

14.01

Eight-membered Rings with One Nitrogen Atom

D. C. Oniciu

University of Florida, Gainesville, FL, USA

© 2008 Elsevier Ltd. All rights reserved.

14.01.1	Introduction	2
14.01.1.1	Scope	2
14.01.1.2	Structure and Nomenclature	2
14.01.2	Theoretical Methods	2
14.01.3	Experimental Structural Methods	3
14.01.3.1	NMR Spectroscopy	3
14.01.3.2	Mass Spectrometry	4
14.01.3.3	X-Ray Diffraction	4
14.01.3.4	HPLC, IR, and UV Spectroscopy, and Other Techniques	5
14.01.4	Thermodynamic Aspects	6
14.01.4.1	Azocines	6
14.01.4.2	Hydroazocines, Azocanes (perhydroazocines), Benzazocines, Dibenzazocines	7
14.01.5	Synthesis	7
14.01.5.1	Azocines	7
14.01.5.2	Hydroazocines	7
14.01.5.3	Azocanes (Perhydroazocines)	20
14.01.5.4	Benzazocines	30
14.01.5.5	Dibenzazocines	31
14.01.6	Reactivity of Unsaturated Derivatives	34
14.01.7	Reactivity of Partially Unsaturated Derivatives (Hydroazocines, Benzazocines, Dibenzazocines)	34
14.01.8	Reactivity of Fully Saturated Derivatives (Azocanes) and of the Ring Nitrogen	36
14.01.9	Applications	41
14.01.9.1	Azocines	41
14.01.9.2	Hydroazocines	42
14.01.9.3	Azocanes (Perhydroazocines)	42
14.01.9.4	Benzazocines	42
14.01.9.5	Dibenzazocines	42
14.01.10	Further Developments	42
14.01.10.1	Properties	42
14.01.10.2	Syntheses	42
14.01.10.3	Applications	44
References		44

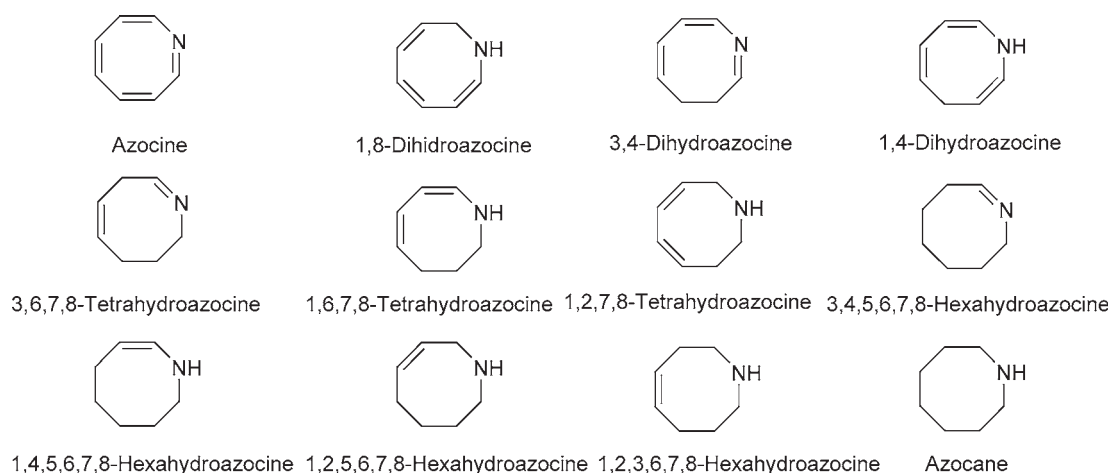
14.01.1 Introduction

14.01.1.1 Scope

Eight-membered rings with one nitrogen atom were discussed in CHEC(1984) <1984CHEC(7)653> and CHEC-II(1996) <1996CHEC-II(9)403>. This chapter covers the chemical literature following the publication of CHEC-II(1996), specifically the years 1996–2006. In the reader's benefit, one has preserved the structure and layout of the CHEC-II(1996) chapter. The updates in this review include structural information, molecular calculations related to ground states and reaction energetics, conformation and aromaticity, preparations, and reactivity.

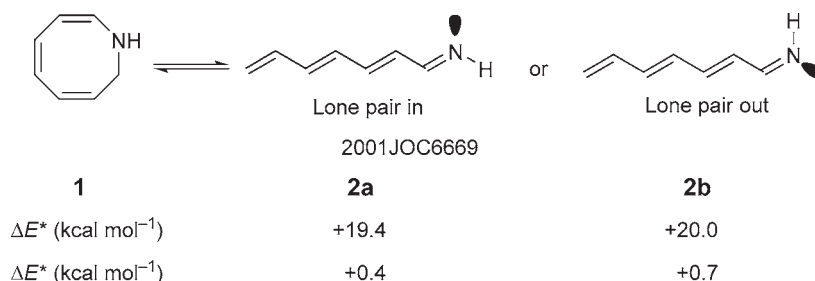
14.01.1.2 Structure and Nomenclature

As in the previous volumes, the current review classifies the eight-membered ring systems with one nitrogen atom in: unsaturated, partially saturated, fully saturated, bridge-head, and fused ring. The system nomenclature followed the Hantzsch–Widman system, which is explained in detail in the previous volumes. As a single distinction from the previous reviews, the term azocane will be used instead of perhydroazocine. A few examples of eight-membered rings with one N atom and their nomenclature are presented.



14.01.2 Theoretical Methods

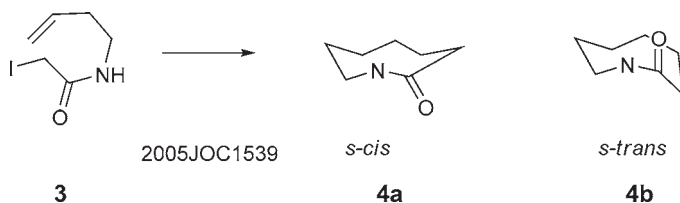
Theoretical methods have been extensively reviewed for the first time in CHEC-II(1996) <1996CHEC-II(9)403>. A new theoretical study of the ring opening of 1-azapolyenes performed using HF, MP2, and B3LYP calculations <2001JOC6669> confirmed that there are two transition states for the azocine ring-opening process: one with the nitrogen electron lone pair 'in' (Scheme 1, 2a) and the other with the electron lone pair 'out' (Scheme 1, 2b). The ring opening is an eight-electron, therefore conrotatory, process. The first transition state 2a with an inwardly rotating lone pair has a barrier of 19.4 kcal mol⁻¹, while 2b has a barrier of 20 kcal mol⁻¹. 1,3,5-Cyclooctatriene has a lower barrier of 16.5 kcal mol⁻¹ as calculated earlier by the same group using B3LYP/6-31G* <1995JA8594>. The ring openings



Scheme 1

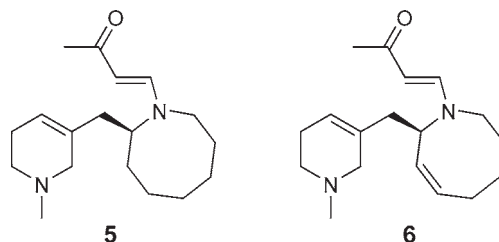
calculated for azocine by the same method used for 1,3,5-cyclooctatriene were shown to be endothermic (0.4 and 0.7 kcal mol⁻¹, respectively). However, the same energies calculated by MP2/6-31G* are exothermic (0.9 and 0.1 kcal mol⁻¹, respectively), while the opening of 1,3,5-cyclooctatriene calculated by B3LYP/6-31G* <1995JA8594> is endothermic (0.9 kcal mol⁻¹). These similar values may be explained by the lower energetic demands during the ring opening of eight-electron rings than for smaller cycles. As for lower energetic demands for the 1,3,5-cyclooctatriene compared to azocine, this can be explained by the fact that the transition state involves only a simple stretching of the breaking C–C bond, and therefore the inward and outward positions have similar interactions with that bond.

The 8-*endo* cyclization of *N*-(4-pentyl) iodoacetamides was investigated by density functional theory calculations at the B3LYP/6-31G* level (Scheme 2 <2005JOC1539>) (see also Section 12.8.5.3). The calculations revealed the propensity of *N*-alkenyl-substituted α -carbamoyl radicals for 8-*endo* cyclization of both *s-cis* and *s-trans* conformational transition structures, while 7-*exo* transition structures were less stable, although both of comparable energy. Theoretical assessments are in agreement with experimental findings.



Scheme 2

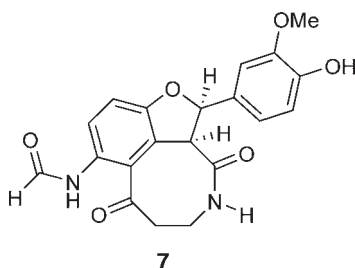
Ground-state conformations for cycloadditions involving 5 and 6 were analyzed by energy minimization of reactant conformations using MM2 force field to explain the effect on unsaturation in the stereoselectivity of cycloaddition <1998T7045>.



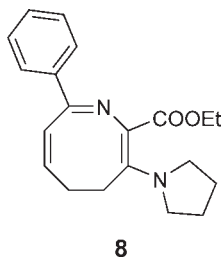
14.01.3 Experimental Structural Methods

14.01.3.1 NMR Spectroscopy

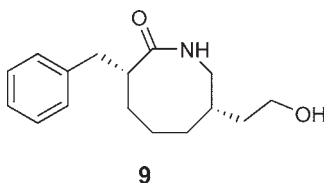
Nuclear magnetic resonance (NMR) techniques have been particularly useful in the structure elucidation of benzazocines or other eight-ring derivatives with multiple substituents. The structure of 3*H*-furo[2,3,4-*k*][3]benzazocine-3,7(4*H*)-dione derivative 7 (named moschamide) was assigned by NMR methods <1998TL1421>. ¹H-NMR and ¹H–¹H COSY45 revealed the number of hydrogen atoms and their connectivity. The carbon skeleton and hydrogen assignments were determined by ¹H–¹³C heteronuclear multiple quantum correlation (HMQC) and ¹H–¹³C heteronuclear multiple bond correlation (HMBC) correlations. The stereochemistry of 7 was elucidated by ¹H–¹H nuclear Overhauser enhancement spectroscopy (NOESY), which completed its full structure elucidation by NMR techniques.



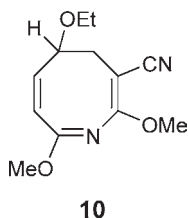
Diverse NMR techniques have been used in the elucidation of reaction mechanisms in azocine and azocane syntheses. For instance, 4,5-dihydroazocine **8** displays a *cis* stereochemistry of the C6/C7 alkene and consequently of the C2/C3 double bond as confirmed by NMR techniques [<2004TL8607>](#), which was in agreement with the disrotatory [4+2] electrocyclic reaction mechanism (see [Section 14.01.5.2](#), [Scheme 6](#)).



The *cis* stereochemistry adopted by lactam **9** in the course of synthesis was elucidated by ^1H NMR, ^1H – ^1H correlation spectroscopy (COSY), and nuclear Overhauser effect (NOE) experiments taking into account the signals for the hydroxyethyl and benzyl fragments [<2002OL2637>](#).



Multi-dimensional NMR was also the tool in the structure elucidation of dihydroazocine **10** in order to prove the addition regioselectivity [<2003JOC1447>](#), and in the synthesis of various benzazocines via Beckmann rearrangement [<2006TL4721>](#).



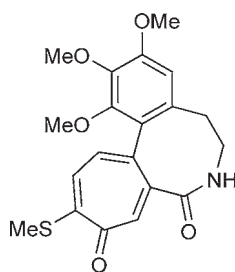
Other examples refer to the confirmation by NMR of reaction mechanisms by structure elucidation of by-products [<1999TL6657>](#), or to conformational analysis by solution NMR. As an example of the latest, solution NMR studies in $\text{CDCl}_2\text{CDCl}_2$ showed a propensity of some eight-membered lactams to dimerize [<2000J\(P1\)2943>](#).

14.01.3.2 Mass Spectrometry

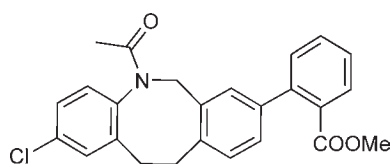
The mass spectra of compounds described in this chapter usually show the molecular ion in traditional techniques. For instance, **10** shows the molecular ion peak 237 (MH^+) by FAB. Other mass spectroscopy techniques have been successfully used for compounds in this class, such as electrospray ionization (ESI) (MNa^+) [<2006T9043>](#) or EI (M^+) [<2000BMC557>](#). Nowadays mass spectroscopy has become a common tool in organic chemistry and mass spectral data are presented for most structures described in this chapter.

14.01.3.3 X-Ray Diffraction

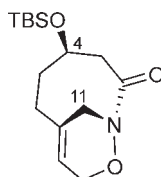
X-Ray diffraction studies have been reported for the first colchicine derivative **11** with an eight-membered *B*-ring lactam [<1997BML2771>](#). There is an intramolecular hydrogen bond $\text{N1-H}\cdots\text{O4}$ with an $\text{N}\cdots\text{O}$ distance of 2.787(6) Å and a $\text{N1-H}\cdots\text{O}$ angle of 167(6)°. The A and C rings are almost planar with a parallel orientation of the 1,2-dimethoxy groups. According to molecular calculations MM2, the antiparallel conformation is favored with 1 kcal mol $^{-1}$.

**11**

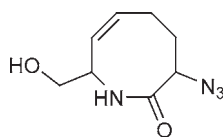
X-Ray data are also useful for molecular modeling of the biological potency. Thus, the X-ray data of benzazocine **12** were manipulated in connection with its inhibitory effect on 17β -hydroxysteroid dehydrogenase type 3 to support structure–activity relationship considerations <2006BML1532>.

**12**

The syn stereochemistry between the silyloxy group at C-4 and the methylene bridge at C-11 in oxazinolactam **13** was established by X-ray <2002OL2637>.

**13**

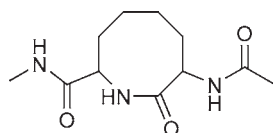
X-Ray crystallographic data for azide **14** revealed a pseudo-boat conformation in solid state <2000J(P1)2943>.

**14**

14.01.3.4 HPLC, IR, and UV Spectroscopy, and Other Techniques

High-performance liquid chromatography (HPLC) techniques have been used lately for enantiomeric separations of benzazocine having a chiral biaryl axis <1998TA3497> and in analytical methods for purity determination <1996JME669, 1997JME1578, 2000JME2362>.

IR and vapor pressure osmometry were utilized in the structure elucidation of lactam **15** <2000J(P1)2943>. It was shown that **15** exists in a semi-extended conformation and exhibits a head-to-tail self-recognition in $\text{CDCl}_2\text{CDCl}_2$.

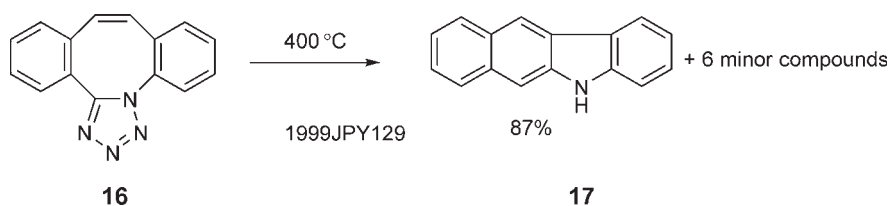
**15**

Ultraviolet (UV) spectra in cyclohexane of some azocine derivatives displayed absorption bands slightly above 300 nm <2003JOC1447>.

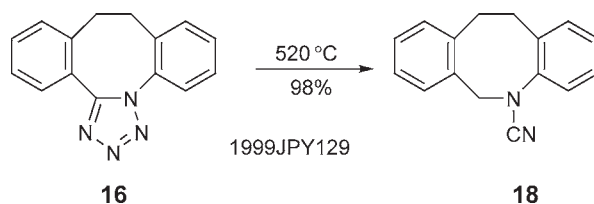
14.01.4 Thermodynamic Aspects

14.01.4.1 Azocines

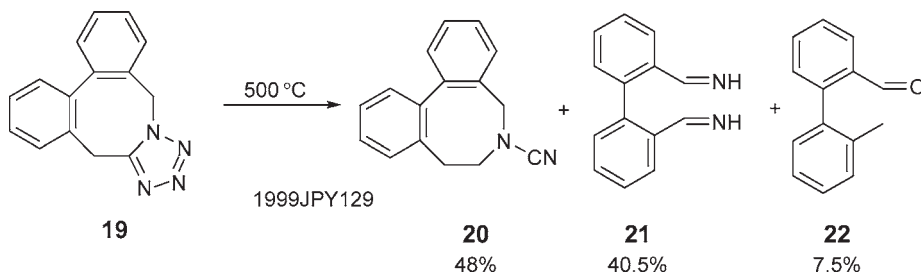
Thermal stability of various tetrazole-substituted dibenzazocines has been extensively studied by flow-vacuum pyrolysis in order to determine the decomposition temperatures (Schemes 3–5 <1999JPY129, 2005RRC153, 2006RRC345>). However, thermodynamic parameters were not reported. Decomposition occurred via nitrene intermediates and the ease of decomposition was attributed to structural factors: bridging of benzene rings, aryl/alkyl neighboring groups, continuous conjugation.



Scheme 3



Scheme 4



Scheme 5

14.01.4.2 Hydroazocines, Azocanes (perhydroazocines), Benzazocines, Dibenzazocines

There are no relevant data reported in this period.

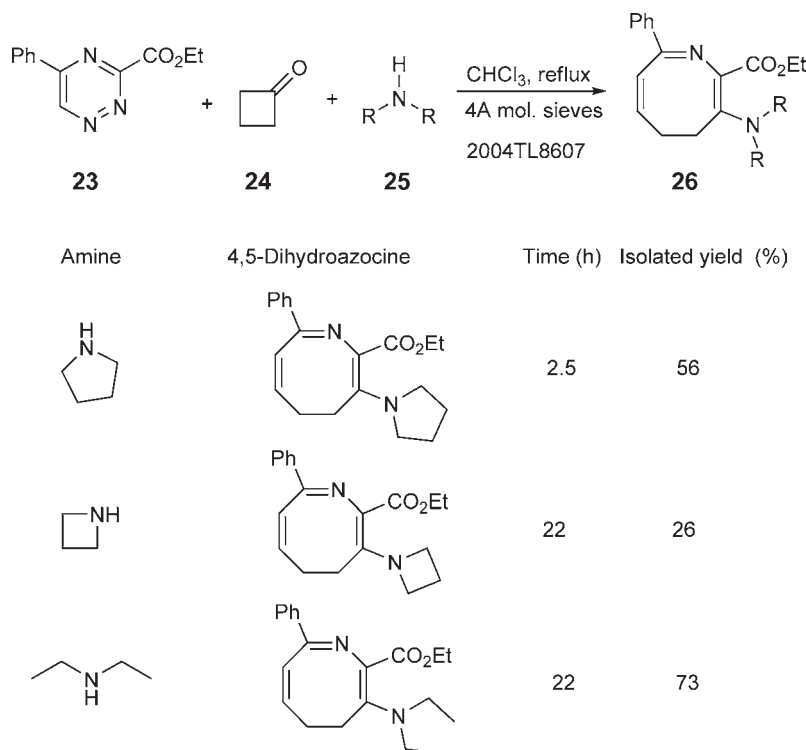
14.01.5 Synthesis

14.01.5.1 Azocines

Methods for the preparation of eight-membered hetarenes and heteroannulenes have been reviewed, including cyclization, ring transformation, aromatization, and substituent modification of azocine and 2-benzazocin-1(2*H*)-one <2004SOS(17)1979>.

14.01.5.2 Hydroazocines

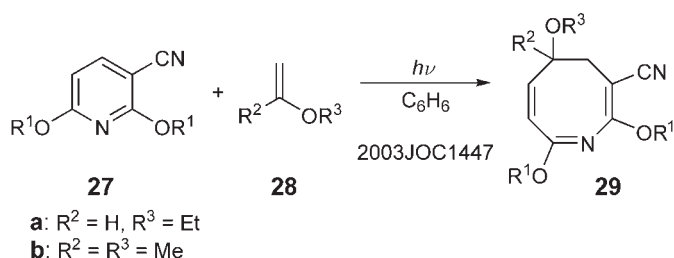
4,5-Dihydroazocines. A one-pot cascade reaction of the easily accessible 3-(ethoxycarbonyl)-5-phenyl-1,2,4-triazine, cyclobutanone, and secondary amines provided easy access to 4,5-dihydroazocines. The reaction, performed in refluxing chloroform in the presence of molecular sieves, is versatile and afforded **26** in moderate to very good yields (Scheme 6 <2004TL8607>). Under these conditions, cyclobutylamine reacted in 26% yield, while diethylamine in 73% yield.



Scheme 6

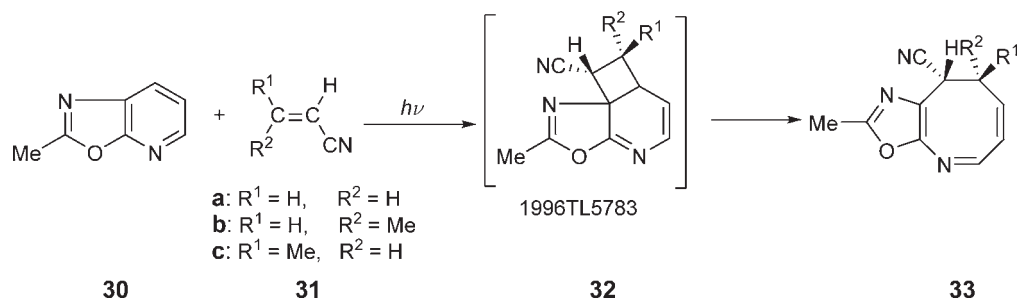
4,5-Dihydroazocines are also obtained by irradiation of a benzene solution of 3-cyano-2,6-dimethoxypyridine (0.2 M) in the presence of a solution of ethyl vinyl ethers 0.1 M at room temperature (Scheme 7 <2003JOC1447>). The irradiation was performed with a high-pressure mercury lamp for 6 h. Adducts **29** were obtained in good yields.

Acrylonitrile **31a** and butendionitriles **31b** and **31c** underwent cycloadditions to methyloxazolo[5,4-*b*]pyridine **30** followed by ring opening to afford 2-methyloxazolo[5,4-*b*]dihydroazocines **33** as main products. The reaction is regio- and stereospecific (Scheme 8 <1996TL5783>). Other oxazolopyridines, such as [4,5-*b*], [4,5-*c*], and [5,4-*c*], were not reactive under these conditions, which was explained by the different nature of the lowest electronic level based on fluorescence data: for the [5,4-*b*], it is $\pi-\pi^*$, and for instance for the [4,5-*b*] derivative, it is $n-\pi^*$ (or mixed).



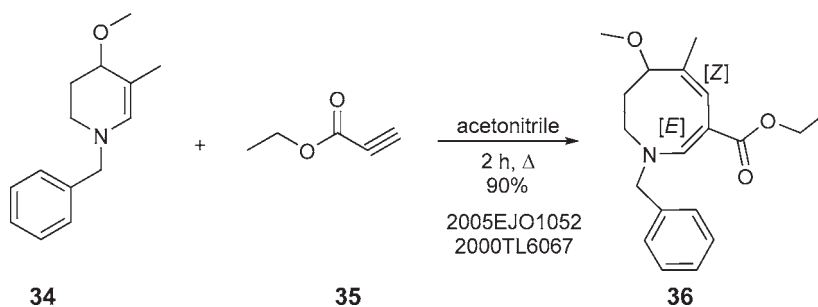
R^1	Alkene	Conv (%)	Yield (%)
Me	a	95	83
Et	a	96	70
<i>i</i> -Pr	a	93	70
Me	b	64	60

Scheme 7



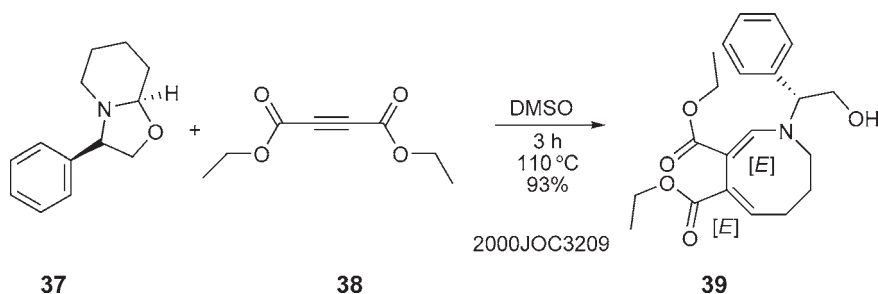
Scheme 8

1,6,7,8-Tetrahydroazocines. Tetrahydropyridines **34**, obtained in four steps from readily available 3-alkyl-*N*-benzylpyridinium salts, were used in the preparation of functionalized azocine derivatives **36** via their corresponding iminium salts (Scheme 9 <2005EJO1052, 2000TL6067>). Tetrahydropyridines were heated with ethyl propiolate in refluxing MeCN for 2 h to yield compounds such as **36** in good to excellent yields.



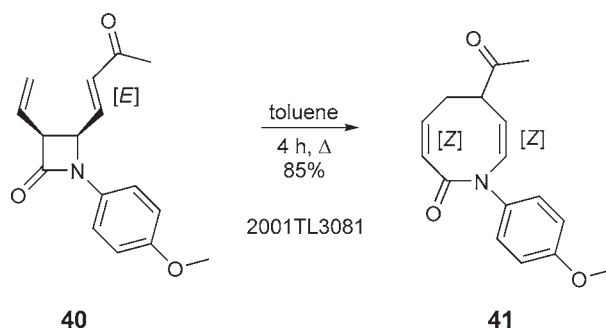
Scheme 9

Tetrahydroazocines such as **39** were obtained in excellent yields by heating phenyloxazolopiperidine **37** with diethyl acetylenedicarboxylate **38** in dimethyl sulfoxide (DMSO) (Scheme 10 <2000JOC3209>).

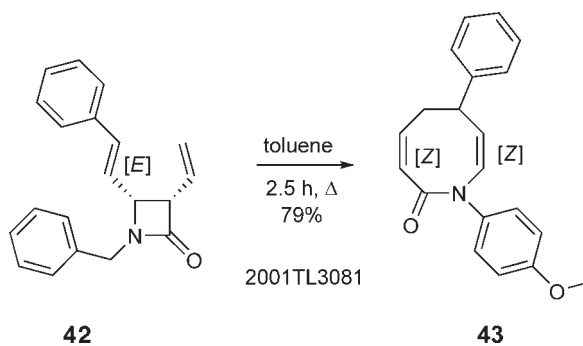


Scheme 10

1,4,5,8-Tetrahydroazocines. *Cis*-divinyl- β -lactams **40** and **42** with alkenyl groups at both C-3 and C-4 positions underwent thermally induced [3,3]sigmatropic (Cope) rearrangement to produce tetrahydroazocinones **41** (Scheme 11 <2001TL3081>) and **43** (Scheme 12 <2001TL3081>), respectively, by a concerted C(3)–C(4) bond breakage of the azetidine ring. The process is thermodynamically favored by the four-membered ring strain.



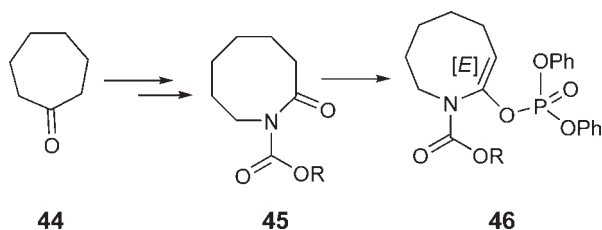
Scheme 11



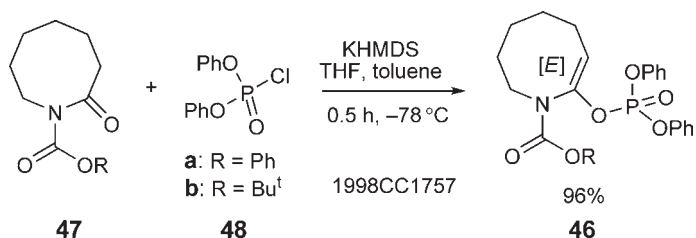
Scheme 12

1,4,5,6,7,8-Hexahydroazocines. The synthesis of stable ketene aminal diphenylphosphates **46** was accomplished departing from the eight-membered *N*-BOC or *N*-COOPh protected lactams **45** via their potassium enolates (Scheme 13 <1998CC1757>). Azocane-2-one **45** was easily obtained from cycloheptanone **44** by Beckmann rearrangement of its cycloheptanone-oxime and subsequent protection of the amino moiety.

The synthesis of diphenylphosphates **46a** and **46b** proceeded in good yields in the presence of KHDMS in a mixture of solvents (e.g., tetrahydrofuran (THF) and toluene) (Scheme 14 <1998CC1757>) and generated products that are stable at room temperature and to various manipulations, such as silica gel flash chromatography.

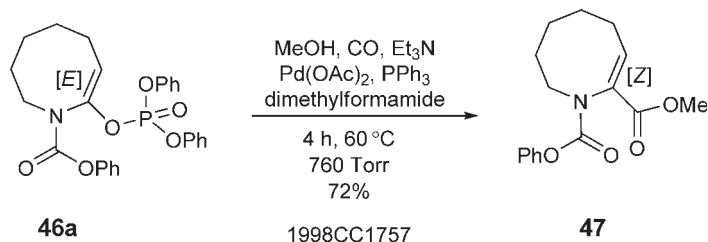


Scheme 13



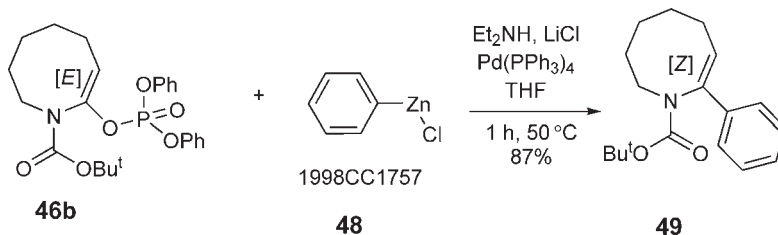
Scheme 14

Diphenylphosphates **46a** and **46b** were shown to be excellent substrates for the synthesis of functionalized tetrahydroazocines by nucleophilic substitution. Thus, phenyl ester **46a** underwent carbonylation at atmospheric pressure in the presence of Pd(OAc)₂ (Scheme 15 <1998CC1757>).

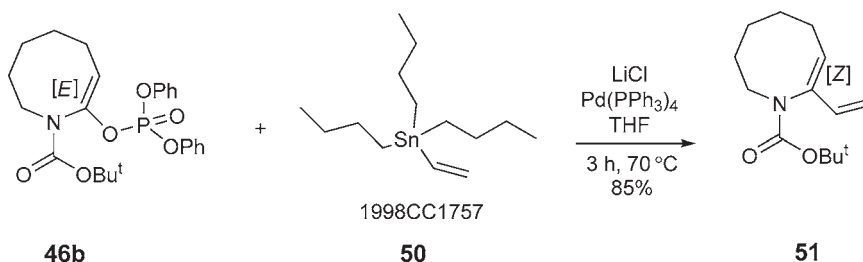


Scheme 15

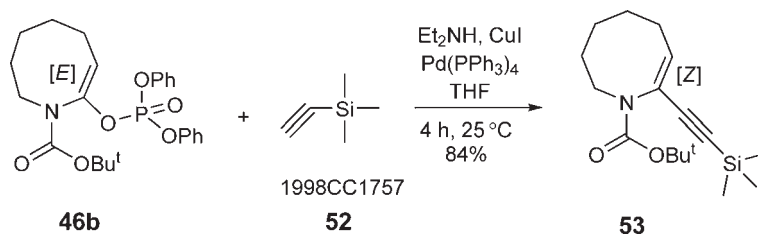
Diphenylphosphates **46b** reacted with various nucleophiles in the presence of Pd(0) and Ni(0) catalysts to produce a variety of functionalized hexahydroazocines in good to excellent yields. The (*E*)-stereochemistry of the diphenylphosphonate double bond was changed into a (*Z*)-stereochemistry in the reaction product **49**. The *N*-BOC-protected diphenylphosphate **46a** reacted with arylzinc **48** in the presence of Pd(PPh₃)₄ to give 2-aryl-substituted hexahydroazocine **49** (Scheme 16 <1998CC1757>). It also underwent alkenylation with stannum derivative **50** in the presence of LiCl (Scheme 17 <1998CC1757>) to produce diene **51**, and with silyl alkyne **52** in the presence of CuI/Et₂NH to produce alkyne **53** (Scheme 18 <1998CC1757>).



Scheme 16

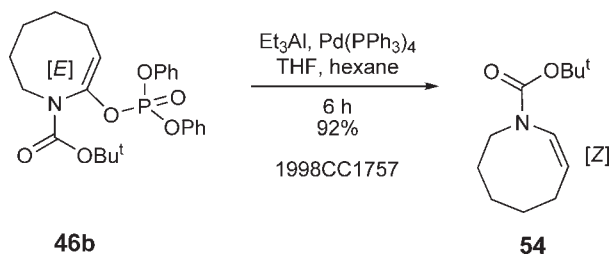


Scheme 17



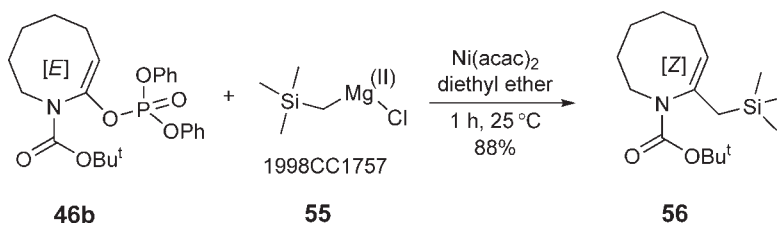
Scheme 18

Diphenylphosphate **46b** was also reduced to the parent 1,4,5,6,7,8-hexahydroazocine **54** by reaction with Et_3Al /hexane in the presence of $\text{Pd}(\text{PPh}_3)_4$ (Scheme 19 <1998CC1757>).



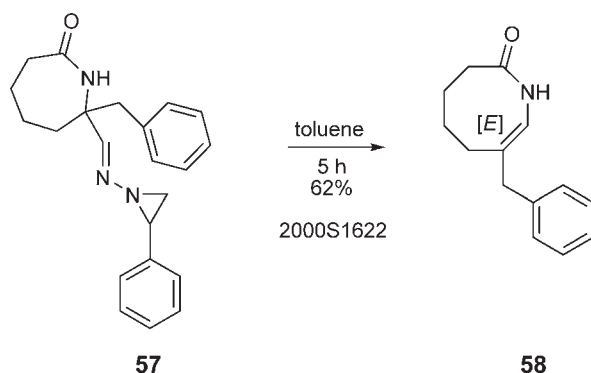
Scheme 19

Grignard reagent **55** reacted with diphenylphosphate **46b** (Scheme 20 <1998CC1757>) in the presence of $\text{Ni}(\text{acac})_2$ to afford **56** capable of further functionalization.



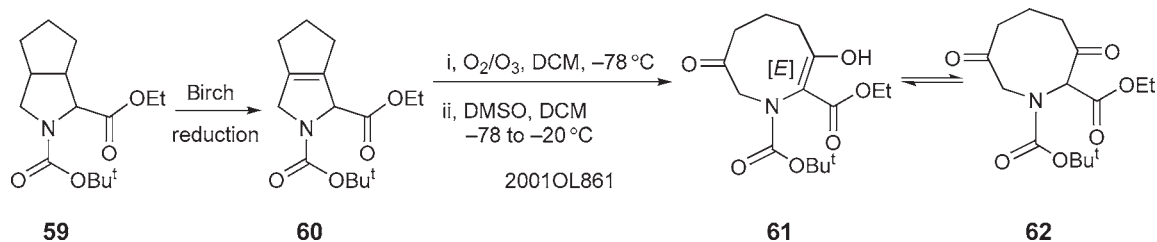
Scheme 20

α -Azacyclo-*N*-aziridinylimines, such as **57**, generated carbenes by thermolysis in refluxing toluene, and underwent ring expansions via intramolecular ammonium ylide formation to produce hexahydroazocines (e.g., **58**) with an (*E*)-stereoconfiguration (Scheme 21 <2000S1622>).

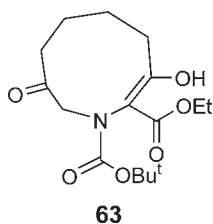


Scheme 21

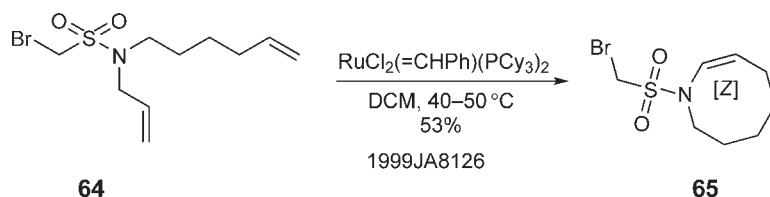
Medium-ring heterocycles were obtained starting from annulated pyrroles by a Birch reduction and subsequent oxidative cleavage [2001OL861](#). Although experimental data for **61** were not included, the authors claimed that it could be obtained as shown in [Scheme 22](#). Only the synthesis and characterization of its nine-membered ring analogue **63** was described, which were isolated as its enol tautomer. Given the availability of annulated pyrroles and the ease of their functionalization, such a sequence has a great synthetic potential.



Scheme 22

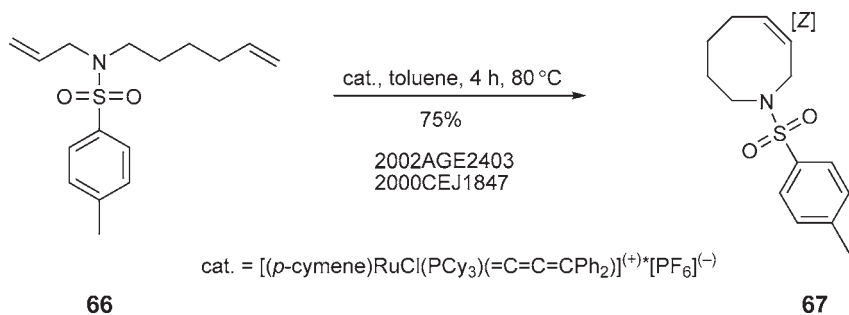


Ring-closing metathesis of the readily accessible doubly unsaturated sulfonamide **64** proceeded in the presence of the Grubbs catalyst in 53% yield to produce azocine **65** ([Scheme 23](#) [1999JA8126](#)).

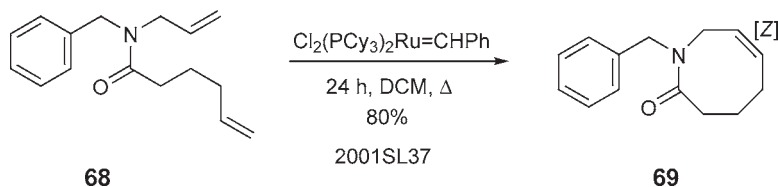


Scheme 23

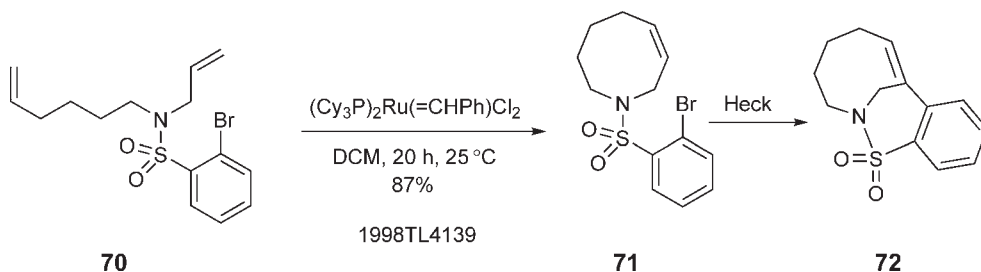
1,2,5,6,7,8-Hexahydroazocines were obtained in good to excellent yields by olefin metathesis in aprotic or protic media, in the presence of efficient catalysts under an air atmosphere. A large variety of catalysts were explored for this purpose and various *N*-functionalized hexahydroazocines were obtained by this versatile reaction (**Scheme 24** <2000CEJ1847, 2002AGE2403>, **Scheme 25** <2001SL37>, **Scheme 26** <1998TL4139>). The method was extensively reviewed <2003ASC572>. Reported yields were good to excellent.



Scheme 24



Scheme 25



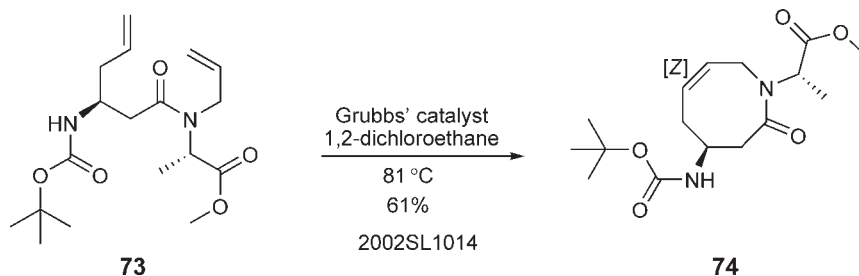
Scheme 26

The sequential or cascade combination of olefin metathesis with intramolecular Heck reactions (in the presence of 10 mmol% $\text{Pd}(\text{OAc})_2$, 20 mmol%, 1 mol equiv Et_4NCl , 2 mol equiv K_2CO_3 in DMF at 100°C for 2–4 h) provided access to fused eight-membered rings. Mixtures of double bonds were produced during metathesis in the presence of $(\text{Cy}_3\text{P})_2\text{Ru}(=\text{CHPh})\text{Cl}_2$ (**Scheme 26** <1998TL4139>).

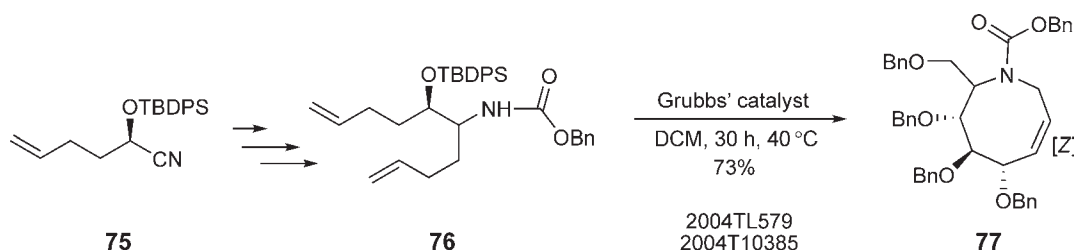
Other examples of metathesis reactions using various generations of the Grubbs's catalyst were also reported (**Scheme 27** <2002SL1014>, **Scheme 28 and 29** <2004TL579, 2004T10385>, **Scheme 30** <2004JA9524>). In the synthesis of unsaturated Homo-Freidinger lactam (lactam-bridged dipeptide mimic) **74** the metathesis of precursor **73** was the key step (**Scheme 27** <2002SL1014>).

Substrates **76** prepared from readily affordable chiral unsaturated cyanohydrins **75** were transformed into eight-membered rings by combining a diisobutylaluminum hydride (DIBAL) reduction–allylamine transimination– NaBH_4 reduction sequence (not shown) with a ring-closing metathesis. The sequence afforded hexahydroazocinols **77** in high yields and excellent ee (97–99%) (**Scheme 28 and 29** <2004TL579, 2004T10385>). Eight-membered

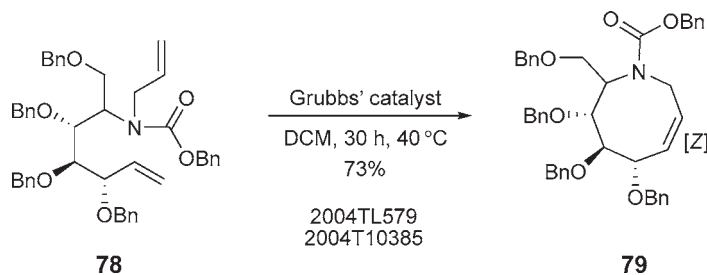
iminoalditol **78** was synthesized from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose by ring-closing metathesis. Dehydroazocane **79** was thus formed in a *D-gluco* configuration for C(2)–C(5), and appears to exist predominantly in a boat–chair conformation (**Scheme 29** <2004TL579>).



Scheme 27

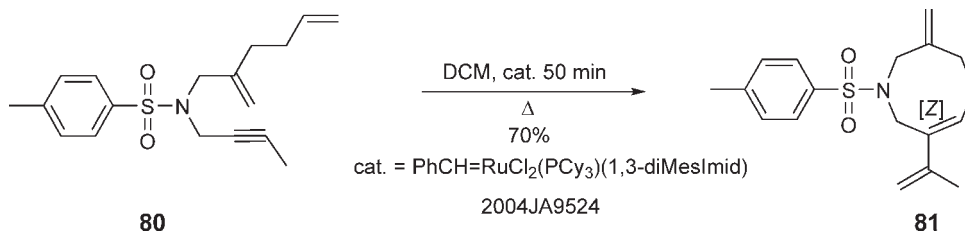


Scheme 28



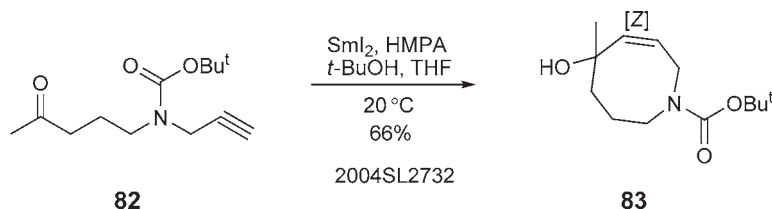
Scheme 29

A catalytic tandem cyclopropanation-ring-closing metathesis of dienyne **80** led to derivative **81** in good yield (**Scheme 30** <2004JA9524>). For internal alkynes, carbene-mediated ring-closing enyne metathesis was observed. Less favorable alkyne binding leads to preferential reactions of the metal carbene with the 1-alkene moiety.



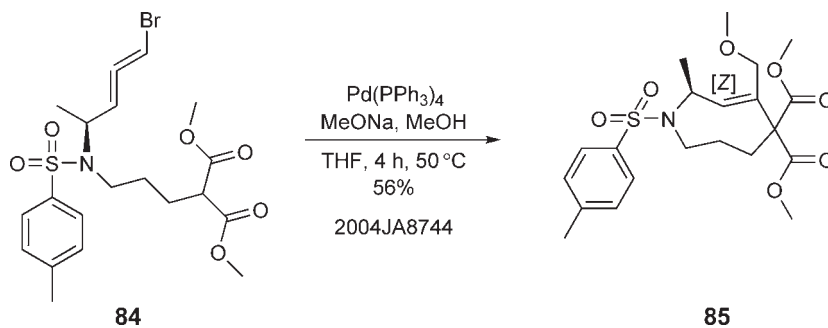
Scheme 30

Hexahydroazocines were prepared by ketyl-alkyne coupling starting from alkynyl-substituted ketones. Thus, by using SmI_2 as a catalyst in the presence of hexamethylphosphoramide (HMPA), ketone **82** was transformed into **83** (Scheme 31 <2004SL2732>). Reported yields for the synthesis of eight-membered rings using this methodology range from 43% to 78%.



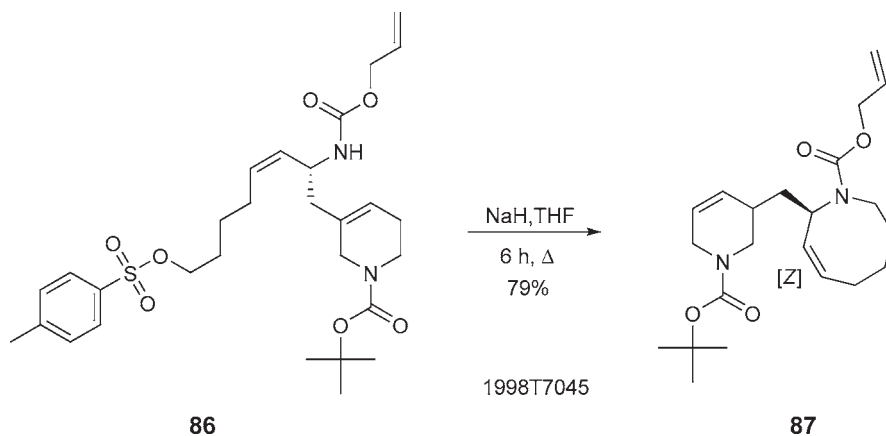
Scheme 31

The first example to demonstrate the synthesis of medium-sized rings via cyclization of bromoallenes is illustrated in Scheme 32 <2004JA8744>. *N*-Protected bromoallene **84** acted as an allyl dication equivalent and afforded eight-membered ring **85** with a *trans*-configuration. The reaction was conducted without using high dilution conditions, as it is usually necessary for medium- and large-membered rings.

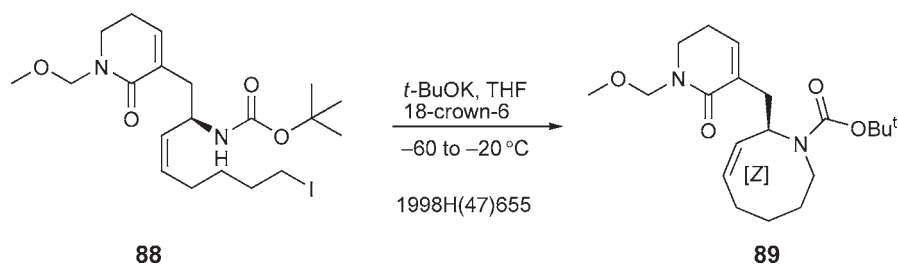


Scheme 32

Dehydrocyclizations (Scheme 33 <1998T7045>) and dehydrohalogenations (Scheme 34 <1998H(47)655>) produced hexahydroazocines in good yields.

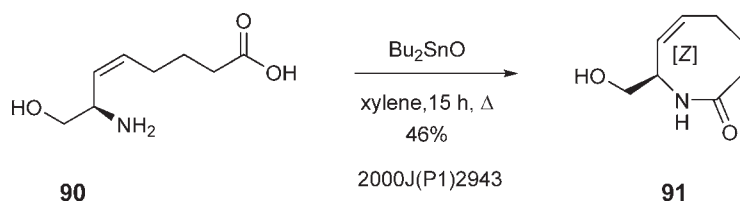


Scheme 33

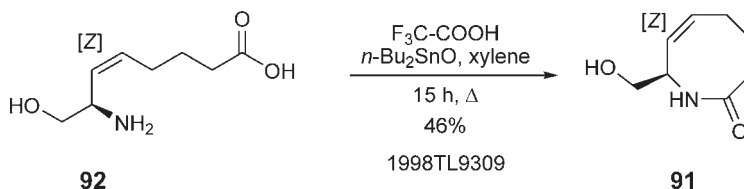


Scheme 34

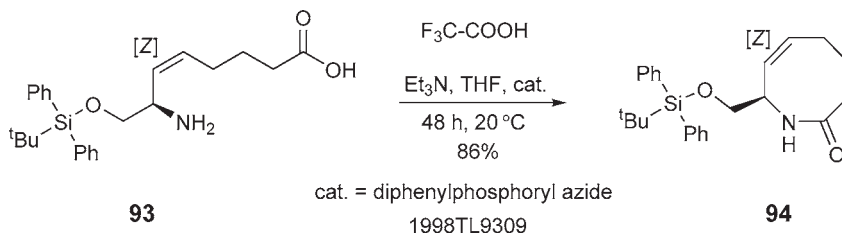
Cyclic amides were also obtained by amidation reactions in various conditions in good to moderate yield (Scheme 35 <2000J(P1)2943>, Scheme 36 <1998TL9309>, Scheme 37 <1998TL9309>, and Scheme 38 <1998TL9309>). Hydroxymethyl-substituted eight-membered lactam **91** was prepared by the cyclization of amino acid **90** in the presence of dibutyltin oxide in refluxing xylene (Scheme 35). In this reaction, the yield never exceeded 50%, while for the similar reaction to produce the corresponding seven-membered lactam the yield increased to 89%.



Scheme 35

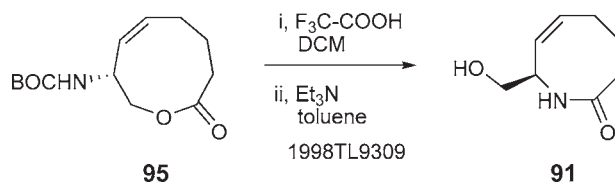


Scheme 36



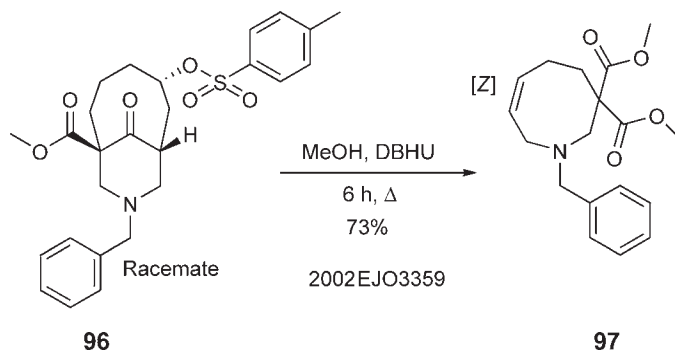
Scheme 37

N-Protected 7-amino-8-hydroxyoctenoic acids, such as **92**, were cyclized to their corresponding nine-membered ring lactones, which underwent intramolecular *O*-to-*N*-acyl (lactone-to-lactam) ring contraction in the presence of trifluoroacetic acid to yield 8-hydroxymethyl-6,7-dehydroazocane **91** (Schemes 36 and 37 <1998TL9309>). The reaction was shown to occur via intermediate nine-membered lactone **95**, which was obtained separately from the above-mentioned acid and rearranged to the corresponding azocine (Scheme 38 <1998TL9309>).



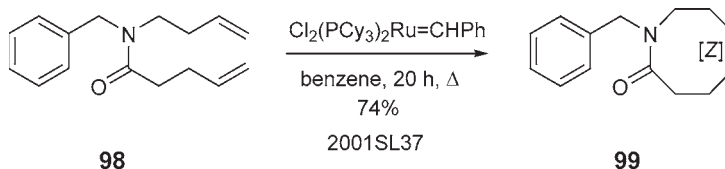
Scheme 38

Ring opening of bicyclic ketone derivative **96** provided dehydroazocane **97** in good yields (Scheme 39 <2002EJO3359>).



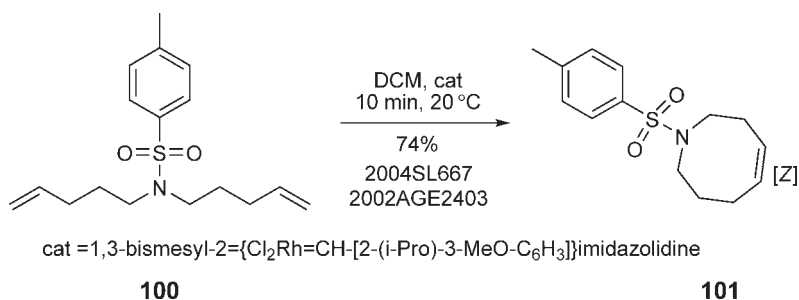
Scheme 39

1,2,3,4,7,8-Hexahydroazocines, such as **99**, were prepared by a metathesis process similar to other isomers described above (Scheme 40 <2001SL37>).



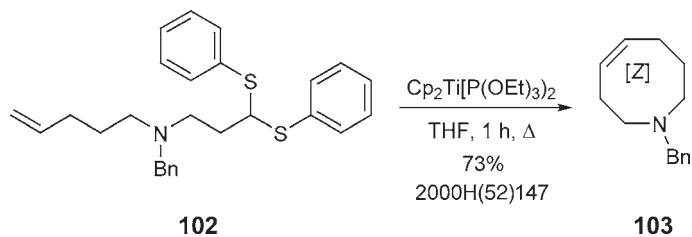
Scheme 40

Lately, hexahydroazocines, such as **101**, were prepared by olefin metathesis using novel ruthenium alkylidene catalysts (Scheme 41 <2002AGE2403, 2004SL667>). Reactions were carried out at room temperature using 1 mol% of catalysts. Yields were moderate to excellent.



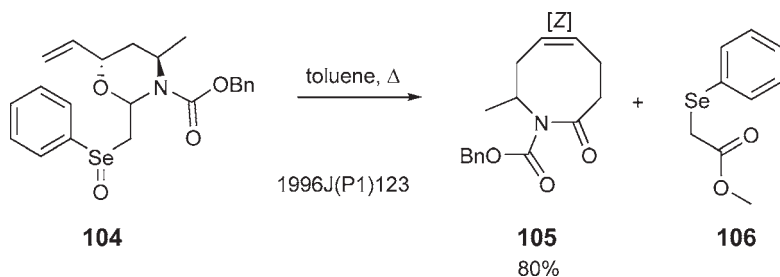
Scheme 41

The substrate for metathesis leading to product **103** was prepared *in situ* prior to cyclization in the form of a titanium–carbene complex, by desulfurization of thioacetals with low-valent titanium catalysts, such as $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$ (Scheme 42 <2000H(52)147>).



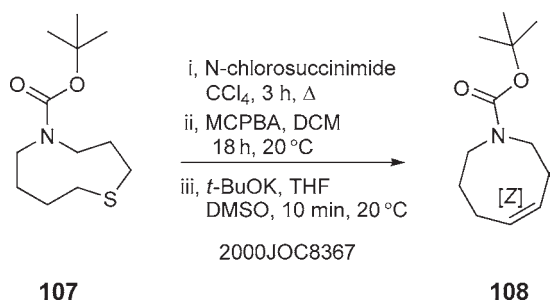
Scheme 42

Unsaturated eight-membered lactams **105** were prepared in good yields by the Claisen rearrangement of vinyl-substituted precursors **104** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 43 <1996J(P1)123>).



Scheme 43

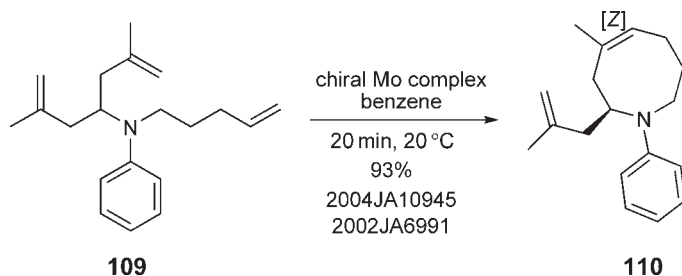
A Ramberg–Bäcklund rearrangement of azacycle **107** catalyzed by *t*-BuOK introduced *cis*-stereoselectively a double bond (Scheme 44 <2000JOC8367>). In order for the reaction to occur, macrocycle **107** was prior converted to the appropriate α -chlorosulfone.



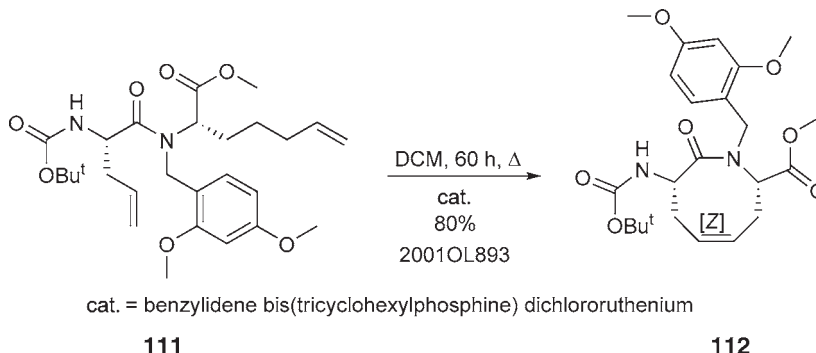
Scheme 44

Asymmetric ring-closing metathesis (performed in the presence of asymmetric Mo complexes as catalysts and in the absence of solvents) produced eight-membered rings in high yield and exceptional enantioselectivity (Scheme 45 <2004JA10945, 2002JA6991>). The catalysts were prepared *in situ* from commercially available reagents.

Ring-closing metathesis of diallylglycine **111** in the presence of a ruthenium catalyst was promoted by the 2,4-dimethoxybenzyl group, which constrained the stereochemistry to the appropriate rotamer (Scheme 46 <2001OL893>). The product **112** obtained in 80% yield was further deprotected to give a cyclic dipeptide useful in peptidomimetic research. Same lactam with *trans*-amide and *trans*-olefin configuration was obtained in 75% yield by using a 20 mol% of the first generation Grubbs' catalyst in refluxing DCM for 75 h.

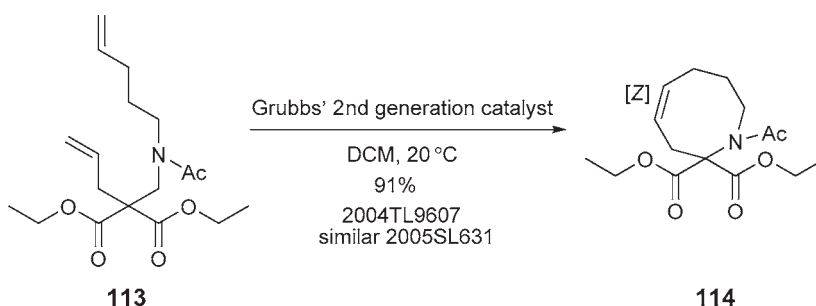


Scheme 45



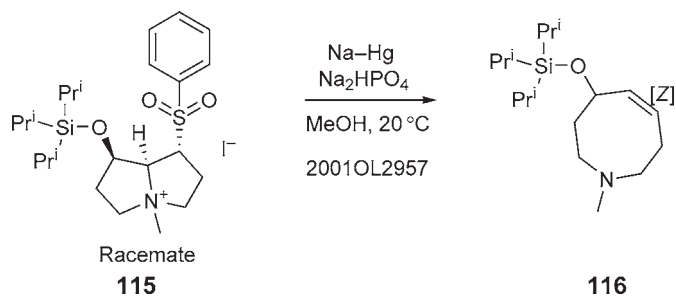
Scheme 46

Ring-closing metathesis of derivative **113** in the presence of the second generation Grubbs' catalysts produced cyclic amino acid derivative **114** in excellent yield (Scheme 47 <2004TL9607, 2005SL631>). By using the first generation, only mixtures of products were isolated. The starting material was obtained by subsequent *C*-alkylation (in the presence of Cs_2CO_3 in refluxing MeCN) and *N*-alkylation (in the presence of KH in refluxing DMF) of diethyl acetamidomalonate.



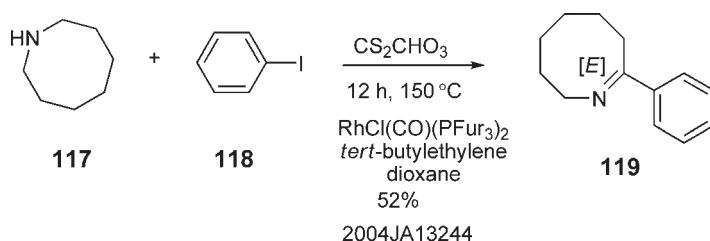
Scheme 47

Medium-sized cyclic amines (eight- to ten-membered ring) were prepared by selective ring opening of sulfonated bicyclic pyrrolizines, indolizines, and quinolizines, which occurred by selective cleavage of the central C–N bond of the bicyclic amine by means of a Julia-like olefin-forming desulfonation <2001OL2957>. Thus, *N*-methylated pyrrolizine **115** was treated with Na–Hg at room temperature under typical desulfonation conditions (Na_2HPO_4 , MeOH) to afford product **116** in 70% yield (Scheme 48 <2001OL2957>).

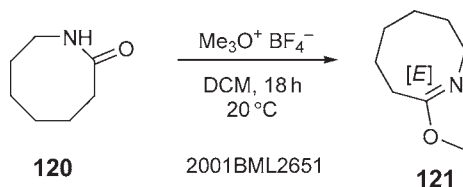


Scheme 48

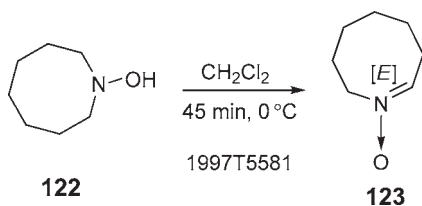
3,4,5,6,7,8-Hexahydroazocines were obtained by various functionalizations of unsubstituted azocane **117** (Scheme 49 <2004JA13244>), its lactam: azocane-2-one **120** (Scheme 50 <2001BML2651>), and its hydroxylamine **122** (Scheme 51 <1997T5581>) using common methodologies.



Scheme 49



Scheme 50

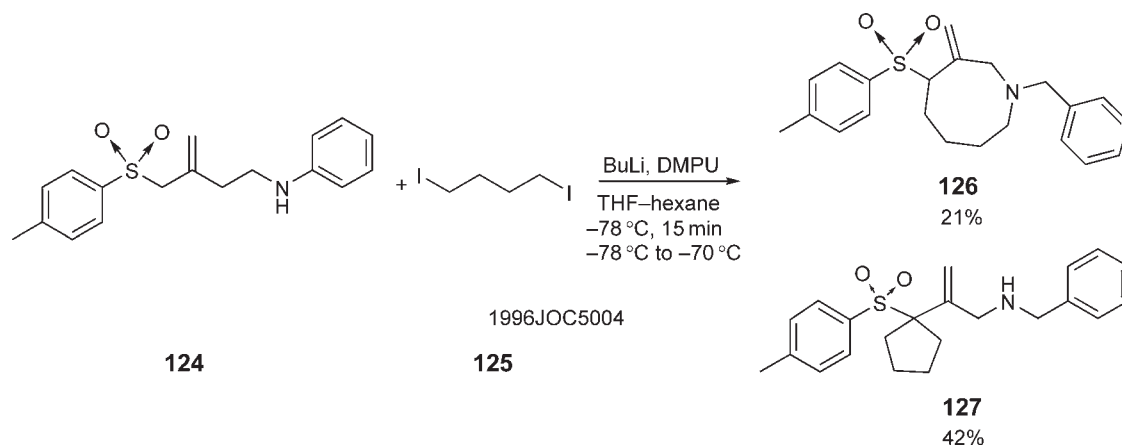


Scheme 51

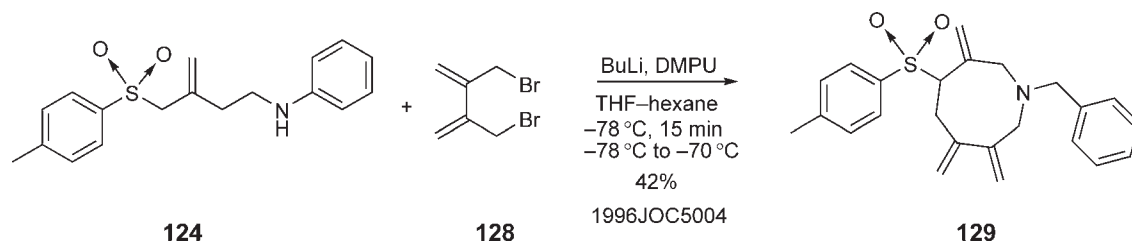
14.01.5.3 Azocanes (Perhydroazocines)

Syntheses of azocanes usually revolve around inter- or intramolecular cyclizations and rearrangements. Intermolecular cyclizations usually imply two reactive centers on each component. Intramolecular cyclizations involve two steps: (1) preparation of a building block with reactive ends (either multiple bonds or reactive functionalities containing the nitrogen atom) and (2) intramolecular cyclization or elimination. Among other synthetic methods reported are carbon insertions using various synthons, Beckmann rearrangements, ring-opening reactions, etc.

Intermolecular cyclizations. One-pot alkylation–cyclization of γ -tosyl-substituted benzyl-methallylamines afforded eight-membered derivatives via γ -amino-methallyl sulfone anions <1996JOC5004>. The dilithiation of benzyl[2-(tosylmethyl)propenyl]amine **124** with BuLi at -78°C led to a mono- and di-anion; the dianion further reacted with α,δ -dihalo derivatives to produce azocanes (Schemes 52 and 53 <1996JOC5004>). Thus, reacting the methallyl sulfone anion of **124** with 1,4-diiodobutane, **126** was obtained in 21% yield, while the main product **127** obtained in 42% yield was the result of monoalkylation. Similarly, 2,3-bis(bromomethyl)buta-1,3-diene **128** reacted with the same dianion to afford only azocane **129** in 42% yield (Scheme 53).

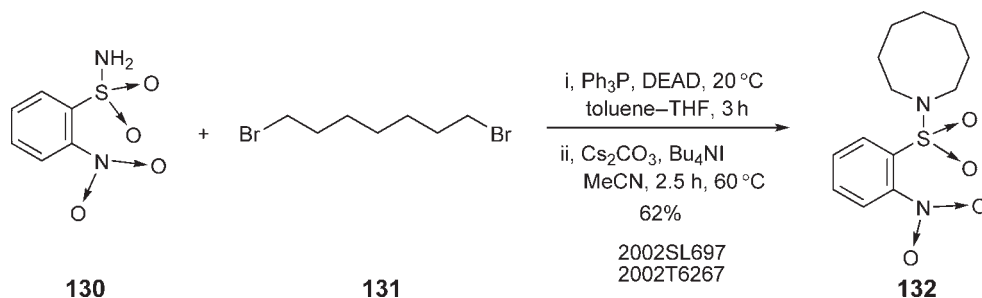


Scheme 52



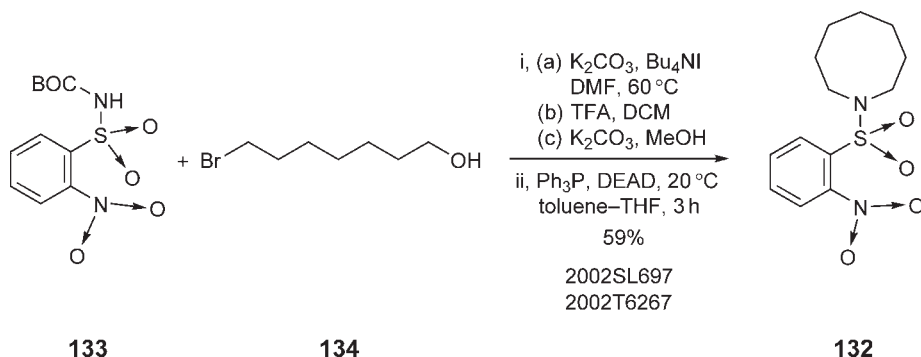
Scheme 53

An efficient synthesis of the azocane cycle was accomplished by alkylation of 2-nitrobenzenesulfonamide **130** with dibromoheptane **131** and subsequent cyclization of the sulfonamide thus obtained (Scheme 54 <2002SL697, 2002T6267>). The synthesis of the N-substituted azocane **132** took place under conventional alkylation conditions followed by cyclization (dehydrohalogenation) in the presence of Cs_2CO_3 (Scheme 54), with a yield of 62%. When using α,ω -diols or haloalcohols, as alkylating agents (Scheme 55), the alkylation was performed in basic conditions,



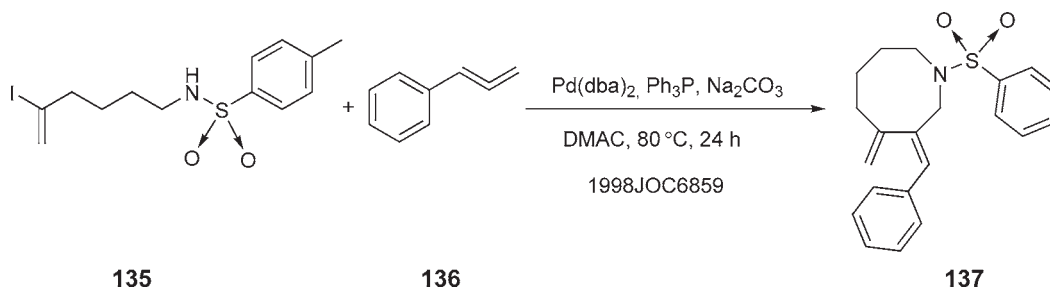
Scheme 54

and construction of the azocane ring **132** was performed by dehydration in Mitsunobu conditions. The ring closure proceeded without secondary reactions or branching effects in both conventional alkylation and Mitsunobu conditions <2002T6267>.



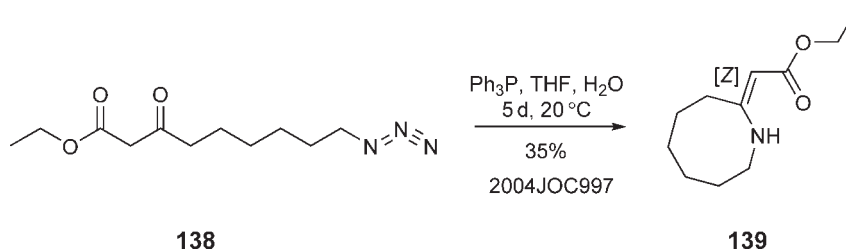
Scheme 55

Palladium-catalyzed heteroannulation of a variety of 1,2-dienes (i.e., allene **136**) by tosylamide-containing aryl or vinyl halides produced eight-membered heterocycles such as **137** (Scheme 56 <1998JOC6859>). The yields are dependent on the reaction conditions: palladium catalyst utilized [PdCl_2 , $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{PPh}_3)_4$ etc.], base [Na_2CO_3 (2–5 equiv), KOAc (5 equiv), K_2CO_3 (5 equiv), etc.], and solvent [DMAC, DMSO, DMF], and varies from 0% [Li_2CO_3 (5 equiv)/ $\text{Pd}(\text{dba})_2$ in DMA] to 61% [Na_2CO_3 (5 equiv)/ $\text{Pd}(\text{dba})_2$ in DMAC]. The best results are obtained when using 1 equiv organic iodide, 2 equiv of allene, 5 mol% of $\text{Pd}(\text{dba})_2$, 5 mol% of Ph_3P , 1 equiv Bu_4NCl , and 5 equiv Na_2CO_3 in DMAC at 80°C for 1 day.



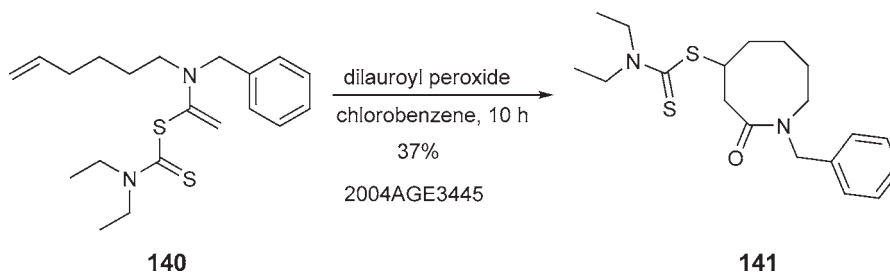
Scheme 56

Intramolecular cyclizations. Cyclizations of ω -azido- β -ketoesters, such as **138** (obtained by a multistep reaction starting from cyclohexanone), produced eight-membered enamines **139** (Scheme 57 <2004JOC997>). Preparations of **138** are based on a method developed from the formal ring expansion of cyclic ketones via retro-Reformatsky fragmentation <2004JOC997>.



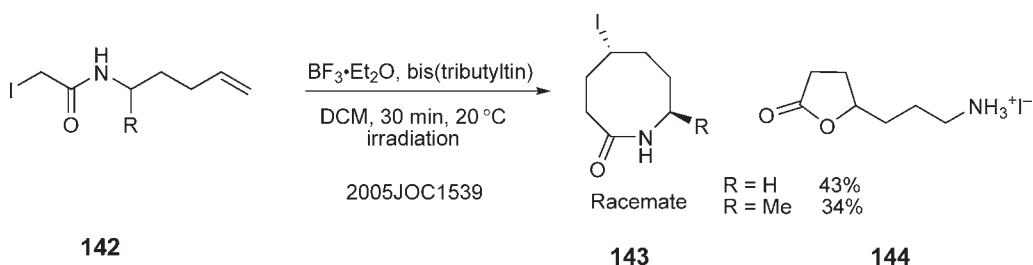
Scheme 57

Metathesis of dithiocarbamate **140** in chlorobenzene in the presence of lauroyl peroxide produced azocane **141** in modest yields (Scheme 58 <2004AGE3445>). The use of a higher-boiling solvent was found to be beneficial in this case. There are no earlier reports of the cyclization of carbamoyl radicals for rings larger than six in the radical chemistry literature, and few reports of direct formation of any eight-membered ring in the radical chemistry literature <2003OL325>.

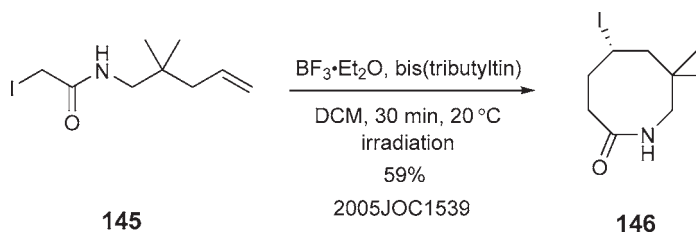


Scheme 58

N-(4-Pentenyl)iodoacetamides (i.e., **142** and **145**) underwent atom transfer radical cyclization reactions in the presence of trifluoroborate etherate at room temperature, usually with an excellent 8-*endo* regioselectivity (Schemes 59 and 60 <2005JOC1539>). It was thus shown that 8-*endo* cyclization of *N*-alkenyl α -carbamoyl radicals is an intrinsically favored process easily promoted by a Lewis acid, such as $\text{BF}_3 \cdot \text{OEt}_2$.



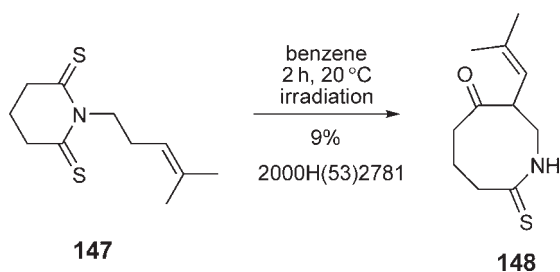
Scheme 59



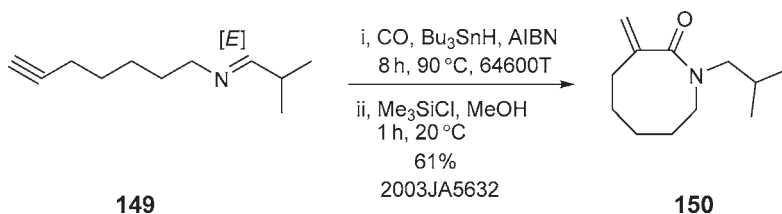
Scheme 60

Intramolecular photoreaction of dithioimides of type **147** yielded substituted azocanes **148** in low yields (Scheme 61 <2000H(53)2781>).

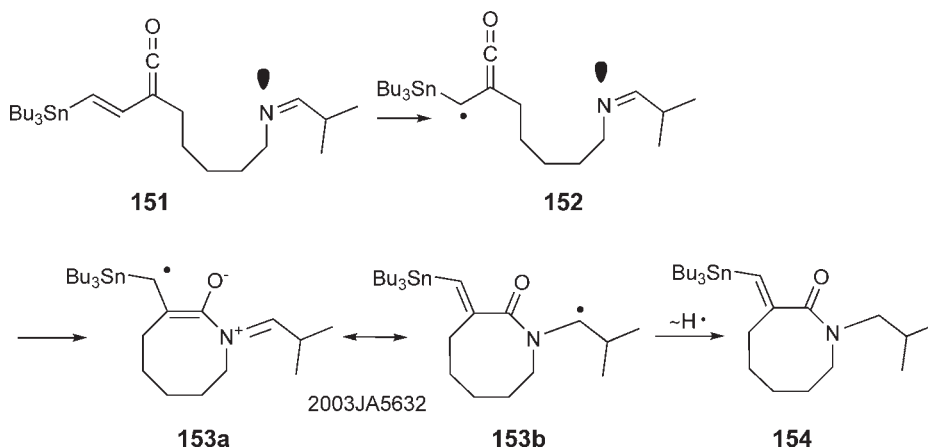
Insertion reactions using CO and CH₂N₂. Radical cyclization reactions of azaenynes in the presence of butyl stannanes in carbonylation conditions furnished β -lactams <2003JA5632>. Azocanone **150** (Scheme 62) was prepared in good yield from enyne **149**. The reaction occurred via α -stannylmethylene lactam of type **154** (Scheme 63). This free radical-mediated stannyl carbonylation is quite versatile and provides a general [*n*+1]-type annulation leading to 4-*exo* and 8-*exo* systems. The yield of the isolated stannylene lactam intermediate **154** was reported as 61%, while the destannylation to lactam **150** was quantitative.



Scheme 61



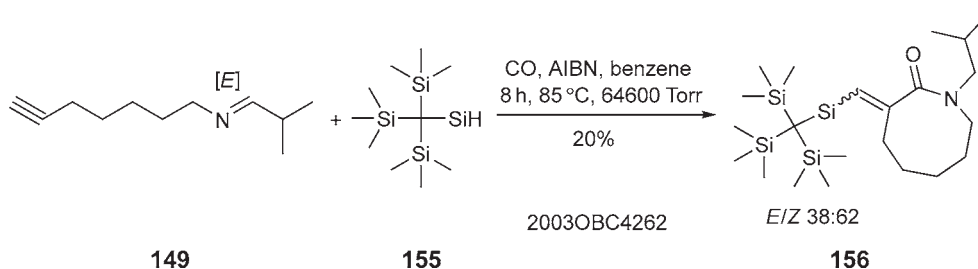
Scheme 62



Scheme 63

The reaction mechanism is presumed to rely on the ability of the α,β -unsaturated acyl **151** to generate an α -ketenyl radical **152**, which reacted as an electrophile toward the imino functionality to produce the radical-zwitterion **153** (Scheme 63 <2003JA5632>).

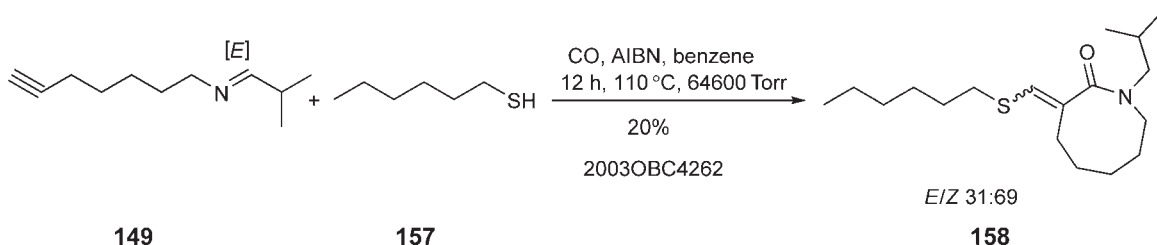
Similar free radical-mediated cyclo-oxidations of azaenynes were performed in the presence of *tris*(trimethylsilyl)silane **155** and afforded β -lactams **156** in moderate yields (Scheme 64 <2003OBC4262>). The (*Z*)-diastereoselectivity



Scheme 64

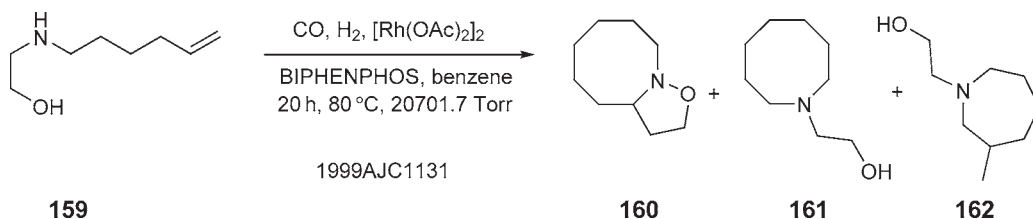
of this reaction is similar to the Sn-mediated cyclization of the system described in [Scheme 62](#) <2003JA5632>. However, this is an exceptional case, as (*E*)-diastereoselectivity is characteristic for the generation of four- to seven-membered rings α -silylmethylene lactams, in contrast to the Sn-mediated cyclizations that provide (*Z*)-diastereomers for all those systems.

Using hexane-1-thiol **157** as the radical mediator, α -thiomethylene lactam **158** was formed, bearing the same (*Z*)-diastereoselectivity ([Scheme 65](#) <2003OBC4262>). Similarly, for lower rings the reaction afforded (*E*)-diastereomers only.



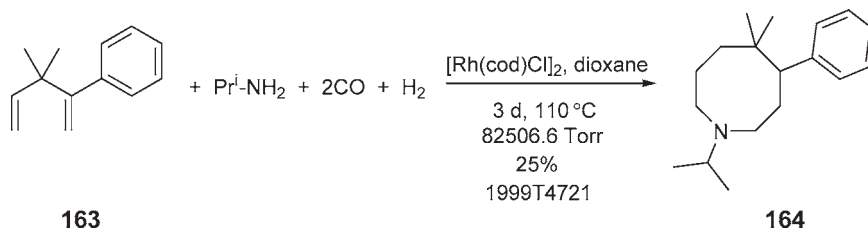
Scheme 65

A hydroformylation–cyclocondensation of *N*-alkenylpropane-1,3-diamines, such as **159** (prepared by reductive amination of the appropriate unsaturated aldehyde with either propane-1,2-diamine or 2-aminoethanol and subsequent borohydride reduction), in the presence of PPh₃ and BIPHENPHOS as ligand provided different reaction products depending on the H₂/CO ratio <1999AJC1131>. The bicyclic system **160** was accompanied by 10% branched **162** when H₂/CO was 1:1 ([Scheme 66](#)). Reaction with H₂/CO in a 1:5 ratio provided solely the bicyclic system, while only a mixture of monoalcohols **161** and **162** was isolated when the reaction was performed in the absence of PPh₃.



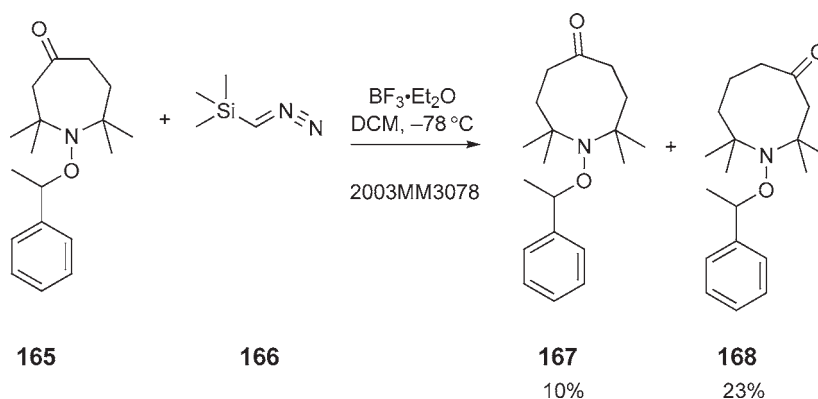
Scheme 66

Ruthenium-catalyzed hydroformylation of 1,4-dienes in the presence of amines produced eight-membered heterocycles in modest yields, and an example is presented in [Scheme 67](#) <1999T4721>.



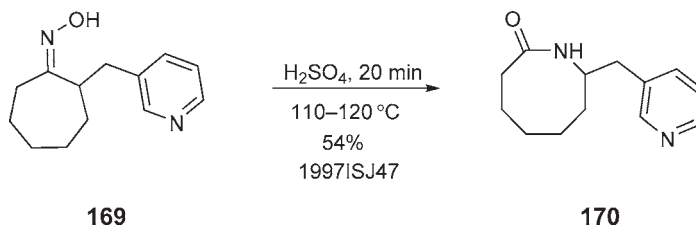
Scheme 67

Carbon insertion by diazomethane derivative **166** was achieved with a low regioselectivity in the presence of BF₃·OEt₂ yielding the two isomers **167** and **168** in a 1:2 ratio ([Scheme 68](#) <2003MM3078>).



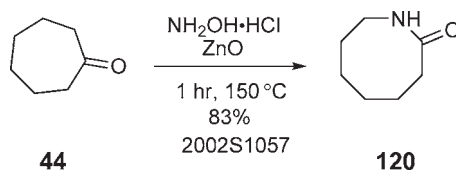
Scheme 68

Beckmann rearrangement. A classical synthesis of eight-membered cyclolactam rings was accomplished by the Beckmann rearrangement of cycloheptanone oximes. Thus, substituted oxime **169** gave lactam **170** in good yields (Scheme 69 <1997ISJ47>).



Scheme 69

Beckman rearrangement of cyclohexanone oxime in the presence of zinc oxide and without any additional solvent afforded the azocane-2-one **120** (Scheme 70 <2002S1057>). This is an environmentally friendly alternative to the usual Beckmann rearrangement performed with highly corrosive, strong Brönsted and Lewis acids, such as conc. sulfuric acid, phosphorus pentachloride in Et_2O , or HCl in acetic anhydride.

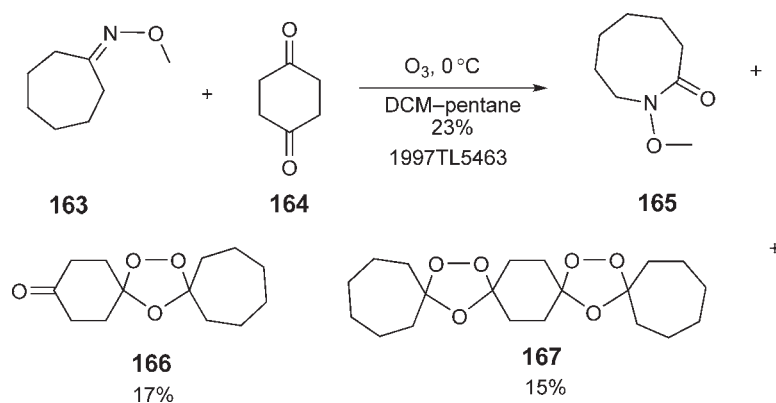


Scheme 70

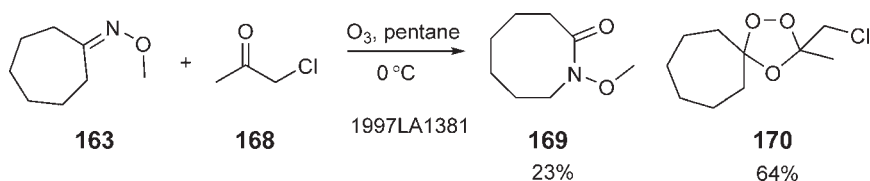
Ozonolysis. Ozonolysis of cyclohexanone *O*-methyl oxime **163** in the presence of 1,4-cyclohexanedione **164** gave a complex reaction mixture containing hydroxylamines **164**, as a main product (Scheme 71 <1997T5463>).

Reaction of cyclohexanone *O*-methyl oxime **163** with chloroacetone gave a similar spectrum of products with a similar ratio and yield (Scheme 72 <1997LA1381>).

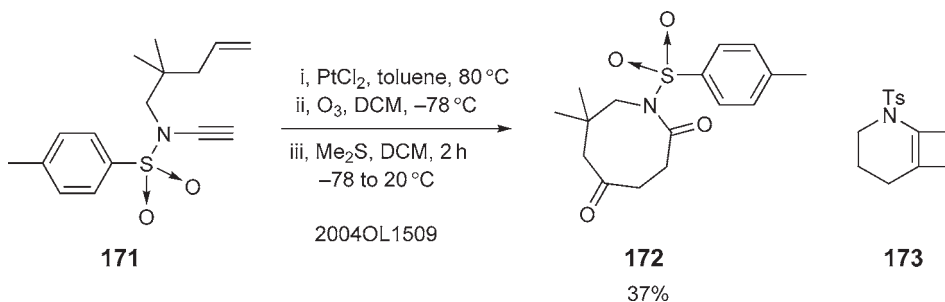
Ring-openings of bridged heterocycles. Ene-tosylamines underwent cyclization to ketolactams via a multistep reaction <2004OL1509>. In the example given in Scheme 73, the main step was the intramolecular cyclization of **171** to bicyclic nitrogen heterocycle **173**, which was subjected *in situ* to ring opening by ozonolysis to provide azocane derivative **172** <2004OL1509>.



Scheme 71

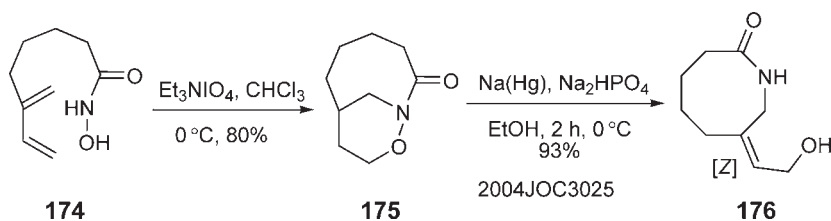


Scheme 72



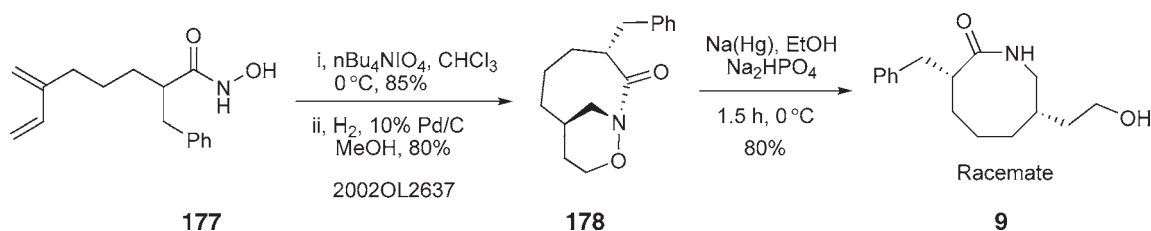
Scheme 73

Diels–Alder precursor hydroxamic acid **174** (prepared by a multistep reaction) was subjected to subsequent oxidation and cycloaddition to provide bicyclic intermediates **175**, which underwent ring cleavage by reduction with Na(Hg) amalgam, affording the eight-membered heterocycle **176** (Scheme 74 <2004JOC3025>).



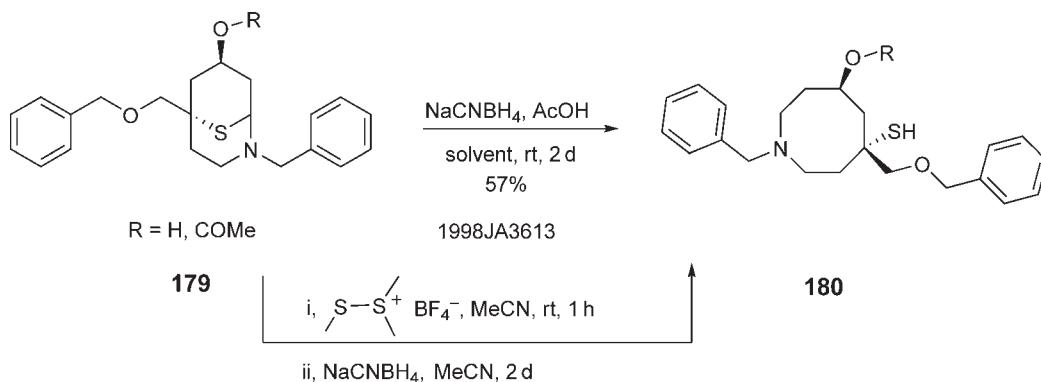
Scheme 74

A type 2 intramolecular *N*-acylnitroso Diels–Alder reaction of hydroxamic acid **177** followed by catalytic hydrogenation of the double bond was employed for the synthesis of substituted bridged bicyclic derivative **178**, as a single diastereomer (Scheme 75 <2002OL2637>). Cleavage of the N–O bond was performed by reduction with Na(Hg) amalgam and provided *cis*-3,7-disubstituted azocane **9**, as a single isomer in 80% yield.



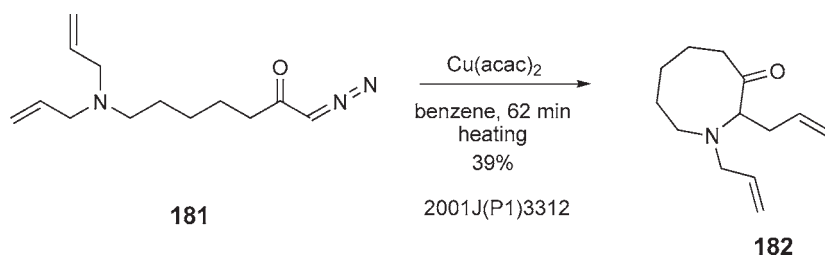
Scheme 75

Similarly, heterocycle **180** was obtained from bicyclic derivative **179** (Scheme 76 <1998JA3613>).



Scheme 76

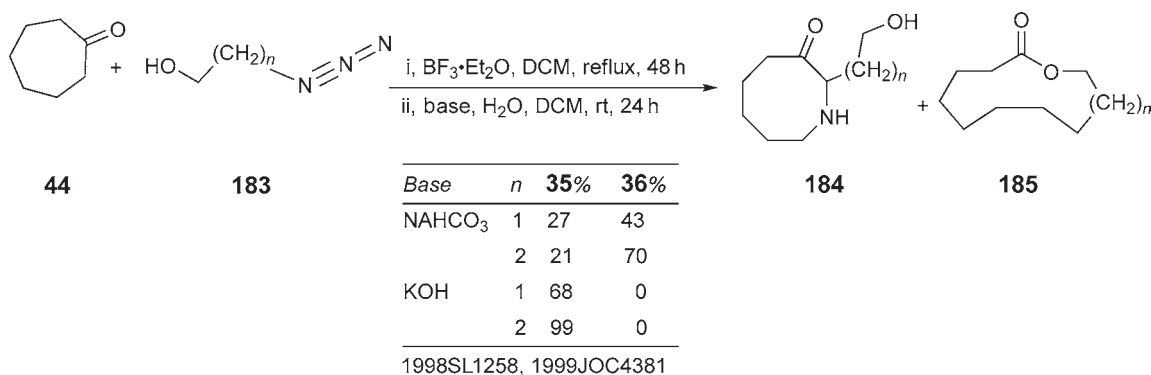
Other reactions. β -Lactams, such as **182**, were prepared in moderate to good yields by [2,3]-rearrangement of ammonium ylides produced by the reaction of copper carbenoids tethered to allylic amines (Scheme 77) <2001J(P1)3312>. The catalyst of choice in the generation of carbenoid/ylide from α -diazoketone precursor is copper(II) acetylacetonate. α -Diazoketone building blocks, such as **181**, were prepared by a multistep synthesis departing from appropriate ω -aminoacids.



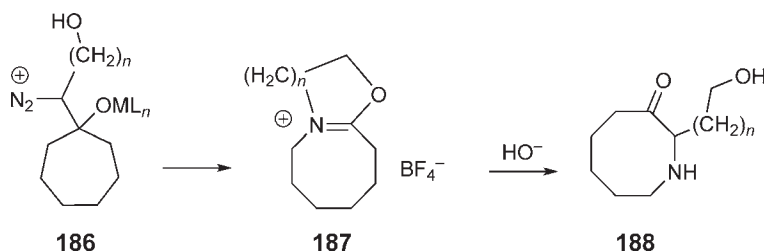
Scheme 77

The synthesis of eight-membered lactams and lactones could be achieved by hydrolysis of iminium ethers obtained by reacting ketones with hydroxyl azides (Scheme 78 <1998SL1258, 1999JOC4381>). This reaction is general and versatile for 6- to 12-membered rings, and produced eight-membered rings in good to excellent yields

(Scheme 78 <1999JOC4381>). The reaction afforded lactams and lactones in a ratio dependent upon the base used in the hydrolysis of iminium ether intermediates **187** (Scheme 79). When the hydrolysis is performed in the presence of NaHCO_3 , lactone derivative **185** was predominant; while in the presence of KOH , azocane **184** was the sole reaction product (Scheme 78).

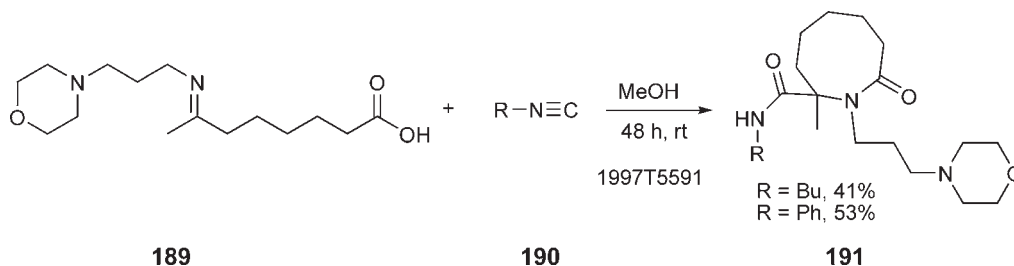


Scheme 78



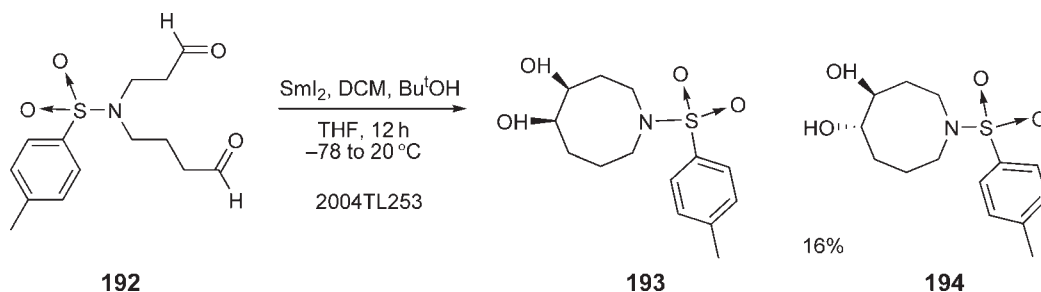
Scheme 79

A modified Ugi reaction was used in the synthesis of lactams of type **191** (Scheme 80 <1997T5591>). The acid and carbonyl functionalities required for the Ugi reaction are tethered with the appropriate spacing to afford the eight-membered ring in good yields, and the other two components – the amine and the nitrile – are introduced stepwise. Methanol plays a crucial catalytic role in the reaction as it adds to the acyl center and facilitates the lactam formation.



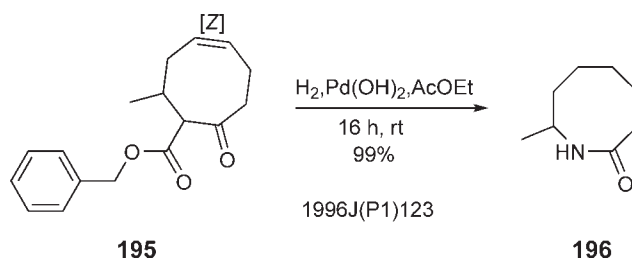
Scheme 80

Eight-membered heterocyclic diols were prepared from acyclic dicarbonyls via pinacol reactions (Scheme 81 <2004TL253>). The *cis*- or *trans*-diol stereoselectivity was controlled by the low-valent metal catalyst used. For instance, when using SmI_2 , the *cis*-*trans* ratio **193**:**194** was 3:1 (Scheme 28 <2004TL579, 2004T10385>). This method is a viable alternative to the metathesis-dihydroxylation strategy presented earlier.



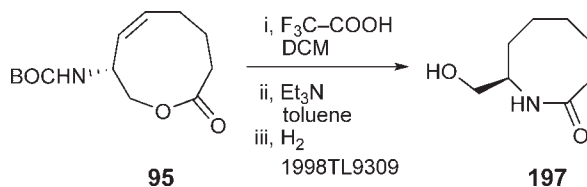
Scheme 81

Azocanes are also obtained in excellent yields from the appropriate unsaturated derivatives by hydrogenation (Scheme 82 <1996J(P1)123>).



Scheme 82

N-Protected 7-amino-8-hydroxyoctenoic acids were cyclized to their corresponding nine-membered ring lactones (Scheme 38, Section 14.01.5.2). Subsequent hydrogenation of the double bond using Pd/C in MeOH afforded the saturated lactone **95**, which underwent intramolecular *O*-to-*N*-acyl (lactone-to-lactam) ring contraction to 8-hydroxymethyl-6,7-dehydro-2-azocanone **197** (Scheme 83 <1998TL9309>).

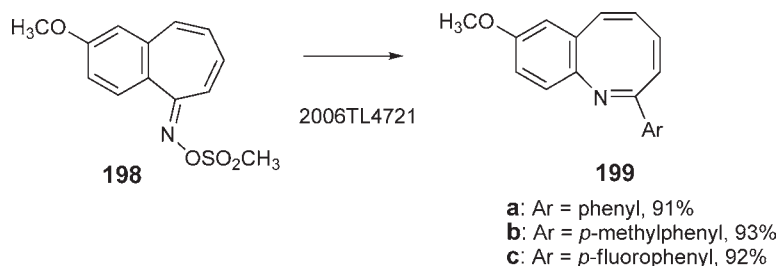


Scheme 83

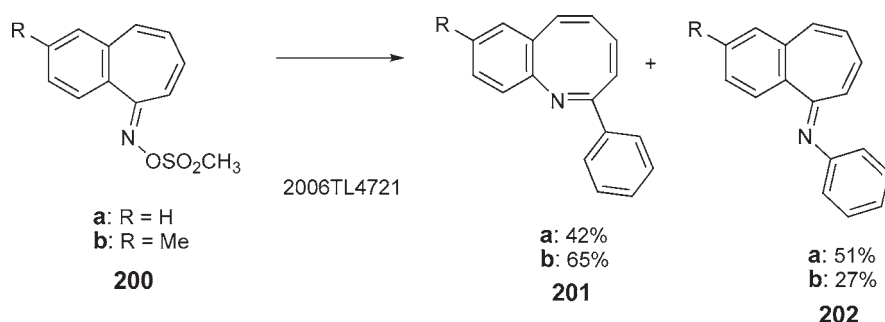
14.01.5.4 Benzazocines

2-Arylated 1-benzazocines **199** were prepared via Beckmann rearrangement of 5*H*-benzocyclohepten-5-one oxime mesylates **198** in dry toluene using aryl Grignard reagents or iodotrimethylsilane to induce rearrangement in the absence of a protic agent (Scheme 84 <2006TL4721>). Dry toluene and benzene were found to be the best solvents for the reaction, but THF and Et_2O worked as well. Low yields were reported when the reaction was performed in DCM. The conversion in final product was strongly dependent on the oxime substitution: only benzazocines of type

199 in excellent yields were reported for methoxy-substituted oximes **198**, while for unsubstituted or methyl-substituted oximes **200** seven-membered ring derivatives **202** were formed along with benzazocines **201** (Scheme 85).

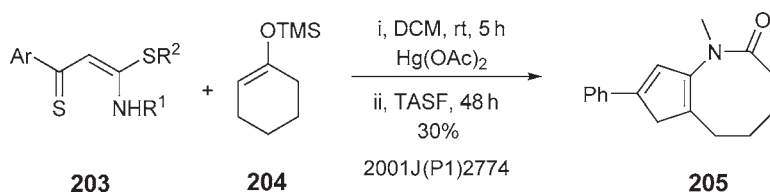


Scheme 84



Scheme 85

Thienolactam **205** was prepared from thioaroylketene *S,N*-acetal **203**, Hg(OAc)₂, and cyclohexanone enol ether **204** in the presence of either tris(dimethylamino)(trimethylsilyl)sulfur difluoride (TASF), or TBAF, with a yield of 30% and 28%, respectively (Scheme 86 <2001J(P1)2774>).

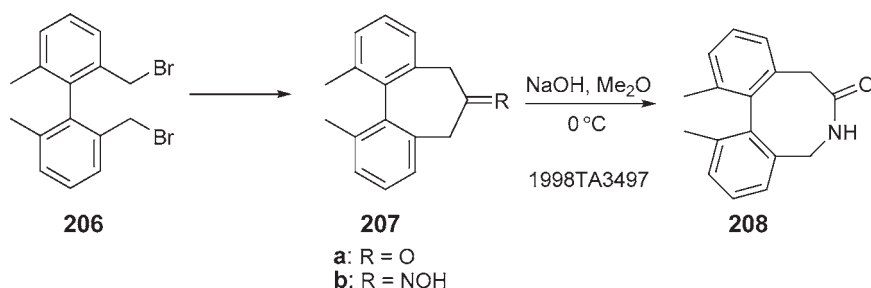


Scheme 86

Benzazocines were also prepared on a solid support from otherwise unstable dihydroisoquinolines. Syntheses of a variety of alkaloid-like benzoazocines were reported to occur in very good yields <2004AGE1681>.

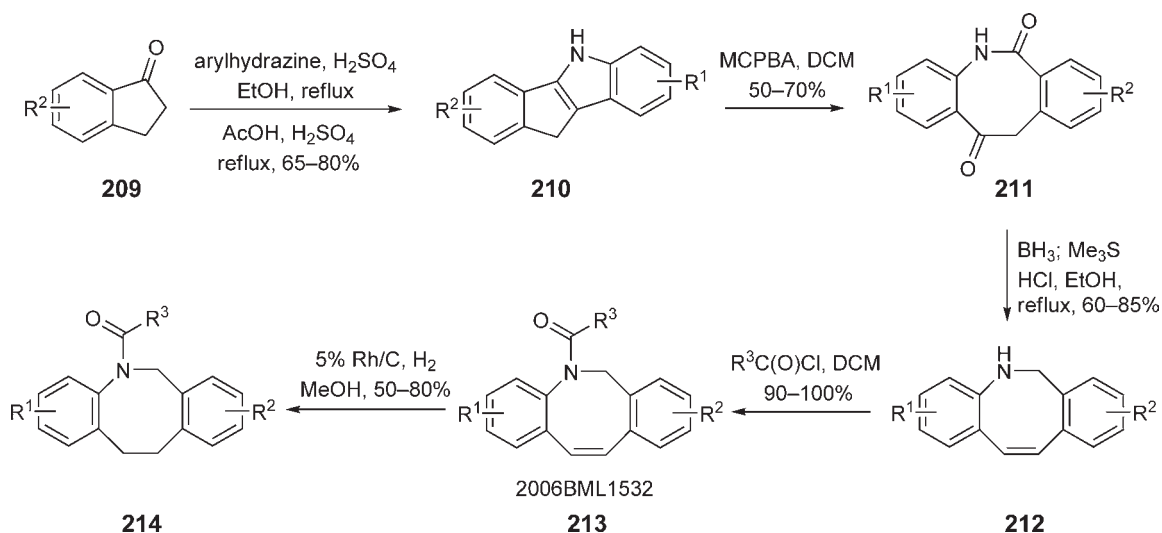
14.01.5.5 Dibenzazocines

The optically active dibenzazocine (*S*)-**208** was prepared by the Beckmann rearrangement of oxime **207b**, which was obtained by reacting dibromide (*R,S*)-**206** with tosylmethyl isocyanide (Scheme 87 <1998TA3497>). The Beckmann rearrangement was performed in classical conditions (NaOH in acetone at 0 °C). Ketone **207a** was obtained by preparative HPLC resolution on triacetylcellulose of the racemate obtained from dibromide (*R,S*)-**206** and having therefore a known absolute configuration. Dibenzazocine (*S*)-**208** was designed for application in the synthesis of homochiral polyamide polymers.



Scheme 87

A series of tetrahydrodibenzazocines identified as inhibitors of 17 β -hydroxysteroid dehydrogenase type 3 were prepared using the reaction sequence presented in [Scheme 88](#) <2006BML1532> departing from indanones. Indanone **209** was reacted with an arylhydrazine to give the corresponding arylhydrazone **210**, which underwent indole cyclization followed by oxidation to afford dibenzazocine **211**. Further manipulation of the keto groups and of the double bond and functionalization of the amino nitrogen produced dibenzazocine derivatives **212–214**.

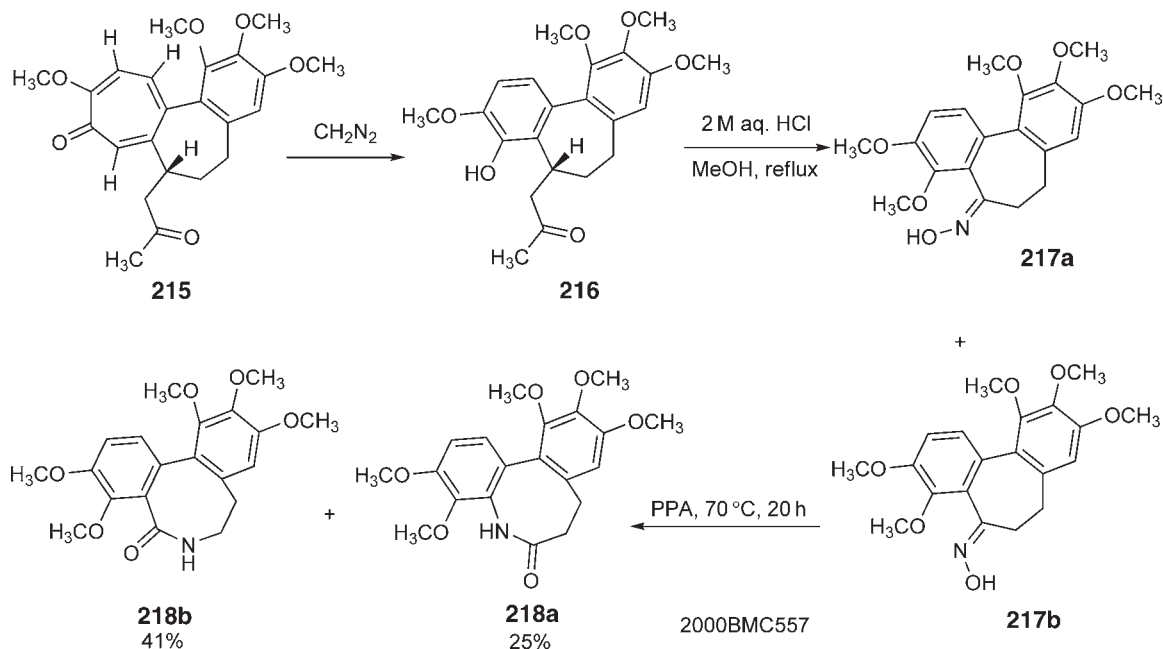


Scheme 88

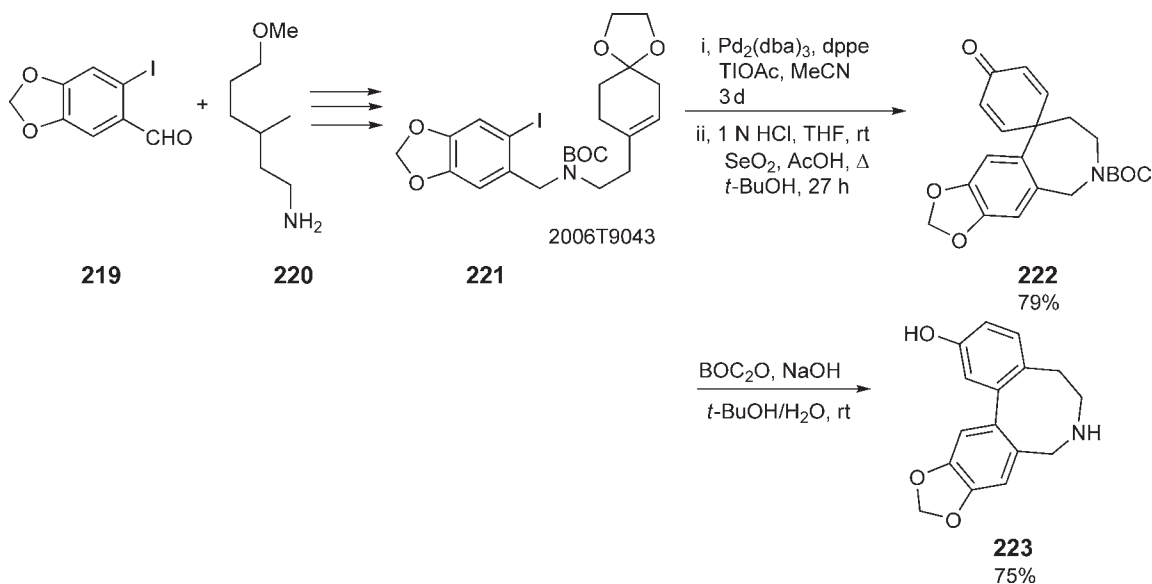
The Beckmann rearrangement was applied to the synthesis of novel allocolchicinoids designed as inhibitors of tubulin assembly <2000BMC557>. The multistep synthesis departed from (–)-colchicine **215** ([Scheme 89](#)). The key reaction was the Beckmann rearrangement of oximes **217a/217b** using polyphosphoric acid at 70 °C for 20 h affording the *syn/anti* mixture of lactams **217a/217b** in a total yield of 68%. The mixture was separated by column chromatography and yielded 41% of oxime **217a** and 25% oxime **217b**, both atropisomers and racemic mixtures, with their chiral biphenyl backbone in an (M)/(P) equilibrium.

Apogalanthamine analogues (e.g., **223**) have a tetrahydrodibenz[*c,e*]azocine structure, in which one benzene can be regarded as a part of benzylamine and other as a part of phenethylamine. From the pharmacological point of view, the phenethylamine in the azocine structure is demonstrated to contribute toward the α -adrenolytic activity and the benzylamine having two methoxy groups contributes toward the anti-serotonin activity. Therefore, such structures are sought after for their interesting biological potential. An alkaloid analogue of apogalanthamine was synthesized by

a dienone/phenol rearrangement from spirodienone **222** (obtained by a multistep reaction departing from readily available aldehyde **219** and 2-(4-methoxyphenyl)ethylamine **220**) by treatment with HCl in MeOH at room temperature (Scheme 90 <2001ARK191>).

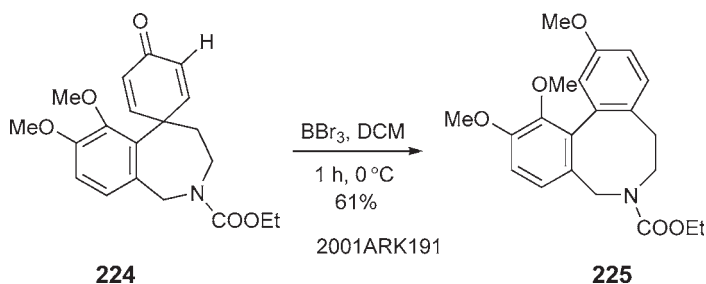


Scheme 89



Scheme 90

Another apogalanthamine analogue **225** was synthesized by ring expansion of an intermediate in the synthesis of apogalanthamine, **224**, performed in the presence of BBR_3 in DCM (Scheme 91 <2001ARK191>).



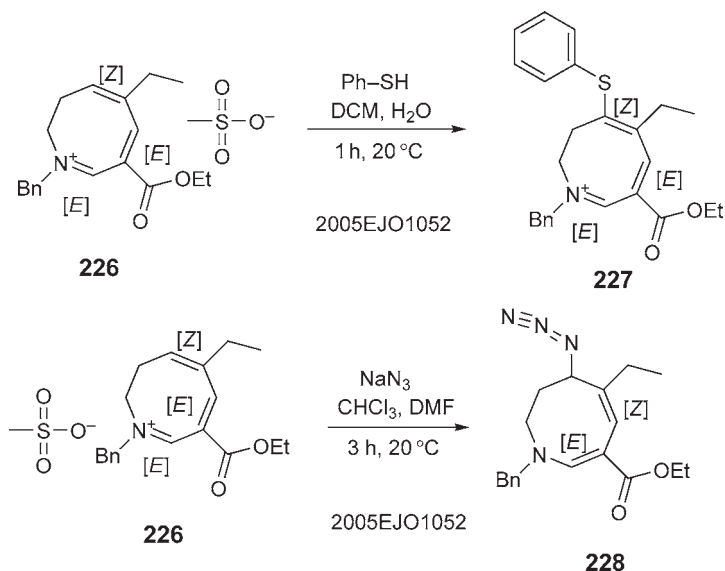
Scheme 91

14.01.6 Reactivity of Unsaturated Derivatives

Unsaturated eight-membered rings with one nitrogen have been subjected to specific reactions of conjugated double bonds as described in CHEC(1984) and CHEC-II(1996). No new developments have been described after 1995.

14.01.7 Reactivity of Partially Unsaturated Derivatives (Hydroazocines, Benzazocines, Dibenzazocines)

Dihydroazocines. Azocines can be converted into the corresponding iminium salts by treatment with 1 equiv of acid, such as methanesulfonic acid, in CHCl_3 . Nucleophilic additions to iminium salt **226** afforded substituted azocine derivatives: reaction with thiophenol in $\text{DCM}/\text{H}_2\text{O}$ at room temperature provided **227**, while reaction with sodium azide in CHCl_3/DMF provided **228** (Scheme 92 <2005EJO1052>).

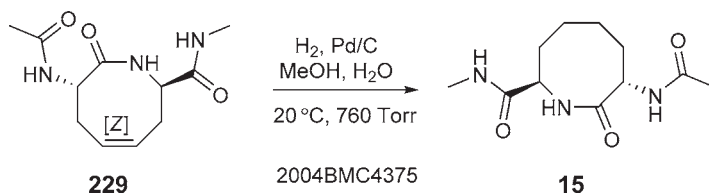


Scheme 92

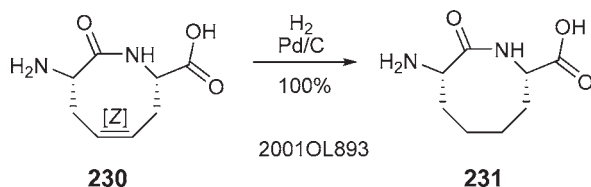
Hexahydroazocines. ‘Hydrogenation’ of the double bond is performed in standard conditions (Scheme 93 <2004BMC4375>).

Unsaturated cyclic dipeptide **230** was subjected to quantitative hydrogenation in the presence of Pd/C to produce cyclic dipeptide **231** (Scheme 94 <2001OL893>). It was expected that incorporation of this peptide instead of the oxidized, cyclic Cys–Cys will provide stable and potentially useful peptidomimetics.

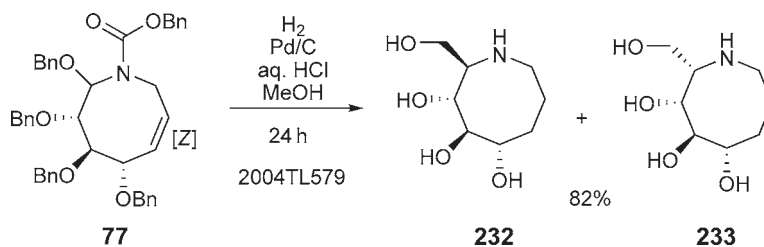
Similarly, derivative **77** was simultaneously reduced and deprotected by catalytic hydrogenation in MeOH to provide a mixture of isomers **232** and **233** (Scheme 95 <2004TL579>).



Scheme 93

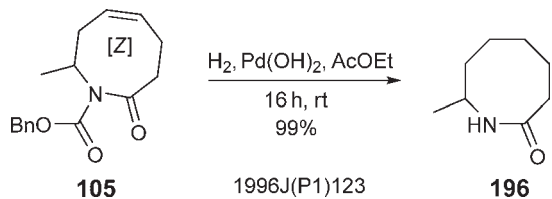


Scheme 94



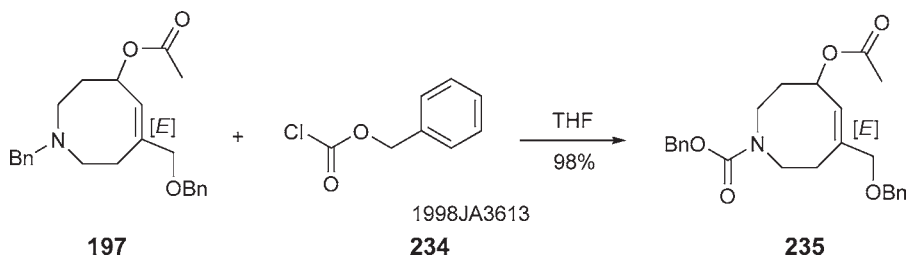
Scheme 95

Catalytic hydrogenation of unsaturated benzyloxycarbonyl-protected lactam **105** using Pearlman's catalyst gave saturated lactam **196** in 99% yield (Scheme 96 <1996J(P1)123>).



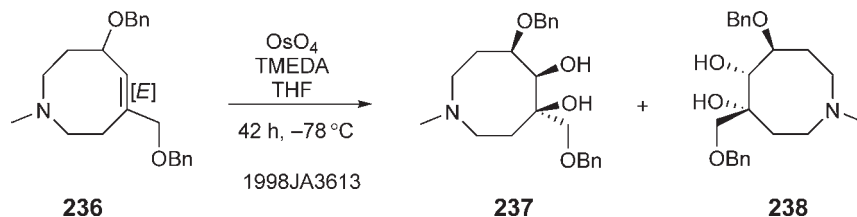
Scheme 96

Reactions to the ring nitrogen. Substituents to the ring nitrogen showed reactions typical for secondary amines (Scheme 97 <1998JA3613>).



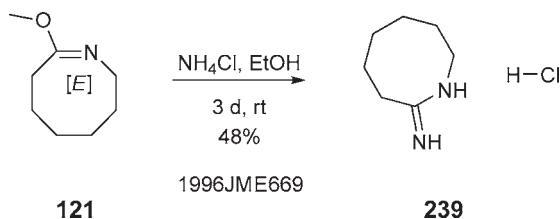
Scheme 97

Other reactions. The double bond in the azocine **236** underwent *trans*-oxidation in the presence of OsO₄ to give a mixture of stereoisomers **237** and **238** (Scheme 98 <1998JA3613>).



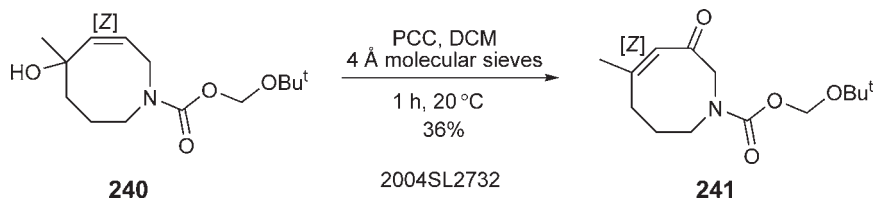
Scheme 98

Iminoether **121** (prepared from 2-azacyclooctanone, Scheme 50) was treated with ammonium chloride in EtOH for 3 days to afford 2-azacyclooctanone imine as a hydrochloride (Scheme 99 <1996JME669>).



Scheme 99

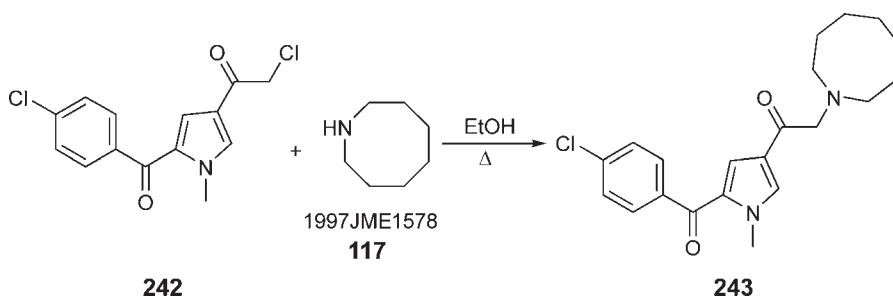
Oxidation of the allyl alcohol system of hexahydroazocine **240** in the presence of PCC produced α,β -unsaturated ketone **241** (Scheme 100 <2004SL2732>).



Scheme 100

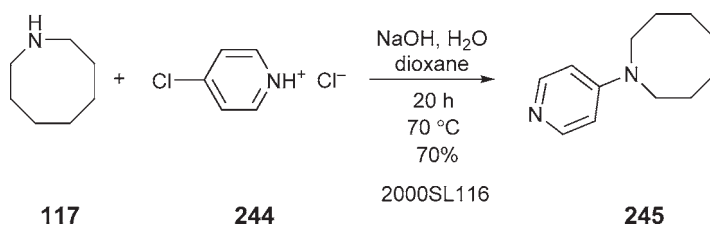
14.01.8 Reactivity of Fully Saturated Derivatives (Azocanes) and of the Ring Nitrogen

The azocane nitrogen undergoes reactions characteristic for secondary amines: nucleophilic substitutions (alkylations and acylations), oxidations, and modifications to ring substituents. *Alkylations.* Halo derivatives were reported to react readily with azocanes to afford in good yields compounds with diverse applications in life sciences (Scheme 101 <1997JME1578>).

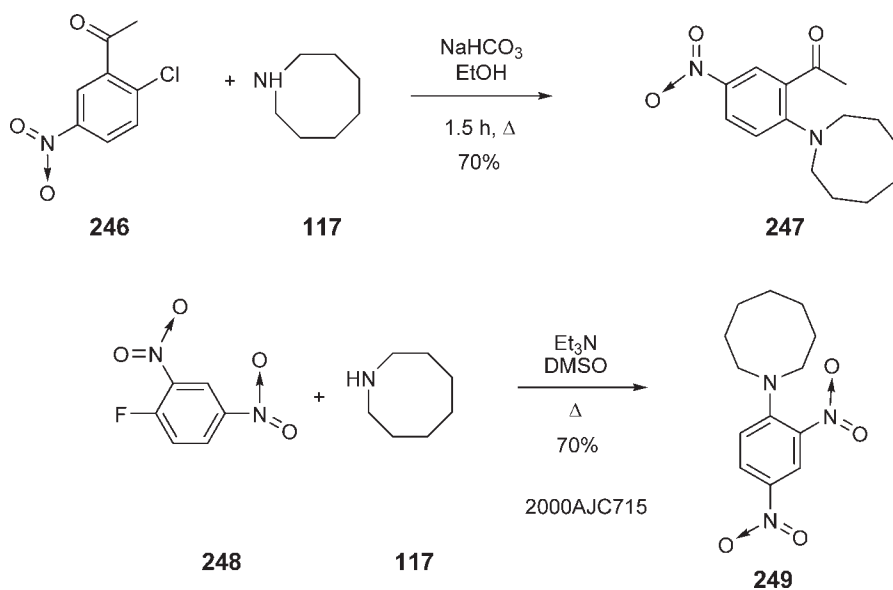


Scheme 101

Halogens on activated aromatic rings react with the azocane nitrogen to provide *N*-aryl-substituted azocanes in good yields. For instance (Scheme 102 <2000SL116>), 4-(di)alkylaminopyridine derivative **245** was obtained in high yield by the high-pressure-promoted nucleophilic aromatic substitution (S_NAr) of 4-chloropyridine with unsubstituted azocane **117**. Unsubstituted azocane reacted in good yields with activated chloro- **246** and fluoro- **248** arenes in conditions typical for S_NAr (Scheme 103 <2000AJC715>) and with activated chloropyrazine **250** (Scheme 104 <1997CCC800>).

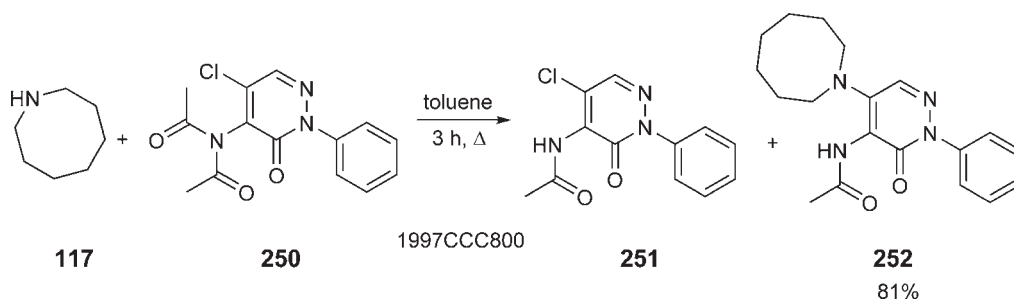


Scheme 102

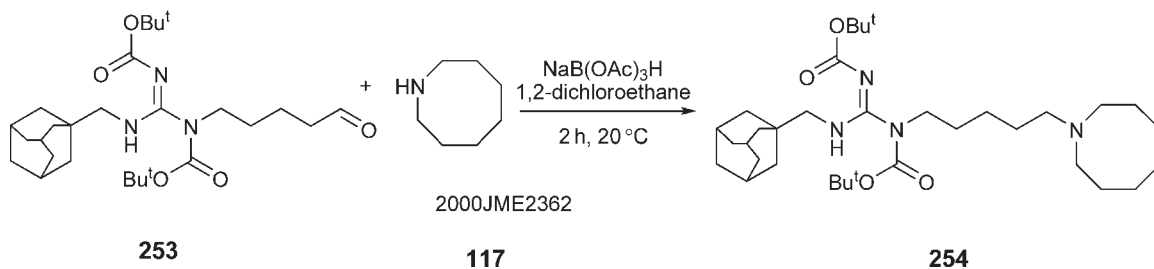


Scheme 103

An alkylation by reductive amination using aldehyde **253** in the presence of sodium triacetoxyborohydride in 1,2-dichloroethane afforded the adamantyl compound **253**, which after further deprotection produced an *N,N'*-disubstituted guanidine derivative **254** interesting for potential biological activity (Scheme 105 <2000JME2362>).

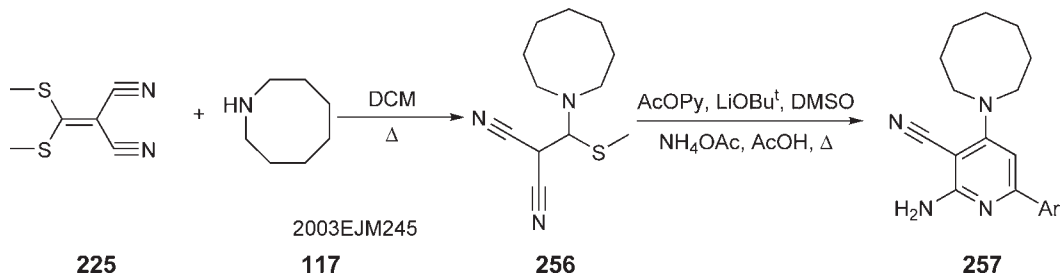


Scheme 104



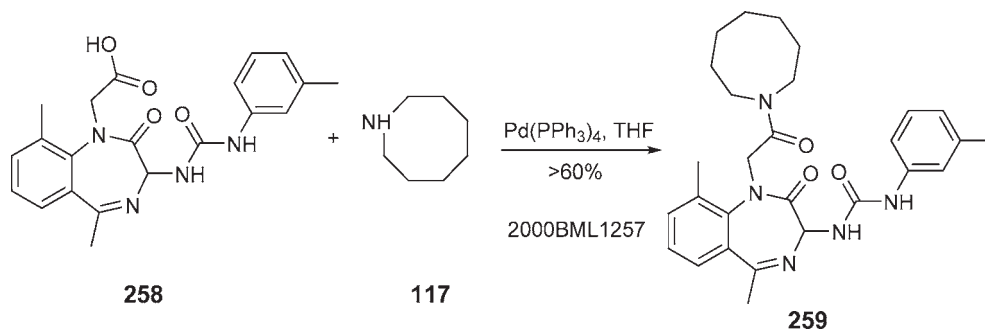
Scheme 105

2-(Bis(methylsulfanyl)methylene)malononitrile **255** reacted with azocane to afford the alkylated product **256**, which was further subjected to treatment with acetylpyridine in DMSO in the presence of *t*-BuOLi and quenched with NH_4OAc in AcOH to give **257** studied for its adenosine kinase inhibition properties (Scheme 106 <2003EJM245>).

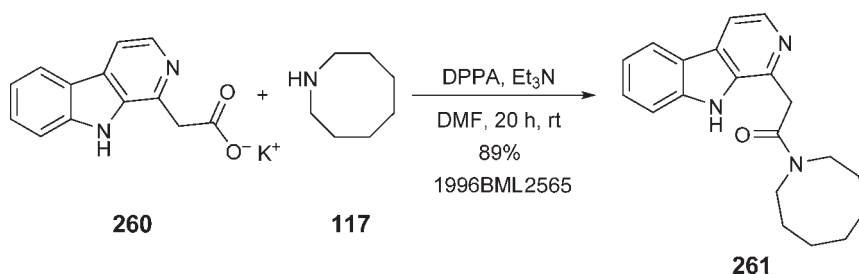


Scheme 106

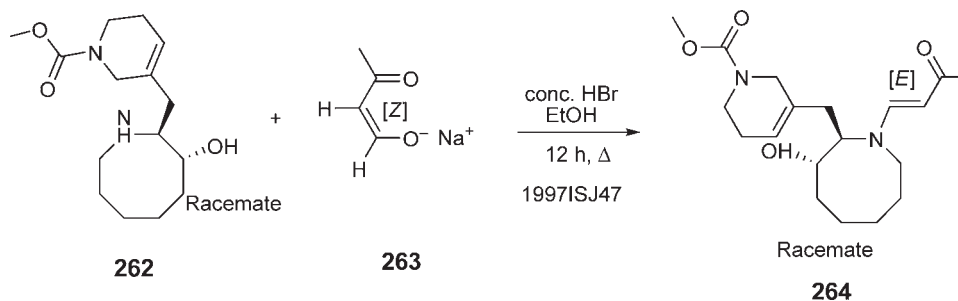
Acylation. The ring nitrogen behaves as a typical secondary amine. Thus, it could be protected with an acyl moiety. Unsubstituted azocane reacts with acids (Scheme 107 <2000BML1257>, Scheme 108 <1996BML2565> and Scheme 109 <1997ISJ47>) under diverse catalytic conditions to provide acyl derivatives in good to excellent yields.



Scheme 107

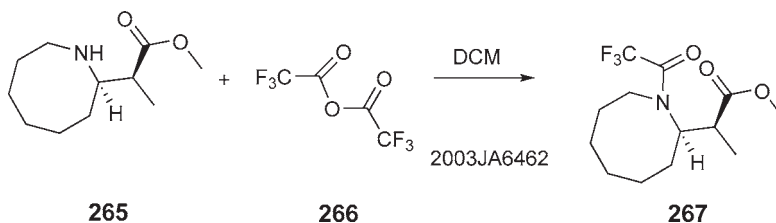


Scheme 108

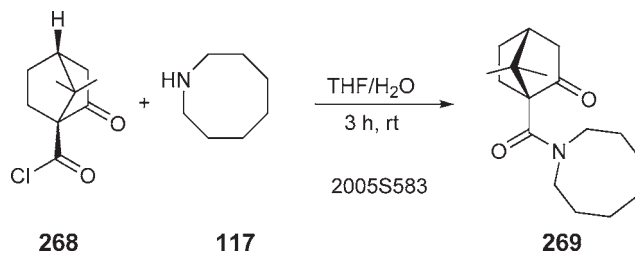


Scheme 109

Reactions with acid anhydrides ([Scheme 110](#) <2003JA6462>) and acyl chlorides ([Scheme 111](#) <2005S583>) occurred at room temperature in various solvents, and furnish acyl-azocanes in reportedly good to excellent yields (specific yields not given). Compounds of type **267** were studied as inhibitors of the Hepatitis B virus replications. Compound **269** was used as a chiral ligand for the enantioselective addition of diethyl zinc to aromatic aldehydes.

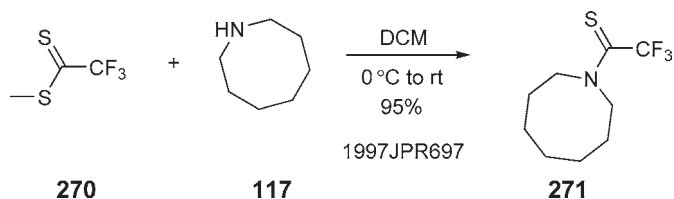


Scheme 110



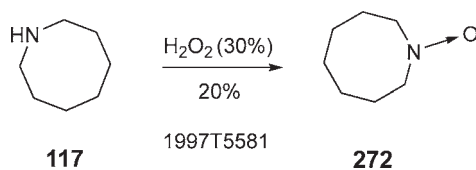
Scheme 111

Unsubstituted azocane **117** was reacted with methyl trifluoromethyldithioacetate **270** to yield the thioester **271** in excellent yield ([Scheme 112](#) <1997JPR697>).



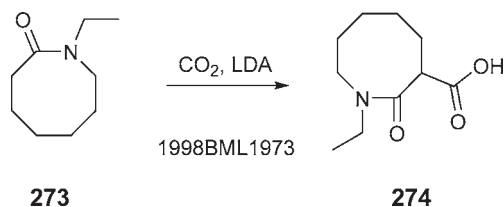
Scheme 112

Oxidations. In previous chapters, oxidation reactions of azocanes to their corresponding *N*-oxides have been described (CHEC(1984) and CHEC-II(1996)). Later reports on the oxidation of azocane **117** to the corresponding nitroxide **272** with H_2O_2 proved the versatility of the method (Scheme 113 <1997T5581>).



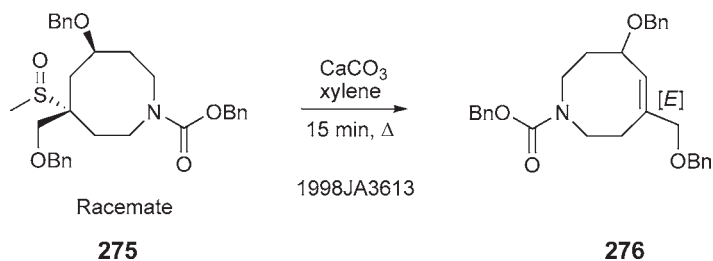
Scheme 113

Lithium diisopropylamide (LDA)-assisted nucleophilic substitution adjacent to the lactam carbonyl in **273** produced α -ketocarboxylic acids **274** (Scheme 114 <1998BML1973>).



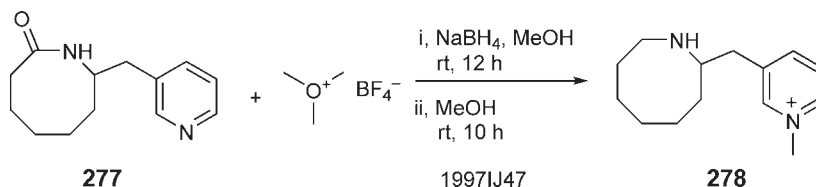
Scheme 114

Reductions. Dehydrogenation of azocane **275** was performed in the presence of CaCO_3 and produced hexahydroazocine **276** (Scheme 115 <1998JA3613>).

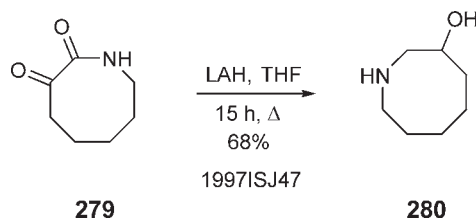


Scheme 115

The carbonyl group attached to the azocane ring in **277** was reduced by conventional methods (Schemes 116 and 117 <1997ISJ47>).

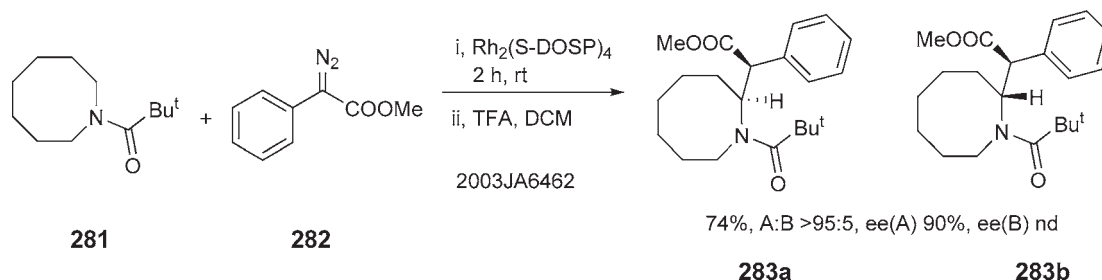


Scheme 116



Scheme 117

Other reactions. *N*-BOC-protected azocane **281** was reacted with aryl diazoacetate **282** in the presence of 1 mol% of dirhodium tetraproline catalyst to produce a very efficient C–H insertion with a high diastereoselectivity and enantioselectivity (Scheme 118 <2003JA6462>). The *erythro* C–H insertion product **283a** was formed in 90% ee and 90% de, which infers that the flexibility of the eight-member ring sterically favors the accommodation of the transition state for the C–H activation.



Scheme 118

14.01.9 Applications

The abundance in natural products of medium ring heterocycles, particularly eight-membered heterocycles with one nitrogen atom, ensures the chemists' interest for such a popular target. Efforts to diversify the syntheses of azocines, hydrazocines, and azocanes are intrinsically linked to their potentially useful biological activities <2006WO2006001463>.

14.01.9.1 Azocines

Some azocine derivatives showed insecticidal activity as assayed by oral administration to silkworms larvae <2000BBB1519>. The azocine ring was shown to be indispensable to form the active conformation. Benzazocine with the lactam structure was evaluated in the syntheses of homochiral polyamide polymers <1998TA3497>.

14.01.9.2 Hydroazocines

Eight-membered iminoalditols have been evaluated as inhibitors of glucuronidases <2004TL579>.

14.01.9.3 Azocanes (Perhydroazocines)

Compounds in this class have been used as herbicides, drugs, and catalysts, as described earlier in CHEC-(1984) and CHEC-II(1996). New research showed that they can be used for the dyeing of keratinous fibers, and in particular of human keratinous fibers, such as the hair <2005WO2005068431>. New azocane derivatives have been shown to have sphingosine-1-phosphate (SP1) receptor binding potency <2006WO2006001463> and therefore they are evaluated in the prevention or therapy of various autoimmune diseases, transplant rejections, allergic disorders, etc. Azocanes were also prepared as neurokinin NK-1 antagonists/selective serotonin reuptake inhibitors, showing NK-1 binding activities with $IC_{50} < 20 \mu M$ <2006WO2006023187>. Azocane derivatives bearing pyridine substituents were also described as hypoglycemic agents for treating diabetes and obesity <2004WO2004043947>. 2-Iminoazocanes were reported as inhibitors of human nitric oxide synthase isoforms <1996JME669>. There are reports on the structure elucidation of natural compounds of *Stemona* plants, such as an unusual bridged azepinyl azocane used in Chinese and Japanese folk medicine as insecticides, drugs for the treatment of respiratory diseases such as bronchitis, pertussis, and tuberculosis, and as antihelmintics <1998MI1>.

14.01.9.4 Benzazocines

Tetrahydropyrido[2,3-*b*]azocines have been synthesized for their excellent antagonistic activity against CCR5 and/or CCR2 and are useful as preventive/therapeutic agents for HIV infection in human peripheral blood mononuclear cells, especially for AIDS <2004WO200469833>.

14.01.9.5 Dibenzazocines

A series of dibenzazocines was designed for application in the synthesis of homochiral polyamide polymers <1998TA3497>. Bis-oxo-tetrahydridibenzazocines showed picomolar to nanomolar inhibition of 17 β -hydroxysteroid dehydrogenase of type 3 <2006BML1532>. Colchicine derivatives that contain the dibenzazocine moiety have been studied for their biological properties <2000BMC557>.

14.01.10 Further Developments

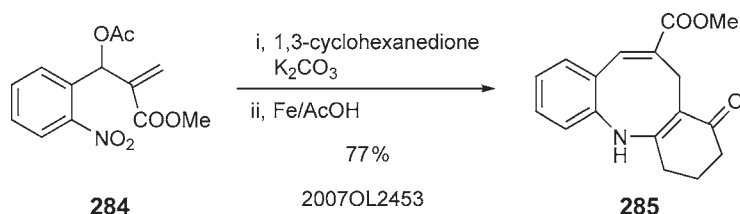
There were various reports on the properties and syntheses of azocanes and azocines during the year 2007. The most relevant are illustrated below.

14.01.10.1 Properties

The binding of unsubstituted azocane to a deep cavitand substituted with multiple terminal amide groups was demonstrated by ^1H NMR <2007CC1605>. It was further shown that binding accelerated its subsequent S_NAr reactions in *p*-xylene, presumably due to the solvation of the intermediate Meisenheimer complex. The solvation may be facilitated by the cavitand terminal amide groups. These findings are supported by ^1H NMR resonances in the far upfield region of the spectra.

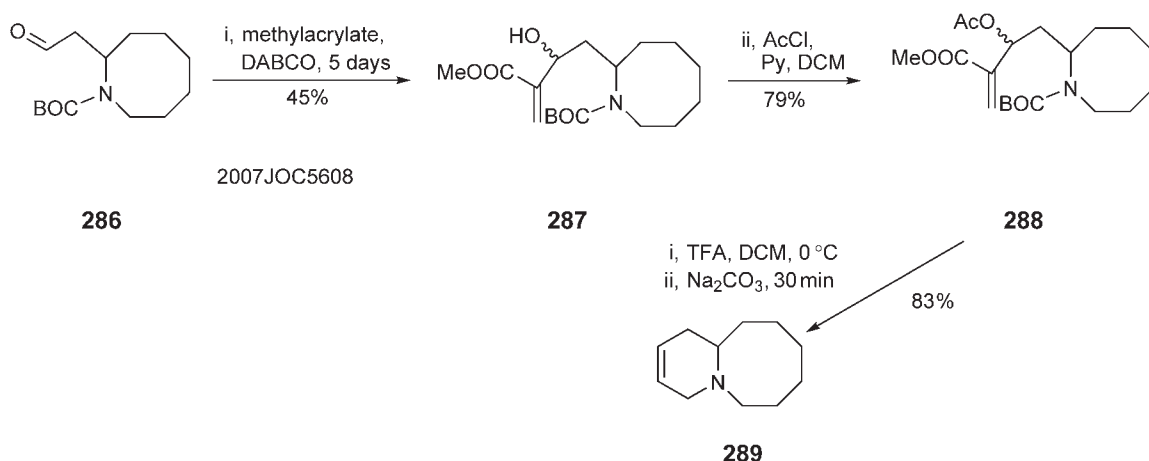
14.01.10.2 Syntheses

Baylis–Hillman acetates have been conveniently transformed into tri/tetracyclic heterocyclic frameworks containing an azocine moiety *via* a one-pot multistep protocol involving alkylation, reduction, and cyclization sequence <2007OL2453>. Treatment of Baylis–Hillman acetate **284** with 1,3-cyclohexanedione in the presence of K_2CO_3 , followed by treatment of the resulting product with $Fe/AcOH$, gave 77% fused azocine **285** (Scheme 119).



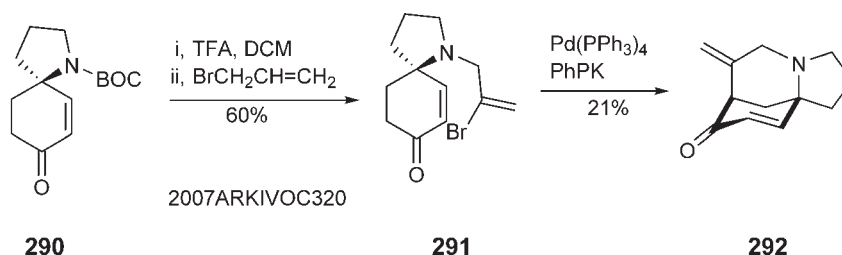
Scheme 119

Azocanes with nitrogen at a bridgehead such as fused azocane **289** were prepared starting from *N*-protected amino aldehydes **286**. Those amino aldehydes were converted into allylic alcohols by the classical Morita–Baylis–Hillman reaction or by condensation with selenium-stabilized carbanions, followed by oxidation <2007JOC5608>. Fused azocane **289** was prepared in good yield as described in Scheme 120. Formation of [*m,n*,0]-bicyclic structures via these reactions is general and the stereochemistry of the starting amino-aldehyde is preserved.



Scheme 120

Studies in the synthesis of the immunosuppressant FR901483 tricyclic skeleton showed that by palladium- and radical-mediated cyclizations of azaspiro-decanes the formation of azatricyclic derivatives was possible. Depending on the reaction conditions, 7,10*a*-methanopyrrolo[1,2-*a*]azocine **292** could be obtained from *N*-(2-bromoprop-2-enyl)-1-azaspiro[4.5]decane **291** (Scheme 121) <2007ARKIVOC320>. When the reaction was performed in the presence of Bu₃SnH, pyrrolo[2,3-*i*]indoles were obtained instead.



Scheme 121

14.01.10.3 Applications

Some azocane-substituted pyrazoline compounds have been reported as cannabinoid receptor modulators <2007WO0009723, 2007WO131538>. An azocane derivative with a 3,3-diphenylpentane skeleton was reported to be an inhibitor of human 5 α -reductase 1 <2007BMCL5414>. A dipyridamole analog having a bis-azocane structure was identified as a highly potent Nucleoside Transporter 1 inhibitor <2007JMC3906>.

References

- 1984CHEC(7)653 J. A. Moore and F. A. L. Anet; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon Press, Oxford, 1984, vol. 7, p. 653.
- 1995JA8594 O. Wiest, K. N. Houk, K. A. Black, and B. E. Thomas, IV, *J. Am. Chem. Soc.*, 1995, **117**, 8594.
- 1996BML2565 Y. Torisawa, A. Hashimoto, M. Okouchi, T. Iimori, and M. Nagasawa, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2565.
- 1996CHEC-II(9)403 M. Sutharchanadevi and R. Murugan; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; vol. 9, p. 403.
- 1996JME669 W. M. Moore, R. K. Webber, K. F. Fok, G. M. Jerome, and J. R. Connor, *J. Med. Chem.*, 1996, **39**, 669.
- 1996JOC5004 D. A. Alonso, L. R. Falvello, B. Mancheno, C. Najera, and M. Tomas, *J. Org. Chem.*, 1996, **61**, 5004.
- 1996J(P1)123 P. A. Evans, A. B. Holmes, R. P. McGeary, P. Ross, A. Nadin, K. Russel, P. J. O'Hanlon, and N. D. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1996, 123.
- 1996TL5783 D. Donati, S. Fusi, and F. Ponticelli, *Tetrahedron Lett.*, 1996, **37**, 5783.
- 1997BML2771 U. Berg, H. Bladh, C. Svensson, and M. Wallin, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2771.
- 1997CCC800 V. Konecny, J. Zuziova, S. Kovac, and T. Liptaj, *Collect. Czech. Chem. Commun.*, 1997, **5**, 800.
- 1997ISJ47 J. D. Winkler, J. E. Stelmach, M. G. Siegel, N. Haddad, J. Axten, and W. P. Dailey, *Isr. J. Chem.*, 1997, **37**, 47.
- 1997JME1578 J. R. Carson, R. J. Carmosin, P. M. Pitis, J. L. Vaught, and H. R. Almond, *J. Med. Chem.*, 1997, **40**, 1578.
- 1997JPR697 F. Laduron, C. Nyns, Z. Janousek, and H. G. Viehe, *J. Prakt. Chem.*, 1997, **8**, 697.
- 1997LA1381 K. Griesbaum, X. Liu, A. Kassiaris, and M. Scherer, *Liebigs Ann.*, 1997, 1381.
- 1997T5463 K. Griesbaum, X. Liu, and Y. Dong, *Tetrahedron*, 1997, **53**, 5463.
- 1997T5581 S. S. Al-Jaroudi, H. P. Perzanovski, M. I. Wazeer, and S. A. Ali, *Tetrahedron*, 1997, **53**, 5581.
- 1997T5591 G. C. B. Harriman, *Tetrahedron Lett.*, 1997, **38**, 5591.
- 1998BML1973 Y. Hirokawa, H. Yamazaki, N. Yoshida, and S. Kato, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1973.
- 1998CC1757 K. C. Nicolaou, G.-Q. Shi, K. Namoto, and F. Bernal, *Chem Commun.*, 1998, **16**, 1757.
- 1998H(47)655 Y. Torisawa, T. Soe, C. Katoh, Y. Motohashi, A. Nishida, T. Hino, and M. Nakagawa, *Heterocycles*, 1998, **47**, 655.
- 1998JA3613 E. Vedejs, R. J. Galante, and P. G. Goeckjian, *J. Am. Chem. Soc.*, 1998, **120**, 3613.
- 1998JOC6859 R. C. Larock, C. Tu, and P. Pace, *J. Org. Chem.*, 1998, **63**, 6859.
- 1998MI1 P. Wipf, Book of Abstracts, 216th ACS National Meeting, Boston, 23–27 Aug. (1998) ORGN-323.
- 1998RRC649 M. D. Banciu, C. Draghici, A. Popescu, A. Banciu, and A. Simion, *Rev. Roum. Chim.*, 1998, **43**, 649.
- 1998SL1258 J. E. Forsee, B. T. Smith, T. Brent, K. E. Frank, and J. Aube, *Synlett*, 1998, 1258.
- 1998TA3497 M. Tichy, J. Holanova, and J. Zavada, *Tetrahedron Asymmetry*, 1998, **9**, 3497.
- 1998T7045 J. D. Winkler, J. Axten, A. H. Hammach, Y.-S. Kwak, U. Lengweiler, M. J. Luccio, and K. N. Houk, *Tetrahedron*, 1998, **54**, 7045.
- 1998TL1421 S. D. Sarker, L. Dinan, V. Sik, E. Underwood, and P. V. Watermann, *Tetrahedron Lett.*, 1998, **39**, 1421.
- 1998TL139 R. Grigg, V. Sridharan, and M. York, *Tetrahedron Lett.*, 1998, **39**, 4139.
- 1998TL9309 S. Derrer, N. Feeder, S. J. Teat, J. E. Davies, and A. B. Holmes, *Tetrahedron Lett.*, 1998, **39**, 9309.
- 1999A8126 L. A. Paquette and S. M. Leit, *J. Am. Chem. Soc.*, 1999, **121**, 8126.
- 1999JOC4381 J. E. Forsee and J. Aube, *J. Org. Chem.*, 1999, **64**, 4381.
- 1999JPY129 M. D. Banciu, A. Popescu, A. Simion, C. Draghici, C. Mangra, D. Mihaiescu, and M. Pocol, *J. Anal. Appl. Pyrolysis*, 1999, **48**, 129.
- 1999T4721 C. L. Kranemann, B. E. Kitos-Rzychon, and P. Eilbracht, *Tetrahedron*, 1999, **55**, 4721.
- 1999TL6657 F. M. Cordero, I. Barile, F. De Sarlo, and A. Brandi, *Tetrahedron Lett.*, 1999, **40**, 6657.
- 1999AJC1131 D. J. Bergmann, E. M. Campi, R. V. Jackson, and A. F. Patti, *Aust. J. Chem.*, 1999, **52**, 1131.
- 2000AJC715 M. F. Mackay, D. J. Gale, and J. F. Wilshire, *Aust. J. Chem.*, 2000, **53**, 715.
- 2000BBB1519 Y. Shiono, K. Akiyama, and H. Hayashi, *Biosci. Biotechnol. Biochem.*, 2000, **64**, 1159.
- 2000BMC557 R. Brecht, G. Seitz, D. Guénard, and S. Thoret, *Bioorg. Med. Chem.*, 2000, **8**, 557.
- 2000BML1257 W. Lew, H. Wu, X. Chen, B. J. Graves, P. A. Escarpe, H. L. McArthur, D. B. Mendel, and C. U. Kim, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1257.
- 2000CEJ1847 A. Furstner, M. Liebl, C. W. Lehmann, M. Picquet, R. Kunz, C. Bruneau, D. Touchard, and P. H. Dixneuf, *Chem. Eur. J.*, 2000, **6**, 1847.
- 2000H(52)147 T. Fujiwara, Y. Kato, and T. Takeda, *Heterocycles*, 2000, **52**, 147.
- 2000H(53)2781 K. Oda, T. Kazuaki, Y. Fukuzawa, N. Nishizono, and M. Machida, *Heterocycles*, 2000, **53**, 2781.
- 2000JME2362 I. D. Linney, I. M. Buck, E. A. Harper, S. B. Kalindjian, M. J. Pether, N. P. Shankley, G. F. Watt, and P. T. Wright, *J. Med. Chem.*, 2000, **43**, 2362.
- 2000J(P1)2943 S. Derrer, J. E. Davies, and A. B. Holmes, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2943.
- 2000JOC3209 D. Francois, E. Poupon, M.-C. Lallemand, N. Kunesch, and H. P. Husson, *J. Org. Chem.*, 2000, **65**, 3209.
- 2000JOC8367 D. I. MaGee and E. J. Beck, *J. Org. Chem.*, 2000, **65**, 8367.
- 2000S1622 S. Kim and J.-Y. Yoon, *Synthesis*, 2000, 1622.
- 2000SL116 H. Kotsuki, H. Sakai, and T. Shinohara, *Synlett*, 2000, 116.
- 2000TL6067 L. Gil, R. P. de Freitas Gil, D. C. dos Santos, and C. Marazano, *Tetrahedron Lett.*, 2000, **41**, 6067.
- 2001ARK191 L. Czollnera, M. Treub, J. Froehlichb, B. Kueenburger, and U. Jordis, *ARKIVOC*, 2001, i, 191.

- 2001BML2651 A. E. Moormann, S. Metz, M. V. Toth, W. M. Moore, G. Jerome, C. Kornmeier, P. Manning, D. W. Hansen, Jr, B. S. Pitzele, and R. K. Webber, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2651.
- 2001J(P1)2774 J. S. Lee, D. J. Lee, B. S. Kim, and K. Kim, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2774.
- 2001J(P1)3312 J. S. Clark, P. B. Hodgson, M. D. Goldsmith, and L. J. Street, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3312.
- 2001OL861 T. J. Donohoe, A. Raof, and J. D. Linney, *Org. Lett.*, 2001, **3**, 861.
- 2001OL893 C. J. Creighton and A. B. Reitz, *Org. Lett.*, 2001, **3**, 893.
- 2001OL2957 F. Iradier, G. Arrayas, and J. C. Carretero, *Org. Lett.*, 2001, **3**, 2957.
- 2001JOC6669 M. J. Walker, B. N. Hietbrink, B. E. Thomas IV, K. Nakamura, E. A. Kallel, and K. N. Houk, *J. Org. Chem.*, 2001, **66**, 6669.
- 2001SL37 G. Vo-Thang, V. Boucard, H. Sauriat-Dorizon, and F. Guibe, *Synlett.*, 2001, 37.
- 2001TL3081 B. Alcaide, C. Rodriguez-Ranerc, and A. Rodriguez-Vicente, *Tetrahedron Lett.*, 2001, **42**, 3081.
- 2002AGE2403 S. Blechert and H. Wakamatsu, *Angew. Chem., Int. Ed.*, 2002, **41**, 2403.
- 2002EJO3359 C. Simon, J.-F. Peyronel, F. Clerc, and J. Rodriguez, *Eur. J. Org. Chem.*, 2002, **19**, 3359.
- 2002JA6991 S. J. Dolman, E. S. Sattely, A. H. Hoveyda, and R. R. Schrock, *J. Am. Chem. Soc.*, 2002, **124**, 6991.
- 2002OL2637 C. P. Chow, K. J. Shea, and S. M. Sparks, *Org. Lett.*, 2002, **4**, 2637.
- 2002S1057 H. Shargi and M. Hosseini, *Synthesis*, 2002, **8**, 1057.
- 2002SL1014 T. Hoffmann and P. Gmeiner, *Synlett.*, 2002, 1014.
- 2002SL697 T. Kan, H. Kobayashi, and T. Fukuyama, *Synlett.*, 2002, 697.
- 2002T6267 T. Kan, A. Fujiwara, H. Kobayashi, and T. Fukuyama, *Tetrahedron*, 2002, **58**, 6267.
- 2003ASC572 S. J. Connon, M. Rivard, M. Zaja, and S. Blechert, *Adv. Synth. Catal.*, 2003, **345**, 572.
- 2003EJM245 G. A. Gfesser, E. K. Bayburt, M. Cowart, S. DiDomenico, A. Gomtsyan, C.-H. Lee, A. O. Stewart, M. F. Jarvis, E. A. Kowaluk, and S. S. Bhagwat, *Eur. J. Med. Chem.*, 2003, **38**, 245.
- 2003JA5632 I. Ryu, H. Miyazato, H. Kuriyama, K. Matsu, M. Tojino, T. Fukuyama, S. Minakata, and M. Komatsu, *J. Am. Chem. Soc.*, 2003, **125**, 5632.
- 2003JA6462 H. M. L. Davies, C. Venkataramani, T. Hansen, and D. W. Hopper, *J. Am. Chem. Soc.*, 2003, **125**, 6462.
- 2003JOC1447 M. Sakamoto, T. Sano, S. Fujita, M. Ando, K. Yamaguchi, T. Mino, and T. Fujita, *J. Org. Chem.*, 2003, **68**, 1447.
- 2003MM3078 T. Schulte and A. Studer, *Macromolecules*, 2003, **36**, 3078.
- 2003OBC4262 M. Tojino, N. Otsuka, T. Fukuyama, H. Matsubara, K. H. Schiesser, H. Kuriyama, H. Miyazato, S. Minakata, M. Komatsu, and I. Ryu, *Org. Biomol. Chem.*, 2003, **1**, 4262.
- 2003OL325 E. Bacqué, F. Pautrat, and S. Z. Zard, *Org. Lett.*, 2003, **5**, 325.
- 2004AGE1681 S. J. Taylor, A. M. Taylor, and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2004, **43**, 1681.
- 2004AGE3445 R. S. Grainger and P. Innocenti, *Angew. Chem., Int. Ed.*, 2004, **43**, 3445.
- 2004BMC4375 C. J. Creighton, G. C. Leo, Y. Du, and A. B. Reitz, *Bioorg. Med. Chem.*, 2004, **12**, 4475.
- 2004JA8744 H. Ohno, H. Hamaguchi, M. Ohata, S. Kosaka, and T. Tanaka, *J. Am. Chem. Soc.*, 2004, **126**, 8744.
- 2004JA9524 B. P. Peppers and S. T. Diver, *J. Am. Chem. Soc.*, 2004, **126**, 9524.
- 2004JA13244 B. Sezen and D. Sames, *J. Am. Chem. Soc.*, 2004, **126**, 13244.
- 2004JA10945 S. J. Dolman, K. C. Hultsch, F. Pezet, X. Teng, A. H. Hoveyda, and R. R. Schrock, *J. Am. Chem. Soc.*, 2004, **126**, 10945.
- 2004JOC997 M.-X. Zhao, M.-X. Wang, C.-Y. Yu, Z.-T. Huang, and G. W. J. Fleet, *J. Org. Chem.*, 2004, **69**, 997.
- 2004JOC3025 S. M. Sparks, C. P. Chow, L. Zhu, and K. J. Shea, *J. Org. Chem.*, 2004, **69**, 3025.
- 2004OL1509 F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, and M. Malacria, *Org. Lett.*, 2004, **6**, 1509.
- 2004SL667 N. Buschmann, H. Wakamatsu, and S. Blechert, *Synlett.*, 2004, 667.
- 2004SL2732 A. Hoelemann and H.-U. Reissig, *Synlett.*, 2004, 2732.
- 2004SOS(17)979 R. M. Borzilleri; in 'Science of Synthesis', S. M. Weinreb, Ed.; Thieme, Stuttgart, 2004, vol. 17, p. 979.
- 2004T10385 A. M. C. H. van Nieuwendijk, A. B. T. Ghisaidoobe, H. S. Overkleef, J. Brussee, and A. van der Gen, *Tetrahedron*, 2004, **60**, 10385.
- 2004TL253 S. Handa, M. S. Kachala, and S. L. Lowe, *Tetrahedron Lett.*, 2004, **45**, 253.
- 2004TL579 G. Godin, E. Gamier, P. Compain, O. R. Martin, K. Ikeda, and N. Asano, *Tetrahedron Lett.*, 2004, **45**, 579.
- 2004TL8607 S. A. Raw and R. J. K. Taylor, *Tetrahedron Lett.*, 2004, **45**, 8607.
- 2004TL9607 S. Kotha and K. Singh, *Tetrahedron Lett.*, 2004, **45**, 9607.
- 2004WO2004043947 S. Rault, M. Kopp, J. C. Lancelot, S. Lemaire, B. Pfiffer, E. Bizot, J. G. Espiard, and P. Renard, WO 2004043947 (2004) (*Chem. Abstr.*, 2004, **140**, 375 078).
- 2004WO200469833 M. Shiraishi, K. Aikawa, N. Kanzaki, and M. Baba, WO200469833 (2004) (*Chem. Abstr.*, 2004, **141**, 207 192).
- 2005EJO1052 A. C. L. B. Trindade, D. C. dos Santos, L. Gil, C. Marazano, and R. P. de Freitas Gil, *Eur. J. Org. Chem.*, 2005, **6**, 1052.
- 2005JOC1539 L. Liu, Q. Chen, Y.-D. Wu, and C. Li, *J. Org. Chem.*, 2005, **70**, 1539.
- 2005RRC153 M. D. Banciu, A. Popescu, A. Banciu, D. Mihaiescu, C. Draghici, A. Lariand, and I. Oprean, *Rev. Roum. Chim.*, 2005, **50**, 153.
- 2005SS583 Y. Hari and T. Aoyama, *Synthesis*, 2005, **4**, 583.
- 2005SL631 T. Yamanaka, M. Ohkubo, M. Kato, Y. Kawamura, A. Nishi, and T. Hosokawa, *Synlett.*, 2005, 631.
- 2005WO2005068431 S. Sabelle, WO2005068431 (2005) (*Chem. Abstr.*, 2005, **143**, 138613).
- 2006BML1532 B. E. Fink, A. V. Gavai, J. S. Tokarski, B. Goyal, R. Misra, H.-Y. Xiao, S. D. Kimball, W.-C. Han, D. Norris, T. E. Spire, D. You, M. M. Gottardis, M. V. Lorenzi, and G. D. Vite, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1532.
- 2006RRC345 A. Popescu, A. Lari, A. Banciu, C. Draghici, D. Ciuculescu, D. Istrati, and M. D. Banciu, *Rev. Roum. Chim.*, 2006, **51**, 345.
- 2006T9043 C. Bru and C. Guillou, *Tetrahedron*, 2006, **62**, 9043.
- 2006TL4721 Z. Ma, S. Dai, and D. Yu, *Tetrahedron Lett.*, 2006, **47**, 4721.
- 2006WO2006001463 H. Habashita and S. Nakade, WO2006001463 (2006) (*Chem. Abstr.*, 2006, **144**, 108 361).
- 2006WO2006023187 Y.-L. Wu and H. He, WO2006023187 (2006) (*Chem. Abstr.*, 2006, **144**, 170 897).
- 2007ARKIVOC320 F. Diaba, E. Ricou, D. Sole, E. Teixido, N. Valls, and J. Bonjoch, *ARKIVOC*, 2007, 320.
- 2007BMCL5414 S. Hosoda and Y. Hashimoto, *Bioorg. & Med. Chem. Lett.*, 2007, **17**, 5414.
- 2007CC1605 S. M. Butterfield and J. Jr. Rebek, *Chem. Commun.*, 2007, 1605.
- 2007JMC3906 W. Lin and J. K. Buolamwini, *J. Med. Chem.*, 2007, **50**, 3906.
- 2007JOC5608 D. L. J. Clive, Z. Li, and M. Yu, *J. Org. Chem.*, 2007, **72**, 5608.

- 2007OL2453 D. Basavaiah and K. Aravindu, *Org. Lett.*, 2007, **9**, 2453.
2007WO0009723 J. A. Torrens and S. Minguez, WO0009723 (2007) (*Chem. Abstr.*, 2007, **146**, 184 443).
2007WO131538 J. A. Torrens and S. Minguez, WO07131538 (2007) (*Chem. Abstr.*, 2007, **147**, 541 871).

Biographical Sketch



Daniela Carmen Oniciu received her MS in organic chemistry and chemical engineering, then her PhD in organic chemistry from the University “Polytechnica” of Bucharest (Romania), where she worked as a scientist until 1997. Her postdoctoral experience was gained with Alan R. Katritzky at the University of Florida and Hiizu Iwamura at the University of Tokyo. In 1998, she joined Alchem Laboratories in Alachua (Gainesville) (USA) as director of chemistry, working in pharmaceutical research and development. From 2001 to 2005 she was director of Chemical R&D at Esperion Therapeutics, Inc. in Ann Arbor (USA), which became a Division of Pfizer Global Research and Development in 2004. Since 2004 she is courtesy professor of chemistry at the University of Florida at Gainesville (USA). Currently, she is senior director of chemistry at Cerenis Therapeutics SA (France), a pharmaceutical company focused on developing pharmaceuticals to treat cardiovascular disease. Her research interests encompass a broad area: heterocyclic chemistry, the chemistry of free radicals, and medicinal chemistry.

14.02

Eight-membered Rings with One Oxygen Atom

A. M. S. Silva and A. C. Tomé

University of Aveiro, Aveiro, Portugal

© 2008 Elsevier Ltd. All rights reserved.

14.02.1	Introduction	49
14.02.2	Theoretical Models	50
14.02.3	Experimental Structural Methods	51
14.02.3.1	Natural Products	51
14.02.4	Thermodynamic Aspects	61
14.02.5	Reactivity of Fully Conjugated Rings	61
14.02.6	Reactivity of Nonconjugated Rings	61
14.02.7	Reactivity of Substituents Attached to Ring Carbon Atoms	62
14.02.8	Reactivity of Substituents Attached to the Ring Heteroatoms	62
14.02.9	Ring Syntheses Classified by Number of Ring Atoms in Each Component	63
14.02.9.1	Hydroxydithioketal Cyclization	63
14.02.9.2	Ring-Closing Metathesis	64
14.02.9.3	1,3-Dipolar Cyclizations	67
14.02.9.4	Haloetherification of Unsaturated Alcohols	67
14.02.9.5	Aldehyde-Allylboration Reaction	67
14.02.9.6	Titanocene-Promoted Cyclizations	68
14.02.9.7	Sml₂-Promoted Cyclizations	69
14.02.9.8	Cyclization of Hydroxy Epoxides	70
14.02.9.9	Lactonization	70
14.02.9.10	Other Cyclization Methods	72
14.02.10	Ring Syntheses by Transformation of Another Ring	76
14.02.10.1	Ring Expansions of One Atom	76
14.02.10.2	Ring Expansions of Two Atoms	77
14.02.10.3	Ring Expansions of Three or More Atoms	77
14.02.10.4	Ring Contractions	81
14.02.11	Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	83
14.02.12	Important Compounds and Applications	83
14.02.13	Further Developments	84
	References	84

14.02.1 Introduction

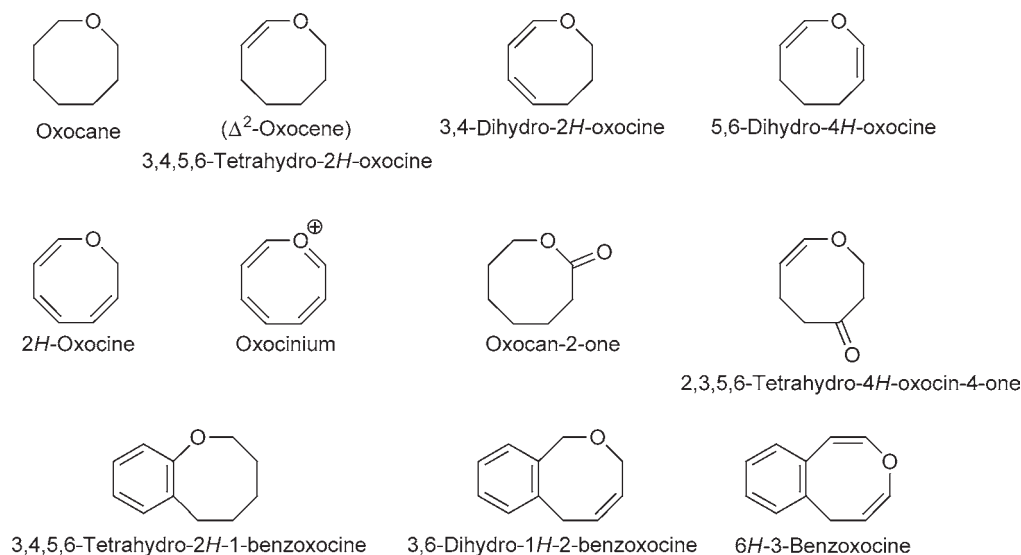
Previously published information regarding the compounds of this class can be found in CHEC-II(1996) <1996CHEC-II429>. Other important reviews on the chemistry and biological properties of these compounds are also available <1995CRV1953, 2000NPR293, 2005CRV4379>. During the last decade, this class of compounds has been the subject of numerous research articles related with the chemical and biological properties of the eight-membered cyclic ethers. The interest in this ring system is mainly due to their occurrence in nature, particularly in

marine-based natural products. Many of these natural products are the cause of human poisoning by ingestion of shellfish. Accordingly, this chapter emphasizes the characterization and the synthesis of structures found in nature.

The eight-membered cyclic ethers are found in alkaloids, aromatic bisabolene sesquiterpenes, physalins, and other complex molecules; they are also frequently fused in other ring systems. Typically these natural compounds possess either a saturated eight-membered ring or one double bond in the ring. The most studied systems are the brevetoxins, ciguatoxins, yessotoxins, and related compounds, which are produced by dinoflagellates and algae. These compounds accumulate (or are metabolized) in shellfish. The extreme difficulty to isolate these toxins or their metabolites from their natural sources, due to small quantities present, led to the development of several bioassays or chromatographic methods for their monitoring, identification, and quantitative determination. The availability of these compounds in very limited quantities, associated to their unusual molecular structures, make them challenging targets to study. Efficient routes for their synthesis are thus required in order to make them available in larger quantities for pharmacological and toxicological studies.

The progress in nuclear magnetic resonance (NMR) hardware and pulse technology improves and accelerates the structure determination of complicated natural compounds, in particular high field spectrometers and heteronuclear multiple bond correlation (HMBC) spectra. The combination of the NMR techniques, mainly nuclear Overhauser effect (NOE) information, with molecular mechanics calculations allows the estimation of the three-dimensional (3-D) structures of the larger molecules [<2005TL1855>](#). Accordingly, the structures of the major part of the described complex molecules are assigned by extensive 1-D and 2-D NMR studies complemented or supported by mass spectrometry (MS) data, mainly electrospray ionization (ESI), which facilitates the determination of their molecular masses. The small quantities of the larger molecules hampered the determination of their absolute configuration by X-ray diffraction, but this problem was circumvented by the development of new chiral reagents and methods for their assignment by NMR.

Eight-membered rings with one oxygen atom are named as oxocanes, oxocenes, or oxocines. The name Δ^n -oxocene is frequently used for compounds with one double bond; $n=2-4$ indicates the position of the double bond. Oxocenes, however, are preferentially named as dihydro- or tetrahydrooxocines. The names of some selected oxocane and oxocine compounds are shown.



14.02.2 Theoretical Models

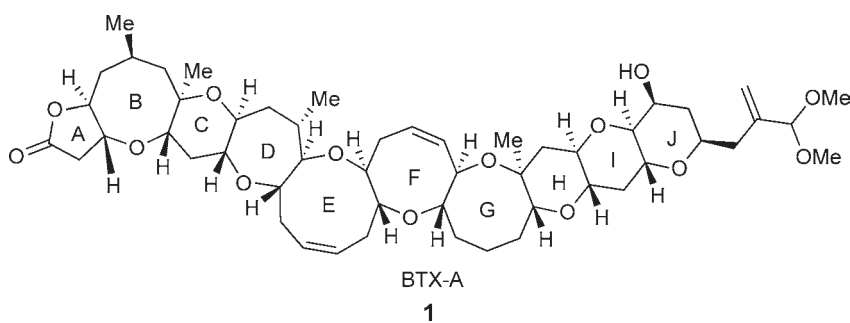
Eight-membered ring systems were the subject of extensive theoretical effort until 1994 [<1996CHEC-II429>](#). Since then, there are a few studies combining molecular mechanics calculations and NMR studies to rationalize the observed conformations and various conformational processes [<2000T10209, 2005TL1855>](#). There is also a study on the determination of the 3-D molecular structure of brevetoxin-B, a molecule containing 23 chiral centers (see [Section 14.02.3](#)), based on the NOE data and the application of a stochastic genetic algorithm [<2005T9980>](#).

14.02.3 Experimental Structural Methods

14.02.3.1 Natural Products

Brevetoxins are lipid-soluble polyether neurotoxins produced by marine algal dinoflagellates, which are responsible for massive fish kills and severe human health problems. Brevetoxins type A exhibit the highest toxicity while there are some subtle toxicity differences between the brevetoxins type B <1988MI97, B-1990MI397>. Until recently, shellfish toxicity was presumed to be due to unmodified brevetoxins produced by the red tile dinoflagellate *Karenia brevis* (the actual name of this organism, also known as *Ptychodiscus brevis* and *Gymnodinium breve* <2000MI302>) and accumulated in shellfish. However, several metabolites of brevetoxins analogues have been isolated from shellfish that feed dinoflagellates and their structure assigned <1995TL725, 1995TL8995, 1998T735, 2004TL29>.

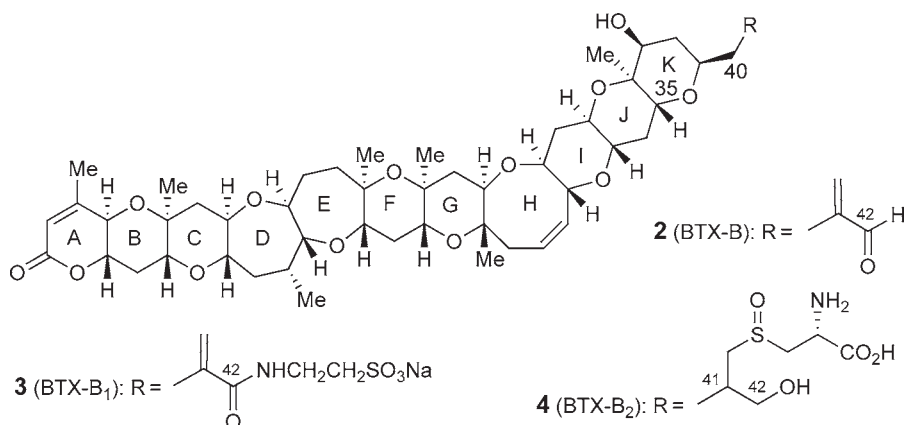
The structures of numerous brevetoxins and structurally similar toxins have been determined in the 1980s and were reported in the CHEC-II(1996) <1996CHEC-II429>. These studies considered the X-ray crystal structure of brevetoxin A (BTX-A, **1**) and of a chiral 1,3-dioxolane derivative of brevetoxin B (BTX-B also identified as PbTx-2, **2**). It is important to notice that BTX-A has two oxocane and one oxocene subunits. Another important feature is the 90° bend of the eight-membered oxygen-containing G-ring. By the contrary, BTX-B **2** was described to be essentially planar in which the G-ring possesses the boat-chair conformation. The conformational flexibility of this ring, a possible boat-chair-to-crown interconversion indicated by NMR, has been postulated to account for its greater toxicity <1996CHEC-II429>.



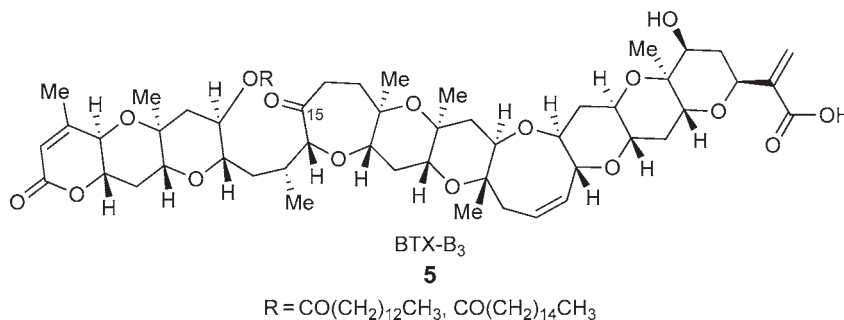
After the 1992–93 outbreak of neurotoxic shellfish poisoning (NSP) in New Zealand, several metabolites of brevetoxins were isolated from seafood <B-1993MI(24)35>. NSP is a term applied to an illness resulting from the ingestion of shellfish exposed to blooms of dinoflagellate *K. brevis* <1965MI111, 1991MI471>.

Brevetoxin B₁ (BTX-B₁, **3**) was isolated from the New Zealand toxicated shellfish, *Austrovenus stutchburyi* <1995TL725>. Its structure differs from that of BTX-B **2** only in the functional group of the ring K side chain. The structure of BTX-B₁ **3** was based on detailed NMR analysis, namely 2-D correlation spectroscopy (COSY) and HMBC spectra and NOE measurements, and by comparison of the high and low field regions of the ¹³C NMR spectra where the signal at 197.1 ppm (C-42) in BTX-B is replaced by three new signals at 171.7, 52.0, and 37.5 ppm in the spectrum of BTX-B₁. The acid hydrolysis of BTX-B₁ afforded 1 equiv of 2-aminoethanesulfonic acid, the functional group at C-42 in its side chain, and the high-resolution fast atom bombardment mass spectrometry (HRFABMS) gave the molecular formula C₅₂H₇₄O₁₇NSNa.

Brevetoxins B₂ **4**, B₃ **5**, and B₄ **6** were isolated from excised hepatopancreas of greenshell mussels, *Perna canaliculus*, from North Island of New Zealand. The residue obtained from the acetone extract by solvent evaporation was first partitioned between water and AcOEt. From the organic layer, BTX-B₃ **5** and BTX-B₄ **6** were obtained while BTX-B₂ **4** was retained in the aqueous layer and then extracted with BuOH <1995TL8995, 1998T735, 1999MI45>. The ¹H NMR spectrum of BTX-B₂ **4** is similar to that of BTX-B **2**, except the lacking signals due to the formyl and exomethylene groups of the side chain of **2**. All of the NMR data of **2** and **4** showed that both compounds have the same backbone structure including its stereochemistry. The HRFABMS revealed a parent mass ion consistent with a molecular formula of C₅₃H₈₀O₁₇NS. The positive ninhydrin test and the infrared (IR) spectrum (1610 cm⁻¹) suggested that an α-amino group exists in the molecule, whereas the presence of a sulfur atom was confirmed by dispersive X-ray analysis. BTX-B₂ **4** oxidizes HI to liberate iodine and produces a sulfone by *m*-chloroperbenzoic acid (MCPBA) oxidation, indicating that the sulfur atom exists as a sulfoxide. The proton and carbon signals arising from the side chain were split and broadened even after changing temperature and radiowave frequency, suggesting that BTX-B₂ **4** exists as a diastereomeric mixture based on the stereogenic centers at C-41 and sulfoxide. All the attempts to separate these diastereomers were unsuccessful. The NOE effects between H-35 and CH₂-40 indicated that the side chain is in the β-orientation, as in **2**.

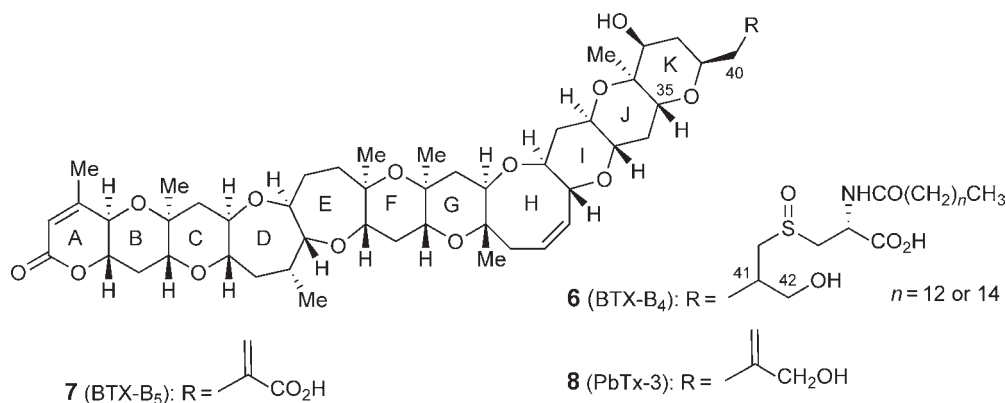


Brevetoxin B₃ **5** was isolated as a mixture of two homologues differing in their acyl moieties, as was evidenced by the FAB negative mass spectrum, m/z at 1135 and 1163 (M-H)⁻ <1995TL8995>. Their structures are similar to that of BTX-B **2** in which the terminal aldehyde is oxidized to a carboxylic acid, the oxepane ring D is cleaved to a keto alcohol moiety, and the resulting alcohol is esterified. The ¹H NMR spectrum of BTX-B₃ **5** resembles that of BTX-B **2**, but presents a large envelope of signals at δ 1.2 ppm, indicative of a long-chain fatty acid. A basic hydrolysis of BTX-B₃ **5** and fluorometric high-performance liquid chromatography (HPLC) analysis of the hydrolysate confirmed that its structure contained one molecule of either palmitic or myristic acid. The relative ratio of the two fatty acids was approximately 1:1. The detailed NMR data of BTX-B₃ **5** (COSY, total correlated spectroscopy (TOCSY), heteronuclear single quantum correlation (HSQC), and HMBG spectra, and NOE correlations) led to the assignment of BTX-B₃ structure. The ¹³C NMR spectrum of BTX-B₃ **5** was distinct from that of BTX-B **2** by a ketone (216.3 ppm, C-15) and a carboxyl carbon (171.2 ppm) signals. The structure of BTX-B₃ **5** was further supported by negative ion FAB MS/MS studies (molecular formulas of C₆₄H₉₆O₁₇ and C₆₆H₁₀₀O₁₇ for the two homologues).



Brevetoxin B₄ (BTX-B₄, **6**) was identified as the major toxin in greenshell mussels, *P. canaliculus*, and obtained as a mixture of *N*-myristoyl-BTX-B₂ and *N*-palmitoyl-BTX-B₂, as was evidenced by negative ion FABMS in the ratio of 4:3. The presence of a sulfur atom(s) in the molecule was confirmed by energy-dispersive X-ray analysis while the ¹H NMR spectrum resembled that of BTX-B **2** but lacking the signals due to the formyl and exomethylene groups in the side chain of BTX-B **2**, and showed a large methylene assembly at 1.2 ppm, indicative of a long-chain fatty acid. The 2-D NMR measurements revealed good agreements between BTX-B₄, BTX-B₂ **4**, and BTX-B **2** in the connectivities and coupling constants of protons, allowing assignment of the same backbone structure including the stereochemistry; however, precise NMR assignments of the side-chain part were impossible because BTX-B₄ is a diastereo-mixture having chiral centers at C-41 and sulfoxide. *N*-Palmitoyl-BTX-B₂ was synthesized from BTX-B₂ **4** and showed an ¹H NMR spectrum identical with that of BTX-B₄, thus strongly supporting that BTX-B₄ was a mixture of *N*-myristoyl and *N*-palmitoyl-BTX-B₂ <1999MI45>.

Brevetoxin B₅ (BTX-B₅, **7**) was identified together with BTX-B₁ and PbTx-3 (**8**, a BTX-B derivative where the formyl group was reduced to a hydroxymethyl group) from the New Zealand toxicated shellfish, *A. stutchburyi* <2004TL29>. Its structure was elucidated by comparison of their spectral data (NMR and FAB collisionally activated dissociation (CAD) MS/MS spectra) with those of BTX-B **2**. These data suggested that **7** have the same polycyclic ether part, including the stereochemistry, of **2** in which the terminal formyl group was oxidized to a carboxylic acid. The BTX-B₅ **7** was also obtained in 100% yield by oxidation of **2** with SeO₂ and 30% H₂O₂ in *tert*-butyl alcohol.



Several new brevetoxin derivatives have been isolated and identified in *K. brevis* and natural blooms by solid-phase extraction and liquid chromatography (LC)–MS(MS) techniques [\[2006MI104\]](#). These analogues are more polar than the previously reported brevetoxin derivatives and are poorly extractable by nonpolar solvents. They are novel derivatives and result from the hydrolysis of the A-ring and/or oxidation of the formyl group of some known derivatives.

The brevetoxins BTX-B **2** and PbTx-3 **8** are produced by the red tile dinoflagellate *K. brevis* and were isolated in the 1980s [\[1981JA6773, 1982TL5521\]](#); however, in 1996, they were isolated from oysters, *Crassostrea gigas*, at North Island of New Zealand [\[1996MI1050\]](#). Although brevetoxins produced by the dinoflagellate itself have been extensively studied, those of shellfish received little attention until 1990s. The occurrence of several brevetoxin derivatives (A and B types) and some of their conjugates in shellfish put in evidence that *Karenia* species produce the toxins that accumulate directly or after metabolism in shellfish, although some of them were eliminated [\[2002MI721, 2004MI455, 2004MI677, 2004MI701\]](#). A possible metabolic pathway of brevetoxin BTX-B **2** in shellfish was recently proposed ([Figure 1](#)) [\[2003MI191\]](#).

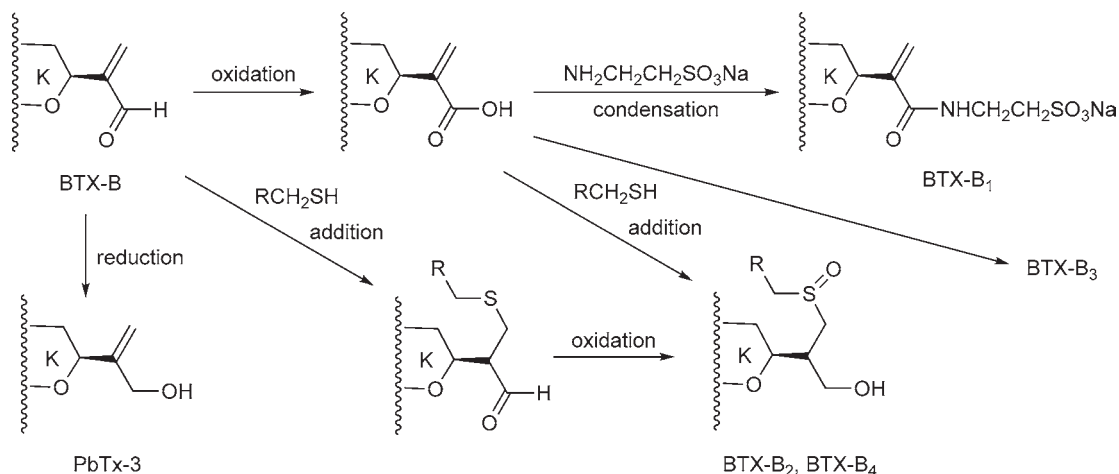
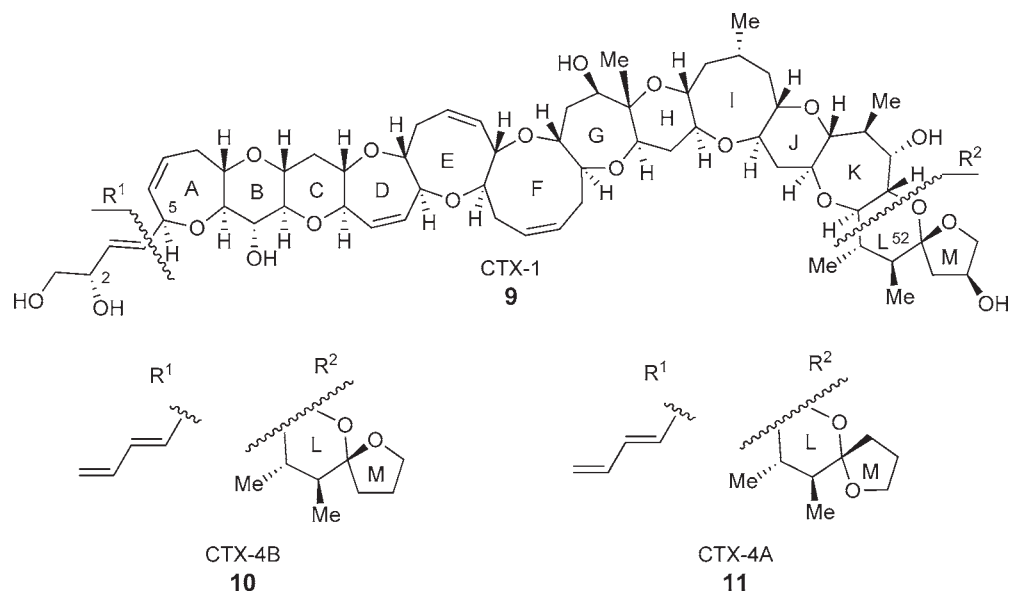


Figure 1 Possible metabolic pathway of BTX-B **2** in shellfish.

The extreme difficulty of brevetoxins' isolation from shellfish, due to the small quantities present, led to the development of several bioassays and chromatographic methods for their monitoring, identification, and quantitative determination [\[1999MI157, 2003MI191, 2004MI669, 2004MI779, 2005MI441\]](#). Some of them can discriminate ciguatoxins from brevetoxins [\[2005MI261\]](#).

Since the isolation and structural characterization of ciguatoxin (CTX or CTX-1 as described by many authors, **9**), the principal toxin causing ciguatera (a term applied to food poisoning caused by ingestion of coral reef fish), and ciguatoxin 4B (CTX-4B, **10**, first identified as gambertoxin-4b, GT-4b) <1990JA4380, 1996CHEC-II429>, other ciguatoxin derivatives have been identified <1993TL1975, 1997BBB2103, 1998TL1197, 2001MI228>. Ciguatoxin 4A (CTX-4A, **11**) was isolated from cultures of marine dinoflagellate *Gambierdiscus toxicus* and its structure assigned as 52-*epi*-CTX-4B based on the spectroscopic data. The authors claimed that CTX-4A **11** was chromatographic and spectroscopic identical to the unelucidated congener scaritoxin (SG-1) <1997BBB2103>.

The relative stereochemistry of **9–11** was elucidated when they were isolated, but further chemical studies to determine the absolute configuration of these toxins were hampered because of the extremely limited availability of the toxins. Configuration 5*R* of CTX-4B **10** was initially assigned by comparing its CD spectrum with that of a synthetic fragment bearing the butadienyl side chain and the AB rings of **10**, but uncertainty remained due to the observed small Cotton effects <1991TL4505>. The (2*S*)-configuration of CTX-1 **9** assigned on the basis of the CD exciton chirality data of tetrakis-*p*-bromobenzoates of **9** and tris-*p*-bromobenzoates of AB fragments also needed further confirmation due to the difficulty to assign the position of the tetrakis-*p*-bromobenzoates of **9** <1995SL1252, 1997T3057>. The use of new fluorescent reagents ((*S*)- and (*R*)-*tert*-butyl-2-methyl-1,3-benzodioxole-4-carboxylic acid) in conjugation with the CD exciton chirality method allowed the unambiguous determination of (2*S*)-configuration to CTX-1 **9** and 5*R* for CTX-4A **11** using very small amounts of toxins <1997JA11325>. Since CTX-1 **9** is an oxidized metabolite of CTX-4A **11**, the configuration of its C-5 must be the same (i.e., *R*).

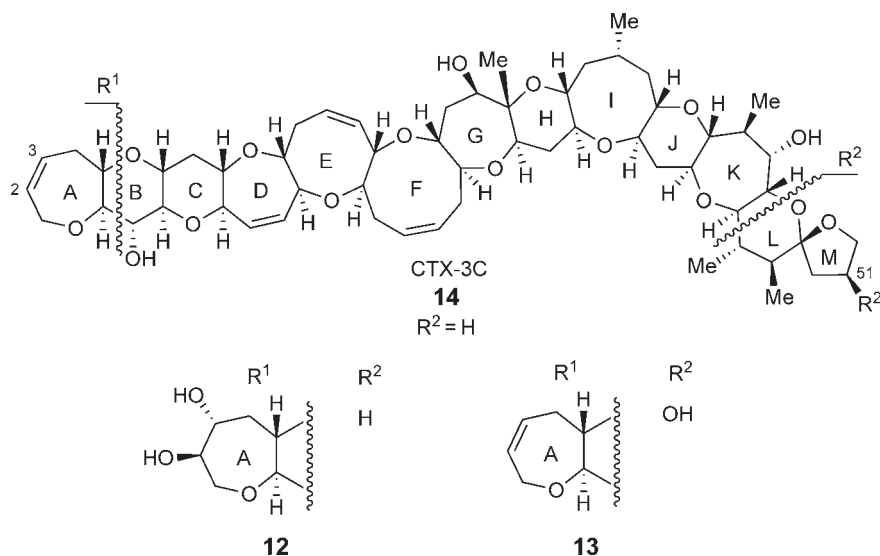


Like ciguatoxin **9**, 2,3-dihydroxy-CTX-3C **12** and 51-hydroxy-CTX-3C **13** were also isolated from the viscera of the moray eel *Gymnothorax javanicus* <1998TL1197>. The HR-FABMS of **12**, ($M+Na$)⁺ 1079.5510 (calcd. for C₅₇H₈₄O₁₈Na: 1079.5560), indicated that it is larger than CTX-3C (**14**, C₅₇H₈₂O₁₆) by two hydroxyl groups. This information along with the NMR data (namely COSY and TOCSY spectra and NOE correlations) in C₅D₅N confirm that two olefinic proton signals due to H-2 and H-3 in CTX-3C **14** were replaced by new oximethine signals at ca. 4.3 ppm in **12**, also assigned to the resonances H-2 and H-3 of **12**. The HRFABMS of **13**, ($M+Na$)⁺ 1061.5460 (calcd. for C₅₇H₈₂O₁₇Na: 1061.5450), showed that it is larger than CTX-3C **14** by one oxygen atom. The structure of **13** was determined by comparing their NMR data with those of CTX-1 **9** and CTX-3C **14**. The main difference is the new signal assignable to an oximethine proton H-51 (4.86 ppm).

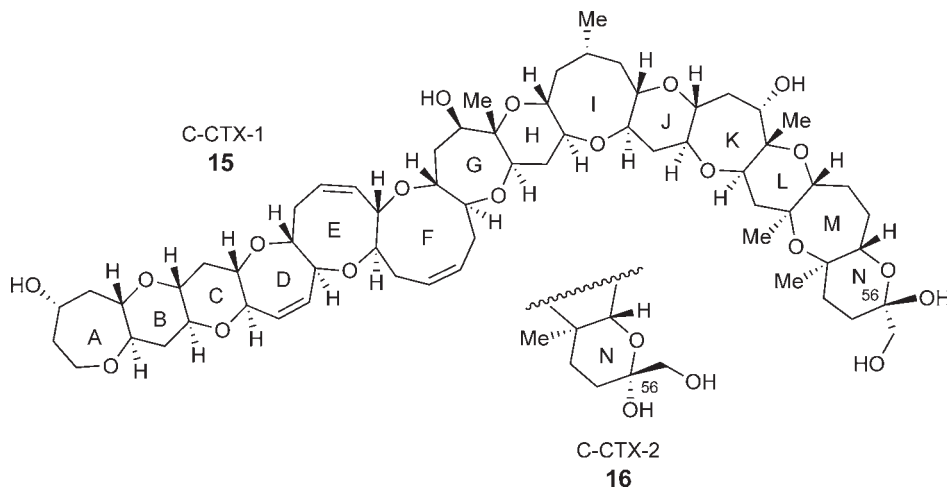
The occurrence of **12** and **13** in fish but not in *G. toxicus* implies that CTX-3C **14** produced by this dinoflagellate was oxidized in fish to **12** and **13**, supporting the theory for oxidative modification of ciguatera toxins during the food chain transmission.

Many of ciguatoxin congeners remained unidentified because of the extreme difficulty to obtain enough material for NMR studies. However, Yasumoto *et al.* developed a method to identify ciguatoxin congeners by FAB/MS/MS, based on the fact that the (Na -adduct)⁺ of ciguatoxin congeners facilitates charge-remote fragmentations from both termini induced by high-energy (8 kV) collision activation. The FAB/MS/MS spectra of CTX-1 **9** and CTX-3C **14**

and their 2-sulfobenzoates allowed assigning typical fragment ions, which were used in the identification of many new congeners of ciguatoxin <2000JA4988, 2001MI228>.



In 1997, Vernoux and Lewis reported the isolation of several ciguatoxins from the horse-eye jack, *Caranx latus*, of the Caribbean Sea. Based on turbo-assisted HPLC MS, they identified five C-ciguatoxins, C-CTX-1 and C-CTX-2, assigned as diastereomers and being different from Pacific ciguatoxins, and three C-CTX-1-related compounds <1997MI889>. In the same year, there was a report where C-CTX-1 was identified as the cause of an outbreak of fish poisoning among US soldiers in Haiti <1997MI733>. Only in 1998, Lewis *et al.* assigned the structure of C-ciguatoxin-1 (C-CTX-1, **15**), isolated from horse-eye jack, *C. latus*, from the Caribbean Sea, based on MS and exhaustive 2-D NMR studies at high NMR field (500 and 750 MHz) <1998JA5914>. It was demonstrated that C-CTX-1 **15** has a ciguatoxin/brevetoxin structure comprising 14 *trans*-fused ether-linked rings (7/6/6/7/8/9/7/6/8/6/7/6/7/6), with a molecular formula of C₆₂H₉₂O₁₉ determined by ISMS, (M+H)⁺ *m/z* 1141.6. Comparing the structure of CTX-1 (**9**), or P-CTX-1, since it was identified from Pacific Ocean) with that of C-CTX-1 **15**, one can conclude that the latter possesses a flexible nine-membered ring (which is a structural feature among the ciguatoxins), it has a longer contiguous carbon backbone (57 vs. 55 for P-CTX-1, **9**), one extra ring, and a hemiketal in ring N but no spiroketal. In the same study, a 56-*epi*-C-CTX-1 (C-CTX-2, **16**) was also identified, and it was shown to rearrange to C-CTX-1 in solution. The structural similarities between Caribbean and Pacific ciguatoxins led the authors to propose that C-CTX-1 **15** and C-CTX-2 **16** arise from a Caribbean strain of the dinoflagellate *G. toxicus* <1998JA5914>.



In 2002, Lewis and co-workers reported the isolation and initial characterization of Indian Ocean ciguatoxin (I-CTX) from toxic lipid-soluble extracts of ciguateric fishes of Indian Ocean <2002MI685>. This compound eluted later than P-CTX-1 but was practically indistinguishable from C-CTX-1 on reverse-phase HPLC while TSK HW-40S column chromatography differentiates I-CTX-1 from the later-eluting C-CTX-1. The electrospray mass spectrometry identified their $[M+H]^+$ ion at m/z 1141.58, which also corresponds to the mass of C-CTX-1, but the fragmentation pattern of I-CTX-1 showed a different ratio of pseudomolecular and product ions. Later in that same year, the presence of several I-CTX, namely I-CTX-1, I-CTX-2, I-CTX-3, and I-CTX-4, from a partially purified extract of a highly toxic *Lutjanus sebae* (red emperor) from the Indian Ocean was reported <2002MI1347>. It seems that I-CTX-1 and I-CTX-2 (1140.6 Da for both) may arise from separate dinoflagellate precursors that may be oxidatively biotransformed to I-CTX-3 and I-CTX-4 (1156.6 for both) in fish.

Yessotoxin (**17**, YTX) was isolated in Japan from the scallop *Patinopecten yessoensis* as a diarrhetic shellfish poison. Its planar structure was elucidated by NMR and negative FAB MS/MS <1987TL5869, 1993RCM179>. Although the structural resemblance with brevetoxin B **2** and ciguatoxin 4B **10**, potent activators of voltage-gated sodium channels and not cytotoxins, YTX **17** does not potentiate those channels and shows cytotoxicity and toxicological properties <1990JA4380>. The relative configuration and ring conformations of YTX were determined in 1996 by NMR experiments, mainly NOEs and typical coupling constants, namely those of angular protons ($J = 9\text{--}10$ Hz) of *anti*-periplanar substitution on oxycarbons indicating that all ether rings have a *trans*-fusion <1996TL5955>. Their absolute configuration was determined in the same year by NMR spectroscopy using the chiral anisotropic reagent methoxy(2-naphthyl)acetic acid (2-NMA), which was applied to a monoacetate of bisdesulfated yessotoxin **18** <1996TL7087>. This chiral reagent was used because it is the most convenient one for secondary alcohols and the anisotropy of its naphthalene ring is much greater than others bearing benzene rings. The reaction of **18** with (*R*)- and (*S*)-2-NMA led to the formation of the corresponding esters on C-4 which allowed the assignment of the absolute configuration of this carbon to be (*S*), which was enough to assign all the absolute configuration of YTX **17** (the relative configuration was determined previously).

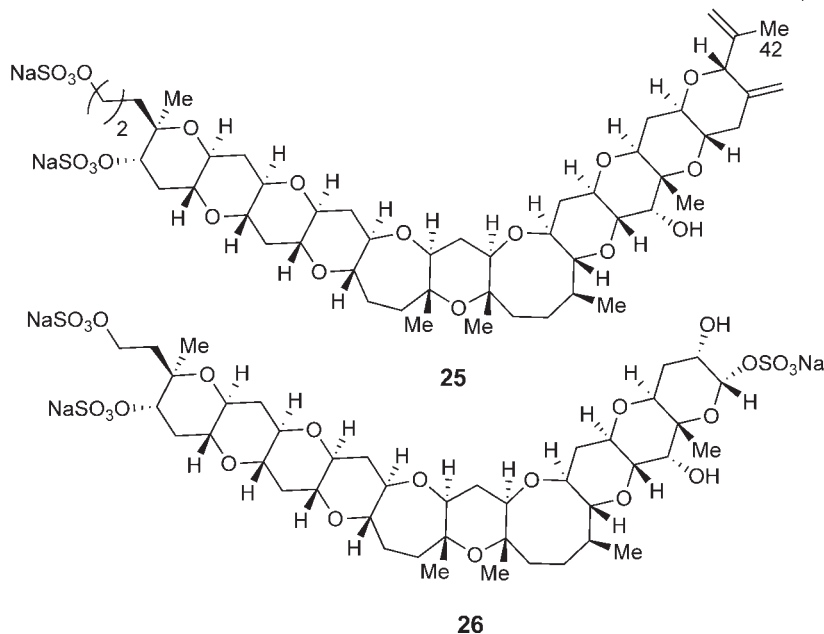
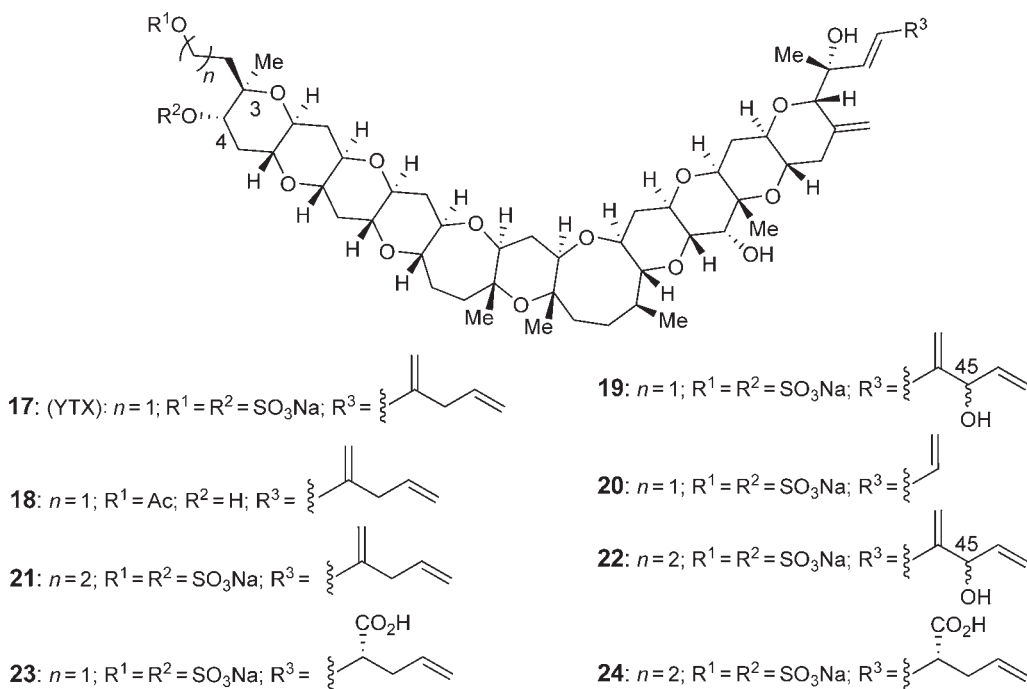
Two other yessotoxin analogues, 45-hydroxy-YTX **19** and 45,46,47-trinor-YTX **20**, have been isolated from the toxic scallop *P. yessoensis* <1996TL5955>. The negative ESI-MS spectrum suggested that **19** is larger than YTX by one oxygen atom and the NMR data allowed the assignment of the extra 45-OH group, but a very small amount prevented the determination of C-45 configuration. Once again, in the case of **20**, the MS data (40 Da smaller than **17**) and the absence of protons signals from H-45 to H-47 led to the assignment of its structure as 45,46,47-trinor-YTX.

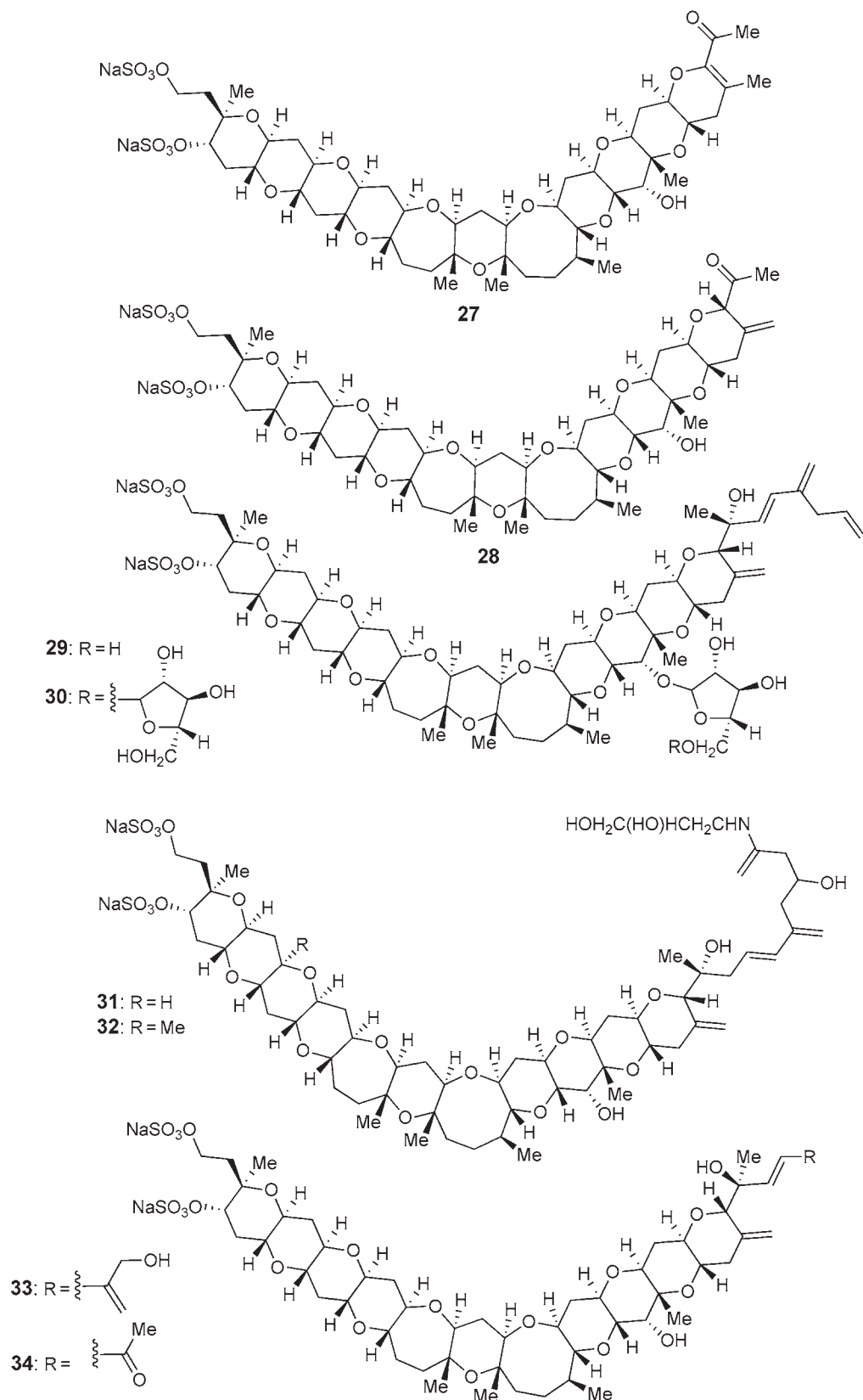
After 1997, several new YTX analogues, homoyessotoxin **21**, 45-hydroxyhomoyessotoxin **22**, carboxyessotoxin **23**, carboxyhomoyessotoxin **24**, 42,43,44,45,46,47,55-heptanor-41-oxohomoyessotoxin **25**, and adriatoxin **26** have been isolated from mussels, *Mytilus galloprovincialis*, of the Adriatic Sea <1997MI107, 1998TL8897, 1999MI689, 2000EJO291, 2000CRT770, 2001MI596>. The structures of **21** and **22** were identified by MS, which presented 14 Da larger than the corresponding YTX **17** and 45-hydroxyYTX **19**, and NMR, mainly HMBC connectivities around C-3 <1997MI107>. The molecular formulas of **23** and **24** were deduced from their negative HRFABMS spectrum and their structures were established by exhaustive NMR studies, including the absolute configuration of C-44 assigned by the method for chiral carboxylic acids <1995TL1853, 2000EJO291, 2000CRT770>. The ^1H NMR spectrum of **25** showed a close resemblance to those of other YTXs, suggesting that it has the same basic polycyclic ether skeleton, but with two basic differences, the lack of the characteristic signals of the side chain at C-40 in the olefinic region of the spectrum and the presence of an additional methyl signal at relatively low field (2.22 ppm due to H-42) <2001MI596>. The FABMS spectrum of adriatoxin **26** suggested the presence of three sulfate groups and the comparison of their ^1H NMR spectrum with that of YTX **17** allowed observing the lack of the characteristic signals of the terminal part of the molecule <1998TL8897>.

Yessotoxin and its analogues are disulfonated polyether toxins reported from shellfish from different countries, but a new derivative lacking a 1-sulfated substituent, 1-desulfoyessotoxin (YTX with $R^1 = \text{H}$), has been isolated from mussels from Norway <1998MI235>. Its ESI-MS spectrum showed that this compound is 102 Da smaller than YTX **17**, implying that one of the sulfate esters in YTX was desulfonated. The NMR data of 1-desulfoyessotoxin are similar to that of YTX **17** except for the 1-methylenic protons where desulfonation occurred; they are shifted to upfield by 0.49 ppm and their chemical shifts (3.72 and 3.78 ppm) are typical of hydroxymethyl protons.

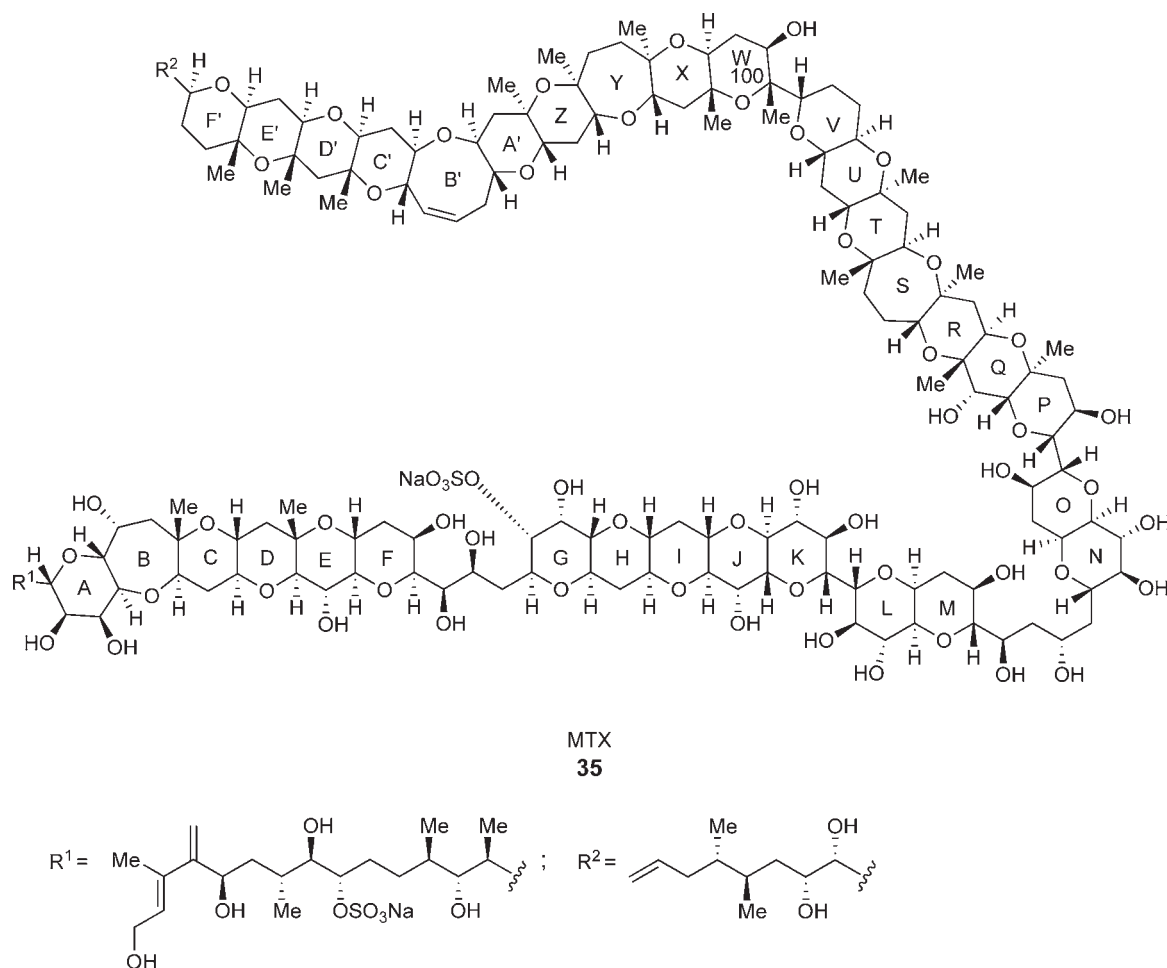
Numerous studies have been conducted with cultures of the marine dinoflagellate *Protoceratium reticulatum* not only to confirm the biogenetic origin of yessotoxin **17** and 45,46,47-trinoryessotoxin **20** <1997MI164, 1999MI147>, but also to isolate and assign the structure of known and new YTX analogues, such as **27** (a 1-en-3-one isomer of

42,43,44,45,46,47,55-heptanor-41-oxoyessotoxin, **28**), yessotoxin glycosides (**29** and **30**), trihydroxylated amides 41a-homoyessotoxin **31** and 9-methyl-41a-homoyessotoxin **32**, 45-hydroxy-46,47-dinoryessotoxin **33**, and 44-oxo-45,46,47-trinoryessotoxin **34** <2004MI325, 2005MI61, 2005JNP420, 2006MI229, 2006MI510, 2006MI611>. The structures of all of these compounds have been established by NMR (1-D and 2-D experiments) and MS studies. Other minor yessotoxin derivatives were partially characterized by LC-MS studies due to their low abundance. This technique is also extensively used for direct detection and for determination of yessotoxin derivatives in dinoflagellates and shellfish <2002JCH(968)61, 2002JCH(976)329, 2003MI7>.



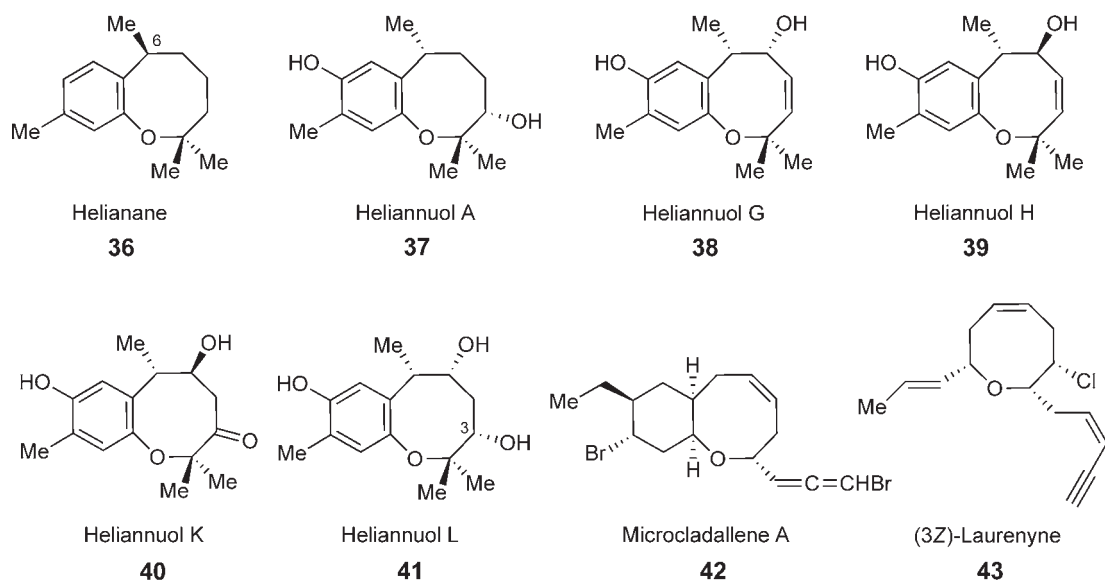


Maitotoxin (MTX, **35**) was found both in the dinoflagellate *G. toxicus* and surgeonfish *Ctenochaetus striatus*. With a molecular weight of 3422 Da, it is the largest natural product known to date besides biopolymers. With exception for a few proteins, maitotoxin is the most potent natural product, having a lethal dose in mice of 50 ng Kg^{-1} when injected intraperitoneally <1996CHEC-II429, 1997JA7928, 2000NPR293, 2001MI228>. The complete structure of **35** was reported in 1993 <1993JA2060> but it has been reviewed recently <2000NPR293>. A partial relative stereochemistry was assigned in 1994 and focused on the fused ring portions of MTX <1994JA7098>. The relative stereochemistry of four acyclic fragments of **35** was published independently by the groups of Yasumoto and Kishi <1994TL5023, 1995JA7019, 1995TL9007, 1995TL9011, 1996TL1269, 1996AGE1672, 1996AGE1675, 1996JA7946>. The stereochemistry of the K/L- and O/P-ring junctions was assigned by Yasumoto and co-workers in 1994 based on the NOE effects and vicinal coupling constants supported by molecular mechanics calculations <1994JA7098>. However, the presence of a 100-methyl group precluded the use of vicinal spin coupling constant between ring-juncture protons in assigning the relative stereochemistry at the V/W-ring juncture. Yasumoto and co-workers relied on NOE data in combination with MM2 force field calculations to distinguish between the two possible diastereomers and assign the relative stereochemistry of the V/W-ring juncture of MTX **35** <1994JA7098>. Kishi and co-workers unambiguously assigned the stereochemistry of the V/W-ring closure by synthesizing two diastereomeric models bearing four six-membered rings including the V/W-rings <1997JA7928>. The NMR data of one of these diastereomers is virtually identical to that of MTX **35**, confirming the stereochemistry proposed by Yasumoto and co-workers <1994JA7098>.



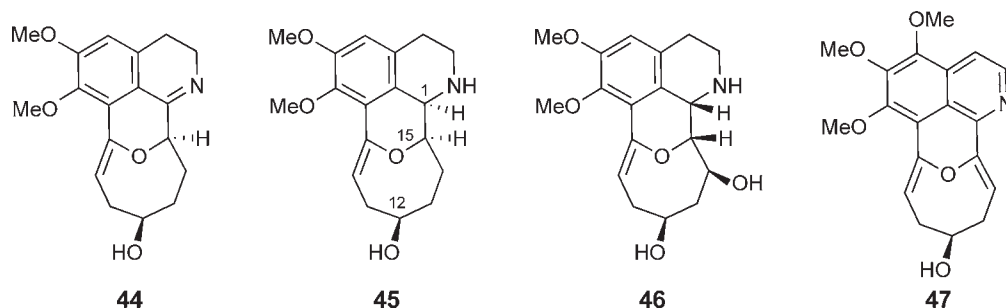
Terrestrial plants, sponges, and other marine organisms are the source of several well-known aromatic bisabolene sesquiterpenes; however, those possessing both an aromatic bisabolene moiety and a heterocyclic ring are less known. From these, one can refer to several new derivatives bearing an eight-membered oxygen heterocyclic ring **36–41**. Helianane **36** has been isolated from the Indo-Pacific sponge *Haliclona fascigera* <1997JOC2646>, and

the stereochemistry at C-6 was established as 6*S*, by comparing their optical rotation with other bisabolenes having only one similar chiral center. This absolute configuration was not consistent with that of heliannuol A **37** reported before and established as 6*R* by X-ray analysis <1993TL1999>. A probable biogenesis pathway has been proposed for the heliannane derivatives; it considered the configuration 6*R* for the derivatives from plants or marine soft coral and 6*S* for marine sponge metabolites. Heliannuol derivatives **37–41** have been isolated from *Helianthus annuus* (sunflower) and their structure fully characterized by extensive NMR and MS studies, in that the stereochemistry was established by NOE experiments and the absolute configuration by the modified Mosher methodology <1999JNP1636, 2000JEL2173, 2002P687>. In the case of heliannuol L **41**, the NOE experiments were not conclusive to establish the stereochemistry at C-3, but a theoretical study for the search of the most stable conformation isomer made by GMMX (PCMODEL, 2000) and refined by PM3 semi-empirical calculations supported their structure as depicted in **41** <2002P687>. The known microcladallene A **42** and the (*Z*)-diastereomer **43** of the known laurenynes have been isolated from Okinawan *Laurencia* algae and their structure established by NMR spectroscopy <2002JNP395, 2002JNP801>.



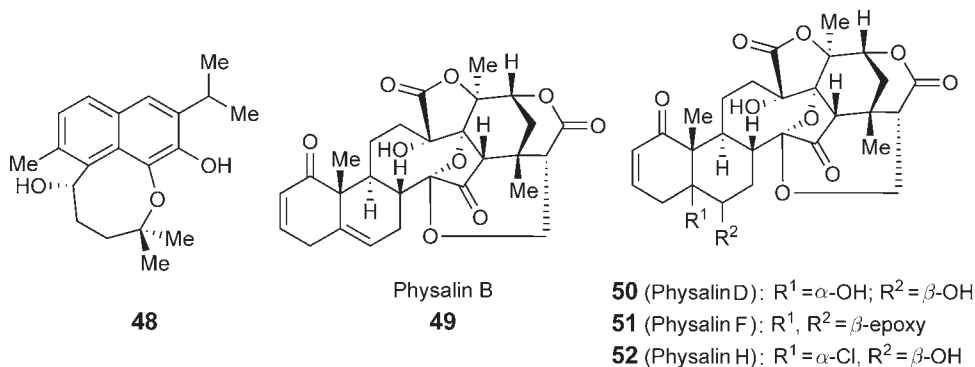
In the last years, some isoquinoline alkaloids bearing oxocane rings have been isolated from Japanese and Brazilian plants <1996JNP803, 1998JNP1140>. The structure of stephaoxocanine **44** was established by spectroscopic data, especially by NMR. The relative stereochemistry of **44** was established by NOESY experiment and the absolute configuration of C-12 and C-15 as *R* (α -H) deduced by the modified Mosher's method <1991JA4092, 1996JNP803>. These data allowed the deduction of the stereochemistry of 1,2-dihydrostephaoxocanine **45**, obtained by reduction of **44** with NaBH₄, and the comparison of the CD spectral data of **45** with that of excentricine **46** led to revision of their absolute stereochemistry to 1*S* (β -H), 12*S* (α -H), 14*S* (α -H), and 15*R* (β -H) as shown in **46**.

Isoquinoline cletefine **47** was described as a mixture of two forms that exist in equilibrium, probably with, or without, an intramolecular hydrogen bonding between the hydroxyl proton and the oxygen atom of the oxocine ether bridge. These two forms could be separated by thin-layer chromatography (TLC) and reverted to the initial mixture in about 48 h. The structure of **47** was established by NMR and MS spectral data; NOE experiments were essential to establish the stereochemistry and HMBC to establish the connections between the oxocine ring and the isoquinoline moiety <1998JNP1140>. The oxidation of **47** with pyridinium dichromate led to the formation of a single compound with a 12-oxo group, confirming that the equilibrium mixture could be somehow related with the 12-hydroxy group.



The new diterpene, 10-isopropyl-2,2,6-trimethyl-2,3,4,5-tetrahydronaphtho[1,8-*bc*]oxocine-5,11-diol **48**, was obtained as colorless crystals from the roots of *Nardostachys chinensis* <2005JNP1131>. The structure of **48**, a naphthalene nucleus fused with an oxocine ring, was established by spectroscopic data, mainly NMR, and confirmed by X-ray crystallographic analysis.

Physalins are 16,24-*cyclo*-13,14-secosteroidal constituents of *Physalis* plants. A study devoted to the structural elucidation of the physalins playing an important role in the antimycobacterial activity of some fractions of an active crude extract of *Physalis angulata* led to identification of physalins B **49**, D **50**, and F **51**, being only physalins B and D isolated as pure substances and their structure completely elucidated by extensive NMR studies <2002MI445>. Phytochemical studies of *Brachistus stramonifolius* guided by *in vitro* cytotoxic activity using human nasopharyngeal cells led also to the isolation and structural elucidation of physalins B **49**, F **51**, and H **52** by using 1-D and 2-D NMR experiments <2003MI520>.



14.02.4 Thermodynamic Aspects

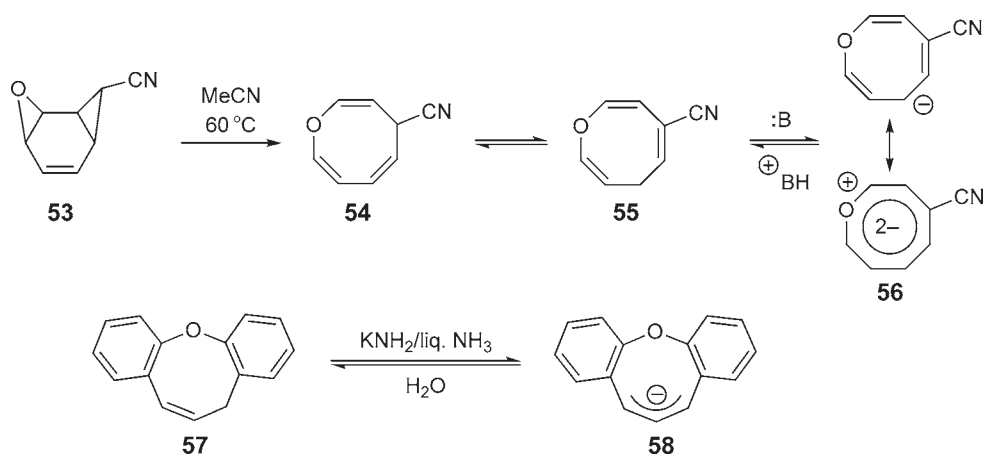
No relevant thermodynamic studies were reported during the last decade.

14.02.5 Reactivity of Fully Conjugated Rings

There are very few fully conjugated molecules (aromatic or antiaromatic), which fall into this ring system. An interesting study (Scheme 1) involved the synthesis of the 4-cyanooxocine **54**, via thermal rearrangement of epoxide **53** <1987TL2513>, and the generation of the oxocinyl anion **56** <1987TL2517>. Compound **55** rapidly polymerizes on exposure to air, but when treated with a strong nonionic phosphinimine base it is converted into **56**, which remains unchanged at room temperature for several hours. NMR studies showed that this aromatic 10 π -anion has planar-diatropic geometry <1987TL2517>. NMR studies also showed that the anion **58**, generated from dibenzo[*h,g*]oxocine **57**, is not an aromatic system, because the negative charge is primarily localized in the allylic moiety of the eight-membered ring <1980AGE393>.

14.02.6 Reactivity of Nonconjugated Rings

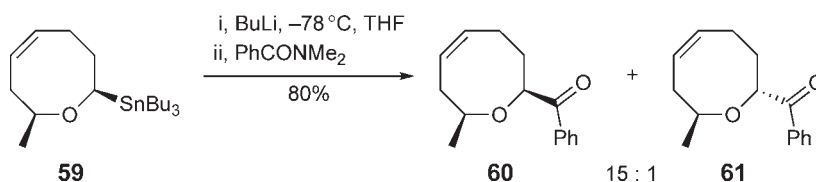
The reactivity of this ring system is dominated by the reactivity at the carbon atoms in the ring and therefore this discussion is relegated to the following section.



Scheme 1

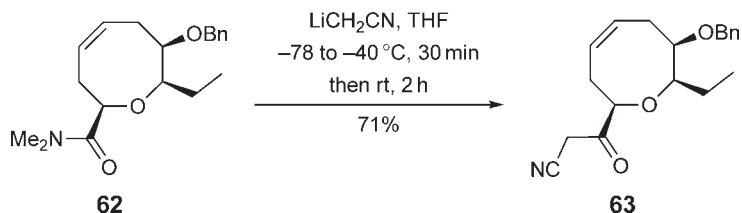
14.02.7 Reactivity of Substituents Attached to Ring Carbon Atoms

cis-Oxocene **59** undergoes transmetalation with butyllithium. Condensation of the resulting anion with *N,N*-dimethylbenzamide provides mainly the benzoyl-substituted oxocene **60** (Scheme 2) <1997JA6919>. The reaction sequence occurs predominantly with retention of configuration, leading to the *cis*-oxocene **60** in 75% isolated yield and 5% isolated yield of the *trans*-isomer **61**.



Scheme 2

Addition of the lithium anion of MeCN (used as an acetaldehyde equivalent) to amide **62** resulted in ketone **63** (71% yield, Scheme 3) <2005OL75>.

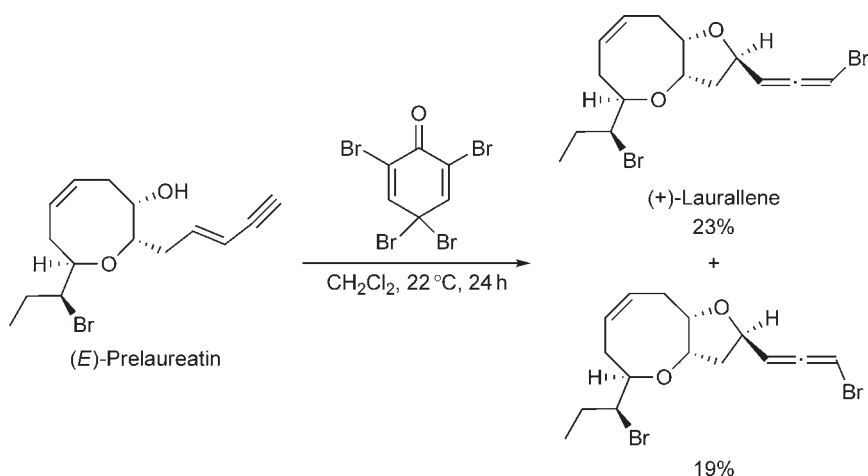


Scheme 3

Treatment of (*E*)-prelaureatin with 2,4,4,6-tetrabromo-2,5-cyclohexadienone, a brominating reagent, provides two isomeric bromoallenes, which can be separated by HPLC. The major compound (23% yield) is identical with natural (+)-laurallene (Scheme 4) <1997T8371>.

14.02.8 Reactivity of Substituents Attached to the Ring Heteroatoms

Oxonium ions and oxonium ylides are invoked in several reaction mechanisms (see Sections 14.02.10.3 and 14.02.10.4).

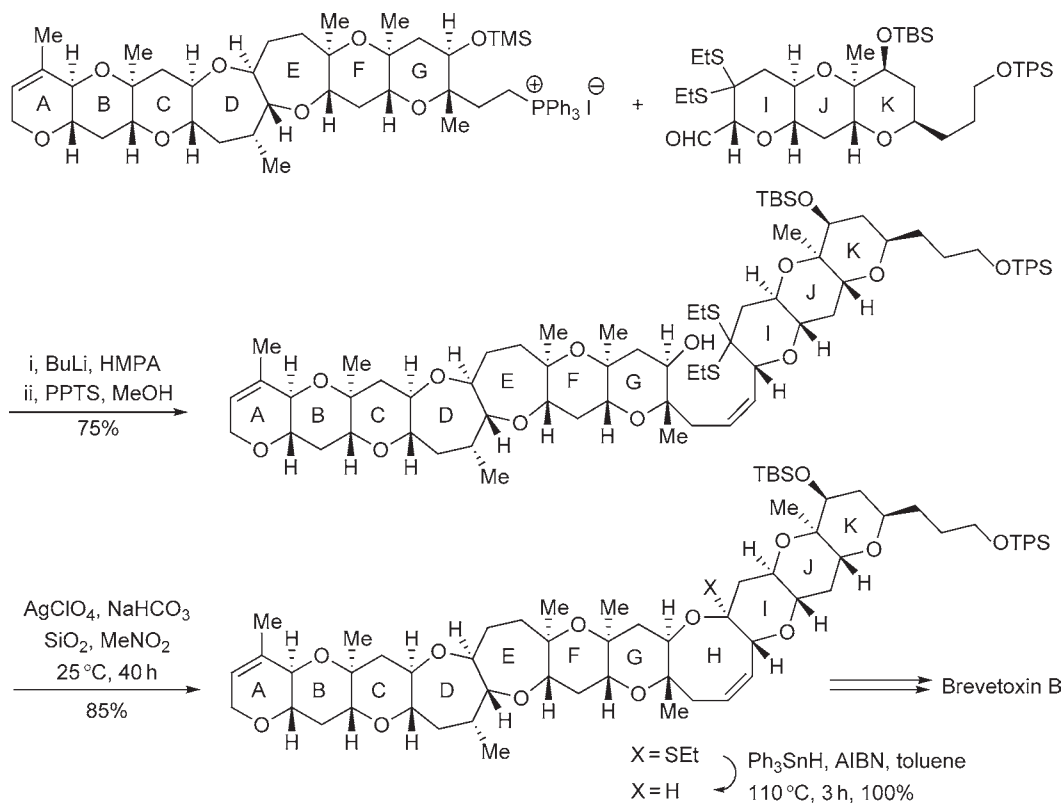


Scheme 4

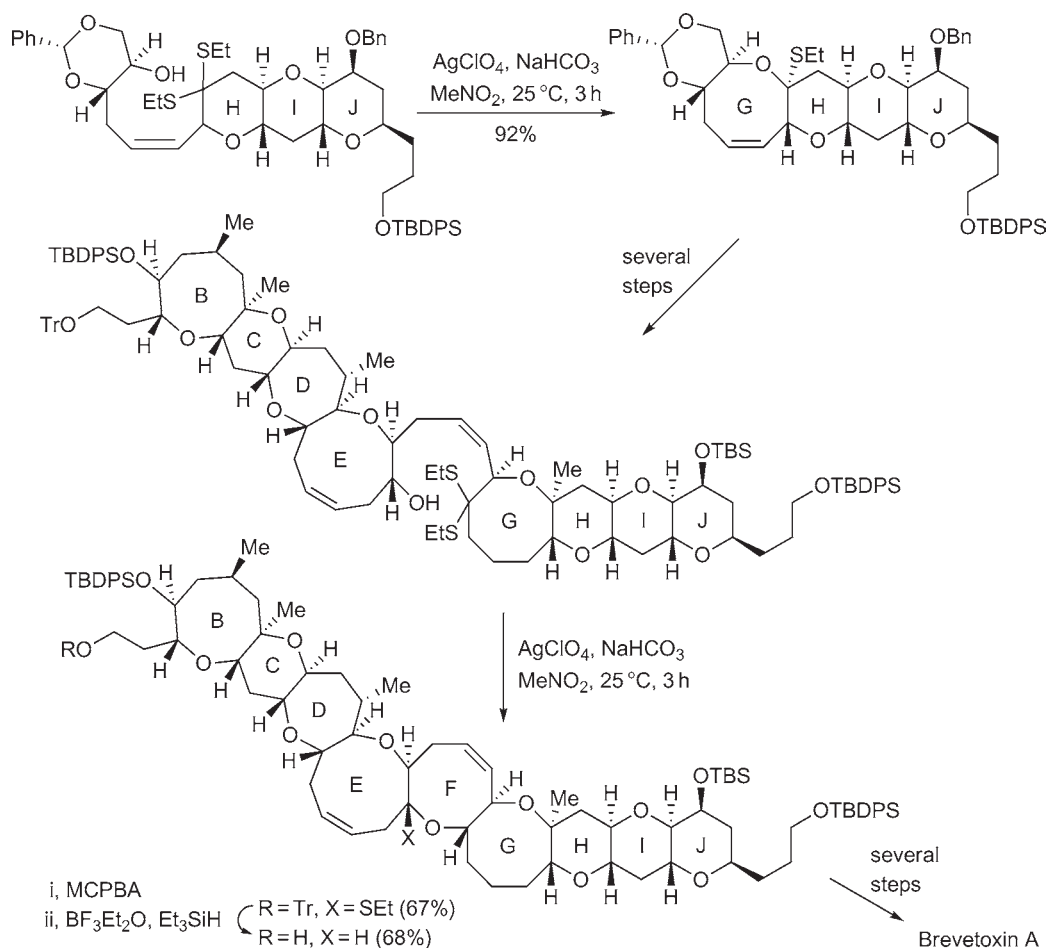
14.02.9 Ring Syntheses Classified by Number of Ring Atoms in Each Component

14.02.9.1 Hydroxydithioketal Cyclization

The hydroxydithioketal cyclization methodology was extensively used by Nicolaou *et al.* to construct the oxocane/oxocene rings in natural fused polycyclic ethers isolated from marine sources. The formation of the H-ring of brevetoxin B (Scheme 5) <1995JA10227, 1995JA10252> and the F- and G-rings of brevetoxin A (Scheme 6) <1999CEJ599, 1999CEJ618, 1999CEJ628, 1999CEJ646> are examples of application of such methodology.



Scheme 5



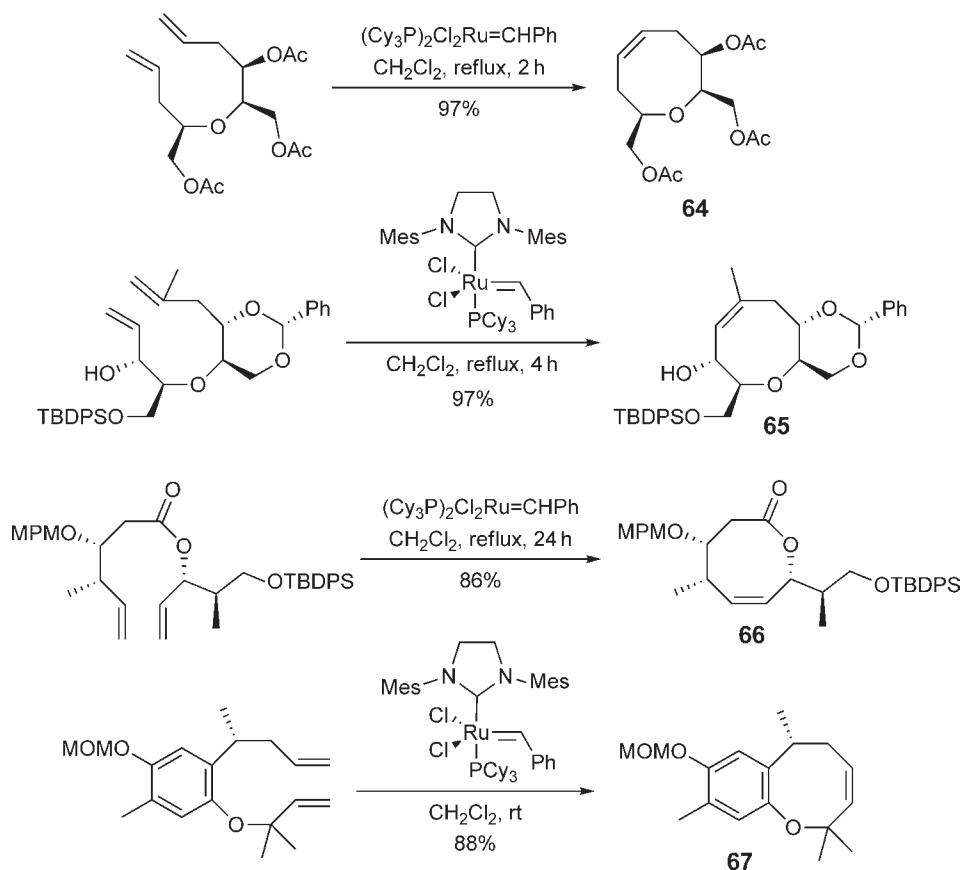
Scheme 6

14.02.9.2 Ring-Closing Metathesis

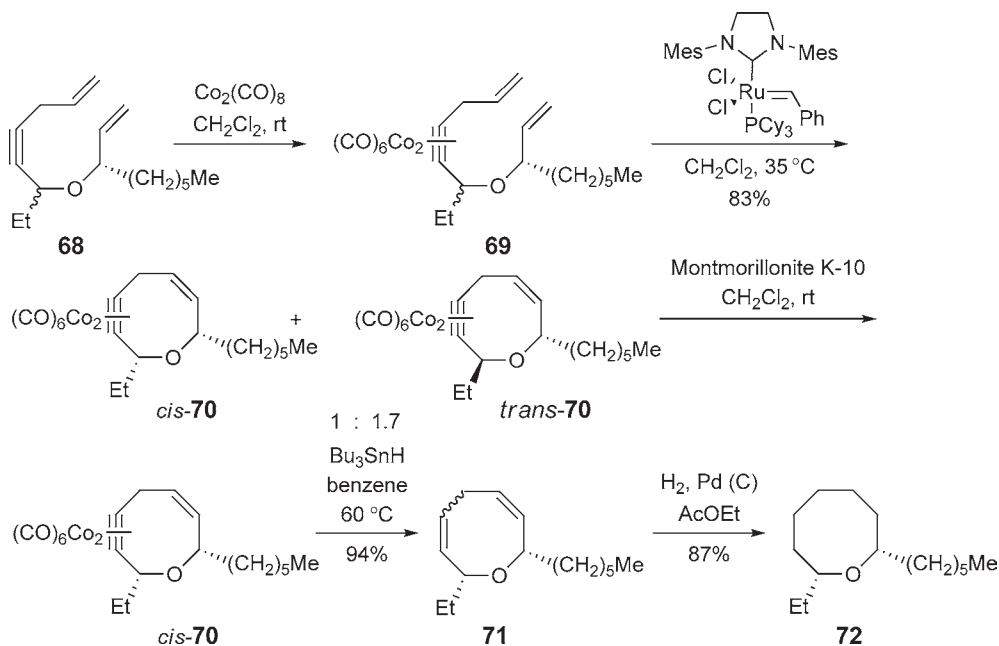
Ring-closing metathesis is being used, increasingly, as the method of choice for the synthesis of medium-sized ring ethers. Many natural products bearing an oxocene or oxocene moiety, or their precursors, were synthesized using such methodology. Examples include (+)-prelaureatin <2000JA5473, 2002SL1493>, (+)-laurallene <2000JA5473>, (+)-laurenyne <2004TL8639>, (+)-laurencyn <1999OL2029, 1999JA5653, 2005TL6819, 2004T7361>, octalactin A <2002TL181>, (+)-*cis*-lauthisan <2006OL871>, (–)-heliannuol A <2003CC350>, brevetoxins and ciguatoxins <1998TL8321, 1999T8231, 2002SL1496, 2005JA9246>, and yessotoxin <2005TL3991>. A range of oxocene-annulated coumarins, 2-quinolones, and carbazoles were also prepared using this methodology <2002TL7781, 2005S403, 2006TL6895>. There are a few interesting works on the synthesis of eight-membered cyclic ethers via ring-closing metathesis <1997JA6919, 1997TL6299, 1997JOC7548, 1999JOC4798, 2001EJO3657, 2002TL7263, 2004OL4787, 2005T7461, 2005TL3465, 2006TL113, 2006OL5897>.

The versatility of the ring-closing metathesis is exemplified in **Scheme 7** with the synthesis of oxocene **64**, a precursor of (+)-laurencyn <1999JA5653>, oxocene **65**, a precursor of the I-ring part of ciguatoxin <2002SL1496>, oxocene **66**, a precursor of octalactin A <2002TL181>, and dihydrobenzoxocine **67**, an intermediate in the synthesis of (–)-heliannuol A <2003CC350>.

A new methodology was developed for the ring-closing metathesis of the dienyl derivative **68** (**Scheme 8**) <2006OL871>. To overcome the unfavorable entropic and enthalpic factors involved in the formation of the eight-membered ring with an endocyclic triple bond, a cobalt complex was previously prepared. This took advantage of the bending in the acetylenic system when the cobalt complex is formed. In addition, the cobalt complex avoided the undesirable participation of the triple bond in the metathesis process. Under diluted conditions (0.001 M) and



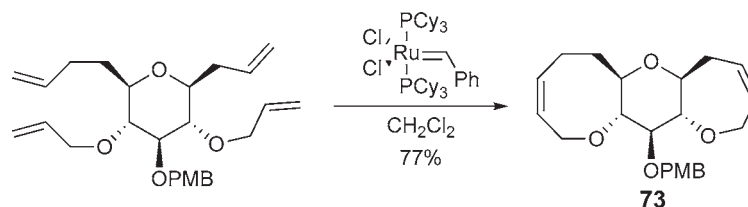
Scheme 7



Scheme 8

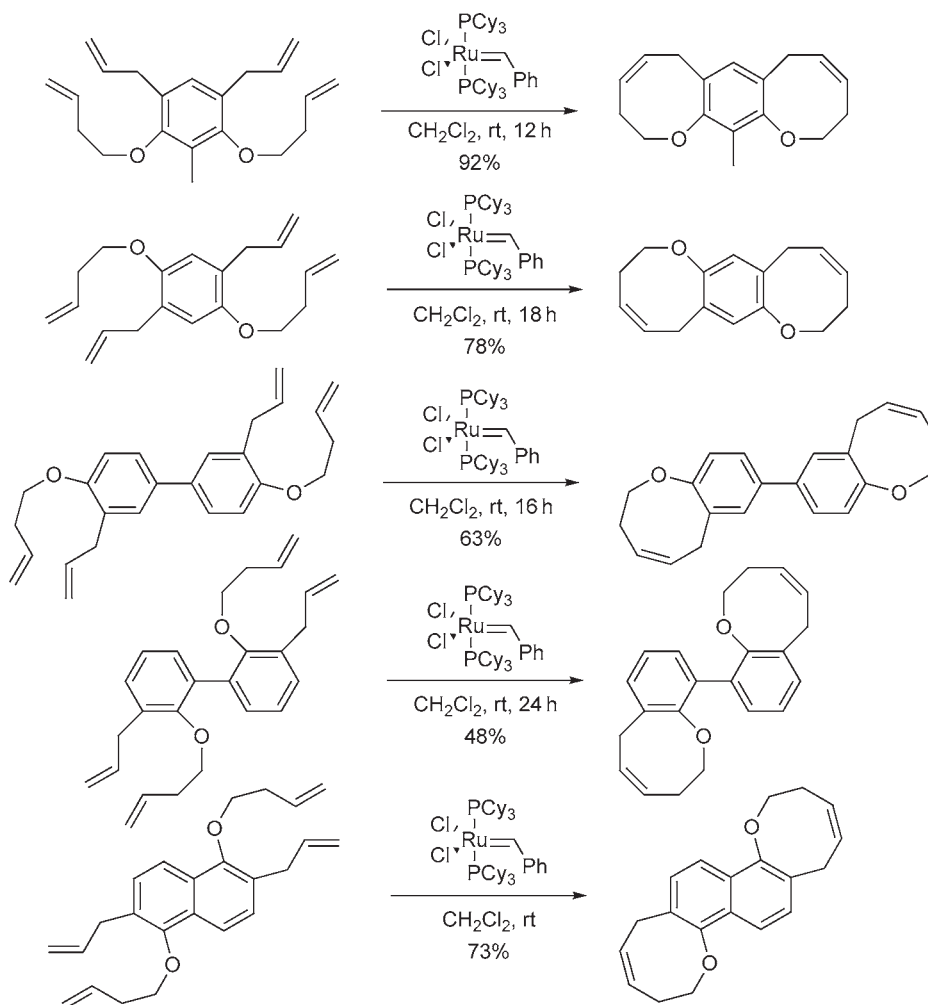
using second-generation Grubbs' catalyst, complex **69** was converted into **70** in 83% yield (as a 1:1.7 mixture of both diastereomers). When treated with Montmorillonite K-10, the mixture evolved quantitatively to a *cis/trans*-ratio of 17:1. Finally, reductive cleavage of the cobalt complex and hydrogenation of the double bonds afforded the target (+)-*cis*-lauthisan **72**, $[\alpha]_D^{25} = +4.1$ (c 0.9, CHCl_3).

The synthesis of polycyclic ethers with variable ring sizes can be conducted by two-directional double ring-closing metathesis. This methodology was used to prepare, in one-step, the tricyclic ether **73**, which has a six-, seven-, and eight-membered ring (Scheme 9) <2000AGE372>.



Scheme 9

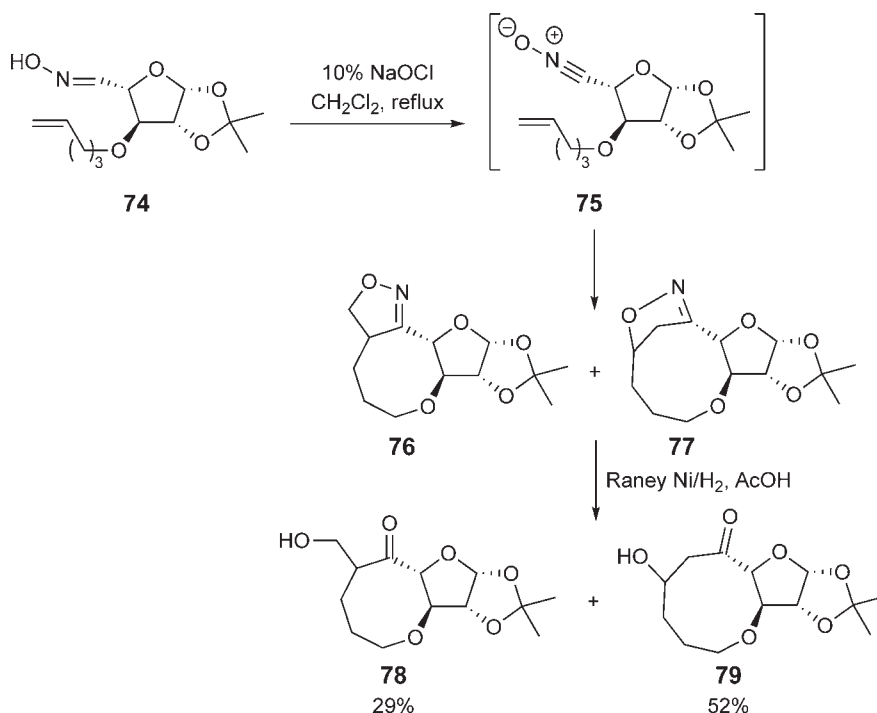
The two-directional double ring-closing metathesis was also used to synthesize a range of benzofused ethers, as exemplified in Scheme 10 <2006SL2211>.



Scheme 10

14.02.9.3 1,3-Dipolar Cyclizations

Nitrile oxide **75**, generated *in situ* from oxime **74**, gives intramolecular 1,3-dipolar cycloaddition affording a mixture of inseparable oxocane **76** and oxonane **77** in a ratio of 1:1.4 (Scheme 11). Hydrogenation of these isoxazolines with Raney nickel leads to keto alcohols **78** and **79**, which can be separated by chromatography <2006SL1205>.



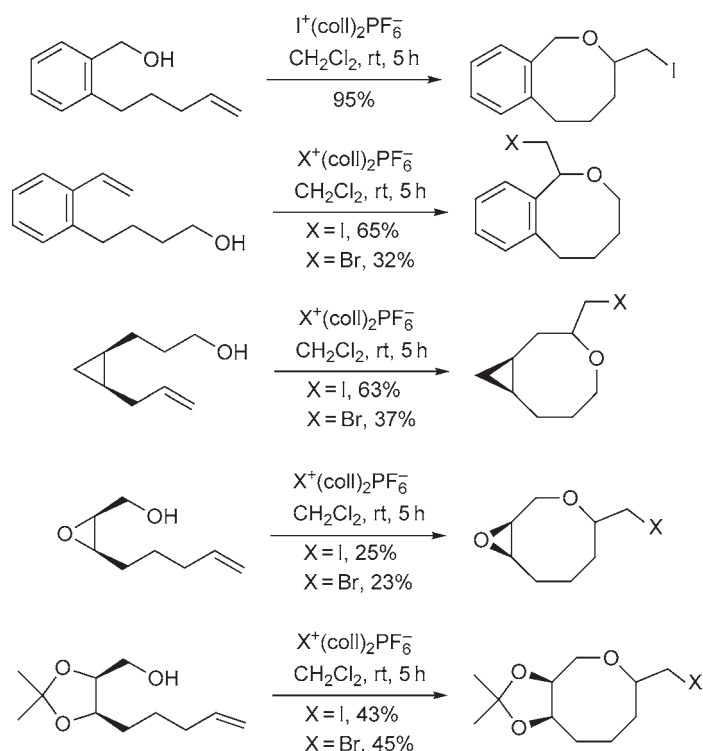
Scheme 11

14.02.9.4 Haloetherification of Unsaturated Alcohols

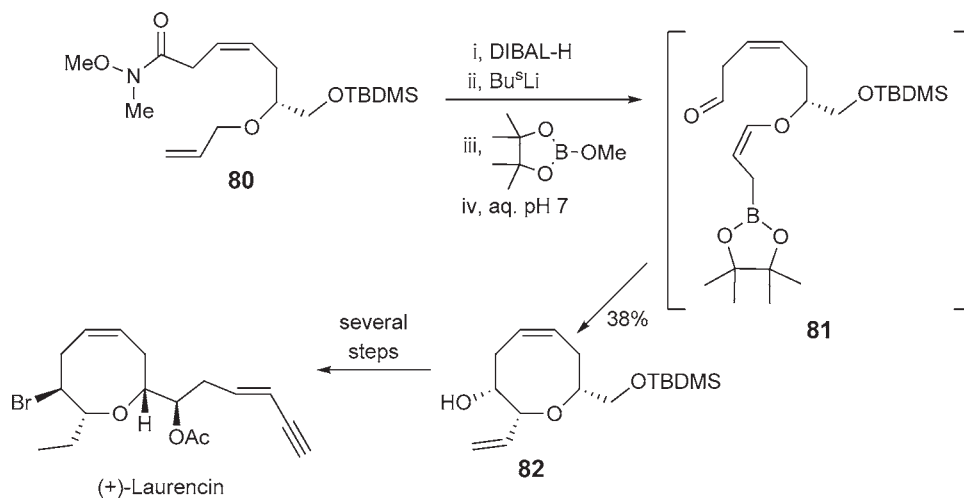
The 7-octen-1-ols substituted with a rigid cyclic moiety (cyclopropane or phenyl) react with bis(collidine)iodonium and -bromonium hexafluorophosphates to afford oxocanes in modest to good yields (Scheme 12). If the cyclic component is an oxirane or a dioxolane ring, the yields are lower. The cyclizations are carried out in dichloromethane (DCM) at room temperature <2003EJO463>.

14.02.9.5 Aldehyde-Allylboration Reaction

The intramolecular allylboration of an aldehyde function leads selectively to *cis*-disubstituted cyclic ethers. It has been shown that both the reactive aldehyde and the allylboronate moiety can be initially generated *in situ* in a masked form and then liberated simultaneously by hydrolysis of the precursor functions <1997JA7499>. This methodology was successfully applied to the one-pot synthesis of the oxocene **82**, a precursor of (+)-laurencin (Scheme 13). A DIBAL reduction of the Weinreb amide **80**, metalation with *sec*-butyllithium, borylation with the pinacol borate ester, and, finally, liberation of both the aldehyde and the allylboronate function by aqueous pH 7 buffer solution generated the reactive **81**, which cyclized in 38% overall yield to the oxocene **82**. Only the all-*cis*-diastereomer is formed, which means that the cyclization proceeds under high asymmetric induction from the resident stereogenic center present in **80**.



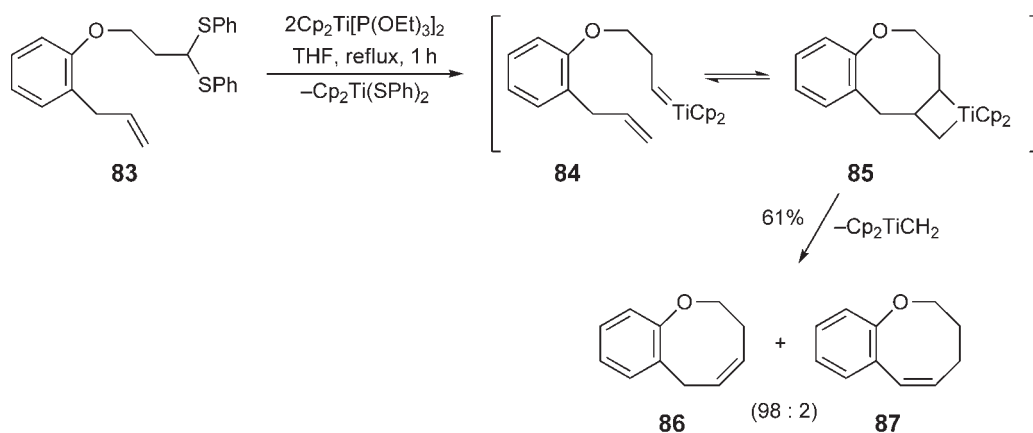
Scheme 12



Scheme 13

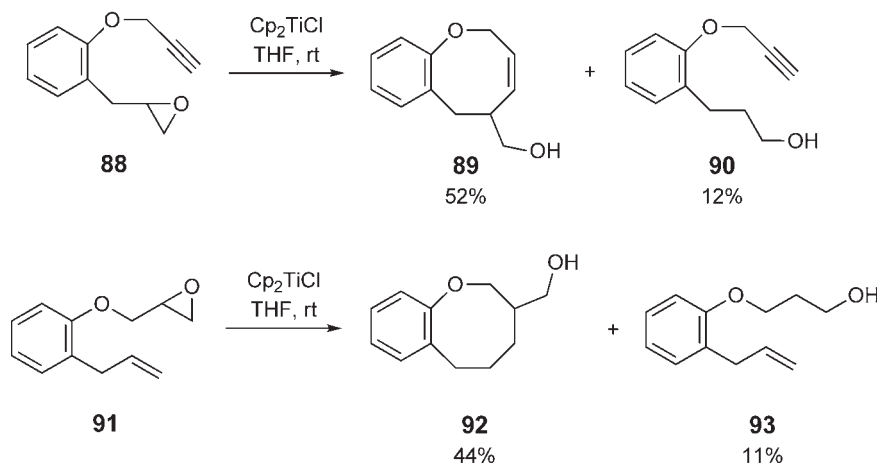
14.02.9.6 Titanocene-Promoted Cyclizations

Titanocene(II) species promote the conversion of unsaturated thioacetals to cyclic compounds. This cyclization proceeds with the loss of the terminal alkene carbon. Treatment of the thioacetal **83** with the low-valent titanium species $Cp_2Ti[P(OEt)_3]_2$ (3 equiv) in refluxing THF afforded benzoxocines **86** and **87** (by isomerization of **86**) in 61% yield (Scheme 14) <1999SL354>. Using 4 equiv of the titanocene(II), the yield is higher (70%) but the selectivity is lower (the ratio **86**:**87** becomes 82:18). The mechanism of the reaction probably involves the formation of the titanium carbene complex **84**, its intramolecular reaction with the double bond to form titanocyclobutane **85**, and the subsequent elimination of methylidenetitanocene <1999SL354>.



Scheme 14

The radical cyclization of epoxides using titanocene(III) chloride, as the radical source, is a new methodology to construct eight-membered ring ethers. Treatment of the epoxide **88** with Cp_2TiCl (prepared *in situ* from commercially available Cp_2TiCl_2 and activated zinc dust) in tetrahydrofuran (THF) under argon affords ether **89** in 52% yield along with the reduced product **90** (12%) and an unidentified product (18–20%) (Scheme 15) <2006TL1599>. Similarly, reductive opening of the epoxide **91** affords ether **92** (44%) along with the reduced product **93** (11%) and two other unidentified products (25%).

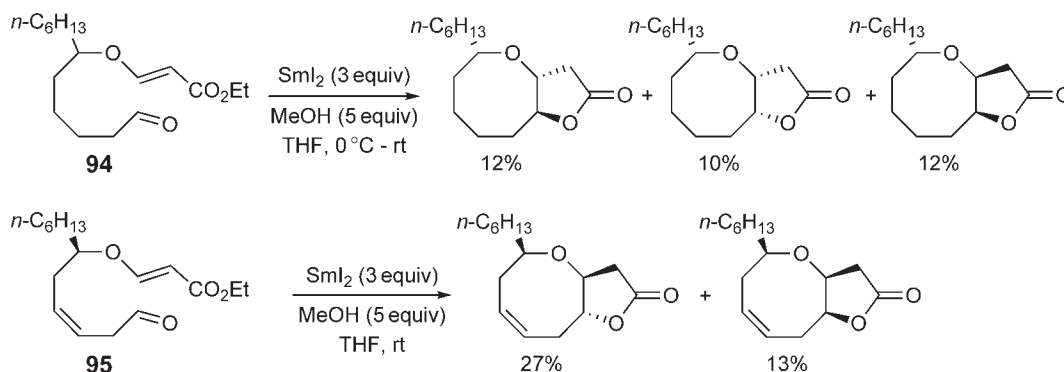


Scheme 15

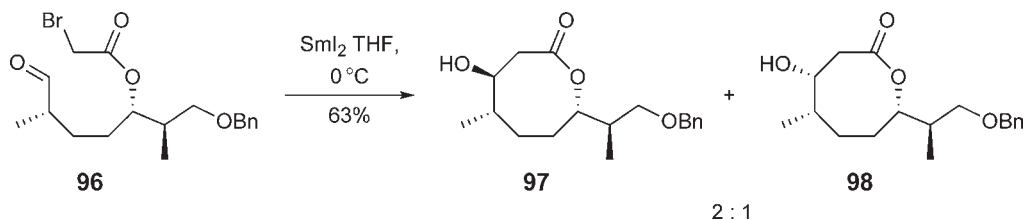
14.02.9.7 SmI_2 -Promoted Cyclizations

Acyclic ethers having an aldehyde and a β -alkoxyacrylate group undergo SmI_2 -induced reductive cyclization to afford oxocanes or oxocenes in moderate yield but with low stereoselectivity (Scheme 16) <2002CL148>.

A SmI_2 -promoted intramolecular Reformatsky-type reaction was used for the cyclization of δ -(bromoacetoxy)aldehyde **96** (Scheme 17) <1998SL735>. This reaction provided a 2:1 epimeric mixture of the oxocan-2-ones **97** and **98** in 63% yield. The isomer **97** could be converted almost quantitatively into **98** (a precursor of (–)-octalactin A) by sequential Dess–Martin oxidation and NaBH_4 reduction.



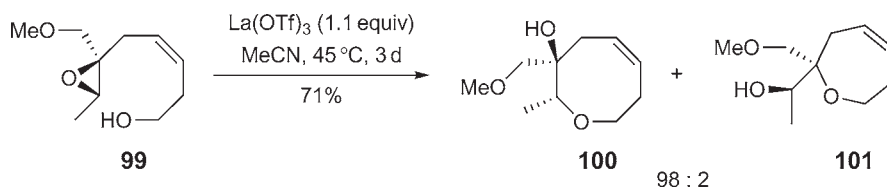
Scheme 16



Scheme 17

14.02.9.8 Cyclization of Hydroxy Epoxides

Hydroxy epoxides, in the presence of $\text{La}(\text{OTf})_3$, undergo selective *endo*-cyclization [<1998TL393>](#). Epoxide **99**, for instance, under the conditions indicated in [Scheme 18](#), affords oxocene **100** and a small amount of 7-*exo*-cyclization product **101**. When the reaction is conducted in DCM, for 8 days at 25°C , only the 8-*endo*-product **100** is formed, albeit in lower yield (55%).



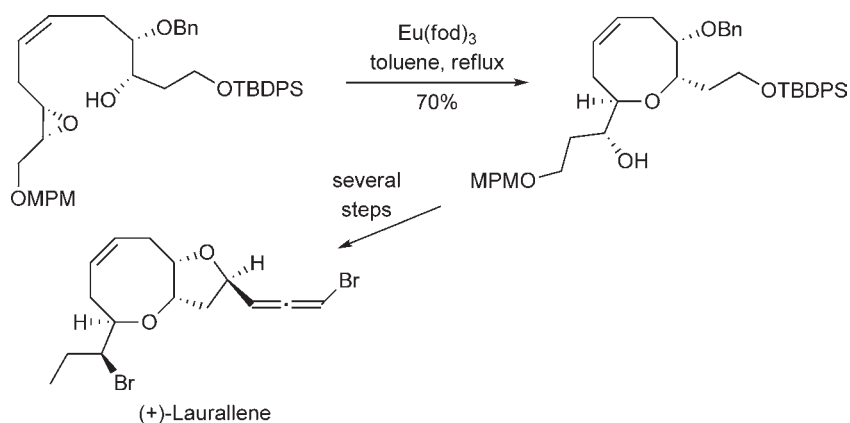
Scheme 18

It was shown that cyclization of the hydroxy epoxides promoted by $\text{Eu}(\text{fod})_3$ ($\text{fod} = 6,6,7,7,8,8,8\text{-heptafluoro-2,2-dimethyl-3,5-octanedionato}$) proceeds via an *exo*-mode, providing the corresponding disubstituted eight- and nine-membered cyclic ethers in excellent yields [<2003TL2709>](#). This method was used for the stereoselective total synthesis of (+)-laurallene, as indicated in [Scheme 19](#) [<2003TL3175>](#).

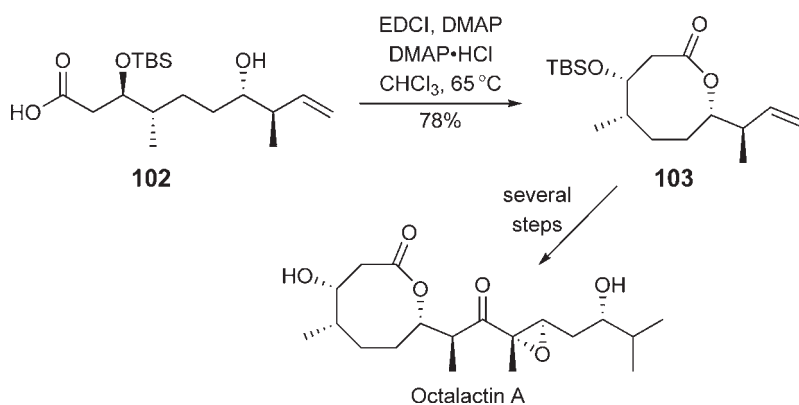
14.02.9.9 Lactonization

Lactone **103**, an intermediate in the synthesis of (+)-octalactin A, a potent cytotoxic natural product, was obtained in 81% yield by lactonization of the hydroxy acid **102**. The cyclization was conducted with the water-soluble carbodiimide EDCI (ethyl dimethylaminopropyl carbodiimide hydrochloride, 5 equiv), DMAP (4-*N,N*-dimethylaminopyridine, 5 equiv) and DMAP·HCl (5 equiv) in refluxing CHCl_3 ([Scheme 20](#)) [<1996TL5049>](#).

Scandium triflate ($\text{Sc}(\text{OTf})_3$), which is commercially available, is a practical and useful Lewis acid catalyst for acylation of alcohols with acid anhydrides or the esterification of alcohols by carboxylic acids in the presence of



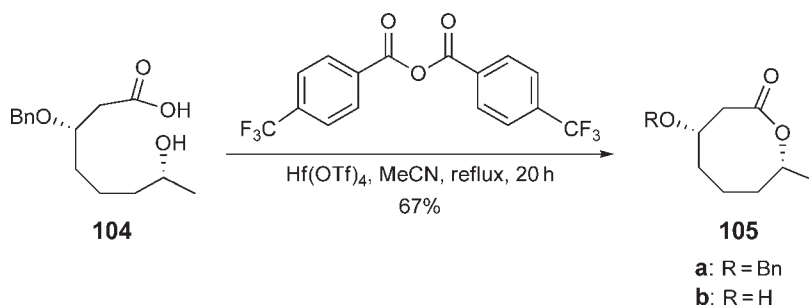
Scheme 19



Scheme 20

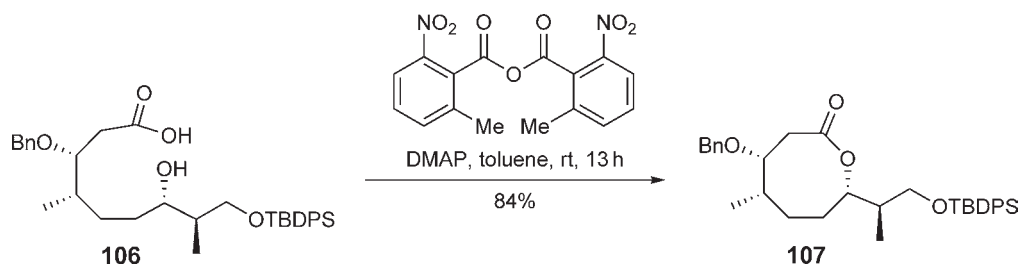
p-nitrobenzoic anhydride. This method is especially effective for selective lactonization of ω -hydroxy carboxylic acids. A series of ω -hydroxy carboxylic acids, $\text{HO}(\text{CH}_2)_n\text{CO}_2\text{H}$ with $n=5-15$, was directly converted into the corresponding lactones by slow addition to a mixed solution of 10–20 mol% of scandium triflate and 2 equiv of *p*-nitrobenzoic anhydride in MeCN at reflux. Lactones were obtained in good to excellent yields in all cases (52–99%); 7-hydroxyheptanoic acid afforded oxocan-2-one in 71% yield [\[1996JOC4560\]](#).

A variation of the above method, which consists in the use of a catalytic amount of $\text{Hf}(\text{OTf})_4$ and 4-(trifluoromethyl)benzoic anhydride, was used to synthesize the eight-membered ring lactone **105a**, a synthetic intermediate of cephalosporolide D **105b** (Scheme 21) [\[2000H\(52\)1105, 2004T1587\]](#).



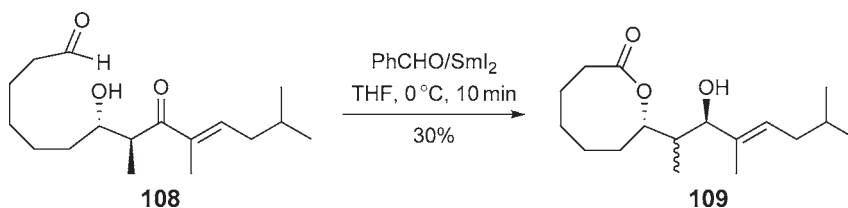
Scheme 21

A variation of the mixed-anhydride lactonization process was developed for the synthesis of lactone **107**, an intermediate in the synthesis of octalactin B. In this case, 2-methyl-6-nitrobenzoic anhydride (MNBA) and a catalytic amount of DMAP are used and the reaction occurs at room temperature (Scheme 22) <2004TL543, 2005SL2851>. The yield of this transformation was increased to 90% by conducting the reaction in DCM and using 4-dimethylaminopyridine 1-oxide (DMAPO) instead of DMAP <2005CEJ6601>.



Scheme 22

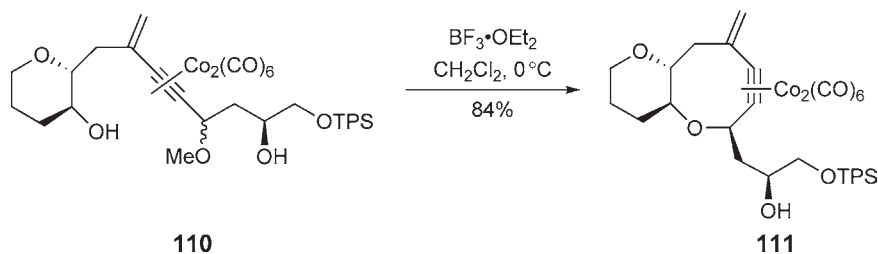
The hydroxy aldehyde **108** was converted into lactone **109** (a 1:1 diastereomeric mixture) by a samarium-mediated cyclization reaction (Scheme 23) <1997TL8245>.



Scheme 23

14.02.9.10 Other Cyclization Methods

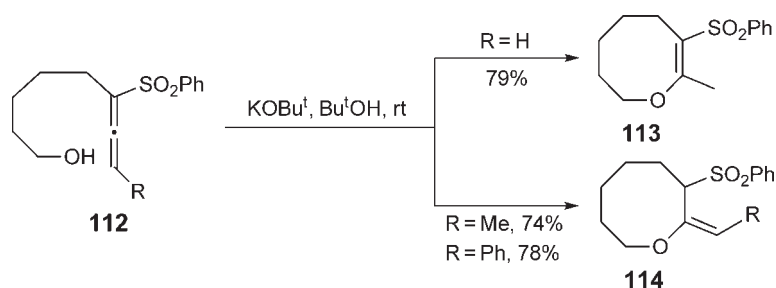
Cobalt complex **110** undergoes smooth ring closure upon treatment with BF₃·Et₂O in degassed DCM at 0 °C (Scheme 24) <2000SL266>.



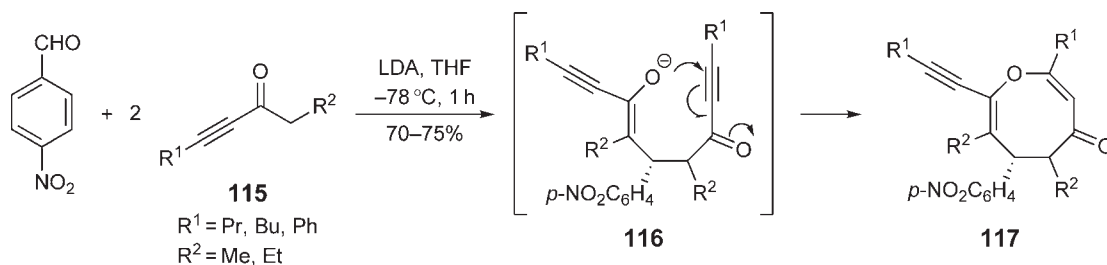
Scheme 24

Treatment of the allenyl sulfones **112** with KO^tBu in ^tBuOH at room temperature provides the oxocenes **113** or **114** in high yields (Scheme 25) <2001OL3385>.

p-Nitrobenzaldehyde reacts with 2 equiv of alkynyl ketones **115**, in the presence of LDA, to afford the highly substituted 5,6-dihydro-4*H*-oxocin-4-ones **117** in good yields (Scheme 26) <2003TL8019>. The enolate **116** is a probable intermediate in this transformation.

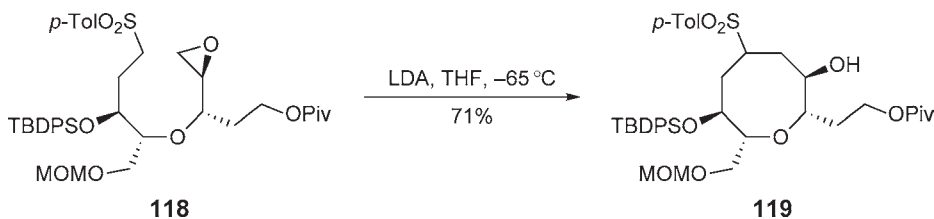


Scheme 25



Scheme 26

Treatment of epoxy sulfone **118** with LDA (4 equiv) in THF at -65°C affords oxocane **119** in 71% yield as a single isomer (Scheme 27) <1998JOC9728, 2001SL117>.

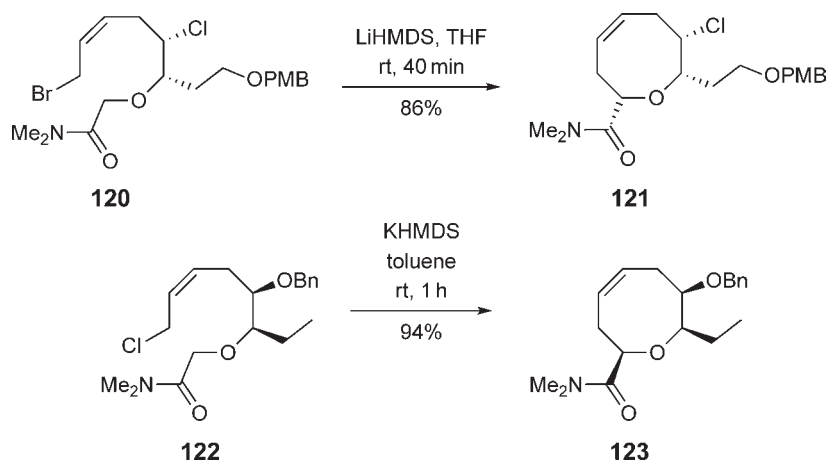


Scheme 27

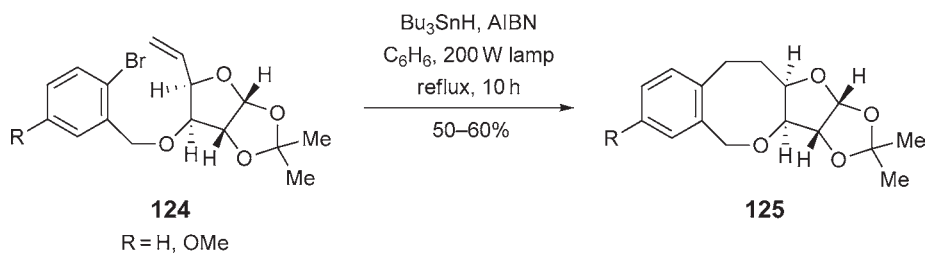
A novel and highly stereo- and regioselective intramolecular amide enolate alkylation was developed to construct the oxocene skeleton <2003JA10238>. Using such methodology, oxocene **121** was obtained in 86% yield, as a single isomer, upon treatment of bromo amide **120** with 1.1 equiv of lithium hexamethyldisilazide (LiHMDS) in THF at room temperature (Scheme 28). Similarly, chloro amide **122** was converted into oxocene **123** with excellent diastereoselectivity (>25:1) and in high yield (94%) <2005OL75>. Compounds **121** and **123** are intermediates in the synthesis of (+)-3-(*E*)- and (+)-3-(*Z*)-pinnatifidenyne and (+)-laurencin, respectively.

Radical cyclization of alkenes **124** in refluxing benzene with Bu_3SnH (1.5 equiv) and a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) furnished the respective crystalline 2-benzoxocine derivatives **125** in 50–60% yield (Scheme 29) <1997CC2139>.

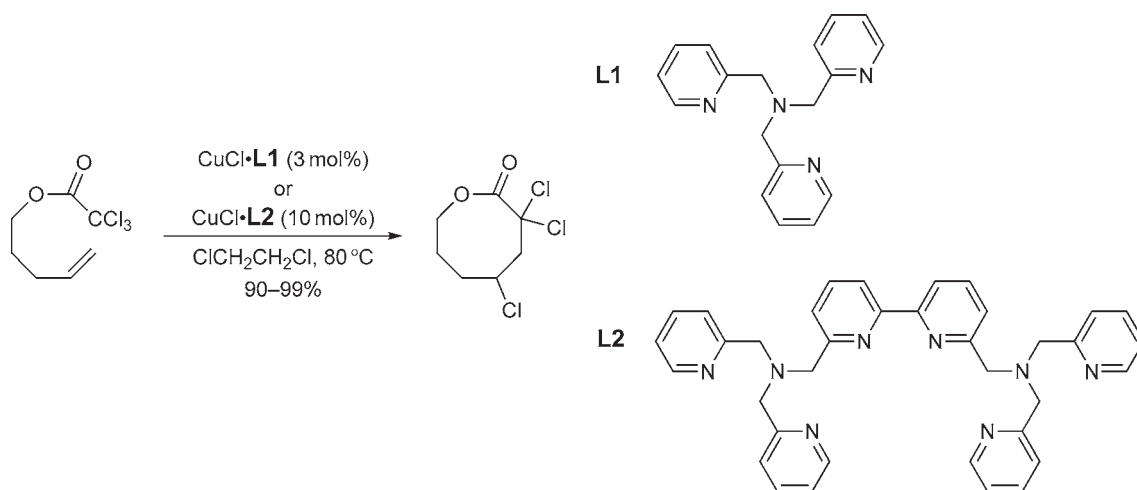
$\text{Cu}(\text{I})$ and $\text{Fe}(\text{II})$ complexes prepared *in situ* by reacting copper(I) or iron(II) chloride with 1 equiv of ligand **L1** (tris(pyridin-2-ylmethyl)amine) or **L2** are efficient catalysts for atom-transfer radical addition reactions. For instance, pent-4-enyl trichloroacetate was converted into 3,3,5-trichlorooxocan-2-one in 90% and 99% yield, respectively, when $\text{CuCl}\cdot\text{L1}$ and $\text{CuCl}\cdot\text{L2}$ were used as catalysts (Scheme 30) <2000J(P1)575>.



Scheme 28

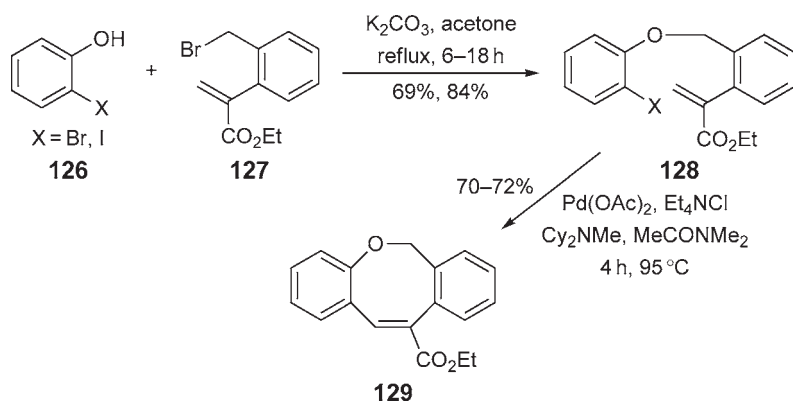


Scheme 29



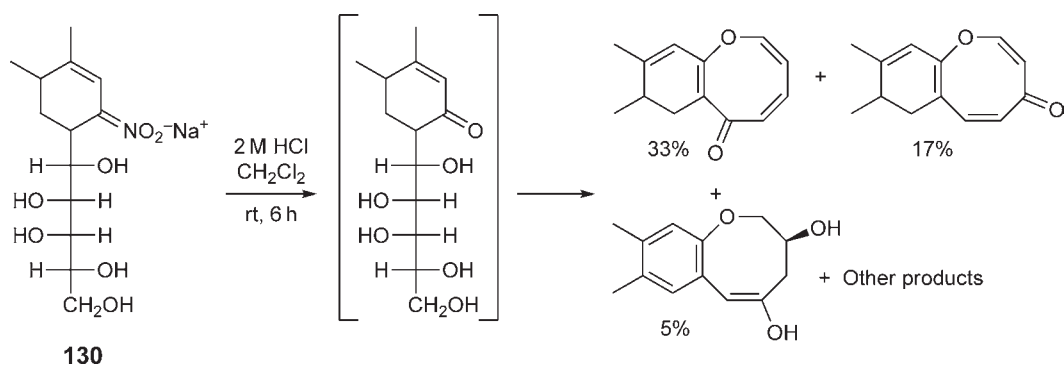
Scheme 30

The dihydrodibenzo[*b,f*]oxocine **129** was obtained in only two steps starting from commercially available starting materials. The strategy involved the alkylation of the 2-halophenol **126** followed by a highly selective intramolecular Heck arylation (Scheme 31) <2004OL3005>. The Heck reaction was carried out in *N,N*-dimethylacetamide using Cy₂NMe as a base, Et₄NCl as a promoter, and Pd(OAc)₂ as precatalyst. The bromo derivative required a longer reaction time (12 h) than the corresponding iodo compound (4 h).



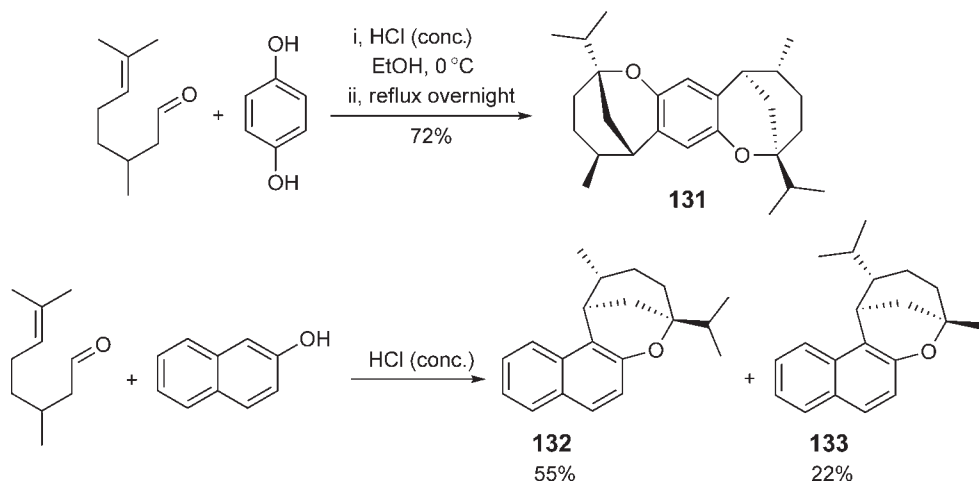
Scheme 31

Treatment of sodium nitronate salt of 5-glyco-4-nitrocyclohexene **130** with hydrochloric acid at room temperature affords a mixture of oxocine derivatives, which can be obtained pure after column chromatography (Scheme 32) <2000TL10201>.



Scheme 32

The acid-catalyzed condensation of citronellal with hydroquinone affords the 2:1 adduct **131** in 72% yield (Scheme 33) <1999CC1117, 2000T9297>. Under similar conditions, the condensation with 2-naphthol gives a mixture of the 1:1 adducts **132** and **133**.

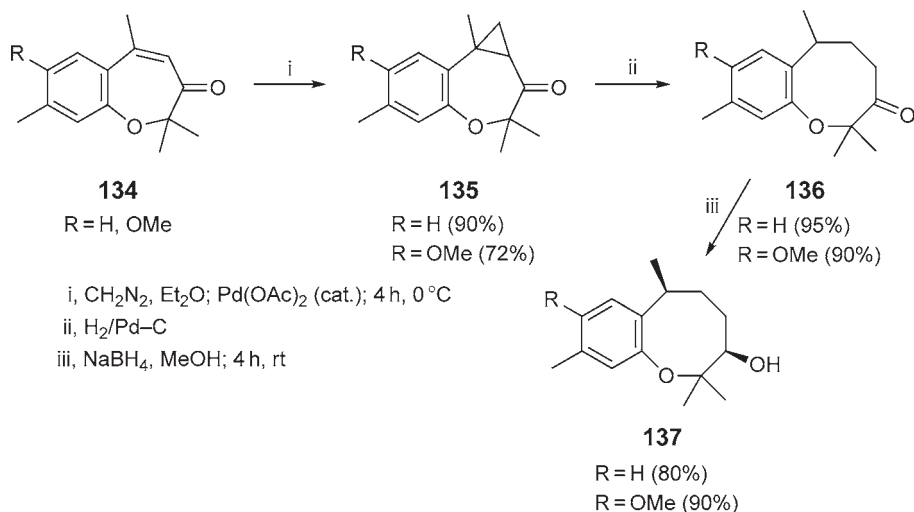


Scheme 33

14.02.10 Ring Syntheses by Transformation of Another Ring

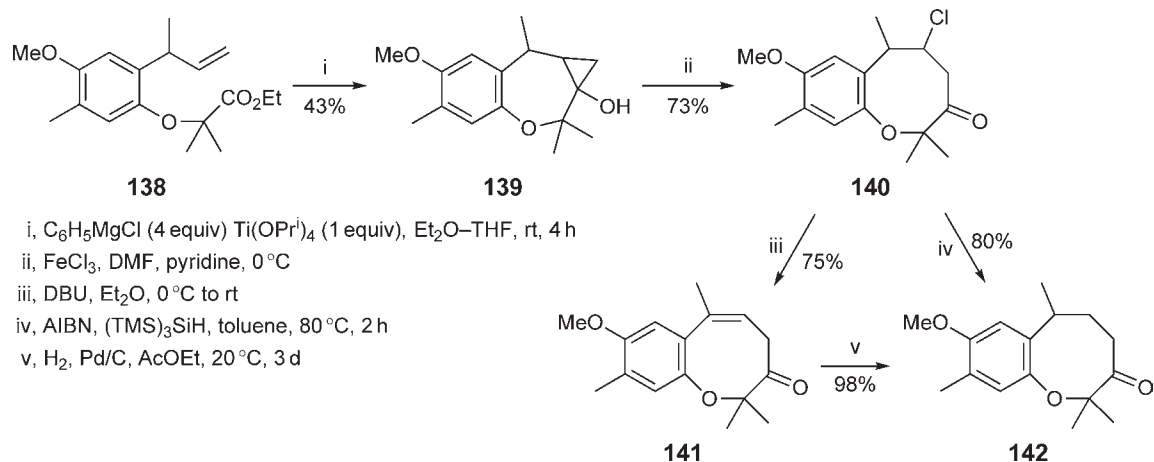
14.02.10.1 Ring Expansions of One Atom

The ring expansion of the benzoxepinones **134** to benzoxocinones **136** involved a cyclopropanation with diazomethane in the presence of palladium acetate and a catalytic hydrogenation. The cleavage of the more labile internal bond in the cyclopropyl derivatives **135** leads to the eight-membered ketones **136** exclusively in excellent yields (90–95%). Reduction of ketones **136** with sodium borohydride affords the hydroxy derivatives **137** in a stereocontrolled manner (Scheme 34) <2002CC634>.



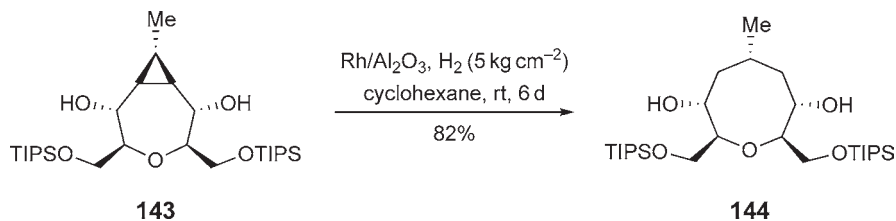
Scheme 34

The intramolecular titanium-mediated cyclopropanation of ester **138** produces a 1:1 diastereomeric mixture of cyclopropanols **139**, which by ring opening afford a diastereomeric mixture (77:23) of β -chloroketones **140** (Scheme 35). Subsequent dehydrohalogenation gives the benzoxocinone **141** <2004SL1613>. Treatment of chloroketones **140** with tris(trimethylsilyl)silane gives the benzoxocinone **142** <2005EJO2589>. The same compound can be obtained in almost quantitative yield by catalytic hydrogenation of **141**.



Scheme 35

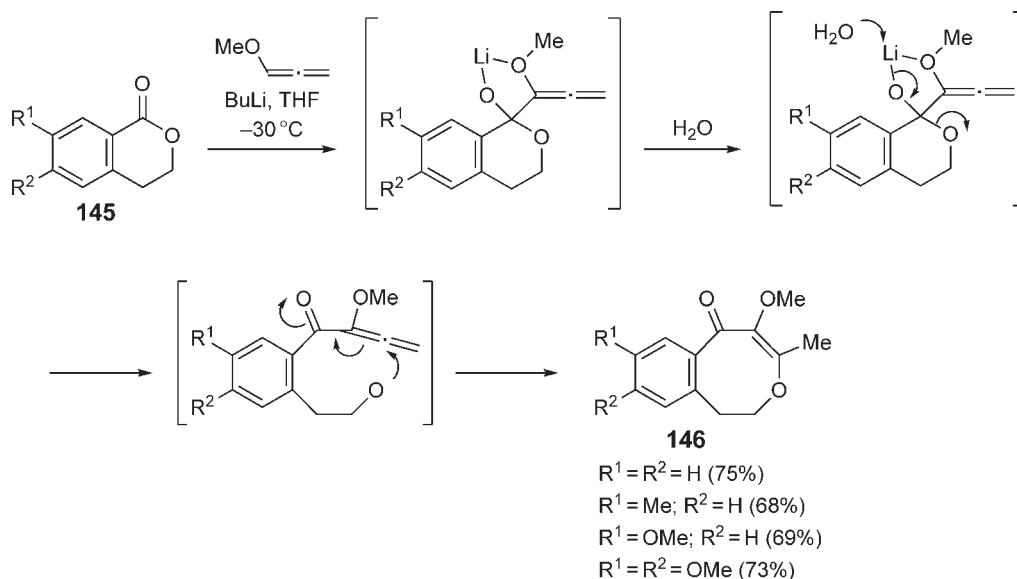
Hydrogenation of **143** using Rh/Al₂O₃ catalyst in cyclohexane at room temperature leads to a regioselective reductive opening of the cyclopropane ring affording oxocane **144**, as a single isomer (Scheme 36) <1996SL1165, 1999T7471>.



Scheme 36

14.02.10.2 Ring Expansions of Two Atoms

Treatment of isochroman-1-one derivatives **145** with lithio methoxyallene followed by quenching the reaction with water furnishes 3-benzoxocin-6-one derivatives **146** in good yields (Scheme 37) <2004SL481>.



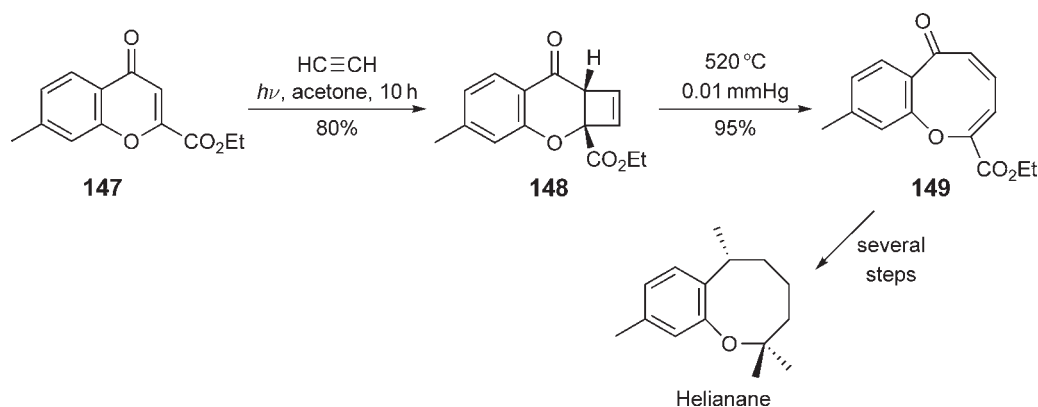
Scheme 37

Ring expansion of the keto ester **148** by flash vacuum thermolysis at 520 °C at 0.01 mmHg afforded the 1-benzoxocin-6-one derivative **149** in an excellent yield (95%) (Scheme 38) <2004TL9653>, which was used as intermediate in the synthesis of helianane, a novel heterocyclic sesquiterpene isolated from the marine sponge *Haliclona fascigera* <1997JOC2646>.

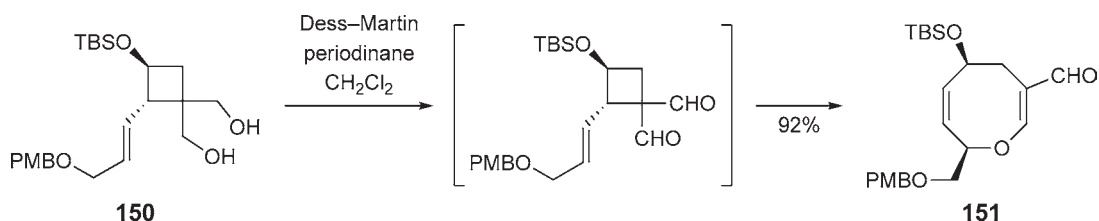
14.02.10.3 Ring Expansions of Three or More Atoms

The Dess–Martin periodinane oxidation of diol **150** and subsequent thermal equilibration at 45 °C gives the dihydrooxocine **151** in 92% yield (Scheme 39) <2002OL3891>.

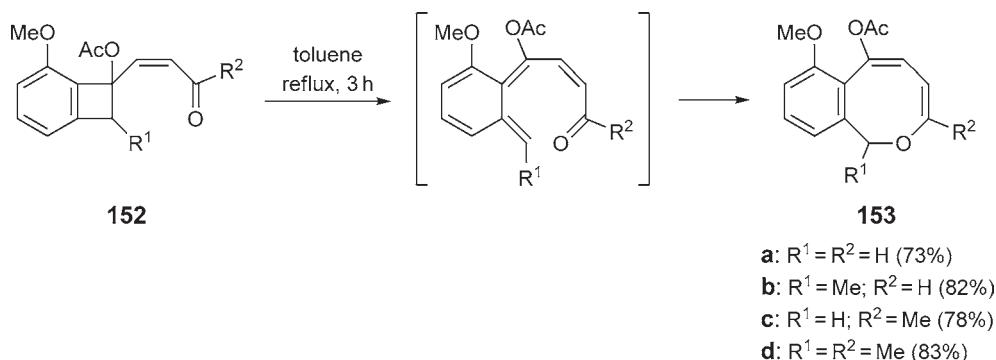
1-Acycloxybenzocyclobutenes **152**, having an α,β -unsaturated carbonyl group at C-1 position, undergo thermal ring expansion to give 2-benzoxocine derivatives **153** in high yield (Scheme 40) <2006CL730>.



Scheme 38



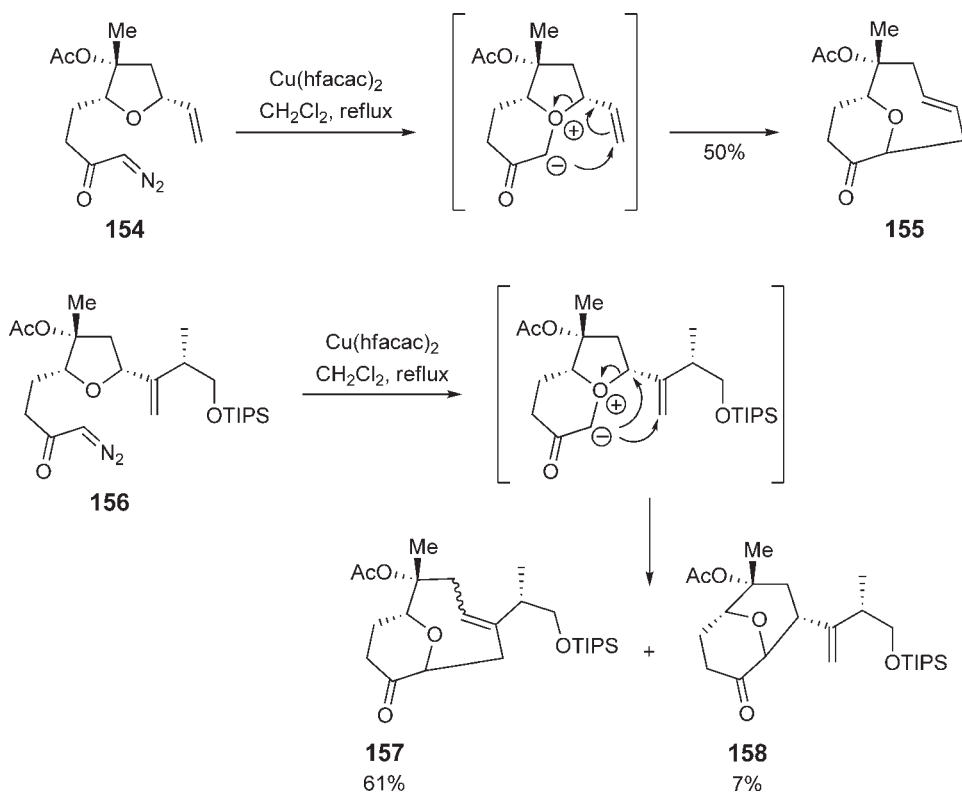
Scheme 39



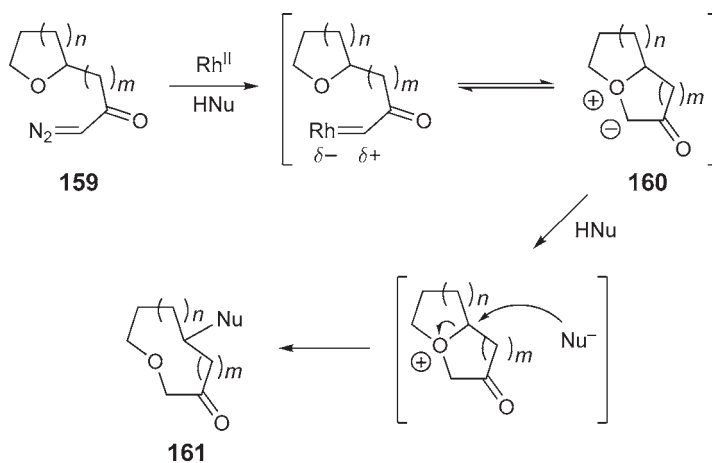
Scheme 40

Exposure of the α -diazo ketone **154** to copper(II) hexafluoroacetylacetonate $[\text{Cu}(\text{hfacac})_2]$ (2 mol%) in DCM at reflux results in sequential carbenoid generation, oxonium ylide formation, and ylide rearrangement to afford the bridged bicyclic (*E*)-alkene **155**, exclusively (Scheme 41) <1996TL5605, 2000CC1079, 2006SL2191; see also 1986JA6060>. Under similar conditions, α -diazo ketone **156** affords the bridged bicyclic ether **157** in 61% yield as a 3:2 mixture of (*Z*) and (*E*)-isomers along with **158** (7% yield) arising from a [1,2]-shift of the intermediate oxonium ylide <1999CC749>. Treatment of **157** (or **155**) with AIBN and a substoichiometric amount of EtSH in benzene at reflux gives the corresponding (*Z*)-alkene isomer in 81% yield <1999CC749>.

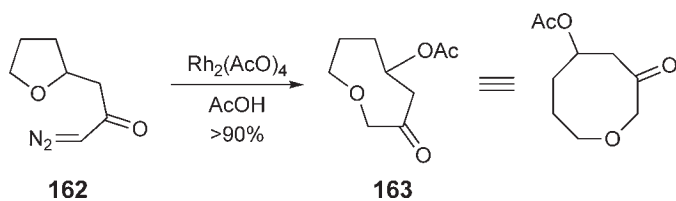
Eight- to eleven-membered cyclic keto ethers **161** can be synthesized in a single step by rhodium(II)-catalyzed three-carbon ring enlargement of diazoacetyl-substituted cyclic ethers **159** via bicyclic ethereal oxonium ylide intermediates **160** (Scheme 42) <1996CC1077, 1998J(P1)3623>. Best results are obtained when $m = n = 1$ and the nucleophile is AcOH; when **162** was treated with a catalytic amount of $\text{Rh}_2(\text{OAc})_4$ in the presence of AcOH, the eight-membered cyclic keto ether **163** was formed in an excellent yield (>90%) (Scheme 43). Oxonium ylides **160** undergo rhodium(II)-catalyzed sigmatropic and stereospecific [3+2] cycloreversion reactions to form alkenyloxyketenes, which can be efficiently trapped by MeOH to form the corresponding esters <2004JOC1331>.



Scheme 41

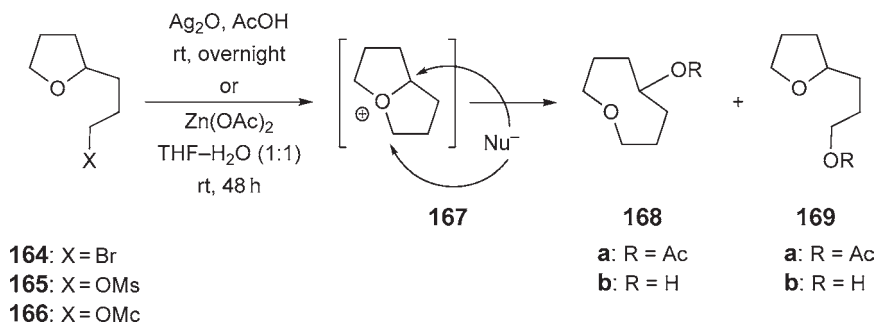


Scheme 42



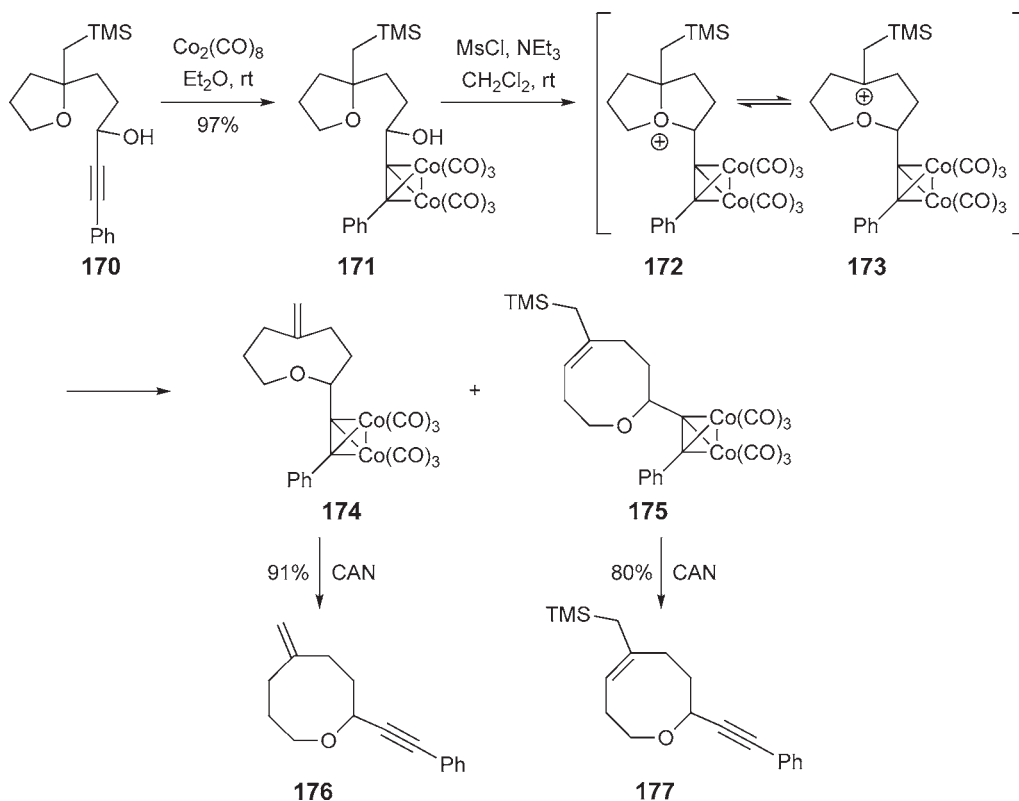
Scheme 43

Treatment of 2-(3-bromopropyl)tetrahydrofuran with Ag_2O in the presence of AcOH , overnight at room temperature, yields the ring-expanded oxocan-5-yl acetate **168a** in 56% yield and 3-(tetrahydrofuran-2-yl)propyl acetate **169b** (21%) (**Scheme 44** <1996J(P1)413>). This transformation probably involves the formation of a bicyclooxonium ion **167**. Mesylate **165**, when treated with zinc acetate in $\text{THF-H}_2\text{O}$ (1:1), affords a mixture of **168a**, **168b**, **169a**, and **169b** in relative proportions 11.7:8.6:2.8:1 and in 93% combined yield <2002OL675>. Monochlate **166** ($\text{OMc} = \text{OSO}_2\text{CH}_2\text{Cl}$), prepared from alcohol **169b** with chloromethanesulfonyl chloride (MeCl) and 2,6-lutidine in DCM , when stirred in $\text{THF-H}_2\text{O}$ (1:1) at room temperature for 2 h, even in the absence of a Lewis acid, affords a 8:1 mixture of **168b** and **169b** in 82% combined yield (two steps) <2002OL675>.



Scheme 44

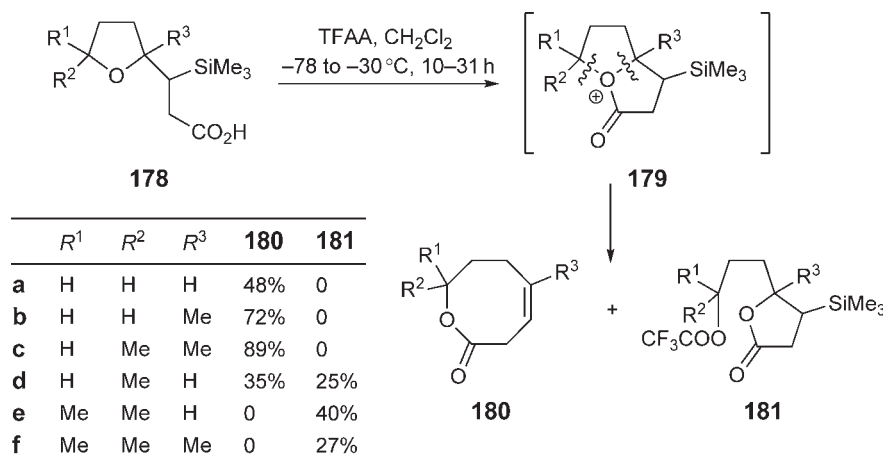
A new ring expansion of THF derivatives to oxocanes based on alkyne- $\text{Co}_2(\text{CO})_8$ complexes (**Scheme 45**) was reported by Mukai *et al.* <2000T2203>. Treatment of THF **170** with $\text{Co}_2(\text{CO})_8$ in Et_2O , at room temperature, affords



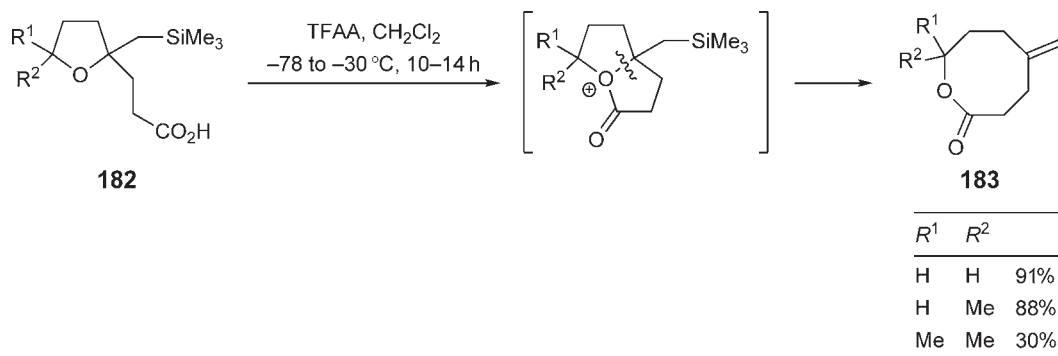
Scheme 45

the corresponding alkyne–Co₂(CO)₈ complex **171** in 97% yield. When this complex is treated with MsCl in DCM in the presence of Et₃N at room temperature, it affords the eight-membered exomethylene product **174** in 54% yield along with the *endo*-alkene **175** in 23% yield. If the reaction is conducted in refluxing DCM, **174** is isolated as the sole product in 72% yield. Carbocation **173** is a probable intermediate for both oxocanes **174** and **175**. Decomplexation of **174** and **175** with cerium ammonium nitrate (CAN) gives **176** and **177** in 91% and 80% yields, respectively.

Exposure of 3-(tetrahydro-2-furyl)-3-trimethylsilylpropanoic acids **178** to trifluoroacetic anhydride allows intramolecular acylative ring-opening reaction to give the corresponding eight-membered lactones **180** in moderate to good yields (Scheme 46) <1999SL1757>. However, when R¹ = R² = Me, lactones **180** are not formed. The acyloxonium ion **179** is a probable intermediate in these reactions. Similarly, acids **182** afford lactones **183** (Scheme 47).



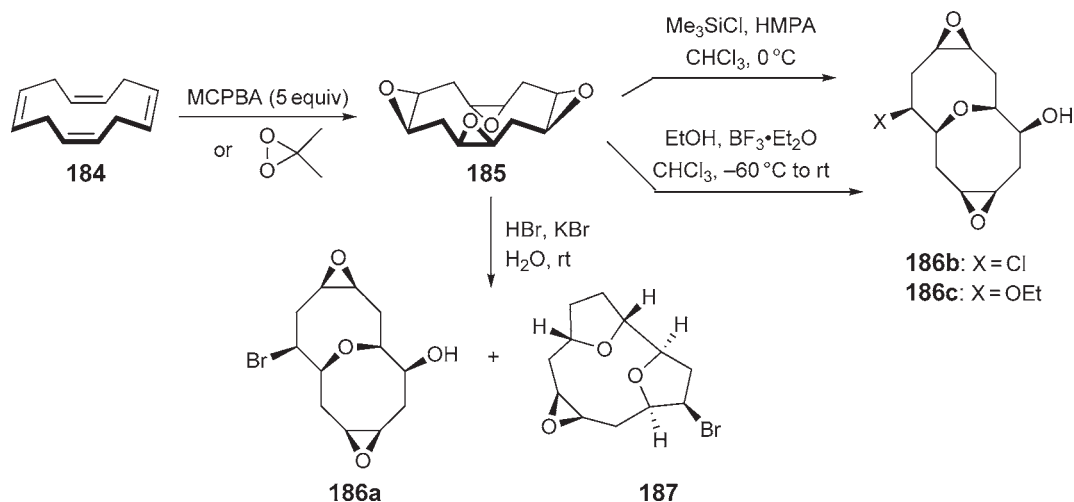
Scheme 46



Scheme 47

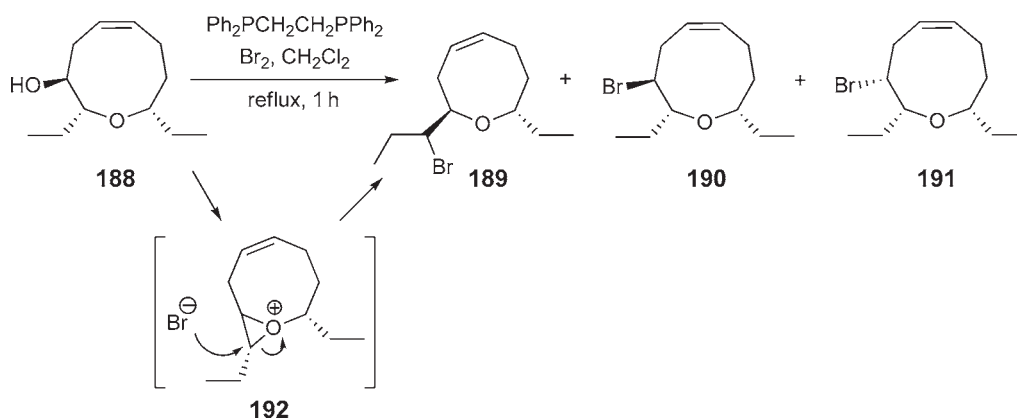
14.02.10.4 Ring Contractions

Epoxidation of *all*-(*Z*)-1,4,7,10-cyclododecatetraene **184** with MCPBA or dimethyldioxirane in anhydrous solvent affords only the *exo,exo,exo,endo*-1,4,7,10-tetraepoxide **185** in 75% and 98% yield, respectively (Scheme 48). Treatment of tetraepoxide **185** with HBr/KBr leads to the bridged bis-oxocane **186a** (27% yield) and **187** (25% yield). The reaction of tetraepoxide **185** with trimethylsilyl chloride in the presence of a catalytic amount of hexamethylphosphoramide (HMPA) at 0 °C gives the oxabicyclo[5.5.1]tridecanol **186b** in 29% yield, as the sole product after aqueous workup. Similarly, reaction of tetraepoxide **185** with EtOH in the presence of BF₃·Et₂O in CHCl₃ at –60 °C provides the ethoxy derivative **186c** in 49% yield <2003JOC3319>.



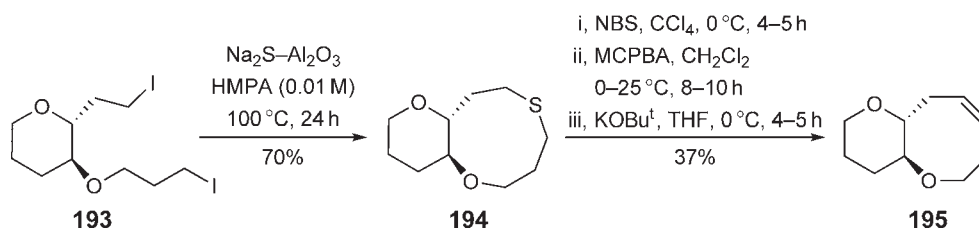
Scheme 48

Refluxing 3-hydroxy- Δ^5 -oxonene **188** with the complex of 1,2-bis(diphenylphosphino)ethane and bromine in DCM for 1 h leads to *trans*-2-(1-bromopropyl)- Δ^4 -oxocene **189** (obtained as a single stereoisomer in 50% yield) along with an inseparable 2:3 mixture of 3-bromo- Δ^5 -oxonenes **190** and **191** in a combined 50% yield (Scheme 49). Formation of oxocene **189** probably involves the nucleophilic attack of a bromide ion to the bridged oxonium cation **192** <1995TL8263>.



Scheme 49

The *trans*-fused oxocene **195** was synthesized from the diiodoalkylpyran derivative **193** via thioannulation to the oxathiacyclic **194**, followed by the Ramberg–Bäcklund olefination process (Scheme 50) <1996TL2865>. This ring-contraction methodology was also applied to the synthesis of *cis*- and *trans*-lauthisan <2002OL3047>.



Scheme 50

14.02.11 Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

As shown in the previous section, during the last decade an impressive number of new methods have been developed for the construction of eight-membered cyclic ethers. Among them, the ring-closing metathesis is, indubitably, the most versatile one. This method has been used to synthesize many natural products, or their precursors, bearing oxocane or oxocene units. The new methods for the lactonization of 7-hydroxy acids are also worth mentioning. Remarkable improvements (yield and selectivity) were obtained by the mixed-anhydride lactonization process catalyzed by Lewis acids ($\text{Sc}(\text{OTf})_3$ or $\text{Hf}(\text{OTf})_4$), DMAP or DMAPO (see Section 14.02.9.9). Copper(II) hexafluoroacetylacetonate and rhodium(II)-catalyzed three-carbon ring enlargement of diazoacetyl-substituted THF derivatives is also an interesting method for oxocanes and oxocenes. The main disadvantage of this method is the less accessibility to the starting diazo compounds.

14.02.12 Important Compounds and Applications

Humans exposed to brevetoxins through beachside marine aerosols during *K. brevis* blooms suffer eye irritation and respiratory distress; the consumption of brevetoxin-contaminated shellfish causes NSP. NSP is characterized by gastrointestinal and neurological sequelae of peripheral and central nervous system injury <1999MI157, 2002MI721>. The great interest generated by brevetoxins, mainly due to their occurrence in bivalves, has spurred the development of fast and effective methods for their detection <2003MI191, 2004MI669, 2005MI261, 2005MI441>.

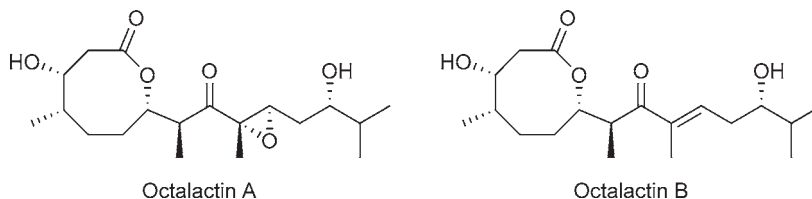
Ciguatoxins are the principal toxins causing ciguatera, a term applied to food poisoning caused by ingestion of certain coral reef fish. They have been isolated from toxic fish or dinoflagellate *G. toxicus*. Ciguatera constitutes one of the largest-scale food poisoning of nonbacterial origin and is characterized by a wide array and variable complex of gastrointestinal, neurological, and cardiovascular signs and symptoms <1990JA4380, 1997MI733, 1998JA5914, 2001MI228>.

The pharmacological effects of ciguatoxins and brevetoxins are similar, both being blocked by tetrodotoxin, implying the involvement of voltage-sensitive Na-channels. Both toxins bind to the same site on the voltage-sensitive sodium channel protein <1998JA5914, 2001MI228, 2003MI919>. However, the binding affinity of ciguatoxin **9** was shown to be ca. 10 times more potent than that of brevetoxins, despite their structural similarity <2002JOC3301>. It was shown that there is a selective resistance to brevetoxin PbTx-3 **8** of cardiac muscle voltage-gated sodium channel of rat compared to that of fish <2006MI702>.

Yessotoxin **17** has been associated with diarrhetic shellfish poisoning (DSP), but there is a controversy about its inclusion in this category, since its activity is as much as 10-fold lower when administered orally to mice compared with intraperitoneal injection <2000EJO291, 2000CRT770, 2002MI77, 2005JNP420>. Yessotoxin derivatives are produced by dinophyceae algae, *P. reticulatum* and *Lingulodinium polyedrum*. Bivalve mollusks, such as mussels and scallops, accumulate them by filter-feeding in waters containing blooms of the algae <2004CRT1251, 2005MI265>. Besides the potent acute toxicity against mice ($\text{LD}_{50} = 286 \mu\text{g kg}^{-1}$, ip) <1990MI1095>, yessotoxins exhibit interesting biological activities in humans, namely: (1) modulation of cytosolic calcium levels of human lymphocytes <2001BP827>, (2) activation of caspases <2002MI357>, and (3) cytotoxicity against human tumor cell lines <2004JNP1309>.

Maitotoxin **35** may play an important role in ciguatera caused by herbivorous fish and presents an extremely potent toxicity against mice; the toxin possesses very potent cytotoxicity, ichthyotoxicity, and hemolytic activity. The various pharmacological activities of this toxin are probably due to the stimulation of calcium influx into the cells <1996CHEC-II429, 2000NPR293>.

Octalactins A and B are two saturated eight-membered lactones isolated from a marine-derived actinomycete of the genus *Streptomyces*, collected from the surface of the gorgonian octocoral *Pacifigorgia* sp. Biological evaluation of these natural products demonstrated that octalactin A was significantly cytotoxic in tests with B-16-F10 murine melanoma and HCT-116 human colon tumor cell lines, whereas octalactin B was completely inactive <1991JA4682, 1998MI97>.



Heliannuols, a group of phenolic allelochemicals isolated from the sunflowers *Helianthus annuus*, exhibit activity against dicotyledon plant species <1993TL1999>. Heliannuols A **37** and C (a 1-benzoxepine derivative), the most active members of the family, inhibit the germination of lettuce and cress, even at concentrations as low as 10^{-9} M <1994JOC8261>. These compounds have potential agricultural importance as natural herbicide models with certain specificity against dicotyledon species. Heliannuols H **39**, G **38**, and K **40** show inhibitory effects on the germination of dicotyledon species and, in contrast, have stimulatory effects on the growth of monocotyledon species <1999JNP1636, 2000JEL2173>.

(3Z)-Laurenynne **43** showed toxicity toward brine shrimp with an LC_{50} value of $467.0\text{ }\mu\text{M}$ <2002JNP395>.

Physalins B **49** and D **50** presented antimycobacterial activity against *Mycobacterium tuberculosis* H₃₇Rv strain, the latter being the most potent one <2002MI445>. Physalins B **49**, F **51**, and H **52** showed broad cytotoxicity against a panel of human and murine cancer cell lines. Among these compounds, physalin B was the most potent cytotoxic agent against human nasopharyngeal carcinoma and hormone-dependent human prostate cancer cell lines (IC_{50} of $0.6\text{ }\mu\text{M}$ in both cases) <2003MI520>.

14.02.13 Further Developments

Recent NMR and computational studies corroborate the initially proposed structure of maitotoxin <2007AG(E)5278>. Two independent stereoselective syntheses of (+)-(Z)-isolaureatin and (+)-(Z)-laureatin were reported <2007JA2269, 2007TL1109>. The stereocontrolled formation of a highly-functionalized eight-membered cyclic ether from an enantiopure camphor-derived bis(spiroepoxide) 1-norbornyl triflate was described <2007TL5185>. Full details of a previously described synthesis of heliannuols A and K were reported <2002CCC634, 2007T644>.

References

- 1965MI111 E. F. McFarren, H. Tanabe, E. J. Silva, W. B. Wilson, J. E. Campbell, and K. H. Lewis, *Toxicon*, 1965, **3**, 111.
 1980AGE393 A. G. Anastassiou and H. S. Kasmai, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 393.
 1981JA6773 Y. Y. Lin, M. Risk, S. M. Ray, D. V. Engen, J. Clardy, J. Golik, J. C. James, and K. Nakanishi, *J. Am. Chem. Soc.*, 1981, **103**, 6773.
 1982TL5521 H. N. Chou and Y. Shimizu, *Tetrahedron Lett.*, 1982, **23**, 5521.
 1986JA6060 M. C. Pirrung and J. A. Werner, *J. Am. Chem. Soc.*, 1986, **108**, 6060.
 1987TL2513 B. Zipperer, M. Fletschinger, D. Hunkler, and H. Prinzbach, *Tetrahedron Lett.*, 1987, **28**, 2513.
 1987TL2517 M. Fletschinger, B. Zipperer, H. Fritz, and H. Prinzbach, *Tetrahedron Lett.*, 1987, **28**, 2517.
 1987TL5869 M. Murata, M. Kumagai, J. L. Lee, and T. Yasumoto, *Tetrahedron Lett.*, 1987, **28**, 5869.
 1988MI97 D. G. Baden, T. J. Mende, A. M. Szmant, V. L. Trainer, R. A. Edwards, and L. E. Rozell, *Toxicon*, 1988, **26**, 97.
 1990JA4380 M. Murata, A. M. Legrand, Y. Ishibashi, M. Fukui, and T. Yasumoto, *J. Am. Chem. Soc.*, 1990, **112**, 4380.
 B-1990MI397 R. H. Pierce, M. S. Henry, L. S. Proffitt, and P. A. Hasbrouck; in 'Toxic Marine Phytoplankton', E. Granéli, B. Sundström, L. Edler, and D. Anderson, Eds.; Elsevier, New York, 1990, p. 397.
 1990MI1095 K. Terao, E. Ito, M. Oarada, M. Murata, and T. Yasumoto, *Toxicon*, 1990, **28**, 1095.
 1991JA4092 I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
 1991JA4682 D. M. Tapiolas, M. Roman, W. Fenical, T. J. Stout, and J. Clardy, *J. Am. Chem. Soc.*, 1991, **113**, 4682.
 1991MI471 P. D. Morris, D. S. Campbell, T. J. Taylor, and J. Freeman, *Am. J. Pub. Health*, 1991, **81**, 471.
 1991TL4505 T. Suzuki, O. Sato, M. Hirma, Y. Yamamoto, M. Murata, T. Yasumoto, and N. Harada, *Tetrahedron Lett.*, 1991, **32**, 4505.
 1993JA2060 M. Murata, H. Naoki, T. Iwashita, S. Matsunaga, M. Sasaki, A. Yokoyama, and T. Yasumoto, *J. Am. Chem. Soc.*, 1993, **115**, 2060.
 B-1993MI(24)35 M. Bates, M. Baker, N. Wilson, L. Lane, and S. Handford; in 'The Royal Society of New Zealand Miscellaneous Series: Marine Toxins and New Zealand Shellfish', J. Jasperse, Ed.; Royal Society of New Zealand, Wellington, 1993, vol. 24, p. 35.
 1993RCM179 H. Naoki, M. Murata, and T. Yasumoto, *Rapid Commun. Mass Spectrom.*, 1993, **7**, 179.
 1993TL1975 M. Satake, M. Murata, and T. Yasumoto, *Tetrahedron Lett.*, 1993, **34**, 1975.
 1993TL1999 F. A. Macías, R. M. Varela, A. Torres, J. M. G. Molinillo, and F. R. Fronczek, *Tetrahedron Lett.*, 1993, **34**, 1999.
 1994JA7098 M. Murata, H. Naoki, S. Matsunaga, M. Satake, and T. Yasumoto, *J. Am. Chem. Soc.*, 1994, **116**, 7098.
 1994JOC8261 F. A. Macías, J. M. G. Molinillo, R. M. Varela, A. Torres, and F. R. Fronczek, *J. Org. Chem.*, 1994, **59**, 8261.
 1994TL5023 M. Sasaki, T. Nonomura, M. Murata, and K. Tachibana, *Tetrahedron Lett.*, 1994, **35**, 5023.
 1995CRV1953 E. Alvarez, M.-L. Cadenas, R. Perez, J. L. Ravelo, and J. D. Martin, *Chem. Rev.*, 1995, **95**, 1953.
 1995JA7019 M. Satake, S. Ishida, and T. Yasumoto, *J. Am. Chem. Soc.*, 1995, **117**, 7019.
 1995JA10227 K. C. Nicolaou, C.-K. Hwang, M. E. Duggan, D. A. Nugiel, Y. Abe, K. B. Reddy, S. A. DeFrees, D. R. Reddy, R. A. Awartani, S. R. Conley, F. P. J. T. Rutjes, and E. A. Theodorakis, *J. Am. Chem. Soc.*, 1995, **117**, 10227.
 1995JA10252 K. C. Nicolaou, F. P. J. T. Rutjes, E. A. Theodorakis, J. Tiebes, M. Sato, and E. Untersteller, *J. Am. Chem. Soc.*, 1995, **117**, 10252.
 1995SL1252 H. Oguri, S. Hishiyama, T. Oishi, and M. Hirma, *Synlett*, 1995, 1252.

- 1995TL725 H. Ishida, A. Nozawa, K. Totoribe, N. Muramatsu, H. Nukaya, K. Tsuji, K. Yamaguchi, T. Yasumoto, H. Kaspar, N. Berkett, and T. Kosuge, *Tetrahedron Lett.*, 1995, **36**, 725.
- 1995TL1853 Y. Nagai and T. Kusumi, *Tetrahedron Lett.*, 1995, **36**, 1853.
- 1995TL8263 K. Fujiwara, M. Tsunashima, D. Awakura, and A. Murai, *Tetrahedron Lett.*, 1995, **36**, 8263.
- 1995TL8995 A. Morohashi, M. Satake, K. Murata, H. Naoki, H. F. Kaspar, and T. Yasumoto, *Tetrahedron Lett.*, 1995, **36**, 8995.
- 1995TL9007 M. Sasaki, T. Nonomura, M. Murata, and K. Tachibana, *Tetrahedron Lett.*, 1995, **36**, 9007.
- 1995TL9011 M. Sasaki, N. Matsumori, M. Murata, K. Tachibana, and T. Yasumoto, *Tetrahedron Lett.*, 1995, **36**, 9011.
- 1996AGE1672 M. Sasaki, N. Matsumori, T. Maruyama, T. Nonomura, M. Murata, K. Tachibana, and T. Yasumoto, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1672.
- 1996AGE1675 T. Nonomura, M. Sasaki, N. Matsumori, M. Murata, K. Tachibana, and T. Yasumoto, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1675.
- 1996CC1077 A. Oku, S. Ohki, T. Yoshida, and K. Kimura, *Chem. Commun.*, 1996, 1077.
- 1996CHEC-II429 T. P. Smith; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky, C. W. Rees, and E. F. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 429.
- 1996JA7946 W. Zheng, J. A. DeMattei, J.-P. Wu, J. J.-W. Duan, L. R. Cook, H. Oinuma, and Y. Kishi, *J. Am. Chem. Soc.*, 1996, **118**, 7946.
- 1996JNP803 N. Kashiwaba, S. Morooka, M. Kimura, M. Ono, J. Toda, H. Suzuki, and T. Sano, *J. Nat. Prod.*, 1996, **59**, 803.
- 1996JOC4560 K. Ishihara, M. Kubota, H. Kurihara, and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4560.
- 1996J(P1)413 T. Kamada, Ge-Qing, M. Abe, and A. Oku, *J. Chem. Soc., Perkin Trans. 1*, 1996, 413.
- 1996MI1050 H. Ishida, N. Muramatsu, H. Nukaya, T. Kosuge, and K. Tsuji, *Toxicon*, 1996, **34**, 1050.
- 1996SL1165 T. Oishi, M. Shoji, K. Maeda, N. Kumahara, and M. Hiram, *Synlett*, 1996, 1165.
- 1996TL1269 N. Matsumori, T. Nonomura, M. Sasaki, M. Murata, K. Tachibana, M. Satake, and T. Yasumoto, *Tetrahedron Lett.*, 1996, **37**, 1269.
- 1996TL2865 E. Alvarez, M. Delgado, M. T. Díaz, L. Hanxing, R. Pérez, and J. D. Martín, *Tetrahedron Lett.*, 1996, **37**, 2865.
- 1996TL5049 M. B. Andrus and A. B. Argade, *Tetrahedron Lett.*, 1996, **37**, 5049.
- 1996TL5605 J. S. Clark, A. G. Dossetter, and W. G. Whittingham, *Tetrahedron Lett.*, 1996, **37**, 5605.
- 1996TL5955 S. Masayuki, K. Terasawa, Y. Kadowaki, and T. Yasumoto, *Tetrahedron Lett.*, 1996, **37**, 5955.
- 1996TL7087 H. Takahashi and T. Kusumi, *Tetrahedron Lett.*, 1996, **37**, 7087.
- 1997BBB2103 M. Satake, Y. Ishibashi, A.-M. Legrand, and T. Yasumoto, *Biosci. Biochem. Biotech.*, 1997, **60**, 2103.
- 1997CC2139 P. Chattopadhyay, M. Mukherjee, and S. Ghosh, *Chem. Commun.*, 1997, 2139.
- 1997JA6919 R. J. Linderman, J. Siedlecki, S. A. O'Neill, and H. Sun, *J. Am. Chem. Soc.*, 1997, **119**, 6919.
- 1997JA7499 J. Kruger and R. W. Hoffmann, *J. Am. Chem. Soc.*, 1997, **119**, 7499.
- 1997JA7928 L. R. Cook, H. Oinuma, M. A. Semones, and Y. Kishi, *J. Am. Chem. Soc.*, 1997, **119**, 7928.
- 1997JA11325 M. Satake, A. Morohashi, H. Oguri, T. Oishi, M. Hiram, N. Harada, and T. Yasumoto, *J. Am. Chem. Soc.*, 1997, **119**, 11325.
- 1997JOC2646 B. Harrison and P. Crews, *J. Org. Chem.*, 1997, **62**, 2646.
- 1997JOC7548 M. T. Crimmins and A. L. Choy, *J. Org. Chem.*, 1997, **62**, 7548.
- 1997MI107 M. Satake, A. Tubaro, J.-S. Lee, and T. Yasumoto, *Nat. Toxins*, 1997, **5**, 107.
- 1997MI164 M. Satake, L. MacKenzie, and T. Yasumoto, *Nat. Toxins*, 1997, **5**, 164.
- 1997MI733 M. A. Poli, R. J. Lewis, R. W. Dickey, S. M. Musser, C. A. Buckner, and L. G. Carpenter, *Toxicon*, 1997, **35**, 733.
- 1997MI889 J.-P. Vernoux and R. J. Lewis, *Toxicon*, 1997, **35**, 889.
- 1997T3057 H. Oguri, S. Hishiyama, O. Sato, T. Oishi, M. Hiram, M. Murata, T. Yasumoto, and N. Harada, *Tetrahedron*, 1997, **53**, 3057.
- 1997T8371 K. Ishihara, Y. Shimada, N. Kanoh, Y. Takasugi, A. Fukuzawa, and A. Murai, *Tetrahedron*, 1997, **53**, 8371.
- 1997TL6299 M. Delgado and J. D. Martín, *Tetrahedron Lett.*, 1997, **38**, 6299.
- 1997TL8245 A. N. Hulme and G. E. Howells, *Tetrahedron Lett.*, 1997, **38**, 8245.
- 1998JA5914 R. L. Lewis, J.-P. Vernoux, and I. M. Brereton, *J. Am. Chem. Soc.*, 1998, **120**, 5914.
- 1998JNP1140 E. V. L. da-Cunha, M. L. Cornélio, J. M. Barbosa-Filho, R. Braz-Filho, and A. I. Gray, *J. Nat. Prod.*, 1998, **61**, 1140.
- 1998JOC9728 M. T. Mujica, M. M. Afonso, A. Galindo, and J. A. Palenzuela, *J. Org. Chem.*, 1998, **63**, 9728.
- 1998J(P1)3623 T. Mori, M. Taniguchi, F. Suzuki, H. Doi, and A. Oku, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3623.
- 1998MI97 J.-P. Perchellet, E. M. Perchellet, S. W. Newell, J. A. Freeman, J. B. Ladesich, Y. Jeong, N. Sato, and K. Buszek, *Anticancer Res.*, 1998, **18**, 97.
- 1998MI235 M. Daiguji, M. Satake, H. Ramstad, T. Aune, H. Naoki, and T. Yasumoto, *Nat. Toxins*, 1998, **6**, 235.
- 1998SL735 S. Inoue, Y. Iwabuchi, H. Irie, and S. Hatakeyama, *Synlett*, 1998, 735.
- 1998T735 K. Murata, M. Satake, H. Naoki, H. F. Kaspar, and T. Yasumoto, *Tetrahedron*, 1998, **54**, 735.
- 1998TL393 K. Fujiwara, H. Mishima, A. Amano, T. Tokiwano, and A. Murai, *Tetrahedron Lett.*, 1998, **39**, 393.
- 1998TL1197 M. Satake, M. Fukui, A.-M. Legrand, P. Cruchet, and T. Yasumoto, *Tetrahedron Lett.*, 1998, **39**, 1197.
- 1998TL8321 J. S. Clark, O. Hamelin, and R. Hufton, *Tetrahedron Lett.*, 1998, **39**, 8321.
- 1998TL8897 P. Ciminiello, E. Fattorusso, M. Forino, S. Magno, R. Poletti, and R. Viviani, *Tetrahedron Lett.*, 1998, **39**, 8897.
- 1999CC749 J. S. Clark, A. G. Dossetter, A. J. Blake, W.-S. Li, and W. G. Whittingham, *Chem. Commun.*, 1999, 749.
- 1999CC1117 B. Forier, S. Toppet, L. Van Meervelt, and W. Dehaen, *Chem. Commun.*, 1999, 1117.
- 1999CEJ599 K. C. Nicolaou, M. E. Bunnage, D. G. McGarry, S. Shi, P. K. Somers, P. A. Wallace, X.-J. Chu, K. A. Agrios, J. L. Gunzner, and Z. Yang, *Chem. Eur. J.*, 1999, **5**, 599.
- 1999CEJ618 K. C. Nicolaou, P. A. Wallace, S. Shi, M. A. Ouellette, M. E. Bunnage, J. L. Gunzner, K. A. Agrios, G.-Q. Shi, P. Gartner, and Z. Yang, *Chem. Eur. J.*, 1999, **5**, 618.
- 1999CEJ628 K. C. Nicolaou, G.-Q. Shi, J. L. Gunzner, P. Gartner, P. A. Wallace, M. A. Ouellette, S. Shi, M. E. Bunnage, K. A. Agrios, C. A. Veale, C.-K. Hwang, J. Hutchinson, C. V. C. Prasad, W. W. Ogilvie, and Z. Yang, *Chem. Eur. J.*, 1999, **5**, 628.
- 1999CEJ646 K. C. Nicolaou, J. L. Gunzner, G.-Q. Shi, K. A. Agrios, P. Gartner, and Z. Yang, *Chem. Eur. J.*, 1999, **5**, 646.
- 1999JA5653 M. T. Crimmins and A. L. Choy, *J. Am. Chem. Soc.*, 1999, **121**, 5653.
- 1999JNP1636 F. A. Macías, R. M. Varela, A. Torres, and J. M. G. Molinillo, *J. Nat. Prod.*, 1999, **62**, 1636.
- 1999JOC4798 M. Delgado and J. D. Martín, *J. Org. Chem.*, 1999, **64**, 4798.
- 1999MI45 A. Morohashi, M. Satake, H. Naoki, H. F. Kaspar, Y. Oshima, and T. Yasumoto, *Nat. Toxins*, 1999, **7**, 45.

- 1999MI147 M. Satake, T. Ichimura, K. Sekiguchi, S. Yoshimatsu, and Y. Oshima, *Nat. Toxins*, 1999, **7**, 147.
- 1999MI157 R. Dickey, E. Jester, R. Granade, D. Mowdy, C. Moncreiff, D. Rebarchik, M. Robl, S. Musser, and M. Poli, *Nat. Toxins*, 1999, **7**, 157.
- 1999MI689 P. Ciminiello, E. Fattorusso, M. Forino, R. Poletti, and R. Viviani, *Toxicon*, 1999, **37**, 689.
- 1999OL2029 M. T. Crimmins and K. A. Emmitte, *Org. Lett.*, 1999, **1**, 2029.
- 1999SL354 T. Fujiwara and T. Takeda, *Synlett*, 1999, 354.
- 1999SL1757 H. Ohi, S. Inoue, Y. Iwabuchi, H. Irie, and S. Hatakeyama, *Synlett*, 1999, 1757.
- 1999T7471 T. Oishi, M. Maruyama, M. Shoji, K. Maeda, N. Kumahara, S.-I. Tanaka, and M. Hirama, *Tetrahedron*, 1999, **55**, 7471.
- 1999T8231 J. S. Clark and J. G. Kettle, *Tetrahedron*, 1999, **55**, 8231.
- 2000AGE372 J. S. Clark and O. Hamelin, *Angew. Chem., Int. Ed.*, 2000, **39**, 372.
- 2000CC1079 J. S. Clark and Y.-S. Wong, *Chem Commun.*, 2000, 1079.
- 2000CRT770 P. Ciminiello, E. Fattorusso, M. Forino, R. Poletti, and R. Viviani, *Chem. Res. Toxicol.*, 2000, **13**, 770.
- 2000EJ0291 P. Ciminiello, E. Fattorusso, M. Forino, S. Magno, R. Poletti, and R. Viviani, *Eur. J. Org. Chem.*, 2000, 291.
- 2000H(52)1105 I. Shiina, H. Fujisawa, T. Ishii, and Y. Fukuda, *Heterocycles*, 2000, **52**, 1105.
- 2000JA4988 T. Yasumoto, T. Igarashi, A.-M. Legrand, P. Crochet, M. Chinain, T. Fujita, and H. Naoki, *J. Am. Chem. Soc.*, 2000, **122**, 4988.
- 2000JA5473 M. T. Crimmins and E. A. Tabet, *J. Am. Chem. Soc.*, 2000, **122**, 5473.
- 2000JEL2173 F. A. Macías, R. M. Varela, A. Torres, and J. M. G. Molinillo, *J. Chem. Ecol.*, 2000, **26**, 2173.
- 2000J(P1)575 F. De Campo, D. Lastécouères, and J.-B. Verlhac, *J. Chem. Soc., Perkin Trans. 1*, 2000, 575.
- 2000MI302 N. Daugbjerg, G. Hansen, J. Larsen, and Ø. Moestrup, *Phycologia*, 2000, **39**, 302.
- 2000NPR293 M. Murata and T. Yasumoto, *Nat. Prod. Rep.*, 2000, **17**, 293.
- 2000SL266 T.-Z. Liu and M. Isobe, *Synlett*, 2000, 266.
- 2000T2203 C. Mukai, H. Yamashita, T. Ichiryu, and M. Hanaoka, *Tetrahedron*, 2000, **56**, 2203.
- 2000T9297 R. Goossens, G. Lhomeau, B. Forier, S. Toppet, L. Van Meervelt, and W. Dehaen, *Tetrahedron*, 2000, **56**, 9297.
- 2000T10209 T. Z. Liu, J.-M. Li, and M. Isobe, *Tetrahedron*, 2000, **56**, 10209.
- 2000TL10201 M. V. Gil, E. Román, and J. A. Serrano, *Tetrahedron Lett.*, 2000, **41**, 10201.
- 2001BP827 L. A. de la Rosa, A. Alfonso, N. Vilariño, M. R. Vieytes, and L. M. Botana, *Biochem. Pharmacol.*, 2001, **61**, 827.
- 2001EJO3657 P. Langer, T. Eckardt, N. N. R. Saleh, I. Karimé, and P. Müller, *Eur. J. Org. Chem.*, 2001, 3657.
- 2001MI228 T. Yasumoto, *Chem. Rec.*, 2001, **1**, 228.
- 2001MI596 P. Ciminiello, E. Fattorusso, M. Forino, and R. Poletti, *Chem. Res. Toxicol.*, 2001, **14**, 596.
- 2001OL3385 C. Mukai, H. Yamashita, and M. Hanaoka, *Org. Lett.*, 2001, **3**, 3385.
- 2001SL117 M. Martín, M. M. Afonso, A. Galindo, and J. A. Palenzuela, *Synlett*, 2001, 117.
- 2002CC634 K. Tuhina, D. R. Bhowmik, and R. V. Venkateswaran, *Chem. Commun.*, 2002, 634.
- 2002CL148 G. Matsuo, H. Kodahama, and T. Nakata, *Chem. Lett.*, 2002, 148.
- 2002JCH(968)61 P. Ciminiello, C. Dell'Aversano, E. Fattorusso, M. Forino, S. Magno, and R. Poletti, *J. Chromatogr. A*, 2002, **968**, 61.
- 2002JCH(976)329 M. F. Amandi, A. Furey, M. Lehan, H. Ramstad, and K. J. James, *J. Chromatogr. A*, 2002, **976**, 329.
- 2002JNP395 Y. Takahashi, M. Daitoh, M. Suzuki, T. Abe, and M. Masuda, *J. Nat. Prod.*, 2002, **65**, 395.
- 2002TL1801 M. Suzuki, S. Nakano, Y. Takahashi, T. Abe, M. Masuda, H. Takahashi, and K. Kobayashi, *J. Nat. Prod.*, 2002, **65**, 801.
- 2002JOC3301 M. Sasaki, T. Noguchi, and K. Tachibana, *J. Org. Chem.*, 2002, **67**, 3301.
- 2002MI77 T. Aune, R. Sorby, T. Yasumoto, H. Ramstad, and T. Landsverk, *Toxicon*, 2002, **40**, 77.
- 2002MI357 C. Malaguti, P. Ciminiello, E. Fattorusso, and G. P. Rossini, *Toxicol. In Vitro*, 2002, **16**, 357.
- 2002MI445 A. H. Januário, E. R. Filho, R. C. L. R. Pietro, S. Kashima, D. N. Sato, and S. C. França, *Phytother. Res.*, 2002, **16**, 445.
- 2002MI685 B. Hamilton, M. Hurbungs, J.-P. Vernoux, A. Jones, and R. J. Lewis, *Toxicon*, 2002, **40**, 685.
- 2002MI721 S. M. Plakas, K. R. El Said, E. L. E. Jester, H. R. Granade, S. M. Musser, and R. W. Dickey, *Toxicon*, 2002, **40**, 721.
- 2002MI1347 B. Hamilton, M. Hurbungs, A. Jones, and R. J. Lewis, *Toxicon*, 2002, **40**, 1347.
- 2002OL675 Y. Sakamoto, K. Tamegai, and T. Nakata, *Org. Lett.*, 2002, **4**, 675.
- 2002OL3047 M. J. Coster and J. J. De Voss, *Org. Lett.*, 2002, **4**, 3047.
- 2002OL3891 R. K. Boeckman, Jr., J. Zhang, and M. R. Reeder, *Org. Lett.*, 2002, **4**, 3891.
- 2002P687 F. A. Macías, A. Torres, J. L. G. Galindo, R. M. Varela, J. A. Álvarez, and J. M. G. Molinillo, *Phytochemistry*, 2002, **61**, 687.
- 2002SL1493 K. Fujiwara, S.-I. Souma, H. Mishima, and A. Murai, *Synlett*, 2002, 1493.
- 2002SL1496 K. Fujiwara, Y. Koyama, E. Doi, K. Shimawaki, Y. Ohtaniuchi, A. Takemura, S.-I. Souma, and A. Murai, *Synlett*, 2002, 1496.
- 2002TL181 K. R. Buszek, N. Sato, and Y. Jeong, *Tetrahedron Lett.*, 2002, **43**, 181.
- 2002TL7263 J. Cossy, C. Taillier, and V. Bellosta, *Tetrahedron Lett.*, 2002, **43**, 7263.
- 2002TL7781 S. K. Chattopadhyay, S. Maity, and S. Panja, *Tetrahedron Lett.*, 2002, **43**, 7781.
- 2003CC350 H. Kishuku, M. Shindo, and K. Shishido, *Chem. Commun.*, 2003, 350.
- 2003EJO463 C. Mendès, S. Renard, M. Rofoo, M.-C. Roux, and G. Rousseau, *Eur. J. Org. Chem.*, 2003, 463.
- 2003JA10238 H. Kim, W. J. Choi, J. Jung, S. Kim, and D. Kim, *J. Am. Chem. Soc.*, 2003, **125**, 10238.
- 2003JOC3319 S. Guiard, M. Giorgi, M. Santelli, and J.-L. Parrain, *J. Org. Chem.*, 2003, **68**, 3319.
- 2003MI7 P. Ciminiello, C. Dell'Aversano, E. Fattorusso, M. Forino, S. Magno, F. Guerrini, R. Pistocchi, and L. Boni, *Toxicon*, 2003, **42**, 7.
- 2003MI91 A. Nozawa, K. Tsuj, and H. Ishida, *Toxicon*, 2003, **42**, 91.
- 2003MI191 L. S. David, S. M. Plakas, K. R. El Said, E. L. E. Jester, R. W. Dickey, and R. A. Nicholson, *Toxicon*, 2003, **42**, 191.
- 2003MI520 L. Fang, H.-B. Chai, J. J. Castillo, D. D. Soejarto, N. R. Farnsworth, G. A. Cordell, J. M. Pezzuto, and A. D. Kinghorn, *Phytother. Res.*, 2003, **17**, 520.
- 2003MI919 M.-Y. B. Dechraoui and J. S. Ramsdell, *Toxicon*, 2003, **41**, 919.
- 2003TL2709 T. Saitoh, T. Suzuki, N. Onodera, H. Sekiguchi, H. Hagiwara, and T. Hoshi, *Tetrahedron Lett.*, 2003, **44**, 2709.
- 2003TL3175 T. Saitoh, T. Suzuki, M. Sugimoto, H. Hagiwara, and T. Hoshi, *Tetrahedron Lett.*, 2003, **44**, 3175.
- 2003TL8019 N. Rosas, P. Sharma, C. Alvarez, E. Gómez, Y. Gutiérrez, M. Méndez, R. A. Toscano, and L. A. Maldonado, *Tetrahedron Lett.*, 2003, **44**, 8019.

- 2004CRT1251 S. Ferrari, P. Ciminiello, C. Dell'Aversano, M. Forino, C. Malaguti, A. Tubaro, R. Poletti, T. Yasumoto, E. Fattorusso, and G. P. Rossini, *Chem. Res. Toxicol.*, 2004, **17**, 1251.
- 2004JNP1309 M. Konishi, X. Yang, B. Li, C. R. Fairchild, and Y. Shimizu, *J. Nat. Prod.*, 2004, **67**, 1309.
- 2004JOC1331 A. Oku, Y. Sawada, M. Schroeder, I. Higashikubo, T. Yoshida, and S. Ohki, *J. Org. Chem.*, 2004, **69**, 1331.
- 2004MI325 C. O. Miles, A. L. Wilkins, A. D. Hawkes, A. Selwood, D. J. Jensen, J. Aasen, R. Munday, I. A. Samdal, L. R. Briggs, V. Beuzenberg, and A. L. MacKenzie, *Toxicol.*, 2004, **44**, 325.
- 2004MI455 Z. Wang, S. M. Plakas, K. R. El Said, E. L. E. Jester, H. R. Granade, and R. W. Dickey, *Toxicol.*, 2004, **43**, 455.
- 2004MI669 N. V. Kulagina, T. J. O'Shaughnessy, W. Ma, J. S. Ramsdell, and J. J. Pancrazio, *Toxicol.*, 2004, **44**, 669.
- 2004MI677 S. M. Plakas, Z. Wang, K. R. El Said, E. L. E. Jester, H. R. Granade, L. Flewelling, P. Scott, and R. W. Dickey, *Toxicol.*, 2004, **44**, 677.
- 2004MI701 H. Ishida, A. Nozawa, H. Nukaya, L. Rhodes, P. McNabb, P. T. Holland, and K. Tsuji, *Toxicol.*, 2004, **43**, 701.
- 2004MI779 H. Ishida, A. Nozawa, H. Nukaya, and K. Tsuji, *Toxicol.*, 2004, **43**, 779.
- 2004OL3005 L. A. Arnold, W. Lu, and R. K. Guy, *Org. Lett.*, 2004, **6**, 3005.
- 2004OL4787 C. M. Rodríguez, J. L. Ravelo, and V. S. Martín, *Org. Lett.*, 2004, **6**, 4787.
- 2004SL481 Y. Nagao, S. Tanaka, K. Hayashi, S. Sano, and M. Shiro, *Synlett*, 2004, 481.
- 2004SL1613 F. Lecornué and J. Ollivier, *Synlett*, 2004, 1613.
- 2004T1587 I. Shiina, *Tetrahedron*, 2004, **60**, 1587.
- 2004T7361 I. Kadota, H. Uyehara, and Y. Yamamoto, *Tetrahedron*, 2004, **60**, 7361.
- 2004TL29 H. Ishida, A. Nozawa, H. Hamano, H. Naoki, T. Fujita, H. F. Kaspar, and K. Tsuji, *Tetrahedron Lett.*, 2004, **45**, 29.
- 2004TL543 I. Shiina, H. Oshiumi, M. Hashizume, Y.-S. Yamai, and R. Ibuka, *Tetrahedron Lett.*, 2004, **45**, 543.
- 2004TL8639 L. S. Clark, R. P. Freeman, M. Cacho, A. W. Thomas, S. Swallow, and C. Wilson, *Tetrahedron Lett.*, 2004, **45**, 8639.
- 2004TL9653 S. K. Sabui and R. V. Venkateswaran, *Tetrahedron Lett.*, 2004, **45**, 9653.
- 2005CEJ6601 I. Shiina, M. Hashizume, Y.-S. Yamai, H. Oshiumi, T. Shimazaki, Y.-J. Takasuna, and R. Ibuka, *Chem. Eur. J.*, 2005, **11**, 6601.
- 2005CRV4379 M. Inoue, *Chem. Rev.*, 2005, **105**, 4379.
- 2005EJO2589 F. Lecornué, R. Paugam, and J. Ollivier, *Eur. J. Org. Chem.*, 2005, 2589.
- 2005JA9246 I. Kadota, H. Takamura, H. Nishii, and Y. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 9246.
- 2005JNP420 M. L. Souto, J. J. Fernández, J. M. Franco, B. Paz, L. V. Gil, and M. Norte, *J. Nat. Prod.*, 2005, **68**, 420.
- 2005JNP1131 Y. Zhang, Y. Lu, L. Zhang, Q.-T. Zheng, L.-Z. Xu, and S.-L. Yang, *J. Nat. Prod.*, 2005, **68**, 1131.
- 2005MI61 C. O. Miles, A. L. Wilkins, A. D. Hawkes, A. I. Selwood, D. J. Jensen, R. Munday, J. M. Cooney, and V. Beuzenberg, *Toxicol.*, 2005, **45**, 61.
- 2005MI261 M.-Y. B. Dechraoui, J. A. Tiedeken, R. Persad, Z. Wang, H. R. Granade, R. W. Dickey, and J. S. Ramsdell, *Toxicol.*, 2005, **46**, 261.
- 2005MI265 J. Aasen, I. A. Samdal, C. O. Miles, E. Dahl, L. R. Briggs, and T. Aune, *Toxicol.*, 2005, **45**, 265.
- 2005MI441 P. Truman, R. A. Keyzers, P. T. Northcote, V. Ambrose, N. A. Redshaw, and F. H. Chang, *Toxicol.*, 2005, **46**, 441.
- 2005OL75 S. Baek, H. Jo, H. Kim, H. Kim, S. Kim, and D. Kim, *Org. Lett.*, 2005, **7**, 75.
- 2005S403 S. K. Chattopadhyay, R. Dey, and S. Biswas, *Synthesis*, 2005, 403.
- 2005SL2851 M.-T. Dinh, S. BouzBouz, J.-L. Peglion, and J. Cossy, *Synlett*, 2005, 2851.
- 2005T7461 K. P. Kaliappan and N. Kumar, *Tetrahedron*, 2005, **61**, 7461.
- 2005T9980 Y. D. Smurnyy, M. E. Elyashberg, K. A. Blinov, B. A. Lefebvre, G. E. Martin, and A. J. Williams, *Tetrahedron*, 2005, **61**, 9980.
- 2005TL1855 T. Ishida and K. Tachibana, *Tetrahedron Lett.*, 2005, **46**, 1855.
- 2005TL3465 K. Fujiwara, A. Goto, D. Sato, H. Kawai, and T. Suzuki, *Tetrahedron Lett.*, 2005, **46**, 3465.
- 2005TL3991 K. Watanabe, M. Suzuki, M. Murata, and T. Oishi, *Tetrahedron Lett.*, 2005, **46**, 3991.
- 2005TL6819 K. Fujiwara, S. Yoshimoto, A. Takizawa, S.-I. Souma, H. Mishima, A. Murai, H. Kawai, and T. Suzuki, *Tetrahedron Lett.*, 2005, **46**, 6819.
- 2006CL730 T. Hamura, N. Kawano, T. Matsumoto, and K. Suzuki, *Chem. Lett.*, 2006, 730.
- 2006MI104 A. Abraham, S. M. Plakas, Z. Wang, E. L. E. Jester, K. R. El Said, H. R. Granade, M. S. Henry, P. C. Blum, R. H. Pierce, and R. W. Dickey, *Toxicol.*, 2006, **48**, 104.
- 2006MI229 C. O. Miles, A. L. Wilkins, A. D. Hawkes, A. I. Selwood, D. J. Jensen, J. M. Cooney, V. Beuzenberg, and A. L. MacKenzie, *Toxicol.*, 2006, **47**, 229.
- 2006MI510 C. O. Miles, A. L. Wilkins, A. I. Selwood, A. D. Hawkes, D. J. Jensen, J. M. Cooney, V. Beuzenberg, and A. L. MacKenzie, *Toxicol.*, 2006, **47**, 510.
- 2006MI611 B. Paz, P. Riobó, M. L. Souto, L. V. Gil, M. Norte, J. J. Fernández, and J. M. Franco, *Toxicol.*, 2006, **48**, 611.
- 2006MI702 M.-Y. B. Dechraoui, J. J. Wacksman, and J. S. Ramsdell, *Toxicol.*, 2006, **48**, 702.
- 2006OL871 N. Ortega, T. Martín, and V. S. Martín, *Org. Lett.*, 2006, **8**, 871.
- 2006OL5897 S. V. Pansare and V. A. Adsool, *Org. Lett.*, 2006, **8**, 5897.
- 2006SL1205 T. K. M. Shing and Y.-L. Zhong, *Synlett*, 2006, 1205.
- 2006SL2191 J. S. Clark, L. J. Winfield, C. Wilson, and A. J. Blake, *Synlett*, 2006, 2191.
- 2006SL2211 S. K. Chattopadhyay, T. Biswas, and S. Maity, *Synlett*, 2006, 2211.
- 2006TL113 V. T. H. Nguyen, E. Bellur, and P. Langer, *Tetrahedron Lett.*, 2006, **46**, 113.
- 2006TL1599 S. K. Mandal and S. C. Roy, *Tetrahedron Lett.*, 2006, **47**, 1599.
- 2006TL6895 S. K. Chattopadhyay, S. P. Roy, D. Ghosh, and G. Biswas, *Tetrahedron Lett.*, 2006, **47**, 6895.
- 2007AG(E)5278 K. C. Nicolaou and M. O. Frederick, *Angew. Chem. Int. Ed.*, 2007, **46**, 5278.
- 2007JA2269 H. Kim, H. Lee, D. Lee, S. Kim, and D. Kim, *J. Am. Chem. Soc.*, 2007, **129**, 2269.
- 2007T644 S. Ghosh, K. Tuhina, D. R. Bhowmik, and R. V. Venkateswaran, *Tetrahedron*, 2007, **63**, 644.
- 2007TL1109 M. Sugimoto, T. Suzuki, H. Hagiwara, and T. Hoshi, *Tetrahedron Lett.*, 2007, **48**, 1109.
- 2007TL5185 A. G. Martínez, E. T. Vilar, A. G. Fraile, S. M. Cerero, and C. D. Morillo, *Tetrahedron Lett.*, 2007, **48**, 5185.

Biographical Sketch



Artur Manuel Soares da Silva was born in Marco de Canaveses, Porto, Portugal, in 1963. He studied chemistry-physics for teaching at the University of Aveiro where he obtained his B.Sc. degree in 1987. He obtained his Ph.D. (1993) at the University of Aveiro, under the supervision of Prof. J. Cavaleiro, working on the synthesis of flavonoid-type compounds and was approved in the Habilitation in 1999.

He joined the Department of Chemistry of the University of Aveiro as Assistente Estagiário in 1987 and he was appointed as auxiliary professor in 1996, associate professor in 1999, and full professor in 2001. He has been lecturing organic and natural products chemistry and NMR courses and supervising several master's and Ph.D. students and postdoctoral researchers.

His research interests range over the chemistry of polyphenolic and nitrogen heterocyclic compounds, with special emphasis on the development of new synthetic routes. He has published more than 180 SCI papers, 7 book chapters, and delivered more than 20 lectures in scientific meetings.

He was the chairman of the Chemistry Department, University of Aveiro, for 2001–06 and was also president and vice-president of the Organic Chemistry Division of the Portuguese Chemical Society. He belongs to the advisory board of the *European Journal of Organic Chemistry* and is referee of more than 10 international scientific journals.



Augusto C. Tomé was born in Aveiro, Portugal, in 1963. He studied chemistry at the University of Aveiro where he obtained his B.Sc. degree (1985), Ph.D. (1994), and Habilitation (2005). He joined the Department of Chemistry of the University of Aveiro as Assistente Estagiário (1985) and he was then promoted to auxiliary professor (1994), associate professor (1998), and associate professor with Habilitation (2005). He has been lecturing organic and bioorganic chemistry courses and supervising master's and Ph.D. students and postdoctoral researchers. His research interests range over fullerene chemistry and heterocyclic chemistry, with special emphasis on the functionalization of porphyrins. He has published over 80 peer-reviewed papers and three chapters in collective volumes.

14.03

Eight-membered Rings with One Sulfur Atom

H. Eckert

Technical University of Munich, Garching, Germany

© 2008 Elsevier Ltd. All rights reserved.

14.03.1	Introduction	89
14.03.2	Theoretical Methods	89
14.03.2.1	Fully Conjugated Rings	89
14.03.2.2	Dihydro Derived Rings	90
14.03.3	Experimental Structural Methods	90
14.03.3.1	X-Ray Diffraction Studies	91
14.03.3.2	NMR Studies	91
14.03.4	Thermodynamic Aspects	91
14.03.5	Reactivity of Fully Conjugated Rings	91
14.03.6	Reactivity of Nonconjugated Rings	91
14.03.7	Reactivity of Substituents Attached to Ring Carbon Atoms	92
14.03.8	Reactivity of Substituents Attached to Ring Heteroatoms	93
14.03.9	Ring Syntheses	93
14.03.9.1	Fully Conjugated Rings	93
14.03.9.2	Dihydro Derived Rings	94
14.03.9.3	Tetrahydro Derived Rings	94
14.03.9.4	Fully Saturated Rings	95
References		96

14.03.1 Introduction

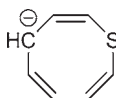
This ring system and its nomenclature were reviewed in the CHEC-II(1996) <1996CHEC-II(9)449> and the literature was covered up to 1994. This chapter covers the intervening time through 2006 and the beginning of 2007. In general, eight-membered rings with one S-atom are not easy to make, and there are only a few references on synthetic literature in the period 1995–2006. Since the publication of CHEC-II(1996), syntheses of fully conjugated heterocycles have been reported (Section 9.20.9.1), as have dihydro-, tetrahydro-, and saturated thiocines.

14.03.2 Theoretical Methods

14.03.2.1 Fully Conjugated Rings

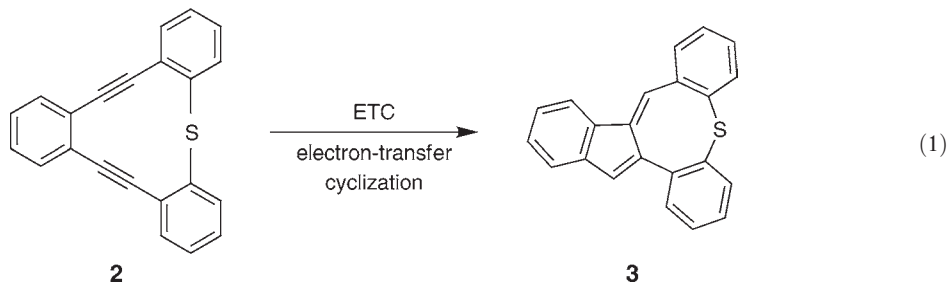
Some theoretical calculations on S-containing eight-membered rings have been performed using commonly used Becke–Lee–Yang–Parr (BLYP) density-functional theory <1993MI5648, 2005MI848> and recent Kang–Musgrave method of the Lee–Yang–Parr (KMLYP) density functional theory <1993MI5648, 2001MI1040> *ab initio* molecular orbital (MO) studies.

Thus, **1** has been predicted to be planar and diatropic in an *ab initio* study using recent KMLYP hybridization, which is qualitatively superior to the B3LYP hybrid for modeling the aromaticity of such systems <2004PCP310>.



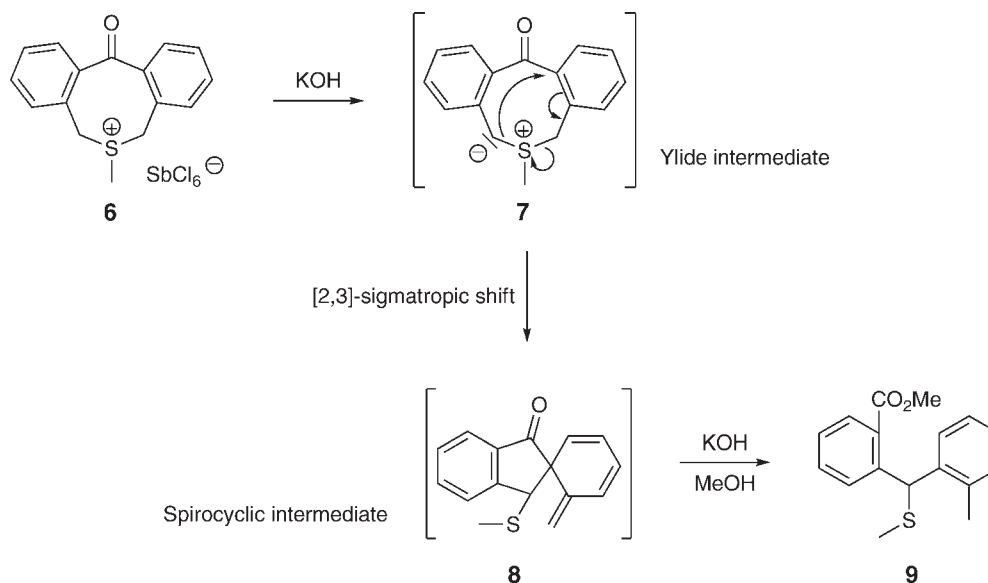
1

Under calculation using B3LYP/6, the thiocine derivative **3** should be possible to be generated according to Equation (1) from the 11-membered ring **2** by electron transfer cyclization (ETC) <2002JOC388>. Structure **3** is with a calculated relative energy of $32.7 \text{ kcal mol}^{-1}$ even less stable than **2** due to the unfavorable bond angles in the eight-membered ring.



14.03.2.2 Dihydro Derived Rings

Molecular orbital (MO) calculations have been performed on various intermediates of Scheme 1 in Section 14.03.6. *Ab initio* calculations were carried out at the Hartree–Fock (HF) level with the 6-31G* basis set using the HONDO-2001 program package <2002J(P1)2704>.



Scheme 1

The density functional calculations at BLYP/6-31G* level of theory on **11** and **12** support the X-ray-crystallographic findings in Section 14.03.3.1. The *anti*-conformer of **11** is predicted to be more stable than the *syn*-conformer by $5.0 \text{ kcal mol}^{-1}$, and the *anti*-conformer of **12** less stable than the *syn*-conformer by $4.9 \text{ kcal mol}^{-1}$, supporting experimental facts <2002T3647>.

14.03.3 Experimental Structural Methods

Detailed spectroscopic data as ^1H and ^{13}C NMR (NMR – nuclear magnetic resonance), infrared (IR), ultraviolet (UV), and mass spectrometry (MS) on structures are reported for **4**, **5** and **10** (<2001H(54)159>, **6** <2002J(P1)2704>,

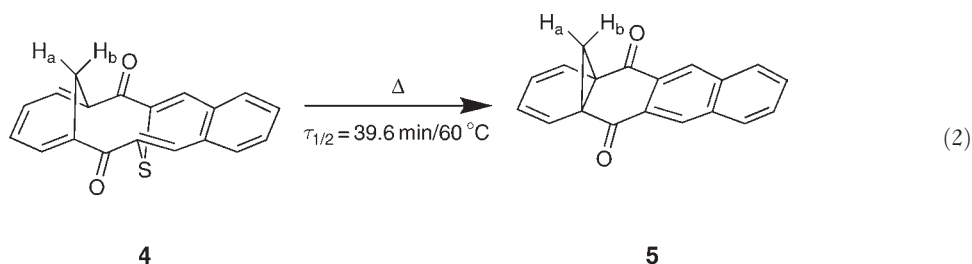
11 and **12** <2002T3647>, **22** <2005T9082>, and **33** <1999SL735>. Some methods for constructing and analyzing new structures and kinetics of eight-membered rings with one S-atom have been applied as X-ray diffraction, ^1H NMR spectroscopy, and cyclic voltametry.

14.03.3.1 X-Ray Diffraction Studies

The molecular structures of the compounds **11** and **12** were elucidated by X-ray crystallographic analysis. There are two independent molecules with C_i symmetry in the crystals of **11**, which has an *anti*-conformation. The X-ray structure of **12** shows C_s symmetry and has the *syn*-conformation <2002T3647>.

14.03.3.2 NMR Studies

Thermolysis of diketothiocane **4** (described in Section 14.03.6) has been monitored by the ^1H NMR spectroscopic measurement of the decreasing integration of the bridged methylene protons of **4**. Thus, the half-life (τ) of **4** was determined as 40 min at 60 °C. The cyclopropanation in **5** is proved by the strong decrease of the chemical shift of $H_a(\mathbf{4}) = 2.04$ to $H_a(\mathbf{5}) = 0.92$ (Equation 2) <2001H(54)159>.



14.03.4 Thermodynamic Aspects

Physical properties and solubilities of thiocanes and thiocines were reviewed in CHEC-II(1996). Conformational studies on molecular structures of dihydrothiocines **11** and **12** have been performed by X-ray crystallography (see Section 14.03.3.1) and by density functional calculations (Section 14.03.2.2), both methods provided the same results <2002T3647>.

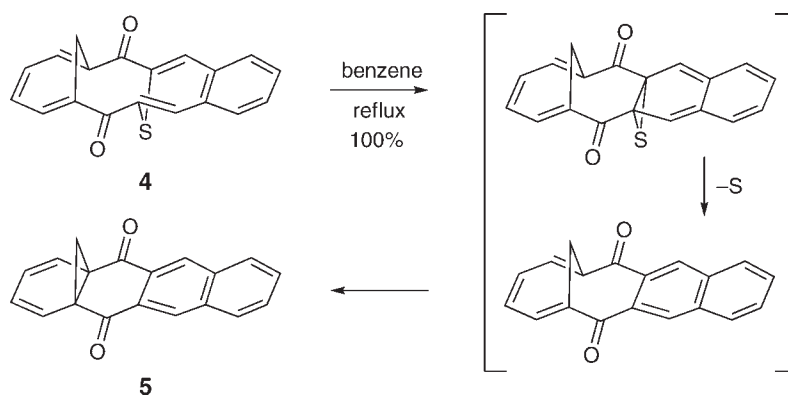
14.03.5 Reactivity of Fully Conjugated Rings

No literature was reported about this item.

14.03.6 Reactivity of Nonconjugated Rings

S-Methylthiocinium salt **6** (preparation in Section 14.03.9.2) is transformed by base influence into an ylide intermediate **7**, which undergoes a [2,3]-sigmatropic shift forming the spirocyclic intermediate **8**, which is attacked by methoxide ion affording stable **9** <2002J(P1)2704> as shown in Scheme 1.

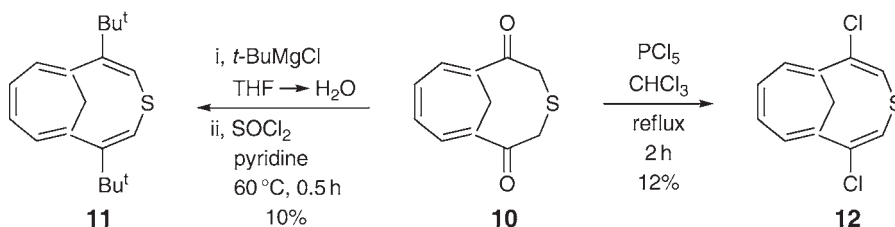
Diketothiocane **4** (preparation in Section 14.03.9.4) can be transformed quantitatively into the desulfurized diketoannulene **5** by thermolysis in refluxing benzene according to Scheme 2 <2001H(54)159>. The kinetic data of the reaction have been measured (Section 14.03.3).



Scheme 2

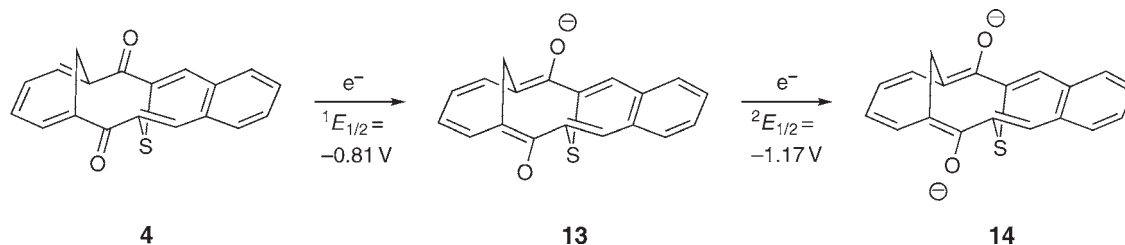
14.03.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Diketothiocane **10** (Section 14.03.9.4) reacts both with Grignard reagents and halogenating reagents at both keto functions providing dihydrothiocines **11** and **12**. Reaction of **10** with *t*-butylmagnesium chloride affords 3,10-di(*t*-butyl)-4,9-methanothia[11]-annulene **11**, reaction with phosphorus pentachloride gives 3,10-dichloro-4,9-methanothia[11]-annulene **12** (Scheme 3) <2002T3647>.



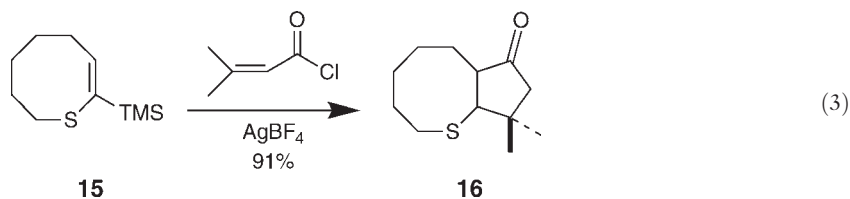
Scheme 3

The transformation of the diketothiocane **4** (Section 14.03.9.4) into a thiocine derivative could be achieved by the electrical reduction of both keto functions in **4**. The cyclic voltograms (CV) of **4** in dimethyl sulfoxide (DMSO) show two reversible half-wave reduction potentials ($^1E_{1/2} = -0.78$ V, $^2E_{1/2} = -1.17$ V) and a little difference between two potentials compared with those of anthraquinone was observed, indicating greater stability of the radical anion **13** and dianion **14** in Scheme 4 than corresponding species of anthraquinone <2001H(54)159>.



Scheme 4

Dihydrothiocienes attached with a trialkylsilyl group react with acylchlorides to form bicyclic thiofunctionalized enones. Thus, the α -silylvinylsulfide **15** reacts with 3,3-dimethyl acryloyl chloride according to Equation (3) to provide the bicycle **16** in 91% yield <1997PS451>.



14.03.8 Reactivity of Substituents Attached to Ring Heteroatoms

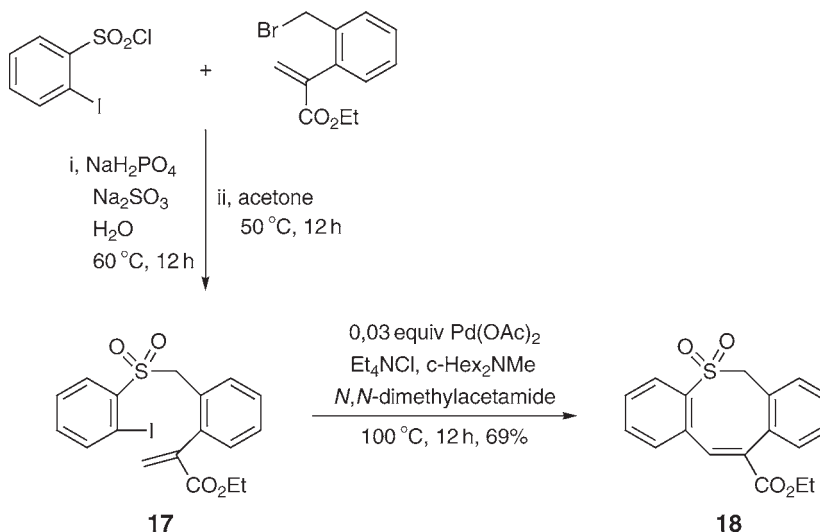
There was no literature concerning this item.

14.03.9 Ring Syntheses

In all subsections syntheses have been performed. Particularly, new methods to prepare fully conjugated eight-membered were reported.

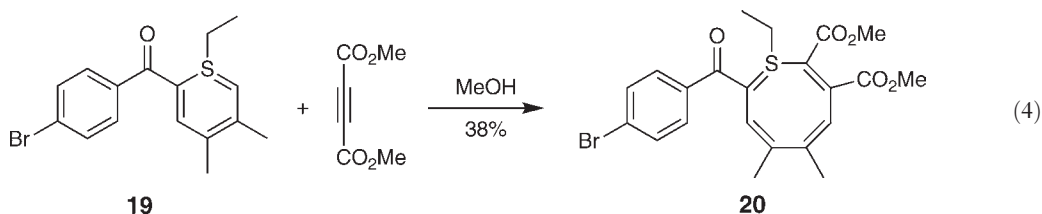
14.03.9.1 Fully Conjugated Rings

As yet no satisfactory syntheses to form dibenzothiocienes were noted (as in CHEC-II(1996)). However, using intramolecular Heck coupling between aryl halide and acrylate moieties in **17** affords 1,1-dioxo-2*H*-dibenzo[*b,f*]thiocine-5-carboxylic acid ethyl ester **18** in 69% yield (Scheme 5) <2004OL3005>.



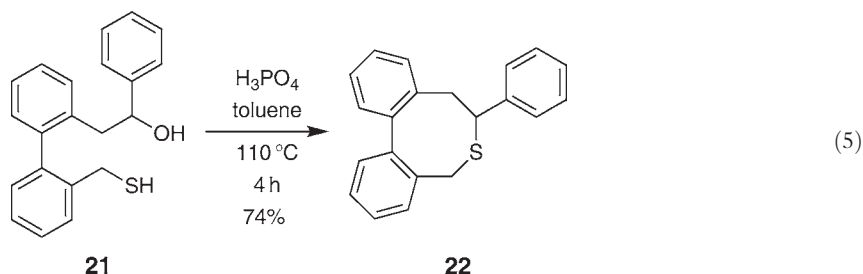
Scheme 5

The chemical reactivities of 1-alkylthiabenzene were investigated. The electrophilic addition of dimethyl acetylenedicarboxylate (DMAD) to 1-ethylthiabenzene **19** affords the fully conjugated thiocine derivative **20** in 38% yield (Equation 4) <2000ITE50>.

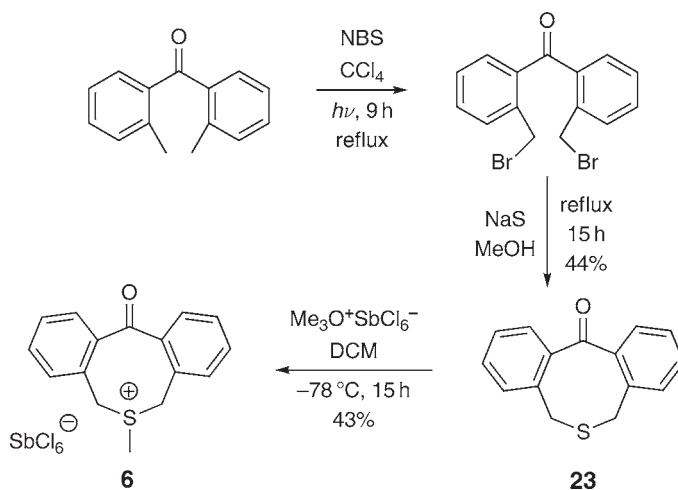


14.03.9.2 Dihydro Derived Rings

The cyclization of the sulfanylalcohol **21** under acidic conditions gives the sulfide 7-phenyl-7,8-dihydro-5-*H*-dibenzo[*c,e*]thiocine **22** in good yield of 74% (Equation 5) <2001TL2469, 2005T9082>.



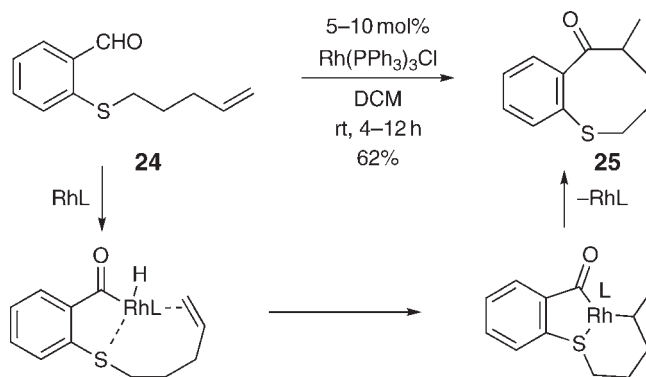
Preparations of 5-oxo-2,8-dihydro-5-*H*-dibenzo[*b,e*]thiocin **23** and the corresponding *S*-methylthiocinium hexachloroantimonate **6** have been described (Scheme 6) <2002J(P1)2704>. The methylthiocinium salt **6** has been employed in a [2,3]-sigmatropic shift reaction (Section 14.03.6).



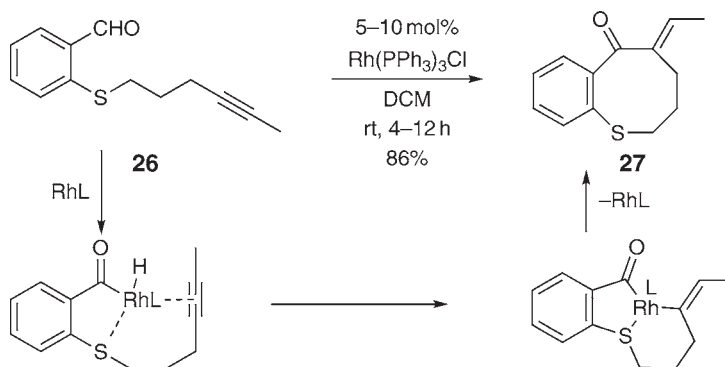
Scheme 6

14.03.9.3 Tetrahydro Derived Rings

Tetrahydrothiocines **25** or **27** can be synthesized from S-containing ω -alkenals **24** or alkynals **26** via chelation-assisted hydacylation catalyzed by rhodium(I) (Schemes 7 and 8), respectively <2002TL7031>.



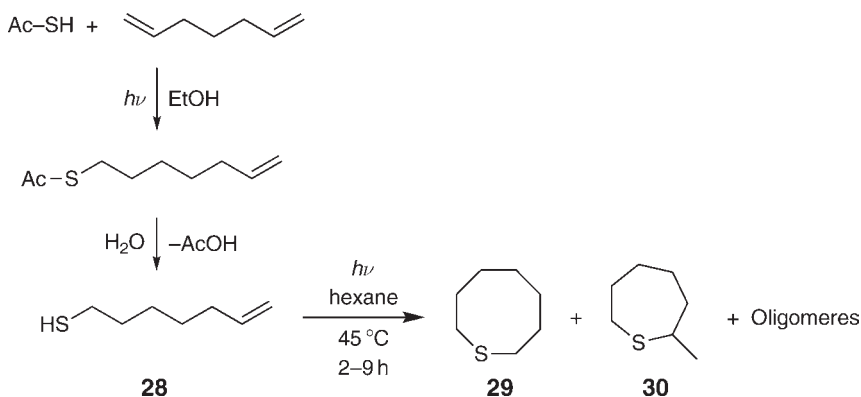
Scheme 7



Scheme 8

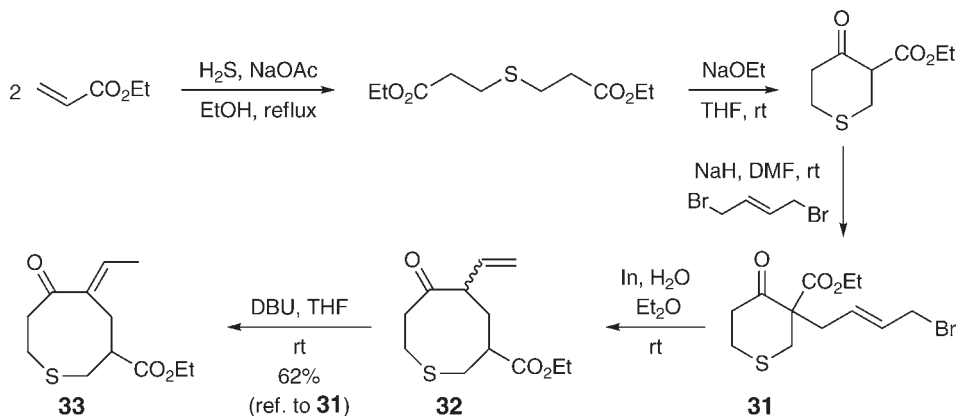
14.03.9.4 Fully Saturated Rings

Thiocane **29** can be synthesized by a photoinduced intramolecular cyclization reaction of 1-heptene-7-thiol **28** in an *endo*- and an *exo*-mode (Scheme 9). Thereby **29** and its *exo*-isomer **30** are formed in the ratio 1 : 1.2. However, **28** mainly undergoes intermolecular addition resulting in oligomeric compounds (65%) [1995PS47].



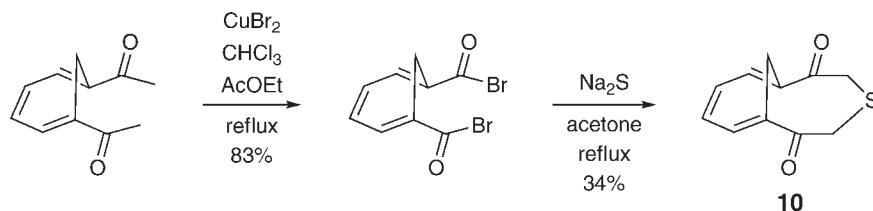
Scheme 9

An indium-mediated ring-expansion reaction of a cyclic thioether derivative **31** in aqueous medium leads to the eight-membered cyclic thioether derivative **32**, which isomerizes to the more stable conjugated product **33** in 62% yield (referred to **31**) (Scheme 10) <1999SL735>. For a review of such Barbier–Grignard type reactions in water see <1996T5643>.

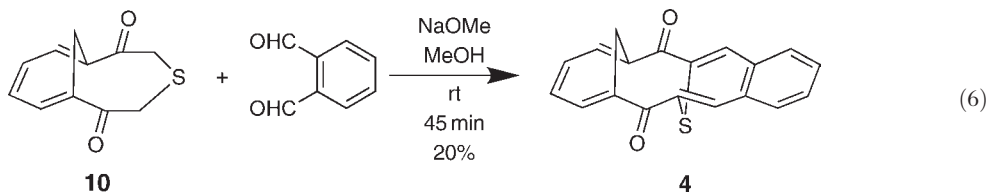


Scheme 10

The diketothiocane 4-thia-1,7-methano[11]annulene-2,6-dione **10** has been prepared according to Scheme 11 in a simple reaction sequence <2001H(54)159>. It is the starting material for further syntheses of enlarged diketothiocanes as *anti*-6,15-epithia-8,13-methanobenzo[e][14]annulene-7,14-dione **4** (Equation 6). Both diketothiocanes **10** and **4** have also been transformed into dihydro thiocines by reaction of keto functions (Section 14.03.7).



Scheme 11



Saturated sulfides have been prepared from unsaturated sulfides by low-pressure hydrogenation with a combination of heterogeneous and homogeneous ruthenium catalysts as Ru_2O and $\text{Ru}_3\text{O}(\text{OAc})_6^+ \text{AcO}^-$ in satisfactory to good yields, thus minimizing side reactions <1996SC899>.

References

- 1993MI5648 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
 1995PS47 S. Kirpichenko, L. Tolstikova, E. Suslova, A. Albanov, and M. Voronkov, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1995, **106**, 47.
 1996CHEC-II(9)449 J. E. Toomey; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 449.

- 1996SC899 V. Cere, F. Massaccesi, S. Pollicino, and A. Ricci, *Synth. Commun.*, 1996, **26**, 899.
- 1996T5643 C.-J. Li, *Tetrahedron*, 1996, **52**, 5643.
- 1997PS451 B. F. Bonini, M. Fochi, and G. Mazzanti, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1997, **120–121**, 451.
- 1999SL735 C.-J. Li and D.-L. Chen, *Synlett*, 1999, 735.
- 2000ITE50 H. Shimizu, N. Kudo, T. Kataoka, and M. Hori, *ITE Lett. Batteries, New Technol. Med.*, 2000, **1**, 50.
- 2001H(54)159 S. Zuo, S. Kuroda, M. Oda, S. Kuramoto, Y. Mizukami, A. Fukuta, Y. Hirano, T. Nishikawa, S. Furuta, R. Miyatake, S. I. Shaheen, T. Kajioka, and M. Kyogoku, *Heterocycles*, 2001, **54**, 159.
- 2001MI11040 J. K. Kang and C. B. Musgrave, *J. Chem. Phys.*, 2001, **115**, 11040.
- 2001TL2469 M. Yus and F. Foubelo, *Tetrahedron Lett.*, 2001, **42**, 2469.
- 2002JOC388 H. Wandel and O. Wiest, *J. Org. Chem.*, 2002, **67**, 388.
- 2002J(P1)2704 K. Okada and M. Tanaka, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2704.
- 2002T3647 R. Miyatake, S. Kuroda, A. Taketani, and M. Oda, *Tetrahedron*, 2002, **58**, 3647.
- 2002TL7031 H. D. Bendorf and Ch. M. Colella, *Tetrahedron Lett.*, 2002, **43**, 7031.
- 2004OL3005 L. A. Arnold, W. Luo, and R. K. Guy, *Org. Lett.*, 2004, **6**, 3005.
- 2004PCP310 H. S. Rzepa and N. Sanderson, *Phys. Chem. Chem. Phys.*, 2004, **6**, 310.
- 2005MI848 T. Strassner and M. A. Taige, *J. Chem. Theory Comput.*, 2005, **1**, 848.
- 2005T9082 F. Foubelo, B. Moreno, T. Soler, and M. Yus, *Tetrahedron*, 2005, **61**, 9082.

Biographical Sketch



Heiner Eckert was born in Munich, Germany, where he gained his diploma in chemistry at the Technical University of Munich (TUM) in 1973, going on to receive his Ph.D. with *summa cum laude* under Prof. Ugi 3 years later. In 1977 he founded *Dr. Eckert GmbH*, a company specializing in developing fine chemicals and processes for chemical production, which he sold in 2002. In 2005 Eckert gained his Habilitation and the *venia legendi* in Chemistry at the TUM. At present he is working as *Privatdozent* at the TUM, with his research interest in development of new methods and reactions in chemical syntheses. Eckert has published numerous scientific papers and patents (natural product syntheses, metal phthalocyanine catalysts) as well as the book *Phosgenations – A Handbook*, and indeed the *Eckert hydrogenation catalysts* are named for him. His invention of the solid reagent triphosgene as a safe and effective substitute for the dangerous gas phosgene is nowadays commonly used in every laboratory worldwide. His current research is focused on developing additional functionalizing of selected components of *Multi-Component-Reactions*.

14.04

Eight-membered Rings with Two Heteroatoms 1,2

G. Cirrincione and P. Diana

Università degli Studi di Palermo, Palermo, Italy

© 2008 Elsevier Ltd. All rights reserved.

14.04.1	Introduction	100
14.04.2	Rings with Two Nitrogens (1,2-Diazocines)	101
14.04.2.1	Theoretical Methods	101
14.04.2.2	Experimental Structural Methods	102
14.04.2.3	Thermodynamic Aspects	107
14.04.2.4	Reactivity of Nonconjugated Rings	108
14.04.2.5	Reactivity of Substituents Attached to Ring Carbon Atoms	110
14.04.2.6	Reactivity of Substituents Attached to Ring Heteroatoms	111
14.04.2.7	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	112
14.04.2.7.1	Ring syntheses from C_6N_2 units	112
14.04.2.7.2	Ring syntheses from $C_6 + N_2$ units	114
14.04.2.7.3	Ring syntheses from $C_3N + C_3N$ units	117
14.04.2.8	Ring Syntheses by Transformation of Another Ring	118
14.04.2.9	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	120
14.04.2.10	Important Compounds and Applications	120
14.04.3	Rings with One Nitrogen and One Oxygen (2H-1,2-Oxazocines)	121
14.04.3.1	Theoretical Methods	121
14.04.3.2	Experimental Structural Methods	122
14.04.3.3	Thermodynamic Aspects	124
14.04.3.4	Reactivity of Nonconjugated Rings	124
14.04.3.5	Reactivity of Substituents Attached to Ring Carbon Atoms	126
14.04.3.6	Reactivity of Substituents Attached to Ring Heteroatoms	127
14.04.3.7	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	127
14.04.3.7.1	Ring syntheses from C_6NO units	127
14.04.3.7.2	Ring syntheses from $C_6 + NO$ units	127
14.04.3.8	Ring Syntheses by Transformation of Another Ring	131
14.04.3.9	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	133
14.04.3.10	Important Compounds and Applications	133
14.04.4	Rings with One Nitrogen and One Sulfur (2H-1,2-Thiazocines) or One Oxygen and One Sulfur (1,2-Oxathiocins)	134
14.04.4.1	Experimental Structural Methods	134
14.04.4.2	Thermodynamic Aspects	135
14.04.4.3	Reactivity of Nonconjugated Rings	135
14.04.4.4	Reactivity of Substituents Attached to Ring Carbon Atoms	137
14.04.4.5	Reactivity of Substituents Attached to Ring Heteroatoms	137

14.04.4.6	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	137
14.04.4.6.1	Ring syntheses from C ₆ NS units	137
14.04.4.6.2	Ring syntheses from C ₄ S + C ₂ N units	138
14.04.4.6.3	Oxathiocin ring synthesis	138
14.04.4.7	Ring Syntheses by Transformation of Another Ring	138
14.04.4.8	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	138
14.04.4.9	Important Compounds and Applications	139
14.04.5	Rings with Two Oxygens (1,2-Dioxocins)	139
14.04.5.1	Theoretical Methods	139
14.04.5.2	Experimental Structural Methods	140
14.04.5.3	Thermodynamic Aspects	144
14.04.5.4	Reactivity of Nonconjugated Rings	145
14.04.5.5	Reactivity of Substituents Attached to Ring Carbon Atoms	148
14.04.5.6	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	150
14.04.5.6.1	Natural products	150
14.04.5.6.2	Ring syntheses from C ₆ O ₂ units	151
14.04.5.6.3	Ring syntheses from C ₆ + O ₂ units	151
14.04.5.7	Ring Syntheses by Transformation of Another Ring	152
14.04.5.8	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	158
14.04.5.9	Important Compounds and Applications	158
14.04.6	Rings with Two Sulfurs (1,2-Dithiocins)	160
14.04.6.1	Theoretical Methods	160
14.04.6.2	Experimental Structural Methods	160
14.04.6.3	Thermodynamic Aspects	161
14.04.6.4	Reactivity of Nonconjugated Rings	161
14.04.6.5	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	161
14.04.6.5.1	Ring syntheses from C ₆ S ₂ units	161
14.04.6.5.2	Ring syntheses from C ₆ + S ₂ units	163
14.04.6.6	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	164
14.04.6.7	Important Compounds and Applications	164
14.04.7	Further Developments	164
References		164

14.04.1 Introduction

Eight-membered rings with two heteroatoms adjacent to each other were treated previously in few pages in CHEC(1984) that covered the literature through 1982, in volume 7 in which all eight-membered heterocycles with one or more heteroatoms were treated in a single chapter (5.19). The Section 5.19.4 was essentially directed to diazocines, the best known members of this class of heterocycles. Also oxazocines (Section 5.19.5), dioxocanes (Section 5.19.7.1), and dithiocanes (Section 5.19.8.3) have been very briefly reviewed. In CHEC-II(1996), which covered the literature from 1983 to 1995, the eight-membered rings with two heteroatoms in a 1,2-relationship were

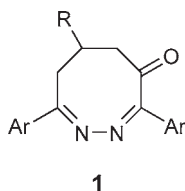
treated in volume 9 in the dedicated chapter 21 of 36 pages. That chapter did not cover compounds in which the ring heteroatoms were members of another fused ring and bridged polycycles. This chapter covers the literature from 1996 to 2006 and also reports the articles published in 1995 that were not reported in CHEC-II(1996). In this edition, in addition to the uncondensed derivatives, eight-membered 1,2-heterocycles fused to five-, six-, and seven-membered carbocycles or heterocycles are covered, although in one case a four-membered fused ring was occasionally reported. Bridged heterocines, which actually constitute the majority of the compounds reported, are covered. Also, in this chapter, as happened in the previous one, the interest in this class of heterocycles has been driven by the pharmacological activity shown by some compounds or some potentially important industrial energy applications. In particular, the oxygen-bridged pyrazolo-fused 1,2-diazocines were active as herbicides and growth-inhibitors; dibenzo-1,2-diazocine dioxides showed anticancer activity; methylene bridged 1,2-dioxocins showed remarkable antimalarial activity against chloroquine-resistant *Plasmodium* strains; and 1,2-oxathiocin derivatives are the key components for the synthesis of a polymer used for proton-exchange membrane fuel cells (PEMFCs). As in CHEC-II(1996), nomenclature for the eight-membered rings with two heteroatoms possessing a 1,2-relationship follows the standard system, with the exceptions introduced for the completely reduced derivatives. The six parent unsaturated systems are 1,2-diazocine, 2*H*-1,2-oxazocine, 2*H*-1,2-thiazocine, 1,2-dioxocin, 1,2-oxathiocin, and 1,2-dithiocin. Only three ‘fully conjugated’ 1,2-diazocines have been prepared and the section “Reactivity of Fully Conjugated Rings” is absent from all six system sections. Hydrogenated analogues are generally named as di-, tetra-, hexa-, or, in the case of diazocines, octa- or perhydro-derivatives. The completely saturated derivatives are referred to as diazocane, oxazocane, thiazocane, dioxocane, oxathiocane, and dithiocane. The main change in this chapter with respect to CHEC-II(1996) is related to the “Theoretical Methods” section. Such a section in CHEC-II(1996) was unique, placed immediately after the introduction, and dealt with all the classes of eight-membered heterocycles with two heteroatoms. In this edition, each paragraph dealing with a single class of heterocycles has its own theoretical methods section. The “Experimental Structural Methods” section has received a strong emphasis with some exceptions; the great majority of the reported derivatives have been adequately characterized. As previously done in CHEC-II(1996), all six systems are discussed separately with each discussion following the same general format. In the case that a particular section is not mentioned, it means that no chemistry has been reported. In the past decade, comprehensive reviews on 1,2-heterocines did not appear due to the complete coverage that these systems received in CHEC-II(1996); however, the antimalarial activity and the related mode of action of some 1,2-dioxocins has been reviewed <2001CME1803, 2002MI1661>.

14.04.2 Rings with Two Nitrogens (1,2-Diazocines)

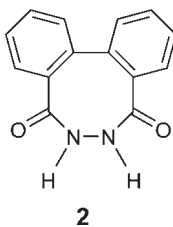
14.04.2.1 Theoretical Methods

Only a limited number of papers reporting theoretical studies on 1,2-diazocines has appeared in the past decade. All have dealt with conformational preferences of partially reduced derivatives. Of course, cross-references will be given to the section on experimental structural methods, in which the theoretical results will be compared with those obtained by experimental structural methods. Also, in the section on thermodynamic aspects, the theoretical results can have a relevant role.

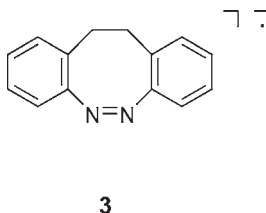
To identify the explicit conformation of the dihydrodiazocine **1** (R = 3-Ph-isoxazol-5-yl; Ar = Ph) as well as the orientation of the C-6 substituent, electronic structure calculations were performed on a model dihydrodiazocine substituted with Ar = R = H. Density functional calculations at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level showed several conformations for the eight-membered ring. The lower energy conformations have a *cis,cis*-orientation of the two C=N bonds. The *cis,trans*- and *trans,cis*-isomers are higher in energy by 7–15 kcal mol⁻¹. For the *cis,cis*-isomer, the two conformations corresponding to energy minima are the twist-boat and twist-boat-chair. The latter conformation, in agreement with the spectral, crystallographic, and kinetic studies (see Sections 14.04.2.2 and 14.04.2.3), was shown to be the major contributor to the thermodynamic isomer <2006JOC2480>.



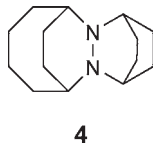
The enantiomerization of 6,7-dihydro-dibenzo[*d,f*][1,2]diazocine-5,8-dione **2** was investigated using quantum-mechanical methods. At the density functional theory (DFT) B3LYP/6-31G(d,p) level, two enantiomeric C_2 -symmetric transition states (TSs) and two enantiomeric pathways were found with a calculated barrier of $155.6 \text{ kJ mol}^{-1}$. The pathways can be divided into two steps: one involving primarily inversion of the amidic bridge and the other movement of the aromatic rings <2004TA537>.



Molecular geometries for the radical anion **3** and related carbocyclic system were optimized using theoretical calculations by semi-empirical modified neglect of diatomic overlap (MNDO) and AM1 procedures. For these compounds, two geometric forms have to be considered, the twisted form and the tub form. The twisted form, in which the benzene rings are only slightly rotated out of coplanarity with the central N=N (or C=C) bond, is predicted to be more stable than its tub counterpart (energy difference: 6 and 28 kJ mol^{-1} by MNDO and AM1, respectively, for **3** as well as 26 and 28 kJ mol^{-1} by MNDO and AM1, respectively, for the carbocyclic system) <1996HCA307>.



NCG calculations on the AM1-UHF geometry-optimized structure of the radical cation of the perhydrodiazocine **4** were performed; the relationships between the calculated energy differences and the observed were examined and led to a *syn*-pyramidal geometry possessing an N–N lone pair–lone pair twist angle $\theta = 9.3^\circ$ (see Section 14.04.2.3) <1998JOC2536>.



14.04.2.2 Experimental Structural Methods

X-Ray crystallography studies on 1,2-diazocines are limited to six derivatives. A single crystal X-ray analysis was performed on 3,8-diphenyl-6-(3-phenylisoxazol-5-yl)-6,7-dihydro-5*H*-[1,2]diazocin-4-one **1** and confirmed the results obtained with theoretical calculations conducted on a model of **1** in which Ar = R = H (*vide infra*). In fact, the major contribution to the thermodynamic isomer is given by the twist-boat-chair conformer having the substituent in position 6 in a pseudoequatorial orientation relative to the eight-membered ring <2006JOC2480>.

The X-ray diffraction of racemic 1,2-diazocinone **2** was examined to elucidate the conformation, configuration, and solid-state H-bonding capabilities, which might be important for understanding the analgesic activity of its homologues. Compound **2** forms isomorphous inclusion compounds with MeCN and EtOH. The density of the EtOH solvate is higher than that of the MeCN solvate. The cell dimensions of both are very close to each other. The H-bonding network in both structures is typical for racemic chiral dilactams, since this heterocycle forms H-bonded centrosymmetric zigzag tapes with $R^2_2(8)$ eight-membered rings and strictly alternating enantiomers. Also **2** shows the N–N bond length, $1.393 \text{ \AA}$, and the C(8)–N(1)–N(2)–C(3) torsion angle, 93.8° , close to the values found in acyclic dibenzoylhydrazine, and the two nonequivalent N–H $\cdots$ O hydrogen bonds (2.837 and $2.898 \text{ \AA}$). The dihedral angle C(4)–C(5)–C(6)–C(7) (63.7° for the (*S*)-enantiomers) characterizes the twist of the biphenyl core (Figure 1) <2004TA537>.

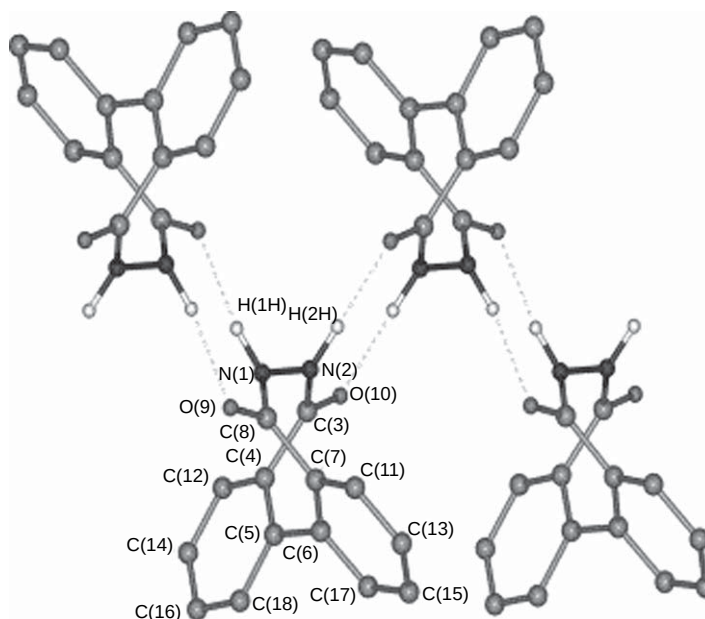
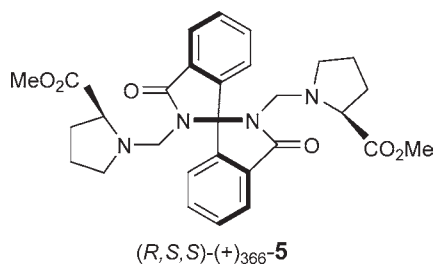


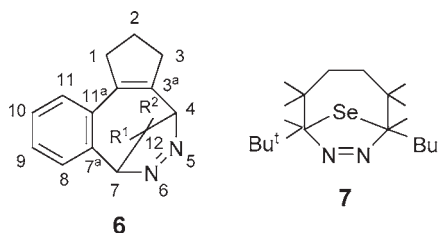
Figure 1 Centrosymmetric zigzag tapes and atom numbering in the crystal structure of **2**.

The X-ray diffraction analysis established that the structure of **4** is antipyramidal having the N–N lone pair–lone pair twist angle of $\theta = 164.4^\circ$ <1998JOC2536>.

The X-ray diffraction analysis was conducted on the proline-methylated **5**, the diastereomer (*R,S,S*)-(+)₃₆₆-**5**, which was obtained by reaction of racemic **2** with the chiral derivatizing agent (*S*)-(-)-*N*-(methoxymethyl)proline methyl ester, followed by crystallization from MeCN. The absolute configuration of **5** was unambiguously determined with the known (*S*)-configuration of the prolinomethyl residue (Figure 2) <2004TA537>.



The X-ray crystallography was also utilized to determine the structure of 2,3,4,7-tetrahydro-4,7-methano-12-phenyl-1*H*-cyclopenta[*e*][2,3]benzodiazocine **6a** ($R^1 = \text{H}$, $R^2 = \text{Ph}$) <2000J(P1)1139> and 7,8-diaza-1,6-di-*t*-butyl-2,2,5,5-tetramethyl-9-selenabicyclo[4.2.1] nonan-7-ene **7** <2000JOC1799>.



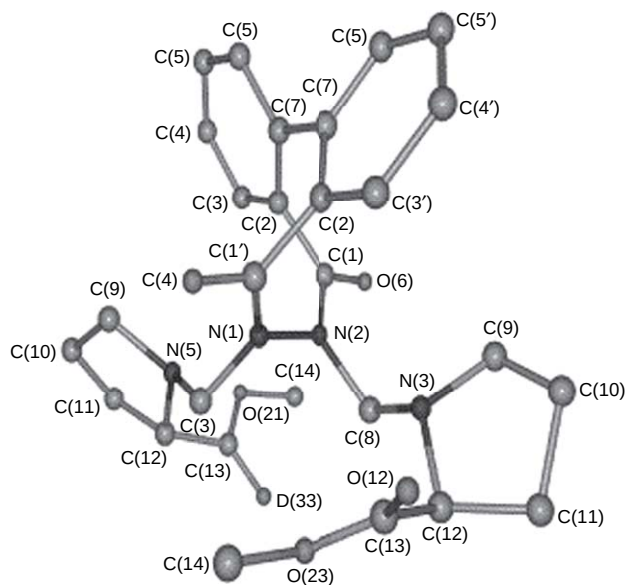
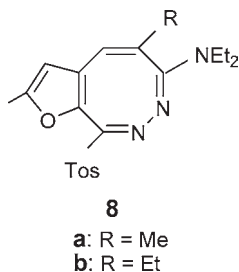


Figure 2 Crystal structure of **5**.

Besides several nuclear magnetic resonance (NMR) studies directed toward conformational analysis and interaction with proteins reported below, most NMR data have been regarded as routine in the characterization of these heterocycles. The chemical shifts of the only ring hydrogen of the two fully conjugated 1,2-diazocines **8** were found in the expected range, 5.91–5.93 ppm <1996H(43)199>. The reduced diazocines showed their protons adjacent to nitrogen resonances in the range 3–5 ppm depending on the functionality present. The other methylene protons signals were found in the range 0.8–2.6 ppm <1995J(P1)167, 1996T13695, 1998CPB674, 2000H(53)151>. In the case of diazocines having bridged hydrogens, the signals of the protons adjacent to nitrogen are found in the range 4.80–6.00 ppm and the bridged hydrogens resonate at 5.3–5.9 ppm <2000J(P1)1139, 2002ARK67>. Regarding the signals of N-substituents, the methyl was found at 3.0–3.3 ppm <1996T13695>, while in the case of the N-unsubstituted diazocinone **2**, the NH signal was found to be at ~10 ppm <2004TA537>. In diazocines with a greater degree of hydrogenation, the NH peaks were found at higher fields 3.7–8.0 ppm <2004OL4351>.



Although the ^{13}C resonances of the fully conjugated **8** were reported, the authors neither assigned the signals nor reported the signal multiplicities <1996H(43)199>. The ^{13}C resonances of carbons adjacent to nitrogen in hydrogenated diazocines were found in the range 53–71 ppm, whereas the other ring carbons were found at 22–32 ppm <1998CPB674, 2004OL4351>. The resonances of carbons adjacent to nitrogen in bridged diazocines were generally at 83–98 ppm <2000J(P1)1139, 2002ARK67>. The carbonyl carbons in position 3 and/or 8 had chemical shifts of typical amides, 172–182 ppm <2004TA537, 2004OL4351>. Carbonyl carbon resonances in other ring positions were found at values compatible with those of cyclic ketones, 202–204 ppm <2006JOC2480>. Carbonyl carbons bounded

to nitrogen resonate at 151–155 ppm in the case of carbamoyl esters <2004OL4351> or 174–175 ppm in the case of benzoyl derivatives <1998CPB674>.

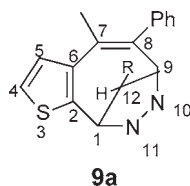
The ^{77}Se NMR spectrum of **7** was measured and the signal was found at 228 ppm <2000JOC1799>.

The ^1H NMR spectrum of dihydrodiazocinone **1** bearing phenyl moieties at C-3 and C-8 revealed two conformations of the eight-membered ring that were non-interconverting on the NMR timescale at 25 °C showing two distinct singlets for the C-4 proton of the isoxazole ring bound at the C-6 of the diazocine ring. This observation was strengthened by the doubling of the signals in the ^{13}C NMR spectrum. Coupling constants for the C-6 methyne proton to the adjacent C-5 and C-7 methylene protons provided further conformational insight. These coupling constants indicated that the dihedral angles involving the methyne proton and adjacent methylene protons differ between the two conformers. This could result from conformer differences in the geometry of the dihydrodiazocinone ring and/or in the orientation of the isoxazole substituent. Monitoring of the ^1H NMR signal of the isoxazole C(4)H of both conformers was utilized to investigate the kinetics of the interconversion between the kinetic and thermodynamic conformers <2006JOC2480>.

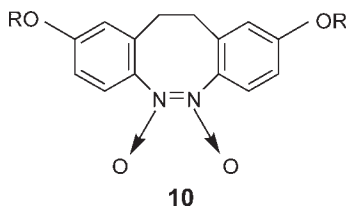
The ^1H NMR analysis was used for (*R*)-(+)-**2**, obtained from (*R,S,S*)-(+)-**366-5** by acid cleavage of the chiral auxiliary. The ee (>90%) was estimated with shift reagent europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] ($\text{Eu}(\text{tfc})_3$) in CDCl_3 : in the enantiomer, there appeared a doublet at 7.27 ppm with no additional splitting, whereas for the racemate there was a 0.05 ppm shift <2004TA537>.

The ^1H NMR spectra of **6** were at first glance unusual since no coupling was observed between the protons at C-4 and C-7 and the bridged protons *trans* to the azo group as in **6a** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$), but in compounds, in which the other bridged proton was present, as in **6b** ($\text{R}^1 = \text{R}^2 = \text{H}$), a strong coupling of this latter was observed ($J = 7\text{--}8\text{ Hz}$). This confirmed that in **6** having a chiral bridged carbon atom ($\text{R}^1 = \text{H}$, $\text{R}^2 \neq \text{H}$), the hydrogen atoms at C-4 and C-12 have the same relative stereochemistry as in **6a** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$), which was confirmed by X-ray crystallography (see above) <2000J(P1)1139>.

The lack of the spin coupling between the H-12 and its adjacent protons was also observed in the ^1H NMR spectrum of the methano-bridged thieno[2,3-*d*][1,2]diazocine **9a** ($\text{R} = \text{Ph}$), due to their nearly orthogonal orientation <2002ARK67>.



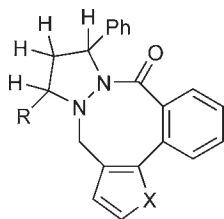
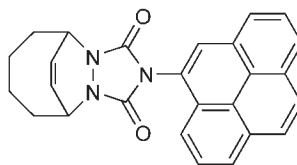
NMR methods were useful to demonstrate that 2,9-dimethoxy-11,12-dihydrodibenzo[*e,g*] [1,2]diazocine 5,6-dioxide **10a** ($\text{R} = \text{Me}$) binds to Bcl-XL, a protein which regulates programmed cell death (apoptosis). Thus, the heteronuclear single quantum correlation (HSQC) spectrum of ^{15}N -labeled Bcl-XL with **10a** showed that most of the residues, whose chemical shifts are affected by the binding of **10a**, were around the BH3 binding pocket of Bcl-XL <2001JME4313>.



The NMR techniques, such as nuclear Overhauser effect (NOE) or two-dimensional total correlated spectroscopy (2-D TOCSY), were utilized to establish the stereochemistry of hydrogenated <1996T13695> or condensed 1,2-diazocines <2003T4451>. No studies on fragmentation patterns of 1,2-diazocines have been reported in the past decade. Unfortunately, the majority of the papers dealing with 1,2-diazocines reporting mass spectral data in their experimental sections only mentioned the molecular or quasi-molecular ions <1996T13695, 1998CPB674, 2000H(53)151, 2001JME4313, 2002ARK67, 2003T4451, 2003WO038060, 2004WO099162, 2004TL3757>. In fact, for all of the 1,2-diazocines, their mass spectra show the parent ions with the exception of **7**, which lost nitrogen <2000JOC1799>.

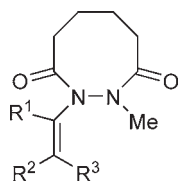
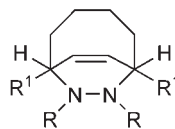
The fast atom bombardment (FAB) mass spectra of **6** ($\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CO}_2\text{Me}$; $\text{R}^1 = \text{R}^2 = \text{Me}$) exhibited the MH^+ and molecular ions as well as the common major fragmentations of

m/z M-28, likely due to loss of nitrogen and m/z M-58 probably obtained from the M-28 ion upon cleavage of the cyclopentene ring <2000J(P1)1139>. The electron ionization mass spectra of furano- or thieno-fused benzodiazocines **11** (R = H, X = S; R = Ph, X = S; R = 4-O₂N-C₆H₄, X = O; R = 2-F-C₆H₄, X = O; R = 4-Me₂N-C₆H₄, X = S; R = 3-F₃C-C₆H₄, X = S; R = 3-F₃C-C₆H₄, X = O; R = 3-MeO-C₆H₄, X = S; R = 3-MeO-C₆H₄, X = O), in addition to the molecular ion, show main fragments of M-105 probably involving rupture of the diazocine ring and extrusion of the CPh portion, and ions of m/z 200 or 184 in the case of thieno or furano derivatives, respectively, likely originating by cleavage of the diazocine ring with extrusion of the pyrazoline moiety <2003T4451>. The chemical ionization mass spectra of triazolodiazocine **12** displayed the quasi-molecular (m/z = 408), the molecular ion (m/z = 407), and a major fragment of m/z 243 (M-CON-Pyrenyl), which shows the m/z 214 ion by CO loss <1995J(P1)167>.

**11****12**

Infrared (IR) data reported for the 1,2-diazocine derivatives are fragmentary. Compounds **1** (R = 3-Ph-isoxazol-5-yl, Ar = Ph, 4-Cl-C₆H₄, 4-Br-C₆H₄, 4-Me-C₆H₄; R = 3-(4-MeO-C₆H₄)-isoxazol-5-yl, Ar = Ph, 4-Cl-C₆H₄, 4-Br-C₆H₄, 4-Me-C₆H₄) showed the stretching of the carbonyl at position 4 in the range 1697–1714 cm⁻¹, while the N=C vibrations were found at 1428–1529 cm⁻¹ <2006JOC2480>. The carbonyl stretching in **12** was observed at 1760 cm⁻¹ <1995J(P1)167>.

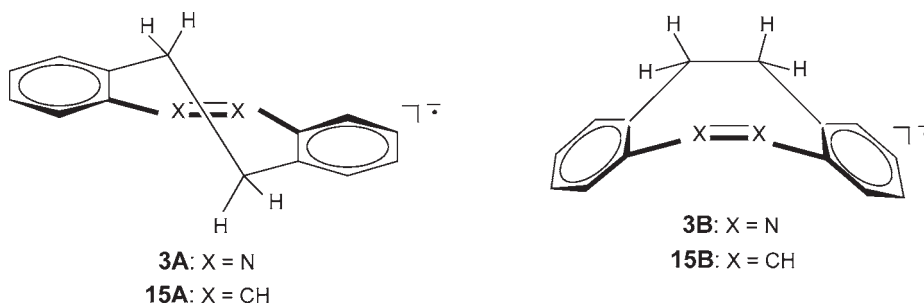
Dicarbonyl-1,2-diazocines **13** exhibited carbonyl absorptions in the range 1656–1661 cm⁻¹ <1996T13695>. Bridged 1,2-diazocines **14** having R = CPh and R¹ = CO₂Me showed the benzoyl carbonyl and ester carbonyl absorptions at 1684 and 1750 cm⁻¹, respectively. The N-unsubstituted derivatives (R = H) having R¹ = CO₂H showed the NH and OH stretching at 3462 and 3312 cm⁻¹, while the carbonyl band was found at 1714 cm⁻¹ <1998CPB674>. Other diazocine NH vibrations were observed at 3298 cm⁻¹ <2004T3757>. The N=N absorption was observed at 1472 cm⁻¹ <2000JOC1799>.

**13****14**

The ultraviolet (UV) spectrum of **2** has an absorption maximum at 202 nm in either MeOH or MeCN and two shoulders at 270 and 235 nm, while the circular dichroism (CD) spectrum shows two positive bands ca. 240 and 220 nm ($\Delta\epsilon$ 30 and 42, respectively) and negative absorbance below 200 nm. The long-wavelength positive band at 240 nm was assigned to the A-band of a negatively twisted biphenyl moiety (angle $-90^\circ < \theta < 0^\circ$). The high-energy positive band at 220 nm and the negative CD-absorbance below 200 nm correlate in magnitude and shape to bands observed in the (*R*)-configured bridged biphenyl derivatives. Both assignments agree with the configuration for (+)-**2** derived from X-ray analysis (see above) <2004TA537>.

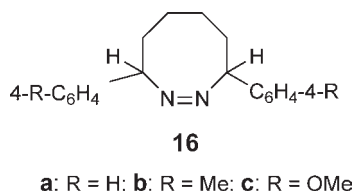
The radical anions of 5,6-dihydro-dibenzo[*c,g*][1,2]diazocine **3** and its carbocyclic analogue **15** (X = CH) were characterized by electron spin resonance (ESR) and electron-nuclear double resonance (ENDOR) spectroscopy. The radical anions were generated from their neutral precursors with potassium in 1,2-dimethoxyethane (DME). In contrast with the well-resolved ESR spectrum of the hydrocarbon radical anion **15**, that of its azo counterpart **3** suffers from line broadening by a pronounced ¹⁴N-hyperfine anisotropy, which particularly affects the outer components. Thus, while the ENDOR technique was very helpful but not indispensable for the analysis of the ESR spectrum of **15**, it proved crucial for unraveling the incompletely resolved hyperfine pattern of **3**. The coupling constants observed for **3** are characteristic of π -radicals in which the benzene rings are strongly tilted out of the coplanarity with the π -system bearing the bulk of the spin population (tilt angle $> 50^\circ$). Such a tilt was predicted by semi-empirical MNDO and AM1 calculations for the benzene rings in the tub form **3B** but not in its twisted counterpart (see Section 14.04.2.1). Thus, the hyperfine data for **3** strongly suggest that, unlike **15** and at some variance with the results of the theoretical calculations, this radical anion

prefers the tub **B** over twisted **A** form. The driving force for such a preference must be the tendency to shift the charge and spin population from the benzene moieties to the electronegative azo group [<1996HCA307>](#).



The ESR spectrum of the radical cation of **4** showed a hydrogen splitting over 10G, requiring that it is a significant twist of the N–N bond. Such data are coherent with the X-ray data but in disagreement with theoretical calculations (see above) [<1998JOC2536>](#).

The electron paramagnetic resonance (EPR) spin-trapping technique was used to study the photochemical-, thermal-, and electrochemical-initiated decomposition of hydrogenated 1,2-diazocines **16** [<1998MRC13>](#).

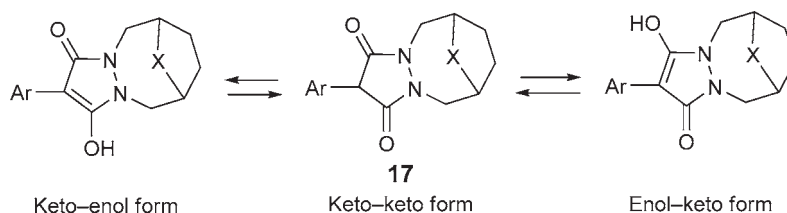


14.04.2.3 Thermodynamic Aspects

The 1,2-diazocine derivatives, reported since 1995, show a variety of phase behavior. Several compounds are reported to be oils, generally colorless or yellow [<2004OL4351, 2000J\(P1\)1139, 2002ARK67>](#). Most compounds, for example **11**, are colorless gums [<2003T4451>](#), while others have low melting points (43–77 °C) [<2000H\(53\)151>](#). Several derivatives melt in the range 87–190 °C depending on the functionality present [<1996H\(43\)199, 1996T13695, 2000JOC1799, 2000J\(P1\)1139, 2004TL3757, 2006JOC2480>](#). Derivatives with higher melting points have functionality that allows intermolecular interactions that stabilize the solid state. Thus, the N-unsubstituted diazocine-dione **2** melts at 310–311 °C, whereas the corresponding proline-methylated derivative **5** melts at 167–170 °C [<2004TA537>](#); **14**, with R = H and R¹ = CO₂H, melts at 188 °C, and the corresponding methyl ester *N*-benzyl substituents (R = Bn, R¹ = CO₂Me) melt at 102–103.5 °C [<1998CPB674>](#). The seleno-bridged diazocine **7** is thermally stable up to 105 °C, its melting point in the dark [<2000JOC1799>](#).

The reported chromatographic behavior indicates that 1,2-diazocines have good solubility in several common organic solvents. The solvent mixtures for elution in chromatographic purification have generally low to medium polarity, being hexane/EtOAc [<2001JME4313>](#), hexane/Et₂O [<1998CPB674>](#), and dichloromethane (DCM)/MeOH [<2004OL1313>](#).

Pyrazolo-diazocines **17** (X = O, CH₂) exist in equilibrium of the keto–keto, enol–keto, and keto–enol forms (**Scheme 1**) [<1999WO47525, 2000WO47585, 2001WO17351, 2001WO17352, 2001WO17972>](#). Also, pyrazolo-diazocines in which the oxygen or methylene bridge is missing show the same tautomerism [<2001WO17973>](#).



Scheme 1

The NMR spectra of 1,2-diazocine **10a–c** indicated that they exist in an equilibrium mixture of ring-cyclized isomer **A** (diazocine dioxide form) and ring-open isomer **B** (bis-nitroso form) (Scheme 2). The ratio of the two isomers in dimethyl sulfoxide (DMSO- d_6) and CDCl_3 are reported in Table 1. More polar solvents stabilize the cyclized isomer **A** and electron-withdrawing substituents disfavor the ring opening.



Scheme 2

Table 1 Relative abundances of forms **A** and **B** of **10** (Scheme 2)

	<i>A</i>			<i>B</i>		
	<i>DMSO-d</i> ₆	<i>CDCl</i> ₃	<i>R</i>	<i>DMSO-d</i> ₆	<i>CDCl</i> ₃	References
1	1	1	a: Me	2.5	3.7	2001JME4313, 2003WO038060
		1	b: CH_2CF_3		1.5	2004WO099162
		2.9	c: CHF_2		1	2004WO099162

The crude **1** ($R = 3\text{-Ph-isoxazol-5-yl}$; $\text{Ar} = \text{Ph}$) is formed by a mixture of two conformers, as demonstrated by NMR studies (see Section 14.04.2.2). The ratio of the thermodynamic to kinetic conformers is 1.4:1. Heating such a mixture at 119°C for 20 min, the two conformers equilibrated to a 10:1.8 mixture (^1H NMR). Recrystallization of the crude reaction mixture (1.4:1 ratio) from MeOH led to the isolation of the thermodynamic conformer in pure form. The kinetics of this interconversion was studied by NMR in the temperature range of $21\text{--}70^\circ\text{C}$. No evidence of an intermediate was observed indicating a simple isomerization process wherein the conformers approached their equilibrium concentrations by a first-order process. The observed rates yield a kinetic to thermodynamic activation energy of $\sim 21\text{ kcal mol}^{-1}$. The equilibrium constant does not change, within the experimental uncertainties, over the studied temperature range indicating that the energies of the two conformers differ by $\leq 2\text{ kcal mol}^{-1}$ <2006JOC2480>.

The free activation energy for the enantiomerization of **2** in MeCN at 373 K was determined as $\Delta G^\ddagger = 126.7 \pm 0.8\text{ kJ mol}^{-1}$. Compound **2** was obtained in the enantiomerically pure form from one of its prolino-methylated derivatives **5**, the diastereomer (R,S,S)-(+)-₃₆₆-**5**, by cleavage of the chiral auxiliary <2004TA537>.

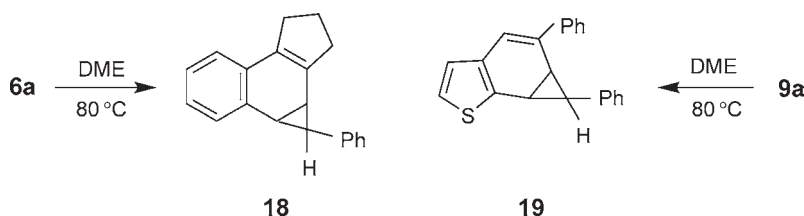
The calculated energy differences for the radical cation of **4** were 5.5 kcal mol^{-1} above the observed values for other bis- N,N' -bicycles. Such a deviation is due to AM1 calculations obtaining untwisted structures, while the real structures are significantly twisted as demonstrated by X-ray analysis of **4** and the ESR spectrum of the radical cation of **4** (see Sections 14.04.2.1 and 14.04.2.2) <1998JOC2536>.

The ^1H NMR spectrum of the diazocine **12** provided clear evidence for a restricted rotation about the pyrenyl–N bond, although the rotamer ratio was not reported <1995J(P1)167>.

In **13**, the prevalent formation of the (*E*)-isomer was observed (*E*):(*Z*) ratio of ca. 9:1 at the end of the reaction). It is worthy to note that in the early part of the reaction the exclusive formation of the (*E*)-isomer was detected. The (*Z*)-isomer was formed by isomerization in the acidic reaction medium. The (*E*)-configuration was deduced from NOE experiments carried out on a (*E*)/(*Z*)-mixture <1996T13695>.

14.04.2.4 Reactivity of Nonconjugated Rings

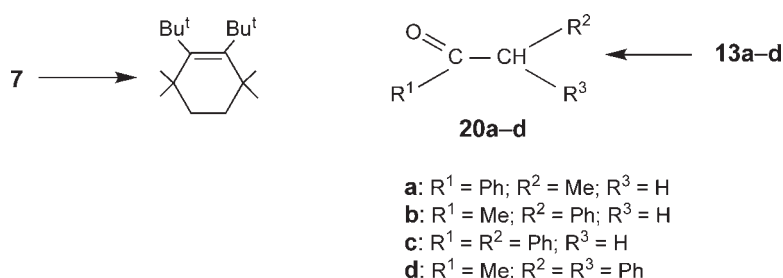
The chemistry of the nonconjugated 1,2-diazocines reported in the past decade essentially involves thermal or hydrolytic elimination of nitrogen and reductive cleavage of the N–N bond to produce diamino derivatives. Thus, thermolysis of methano-bridged 1,2-diazocine **6a** led, by extrusion of nitrogen, to the hydrocarbon **18** as the only product (Scheme 3) <2000J(P1)1139>.



Scheme 3

The same extrusion of nitrogen from thienodiazocine **9a**, under the same reaction conditions, produced the corresponding cyclopropabenzothiophene **19** (Scheme 3) <2002ARK67>.

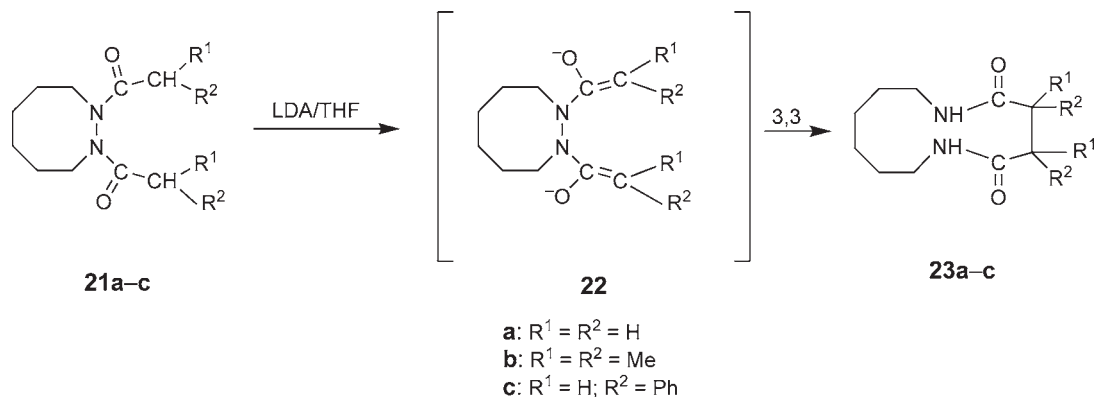
Thermolysis of the seleno-bridged 1,2-diazocine **7**, in absence of solvent at 115–130°C, led by simultaneous extrusion of nitrogen and selenium to the 1,2-di-*t*-butyl-3,3,6,6-tetramethylcyclohexene in 43% yield. The same compound was obtained in lower yield (7%) when the thermolysis of **7** was conducted in refluxing 1,3-dimethyl-2-imidazolidinone (DMI; Scheme 4) <2000JOC1799>.



Scheme 4

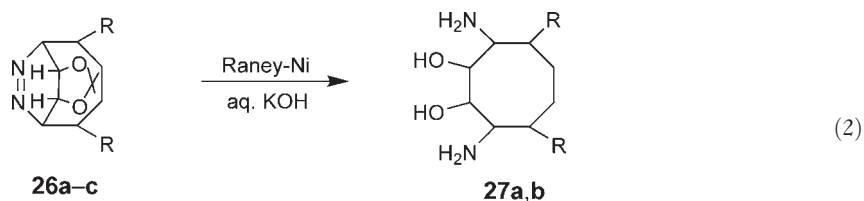
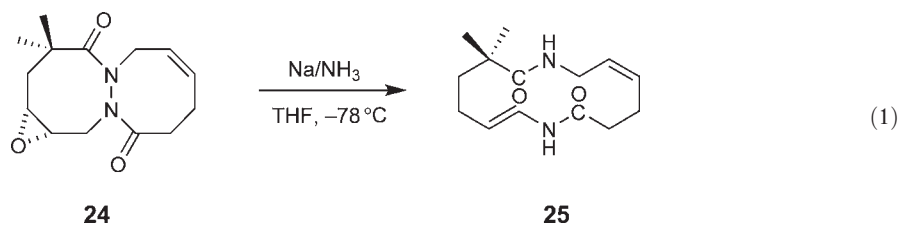
Slow hydrolysis of **13a-d** gave **20a-d**, the ketones of the corresponding starting hydrazones (Scheme 4) <1996T13695>. 1,2-Diazocines **16a-c** showed a remarkable stability to thermally and photochemically initiated decompositions. In the cathodic reduction, **16a-c** decomposed by a route similar to that found in the photochemically and thermally initiated decompositions, forming reactive radicals corresponding to synchronous splitting <1998MRC13>.

N,N'-Diacyl-octahydro-1,2-diazocines **21a-c** were converted into the 1,2-disubstituted succinamides **23a-c** upon treatment with lithium diisopropylamide (LDA) in excess tetrahydrofuran (THF). The C–C bond-forming rearrangement was rationalized in terms of hetero[3,3]sigmatropic shifts of the dienolate precursor of type **22**. The yields of **23a,b** were, however, poor, that is, 12% and 20%, respectively, since the substituents ($\text{R}^1 = \text{R}^2 = \text{H}, \text{Me}$) weakly stabilize the α -carbanion (Scheme 5). In the case of **23c**, the rearrangement furnished the final product in higher yield (87%) due to the stabilizing effect of the phenyl group, adjacent to the enolate. Such an effect compensates for the disadvantage due to the conformation of the starting eight-membered ring, that is not favorable for the rearrangement <2000H(53)151>.



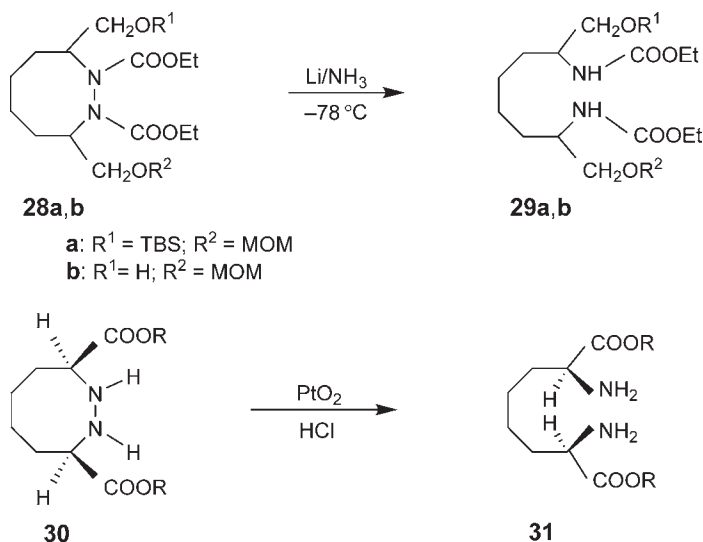
Scheme 5

A further example of N–N reductive cleavage leading to a macrocycle is furnished by the diazocino[1,2-*a*]diazocine **24**, which upon reaction with Na/NH₃ afforded the 14-membered macrocycle enamide **25** in high yield (85%) (Equation 1) <2004OL4351>. Bridged 1,2-diazocines **26a–c** underwent N–N cleavage by catalytic hydrogenation over Raney nickel in aqueous KOH to give the diaminopolyols **27a** and **27b** in high yields (83–96%; Equation 2) <1997TL5485>.



a: R = H; **b:** R = OH; **c:** R = OAc

Reductive N–N cleavage of derivatives **28a** and **28b** gave the open-chain bis-carbamates **29a** and **29b** (Scheme 6) <1998AGE2242>. Another example of N–N reductive cleavage is observed in diazocines **30** (R = H, Me), which were converted into the *meso*-diaminodicarboxylic acid **31** (R = H) or ester (R = Me) by hydrogenolysis with PtO₂ in 2 N HCl (Scheme 6) <1998CPB674>.

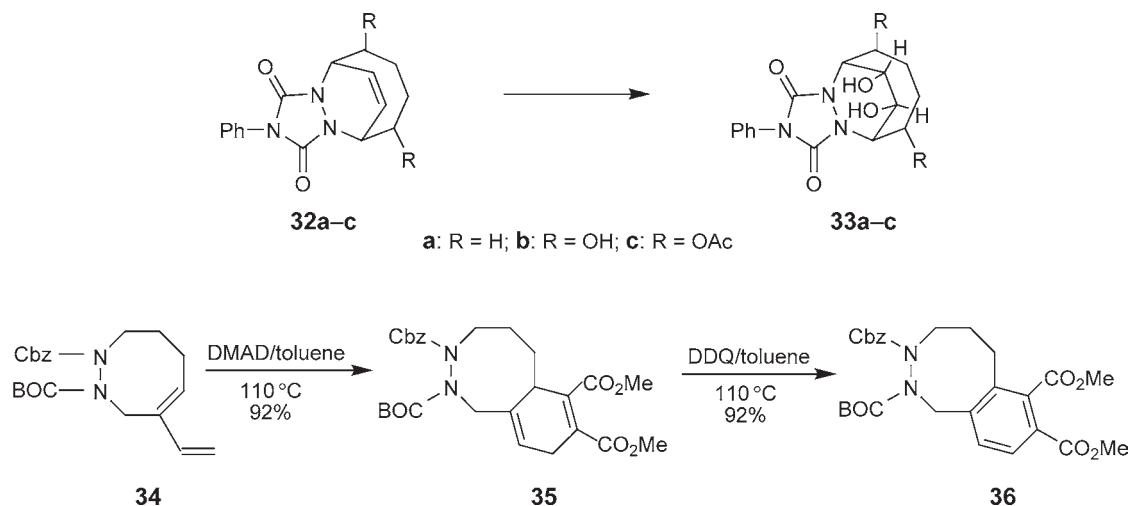


Scheme 6

14.04.2.5 Reactivity of Substituents Attached to Ring Carbon Atoms

Bridged 1,2-diazocines **32a–c**, obtained from cyclooctadienes and 4-phenyl-1,2,4-triazoline-3,5-dione, were useful intermediates for the synthesis of diaminopolyols, core units of various bioactive aminoglycoside antibiotics and antiviral

nucleosides. Thus, **32a–c** were dihydroxylated by standard procedures (OsO_4 , *N*-methylmorpholine oxide) to give **33a–c**. The stereoselectivity of this reaction was excellent ([2.2.4]: >97% *endo*-**33a–c**) (Scheme 7) <1997TL5485>.



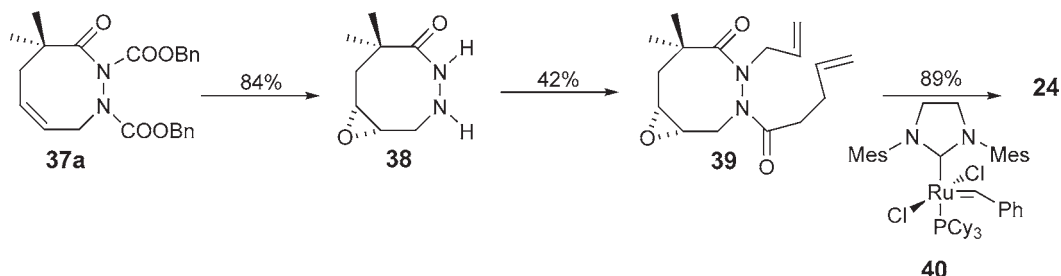
Scheme 7

N-Substituted 1,2-diazocine **34**, containing a conjugated diene moiety, was reacted with dimethyl acetylenedicarboxylate (DMAD) to give the cycloaddition adduct **35** in excellent yield. The latter was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the benzodiazocine **36** (Scheme 7) <2004TL3757>.

14.04.2.6 Reactivity of Substituents Attached to Ring Heteroatoms

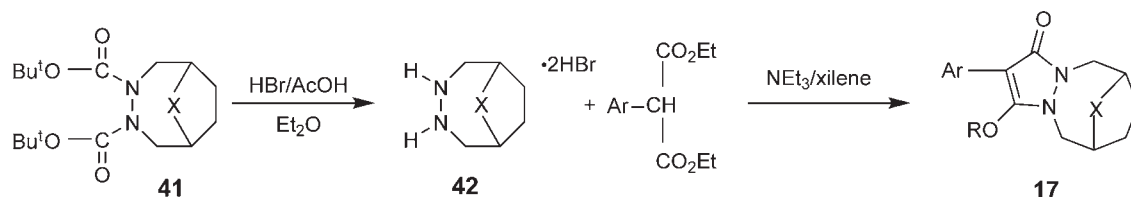
Reaction of racemic 1,2-diazocinone **2** with (*S*)-(-)-*N*-(methoxymethyl)proline methyl ester, followed by crystallization from MeCN, gave the diastereomer (*R,S,S*)-(+)-**5** <2004TA537>. The diazocinone **37a** was subjected to epoxidation conditions (oxone, acetone, NaHCO_3) and subsequent deprotection of the *N*-carbobenzyloxy moieties with Pd/C- H_2 to give **38**.

Acylation of the amino functionality and allylation of the amide nitrogen afforded the ring-closing metathesis (RCM) substrate **39** in moderate yield. Its treatment with 5–10 mol% of Grubbs' catalyst **40** furnished the diazocino[1,2-*a*]diazocine **24** in good yield as a single atropisomer (Scheme 8) <2004OL4351>.



Scheme 8

N,N'-Dicarboxylate-substituted 1,2-diazocine **41** ($\text{X}=\text{O}$, CH_2), through a sequence of typical reactions of the substituents attached to the ring heteroatoms, led to compounds which were patented as herbicides and growth inhibitors. Thus **41**, upon action of hydrogen bromide in AcOH, gave in good yields the *N*-unsubstituted diazocine **42** ($\text{X}=\text{O}$, CH_2), which was reacted with aryl-substituted malonates to give the pyrazolo-diazocines **17** ($\text{R}=\text{H}$; $\text{X}=\text{O}$, CH_2) (Scheme 9). These diazocines were reacted with acyl chlorides or chloroformates to give 28 herbicide and growth inhibitor derivatives (the substituents of all derivatives are reported in Section 14.04.2.10, Table 3).

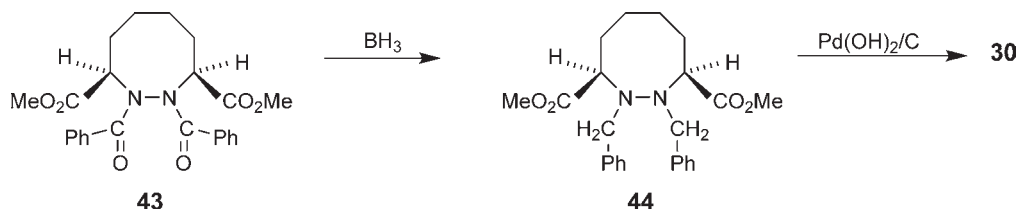


Scheme 9

<1999WO47525, 2000WO47585, 2001WO17351, 2001WO17352, 2001WO17972>. In the case of related compounds in which the oxygen or methylene bridge was missing, the unsubstituted diazocine were obtained with hydrochloric acid formed *in situ* from dry MeOH and acetyl chloride; the formation of the pyrazolo-diazocine was also achieved with malondiamides instead of malonate diesters <2001WO17973>.

The urazole ring of **33**, after their conversion to the corresponding acetonides, was transformed into the azo-bridge of **26** with alcoholic KOH <1997TL5485>. The *t*-butoxycarbonyl (BOC) group of **34** was removed in trifluoroacetic acid (TFA) to give the corresponding N-unsubstituted compound in 50% yield <2004TL3757>.

The benzoyl groups of **43** were reduced using a borane–dimethylsulfide complex to give the corresponding *N*-benzyl-diazocine **44**, which, upon hydrogenolysis with 20% Pd(OH)₂ followed by acid hydrolysis, afforded the NH diazocine **30** (R = H) (Scheme 10) <1998CPB674>.



Scheme 10

14.04.2.7 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.04.2.7.1 Ring syntheses from C₆N₂ units

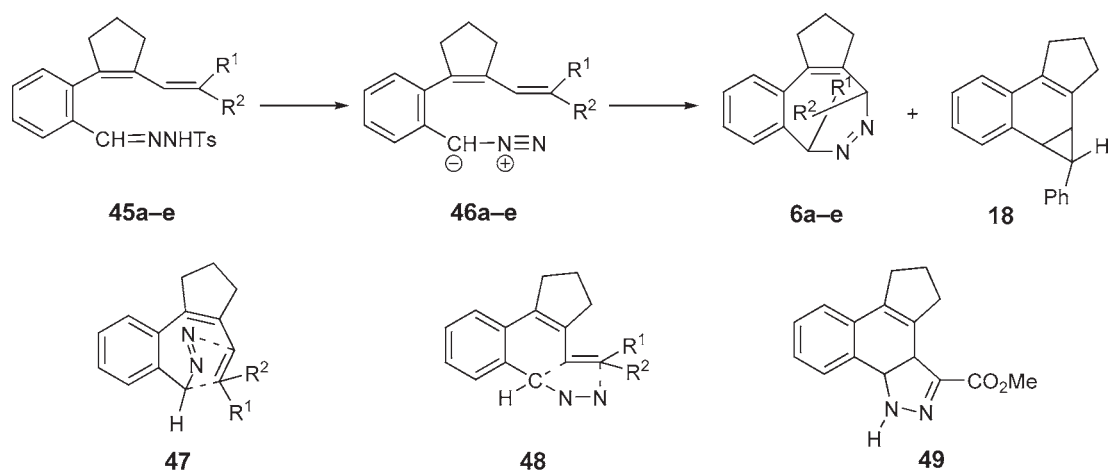
Thermal decomposition of the sodium salts of tosylhydrazones **45a–e** gave the triene-conjugated diazo **46a–e**, which have α,β aromatic and $\gamma,\delta;\epsilon,\zeta$ olefinic unsaturation. Such diazo compounds react at 25 °C via an intramolecular [3+2] cycloaddition with unprecedented regioselectivity to give the bridged benzodiazocine **6a–e**.

These derivatives were the sole or major products from **46a–d** when the reactions were conducted at 25 °C; whereas, when carried out by heating **46a** at 80 °C in DME, as solvent, derivative **6a** (27%) and **18**, as the major product (46%), were obtained. This latter compound was generated via the extrusion of nitrogen from **6a** as already pointed out in Section 14.04.2.4.

Products **6** were formed by a concerted [3+2] cycloaddition via a helical TS of type **47**; however, it was unexpected that the cycloaddition should show this regioselectivity rather than that shown in structure **48**. The only example to show the expected regioselectivity was the case of **46e** in which the formation of **6e** was observed (28%) and the major product was the indazole **49** (59%) (Scheme 11). It is worthy to mention that diazo compounds in which the cyclopentene was not present are stable at 25 °C and gave compounds of type **18** as the main products. The presence of the cyclopentene ring serves in some way to expedite the cycloaddition reaction through the TS **47** <2000J(P1)1139>.

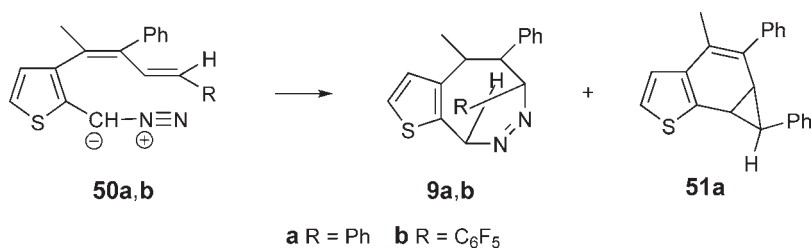
Reactivity parallel to that of **46** was exhibited by the γ,δ -*cis* diazo **50a** and **50b**. In fact, at 25 °C, **9a** and **9b** were isolated as the sole products (63–70%), whereas, in refluxing DME, **50a** gave **51a** as main product (56%) and **9a** in 38% yield (Scheme 12) <2002ARK67>.

The seleno-bridged 1,2-diazocine **7** was obtained from the reaction of Se₂Cl₂ with bis-hydrazone **52**, which was obtained from 2,5-dicyano-2,5-dimethylhexane and *t*-BuLi followed by reaction with hydrazine hydrate. Actually, from the reaction mixture together with the diazocine derivative, diselenetane **54** and the monoselenodiketone **55**, as the major product, were also isolated. The formation of **7** was explained in terms of an intramolecular [3+2] cyclization of the intermediate diazoselenoketone **53** (Scheme 13) <2000JOC1799>.

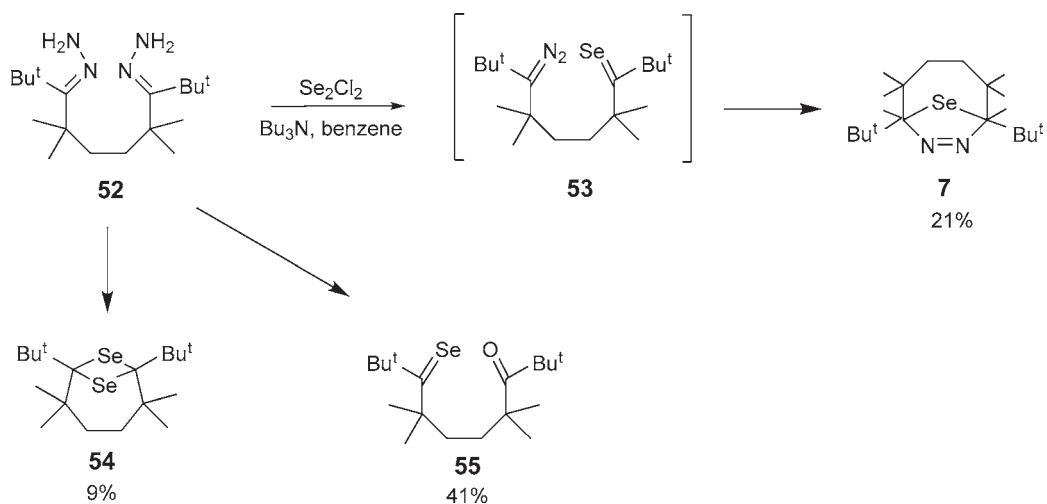


a: $R^1 = H$, $R^2 = Ph$; **b:** $R^1 = R^2 = H$; **c:** $R^1 = H$, $R^2 = Me$; **d:** $R^1 = R^2 = Me$; **e:** $R^1 = H$, $R^2 = CO_2Me$

Scheme 11

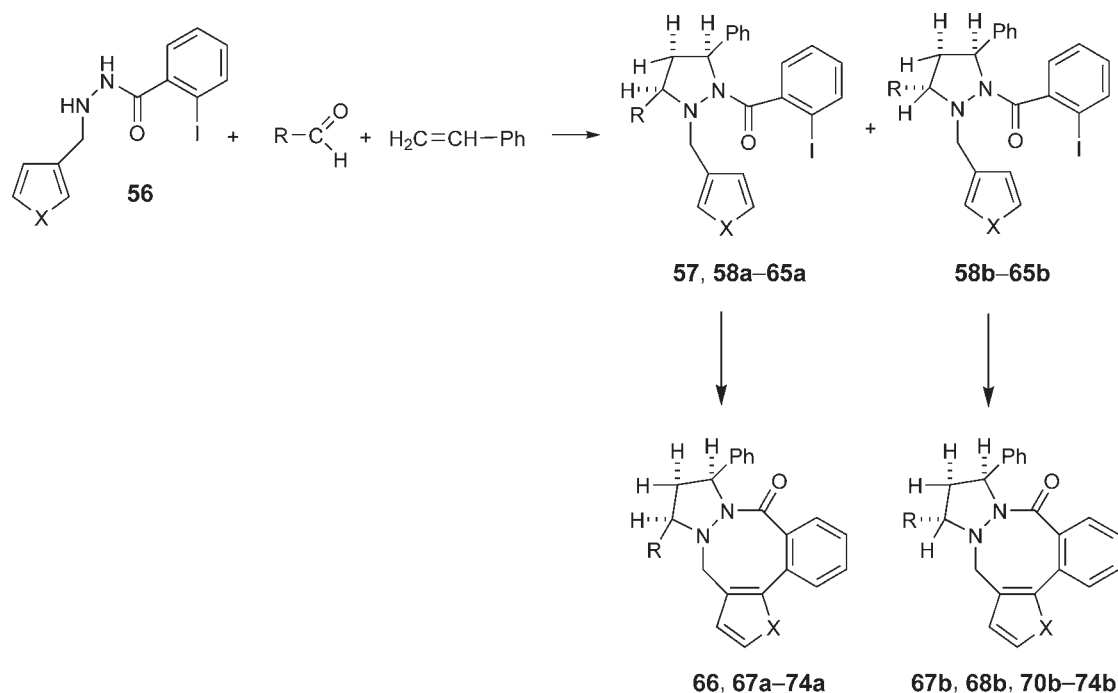


Scheme 12



Scheme 13

Pyrazolo-dibenzo-1,2-diazocines of type **66–74** were obtained by the cycloaddition of azomethine imines, generated *in situ* by condensation of aryl/heteroaryl aldehydes and *N,N'*-disubstituted hydrazines with styrene to give pyrazolidines, which contain suitable functionality for subsequent Pd-catalyzed cyclization involving the aldehyde and hydrazine substituents, with formation of the eight-membered rings in good yields. Thus, hydrazines **56**, obtained from 2-iodobenzoic hydrazide and 3-thiophenecarboxaldehyde or -furaldehyde, via reductive amination, reacted with paraformaldehyde and styrene in boiling xylene to give the cycloadduct **57**, which, in toluene using [Pd(OAc₂)] (10%), phosphine (20%), and thallium acetate (1.2 equiv), cyclized to **66** in 85% yield. When the reaction was repeated using arylaldehydes, a mixture of cycloadducts **58a,b–65a,b** were formed. Cyclization to form eight-membered ring products **67a,b–74a,b** was extraordinarily facile. These products were obtained in excellent yields upon treatment of the corresponding cycloadducts with the same catalyst used for that of adduct **57** (Scheme 14). The results are collected in Table 2. The sequential azomethine imine cycloaddition–palladium-catalyzed cyclization process is very versatile and of general application and can also lead to six-membered and seven-membered rings <2003T4451>.



Scheme 14

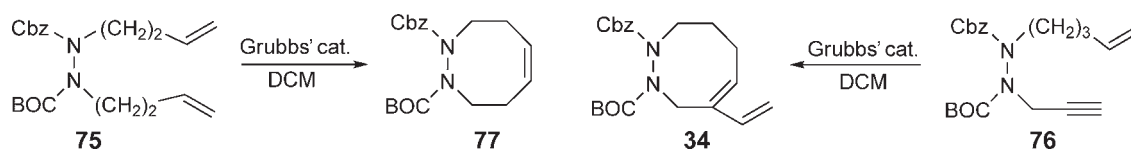
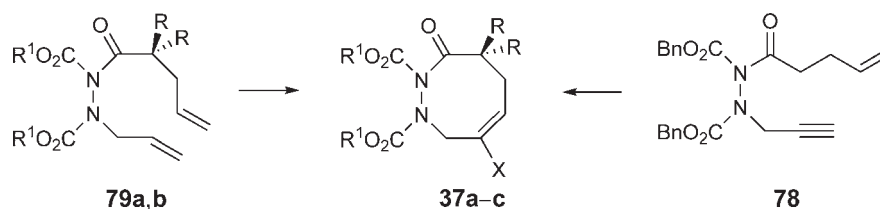
RCM of diene **75** and enyne **76** tethered by an N–N bond in refluxing DCM and in the presence of Grubbs' catalyst gave the 1,2-diazocines **77** and **34**, respectively, in good yields (70–74%; Scheme 15) <2004TL3757>. Dienes **79a**, **79b**, and enyne **78** furnished another example of the RCM approach. Thus, 1,2-diazocines **37a** and **37b** were obtained in 93% and 88% yield, respectively, under typical RCM conditions from the dienes **79a** and **79b**. The fact that **37b**, which lacks the geminal dimethyl groups, was obtained in slightly lower yield is probably due to the *gem*-dialkyl effect. Moreover, it was proved that the RCM is more efficient in the presence of a terminal alkene rather than an internal alkene. The enyne **78** afforded the diazocine **37c** in moderate yield (47%; Scheme 16) <2004OL4351>.

14.04.2.7.2 Ring syntheses from C₆ + N₂ units

Triazolo-diazocine **12** was obtained through a [6+2] cycloaddition of cycloocta-1,3-dione and 4-pyren-1-yl-1,2,4-triazole-3,5-dione **80**. Such a triazole derivative was obtained by *in situ* oxidation of 1,2,4-triazolidine-3,5-dione **81**, which was in turn obtained by reacting isocyanates and semicarbazides, followed by base-catalyzed cyclization

Table 2 Cycloadducts from the reaction of **56** and aldehydes and styrene and related Pd-catalyzed cyclization products (Scheme 14)

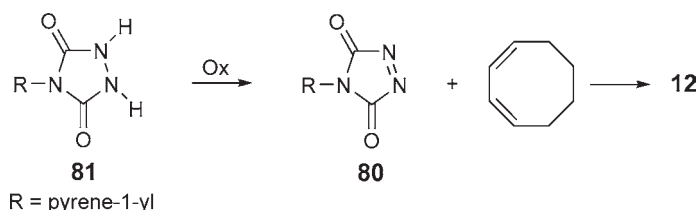
<i>R</i>	<i>X</i>	Cycloadduct	Yield (%)	Cyclization product	Yield (%)
H	S	57	94	66	85
Ph	S	58a	38	67a	82
		58b	30	67b	84
4-O ₂ N-C ₆ H ₄	O	59a	46	68a	72
		59b	14	68b	69
2-F-C ₆ H ₄	O	60a	35	69a	71
		60b	13		
4-Me ₂ N-C ₆ H ₄	S	61a	37	70a	81
		61b	25	70b	77
3-F ₃ C-C ₆ H ₄	S	62a ^a	55	71a ^b	79
		62b ^a	22	71b ^b	79
3-F ₃ C-C ₆ H ₄	O	63a ^a	54	72a ^c	73
		63b ^a	22	72b ^c	73
3-MeO-C ₆ H ₄	S	64a ^a	46	73a ^d	85
		64b ^a	30	73b ^d	83
3-MeO-C ₆ H ₄	O	65a ^a	42	74a ^c	70
		65b ^a	31	74b ^c	70

^aAn inseparable mixture.^bA mixture of **71a** and **71b** (2.5:1) from a mixture of **62a** and **62b** (2.5:1).^cA mixture of **72a** and **72b** (2.5:1) from a mixture of **63a** and **63b** (2.5:1).^dA mixture of **64a** and **64b** (1.5:1).^eA mixture of **65a** and **65b** (1.3:1).**Scheme 15**

a: X = H, R = Me, R¹ = Bn; **b:** X = H, R = H, R¹ = *i*-Pr; **c:** X = CH=CH₂, R = H, R¹ = Bn

Scheme 16

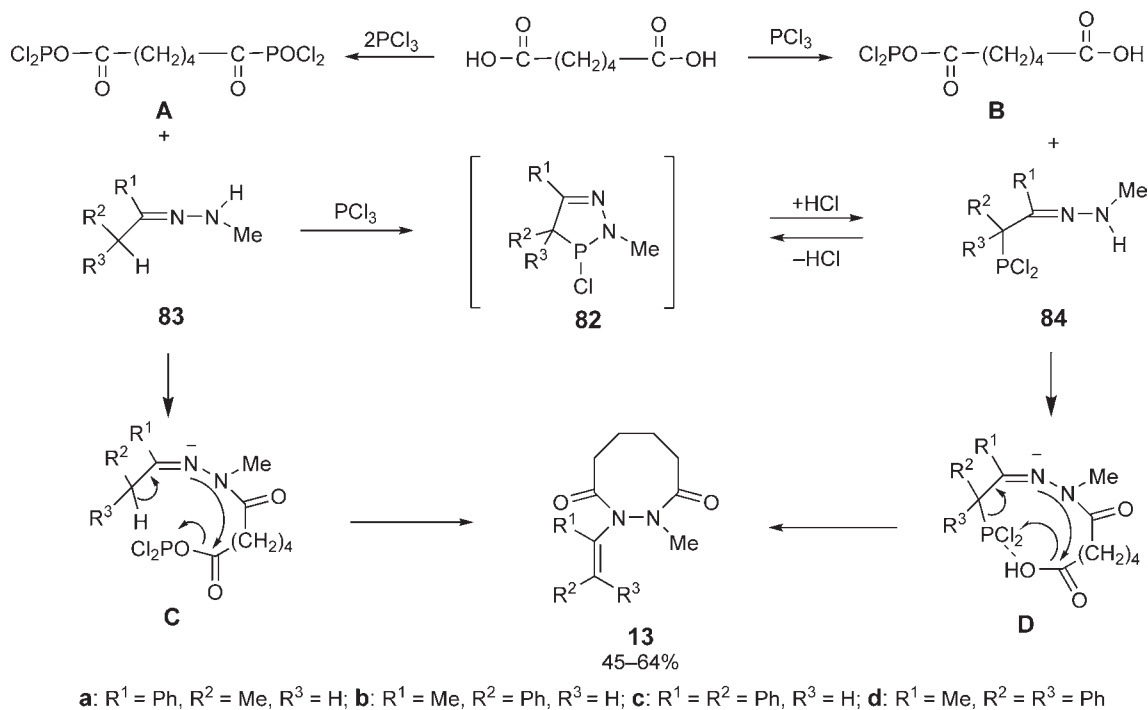
(Scheme 17). This oxidation was studied in details using 17 different oxidizing agents; however, the more convenient one was *t*-butyl hypochlorite <1995J(P1)167>. The common strategy of condensation of 1,6-dicarbonyl compounds with hydrazine was utilized to get 3,8-diaryl substituted tetrahydro-1,2-diazocine <1995MI811>. A valid variation on this [6+2] synthesis is furnished by the use of diazophosphole derivatives **82**, generated *in situ*, or the PCl₃/hydrazone combination, in a one-pot procedure for the synthesis at 25 °C of *N*-alkenyl derivatives of perhydro-1,2-diazocin-3,8-dione **13**.



Scheme 17

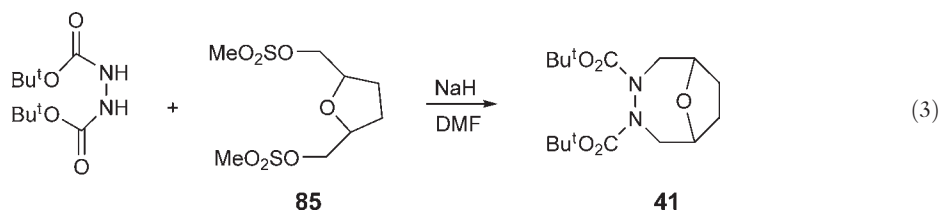
Thus, such eight-membered rings were obtained by reaction of PCl_3 , ketone methylhydrazones **83**, and adipic acid in good yields (45–64%) after a few hours at 25 °C. A different procedure, leading to the final products with the same yields, consisted of the addition of a THF solution of adipic acid and equimolecular amount of PCl_3 to a DCM solution of hydrazones **83** and an equimolar amount of PCl_3 . The first experiments were carried out with a low concentration of reagents in order to avoid polymerization, but the formation of adipic anhydride was observed as the major product. Good results were also obtained using a high concentration of reagents. The explanation of this facile formation of eight-membered rings without the use of high-dilution techniques is probably due to the different nature of the two nitrogen atoms in **83** or the ring-opened intermediate **84** derived from **82**. The amine nitrogen in **83** or **84** is more prone to react with the activated acids **A** and **B**, respectively, than the less nucleophilic imine nitrogen.

Consequently, only after the first attack, which gives intermediates **C** or **D**, is the imine nitrogen activated to give the second site for subsequent cyclization. In this manner, the condensation to give **C** or **D** is favored over the competing reaction, which gave the anhydride (Scheme 18) <1996T13695>.



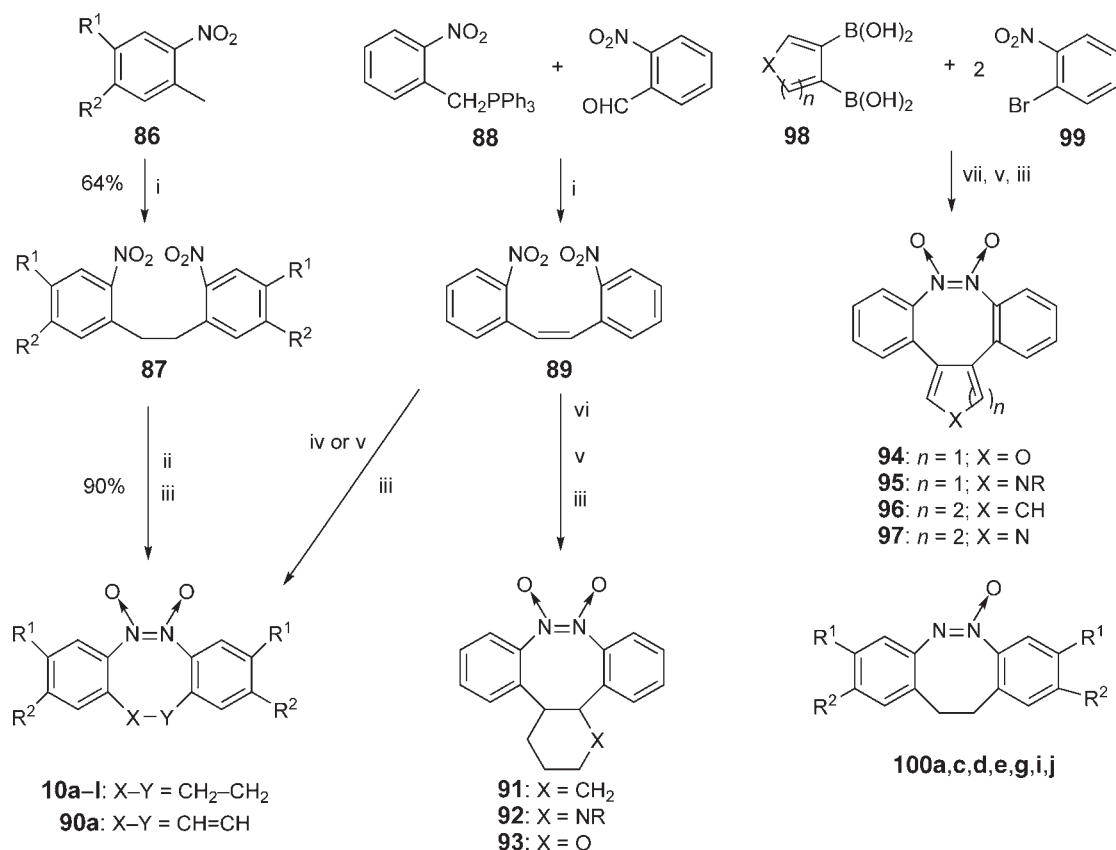
Scheme 18

1,2-Dicarboxylate-substituted diazocine **41**, key intermediate for the synthesis of pyrazolo-diazocine possessing herbicidal and growth-inhibiting properties, was prepared, in appreciable yield (66%), from di-*t*-butyl hydrazine-1,2-dicarboxylate and dimesylate **85** with 2 equiv of NaH in dimethylformamide (DMF; Equation 3) <1999WO47525, 2000WO47585, 2001WO17351, 2001WO17352>. A variation of this sort of synthesis leading to an intermediate without the oxygen bridge involves the use of 1,6-dichlorohexane instead of the dimesylate <2001WO17973>.



14.04.2.7.3 Ring syntheses from C₃N + C₃N units

Dibenzo-1,2-diazocine dioxides **10a–l** (X–Y = CH₂–CH₂) were obtained from substituted 2-nitrotoluene **86**, which by action of *t*-butoxide in Et₂O/DMSO afforded the dinitro derivatives **87**, which were reduced to the corresponding amines, followed by oxidation catalyzed by sodium tungstate to give **10** (Scheme 19) <2001JME4313, 2004WO099162, 2003WO038060>. Alternatively, **10** can be obtained via a Wittig reaction of **88** with substituted 2-nitroaldehyde affording **89**. Catalytic reduction, followed by the sodium tungstate-catalyzed oxidation, led to **10** in moderate yield <2004WO099162>.



i, K-OBu^t, ether/DMSO; ii, NH₂NH₂, H₂O/10%Pd/C, ethanol; iii, Na₂WO₄, ethanol/water 3:1, 30% H₂O₂;

iv, Na₂S₂O₃; v, H₂/Pd/C, ethanol; vi, (X = CH₂, NR, O); vii, TEA, Pd(OAc)₂

R¹ = H

a: R² = H; **b**: R² = OMe; **c**: R² = OCH₂CF₃; **d**: R² = OCHF₂; **e**: R² = OCH₂Ph; **f**: R² = OCF₂CHClF;
g: R² = OCF₂CHFClF₃; **h**: R² = O-(3-CF₃-pyridin-2-yl); **i**: R² = F; **j**: R² = SO₂Et

R² = H

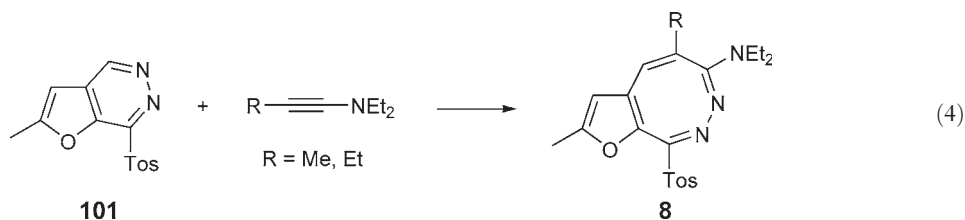
k: R¹ = NHCOMe; **l**: R¹ = NHCOCF₃

Scheme 19

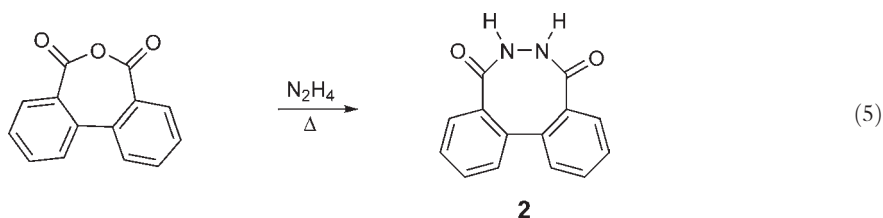
When the reduction of **89** was conducted with sodium hyposulfite, the fully conjugated dibenzo-1,2-diazocine dioxide **90a** ($X-Y = CH=CH$) was obtained <2004WO099162>. The same intermediate **89** furnished 1,2-dibenzodiazocines annelated with carbocyclic or heterocyclic rings at the position 11-12 if the usual synthetic procedure leading to the eight-membered ring is preceded by a Diels–Alder reaction with 1,3-butadienes, azabutadienes, or α,β -unsaturated aldehydes. Thus, in the case of 1,3-butadienes, the tetracycle **91** ($X = CH_2$) was obtained, while the azabutadienes or α,β -unsaturated aldehydes furnished the heterofused dibenzo-1,2-diazocines **92** ($X = NR$) and **93** ($X = O$), respectively <2004WO099162>. Dibenzo-1,2-diazocines **94–97**, annelated with aromatic or heteroaromatic moieties, can be obtained by the coupling reaction between **98** and **99** via Suzuki conditions where the boronic acid derivative was treated with the halide in the presence of a base and transition metal catalyst, such as $[Pd(OAc)_2]$. The annelated dinitro derivatives, analogues of **89**, underwent the usual sequence to give furo- and pyrrolo-1,2-diazocines **94** ($X = O$, $n = 1$) and **95** ($X = NR$, $n = 1$) or the benzo- and pyrido-fused systems **96** ($X = CH$, $n = 2$) and **97** ($X = N$, $n = 2$) (Scheme 19). The same approach resulted in the case of annelation of pyrazole, imidazole, thiazole, or isoxazole <2004WO099162>. It is worthy to mention that in several cases, in addition to the dioxides, the monoxides **100** were also isolated as minor products <2004WO099162>; however, a monoxide **100** ($R^1 = F$, $R^2 = H$) could be obtained in 92% yield by heating or irradiating with a UV lamp ($\lambda \geq 300$ nm) an EtOH solution of the ethane-1,2-bis(4-fluorobenzene-2-nitrosohydroxylamine ammonium salt) <1997TL9001>.

14.04.2.8 Ring Syntheses by Transformation of Another Ring

Two derivatives of the fully conjugated 1,2-diazocine system **8** were reported in the past decade but in poor yields (14–20%) from the reaction of 2-methyl-7-tosylfuro[2,3-*d*]pyridazine **101** with ynamines by a [2+2] cycloaddition–ring-expansion sequence (Equation 4). From the reaction mixture, the penta-substituted pyridine derivatives (14%) by an N–N bond cleavage of the pyridazine ring and benzofuranes, as the major products (31–34%) by a [4+2] cycloaddition–denitrogen reaction, were also isolated <1996H(43)199>.



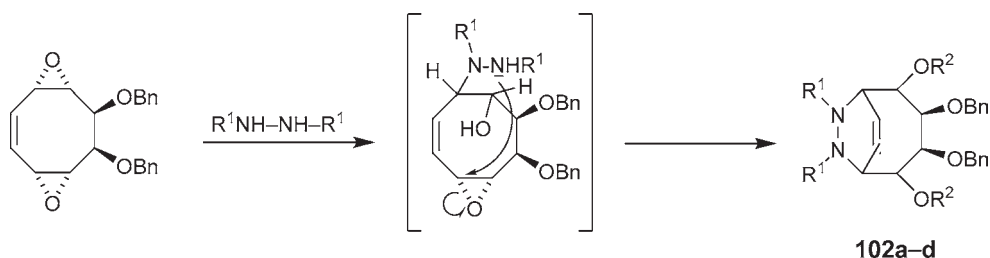
The dihydro-1,2-diazocine **2** was synthesized in low yield (10%) from diphenic anhydride and anhydrous hydrazine (Equation 5) <2004TA537>.



Eight derivatives of the dihydrodiazocine, for example **1**, were prepared utilizing the known reaction of 1,2,4,5-tetraazines with the enolate of cyclobutanones with the aim to obtain the isoxazolyl eight-membered diazaheterocycles with relatively few low-energy conformationally accessible states and, in turn, limited conformational flexibility <2006JOC2480>.

Nucleophilic addition of 1,2-disubstituted hydrazines (1,2-dimethyl- and 1,2-dibenzyl-) to diepoxy-cyclooctene-dibenzyloxy, in refluxing MeOH/water, gave monoadducts, which rapidly cyclized in a highly selective manner (up to 95%) to give the bridged 1,2-diazocines **102a** and **102c** (derivatized as **102b** and **102d** invertomers) (Scheme 20). This reaction depends on the nature of the substituents in position 3 and 4 and on the nucleophile. In fact, reaction of the same diepoxy compound with hydrazine hydrate led to a bridged azepine, whereas in the reaction of substituted hydrazine with diepoxy-3,4-dimethoxycyclooctene no selectivity was observed <2000TL5483>.

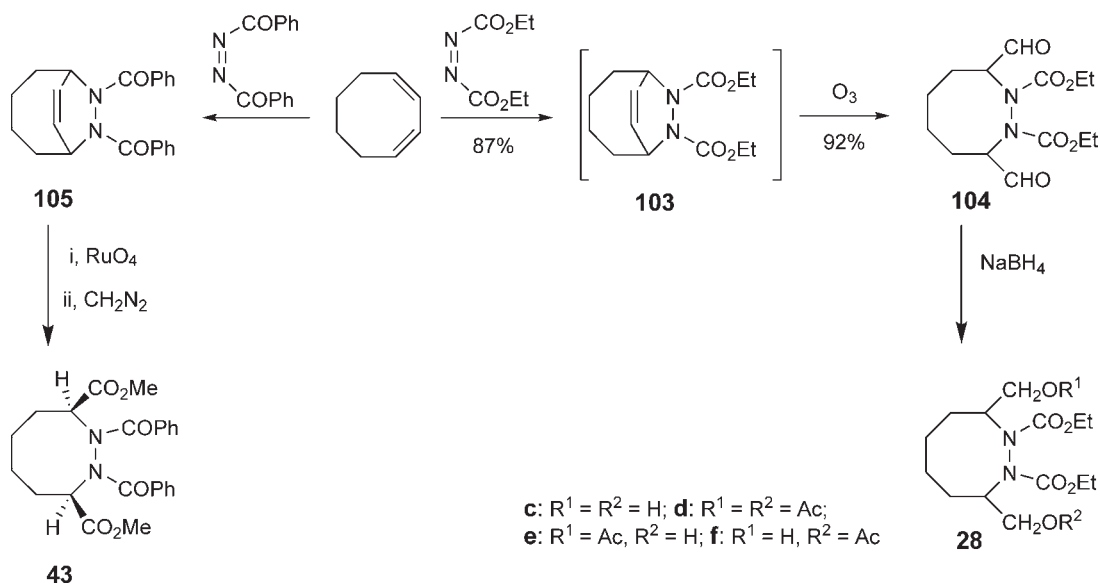
1,2-Perhydro-diazocines **28**, for the preparation of 1,4-diamino-2,3-diol units that are the central structural elements in numerous biomaterials, were obtained from 1,3-cyclooctadiene, by reaction with diethyl azodicarboxylate (DEAD) to give the bridged 1,2-diazocine **103**, which by ozonolysis gave the dialdehyde **104** that underwent



a: $R^1 = \text{Me}$, $R^2 = \text{H}$; **b:** $R^1 = \text{Me}$, $R^2 = \text{Ac}$; **c:** $R^1 = \text{Bn}$, $R^2 = \text{H}$; **d:** $R^1 = \text{Bn}$, $R^2 = \text{Ac}$

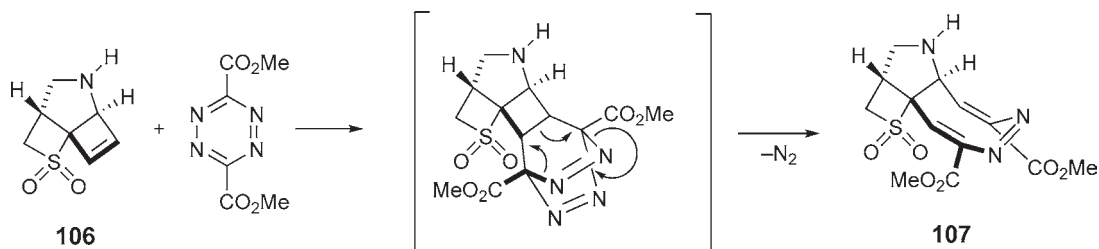
Scheme 20

reduction with NaBH_4 to give **28c** and **28d**. Subsequent enzymatic asymmetrization with lipozyme IM, either by esterification of **28c** or hydrolysis of diacetate **28d**, gave **28e** and **28f** (Scheme 21) <1998AGE2242>. Reaction of 1,3-cyclooctadiene with azodibenzoyl gave in low yield (37%) the bridged diazocine **105**, which upon oxidation with ruthenium tetroxide, followed by treatment with diazomethane, afforded the dimethyl 1,2-dibenzoyldiazocine-*cis*-3,8-dicarboxylate **43** in 91% yield (Scheme 21) <1998CPB674>.



Scheme 21

The spiro compound **106** underwent a Diels–Alder cycloaddition with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate to give the condensed 1,2-diazocine **107**, presumably via retrograde deazotization of the initial [4+2] cycloadduct with cleavage of the cyclobutane ring (Scheme 22) <2004OL1313>.



Scheme 22

14.04.2.9 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Among the five unimolecular cyclizations reported, two of them showed versatility in functionalizing the eight-membered ring. The sequential azomethine imine cycloaddition–palladium-catalyzed cyclization process seems the most versatile, since it can also lead to pyrazine and 1,2-diazepine ring systems. Also the RCM of dienes and enynes offers good potential for ring construction. This sort of reaction has wide application. In fact, dibenzodiazocine derivatives **90** can also be prepared from intermediates obtained by olefin metathesis of 2-nitrostyrene <2004WO099162>. Probably this very interesting cyclization route has a limitation, that is the cost of the Grubbs' catalyst, especially the second generation. Other unimolecular cyclizations, either in terms of yields or in terms of mixture of compounds obtained, have diminished preparative interest. The condensation of hydrazine with 1,6-dicarbonyl compounds still finds application in its interesting variation, which utilizes adipic acid, activated by reaction with 1 or 2 mole of phosphorus trichloride, and hydrazones. The reaction conditions (e.g., 25 °C) are certainly milder than those utilized for the classical condensation and the yields are reasonable. The cyclization of two C₃N units leading to dibenzodiazocines with antineoplastic properties appears to be very attractive and allows a large variety of substituents at the benzene moiety. The reported ring transformations have no preparative interest except for the cycloaddition of DEAD to 1,3-cyclooctadiene leading in an 80% overall yield of key intermediates for the synthesis of bioactive materials.

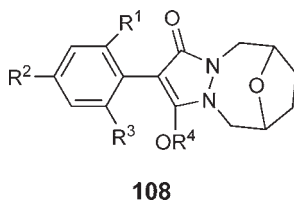
14.04.2.10 Important Compounds and Applications

Twenty-eight 1,2-diazocines of type **108** were active as herbicides and growth inhibitors. The weeds to be controlled can be of either the monocotyledonous or dicotyledonous variety. Compounds **108** are particularly suitable for controlling alopecurus, avena, agrostis, setaria, phalaris, Ionium, panicum, echinocloa, brachiaria, and digitaria <1999WO47525>. These 1,2-diazocine derivatives are utilized for combating grass and weeds in crop plant cultures, since they can be used in combination with the herbicide-antagonistically effective compounds, safeners, which protect the useful plants against the phytotoxic effect of the herbicides <2000WO47585, 2001WO17351, 2001WO17352, 2001WO17973>. All of the synthesized derivatives with herbicide activity are listed in Table 3.

Table 3 1,2-Diazocine derivatives **108** with herbicide and growth-inhibiting properties

Compounds	R ¹	R ²	R ³	R ⁴
108-1	Me	Me	Me	H
108-2	Me	Me	Me	CO- <i>t</i> -Bu
108-3	Me	Me	Me	CO ₂ Et
108-4	Et	Me	Et	H
108-5	Et	Me	Et	CO- <i>t</i> -Bu
108-6	Et	Me	Et	CO ₂ Et
108-7	Et	Me	Br	H
108-8	Et	Me	Br	CO- <i>t</i> -Bu
108-9	Et	Me	Br	CO ₂ Et
108-10	C≡CH	Me	Me	H
108-11	C≡CH	Me	Me	CO- <i>t</i> -Bu
108-12	C≡CH	Me	Me	CO ₂ Et
108-13	C≡CH	Me	Et	H
108-14	C≡CH	Me	Et	CO- <i>t</i> -Bu
108-15	C≡CH	Me	Et	CO ₂ Et
108-16	C≡CH	Me	C≡CH	H
108-17	C≡CH	Me	C≡CH	CO- <i>t</i> -Bu
108-18	C≡CH	Me	C≡CH	CO ₂ Et
108-19	OMe	Me	Et	H
108-20	OMe	Me	Et	CO- <i>t</i> -Bu
108-21	OMe	Me	Et	CO ₂ Et
108-22	OMe	Me	Br	H
108-23	OMe	Me	Br	CO- <i>t</i> -Bu
108-24	OMe	Me	Br	CO ₂ Et
108-25	OMe	Me	C≡CH	H
108-26	OMe	Me	C≡CH	CO- <i>t</i> -Bu
108-27	OMe	Me	C≡CH	CO ₂ Et
108-28	Et	Ph	OMe	H

Also 1,2-diazocines, closely related to **108** bearing a methylene bridge instead of the oxygen bridge, were also active as herbicides and growth inhibitors <2001WO17972>. The same biological activities were maintained in 1,2-diazocine derivatives in which the oxygen or methylene bridge is missing <2001WO17973>.

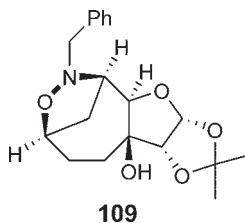


1,2-Diazocine dioxides of type **10** and corresponding monoxides **100** were tested for acute cytotoxicity (apoptotic activity) using two human cancer cell lines expressing high levels of either Bcl-2 or Bcl-X_L: HL60 human leukemia cell expressing high Bcl-2 and low Bcl-X_L levels and A549 human lung cells expressing low Bcl-2 and high Bcl-X_L levels. Compounds **10** were more active than the corresponding monoxides **100** having LC₅₀ < 50 μM. 1,2-Diazocine dioxides were more active with respect to the HL60 leukemia cell line than A549 lung cell line. It was proposed that **10** can bind to a pocket in Bcl-2/Bcl-X_L, formed by BH1, BH2, and BH3 domains that block the anti-apoptotic function of these proteins in cancer cells and tumor tissues exhibiting Bcl-2 protein over expression. 1,2-Diazocines **10** that find use in the breast cancer and myeloid leukemia as well as acquired immune deficiency syndrome (AIDS), degenerative conditions, and vascular diseases, exhibit distinct advantages including good oral availability, *in vivo* stability, and low cost <2001JME4313, 2002WO13833, 2003WO038060, 2004WO099162>.

14.04.3 Rings with One Nitrogen and One Oxygen (2H-1,2-Oxazocines)

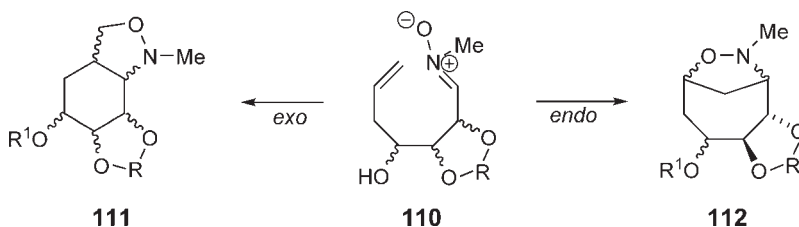
14.04.3.1 Theoretical Methods

To establish the relative configuration of the newly formed stereocenters of the bridged 1,2-oxazocine **109**, obtained from an alkene–aldehyde intermediate, a computer-assisted molecular modeling coupled with ³J_{HH} calculations was utilized.



Some of the plausible conformations were created in a Desktop Molecular Modeller, the energy was minimized to a large extent, the resulting structure transferred for full energy minimization in the MMPMI program of QCPE (Indiana University), and the ³J_{HH} values calculated using the 3JHHPC program of QCPE. The agreement with experimental *J* values could be unambiguously determined from high-field NMR spectral analysis <1996T11265>.

The intramolecular nitronc–alkene cycloaddition (INAC) of hept-6-enoses **110** can proceed either via the *exo*-mode to give fused isoxazolidines **111** or the *endo*-mode to give the bridged 1,2-oxazocines **112** (Scheme 23).

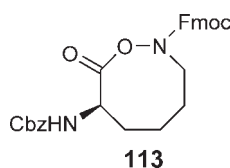


Scheme 23

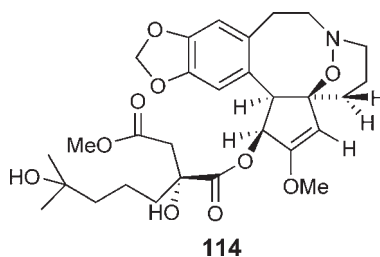
The blocking group O–R–O affected the regio- and stereoselectivity of such cycloadditions. Thus, when the blocking group was a 2,3-*O*-isopropylidene moiety, the only reaction observed was the *exo*-mode of INAC cyclization to give **111**. In the case of the 2,3-*O*-*trans*-diacetal blocking group, the formation of a mixture of fused oxazolidine **111** and bridged oxazocine **112** was observed (see Section 14.04.3.8). The stereo- and regioselectivity of these reactions were rationalized on the basis of TS energies obtained by computation. The TS energies were obtained by calculating, at first, the ground-state structures with molecular mechanics by using CONFLEX program for conformational search. Among the many conformers obtained, the relatively stable ones (within 10 kcal mol^{−1} compared to the more stable conformer) were selected for further analysis. Then, the ground state structures were calculated by B3LYP/6-31G* with a suite of Gaussian 98 programs. The obtained TS energies were compared and the results of this theoretical analysis were consistent with the experimental results <2006JOC3253>.

14.04.3.2 Experimental Structural Methods

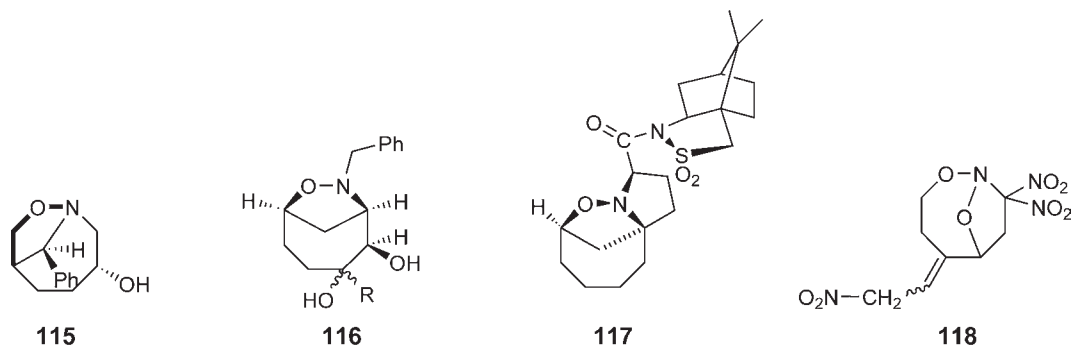
No detailed X-ray crystallography studies of 2*H*-1,2-oxazocines have been reported. Only in two cases was this technique utilized to confirm the structure of **112** (R = –CH(Me)–CH(Me)–; R¹ = H and TBS) <2006JOC3253> and the structure of the perhydro-oxazocinone **113** <1995TL6379>.



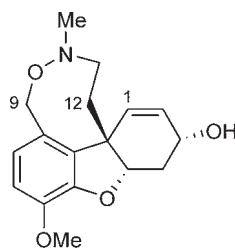
Contrary to what was reported in Section 9.21.4.1 of CHEC-II(1996), in the papers of the last decade dealing with 1,2-oxazocines and reviewed in this chapter, the NMR spectral data were provided for the majority of the synthesized compounds, although, with some exceptions below reported, both ¹H and ¹³C NMR spectra were not assigned. However, from the available data, it is only possible to assign a range for the protons bound to carbons adjacent to the nitrogen or the oxygen of the oxazocine rings. Protons adjacent to nitrogen were found at 3.09–3.86 ppm <1996T11265, 1997T13165, 2005JOC6995> or, in case of N–C double bond at 7.46 ppm <2003CHE388>. Protons adjacent to the oxygen were found in the range of 3.78–4.75 ppm <1996T11265, 1997T13165, 2005JOC6995>. NMR techniques were essentially utilized for the characterization of the synthesized compounds. For **109**, the experimental ³J_{HH} values were unambiguously determined. Thus, *J*_{1,2} and *J*_{4,5} were 3.7 and 2.4 Hz, respectively, while H-7 showed two *J* values of 8.8 and 4.1 Hz. Such experimental values were in agreement with those calculated using the ³JHPC program of QCPE <1996T11265>. The ratio of **112** (R = –CH(Me)–CH(Me)–; R¹ = H, TBS) (TBS, *t*-butyldimethylsilyl) and the isomeric fused oxazolidines **111** (R = –CH(Me)–CH(Me)–; R¹ = H, TBS) was achieved by measuring the integration of the individual *N*-methyl group in the ¹H NMR spectrum of the mixture of cycloadducts. Instead the ring size was based on ¹³C distortionless enhancement by polarization transfer (DEPT) experiments in which **111** showed one resonance in the upfield region assigned to a methylene group (25–40 ppm), whereas **112** have two methylene resonances in that region. The strong NOE effects in **112** indicated that the bridgehead was pointing upward <2006JOC3253>. The framework of polycondensed oxazocine **114**, obtained from the *N*-oxide of the corresponding seven-membered ring azepine, was confirmed by its heteronuclear multiple bond correlation (HMBC) spectrum. ¹H and ¹³C NMR spectra showed the ester side chain, the methylenedioxy group, and the methyl enol ether moiety. The low-field shift (87.5 ppm) of the C-1 resonance indicated that the oxazocine oxygen atom is bound to this carbon. Moreover, the nuclear Overhauser enhancement spectroscopy (NOESY) correlations were observed between H-2 and H-20β and between H-5 and H-20α <1997JOC8251>.



The structure of the bridged oxazocine **115** was unambiguously assigned on the basis of 2-D correlation spectroscopy (COSY) and NOE data <1997T13165>. The structure of oxazocine **116b** was based upon the presence of a one-proton doublet at 2.06 ppm and a one-proton doublet of triplet at 2.44 ppm in its ^1H NMR spectrum as well as an upfield triplet at 29.4 ppm in its ^{13}C NMR spectrum assigned to the bridge methylene group <1999JOC2304>. Structural identification of oxazocine **117** was elucidated by ^1H , COSY, ^{13}C , and $^1\text{H}/^{13}\text{C}$ heteronuclear correlation NMR studies. The stereochemistry of **117** was established by a NOESY irradiation experiment that indicated a significant enhancement of the signal at 4.31 ppm arising from the irradiation of the isoxazoline methyne resonance at 4.72 ppm <2000TA2625>. The ^1H and ^{13}C NMR spectra of **118** showed two set of signals corresponding to two geometrical isomers (*E*) and (*Z*). The *cis*-arrangement of the proton at the double bond and the proton in position 6 for the major isomer was proven by the NOE. Signal assignments in the ^1H and ^{13}C NMR spectra were made with the use of 2-D ^1H - ^1H and ^1H - ^{13}C COSY spectroscopy <2002DOC9>. In the ^1H NMR spectrum of **119**, it was found that the *N*-methyl group showed strong NOE interactions with H-9 and H-12 α suggesting that the methyl group is α -oriented. In addition, there is a strong interaction between H-1 and H-12 α , which hinders the α -face of the molecule, where the nitrogen atom is localized <2003BML2389>.



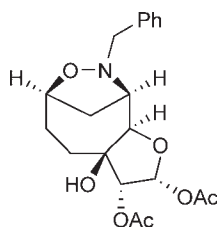
a: R = H; b: R = CH₂OH



119

Also for 1,2-oxazocines, no studies on fragmentation patterns have been reported. Several papers do not report a detailed mass spectra or report, in the experimental section, the high-resolution FAB mass spectrometry (HRFABMS) data but only mention the quasi-molecular ion, instead of the elemental analysis <1997T13165, 1999JOC2304, 2003ARK75, 2005JOC6995>. All of the 1,2-oxazocines, with one exception (*vide infra*), show the parent ions in their mass spectra. Below, unless otherwise specified, are described electron ionization mass spectra. The mass spectrum of the bridged oxazocine **109** showed, beside the molecular ion, main fragments of m/z M-15 and m/z M-90 probably due to loss of the methyl and benzyl moieties, respectively, and an ion of m/z 160 most likely involving the rupture of the bridged oxazocine ring <1996T11265>. The FAB mass spectra of **112** (R = -CH(Me)-CH(Me)-; R¹ = H, TBS) showed the quasi-molecular (MH⁺), the molecular ions, and a fragmentation originated by the loss of the methoxy moiety <2006JOC3253>. The mass spectrum of the polycondensed oxazocine **114** showed, beside the parent ion, a fragment of m/z 545 by extrusion of oxygen, the base peak at m/z 314 due to loss of the ester moiety, and a fragment of m/z 298 likely due to loss of oxygen from the base peak <1997JOC8251>. In its mass spectrum, **116b** (R = CH₂OH) showed the molecular ion and a fragmentation of m/z 159 likely due to the cycloheptane moiety upon cleavage of the oxazocine ring <1997JOC8948>. The mass spectrum of **117** showed a very low parent ion (1%) and a base peak of m/z 166 due to the elimination of the acyl substituent <2000TA2625>. The mass spectrum of **118** showed no parent ion but rather peaks of

m/z 244 and 198 due to loss of one or two nitro groups, respectively <2002DOC9>. The mass spectrum of **120** showed the parent ion and fragmentations due to the loss of substituents, the acetyl and benzyl moieties <1997T4727>.



120

14.04.3.3 Thermodynamic Aspects

Over the last decade, the physical properties of 1,2-oxazocines reported did not improve with respect to that reported in CHE-II(1996); in fact, they still remain scarce and fragmentary. All 1,2-oxazocines are bridged and/or annelated to carbocycles or heterocycles. Also, 1,2-oxazocines show a varied phase behavior. Several compounds are colorless oils <1997JOC8251, 1997JOC8948, 1997T13165, 2005JOC6995, 2000TA2625, 2006JOC3253>, while other derivatives show a gummy or foamy consistence <1999JOC2304, 1997T4727, 2003ARK75>. Compound **112** (R = -CH(Me)-CH(Me)-, R¹ = TBS) has a low melting point of 53–54 °C, while the derivative, in which R¹ = H, increasing the intermolecular interactions, raises its melting point to 207–208 °C <2006JOC3253>. Also **109**, bearing functionality that allows the stabilization of the solid state, melts at 180–181 °C <1996T11265>. From the experimental parts of the reports dealing with 1,2-oxazocines, it is evident that such compounds are soluble in most common organic solvents. The eluents for chromatography, either column or thin-layer chromatography (TLC), range from low to medium polarity being CHCl₃ <1996T11265, 1997JOC8948, 1997T4727, 2002DOC9>, CHCl₃/MeOH <1999JOC2304, 2003ARK75>, hexane/EtOAc <2000TA2625, 2005JOC6995, 2006JOC3253>, and Et₂O/petroleum ether <1997T13165>. There appeared only one report on thermal behavior of 1,2-oxazocine which indicated that they are stable. In fact, three isomers of oxazocine **112** (R = -CH(Me)-CH(Me)-, R¹ = H), heated in a sealed tube to 210 °C in toluene for 24 h, were recovered unchanged <2006JOC3253>.

14.04.3.4 Reactivity of Nonconjugated Rings

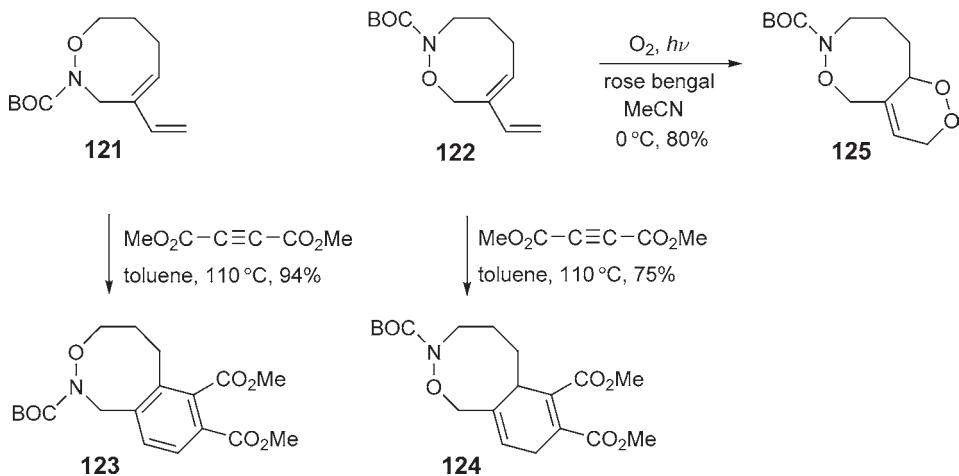
1,2-Oxazocine derivatives **121** and **122**, being 1,3-dienes, underwent a Diels–Alder reaction with DMAD to give the bicyclic derivatives **123** and **124**, respectively, in excellent yields. Compound **123** turned out to be aromatic, which could have resulted from the air oxidation during reaction workup; interestingly, the isomer **124** was not oxidized under the same conditions (Scheme 24) <2003SL2017>. Derivative **122** underwent a Diels–Alder reaction with singlet oxygen by irradiation with a tungsten lamp in the presence of catalytic amount of rose bengal, as sensitizer, while a steady flow of oxygen was passed through the solution to give the 1,2-dioxine derivative **125** <2004BKC1307>.

The furan-fused 1,2-oxazocine **126** cleaved the N–O bond when treated with NaBH₄ catalyzed by Mo(CO)₆ to give the furan **127** (Equation 6). It is noteworthy that hydrogenation conditions, such as activated zinc and samarium iodide, failed to cleave the N–O bond <2005JOC6995>.

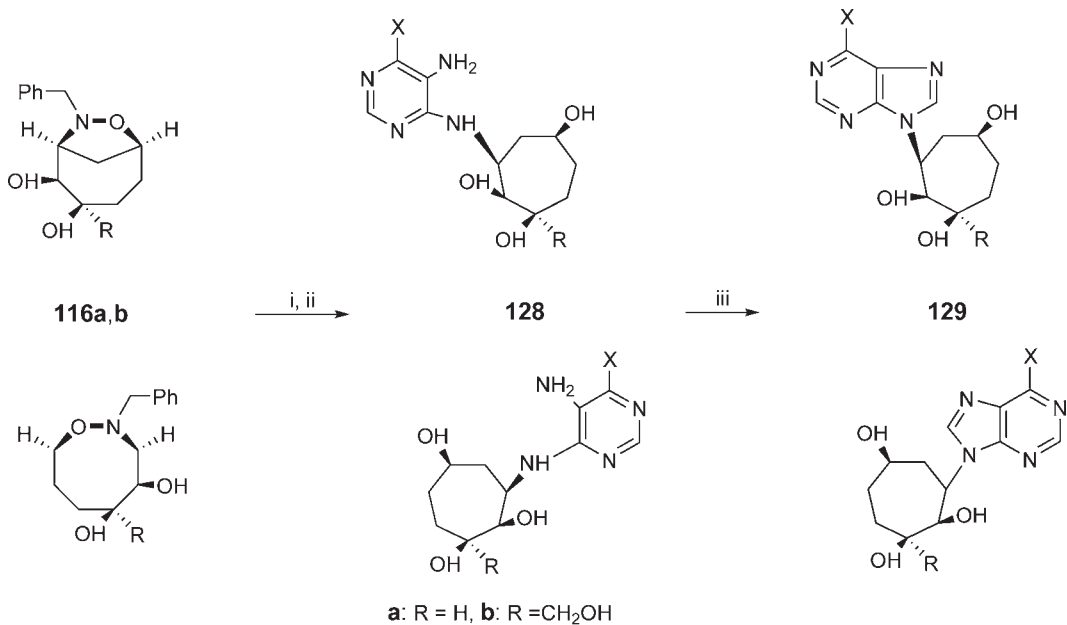
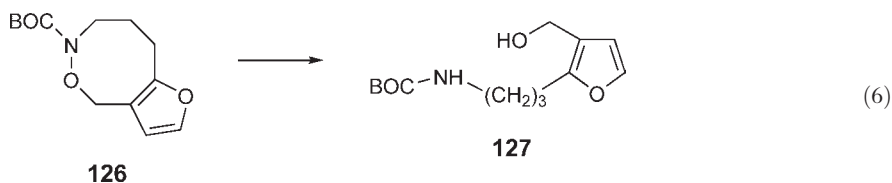
The enantiomeric pair of the bridged 1,2-oxazocines **116a** and **116b**, by catalytic transfer hydrogenation (Pd–Cl/cyclohexene) followed by reaction with 5-amino-4,6-dichloropyrimidine, gave the corresponding polyhydroxyamino carbocycles **128a** and **128b** (X = Cl), which underwent ring closure by the reaction with triethyl orthoformate to give the chloro nucleosides **129a** and **129b** (X = Cl) (Scheme 25). These latter, in turn, can be converted to the corresponding enantiomeric pair of the seven-membered carbocyclic nucleoside analogues **129a** and **129b** (X = NH₂).

In the case of **116a** (R = H), the dimethylamino nucleoside pair **129** (X = NMe₂), conceivably formed from chloropurine **129** (X = Cl) with Me₂NH derived from DMF, was also isolated. The formation of these products can be due to H-bonding between the N-3 of the purine ring and hydroxyl substituent at C-2 of the carbocyclic moiety facilitating nucleophilic attack at C-6 <1997JOC8948, 1999JOC2304, 2003ARK75>. Also, furano-1,2-oxazocine fused at the 4-5 positions, an analogue of **116**, underwent hydrogenolysis, under the same reaction conditions, to give the corresponding furano-fused seven-membered tetrahydrocarbocyclic nucleoside, which was characterized as its

tetraacetate <1997T4727>. Reaction of the polycondensed azocine **119** with ethyl chloroformate cleaved the N–O bond, affording **130** by benzylic cleavage (Scheme 26). The same N–O bond could not be cleaved by reduction under several reaction conditions or by quaternization with dimethyl sulfate <2003BML2389>.

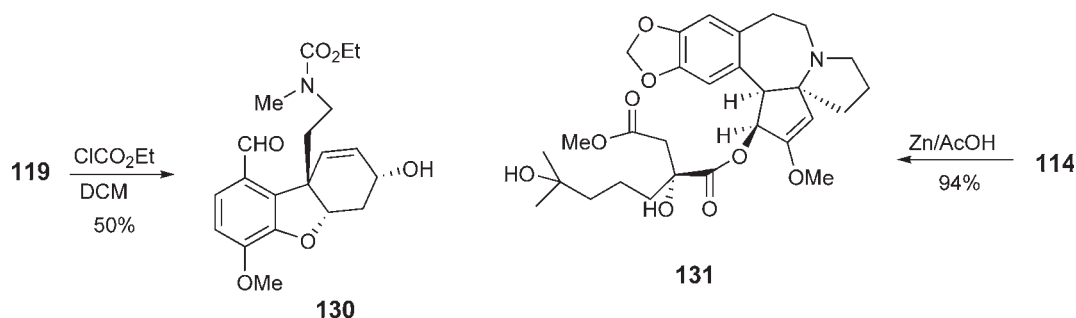


Scheme 24



i, 10% Pd/C, cyclohexene, EtOH; ii, 5-amino-4,6-dichloropyrimidine, Et₃N, *n*-BuOH, reflux, 24 h; iii, HC(OEt)₃, *p*-TSA, DMF, 32–35 °C, 24 h

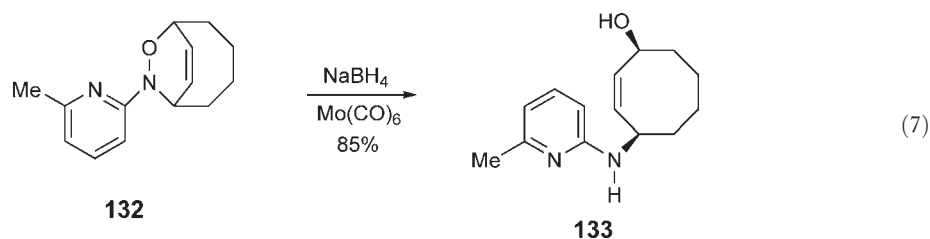
Scheme 25



Scheme 26

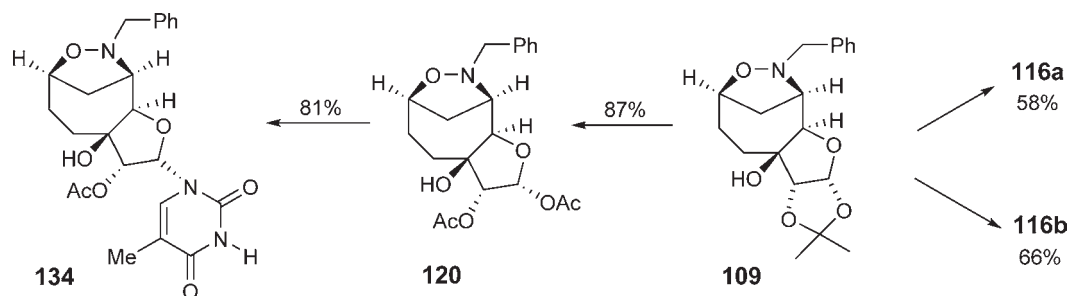
Cleavage of the N–O bond of the polycondensed 1,2-oxazocine **114** by reduction with zinc in AcOH gave homoarringtonine **131**, the corresponding azepine from which it was synthesized (Scheme 26) <1997JOC8251>.

The bridged oxazocine **132** underwent cleavage of the N–O bond to give the amino, hydroxy-substituted eight-membered carbocyclic ring **133** (Equation 7) <2005WO068457>.



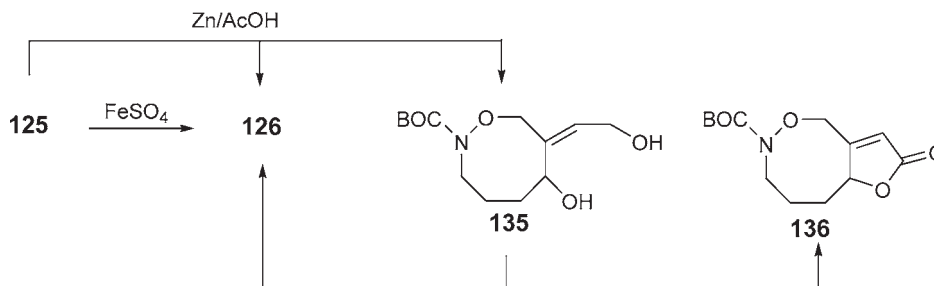
14.04.3.5 Reactivity of Substituents Attached to Ring Carbon Atoms

The bridged oxazocine **109**, upon acid hydrolysis followed by acetylation, was converted into the furano-oxazocine **120**, which reacted with bis-*O*-(trimethylsilyl)uracil in dichloroethene (DCE) to give **134** (Scheme 27) <1997T4727>. The same oxazocine **109** by trimming the furanose led to **116**. The reaction sequence involved opening of the isopropylidene moiety with acid, cleavage of the triol with NaIO_4 , followed by reduction with NaBH_4 . When the reduction was carried out at 10°C , **116a** ($\text{R} = \text{H}$) <1999JOC2304, 2003ARK75> was obtained; whereas at 0°C , the hydroxymethyl derivative **116b** ($\text{R} = \text{CH}_2\text{OH}$) was obtained (Scheme 27) <1997JOC8948>. The ring-opening reaction of the dioxine-fused oxazocine **125** catalyzed by FeSO_4 led to the furan[3,2-*d*]azocine **126** in high yield. It is noteworthy that attempts for a direct conversion of **125** to **126** using strong bases, for example *t*-BuOK or $\text{LiN(SiMe}_3)_2$, were unsuccessful.



Scheme 27

When **125** was subjected to a two-step sequence, reductive cleavage of the O–O bond and subsequent oxidative dehydration, by treatment with zinc in AcOH, the allylic diol **135** and the 1,2-oxazocine **126**, as minor product, were isolated. Oxidation of the diol **135** under several different reaction conditions (pyridinium chlorochromate (PCC), 2-iodoxybenzoic acid (IBX)/EtOH, IBX/DMSO, Pyr/SO₃) gave **126** in high yield (68–92%), while with tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide (TPAP/NMO) as oxidizing agent **126** was the minor product and the α,β -unsaturated γ -butyrolactone **136** was obtained in 68% yield (Scheme 28) <2005JOC6995>.



Scheme 28

14.04.3.6 Reactivity of Substituents Attached to Ring Heteroatoms

Only the copper-catalyzed reaction with aryl, heteroaryl, and alkenyl halides (Cl, Br, I) of 2*H*-1,2-oxazocine to give the corresponding *N*-substituted derivatives has been reported <2002WO085838>.

14.04.3.7 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

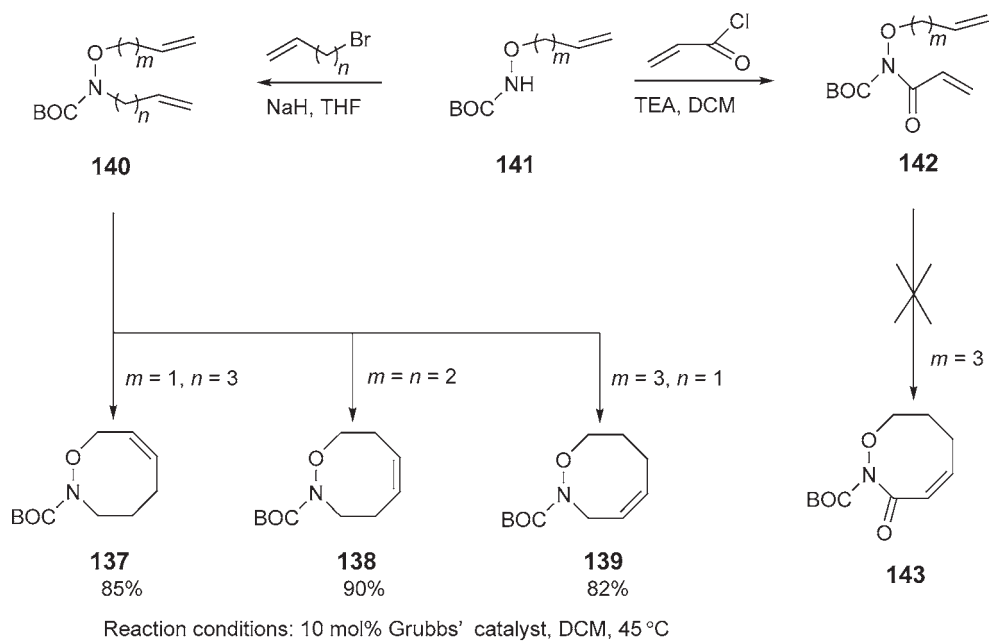
14.04.3.7.1 Ring syntheses from C₆NO units

1,2-Oxazocine derivatives **137–139** were prepared by the RCM of alkenes. The key intermediates **140** were obtained by a double alkylation of *N*-BOC-hydroxylamine with suitable bromoalkenes. The first alkylation led to **141**, which were further reacted with the second bromoalkene to give **140**. Such substrates were reacted under the usual RCM conditions to give the eight-membered rings in excellent yields (82–90%). Interestingly, the position of the double bond in the 1,2-oxazocine products can have an effect on the course of the metathesis reaction. Replacement of the BOC protecting group with the benzoyl moiety resulted in a faster cyclization and higher yields. Reaction of **141** with acryloyl chloride led to the corresponding amide **142**, which could not be cyclized to the oxazocine **143** (Scheme 29) <2003SL1043>.

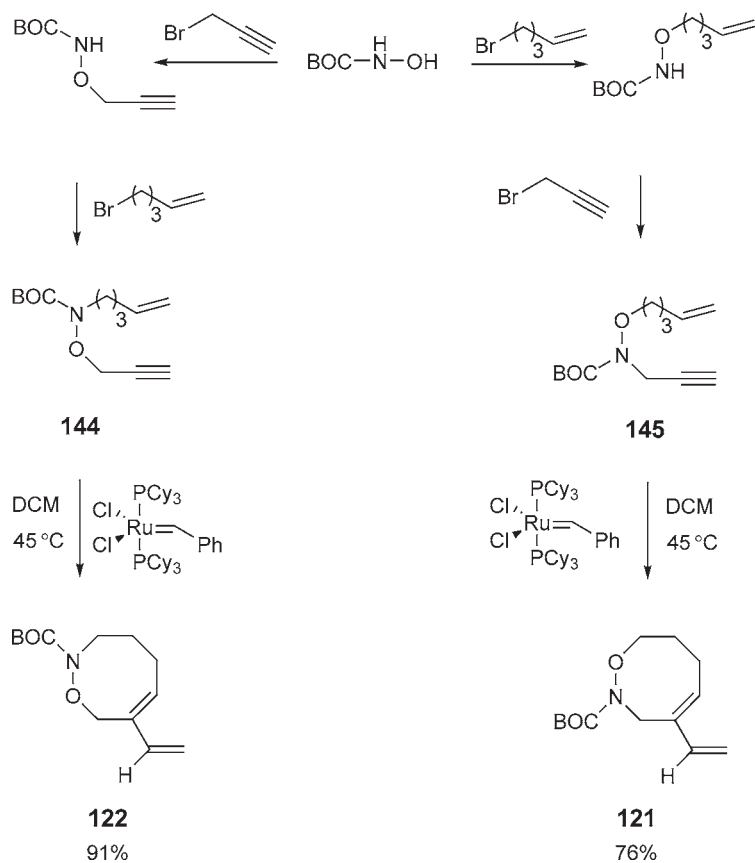
The RCM is also efficient in the case of enynes of type **144** and **145**, obtained from *N*-BOC-hydroxylamine, which underwent a sequence of two alkylation reactions. The enyne **144** was obtained if the bromoalkyne is initially employed and then the bromoalkene. Enyne **145** was obtained when the first alkylation was carried out with bromoalkene and the second with bromoalkyne. Both enynes **144** and **145** cyclized in the presence of Grubbs' catalyst to give the oxazocines **122** and **121**, respectively, in good yields, although it was necessary to conduct the reaction under high-dilution conditions (0.007 M). It was observed that when the alkyne moiety is bound to the oxygen the cyclization is faster with increased yields (Scheme 30) <2003SL2017>.

14.04.3.7.2 Ring syntheses from C₆ + NO units

The 1,2-oxazocinone derivative **113** was accidentally obtained in the attempt to synthesize cobactin T, an *N*-hydroxyazepinone, key component of the mycobactins (a family of siderophores (microbial iron chelators),

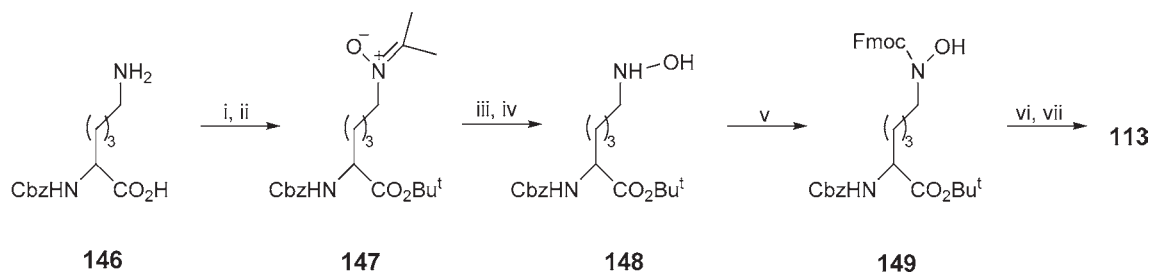


Scheme 29



Scheme 30

essential for growth of pathogenic strains such as *M. tuberculosis*). The starting material was *N*^α-Cbz-lysine **146**, which was reacted in a sealed tube with *t*-butoxy acetate in the presence of HClO₄ to give the corresponding ester, which underwent oxidation by dimethyldioxirane to afford nitron **147**. Treatment of **147** with hydroxylamine hydrochloride afforded **148**, which reacted with FmocCl to give the corresponding substituted hydroxylamine **149** (Fmoc = 9-fluorenylmethyloxycarbonyl group). This intermediate was transformed into the corresponding acid and then cyclized to the eight-membered ring **113** (Scheme 31) <1995TL6379>. The INAC permitted the synthesis of both the pure enantiomers of a nucleoside analogue incorporating seven-membered carbocyclic rings through the intermediacy of bridged oxazocine derivatives.



i, AcOBu^t/HClO₄, rt or SOCl₂/MeOH; ii, dimethyldioxirane, acetone, −78 °C, 60%; iii, NH₂OH·HCl, MeOH, 40 °C, 10 min; iv, NaHCO₃; v, FmocCl/NaHCO₃, 62% of **149** from **147**; vi, TFA, DCM, rt, 1 h; vii, DCC, DMAP·HCl, CHCl₃, reflux, 3 h, 39%

Scheme 31

Thus, the D-glucose derived substrate **150**, through sequence A, gave intermediate **151** bearing a nitron functionality at C-5 with an alkene moiety at C-3 (glucose numbering). INAC of the intermediate **151** led to the bridged oxazocine **109** (Scheme 32). The reaction was conducted in seven different solvents and although the yields were all excellent (80–98%), the best results were obtained with protic solvents <1996T11265>. Diazocine **109**, by the reaction sequence described in Section 14.04.3.5, gave (1*R*,2*R*,5*R*,7*R*)-**116b**. Alternatively **150**, through sequence B, afforded the intermediate **152** bearing the nitron functionality at C-1 and the alkene moiety still at C-3. INAC of this nitron led to (1*S*,2*S*,5*S*,7*S*)-**116b** with 50% overall yield (Scheme 32) <1999JOC2304>.

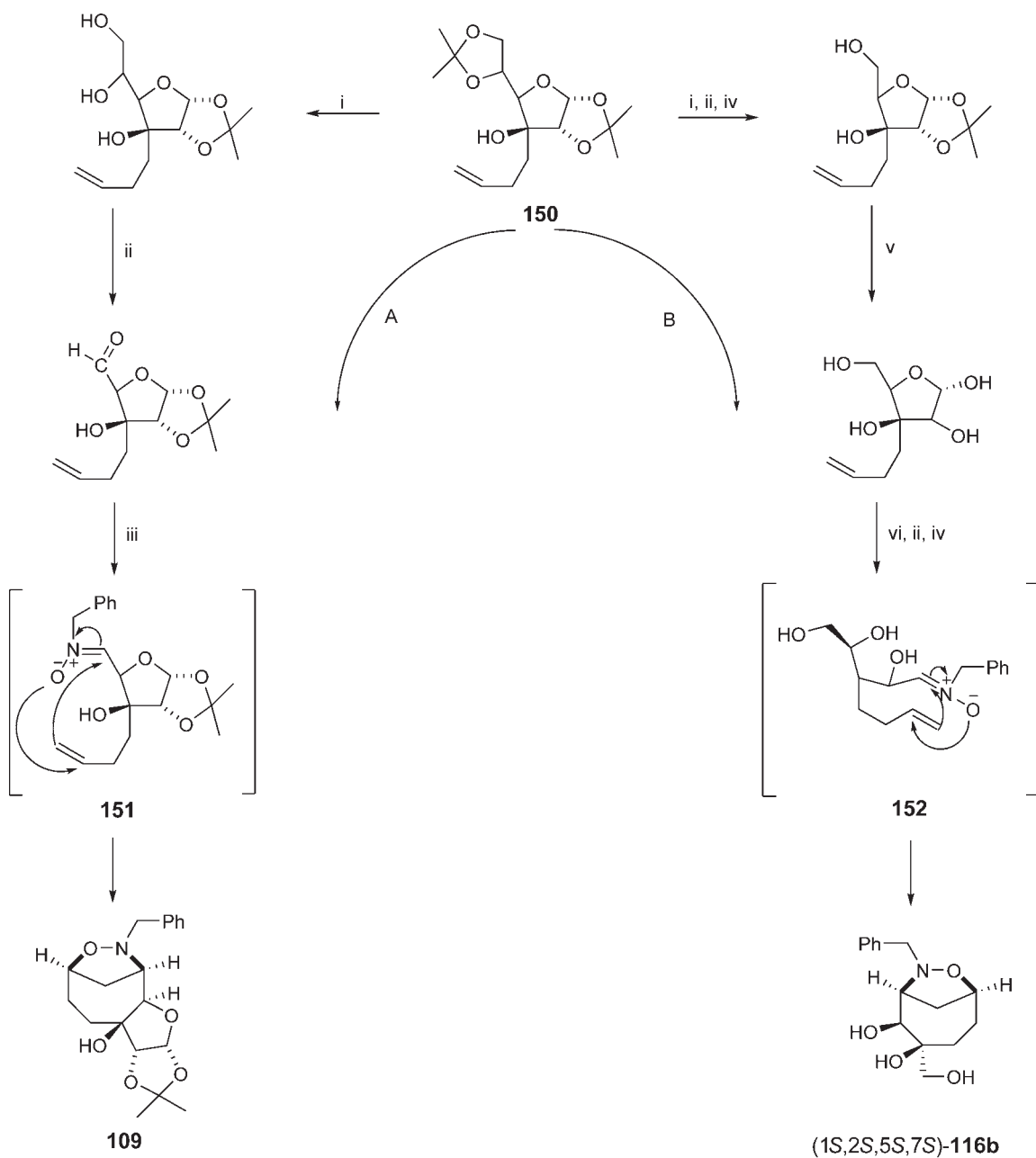
Both enantiomers of **116b**, through the sequence described in Section 14.04.3.4, led to the enantiomeric pair of the seven-membered carbocyclic nucleosides **129** <1997JOC8948, 1999JOC2304, 2003ARK75>.

Nitron **153**, obtained by a regiospecific nucleophilic substitution of the nitrogen atom of the (*Z*)-benzaloxime and excess of 1,2-epoxy-5-hexene, gave as by-product the oxazocine **115**, through a 1,3-dipolar cycloaddition as a result of 1a/3b bonding. The main products were a mixture of three oxazepine cycloadducts **154** as a result of 1b/3a bonding (Scheme 33) <1997T13165>.

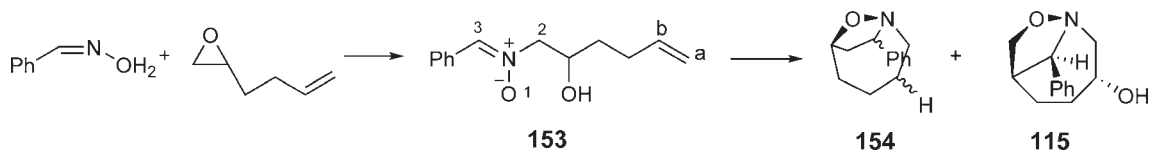
The analogous intramolecular 1,3-dipolar cycloaddition of the cyclic nitron **155**, in an attempt to get to intermediates useful for the synthesis of the cylindricine or lepadiformine natural products, unexpectedly gave by 1b/3a bonding the bridged cycloadduct oxazocine **117** in 49% yield with total diastereocontrol. From this reaction, the fused cycloadduct through 1a/3b bonding (41%) was also isolated (Equation 8) <2000TA2625>.

In a study of vinylcyclopropanes with tetranitromethane (TNM), from 1,1-divinylcyclopropane **156**, a specific 1,4-diene, the unexpected product **118**, was obtained. The formation of the nitronic ester was accompanied by homoallylic rearrangement, followed by the intramolecular 1,3-dipolar cycloaddition (Equation 9) <2002DOC9>.

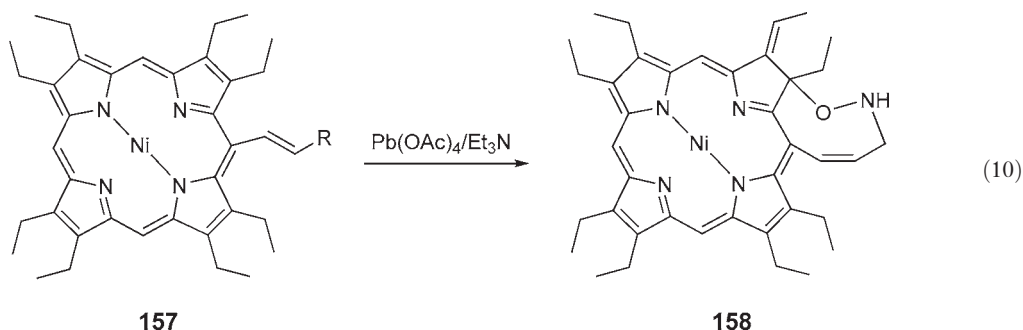
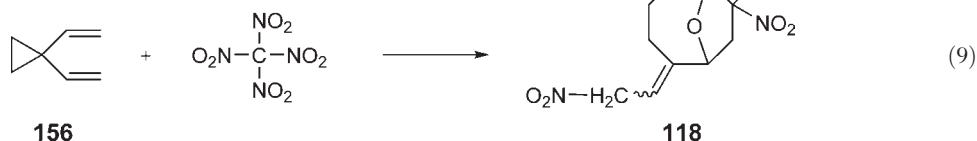
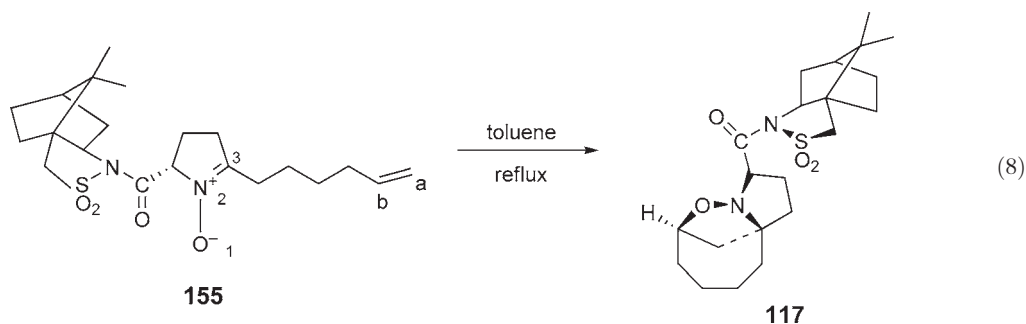
The oxime **157** (R = CH=NOH), quantitatively obtained as a mixture of the *syn*- and *anti*-isomers from the *meso-trans*-formylvinylporphyrin **157** (R = CHO), was reacted with lead tetraacetate in the presence of Et₃N to give the macrocycle with a condensed oxazocine **158**, as the result of oxidative cyclization as a single isomer relative to the *exo*-ethyldiene bond (Equation 10) <2003CHE388>.



Scheme 32

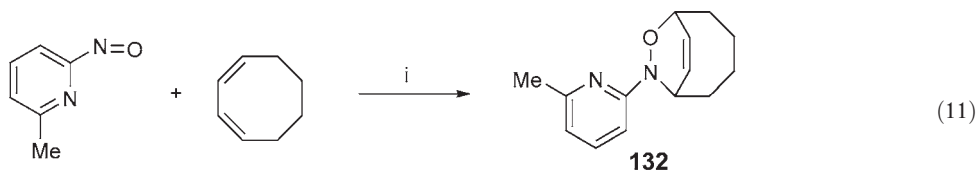


Scheme 33



14.04.3.8 Ring Syntheses by Transformation of Another Ring

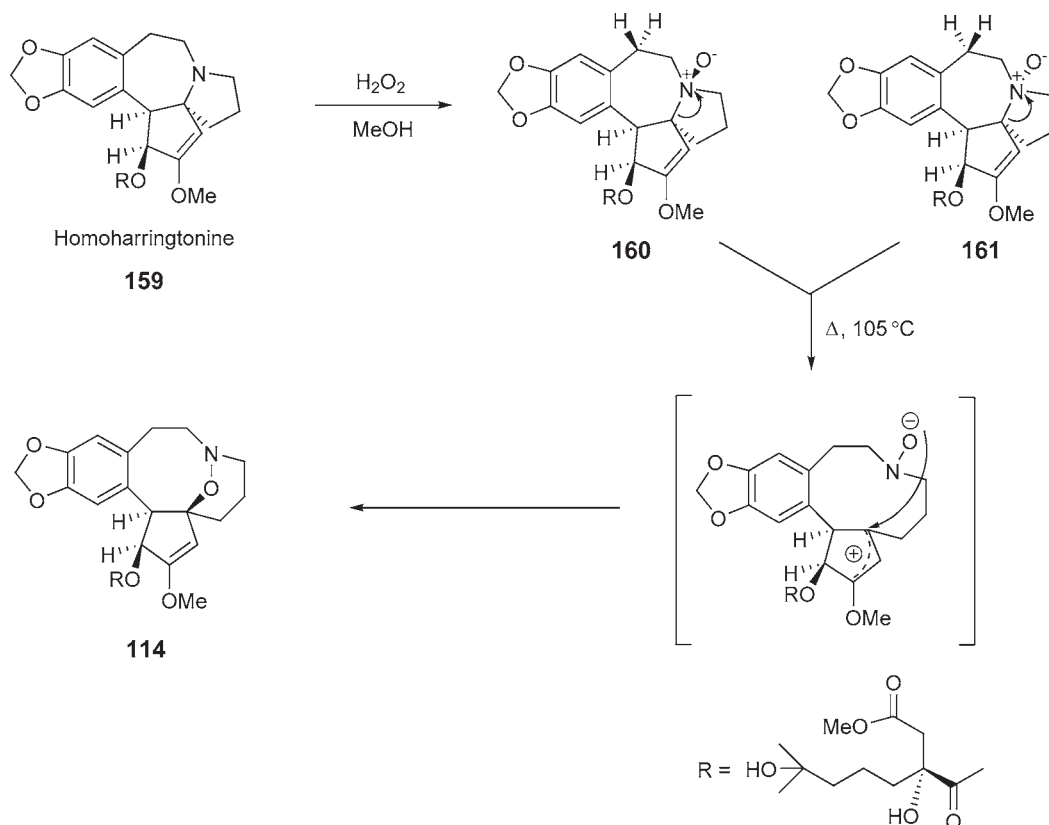
6-Methyl-2-nitrosopyridine reacted with (1*Z*,3*Z*)-cycloocta-1,3-diene to give the *N*-pyridyl-1,2-oxazocine **132**. Such a Diels–Alder reaction was conducted in the presence of a catalytic amount of an asymmetric bidentate ligand and a metal to provide an enantiomerically enriched cycloadduct; however, the ee observed was only 4% (Equation 11) <2005WO068457>.



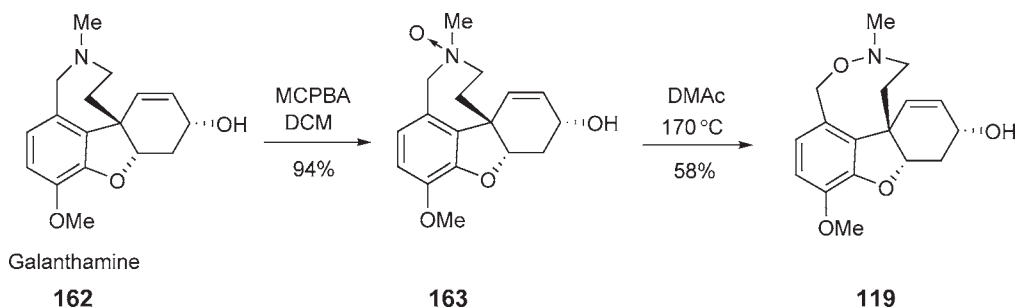
i, CuPF₆(MeCN)₄, (S)-DIFLUOROPHOS or (S)-SEGPPOS (10 mol%)-DCM, −80 to −20 °C, yield >95%

The polycondensed 1,2-oxazocine **114** was obtained from homoharringtonine **159**, an antileukemic alkaloid, during the attempt to produce analogues of the natural compound. Thus **159** was oxidized to the β-*N*-oxide **160** and α-*N*-oxide **161**, which when heated in a sealed tube in 1,2-dichloroethane gave **114** in 65% and 58% yields, respectively. The formation of **114** was explained in terms of thermal cleavage of the C(5)–N(9) bond to give a stable carbocation and subsequent attack of the oxygen anion to C-5 (Scheme 34) <1997JOC8251>.

Galanthamine **162** was converted into its *N*-oxide **163** by treatment with *m*-chloroperbenzoic acid (MCPBA) in nearly quantitative yield. Heating of *N*-oxide **163** afforded the oxazocine **119** as a result of the Meisenheimer rearrangement (Scheme 35) <2003BML2389>.



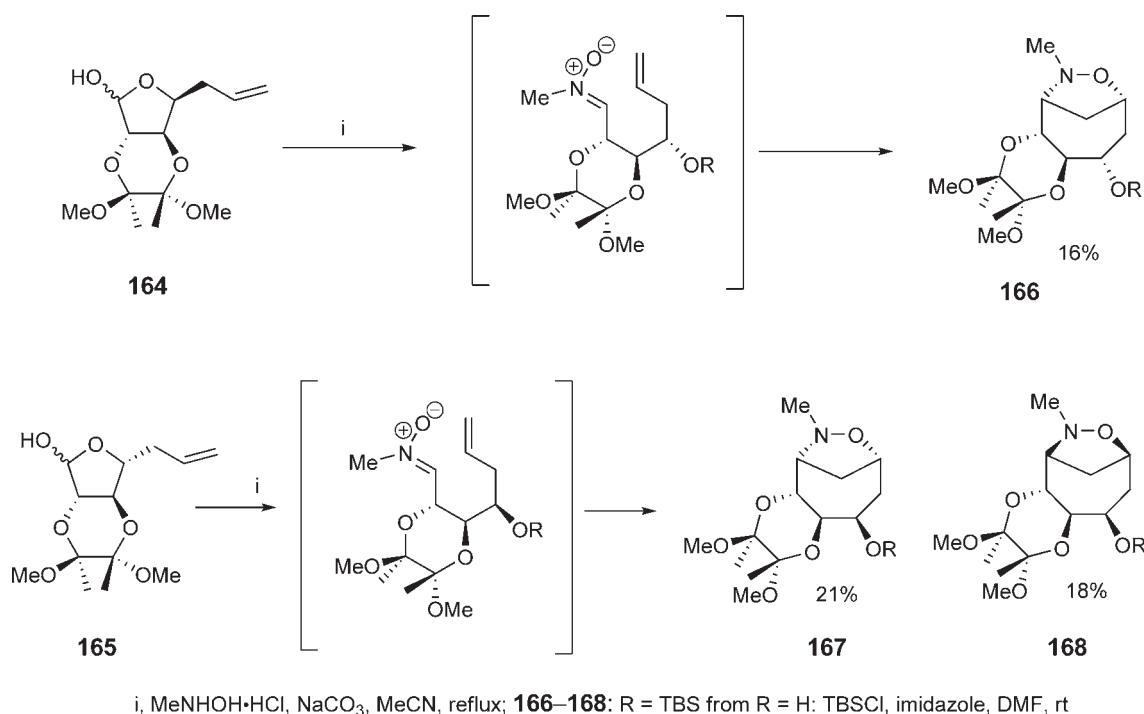
Scheme 34



Scheme 35

The *endo*-mode of INAC reaction (see Section 14.04.3.1) of lactols **164** and **165** gave the bridged 1,2-oxazocines **166** (R = H) and **167** (R = H), **168** (R = H), respectively, in poor yield. Actually, these compounds were obtained together with the *cis*- and *trans*-fused isoxazoline **112** originating by the *exo*-mode of INAC reaction, as major products (Scheme 36). The products could be characterized after their conversion into the corresponding silyl ethers **166** (R = TBS), **167** (R = TBS), and **168** (R = TBS) for ease in chromatographic separation and final desilylation. This INAC showed trivial temperature, but significant solvent, dependence. In fact, in 2-propanol, the *exo*-mode of the INAC is favored, whereas in DCM the best yields of bridged 1,2-oxazocines were obtained <2006JOC3253>.

The 5,6,7,8-tetrahydro-2*H*-1,2-oxazocine-3(4*H*)-one was detected by gas chromatography–mass spectrometry (GC/MS) in traces after a reaction sequence starting from ϵ -caprolactone, which was sequentially transformed with HBr in AcOH and MeOH into the corresponding ω -bromo methyl ester, subsequent reaction with *N*-hydroxyphthalimide, removal of the protecting group with methylhydrazine, and final cyclization with AlMe_3 <2003CJC937>.



Scheme 36

14.04.3.9 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

The RCM of alkenes or enynes represents the only strategy in the unimolecular cyclization leading to 1,2-oxazocine derivatives. The method is efficient and allows the isolation of the eight-membered heterocycles in excellent yields starting from a wide variety of alkenes and enynes. However, alkene RCM produces the cycles in higher yields. Other synthetic pathways for ring construction essentially involve INAC. Such a strategy allows for the isolation of the 1,2-oxazocines with different degree of efficacy. In some cases the yields are reasonable <1996T11265, 1999JOC2304, 2000TA2625>, whereas in other cases the approach is of no preparative interest <1997T13165, 2002DOC9>. The syntheses of 1,2-oxazocines by transformation of other rings of interest essentially involve the N-oxidation of natural polycondensed azepines and subsequent thermally driven rearrangement into the eight-membered ring. The INAC approach on hept-6-enoses shows interesting mechanistic aspects but, with yields in the range 16–21%, there would appear to be a very limited preparative interest.

14.04.3.10 Important Compounds and Applications

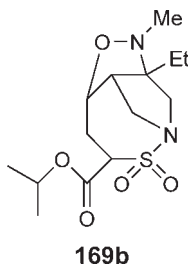
Polycondensed oxazocine **114**, the synthetic analogue of homoarringtonine **159**, was tested against P-388 leukemia cells and showed a $GI_{50} = 4.0 \mu\text{g ml}^{-1}$. This value is far higher than that shown by **159**. This indicated that the nitrogen lone pair is essential for the antitumor activity as the natural compound appears to be more keenly shared with the biologic macromolecule (via hydrogen bonding) than the oxazocine analogue <1997JOC8251>.

Oxazocine **119** is a synthetic derivative of galanthamine **162**. The latter is a tertiary alkaloid, isolated from amaryllidaceae, which is a central acting competitive and reversible inhibitor of acetylcholinesterase that enhances cognitive functions in Alzheimer's patients. However, oxazocine **119** showed a decreased potency as an acetylcholinesterase inhibitor and a marked selectivity with respect to butyrylcholinesterase, probably because butyrylcholinesterase accommodates steric bulk around the catalytic site, better than acetylcholinesterase <2003BML2389>.

14.04.4 Rings with One Nitrogen and One Sulfur (2*H*-1,2-Thiazocines) or One Oxygen and One Sulfur (1,2-Oxathiocins)

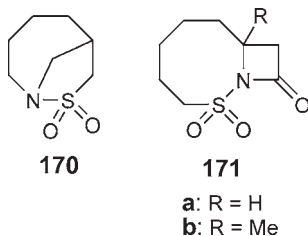
14.04.4.1 Experimental Structural Methods

No detailed X-ray crystallography study of either 2*H*-1,2-thiazocines or 1,2-oxazocins has been reported. Such a technique was utilized, only in the case, in which the unequivocal molecular framework and structural conformation of the bridged thiazocine **169b** were confirmed.

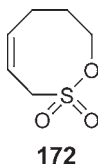


The same results were achieved by a complete assignment of the ^1H and ^{13}C NMR spectra of thiazocines **169** as well as the corresponding starting seven-membered rings bearing a nitronium moiety (see Section 14.04.4.7) to obtain their ‘fingerprints’. The NMR techniques utilized were gradient COSY, gradient heteronuclear multiple quantum-coherence spectroscopy (HMQC), and gradient HMBC. Moreover, double pulsed field gradient spin echo NOE experiments were performed in order to study their spatial conformation and to assess the stereo- and regioselectivity of the intramolecular cycloaddition leading to **169** <2002MRC307>.

For all of the thiazocines synthesized, the ^1H NMR spectra (although most were not assigned) were reported. However, derivatives **169** and the other bridged sultams of type **170** that are monosubstituted alternatively in positions 3, 4, and 8 show the methylene bridge protons in the range 3.39–4.04 ppm. The methylene protons adjacent to the sulfone moiety are found at 2.96–4.77 ppm; the methylene protons adjacent to the nitrogen resonate in the range 2.64–3.45 ppm; and the other methylene protons lie in the normal range for hydrogens bound to sp^3 carbons, 1.26–3.03 ppm, depending on the effects of the substituents present in the molecule. In the case of analogues of **170**, bearing unsaturation in position 3-4 and/or 5-6, the alkene protons resonate in the range 5.61–6.44 ppm; in these compounds, the methylene bridge protons resonate at 3.90–4.25 ppm, downfield with respect to those of the saturated ring <2001JOC3564, 2002MRC307, 2004OL1313>. The β -lactam moiety in **171** and related compounds with one unsaturation in position 6-7 does not affect the chemical shift of the thiazocine protons. Thus, the methylene protons adjacent to the sulfone group resonate in the range 3.21–3.39 ppm. The other methylene protons are found in the range 1.48–3.03 ppm. The alkene protons in the unsaturated derivatives resonate at 5.63–5.90 ppm. The methylene of the β -lactam moiety is found at 4.38–4.68 ppm when $\text{R} = \text{H}$ and 3.20–3.31 ppm in the case of $\text{R} = \text{Me}$ <2004S1696>.



Compound **172** represents the sole oxathiocin synthesized in the past decade. Its ^1H NMR spectrum showed the protons adjacent to oxygen and sulfone moiety at 4.36 and 3.90 ppm, respectively. The other methylene protons resonated at 1.94–2.41 ppm, while the alkene protons were found at 5.71–6.00 ppm <2004S1696>.



Also, ^{13}C NMR spectra were reported for all the compounds synthesized, although for some the signal multiplicities are not reported. For **169** and **170**, the resonances of the bridge methylene carbons are found at 46.8–54.2 ppm. The signals of the carbons adjacent to the sulfone moiety can be found in the range 52.0–64.7 ppm. The resonances due to carbons adjacent to nitrogen can be found at 39.5–54.1 ppm. The other carbons of the eight-membered ring resonate at 18.4–41.5 ppm. The sp^2 carbons in unsaturated thiazocine can be found in the range 119–138 ppm. The carbonyl carbon in **170**, bearing a carbonyl functionality in position 3, resonated at 174.9 ppm, while the carbonyl resonance of the β -lactams **171** can be found in the range 163.0–164.6 ppm. The methylene carbon of the four-membered ring resonated at 40.3–46.3 ppm in the case of saturated thiazocines and 45.0–50.8 ppm in the case of the 3,4-unsaturated ones. The carbons belonging to the eight-membered rings fall in the ranges already seen for other sultams <2001JOC3564, 2002MRC307, 2004OL1313, 2004S1696>. The ^{13}C NMR spectrum of oxathiocin **172** showed the carbons adjacent to the oxygen and sulfone groups at 71.1 and 48.66 ppm, respectively, the other sp^3 carbons signals in the range 23.00 and 26.7 ppm, and the sp^2 carbon resonances at 118.7–136.7 ppm <2004S1696>.

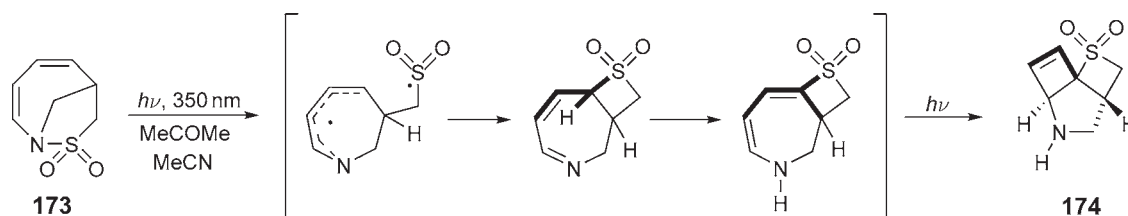
No fragmentation study has been undertaken on thiazocines and oxathiocins but in one case liquid chromatography–mass spectrometry (LC/MS) methods were used to purify **169** <2002MRC307>. All the papers with an experimental section, report data, although limited to molecular or quasi-molecular ions, for all synthesized derivatives. In particular, for **171** LC/MS data, the $\text{M} + \text{K}^+$, $\text{M} + \text{Na}^+$, $\text{M} + \text{NH}_4^+$, and $\text{M} + \text{H}^+$ quasi-molecular ions have appeared <2004S1696>. The electrospray high-resolution mass spectrometry (ES HRMS) and electron ionization high-resolution mass spectrometry (EI HRMS) data for **170** reported the $\text{M} + \text{Na}^+$ quasi-molecular and molecular ions, respectively <2004OL1313, 2001JOC3564>. The GC/MS spectrum of the oxathiocin **172** showed the molecular ion of m/z 162, a peak at m/z 98 due to the extrusion of SO_2 , which is probably the origin of the m/z 80 peak for the loss of water. There are also present consecutive peaks typical of aliphatic chains <2004S1696>. Since all the thiazocine derivatives are cyclic sulfonamide, sultams, authors have reported the asymmetric and symmetric stretching of the sulfone moiety generally in the ranges 1371–1323 and 1151–1128 cm^{-1} , respectively <2001JOC3564, 2004CC1848, 2004OL1313, 2004S1696>. Also, the two stretching bands for the oxathiocin **172** fall in the range above indicated <2004S1696>.

14.04.4.2 Thermodynamic Aspects

Also in this chapter, as in CHEC-II(1996), all of the synthesized thiazocine derivatives reported are sulfonamides, in particular, bridged and/or fused. Unsubstituted bridged thiazocine **170** is a white hydrolytically stable crystalline solid having the melting point at 111–112 °C. This is strange considering that the corresponding unsubstituted hexahydro-1,2-thiazocine 1,1-dioxide, which is supposed to guarantee a better solid-state packing, melts at 70–71 °C, as reported in CHEC-II(1996). Substitution at position 3 or 8 with acetoxy, propenyl, or benzyl groups resulted in colorless oils as well as for the 3-carbonyl derivative <2001JOC3564>. The 4-bromo derivative is a white solid; however, no melting point was reported. Also, unsaturation at the position 3,4 and/or 5,6 of **170** produced colorless oils <2004OL1313>. Condensation with a β -lactam moiety at the position 2,3 of the eight-membered ring produced **171** as white solids melting at 184–185 °C ($\text{R} = \text{H}$) and 94–96 °C ($\text{R} = \text{Me}$). Unsaturation at the positions 6,7 of the thiazocine ring lowered the melting points to 121–123 and 85–89 °C, respectively <2004S1696>. The sole oxathiocin derivative synthesized in the past decade, **172**, has a low melting point (38 °C), which is practically the same as that of the corresponding saturated derivative reported in CHEC-II(1996) (37–37.5 °C) <2004S1696>. Data reported in the experimental sections of the papers dealing with thiazocines indicate that such compounds are soluble in common organic solvents. They are generally purified by flash chromatography on silica gel with a variety of eluents: Et_2O , Et_2O /petroleum ether <2004CC1848, 2004S1696>, EtOAc , EtOAc /hexane <2001JOC3564, 2004OL1313>, DCM /hexane <2001JOC3564>. Compounds **169** were purified through a high-performance liquid chromatography (HPLC) column C-18 YMC and aqueous TFA (0.05–0.035%) <2002MRC307>. Oxathiocin **172** was purified in silica gel with Et_2O /pentane 2:3 <2004S1696>. As in CHEC-II(1996), conformational issues have scarcely been addressed for the thiazocines and oxathiocins, and in this edition neither crystallographic data nor calculation studies have been reported.

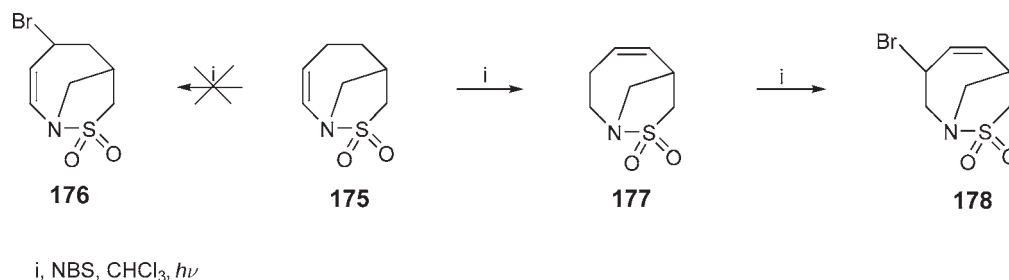
14.04.4.3 Reactivity of Nonconjugated Rings

The conjugated diene **173**, irradiated at 350 nm, isomerized via a two-photon process, to give the spiro heterocycle **174** (Scheme 37). The reaction, carried out in pure acetone, produced the spiro **174** in 52% yield but polymer formation on the wall of the reaction vessel was also evident. This tendency was significantly reduced upon dilution with MeCN (acetone/MeCN 2:1); the photoisomerization was slower with lower yield (42%) but the starting material was easily recycled <2004OL1313>.



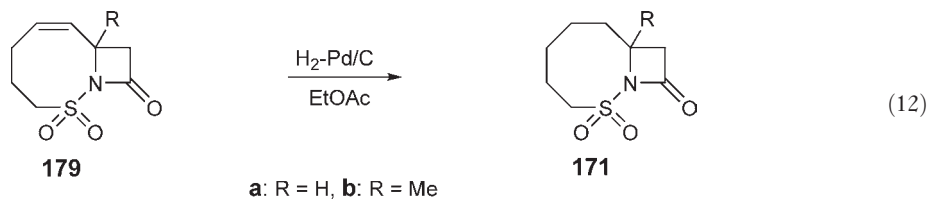
Scheme 37

Attempted allylic bromination of the bridged thiazocine **175** did not give the expected product **176** but rather generated the monounsaturated sultam **177**, which, however, could be brominated to give **178** (Scheme 38) <2004OL1313>.

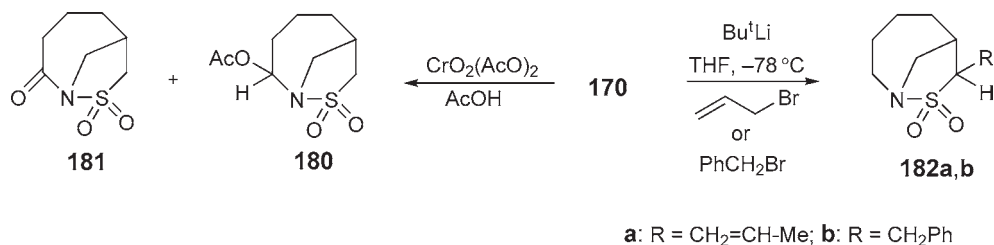


Scheme 38

The β -lactam-fused thiazocines **179** were catalytically hydrogenated in EtOAc to give the saturated **171** (Equation 12). A proper choice of solvent was crucial to the success of this reduction, since the experiment failed when conducted in MeOH <2004S1696, 2004TL3589>.



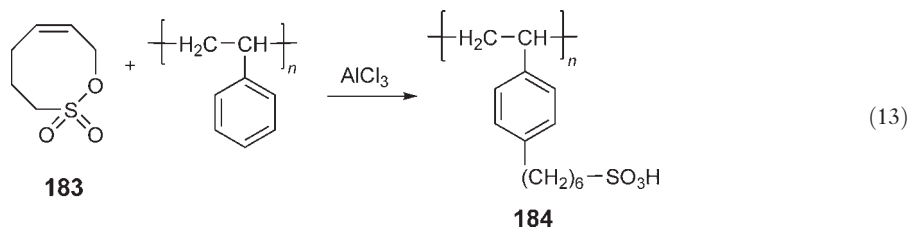
Chromyl acetate oxidation in glacial acetic acid admixed with Ac₂O of oxazocine **170** led, via a rapid exothermic reaction, to acetate **180** (42%) and ketone **181** (28%) (Scheme 39). Although the combined yields of these two products make it possible that other positional isomers could have been formed, none were found, confirming that the methylene group α to nitrogen in such ring is inherently the most reactive toward this peculiar oxidant. Such reactivity is unusual since chromyl acetate is recognized to be capable of oxidizing inactivated CH bonds in either bicycloalkanes or polycycloalkanes as well as reacting more rapidly with tertiary CH than with methylene groups.



Scheme 39

In **170**, the only tertiary hydrogen is positioned at the bridged site and is inert <2001JOC3564>; however, dilution of the reaction medium with DCM enhanced the level of the ketone production and gave rise to an inverted distribution of **180** and **181**, in 23% and 70% yield, respectively <2004OL1313>. Although attempts to deprotonate thiazocine **170** with a variety of bases failed; with *t*-butyllithium, regio- and stereoselective allylation and benzylation took place affording the corresponding derivatives **182a** and **182b** (Scheme 39) <2001JOC3564>.

Tetrahydro-oxathiocin 2,2-dioxide **183** was used for the production of the polymer **184** by reaction with polystyrene in the presence of aluminium trichloride (Equation 13) <2006USP0135702>.



14.04.4.4 Reactivity of Substituents Attached to Ring Carbon Atoms

Flash vacuum pyrolysis of the 3-acetoxythiazocine **180** produced the 3,4-unsaturated thiazocine **175** in poor yield (8%) <2004OL1313>, whereas the bromothiazocine **178** underwent E₂ elimination to give the conjugated diene **173** in good yield (80%) <2004OL1313>.

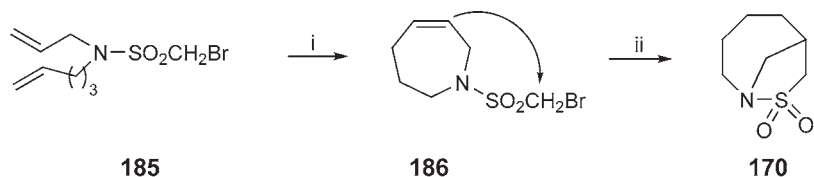
14.04.4.5 Reactivity of Substituents Attached to Ring Heteroatoms

The only report dealing with 2*H*-1,2-thiazocine showed that it underwent copper-catalyzed reaction with aryl, heteroaryl, and alkenyl halides (Cl, Br, I) to give the corresponding N-substituted derivatives <2002WO085838>.

14.04.4.6 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.04.4.6.1 Ring syntheses from C₆NS units

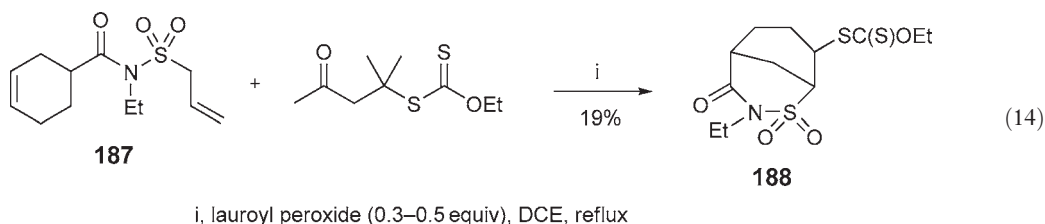
The doubly unsaturated sulfonamide **185**, obtained in excellent yield from *N*-allyl-1-bromomethanesulfonamide and pent-4-en-1-ol by Mitsunobu alkylation, underwent a smooth RCM to give the bromomethylsulfonamide derivative **186** in nearly quantitative yield. Its free radical cyclization afforded the bridged thiazocine **170** together with the reduction product *N*-methylsulfonamidoazepine, as a minor component (12%) (Scheme 40) <1999JA8126>. When **186** was heated in the presence of Pd(OAc)₂ in DMF containing K₂CO₃, tri-2-furylphosphine, and 4 Å molecular sieves at 100 °C for 72 h, the alkene **177** and conjugated diene **173** in 67% and 5% yield, respectively, together with a minor amount of the reduction product were isolated <2004OL1313>.



i, RuCl₂(=CHPh)(PCy₃)₂, DCM, 40–50 °C, 98%; ii, Bn₃SnH, AIBN, benzene, 60 °C, 69%

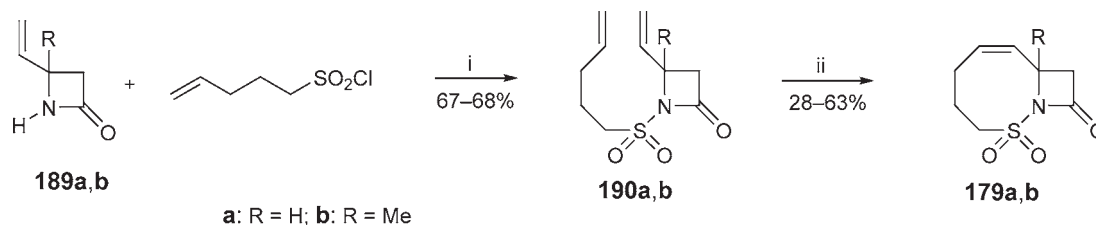
Scheme 40

In the study of amidyl radicals, obtained from *N*-amidosulfonyl radicals by extrusion of sulfur dioxide, sulfonamide **187** reacted with *S*-(1,1-dimethyl-3-oxobutyl) *O*-ethyl dithiocarbonate to give, as minor product, the thiazocinone **188** via cyclization of the *N*-amido sulfonyl radical. The major product (55%) was the corresponding seven-membered azepinone from the cyclization of the amidyl radical (Equation 14) <2004CC1848>.



14.04.4.6.2 Ring syntheses from C₄S + C₂N units

Rapid access to β -lactams fused to a sultam moiety was developed from azetidinone derivatives **189a** and **189b**, which were conveniently prepared by cycloaddition of chlorosulfonyl isocyanate with 1,3-butadiene and isoprene. Reaction of the four-membered ring with pent-4-ene-1-sulfonyl chloride produced the *N*-sulfonyl derivatives **190a** and **190b**, which underwent an RCM to give the heterobicycles **179a** and **179b**. The eight-membered sultam **179b** (R = Me) was isolated in good yield (63%), whereas the unsubstituted **179a** (R = H) was obtained in low yield (28%) (Scheme 41). This latter reactivity difference is not immediately apparent, but may be attributed to the conformational requirements imposed by the azetidin-2-one template <2004S1696, 2004TL3589>.



i, **189** + BuLi, THF, –78 °C, then pentenyl sulfonylchloride, –78 °C to rt 16 h; ii, Grubbs' catalyst, DCM, reflux

Scheme 41

14.04.4.6.3 Oxathiocin ring synthesis

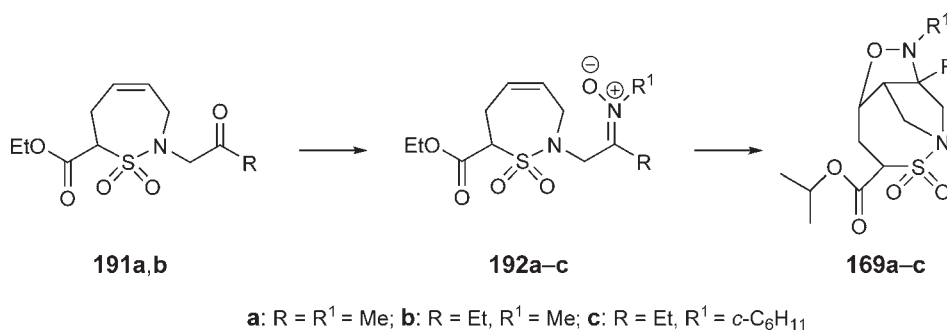
The β,γ -unsaturated eight-membered sultone **172** was efficiently prepared from vinylsulfonyl chloride and pent-4-en-1-ol to give, in 91% yield, the corresponding sulfonate, which underwent an RCM, using a second-generation Grubbs' catalyst, to give the final product in high yield (82%). Attempted cyclization of hex-5-enyl ethenesulfonate to give α,β -unsaturated eight-membered sultone failed <2004S1696>.

14.04.4.7 Ring Syntheses by Transformation of Another Ring

Thiazepines **191a** and **191b**, bearing an exocyclic ketone function and endocyclic alkene moiety, reacted with hydroxylamines to give the bridged thiazocines **169a–c** by an INAC. Thiazocines **169** were obtained in good yields when the reaction was carried out in EtOH, whereas, in benzene, a mixture of the cyclized products and uncyclized intermediate nitron–alkenes **192a–c** was obtained (Scheme 42) <2002MRC307>.

14.04.4.8 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

None of the four reported syntheses of 1,2-thiazocine derivatives can be considered particularly advantageous in terms of yield; however, with the exception of the cyclization of the *N*-amidosulfonyl radical, bridged and/or fused thiazocines are generally obtained in two steps in ca. 60% yield. The synthesis of the oxathiocin is, however, convenient, since the two steps led to the final heterocycle with 75% yield.



Scheme 42

14.04.4.9 Important Compounds and Applications

The 3,4,5,6,7,8-hexahydro-1,2-oxathiocin 2,2-dioxide is the key component for the synthesis of a polymer used for proton exchange membrane fuel cells (PEMFCs). Membranes made with this polymer are pliant, do not expand much during wet conditions, and are chemically, hydrolytically, and thermally stable <2006USP0135702>.

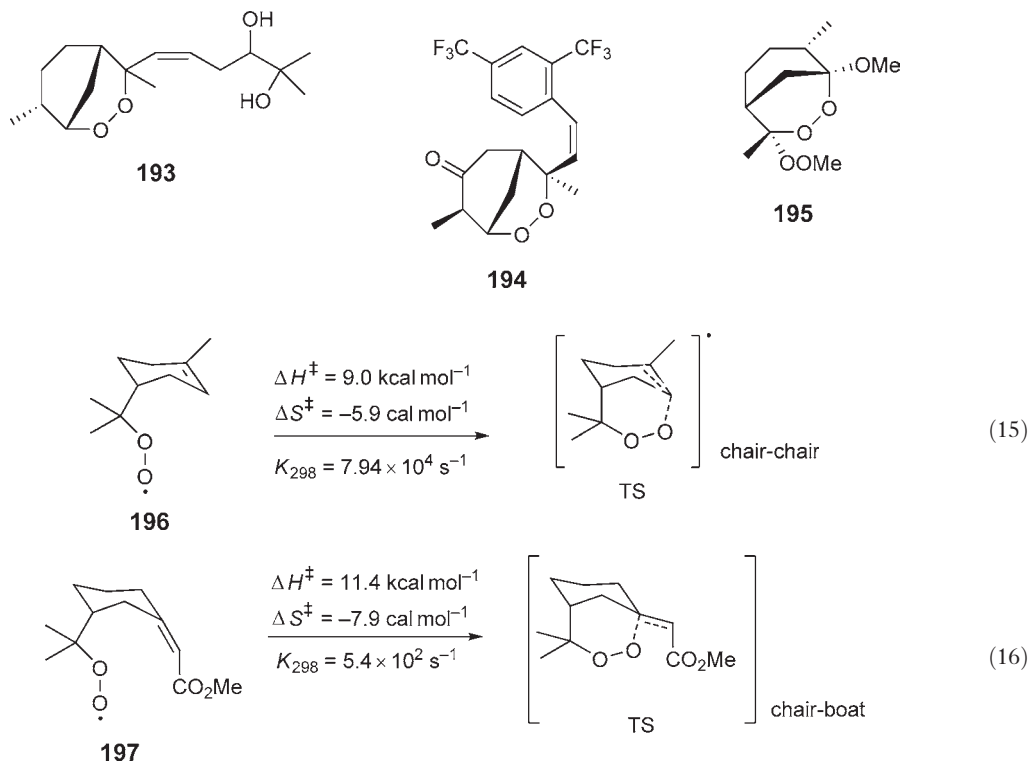
14.04.5 Rings with Two Oxygens (1,2-Dioxocins)

14.04.5.1 Theoretical Methods

Theoretical calculations dealing with 1,2-dioxocins are related to the remarkable antimalarial activity showed by both natural and synthetic compounds containing the eight-membered ring. Thus, two reports propose quick *in silico* discovery of new candidates as possible antimalarial agents and a third report gives a contribution to clarify the mechanism of action of antimalarial agents. Of which, only one utilizes theoretical calculations to determine the conformation of a 1,2-dioxocin derivative.

The molecular electrostatic potentials (MEPs) of the natural dioxocin yingzhaosu A **193** and some synthetic analogues have been calculated and studied as a means of distinguishing between high and low antimalarial activity. To facilitate a comparison, the dimensionality of the MEP was reduced by Kohonen neural network transforms. The reduction revealed that peroxides exhibiting high antimalarial activity are characterized by a continuous strip of negative electric potential surrounding the molecule, whereas less active compounds show a broken strip <2000JCI354>. Simple linear discriminant-based quantitative structure–activity relationship (QSAR) models for the classification and prediction of antimalarial activity use TOMOCOMD-CARDD (Topological Molecular Computer Design-Computer Aided ‘Rational’ Drug Design) fingerprints, so as to enable computational screening from virtual combinatorial data sets. Thus, a database of 1562 organic compounds having large structural variability, 597 of them antimalarial agents, such as the dioxocins yingzhaosu A **193** and arteflene **194**, and 965 compounds having other clinical uses, was processed by a k-means cluster analysis in order to design training and predicting sets. Subsequently, two linear classification functions to discriminate between antimalarial and non-antimalarial compounds were derived. The models, including nonstochastic and stochastic indexes, correctly classified more than 93% of the data set, in both training and external prediction data sets <2005MI1082>. Theoretical calculations have been performed on the interactions of several endoperoxides, which are potential antimalarial agents, including arteflene **194**, with two possible sources of iron in the parasite: the hexa-aquo ferrous ion $[\text{Fe}(\text{H}_2\text{O})_6]^{2+}$ and heme. DFT calculations showed that both iron sources, upon reaction with all endoperoxides considered, initially generating a Fe–O bond, followed by cleavage of the O–O bond to oxygen radical species. Afterward, they can be transformed into carbon-centered radicals of greater stability. In the case of $[\text{Fe}(\text{H}_2\text{O})_6]^{2+}$, as the iron source, the oxygen-centered radical species are more likely to react further akin to Fenton’s reagent, whereby iron salts favor hydrogen peroxide to act as an oxidizing agent and that solvent plays a major role; whereas, when reacting with heme, the oxygen-centered radicals interconvert into more stable carbon-centered radicals, which can then alkylate heme. Successive cleavage of the Fe–O bonds led to stable and inactive antimalarial products. Thus, the reactivity of the endoperoxides, as antimalarial agents, is greater with iron hexahydrates for radical-mediated damage than heme, which leads to unreactive species. Considering that nanomolar concentrations of hydrated metal ions could catalyze the reactions leading to damage of the parasites, this might be an alternative or competitive reaction responsible for the antimalarial

activity <2005JST87>. PM3 calculations indicated that the 1,2-dioxane portion of the bridged 1,2-dioxocin **195** adopts a boat conformation <2000TL3145>. The activation enthalpies and entropies in the intramolecular cyclization of the unsaturated peroxy radical **196** and **197** were calculated at the UB3LYP/6-31G(d) level of theory with Gaussian 98 package. These results suggested that the cyclization of the peroxy radical **196** seems to proceed via the TS with a chair-chair conformation (Equation 15), while in the case of peroxy radical **197** the chair-boat TS is more favorable (Equation 16), and the intramolecular cyclization of peroxy radical **196** is much easier than that of **197** (due to the larger steric congestion in the TS from **197**) <2003JOC7361>.



14.04.5.2 Experimental Structural Methods

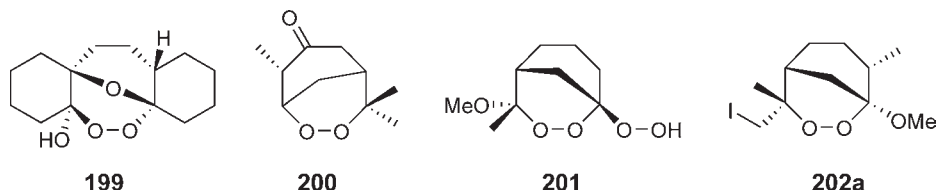
The structure of several 1,2-dioxocin derivatives was determined by using X-ray crystallography techniques and some detailed X-ray studies were reported.

Single crystal X-ray analysis of sulfonyl endoperoxide **198a** provided the 3-D structure, in which the absolute configuration of stereocenters 1*S*, 4*S*, and 5*S* in the bicyclic system was the same as that reported for the corresponding stereocenters in yingzhaosu A **193** (*vide infra*) as well as the methyl group on the 8*S* carbon, which is equatorially positioned. Both rings adopt the chair conformation. Evaluation of the data revealed a difference in the through-space distances between the nonequivalent hydrogen atoms of the C(12)HH' moiety and the oxygen atoms. In the case of C(12)H proton, the through-space distances were 3.175 Å for H(12)–O(2) and 2.528 Å for H(12)–O(3); on the other hand, for C(12)H' proton, the corresponding distances were shorter and very close to each other: 2.431 Å for H'(12)–O(2) and 2.491 Å for H'(12)–O(3). Compound **198a** is characterized by *syn*-arrangement of O(2)–O(3)–C(4)–C(12) bonds, while **198b** is characterized by *anti*-arrangement of O(2)–O(3)–C(4)–C(12) bonds <2002T2449>.

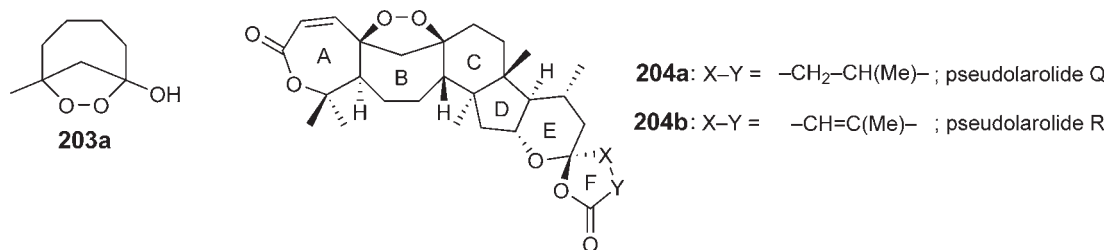


X-Ray diffraction determined the structure of **199**, in which the bond lengths have standard values, 1.513–1.538 Å for C–C and 1.429–1.465 Å for C–O and O–O. Most of the angles are in the range 108.1–113.9°. There is an

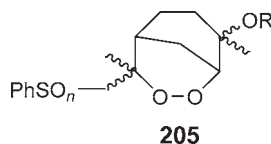
intermolecular H-bond between the hydroxyl of any molecule with the O-4 oxygen bridge of the next b-translated molecule ($\text{O}-\text{H}\cdots\text{O}(4)=3.035\text{ \AA}$). All other contributions to the packing cohesion are through van der Waals interactions. The molecular conformation is rigidly fashioned because of the sp^3 hybridization. Examination of the region surrounding the peroxide showed that the local accessible surface including O-1, O-2, and the next hydrogen is almost planar so that there is no steric hindrance for an attack of the peroxide moiety <2003OBC2859>. X-Ray crystal structure of **200** showed the peroxide ring in the chair form with axial and equatorial methyl groups <1998TL6065>. X-Ray crystallographic analysis of **201** showed that the two rings adopted a chair-boat arrangement. The dioxane ring exhibited significant distortion from the ideal boat conformation and the methoxy substituent was located at the *endo*-position favoring an anomeric interaction with the ring. The molecular skeleton of another analogue of yingzhaosu A **193**, **202a**, also determined by X-ray crystallographic analysis, has the same chair-boat arrangement while the natural compound, in its crystal structure, adopted the alternative chair-chair arrangement <2001T5979>.



The ORTEP plot of **203** shows that in the asymmetric unit there are two independent molecules <2005T4831>. X-Ray crystallography was also useful in the determination of the structure of pseudolarolides Q and R, **204a** and **204b**, which were obtained from natural sources containing a dioxocin moiety <2004T4931>. The X-ray crystallography data were reported for the natural occurring yingzhaosu A **193**, <2005JOC3618> as well as for other synthetic bridged 1,2-dioxocins, mainly yingzhaosu A analogues <1995JA9927, 1998SL122, 2004AGE4193, 2006BML2991>.

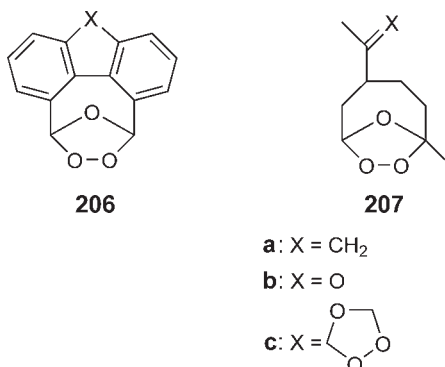


All of the 1,2-dioxocin derivatives reported in the past decade were structurally supported with ^1H NMR spectra. Compounds belonging to the general formula **205** are analogues and/or precursors of the natural **193**. Such a general formula includes three series of compounds: sulfonyl ($n=2$), sulfinyl ($n=1$), and sulfenyl ($n=0$) derivatives. The chemical shifts of the eight-membered ring protons are unaffected or marginally affected by the oxidation state of the sulfur with the exception of the methyne of position 5. Thus, C-1 protons resonate in the range 3.59–4.52 ppm. The methylene protons in position 6 can be found in the range 1.67–2.02 ppm with the sulfenyl series ($n=0$) that lies in the lower figures of the range. The C-7 protons resonate at 1.58–2.39 ppm and the sulfonyl series ($n=2$) occupies the upper part of the range. The bridge C-9 protons resonate at 1.76–2.39 ppm. The C-5 protons of the sulfonyl series ($n=2$) resonate at 2.03–2.39 ppm, while those of the sulfinyl series ($n=1$) can be found at 1.80–2.25 ppm and the sulfenyl series ($n=0$) at 1.74–1.91 ppm <1998BML903, 1998SL122, 2000TL3145, 2002JME4732, 2002T2449, 2003JOC7361, 2003JME2516, 2005JOC3618>.



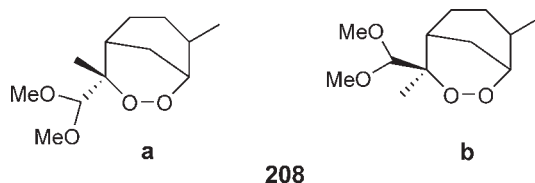
In oxygen-bridged 1,2-dioxocin fused to phenanthrene system **206** ($\text{X}=\text{CH}=\text{CH}$) and related derivatives, the protons adjacent to the oxygen centers resonate at 5.63–6.67 ppm and the aromatic protons can be found in the range 7.57–8.05 ppm <2000EJO335, 2002HCA1, 2004JKC207>. In the case of fluorene-fused 1,2-dioxocin **206** ($\text{X}=\text{CH}_2$), the protons adjacent to the oxygen atoms resonate in the same range, whereas the aromatic protons can be found at

7.24–7.59 ppm <2000EJO335, 1999MIBKC969>. The uncondensed oxygen-bridged 1,2-dioxocins **207** and related compounds fused to nonconjugated rings exhibit the oxygen-adjacent protons at higher fields, 5.34–5.62 ppm <1996T14813, 2000JBS59, 2001EJO1899, 2005HCA2865>. The two perhydro-1,2-dioxocins derivatives di- or poly-substituted with methyl, chloro, or iodomethyl groups in 3,4,5,8-positions show the oxygen-adjacent protons in the range 3.60–4.20 ppm and the other methylene or methyne protons at 1.10–2.42 ppm <2000JOC8407, 2003T525>.



Analysis of the ¹H and ¹³C NMR spectra of sulfonyl endoperoxides **198a** and **198b** and the corresponding sulfinyl (–CH₂–SO–Ph) and sulfenyl derivatives (–CH₂–S–Ph), coupled with the COSY, HMQC, and NOE difference data, allowed a full assignment of the resonance signals. It was shown that diastereomers **a** and **b** exhibited very similar NMR patterns for atoms and groups attached to the C-8 stereogenic center. However, the NMR patterns related to atoms and groups bound to the stereogenic center C-4 are significantly different for **a** and **b** diastereomers. This indicates that all the diastereomers have the same configuration at C-8 and differ in their configurations only at C-4 <2002T2449, 2003JME2516>.

The configuration of the substituents on the stereogenic atoms C-4 and C-8 was further corroborated by the NOE difference experiments as shown for **208a** and **208b**, intermediates in the total synthesis of yingzhaosu A **193**. Thus, hydrogen atoms of **208a** and **208b** showed a remote NOE, upon irradiation of the corresponding axial C-9 hydrogen atom, confirming the (8*R*)-configuration of this stereogenic center. The signal of the C-10 methyl protons of **208b** showed an enhancement through interaction with the axial C-7 proton. The NOE data confirmed the stereochemistry at C-4 on the basis of the enhancement of the acetal proton signal of **208a** upon irradiation of the equatorial C-9 proton, indicating an (*S*)-configuration. Such an interaction was not observed in the case of **208b** in which the acetal proton showed an NOE with the equatorial C-6 hydrogen and axial C-7 proton <2005JOC3618>. The difference in through-space distances between the diastereotopic C(12)HH' protons and the O-2 atom, observed in the single crystal X-ray analysis of **198a**, is reflected in the ¹H NMR spectrum. The additional deshielding effect of O-2 atom is stronger on the H'(12) proton than on its geminal H(12) proton. Thus, the typical AB quartet appeared at 4.23 and 3.27 ppm. In contrast with **198b**, due to the *anti*-arrangement between O-2 and C(12)HH', both distances are more remote through-space from O-2 and are less deshielded; the corresponding AB quartet appeared at 3.14 and 3.33 ppm. A long-range coupling was observed as a cross-peak of the H'-12 proton and Me-11 in the COSY spectra; such an interaction usually resulted in the broadening or splitting (*J* = 0.3–0.7 Hz) of Me-11 and the downfield component of the C(12)HH' pattern. The chemical shift values of the Me-10 are always very similar for both **a** and **b** diastereomers and are not influenced by the oxidation state of the sulfur atom. Distinctive features for the **a** series in the ¹H NMR spectra are a downfield chemical shift for C(12)HH' AB quartet of Δ(δ H'–H) values of ca. 1 ppm for sulfonyl endoperoxides, and 0.4 ppm for sulfenyl and sulfinyl endoperoxides as well as a chemical shift of the Me-11 at 1.5 ppm for the sulfonyl and sulfinyl series and 1.25 ppm for the sulfenyl series. For the series **b**, the chemical shift difference C(12)HH' AB quartet of Δ(δ H'–H) is ca. 0.2 ppm for sulfonyl series and 0.1 ppm for sulfenyl and sulfinyl series. Typically a singlet at 1.8 ppm is observed for the Me-11 in the sulfonyl and sulfinyl series and at ca. 1.55 ppm for the sulfenyl series <2002T2449, 2003JME2516>. The two methyl groups at C-4 of **200** have characteristic and quite different ¹H chemical shifts (1.10 and 1.52 ppm). Significantly the C-4 axial methyl group of arteflene **194** (*R*)-configuration at C-4) has chemical shift of 1.54 ppm. Such an assignment was useful to assign configuration of endoperoxides, analogues of **193**, with antimalarial activity bearing a methyl and vinyl at C-4 <1998TL6065>. The NMR techniques such as ¹H–¹H COSY, HMQC, HMBC, as well as NOESY experiments, also performed at variable temperature, had a fundamental role in determining the structure and configuration of bridged and/or fused 1,2-dioxocins <1999TL8391, 2004T4931, 2005P599>.



208

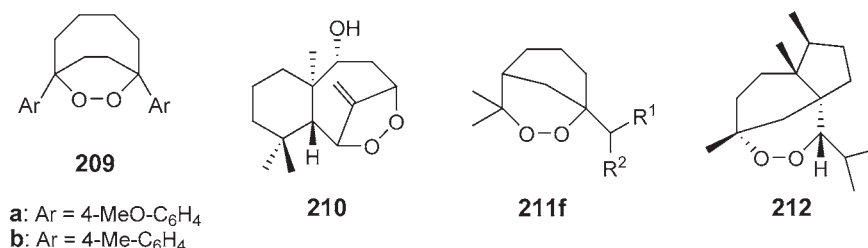
The ^{13}C NMR spectra, with some rare exception, were recorded in all reports dealing with 1,2-dioxocins. The ^{13}C chemical shifts of the ring carbon atoms of **205** are practically unaffected by the oxidation state of the sulfur. Thus, C-1 resonances can be found in the range 77.3–82.5 ppm; at lower field, there are the C-4 signals (82.3–83.9 ppm), whereas the methylene bridge carbons C-9 resonate at 23.2–24.6 ppm. In the same region, C-5, C-6, and C-7 carbons resonate at 28.4–36.0 ppm and the C-8 carbons, bearing an oxygen, at 71.2–86.6 ppm <1998BML903, 1998SL122, 2000TL3145, 2002JME4732, 2002T2449, 2003JOC7361, 2003JME2516, 2005JOC3618>.

The phenanthrene-fused oxygen bridged 1,2-dioxocin **206** ($\text{X} = \text{CH}=\text{CH}$) and related derivatives showed the carbon atoms adjacent to the oxygens at 99.3–106.6 ppm and the aromatic carbons in the usual range, 125.5–135.1 ppm <2000EJO335, 2002HCA1, 2004JKC207>. Oxygen-bridged 1,2-dioxocin fused to the fluorene system **206** ($\text{X} = \text{CH}_2$) exhibited the carbons adjacent to oxygens at 104.3 ppm, the aromatic carbons at 125.9–144.4 ppm, whereas the methylene carbon was found at 37.6 ppm <2000EJO335, 1999MIBKC969>. The uncondensed oxygen-bridged 1,2-dioxocins **207** and related compounds fused to nonconjugated rings exhibited the oxygen-adjacent carbons over a wider range, 94.1–112.5 ppm <1996T14813, 2000JBS59, 2001EJO1899>. The ring carbon atoms adjacent to the oxygens of perhydro-1,2-dioxocins alternatively di- or polysubstituted in 3,4,5,8-positions resonate in the range 74.7–86.1 ppm, while the other methylene or methyne carbons can be found at 20.9–34.4 ppm <2000JOC8407, 2003T525>. The carbonyl carbon in **200** and related derivatives is found at ca. 208 ppm <1998TL6065>. In particular, ^{13}C NMR data offered further diagnostic indications for the **a** and **b** series of the endoperoxides **198**. Thus, chemical shift values of C-1 and C-5 were always higher, by ca. 0.4 and 1.5 ppm, respectively, in the **b** series than in the corresponding **a** diastereomers independent of the oxidation state of the sulfur atom <2002T2449, 2003JME2516>.

The ^{17}O NMR spectrum was measured only for **207a** and **207b** in which the oxygen bridge was found at 112–115 ppm and the O–O signals at 290–299 ppm. The carbonyl oxygen of **207b** resonated at 563 ppm <1996T14813>.

Studies on fragmentation patterns of 1,2-dioxocins have not been reported in the past decade, although the majority of the papers report mass spectra data often limited to the molecular or quasi-molecular ions. Thus, the electron ionization mass spectra <2000JBS59, 2003T525, 2005T48319> showed molecular ions, FAB mass spectra showed $(\text{M}+\text{H})^+$ ions <1996USP5543406>, chemical ionization mass spectra presented $(\text{M}+\text{H})^+$ or $(\text{M}+\text{CH}_3)^+$ ions <1995JA9927, 1998BML903, 1999TL8391>, desorption chemical ionization mass spectra possessed $(\text{M}+\text{NH}_4)^+$ and/or $(\text{M}+\text{H})^+$ ions <2002T2449, 2003OBC2859>, and GC/mass or LC/mass spectra reported $(\text{M}+\text{NH}_4)^+$ and/or $(\text{M}+\text{H})^+$ ions <1996T14813, 2000JOC1578>. Several other papers reported partial fragmentation data. The electron ionization mass spectra of pseudolarolides Q and R, **204a** and **204b**, besides the weak molecular peaks at m/z 514 and 512 respectively, revealed a peak $(\text{M}-\text{O}_2)^+$ (m/z 482 and 480, respectively) characteristic of the cleavage of a peroxy group and a base peak at m/z 139 and 137, typical of the spiro ring E and the γ -lactone F <2004T4931>.

The ethylene-bridged 1,2-dioxocin **209a** in the electronic ionization mass spectrum showed a low molecular ion, a peak at m/z 322 due to loss of oxygen, and the base peak at m/z 135 due to the acylium ion $4\text{-MeO-C}_6\text{H}_4\text{CO}^+$ <1995TL1889>. The chemical ionization mass spectrum of dioxocin **210** showed a low quasi-molecular ion of m/z 253, which gave rise to peaks of m/z 237 and 235 due to loss of oxygen and water, respectively. The electron ionization mass spectrum of **210** did not show the molecular ion but rather a peak at m/z 236, due to loss of oxygen. The presence of peaks of m/z 234, 203, and 175 probably due to a sequential loss of water, oxygen and hydroxyl group, and the $\text{C}=\text{CH}_2$ moiety <1999T759> was also observed. The electronic ionization mass spectrum of **211** ($\text{R}^1 = \text{CO}_2\text{Et}$, $\text{R}^2 = \text{I}$) showed, besides the molecular ion, two peaks of m/z 241 and 155 due to loss of iodine and the complete side chain, respectively <2002JME4732>. A similar behavior for **211** ($\text{R}^1 = \text{CO}_2\text{Et}$, $\text{R}^2 = \text{OH}$) in the electron ionization mass spectrum has been reported, which showed a low molecular ion at m/z 258 and the base peak at m/z 155 due to loss of the side chain <2003JOC7361>. Compound **212** showed fragmented ion peaks at m/z 222, 221, and 220 as the heaviest ions detected under direct inlet electronic ionization mass spectrum and a chemical ionization fragmented ions m/z 221 ($\text{M}^+ + 1 - \text{H}_2\text{O}$) and m/z 223 ($\text{M}^+ + 1 - \text{O}$) using *iso*-butane and ammonia as reactant gases, respectively. The molecular formula was concluded using the atmospheric pressure chemical ionization (APCI) techniques, which revealed a very weak peak at m/z 239 ($\text{M}+1$)⁺ <2005P599>.



The EPR spin-trapping techniques were used to obtain evidence for the formation of a radical intermediate in the biomimetic Fe(II)-induced degradation of artefene **194** in the presence of sodium 3,5-dibromo-4-nitrosobenzene-sulfonate (DBNBS) and 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) <2000JOC1578>.

14.04.5.3 Thermodynamic Aspects

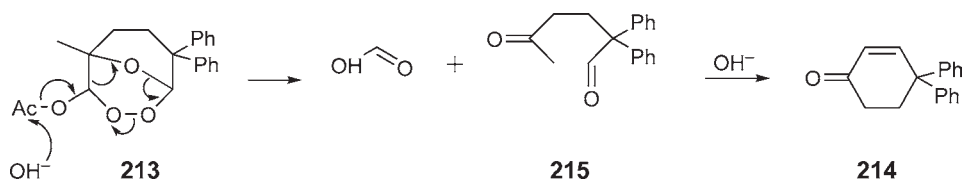
In CHEC-II(1996), only one bridged 1,2-dioxocane and a limited number of benzo- or dibenzo-fused 1,2-dioxocanes as well as few uncondensed derivatives were reported. In the past decade, due to the discovery of the antimalarial activity of yingzhaosu A **193**, a natural material with the 1,2-dioxocane skeleton, the interest on this ring system received strong encouragement and this is reflected in the increased number of published papers as well as the new compounds, analogues of **193**, synthesized. Among the 1,2-dioxocanes, only two reported derivatives are unbridged and uncondensed. One of these, 5-chloro-3,3,4,4,8-pentamethyl-1,2-dioxocane, obtained as a mixture of 2.4:1 ratio diastereomers that were separated by HPLC, was described; neither the consistency nor melting point of the compounds in two different reports by the same group <1995JOC784, 2000JOC8407> was given. The other, 3-iodomethyl-3-methyl-1,2-dioxocane, is an oil <2003T525>. All the remaining 1,2-dioxocanes reported are bridged and/or fused to other cycles. Uncondensed oxygen-bridged 1,2-dioxocanes of type **207** are colorless oils <1996T14813>, but annelation with an epoxy functionality or benzofuran moiety generated colorless solids melting at 73–74 °C and 142–152 °C, respectively <2001EJO1899, 2005HCA2865>. Condensation of the same oxygen-bridged dioxocane with pyrene or fluorene systems **206** kept the melting point in the range 141–164 °C <1999MIBKC969, 2000EJO335, 2004JKC207>. When the oxygen bridge is replaced by a *t*-butyl-substituted nitrogen, the corresponding pyrene-fused dioxocane caused a rise in its melting point to 195–200 °C <1997J(P1)1939>. Methylene-bridged 1,2-dioxocanes of type **201**, **202**, and related derivatives are generally oils with the exception of those bearing a 4-*endo*-oriented methoxy group, which underwent a stabilizing anomeric interaction with the ring <2001T5979, 2002JME4732>. For instance, the *endo*-isomer **201** is a stable solid melting at 73–74 °C, whereas the other (oily) *exo*-isomer lacking any stabilizing anomeric effect was found to be thermally labile and underwent extensive decomposition in less than a week on storage at <5 °C <2001T5979>. It is difficult to predict the phase behavior of analogues of **193** belonging to the general formula **205**. The majority of them are colorless oils, independent of the oxidation state of the sulfur and substituents, and capable of intermolecular interactions. Some derivatives melt in the range 97–118 °C and only few sulfinyl compounds have melting point ca. 150 °C <1998BML903, 1998SL122, 2000TL3145, 2002JME4732, 2002T2449, 2003JOC7361, 2003JME2516, 2005JOC3618>. Such compounds are, however, generally stable. For instance, both diastereomers **205** (*n* = 2, R = H) showed no changes in the NMR spectra for samples that were kept for 4 years at 25 °C <2002T2449>. Also, the sulfenyl diastereomers **205** (*n* = 0, R = H) are stable at 25 °C for at least 6 months and in solution of inert organic solvent at 60 °C for at least 5 h and the individual racemic diastereomers could be separated by flash chromatography <1998SL122>. Such chromatographic separation was also efficient in the case of a couple of diastereomer intermediates in the total synthesis of yingzhaosu A **193**, which could be separated from its epimer by fractional recrystallization <2005JOC3618>. Discordant information on the stability of **209a**, synthesized via the same pathway, was reported in two different papers. One of them reported its melting point (127–130 °C) and suitable ¹H and ¹³C NMR data and it was obtained in poor yield (11%). Other authors obtained **209a** in 95% yield and showed it to be unstable at 25 °C and directly analyzed through its ¹H and ¹³C NMR data (practically identical with those reported in the first report) <1996LA545>. Compound **212** was also stable to rearrangements on addition of acidic ion-exchange resin (Amberlyst) and few drops of concentrated hydrochloric acid in MeOH for 2 h. The peroxy functionality was also resistant to catalytic hydrogenation and treatment with lithium aluminium hydride (LAH) <2005P599>.

The 1,2-dioxocanes are soluble in the common organic solvents and are generally purified on silica gel using several elution mixtures: hexane/EtOAc <1998TL6065, 1999T759, 2002T2449, 2005T4831, 2005JOC3618>, EtOAc/

petroleum ether <2001OL3733, 2005HCA2865>, CHCl_3 <1997J(P2)2313>, $\text{CHCl}_3/\text{hexane}$ <2005T4831>, $\text{C}_6\text{H}_6/\text{hexane}$ <1997J(P1)1939>, pentane/ Et_2O <2001EJO1899, 2004JKC207>.

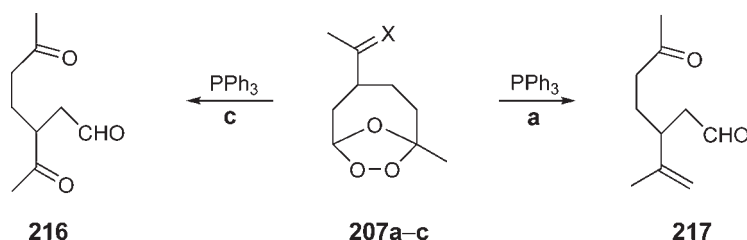
14.04.5.4 Reactivity of Nonconjugated Rings

Oxygen-bridged dioxocin **213** reacted with methanolic NaOH to give the enone **214** in 90% yield. The reaction went through the intermediacy of the ketoaldehyde **215** by cleavage of the O–O bond (Scheme 43). The base catalyzed not only the deformylation but also the aldolization and dehydration. When the base was added to the corresponding nonacetylated derivative obtained from the crude ozonolysis mixture, the yield was 42% <1995JA9927>.



Scheme 43

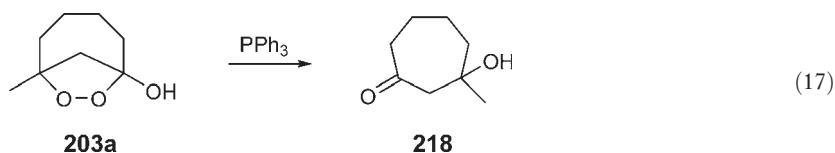
Reduction of derivatives **207a** ($\text{X} = \text{CH}_2$) and **207c** ($\text{X} = 1,2,4\text{-trioxolane-3-yl}$) using an excess of $(\text{C}_6\text{H}_5)_3\text{P}$ (PPh_3) gave **217** and **216**, respectively (Scheme 44). When the reduction of **207c** was conducted using only 1 equiv of PPh_3 , **207b** ($\text{X} = \text{O}$) was isolated and subsequently reduced with PPh_3 to afford **217** <1996T14813>.



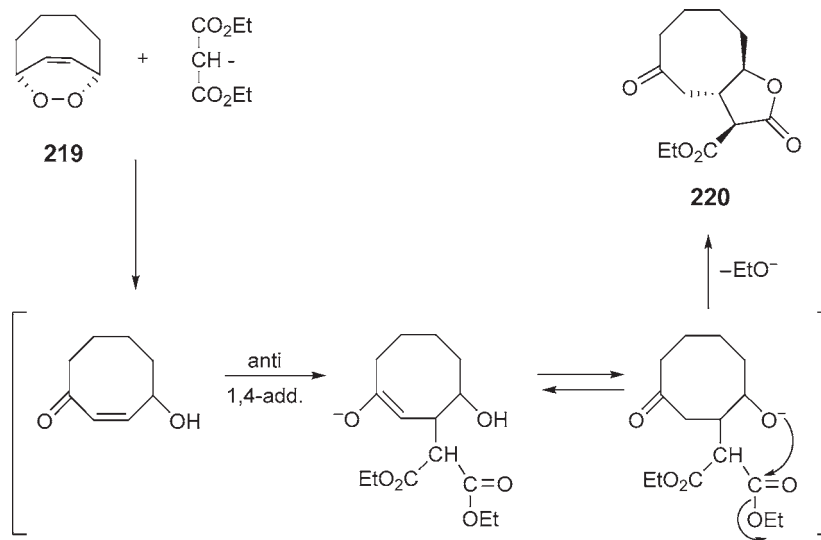
Scheme 44

The same reactivity with PPh_3 was shown by a benzo-fused dioxocin <2004JKC207> and derivatives **206** ($\text{X} = \text{CH}_2$ and $\text{X} = \text{CH=CH}$) to give 9*H*-fluorene-4,5-dicarbaldehyde and 4,5-phenanthrene dicarbaldehyde, respectively <2000EJO335>, which was also obtained in lower yield (25%) when **206** ($\text{X} = \text{CH=CH}$) was treated with NaI in AcOH <2002HCA1>. Analogous cleavage of the peroxy functionality to a diketone was observed by reduction of an oxygen-bridged dioxocin with triphenylphosphine <2001EJO1899>. Other reducing agents that caused the formation of a dicarbonyl compound from a polycondensed dioxocin was zinc in AcOH <1996USP5543406>.

Compound **203** was totally transformed into the hydroxycycloheptanone **218** by treatment with PPh_3 (Equation 17) <1999TL4045>. Interestingly, the same β -hydroxy ketone **218** was obtained, although in lower yield (75%), upon reaction of **203** with a catalytic amount of vanadyl acetylacetonate ($\text{VO}(\text{acac})_2$) in EtOH and oxygen <2005T4831>. Cleavage of the peroxy functionality to give hydroxy ketones was observed in a bridged dioxocin, bearing hydrogen atoms adjacent to oxygen, by reaction with Et_3N <2003MI145>.



The intermediacy of hydroxy ketone was invoked in the case of the addition of the enolate of diethyl malonate to dioxocin **219**, which gave the *trans*-fused lactone **220** with high diastereoselectivity in good yield (65%; [Scheme 45](#)) [<2002JOC5307>](#).

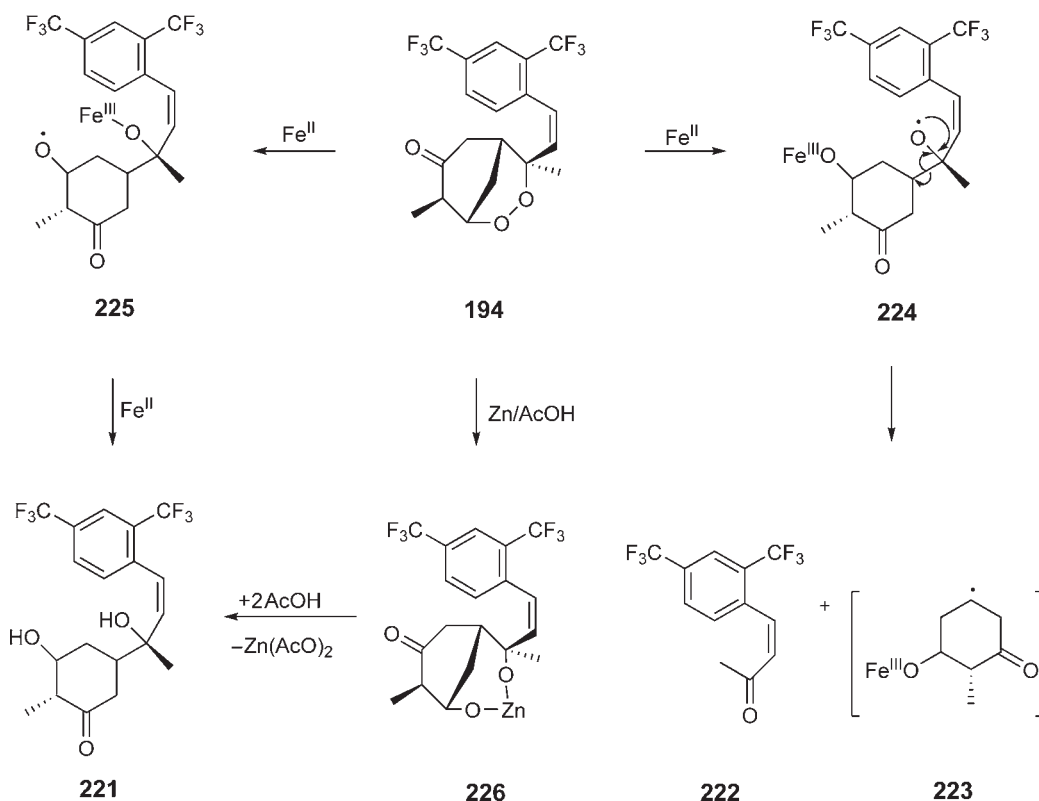


Scheme 45

Treatment of arteflene **194** with $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ in MeCN led to diol **221**, enone **222**, a polymeric material, and unreacted **194** ([Scheme 46](#)). Increasing the concentration of $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ led to an increased turnover while the use of anhydrous FeCl_2 led to lower yields. When the reaction was conducted with hemin FeCl_3 and 1 equiv of *N*-acetylcystein, as Fe(III) -reducing agent in aqueous MeCN, the same products **221** and **222** were obtained but in lower yields. Instead, treatment of **194** with zinc in AcOH led to the production of diol **221** as the only product (80%) [<1997TL4263>](#). The mechanism of such reductive activation of arteflene attracted the attention of several research groups, since its rationalization was considered of primary importance in understanding the mechanism of action of this antimalarial agent.

The proposed mechanism for the formation of **222** involves homolytic cleavage of the peroxy moiety by single-electron donation from Fe(II) to give the oxyl radical **224**. Such an intermediate collapses to produce enone **222** and the nonstabilized cyclohexyl radical **223**, which polymerizes under the reaction conditions. The formation of **221** can be rationalized by association of Fe(II) with oxygen to produce oxyl radical **225**, which by further reduction and subsequent protonation gave **221**. It is also reasonable that **221** may be derived from similar reduction of the oxyl radical **224** by Fe(II) and subsequent protonation. The formation of **221** from zinc in AcOH is explained by the oxophilic nature of zinc. The reaction is initiated by donation of a pair of electrons to the peroxide bond to give **226**. Reaction of such a species with AcOH produces **221** [<1997TL4263>](#). The proposed mechanism which involved the oxygen-centered radical **224**, which rearranges to the enone **222** and the carbon-centered radical **223**, appeared to be valid also in the case of an analogue of arteflene in which the 2,4-bis(trifluoromethyl)-1-vinyl benzene moiety was replaced by an octyloxy group and instead of the enone **222** the octyl acetate was isolated [<1998TL6065>](#). However, direct evidence for the formation of the *C*-centered radical **223** was provided when the reaction of **194** with Fe(II) was carried out in the presence of sodium DBNBS or DMPO; a strong EPR signal was observed [<2000JOC1578, 2001CME1803>](#). Moreover, the *C*-centered radical **223**, obtained by reductive activation of **194** with Mn(II) tetraphenylporphyrin, was trapped by 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) and characterized by its ^1H NMR spectrum [<1999JOC6776>](#). Upon reductive activation with Mn(II) tetraphenylporphyrin, **199** produced a radical that reacted with tetraphenylporphyrin to give stable compounds that could be analyzed and identified [<2003OBC2859>](#).

Also, for the Fe(II) -induced degradation of the antimalarial sulfonyl dioxocin **227** (an analogue of yingzhaosu A), a parallel mechanism was proposed with the difference that the carbon-centered radical **235**, an analogue of **223**, instead of undergoing polymerization, gives well-defined monomeric products. Thus, the cleavage of the peroxide

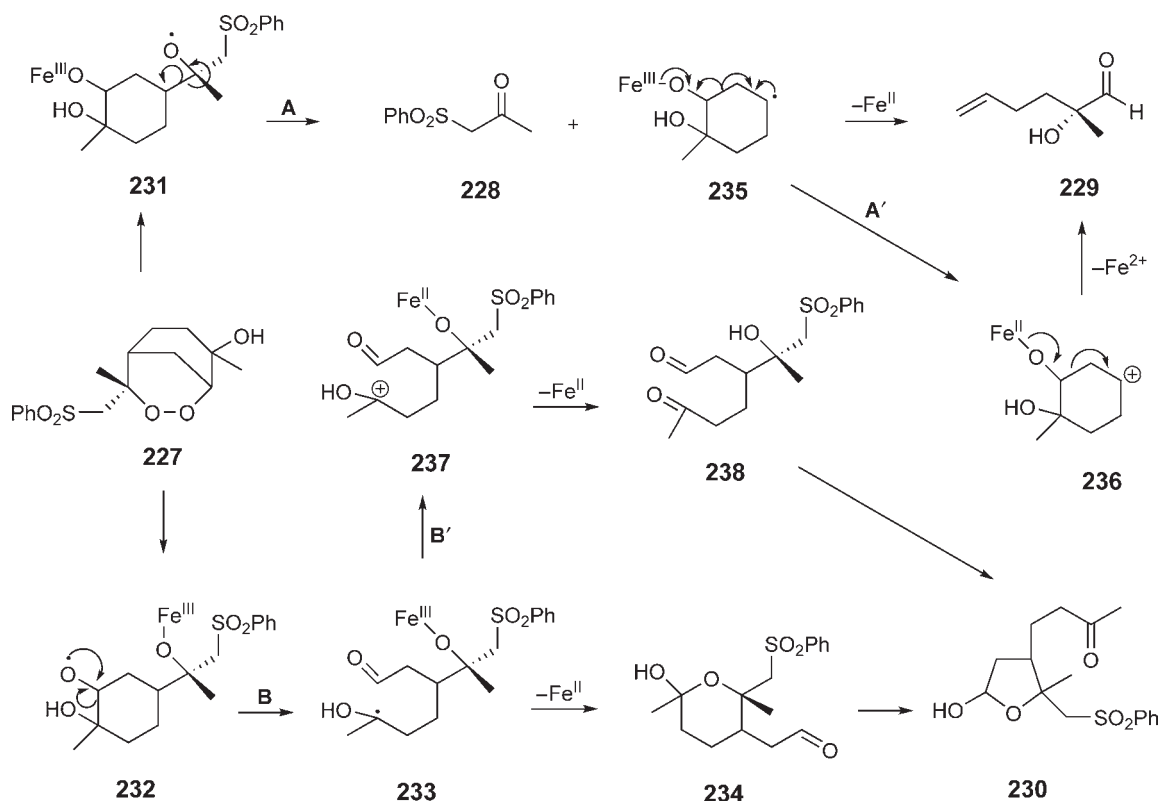


Scheme 46

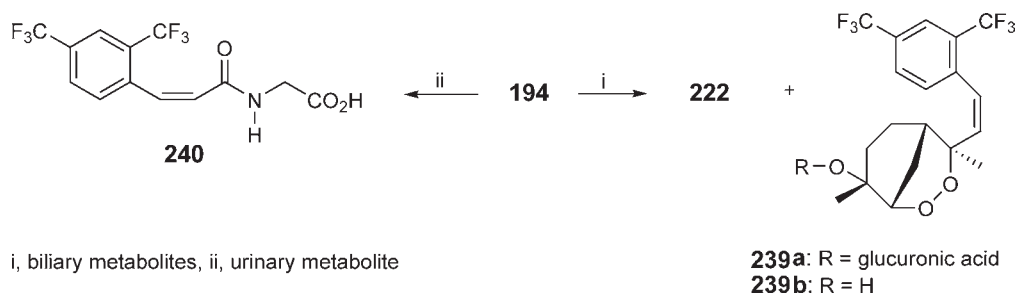
bond in **227** led to oxygen-centered radicals **231** and **232** (Scheme 47). Radical **231** (path A) underwent β -scission to give ketosulfone **228** and cyclohexyl radical **235**, which underwent oxidative β -cleavage to give the unsaturated hydroxyl aldehyde **229** with concomitant regeneration of Fe(II) that continues the chain reaction. β -Cleavage of oxygen-centered radical **232** (path B) afforded the oxygen-stabilized carbon-centered radical **233**, which underwent oxidative ring closure to give the six-membered lactol **234** with the regeneration of Fe(II). Acid-catalyzed, heterolytic rearrangement took place to afford five-membered lactol **230**. An alternative mechanism that accounts for the formation of **229** and **230** is outlined in paths A' and B'. Carbocations **236** and **237** were formed through single-electron transfer from carbon-centered radicals **235** and **233**, respectively. In path A', carbocation **236**, in absence of an effective nucleophile, undergoes β -cleavage to give the unsaturated hydroxyl aldehyde **229**. In path B', an instantaneous proton shift in carbocation **237** resulted in the dicarbonyl **238**, which undergoes spontaneous acid-catalyzed cyclization to five-membered lactol **230** <2000JHC639, 2001JOC6531>.

Parallel reactivity in the biomimetic Fe(II)-induced degradation was shown via an analogue of **227** bearing a phenyl group instead of methyl in position 4 <2006BML2991>, or phenyl and styrene moieties in position 4 as well as methyl and acetoxy groups in position 8 <2004AGE4193>. The activation of arteflene was also studied *in vivo* in nonparasitized rats. The principal biliary metabolites were 8-hydroxyarteflene glucuronide **239** and the *cis*- and *trans*-isomers of enone **222**. The principal urinary metabolite appeared to be **240**, a glycine conjugate of a derivative of the enone (Scheme 48). Biliary excretion of the glucuronide was inhibited by ketoconazole. 8-Hydroxyarteflene **239b** (R = H) was extensively formed by rat and human liver microsomes but no enone was found. Bioactivation is a major pathway of arteflene's metabolism in the rat; although the mechanism of *in vivo* bioactivation is yet unclear, the reaction is not catalyzed by microsomal cytochrome P450 enzymes <1999MI511>.

It was later reported that both metabolic activation (reduction of the endoperoxide bridge) and the deactivation (hydroxylation plus O-glucuronylation) of arteflene occur in the rat liver. The balance of these pathways is associated with cytotoxicity, although only at relatively high concentrations in the cultured hepatocyte. The hepatic metabolism may restrict the therapeutic effectiveness of arteflene because 8-hydroxyarteflene retains only about 25% of the parent drug's antimalarial activity, while the enone is inactive <2004173>.



Scheme 47

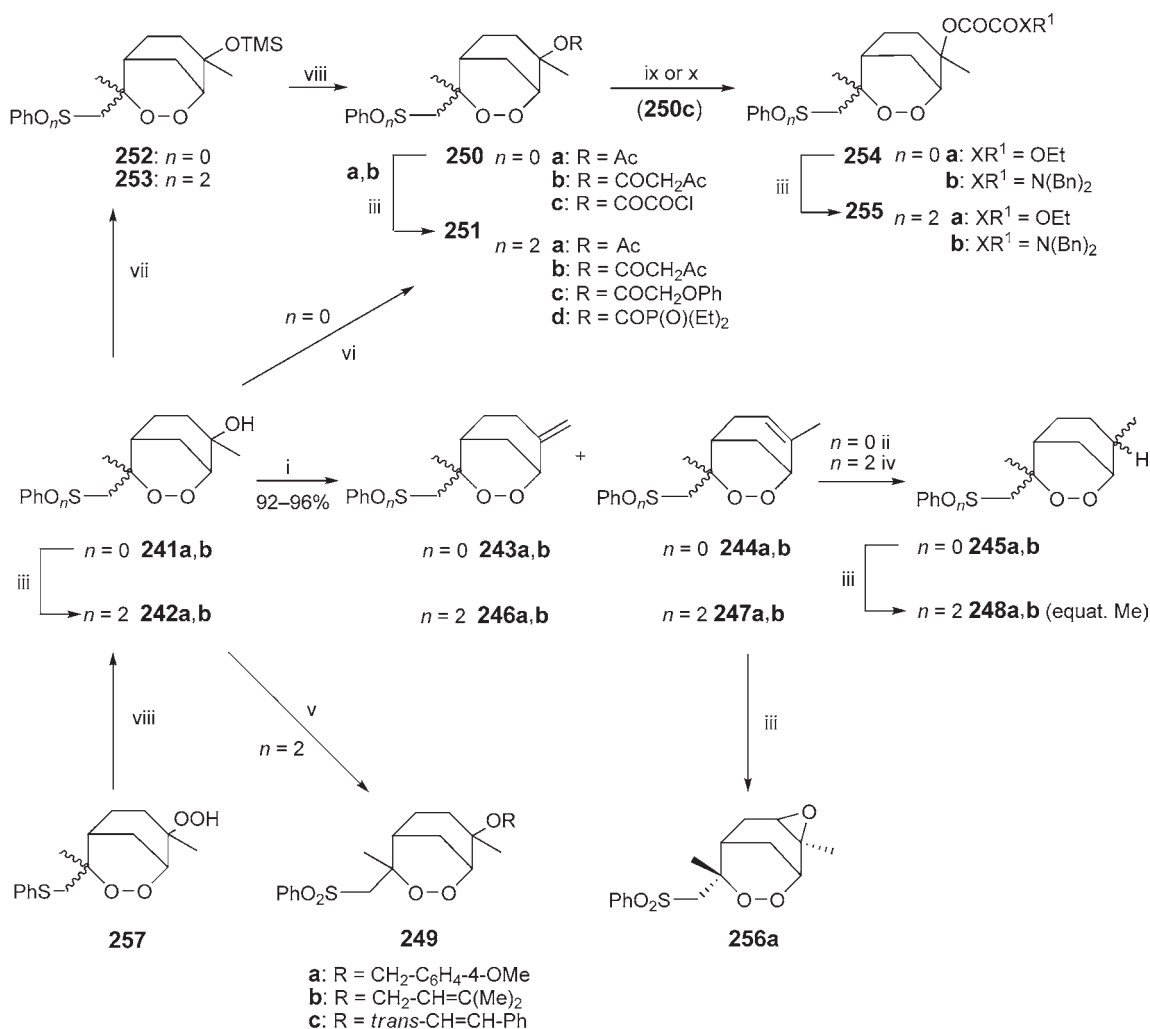


Scheme 48

14.04.5.5 Reactivity of Substituents Attached to Ring Carbon Atoms

All the reactions reported in this section deal with modification of substituents of dioxocins, analogues of the natural antimalarial agent yingzhaosu A, possessing antimalarial activity or utilized in the total synthesis of the natural product.

Dehydration of the mixture of the diastereomers **241a** and **241b** afforded a mixture of the exocyclic alkenes **243a** and **243b** and the endocyclic alkenes **244a** and **244b** (15:85) (each as a mixture of (4*R*)- and (4*S*)-diastereomers) in 93% combined yield (Scheme 49). Treatment of this blend with excess of diimide, generated *in situ* from potassium azodicarboxylate, resulted in the selective hydrogenation of the exocyclic alkenes **243a** and **243b** to give a mixture of four saturated derivatives **245a** and **245b**. The endocyclic C=C bond in **244a** and **244b** is less reactive and remains unchanged. Attempts to reduce such a double bond with additional diimide or hydrogenation catalyzed by PtO₂, Pd/C, Rh/Al₂O₃, as well as homogeneous Wilkinson and Crabtree catalysts have failed. These failures are probably due to the poisoning of the catalysts by the divalent sulfur. Sulfone derivatives **242a** and **242b**, as single isomers, underwent



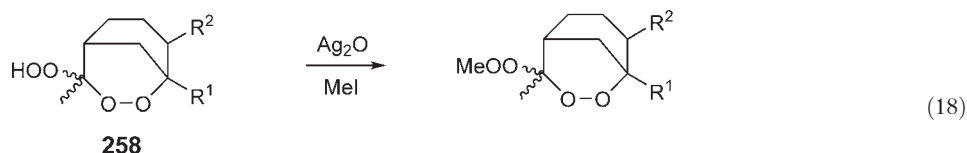
i, SO_2Cl_2 , pyridine, DCM, 0°C to rt; ii, potassium azodicarboxylate, AcOH; MeOH, DCM, 0°C ; iii, MCPBA, EtOAc, rt;
 iv, $\text{H}_2/\text{PtO}_2\text{-H}_2\text{O}$, EtOAc, -10°C ; v, trichloroacetamide, TfOH, Et_2O , $0\text{--}10^\circ\text{C}$; vi, AcCl, DMAP, DCM, 0°C to rt;
 vii, TMSOTf, 2,6-lutidine, DCM, 5°C ; viii, acyl chlorides, rt; ix, EtOH, 2,6-lutidine, DCM, 4°C ; x, Bn_2NH , 2,6-lutidine, DCM, 0°C

Scheme 49

dehydration to give a mixture of the exocyclic and endocyclic alkenes **246a/247a** and **246b/247b**, respectively. The mixture **246a** and **247a** was hydrogenated over PtO_2 at -10°C giving chemo- and diastereoselectively a single sulfone **248a** in excellent yield. Using the same procedure, **242b** gave **248b** <2003JME2516, 2005JOC3618>. Treatment of the single sulfone **242a** with trichloroacetamides followed by TfOH afforded the corresponding diastereomer of O-alkylated **249** <1998BML903, 2003JME2516>. Direct acylation with acyl chlorides and 4-dimethylaminopyridine (DMAP) of the sterically hindered hydroxyl group of **241** and **242** is slow and consequently prone to secondary reactions. For instance, reaction of **241a** and **241b** with acetyl chloride and DMAP gave the acetoxy derivative **250a** (53%) and the bis-acetylated derivative acetoacetate **250b** (13%) as a pair of diastereomers. A more efficient method involved silylation of **241** and **242** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) to give quantitative yields of **252** and **253**, followed by treatment with excess of acyl chlorides to give **250** and **251** as a pair of diastereomers in excellent yields. A similar procedure was applied for the preparation of oxalyl chloride derivative **250c**, which afforded ester **254a** and amide **254b** upon treatment with EtOH and benzylamine, respectively <1998BML903, 1999WO12900, 2002T2449, 2003JME2516>. The above two-step acylation procedure was successfully utilized in the case of other yingzhaosu A analogues bearing an hydroxyl group in position 8 <2003JOC7361> or compounds belonging to the same series of **241** but bearing a phenyl instead of a methyl in position 4 <2004AGE4193, 2006BML2991>. Other efficient

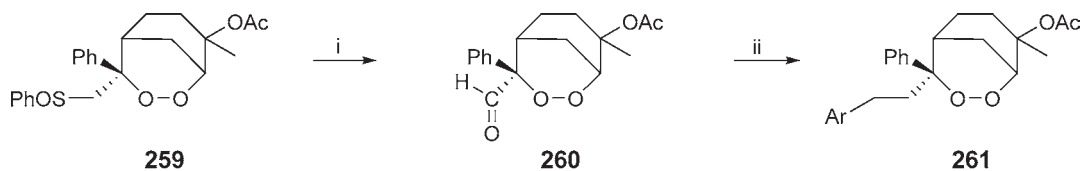
alkylations under very mild conditions of the hydroxyl group of **242** involved the reaction of diethylphosphonoacetic acid and dicyclohexylcarbodiimide (DCC) to give the corresponding acyl derivative **251** ($R = \text{COP(O)(OEt)}_2$) in 92% yield <2001OL3733, 2002JOC8975>. Oxidation of sulfenyl derivatives **241a,b** (and related compound bearing a phenyl in position 4), **250a,b**, and **254a,b** (each as a mixture of (4*R*)- and (4*S*)-diastereomers) with an excess of MCPBA afforded the corresponding pairs of the sulfone dioxocins **242a,b**, **251a,b**, and **255a,b**, respectively <1998BML903, 1998SL122, 1999WO12900, 2002T2449, 2003JME2516, 2006BML2991>. Also **245a** and **245b**, with an equatorially positioned methyl group (10), separated from **245c** and **245d** (axial methyl) by medium-pressure liquid chromatography (MPLC), gave a mixture of sulfone derivatives **248a** and **248b** upon treatment with MCPBA <2003JME2516>. When **241a**, **241b**, and **250a** were oxidized with 1 equiv of MCPBA, the corresponding sulfinyl derivatives **241a** and **241b** ($n = 1$) and **250a** ($n = 1$) were isolated <1999WO12900, 2003JME2516>. The endocyclic alkene **247a** was diastereoselectively epoxidized from the less-hindered side of the cycle to give the epoxy derivative **256a** as a single diastereomer <2003JME2516>. The 8-hydroxy-substituted sulfenyl dioxocin **257** and other analogues of yingzhaosu A were chemoselectively reduced with $(\text{C}_6\text{H}_5)_3\text{P}$ to the corresponding hydroxyl derivative of type **241** <2002T2449, 2003JME2516, 2004AGE4193>. Catalytic hydrogenation over PtO_2 of arteflene **194** reduced the $\text{C}=\text{C}$ bond of the side chain originating from the ‘dihydroarteflene’ <2000JOC1578>. Acetylation of the hydroxyl group of the antimalarial agent **199** was achieved with Ac_2O and pyridine, as the base, while the methylation of the same hydroxyl group was achieved with KO^tBu and subsequent reaction with MeI <2003OBC2859>.

The hydroperoxy group of dioxocins **258** underwent methylation with a mixture of Ag_2O and MeI (Equation 18). The same methylation was performed on dioxocin **201** <2000TL3145, 2001T5979>.



a: $R^1 = \text{OMe}$, $R^2 = \text{H}$; **b:** $R^1 = \text{OMe}$, $R^2 = \text{Me}$; **c:** $R^1 = \text{Me}$, $R^2 = \text{H}$; **d:** $R^1 = R^2 = \text{H}$

Sulfinyl dioxocin **259** underwent Pummerer-type oxidative desulfuration to give the aldehyde derivative **260**, which, through a Wittig *cis*-olefination, gave **261** in low to moderate yields (Scheme 50) <2004AGE4193>.



i, TFAA (2 equiv), morpholine, MeCN , 40%

ii, $(\text{ArCH}_2)\text{Ph}_3\text{P}^+\text{Br}^-$ (1.4 equiv), KHMDS (1.4 equiv), THF , -10°C to rt

a: $\text{Ar} = \text{Ph}$ (20%)

b: $\text{Ar} = \text{C}_6\text{H}_4\text{-4-F}$ (31%)

c: $\text{Ar} = \text{C}_6\text{H}_4\text{-4-Cl}$ (40%)

Scheme 50

14.04.5.6 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

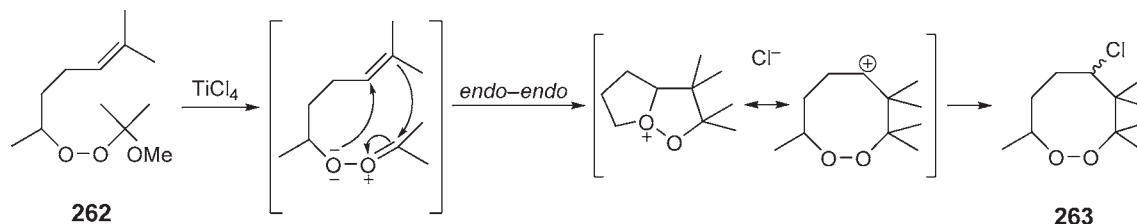
14.04.5.6.1 Natural products

The dioxocin ring is the only, among the eight-membered rings with two heteroatoms in a 1,2-relationship, to be isolated from natural sources. The most important natural product is yingzhaosu A **193**. Actually it was isolated in the late 1970s from an extract of *Artabotrys uncinatus* that was used in China as a traditional remedy for treatment of malaria, but in the last decade the majority of dioxocin derivatives synthesized and tested as antimalarial agents are analogues of this natural product. The triterpene lactones, pseudolarolides **Q** and **R**, **204a** and **204b**, containing a

dioxocin moiety, were isolated from the root bark of *Pseudolarix kaempferi*, a plant indigenous to eastern China used for treatment of dermal infections caused by fungi <2004T4931>. The sesquiterpene **210** was obtained, by extraction with DCM, from the aerial parts of *Illicium tsanggii*, a poisonous shrub from southern China used in traditional medicine for treating pain <1999T759>. The bridged dioxocin **212** was isolated from the essential oil of the liverwort *Plagiochila asplenioides* from northern Germany <2005P599>.

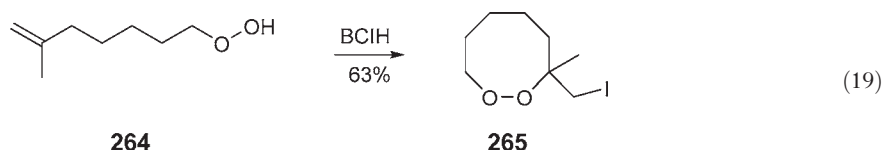
14.04.5.6.2 Ring syntheses from C₆O₂ units

Monoperoxyacetal **262**, when treated with TiCl₄, produced an intermediate, presumably a peroxycarbenium ion, that was capable of undergoing a *endo-endo*-intramolecular cyclization with the alkene moiety to give, in low yield, a 2,4:1 mixture of diastereomers of the perhydro-dioxocin **263** (Scheme 51) <1995JOC784, 2000JOC8407>.



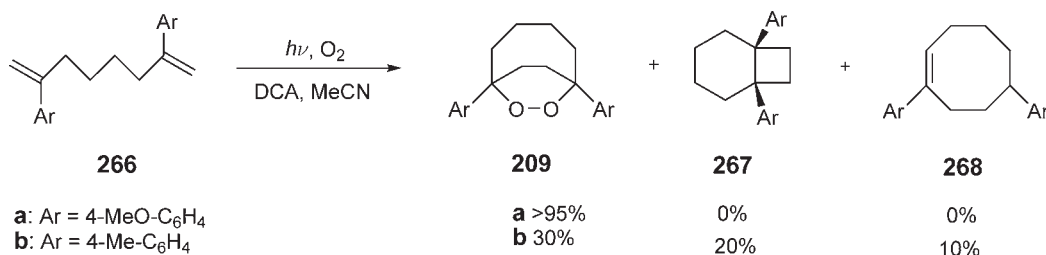
Scheme 51

The bis(*sym*-collidine)iodine(i)hexafluorophosphate-promoted cyclization of unsaturated hydroperoxide **264** provided an excellent method for the production of the perhydro-dioxocin **265** in good yield (Equation 19) <2003T525>.



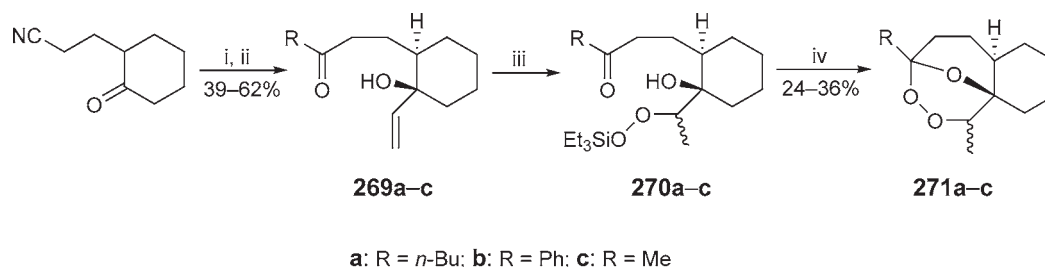
14.04.5.6.3 Ring syntheses from C₆ + O₂ units

The preparation of the bridged diaryldioxocins **209** from a photoinduced electron transfer cyclization of 2,7-diaryl-1,7-octadienes is somehow controversial. Two different research groups reported different data either for the reaction products and the physical properties of one of the reaction products (see Section 14.04.5.3). Thus, electron-rich diene **266a**, upon irradiation for 3 h in the presence of the photosensitizer 9,10-dicyanoanthracene (DCA) and under constant oxygen pressure, with oxygen uptake monitoring, quantitatively gave the bridged perhydro-dioxocin **209a** (Scheme 52). More complex was the product pattern for octadiene **266b**. In this case, a mixture of cyclobutane **267b** and cyclooctene **268b** was formed as a result of the nonoxidative path and a mixture of the dioxocin **209b** with 1,6-bis(4-methylphenyl)hexane-1,6-dione (40%) <1996LA545>. The other research group irradiated the diene **266a** for 20 min, under the same reaction conditions, to get dioxocin **209a** (9%), cyclooctene **268a**, and unreacted starting material (28%) <1995TL1889>.



Scheme 52

Allylic alcohols **269a–c**, obtained from 3-(2-oxocyclohexyl)propane nitrile by a one-pot two-step procedure, underwent Co(II)-catalyzed triethylsilylperoxygenation to give a 1:1 diastereomeric mixture of the corresponding peroxy alcohols **270a–c**. These latter, by acid-catalyzed cyclization, furnished a 1:1 diastereomeric mixture of the oxygen-bridged 1,2-dioxocins **271a–c** in low yields (Scheme 53) <1999TL8391>.



i, $\text{H}_2\text{C} = \text{CHMgBr}$, THF, 0 °C; ii, RLi, Et_2O , rt; iii, $\text{Co}(\text{acac})_2$ (0.1 equiv), Et_3SiH (1.5 equiv), EtOH under O_2 ; iv, pTsOH (cat), DCM

Scheme 53

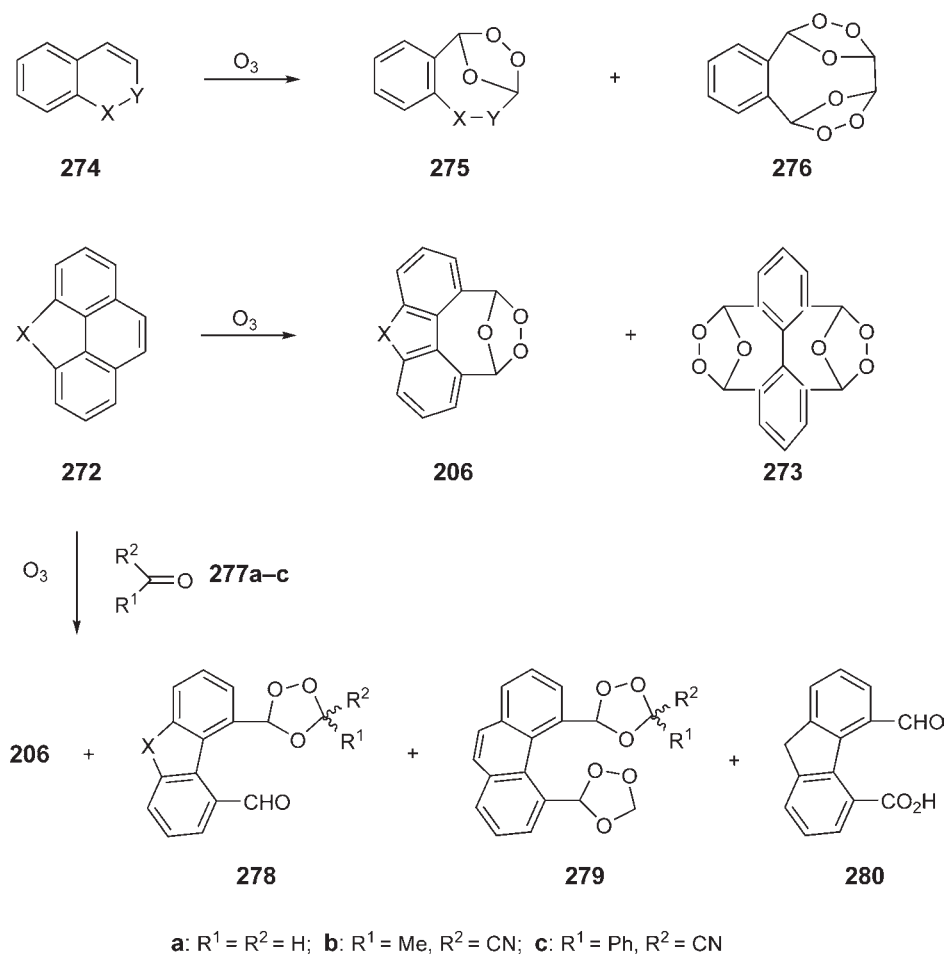
14.04.5.7 Ring Syntheses by Transformation of Another Ring

Ozonolysis of pyrene **272** ($\text{X} = \text{CH}=\text{CH}$) at -70°C with a stoichiometric amount of ozone afforded dihydro-4,7-epoxyphenanthro[4,5-*d,e,f*][1,2]dioxocin **206** ($\text{R} = \text{CH}=\text{CH}$) in 48% yield (Scheme 54) <2002HCA1>. When the ozonolysis of pyrene was conducted on polyethylene at -78°C with a large excess of ozone (1:32), **206** ($\text{X} = \text{CH}=\text{CH}$) was isolated in 10% yield together with the dioxocin–dioxocin **273** isolated in 14% yield <2004JKC207>. Naphthalene **274** ($\text{X}-\text{Y} = \text{CH}=\text{CH}$) under the same reaction conditions produced the dioxocin **275** ($\text{X}-\text{Y} = \text{CH}=\text{CH}$) in 9% yield and **276** in 12% yield. Ozonolysis of dihydronaphthalene **274** ($\text{X}-\text{Y} = \text{CH}_2-\text{CH}_2$) gave only the dioxocin **275** ($\text{X}-\text{Y} = \text{CH}_2-\text{CH}_2$) in 15% yield <2004JKC207>. A polycondensed dioxocin derivative was formed from benzo[*a*]pyrene in a continuous ozonator system for an aerobic biological degradation of polycyclic hydrocarbons <1999MI107>. When the ozonolysis of pyrene was conducted in the presence of **277a–c**, the reaction mixture that resulted was complex and dioxocin **206** ($\text{X} = \text{CH}=\text{CH}$) was isolated in 17–24% yields; in the presence of **277a** and **277b**, **278** ($\text{X} = \text{CH}=\text{CH}$) and **279** were also isolated as major products <2000EJO335>. When the same sort of ozonolysis was conducted on 4,5-methylenepheneanthrene **272** ($\text{X} = \text{CH}_2$), the dioxocin **206** ($\text{X} = \text{CH}_2$) was also isolated in the presence of compounds **277b** and **277c** in 13–60% yields besides **278** ($\text{X} = \text{CH}_2$) and **280** <1999MIBKC969, 2000EJO335>. When the ozonolysis of pyrene was conducted in the presence of *t*-butylamine or *c*-hexylamine instead of the oxygen-bridged dioxocin **206**, the corresponding N–R-bridged derivative was isolated in 12% yield <1997J(P1)1939>.

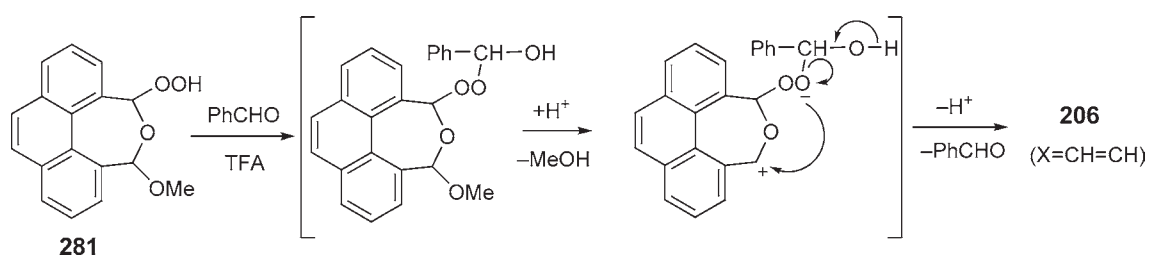
Dioxocin **206** ($\text{X} = \text{CH}=\text{CH}$) was also obtained from the hydroperoxide-substituted phenanthrene-fused oxepine **281** upon reaction with stoichiometric amount of benzaldehyde or acetone and TFA. The formation of the dioxocin goes through the elimination of MeOH and consequent intramolecular cyclization of the oxygen on the stabilized carbocation (Scheme 55) <1998J(P1)3053>.

The largest series of yingzhaosu A analogues was synthesized through a free radical, four-component sequential thiol–olefin co-oxygenation (TOCO) procedure. Thus, treatment of (*S*)-limonene and related monoterpenes with aliphatic or aromatic thiols, oxygen, and radical initiator afforded the diastereomeric hydroperoxide derivatives **282a** and **282b** ($\text{R}^2 = \text{OH}$) (Equation 20). Such intermediates can be isolated or directly subjected to selective reduction to give the corresponding hydroxyl compounds **282a** and **282b** ($\text{R}^2 = \text{H}$). The decrease of the yields in the reaction with some derivatives arises from steric interference at one of the TSs by the X or R^1 substituents (see Table 4).

The TOCO procedure requires an initial step where $\text{R}^1\text{S}^\bullet$ is obtained from R^1SH and a radical initiator, followed by regioselective addition to the terminal end of the isopropenyl double bond of limonene. The emerging carbon-centered radicals should be rapidly trapped by molecular oxygen to give peroxy radicals, which should undergo a 6-*exo*-intramolecular addition to endocyclic double bond generating the tertiary carbon-centered radicals. These latter radicals should be trapped by a second equivalent of oxygen, thus giving peroxy radicals, which should abstract a hydrogen atom from R^1SH , giving the target hydroperoxides and $\text{R}^1\text{S}^\bullet$ that continues the chain reaction (Scheme 56) <1998SL122, 1999WO12900, 2000JHC639, 2002T2449, 2006BML2991>.



Scheme 54



Scheme 55

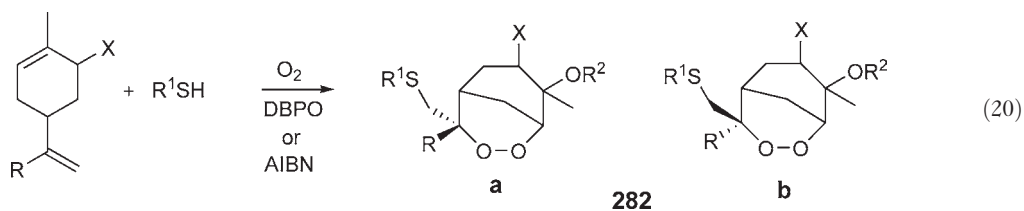
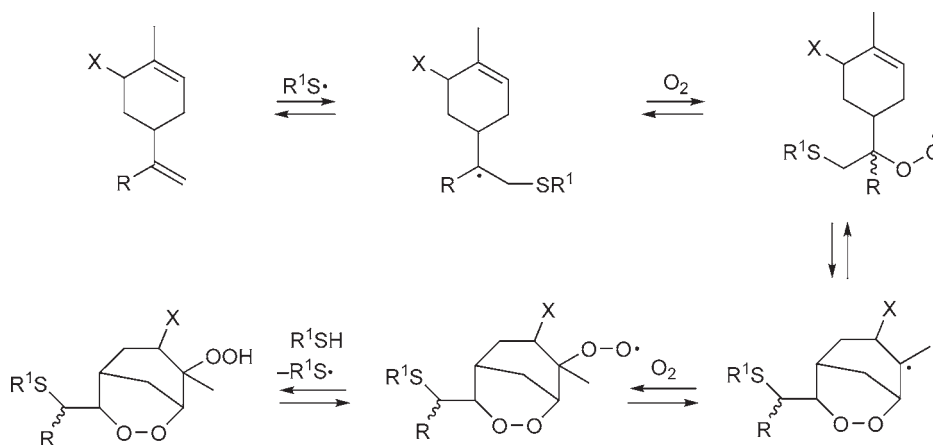
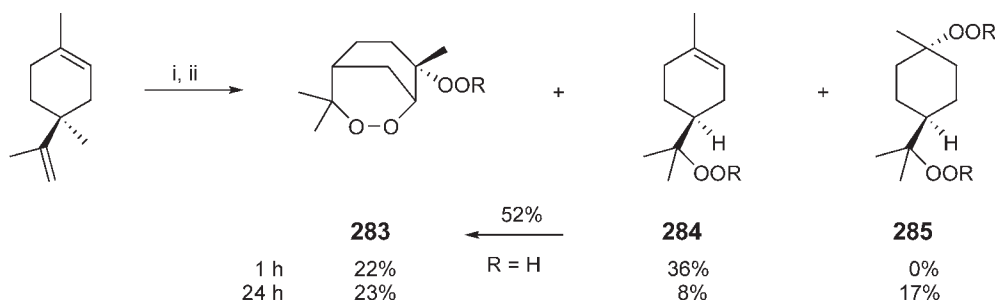


Table 4 Compounds **282** synthesized by TOCO procedure (Equation 20)

<i>R</i>	<i>R</i> ¹	<i>R</i> ²	<i>X</i>	Yield (%)	References
Me	Ph	OH	H	n.r. ^a	2002T2449
Me	4-F-C ₆ H ₄	OH	H	n.r.	2002T2449
Me	<i>n</i> -Bu	OH	H	n.r.	2002T2449
Me	CH ₂ CO ₂ H	OH	H	n.r.	2002T2449
Me	<i>c</i> -Hex	OH	H	n.r.	2002T2449
Me	<i>t</i> -Bu	OH	H	n.r.	2002T2449
Me	Tr	OH	H	n.r.	2002T2449
Ph	Ph	OH	H	n.r.	2004AGE4193
Me	Ph	H	H	55	2002T2449, 1998SL122
Me	4-F-C ₆ H ₄	H	H	47	2002T2449
Me	<i>n</i> -Bu	H	H	25	2002T2449
Me	CH ₂ CO ₂ H	H	H	18	2002T2449
Me	<i>c</i> -Hex	H	H	16	2002T2449
Me	<i>t</i> -Bu	H	H	29	2002T2449
Me	Tr	H	H	41	2002T2449
Me	Ph	H	β -OBz	22	2002T2449, 1999WO12900
Me	<i>n</i> -Bu	H	β -OBz	6	2002T2449, 1999WO12900
Me	Ph	H	α -OBz	6	2002T2449, 1999WO12900
Me	Ph	H	α -OH	13	2002T2449, 1999WO12900
Ph	Ph	H	H	70	2004AGE4193
Ph	4-Cl-C ₆ H ₄	H	H	21	2006BML2991

^aNot reported.**Scheme 56**

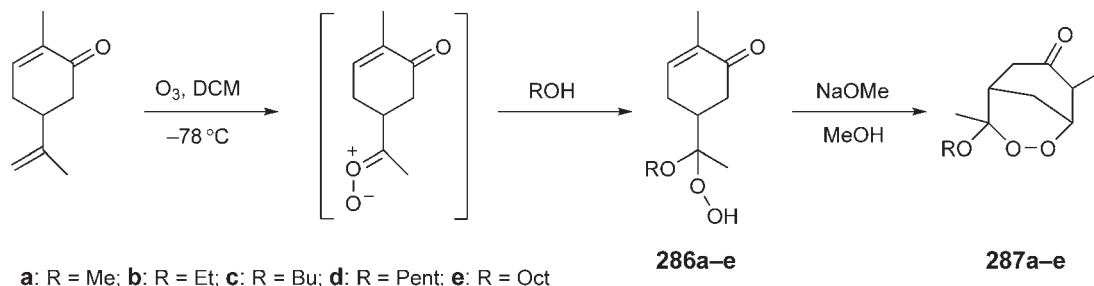
Limonene was the starting material for other syntheses. Reaction of (*S*)-limonene with oxygen and Et₃SiH in DCE in the presence of bis(1-morpholinocarbonyl-4,4-dimethyl-1,3-pentaneditionato)Co(II) [Co(modp)₂] gave a mixture of three triethylsilyl peroxides **283–285** (R = triethylsilyl (TES)), which were easily desilylated to the corresponding hydroperoxides **283–285** (R = H) (**Scheme 57**). After 1 h, the limonene was completely consumed and the major product was **284** (R = H) (36%), while the dioxocin **283** (R = H) was obtained in 22% yield. After 24 h, the reaction gave the bis-hydroperoxide **285** (R = H) in 17% yield with the concomitant decrease in the yield of **284** (R = H) (8%) whereas the yield of dioxocin **283** (R = H) remained the same. For the formation of **283**, a mechanism parallel to that described for **282** was proposed. When the reaction was conducted in the presence of Co(acac)₂ in EtOH, the reaction mixture gave **283** (R = H) (22%), **283** (R = TES) (18%), and **284** (R = TES) (9%) and was shown to be time independent. Interestingly, **284** (R = H) underwent spontaneous transformation into dioxocin **283** (R = H) in 52% yield <2003JOC7361>. Treatment of (*R*)-limonene with 1 molar equiv of ozone in pentane afforded a mixture of **207a** (X = CH₂) (7%) and two diastereomers of **207c** (X = 1,2,4-trioxolane-3-yl) (6%). When 2 equiv of ozone were used, the reaction gave the two diastereomers of **207c** as the sole product <1996T14813>.



i, O₂, Co(modp)₂, Et₃SiH, DCE, rt; ii, HCl/MeOH

Scheme 57

Ozonolysis of (*R*)-carvone and *in situ* trapping with primary alcohols produced hydroperoxy ketals **286**, as a 1:1 mixture of diastereomers. Cyclization of these latter with catalytic amount of NaOMe in MeOH gave the corresponding bridged dioxocins **287** in 24–38% yields ([Scheme 58](#)) <1998TL6065>.

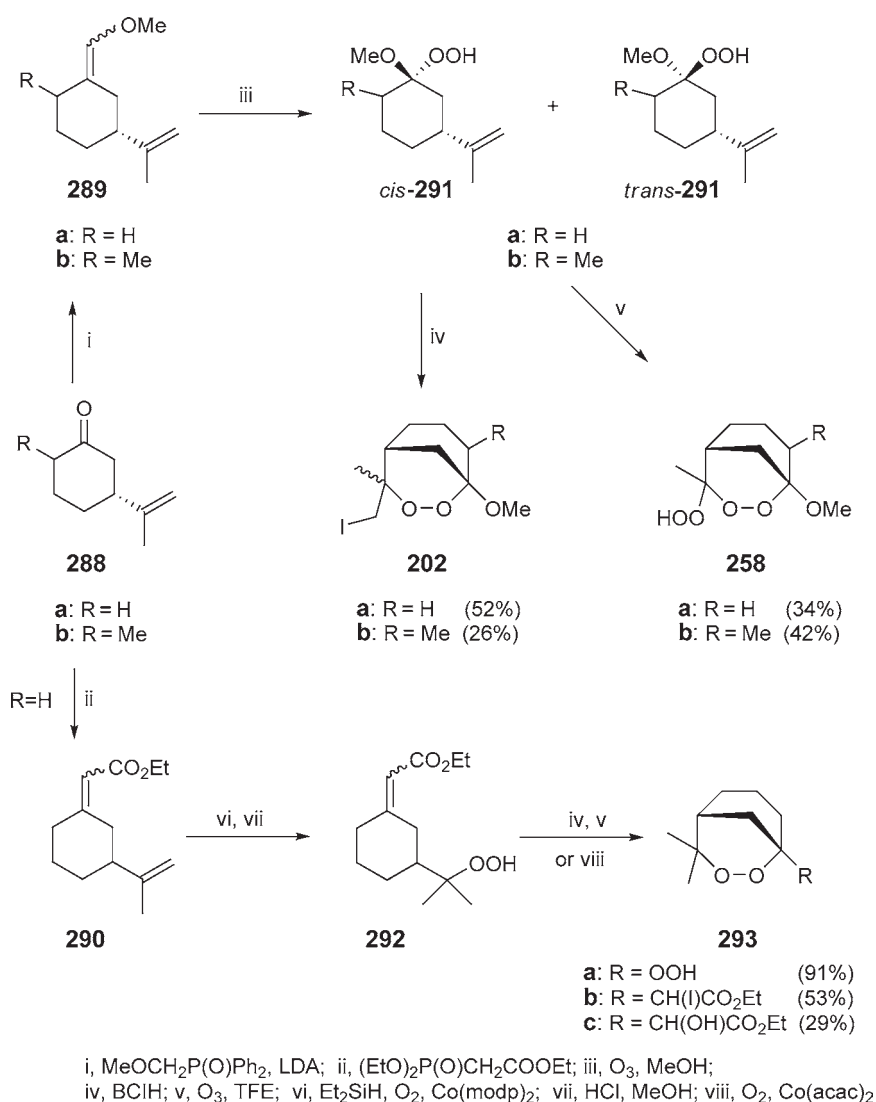


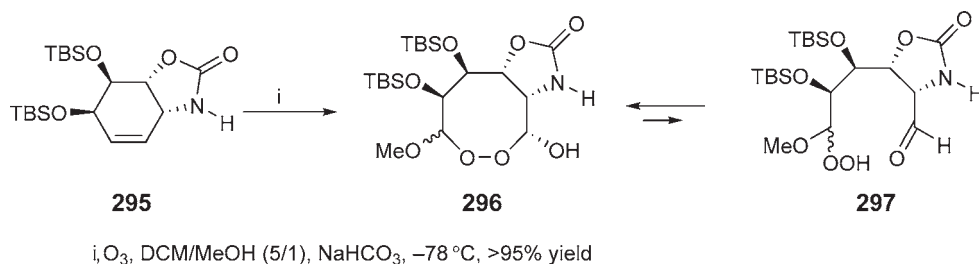
Scheme 58

Olefination of ketones **288a** and **288b** by the Horner–Emmons reaction in MeOH gave the dienes **289a**, **289b**, and **290**. Selective ozonolysis of the electron-rich vinyl ether group of **289** in MeOH gave two isomeric hydroperoxides, *cis*-**291a,b** and *trans*-**291a,b** ([Scheme 59](#)). The *cis*-**291a** and *cis*-**291b** isomers underwent BCIH-promoted cyclization to give the iodomethyl-substituted dioxocins **202a** and **202b** in 26–52% yields, as a mixture of two isomers. Treatment of *cis*-**291a** and *cis*-**291b** with ozone in trifluoroethanol (TFE) gave the expected hydroperoxy derivatives **258a** and **258b** as single isomers in 34–42% yields <2000TL3145, 2001T5979>. The Co(II)-catalyzed autoxidation of the alkene moiety of **290** produced the *tert*-hydroperoxide **292**, which cyclized to **293a** (R=OOH), **293b** (R=CH(I)CO₂Et), or **293c** (R=CH(OH)CO₂Et) upon reaction with ozone in TFE, BCIH, or O₂/Co(acac)₂, respectively <2001T5979, 2002JME4732, 2003JOC7361>.

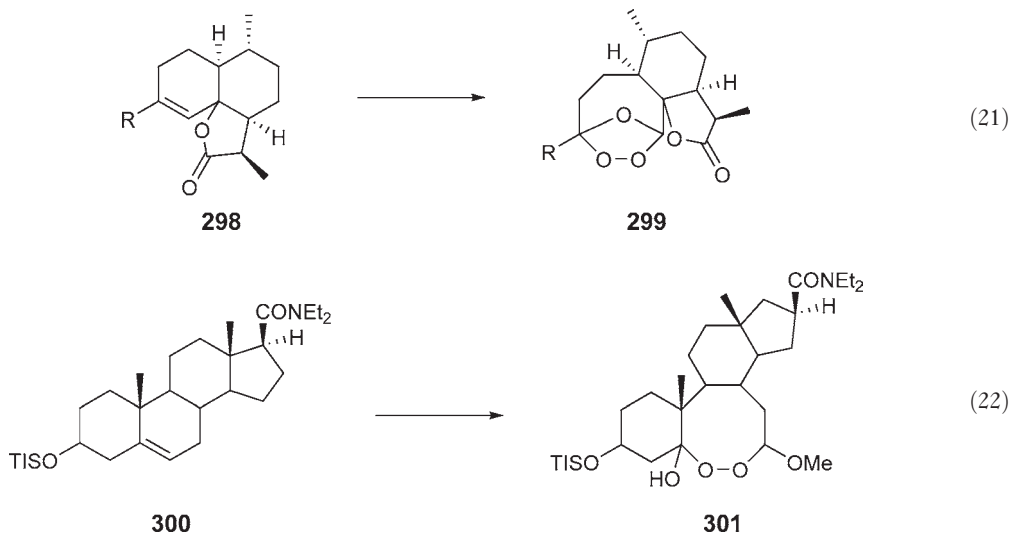
Ozonolysis of 4,4-diphenyl-1-methyl-cyclohex-2-ene-1-ol in DCM at –78 °C in the presence of Ac₂O led to the oxygen-bridged 1,2-dioxocin **213** in 30% yield. Its formation is explained in terms of intramolecular trapping of the carbonyl oxide intermediate, followed by cyclic acetal formation. Since **294** is unstable and spontaneously decomposed to ketoaldehyde **215** (see [Section 14.04.5.4](#)), it was necessary to acetylate it in order to have the stable 1,2-dioxocin **213** ([Scheme 60](#)) <1995JA9927>.

Treatment of oxazolidinone-fused cyclohexene **295** with ozone in DCM/MeOH afforded in nearly quantitative yield a ca. 3:1 mixture of 1,2-dioxocin **296** and hydroperoxy aldehyde **297** (both as 1:1 epimeric mixture) ([Scheme 61](#)) <2000TL7863>.



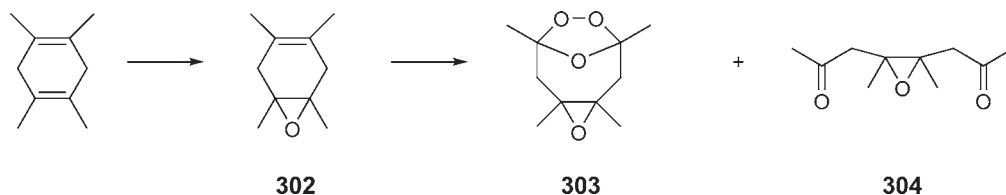


Scheme 61



Ozonolysis of maleopimaric anhydride methyl ester in the presence of tetracyanoethylene gave in very poor yield the corresponding ozonide together with an epoxy derivative, as the major product [\[2000JBS59\]](#). By treatment of 3,4,5,6,7,8-hexahydro-2'*H*-spiro[chromene-2,1'-cyclohexan]-2'-one with hydrogen peroxide in acidic medium, the oxygen-bridged 1,2-dioxocin **199** was obtained as a mixture of diastereomers in 46% yield [\[2003OBC2859\]](#). Dioxocin **219** was obtained, in 24% yield, from 1,3-cyclooctadiene by a seco-porphyrazine-catalyzed [4+2] cycloaddition of singlet oxygen [\[2000SL1010\]](#).

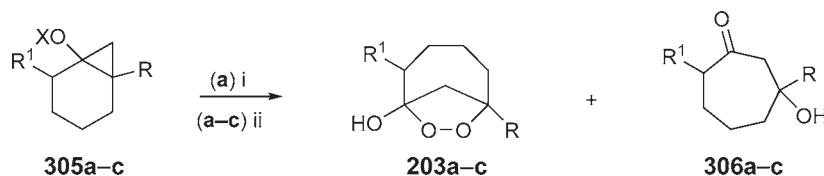
Epoxidation of 1,2,4,5-tetramethyl-1,4-cyclohexadiene with MCPBA provided the epoxide **302** in 65% yield. Subsequent ozonolysis of **302** gave a mixture containing 84% of the 1,2-dioxocin **303** and 16% of the epoxy ketone **304**, from which **303** was isolated in 38% yield ([Scheme 62](#)) [\[2001EJO1899\]](#).



Scheme 62

Treatment of bicycloheptane **305a** (X=H) with oxygen, catalytic amount of Fe(acac)₃, silica gel, and light produced the bridged 1,2-dioxocin **203a** in 54% yield, as the sole product. Omission of either of the reagents or light decreased the reaction rate and/or gave lower yield of the product ([Scheme 63](#)) [\[1999TL4045\]](#). The same dioxocins **203** were obtained from the reaction of tertiary trimethylsilyl ethers **305** (X=TMS) with oxygen, catalytic

amount of VO(acac)₂, and TFE as a solvent. Under such conditions, **203** were obtained in 43–86% yields, but the formation of β -hydroxyketones **306** was also observed (traces to 26%). When the reaction of **305a** (X = TMS) was conducted in EtOH, the yield of **203a** was lowered from 86% to 45% and the yield of **306a** increased from 10% to 53% <2005T4831>.



a: R = Me, R¹ = H; **b:** R = Bn, R¹ = H; **c:** R = R¹ = Me

i, O₂, silica gel, Fe(acac)₃, *hν*, 36 h, rt; ii, O₂, VO(acac)₂, TFE, 20 h, rt

Scheme 63

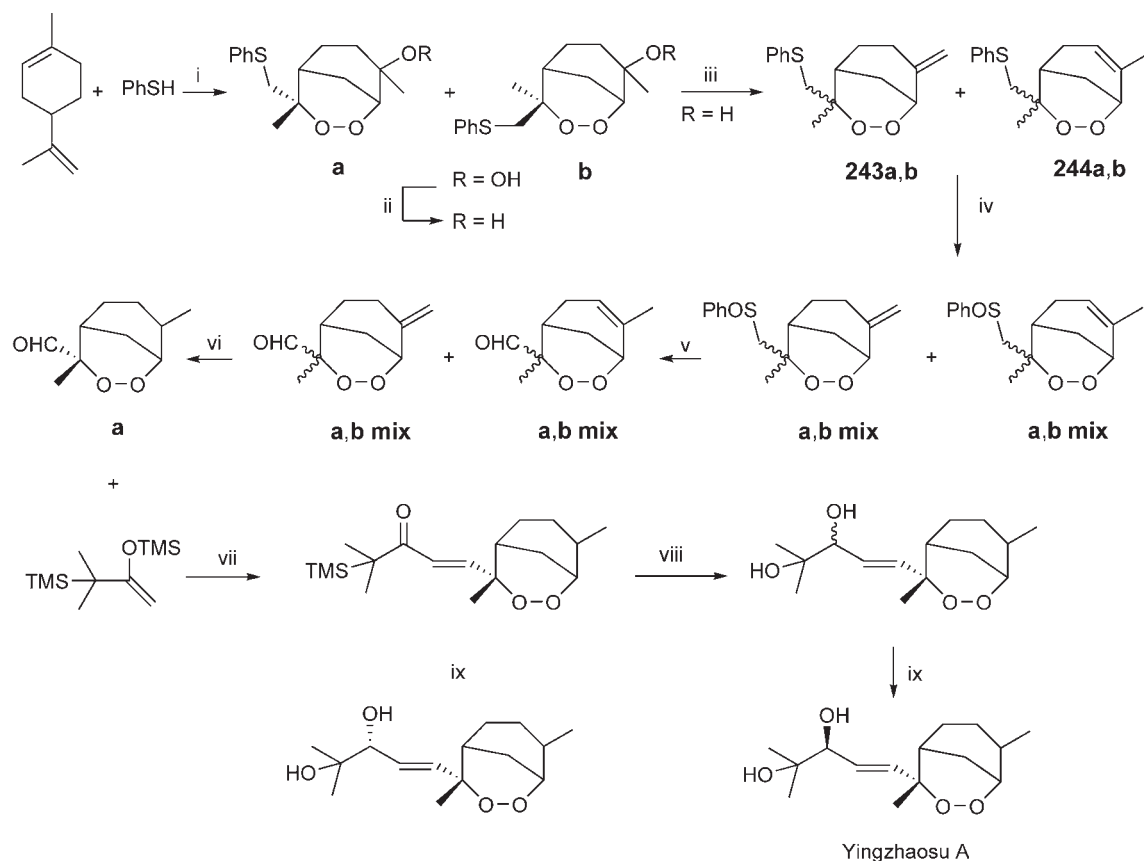
14.04.5.8 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

At variance with the other five series of 1,2-heterocines, the syntheses by transformation of other rings represent the majority of the reported synthetic pathways for 1,2-dioxocins. The sole unimolecular cyclization to the perhydrodioxocin system is not of preparative interest. The cyclization BCIH-promoted of unsaturated hydroperoxides is more interesting from the preparative point of view but is still only one example. Among the transformations of other rings, the most common route to 1,2-dioxocins involved the addition of ozone or oxygen to endocyclic or exocyclic alkenes followed by ring closure. With the exception of the TOCO procedure, that with selected substituents can lead to bridged dioxocins in good yields; all the dioxocins reported are obtained in poor yields and generally together with other compounds, often as major products.

However, in this section, the total synthesis of yingzhaosu A, the lead compound of a particular class of antimalarial 1,2-dioxocins, is reported. The synthesis involves eight steps and a 7.3% overall yield starting from (*S*)-limonene (Scheme 64). Besides the TOCO procedure that allowed the formation of five bonds in one step, the most intriguing steps involved the selective hydrogenation of a C–C double bond in the presence of a peroxide and an aldehyde functionalities (step vi) and the stereoselective reduction of the side-chain carbonyl with (*R*)-CBS catalyst (step viii). Last but not least, the old classical fractional recrystallization allowed the separation of yingzhaosu A from its C-14 epimer and saved two synthetic steps <2005JOC3618>.

14.04.5.9 Important Compounds and Applications

Nearly all applications for dioxocins are related to the antimalarial activity of several synthetic derivatives, analogues of the natural products yingzhaosu A **193**. Although isolated in the late 1970s, only 30 years later, the first *in vitro* and *in vivo* quantitative data for the antimalarial activity of **193** and its C-14 epimer were reported. The epiyingzhaosu A exhibited potent *in vitro* cytotoxic activity against the KB nasal-pharyngeal cancer cell line <2005JOC3618>. More than 50 compounds of type **205** were tested *in vitro* as antimalarial agents. Ten β -sulfonyl derivatives (*n* = 2) and one β -sulfinyl derivative (*n* = 1) showed IC₅₀ values lower than 25 nM against *Plasmodium falciparum*. Upon subcutaneous administration, four sulfonyl derivatives, namely the diastereomer **a** of **251a** and **249a** and both diastereomers of **251** (R = Bn), are highly active *in vivo* against *Plasmodium yoelii* and *Plasmodium berghei* strains of malaria parasites. The most potent **251** (R = Bn) are twice as efficacious against chloroquine-sensitive *P. berghei* and 3–5 times more efficacious against chloroquine-resistant *P. yoelii* than artemisinin. Thus, their potency is comparable to some of the best drugs currently used as antimalarials <1998SL122, 1998BML903, 1999WO12900, 2003JME2516>. SAR studies revealed that sulfonyl derivatives are generally more active than the corresponding sulfenyl ones <1998BML903>. Replacement of the methyl in position 4 with a phenyl provides no advantages in terms of enhancing antimalarial activity <2006BML2991>, but derivatives **261**, bearing a phenyl in position 4 and a benzyl or substituted benzyl moiety instead of a sulfonyl group, maintain the antimalarial activity at nanomolar level



i, O_2 , AIBN, $h\nu$, MeCN; ii, Ph_3P ; iii, 4.3 equiv of $SOCl_2$, 11 equiv of pyridine, DCM, $0^\circ C$; iv, 1.1 equiv MCPBA, EtOAc, $-40^\circ C$; v, (a) 5 equiv TFAA, 10 equiv of 2,6-lutidine, DCM, $-35^\circ C$, (b) 1.1 equiv morpholine, MeOH/DCM, $-10^\circ C$ to $0^\circ C$, (c) separation by flash chromatography to separate the diastereomers **a** of the two compounds from the corresponding diastereomers **b**; vi, H_2 , 0.15 equiv of PtO_2 , -11 to $-12^\circ C$, EtOAc; vii, (a) 3–4 equiv of $TiCl_4$, $-78^\circ C$, DCM, 4 h, (b) 21 equiv of pyridine, -20 to $-30^\circ C$, 11 h; viii, 1.2 equiv of (*R*)-CBS catalyst, 1.2 equiv of $BH_3 \cdot THF$, $-55^\circ C$, 47 h; ix, fractional recrystallization: yingzhaosu A from *t*-butylmethylether/pentene; its C-14 epimer from EtOAc/hexane

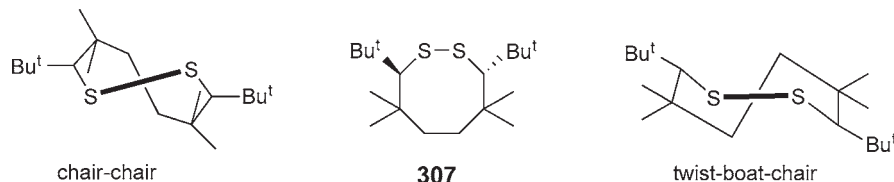
Scheme 64

<2004AGE4193>. The *O*-methyl derivatives obtained from **258a–d** were tested against *P. falciparum* and the derivative **b** showed an IC_{50} value of 1×10^{-7} M, approximately a tenth of the antimalarial potency of artemisinin (7.8×10^{-9}). Moreover, the selectivity, determined by comparison with the cytotoxicity against mouse mammary FM3A cells (3.3×10^{-5} M) was as high as 330 <2000TL3145, 2001T5979>. Even better *in vitro* activity against the same strains was shown by analogues of **202a** and **202b**, bearing a methyl group instead of a methoxy moiety at the position 8 and by **293b** and **293** ($R = CH_2I$) which, reaching nanomolar concentrations, and showing selectivity index values of 282 and 1700, were tested *in vivo* showing, on intramuscular administration, significant antimalarial activity <2002JMC4732>. Other related dioxocin derivatives showed IC_{50} values ($1\text{--}3 \times 10^{-9}$ M) better than artemisinin although with a lower selectivity index <2003JOC7361>. The *in vivo* tests confirmed an activity very similar to that of the reference drug <2005T9961>. Dioxocins **287a–e** were tested against the HB3 strain of *P. falciparum* and the results compared to arteflene **194**. The IC_{50} were in the range 666–123 nM. The most active compounds were **287d** and **287e**, showing that the activity increases by lengthening the side chain <1997TL4263, 1998TL6065>. Also, dihydroarteflene maintains antimalarial activity in the nanomolar range <2000JOC1578>. Arteflene was also utilized in studies directed to elucidate the mechanism of resistance of *P. falciparum* to drugs <2000MI955>. Also, dioxocin derivatives **199** showed antimalarial activity <2003OBC2859>. Compounds **299** showed *in vivo* antischistosomal activity against schistosoma japonicum <2005HCA2865>.

14.04.6 Rings with Two Sulfurs (1,2-Dithiocians)

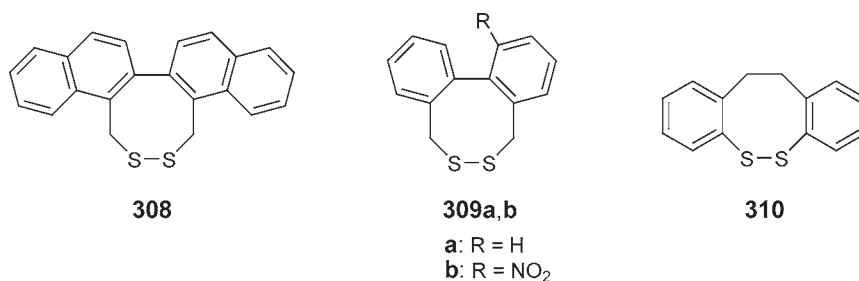
14.04.6.1 Theoretical Methods

The PM3 calculations showed that the twist-boat-chair conformation of dithiocin **307** is more stable by $5.9 \text{ kcal mol}^{-1}$ than the corresponding chair-chair conformation. For the same compound, coupling constants for the AA'XX' system of the ethylene chain were simulated to be $J(\text{AA}') = 10.15 \text{ Hz}$, $J(\text{XX}') = 0 \text{ Hz}$, $J(\text{AX}) = -14.0 \text{ Hz}$, $J(\text{AX}') = 9.4 \text{ Hz}$ <2002HAC351>.



14.04.6.2 Experimental Structural Methods

The structure of dithiocin **307** was unambiguously determined by X-ray crystallography to be the *trans*-isomer, which takes the twist-boat-chair conformation, confirming the calculation performed on this molecule (see Section 14.04.6.1). The authors, because of the low quality of the crystals, which did not provide satisfactory *R* values, did not discuss the bond length and angle data, but reported, for tentative information, some relevant data such as S–S bond length ($2.0388 \text{ \AA}$) and C–S bond lengths (1.836 and $1.858 \text{ \AA}$). Such figures are, however, in good agreement with those reported in CHEC-II(1996) for dibenzodithiocin **309a** <2002HAC351>. In all the reports related to dithiocians, the ^1H NMR spectra are described, although only in two cases do the authors describe in details the features of the ^1H NMR spectra. The methylene protons in **308** and **309a** in which the position 4-5 and 6-7 of the dithiocin ring are fused with naphthalene and benzene moieties, respectively, were found in the range $3.39\text{--}4.03 \text{ ppm}$. In CHEC-II(1996), the chemical shifts of the benzylic protons of the nitro derivative of **309b** were reported and are in perfect agreement ($3.5\text{--}4.0 \text{ ppm}$) with the values herein reported. The protons bound to the aromatic rings of these molecules can be found in the expected range ($7.03\text{--}7.97 \text{ ppm}$) <1995JOC7142, 1995T787>. The bridge methylene protons in **310** resonate at 3.31 ppm . Actually, this compound was already known, and it is discussed in CHEC-II(1996), the chemical shift of which was reported to be 3.15 ppm . There are also differences in the physical parameters in the reports of the two research groups (see Section 14.04.6.3) concerning **310**; however, the chemical shift of H-4, the closest proton to sulfur, is 7.44 ppm , while the other protons resonate in the range $7.04\text{--}7.17 \text{ ppm}$ <2004OBC1528>.



The ^1H NMR spectrum of dithiocin **307** showed that the two *t*-butyl groups are equivalent as well as the two methyne protons resonating at 1.16 and 2.97 ppm , respectively. The four methyl groups appeared as two singlets at 1.01 and 1.14 ppm . The ethylene chain resonated as an AA'XX' system centered at 0.91 and 2.23 ppm <2002HAC351>. The ^1H NMR spectrum of dinaphthodithiocin **308** showed a four-proton AB pattern at 3.54 and 4.03 ppm ($J = 12.3 \text{ Hz}$), while the ^{13}C NMR spectrum showed only one aliphatic resonance (41.42 ppm) and 10 aromatic resonances indicating a complete equivalence of the two naphthalene rings <1995T787>. At variance with CHEC-II(1996), for all 1,2-dithiocians described herein, the ^{13}C NMR spectra are reported. Thus the methylene carbons in **308** and **309a** can be found at $41.25\text{--}42.50 \text{ ppm}$. The quaternary carbons of dibenzodithiocin **309a** resonate at 138.2 and 140.0 ppm while the other sp^2 carbons lie in the usual range, $126.7\text{--}130.3 \text{ ppm}$ <1995JOC7142>. The dinaphthodithiocin **308** exhibited the methylene carbons at 41.4 ppm and the other carbons in the range

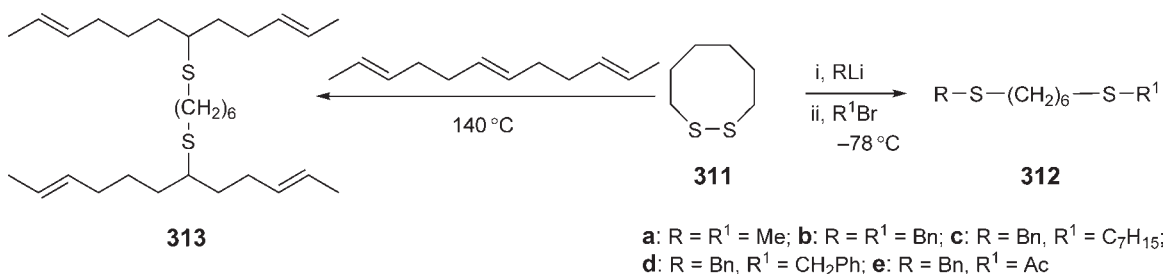
133.0–136.0 ppm <1995T787>. The controversial derivative **310** showed the methylene protons at 33.4 ppm, the quaternary carbons, C-4a and C-12a, at 142.2 and 134.5 ppm, respectively, and the other sp^2 carbons in the range 126.2–130.3 ppm <2004OBC1528>. As in CHEC-II(1996), no ^{33}S NMR data were reported for any 1,2-dithiocin derivatives. Data related to mass spectra are limited to two derivatives, **307** and **310**. The electron ionization mass spectra showed the molecular ions for both, and, in the case of the dibenzo derivative **310**, the base peak at m/z M-32 due to loss of sulfur was also reported <2002HAC351, 2004OBC1528>. Although little useful information is obtained from the IR spectrum for the disulfide moiety, in one case the S–S vibration absorption at 683 cm^{-1} was reported <2004OBC1528>.

14.04.6.3 Thermodynamic Aspects

It is impossible to outline the phase behavior of 1,2-dithiocins on the basis of the physical data reported on four derivatives among which two were already known. However, the hexahydrodithiocin **303** is a colorless crystalline solid, from EtOH, melting at 110–111 °C <2002HAC351>. Also, the dibenzodithiocin **309a** and dinaphthodithiocins **308** are solids melting at 131 and 175 °C, respectively <1995T787, 1995JOC7142>. Compound **310** has been reported to be a yellow powder, obtained from petroleum ether, melting at 41–42.5 °C <2004OBC1528>. These data contrast with those reported in CHEC-II(1996) and the references cited therein that describe **310** as a colorless solid that, recrystallized from AcOH, melts at 192–193 °C. Probably this discrepancy is due to dimorphism. The reported dithiocins were generally purified on silica gel and petroleum ether/EtOAc <2004OBC1528>, pentane <2002HAC351>, hexane <1995T787>, or DCM/hexane <1995JOC7142>, as eluents. Conformation data are limited only to dithiocin **307** which was obtained as a single isomer of two possible *cis*- (*meso*-) and *trans*- (*dl*-) stereoisomers. Either PM3 calculations (see Section 14.04.6.1) or X-ray crystallography (see Section 14.04.6.2) demonstrated that **307** is the *trans*-isomer, which possesses the twist-boat-chair conformation having the C_2 symmetry <2002HAC351>.

14.04.6.4 Reactivity of Nonconjugated Rings

In this section, reactions involving the ring-opening of the 1,2-dithiocin are reported. Thus, perhydro derivative **311** underwent nucleophilic ring opening with organolithium reagents (e.g., MeLi, BuLi). The intermediates can be reacted with alkyl or acyl halides to give either symmetrical or unsymmetrical dithia compounds **312** in good yields (67–85%). Alkylation did not occur, under the same reaction conditions, with tertiary alkyl halides, which, after workup, produced the corresponding thiols (Scheme 65) <1995J(P1)2381>. The same **311** reacted with *cis*-butadiene rubber (BR) to form cross-links by addition to the carbon double bonds under the influence of zinc dimethyl dithiocarbamate and 1,12-diaminododecane, producing the BR vulcanizates **313** <1999MM7509>.



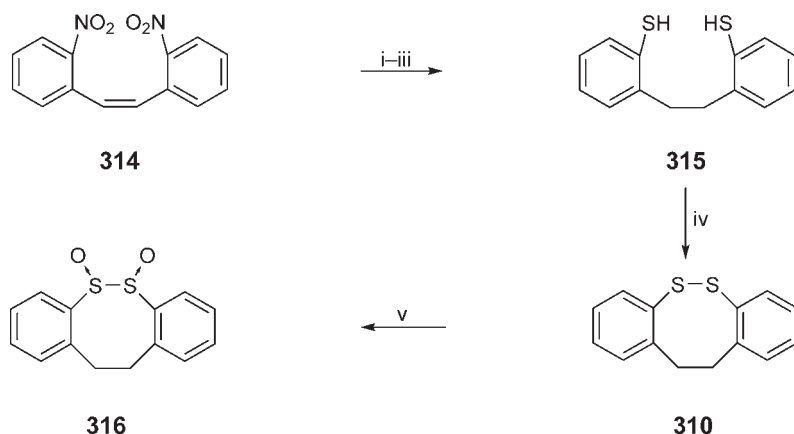
Scheme 65

14.04.6.5 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.04.6.5.1 Ring syntheses from C_6S_2 units

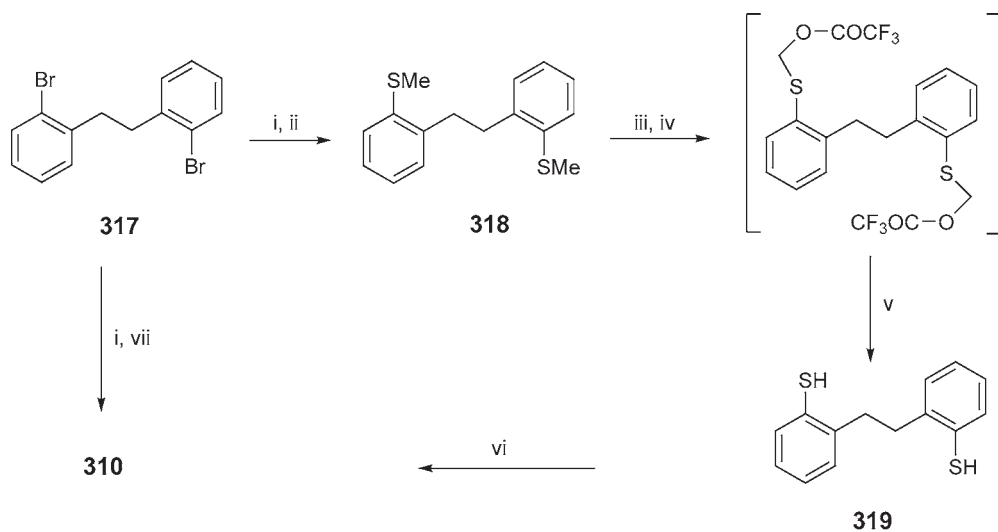
The dithiophenol derivative **315**, prepared from the dinitro **314** via reduction, diazotization, and subsequent reaction with sulfide, under mild oxidative conditions, afforded the cyclic disulfide **310**, which was converted into dioxide **316** with hydrogen peroxide or a peracid (Scheme 66) <2004WO099162>. The already known, dithiocin **310**, obtained

in five steps from 2-methyl-4-nitrobenzenesulfonic acid in 14% yield, can be synthesized by two different routes. Both routes start from dibromide **317**. Using the first strategy, the two sulfur atoms are introduced independently and the sulfur–sulfur bond is made later. Thus, double lithiation of dibromide **317** followed by reaction with Me_2S_2 , as the sulfur reagent, gave the double sulfide **318**, which via a double Pummerer reaction, followed by immediate treatment with the bis-trifluoroacetoxy derivative with methanolic ammonia, gave the thiol **319** (which by oxidation with KI_3 gave the dithiocin **310**; Scheme 67). The overall yield from dibromide **317** was 28% since the yield-limiting step, the demethylation of **318**, occurred in only 30% yield. Instead, the yield of the second synthetic pathway, in which the sulfur–sulfur portion is already in place, was much higher, 85%.



i, $\text{H}_2/\text{Pd}-\text{C}$; ii, HNO_2 ; iii, $\text{H}_2\text{S}/\text{NaOH}$; iv, H_2O_2 or FeCl_3/H^+ ; v, peracid

Scheme 66

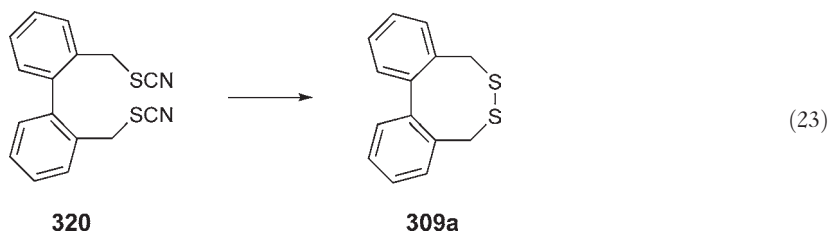


i, BuLi ; ii, Me_2S_2 ; iii, MCPBA; iv, TFAA, 40°C ; v, MeOH/NH_3 ; vi, KI_3 ; vii, $6 \times \text{S}_2\text{Im}_2$

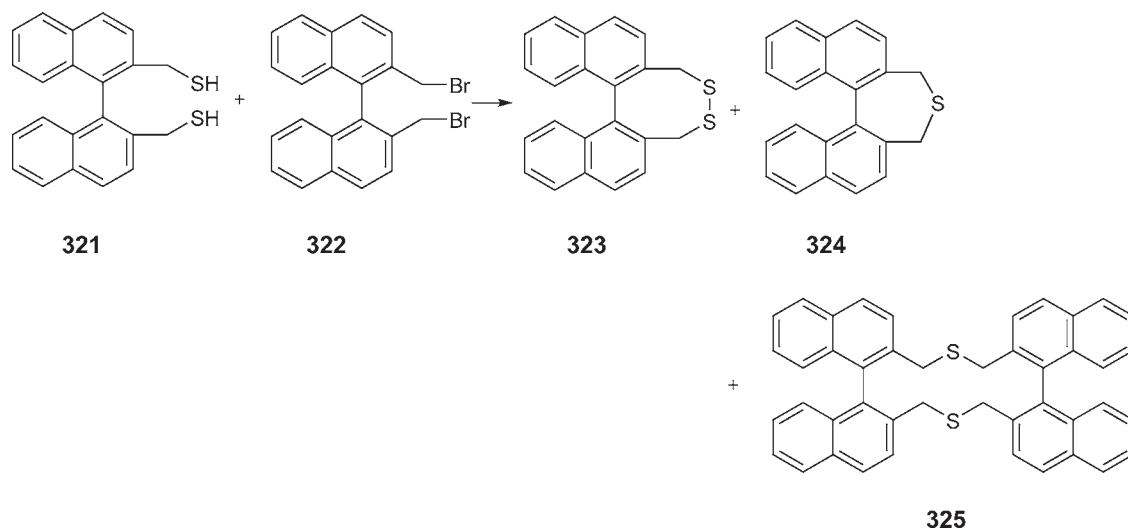
Scheme 67

It involved the use of sulfur diimidazole (S_2Im_2), as a doubly electrophilic source of sulfur, in the reaction with lithiated derivatives **317** to give directly the dibenzodithiocin **310** <2004OBC1528>.

Also, the yield of the already known dihydrodibenzo[*d,f*][1,2]dithiocin **309a** was improved by the cyclization of bis-thiocyanate **320**, obtained from the corresponding aralkyl bromides and potassium thiocyanate, in the presence of benzyltriethylammonium tetrathiomolybdate (Equation 23) <1995JOC7142>.



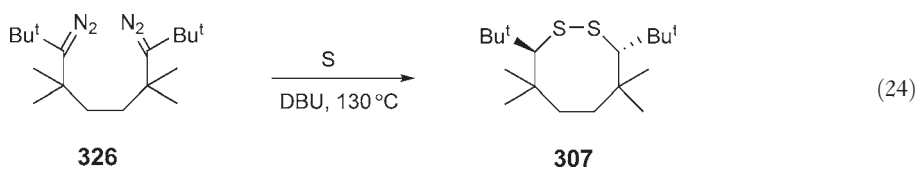
Dinaphthodithiocin **323** was unexpectedly obtained from the reaction of 1,1'-binaphthalene-2,2'-bis-methylenethiol **321** and 2,2'-bis-bromomethyl-1,1'-binaphthalene **322**. The dinaphthothiepine **324** and macrocycle **325** were the major products (Scheme 68) <1995T787>. Oxidation of 1,6-hexanedithiol with molecular bromine on hydrated silica gel gave 1,2-dithiacyclooctane in high yield (91%) and high purity after an easy workup. The procedure utilized organic media and does not require a base to neutralize HBr by-product since silica gel acts as the HBr scavenger <2002TL6271>.



Scheme 68

14.04.6.5.2 Ring syntheses from C₆ + S₂ units

1,6-Bis-diazoheptane **326** was prepared from the corresponding bis-hydrazone **53** by oxidation with nickel peroxide. Reaction of the bis-diazo compound **326** with elemental sulfur gave the hexahydro-1,2-dithiocin **307** in 77% yield (Equation 24) <2002HAC351>.



14.04.6.6 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Among the six reported syntheses of 1,2-dithiocins, four are relative to unimolecular cyclizations mainly involving oxidation of 1,6-dithiols. The most efficient cyclization appears to be the oxidation by bromine in hydrated silica gel both in terms of workup and yield. The cyclization of 1,6-dithiocyanate derivative catalyzed by tetrathiomolybdate seems less efficient, although preparatively interesting. Sulfurization of 1,6-dibromo derivative with sulfur diimidazole is certainly the best and immediate synthesis, which produces in a single step the dithiocins from dihalo compounds, generally used as starting materials for the unimolecular cyclizations. The sulfurization of the bis-diazo compound with elemental sulfur is obtained in lower, but still good, yield, but to get the bis-diazo compound a multistep procedure is necessary.

14.04.6.7 Important Compounds and Applications

Dithiocins have not received a great deal of attention from the practical application point of view except the possible utilization of the perhydropyridothiocin **311**, which was used for vulcanization of high *cis*-butadiene rubber <1999MM7509>.

14.04.7 Further Developments

A SciFinder search performed on 26 July 2007 gave no answers for 1,2-diazocines, 1,2-thiazocines, or 1,2-oxathiocins.

Instead the reactivity of a 3,8-ethylene bridged perhydro-oxazocine with benzylazide which gave traces of a triazoline adduct upon cycloaddition to the bridge double bond was reported <2007JOC3929>. High-yielding endo-selective intramolecular nitron-alkene cycloaddition (INAC) reaction of hept-6-enones, controlled by a *trans*-acetone, to give methylene-bridged perhydro-oxazocines which were readily transformed into calystegine, tropane and hydroxylated aminocycloheptane frameworks was also reported <2007OL207>.

Regarding 1,2-dioxocins, a computational study of the reaction between an oxygen-bridged 1,2-dioxocin and sulfuric acid <2007JPC3394> and the isolation of Walsuronoid A, a limonoid featuring a condensed methylene-bridged 1,2-dioxocin, from *Walsura robusta* was reported <2007OL2353>.

Regarding 1,2-dithiocins, the chemo-enzymatic preparation of copolymeric polythioesters containing branched-chain thioether groups <2007MI357>, and the photolysis of hexahydro-1,2-dithiocins in the presence of diamond films which led to a surface modification that introduced thioalkylthiol functional groups was also reported <2007MI348>.

References

- 1995JA9927 M. P. DeNinno, *J. Am. Chem. Soc.*, 1995, **117**, 9927.
 1995JOC784 P. H. Dussault, H. J. Lee, and Q. J. Niu, *J. Org. Chem.*, 1995, **60**, 784.
 1995JOC7142 K. R. Prabhu, A. R. Ramesha, and S. Chandrasekaran, *J. Org. Chem.*, 1995, **60**, 7142.
 1995J(P1)167 G. Read and N. R. Richardson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 167.
 1995J(P1)2381 K. Smith and M. Tzimas, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2381.
 1995MI811 C. G. Calin, *Revista De Chimie*, **46**, 811 (*Chem. Abstr.*, 1995, **124**, 55930).
 1995T787 U. K. Bandarage, L. R. Hanton, and R. A. J. Smith, *Tetrahedron*, 1995, **51**, 787.
 1995TL1889 Y. Takahashi, M. Ando, and T. Miyashi, *Tetrahedron Lett.*, 1995, **36**, 1889.
 1995TL6379 J. Hu and M. J. Miller, *Tetrahedron Lett.*, 1995, **36**, 6379.
 1996H(43)199 K. Iwamoto, S. Suzuki, E. Oishi, A. Miyashita, and T. Higashino, *Heterocycles*, 1996, **43**, 199.
 1996HCA307 F. Gerson, A. Lamprecht, M. Scholz, and H. Troxler, *Helv. Chim. Acta*, 1996, **79**, 307.
 1996LA545 A. G. Griesbeck, O. Sadlek, and K. Polborn, *Liebigs Ann. Chem.*, 1996, 545.
 1996MI79 S. R. Meshnick, C. W. Jefford, G. H. Poster, M. A. Avery, and W. Peters, *Parasitol. Today*, 1996, **12**, 79 (*Chem. Abstr.*, 1996, **124**, 249418).
 1996T11265 R. Patra, N. C. Bar, A. Roy, B. Achari, N. Ghoshal, and S. B. Mandal, *Tetrahedron*, 1996, **52**, 11265.
 1996T13695 G. Baccolini, A. Munyaneza, and C. Boga, *Tetrahedron*, 1996, **52**, 13695.
 1996T14813 K. Griesbaum, M. Hilß, and J. Bosch, *Tetrahedron*, 1996, **52**, 14813.
 1996USP5543406 R. C. A. Durham, C. M. C. Raleigh, S. V. F. Durham, C. D. H. Cary, and P. R. M. Durham, *US Pat.* 5 543 406 (1996) (*Chem. Abstr.*, 1996, **125**, 204519).
 1997JOC8251 I. Takano, I. Yasuda, M. Nishijima, Y. Hitotsuyanagi, K. Takeya, and H. Itokawa, *J. Org. Chem.*, 1997, **62**, 8251.
 1997JOC8948 N. C. Bar, A. Roy, B. Achari, and S. B. Mandal, *J. Org. Chem.*, 1997, **62**, 8948.
 1997J(P1)1939 Y. Ushigoe, S. Satake, A. Masuyama, M. Nojima, and K. J. McCullough, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1939.

- 1997J(P2)2313 Z. Paryzek and U. Rychlewska, *J. Chem. Soc., Perkin Trans 2*, 1997, 2313.
- 1997T4727 N. C. Bar, R. Patra, B. Achari, and S. B. Mandal, *Tetrahedron*, 1997, **53**, 4727.
- 1997T13165 J. Markandu, H. A. Dondas, M. Frederickson, and R. Grigg, *Tetrahedron*, 1997, **53**, 13165.
- 1997TL4263 P. M. O'Neill, L. P. Bishop, N. L. Searle, J. L. Maggs, S. A. Ward, P. G. Bray, R. C. Storr, and B. K. Park, *Tetrahedron Lett.*, 1997, **38**, 4263.
- 1997TL5485 S. Grabowski, J. Armbruster, and H. Prinzbach, *Tetrahedron Lett.*, 1997, **38**, 5485.
- 1997TL9001 J. R. Hwu, C. S. Yau, S.-C. Tsay, and T.-I. Ho, *Tetrahedron Lett.*, 1997, **38**, 9001.
- 1998AGE2242 J. Armbruster, S. Grabowski, T. Rush, and H. Prinzbach, *Angew. Chem. Int. Ed.*, 1998, **37**, 2242.
- 1998BML903 M. D. Bachi, E. E. Korshin, P. Ploypradith, J. N. Cumming, S. Xie, T. A. Shapiro, and G. H. Posner, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 903.
- 1998CPB674 Y. Arakawa, T. Goto, K. Kawase, and S. Yoshifuji, *Chem. Pharm. Bull.*, 1998, **46**, 674.
- 1998JOC2536 S. F. Nelsen, H. Q. Tran, R. F. Ismagilov, M. T. Ramm, L. Chen, and D. R. Powell, *J. Org. Chem.*, 1998, **63**, 2536.
- 1998J(P1)3053 K. J. McCullough, Y. Ushigoe, S. Tanaka, A. Masuyama, and M. Nojima, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3053.
- 1998MRC13 A. Stasko, K. Erentova, P. Rapta, O. Nuijken, and B. Voit, *Magn. Reson. Chem.*, 1998, **36**, 13.
- 1998SL122 M. D. Bachi and E. E. Korshin, *Synlett*, 1998, 122.
- 1998TL6065 P. M. O'Neill, N. L. Searle, K. J. Raynes, J. L. Maggs, S. A. Ward, R. C. Storr, B. K. Park, and G. H. Posner, *Tetrahedron Lett.*, 1998, **39**, 6065.
- 1999BKC969 C. W. Lee and T. S. Huh, *Bull. Korean Chem. Soc.*, 1999, **20**, 969 (*Chem. Abstr.*, 1999, **131**, 351069).
- 1999JA8126 L. A. Paquette and S. M. Leit, *J. Am. Chem. Soc.*, 1999, **121**, 8126.
- 1999JOC2304 A. Roy, K. Chakrabarty, P. K. Dutta, N. Bar, N. Basu, B. Achari, and S. B. Mandal, *J. Org. Chem.*, 1999, **64**, 2304.
- 1999JOC6776 J. Cazelles, A. Robert, and B. Meunier, *J. Org. Chem.*, 1999, **64**, 6776.
- 1999MI107 A. Kornmüller and U. Wiesmann, *Wat. Sci. Tech.*, 1999, **40**, 107 (*Chem. Abstr.*, 2000, **132**, 5948).
- 1999MI511 L. P. D. Bishop, J. L. Maggs, P. M. O'Neill, and B. K. Park, *J. Pharm. Exp. Ther.*, 1999, **289**, 511 (*Chem. Abstr.*, 1999, **131**, 39147).
- 1999MM7509 R. Hulst, R. M. Seyger, J. P. M. van Duynhoven, L. van der Does, J. W. M. Noordermeer, and A. Bantjes, *Macromolecules*, 1999, **32**, 7509.
- 1999T759 K. S. Ngo and G. D. Brown, *Tetrahedron*, 1999, **55**, 759.
- 1999TL4045 V. Morisson, J. P. Barnier, and L. Blanco, *Tetrahedron Lett.*, 1999, **40**, 4045.
- 1999TL8391 C. H. Oh, H. J. Kim, S. H. Wu, and H. S. Won, *Tetrahedron Lett.*, 1999, **40**, 8391.
- 1999WO12900 M. Bachi, G. H. Posner, and E. Korshin, *PCT Int. Appl. WO 12900* (1999) (*Chem. Abstr.*, 1999, **130**, 237573).
- 1999WO47525 M. Muhlebach, J. Glock, T. Maetzke, and A. Stoller, *PCT Int. Appl. WO 47525* (1999) (*Chem. Abstr.*, 1999, **131**, 228720).
- 2000EJO335 H. S. Shin, C. won Lee, J. Y. Lee, and T. S. Huh, *Eur. J. Org. Chem.*, 2000, 335.
- 2000H(53)151 Y. Endo, T. Uchida, and K. Yamaguchi, *Heterocycles*, 2000, **53**, 151.
- 2000JBS59 S. C. Hess, M. I. S. Farah, S. Y. Eguchib, and P. M. Imamura, *J. Braz. Chem. Soc.*, 2000, **11**, 59 (*Chem. Abstr.*, 2000, **133**, 177319).
- 2000JCI354 C. W. Jefford, M. Grigorov, J. Weber, H. P. Lüthi, and J. M. J. Tronchet, *J. Chem. Inf. Comput. Sci.*, 2000, **40**, 354.
- 2000JHC639 M. D. Bachi, E. E. Korshin, R. Hoos, and A. M. Szpilman, *J. Heterocycl. Chem.*, 2000, **37**, 639.
- 2000JOC1578 P. M. O'Neill, L. P. D. Bishop, N. L. Searle, J. L. Maggs, R. C. Storr, S. A. Ward, B. K. Park, and F. Mabbs, *J. Org. Chem.*, 2000, **65**, 1578.
- 2000JOC1799 A. Ishii, C. Tsuchiya, T. Shimada, K. Furusawa, T. Omata, and J. Nakayama, *J. Org. Chem.*, 2000, **65**, 1799.
- 2000JOC8407 P. H. Dussault, I. Q. Lee, H. J. Lee, R. J. Lee, Q. J. Niu, J. A. Schultz, and U. R. Zope, *J. Org. Chem.*, 2000, **65**, 8407.
- 2000J(P1)1139 J. T. Sharp, P. Wilson, S. Parsons, and R. O. Gould, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1139.
- 2000MI955 M. T. Duraisingh, C. Roper, D. Walliker, and D. C. Warhurst, *Mol. Microbiol.*, 2000, **36**, 955 (*Chem. Abstr.*, 2000, **133**, 132352).
- 2000SL1010 A. A. Trabanco, A. G. Montalban, G. Rumbles, A. G. M. Barrett, and B. M. Hoffman, *Synlett*, 2000, 1010.
- 2000TA2625 M. C. Bagley and W. Oppolzer, *Tetrahedron Asymmetry*, 2000, **11**, 2625.
- 2000TL3145 T. Tokuyasu, A. Masuyama, M. Nojima, H. S. Kim, and Y. Wataya, *Tetrahedron Lett.*, 2000, **41**, 3145.
- 2000TL5483 J. Armbruster, F. Stelzer, P. Landenberger, C. Wieber, D. Hunkler, M. Keller, and H. Prinzbach, *Tetrahedron Lett.*, 2000, **41**, 5483.
- 2000TL7863 D. Spielvogel, J. Kammerer, M. Keller, and H. Prinzbach, *Tetrahedron Lett.*, 2000, **41**, 7863.
- 2000WO47585 M. Muhlebach, J. Glock, T. Maetzke, W. Haas-Weg, and A. Stoller, *PCT Int. Appl. WO 47585* (2000) (*Chem. Abstr.*, 2000, **133**, 164053).
- 2001CME1803 C. W. Jefford, *Curr. Med. Chem.*, 2001, **8**, 1803 (*Chem. Abstr.*, 2002, **136**, 177399).
- 2001EJO1899 I. C. Jung, *Eur. J. Org. Chem.*, 2001, 1899.
- 2001JME4313 I. J. Enyedy, Y. Ling, K. Nacro, Y. Tomita, X. Wu, Y. Cao, R. Guo, B. Li, X. Zhu, Y. Huang, *et al.*, *J. Med. Chem.*, 2001, **44**, 4313.
- 2001JOC3564 L. A. Paquette, C. S. Ra, J. D. Schloss, S. M. Leit, and J. C. Gallucci, *J. Org. Chem.*, 2001, **66**, 3564.
- 2001JOC6531 A. M. Szpilman, E. E. Korshin, R. Hoos, G. H. Posner, and M. D. Bachi, *J. Org. Chem.*, 2001, **66**, 6531.
- 2001OL3733 M. Nahmany and A. Melman, *Org. Lett.*, 2001, **3**, 3733.
- 2001T5979 T. Tokuyasu, A. Masuyama, M. Nojima, K. J. McCullough, H. S. Kim, and Y. Wataya, *Tetrahedron*, 2001, **57**, 5979.
- 2001WO17351 J. Glock, A. A. Friedmann, and D. Cornes, *PCT Int. Appl. WO 17351* (2001) (*Chem. Abstr.*, 2001, **134**, 218317).
- 2001WO17352 J. Glock, A. A. Friedmann, and D. Cornes, *PCT Int. Appl. WO 17352* (2001) (*Chem. Abstr.*, 2001, **134**, 203787).
- 2001WO17972 T. Maetzke, A. Stoller, S. Wendeborn, and H. Szczepanski, *PCT Int. Appl. WO 17972* (2001) (*Chem. Abstr.*, 2001, **134**, 237482).
- 2001WO17973 T. Maetzke, S. Wendeborn, and A. Stoller, *PCT Int. Appl. WO 17973* (2001) (*Chem. Abstr.*, 2001, **134**, 222711).
- 2002ARK67 J. T. Sharp, A. G. Cessford, and A. R. Stewart, *ARKIVOC*, 2002, **6**, 67.
- 2002DOC9 O. A. Ivanova, E. B. Averina, Yu. K. Grishin, T. S. Kuznetsova, and N. S. Zefirov, *Dokl. Chem. (Engl. Transl.)*, 2002, **382**, 9.
- 2002HAC351 A. Ishii, K. Furusawa, T. Omata, and J. Nakayama, *Heteroatom Chem.*, 2002, **13**, 351.
- 2002HCA1 T. Caronna, S. Gabbiadini, A. Mele, and F. Recupero, *Helv. Chim. Acta*, 2002, **85**, 1.
- 2002JME4732 H. S. Kim, K. Begum, N. Ogura, Y. Wataya, T. Tokuyasu, A. Masuyama, M. Nojima, and K. J. McCullough, *J. Med. Chem.*, 2002, **45**, 4732.
- 2002JOC5307 B. W. Greatrex, M. C. Kimber, D. K. Taylor, G. Fallon, and E. R. T. Tiekink, *J. Org. Chem.*, 2002, **67**, 5307.
- 2002JOC8975 R. Shelkov, M. Nahmany, and A. Melman, *J. Org. Chem.*, 2002, **67**, 8975.

- 2002MI1661 K. Borstnik, I. Paik, T. A. Shapiro, and G. H. Poster, *Int. J. Parasitol.*, 2002, **32**, 1661 (*Chem. Abstr.*, 2003, **139**, 159214).
- 2002MRC307 C. Jolivet, D. D. Long, R. S. Dahl, and A. P. Termin, *Magn. Reson. Chem.*, 2002, **40**, 307.
- 2002T2449 M. D. Bachi, E. E. Korshin, R. Hoos, A. M. Szpilman, P. Ploypradith, S. Xie, T. A. Shapiro, and G. Posner, *Tetrahedron*, 2002, **58**, 2449.
- 2002TL6271 M. H. Ali and M. McDermott, *Tetrahedron Lett.*, 2002, **43**, 6271.
- 2002WO13833 S. Wang, D. Yang, and I. J. Enyedy, *PCT Int. Appl.* WO 13833 (2002) (*Chem. Abstr.*, 2002, **136**, 194235).
- 2002WO085838 S. Buchwald, A. K. Lapars, J. Cantilla, G. E. Job, M. Wolter, F. Y. Kwong, G. Nordmann, and E. J. Hennessy, *PCT Int. Appl.* WO 085838 (2002) (*Chem. Abstr.*, 2002, **137**, 352492).
- 2003ARK75 K. Singha, B. Achari, and S. B. Mandal, *ARKIVOC*, 2003, **9**, 75.
- 2003BML2389 D. Herlem, M. T. Martin, C. Thal, and C. Guillou, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2389.
- 2003CHE388 Yu. V. Morozova, D. V. Yashunsky, B. I. Maksihov, and G. V. Ponomarev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 388.
- 2003CJC937 S. Wolfe, M. C. Wilson, M. H. Cheng, G. V. Shustov, and C. I. Akuche, *Can. J. Chem.*, 2003, **81**, 937.
- 2003JME2516 E. E. Korshin, R. Hoos, A. M. Szpilman, Konstantinovskii, G. H. Posner, and M. D. Bachi, *J. Med. Chem.*, 2003, **46**, 2516.
- 2003JOC7361 T. Tokuyasu, S. Kunikawa, M. Abe, A. Masuyama, M. Nojima, H. S. Kim, K. Begum, and Y. Wataya, *J. Org. Chem.*, 2003, **68**, 7361.
- 2003MI145 E. Mete, R. Altundaş, H. Seçen, and M. Balci, *Türk. J. Chem.*, 2003, **27**, 145 (*Chem. Abstr.*, 2003, **139**, 179661).
- 2003OBC2859 J. F. Berrien, O. Provot, J. Mayrargue, M. Coquillay, L. Cicerón, F. Gay, M. Danis, A. Robert, and B. Meunier, *Org. Biomol. Chem.*, 2003, **1**, 2859.
- 2003SL1043 Y.-K. Yang and J. Tae, *Synlett*, 2003, 1043.
- 2003SL2017 Y.-K. Yang and J. Tae, *Synlett*, 2003, 2017.
- 2003T525 T. Ito, T. Tokuyasu, A. Masuyama, M. Nojima, and K. J. McCullough, *Tetrahedron*, 2003, **59**, 525.
- 2003T4451 C. W. G. Fishwick, R. Grigg, V. Sridharan, and J. Virica, *Tetrahedron*, 2003, **59**, 4451.
- 2003WO038060 S. Wang, *PCT Int. Appl.* WO 038060 (2003) (*Chem. Abstr.*, 2003, **138**, 348698).
- 2004AGE4193 P. M. O'Neill, P. A. Stocks, M. D. Pugh, N. C. Araujo, E. E. Korshin, J. F. Bickley, S. A. Ward, P. G. Bray, E. Pasini, J. Davies, *et al.*, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 4193.
- 2004BKC1307 Y.-K. Yang, S. Lee, and J. Tae, *Bull. Korean Chem. Soc.*, 2004, **25**, 1307 (*Chem. Abstr.*, 2005, **142**, 336310).
- 2004CC1848 C. Moutrille and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 2004, 1848.
- 2004JKC207 A. Y. Lee, T. S. Huh, and K. R. Lee, *J. Korean Chem. Soc.*, 2004, **48**, 207 (*Chem. Abstr.*, 2004, **141**, 350034).
- 2004MI173 J. L. Maggs, L. P. D. Bishop, K. T. Batty, C. C. Dodd, K. F. Ilett, P. M. O'Neill, G. Edwards, and B. K. Park, *Chem. Biol. Interact.*, 2004, **147**, 173 (*Chem. Abstr.*, 2004, **141**, 116381).
- 2004OBC1528 P. Wyatt and A. Hudson, *Org. Biomol. Chem.*, 2004, **2**, 1528.
- 2004OL1313 L. A. Paquette, W. R. S. Barton, and J. C. Gallucci, *Org. Lett.*, 2004, **6**, 1313.
- 2004OL4351 Y. J. Kim and D. Lee, *Org. Lett.*, 2004, **6**, 4351.
- 2004S1696 S. Karsch, D. Freitag, P. Schwab, and P. Metz, *Synthesis*, 2004, 1696.
- 2004T4931 T. Zhou, H. Zhang, N. Zhu, and P. Chiu, *Tetrahedron*, 2004, **60**, 4931.
- 2004TA537 D. A. Lenev, K. A. Lyssenko, D. G. Golovanov, O. Wingart, V. Bub, and R. G. Kostnanovsky, *Tetrahedron Asymmetry*, 2004, **60**, 537.
- 2004TL3589 D. Freitag, P. Schwab, and P. Metz, *Tetrahedron Lett.*, 2004, **45**, 3589.
- 2004TL3757 J. Tre and D. Hahn, *Tetrahedron Lett.*, 2004, **45**, 3757.
- 2004WO099162 S. Gupta, R. Rajagopalan, D. M. Carrig, and P. Fernandes, *PCT Int. Appl.* WO 099162 (2004) (*Chem. Abstr.*, 2004, **141**, 424217).
- 2005HCA2865 Z. S. Yang, W. M. Wu, Y. Li, and Y. L. Wu, *Helv. Chim. Acta*, 2005, **88**, 2865.
- 2005JOC3618 A. M. Szpilman, E. E. Korshin, H. Rozenberg, and M. D. Bachi, *J. Org. Chem.*, 2005, **70**, 3618.
- 2005JOC6995 Y.-K. Yang, J.-H. Choi, and J. Tae, *J. Org. Chem.*, 2005, **70**, 6995.
- 2005JST87 M. G. B. Drew, J. Metcalfe, and F. M. D. Ismail, *J. Mol. Struct.*, 2005, **756**, 87.
- 2005MI1082 Y. Marrero-Ponce, M. Iyarreta-Veitia, A. Montero-Torres, C. Romero-Zaldivar, C. A. Brandt, P. E. Avila, K. Kirchgatter, and Y. Machado, *J. Chem. Inf. Model*, 2005, **45**, 1082 (*Chem. Abstr.*, 2005, **143**, 165983).
- 2005P599 A. M. Adio and W. A. König, *Phytochemistry*, 2005, **66**, 599.
- 2005T4831 M. Kirihaara, H. Kakuda, M. Ichinose, Y. Ochiai, S. Takizawa, A. Mokuya, K. Okubo, A. Hatano, and M. Shiro, *Tetrahedron*, 2005, **61**, 4831.
- 2005T9961 J. M. Wu, S. Kunikawa, T. Tokuyasu, A. Masuyama, M. Nojima, H. S. Kim, and Y. Wataya, *Tetrahedron*, 2005, **61**, 9961.
- 2005WO068457 Y. Yamamoto and H. Yamamoto, *PCT Int. Appl.* WO 068457 (2005) (*Chem. Abstr.*, 2005, **143**, 172883).
- 2006BML2991 P. M. O'Neill, E. Verissimo, S. A. Ward, J. Davies, E. E. Korshin, N. Araujo, M. D. Pugh, M. L. S. Cristiano, P. A. Stocks, and M. D. Bachi, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2991.
- 2006JOC2480 L. I. Robins, R. D. Carpenter, J. C. Fettingner, M. J. Haddadin, D. S. Tinti, and M. J. Kurth, *J. Org. Chem.*, 2006, **71**, 2480.
- 2006JOC3253 T. K. M. Shing, A. W. F. Wong, T. Ikeno, and T. Yamada, *J. Org. Chem.*, 2006, **71**, 3253.
- 2006USP0135702 C. Wang and J. Dong, *US Pat.* 0135702 (2006) (*Chem. Abstr.* 2006, **145**, 47060).
- 2007JOC3929 B. S. Bodnar and M. J. Miller, *J. Org. Chem.*, 2007, **72**, 3929.
- 2007JPC3394 T. Kurtén, B. Bonn, H. Vehkamäki, and M. Kulmala, *J. Phys. Chem.*, 2007, **111**, 3394.
- 2007MI348 T. Nakamura, T. Ohana, M. Hasegawa, and Y. Koga, *Japanese Journal of Applied Physics*, 2007, **46**, 348 (*Chem. Abstr.*, 2007, **146**, 120786).
- 2007MI357 E. Fehling, E. Klein, N. Weber, C. Demes, and K. Vosman, *Applied Microbiology and Biotechnology*, 2007, **74**, 357 (*Chem. Abstr.*, 2007, **146**, 128278).
- 2007OL207 T. K. M. Shing, W. F. Wong, T. Ikeno, and T. Yamada, *Org. Lett.*, 2007, **9**, 207.
- 2007OL2353 S. Yin, X.-N. Wang, C.-Q. Fan, S.-G. Liao, and J.-M. Yue, *Org. Lett.*, 2007, **9**, 2353.

Biographical Sketch



Girolamo Cirrincione was born in Palermo in 1948. In March 1974, he graduated in chemistry from the University of Palermo. After completing one year of military service, he did his postdoctoral fellowship at the Medicinal Chemistry Department of the University of Palermo from May 1975 to March 1976; from April 1976 to October 1981, he was a research fellow and from November 1981 to October 1994 an associate professor of medicinal chemistry at the same institution. Since November 1994, he has been a full professor of medicinal chemistry at the University of Palermo. He has obtained CNR-NATO Fellowships (September 1982–May 1983, July–August 1986, July–September 1989) and British Council Fellowship (August 1984), from the School of Chemical Sciences of the University of East Anglia (Norwich, UK).

He has served as the director of the Istituto Farmacochimico (March 1995–June 1999) and director of the Dipartimento Farmacochimico Toss. Biol. (July 1999–December 2004 and July 2005–to date). He is responsible for ERASMUS exchanges of the Faculty of Pharmacy of the University of Palermo; for the research sector ‘Synthetic Analogues of Natural Structure of Biological Interest’ of the ICTPN-CNR in a scientific capacity (January 1994–December 1998). He has been Member of the Drug Discovery Committee of the European Organization for Research and Treatment of Cancer, the Società Chimica Italiana, Member, and the International Society of Heterocyclic Chemistry (which he has also served in the capacity of vice-president for the period 2004–05). He is a scientific editor of the journal *ARKIVOC*.



Patrizia Diana was born in Palermo in 1967. She graduated in pharmacy with honors at the University of Palermo in March 1990. From April 1990 to August 1992, she was a research fellow at the Medicinal Chemistry Department of the University of Palermo. She has been working as researcher in medicinal chemistry (September 1992–March 2000) and associate professor of medicinal chemistry (April 2000–to date) at the University of Palermo. From May 1994 to May 1995, she worked with Professor Malcolm F. G. Stevens at the CRC Experimental Cancer Chemotherapy Research Group for a fellowship. Since 2005, she has been vice-director of the Dipartimento Farmacochimico Toss. e Biol. She is a member of the Società Chimica Italiana and International Society of Heterocyclic Chemistry.

14.05

Eight-membered Rings with Two Heteroatoms 1,3

G. Cirrincione and P. Diana

Università degli Studi di Palermo, Palermo, Italy

© 2008 Elsevier Ltd. All rights reserved.

14.05.1	Introduction	170
14.05.2	Rings with Two Nitrogens (1,3-Diazocines)	171
14.05.2.1	Theoretical Methods	171
14.05.2.2	Experimental Structural Methods	172
14.05.2.3	Thermodynamic Aspects	174
14.05.2.4	Reactivity of Nonconjugated Rings	175
14.05.2.5	Reactivity of Substituents Attached to Ring Carbon Atoms	176
14.05.2.6	Reactivity of Substituents Attached to Ring Heteroatoms	178
14.05.2.7	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	179
14.05.2.7.1	Ring syntheses from C_6N_2 units	179
14.05.2.7.2	Ring syntheses from $C_6N + N$ units	183
14.05.2.7.3	Ring syntheses from $C_5N_2 + C$ units	184
14.05.2.7.4	Ring syntheses from $C_5 + CN_2$ units	186
14.05.2.8	Ring Syntheses by Transformation of Another Ring	186
14.05.2.9	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	189
14.05.2.10	Important Compounds and Applications	190
14.05.3	Rings with One Nitrogen and One Oxygen (2H-1,3-Oxazocines)	191
14.05.3.1	Theoretical Methods	191
14.05.3.2	Experimental Structural Methods	192
14.05.3.3	Thermodynamic Aspects	196
14.05.3.4	Reactivity of Nonconjugated Rings	197
14.05.3.5	Reactivity of Substituents Attached to Ring Carbon Atoms	205
14.05.3.6	Reactivity of Substituents Attached to Ring Heteroatoms	213
14.05.3.7	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	213
14.05.3.7.1	Natural products	213
14.05.3.7.2	Ring syntheses from C_6NO units	213
14.05.3.7.3	Ring syntheses from $C_5NO + C$ units	221
14.05.3.7.4	Ring syntheses from $C_5O + CN$ units	221
14.05.3.7.5	Ring syntheses from $C_5O + C + N$ units	221
14.05.3.7.6	Ring syntheses from $C_4N + C_2O$ units	222
14.05.3.7.7	Ring syntheses from $C_4O + C_2N$ units	224
14.05.3.7.8	Ring syntheses from $C_3O + C_3 + N$ units	225
14.05.3.8	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	225
14.05.3.9	Important Compounds and Applications	225
14.05.4	Rings with One Nitrogen and One Sulfur (2H-1,3-Thiazocines) or with Two Sulfurs (4H-1,3-Dithiocins)	226

14.05.4.1	Theoretical Methods	226
14.05.4.2	Experimental Structural Methods	227
14.05.4.3	Thermodynamic Aspects	229
14.05.4.4	Reactivity of Nonconjugated Rings	229
14.05.4.5	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	230
14.05.4.5.1	Ring syntheses of thiazocines from C ₆ NS units	230
14.05.4.5.2	Ring syntheses of thiazocines from C ₄ NS + C ₂ units	230
14.05.4.5.3	Ring syntheses of thiazocines from C ₄ N + C ₂ S units	231
14.05.4.5.4	Ring syntheses of dithiocins from C ₅ S ₂ + C units	232
14.05.4.5.5	Ring syntheses of dithiocins from C ₂ S + C ₂ S + C ₂ units	233
14.05.4.6	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	233
14.05.4.7	Important Compounds and Applications	234
14.05.5	Rings with Two Oxygens (4<i>H</i>-1,3-Dioxocins)	234
14.05.5.1	Theoretical Methods	234
14.05.5.2	Experimental Structural Methods	234
14.05.5.3	Thermodynamic Aspects	236
14.05.5.4	Reactivity of Nonconjugated Rings	237
14.05.5.5	Reactivity of Substituents Attached to Ring Carbon Atoms	240
14.05.5.6	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	241
14.05.5.6.1	Ring syntheses from C ₆ O ₂ units	241
14.05.5.6.2	Ring syntheses from C ₅ O ₂ + C units	243
14.05.5.6.3	Ring syntheses from C ₄ O + C ₂ O units	246
14.05.5.6.4	Ring syntheses from C ₂ O + C ₂ O + C ₂ units	246
14.05.5.7	Ring Syntheses by Transformation of Another Ring	247
14.05.5.8	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	249
14.05.5.9	Important Compounds and Applications	249
14.05.6	Further Developments	249
References		250

14.05.1 Introduction

CHEC(1984), which covered the literature through 1982, treated all eight-membered heterocycles with one or more heteroatoms in Volume 7 in a single chapter (5.19). Within that chapter, little attention was given to eight-membered rings with two heteroatoms in a 1,3-relationship. In fact, few lines were dedicated to 1,3-diazocines (Section 5.19.4.2); only one 1,3-oxazocine was reported in Section 5.19.5; and Section 5.19.7.2 dealing with 1,3-dioxocanes, the largest class of 1,3-heterocines, was contained in less than one page. In Section 5.19.5, dedicated to "Conformations of heterocyclic eight-membered rings," the conformational behavior of 1,3-dioxocanes was reported. In CHEC-II(1996), which covered the literature from 1983 to 1995, the eight-membered rings with two heteroatoms in a 1,3-relationship were treated in Volume 9 in the dedicated chapter 22 of 31 pages. That chapter covered those compounds with nitrogen, oxygen, and sulfur as heteroatoms and did not cover compounds in which the ring heteroatoms were members of another fused ring and bridged polycyclic compounds. The most important sections regarded the diazocines and the dioxocins. This chapter covers the literature from 1996 to 2006 and also reports those articles published in 1995 which were not reported in CHEC-II(1996). In this edition, in addition to the uncondensed derivatives, eight-membered 1,3-heterocycles fused to five-, six-, and seven-membered carbocycles or heterocycles are covered. Bridged 1,3-heterocines, which actually constitute the majority of the compounds reported, were covered as well. Also, in this edition, as happened in the

previous one, the interest in this class of compounds has been driven by their pharmacological activity. In fact, the most important section of this chapter deals with oxazocines due to studies conducted on bicyclomycin, an antibiotic, which was introduced in the market with the trade name Bicozamycin, and the huge number of analogues synthesized. Another important class of compounds is represented by purine-fused 1,3-diazocines and related isomers, aza- or deaza- analogues also called anhydronucleosides or cyclonucleosides. Such compounds exhibited good and selective activity against *Flaviviridae* infections and in particular against hepatitis C virus (HCV). On the contrary, the 1,3-oxazocine analogues of this latter class showed remarkable anti-HIV activity (HIV = human immunodeficiency virus). The 1,3-dioxocin nucleus proved to be a good pharmacophoric moiety as, depending on the substituents and annelations, showed a wide range of biological activities such as antitumor, anti-inflammatory, hypolipidemic, antidiabetic, and herbicide properties. Dioxocins are also studied as components of bridged calixarenes and cavitand for molecular recognition and metal binding, but the large number of references found in the past decade (as much as the other 1,3-heterocines) and editorial constraints induced us to neglect this topic and limit our attention to some representative references only <1997CRV1713, 2005AGE7107, 2006JOC1289, 2006JA1531>. As in CHEC-II(1996), nomenclature for the eight-membered rings with two heteroatoms in a 1,3-relationship follows the usual standard system, with the exceptions introduced for the completely reduced derivatives. The six parent unsaturated systems are 1,3-diazocine, 2*H*-1,3-oxazocine, 2*H*-1,3-thiazocine, 4*H*-1,3-dioxocin, 4*H*-1,3-oxathiocin, and 4*H*-1,3-dithiocin.

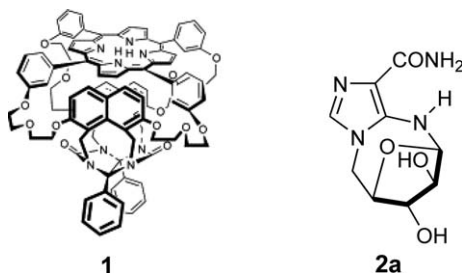
No ‘fully conjugated’ 1,3-heterocines have been prepared and the section “Reactivity of fully conjugated rings” is absent from all six system subchapters. The subchapter of the 4*H*-1,3-oxathiocins is also missing. Hydrogenated analogues are generally named as di-, tetra-, hexa-, or in the case of diazocines octa- or perhydro derivatives. The completely saturated derivatives are generally referred to as diazocane, oxazocane, thiazocane, dioxocane, oxathiocane, and dithiocane in the literature. The main change in this chapter, with respect to CHEC-II(1996), is related to the “Theoretical methods” section. Such a section in CHEC-II(1996) was a unique section, placed immediately after the introduction, dealing with all the classes of eight-membered heterocycles with two heteroatoms. In this edition, each paragraph dealing with a single class of heterocycles has its own theoretical methods section. The “Experimental Structural Methods” section has received a strong impulse as, with some exceptions, the great majority of the reported derivatives has been adequately characterized. As already done in CHEC-II(1996), all five reported systems are discussed separately with each discussion following the same general format. In the case where particular sections are not mentioned, it means that no chemistry has been reported. In the last decade, comprehensive reviews on 1,3-heterocines did not appear due to their complete coverage received in CHEC-II(1996).

14.05.2 Rings with Two Nitrogens (1,3-Diazocines)

14.05.2.1 Theoretical Methods

The naphthalene-fused 1,3-diazocine **1** is a glycoluril-based host with a nearby porphyrin, bound through a crown ether spacer, that exists in chloroform as a mixture of three slowly interconverting conformers, which differ in the orientation of the naphthalene sidewalls of the cavity with respect to the phenyl groups of the glycoluril framework. Molecular modeling predicted that the flexible crown ethers allow the porphyrin to move freely with regard to the receptor, and that it is not possible for the porphyrin to be situated on the convex side of the host. A combined utilization of molecular modeling and the observed chemical shifts as well as the nuclear Overhauser effects (NOEs) in the two-dimensional nuclear Overhauser enhancement spectroscopy (2-D NOESY) spectrum allowed the calculation of the 3-D structures of the *syn-anti* (*sa*) and *syn-syn* (*ss*) conformers of **1** (78% and 20% of the population). Due to the low abundance of the *anti-anti* (*aa*) conformer (2%), its exact structure could not be derived from nuclear magnetic resonance (NMR) shifts, and it was computer-modeled assuming that in this conformer also, like the *sa* conformer, the porphyrin is situated over the sidewalls. Moreover, the molecular modeling studies indicated that potassium ions can be nicely accommodated between two crown ether spacer at the sides of the cavity where the carbonyl functions are located. Also, molecular modeling of the 1:1 complex formed upon addition of *N,N'*-dimethyl-4,4'-dipyridinium (MV) indicated that the lifting of the porphyrin moiety is necessary to accommodate the bipyridine ring system of the guest and that the MV is bound orthogonal to the porphyrin plane and parallel to the cavity of the side walls <2002MI151>. Molecular modeling studies made on the oxygen-bridged imidazo-fused 1,3-diazocine **2a** showed that the eight-membered ring adopts a distorted boat conformation with the imidazole ring essentially coplanar with and end face of the boat. The angle between the bottom face and the end face attached to the imidazole ring is ca. 140°. The oxygen bridge is on the bottom face of the boat. Variation in the position of the hydroxyl groups gives rise to a range of conformational energies (ca. 13 kJ mol⁻¹). The two lowest energy forms have

the 3-OH group in either *gauche* conformations with respect to the C(3)–C(2) bond with the 4-OH group in the *trans*-position with respect to the C(4)–C(5) bond. The amide group adopts the conformation, which allows a hydrogen bond to the imidazole nitrogen. Diazocine **2a** can also exist with the eight-membered ring in a distorted chair conformation; however, this conformation is about 12 kJ mol^{−1} higher in energy and will not be significantly populated <1999MI441>.

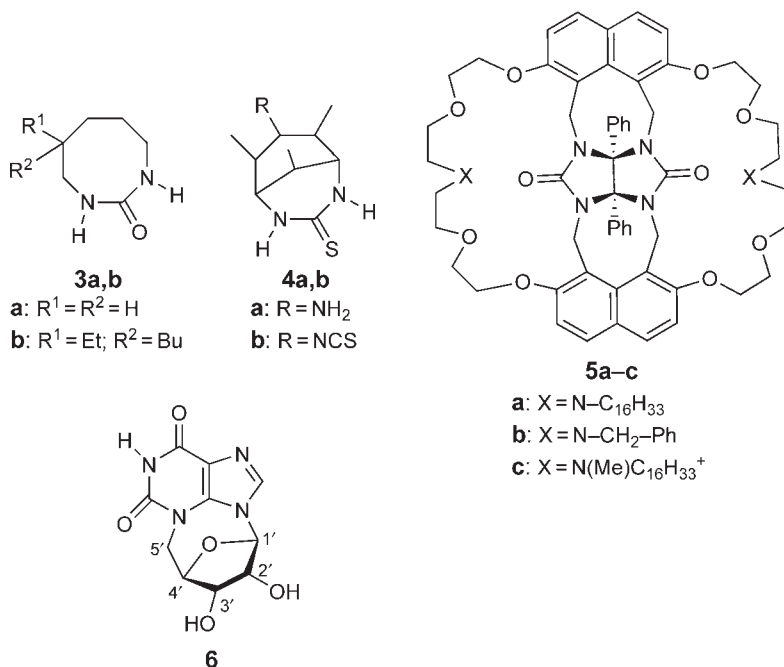


14.05.2.2 Experimental Structural Methods

No X-ray crystallography studies were reported in the past decade for 1,3-diazocines. The NMR techniques were instead widely used to establish the structure of the 1,3-diazocines, which are generally part of condensed and/or bridged systems. Very few uncondensed derivatives have been reported. Among them, **3b** showed the methylene resonances adjacent to nitrogen atoms at 3.00–3.31 ppm and the other ring methylene or methyne signals were found in the range 0.70–1.66 ppm. The NH protons resonated at 5.32–5.59 ppm <2002JOC4086>. An alkyl bridge between positions 4 and 8 experienced a downfield shift for all the signals. Thus in **4**, the protons adjacent to nitrogens resonated at 3.09–4.05 ppm, the other ring methyne signals could be found at 1.74–1.88 ppm, while the NH protons resonate in the range 6.95–7.46 ppm <1997J(P2)1445>. Benzo-condensation on positions 5 and 6 further shifted downfield all the signals with the protons adjacent to nitrogen that could be found at 3.56–4.44 ppm, other ring protons resonated at 1.95–3.05 ppm, and the NH signals at 7.56–8.16 ppm <1995JME2946, 2002BMC599>.

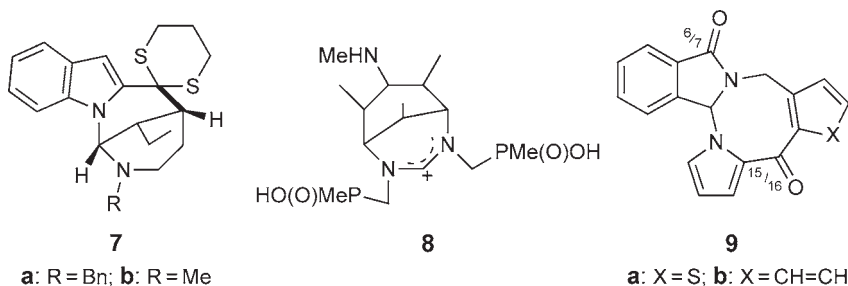
NMR techniques were also utilized to study the conformational behavior of several 1,3-diazocines. As already mentioned in Section 14.05.2.1, **1** showed a very complex ¹H NMR spectrum since the receptor moiety (naphthalene-fused 1,3-diazocine) exists in three conformations, which interconvert slowly on the NMR timescale and were observed separately. With the help of correlation spectroscopy (COSY) and NOESY 2-D spectra, most of the resonances in the spectrum could be assigned. By comparison with the spectra of related compounds and the help of tables to calculate the ring current shifts, the different conformers could be identified. The *sa* conformer was the predominant one at 25 °C, being 78% of the population, while the *ss* conformer (20%) and the *aa* conformer (2%) were the less abundant species. From the strongly upfield shifted signals of the H-4 protons on the *anti*-positioned sidewall in the *sa* conformer, it was concluded that the center of the porphyrin was positioned closely above the sidewall proton in an edge-to-face geometry. Such a conclusion was predicted by the molecular modeling studies (see Section 14.05.2.1). In the *ss* conformer, the porphyrin was situated over the glycouril skeleton, which was indicated by the strong upfield shift of the signals of the NCH₂Ar out-protons <2002MI151>. Less complex ¹H NMR spectra were shown by **5a–c**, amphiphilic receptors, as well as **1**. In these cases, it was not necessary to resort to molecular modeling, and COSY and NOESY 2-D spectra led to the exact structure of the conformers. Thus, in CDCl₃, **5a** existed 90% in the *sa* conformation and 10% in the *ss* conformation; **5b** existed as 88% in the *sa* conformation and 12% in the *ss* conformation; **5c** instead was present in all the three conformations: *aa* 25%, *sa* 60%, and *ss* 15%. The *β*-configuration of the sugar moiety of **2a** was confirmed by the magnitude of the coupling constant between H-2 and H-3, H-1 and H-2 of the furanose ring, which was ~0 Hz showing that the torsion angle ϕ [H-2,H-3] was ca. 90°. Coupling constant between H-3 and H-4 was 3.0 Hz, indicating that this end of the molecule adopted an eclipsing conformation, that is, ϕ (H-3,H-4) was ca. 120°. The *xylo* configuration was confirmed by the large coupling constant between H-4 and H-5 (*J*_{4,5} = 7.8 Hz) <1999MI441>. The structure of purine-fused oxygen-bridged 1,3-diazocine **6** and related compounds was also determined by 1-D and 2-D ¹H NMR. Usually the chemical shifts of protons of the sugar moiety in ribonucleosides are downfield in the order of 1' > 2' > 3' > 4' > 5'; however, chemical shifts of those protons in **6** were reversed except for 1'-proton where the order was 5' > 4' > 5'' > 3' > 2'. This change in chemical

shifts indicated that the deshielding heterocycle moiety was linked to 5'-carbon, which resulted in lower field resonances for 5'-, 4'-, and 3'-protons due to their relative proximity to the base compared with those of normal ribonucleosides. Another feature of the ^1H NMR of **6** and related compounds was the large difference in chemical shifts of the 5'- and 5''- protons. For instance, the chemical shifts of H-5' and H-5'' of **5** were 4.62–4.55 and 3.72 ppm, respectively, reflecting the rigid structures of the anhydro-nucleosides due to the additional linkage between the base and sugar moiety. Both protons H-5' and H-5'' coupled with H-4' proton and this was consistent with the reported bifurcation of the two protons by the plane of the purine ring <2004NN347, 2005JNP1689, 2005TL2825>.



The structural assignment of the indolo-fused 1,3-diazocines **7** and related compounds was accomplished by 2-D NMR experiments. The most characteristic ^1H NMR data were a singlet at 6.90 ppm corresponding to H-7 and a deshielded singlet at 5.20 ppm for the angular H-1 <1995TL1693, 1995S592, 1996T3563>. The ^1H NMR spectrum of the diazocinium salt **8** showed a downfield singlet at 8.20 ppm typical of an amidinium group <1997J(P2)1445>.

The polycondensed 1,3-diazocines **9a** and **9b** showed in their ^1H NMR spectra the N-CH₂ signals as two doublets at 3.91–4.12 and 5.21–5.33 ppm with a coupling constant of $J = 14$ Hz. The N-CH-N protons appeared as a singlet at 6.35–6.64 ppm and the pyrrole rings presented an AMX system characteristic of a 1,2-disubstituted pyrrole <1999JHC735>.



The ^{13}C NMR data were not provided for all the 1,3-diazocine reported. In some cases, the ^{13}C signals were not assigned and the signal multiplicities were missing. However, the uncondensed diazocine **3b** exhibited the methylene adjacent to nitrogens at 41.4–48.7 ppm, the other ring carbons at 27.0–40.4 ppm, and the carbonyl carbon at

160.7 ppm <2002JOC4086>. In the ^{13}C NMR spectrum of **4b**, the carbon adjacent to nitrogens could be found at 55.6 ppm, the C-5 and C-7 at 41.1 ppm, the carbon bridge at 32.4 ppm, while the thiocarbonyl resonated at 151.0 ppm <1997J(P2)1445>. The purine-fused oxygen-bridged 1,3-diazocine **6** and related compounds in their ^{13}C NMR spectra exhibited the C(1') resonances at 88.8–93.1 ppm, the C-5' signals at 83.9–85.8 ppm, while the C-2', C-3', and C-4' signals could be found in the range 45.1–76.2 ppm <2004NN347, 2005JNP1689, 2005TL2825>. For **2a**, the ^{13}C chemical shifts of the carbons of the sugar moiety were consistent with those reported for **6** with the exception of C-5', which was reported to resonate at 49.1 ppm, probably due to the missing effect that the pyrimidindione moiety exerts on the corresponding carbon in **6** <1999MI441>. The ^{13}C NMR spectra of the indolo-fused diazocines **7** showed the N–CH–N carbon at 69.1–69.8 ppm, the other carbon adjacent to nitrogen at 42.6–45.4 ppm, and the other eight-membered ring sp^3 carbons in the range 24.5–52.8 ppm <1995TL1693, 1995S592, 1996T3563>. The ^{13}C NMR spectrum of the diazocinium salt **8** showed the amidinium carbon at 154.0 ppm <1997J(P2)1445>. The polycondensed 1,3-diazocines **9** in their ^{13}C NMR spectra showed the N–CH₂ resonance at 36.3–41.7 ppm, the other sp^3 carbon of the eight-membered ring (N–CH–N) at 67.7–68.2 ppm, while the two carbonyls at positions 5/15 for **9a** and 7/16 for **9b** could be found at 175.4–182.5 and 164.0–164.4 ppm, respectively <1999JHC735>.

No ^{15}N NMR data have been provided for the reported 1,3-diazocines. Instead, ^{31}P NMR data were reported for **8** and the spectrum revealed two resonances at 33.5 and 36.8 ppm, at pD = 1.5, in an approximately 45:55 ratio <1997J(P2)1445>.

The majority of the papers dealing with 1,3-diazocines reporting mass data in their experimental sections only mentioned the molecular or quasi-molecular ions. Thus fast atom bombardment (FAB) spectra <1995JME2946, 1999JOC9289, 2002JOC4086, 2002CME1, 2004JME6100, 2005TL2825, 2005JME6454>, configuration interaction (CI) spectra <1997J(P1)901, 1997J(P2)1445>, electrospray ionization (ESI) spectra <2005JNP1689>, and electron ionization (EI) spectra <1995S592, 1996T3563, 1997JHC135, 2002TL6653, 2004JIC598, 2004JOC8681, 2004NN347> were reported. However, all of the 1,3-diazocines showed the parent ions in their mass spectra. For **7b**, besides the parent ion (m/z 358), fragmentations of m/z 252 and 224 were reported, probably due to sequential loss of the propylenedisulfanyl moiety and the ethyl group from the bridge, respectively <1996T3563>.

Infrared (IR) data provided for the reported 1,3-diazocines were highly fragmentary; on several occasions they were not reported at all. However, for **3b**, only the carbonyl stretching at 1651 cm^{-1} was reported <2002JOC4086>. The bridged diazocine **4a** had the NH stretching overlapping with the NH₂ absorptions ($3182, 2959\text{ cm}^{-1}$) while **4b** showed the NH stretching at 3191 cm^{-1} and the isothiocyanate absorption at 2123 cm^{-1} ; both derivatives exhibited the C=S stretching at 1550 cm^{-1} <1997J(P2)1445>. The 1,3-diazocinone carbonyl stretchings in **9** could be found at $1696\text{--}1699\text{ cm}^{-1}$ <1999JHC735>. Data on IR carbonyl or NH absorptions for other 1,3-diazocine derivatives have also been reported <1997JHC135, 1997J(P1)901, 2004JIC598, 2004JOC8681>.

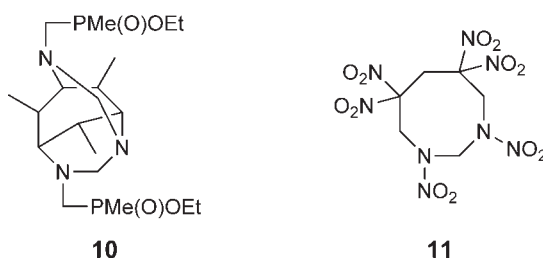
14.05.2.3 Thermodynamic Aspects

The phase behavior of 1,3-diazocine is characterized by relatively high melting points. There are some exceptions as in the case of **7a** which is an oil <1996T3563> or **3b**, which melts at $55\text{--}57^\circ\text{C}$ <2002JOC4086>. In fact, uncondensed 1,3-diazocines **4a** and **4b** also showed melting points at $174\text{--}175$ and $236\text{--}237^\circ\text{C}$, respectively. Annellation of the eight-membered ring with a benzene led to compounds melting in the range $218\text{--}287^\circ\text{C}$ <1995JME2946, 2002BMC599>. Condensation with one or more heterocycles generally produced compounds with melting points $>200^\circ\text{C}$ <1997JHC135, 1999JHC735, 1999MI441, 2004NN347, 2004JME6100> or even $>300^\circ\text{C}$ <2004NN117, 2002MI151>.

1,3-Diazocines are generally soluble in most common organic solvents and were generally purified in silica gel with eluent of medium to high polarity: EtOH/MeOH <2004NN117>, toluene/EtOH <2004NN117>, MeOH dichloromethane (DCM) <2004JME6100, 2004JOC8681, 2005JME6454>, EtOH/acetone <1999MI441>, EtOAc/hexane <1996T3563>, DCM/hexane <1995JME2946>. As already determined by NMR studies, the amphiphilic receptors **1** and **5a–c** can exist, in CHCl_3 solution, as a mixture of three slowly interconverting *aa*, *sa*, *ss* conformers. Generally the most abundant conformation is that of *sa*; however, after addition of potassium ions, **5a** and **5b** were found to be converted to the *aa* conformation forming a complex with two K^+ ions in a strongly cooperative manner. The first ion, which induces a change to the *aa* conformer of the host, is bound with a relatively low association constant, making the second ion more strongly bound. Compound **1** had a different behavior by forming a complex with only one K^+ ion. This first ion was bound much stronger than it was in **5a** or **5b**. This might be due to a better fit of this ion between the crown ether spacers in the former hosts <2001JOC1538, 2002MI151>. Compounds **1** and **5a–c** could bind aromatic substrates such as resorcinol. Binding occurred by π – π -stacking interactions between the two aromatic

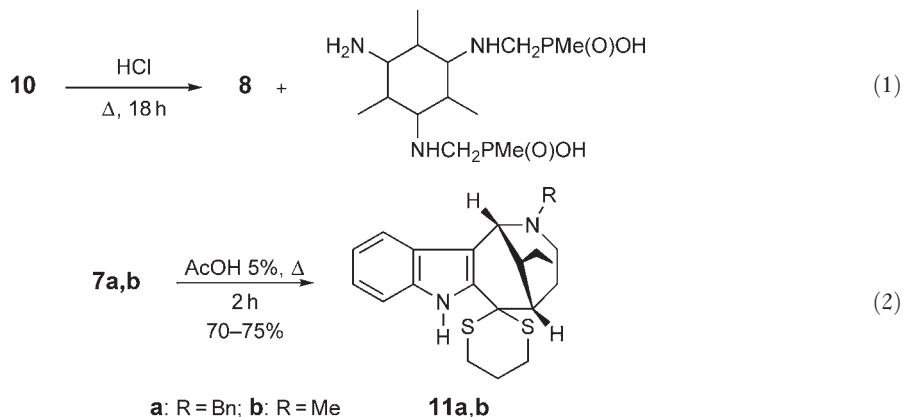
walls (naphthalene) of the cavity and the aromatic ring of the guest and by hydrogen bonding of the phenolic OH groups of the guest and the urea carbonyl groups of the host. Thus, **5a** and **5c** formed 1:1 inclusion complexes with resorcinol and magneson [4-(4-nitrophenylazo)resorcinol] and **5b** formed 1:1 inclusion complexes with dinitrobenzenes and 1,3-dihydroxybenzenes. Upon binding in all the cases, the amount of *aa* conformer increased. Compound **1** showed a different binding behavior. Upon addition of 1,3-dinitrobenzene, no increase of the *aa* conformer was detected in the NMR spectrum. Probably, the inability of **1** to bind this aromatic guest is due to the fact that the energy to push up the porphyrin and generate the *aa* conformer is too high. However, upon addition of MV, **1** formed very stable 1:1 host–guest complex. Interestingly, depending on the solvent, 1,3-dinitrobenzene was bound 2–6 times more strongly to host **5b** containing K^+ ions than when these ions were absent, mimicking the allosteric effect observed in enzymes. Also **1**, in the presence of K^+ ions, weakly complexed 1,3-dinitrobenzene to its *aa* conformer. Moreover, dispersion of amphiphilic receptors **5a** and **5c** in water led to the formation of aggregates. Thus, **5a** yielded vesicle structures with diameters in the range 50–250 nm and **5c** gave vesicles with diameters 50–200 nm <2001JOC1538, 2002MI151>.

In **10**, there are two remote stereogenic centers at phosphorus and it was isolated as an almost equimolecular mixture of the two sets of diastereoisomers, that is, (*RR*/*SS*) and (*RS*/*SR*). In each chiral diastereoisomer, the phosphorus atoms are nonequivalent and four distinct ^{31}P resonances were obtained almost in a 1:1:1:1 ratio <1997J(P2)1445>. The kinetics of the thermal decomposition of **11** in dibutyl phthalate was studied. The high rate of decomposition was probably determined by mutual steric influence of the bulky dinitromethylene moieties <2006RJC499>.

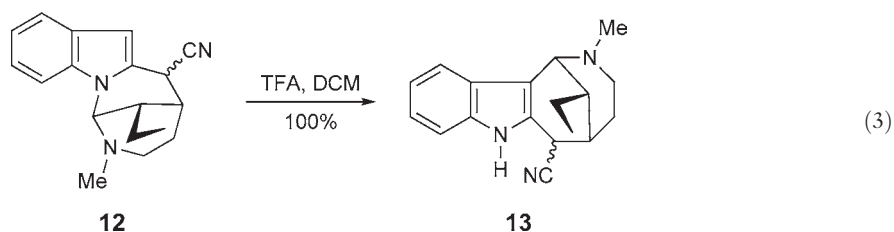


14.05.2.4 Reactivity of Nonconjugated Rings

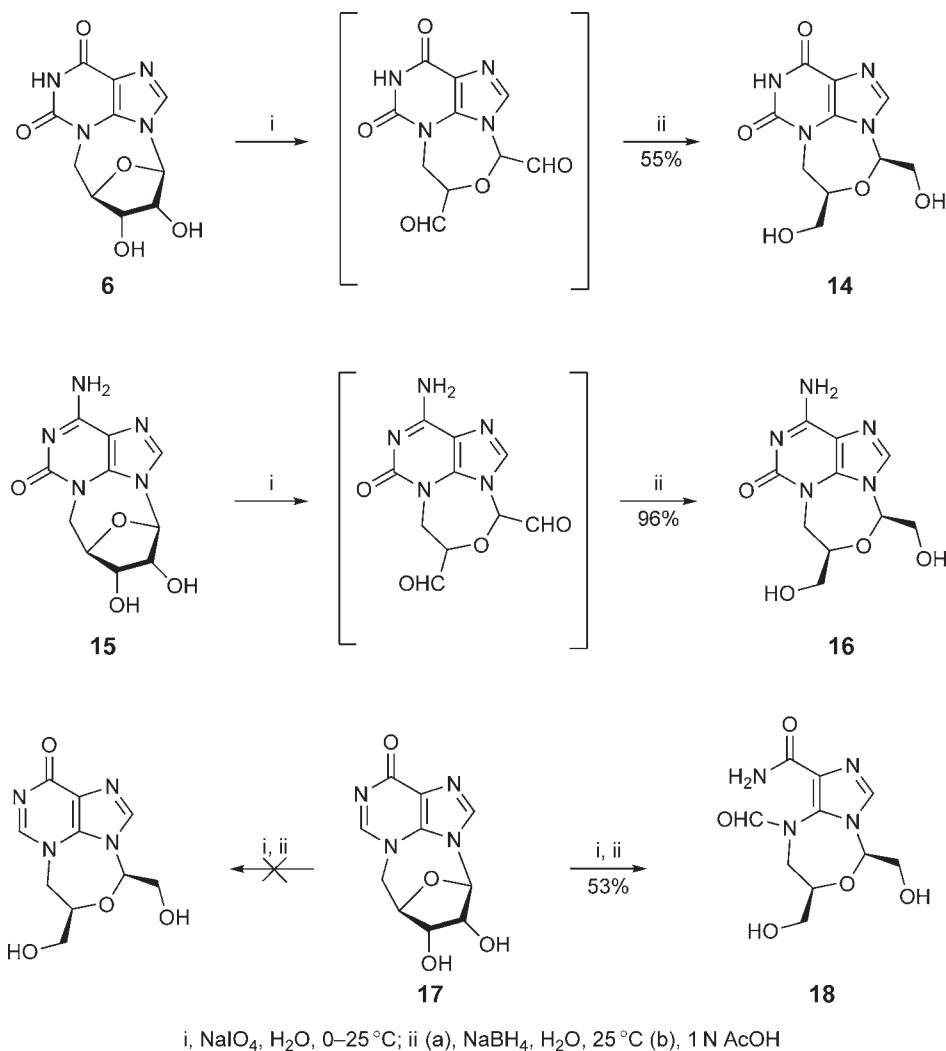
Acid hydrolysis of the diester **10** gave a 1:1 mixture of the diazocinium salt **8** and a triamino-substituted cyclohexane derivative (Equation 1) <1997J(P2)1445>; whereas, acid hydrolysis of the indolo-fused diazocines **7a** and **7b** afforded, in good yields, the isomerization products indolo-fused bridged diazocines **11a** and **11b** (Equation 2) <1995TL1693, 1996T3563>.



The same type of isomerization was observed in the case of the indolo-fused bridged 1,3-diazocines **12**, which, upon action of trifluoroacetic acid (TFA), quantitatively rearranged to the indolo-azocine **13** (Equation 3) <1995S592>.



The purine-fused oxygen-bridged 1,3-diazocines **6** and **15** underwent oxidative cleavage of the eight-membered ring, by sodium periodate, to give the dialdehyde-substituted oxadiazepines, which were not stable and were directly reduced to the corresponding diols **14** and **16**, respectively. Derivative **17**, subjected to the same reaction condition, did not lead to the expected diol but to the ring-opened derivative **18** (Scheme 1) <2004NN347>.



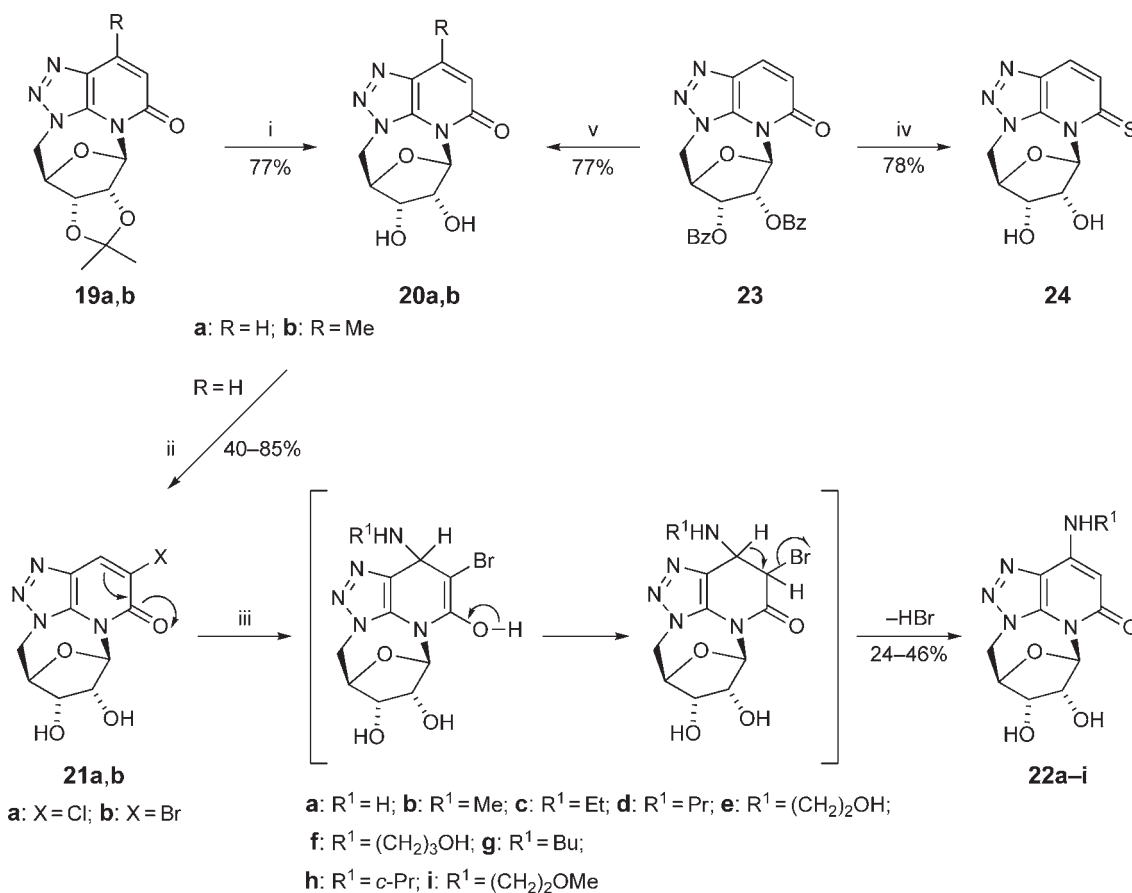
Scheme 1

14.05.2.5 Reactivity of Substituents Attached to Ring Carbon Atoms

Acid hydrolysis of **19a** and **19b** led to the corresponding dihydroxy derivatives **20a** and **20b** in high yield <2005JME6454>. The same acid hydrolysis led to derivative **6** from the corresponding 2,3-*O*-isopropylidene

derivative <2005TL2825>. The *O*-isopropylidene moiety was also removed, in the same acidic medium, from pyrimido-diazocines and purine-fused 1,3-diazocine isomers of **6** <2005TL2825>. Halogenation of **20a** led to the 6-substituted halides **21a** and **21b**. Treatment of the bromo derivative **21b** with various amines gave the 7-substituted amino derivatives **22a-i**.

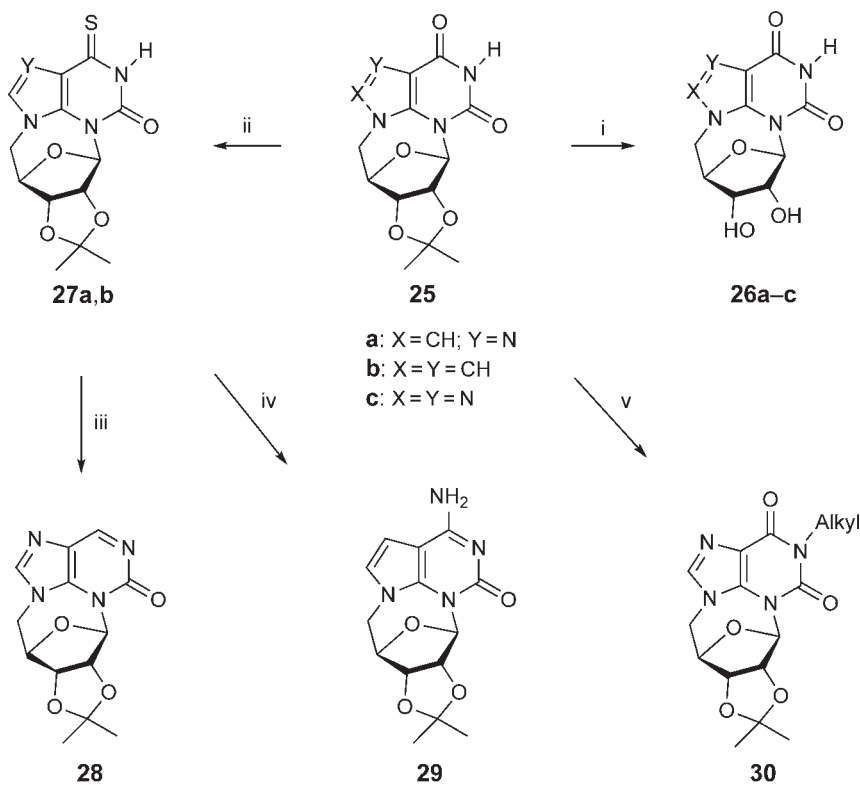
The reaction went through a Michael addition of the amine to give the saturated intermediates which, by elimination of HBr, led to the thermodynamic products <2005JME6454>. Treatment of the dibenzoyl derivative **23** with Lawesson's reagent afforded the corresponding thio derivative which, without purification, was debenzoylated in alkaline conditions to give **24** in high yield <2005JME6454>. Alkaline hydrolysis of **23** afforded the corresponding dihydroxy derivative **20a** in yields that were as good as that observed in the case of the acid hydrolysis (Scheme 2) <2004JME6100, 2005JME6454>. Basic hydrolysis of the isothiocyanate group of **4b** gave the corresponding amine **4a** in 80% yield <1997J(P2)1445>.



i, HCl/dioxane, 50 °C, 12 h; ii, NCS/AcOH reflux (X = Cl) or Br₂/H₂O (X = Br); iii, R¹NH₂, heating;
 iv, (a), Lawesson's reagent/DCE, reflux (b), NH₃/MeOH, 25 °C; v, 0.5 M NaOMe/MeOH, 25 °C

Scheme 2

Also purine-fused diazocine **25a**, deazapurine-fused diazocine **25b**, and azapurine-fused diazocine **25c** underwent several of the above reactions. Thus, **25a–c** underwent deisopropylidenation in acid medium to give the corresponding dihydroxy derivative **26a–c**. Treatment of **25a** and **25b** with Lawesson's reagent produced the thio derivatives **27a** and **27b**. The thio derivative **27a**, upon reduction with Raney nickel, afforded **28**, while **27b** reacted with ammonia to give the amino derivative **29**. Diazocine **25a** could be alkylated to give the corresponding alkyl derivatives **30** (Scheme 3) <2004WO013300>.

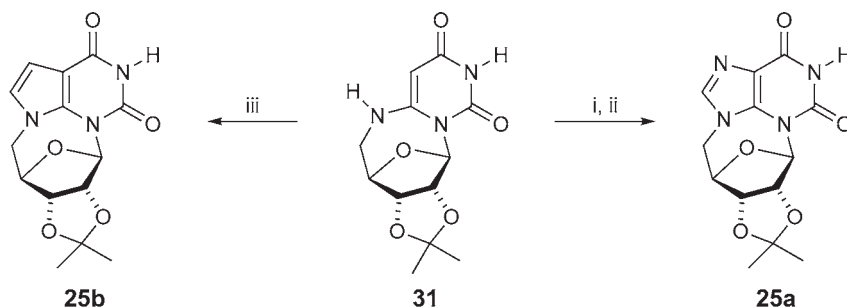


i, 5 N HCl 25 °C, 2 h; ii, Lawesson's reagent, DCE, reflux 15 h;
 iii, Raney-Ni, H₂O, reflux, 1.5 h; iv, ammonia, reflux; v, NaOH, alkyl halide, DMF

Scheme 3

14.05.2.6 Reactivity of Substituents Attached to Ring Heteroatoms

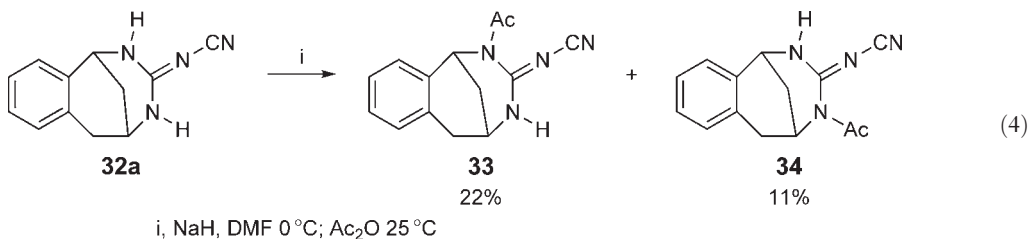
The purine-fused oxygen-bridged 1,3-diazocine **25a** was obtained in good yield from the pyrimido-diazocine **31** by nitrosation of the 5-position of the pyrimidine ring, followed by reduction and annelation of the imidazole ring with diethoxymethyl acetate [<2004WO013300, 2005TL2825>](#). Instead, reaction of **31** with chloroacetaldehyde afforded the deazapurine-fused diazocine **25b** in low yield (32%) ([Scheme 4](#)) [<2004WO013300>](#).



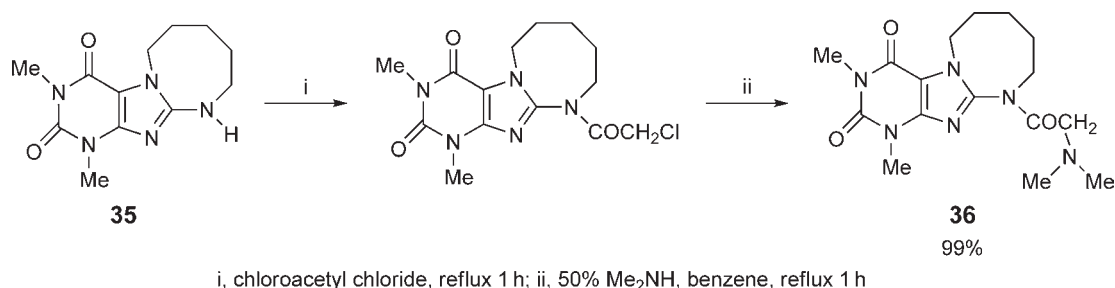
i (a), NaNO₂, HCl, THF/H₂O, 0 °C, 15 min (b), NaHCO₃ (c), Zn, HCl, MeOH, 90 °C, 30 min, NaHCO₃, chloroacetaldehyde; ii, diethoxymethyl acetate, 90 °C, 30 min; iii, ClCH₂CHO, EtOH, 70 °C, 15 h

Scheme 4

The methylene-bridged 1,3-benzodiazocine **32a** reacted with sodium hydride and acetic anhydride to give, in low yields, a mixture of the two monoacetyl derivatives **33** and **34** (Equation 4) <2002BMC599>.



The *N*-dimethylglycyl substituted purino-fused 1,3-diazocine **36** was obtained, in nearly quantitative yield, from the corresponding *N*-unsubstituted derivative **35** by sequential reaction with chloroacetyl chloride and dimethylamine (Scheme 5) <1997JHC135>.

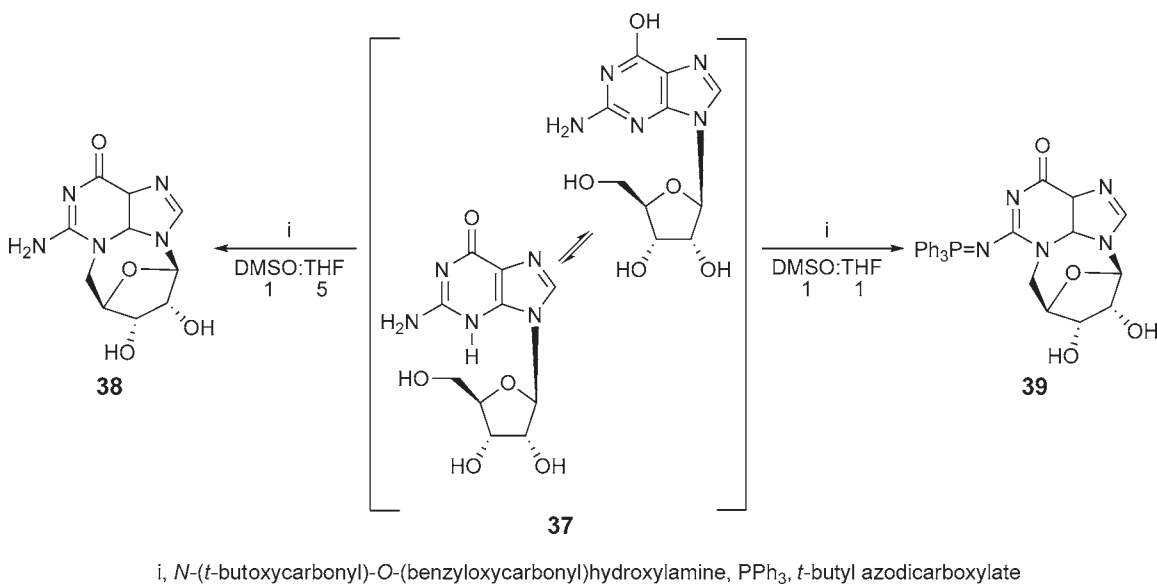


Scheme 5

14.05.2.7 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.05.2.7.1 Ring syntheses from C₆N₂ units

Guanosine **37** underwent Mitsunobu reaction in a 1:5 mixture of DMSO:THF to give the purine-fused oxygen bridged 1,3-diazocine **38** in 90% yield (DMSO = dimethyl sulfoxide; THF = tetrahydrofuran). Increasing the DMSO concentration (DMSO:THF 1:1) resulted in formation of the corresponding iminophosphorane **39** in 35% yield (Scheme 6).

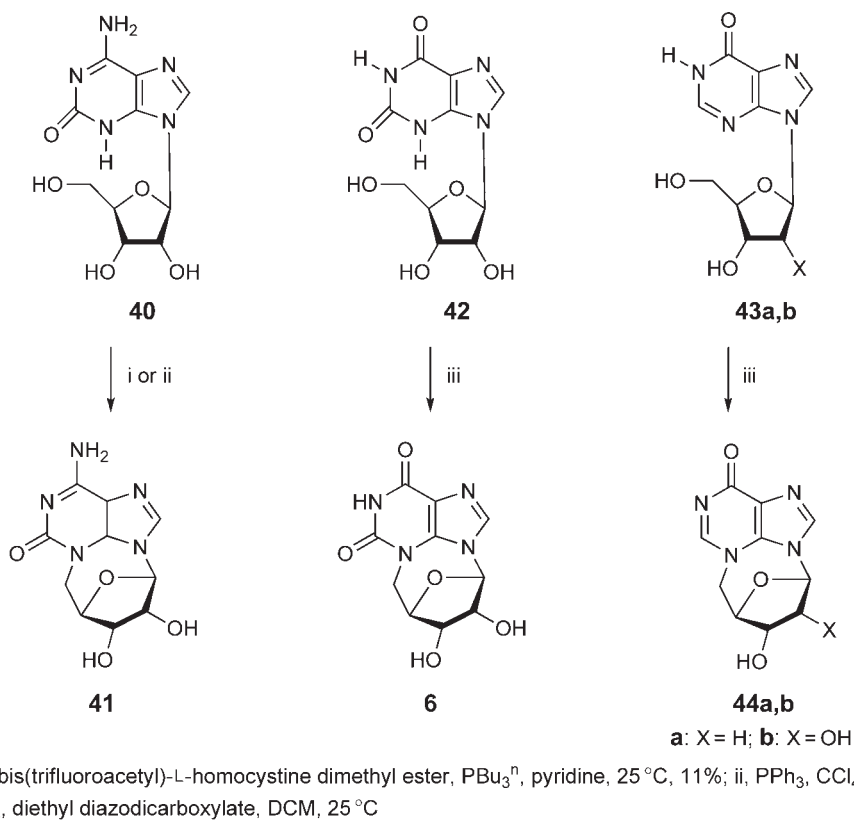


Scheme 6

The presence of the acidic 6-OH of the guanine was essential for the formation of the eight-membered ring. In fact, the 6-benzyl derivative of **37**, under Mitsunobu conditions, did not lead to cyclized products (Scheme 6) <1999JOC9289>.

In the attempt to functionalize the hydroxyl group at C-5' of the ribose moiety, isoguanosine **40** was treated with *N,N*-bis(trifluoroacetyl)-L-homocystine dimethyl ester in the presence of tri-*n*-butylphosphine and pyridine as the solvent, but, instead of the expected product, the cyclized **41** was obtained in 11% yield.

Improvement of the yield of **41** was observed when **40** was treated with PPh₃ and CCl₄ in pyridine (75%). Attempted cyclization of xanthosine **37** under the same reaction conditions failed due to the chlorination of the 6-position. However, **42**, **43a**, and **43b**, subjected to Mitsunobu reaction, in one step, gave the diazocines **6**, **44a** and **44b**, respectively, in good yields (67–86%) (Scheme 7) <2004NN347>. The purine-fused diazocine **6** was also isolated from an *Eryus* sp. of marine sponge from the Great Australian Bight <2005JNP1689>. Under the above mentioned reaction conditions, **37** led to the iminophosphorane **39** in 65% yield <2004NN347>.

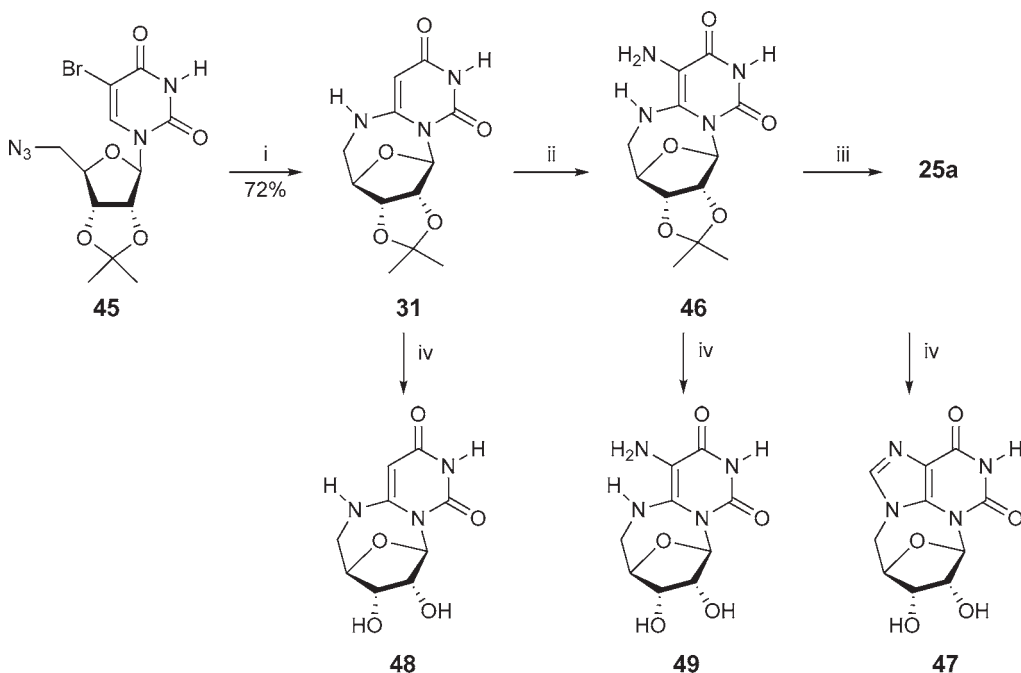


Scheme 7

Synthesis of **47**, a positional isomer of **6**, could be achieved from **45**, which upon reduction and nucleophilic attack of the formed amino group, followed by HBr extrusion, gave the pyrimido-diazocine **31** (a similar Michael addition was described in Section 14.05.2.5 (Scheme 2)).

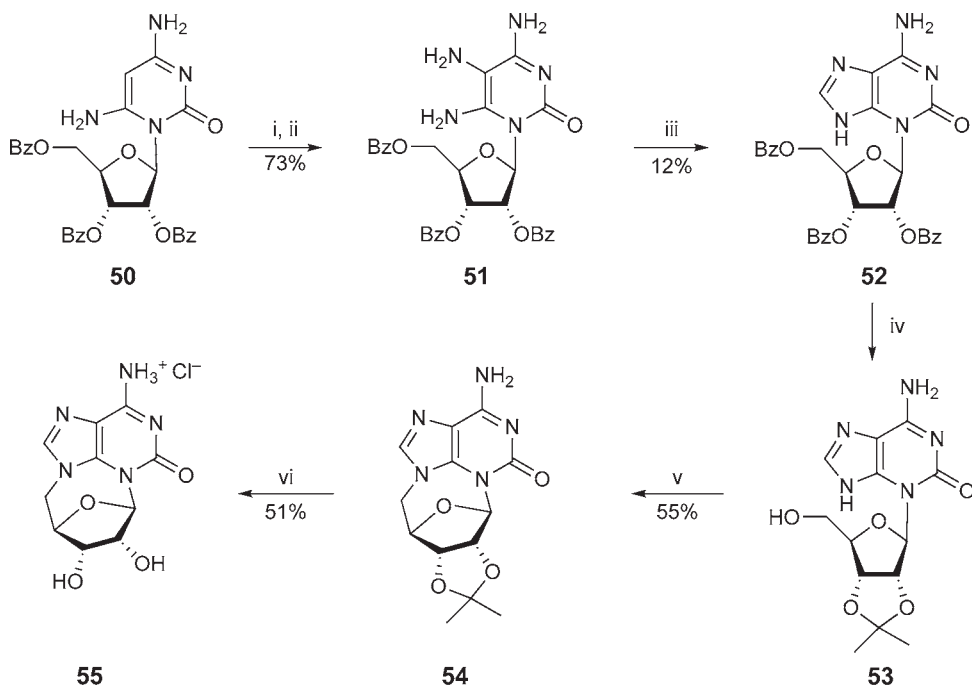
The pyrimidine moiety of **31** was nitrosated and then reduced to give amino derivative **46**, which was transformed into **25a** as described in Section 14.05.2.6 (Scheme 4). Deprotection of the ribose moiety in acid medium led to **47**. The same acidic deprotection conducted on intermediates **31** and **46** led to the pyrimido-1,3-diazocines **48** and **49**, respectively (Scheme 8). Starting from xanthosine **42**, through isopropylidene protection, the Mitsunobu reaction and deprotection sequence derivative **6** was also synthesized <2004WO013300, 2005TL2825>.

Purine-fused diazocine **55**, the positional isomer of **41**, was synthesized starting from diaminopyrimidino-1-pentafuranosyl-substituted **50**, which upon nitrosation and successive reduction gave the triamino derivative **51** in good yield. The annelation of the imidazole ring onto the pyrimidine ring to give **52** took place in low yield. De-O-benzoylation in base medium followed by isopropylidenation of **52** afforded **53**, which underwent intramolecular Mitsunobu reaction to give the diazocine **54** that, upon hydrolysis, gave the desired **55** (Scheme 9) <2004WO013300>.



i, PPh_3 , THF, 25°C , 6 h, then NH_4OH , 25°C , 6 h; ii (a), NaNO_2 , HCl, THF– H_2O , 0°C , 15 min (b), NaHCO_3 (c), Zn, HCl, MeOH, 90°C , 30 min (d), NaHCO_3 ; iii, diethoxymethyl acetate, DMF, 90°C , 30 min; iv, HCl, H_2O

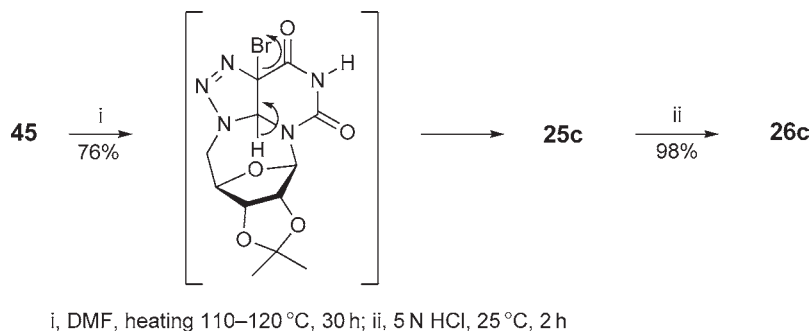
Scheme 8



i, NaNO_2 , $\text{H}_2\text{O}/\text{AcOH}$ (1:10), 0°C , 5 h; ii, crude nitroso, DMF/ H_2O (1:1), NaHSO_3 , 150°C , 2 h; iii, DMF, POCl_3 , 25°C , 30 min, then NaHCO_3 ; iv, $n\text{-BuNH}_2$, MeOH, 25°C , 24 h, dried, 2,2-dimethoxypropane, $p\text{-TsOH}$, acetone; v, PPh_3 , DMF, DEAD, 25°C ; vi, 5 N HCl, 25°C , 2 h

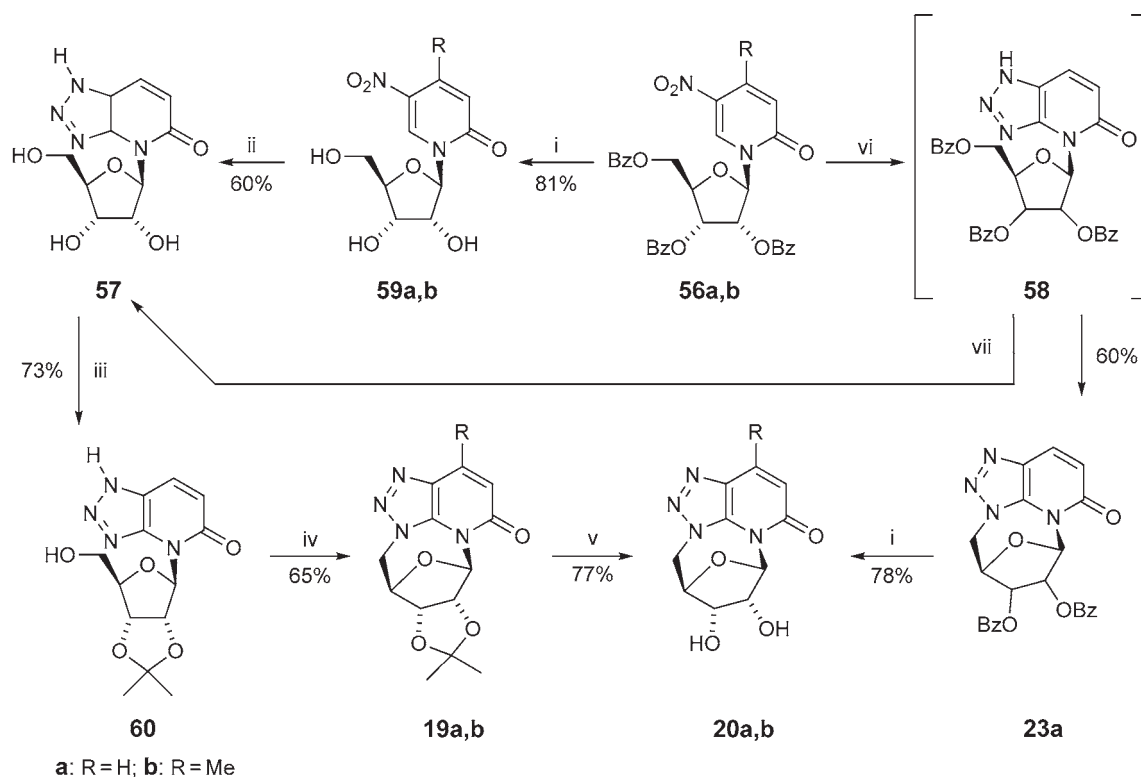
Scheme 9

The azapurine-fused 1,3-diazocine **26c** was obtained from the azido derivative **45** in 75% overall yield. Upon heating **45** in an inert solvent, **25c** is produced likely through a [2,3]-dipolar addition of the 5'-azidomethyl moiety to the 5,6-double bond of the pyrimidine ring and elimination of HBr from the adduct. Deisopropylidenation under acid conditions gave diazocine **26c** (Scheme 10) <2004WO013300>.



Scheme 10

The synthesis of the triazolo-pyridine-fused 1,3-diazocine **20a** was achieved starting from **56a**, which by de-*O*-benzoylation followed by reaction with NaN_3 in DMF afforded the triazolo-pyridine **57**. The latter by treatment with a mixture of acetone and 2,2-dimethoxypropane in the presence of acid afforded the *O*-isopropylidene derivative **60**. The Mitsunobu reaction led to the diazocine **19a**, which, as mentioned in Section 14.05.2.5 (Scheme 2), afforded **20a** in 19% overall yield (Scheme 11) <2005JME6454>.

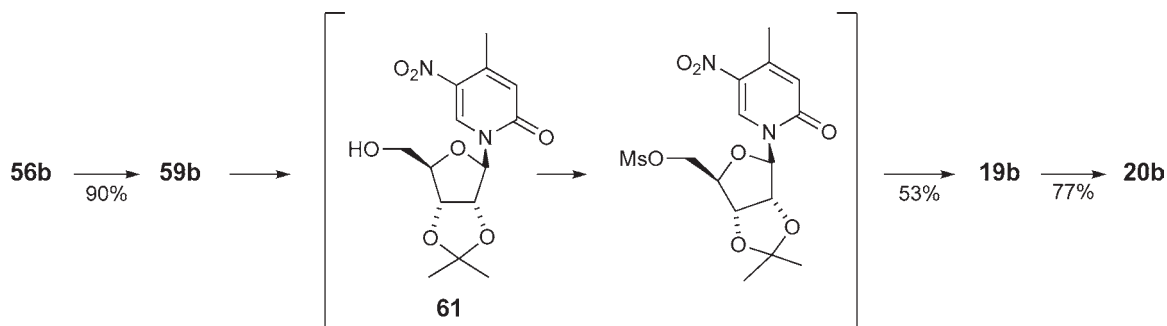


i, NH_3/MeOH , 25 °C; ii, NaN_3 , DMF, 110–120 °C, 12 h; iii, DMP/DMF/acetone/*p*-TsOH, 25 °C; iv, $\text{PPh}_3/\text{DEAD}/\text{DMF}$, 25 °C; v, $\text{HCl}/\text{dioxane}$, 50 °C, 12 h; vi, NaN_3 , DMF (80–95 °C), 24 h from **56** to **58**; 110–120 °C, 72 °C from **56** to **23a**; vii, 0.5 M NaOMe, MeOH, 25 °C

Scheme 11

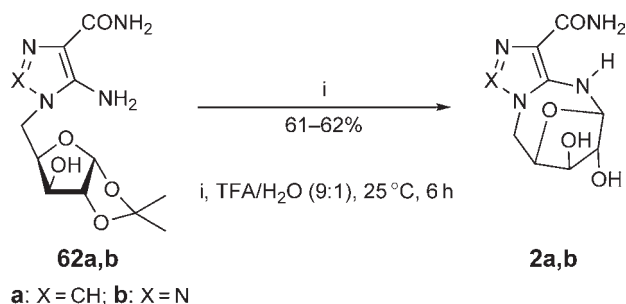
When **56a** was directly treated with NaN_3 , followed by de-O-debenzoylation with methoxide ion, a mixture of **57** and diazocine **20a** was obtained. In this reaction, **57** was formed by solvolysis of **58**. Reaction of **56** with NaN_3 in DMF at 90°C afforded only triazolo-pyridine **58** (84%). Increasing either the temperature and the reaction time led, in 60% yield, to the 1,3-diazocine **23**, which was O-debenzoylated to give **20a** (Scheme 11). This method proved the most convenient to get **20a** (47% overall yield) <2004JME6100, 2005JME6454>.

To obtain the methyl analogue **20b** it was necessary to use a different approach. Thus, **56b** was O-debenzoylated and then reacted with acetone to give the isopropylidene derivative **61**, which was directly mesylated and treated with NaN_3 affording the diazocine **19b**, which was hydrolyzed in acidic medium to give **20b** (Scheme 12) <2004JME6100>.



Scheme 12

Epoxyimidazo- and epoxy[1,2,3]triazolo-1,3-diazocine **2a** and **2b** were obtained from reversed nucleoside analogues **62a** and **62b** bearing an amino group, which cyclized spontaneously when the isopropylidene protecting group is removed from the xylofuranose moiety under acid conditions. This cyclization is regioselective since the only isolated product was the cyclonucleoside corresponding to displacement of the anomeric hydroxyl group (Scheme 13) <1999MI441>.



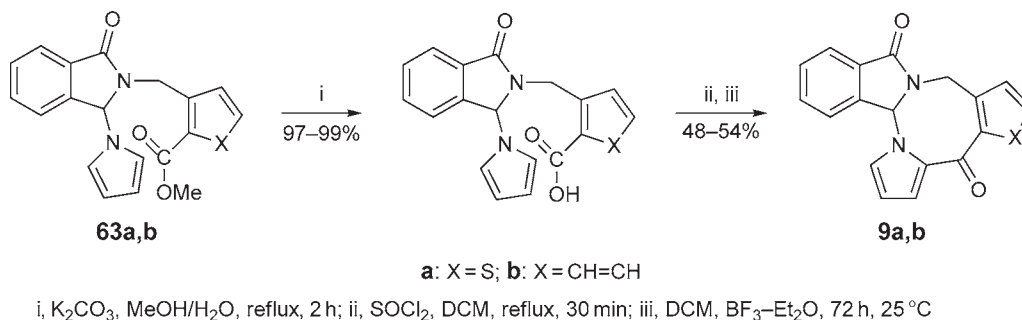
Scheme 13

Saponification of the pyrroles **63a** and **63b** furnished the corresponding acids that were treated with SOCl_2 to give the corresponding acid chlorides that, under Friedel–Crafts cyclization conditions, afforded the benzodiazocines **9a** and **9b** in 48–54% overall yield (Scheme 14) <1999JHC735>.

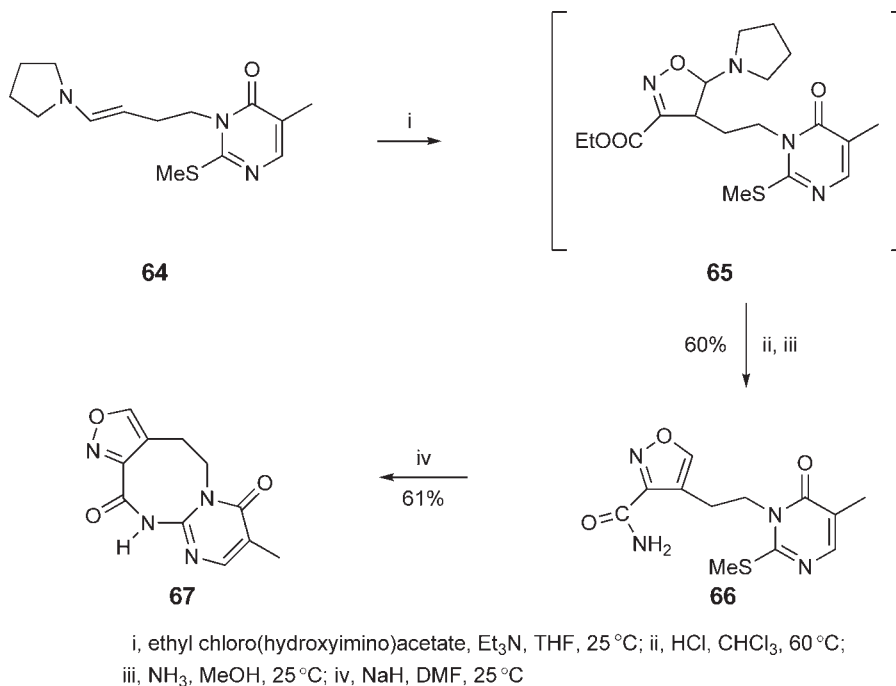
14.05.2.7.2 Ring syntheses from $\text{C}_6\text{N} + \text{N}$ units

A [3+2] cycloaddition of *N*-3-thymine-substituted enamine **64** with ethoxycarbonyl nitrile oxide, generated *in situ* from ethyl chloro(hydroxyimino)acetate, gave the dihydroisoxazole **65**. Subsequent aromatization and ester-to-amide

conversion afforded **66**. Treatment of amide **66** with NaH in DMF produced the amide anion, which, upon ring closure, gave the condensed diazocine **67** in 61% yield (Scheme 15). When the reaction was conducted using THF as a solvent, **67** was not isolated but only starting material was recovered <1997J(P1)901>.



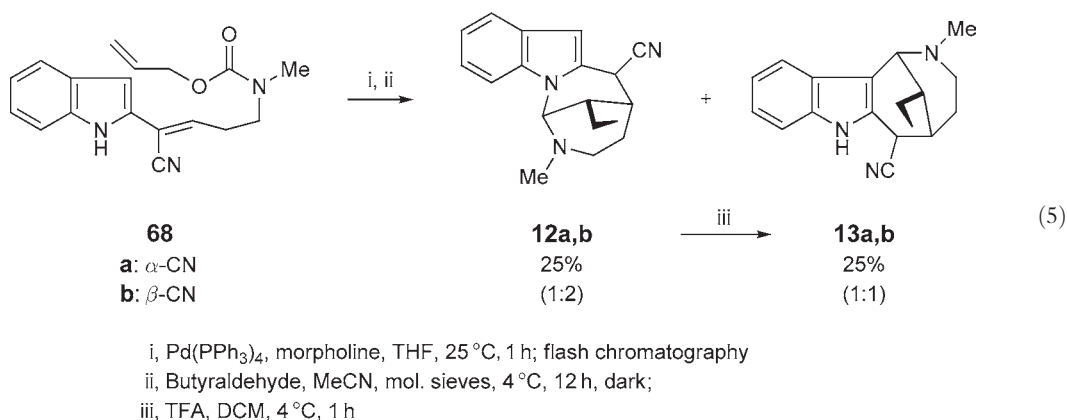
Scheme 14



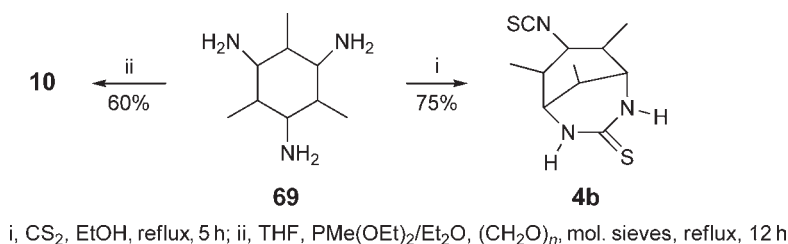
Scheme 15

14.05.2.7.3 Ring syntheses from C₅N₂ + C units

2-Vinylindole **68** was deprotected and the crude product, after purification, was reacted with a large excess of butyric aldehyde in MeCN in the presence of molecular sieves to give **13a** and **13b** and 1,3-ethyl-2,3,4,5-tetrahydro-2-methyl-1,5-methano-1,3-diazocino[1,8-*a*]indole-6-nitrile **12a** and **12b** as a mixture of diastereomers (1:2; α -CN, β -CN) (Equation 5). The formation of these products can be rationalized in terms of a domino process consisting of enamine formation, Michael addition, and Mannich reaction. When TFA was added directly to the reaction mixture, only **13a** and **13b** were obtained since **12a** and **12b** in acidic medium rearrange to **13a** and **13b** (see Section 14.05.2.4 (Equation 3) <1995S592>).

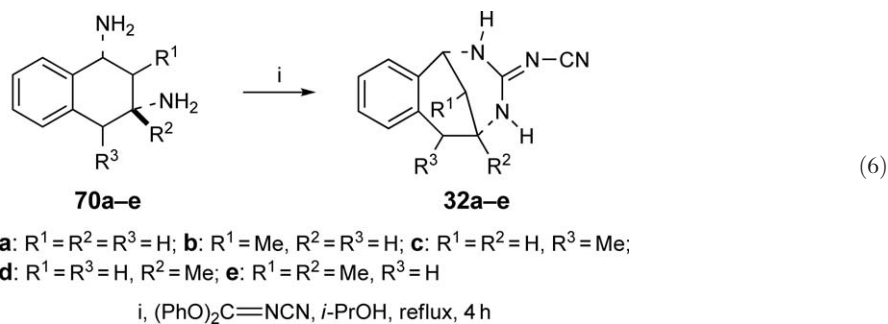


Bridged diazocine **4b** was obtained by reaction of the triaxial conformer of the triaminocyclohexane **69** with carbon disulfide in EtOH (75% yield). Condensation reaction of **69** with paraformaldehyde in the presence of $\text{MeP}(\text{OEt})_2$ resulted in the formation of the bridged diazocine **10** (60% yield) (Scheme 16) <1997J(P2)1445>.

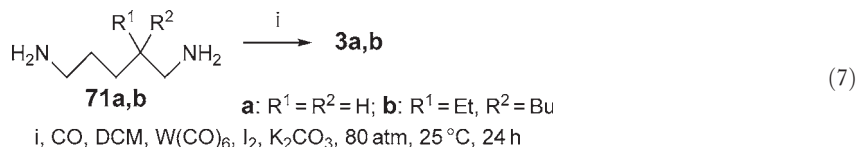


Scheme 16

Bridged diazocines **32a–e** were prepared by cyclization of the appropriate *cis*-1,2,3,4-tetrahydronaphthalene-1,3-diamine **70a–e** with diphenyl cyanocarbonimidate. Diazocine **32b** was obtained as a mixture of two diastereomers (*exo*- and *endo*-isomers) (Equation 6) <2002BMC599>.

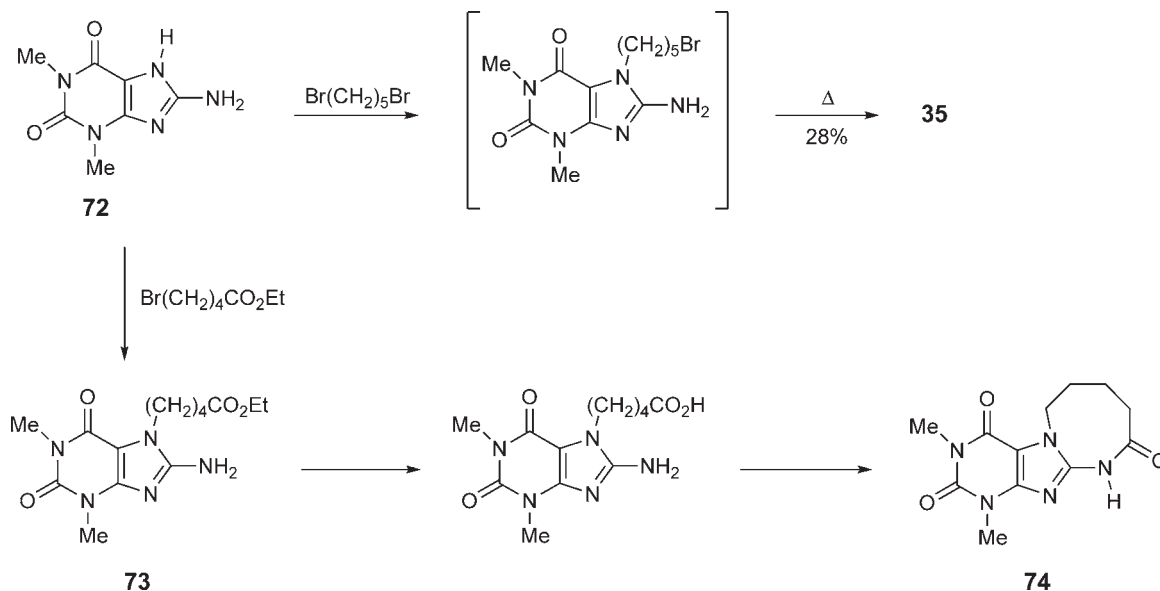


Diazocinones **3a** and **3b** were obtained from 1,5-pentanediamines **71a** and **71b** by reaction with CO (80 atm) in the presence of catalytic amount of $\text{W}(\text{CO})_6$ and nearly stoichiometric I_2 . The parent **3a** was obtained only in traces while **3b** was obtained in 38% yield (Equation 7) <1999OL961, 2002JOC4086>.



14.05.2.7.4 Ring syntheses from C₅ + CN₂ units

Hexahydro-1,3-diazocino[1,2-*f*]purine **35** was prepared in one step from 8-amino-theophylline **72** and 1,5-dibromopentane in dimethylformamide (DMF) in the presence of sodium hydride. The reaction was conducted initially below 90 °C to give the open-chain intermediate and later increased reaction temperatures resulted in the cyclization between the 8-aminotheophylline group and the 7-haloalkyl group. Reaction of **72** with 5-bromovaleric acid did not give the fused eight-membered ring **74** but provided the carboxyester intermediate, which was hydrolyzed to give the corresponding carboxylic acid that could be cyclized to **74** (55% yield) (Scheme 17) <1997JHC135>.

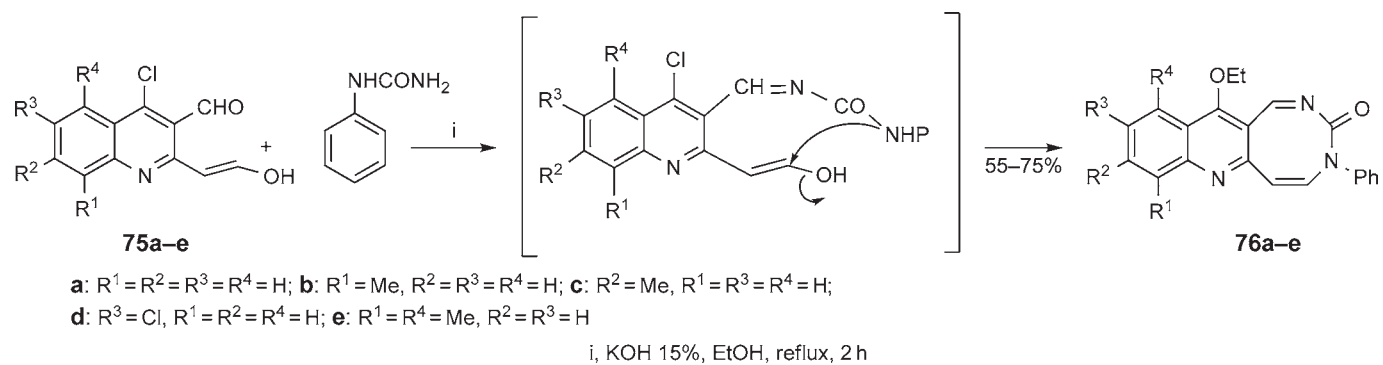


Scheme 17

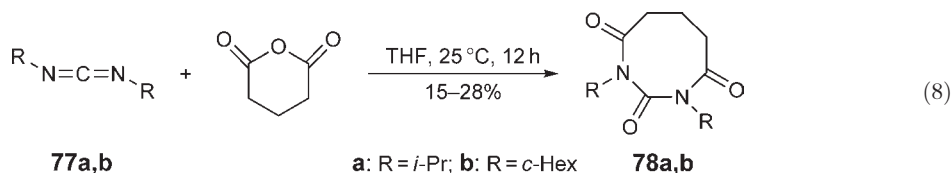
Quinolono[3,2-*c*]-1,3-diazocines **76a–e** were obtained by reaction of 4-chloro-3-formyl-2-(2-hydroxyethene-1-yl)-quinolines **75a–e** with *N*-phenylurea in alcoholic KOH solution. The reaction proceeded via the corresponding *N*-phenylhydrazones. Subsequent cyclization yielded **76a–e** (Scheme 18) <2004JIC598>.

14.05.2.8 Ring Syntheses by Transformation of Another Ring

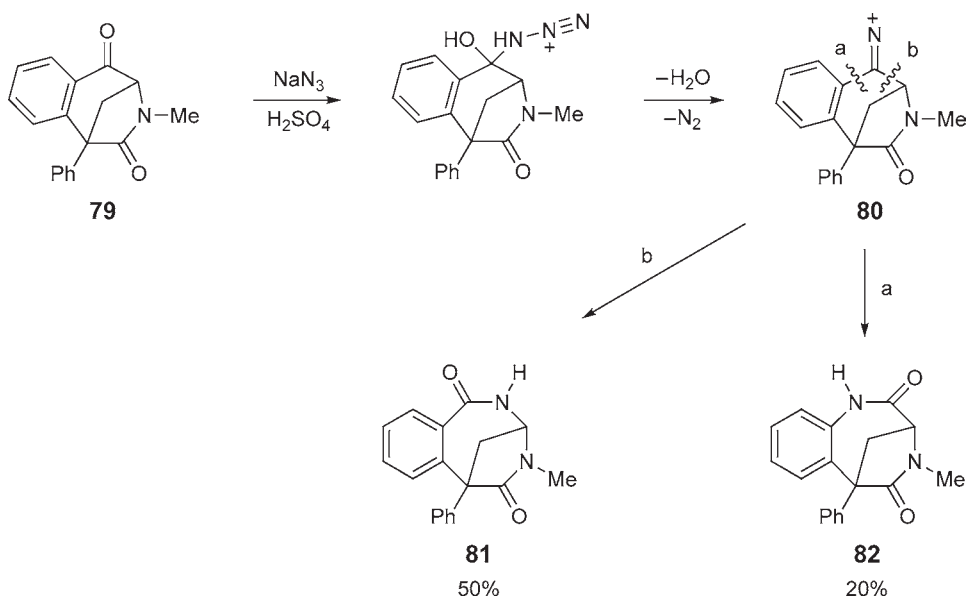
The eight-membered rings **78a** and **78b**, analogues of barbituric acid, are easily accessible, although in low yield, by reaction of *N,N*-dialkylcarbodiimides **77a** and **77b** with glutaric anhydride in the presence of catalytic amounts of $[\text{H}_3\text{Ru}_4(\text{C}_6\text{H}_6)_4(\text{OH})]\text{Cl}_2$ (Equation 8) <2002TL6653>.



Scheme 18



Upon treatment with sodium azide in 98% sulfuric acid, ketone **79** underwent a Schmidt rearrangement, which through the intermediate **80** gave rise to the 1,3-diazocine **81** (50%) and 1,4-diazocine **82**, as minor product (20%) (**Scheme 19**) [<1995JME2946>](#).

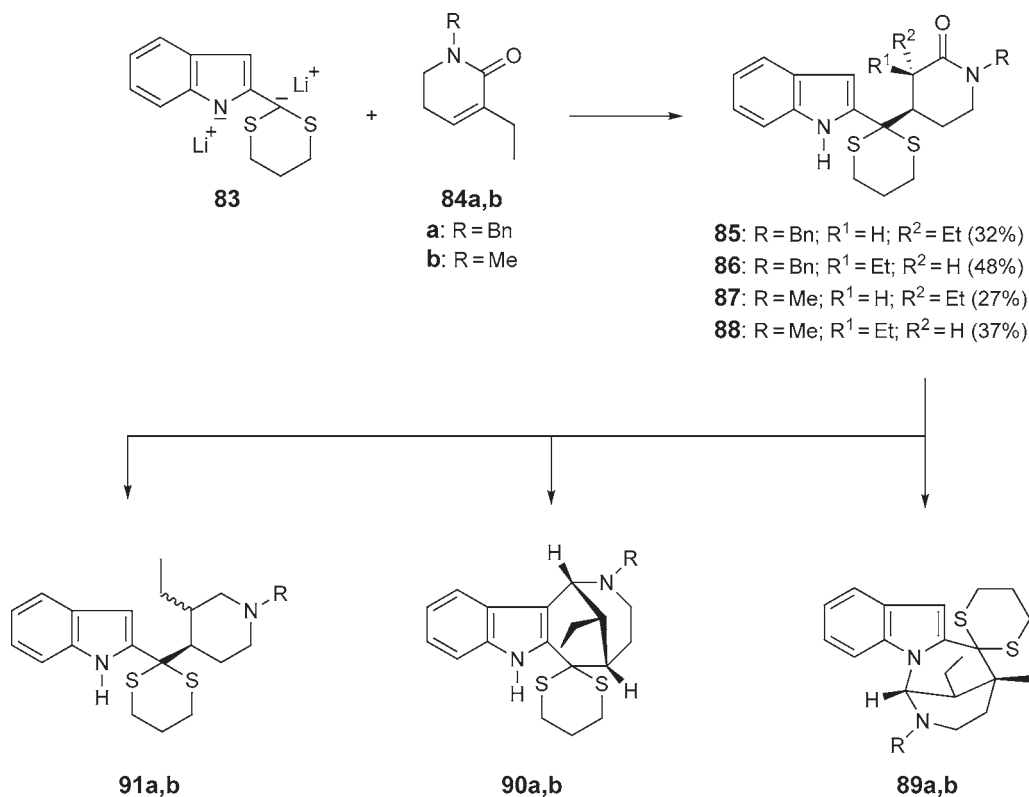


Scheme 19

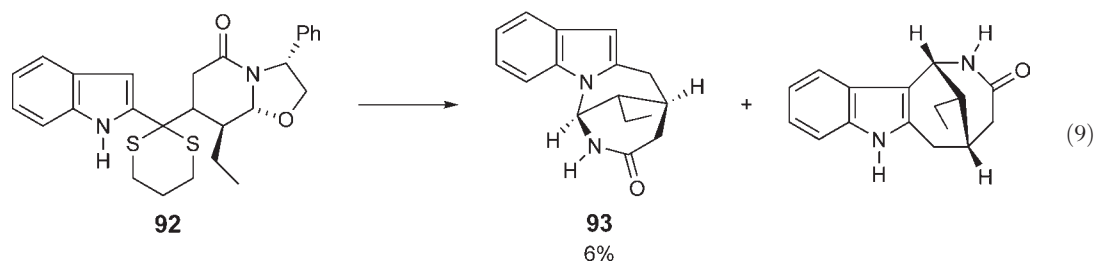
The indolyldithiane dianion **83** reacted with piperidine-2-ones **84a** and **84b** to give, in 64–80% yield, a mixture of diastereoisomeric lactams *trans*-**85**/*cis*-**86** and *trans*-**87**/*cis*-**88** in ratio 1:1.5 and 1:1.4, respectively. Partial reduction of lactams **85–88** afforded the corresponding iminium salts that spontaneously cyclized either on the indole nitrogen or indole 3-position. Thus, treatment of lactam **86** with an excess of Red-Al in THF yielded a 3:1 mixture of diazocinoindole **89a** and **90a** in excellent total yield. Under identical conditions, lactam **88** yielded diazocinoindole **89b** as major product and small amounts of **90b** and **91b** (61%, ratio = 10:1:1). Treatment of lactam **85** with Red-Al gave no reaction, whereas with LiAlH₄ it gave only **91a**.

Lactam **86**, when treated with diisobutylaluminium hydride (DIBAL-H), led to a 6:2:1 mixture of **89b**, **90b**, and **91b** (95% combined yields) (**Scheme 20**) [<1996T3563>](#). In the case of reaction of **83** with 1-(2-hydroxy-1-phenylethyl)-5,6-dihydropyridin-2(1*H*)-one, an equimolecular mixture of *cis*- and *trans*-lactams of type **85** (R = CH(Ph)CH₂OH, R¹ = R² = H) was obtained in 88% yield. Reduction of the *trans*-lactam with Red-Al gave the diazocine **89** (R = CH(Ph)CH₂OH) and an analogue of **91** with an oxazolidine ring annelated to the piperidine moiety [<1995TL1693>](#).

Treatment of **92** with sodium in liquid ammonia brought about the reductive desulfurization and cleavage of the benzylic C–N bond to give an intermediate 6-hydroxylactam, which was cyclized with TiCl₄ to give the diazocine **93** as minor product (6%) and the azocine derived from the cyclization on the 3-position of the indole, as major product (35%) (Equation 9) [<2004JOC8681>](#).



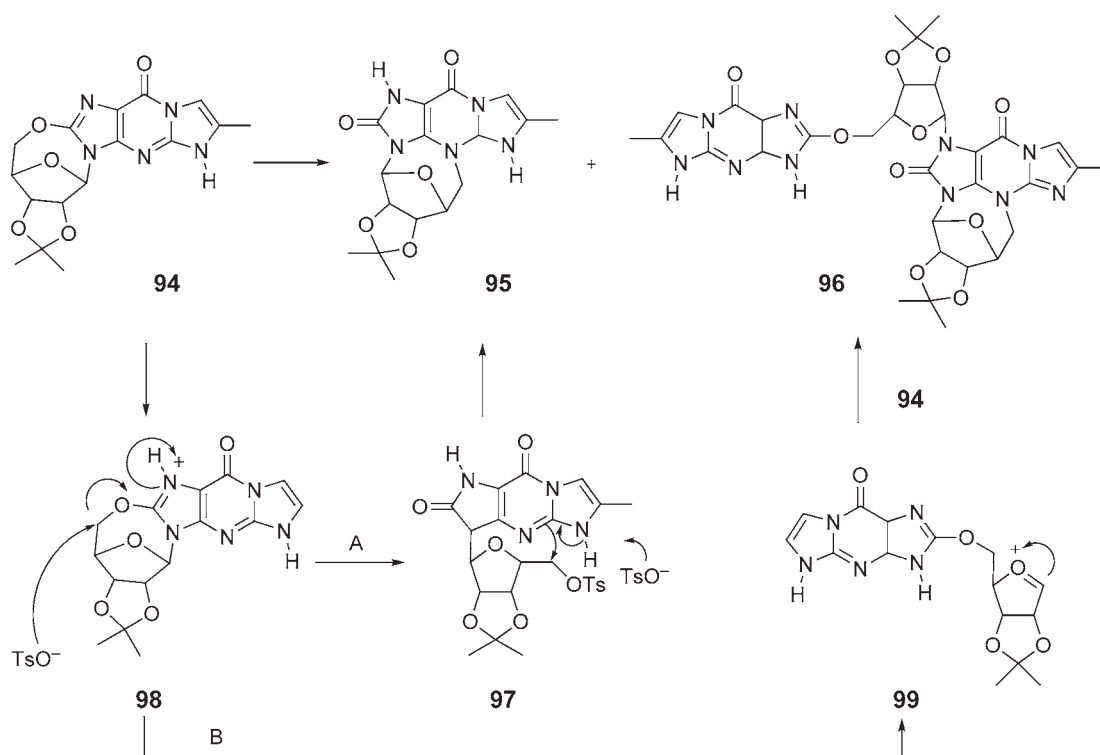
Scheme 20



Nucleoside **94** was subjected to typical acid-catalyzed transglycosylation conditions, that is, heating in chlorobenzene in the presence of *p*-TsOH. When the reaction was conducted at reflux temperature (132 °C), **95** and **96** were isolated in 41% and 8% yields, respectively. Instead, at lower temperature (120 °C), the known **95** and **96** together with **97** were obtained (1.4%). A possible mechanism might involve the protonation of **94** at N-7 to give **98**. This facilitated a nucleophilic attack of the tosyl anion at C-5', leading to the formation of **97** (path A) which underwent a recyclization by intramolecular nucleophilic attack of N-3 at C-5'. The formation of **96** might involve an acid-catalyzed cleavage of the N-glycosylic bond (path B) to give the oxocarbenium cation **99**, which is then attacked by the N-7 center of another molecule of **94** to furnish the dimer, probably after a similar rearrangement of the cyclonucleoside portion as depicted in path A (Scheme 21) <2004NN117>.

14.05.2.9 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Unimolecular cyclizations essentially deal with the synthesis of purine-fused diazocines and the corresponding aza- or deaza-analogues. Such cyclizations occur very often with good yields. Other ring constructions reported are generally



Scheme 21

directed to the synthesis of one derivative and, even if in some instances the yields are not bad, they cannot be considered of general interest. The exceptions are constituted by the annelation of the diazocine moiety to the quinoline system that offers good range of functionalization and interesting yields and by the benzodiazocines synthesized from tetrahydronaphthalenes, which guarantee wide possibilities of substitution (but the yields are not reported for all compounds synthesized). However, such yields should be inconsequential since these compounds are obtained as mixture of diastereomers. None of the ring-transformation syntheses appear interesting since the yields are low and in the cases in which diazocines are formed in reasonable yields, they are always obtained with other compounds.

14.05.2.10 Important Compounds and Applications

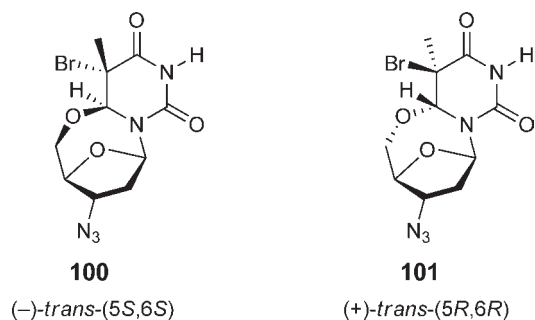
Purine-fused 1,3-diazocines and related isomers, aza- or deaza-analogues, can be regarded as anhydronucleosides or cyclonucleosides. Such compounds exhibited good and selective activity against *Flaviviridae* infections and in particular against HCV. The lead compound of these series was the triazolo[4,5-*b*]pyridine-fused 1,3-diazocine **20a**, which showed EC_{50} and EC_{90} values of 19.7 and 79.8 μ M, respectively, against HCV replicon, with a selectivity index 4 <2004JME6100>. Since then, many other derivatives have been synthesized and tested and improvements in the potency and selectivity were observed. For instance, the thiono **24**, 6-chloro **21a**, 6-bromo **21b**, 7-amino **22a**, 7-alkylamino (**22b-i**), and 7-methyl **20b** derivatives showed more potent anti-HCV activity with EC_{90} values in the range 1.9–2.1 μ M. However, only the 7-amino derivative showed activity at concentrations significantly lower than the cytotoxic activity (CC_{50}). It appears that within the series **22**, the activity would be reduced with increased size of the substituent on the amino group at C-7 <2005JME6454>. Also, purine-fused 1,3-diazocine **47** obtained by dehydration of xanthosine **42** showed enhanced anti-HCV activity compared to the lead compound (EC_{90} 13 μ M) <2005TL2825>. Actually all the above-mentioned compounds and many others have been patented <2004WO013300>. Probably, this potent HCV inhibition has to be ascribed to the fact that these anhydronucleosides are incapable of being phosphorylated at the C-5' position, due to the lack of a free hydroxyl group <2004WO013300>. Benzodiazocines **32a-c**, **33**, and **34** showed insecticidal activity. Structure–activity relationship

(SAR) studies indicated that *exo*-orientation of the bridgehead methyl group gave higher activity than *endo*-orientation and *exo*-methyl substitution on the bridgehead carbon gave higher activity than no substitution. Generally higher insecticidal activities corresponded to lower IC₅₀ levels of acetylcholinesterase (ACHE) assays, indicating cholinesterase inhibition as the primary mode of insecticidal action <2002BMC599>. For the amphiphilic bowl-shaped receptors of type **1** and **5a–c**, possible applications can be foreseen in the fields of sensory systems, drug delivery, and chromatographic separation of organic molecules <2001JOC1538, 2002MI151>. *N*-[(2-Oxo-1,3-diazocan-4-yl)carbon-yl]alanine is a ligand to identify proteins such as protein kinase C, guanine nucleotide-binding protein G, and adenylate cyclase-stimulating G alpha protein <2004WO062553>.

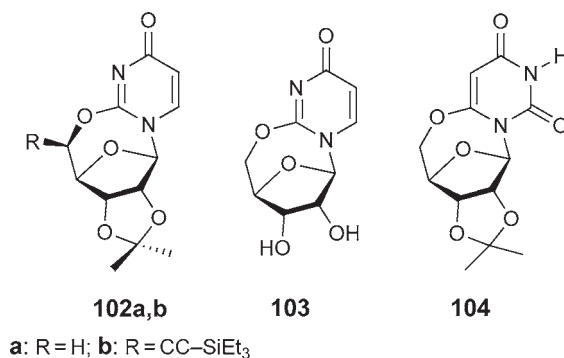
14.05.3 Rings with One Nitrogen and One Oxygen (2*H*-1,3-Oxazocines)

14.05.3.1 Theoretical Methods

Conformation properties of (–)-*trans*-(5*S*,6*S*)- **100** and (+)-*trans*-(5*R*,6*R*)-5-bromo-6,5'-epoxy-5,6-dihydro-3'-azido-3'-deoxythymidine **101**, two diastereoisomer analogues of the antiviral drug AZT, were investigated by AM1 calculations and compared with those of the parent nucleoside. While AZT exhibited a conformational behavior analogous to other pyrimidine nucleosides where the two conformers (north and south) underwent constant transformation, **100** and **101** had a rigid structure as revealed from the estimate of the pseudorotation phase angle which did not give evidence of conformational equilibrium in solution being that the azido moiety is the only group free to rotate. This was due to the presence of the eight-membered oxazocine ring (formed between the sugar and base) which exhibited an extra conformational parameter compared to standard pyrimidine nucleosides: the chair or boat conformation. Theoretical and experimental NMR spectroscopic data for **100** and **101** were also compared and a correlation was observed between them. The calculated ¹H NMR data were obtained with the spectral simulation LAOCOON PC program. The ¹³C NMR chemical shifts were calculated with the ACD program <2000MOL409, 2003NN45>. The rigidity of the skeleton of the pyrimidino-1,3-oxazocine system was also confirmed by MM3* molecular modeling calculations conducted on **102b** <2000HCA1311>.



The relationship between the glycosidic torsion angle χ , the three-bond coupling $^3J_{C(2/4)-H(1')}$, $^3J_{C(6/8)-H(1')}$, and the one-bond coupling $^1J_{C(1')-H(1')}$ in the pyrimido-1,3-oxazocines **102a**, **103**, and **104** were analyzed using density functional theory.

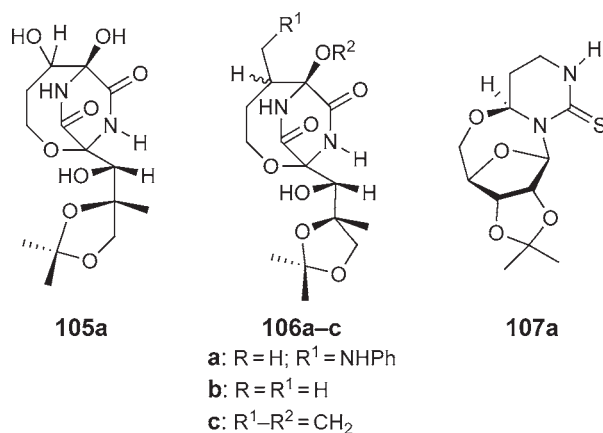


Most of the theoretical $^3J_{C(2/4)-H(1')}$ and $^3J_{C(6/8)-H(1')}$ compare well with available experimental data. The $^3J_{C(6/8)-H(1)}$ couplings for the C-2-bridged nucleosides (**102a** and **103**) are up to 3 Hz smaller than those of the standard nucleosides with the corresponding χ , revealing a nonlocal aspect of the spin-spin interactions across glycosidic bond. Theoretical $^1J_{C(1')-H(1')}$ are underestimated with respect to the experimental values by ca. 10% but reproduce the trends in $^1J_{C(1')-H(1')}$ versus χ <2003JA3649>.

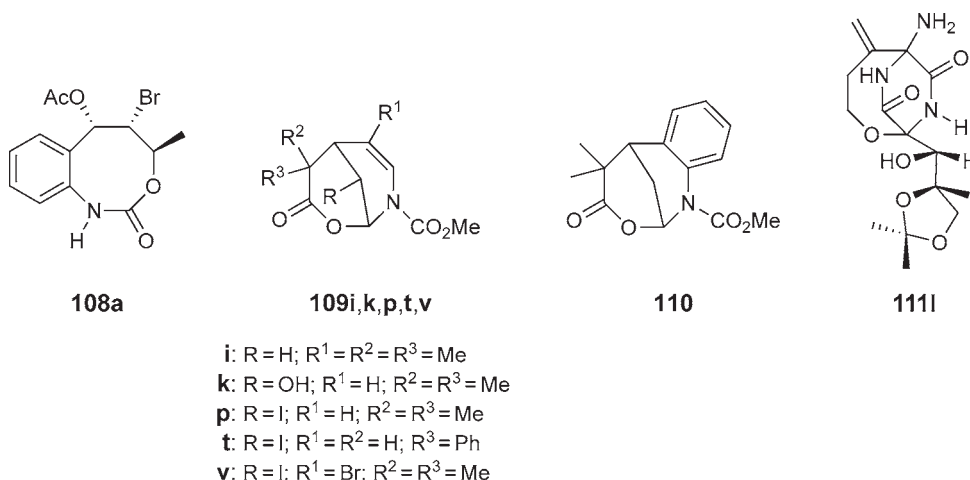
14.05.3.2 Experimental Structural Methods

In spite of the fact that the reports dealing with 1,3-oxazocines, in the past decade, are as much as for the other five series of 1,3-heterocines, no detailed X-ray crystallography studies were reported. This technique was utilized to confirm the structure of 11 derivatives.

X-Ray crystallography studies performed on **102b** established the (*R*)-configuration of C-5' and revealed that the dioxazepane ring adopted a chair-like conformation and the furanose ring possesses an *E*^o conformation (pseudorotational phase angle, $P=270^\circ$). Moreover, the anhydro bond of **102b** (O(4')–C(1')–N(1)–C(2) χ angle = 67.0°) led to a *syn*-conformation <2000HCA1311>. Since it was impossible to establish the orientation of the C-5 hydroxyl group of **105** by 1-D NOE experiments, it was necessary to resort to X-ray crystallographic analysis, which showed the stereochemical orientation of C-5 as (*R*) <1995JOC5346>. The X-ray crystallography allowed an assignment of the (*S*)-configuration to the C-5 of **106a** and the selected ring bond distances were reported: C(5)–C(6) = 1.580(11) Å; C(4)–C(5) = 1.571(12) Å, and the C(6)–C(5)–C(4) angle = $115.7(6)^\circ$ <1996JOC7764>. X-Ray analysis conducted on **106b** and **106c** revealed the identical stereochemical disposition of the C-5 substituent and allowing the clarification of the reaction mechanism for the reduction of an exomethylene group on C-5 <2001JOC2251>. The structure of pyrimido-1,3-oxazocine **107a** was unambiguously established by single crystal X-ray diffraction analysis <1998MI1>. X-Ray crystallographic analysis conducted on two known bridged benzo-1,3-oxazocines corrected the previously proposed <2004SL1584> wrong structures.

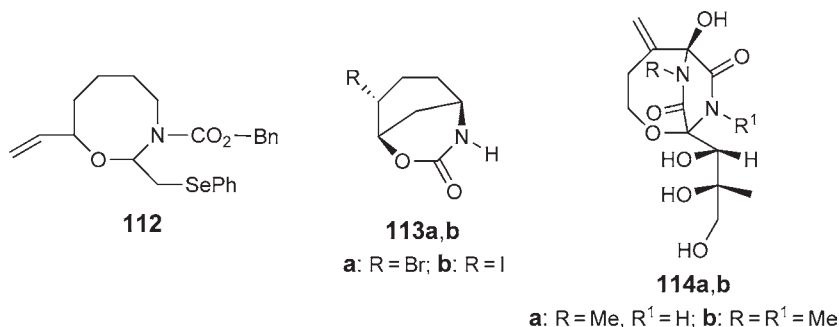


Single crystal X-ray analysis of the benzoxazocine **108a** revealed the *cis*-relationship between the bromo and the acetoxy groups at 5 and 6 positions, respectively <2002TL8025>. X-Ray crystal analysis assessed the structure of the bridged 1,3-oxazocine **109i** (R = H, R¹ = R² = R³ = Me) in which the two hydrogen atoms at the ring junction (positions 2 and 6) were in *cis*-relationship and no major steric hindrance would impede the free rotation of the methoxycarbonyl group, consistent with the presence, according to the NMR spectra (*vide infra*), of two rotamers at room temperature <2005EJO3724>. X-Ray crystal analyses were also performed on derivatives **109t** and **109v** (R = I, R¹ = R² = H, R³ = Ph; R = I, R¹ = Br, R² = R³ = Me), **110** <2002CC940, 2005EJO3724> and **111i** <1998JME1185>.



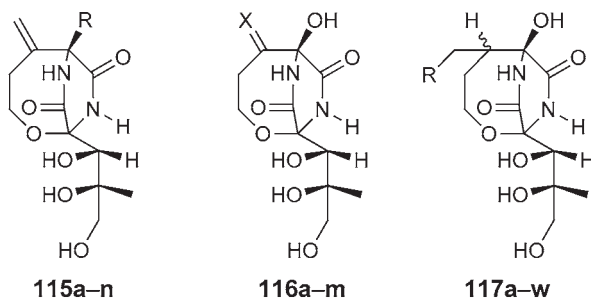
Nearly all reports dealing with 1,3-oxazocines provided ¹H NMR data. The simple unbridged and uncondensed 1,3-diazocine **112**, obtained as an inseparable mixture of diastereoisomers, showed in its ¹H NMR spectrum the signals of CH between the two heteroatoms at 5.45–5.58 ppm, the methyne adjacent to the oxygen at 3.92–4.02 ppm, and the methylene next to nitrogen at 3.49–3.62 ppm. The other ring methylene protons resonated at 1.50–1.76 ppm <1995J(P1)123>. The methylene-bridged 7-halo-1,3-oxazocine **113a** and **113b** showed in their ¹H NMR spectra the CH protons bound to oxygen at 4.64–4.68 ppm and the N–CH protons at 3.62–3.64 ppm. The other methylene or methyne protons resonated at 1.67–2.53 ppm. The NH signal can be found at 6.04–6.49 ppm <1998SL891, 2005T1207>. Other bridged diazocines related to **113** showed the resonances within the ranges above described <1996TA721>. The pseudoaxial C(5')–H of **102b** (D-*allo*-isomer) resonates at higher field (4.86 ppm) than the pseudoequatorial C(5')–H of its L-*talo*-isomer (5.15 ppm). Both C(5')–H show a small *J*(4',5') value (L-*talo*-isomer: 1.6, D-*allo*-isomer: 1.2 Hz), demonstrating the *gauche* orientation of C(4')–H and C(5')–H. The configuration at C-5' was determined by NOE experiments. Irradiation of C(5')–H of the L-*talo*-isomer led to an NOE of 8% for the C(3')–H at 4.95 ppm and of 12% for C(4')–H at 4.63 ppm, evidence for the (5'*S*)-configuration. Irradiation of C(5')–H of **102b** (D-*allo*-isomer) led only to an NOE (19%) for C(4')–H at 4.68 ppm, indicating the (5'*R*)-configuration already established by X-ray analysis (*vide infra*) <2000HCA1311>. Derivative **109k** (R = OH, R¹ = H, R² = R³ = Me), which exists as a mixture of two rotamers, showed in its ¹H NMR spectrum a signal at 6.81 and 6.91 ppm due to NCH=proton and a signal at 5.08–5.15 ppm for the CH=proton. The NCHO proton appeared at 6.25 and 6.40 ppm, whereas the secondary alcohol resonated at 4.79 ppm <2005EJO3724>.

The site of the *N*-methyl group in **114a** was confirmed by 1-D NOE NMR spectroscopy. Irradiation of the C(4)HH' (2.20 ppm) led to a 5% intensity increase of the N(10)–Me signal. Correspondingly, irradiation of the N(10)–Me resonance (2.87 ppm) led to a 3% intensity increase of the C(4)HH' signal <1996JOC7756>. 1,3-Oxazocinones **115b–k**, analogues of the antibiotic bicyclomycin **115a**, showed ¹H NMR data very similar to those of the parent compound and the substituents at position 6 did not affect the chemical shifts of the C-4 and C-5a protons <1996JOC7756>.



Instead, ¹H NMR chemical shifts values for the C-4 methylene protons in the C-5 unsaturated bicyclomycins **116a–j** were sensitive to modifications of the C(5)–C(5a) exomethylene group (X). It was observed that there was a

distinct downfield shift from the parent **115a** ($\Delta \sim 0.5\text{--}1.3$ ppm) <1995JOC5346, 1996JOC7764>. It was also noted that there was a diagnostic appearance of the C-5a proton in the vinylic carboxylic acid derivatives **116a–e** in the range 6.39–6.53 ppm. The C-5a-substituted dihydrobicyclomycins **117a–o** showed an average upfield shift from **115a** ($\Delta \sim 0.32\text{--}0.77$ ppm) for the C-4 methylene protons upon saturation of the C(5)–C(5a) exomethylene group: the appearance of two distinct signals for the diastereotopic C-5a methylene protons and the observation of C-5 proton resonance at 1.85–2.80 ppm. It was also observed that the presence of a sulfur-containing portion at C-5a in **117e–i** led to signals for the C-5a methylene group at 1.85–3.16 ppm. Correspondingly, the presence of an amino substituent at C-5a in **117m–o** led to the appearance of a signal for the C-5a hydrogens at 2.25–3.95 ppm <1996JOC7764>. The stereochemical disposition of further derivatives **116** ($R = C(H)\text{--}C(H)=N\text{--}OMe$, $R = C(H)\text{--}C(Me)=N\text{--}OMe$), obtained as a 70:30 mixture of the *anti*-(5*E*,5*bE*) and *syn*-(5*E*,5*bZ*), and the carboxylic derivatives **116** ($R = C(H)\text{--}C(H)=C(H)CO_2H$, $R = C(H)\text{--}C(H)=C(H)CO_2Me$, $R = C(H)\text{--}C(H)=C(H)CO_2CH_2CH=CH_2$, $R = C(H)\text{--}C(H)=C(H)CO_2Bn$), obtained in a 70–90: 30–10 mixture of (5*E*,5*bE*)- and (5*E*,5*bZ*)-isomers, was achieved utilizing NOE, heteronuclear multiple bond correlation (HMBC), and heteronuclear multiple quantum correlation (HMQC) NMR techniques <2001JOC2251>.



115: **a**: $R = OH$; **b**: $R = OMe$; **c**: $R = OEt$; **d**: $R = CH_2CF_3$; **e**: $R = O\text{--}i\text{-}Pr$; **f**: $R = OAc$; **g**: $R = OBz$; **h**: $R = SETe$; **i**: $R = SPh$; **j**: $R = NPh$; **k**: $R = H$; **l**: $R = NH_2$; **m**: $R = NHOH$; **n**: $R = SH$

116: **a**: $X = C(H)CO_2H$; **b**: $X = C(H)CO_2Me$; **c**: $X = C(H)CO_2Et$; **d**: $X = C(H)CO_2Bn$; **e**: $X = C(H)CO_2t\text{-}Bu$; **f**: $X = NOH$; **g**: $X = NOME$; **h**: $X = NOEt$; **i**: $X = NOBn$; **j**: $X = O$; **k**: $X = CH_2CH_2NH_2$; **l**: $X = CHCH_2NHAc$; **m**: $X = CHCH_2OH$

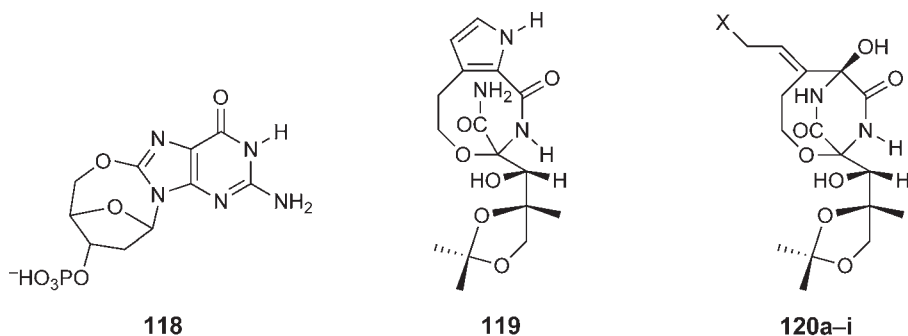
117: **a**: $R = H$; **b**: $R = CO_2H$; **c**: $R = CO_2Me$; **d**: $R = CO_2Et$; **e**: $R = SMe$; **f**: $R = SBu$; **g**: $R = SHex$; **h**: $R = S(CH_2)_2OH$; **i**: $R = S(CH_2)_2NH_2$; **j**: $R = SPh$; **k**: $R = S(O)Me$; **l**: $R = S(O)_2Me$; **m**: $R = N\text{--}morpholine$; **n**: $R = NPh$; **o**: $R = 6\text{-aminoquinoline}$; **p**: $R = CH_2OH$; **q**: $R = CH_2OAc$; **r**: $R = CH_2NH_2$; **s**: $R = CH_2NHAc$; **t**: $R = Me$; **u**: $R = NHC_6H_4\text{-}4\text{-}N_3$; **v**: $R = NHC_6H_4\text{-}3\text{-}CH_2OH$; **w**: $R = NHC_6H_4\text{-}3\text{-}CHO$

The reaction leading to the purine-fused 1,3-diazocine **118** from 2'-deoxyguanosine monophosphate (dGMP) and $[Pt^{IV}Cl_4(dach)]$, as an oxidizing agent, was monitored by ^1H NMR spectroscopy (*dach* = 1,2-diaminocyclohexane). One of the monitored signals was the multiplet peak at 9.11 ppm, due to the H-8 of $Pt(IV)$ bound to the N-7 of guanine, which appeared after 1 h, grew in intensity, and disappeared after 14 h. This indicated that the $Pt^{IV}\text{--}G$ adduct is an intermediate. After a reaction time of 3 h, a new peak at 8.45 ppm appears whose peak intensity continuously grows with a concomitant decrease in intensity of the 8.17 ppm peak due to H-8 of the free-3'-dGMP. The 8.45 ppm peak was assigned to H-8 of the $Pt^{II}\text{--}3'\text{-dGMP}$ adduct <2005JA1773>. The ^1H NMR spectrum of **119**, besides the expected signals due to the bicyclomycin moiety, showed two downfield doublets ($J = 2.4$ Hz) at 5.88 and 6.84 ppm indicative of a 2,3-disubstituted pyrrole. A comparison of the ^1H NMR chemical shifts for the C-1' methyne in **119** and with those typically observed for N(10)–C(6) ring-closed bicyclomycin acetone (i.e., **106** or **111i**) revealed that this signal in **119** appeared upfield (~ 0.42 ppm) from the chemical shift value observed for this signal <1998JOC1290>.

More or less 50% of the papers dealing with oxazocines reporting NMR spectra provided ^{13}C NMR data. The ^{13}C NMR spectra of the methylene-bridged 7-halo-1,3-oxazocines **113a** and **113b** showed the carbon resonance next to oxygen at 75.4–76.6 ppm, the carbon adjacent to nitrogen at 44.9–45.2 ppm, and the carbon bound to halogen at 48.1 (Br) and 24.8 ppm (I). The other methyne or methylene carbon can be found at 24.0–27.7 ppm <1998SL891, 2005T1207>.

The *trans*-configuration of **100** and **101** was determined by comparison of their ^{13}C NMR spectra with that of 6-azido-5-bromo-5,6-dihydrozidovudine. In this latter, the chemical shift of C-5 constitutes the most significant difference between the *cis*- and *trans*-isomers. The C-5 signal appeared at ~ 52 and ~ 62 ppm for the *trans*- and *cis*-isomers, respectively. On the other hand, the C-3' signal of both isomers remained unchanged at ~ 62 ppm. Thus, the upfield shifting of the C-5 signals of both **100** (C-5 = 56.6 ppm) and **101** (C-5 = 52.3 ppm) with respect to that of C-3' (**100** C-3' = 61.9 ppm and **101** C-3' = 66.6 ppm) was taken as main evidence for the *trans*-assignment of both compounds <2003NN45>. The pyrimido-1,3-oxazocine **102b** (*D-allo*-isomer) and corresponding *L-talo*-isomer showed in their ^{13}C NMR spectra the C-2 resonance adjacent to three heteroatoms at 171.0–171.2 ppm, the C-5' carbon adjacent to the ring oxygen at 74.4–75.7 ppm, the C-1' carbon next to nitrogen at 99.0–99.1 ppm. The other resonances of the oxazocine carbons could be found at 81.5–87.3 ppm <2000HCA1311>.

The ^{13}C NMR spectrum of **109k** (R = OH, R¹ = H, R² = R³ = Me) exhibited a signal at 152.7–152.8 ppm due to carbonyl ester of the two rotamers and a singlet at 174.1 ppm for the ring carbonyl. The NCHO appeared at 80.8–81.2 ppm and the bridge carbon at 45.6 ppm. In **109t** and **109p** (R = I, R¹ = R² = H, R³ = Ph; R = I, R¹ = H, R² = R³ = Me), their ^{13}C NMR spectrum showed, besides the carbonyl signals in the same range of **109k**, a bridge carbon bound to iodine at 13.6 ppm <2002CC940, 2005EJO3724>. Also the ^{13}C NMR spectra of the 1,3-oxazocinones **115b–k**, were very similar to those of the antibiotic bicyclomycin **115a**. Only the C-6 ^{13}C NMR chemical shift value in **115b–k** varied with the structure of the C-6 substituent. The differences in C-6 chemical shift values with C-6 substituent was consistent with literature but the magnitude of these differences were attenuated. For example, replacement of the hydrogen substituent in C-6–deoxybicyclomycin **115k** by an ethanethiolate group or an ethoxy unit produced only modest increases in the C-6 chemical shift value (e.g., **115h**, +8.6 ppm; **115c**, +24.9 ppm) <1996JOC7756>. In bicyclomycins **116a–j**, the C-4 carbon resonances were sensitive to the modification at C-5 and C-5a exomethylene group (X). Thus, the vinylic carboxylic acid derivatives **116a–e** and imine analogues **116f–i** showed C-4 resonances upfield from **115a** ($\Delta \sim 6.2$ –10.9 ppm) <1996JOC7764>. The C-5 carbonyl resonance of **116j** was located at 203.9 ppm <1995JOC5346>. The C-5a-substituted dihydrobicyclomycins **117a–o** showed the C-5 carbon signal at 45–56 ppm. Placement of a sulfur-containing moiety at C-5a (**117e–j**) led to signals for the C-5a carbon at 29.9–31.9 ppm. An amino substituent in the same position (**117m–o**) led to C-5a carbon signals at 43.5–61.4 ppm <1996JOC7764>. Oxidation of the 6-hydroxyl group of **117** (R = Br) led to a tricarbonyl compound, which showed the corresponding signals at 165.1, 172.8, and 197.8 ppm <1996T833>. The attached proton test (APT) spectrum of **119** showed two unsubstituted aromatic carbon signals at 111.3 and 123.9 ppm and two substituted aromatic carbon resonances at 123.0 and 126.2 ppm. The chemical shifts of the C-1 and C-1' resonances, with respect to N(10)–C(6) ring-closed bicyclomycin acetonides (i.e., **106** or **111i**), were shifted 3–7 ppm downfield. The magnitude and direction of the ^{13}C as well as ^1H NMR shifts for **119** were reminiscent of sterically induced polarization effects that accompany the relief of the steric strain <1998JOC1290>. Introduction of a methyl or a substituted methyl unit at C-5a of bicyclomycin **115a** gave **120a–i**, which showed in their ^{13}C NMR spectra upfield shifts (4–9 ppm) for the C-5 resonances and downfield shifts for the C-5a signals <1998JOC1290>.



a: X = H; **b:** X = OH; **c:** X = OAc;
d: X = OC(O)-2,6-CF₃-C₆H₃; **e:** X = Cl;
f: X = Br; **g:** X = N₃; **h:** X = NH₂; **i:** X = NHAc

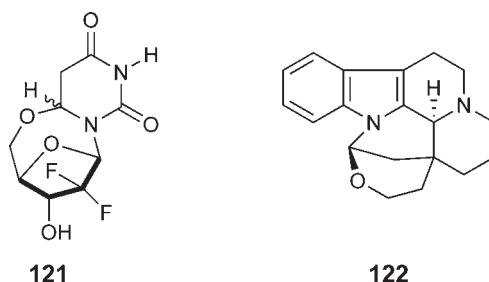
No ^{15}N NMR data have been provided for the reported 1,3-oxazocines.

Only one report utilized ^{31}P NMR spectra. Thus, the time course of ^{31}P NMR spectra of the reaction leading to **118** indicates that the phosphorus atom in this compound is in an environment similar to that of the phosphorus atom

in 3'-dGMO. After 1.5 h, the new peak observed at 0.46 ppm downfield from the main peak (4.9 ppm at 0 h) is due to **118**, and its intensity grows with time. Since the pH drops from 8.6 ($t=0$ h) to 4 ($t=14$ h), both peaks gradually shifted upfield as the reaction progressed. It is known that both inorganic and nucleotide phosphate shift upfield at lower pH. This also confirmed that the phosphate group in **118** was not phosphodiester, whose ^{31}P NMR peak at -5.5 ppm was insensitive to pH <2005JA1773>.

No studies on fragmentation patterns of 1,3-oxazocines have been reported in the past decade. Most of the papers reported only molecular or quasi-molecular ions utilizing different mass spectrometry (MS) techniques. There were reported EI spectra <1995JHC627>, FAB spectra <1996HCA426, 1996T833, 1999JOC9289, 2000HCA1311>, ESI spectra <1998SL891, 2005JME8182>, and CI spectra <1995JOC5346, 1996JOC7750, 1996JOC7756, 1996JOC7764, 1996T833, 1997JOC5432, 1998JME1185, 1998JOC1290, 2000B9067, 2000J(P1)3603, 2000T9885, 2001JOC2251, 2002TL8025, 2003JOC5575, 2005EJO3724, 2005T1207>.

The EI mass spectrum of **121** showed the molecular ion at m/z 264 and three main peaks. The peak at m/z 244 indicated loss of HF and gave rise to the peak at m/z 170 ($\text{C}_7\text{H}_5\text{NO}_3\text{F}$), probably through cleavage of the pyrimidine moiety. The peak at m/z 120 ($\text{C}_4\text{H}_4\text{N}_2\text{O}_2$) is likely due to loss of the oxazocine portion <2000JPS885>. The EI mass spectrum of isolarutensine **122** showed the molecular ion at m/z 294, the base peak at m/z 293 (M-H), and two peaks ($\text{M}-\text{C}_2\text{H}_4$ and $\text{M}-\text{OC}_2\text{H}_4$) due to the cleavage of the oxazocine ring <1998H(48)249>.



In the large number of bicyclomycin analogues synthesized, that is, **105**, **106**, **114–117**, and **120**, the NH stretchings were observed in the usual range $3512\text{--}3226\text{ cm}^{-1}$. The carbonyl absorptions of these series were observed in the range $1728\text{--}1630\text{ cm}^{-1}$ <1995JOC5346, 1996JOC7750, 1996JOC7756, 1996JOC7764, 1997JOC5432, 1998JHC1185, 1998JOC1290>. On some occasions, broad absorptions originated by hydrogen bonding were also observed ($2992\text{--}2956\text{ cm}^{-1}$) <1996JOC7764, 2000B9067, 2001JOC2251>. The pyrimido-oxazocine **103** showed the OH absorptions at 3496 and 3225 cm^{-1} in both free and associate forms and the pyrimidinone carbonyl stretching at 1634 cm^{-1} <1999JOC9289>. The halo-oxazocine **113b** showed the NH stretching at 3427 and 3224 cm^{-1} in the free and associate form, respectively, and the carbonyl stretching at 1696 cm^{-1} <2005T1207>.

In the ultraviolet–visible (UV–Vis) spectra of compounds of type **117**, bearing R-substituents with a sulfur bound to mono-, bi-, and tricyclic aromatic systems, a progressive increase was observed in the λ_{max} for the highest-wavelength absorption from C-5a substituents with an appended monocyclic ring to those with tricyclic substituents. The longest λ_{max} observed was for the δ -anthracene derivative (403 nm). Several derivatives displayed fluorescent properties. The λ_{max} for fluorescent excitation ranged from 257 to 383 nm while the λ_{max} for fluorescent emission was from 336 to 444 nm. The quantum yield (Φ) for fluorescent emission ranged from 0.03 to 0.49 <2003JOC5575>.

14.05.3.3 Thermodynamic Aspects

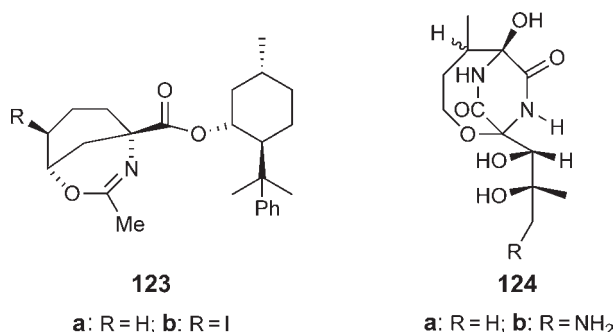
The phase behavior of the 1,3-oxazocines strongly depends on the substituents, condensation with other rings, and the presence of bridges. The consistence of the mixture of diastereoisomers of the unbridged and uncondensed perhydro-1,3-oxazocine **112** was not reported <1995J(P1)123>. The methylene-bridged oxazocines **123a** and **123b** are oils <1996TA721> but similar compounds such as **113**, having only one substituent and lower molecular weight but with a lactam moiety that ensures intermolecular interactions, are solids and **113a** melts at 157°C <1998SL891>. Derivative **109k** ($\text{R}=\text{OH}$, $\text{R}^1=\text{H}$, $\text{R}^2=\text{R}^3=\text{Me}$) is a liquid, whereas the annelation on the ring double bond of a benzene ring exists as a solid melting at 140°C . The same trend is observed in the case of the corresponding methylene-bridged **109b** ($\text{R}=\text{R}^1=\text{H}$, $\text{R}^2=\text{R}^3=\text{Me}$), which is a liquid, and **110**, which is a solid melting at 130°C <2005EJO3724>. The crowded series of bicyclomycin analogues, that is, **105**, **106**, **114–117**, and **120**, bearing functionalities capable of intense intermolecular interactions, generally melt in the range $100\text{--}200^\circ\text{C}$ <1995JOC5346, 1996JOC7750, 1996JOC7764, 1996T833, 1997JOC5432, 1998JHC1185, 1998JOC1290, 2001JOC2251,

2003JOC5575> and in some cases $>200^{\circ}\text{C}$ <1996JOC7756, 2000B9067>. The series of anhydronucleosides, such as pyrimido-fused 1,3-oxazocines **102–104**, have high melting points starting from 200°C . Thus, **102b** melts at $219\text{--}222^{\circ}\text{C}$ <2000HCA1311>, **103** melts at 200°C , and its 2',3'-deoxy derivative maintains the melting point at $199\text{--}201^{\circ}\text{C}$ <1998TL1807>. The corresponding imidato-fused 1,3-diazocine melts at $241\text{--}242^{\circ}\text{C}$ <2000J(P1)3603> and the thienopyrimidine-fused derivative melts at 250°C <1995JHC627>. Annelation with a tricyclic system led to a compound melting at $>300^{\circ}\text{C}$ <2004NN117>.

From the experimental procedures and workup of the reaction in which 1,3-oxazocines are involved, it is clear that these compounds are soluble in most common solvents. They were generally purified in silica gel with eluent of medium to high polarity: $\text{CHCl}_3/\text{MeOH}$ <1995BMC397, 1995JOC5346, 1996JOC7750, 1996JOC7756, 1996JOC7764, 1996T833, 1997JOC5432, 1998JHC1185, 1998JOC1290, 2000B9067, 2000J(P1)3603, 2001JOC2251, 2003JOC5575, 2004NN117>, DCM/MeOH <1995JHC627, 2003JOC367>, $\text{AcOEt}/\text{hexane}$ <1995J(P1)123, 1996TA721, 2000HCA1311, 2005EJO3724, 2005JME8182>, acetone/hexane <1995TL2711>, toluene/acetone <1996HCA426>, MeOH <2001JOC2251>.

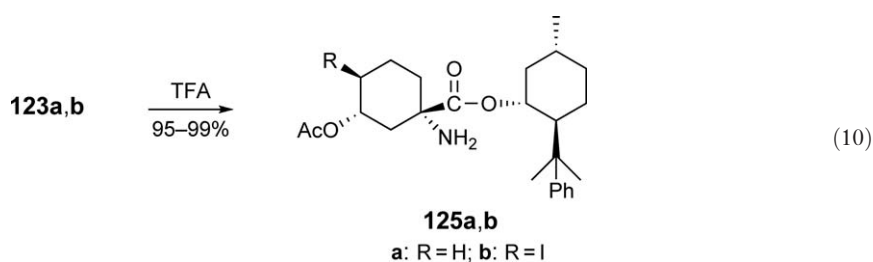
The conformational preferences of the AZT analogues **100** and **101** were different from those exhibited by the lead compound. They showed a high molecular rigidity with practically no changes in the sugar conformation as predicted by AM1 calculation (see Section 14.05.3.1) and demonstrated by comparison of calculated and experimental NMR data (see Section 14.05.3.2) <2003NN45>. The **109d–g** were obtained as mixtures of diastereoisomers: **109d** ($\text{R}=\text{R}^1=\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$) 4:1; **109e** ($\text{R}=\text{R}^1=\text{R}^2=\text{H}$, $\text{R}^3=i\text{-Pr}$) 10:1 (separable); **109f** and **109g** ($\text{R}=\text{R}^1=\text{R}^2=\text{H}$, $\text{R}^3=(\text{CH}_2)_2\text{--CH=CH}_2$; $\text{R}=\text{R}^1=\text{R}^2=\text{H}$, $\text{R}^3=(\text{CH}_2)_3\text{--CH=CH}_2$) 5:2 <2005EJO3724>. The methyl 5a-bicyclomycincarboxylate **116a** was obtained as a 3:1 diastereomeric mixture of the (5*E*)- and (5*Z*)-isomers, which could be separated by repetitive thin-layer chromatography (TLC) <2001JOC2251>. The bicyclomycin analogue **124a** exists in a 6:1 ratio of diastereoisomers as indicated by the two sets of ^{13}C NMR signals, each for C-4, C-5, and C-5a resonances <1996JOC7750>. The presence of mixtures of diastereoisomers is common in most of 5a-substituted C-5,C-5a-dihydrobicyclomycins **117** <1996JOC7764>. The pyrimidine-fused 1,3-oxazocines **107** with $\text{R}\neq\text{R}^1$ exist as a 1:1 mixture of diastereomers, which differ by configuration at the C-6. These diastereomers could be separated by chromatography <1998MI1>.

Bicyclomycin **115a**, **115m**, and **115n** had approximately the same stability in a buffered water solution ($t_{1/2}\sim 28\text{--}31\text{ h}$), whereas **115l** was appreciably more stable ($t_{1/2}\sim 155\text{ h}$) <1998JME1185>. Two dihydrobicyclomycin derivatives **117u** and **117w** ($\text{R}=\text{NHC}_6\text{H}_4\text{--}4\text{--N}_3$ and $\text{NHC}_6\text{H}_4\text{--}3\text{--CHO}$) were stable in D_2O and CD_3OD at 25°C for 1 week. Replacement of the CH_2R moiety at the C-5 of the dihydrobicyclomycins with 4-azidobenzoyloxy and 3-formylbenzoyloxy moieties led to derivatives that either in D_2O and CD_3OD gradually hydrolyzed to the 5-hydroxy-dihydrobicyclomycin. The approximate $t_{1/2}$ value for both compounds in CD_3OD (22°C) was 12 h and in D_2O (22°C) was 24 h <1997JOC5432>. The amine **124b** was stable in aqueous and methanolic solutions at 25°C for short periods of times ($<4\text{ h}$). Maintenance of these solutions for longer times (18 h) led to the formation of a new compound whose structure was not determined <1996JOC7750>.

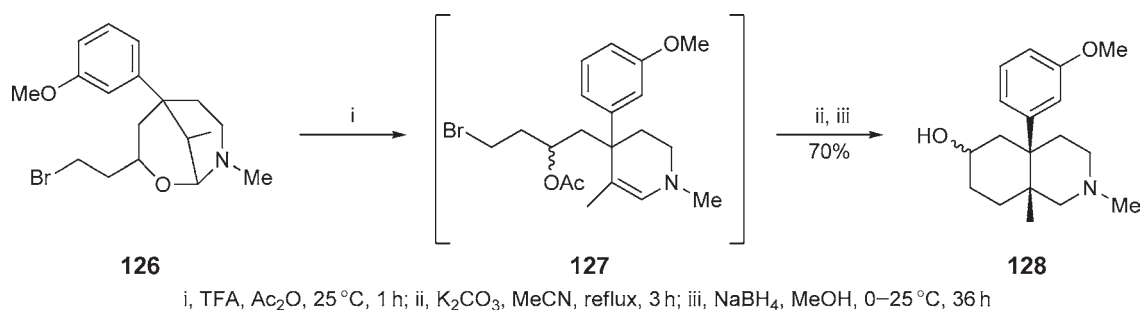


14.05.3.4 Reactivity of Nonconjugated Rings

Treatment of **123a** and **123b** with TFA involved cleavage of the bridged oxazocine ring to give the 8-phenylmenthyl carboxylates **125a** and **125b** (Equation 10) <1996TA721, 1999TA3999>. The same reactivity was exhibited by an analogue of **123b** bearing a methoxycarbonyl group instead of an 8-phenylmenthyloxy moiety to give the carboxymethyl-substituted cyclohexane (98%) <1997S165>.

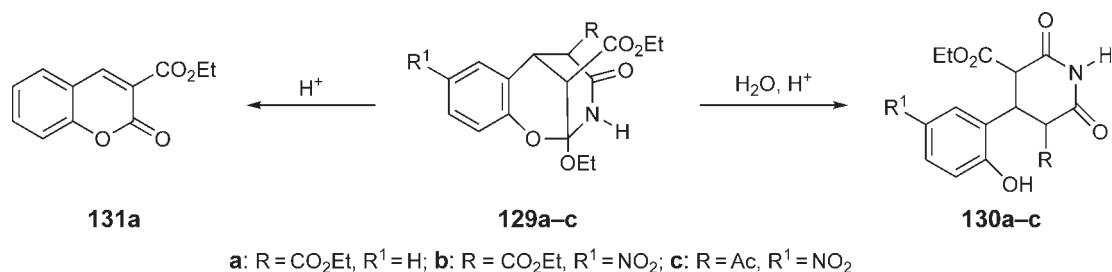


Treatment of **126** with a mixture of TFA and Ac₂O cleaved the oxazocine ring to give the enamine **127**, which was directly cyclized in refluxing MeCN and K₂CO₃, as the base. Treatment of the product with borohydride resulted in concomitant reduction of the enamine and hydrolysis of the acetoxy group to give the 6-hydroxy-octahydroisoquinoline **128** (Scheme 22) <2005JME8182>.



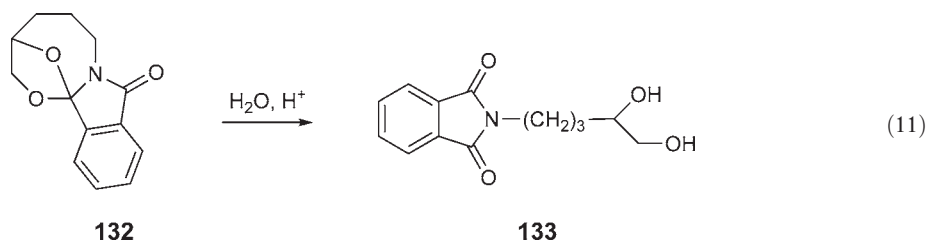
Scheme 22

Benzoxazocinones **129a–c** could be converted by acid hydrolysis into glutarimide derivatives **130a–c**. Instead, in anhydrous acid medium, such as *p*-TsOH or TFA in anhydrous MeCN, **129a** afforded coumarin **131a** from which it was synthesized, demonstrating the full reversibility of the synthetic process (see Scheme 57, Section 14.05.3.7.7) (Scheme 23) <2004SL1584>.



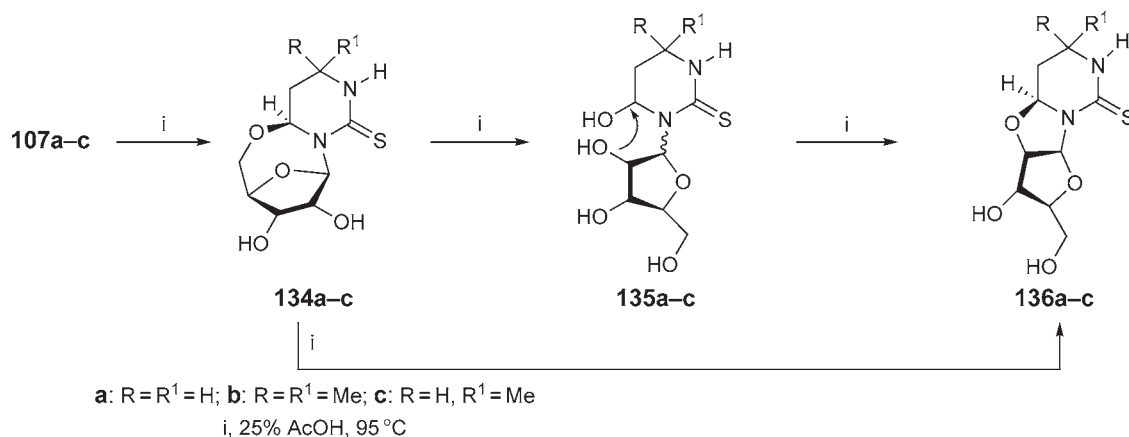
Scheme 23

Acid hydrolysis of the oxygen-bridged isoindole-fused oxazocine **132** led to the phthalimido-substituted ethylene glycol **133** (Equation 11) <2002T7049>.



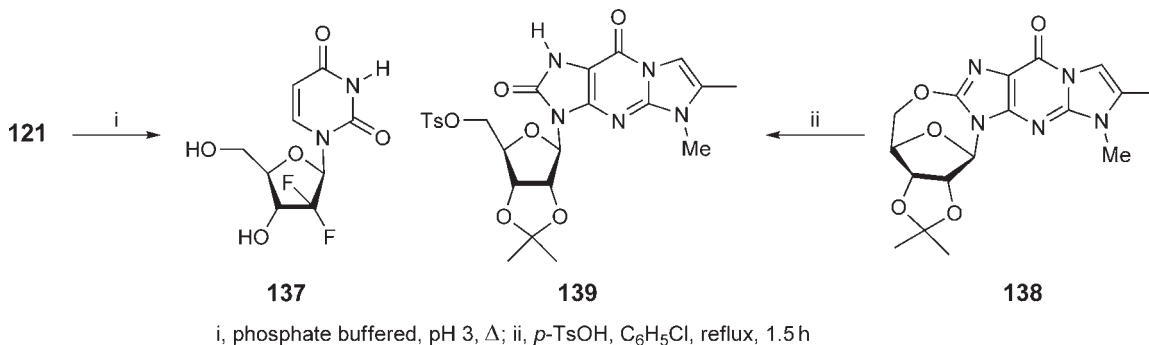
In the attempt to remove the isopropylidene moiety, **107a** was treated with 25% aqueous AcOH. Instead of the expected **135a** from the reaction, **136a** was obtained as the main product (57%) together with the products of cleavage of the glycosidic bond, that is, 4-hydroxyhexahydropyrimidine-2-thione (12%) and D-ribose. The formation of **136a** involves initial deprotection to give **134a**, subsequent cleavage of the O–C(4) bond affording **135a**, which exists in equilibrium mixture of α - and β -ribofuranosides and α - and β -ribofuranosides.

The α -ribofuranose form of **135a** gives the final product as result of an intramolecular cyclization of the 2'-hydroxy group at the 4-position of the pyrimidine ring. Quenching the reaction after ca. 2 h, the reaction mixture consisted of starting material, **136a**, anhydribose **134a**, and riboside **135a**. All the components of the mixture were separated by column chromatography. The proposed route to **136** was confirmed when this compound was obtained from **134a** and **135a** upon reaction with aqueous AcOH. Similarly **107b** and **107c**, under the same reaction conditions, gave **136b** and **136c** although the reactions were slower (Scheme 24). The stability of the oxygen bridge to the hydrolytic cleavage, in fact, decreased in the sequence **134a** > **134c** > **134b** <1998MI1>.



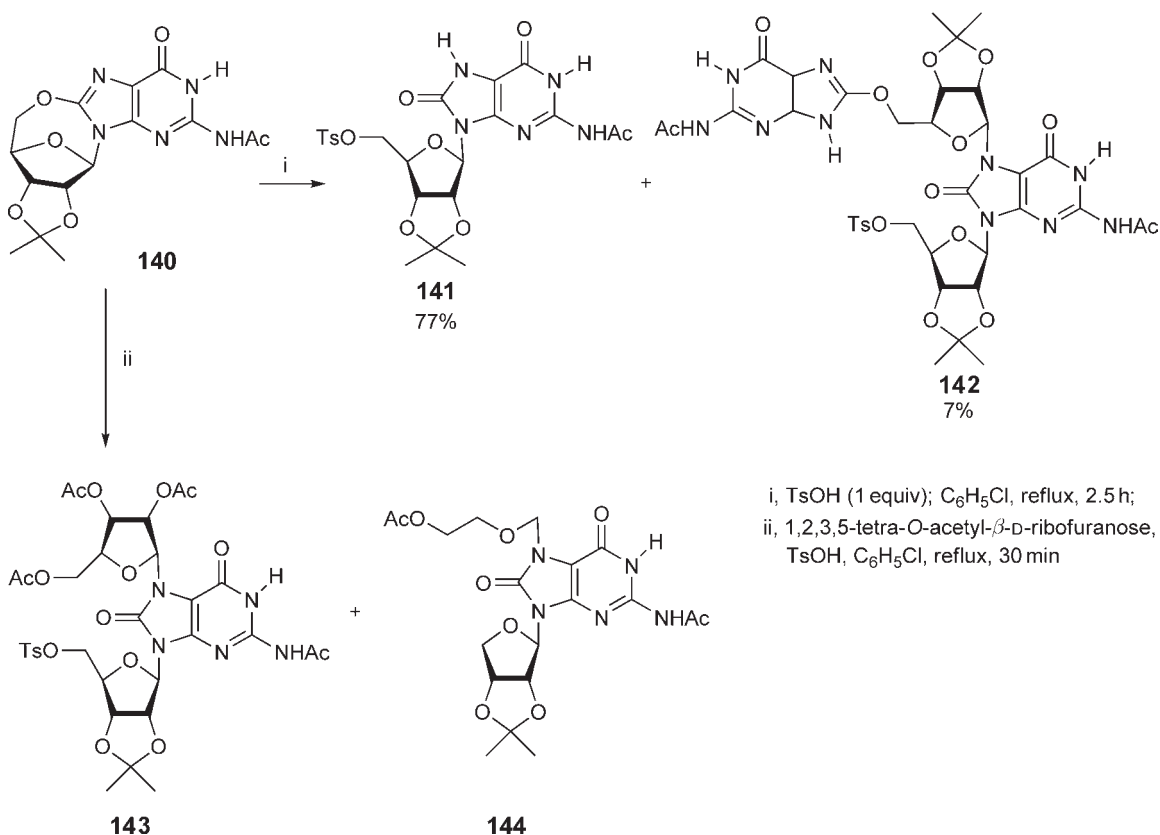
Scheme 24

The pyrimidine-fused oxazocine **121**, upon hydrolysis in acid medium, cleaved the eight-membered ring to give **137** (Scheme 25) <2000JPS885>. Cleavage of the oxazocine ring was also observed when **138**, obtained from **94** by methylation, was reacted in refluxing *p*-TsOH to give **139**, which is incapable of cyclization to the corresponding 1,3-diazocine as did **97**, which furnished **95** (Scheme 25) (the reaction leading to **95** reported in Section 14.05.2.8 (Scheme 21) is also one example of reaction to be reported in this section) <2004NN117>.



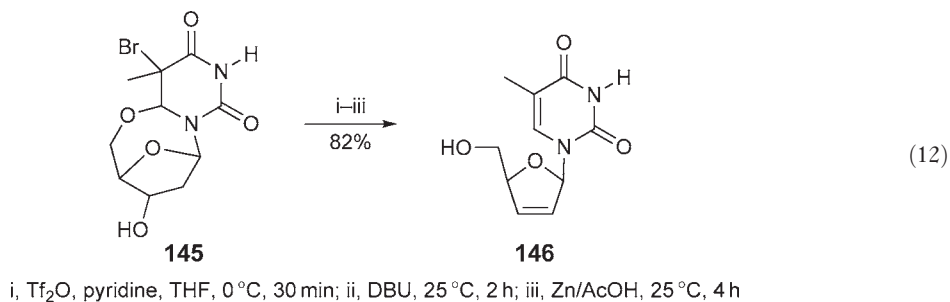
Scheme 25

Another ring cleavage was observed upon treatment of **140** with *p*-TsOH to give **141** and traces of dimer **142**. When the hydrolysis of **140** was performed in the presence of 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose, compounds **143** and **144** were the only products formed (Scheme 26) <2003NN735>. The 5-diazo-anhydro-3'-deoxyuridine was hydrolyzed to give a triazole derivative through a known rearrangement <2002WO32920>.

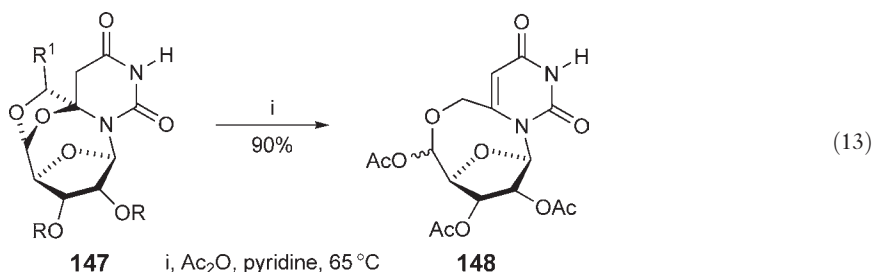


Scheme 26

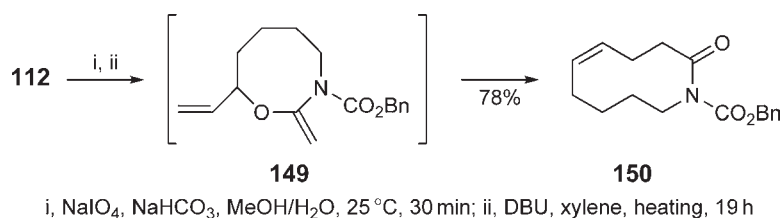
The anti-HIV nucleoside d4T **146** was obtained via a one-pot three-step procedure from the pyrimidine-fused oxazocine **145**, which reacted with Tf₂O followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and final reduction with Zn/AcOH (Equation 12) <1995TL2711>.



The pyrimidino-fused oxazocine **147a** (R = Ac, R¹ = H) underwent an acylative ring opening to give the stable triacetate **148**, which was isolated as a 7:3 mixture of diastereomers (Equation 13) <2000T9885>.



Oxidation of the selenide-substituted oxazocine **112** with NaIO₄ in MeOH/H₂O gave, in quantitative yield, the corresponding selenoxide, which was directly refluxed in xylene with DBU to give the protected lactam **150**, as single product, via the ketene aminal **149** (Scheme 27) <1995J(P1)123>.



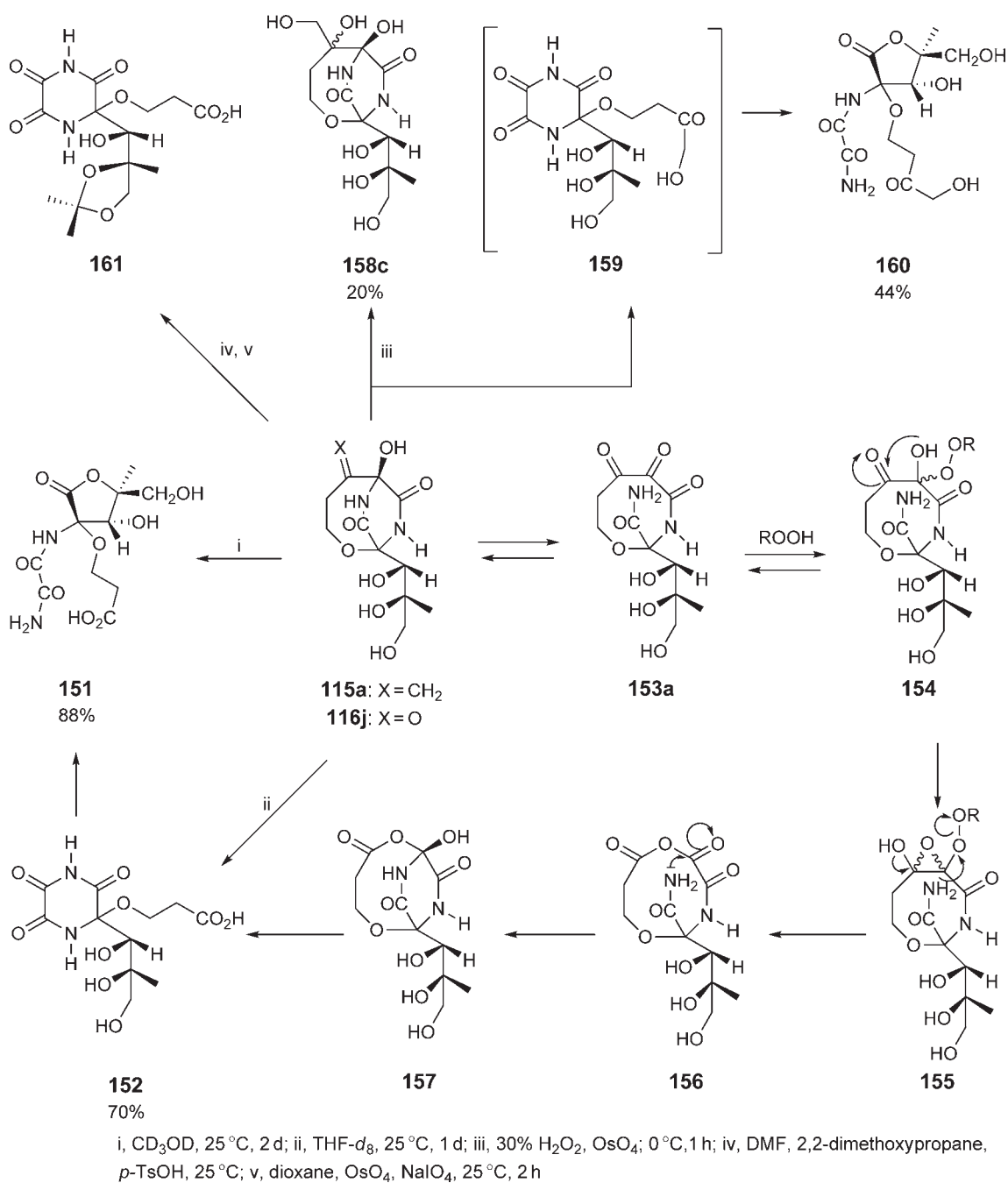
Scheme 27

The attempt to obtain bicyclomycin-5-norketone **116j** by ozonolysis of a methanolic solution of **115a** followed by the addition of dimethylsulfide, on a small scale (0.1 g), produced a complex mixture. NMR analysis of the products in CD₃OD indicated the presence of **116j** along with other adducts. Maintenance of the CD₃OD at 25 °C resulted in **151**, as the sole product. In THF-*d*₈ at 25 °C, **116j** was converted to **152** as major product along with a small amount of **151**. Addition of PPh₃ to a freshly prepared THF-*d*₈ sample of **116j** decreased the extent of conversion to **152** and produced PPh₃O. An evaluation of the above-described reactions indicated that either oxidants entrained in the ozonolysis product mixture or present in the reaction solvents were responsible for these transformations. In fact, addition of H₂O₂ to a freshly prepared CD₃OD solution of **116j** gave **151** as the predominant product. Thus, the mechanism for the conversion of **116j** to **151** and **152** was proposed to go through the hemiketal opening of **116j** to **153a**. Peroxide addition at either of the two ketone carbonyl sites yielded initially an alcohol **154** and then an epoxide **155** intermediate. Subsequent C–C fragmentation produced anhydride **156**, which allowed intramolecular cyclization by the C-9 amide group to give piperazinedione **157**. Ring fragmentation of **157** produced **152** and then **151** by an intramolecular lactonization. Further evidence that bicyclomycin ring framework can undergo oxidative fragmentation was obtained from the reaction of **115a** with H₂O₂ and catalytic amounts of OsO₄, which gave **158** and **160** via **159**. When the oxidative fragmentation with NaIO₄ and OsO₄ was conducted on C-2',C-3'-diol-protected bicyclomycin acetonide, only piperazinetriene **161** was isolated since the intramolecular lactonization was impossible (Scheme 28) <1995JOC5346>.

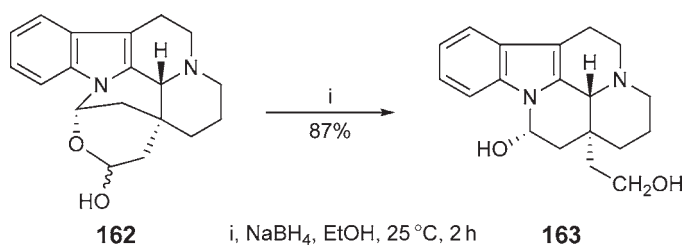
The polycondensed oxazocine **162** by reduction with hydride underwent ring opening at the eight-membered ring to give the diol **163** (Equation 14) <2005HCA2764>.

The benzo-fused oxazocine **108a** smoothly ring-contracted to the rigid [6.5.5]-tricyclic-fused oxazolidinone **164** by an intramolecular S_N2 process (Equation 15) <2002TL8025>.

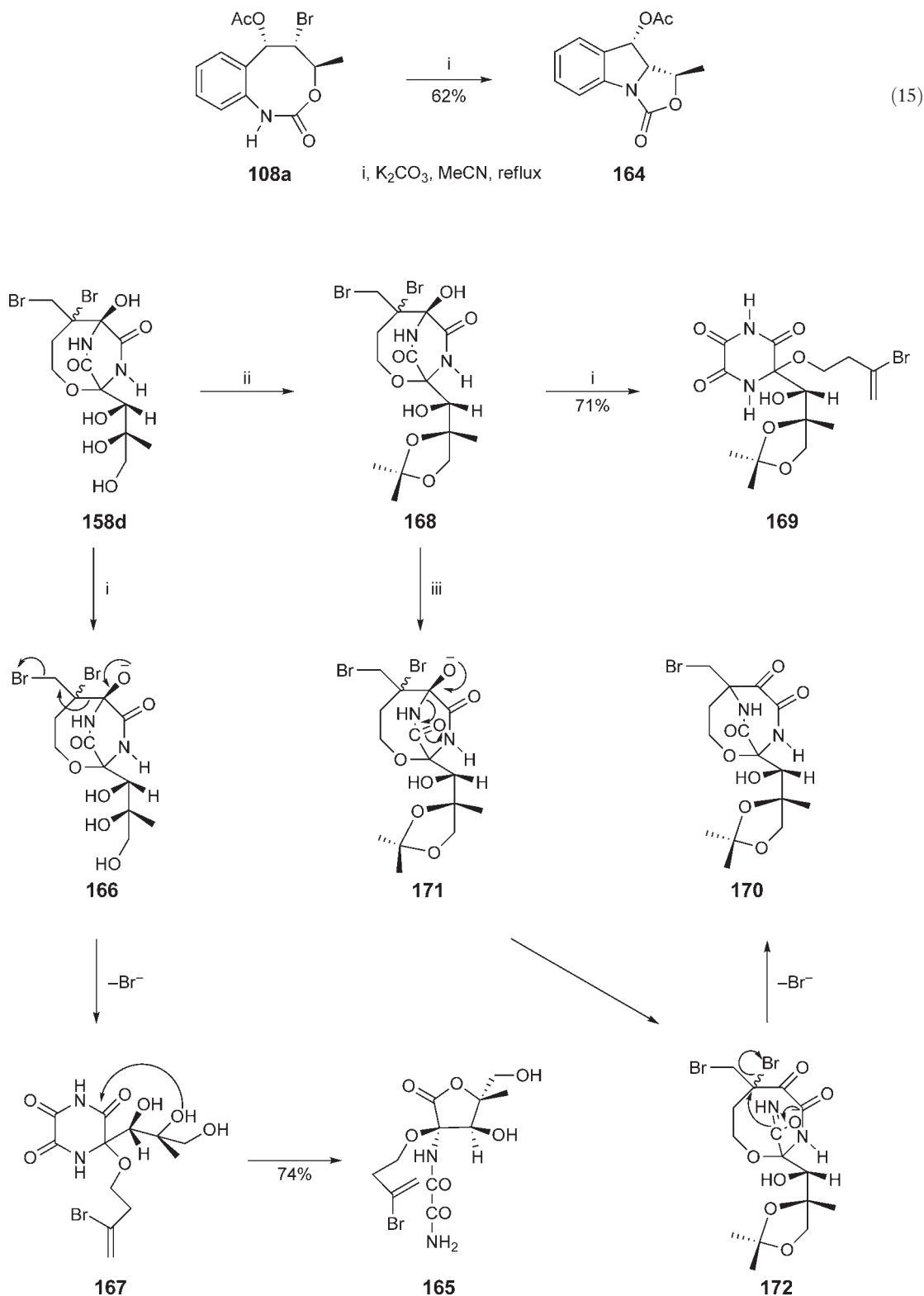
The ring fragmentation observed in bicyclomycin analogues under oxidative conditions (Scheme 28) occurred also in basic medium. Thus, addition of DBU to **158d** in an aprotic solvent generated the rearrangement adduct **165** through the initial abstraction of the C-6 hydroxyl proton in **166** followed by C(5)–C(6) bond cleavage, halide elimination in **167**, and lactonization of the C-2'-hydroxyl group. This pathway was confirmed by treatment of the C-2',C-3'-protected acetonide **168** with DBU, which gave the ring-cleaved piperazinetriene **169**. Use of KF and 18-crown-6 in place of DBU gave a mixture of **169** (48%) and **170** (24%). The pathway to **170** involved cleavage of the C(6)–N(10) bond in **171** to give an amide anion in **172**, which displaced the C-5 bromo group (Scheme 29) <1996T833>.



Scheme 28

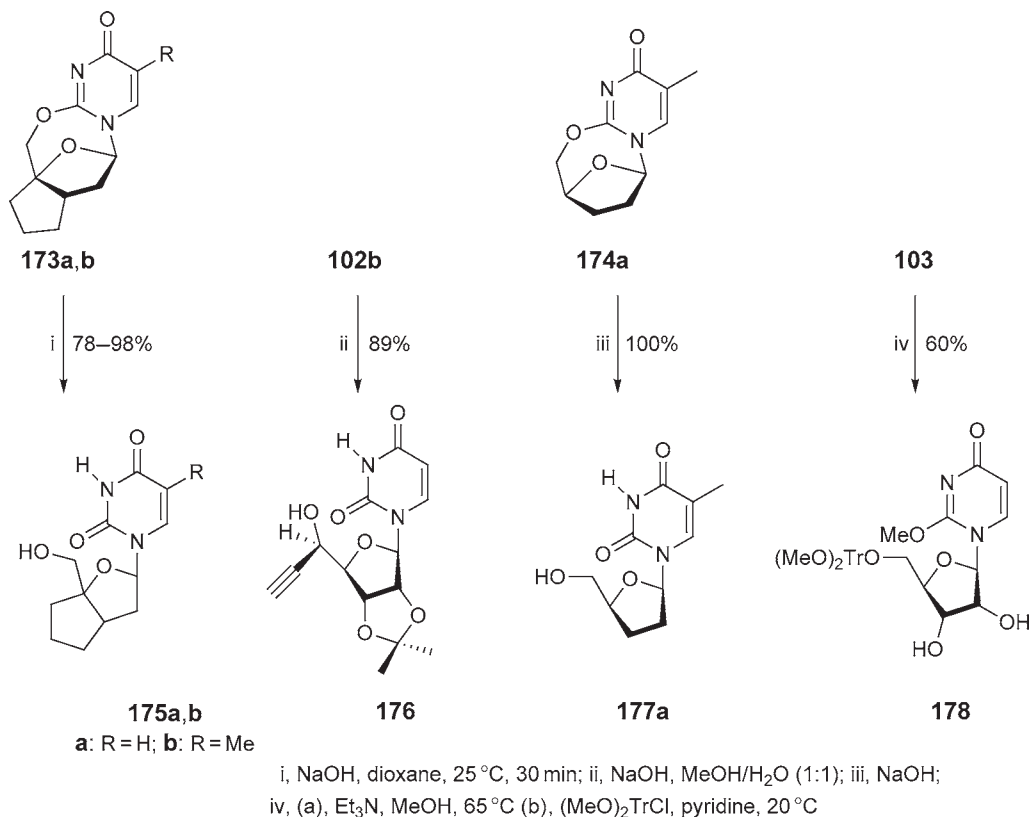


(14)



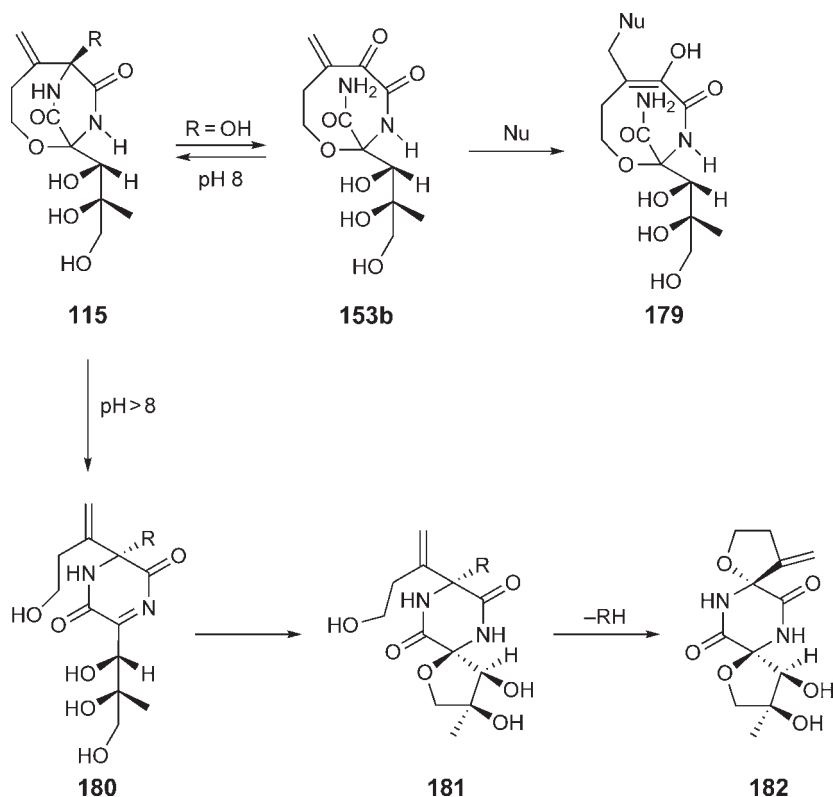
Scheme 29

The cleavage, brought about by acid medium, of the eight-membered ring of the anhydronucleosides was also observed under basic conditions. Thus the pyrimidino-fused oxazocines **102b**, **103**, **173a**, **173b**, and **174a** under the basic conditions indicated in **Scheme 30** gave the corresponding pyrimidine derivatives **176**, **178**, **175a**, **175b**, and **177a**, respectively <1995BMC397, 2000HCA1311, 1998TL1807, 2005HCA2683>. Analogously, ammonolysis of 2,5-anhydro-6-azathymidine and 2,5-anhydro-6-aza-2'-deoxyuridine underwent ring-opening to give 6-aza-5-methyl-2'-deoxyisocytidine and 6-aza-2'-deoxyisocytidine in 80% and 75% yield, respectively <2003JOC367>. The same ring opening of anhydronucleosides was also observed upon nucleophilic attack by phosphorus dithioacids, which produced oligonucleotides containing 3'-S-P(S) and 5'-S-P(S) moieties <2002PS1855>. Reflux with TrCl in pyridine of **174a** cleaved the eight-membered ring <2003WO018599>.



Scheme 30

It was supposed that bicyclomycin would exert its antimicrobial activity by modification of nucleophilic amino acid residues in proteins necessary for bacterial survival. Such modification occurs through a Michael addition of the nucleophile to the exocyclic methylene of the ring-opened β -methylene- α -ketamide **153b** to give **179**. The role of the C-6 hydroxyl group in this mechanism is crucial since its ionization favors the hemiaminal ring-opening to generate **153b**. In fact, replacement of the hydroxyl group with a methoxy moiety in **115b** led to a compound devoid of antimicrobial activity, which at pH ~ 8 in the presence of an excess of EtSH did not react but at higher pH (~ 10) gave the bis-spiro adduct **182** through the initial cleavage of the C(1)–O(2) followed by sequential nucleophilic ring closures by the terminal hydroxyl groups of the two side chains of the piperazinedione ring with final extrusion of RH (MeOH) <1996JOC7756>. Replacement of the hydroxyl group with an amino, hydroxylamino, or mercapto moiety led to **115l–n**, which, in spite of the fact that they have an ionizable proton, lost near-total antimicrobial activity and altered the chemical reactivity of the lead **115a**. Thus, **115l** (R = NH₂) at pH ~ 9 in the presence of excess of EtSH was recovered unchanged while at pH ~ 10.5 gave **182**; **115n** (R = SH) at pH 9.5 gave **182**. However, **115m** (R = NHOH) at both pH ~ 9 and 10 gave only **181** (R = NHOH) (**Scheme 31**) <1998JME1185>.



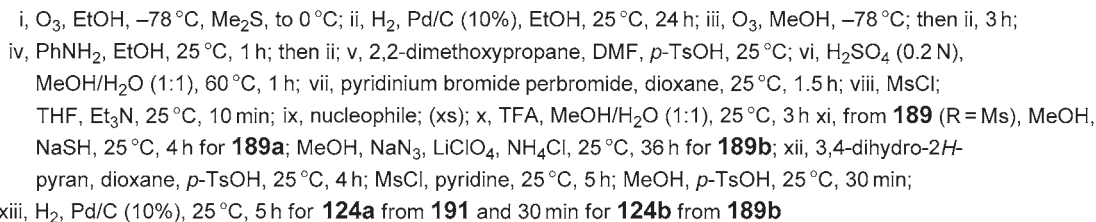
Scheme 31

14.05.3.5 Reactivity of Substituents Attached to Ring Carbon Atoms

More than half of the references cited in this section deal with bicyclomycin and its analogues. A conspicuous number of analogues modifying the substituents in the various positions of the bridged eight-membered ring were synthesized. In particular, modification of the triol side chain, substituents at the 6-position and, more extensively, modification at the 5-position are described. For this series of compounds, the reactivity of substituents attached to ring carbon atoms of bicyclomycin became a tool for the synthesis of the various analogues.

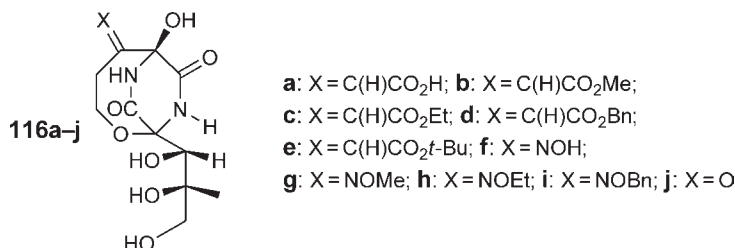
Ozonolysis of **115a** conducted in EtOH gave the bicyclomycin-5-norketone **116j** in an improved yield. Reduction with NaCNBH_3 or H_2 -Pd/C of **116j** led to the stereospecific production of alcohol **183a**, which could, however, be prepared in nearly quantitative yield, by ozonolysis of **115a** at -78°C in MeOH followed by direct catalytic hydrogenation. The alcohol **183a** could also be synthesized by sequential ozonolysis and reduction of the acetonide **111a** and successive removal of the protective group from **105a**. This method allowed the determination of the orientation of the C-5 hydroxyl group. Addition of aniline to an ethanolic solution of **116j** gave the Schiff base **185**, which by catalytic or chemical reduction led to the amine **186**, as a single isomer <1995JOC5346>.

The synthesis of 5,5a-dibromobicyclomycin **158d** was accomplished by treatment of **115a** with pyridinium bromide perbromide <1996T833>. Replacement of the hydroxyl group at position 6 with a wide range of substituents can be achieved by treatment of acetonide **111a** with MsCl, which gave a binary mixture tentatively identified as the mesylate **187** and the dimesylate **188** in a ratio of ca. 9:1. Treatment of **187** and **188** *in situ* with excess of the appropriate nucleophile furnished **111b-n**. Removing the acetonide group from **111b-n** gave the 6-substituted analogues of bicyclomycin **115b-n** <1996JOC7756, 1998JME1185>. Modification of the triol side chain was achieved by mesylation of the C-3' hydroxyl group to give **189** (R = Ms), which, in methanolic solution, reacted with NaSH to give the C-3'-deoxybicyclomycin C-3' thiol **189a** in 52% yield. Similarly when NaN_3 was added to a methanolic solution of **189** (R = Ms), the azide **189b** was obtained in 44% yield. Bicyclomycin C-1'-O-mesylate **190a** was synthesized from **115a** in three steps in 41% overall yield. Compound **115a** was first converted to the C-3' tetrahydropyranyl ether **190c** and then treated with MsCl to give **190b**. Deprotection of the crude **190b** with *p*-TsOH gave **190a**. Dihydrobicyclomycin analogues **124a** and **124b** were prepared by hydrogenation of **191**, obtained from **115a**, and **189b** in 94% and 52% yield, respectively (Scheme 32) <1996JOC7750>.

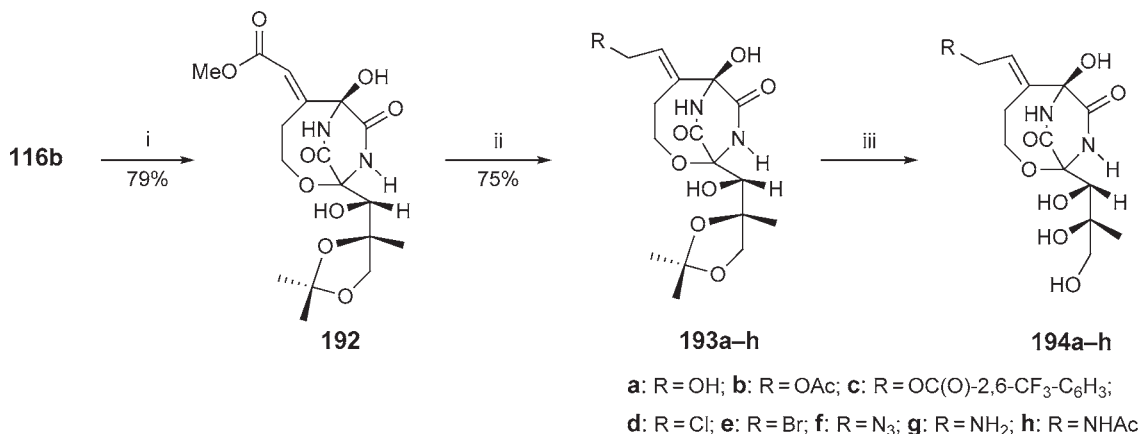


Scheme 32

A great deal of attention has been paid to the synthesis of bicyclomycin analogues with modifications at the C-5 and C-5a positions. Due to the enormous number of derivatives synthesized, different synthetic pathways were used and many derivatives underwent reactions to produce other members of the same series. The series **116a–i** was obtained from the bicyclomycin-5-norketone **116j**. Thus, (5*E*)-isomers of **116b–e** were prepared by the Wittig reaction of **116j** with the corresponding [(arylalkoxycarbonyl)methylene]triphenylphosphoranes in 42–70% yields. When **116j** was reacted with (methoxycarbonylmethyl) tri-*n*-butylphosphonium bromide and NET_3 , a 3:1 diastereomeric mixture of the (5*E*)-**116b** and (5*Z*)-**116b** was produced <2001JOC2251>. Catalytic hydrogenation of **116d** gave the free acid **116a** (50%). The oxime **116f** and substituted oximes **116g–i** were prepared by reacting **116j** with the suitable oxime hydrochloride derivatives in 67–86% yields <1996JOC7764>.



The methyl ester **116b** was transformed into its acetone derivative **192**, which was utilized to prepare the C-5a-substituted bicyclomycins **194a–h** through the intermediacy of **193a–h**. Reduction of **192** with LiEt_3BH gave in good yield the hydroxymethyl derivative **193a**, which was the starting material for the other members in the series. Reaction of **193a** with Ac_2O or 2,6-bis(trifluoromethyl)benzoic acid gave **193b** and **193c** in 46–49% yields, respectively. The preparation of **193d** and **193e** was accomplished by converting the allylic alcohol **193a** *in situ* to the mesylate **193** (R = Ms). Mesylate displacement with LiCl provided **193d** (43% overall yield). Analogous reaction with LiBr led to a 3:1 mixture of **193d** and **193e**. To eliminate the chloride ion content in the reaction, the *in situ* mesylation was conducted with methanesulfonic anhydride, but in this case **193d** and **193e** were obtained as a 9:1 mixture. Even more surprising was that treatment of this 9:1 mixture with TFA gave a 1:1 mixture of **194d** and **194e**. Thus the 9:1 mixture of **193d** and **193e** was utilized to get **193f**, upon reaction with NaN_3 in 82% yield, and **193g**, upon reaction with anhydrous ammonia at -78°C in 69% yield. Treatment of **193g** with Ac_2O gave **193h** (60%). Deprotection of the acetone derivatives **193a–h** with TFA led to **194a–h** in 55–100% yields (Scheme 33) <1998JOC1290>.

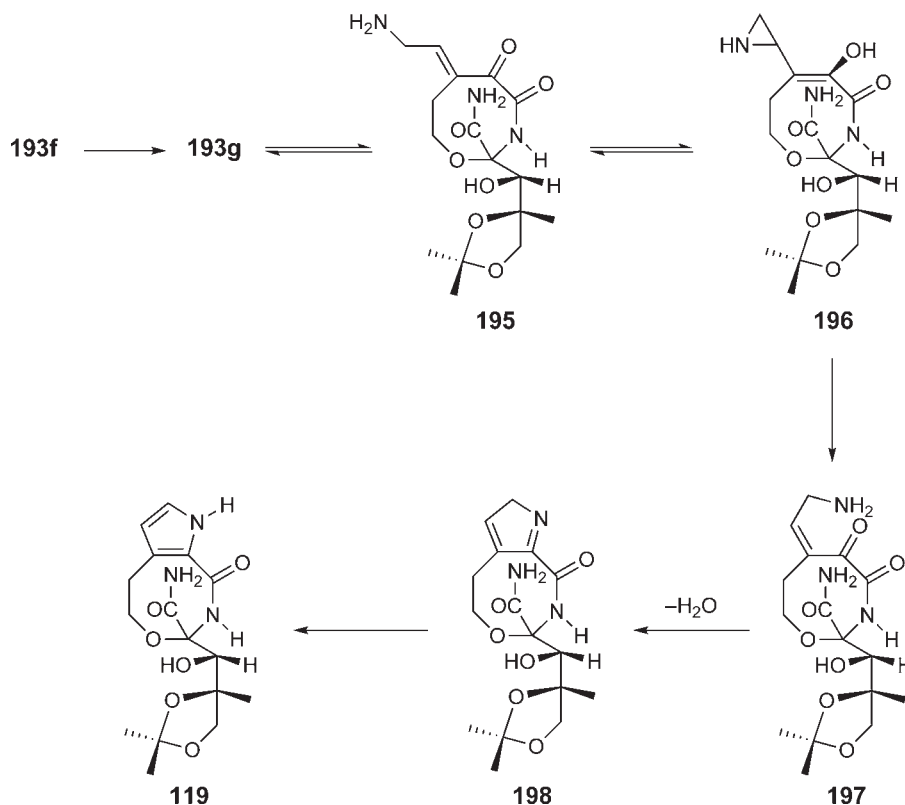


i, 2,2-dimethoxypropane, DMF, *p*-TsOH, 45°C , 2 h; ii, LiEt_3BH , THF, -78°C , 15 h; iii, TFA, $\text{MeOH}/\text{H}_2\text{O}$ (1:1), 25°C , 2 h

Scheme 33

To explore an alternative approach to **193g**, a chemoselective reduction of the azido group in **193f** using Staudinger conditions was attempted. Under such conditions, instead of **193g**, the pyrrolo-oxazocine **119** was isolated. The suggested pathway to **119** involves the initial reduction of **193f** to the desired **193g** and reversible ring opening of **193g** to the (5*E*)-alkene **195**, followed by intramolecular Michael addition to the aziridine **196**. Rotation of the C(5)–C(5a) bond followed by enol-assisted cleavage of the aziridine ring provided the (5*Z*)-alkene **197**.

Intramolecular condensation of **197** gave **198**, which then aromatized to **119**. Alternatively, tautomerization of the allylic amine **195** involving the C-6 carbonyl followed by rotation of the C(5)–C(5a) bond and isomerization gave **197** (Scheme 34) <1998JOC1290>.

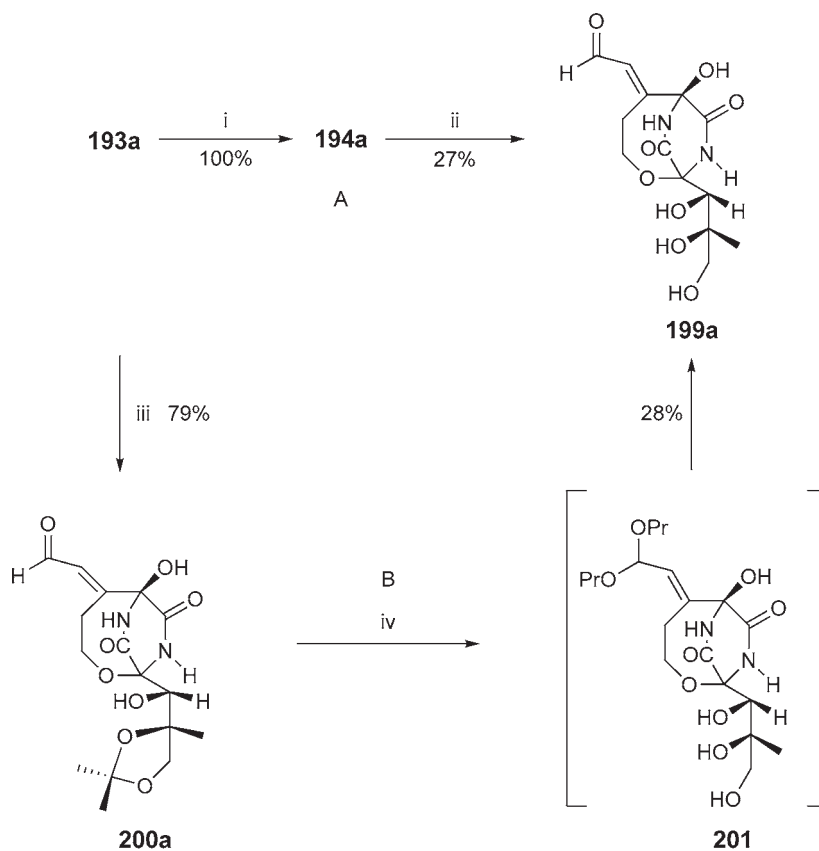


Scheme 34

Synthesis of aldehyde **199a** was accomplished by two different routes, both starting from **193a**. Route A involved removal of the acetonide group to give **194a** and selective oxidation of the allylic alcohol group with Magtrieve to give the aldehyde in 27% overall yield. In route B, the allylic group was first oxidized with Dess–Martin periodinane to give **200a**. Careful deprotection of the acetonide group followed by treatment with propanol and TFA gave the dipropyl acetal **201**, which was converted to **199a** during preparative thin-layer chromatography (PTLC) workup (Scheme 35) <2000B9067>.

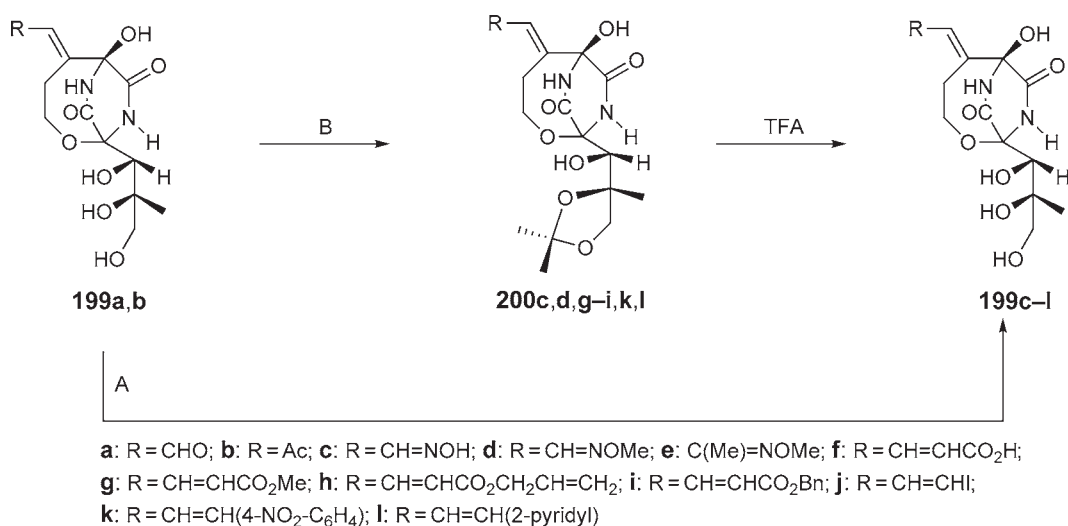
The C-5a-substituted analogues of bicyclomycin **199c–l** were synthesized from the known formyl and acetyl derivatives **199a** and **199b** through two synthetic routes A or B (Scheme 36). Treatment of **199b** with methoxylamine hydrochloride (route A) gave a 7:3 mixture of *anti*-(5*E*,5*bE*)- and *syn*-(5*E*,5*bZ*)-isomers of **199e**. The oximes **199c** and **199d** were obtained by reaction of (5*E*)-isomer of **199a** and the appropriate hydroxylamine hydrochlorides to give **200c** and **200d** (route B).

Deprotection of the acetonide group in **200c** and **200d** afforded **199c** as a single isomer and **199d** as a 7:3 mixture of *anti*-(5*E*,5*bE*) and *syn*-(5*E*,5*bZ*) isomers. Carboxylates **199g–i** were obtained by condensation of the acetonide derivative (5*E*)-isomer of **199a** with the appropriate triphenylphosphorane to give **200g–i** as a 9:1 mixture of (5*E*,5*bE*)- and (5*E*,5*bZ*)-isomers and successive removal of the acetonide group (route B). The carboxylic acid **199f** was obtained as a 9:1 mixture of (5*E*,5*bE*)- and (5*E*,5*bZ*)-isomers by Pd(0)-mediated deprotection of the allylic ester **199g** in the presence of piperidine. The vinyl aromatic analogues **199k** and **199l** were prepared, as single isomers, by Wittig condensation of the acetonide derivative (5*E*)-isomer of **199a** with the appropriate triphenylphosphorane thorough **200k** and **200l**. Addition of chromium dichloride to a solution of acetonide of **199a**, iodoform, and *N*-methylmorpholine, followed by action of TFA, gave an 8:2 mixture of (5*E*,5*bE*)- and (5*E*,5*bZ*)-isomers of **199j** (Scheme 36) <2001JOC2251>.



i, TFA, MeOH/H₂O (1:1), 25 °C, 2 h; ii, Magtrieve, THF, 80 °C, 6 h;
 iii, Dess–Martin periodinane, THF, 25 °C, 1 h; iv, TFA, H₂O to pH 1.8, 25 °C, 18 h

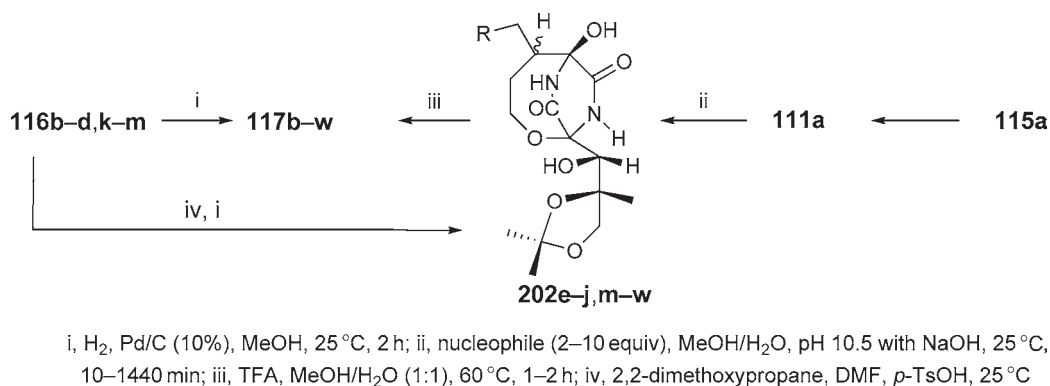
Scheme 35



Scheme 36

Catalytic hydrogenation of **116b** and **116c** gave the C-5,C-5a-reduced analogues **117c** and **117d**, respectively. Reduction of the benzyl ester **116d** under the same condition led to both the hydrogenation of the exomethylene group and removal of the benzyl group to give the free acid **117b** <1996JOC7764>.

Other dihydrobicyclomycins were obtained from **116** through the acetonides **202**. Thus, the methyl carboxylate **116b** was transformed into its acetonide, and reduction gave the primary alcohol **202p**. The allylamine **116k** and the corresponding acetyl derivative **116l** through the same sequence furnished **202r** and **202s**, respectively. Analogously, the allyl alcohol **116m** gave **202t**. Removal of the acetonide group from **202p** and **202r–t** afforded **117p** and **117r–t** <2001JOC2251>. Compounds **117e–j**, **117m–o**, and **117q** were prepared in three steps starting from bicyclomycin which gave, using the known procedure, the acetonide **111a**. Dissolution of **111a** and the appropriate nucleophile in aqueous MeOH, adjusted to pH 10.5, gave the substituted dihydrobicyclomycins acetonides **202e–j,m–o,q,u,v** in 40–100% yields. The Michael addition adduct **202v** (R = C₆H₄-3-CH₂OH) was oxidized to the corresponding **202w** (R = C₆H₄-3-CHO) before undergoing deprotection <1997JOC5432>. The Michael addition reached completion within 1 h (**202e–j**) and 24 h (**202m–o**) at 25 °C and in most cases gave a mixture of diastereomers. In two cases (**202m** and **202o**), the formation of only one isomer was observed. Deprotection of the acetonides **202** furnished the corresponding C-5a-substituted dihydrobicyclomycins **117**. Oxidation of **117e** with 30% H₂O₂ rapidly (30 min) gave, in nearly quantitative yield, the sulfoxide **117k**, whereas longer reaction times (5 h) and higher concentration of H₂O₂ gave the sulfone **117l** in 58% yield (Scheme 37) <1996JOC7764>.



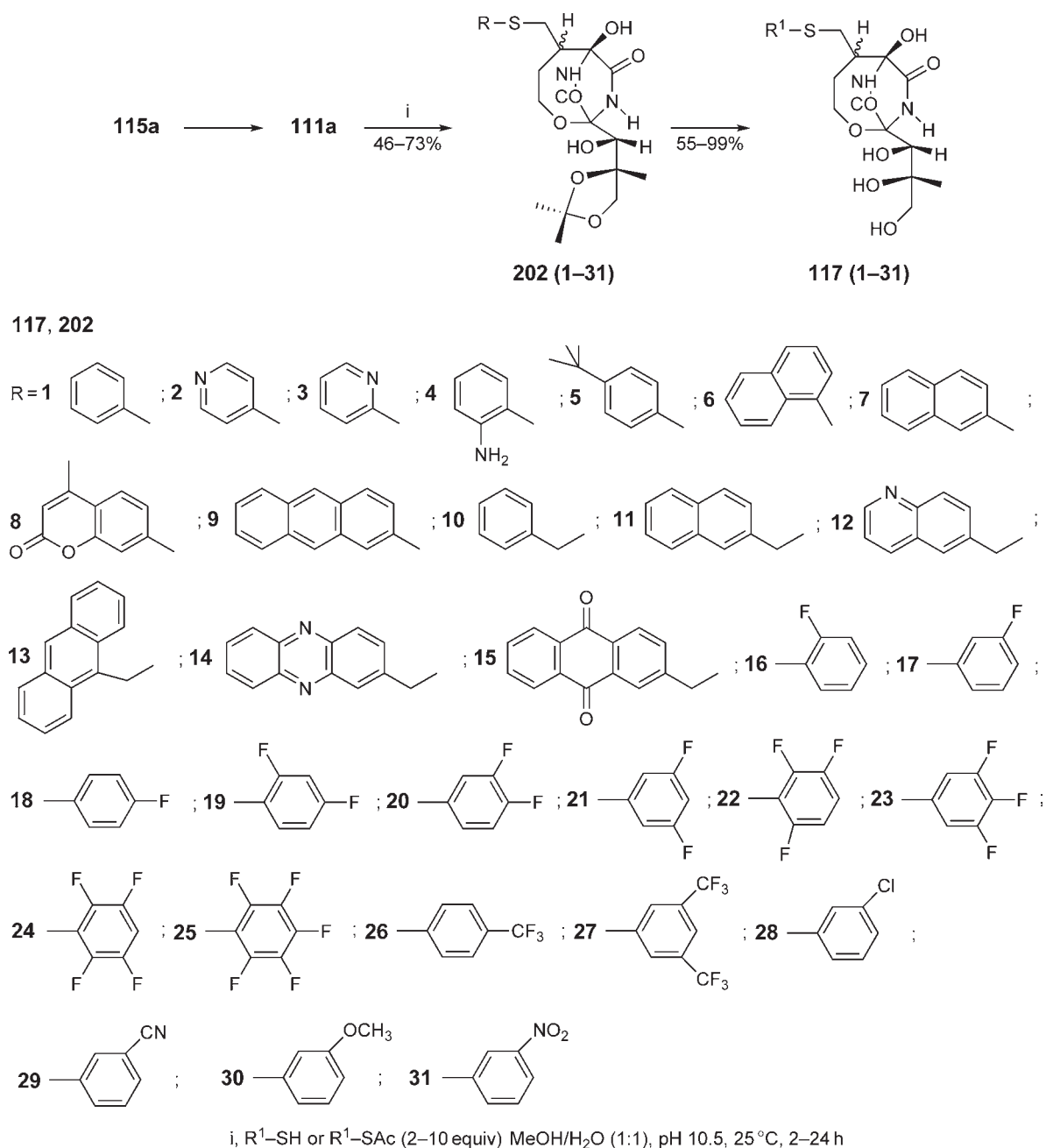
Scheme 37

The Michael addition to the C(5a) position of the acetonide of bicyclomycin **111a** was also utilized to incorporate a fluorophore moiety at the C-5a position of the lead compound. The fluorophore was linked to bicyclomycin through a sulfur atom, considering both the ease with which thiols attack the C-5a position of the bicyclomycin and the excellent biological activity showed by C-5a sulfur-substituted bicyclomycin derivatives. Thus 31 derivatives utilizing sulfides or thioacetate as nucleophiles were synthesized. Usual deprotection of the acetonide group afforded **117(1–31)** (Scheme 38) <2003JOC5575, 2006BMCI>.

Catalytic reduction of the epoxide **158a**, obtained with an improved synthesis from bicyclomycin, TFA, and Na₂WO₄, furnished **158b** as a single isomer. As already reported (Scheme 32), **183a** was obtained in nearly quantitative yield by ozonolysis of bicyclomycin followed by catalytic hydrogenation. Similarly, applying the same procedure to **111a** afforded **105a** in 96% yield. Reaction of **105a** with MsCl and *p*-TsCl in pyridine resulted in the acetonides **105b** and **105c**, respectively. Removal of the acetonide group gave the corresponding **183b** and **183c** (Scheme 39) <1996JOC7764>.

The esters **204a** and **204b** could be obtained from the bicyclomycin acetonide through the oxidation product **105a**, by reaction with 4-azidobenzoic acid or 3-formylbenzoic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to give **203a** and **203b**. Deprotection of the acetonide protecting group led to the final products **204a** and **204b** (Scheme 40) <1997JOC5432>.

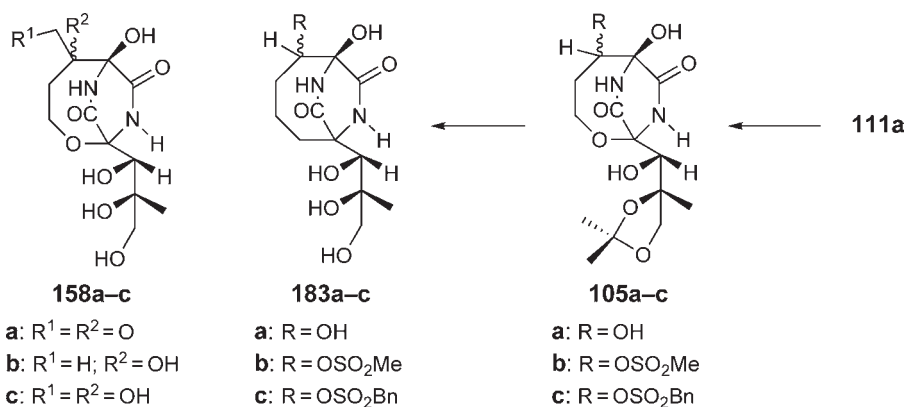
Several other removal procedures of protecting groups were reported. Thus, treatment of the acetonide **147b** (R = C(Me)₂) with 50% aqueous TFA at 23 °C gave the corresponding dihydroxyl **147c** (R = H) <2000T9885>. The *O*-6,*C*-5'-cyclothymidine **145** was obtained in 91% yield by removal of the silyl protecting group from the corresponding 3'-*O*-TBDPS derivative with tetrabutylammonium fluoride (TBAF) in THF (TBDPS = *t*-butyldiphenylsilyl) <1995TL2711>. Also deprotection from chlorotriylpolystyrene resin with 5% aqueous TFA in DCM with 1% triethylsilane, as scavenger, gave 6-benzoxazocine derivatives in moderate to high yields <2001TL6953>.



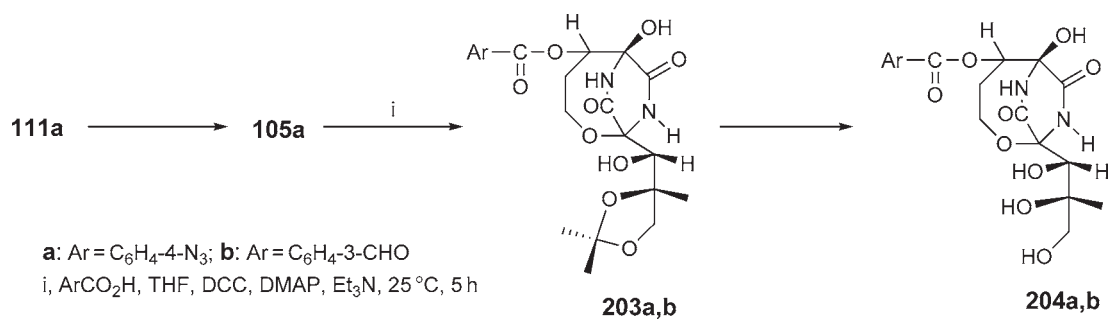
Scheme 38

Treatment of **205** with bromine and PPh₃ removed the tetrahydropyran protecting group and replaced the hydroxyl with bromine to give **126** in a single step <2005JME8182>. Reaction of **109x** with 2 mol of bromine produced **109q** as a result of the transhalogenation of the iodine and bromination at position 6 of the ring (Scheme 41) <2005EJO3724>.

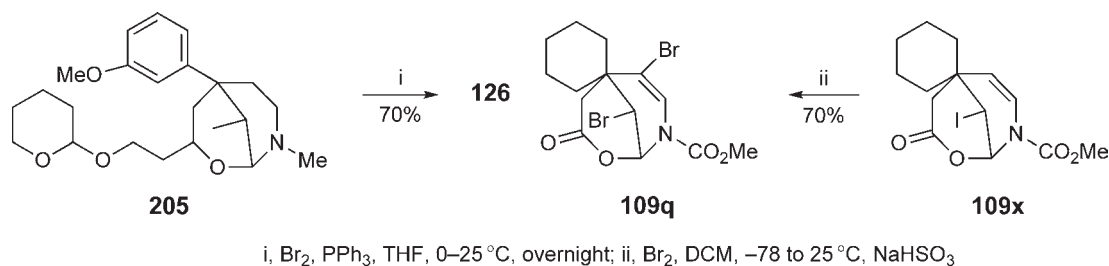
The polyhydroxy bromo-oxazocine **206** was efficiently dehalogenated with NaH₂PO₂, in 91% yield, to give the corresponding methylene-bridged oxazocine **207** (Equation 16) <2006WO126790>. Also, dehalogenation of **123b** was achieved in excellent yield (92%) with tributyltin hydride in DCM at 40 °C <1996TA721>.



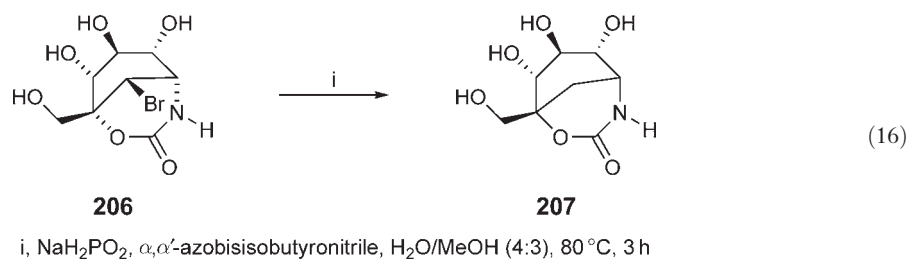
Scheme 39

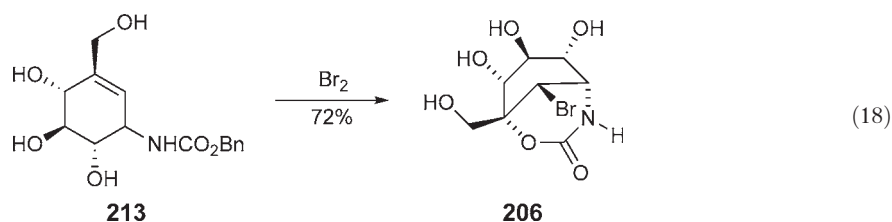


Scheme 40

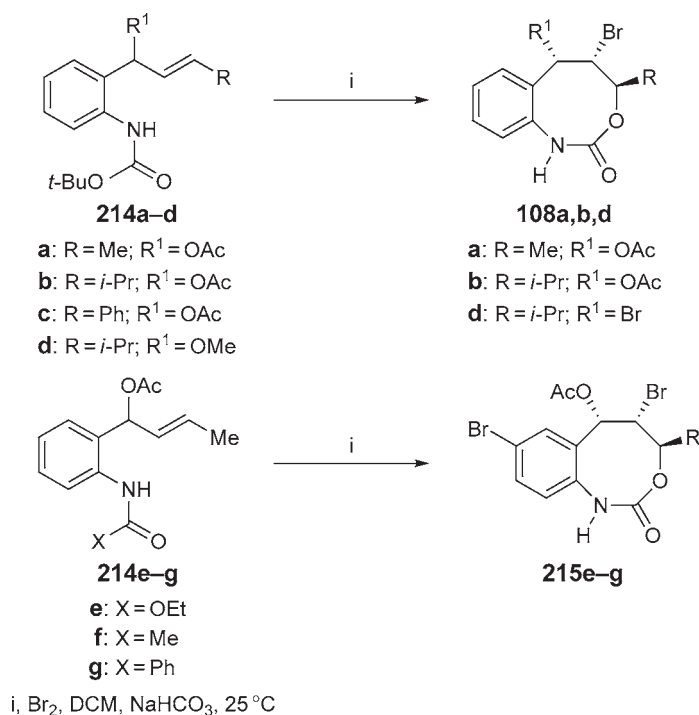


Scheme 41



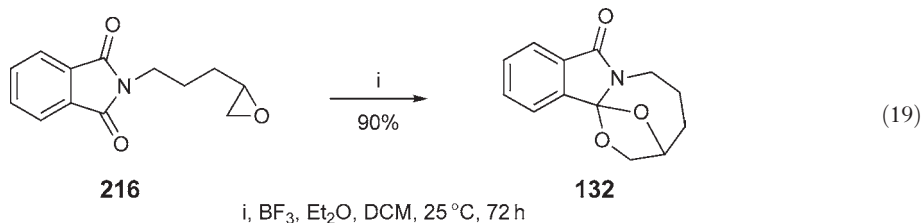


Reaction of aniline **214a** with bromine in the presence of NaHCO_3 unexpectedly gave the benzoxazocine **108a** in 78% yield through an unusual 8-*endo*-trigonal halocyclocarbamoylation, with the oxygen atom of the carbamate acting as the nucleophile instead of the nitrogen atom. No changes in the regioselectivity of the process were observed when the methyl group of the alkene moiety was replaced by an *i*-Pr group and **108b** was isolated (71%), whereas a phenyl group in the same position, **214c**, led to a mixture of several products. Replacement of the acetoxy group with a methoxy functionality gave **214d**, which furnished the benzoxazocine **108d** with no changes associated with the regiochemistry and with a bromine group replacing the methoxy moiety. The nature of the nitrogen protecting group did not affect the process. Thus, **214e–g** gave benzoxazocine **215e–g** bearing a bromine atom in *para* with respect to the nitrogen atom (Scheme 43) <2002TL8025>.

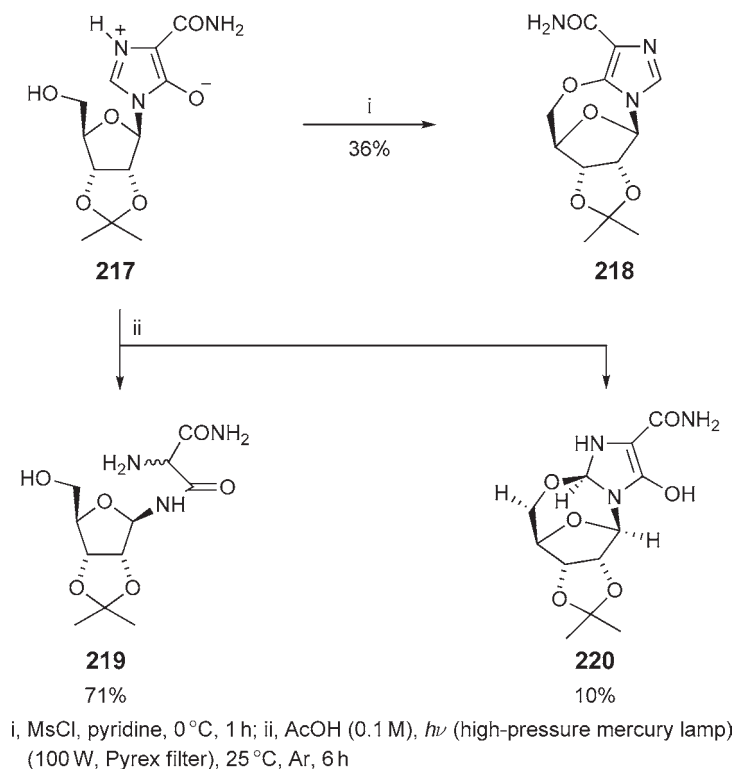


Scheme 43

The epoxide **216**, having a carbonyl functional group, was chemoselectively isomerized to the oxazocine **132** via Lewis acid-promoted 1,7-intramolecular nucleophilic attack of the carbonyl oxygen on the electron-deficient carbon that neighbors the oxonium oxygen (Equation 19) <2002T7049>.

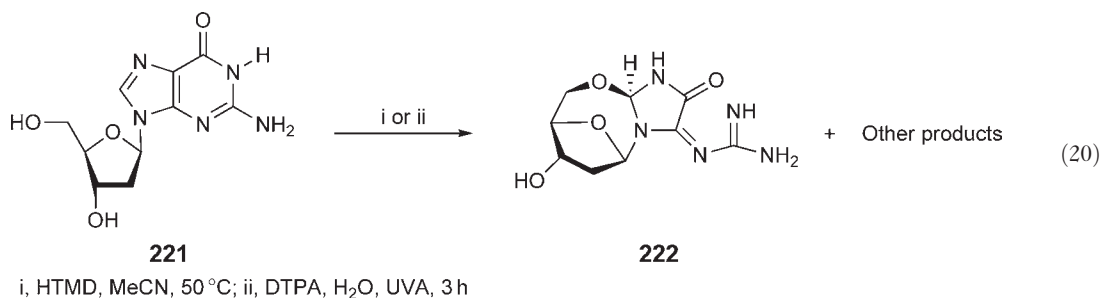


Irradiation of 2',3'-*O*-isopropylidenebredinin **217** furnished **219**, upon imidazole ring cleavage, as the major product and the by-product imidazo-oxazocine **220** as a result of the addition of the 5'-hydroxy group at the 2-position of the imidazole ring <1996TL187, 2000J(P1)3603>. When an electron-withdrawing group was introduced at the 5'-position, intramolecular attack by the 5-oxygen of the imidazole moiety occurred. Thus, under usual mesylation conditions, **217** gave imidazo-oxazocine **218**, as major product (Scheme 44) <2000J(P1)3603>.



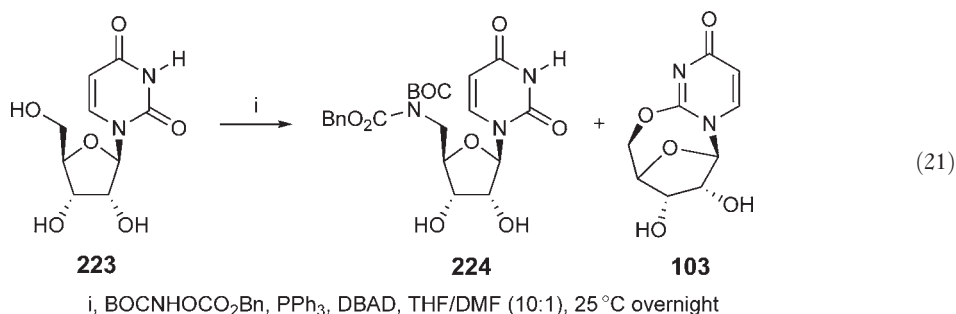
Scheme 44

Photosensitized oxidation of 2'-deoxyguanosine **221**, upon treatment with 3-(hydroxymethyl)-3,4,4-trimethyl-1,2-dioxetane (HTMD), gave the imidazo-oxazocine **222** as a mixture of the (4*R*)- and (4*S*)-diastereomers together with three other products <1997JA719>. Irradiation of an aerated solution of **221** in the presence of decarboxytiaprofenic acid (DTPA), as the sensitizer, resulted in a progressive photodegradation of the purine base to give **222** and three other products that were different from those obtained from the HTMD-promoted photooxidation (Equation 20) <2000MI449>.

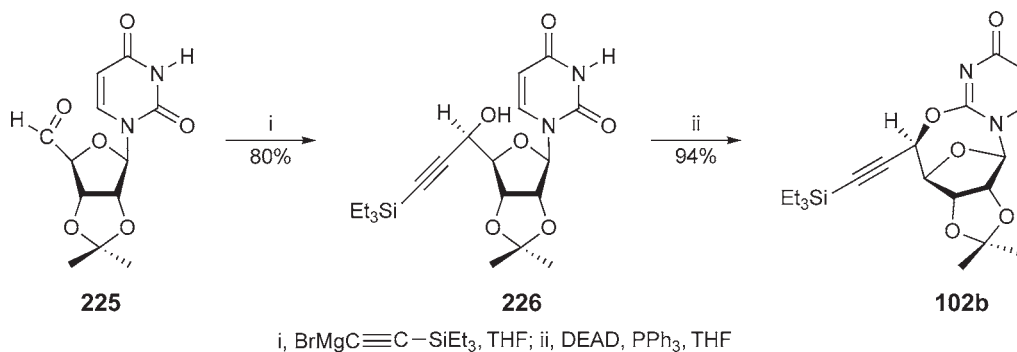


Treatment of uridine **223** with *N*-BOC-*O*-(benzyloxycarbonyl)hydroxylamine, PPh₃, and di-*t*-butyl azodicarboxylate (DBAD) in a mixture of 10:1 THF/DMF gave the pyrimido-oxazocine **103** as the major product (58%) together

with **224** obtained in 32% yield. When THF was used as the solvent, the major product was **224** (60%), and the anhydrouridine **103** was obtained in 33% yield (Equation 21) <1999JOC9289>.

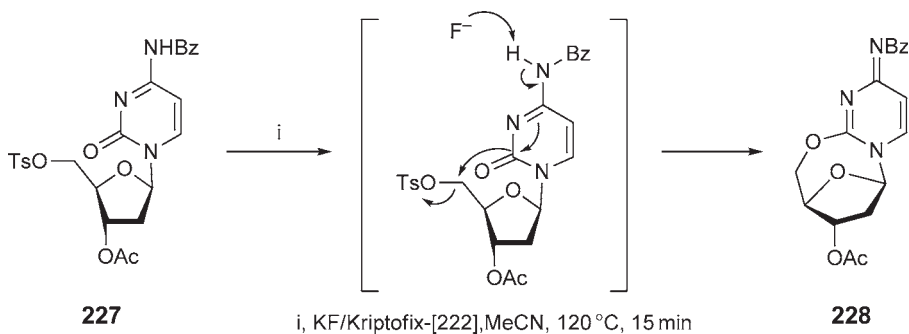


Addition of Et₃SiC≡CMgBr to the aldehyde **225** gave a 1:2 mixture of **226**, which were easily separated. The two isomers separately reacted with PPh₃ and diethyl azodicarboxylate (DEAD) to give the pyrimido-oxazocine **102b** (*D-allo*-isomer) and its *L-talo*-isomer in excellent yields (Scheme 45) <2000HCA1311>.



Scheme 45

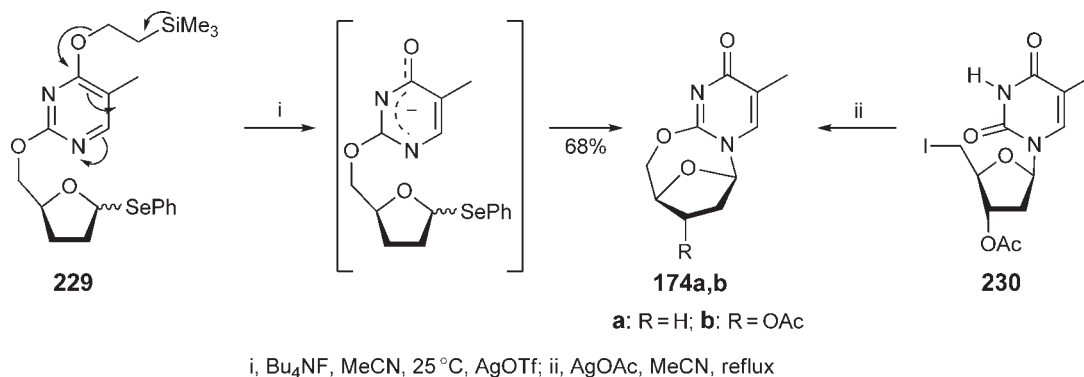
The 5'-*O*-tosyl derivative of cytidine **227**, upon reaction with KF and an azocrown ether, gave, unexpectedly, instead of the nucleophilic substitution product, the oxazocine **228** via nucleophilic attack by the 2-carbonyl oxygen initiated by proton abstraction from N-4 by fluoride (Scheme 46) <1998BML1317>.



Scheme 46

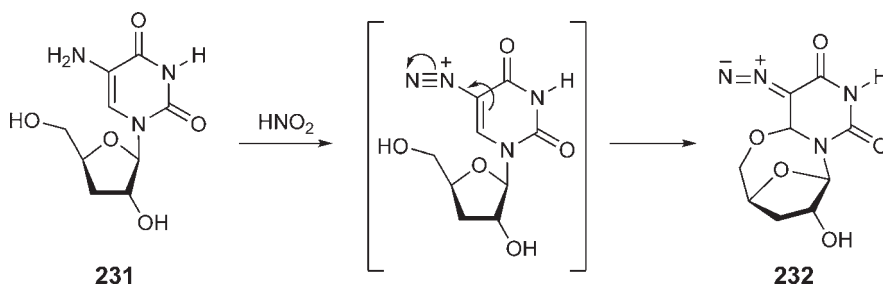
Pyrimido-oxazocines **174** could be obtained both by nucleophilic attack of the N-1 nitrogen of the pyrimidine at the C-1' position of the THF nucleus and by annelation of the oxygen at the 2-position of the pyrimidine moiety onto

the C-5' of the THF ring. Thus, treatment of **229** with Bu_4NF afforded **174a** in good yield <1998TL1807>. Nucleophilic replacement of the C-5' iodine by the 2-carbonyl oxygen of **230** afforded **174b** (Scheme 47) <2003WO18599>.



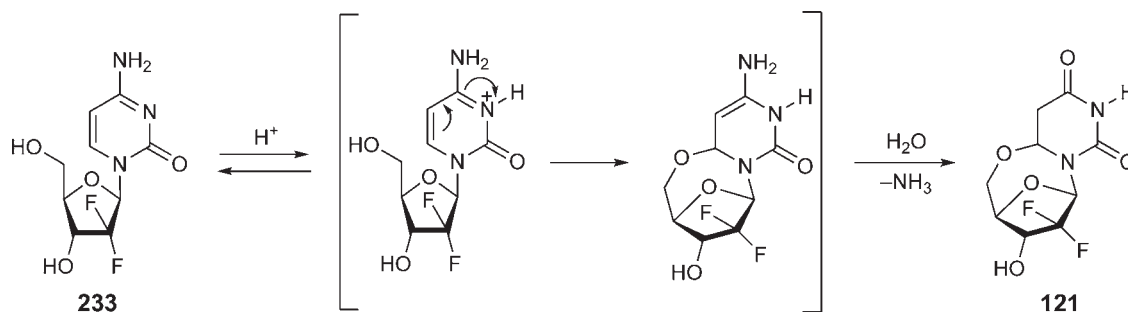
Scheme 47

Diazotization of 5-amino-3'-deoxyuridine **231** gave the 5-diazopyrimidooxazocine **232** through a nucleophilic attack of the C-5' oxygen on the electron-deficient C-4 carbon (Scheme 48) <2002WO32920>.



Scheme 48

Analogous nucleophilic attack by a C-5' hydroxyl group at the 6-position of the pyrimidine ring led to oxazocine **121** by the decomposition in an aqueous solution at pH 3.2 of the antitumor drug gemcitabine **233** (Scheme 49) <2000JPS885>.



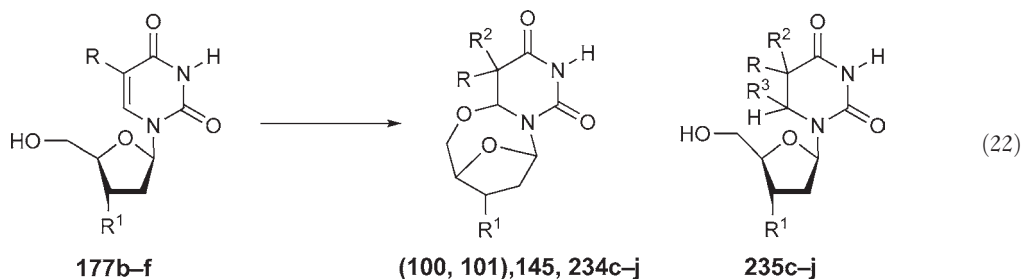
Scheme 49

The halogenation of thymidine **177b** and related **177c–f** allows the isolation of the pyrimido-oxazocines **100/101**, **145**, and **234c–j**. On some occasions, as a result of the addition to the C-5,C-6-double bond of the halogen and the conjugated base of the acid or the solvent present, compounds **235** were also isolated. Table 1 shows the halogenating agents and the products isolated (Equation 22) <1995TL2711, 2002WO094844>.

Table 1 Synthesis of pyrimido-oxazocines **100**, **101**, **145**, **234c–j**, and **235c–j**

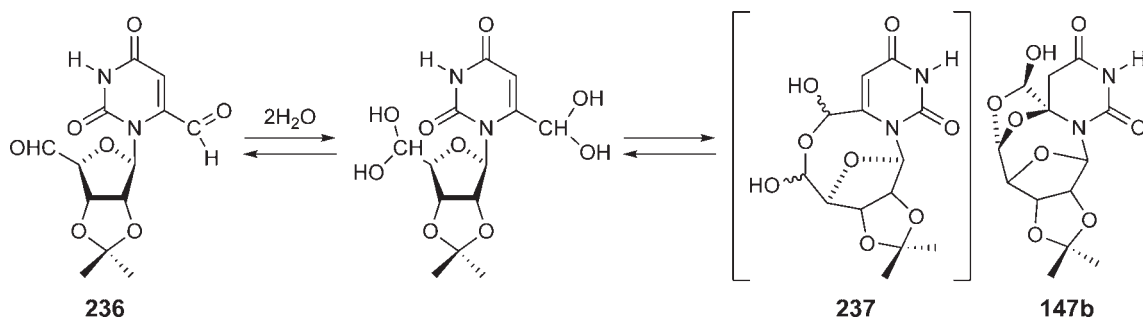
Substrate	Reagent	Products (yield, %)		Reference
		100, 101, 145, 234	235	
177b R = Me; R ¹ = OH	NBS/DMF	145 (62)		1995TL2711
	Cat. TFA	R ² = Br		
177c R = Me; R ¹ = N ₃	NBS/DMF/TFA	100 (5 <i>S</i> ,6 <i>S</i>) (26)		2002WO094844
		101 (5 <i>R</i> ,6 <i>R</i>) (40)		
		R ² = Br		
177c R = Me; R ¹ = N ₃	Br ₂ /dioxane/NaOAc	100 (5 <i>S</i> ,6 <i>S</i>) (25)	235c	2002WO094844
		R ² = Br	R ³ = OAc (nr)	
			Two diastereomers	
177c R = Me; R ¹ = N ₃	NIS/DMF/TFA	234c (5 <i>S</i> ,6 <i>S</i>) (25)		2002WO094844
		234c (5 <i>R</i> , 6 <i>R</i>) (10)		
		R ² = I		
177c R = Me; R ¹ = N ₃	NFTH/MeCN/AcOH	234d (5 <i>R</i> ,6 <i>S</i>) (35)	235d (n.r.)	2002WO094844
		234d (5 <i>R</i> , 6 <i>R</i>) (18)	R ³ = OAc	
		R ² = F	Three diastereomers	
177d R = Me; R ¹ = F	NFTH/MeCN/AcOH	234e (5 <i>R</i> ,6 <i>S</i>) (40)	235e (n.r.)	2002WO094844
		234e (5 <i>R</i> , 6 <i>R</i>) (24)	R ³ = OAc	
		234e (5 <i>S</i> ,6 <i>R</i>) (5)	Two diastereomers	
		R ² = F		
177e R = H; R ¹ = F	NFTH/MeCN/EtOH	234f (5 <i>S</i> ,6 <i>R</i>) (15)	235f (n.r.)	2002WO094844
		234f (5 <i>R</i> ,6 <i>S</i>) (4)	R ³ = OEt	
		R ² = F	Four diastereomers	
177e R = H; R ¹ = F	NBS/CHCl ₃ /AcOH	234g (n.r.)		2002WO094844
		Two diastereomers		
		R ² = Br		
177e R = H; R ¹ = F	NBS excess	234h (6 <i>S</i>) (16)		2002WO094844
	DMF/AcOH	R = R ² = Br		
177e R = H; R ¹ = F	NFTH/MeOH	234i (nr)	235i (n.r.)	2002WO094844
		Two diastereomers	Three diastereomers	
		R ² = F	R ³ = OMe	
177f R = Cl; R ¹ = F	Cl ₂ /AcOH	234j (6 <i>S</i>) (30)	235j (n.r.)	2002WO094844
		R = R ² = Cl	R ³ = OAc	

n.r. = not reported.

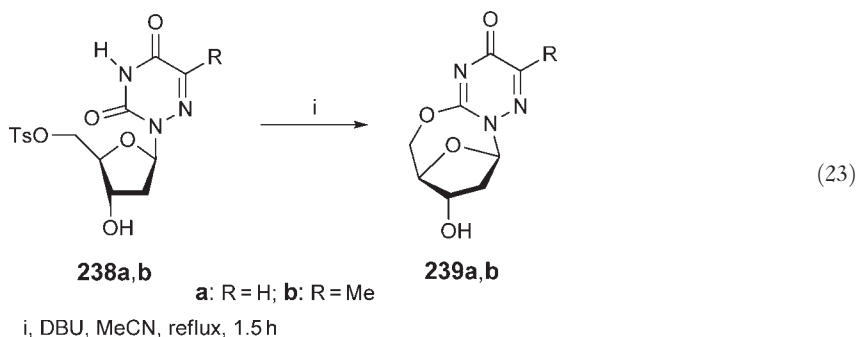


The dialdehyde **236**, dissolved in water, immediately and exclusively formed a dihydrate, which gave the spiro-fused oxazocine **147b** in a moderately facile transformation ($t_{1/2} \sim 2$ h at 23 °C) that likely proceeded through the bridged hydrate **237** as a transient intermediate (Scheme 50) <2000T9885>.

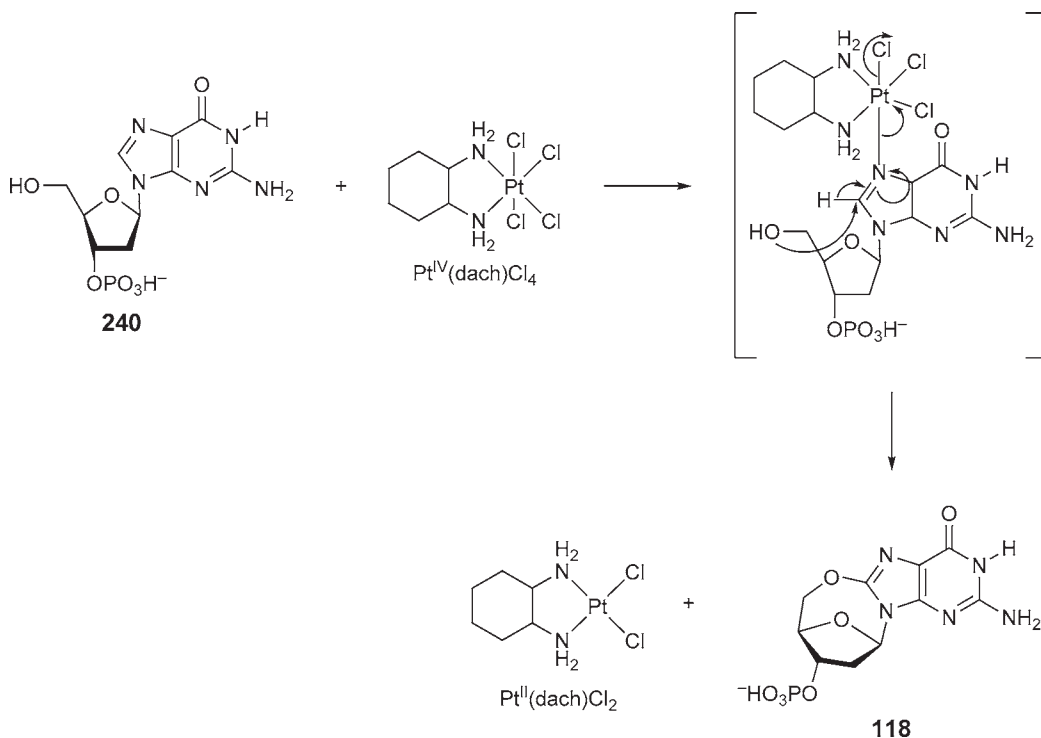
The tosyl derivatives of the azadeoxyisocytidine, **238a** and **238b**, underwent DBU-promoted nucleophilic substitution by the C-3 carbonyl oxygen of the triazine ring at the C-5' carbon to give the triazine-fused oxazocines **239a** and **239b** in 47–50% yield (Equation 23) <2003JOC367>.



Scheme 50

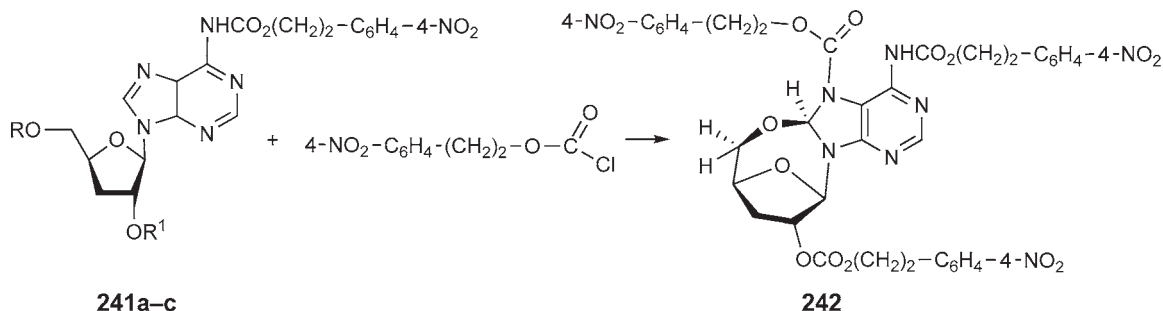


The purine-fused oxazocine **118** was obtained by oxidation of 2'-deoxyguanosine 3'-monophosphate **240** with $\text{Pt}^{\text{IV}}\text{Cl}_4(\text{dach})$. The reaction went through the initial loss of Cl^- from $\text{Pt}^{\text{IV}}\text{Cl}_4(\text{dach})$ followed by binding to **240**. The second step involved nucleophilic attack at C-8 by the C-5' hydroxyl group and an inner-sphere $2e^-$ transfer from **240** to $\text{Pt}(\text{IV})$ to produce **118** and $\text{Pt}^{\text{II}}(\text{dach})\text{Cl}_2$ (Scheme 51) <2005JA1773>. The same ring system **118**, with a hydroxyl group at position 3' was obtained upon decomposition of 7-amino-2'-deoxyguanosine in DMF <1999CRT906>.



Scheme 51

The purine-fused oxazocine **242** was unexpectedly obtained, although in very poor yield (6%), from the direct acylation of **241a** with 2-(4-nitrophenyl)ethyl chloroformate. The other reaction products were **241b** (73%) and **241c** (11%) (Equation 24) <1996HCA426>. Another purine-fused oxazocine was obtained in very poor overall yield (4%) from adenosine in five steps <2005JNP1689>.



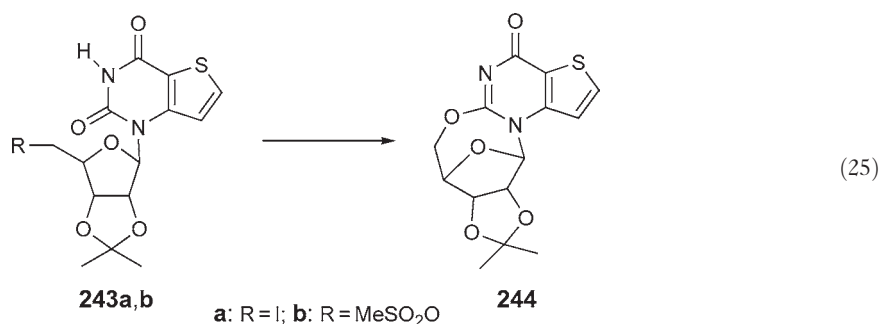
a: R = R¹ = H

b: R = CO₂(CH₂)₂C₆H₄-4-NO₂; R¹ = H

c: R = R¹ = CO₂(CH₂)₂C₆H₄-4-NO₂

(24)

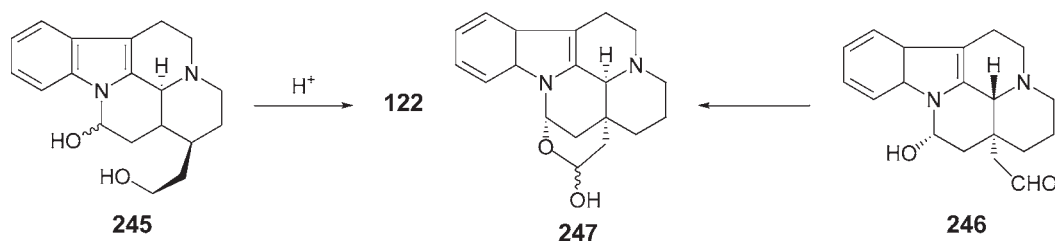
The thienopyrimidine-fused oxazocine **244** was obtained in 19% yield, by nucleophilic attack of the C-2 carbonyl oxygen promoted by *t*-butoxide on the C-5' carbon of **243a** with replacement of iodide in DMSO. A more convenient route to **244** was provided by the reaction of the mesyl derivative **234b** with DBU in MeCN (50% yield) (Equation 25) <1995JHC627>.



(25)

Among the unimolecular reactions leading to oxazocines, it is necessary to mention two reactions that were described in Section 14.05.3.4 (Schemes 25 and 26) which were actually shown to be reversible. Thus, **139**, obtained under acid condition from **138**, in CHCl₃ and NEt₃ at 48 °C for 5 h gave the oxazocine **138** in 92% yield <2004NN117>. Similarly, **141** in CHCl₃ and NEt₃ at 48 °C for 22 h or in DMF and DBU at 65 °C for 30 min gave the oxazocine **140** <2003NN735>.

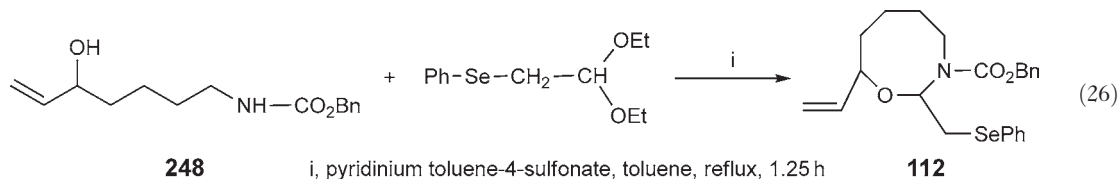
The alkaloid isolarutensine **122** was obtained in 69% yield by acid-induced cyclization of the diol **245** <1998H(48)249>. The aldehyde **246** readily cyclized to the polycondensed oxazocine **247** upon chromatography in silica gel. Attempts to purify **247** failed and its identity was confirmed by NaBH₄ reduction to give a diastereomer of **245** (83% yield) (Scheme 52) <2005HCA2764>.



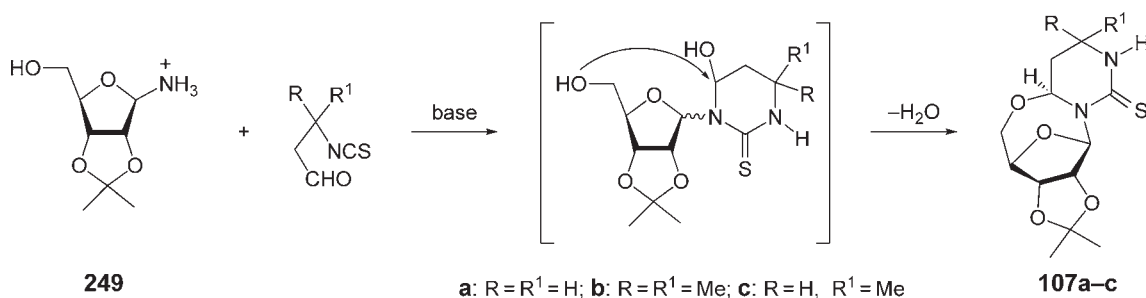
Scheme 52

14.05.3.7.3 Ring syntheses from C₅NO + C units

The unbridged and uncondensed oxazocine **112** was obtained as mixture of diastereomers, in 58% yield, upon refluxing the amino alcohol **248** with phenylselanylacetaldehyde diethyl acetal and a catalytic amount of pyridinium toluene-4-sulfonate (Equation 26) <1995J(P1)123>.



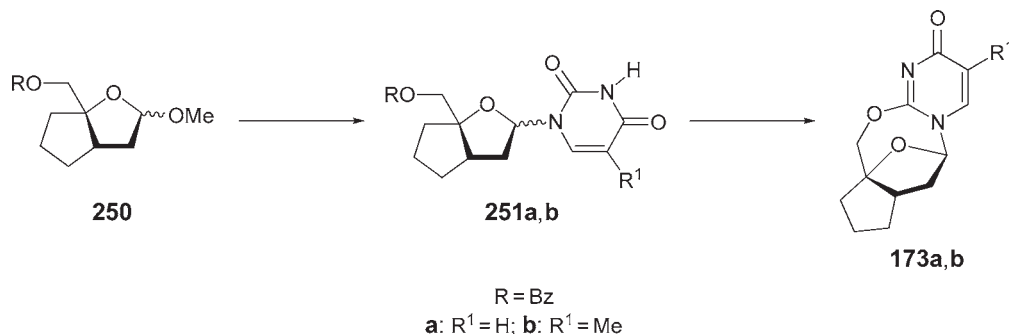
Reaction of 2,3-*O*-isopropylidene- β -ribofuranosylammonium ion **249** with β -isothiocyantoaldehydes in the presence of NEt₃ led to the pyrimido-fused oxazocines **107a–c** in 66–79% isolated yields. The formation of **107a–c** was the result of a spontaneous intramolecular nucleophilic replacement of the hydroxyl group at the pyrimidine ring in β -anomers of the intermediates 4-hydroxy-3-(β -ribofuranosyl) hexahydropyrimidine-2-thiones (Scheme 53) <1998MI1>.



Scheme 53

14.05.3.7.4 Ring syntheses from C₅O + CN units

Reaction of methyl furanoside **250** with bis(trimethylsilyl)thymine and bis(trimethylsilyl)uracil gave **251a** and **251b** in 93% and 96% yield, respectively. The α/β -ratio was 1:2.8 for **251a** and 1:1.2 for **251b**. Deprotection of the benzoyl group with methoxide in MeOH led to **251a** and **251b** (R = H) in 92–98% yields. Conversion of the primary hydroxyl group to the corresponding tosylate by using *p*-TsCl in pyridine and successive refluxing in MeCN in the presence of DBU led to the pyrimidine-fused oxazocines **173a** and **173b** in 43–52% yields (Scheme 54) <1995BMC397>.

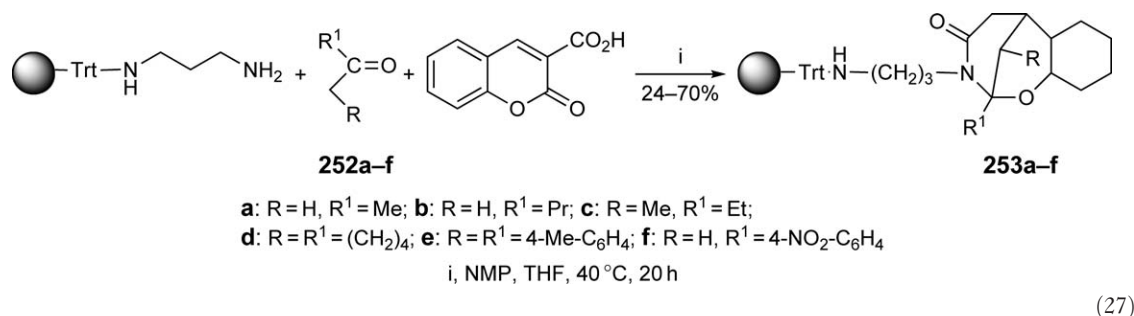


Scheme 54

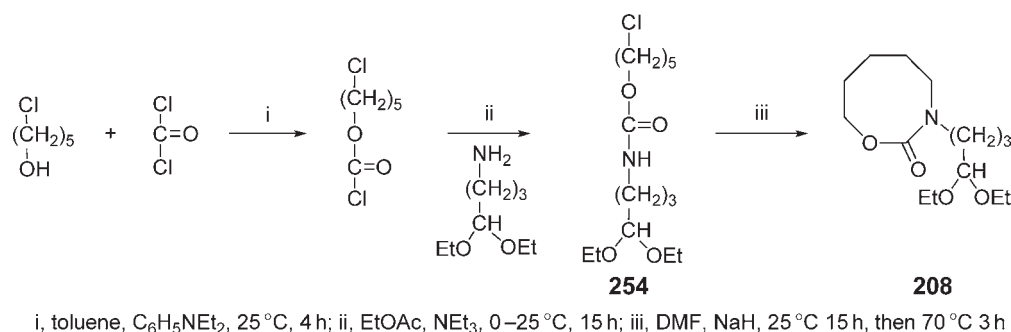
14.05.3.7.5 Ring syntheses from C₅O + C + N units

The synthesis of benzoxazocines **253a–f** was performed by a solid-phase synthesis approach with a three-component reaction. Thus, 1,3-propylenediamine was attached onto a chlorotrityl polystyrene resin and condensed with aliphatic

or aromatic ketones **252a–f** and coumarin-3-carboxylic acid. A large excess of ketones and coumarin-3-carboxylic acid was crucial to get good yields (Equation 27) <2001TL6953>.



The diazocinone **208** was obtained in 18% overall yield starting from 5-chloropentan-1-ol, which reacted with phosgene in the presence of diethylaniline to give the 5-chloropentyl chloroformate. The latter reacted with 4-aminobutanal diethylacetal to give the intermediate **254**, which upon treatment with NaH cyclized to the final eight-membered ring (Scheme 55) <2001WO90081, 2001WO90082>.

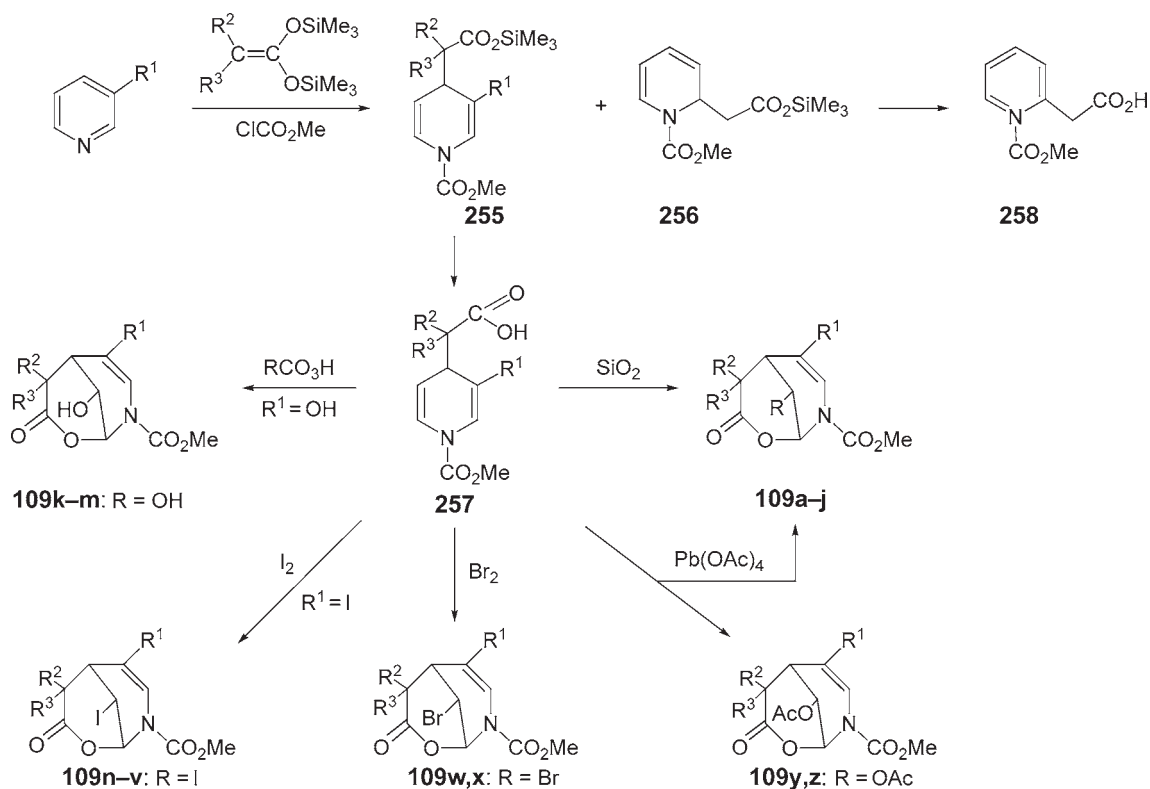


Scheme 55

14.05.3.7.6 Ring syntheses from C₄N + C₂O units

When methyl chloroformate was added to a solution of pyridine (R¹ = H) and bis(trimethylsilyl)ketene acetal (R² = R³ = H) in DCM at 25 °C, the formation of the acid **257** (R² = R³ = H) as major product (48%) and the acid **258** (20%), both as a 1:1 mixture of two rotamers, was observed via trimethylsilyl esters **255** and **256**, which were detected by NMR prior to hydrolysis. The use of substituted bis(trimethylsilyl)ketene acetals and pyridine or 3-substituted pyridines gave exclusively the acid **257**, as a 1:1 mixture of two rotamers. These were shown to be versatile intermediates for the synthesis of numerous bridged oxazocines **109**, upon reaction with reagents capable of reacting with the double bond of the dihydropyridine, and create an electrophilic center at the C-2 of the heterocycle, keen to undergo nucleophilic attack by the carboxylate oxygen. Thus, acids **257** in silica gave the oxazocines **109a–j**, which could be obtained directly and in higher yields when the reaction of pyridine with bis(trimethylsilyl)ketene acetals was conducted in the presence of silica gel. The yields of the reactions were dependent on the nature of the substituents on the ketene acetals (R² and R³): the bulkier the substituents, the better the yields. Reaction of **257** with (4-chloro-2-methylphenoxy)acetic acid (MCPA) gave **109k–m** likely through the intermediacy of C-2,C-3-epoxide, which, upon attack of the carboxylate oxygen, gave the hydroxyl methyne-bridged oxazocines **109k–m**. Iodination of **257** or addition of iodine to the reaction of pyridines with ketene acetals led to **109n–v**. Analogously, bromination of **257** led to **109w**. Similar reactions in which a halogenation brought about an intramolecular cyclization were described in Section 14.05.3.7.2 in Schemes 42 and 43, and Equation 18. Reaction of **257** (R¹ = H, R²–R³ = –(CH₂)₅–) with Pb(OAc)₄ gave, although in very low yield, **109y** and **109e**.

Reaction of the 3-benzoylpyridine-derived acid gave instead only **109z** (Scheme 56) <2002CC940, 2005EJO3724>. Table 2 shows the derivatives synthesized through this reaction as well as isolated yields, which are sometimes much lower than those observed in the crude product due to the low stability of compounds. In



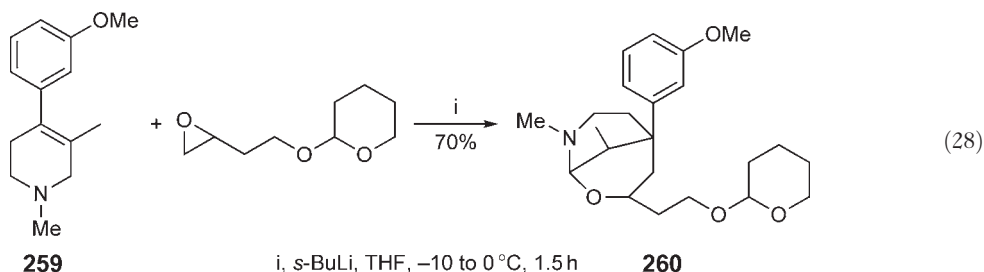
Scheme 56

Table 2 Oxazocines **109** synthesized from pyridines, bis(trimethylsilyl)ketene acetals, and methyl chloroformates
 <2002CC940, 2005EJO3724>

Compound 109	R	R ¹	R ²	R ³	Yield (%)
a	H	H	H	H	15
b	H	H	Me	Me	40
c	H	H	-(CH ₂) ₅ -	Me	45
d	H	H	H	<i>i</i> -Pr	25
e	H	H	H	-(CH ₂) ₂ -CH=CH ₂	32
f	H	H	H	-(CH ₂) ₃ -CH=CH ₂	49
g	H	H	H	H	48
h	H	Me	H	H	16
i	H	Me	Me	Me	50
j	H	Ph	Me	Me	80
k	OH	H	Me	Me	75
l	OH	COPh	Me	Me	50
m	OH	COPh	-(CH ₂) ₅ -	Me	35
n	I	H	H	H	50
o	I	H	H	Me	10
p	I	H	Me	Me	60
q	I	H	-(CH ₂) ₅ -	Me	90
r	I	H	H	-(CH ₂) ₂ -CH=CH ₂	82
s	I	H	H	-(CH ₂) ₃ -CH=CH ₂	50
t	I	H	H	Ph	73
u	I	CO ₂ Me	Me	Me	5
v	I	Br	Me	Me	32
w	Br	H	-(CH ₂) ₅ -	Me	40
x	Br	Br	-(CH ₂) ₅ -	Me	70
y	OAc	H	-(CH ₂) ₅ -	Me	14
z	OAc	COPh	-(CH ₂) ₅ -	Me	14

addition to the reported derivatives, two more derivatives starting from 2-substituted pyridines and two derivatives starting from 4-substituted pyridine were also obtained. Moreover, this synthetic method also starting from quinolines gave the related benzo-fused ring system **110**.

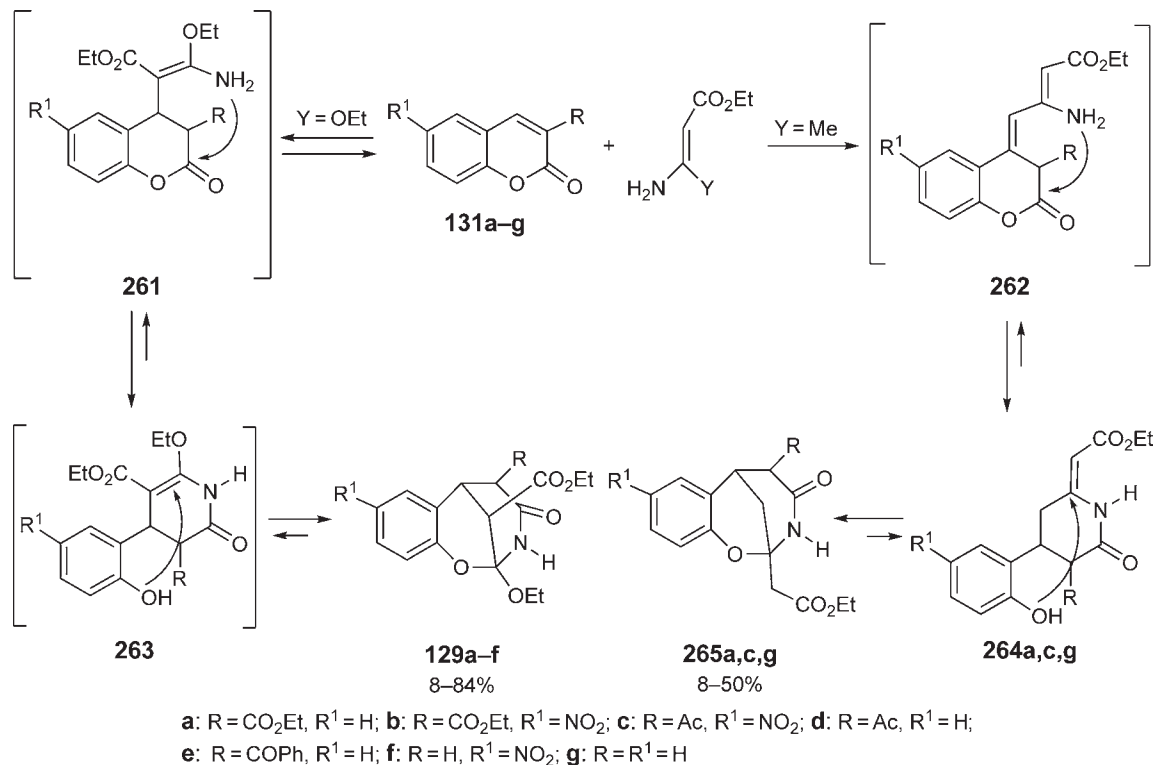
Deprotonation of the tetrahydropyridine **259** with *s*-butyllithium provided the metalated enamine which reacted with tetrahydro-(2-oxiranylethoxy)-2*H*-pyran to give the bridged oxazocine **260** in good yield (Equation 28) <2005JME8182>.



14.05.3.7.7 Ring syntheses from $\text{C}_4\text{O} + \text{C}_2\text{N}$ units

The bridged benzoxazocines **129** and **265** were obtained from the reaction of coumarins **131a–g** with enaminoesters. Thus, 3-amino-3-ethoxypropenoate reacted with its α -carbon to give initially the adduct **261**, whereas the amino-crotonate adds the γ -carbon to give the intermediate **262**. Both adducts, thermodynamically unstable, underwent spontaneous intramolecular rearrangement through an ANRORC mechanism (addition of nucleophile, ring opening, and ring closure) to form the pyridones **263** and **264**, of which **264g** was isolable.

Both **263** and **264**, via further intramolecular Michael addition of the phenolic hydroxyl group to the conjugated double bond, cyclized to the stable final compounds **129a–f** and **265a,c,g**. These processes were fully reversible, since it was observed in their EI mass spectra the presence of peaks with m/z equal to the molecular mass of the starting coumarins and **129a** could be converted into the starting coumarin by refluxing in anhydrous MeCN in *p*-TsOH or TFA (see Section 14.05.3.4) (Scheme 57) <2004SL1584>.



Scheme 57

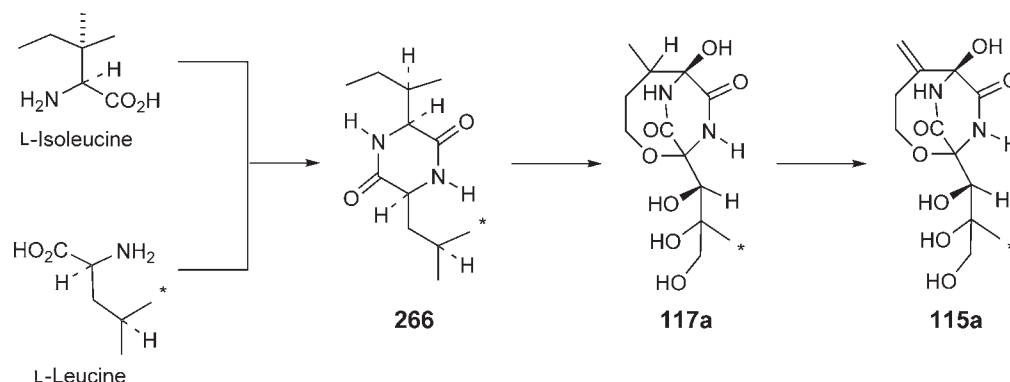
14.05.3.7.8 Ring syntheses from $C_3O + C_3 + N$ units

The only synthesis to be reported in this section has no preparative interest and involves the reaction of malonaldehyde with 2'-deoxyadenosine on a small scale. Such a reaction was monitored by high-performance liquid chromatography (HPLC) and led to 9-(β -D-ribofuranosyl)-6-(5,7-diformyl-2*H*-3,6-dihydro-2,6-methano-1,3-oxazocin-3-yl)purine, which, on the other hand, was a known compound <2005MI637>.

14.05.3.8 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Unimolecular cyclizations were the most popular synthetic routes to get 1,3-oxazocines. The most efficient process appeared to be the intramolecular cyclization of carbamoyl esters (*t*-butoxycarbonyl or benzyloxycarbonyl) bound to a cyclic or acyclic alkene moiety, which, upon halogenation of the double bond, created a positive charge on the carbon that lost the π -bond and underwent cyclization by immediate nucleophilic attack by the carboxylate oxygen. The yields are generally good. Another important class of unimolecular cyclization involved the preparation of pyrimidine- or purine-fused 1,3-oxazocines, both also called either cyclonucleosides or anhydronucleosides, since they are formed by loss of a molecule of water from the 'conventional' nucleosides. The method is of general application, the yields are variable, and the results are obtained when there is an electron-withdrawing group at the C-5' carbon or when a positive charge is created at the carbon adjacent to the purine or pyrimidine nitrogen. Another synthesis of wide application is that involving the reaction of pyridines with methyl chloroformate and silylketene acetals, which originated the intermediates tetrahydropyridine carbamoyl esters that are capable of cyclization, upon suitable activation, as already pointed out. The method gave good yields although the purification procedure sometimes dramatically reduced the yield. Last but not least, it is necessary to mention the syntheses of the numerous analogues of the bicyclomycin, generally obtained in good yields, whose syntheses were treated in Section 14.05.3.5, since they were prepared by modifications of the lead compound or its dihydro derivative. Below is reported the biosynthesis of the antibiotic bicyclomycin.

In fact, bicyclomycin **115a** was biosynthesized in *Streptomyces saprorenensis* from L-leucine and L-isoleucine via the naturally occurring piperazine dione **266** and dihydrobicyclomycin **117a**. The mode of incorporation of (2*S*,4*R*)-[5,5,5- $^2H_3$]leucine into **115a** (and **117a**) showed that the entry of the hydroxyl group at C-2' occurs with unusual inversion of configuration. There was no *in vivo* conversion of **115a** into **117a**; therefore, **117a** was the ultimate irreversible precursor for **115a**. The biosynthesis of **115a** was inhibited by methyrapone at a concentration of 10–20 mM (Scheme 58) <1996TL6935>.



Scheme 58

14.05.3.9 Important Compounds and Applications

Bicyclomycin is certainly the most important compound to be cited in this section. Because of its broad spectrum of activity displayed against Gram-negative bacteria (such as *Escherichia coli*, *Klebsiella*, *Salmonella*, *Shigella*, and *Citrobacter*), coupled with its low toxicity, bicyclomycin was introduced into the market under the trade name Bicozamycin. The mode of action of bicyclomycin was studied in the 1980s and early 1990s, and only information concerning its locus of action in *E. coli*, that is, the rho transcription termination factor (rho is a protein responsible for termination of RNA

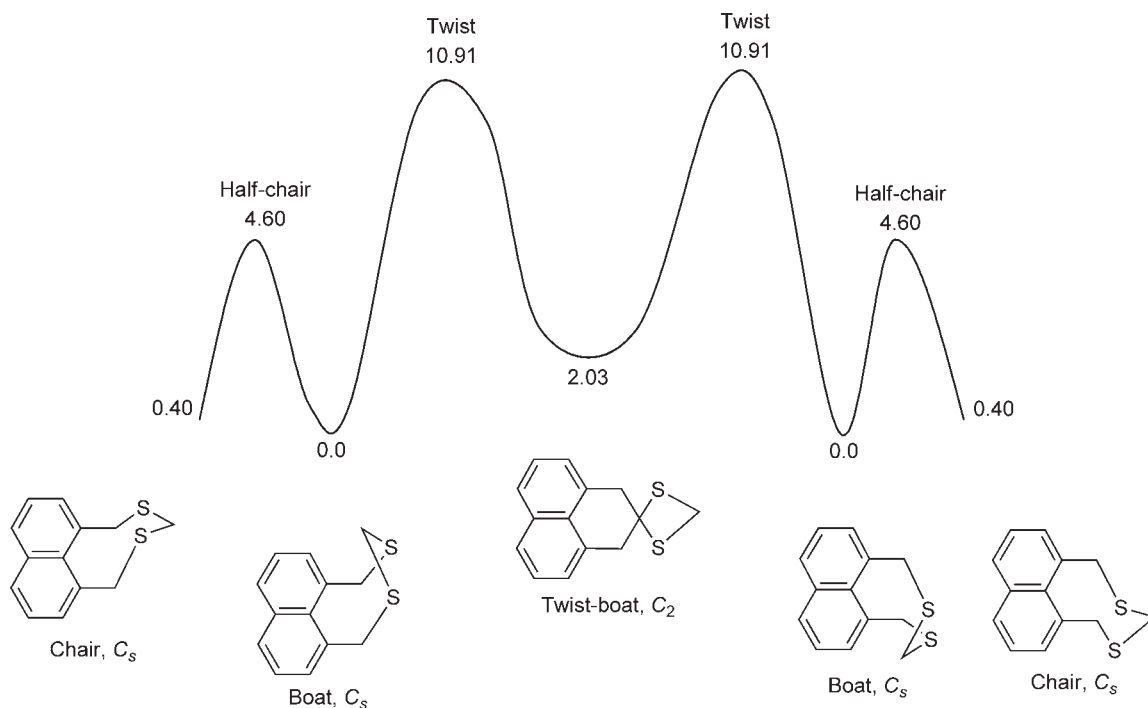
synthesis), was reported. However, those studies have neither revealed the mechanism of rho inhibition nor the site and functional domain(s) on rho where bicyclomycin binds and bonds. In the past decade, many papers appeared to disclose the mechanism of action of this antibiotic, patents dealing with specific pharmaceutical uses and both papers and patents dealing with the synthesis of numerous analogues that helped in clarifying its mode of action. Thus, it was reported that bicyclomycin also inhibited the activity of the Gram-positive bacterium *Micrococcus luteus* transcription termination factor rho <1997MI5238>. Bicyclomycin exerts its activity by binding at the interface of adjacent C-terminal domains of rho <1998JBC34033, 1999JBC7316, 2000B9077, 2003JOC5575>. Specifically, the bicyclomycin binding site has been proposed to lie adjacent to, but distinct from, the ATP site and is thought to partially overlap with the secondary RNA binding sites; in fact, it was a reversible, noncompetitive inhibitor of ATP turnover <1995MI447>. Bicyclomycin also slows rho's movement along RNA and acts as a mixed-type inhibitor for RNA binding at the secondary site <1996JBC25369>. Thus, bicyclomycin may disrupt RNA tracking directly by perturbing the secondary RNA binding sites at the same time that it interferes with rho's ATPase activity <1995MI447, 1996JBC25369, 1998AAC571>. Alternatively, the effects of bicyclomycin may arise because ATP binding and hydrolysis are allosterically coupled to RNA engagement. In the cell, bicyclomycin attenuates the ability of rho to reach and dissociate the RNA polymerase from its DNA template, yielding unnaturally long RNA transcripts <1996JBC25369>. However, bicyclomycin association displaces the catalytic water molecule required for ATP hydrolysis <2002B12377> as demonstrated by X-ray crystallographic images of the antibiotic bound to rho <2005MI99>. Although efficacious, the potency of bicyclomycin is tempered by an IC₅₀ in the low micromolar range <1995MI447, 1996JBC25369, 1999JBC7316>. In attempts to improve inhibitory activity and generate more effective antibiotics, bicyclomycin has been subjected to extensive chemical modifications <1996JOC7750, 1996JOC7756, 1996JOC7764, 1997JOC5432, 1998JBC34033, 1998JME1185, 1998JOC1290, 2000B9067, 2001JOC2251, 2003JOC5575, 2006BMC1>. To a large extent, most modifications at the triol moiety <1996JOC7750> or at the piperazinedione unit <1996JOC7756>, or the substitution of the 6-hydroxyl group with an amino, hydroxylamino, or a mercapto moiety <1998JME1185>, either partially or completely, abrogate the ability of the analogue to inhibit rho. However, selected modifications at the C(5)–C(5a) exomethylene group led to compounds with comparable or better inhibitory activity compared to the parent <1996JOC7764, 2001JOC2251>. Two derivatives in particular, C-5a-formylbicyclomycin **119a** <2000B9067> and C-5a-(3-formylphenylsulfanyl)-dihydrobicyclomycin **117-1** <2000B9077> showed a ~2–15-fold improvement in rho inhibitory activity. The use of bicyclomycin for the manufacture of medicament for treating infections with enterohemorrhagic *E. coli* was patented both in the free form <1999WO027931> and bound to carriers <2000WO61537>. It was included as active principle in veterinary oral drug delivery system <2004WO039172>. The use of bicyclomycin in aquacultures as agent to be concurrently administrated with a cysteamine compound to shellfish to improve their health, immunity, fertility, and growth was also patented <2006WO002868>.

The 2,5'-anhydro-3'-azidodeoxythymidine and 2,5'-anhydro-3'-azidodeoxyuridine were patented as anti-HIV agents <2005USP0026902> while 2,5'-anhydrodeoxyuridine binds to uridine phosphorylase from *Toxoplasma gondii* <1996BPI687>. The 8,5'-O-cycloadenosine was utilized in molecular recognition of cAMP by an RNA aptamer <2000B8983>. Derivatives of the ring system **129** were patented for treatment of migraine headaches, such as those caused by cortical spreading depression <1995WO06468>. The alkaloid **211** inhibited the electrical induced contraction of guinea pig ileum <2002CME1>.

14.05.4 Rings with One Nitrogen and One Sulfur (2H-1,3-Thiazocines) or with Two Sulfurs (4H-1,3-Dithiocins)

14.05.4.1 Theoretical Methods

The conformational properties of the naphthalene-fused dithiocin **267a** were studied by the modified neglect of diatomic overlap (MNDO) semi-empirical self-consistent field (SCF) molecular orbital (MO) method. The most stable conformation was the plane-symmetrical boat. The chair conformation, which has C_s symmetry, was calculated to 0.4 kcal mol⁻¹ less stable than boat conformation. Both were separated by a low-energy barrier (2.03 kcal mol⁻¹). The twist-boat conformation is 3.6 kcal mol⁻¹ higher than the boat conformation. The barrier for chair-to-chair ring inversion in this compound was 10.91 kcal mol⁻¹ (Scheme 59) <1999JST67>. To determine the structure of the minor conformer of **267e**, PM3 calculations were utilized to get the heats of formation of the boat and chair conformers with equatorial and axial orientation of the sulfinyl oxygen atom. The values, which are (kJ mol⁻¹) 27.17 (B-eq), 29.16 (B-ax), 28.80 (C-eq), and 32.36 (C-ax), did not permit to distinguish between C-eq and B-ax but allowed to exclude C-ax <2005RJO1089>.



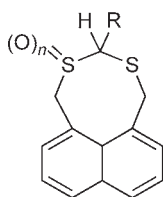
Scheme 59

14.05.4.2 Experimental Structural Methods

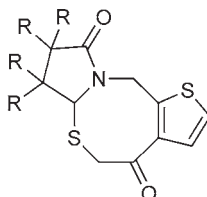
Neither detailed X-ray crystallographic studies nor the mere report of ORTEP representation of both 1,3-thiazocines and dithiocins were observed in the past decade.

NMR data, instead, were provided for all the 1,3-thiazocines and dithiocins reported. The tricyclic thiazocines **268** showed, in their ^1H NMR spectra, the methylene protons next to sulfur at 3.70–3.99 ppm as an AB system as well as the methylene protons adjacent to nitrogen, which resonated at 4.53–5.08 ppm. The methyne proton between the two heteroatoms could be found at 4.58–5.06 ppm. The protons of the annelated rings thiophene and pyrrolidinone lay in the usual ranges <1997SC2241>. Annellation of the benzene ring onto the pyrrolidinone moiety experienced, with the exception of the S-adjacent hydrogens, a downfield shift for all the signals. Thus, in **269a**, the $\text{CH}_2\text{-S}$ protons resonated at 3.90 ppm (no AB system shown), whereas **269d** showed the $\text{CH}_2\text{-S}$ AB system at 2.97–3.48 ppm. The $\text{CH}_2\text{-N}$ protons resonated at 4.80–5.38 ppm and N-CH-S methyne at 5.87 ppm. Different position of the sulfur in the ring system did not affect the chemical shift of the protons with the exception of the $\text{CH}_2\text{-S}$ in **269c** which were found at 3.27–3.38 ppm <1997JHC375>. Replacement of the thiophene moiety with a benzene ring (e.g., **270**) experienced an upfield shift of the $\text{CH}_2\text{-S}$ protons (2.71–3.32 ppm), and a downfield shift of the N-CH-S methyne (4.97–6.17 ppm), whereas the $\text{CH}_2\text{-N}$ protons lay at 4.20–5.41 ppm <2000JHC1543, 2004H33, 2005EJO2758>. The positional isomers of **269**, **271a** and **271b**, showed in their ^1H NMR spectra the $\text{CH}_2\text{-N}$ protons, being also adjacent to sulfur, at 4.20–4.25 ppm in the case of **271a** and 5.70–5.76 ppm in the case of **271b**. The bridged methylene protons were found at 4.95–4.97 ppm, while the methylene next to carbonyl resonated at 3.25–3.26 ppm for **271a** and 4.80–4.95 ppm for **271b** <1997JHC321>.

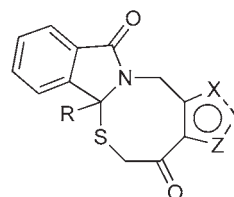
The only two hydrogens present in the decafluoro-substituted tetraoxodithiocin **272** resonated at 5.87 ppm <1995IC792>. The ^1H NMR spectrum of the dibenzodithiocin **273** showed the S-CH-S methyne at 4.25 ppm and the other methyne at 2.64 ppm <1999T7271>. The bis-condensation of the dithiocin ring with naphthalene experienced a large downfield chemical shift for the methyne adjacent to the sulfur atoms, which resonated at 5.60 ppm for **274a** and 7.30–8.10 ppm, overlapping with aromatic protons, in the case of **274b**. Also, the other methyne resonance was found at higher field (4.60–5.40 ppm), whereas the bridge methylene protons resonated at 1.80–2.80 ppm <1995T2109>.

**267a–h**

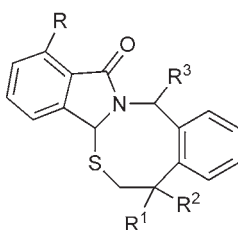
$n=0$ **a**: R=H; **b**: R=Ph; **c**: R=Me; **d**: R=*t*-Bu
 $n=1$ **e**: R=H; **f**: R=Ph; **g**: R=Me; **h**: R=*t*-Bu

**268a,b**

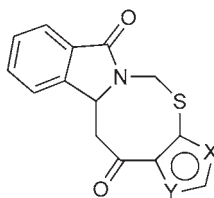
a: R=H; **b**: R=Me

**269a–d**

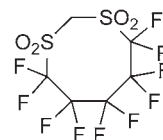
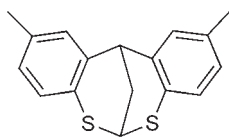
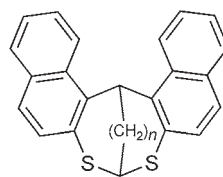
a: R=H; X=S; Y=Z=CH
b: R=H; X=Y=CH; Z=S
c: R=H; X=CCl; Y=S; Z=CH
d: R=Me; X=S; Y=Z=CH

**270a–c**

a: R=R¹=R²=R³=H
b: R=NO₂; R¹–R²=O; R³=H
c: R=H; R¹=R²=O; R³=Me

**271a,b**

a: X=S; Y=CH
b: X=CH; Y=S

**272****273****274a,b**

a: $n=1$; **b**: $n=3$

The naphthathiazocines **267b–d** having a substituent on the C-3 can be regarded as conformationally homogeneous, since their ¹H NMR spectra did not change upon variation of the temperature from 20 to –60 °C. By contrast, the ¹H and ¹³C NMR spectra of **267e** even at 25 °C showed a superposition of signals from two forms at a ratio of 83:17 in CDCl₃. Raising the temperature to 140 °C (DMSO-*d*₆) led to a spectral pattern corresponding to fast exchange on the NMR timescale. Comparison of the chemical shift as well as the geminal coupling constants of the benzylic protons in the ¹H NMR spectra of diastereomers **267f** and **267g** and the predominant conformer of **267e** with those of **267a–d**, which adopted a boat conformation at 25 °C, indicated that **267b–d** and the predominant conformer of **267e** exist in a boat conformation. Determination of the structure of the minor conformer of **267e** was achieved by evaluation of its NOESY spectrum, measured at –60 °C to ensure slow exchange on the NMR timescale, and with the help of the already-known X-ray diffraction data of **267d** <2005RJO1089>.

The ¹³C NMR spectra of **268** showed the CH₂–S signals at 30.4 ppm, the CH₂–N resonance at 58.9–75.5 ppm, and that the two carbonyl carbons resonated at 176.8–178.4 ppm (pyrrolidinone carbonyl) and 188.9–190.6 ppm (thiazocine ring carbonyl). The sp³ carbons of the pyrrolidine moiety resonated, in the usual range, at 19.0–28.7 ppm, as well as the thiophene CH carbons (115.9–125.4 ppm) <1997SC2241>. The pyrrolidinone carbonyl in the tetracyclic thiazocines **269**, due to the benzo-condensation, shifted its chemical shift at higher fields (166.2–166.8 ppm), while the eight-membered ring carbonyl carbon as well as the N–CH–S carbon resonances could be found in the range observed for **268**. Instead, the CH₂–S carbon signals shifted downfield (36.9–39.9 ppm) and the N–CH₂ carbon

resonances were upfield (38.2–40.3 ppm) <1997JHC375>. The same ranges for all described signals were observed in **270** where the thiophene ring was replaced by a benzene moiety <2000JHC1543, 2004H33, 2005EJO2758>.

The ^{13}C NMR spectra was used in determining the conformational composition of **267e**. Thus, comparison of the benzylic carbon resonances of **267a–d** (37.51–38.94 ppm), which adopt a boat conformation as already pointed out by theoretical studies and confirmed by ^1H NMR data, and those of **267e** (36.72–38.18 ppm) confirmed that sulfoxides **267e–h** adopt a boat conformation. Moreover, considering the β -effect of the sulfinyl oxygen atom, the chemical shifts of C-1 in these compounds (55.08–56.40 ppm) suggested that **267f–h** are *trans*-isomers with diequatorial orientation of the substituents <2005RJO1089>.

Neither ^{15}N nor ^{33}S NMR data were reported for thiazocines and dithiocin derivatives. The ^{19}F NMR spectrum (CFCl_3 as internal standard) was measured for **272**, in which the fluorines adjacent to the sulfurs (positions 4 and 8) were displayed at -107.3 ppm, the halogens at positions 5 and 7 at -119.5 ppm, and the C(6)–F at -120.5 ppm <1995IC792>.

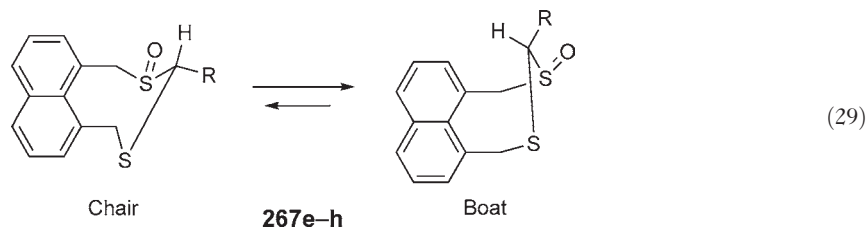
No fragmentation studies of 1,3-thiazocines and 1,3-dithiocins were reported in the past decade. In some cases, only the molecular ion or quasi-molecular ions of their EI spectra <1995T2109, 1999JHC735, 1999T7271, 2004H33, 2005EJO2758> or CI spectra <1995IC792> were provided.

The tricyclic thiazocines **268** as well as the tetracyclic analogues **269–271** showed, in their IR spectra, the pyrrolidinone carbonyl stretching at 1644 – 1695 cm^{-1} and the eight-membered ring carbonyl stretching in the range 1684 – 1711 cm^{-1} <1997JHC321, 1999JHC735, 1997SC2241, 2004H33, 2005EJO2758>.

14.05.4.3 Thermodynamic Aspects

All the thiazocines herein reported are tri- or tetracyclic systems and have melting points in the range 159 – 248°C <1997JHC321, 1999JHC735, 1997SC2241, 2004H33, 2005EJO2758>. The melting points of **270b** and **270c** deviate from this range being 92 and 102°C , respectively <2000JHC1543, 2004H33>. The naphthodithiocin monoxides **267e–h** melted in the range 183 – 217°C <2005RJO1089>. The methylene-bridged tricyclic dibenzodithiocin **273** melted at 148 – 149°C <1999T7271> and the bis-annulation with the naphthalene moiety in **274a** increased its melting point at 169 – 171°C . Instead, in the presence of a larger bridge (three methylene units in **274b**), the melting point decreased probably due to the difficulty in the solid-state packing <1995T2109>. The perfluoro monocycle **272** melted at 137°C <1995IC792>. The reported thiazocines are generally soluble in most common organic solvents as determined from the experimental sections and are usually purified by recrystallization from EtOH <1999JHC735, 2000JHC1543, 2004H33, 2005EJO2758>. In two cases, purification was achieved by silica gel column chromatography with DCM <1997JHC321> or DCM/hexane <1997SC2241> as eluent. Soluble in most common solvent, dithiocins were purified by recrystallization from petroleum ether <1999T7271>, EtOH, or Et_2O <1995T2109>. In some cases, purification was performed by *in vacuo* sublimation <1995IC792> or by silica gel chromatography with $\text{CDCl}_3/\text{EtOAc}$ <2005RJO1089> or $\text{AcOEt}/\text{hexane}$ <2004OL3437> as eluent.

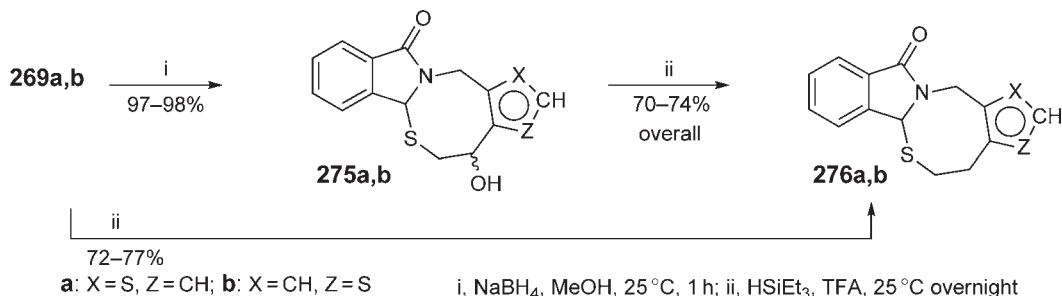
The naphtho-fused 1,3-dithiocins **267a–d**, as predicted by theoretical calculations (see Section 14.05.4.1) and confirmed by NMR studies (see Section 14.05.4.2), adopt a boat conformation in CS_2 and CCl_4 at 25°C . Also, the corresponding sulfinyl derivatives **267f–h** exist in a boat conformation with diequatorial orientation of the substituents. NMR studies evidenced that **267e** exists as a mixture of two conformers: the predominant form has the boat conformation as **267f–h** and the minor conformer has a boat structure with the axial orientation of the sulfoxide oxygen atom (Equation 29) <2005RJO1089>.



14.05.4.4 Reactivity of Nonconjugated Rings

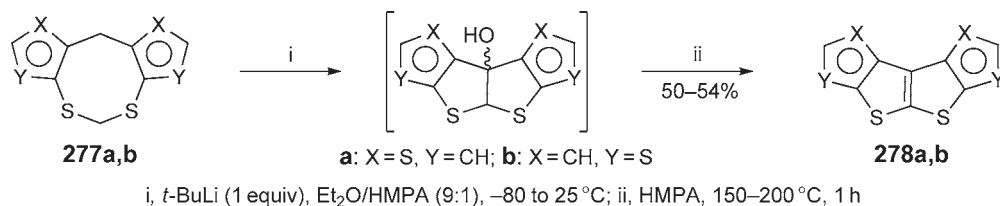
Regioselective reduction of **269a** and **269b** with NaBH_4 in MeOH gave the corresponding alcohols **275a** and **275b**, as a mixture of diastereomers. The ratio depends on the temperature, reaction time, and the position of the sulfur in

the fused thiophene. The mixture **275a** and **275b** treated with triethylsilane in TFA led to the thienothiazocines **276a** and **276b** in good overall yield. Direct reduction of **269a** and **269b** to **276a** and **276b** was possible using triethylsilane in TFA but did not increase the yields (Scheme 60) <1997JHC375>.



Scheme 60

The trithienothiophenes **278a** and **278b** were obtained in good overall yields from the dithienodithiocins **277a** and **277b** upon intramolecular cyclization brought about by strong bases followed by dehydration of the intermediate alcohols. The yield of the reaction was optimized and the reagents of choice are described in Scheme 61 <2004OL3437>. Oxidation of naphthodithiocins **267a-d** with *m*-chloroperbenzoic acid (MCPBA) gave the corresponding monoxides **267e-h** in 32–44% yields (Scheme 61) <2005RJO1089>.



Scheme 61

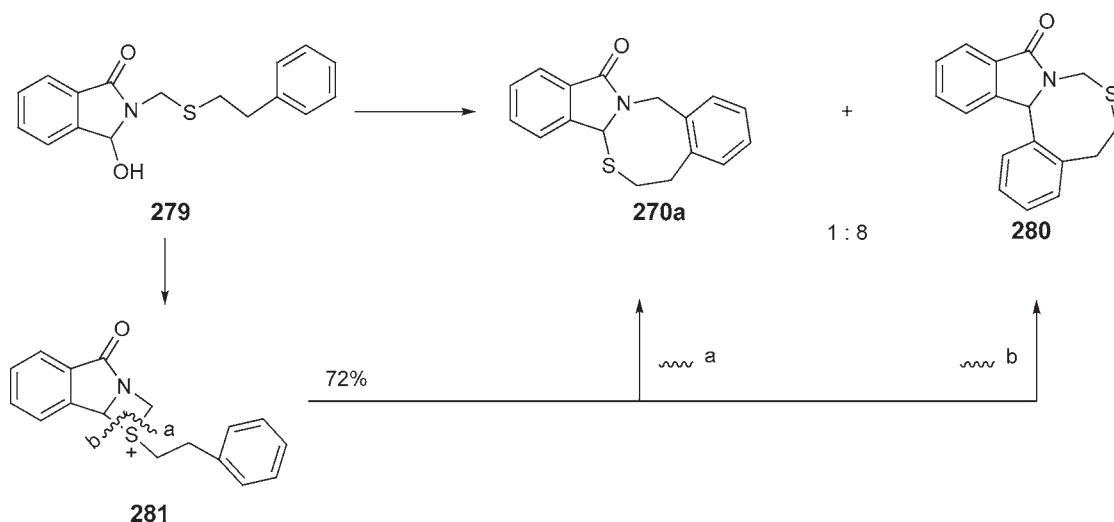
14.05.4.5 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.05.4.5.1 Ring syntheses of thiazocines from C₆NS units

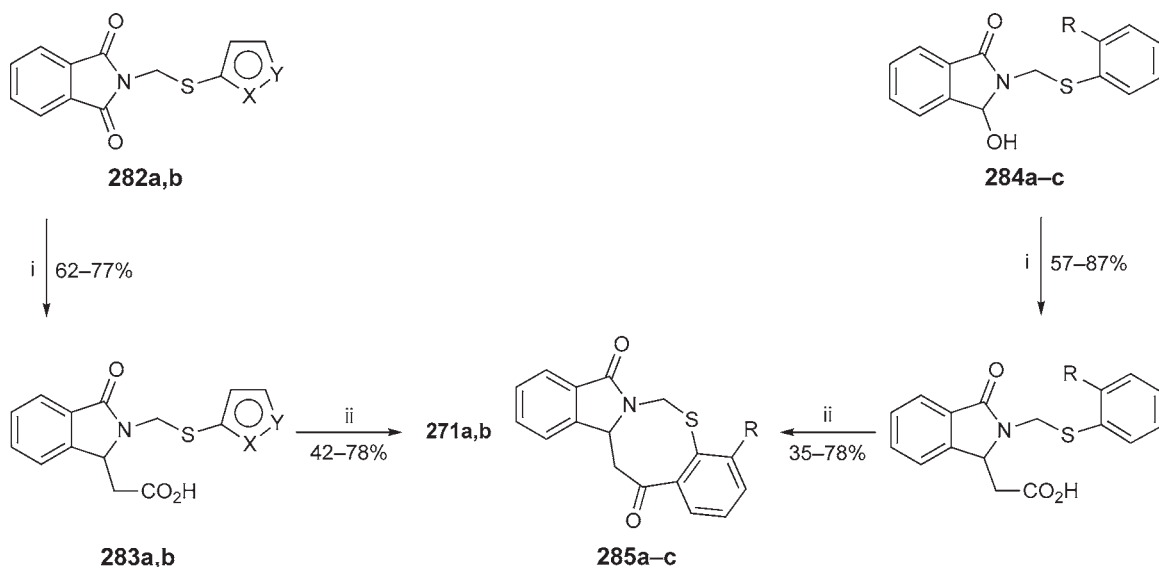
The isoindoleninones **279** upon treatment with neat TFA gave a 1:8 mixture of the thiazocines **270a** and **280**. The reaction went through the initial intramolecular nucleophilic attack by the sulfur to the position 3 of the isoindoleninone moiety with formation of the cyclic azasulfonium cation **281**. Rupture a of the intermediate **281** followed by ring closure of the methylene cation with the phenyl ring gave **270a**. Instead, rupture b produced a positive charge at position 3 of the isoindoleninone moiety, which cyclized with the phenyl ring to originate **280** (Scheme 62) <2005EJO2758>.

14.05.4.5.2 Ring syntheses of thiazocines from C₄NS + C₂ units

The isoindoleninones **282a** and **282b** underwent Wittig reaction using ethoxycarbonylmethylidene triphenyl phosphorane to give the isoindolone acetic acids **283a** and **283b**, which upon transformation into the acyl chlorides underwent intramolecular cyclization to give the tetracyclic thiazocines **271a** and **271b**, positional isomers of **269a** and **269b** (Scheme 63) <1997JHC321>. Analogously, isoindoleninones **284a-c**, when subjected to the same reaction sequence, yielded **285a-c** <2004H33>.



Scheme 62



a: X = S, Y = CH; **b:** X = CH, Y = S

a: R = H; **b:** R = Br; **c:** R = OMe

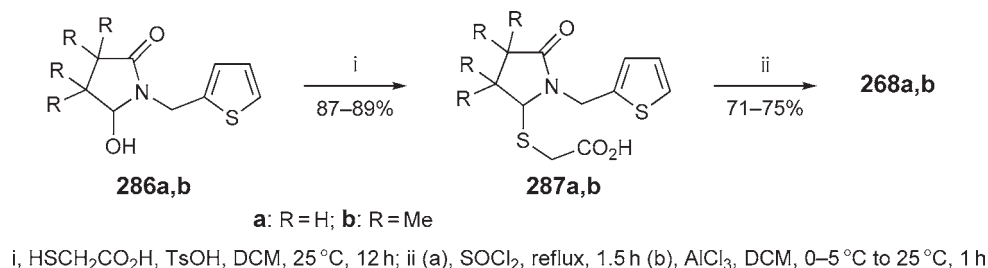
i (a), $\text{Ph}_3\text{PCHCO}_2\text{Et}$, toluene, reflux, 2–3 h (b), K_2CO_3 , MeOH, H_2O , 60 °C, 2 h;

ii (a), SOCl_2 , DCM, reflux, 1–2 h (b), AlCl_3 , DCM, 0–25 °C, 1–2 h

Scheme 63

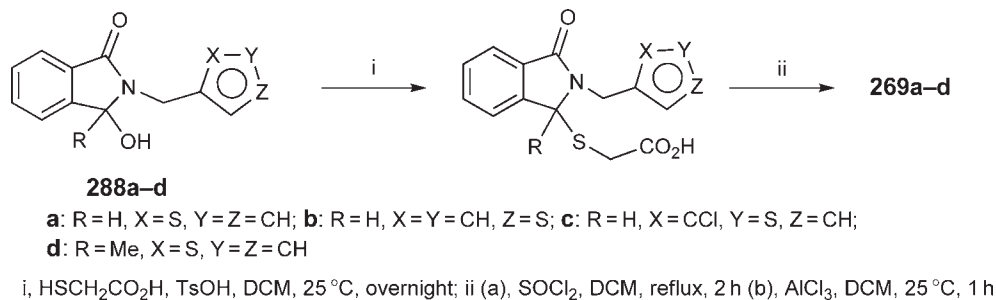
14.05.4.5.3 Ring syntheses of thiazocines from $\text{C}_4\text{N} + \text{C}_2\text{S}$ units

The pyrrolothienodiazocine **268a** and **268b** were efficiently prepared from hydroxyl lactams **286a** and **286b**, which reacted with thioglycolic acid to give, by nucleophilic substitution on the pyrrolidinone moiety, the corresponding thioglycolic acids **287a** and **287b**. These acids were treated with thionyl chloride and the resulting acyl chlorides underwent Friedel–Crafts cyclodehydration to the final ring system in good yields. Cyclization of **287a** was performed at 25 °C, whereas **287b** at the same temperature gave the 5-methylthiopyrrolidinone consequence of a decarboxylation reaction. However, **268b** could be obtained when the cyclization was performed at –5 °C (Scheme 64) <1997SC2241>.



Scheme 64

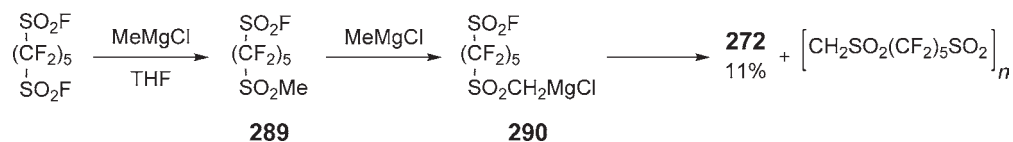
The same synthetic route was utilized for the synthesis of the tetracyclic thiazocines **269a–d** starting from the 3-hydroxyisindoleninones **288a–d** via the thioglycolic acids. The yields with the exception of **288c** (38%) were good (79–88%) (Scheme 65) <1997JHC375>. Analogously, starting from 3-hydroxy-2-(1-phenylethyl)isindolin-1-one, the isindolo-benzothiazocines **270b** and **270c** were obtained in 56–68% yields. Using 3-hydroxy-2-(substituted 1-benzyl)isindolin-1-ones, other derivatives of the same ring system **270** substituted at the benzene moiety were obtained <2000JHC1543, 2004H33>.



Scheme 65

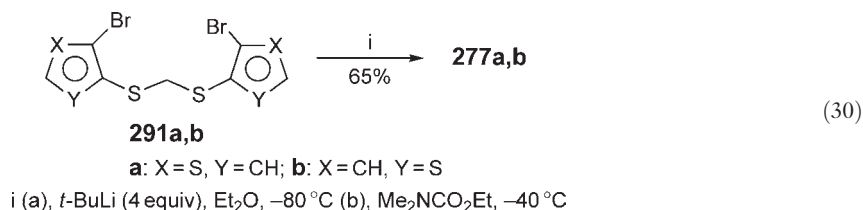
14.05.4.5.4 Ring syntheses of dithiocins from C₅S₂ + C units

Tetraoxodecafluoro-1,3-dithiocin **272** was prepared, in low yield, from α,ω -bis(fluorosulfonyl)perfluoropentane by reaction with methylmagnesium chloride. The synthesis involved the initial formation of the intermediate **289**. The acidic α -hydrogen was easily abstracted by a further molecule of Grignard reagent forming **290**, which underwent either intramolecular cyclization to give **272** or intermolecular reaction with itself or other intermediates to form oligomeric products (Scheme 66) <1995IC792>.



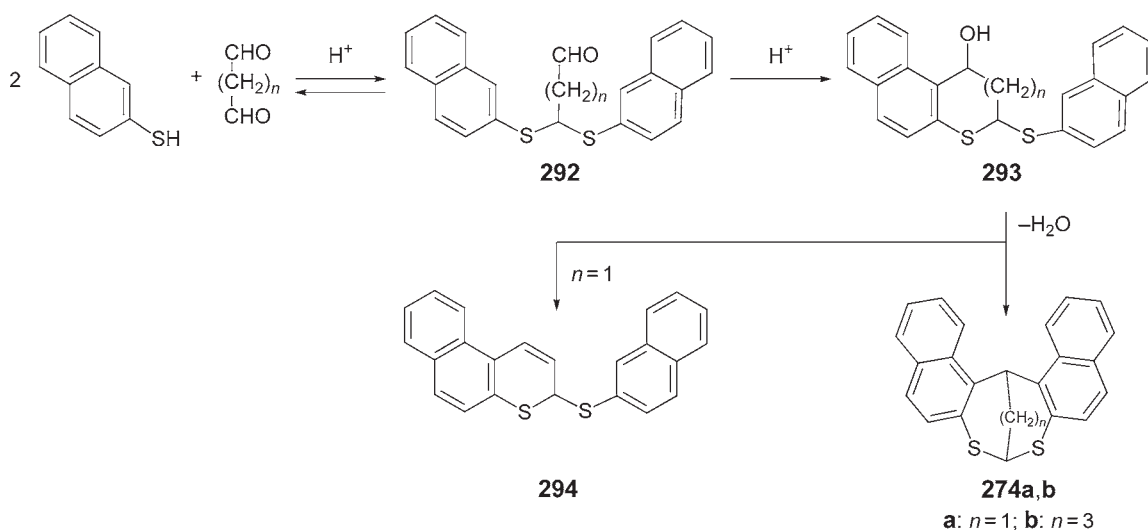
Scheme 66

Dithienodithiocins **277a** and **277b** were prepared by lithiation of the bromo thiophenes **291a** and **291b**, followed by addition of *N,N'*-dimethylethylcarbamate in good yield (Equation 30) <2004OL3437>.



14.05.4.5.5 Ring syntheses of dithiocins from C₂S + C₂S + C₂ units

Thioacetalization of 2 mol of 2-thionaphthol and 1 mol of dialdehyde led to the bis-naphthodithiocins **274a** and **274b** in low yields (12–18%), likely through intermediate **292**, which cyclized at the 1-position of the thionaphthol to give naphthothiocine **293**. Acid catalysis brought about the second cyclization of the other thionaphthol moiety on the carbon bearing the hydroxyl to give the final products. In the case of the malonaldehyde (*n* = 1), the naphthothiopyran **294** (10%) was also isolated (Scheme 67) <1995T2109>. Parallel behavior was observed in the reaction of thiophenol and malonaldehyde, which gave the dibenzodithiocin **273** (25%) together with the benzothiopyran derivative (14%) <1999T7271>.



Scheme 67

14.05.4.6 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

In the four Schemes 62–65, the syntheses of those 10 1,3-thiazocine derivatives are described in which only variants of the same synthetic approach are noted. All of these syntheses concerned the preparation of pyrrolidinone- or isoindoleninone-fused benzo- or thieno-thiazocines and the cyclization involved the α -carbon of the pyrrolidinone or isoindoleninone moieties and the *ortho*-position of the attached benzene or thiophene rings. The sole unimolecular cyclization, in spite of the fact that the cyclic azosulfonium cation intermediate can originate two different ring systems, appears advantageous both for the yields, that are higher than in the two-step syntheses described, and for an easy workup. The paper describing such an approach reported the synthesis of only one 1,3-thiazocine derivative but it was inserted in a general context capable of obtaining 5–8 membered heterocycles and allows wide application. The other processes involving the introduction of a side chain, responsible later for the cyclization, that have appeared in general application warranted cyclizations at the substituted phenyl or differently bound thiophenes with yields, in some case, that are good but in other occasions moderate or low. The only advantageous synthesis of dithiocins involved the insertion of one carbon unit into dibromothiophene derivatives. The yields were good and also prompt entry to the starting materials. The only problem is the dramatic dependence of the yields on the skill of the operator. The synthesis involving the thioacetalization of dialdehydes, although mechanistically interesting, led to the final products in low yields.

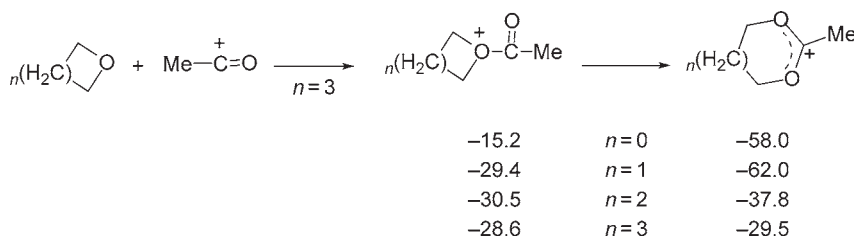
14.05.4.7 Important Compounds and Applications

2,3-Dimethyl-4-thioxo-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,3-benzothiazocine was patented for treating migraine headaches <1995WO06468>. Derivatives of the ring system [1,2,4]triazolo[3,4-*b*]thiazocine were patented due to their capability to inhibit the 11 β -HSD1-mediated conversion of cortisone and other 11-keto-glucocorticoids to cortisol and other 11 β -hydroxyglucocorticoids. The 11 β -HSD1 inhibitors therefore decrease the amount of cortisol in target tissues, thereby modulating the effects of cortisol. Modulation of cortisol may be effective in controlling non-insulin-dependent diabetes mellitus (NIDDM), hyperglycemia, obesity, insulin resistance, dyslipidemia, hypertension, and other symptoms associated with NIDDM or with excess cortisol in the body <2003WO065983>. 1-Methyl-7,8,9,10-tetrahydro-6*H*-[1,3]thiazocino[2,3-*f*]purine-2,4-(1*H*,3*H*)-dione inhibited the *E. coli* MurA enzyme at the concentration of 0.90 μM and *Staphylococcus aureus* at the concentration of 32 $\mu\text{g ml}^{-1}$ <2001AAC3182>.

14.05.5 Rings with Two Oxygens (4*H*-1,3-Dioxocins)

14.05.5.1 Theoretical Methods

Within studies of epoxide ring-expansion reaction promoted by gaseous acylium ions, *ab initio* calculations predicted that the reaction proceeded by initial O-acetylation of the epoxides followed by rapid intramolecular nucleophilic attack that resulted in three- to five-membered ring expansion. *Ab initio* calculations were also utilized to predict the ability of acylium ions to promote analogous ring expansion of larger O-heterocycles. Thus, potential energy surface values were calculated and compared with those obtained for analogous three- to five-, four- to six-, and five- to seven-membered rings. Ring expansion for tetrahydropyran with acetylonium ion was exothermic but, compared with smaller rings, to a lesser extent. From the O-acetylated adduct, however, this ring expansion is just slightly exothermic and likely hampered by substantially higher energy barrier since no alleviation of ring strain occurs, and substantially stronger C–O bonds are disrupted at the corresponding TS_s (Scheme 68) <2000CEJ897>. Four derivatives of the dibenzo[*d,g*]1,3-dioxocin-12-(substituted pyrimidine) were included in a set of obtusifoliol 14 α -methyl demethylase inhibitors to aid in the design of herbicides targeting sterol biosynthesis. The comparative molecular field analysis (CoMFA) was utilized to design compounds that retained the active site shape requirements, but incorporated physical properties that favored soil-applied herbicidal action <1999MI1059>.

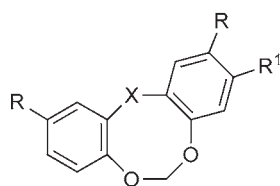


Scheme 68

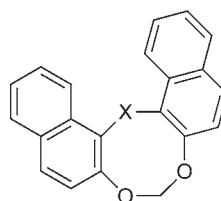
14.05.5.2 Experimental Structural Methods

X-Ray single crystal investigation of dibenzo[*d,g*]1,3-dioxocins **295a–f** and dinaphtho[2,1-*d*;1',2'-*g*]1,3-dioxocins **296a** and **296b** was undertaken to determine their conformation in the crystalline phase. Compounds **295a**, **295b**, and **295d** adopted a boat-chair (BC) conformation. For **295a**, which is free from steric strain, the internal bond angles of all the atoms comprising the eight-membered ring, including the sp² carbons, have normal values (113.0–123.0°). The presence of the equatorial methyl group in **295b** significantly decreased the bond angle at C-6 to 108° with a small elongation of the C(5)–C(6) and C(6)–C(7) bonds, so that the methyl group can avoid steric interaction with the benzo moieties. The axial orientation of the *i*-Pr group in **295d** gives rise to short van der Waals contacts with the endocyclic oxygen atoms. In the **295a,b,d** series, it was observed that a flattening of the eight-membered ring is proportional to the bulkiness of the substituent in the axial position and is reverse to the volume of the group in the equatorial

position. Also, **296a** adopted a BC conformation, which is rather unusual, as strong steric interactions between the two naphtho groups arise in such conformation. However, the torsion angles as well as dihedral angles are nearly the same as in **295a** and **295b**. The closest interatomic contacts between the naphtho groups are not shorter than the sum of the van der Waals radii (3.5 Å). A twist (T) conformation was adopted by **295e** and, due to the flexibility of this conformation, the asymmetric substitution in one of the benzo moieties led to large distortions of the geometry of the ring in **295f** and the twist-boat (TB) form was preferred. The **295c**, bearing two substituents at C-6, ethyl and hydroxyl groups, was found to have a distorted boat (DB) conformation in the crystal. In contrast to **295d** with an isopropyl group at C-6, the distortion of the molecular symmetry in **295c** diminishes steric contacts between the ethyl group and the endocyclic oxygen atoms, so that only one short contact between the ethyl methylene carbon and O-1 was observed. On the contrary, this asymmetry is stabilized by the intramolecular CH $\cdots$ O bond and intermolecular OH $\cdots$ O' hydrogen bonding. Another type of DB conformation is realized in **296b**. For such a molecule, the conformation is determined by the two annulated naphtho groups and by the presence of the phenyl substituent at C-6 <1995JST(344)95>. X-Ray analysis of **297c** established that the ethoxycarbonyl group had an axial orientation and was bound to a ring having a boat conformation <2000S1894>.

**295a–f**

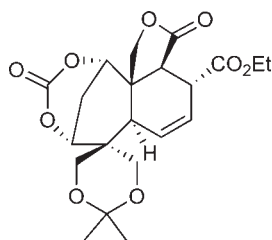
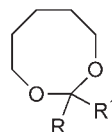
- a:** R = Me; R¹ = H; X = CH₂
b: R = Me; R¹ = H; X = CHMe
c: R = R¹ = H; X = C(OH)Et
d: R = R¹ = H; X = C(OH)-*i*-Pr
e: R = R¹ = H; X = CO
f: R = H; R¹ = *t*-Bu; X = CO

**296a,b**

- a:** X = CH₂
b: X = CHPh

For all reported 1,3-dioxocin derivatives, NMR data have been provided. The ¹H NMR spectra of several uncondensed and unbridged dioxocines **298** and related compounds variously substituted showed the protons at C-2 in the range 4.57–5.10 ppm; the methylene or methyne protons adjacent to the oxygen resonated at 3.00–4.21 ppm, while the other methyne or methylene protons could be found in the usual range at 1.1–2.1 ppm. The methyl groups bound to C(4)–C(8) carbons resonated in the range 0.81–0.99 ppm <1995H(40)607, 1998JNP34, 1999JNP710, 2001MRC657, 2002JOC22, 2005BMC5640>. The NMR spectra of the 4,8-methylene-bridged uncondensed 1,3-dioxocin showed signals consistent with the ranges above described for **298**, and the bridge methylene protons resonated at 2.09–2.14 ppm <1999J(P1)1885>. Annulation of dioxocin ring with benzene or naphthalene moieties experienced a downfield shifts of the protons bound to sp³ carbons. Thus, the ¹H NMR spectra of the dibenzodioxocins **295** and the naphthodioxocins **296** and related compounds bearing a methylene bridge exhibited the protons between the two oxygens (H-6 for **295** and H-8 for **296**) in the range 5.92–6.40 ppm and the other methyne proton of the eight-membered ring (H-12 for **295** and H-16 for **296**) resonated at 3.65–3.90 and 5.20–5.40 ppm, respectively; the methylene-bridged protons, instead, were found at 2.00–2.45 ppm <1997T12621, 1999T7271, 2002JME789, 2004JA12732, 2004T6909>.

For the 2-substituted-1,3-dioxocins **298a–g**, the NMR data indicated that the most favored conformations were the enantiomeric boat-chair forms (see section 14.05.5.3). Owing to symmetry and rapid interconversion on the NMR timescale at 25 °C, only one set of chemical shifts is obtained for the corresponding ¹H and ¹³C nuclei at C-4 and C-8 and at C-5 and C-7. The ¹³C chemical shift effects due to the substituents at C-2 supported the proposed BC conformation. An interesting feature was the distinctly greater deshielding by *t*-Bu group with respect to the Me group (11.6 ppm). The chemical shifts other than C-2 also showed some minor effects but these are not significant for a structural perspective <2001MRC657>.

**297c****298a–g**

a: R=R¹=H; **b:** R=Me, R¹=H; **c:** R=R¹=Me; **d:** R=Et, R¹=H;
e: R=Pr, R¹=H; **f:** R=*i*-Pr, R¹=H; **g:** R=*t*-Bu, R¹=H

The ¹³C NMR spectra of **298** showed that the C-2 carbon resonated in the range 95.5–111.8 ppm, C-4/C-8 next to oxygens in 62.7–70.3, while C-5, C-7, and C-6 carbons were found at 29.6–30.3 and 23.1–26.2 ppm, respectively <2001MRC657>. The sp³ carbon signals in **295** and **296** and related methylene bridged analogues were found at ~92–94 ppm (C-6) and ~25.0–28 ppm (C-12), while the bridged carbon resonated at 31.0–34 ppm <1999T7271>.

The ¹⁷O NMR spectra for **298a–g** were measured and for the unsubstituted derivative the chemical shifts was 32.2 ppm. The α-branching effect, due to the conformational flexibility of the ring, is practically equal for both Et and *i*-Pr groups (−4.3 ppm). The threefold branching effect (*t*-Bu) is almost negligible (−1.9 ppm) <2001MRC657>.

Also for the 1,3-dioxocins, no studies on fragmentation patterns were reported although nearly all the papers dealing with 1,3-dioxocins reporting mass data in their experimental sections only mentioned the molecular or quasi-molecular ions. Thus, FAB spectra <2000EJO2669, 2002JOC22, 2003SL619, 2005BMC5640>, CI spectra <1998JNP34, 1999JNP710>, and EI spectra <1995T2109, 1995H(40)607, 1997JOC3902, 1997T1261, 1999JNP710, 1999J(P1)1885, 1999T7271, 2000S1894, 2003JOC1081, 2004JA12732, 2004TL6909> were reported.

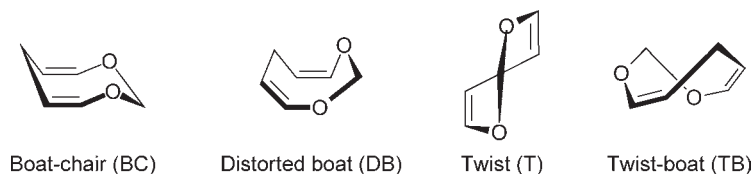
The prediction of *ab initio* calculation on the ring expansion of THF, promoted by acylium ions, was confirmed by sequential product ion mass spectra collected after collision-induced dissociation (CID), which showed that tetrahydropyran failed to undergo six- to eight-membered ring expansion in reaction with [(Me)₂N–C⁺=S] since its adduct (most likely the simple O-acylated ion) dissociated to regenerate exclusively the reactant ion [(Me)₂N–C⁺=S] <2000CEJ897>.

14.05.5.3 Thermodynamic Aspects

The phase behavior of the 1,3-dioxocins varies depending on the substituents and condensation with other rings. Most of the reported dioxocins are fused to another ring and are part of tri-, tetra-, or pentacyclic systems. Simple, substituted, or even methylene-bridged 1,3-dioxocins are generally oils or have low melting points (41–44 °C) <1995H(40)607, 1998JNP34, 1999JNP710, 1999J(P1)1885>. Bis-condensation with benzene ring in **295** increased the melting points in the range 150–200 °C <1999T7271, 2002JME789>. The dinaphthodioxocins further rose in their melting points, >200 °C, and in some cases reached to 300 °C. From the experimental parts of the paper dealing with 1,3-dioxocins, it was clear that such compounds are soluble in most organic solvents. The purification of 1,3-dioxocins was generally performed with columns of silica gel using eluents of medium/high polarity: EtOAc/hexane <1997JOC3360, 1999J(P1)1885, 2000S1894>, EtOAc/CHCl₃ <1999J(P1)1885>, EtOAc/EtOH <1999J(P1)1885>, CHCl₃/MeOH <2000EJO2669>, EtOAc/benzene <2002JME789>, Et₂O/hexane <2003JOC1081>, Et₂O/DCM or MeOH/AcOH/DCM <2004JA12732>.

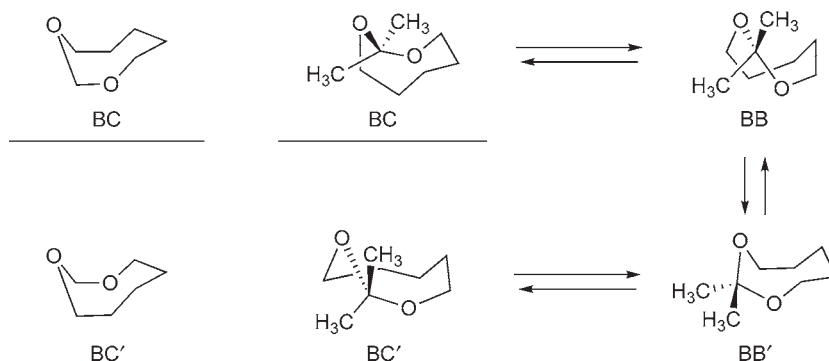
The conformational behavior of **295a–f** and **296a** and **296b** is closer to that of cyclic hydrocarbons than other eight-membered heterocycles. In comparison with cyclic hydrocarbons, the presence of two oxygen atoms in the cycle makes this system more flexible, as the oxygen bond angles are known to vary significantly from one molecule to another. Thus, as expected for **295a**, a BC conformation was observed. The BC conformation is preserved in **295b** in which one of the hydrogens of C-6 is substituted by the methyl group, the latter being in the equatorial position. The introduction of two substituents at C-6, the Et and OH group, in **295c** resulted in the distortion of the BC conformation and the DB became more favorable. The OH and Et groups had pseudoequatorial and pseudoaxial orientation, respectively. Such an asymmetrical conformation is additionally stabilized by both intramolecular and intermolecular hydrogen bonding. The symmetrical substitution (*i*-Pr) resulted in formation of the symmetrical BC conformation with the OH and *i*-Pr groups with the equatorial and axial orientation, respectively, being stabilized

by intramolecular hydrogen bonding. For **296a**, a symmetrical BC conformation, with the molecule lying in a special position on a crystal symmetry plane m , was observed. Both **295e** and **295f** bearing a carbonyl group in the 6-position adopted a T-like conformation, which is nearly symmetrical for the former molecule and significantly distorted for the latter, being closer to the TB form because of the presence of the bulky *t*-Bu group in one of the benzo moieties. The dinaphtho-fused dioxocin **296b**, bearing a Ph group at C-6, adopted the DB form (**Scheme 69**) <1995JST(344)95>.



Scheme 69

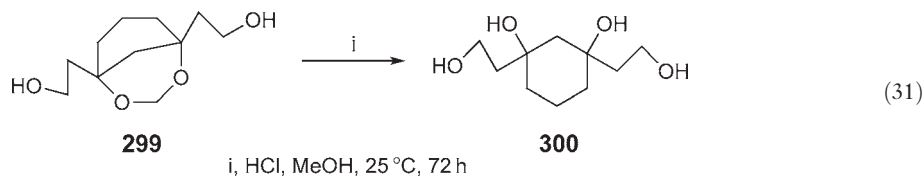
As already mentioned in Section 14.05.5.2 for the 2-substituted 1,3-dioxocins **298a–g**, the preferred conformations are the enantiomeric boat-chair forms BC and BC'. For **298c**, the dimethyl derivative, the pseudorotation of the BC conformation occurred via a boat-boat (BB) form <2001MRC657>. The kinetics of the thermal decomposition of 5,5,7,7-tetranitro-1,3-dioxocin were studied. The steric influence of the bulky dinitromethylene groups probably determined the high rate of decomposition (**Scheme 70**) <2006RJC499>.



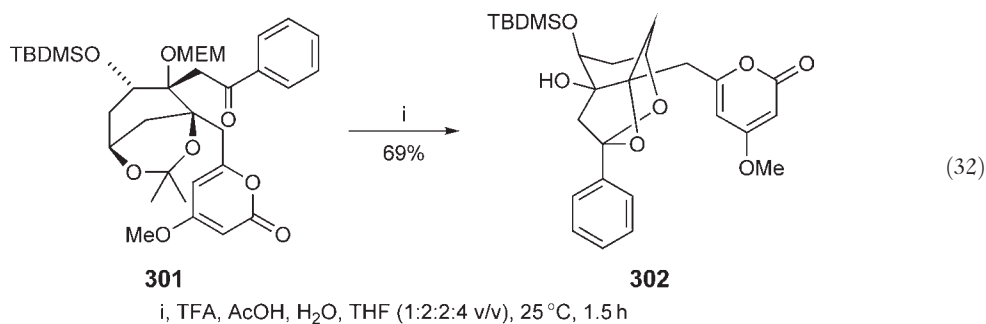
Scheme 70

14.05.5.4 Reactivity of Nonconjugated Rings

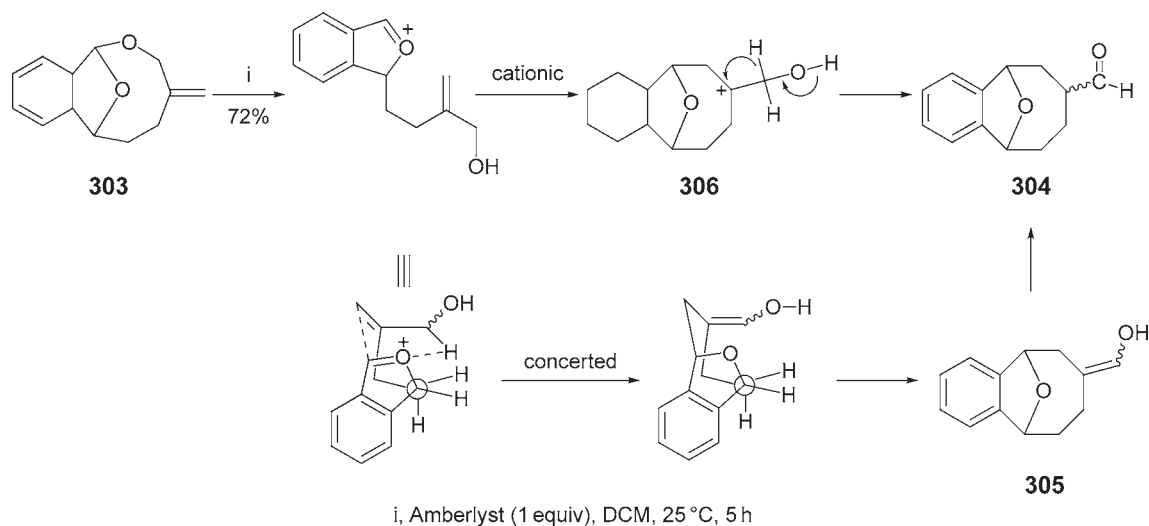
Acid hydrolysis of the bridged dioxocin **299** led to the cyclohexane **300** by cleavage of the acetal moiety (**Equation 31**). Similar cleavage was observed in the case of a dimer of **299**, in which the two units were bound to each other through two diethyloxy moieties, to give *cisoid* tetrahydroxy groups <1999J(P1)1885>.



In the total synthesis of wailupemycin B, the 1,3-dioxocin **301**, upon acid hydrolysis, gave the *t*-butyldimethylsilyl (TBDMS)-protected dihydro wailupemycin B **302** (**Equation 32**) <2003AGE4685>.



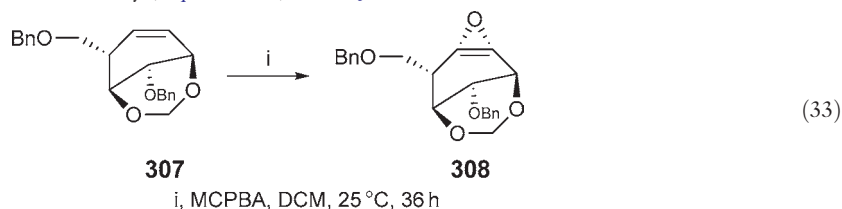
Acid-promoted decomposition of dioxocin **303** led to a 1:1 mixture of *syn*- and *anti*-isomers of the aldehyde **304**. The yield of the reaction was optimized and the best reaction conditions are reported in [Scheme 71](#). Two possible mechanisms are conceivable for this reaction. One is the concerted cyclization, followed by tautomerization of enol **305** to the aldehyde **304**. The other is stepwise cyclization to give the β -hydroxy carbenium ion intermediate **306**, followed by 1,2-hydride shift [<2001TL6859, 2003JOC1081>](#). The rate constants of the acid-catalyzed hydrolysis of **298** ($R = R^1 = \text{Ph}$) monomethyl substituted alternatively in positions 4–6 were determined and compared to those of analogue five- to seven-membered rings. Dioxocins **298** were hydrolyzed 35 times faster than five-membered analogues. This rate dependency on the ring size was explained on the basis of the combination of the ring-strain and the stereoelectronic effects [<1995H\(40\)607>](#).



Scheme 71

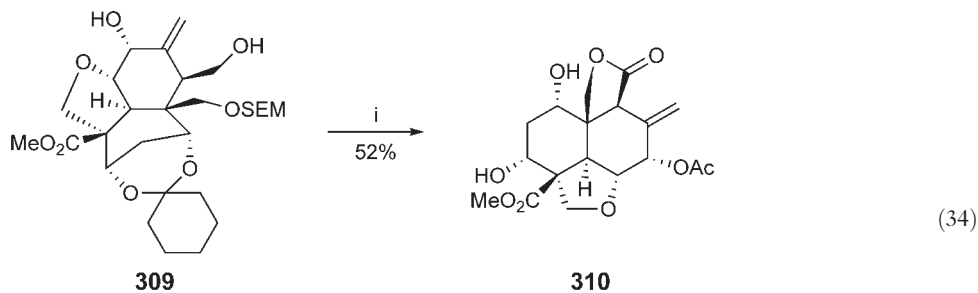
Unsubstituted dibenzodioxocin **295g** ($R = R^1 = \text{H}$, $X = \text{CH}_2$) was brominated with NBS to give the corresponding monobromo derivative **295h** ($R = R^1 = \text{H}$, $X = \text{CHBr}$) in low yield [<2000WO23417>](#).

Epoxidation of **307** with MCPBA gave **308** as a single diastereoisomer due to steric hindrance of the β -face of the double bond by the methylene acetal moiety (Equation 33) [<1997JOC3360>](#).



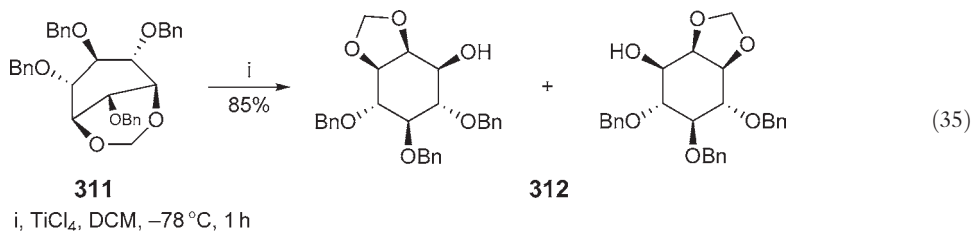
The primary alcohol of the diol **309** was selectively oxidized to the corresponding hydroxyaldehyde through a 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-catalyzed oxidation. The remaining secondary hydroxyl functionality was protected as an acetoxy group and the aldehyde was further oxidized to the acetate carboxylic acid. Treatment of

this latter with ethanolic HCl gave the dihydroxy lactone **310** through cleavage of both the ketal and silyl protecting groups and ring closure (Equation 34) <2005AGE3447>.

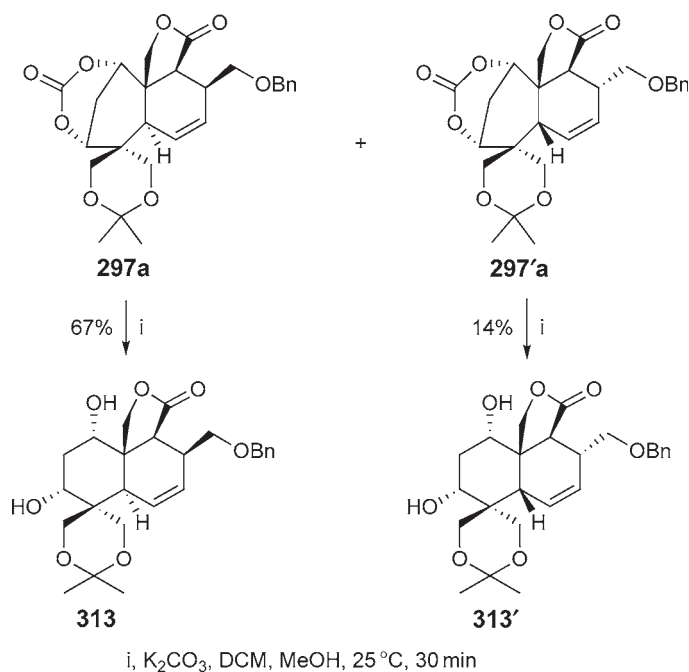


- i, (a) TEMPO (0.8 equiv), polystyrene-supported bromite resin (6 equiv), DCM, 0 °C, 2 h
 (b), Ac₂O (5 equiv), NEt₃ (10 equiv), DMAP (0.2 equiv), DCM, 0–25 °C, 1 h (c), NaClO₂ (4 equiv),
 NaH₂PO₄ (5 equiv), 2-Me-2-butene (75 equiv), THF/*t*-BuOH/H₂O (2:4:1), 25 °C, 1 h
 (d), HCl (0.5 M), EtOH/Et₂O (1:1), 0–25 °C, 3 h

Treatment of **311** with TiCl₄ gave a mixture of **312** through the oxidative cleavage of the eight-membered ring and successive nucleophilic attack of the benzyloxy moiety (Equation 35) <2005CCL171>.

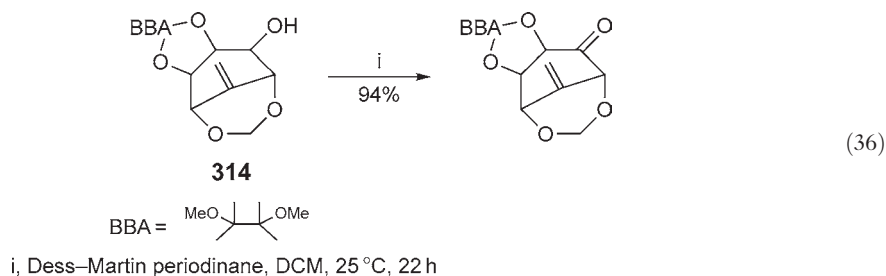


The ring cleavage obtained by acid media was also observed upon action of base. Thus, **297** and **297'** were saponified with K₂CO₃ to give the diols **313** and **313'**, respectively. The latter, to be characterized, was transformed into the bistriethylsilyl (di-TES) ether in quantitative yield (Scheme 72) <2000S1894>.

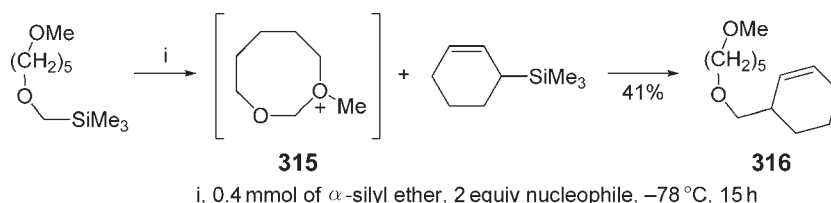


Scheme 72

Within the stereoselective construction of the contiguous tetraol system in tetrodotoxin, the 5-hydroxyl function of BBA-protected 1,3-dioxocin **314** was oxidized, as indicated in Equation (36), to the corresponding carbonyl group in excellent yield <2003SL619>.



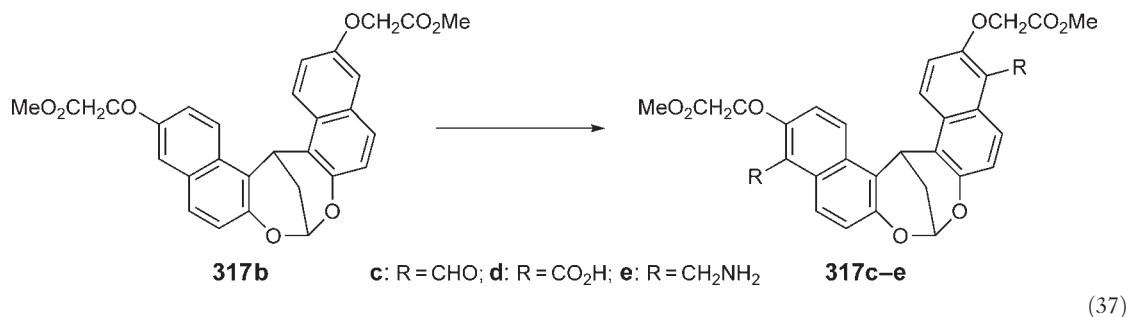
The alkoxy-carbenium ion **315**, obtained by electrochemical oxidation of α -silyl ethers under standard cation pool conditions, underwent ring opening by reaction with the nucleophile cyclohexenyltrimethylsilane to give **316** (Scheme 73) <2005OL4717>.



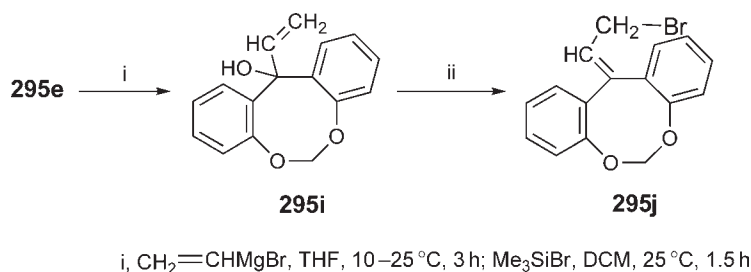
Scheme 73

14.05.5.5 Reactivity of Substituents Attached to Ring Carbon Atoms

Electrophilic formylation of the most activated *peri*-position of each of the naphthalene moieties of the bridged 1,3-dioxocin **317b** led to **317c** in 77% yield. Oxidation of the formyl groups with NaClO₂ led to the diacid **317c** in 95% yield, while reductive amination of the diadehyde gave the diamine **317e** in 66% yield (Equation 37) <2004JA12732>.

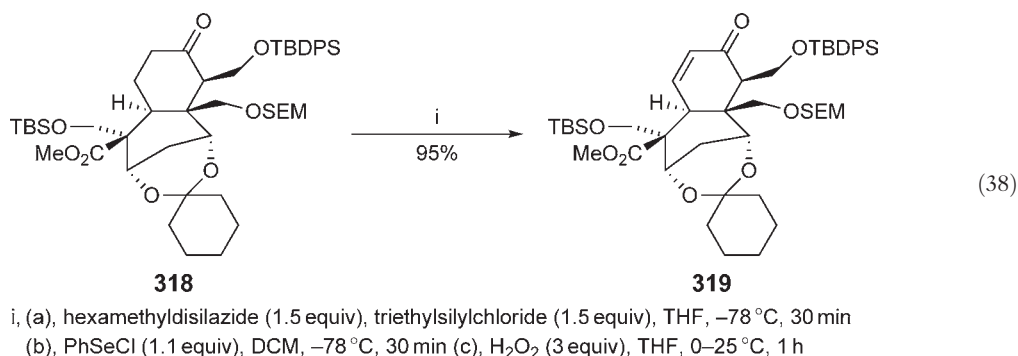


Treatment of 1,3-dioxocinone **295e** with vinylmagnesium bromide led to the 12-hydroxy-12-vinyl-substituted dioxocin **295i**, which was subjected to bromination with Me₃SiBr to give the 12-bromoethylidene dioxocin **295j** in 91% overall yield (Scheme 74) <2002JME789>. This latter underwent nucleophilic substitution by oxygen nucleophiles, ethyl 3-ethoxy-2-(4'-hydroxyphenyl)propionate <2000WO23415>, or nitrogen nucleophiles, piperidine-4-carboxylic acid <1999WO00367>, to give dibenzodioxocins with biological activity. Analogously, the 12-bromo-substituted dibenzodioxocin **295h** (R = R¹ = R² = H, X = CHBr) treated with bromoethanol gave the corresponding 2-bromoethoxy derivative **295k** (R = R¹ = R² = H, X = CH-O(CH₂)₂Br), which, upon nucleophilic substitutions by oxygen nucleophiles, ethyl 3-ethoxy-2-(4'-hydroxyphenyl)propionate <2000WO23416>, or nitrogen nucleophiles, piperidine-3- and -4-carboxylic acid or pyrrolidine-3-acetic acid <1997WO11071, 2000WO23417>, gave dibenzodioxocin with biological activity (see Section 14.05.5.8).



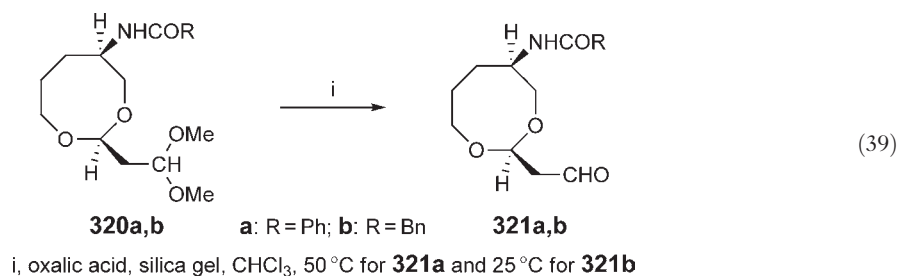
Scheme 74

Within studies toward the synthesis of azadirachtin, the dioxocin **318** was converted into the enone **319** by the standard three-step protocol indicated in Equation (38) in 95% overall yield <2005AGE3447>.



The two hydroxyethyl side chains of dioxocin **299** were obtained by reduction of the corresponding ethyl acetate groups with LiAlH_4 in 92% yield <1999J(P1)1885>. The benzoyl group of the dioxocin **301** was obtained from the corresponding formyl moiety, in 81% overall yield, by reaction with phenylmagnesium bromide, followed by oxidation with Dess–Martin periodinane <2003AGE4685>.

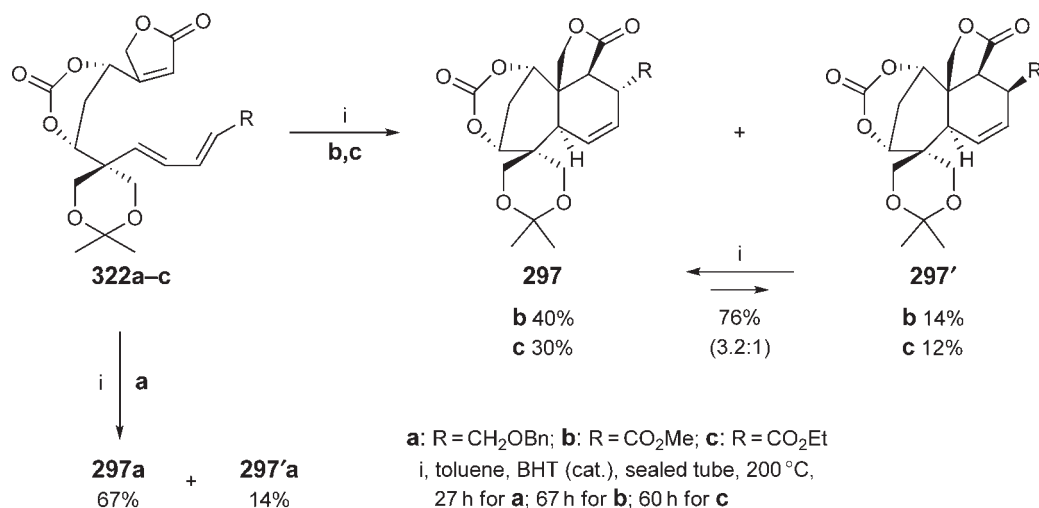
The aldehyde **321a** was obtained in 71% yield from the diacetal **320a** by action of oxalic acid and silica gel (Equation 39) <2002JOC22, 2005BMC5640>.



14.05.5.6 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.05.5.6.1 Ring syntheses from C_6O_2 units

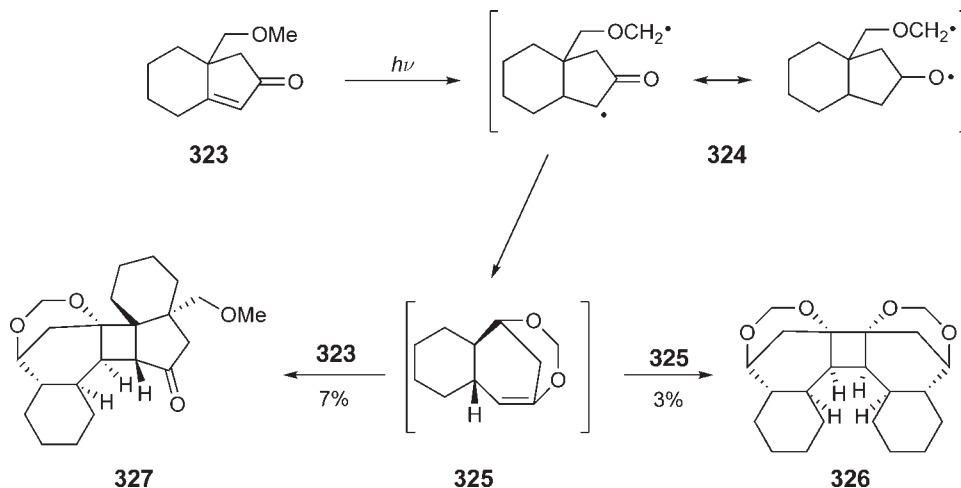
Thermal-induced intramolecular Diels–Alder reaction of **322a** led to the polycondensed dioxocin **297a**, as major adduct, in 67% isolated yield, and the *exo*-adduct **297'a**, as minor product (14%). When **322b** bearing an alkoxycarbonyl group instead of a benzyloxymethyl moiety was heated under the same reaction conditions, a longer time was necessary for completion of the reaction, and the dioxocins **297b** and **297'b** resulted to be both *endo*-adducts in 40% and 14% yield, respectively. Parallel behavior was shown by **322c**, which gave the *endo*-adducts **297c** and **297'c** in 30% and 12% yield, respectively (Scheme 75) <2000S1894>.



Scheme 75

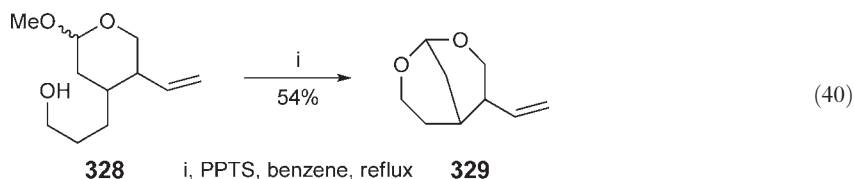
By irradiation of **323**, the polycondensed dioxocins **326** and **327** were obtained in very low yields together with other products; a proposed mechanism for the formation of these products involved intermediate **324**, which originated the dioxocin **325** by ring closure.

Such an intermediate, which possesses great strain, was very reactive and dimerized to give **326** or reacted with **323** to give **327**. It is interesting to note that **326** and **327** showed distinctive regio- and stereochemistry; **326** was a *cis,syn,cis* head-to-head dimer, whereas **327** was a *cis,anti,cis* head-to-tail adduct (Scheme 76) <2000TL3443>.



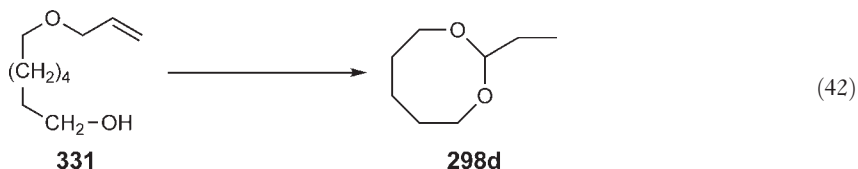
Scheme 76

The last step of the synthesis of the natural product (–)-semburin **329** involved the cyclization of the primary alcohol **328** catalyzed by pyridinium *p*-toluenesulfonate (Equation 40). In analogous fashion, starting from the suitable primary alcohol, the (–)-isosemburine was also obtained <2002SL334>. Similar acid-catalyzed ring-closure was observed in the synthesis of the benzodioxocin **303** from the dialcohol **330** (Equation 41) <2003JOC1081>.



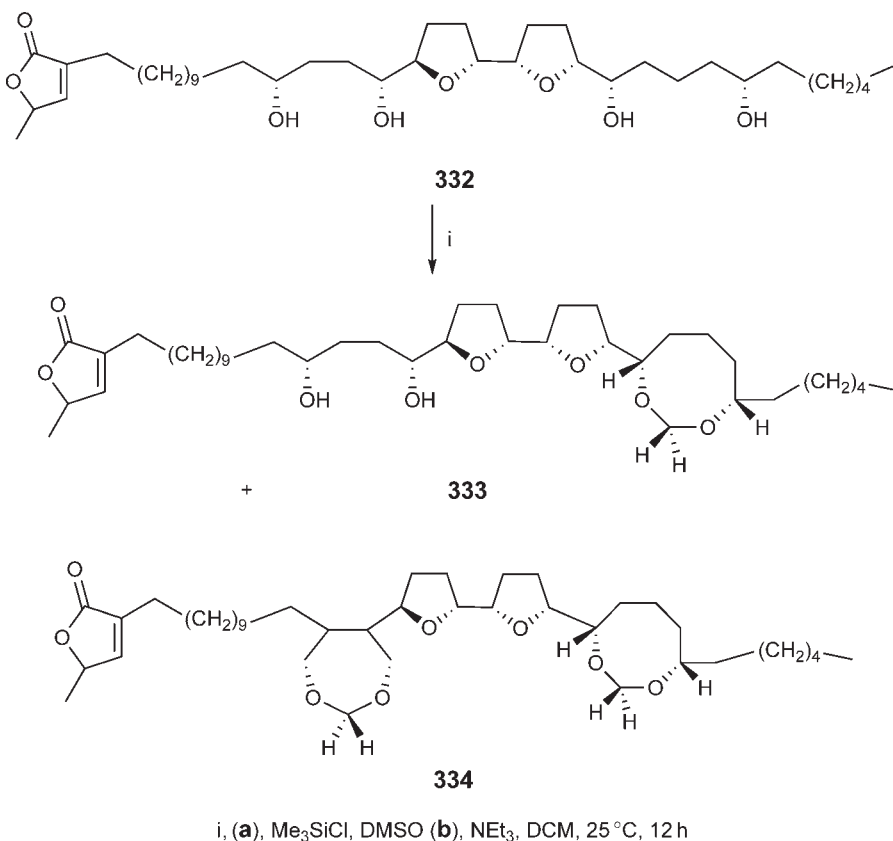


Highly selective cyclization of the allyloxyalcohol **331** using a non-hydride ruthenium complex, $[\text{RuCl}_2(\text{PPh}_3)_3]$, at low concentration, high temperature, and without any solvent afforded dioxocin **298d** with a yield greater than 85% and with a selectivity equal to 94% (Equation 42) <2004SL1203>.



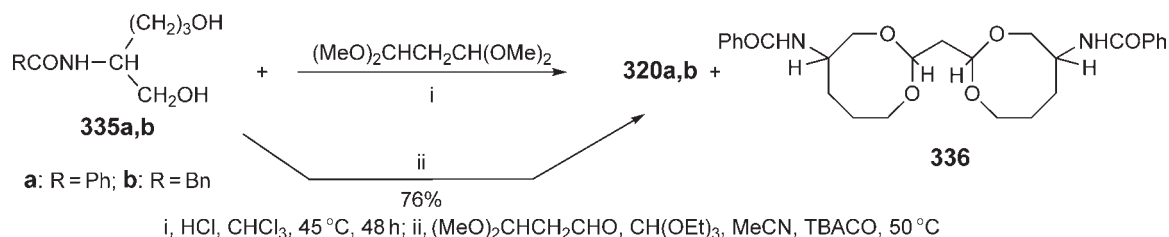
14.05.5.6.2 Ring syntheses from $\text{C}_5\text{O}_2 + \text{C}$ units

Treatment of salzmanin **332**, a bistetrahydrofuran acetogenin, with Me_3SiCl and DMSO, led to the formation of formaldehyde acetal derivatives **333** and **334** in 49% and 25%, respectively. The synthesis has no preparative purpose but served to determine the relative configurations between C-12/C-15 and C-24/C-28 (Scheme 77) <1999JNP710, 1999TL697>. Compounds analogues to **333** and/or **334** were obtained when other bis-THF acetogenins were subjected to the bis-acetalization as in the case of carolins A–C <1998JNP34>, or squamostatin A and squamocin <1995WO34544>.



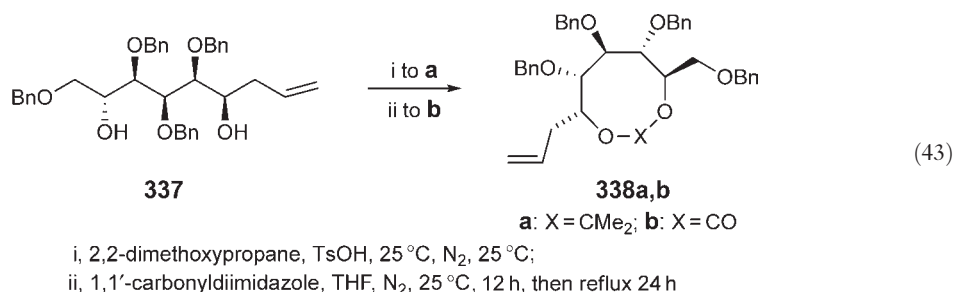
Scheme 77

Reaction of dialcohol **335a** and 1,1,3,3-tetramethoxypropane produced the dioxocin **320a** and the 2,2'-methylenebis-1,3-dioxocin **336** in 14% and 20% yield, respectively <2000EJO2669>. When **335b** was reacted with 3,3-dimethoxypropanal, $\text{CH}(\text{OEt})_3$, and 2,3,3,6-tetrabromo-2,5-cyclohexanedione (TABCO), only **320b** was obtained in 76% yield (Scheme 78) <2005BMC5640>.

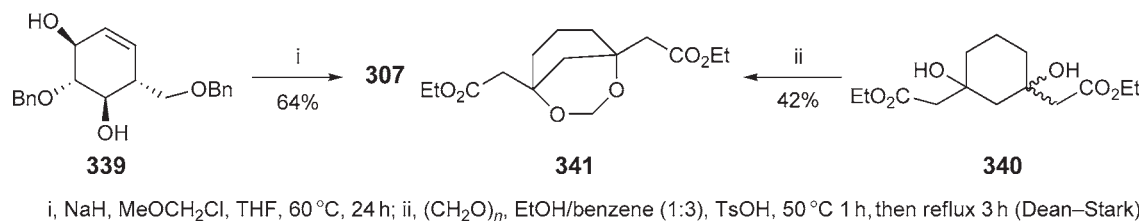


Scheme 78

Acetonization of the dialcohol **337** led to **338a** in 73% yield. Less efficient was the cyclization of **337** with carbonyldiimidazole; therefore, dioxocinone **338b**, even under rather forcing conditions, was obtained in only 29% yield (Equation 43) <2005CEJ6629>. Another example of cyclization of dialcohols, with insertion of a carbon unit, to 1,3-dioxocins, although in poor yield, was furnished by pentane-1,5-diol and β , β -difluoro- α -phenylvinyl sulfide <1995H(41)641>.



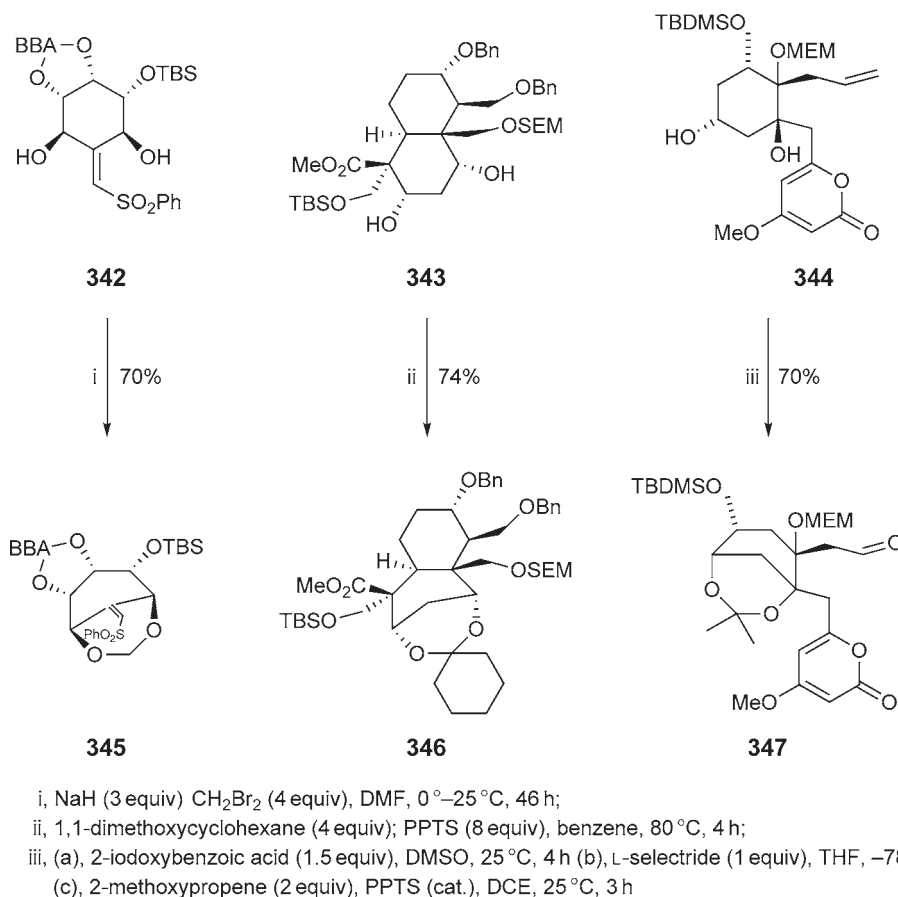
The bridged dioxocin **307** was obtained, in good yield, by treatment of the cyclohexenediol **339** with NaH , which brought about the cyclization of the two unprotected hydroxyl groups with chloro(methoxy)methane <1997JOC3360>. Similar cyclization was observed when the cyclohexane-diol **340** was reacted with paraformaldehyde to give the eight-membered ring **341** (Scheme 79) <1999J(P1)1885>.



Scheme 79

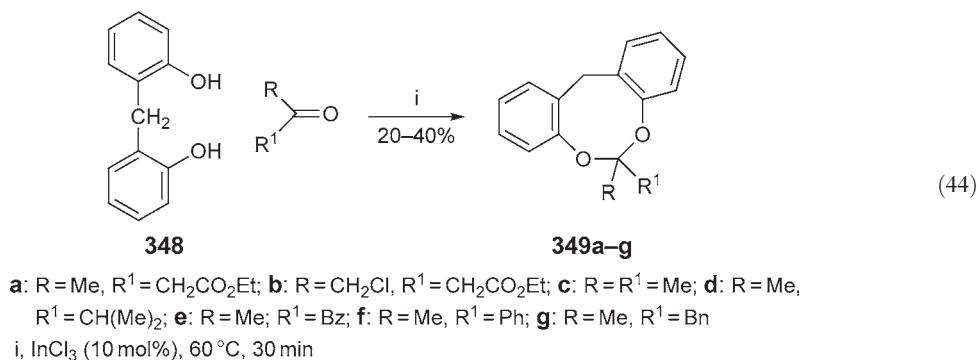
Other examples of dioxocins obtained by cyclization of cyclohexanes bearing two hydroxyl groups in a 1,3-relationship are reported in Scheme 80 along with related reaction conditions. Thus, cyclization of **342**, **343**, and

344 was achieved using CH_2Br_2 , dimethoxycyclohexane, and 2-methoxypropene to give **345**, **346**, and **347**, respectively, in good overall yields <2003SL619, 2005AGE3447, 2003AGE4685>.

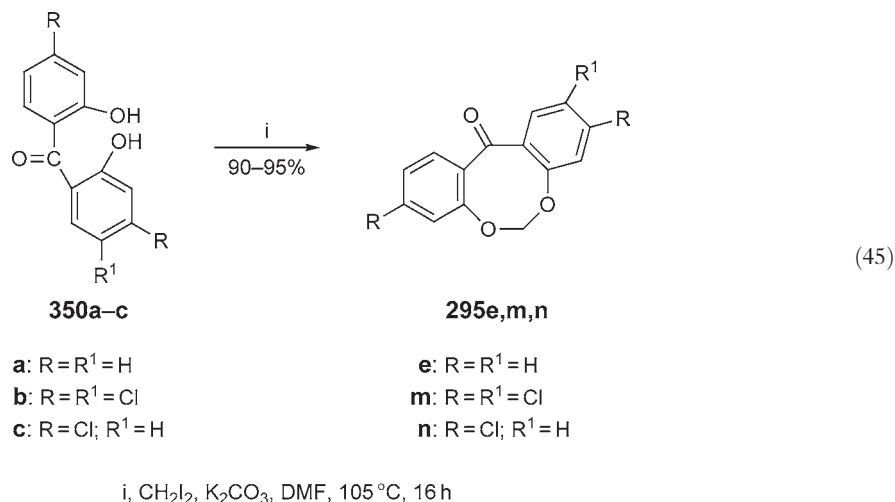


Scheme 80

The 12*H*-dibenzo[*d,g*]1,3-dioxocins **349a–g** were prepared from bis(2-hydroxyphenyl)methane and ketones or β -ketoesters using a catalytic amount (10 mol%) of InCl_3 , without any solvent. For the reaction to take place it is essential that at least one hydrogen atom, belonging to the alkyl group (R), be adjacent to the ketone carbonyl group. Thus, when ethyl 4,4,4-trifluoroacetoacetate, ethyl 4-methoxybenzoylacetate, diethyl malonate, or methyl 4,4-dimethyl-3-oxopentanoate were used as reagents, the reaction did not occur (Equation 44) <2004TL6909>.



Reaction of 2,2'-dihydroxybenzophenones **350a–c** with CH_2I_2 in DMF gave in excellent yields the dibenzodioxocins **295e,m,n** (Equation 45) <1997WO11071, 1998WO15548, 2000WO23416, 2000WO23417>. When the cyclization reaction of **350a–c** was conducted in DMSO with CH_2Br_2 , the yields were lower (~70%) <1997WO37978, 1998USP5780465>, and even worse was the yield of **295b** (20%) obtained from CH_2Br_2 and 2,2'-dioxy-5,5'-dimethyl-1,1'-diphenylethane <1995JST(344)95>. Similar cyclization led to dinaphthodioxocin **296b** by reacting phenyldi(2-naphthol)methane with CH_2Br_2 with nearly quantitative yield <1995JST(344)95>.



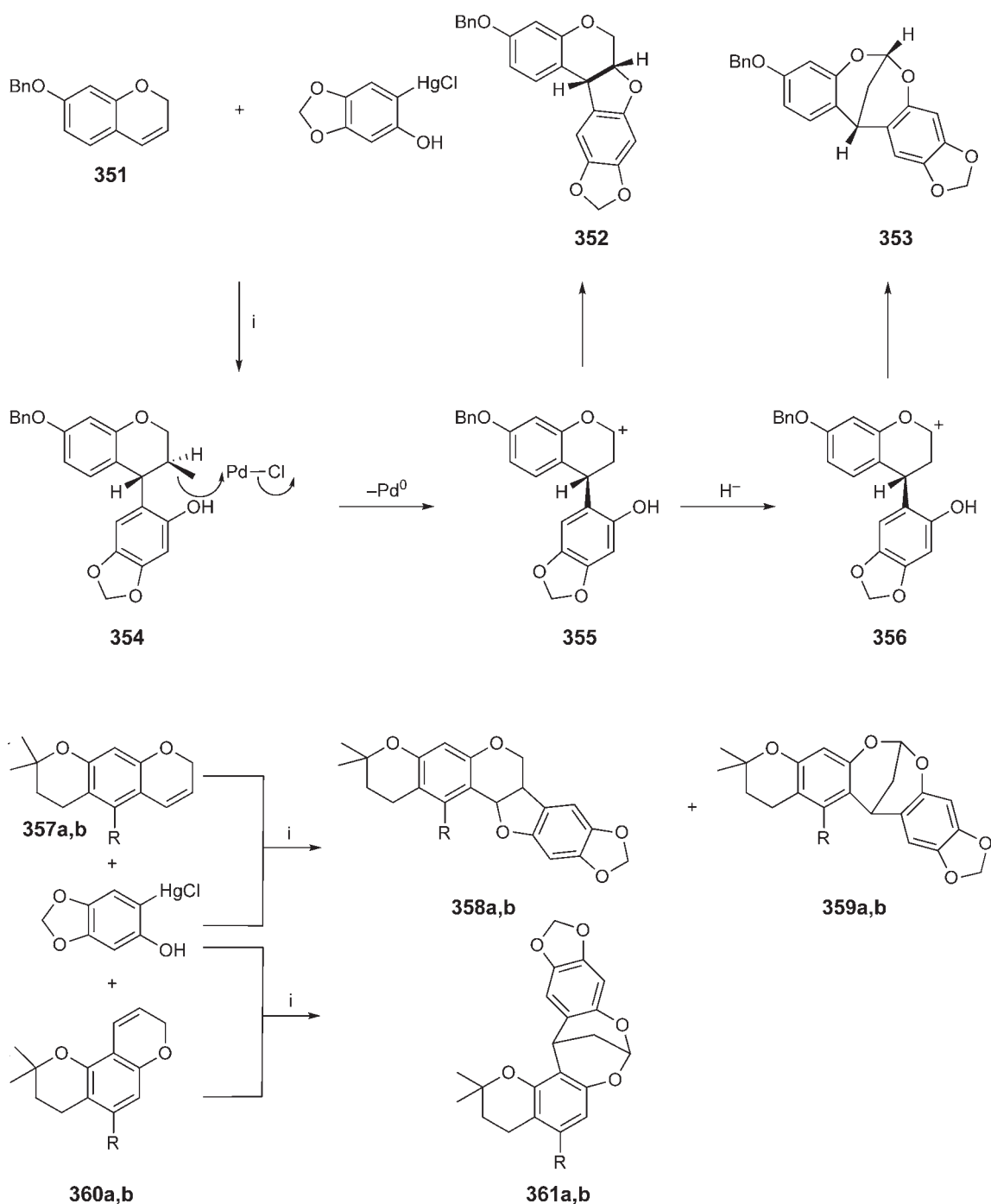
14.05.5.6.3 Ring syntheses from $\text{C}_4\text{O} + \text{C}_2\text{O}$ units

Reaction of 7-benzyloxy-2*H*-1-benzopyran **351** with 2-chloromercurio-3,4-methylenedioxyphenol under the conditions of the Heck oxyarylation procedure afforded the 3-benzylmaackiain, as main product, together with **352** (3%) and dioxocin **353** (8%), as by-products. The formation of these by-products was explained in terms of formation of the organopalladium intermediate **354**, which gave carbocation **355** that cyclized to **352**, upon nucleophilic attack of the hydroxyl group, or rearranged, via a hydride shift, to the more stable carbocation **356**, which cyclized to **353**. The main product, which is a positional isomer of **352**, resulted from the cyclization of organopalladium intermediate bound to the position 4 of the pyran moiety <1999T9283>. Similarly, reaction of chromenes **357a** and **357b**, subjected to a Heck reaction, gave neorautane **358a** and neorautanin **358b** in 37% and 51% yields, respectively. Also, in this case, dibenzodioxocins **359a** and **359b** were obtained as minor products in 26% and 15% yields, respectively. Instead, the angular chromenes **360a** and **360b** gave only the dibenzodioxocins **361a** and **361b** in 58% and 49% yields, respectively (Scheme 81) <1997T12621>.

14.05.5.6.4 Ring syntheses from $\text{C}_2\text{O} + \text{C}_2\text{O} + \text{C}_2$ units

Acetalization of 2 mol of substituted phenols **362a–g** with 1 mol of malonaldehyde bis(dimethylacetal) led, in moderate to excellent yields, to the bridged dibenzodioxocins **365a–g**. The proposed mechanism involved the initial Friedel–Crafts reactions to give the intermediate **363**, which underwent sequential attacks by the hydroxyl groups with elimination of MeOH to give **365a–g** (Scheme 82) <1999T7271>. Such a mechanism is different from that proposed in the case of the thioacetalization leading to the naphthodithiocins from thionaphthol, in which the Friedel–Crafts reaction occurred in the second step and was responsible of the formation of the eight-membered ring (see Section 14.05.4.5.5, Scheme 67).

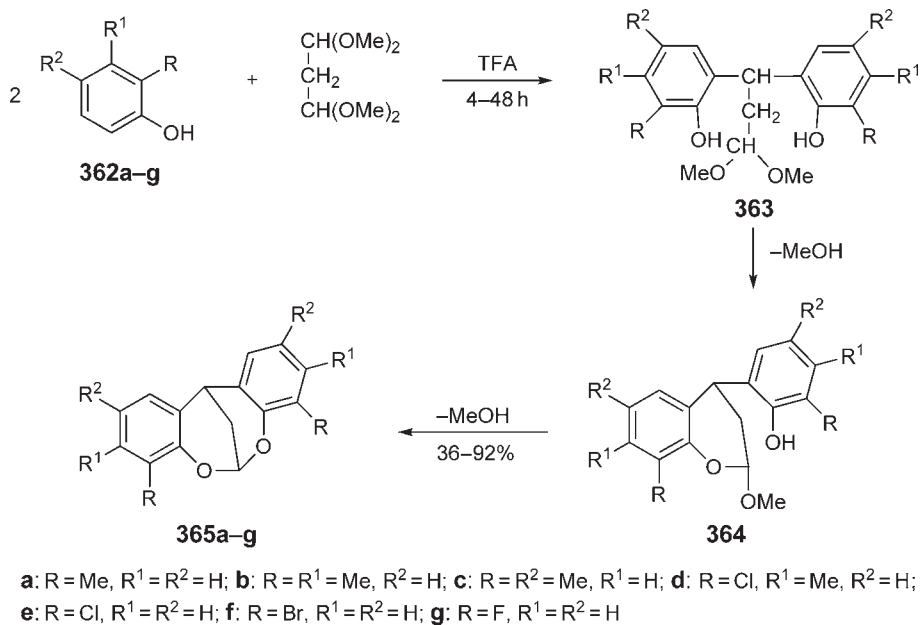
This method, starting from 2-naphthols **366a,b** gave rise to the dinaphthodioxocin **317a,f–h** in 76–81% yield <1999T7271, 2004JA12732> and improved a preceding synthesis, which utilized formic acid as a solvent and malonaldehyde or glutaraldehyde instead of the corresponding diacetals to give **317a,h** in 21–23% yields <1995T2109>. Analogous behavior was shown by the 5-methoxy-1-naphthol **367** and γ -tocopherol **369**, which gave the corresponding dioxocins **368** and **370** in 21% and 35% yields, respectively (Scheme 83) <1995T2109, 2005T9070>.



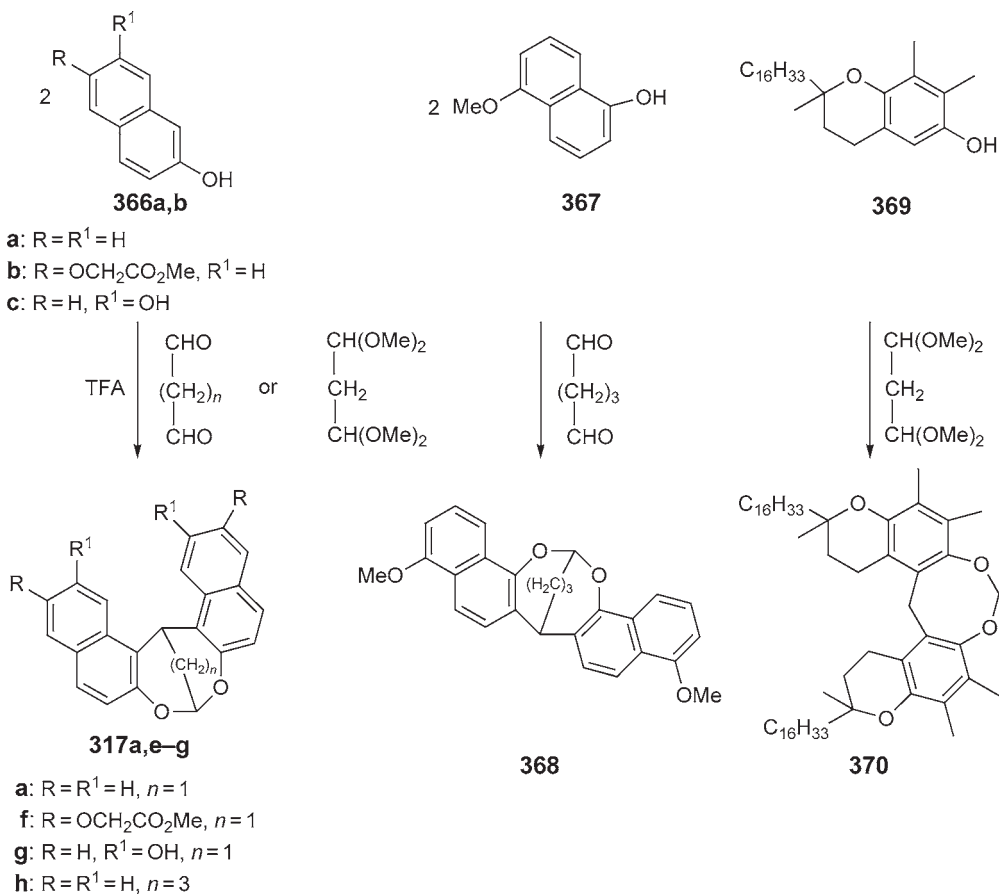
Scheme 81

14.05.5.7 Ring Syntheses by Transformation of Another Ring

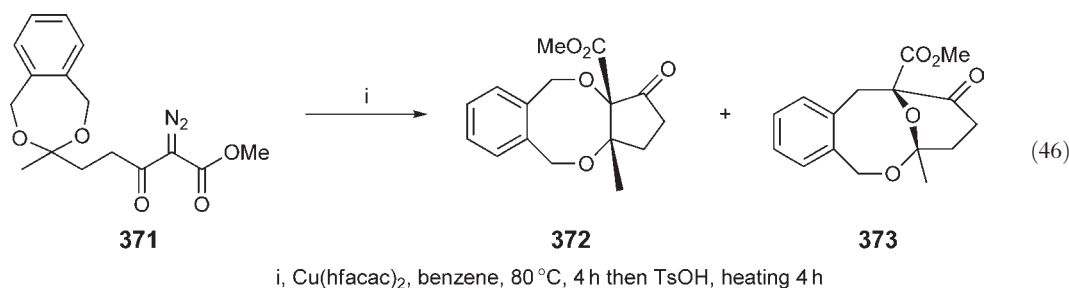
Exposure of the benzodioxepine **371** to catalytic amounts of Cu-(hexafluoroacetylacetonate)₂ [Cu(hfacac)₂] resulted in the formation of the 1,4-benzodioxocin **372**, as main product (56%), and the 1,3-benzodioxocin **373**, as minor product (19%). An endocyclic 1,2-shift to the ketal carbon resulted in the formation of **372**, whereas **373** was the result of an exocyclic 1,2-shift to the benzylic position (Equation 46) <1997JOC3902>.



Scheme 82



Scheme 83



14.05.5.8 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Among the unimolecular cyclizations, the synthesis yielding a single product with excellent yields was the cyclization of allyloxy alcohols brought about by a ruthenium complex. The other unimolecular processes exhibited very low yields and/or mixture of products. The most popular synthesis of 1,3-dioxocins involved the cyclization of 1,5-alcohols with the insertion of a carbon unit. Such acetalization of both acyclic dialcohols or hydroxyl groups bound to rings is particularly efficient and the cyclization of methane-diphenols or dihydroxybenzophenones with dihalomethanes was of wide applications. Palladium-promoted cyclization of chloromercurio compounds showed to be certainly less effective even if it presented some cases in reasonable yields. The sole example synthesis of 1,3-dioxocins by transformation of another ring has no preparative interest.

14.05.5.9 Important Compounds and Applications

Formaldehyde acetal derivatives of squamocin and squamostatin A, analogues of **333** and **334**, exhibited cytotoxicity to human solid tumor cell lines equipotent to adriamycin or orders of magnitude more potent than adriamycin <1995WO34544>. Analogues of **295j**, bearing a piperidine 3- or 4-carboxylic acid or a pyrrolidine-3-acetic acid moieties, were patented for their use for the clinical treatment of painful, hyperalgesic, and/or inflammatory conditions in which C-fibers play a pathophysiological role by eliciting neurogenic pain or inflammation as well as their use for treatment of indications related to the secretion and circulation of insulin antagonizing peptides, for example, NIDDM and ageing-associated obesity <1997WO11071, 1998WO15548, 1999WO00367>. Other analogues of **295**, bearing a variously substituted pyrimidyl moiety at position 12 (35 derivatives), showed excellent herbicidal activity. Such compounds are especially useful for the control of undesirable vegetation in paddy rice <1997WO37978, 1998USP5780465>. An analogue of **295j**, bearing an α -ethoxyphenylpropionic acid side chain at position 12, was showed to be agonist of peroxisome proliferators activated receptor- α (PPAR- α) and - γ (PPAR- γ) with hypolipidemic and antidiabetic activity ($EC_{50} = 3.4 \mu M$) <2000WO23415, 2000WO23416, 2000WO23417, 2002JME789>. Moreover, further 295 analogues were patented for the treatment of patients suffering from a variety of diseases like abnormal tissue growth, neoplasia, hyperplasia, cancer, and diabetic retinopathy <2000WO32193>. Lastly, **320a** showed anti-inflammatory activity against xylene-induced ear edema in mice <2005BMC5640>.

14.05.6 Further Developments

A SciFinder search performed on 12 October 2007 gave no answer for 2*H*-1,3-thiazocines and 4*H*-1,3-oxathiocins.

Regarding the 1,3-diazocines, it was reported that the synthesis of the 'left domain' of haplophytine, a heterodimeric alkaloid endowed with insecticidal activity, contained a pyrrolo-fused carbonyl bridged 1,3-benzodiazocine moiety <2007AG(E)4715>. It was also reported that the synthesis of a pyrazolo-fused 1,3-benzodiazocine and its activity as inhibitor of lymphocyte-specific protein tyrosine kinase (Lck) <2007WO026720>, and the thermal decomposition of a polynitro substituted 1,3-diazocine <2006RJGC499>.

Regarding the 1,3-oxazocines, it was reported that the isolation of 5',8-anhydro-adenosine in an attempt of obtaining 8-fluoroadenosine <2007T3782>, a decaline-fused 1,3-oxazocine, which was unexpectedly obtained in the contest of an attempted synthesis of axinyssamine <2007T1544>, an efficient synthesis and X-ray crystal structure analysis of [1]benzopyrano[4,3-*d*]1,3-benzoxazocin-13-one and its derivatives and 5,6-dihydro-2,4-

disubstituted-2*H*-2,6-methano-1,3-benzoxazocine-5-carbohydrazides <2006SL2791, 2006JCR274>, the utilization of the 4,8-methylene bridged 5,6,7-trihydroxy-8-hydroxymethyl-1,3-oxazocin-2-one as key intermediate for the synthesis of valiolamine <2006JAP232688>, and the unexpected isolation of 4,8-methylene bridged 2-phenyl-7-hydroxy-1,3-oxazocine from the epoxidation of 4-benzamidocyclohexene <2006MI379>.

Regarding the 4*H*-1,3-dioxocins it was reported that the synthesis of 4,8-benzyloxymethane-bridged 5,7-dibenzyloxy-6-hydroxy-2-phenyl-1,3-dioxocin by reduction with diisobutylaluminium hydride (DIBAL-H) of 2,4,6-tri-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate <2007T4149>; analogous reduction of 4,6-di-*O*-benzyl-2-*O*-TBDMS-*myo*-inositol 1,3,5-orthoformate gave the corresponding bridged 1,3-dioxocin <2006CAR897>, the synthesis of 12*H*-dibenzo[*d,g*]-1,3-dioxocins from the reaction bis(2-hydroxyphenyl)methane with aliphatic or aromatic aldehydes <2007H635>, the synthesis of a polycondensed 1,3-dioxocin, analogue of azadirachtin <2007AG(E)1512>, the synthesis of 2-substituted perhydro-1,3-dioxocins by reaction of 1,5-dihydroxypentane with terminal alkynes in the presence of a cationic iridium complex as a catalyst <2006JMO245>, and the synthesis of (±)-diinsininone, a benzopyran-fused 1,3-benzodioxocin <2006T5298>.

Regarding 4*H*-1,3-dithiocins only the synthesis, X-ray single-crystal structure, and electronic properties of two bishienodithiocin derivatives were reported <2007JPC841>.

References

- 1995BMC397 M. Björnsne, T. Szabó, B. Samuelsson, and B. Classon, *Bioorg. Med. Chem.*, 1995, **3**, 397.
 1995H(40)607 T. Oshima, S. Ueno, and T. Nagai, *Heterocycles*, 1995, **40**, 607.
 1995H(41)641 B. T. Kim, Y. K. Min, N. K. Park, K. Y. Cho, and I. H. Jeong, *Heterocycles*, 1995, **41**, 641.
 1995IC792 S. Z. Zhu, W. T. Pennington, and D. D. DesMarteau, *Inorg. Chem.*, 1995, **34**, 792.
 1995JHC627 C. Fossey, D. Ladurée, and M. Robba, *J. Heterocycl. Chem.*, 1995, **32**, 627.
 1995JME2946 P. Herold, J. W. Herzig, P. Wenk, T. Leutert, P. Zbinden, W. Fuhrer, S. Stutz, K. Schenker, M. Meier, and G. Rihs, *J. Med. Chem.*, 1995, **38**, 2946.
 1995JOC5346 Z. Zhang, H. Park, and H. Kohn, *J. Org. Chem.*, 1995, **60**, 5346.
 1995J(P1)123 P. A. Evans, A. B. Holmes, R. P. McGeary, A. Nadin, K. Russell, P. O'Hanlon, and N. D. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 123.
 1995JST(344)95 O. N. Kataeva, I. A. Litvinov, V. A. Naumov, and I. V. Anonimova, *J. Mol. Struct.*, 1995, **344**, 95.
 1995MI447 H. Park, X. Zhang, H. Moon, A. Zwiefka, K. Cox, S. J. Gaskell, W. R. Widger, and H. Kohn, *Arch. Biochem. Biophys.*, 1995, **323**, 447 (*Chem. Abstr.*, 1996, **124**, 310).
 1995S592 S. Blechert, R. Knier, H. Schroers, and T. Wirth, *Synthesis*, 1995, 592.
 1995T2109 A. A. Tunca, N. Talinli, and A. Akar, *Tetrahedron*, 1995, **51**, 2109.
 1995TL1693 L. Micouin, A. Diez, J. Castells, D. Lopez, M. Rubiralta, J. C. Quirion, and H. P. Husson, *Tetrahedron Lett.*, 1995, **36**, 1693.
 1995TL2711 B. H. Lipshutz, K. L. Stevens, and R. F. Lowe, *Tetrahedron Lett.*, 1995, **36**, 2711.
 1995WO34544 J. L. McLaughlin, Z. Gu, and G. Zhao, *PCT Int. Appl. WO 34544* (1995) (*Chem. Abstr.*, 1996, **124**, 256011).
 1995WO06468 P. G. Lysko and R. N. Willette, *PCT Int. Appl. WO 06468* (1995) (*Chem. Abstr.*, 1995, **122**, 306560).
 1996BP1687 M. H. el Kouni, F. N. M. Naguib, R. P. Panzica, B. A. Otter, S. Chu, G. Gosselin, C. K. Chu, R. F. Schinazi, Y. F. Shealy, N. Goudgaon, A. A. Ozerov, T. Ueda, and M. H. Iltzsch, *Biochem. Pharmacol.*, 1996, **51**, 1687 (*Chem. Abstr.*, 1996, **125**, 108579).
 1996HCA426 H. Sigmund and W. Pfeleiderer, *Helv. Chim. Acta*, 1996, **79**, 426.
 1996JBC25369 A. Magyar, X. Zhang, H. Kohn, and W. R. Widger, *J. Biol. Chem.*, 1996, **271**, 25369.
 1996JOC7750 H. Park, X. Zhang, W. R. Widger, and H. Kohn, *J. Org. Chem.*, 1996, **61**, 7750.
 1996JOC7756 A. Santillán, H. Park, X. Zhang, O. Lee, W. R. Widger, and H. Kohn, *J. Org. Chem.*, 1996, **61**, 7756.
 1996JOC7764 H. Park, Z. Zhang, X. Zhang, W. R. Widger, and H. Kohn, *J. Org. Chem.*, 1996, **61**, 7764.
 1996T833 A. Santillán Jr., and H. Kohn, *Tetrahedron*, 1996, **52**, 833.
 1996T3563 P. Forns, A. Diez, M. Rubiralta, X. Solans, and M. Font-Bardia, *Tetrahedron*, 1996, **52**, 3563.
 1996TA721 A. Avenoza, C. Cativiela, M. A. Fernández-Recio, and J. M. Peregrina, *Tetrahedron Asymmetry*, 1996, **7**, 721.
 1996TL187 S. Shuto, K. Haramuishi, and A. Matsuda, *Tetrahedron Lett.*, 1996, **37**, 187.
 1996TL6935 E. L. Bradley, R. B. Herbert, K. W. M. Lawrie, J. A. Khan, C. M. Moody, and D. W. Young, *Tetrahedron Lett.*, 1996, **37**, 6935.
 1997CRV1713 A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713.
 1997JA719 W. Adam, C. R. Saha-Möller, and A. Schönberger, *J. Am. Chem. Soc.*, 1997, **119**, 719.
 1997JHC135 T. Ueda, R. Oh, S.-i. Nagai, and J. Sakakibara, *J. Heterocycl. Chem.*, 1997, **35**, 135.
 1997JHC321 P. Netchitaïlo, M. Othman, and B. Decroix, *J. Heterocycl. Chem.*, 1997, **34**, 321.
 1997JHC375 P. Pigeon and B. Decroix, *J. Heterocycl. Chem.*, 1997, **34**, 375.
 1997JOC3360 J. L. Aceña, O. Arjona, and J. Plumet, *J. Org. Chem.*, 1997, **62**, 3360.
 1997JOC3902 J. B. Brogan and C. K. Zercher, *J. Org. Chem.*, 1997, **62**, 3902.
 1997JOC5432 H. Cho, H. Park, X. Zhang, I. Riba, S. J. Gaskell, W. R. Widger, and H. Kohn, *J. Org. Chem.*, 1997, **62**, 5432.
 1997J(P1)901 C. Perez, Y. L. Janin, D. R. Adams, C. Monneret, and S. Grierson, *J. Chem. Soc., Perkin Trans. 1*, 1997, 901.
 1997J(P2)1445 D. Parker, K. Senanayake, J. Vepsäläinen, S. Williams, A. S. Batsanov, and J. A. K. Howard, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1445.
 1997MI5238 W. L. Nowatzke, E. Keller, G. Koch, and J. P. Richardson, *J. Bacteriol.*, 1997, **179**, 5238 (*Chem. Abstr.*, 1997, **127**, 231798).
 1997SC2241 A. Mamouni, A. Daich, and B. Decroix, *Synth. Commun.*, 1997, **27**, 2241.
 1997S165 A. Avenoza, C. Cativiela, M. A. Fernández-Recio, and J. M. Peregrina, *Synthesis*, 1997, 165.
 1997T12621 K. Subburaj, R. Katoch, M. G. Murugesh, and G. K. Trivedi, *Tetrahedron*, 1997, **53**, 12621.

- 1997WO11071 R. Holweg, T. K. Jorgesen, K. E. Andersen, U. B. Olsen, P. Madsen, Z. Polivka, O. Königova, F. Miksik, M. Kovandova, A. Silhankova, and K. Delar, *PCT Int. Appl. WO 11071* (1997) (*Chem. Abstr.*, 1997, **126**, 305593).
- 1997WO37978 L. D. Markley, P. G. Ray, K. E. Arndt, T. W. Balco, E. N. K. Cressman, J. L. Jackson, D. G. Ouse, and J. Secor, *PCT Int. Appl. WO 37978* (1997) (*Chem. Abstr.*, 1997, **126**, 358870).
- 1998AAC571 L. Carrano, C. Bucci, R. De Pascalis, A. Lavatola, F. Manna, E. Corti, C. B. Bruni, and P. Alitano, *Antimicrob. Agents Chemother.*, 1998, **42**, 571.
- 1998BML1317 D. Pan, S. S. Gambhir, T. Toyokuni, M. R. Iyer, N. Acharya, M. E. Phelps, and J. R. Barrio, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1317.
- 1998H(48)249 A. Lukacs, L. Szabó, E. Baitz-Gács, G. Kalas, and C. Szántay, *Heterocycles*, 1998, **48**, 249.
- 1998JBC34033 I. Riba, S. J. Gaskell, H. Cho, W. R. Widger, and H. Kohn, *J. Biol. Chem.*, 1998, **273**, 34033.
- 1998JME1185 A. Santillán, Jr., X. Zhang, J. Hardesty, W. R. Widger, and H. Kohn, *J. Med. Chem.*, 1998, **41**, 1185.
- 1998JNP34 E. F. Queiroz, F. Roblot, B. Figadère, A. Laurens, P. Duret, R. Hocquemiller, and A. Cavé, *J. Nat. Prod.*, 1998, **61**, 34.
- 1998JOC1290 A. Santillán, X. Zhang, W. R. Widger, and H. Kohn, *J. Org. Chem.*, 1998, **63**, 1290.
- 1998MI1 A. D. Shutalev and G. V. Gurskaya, Electronic Conference on Heterocyclic Chemistry, 29 Jun.–24 Jul. 1998, pp. 497–503 (*Chem. Abstr.*, 2000, **132**, 108207).
- 1998SL891 M. E. Maier and T. Lapeva, *Synlett*, 1998, 891.
- 1998TL1807 J. Lluís, M. I. Matheu, and S. Castillón, *Tetrahedron Lett.*, 1998, **39**, 1807.
- 1998USP5780465 L. D. Markley, K. E. Arndt, P. G. Ray, W. Balko, E. N. K. Cressman, D. G. Ouse, J. L. Jackson, and J. Secor, *US Pat. 5780465* (1998) (*Chem. Abstr.*, 1998, **129**, 105503).
- 1998WO15548 R. Hohlweg, P. Madsen, K. E. Andersen, B. Watson, Z. Polivka, O. Königova, M. Kovandova, A. Silhankova, and V. Valenta, *PCT Int. Appl. WO 15548* (1998) (*Chem. Abstr.*, 1998, **128**, 282847).
- 1999CRT906 F. P. Guengerich, R. G. Mundkowski, M. Voehler, and F. F. Kadlubar, *Chem. Res. Toxicol.*, 1999, **12**, 906 (*Chem. Abstr.*, 1999, **131**, 307809).
- 1999JBC7316 A. Magyar, X. Zhang, F. Abdi, H. Kohn, and W. R. Widger, *J. Biol. Chem.*, 1999, **274**, 7316.
- 1999JHC735 M. Othman, P. Pigeon, and B. Decroix, *J. Heterocycl. Chem.*, 1999, **36**, 735.
- 1999JNP710 E. F. Queiroz, F. Roblot, A. Cavé, R. Hocquemiller, L. Serani, O. Laprèvote, M. De, and Q. Paulo, *J. Nat. Prod.*, 1999, **62**, 710.
- 1999JOC9289 H. Li and M. J. Miller, *J. Org. Chem.*, 1999, **64**, 9289.
- 1999J(P1)1885 H. Takagi, T. Hayashi, T. Mizutani, H. Masuda, and H. Ogoshi, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1885.
- 1999JY1 I. Yavari, D. Tahmassebi, K. Jadidi, D. Nori-Shargh, and S. Balalaie, *J. Mol. Struct.*, 1999, **489**, 67.
- 1999MI441 D. F. Ewing, G. Goethals, G. Mackenzie, P. Martin, G. Ronco, L. Vanbaelinghem, and P. Villa, *J. Carbohydr. Chem.*, 1999, **18**, 441 (*Chem. Abstr.*, 1999, **131**, 59087).
- 1999MI1059 T. M. Bargar, J. Secor, L. D. Markley, B. A. Shaw, and J. A. Erickson, *Pest. Sci.*, 1999, **55**, 1059 (*Chem. Abstr.*, 2000, **132**, 46209).
- 1999OL961 J. E. McCusker, C. A. Grasso, A. D. Main, and L. McElwee-White, *Org. Lett.*, 1999, **1**, 961.
- 1999T7271 A. Banihashemi and A. Rahmatpour, *Tetrahedron*, 1999, **55**, 7271.
- 1999T9283 A. L. Tokes, G. Litkei, K. Gulacsi, S. Antus, E. Baitz-Gacs, C. Szantay, and L. L. Darko, *Tetrahedron*, 1999, **55**, 9283.
- 1999TA3999 A. Avenoza, C. Catiuela, M. A. Fernández-Recio, and J. M. Peregrina, *Tetrahedron Asymmetry*, 1999, **10**, 3999.
- 1999TL697 E. F. Queiroz, E. L. M. Silva, F. Robot, R. Hocquemiller, and B. Figadère, *Tetrahedron Lett.*, 1999, **40**, 697.
- 1999WO00367 K. E. Andersen, T. K. Jorgensen, R. Hohlweg, E. Fischer, U. B. Olsen, Z. Polivka, K. Sindelar, and V. Valenta, *PCT Int. Appl. WO 00367* (1999) (*Chem. Abstr.*, 1999, **130**, 110162).
- 1999WO027931 Y. Matsumoto, A. Ikemoto, C. Morinaga, S. Tawara, and Y. Yocota, *PCT Int. Appl. WO 027931* (1999) (*Chem. Abstr.*, 1999, **131**, 695).
- 2000B8983 M. Koizumi and R. R. Breaker, *Biochemistry*, 2000, **39**, 8983.
- 2000B9067 F. Vincent, W. R. Widger, M. Openshaw, S. J. Gaskell, and H. Kohn, *Biochemistry*, 2000, **39**, 9067.
- 2000B9077 F. Vincent, M. Openshaw, M. Trautwein, S. J. Gaskell, H. Kohn, and W. R. Widger, *Biochemistry*, 2000, **39**, 9077.
- 2000CEJ897 L. A. B. Moraes and M. N. Eberlin, *Chem. Eur. J.*, 2000, **6**, 897.
- 2000EJO2669 L. Bi, M. Zhao, C. Wang, and S. Peng, *Eur. J. Org. Chem.*, 2000, 2669.
- 2000HCA1311 S. Eppacher, N. Solladié, B. Berner, and A. Vasella, *Helv. Chim. Acta*, 2000, **83**, 1311.
- 2000JHC1543 A. Chihab-Eddine, A. Daich, A. Jilale, and B. Decroix, *J. Heterocycl. Chem.*, 2000, **37**, 1543.
- 2000J(P1)3603 S. Shuto, K. Haramuishi, M. Fukuoaka, and A. Matsuda, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3603.
- 2000JPS885 P. Jansen, M. J. Akers, R. M. Amos, S. W. Baertschi, G. G. Cooke, D. E. Dorman, C. A. J. Kemp, S. R. Maple, and K. A. McCune, *J. Pharm. Sci.*, 2000, **89**, 885 (*Chem. Abstr.*, 2000, **133**, 238234).
- 2000MI499 C. Agapakis-Caussè, F. Boscà, J. V. Castell, D. Hernández, M. L. Marin, L. Marrot, and M. A. Miranda, *Photochem. Photobiol.*, 2000, **7**, 499 (*Chem. Abstr.*, 2000, **133**, 116791).
- 2000MOL409 M. T. Baumgartner, M. I. Motura, A. B. Pierini, and M. C. Briñón, *Molecules*, 2000, **5**, 409.
- 2000S1894 Y. Yamamoto, J. Ishihara, N. Kanoh, and A. Murai, *Synthesis*, 2000, 1894.
- 2000T9885 M. P. Groziak and R. Lin, *Tetrahedron*, 2000, **56**, 9885.
- 2000TL3443 A. K. Lai, C. D. Lee, and C. C. Liao, *Tetrahedron Lett.*, 2000, **41**, 3443.
- 2000WO23415 L. Jeppesen, P. S. Bury, and P. Sauerberg, *PCT Int. Appl. WO 23415* (2000) (*Chem. Abstr.*, 2000, **132**, 308360).
- 2000WO23416 L. Jeppesen, P. S. Bury, and P. Sauerberg, *PCT Int. Appl. WO 23416* (2000) (*Chem. Abstr.*, 2000, **132**, 293782).
- 2000WO23417 L. Jeppesen, P. S. Bury, and P. Sauerberg, *PCT Int. Appl. WO 23417* (2000) (*Chem. Abstr.*, 2000, **132**, 308361).
- 2000WO32193 A. J. Hansen, T. K. Jorgensen, and U. Olsen, *PCT Int. Appl. WO 32193* (2000) (*Chem. Abstr.*, 2000, **133**, 34425).
- 2000WO61537 P. Del Soldato, *PCT Int. Appl. WO 61537* (2000) (*Chem. Abstr.*, 2000, **133**, 310142).
- 2001AAC3182 E. Z. Baum, D. A. Montenegro, L. Licata, I. Turchi, G. C. Webb, B. D. Foleno, and K. Bush, *Antimicrob. Agents Chemother.*, 2001, **45**, 3182.
- 2001JOC1538 A. P. H. J. Schenning, B. Escuder, J. L. M. van Nunen, B. de Bruin, D. W. P. M. Löwik, A. E. Rowan, S. J. van der Gaast, M. C. Feiters, and R. J. M. Nolte, *J. Org. Chem.*, 2001, **66**, 1538.
- 2001JOC2251 F. Vincent, J. Srinivasan, A. Santillán, Jr., W. R. Widger, and H. Kohn, *J. Org. Chem.*, 2001, **66**, 2251.
- 2001MRC657 K. Pihlaja, H. Nummelin, K. D. Klika, and J. Czombos, *Magn. Reson. Chem.*, 2001, **39**, 657.
- 2001TL6859 H. Ohmura and K. Mikami, *Tetrahedron Lett.*, 2001, **42**, 6859.

- 2001TL6953 D. Jönsson, M. Erlandsson, and A. Undén, *Tetrahedron Lett.*, 2001, **42**, 6953.
- 2001WO90081 C. A. Dvorak, K. L. Fisher, R. N. Harris, H. Maag, A. Prince, D. B. Repke, and R. S. Stabler, *PCT Int. Appl. WO 90081* (2001) (*Chem. Abstr.*, 2002, **136**, 6016).
- 2001WO90082 A. M. Madera, R. S. Stabler, and R. J. Weikert, *PCT Int. Appl. WO 90082* (2001) (*Chem. Abstr.*, 2002, **136**, 6017).
- 2002B12377 T. P. Weber, W. R. Widger, and H. Kohn, *Biochemistry*, 2002, **41**, 12377.
- 2002BMC599 B. L. Finkelstein, E. A. Benner, M. C. Hendrixson, K. T. Kranis, J. J. Rauh, M. R. Sethuraman, and S. F. McCann, *Bioorg. Med. Chem.*, 2002, **10**, 599.
- 2002CC940 H. Rudler, B. Denise, A. Parlier, and J. C. Daran, *Chem. Commun.*, 2002, 940.
- 2002CME1 A. Capasso, R. Aquino, N. De Tommasi, S. Piacente, L. Rastrelli, and C. Pizza, *Curr. Med. Chem.*, 2002, **2**, 1 (*Chem. Abstr.*, 2002, **137**, 195006).
- 2002JME789 P. Sauerberg, I. Pettersson, L. Jeppesen, P. S. Bury, J. P. Mogensén, K. Wassermann, C. L. Brand, J. Sturis, H. F. Wöldike, J. Fleckner, A. T. Andersen, S. B. Mortensen, L. A. Svensson, H. B. Rasmussen, S. V. Lehmann, Z. Polivka, K. Sindelar, V. Panajotova, L. Ynddal, and E. M. Wulff, *J. Med. Chem.*, 2002, **45**, 789.
- 2002JOC22 L. Bi, M. Zhao, C. Wang, S. Peng, and E. Winterfeldt, *J. Org. Chem.*, 2002, **67**, 22.
- 2002JOC4086 F. Qian, J. E. McCusker, Y. Zhang, A. D. Main, M. Chlebowsky, M. Kokka, and L. McElwee-White, *J. Org. Chem.*, 2002, **67**, 4086.
- 2002MI151 J. A. A. W. Elemans, A. E. Rowan, and R. J. M. Nolte, *J. Supramol. Chem.*, 2002, **2**, 151 (*Chem. Abstr.*, 2004, **140**, 181424).
- 2002PS1855 I. Tworowska, W. Dabkowski, and J. Michalski, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 1855.
- 2002SL334 K. Kadota, T. Taniguchi, and K. Ogasawara, *Synlett*, 2002, 334.
- 2002T7049 S. Kanoh, M. Naka, T. Nishimura, and M. Motoi, *Tetrahedron*, 2002, **58**, 7049.
- 2002TL6653 F. Chérioux and G. Süß-Fink, *Tetrahedron Lett.*, 2002, **43**, 6653.
- 2002TL8025 J. Agejas, F. Delgado, J. J. Vaquero, J. L. Garcia-Navio, and C. Lamas, *Tetrahedron Lett.*, 2002, **43**, 8025.
- 2002WO32920 L. Stuyver and K. A. Watanabe, *PCT Int. Appl. WO 32920* (2002) (*Chem. Abstr.*, 2002, **136**, 340939).
- 2002WO094844 B. Agrawal and D. L. J. Tyrrell, *PCT Int. Appl. WO 094844* (2002) (*Chem. Abstr.*, 2002, **137**, 385074).
- 2003AGE4685 S. Kirsch and T. Bach, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 4685.
- 2003JA3649 M. L. Munzarová and V. Sklenář, *J. Am. Chem. Soc.*, 2003, **125**, 3649.
- 2003JOC367 F. Seela and Y. He, *J. Org. Chem.*, 2003, **68**, 367.
- 2003JOC1081 K. Mikami, H. Ohmura, and M. Yamanaka, *J. Org. Chem.*, 2003, **68**, 1081.
- 2003JOC5575 A. P. Brogan, W. R. Widger, and H. Kohn, *J. Org. Chem.*, 2003, **68**, 5575.
- 2003NN45 M. T. Baumgartner, M. I. Motura, R. H. Contreras, A. B. Pierini, and M. C. Briñón, *Nucleos. Nucleot. Nucleic Acids*, 2003, **22**, 45 (*Chem. Abstr.*, 2003, **139**, 117646).
- 2003NN735 J. Boryski and T. Zandecki, *Nucleos. Nucleot. Nucleic Acids*, 2003, **22**, 735 (*Chem. Abstr.*, 2004, **140**, 199585).
- 2003SL619 Y. Ohtani, T. Shinada, and Y. Ohfuné, *Synlett*, 2003, 619.
- 2003WO018599 J. A. M. Eisenbarth, S. J. Martin, U. Wagner-Utermann, and M. Eisenhut, *PCT Int. Appl. WO 018599* (2003) (*Chem. Abstr.*, 2003, **138**, 205304).
- 2003WO065983 J. M. Balkovec, R. Thieringer, S. S. Mundt, A. Manowski-Vosatka, D. W. Ham, G. F. Patel, S. D. Aster, S. T. Waddell, S. H. Olson, and M. Milana, *PCT Int. Appl. WO 065983* (2003) (*Chem. Abstr.*, 2003, **139**, 180065).
- 2004H33 A. Cul, A. Daich, B. Decroix, G. Sanz, and L. Van Hijfte, *Heterocycles*, 2004, **64**, 33.
- 2004JA12732 B. J. Shorthill, C. T. Avetta, and T. E. Glass, *J. Am. Chem. Soc.*, 2004, **126**, 12732.
- 2004JIC598 R. N. Kumar, T. Suresh, T. Dhanabal, and P. S. Mohan, *J. Indian Chem. Soc.*, 2004, **81**, 598.
- 2004JME6100 P. Wang, L. Hollecker, K. W. Pankiewicz, S. E. Patterson, T. Wtaker, T. R. McBrayer, P. M. Tharnish, R. W. Sidwell, L. J. Stuyver, M. J. Otto, R. F. Schinazi, and K. A. Watanabe, *J. Med. Chem.*, 2004, **47**, 6100.
- 2004JOC8681 M. Amat, M. Pérez, N. Llor, C. Escolano, F. J. Luque, E. Molins, and J. Bosch, *J. Org. Chem.*, 2004, **69**, 8681.
- 2004NN117 T. Zandecki and J. Boryski, *Nucleos. Nucleot. Nucleic Acids*, 2004, **23**, 117 (*Chem. Abstr.*, 2004, **141**, 54556).
- 2004NN347 G. S. Chen, C.-S. Chen, T.-C. Chien, J.-Y. Yeh, C.-C. Kuo, R. S. Talekar, and J.-W. Chern, *Nucleos. Nucleot. Nucleic Acids*, 2004, **23**, 347 (*Chem. Abstr.*, 2004, **141**, 54559).
- 2004OL3437 V. G. Nenajdenko, V. V. Sumerin, K. Y. Chernichenko, and E. S. Balenkova, *Org. Lett.*, 2004, **6**, 3437.
- 2004SL1203 M. Urbala, N. Kuźnik, S. Krompiec, and J. Rzepa, *Synlett*, 2004, 1203.
- 2004SL1584 L. D. Raev, W. Frey, and I. C. Ivanov, *Synlett*, 2004, 1584.
- 2004TL6909 G. Tocco, M. Begala, G. Delogu, C. Picciau, and G. Podda, *Tetrahedron Lett.*, 2004, **45**, 6909.
- 2004WO013300 P. Wang, L. J. Stuyver, K. Watanabe, A. Hassan, B.-K. Chun, and L. Hollecker, *PCT Int. Appl. WO 013300* (2004) (*Chem. Abstr.*, 2004, **140**, 181711).
- 2004WO039172 A. Szöke, *PCT Int. Appl. WO 039172* (2004) (*Chem. Abstr.*, 2004, **140**, 363079).
- 2004WO062553 P. M. Hilarie, H. Yin, S. Surve, and M. Wenckens, *PCT Int. Appl. WO 062553* (2004) (*Chem. Abstr.*, 2004, **141**, 150947).
- 2005AGE3447 K. C. Nicolaou, P. K. Sasmal, T. V. Koftis, A. Converso, E. Loizidou, F. Kaiser, A. J. Roecker, C. C. Dellios, X. W. Sun, and G. Petrovic, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 3447.
- 2005AGE7107 Y. Liu and R. Warmuth, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 7107.
- 2005BMC5640 L. Bi, Y. Zhang, M. Zhao, C. Wang, P. Chan, J. B.-H. Tok, and S. Peng, *Bioorg. Med. Chem.*, 2005, **13**, 5640.
- 2005CC1171 Z. Z. Yue and Y. C. Li, *Chin. Chem. Lett.*, 2005, **16**, 171 (*Chem. Abstr.*, 2005, **143**, 387278).
- 2005CEJ6629 M. Shimizu, M. Kimura, and Y. Tamaru, *Chem. Eur. J.*, 2005, **11**, 6629.
- 2005CPB1355 M. Kitajima, N. Fujii, F. Yoshino, H. Sudo, K. Saito, N. Aimi, and H. Takayama, *Chem. Pharm. Bull.*, 2005, **53**, 1355.
- 2005EJO2758 N. Hucher, A. Pesquet, P. Netchitaïlo and A. Daïch, *Eur. J. Org. Chem.*, 2005, 2758.
- 2005EJO3724 H. Rudler, B. Denise, Y. Xu, A. Parlier, and J. Vaisserman, *Eur. J. Org. Chem.*, 2005, 3724.
- 2005HCA2683 S. Porcher and S. Pitsch, *Helv. Chim. Acta*, 2005, **88**, 2683.
- 2005HCA2764 T. Ho and C. Chen, *Helv. Chim. Acta*, 2005, **88**, 2764.
- 2005JA1773 S. Choi, R. B. Cooley, A. Voutchkova, C. H. Leung, L. Vastag, and D. E. Knowles, *J. Am. Chem. Soc.*, 2005, **127**, 1773.
- 2005JME6454 P. Wang, J. Du, S. Rachakonda, B. K. Chun, P. M. Tharnish, L. J. Stuyver, M. J. Otto, R. F. Schinazi, and K. A. Watanabe, *J. Med. Chem.*, 2005, **48**, 6454.

- 2005JME8182 F. I. Carroll, S. Chaudhari, J. B. Thomas, S. W. Mascarella, K. M. Gigstad, J. Deschamps, and H. A. Navarro, *J. Med. Chem.*, 2005, **48**, 8182.
- 2005JNP1689 R. J. Capon and N. S. Trotter, *J. Nat. Prod.*, 2005, **68**, 1689.
- 2005MI99 E. Skordalakes, A. P. Brogan, B. S. Park, H. Kohn, and J. M. Berger, *Structure*, 2005, **13**, 99 (*Chem. Abstr.*, 2005, **142**, 232335).
- 2005MI637 J. Backman and L. Kronberg, *Chemosphere*, 2005, **58**, 637 (*Chem. Abstr.*, 2005, **142**, 368872).
- 2005OL4717 S. Suga, S. Suzuki, and J. Yoshida, *Org. Lett.*, 2005, **7**, 4717.
- 2005RJO1089 P. A. Kikilo, B. I. Khairutdinov, Y. G. Shtrylin, V. V. Klochkov, and E. N. Klimovitskii, *Russ. J. Org. Chem. (Engl. Transl.)*, 2005, **41**, 1089.
- 2005T1207 E. Gómez-Sánchez and J. Marco-Contelles, *Tetrahedron*, 2005, **61**, 1207.
- 2005T9070 C. Adewöhler and T. Rosenau, *Tetrahedron*, 2005, **61**, 9070.
- 2005TL2825 B. K. Chun, P. Wang, A. Hassan, J. Du, P. M. Tharnish, L. J. Stuyver, M. J. Otto, R. F. Schinazi, and K. A. Watanabe, *Tetrahedron Lett.*, 2005, **46**, 2825.
- 2005USP0026902 T. Maziasz, *US Pat.* 0026902 (2005) (*Chem. Abstr.*, 2005, **142**, 170033).
- 2006BMC1 B. Park, W. Widger, and H. Kohn, *Bioorg. Med. Chem.*, 2006, **13**, 1.
- 2006CAR897 M. Sala, J. Kolar, M. Strlic, and M. Kocevar, *Carbohydr. Res.*, 2006, **341**, 897.
- 2006JA1531 M. Yamanaka, Y. Yamada, Y. Sei, K. Yamaguchi, and K. Kobayashi, *J. Am. Chem. Soc.*, 2006, **128**, 1531.
- 2006JAP232688 G. Wanyoike, K. Kurashima, and H. Sasaki, *Jpn. Pat.*, 232688, 2006 (*Chem. Abstr.* 2006, **145**, 293292).
- 2006JCR274 A. S. Girgis and H. M. Hosni, *J. Chem. Res.*, 2006, 274.
- 2006JMOC245 S. Y. Kim, C. S. Chin, and M.-S. Eum, *J. Mol. Catal.*, 2006, **253**, 245.
- 2006JOC1289 Z. R. Laughery and B. C. Gibb, *J. Org. Chem.*, 2006, **71**, 1289.
- 2006MI379 L. Huang, Y.-J. Zhou, and D.-Y. Ye, *Youji Huaxue*, 2006, **26**, 379 (*Chem. Abstr.* 2006, **145**, 505274).
- 2006RJC499 R. S. Stepanov, L. A. Kruglyakova, and A. M. Astakhov, *Russ. J. Gen. Chem.*, 2006, **76**, 499.
- 2006RJC499 R. S. Stepanov, L. A. Kruglyakova, and A. M. Astakhov, *Russ. J. Gen. Chem. (Engl. Trans.)*, 2006, **76**, 499.
- 2006SL2791 J.-F. Wang, Y.-X. Liao, P.-Y. Kuo, Y.-H. Gau, and D.-Y. Yang, *Synlett*, 2006, 2791.
- 2006T5298 C. Selenski and T. R. R. Pettus, *Tetrahedron*, 2006, **62**, 5298.
- 2006WO002868 F. Chi, *PCT Int. Appl. WO* 002868 (2006) (*Chem. Abstr.*, 2006, **144**, 84538).
- 2006WO126790 T.-A. Lee and K.-C. Kwon, *PCT Int. Appl. WO* 126790 (2006) (*Chem. Abstr.*, 2007, **146**, 27846).
- 2007AG(E)1512 H. Watanabe, N. Mori, D. Itoh, T. Kitahara, and K. Mori, *Angew. Chem. Int. Ed. Engl.*, 2007, **46**, 1512.
- 2007AG(E)4715 K. C. Nicolau, U. Majumder, S. P. Roche, and D. Y.-K. Chen, *Angew. Chem. Int. Ed. Engl.*, 2007, **46**, 4715.
- 2007H635 G. Tocco, M. Begala, G. Meli, and G. Podda, *Heterocycles*, 2007, **71**, 635.
- 2007JPC841 R. P. Ortiz, R. M. Osuna, V. Hernandez, J. T. Lopez Navarrete, B. Vercelli, G. Zotti, V. V. Sumerin, E. S. Balenkova, and V. G. Nenajdenko, *J. Phys. Chem. A*, 2007, **111**, 841.
- 2007T1544 L. Castellanos, C. Duque, J. Rodriguez, and C. Jimenez, *Tetrahedron*, 2007, **63**, 1544.
- 2007T3782 G. Butora, C. Schmitt, D. A. Levorse, E. Streckfuss, G. A. Doss, and M. MacCoss, *Tetrahedron*, 2007, **63**, 3782.
- 2007T4149 C. Murali, M. S. Shashidhar, and C. S. Gopinath, *Tetrahedron*, 2007, **63**, 4149.
- 2007WO026720 H. Umemiya, H. Amada, T. Yabuuchi, T. Koami, F. Shiozawa, Y. Oka, and M. Sato, *PCT Int. Appl. WO* 026720, (2007), *Chem. Abstr.*, 2007, **146**, 259687.

Biographical Sketch



Girolamo Cirrincione was born in Palermo in 1948. In March 1974, he graduated in chemistry from the University of Palermo. After completing one year of military service, he did his postdoctoral fellowship at the Medicinal Chemistry Department of the University of Palermo from May 1975 to March 1976; from April 1976 to October 1981, he was a research fellow and from November 1981 to October 1994 an associate professor of medicinal chemistry at the same institution. Since November 1994, he has been a full professor of medicinal chemistry at the University of Palermo. He has obtained CNR-NATO Fellowships (September 1982–May 1983, July–August 1986, July–September 1989) and British Council Fellowship (August 1984) from the School of Chemical Sciences of the University of East Anglia Norwich (UK).

He has served as the director of the Istituto Farmacochimico (March 1995–June 1999) and director of the Dipartimento Farmacochimico Toss. Biol. (July 1999–December 2004 and July 2005–to date). He is responsible for ERASMUS exchanges of the Faculty of Pharmacy of the University of Palermo; for the research sector 'Synthetic Analogues of Natural Structure of Biological Interest' of the ICTPN-CNR in a scientific capacity (January 1994–December 1998). He has been member of the Drug Discovery Committee of the European Organization for Research and Treatment of Cancer, the Società Chimica Italiana, and the International Society of Heterocyclic Chemistry (which he has also served in the capacity of vice-president for the period 2004–05). He is a scientific editor for the journal *ARKIVOC*.



Patrizia Diana was born in Palermo in 1967. She graduated in pharmacy with honors at the University of Palermo in March 1990. From April 1990 to August 1992, she was a research fellow at the Medicinal Chemistry Department of the University of Palermo. She has been working as researcher in medicinal chemistry (September 1992–March 2000) and associate professor of medicinal chemistry (April 2000–to date) at the University of Palermo. From May 1994 to May 1995, she worked with Professor Malcolm F. G. Stevens at the CRC Experimental Cancer Chemotherapy Research Group for a fellowship. Since 2005, she has been vice-director of the Dipartimento Farmacochimico Toss. E Biol. She is a member of the Società Chimica Italiana and International Society of Heterocyclic Chemistry.

14.06

Eight-membered Rings with Two Heteroatoms 1,4

I. Shcherbakova

MediProPharma, Midvale, UT, USA

© 2008 Elsevier Ltd. All rights reserved.

14.06.1	Introduction	256
14.06.2	Theoretical Methods	256
14.06.3	Rings with Two Nitrogens (1,4-Diazocines)	260
14.06.3.1	Experimental Structural Methods	260
14.06.3.2	Thermodynamic Aspects	261
14.06.3.3	Reactivity of Nonconjugated Rings	262
14.06.3.4	Ring Syntheses	263
14.06.3.4.1	Intramolecular cyclizations	263
14.06.3.4.2	Intermolecular condensation reactions	271
14.06.3.5	Ring Synthesis by Transformation of Another Ring	272
14.06.3.6	Comparison of Synthetic Routes	274
14.06.3.7	Important Compounds and Applications	274
14.06.4	Rings with One Nitrogen and One Oxygen (4<i>H</i>-1,4-Oxazocines)	274
14.06.4.1	Experimental Structural Methods	274
14.06.4.2	Thermodynamic Aspects	274
14.06.4.3	Reactivity of Nonconjugated Rings	276
14.06.4.4	Ring Syntheses	277
14.06.4.5	Ring Synthesis by Transformation of Another Ring	279
14.06.4.6	Comparison of Synthetic Routes	281
14.06.4.7	Important Compounds and Applications	281
14.06.5	Rings with One Nitrogen and One Sulfur (4<i>H</i>-1,4-Thiazocines)	281
14.06.5.1	Reactivity of Nonconjugated Rings	281
14.06.5.2	Ring Syntheses	281
14.06.5.3	Ring Synthesis by Transformation of Another Ring	283
14.06.5.4	Comparison of Synthetic Routes	283
14.06.5.5	Important Compounds and Applications	284
14.06.6	Rings with Two Oxygens (1,4-Dioxocines)	284
14.06.6.1	Experimental Structural Methods	284
14.06.6.2	Thermodynamic Aspects	286
14.06.6.3	Reactivity of Nonconjugated Rings	287
14.06.6.4	Reactivity of Substituents Attached to Ring Carbon Atoms	289
14.06.6.5	Ring Syntheses	289
14.06.6.6	Ring Synthesis by Transformation of Another Ring	293
14.06.6.7	Comparison of Synthetic Routes	294
14.06.6.8	Important Compounds and Applications	294
14.06.7	Rings with One Oxygen and One Sulfur (1,4-Oxathiocines)	295
14.06.8	Rings with Two Sulfurs (1,4-Dithiocines)	296
14.06.9	Further Developments	296
	References	299

14.06.1 Introduction

Eight-membered rings with two N-, O-, or S-atoms or combinations of these heteroatoms in a 1,4-relationship are discussed in this chapter where the publications from 1995 and later chronologically extend coverage of the topic in CHEC(1984) <1984CHEC(5)653> and CHEC-II(1996) <1996CHEC-II(9)527>. For comprehensive coverage of the subject, this chapter should be treated in conjunction with the corresponding publications in CHEC(1984) and CHEC-II(1996). The former, where all eight-membered ring heterocycles were treated in a single chapter, focused primarily on the N-containing compounds, 1,4-diazocines and 1,4-oxazocines, the best-known members of this family of heterocycles. The latter publication extended the overview of the N-containing heterocycles and presented an expanded coverage of the remaining classes, which received little attention in CHEC(1984).

Nomenclature for the eight-membered 1,4-diheterocycles follows IUPAC rules and the names are generated with the ACD software. The parent unsaturated systems are referred to as the corresponding -cines, whereas the fully saturated rings are recognized as -canes. Benzo and dibenzo derivatives follow the standard IUPAC nomenclature. Specific names appear for the individual compounds, where appropriate.

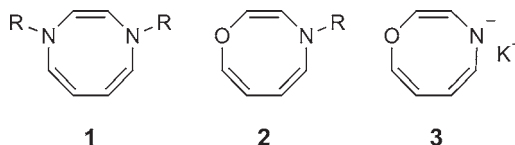
Compounds in which ring heteroatoms are members of another fused ring and bridged polycyclic compounds are, with a few exceptions, not covered in this chapter.

Among eight-membered 1,4-diheterocycles, 1,4-diazo analogs are the largest class based on the number of publications, mostly due to the studies of their pharmacological properties. 1,4-Dioxacines are the second large class, particularly due to an intense interest in the ring-closing metathesis (RCM) reaction, which is being studied in the carbon-carbon bond formation as a powerful method for the synthesis of cyclic systems. 1,4-Oxazocines represent an exciting field of research in medicinal chemistry due to their biological activity <1996CHEC-II(9)527>. Eight-membered 1,4-diheterocycles containing S are less studied, although the recent data suggest their potential applications as biologically active compounds.

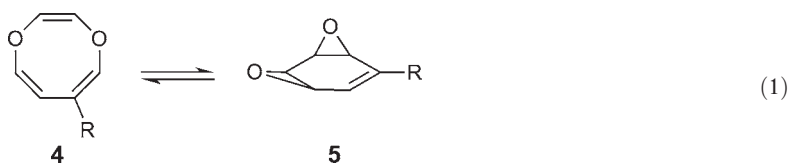
A general discussion of the theoretical studies covers all classes of the title heterocycles followed by each class which is discussed separately in the same general format of this edition. Coverage of each class in the subsections is organized by the type of compounds based on the extent of unsaturation of the diheterocine ring, with fully unsaturated ring systems appearing before those of lower oxidation level and fully saturated derivatives discussed last. Missing section headings (e.g., "Reactivity of fully conjugated rings") are relevant to the cases where no advances have been reported since 1995. Since very few advances occurred for 1,4-oxathiocines and 1,4-dithiocines, these heterocycles are discussed in one section each without subsections.

14.06.2 Theoretical Methods

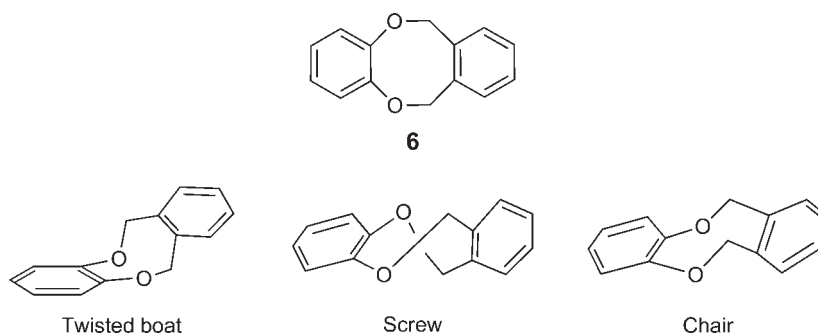
Eight-membered rings with two N-, O-, or S-atoms or combinations of these heteroatoms in a 1,4-relationship and three double bonds possess conjugated π -electron frameworks, are isoelectronic with the cyclooctatetraene dianion, and, if planar, represent potentially aromatic 10π -electron systems. On the basis of topological criteria, Balaban predicted in 1965 the aromaticity of compounds with 10π -electron systems in eight-membered rings with two heteroatoms <1965RRC1059, 2004CR2777>, although since then surprisingly few molecular mechanics (MM) calculations have been reported on 1,4-diheterocines <1996CHEC-II(9)527>. The experimental investigation of the 1,4-diheterocines was started by Schroth *et al.* with the syntheses of 2,5-dihydrobenzo[*b*][1,4]dioxocine and 5,8-dithiadibenzo[*a,c*]cyclooctene <1996CHEC-II(9)527>. 1,4-Diazocines **1** are aromatic when R is a donor group; a ring current was evidenced by nuclear magnetic resonance (NMR). If R is an acceptor group, such as aryl sulfonyl, **1** is nonplanar and showed no ring current <2004CR2777>. 1,4-Oxazocines **2** are planar and diatropic if R = H or alkyl, while the *N*-tosyl derivative is nonplanar <1975AGE348>. The anion **3** possesses an aromatic stabilization as evidenced by NMR <1975AGE348>.



1,4-Dioxocines **4** are paratropic and exist in equilibrium with their $2\sigma \rightarrow 2\pi$ valence isomers, *syn*-benzene dioxides **5** (Equation 1) <1984CHEC(5)653, 2000CC2151, 2004CR2777> (see Section 14.06.6.2).

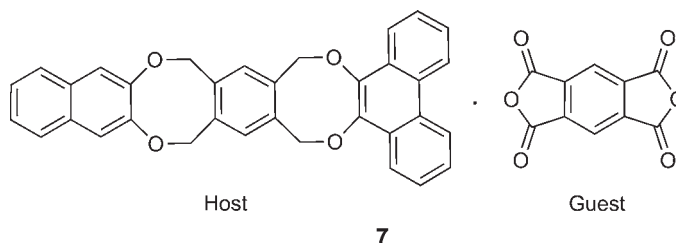


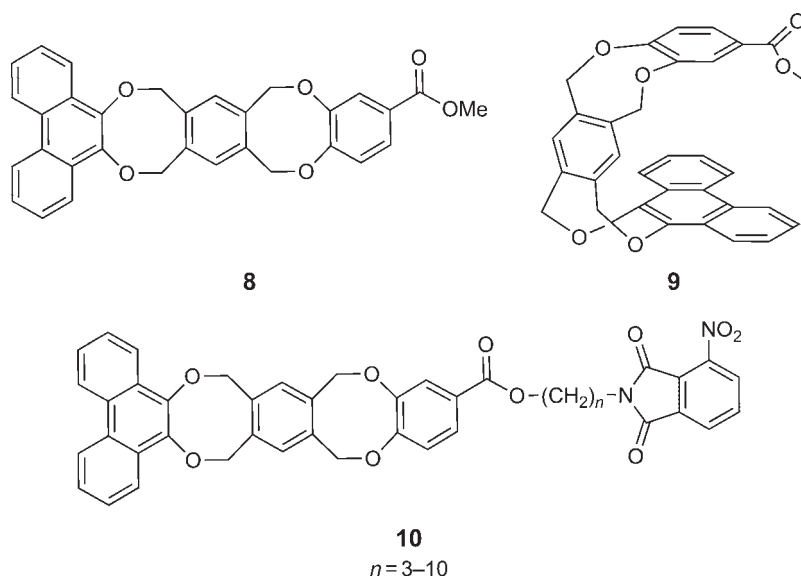
The preferred structural conformation of the dibenzodioxocine **6** could not be identified by NMR spectroscopy due to rapid conformational dynamic process, even at low temperature (-90°C) <1998T13495>. In order to investigate the conformation of **6** and the details of the dynamic conformational process, theoretical calculations both by the MM and molecular orbital (MO) methods were carried out <1998T13495>. Using the low mode conformational search algorithm in the modeling software system, MacroModel V6.0 with MM3* force field, three structures of **6**, twist boat, screw, and chair forms, were found within 5.0 kcal mol^{-1} of the steric energy. The most stable is the twist boat; the screw and the chair forms are higher in steric energy by 1.37 and $2.85\text{ kcal mol}^{-1}$, respectively. These three conformations were optimized also by MO calculations with semi-empirical PM3 and *ab initio* method (RHF/3-21G and Becke3LYP/6-31G*//RHF/3-21G) <1998T13495>. Although the relative stability between the three forms is dependent on the method of calculation, all the methods agreed that the chair form has the highest conformational energy among the three.



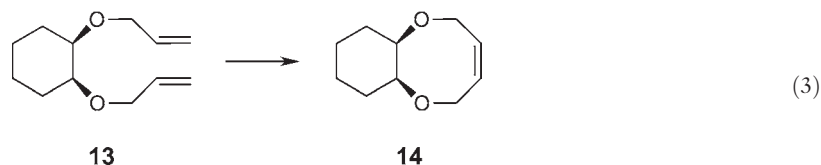
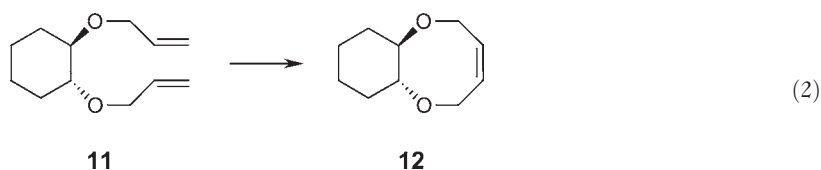
The conformational dynamic process of **6** was analyzed by semi-empirical MO calculation using the torsional drive method. The transition state within interconversion process of the twist boat and screw forms is close to the screw form in energy. The activation energy from the twist boat is very small (1.1 kcal mol^{-1}), and hence the pseudorotational process is extremely facile and almost barrier free. By contrast, the activation energy of the ring-flipping process was predicted to be higher (7.2 kcal mol^{-1}). Hence, the most stable twist boat form can interconvert to its mirror image only by a pseudorotational process via the screw form. The high-energy chair form does not always contribute to the conformational dynamic process of **6** <1998T13495>.

The study of host–guest chemistry found that flexible molecular tweezers (hosts) can bind a π -electron-deficient guest to form the complex **7** <2001T8667>. The modeling study of complex **7** was carried out with AMBER* force field using GB/SA chloroform solvation model in the program package of MacroModel V6.5. Two orientations of the guest, parallel and cross with respect to the phenanthrene ring of the host, were found to have an energy difference of 2.7 kcal mol^{-1} in favor of the parallel orientation. The parallel host–guest orientation was found in the crystalline state for **7** (see Section 14.06.6.1) while the cross complexation was observed in solution <2001T8667>. In the studies of intramolecular complex formation, relative steric energies were calculated for **8** with the second lowest energy conformation **9** (6.07 kJ mol^{-1}) <2001H(54)849>. The conformation of type **9** was realized in the intramolecular complex **10** ($n=3$) where the flexible molecular tweezer can bind intramolecularly a weak electron acceptor, which is linked covalently to the receptor and is entrapped within the host cavity <2001H(54)849>.

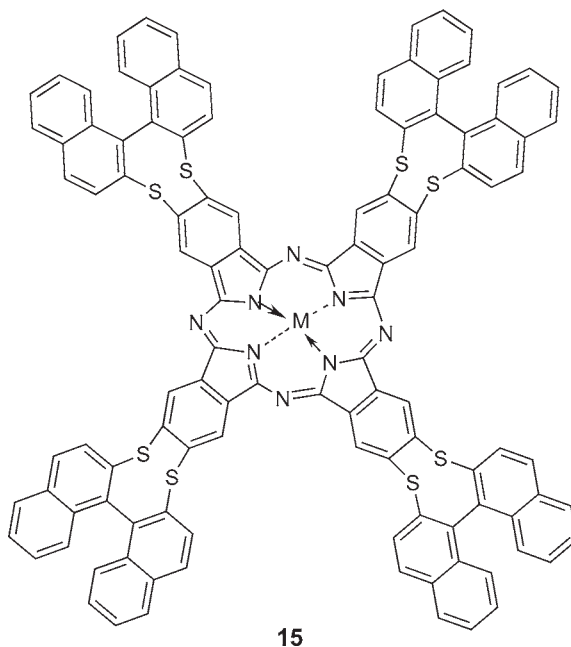




Molecular mechanics (MM3) calculations have been applied to the study of the parameters, which influence the cyclization reactions of the acyclic precursors **11** and **13** under RCM conditions (Equations 2 and 3) <1995JA2108>. Because RCM involves an equilibrium between ring-closed and open-chain products, the relative ratio of cyclic product to acyclic compound might correlate to the relative free energy changes for the reactions. The difference in the free energy changes has been calculated for two reactions (Equations 2 and 3), which are identical except in the stereochemical arrangement at the ring junction. The free energy change for **11** $\rightarrow$ **12** was found to be 1.8 kJ mol^{-1} greater than that for **13** $\rightarrow$ **14**. Greater ring strain was encountered in the formation of bicycle **14** relative to **12**. These data are consistent with the experimental results, where the *trans*-fused bicycle **12** was isolated in 60% yield, while the *cis*-fused counterpart **14** was formed in 20% yield <1995JA2108, 1996CHEC-II(9)527>.

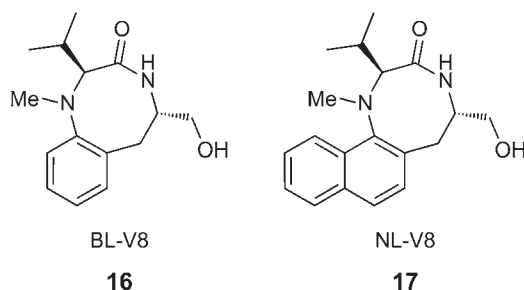


To determine the geometrical parameters that are required in the expressions for the rotary strength, a geometry optimization for the phthalocyanine **15** ($M = \text{Mg}$) was carried out at the PM3 level <1999JA12018>. Also, *R*-**15** ($M = \text{Mg}$) was optimized in tetragonal D_4 symmetry with preliminary optimization of separate fragments in order to reach convergence for the whole macromolecule. The calculated parameters of **15** were used in the interpretation of the observed dichroism results from the interplay of two induction paths, which are both strongly geometry dependent (see Section 14.06.8).

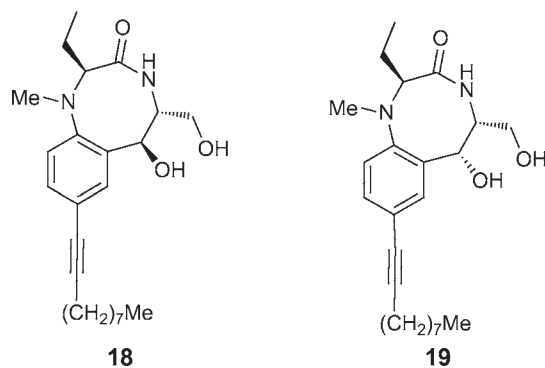


The last two decades have been rich in producing theoretical computational methodology that underpins molecular modeling in the structure-based drug design. Several software applications arose from universities and private or public companies, and those are AMBER, INSIGHT, CHARMM, SYBYL, GRID, DOCK, and HINT [<B-2005MI457>](#). All except AMBER were commercialized, and the pharmaceutical companies develop the proprietary computational programs for ‘in-house’ computer-aided drug design (CADD).

In the study of isozyme-selective modulators for protein kinase C (PKC), docking simulations of the benzolactam **16** (BL-V8) with the crystal structure of the PKC δ C1B domain were performed using the FlexX program in SYBYL [<2005JA5746>](#). The data provided evidence that the CH- π -interaction plays a pivotal role in the binding of **16** to the PKC δ C1B domain. The binding affinity was enhanced in the naphtholactam **17** (NL-V8) by the effective manipulation of the CH- π -interaction.

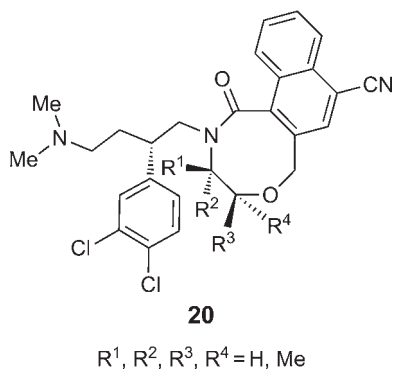


Compounds **18** and **19** were designed with the idea that the extra hydrogen-bond donor group might enhance PKC affinity and selectivity [<2002OL2169>](#). The molecular modeling and docking studies using FlexX program in SYBYL demonstrated that both **18** and **19** are able to form a network of hydrogen bonds with PKC α C1b domain although the binding of the (6*R*)-isomer **19** was considered more favorable. Biological assays revealed that the (6*R*)-ligand **19** is 20-fold more potent than its (6*S*)-counterpart **18** in binding to PKC α [<2002OL2169>](#).



Molecular modeling studies of the substituted 3,8-dioxo[1,4]diazocane with the Accelrys Insight II 2000/Discover 97 modeling package (with the eff91 force field) showed that based upon binding ability, constrained peptides can serve as novel templates for the design of small nonpeptide inhibitors of the SH2 domain of the pp60 (Src), a nonreceptor tyrosine kinase [\[2004JME3131\]](#).

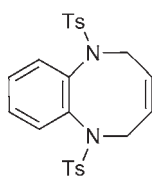
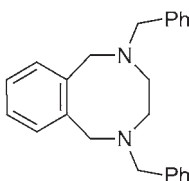
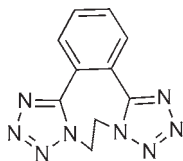
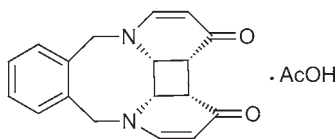
Conformational features of the 1,4-oxazocines **20**, selective NK₁ antagonists, were investigated by MM computations *in vacuo* using the AESOP force field with full geometry optimization of all conformations, and results were visualized using in-house molecular graphics program ENIGMA (AstraZeneca Pharmaceuticals LP) [\[2004BML2653, 2004T4337\]](#). The modeling data, which were consistent with experimental results on biological testing, suggested a detailed model for the NK₁ pharmacophore with the key elements, the aryl–aryl folded geometry, and the positioning of the amide carbonyl, as a hydrogen-bond acceptor (see [Section 14.06.4.2](#)).



14.06.3 Rings with Two Nitrogens (1,4-Diazocines)

14.06.3.1 Experimental Structural Methods

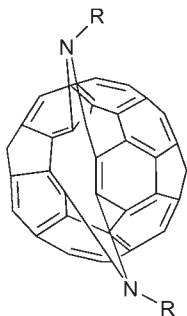
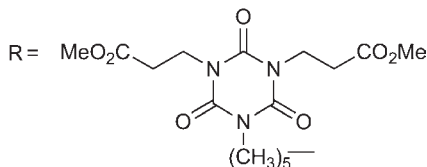
X-Ray diffraction analysis has been extensively used in structural studies of 1,4-diazocines [\[1996CHEC-II\(9\)527\]](#). Confirmation of the structures by a single crystal X-ray structural determination was performed for diazocine **21** with no evidence for bond delocalization in the solid state [\[2004TL9171\]](#). The nonplanar structure of *N,N*-dibenzyl derivative **22**, as the product of Bergman cyclization ([Section 14.06.3.6](#)), was characterized by X-ray crystallography, NMR, and mass spectrometry [\[2003CC1156\]](#). The identity of cyclophane **23**, as a 1-*N*,1-*N'*-intramolecularly bridged tetracycle, was confirmed crystallographically unveiling the lack of rotational freedom, which comes with the shorter *trans*-tetrazole bridge [\[1999J\(P1\)3507\]](#). The ethylene bridge in **23** is the shortest yet incorporated into this family of heterocyclic cyclophanes and includes the first example of 1-*N*,1-*N'*-bridging.

**21****22****23****24**

X-Ray crystallographic analysis of **24**·AcOH established the *cis,syn,cis*-configuration [<1993TL5555>](#). The phenyl rings are positioned in the way that the molecules are cup-shaped in the crystals. Each molecule of **24** has a molecule of AcOH which is hydrogen-bonded to one of the carbonyl oxygen atoms.

Proton and ^{13}C NMR data of a variety of 1,4-diazocine derivatives have been reported in the studies of conformational analysis and assessment of potential aromaticity [<1996CHEC-II\(9\)527, 2004CR2777>](#) as well as routine structural characterization of 9,10-dihydroditetrazolo[5,1- α :1',5'- ϵ][2,5]benzodiazocine [<1999J\(P1\)3507>](#), 5,10-bis[(4-methylphenyl)sulfonyl]-5,6,9,10-tetrahydropyrido[2,3- b][1,4]diazocine [<2004TL9171>](#), substituted 3,8-dioxo[1,4]diazocanes [<2004JME3131>](#), analogs of BL-V8 **16** (see [Section 14.06.2](#)) [<1998JA12459, 1998TL7369, 1999JOC6366, 2001BML99, 2002OL2169, 2002OL2377, 2003JME364, 2003JME4196>](#), 1,3,4,6-tetrahydro-1,6-benzodiazocin-2,5-diones [<2004RJO575>](#), 5,6,11,12-tetrahydrodibenzo[b,f][1,4]diazocin-6,11-diones [<2002SC1929>](#), substituted 1,2,3,4,6,11-hexahydrobenzo[b,f][1,4]diazocines [<2004TA2437>](#), and 1,10-dihydro-11*H*-pyrazolo[3,4- c][1,6]benzodiazocin-11-ones [<2004ARK44>](#).

A single di(azahomo)[60]fullerene isomer **25** was prepared for the first time (see [Section 14.06.3.7](#)) and characterized by NMR, ultraviolet (UV), and infrared (IR) spectroscopy [<2002RCB1491>](#). The ^{13}C NMR spectrum of adduct **25** exhibited 32 signals in the region δ 133–147 ppm, corresponding to sp^2 -hybridized carbon atoms of the fullerene cage. This implies a homofullerene structure of the spheroid with C_s symmetry of the molecule. The IR spectrum of **25** exhibited characteristic absorption bands for the carbonyl groups of the isocyanuric ring (1690 cm^{-1}) and for the methoxycarbonylmethyl substituent (1737 cm^{-1}). The UV spectrum of **25** had no bands with λ_{max} 420–430 nm, which are characteristic of the addition of a dipolarophile to two six-membered rings of the fullerene construct.

**25**

14.06.3.2 Thermodynamic Aspects

Comprehensive coverage of thermodynamic aspects for the 1,4-diazocines was presented in CHEC-II(1996) and included discussion on physical properties, such as melting points, solubility, and chromatographic behavior,

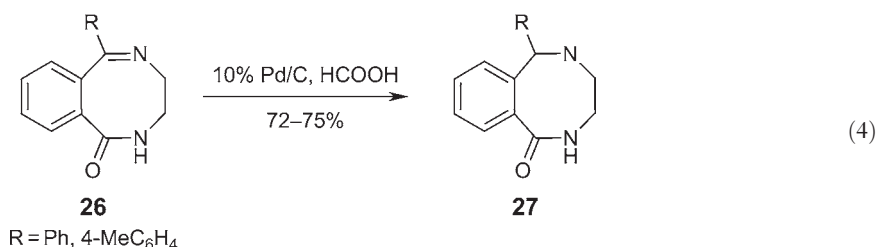
conformational issues, and a few examples of proton-transfer and valence tautomerism <1996CHEC-II(9)527>. These properties remain in the same general trend for the 1,4-diazocines as evidenced by experimental details in the publications, which are cited throughout this chapter.

Melting points, where available, are given throughout this section for the individual compounds. Recent data on conformations of the novel 1,4-diazocines are presented in the context of discussion on the theoretical aspects (Section 14.06.2) and experimental structural methods (Section 14.06.3.1). An excellent review on aromaticity in heterocyclic chemistry, where heteroaromaticity of known and potential monocyclic eight-membered 1,4-diheterocines is a part of discussion, is also recommended <2004CR2777>.

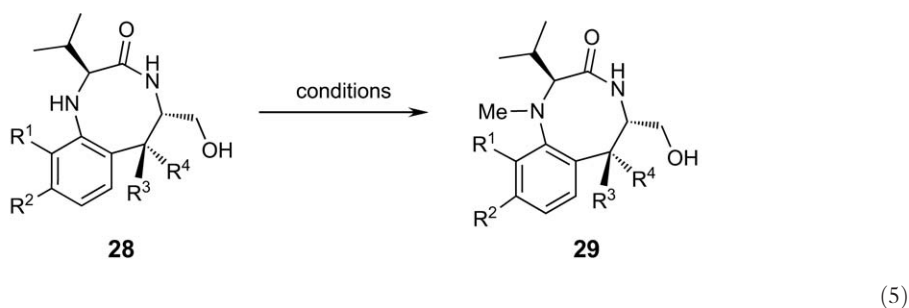
14.06.3.3 Reactivity of Nonconjugated Rings

Since 1995, a few reports involving reactivity of nonconjugated 1,4-diazocines have been published.

The C=N bond in 2,5-benzodiazocin-1-one **26** was saturated using Pd/C in formic acid to give **27** (Equation 4) (see Section 14.06.3.4.2) <2003JOC92>. Attempted transformation of **26** into **27** using other conditions, including Pd/C under a hydrogen atmosphere, NaCNBH₃ in DMF–AcOH, and LiAlH₄, failed to provide satisfactory yields.

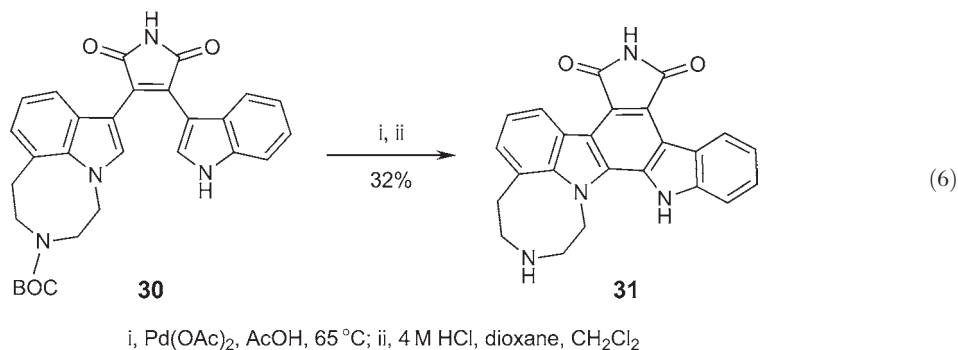


Methylation of the amino group in the 2-oxo-1,4-diazocines **28** afforded the benzolactams **29** (Equation 5), which are structural analogs of BL-V8 **16** and NL-V8 **17** (see Sections 14.06.2 and 14.06.7) <1998TL7369, 1999JOC6366, 2002OL2169, 2005JA5746>.



R ¹	R ²	R ³	R ⁴	Conditions	Yield(%)	Reference
H	BnO	H	H	HCHO, NaCNBH ₃	95	1998T7369
H	H	OH	H	HCHO, AcOH, NaCNBH ₃ , MeCN, 0 °C, 1 h	89	2002OL2169
H	H	H	OH	HCHO, AcOH, NaCNBH ₃ , MeCN, 0 °C, 1 h	90	2002OL2169
AcNH	BnO	H	H	HCHO, NaBH ₄ , 3N H ₂ SO ₄ , 50 °C, 15 min	89	1999JOC6366
–CH=CH–CH=CH–		H	H	(MeO) ₂ CHNMe ₂ , DMF	12	2005JA5746

Bis-indolylmaleimide **30** was transformed into the aza-1,7-annulated indole **31** by an oxidation procedure, followed by the *t*-butoxycarbonyl (BOC) deprotection in one pot (Equation 6) <2004BML3925>.

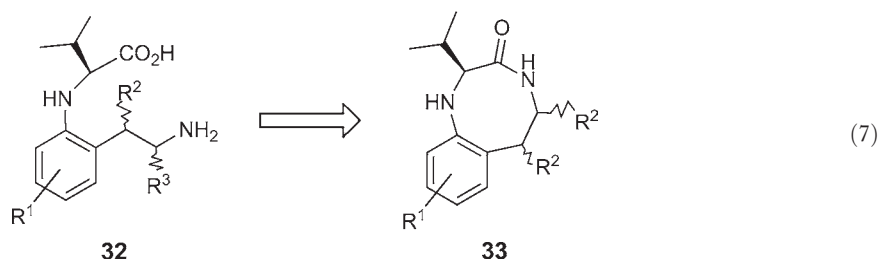


14.06.3.4 Ring Syntheses

There are two general approaches to the construction of the 1,4-diazocine ring from acyclic precursors: (1) via intramolecular cyclization of the appropriately functionalized compound with the formation of one C–N or C–C bond, and (2) by intermolecular condensation with the formation of two C–N bonds.

14.06.3.4.1 Intramolecular cyclizations

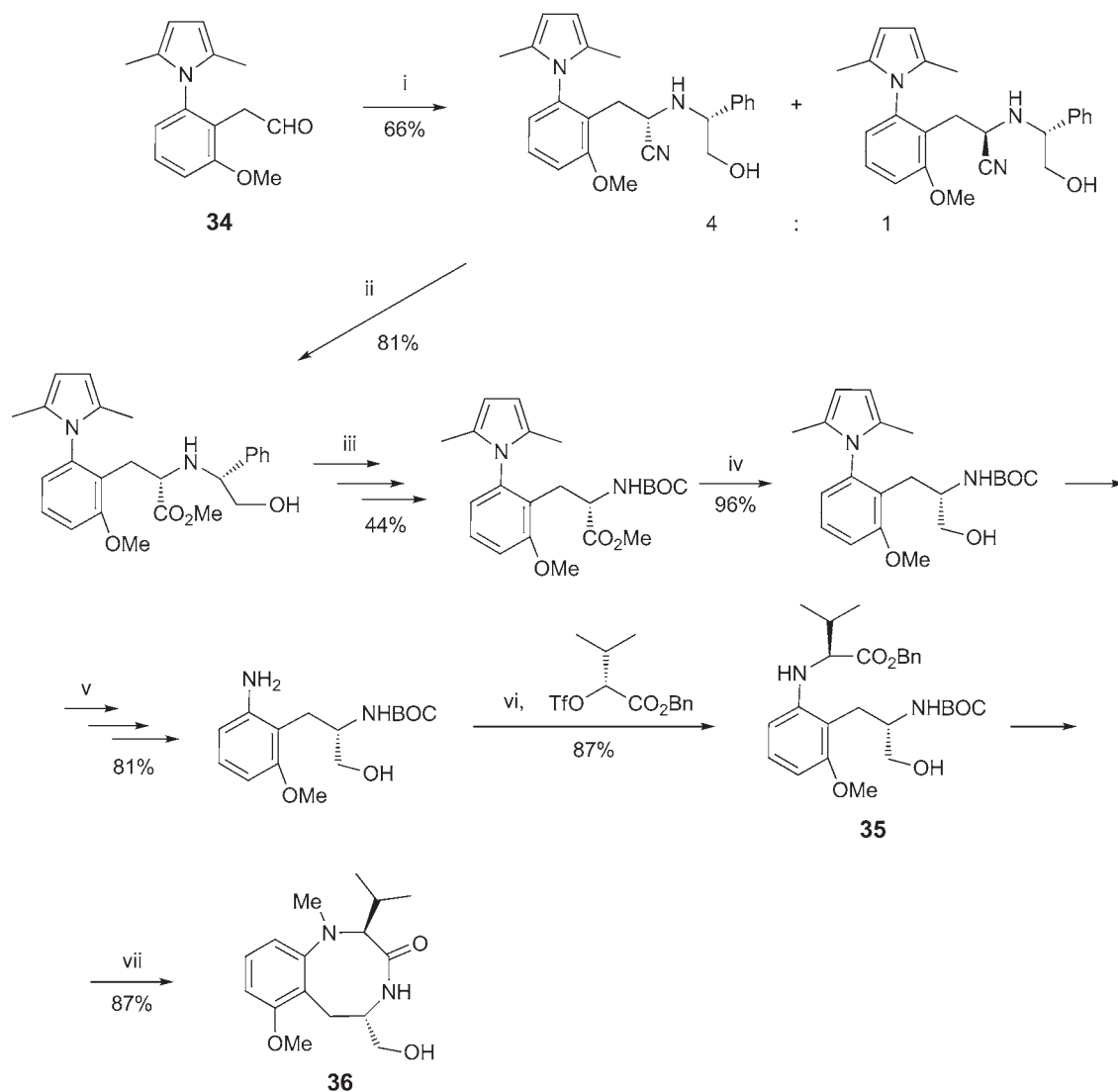
The synthesis of 1,4-diazocines via an intramolecular cyclization with the formation of a C–N bond is generally a result of a stepwise reaction, when a precursor is constructed first. In the synthesis of PKC modulators BL-V8 **16** and NL-V8 **17** and their analogs (see Sections 14.06.2 and 14.06.3.7), challenges exist in the stereoselective construction of the functionalized precursors **32**, which can cyclize via intermolecular amidation to give the target **33** (Equation 7).



Stereoselective syntheses of the amino acids **32** or their functional derivatives have been reported by a number of approaches, which are discussed below.

7-Methoxybenzolactam-V8 **36** was synthesized using a diastereoselective Strecker reaction as the key step employing *ortho*-substituted phenylacetaldehyde **34** and (*R*)-phenylglycinol as the chiral auxiliary (Scheme 1) <2001CC475>. Preparation of the aldehyde **34** involved seven separate steps starting with 3-hydroxyacetanilide. Compound **36** may serve as an intermediate in the preparation of a variety of C-7-substituted analogs of BL-V8 **16**. The asymmetric Strecker reaction was also used in the synthesis of NL-V8 **17** (Section 14.06.2) <2005JA5746>.

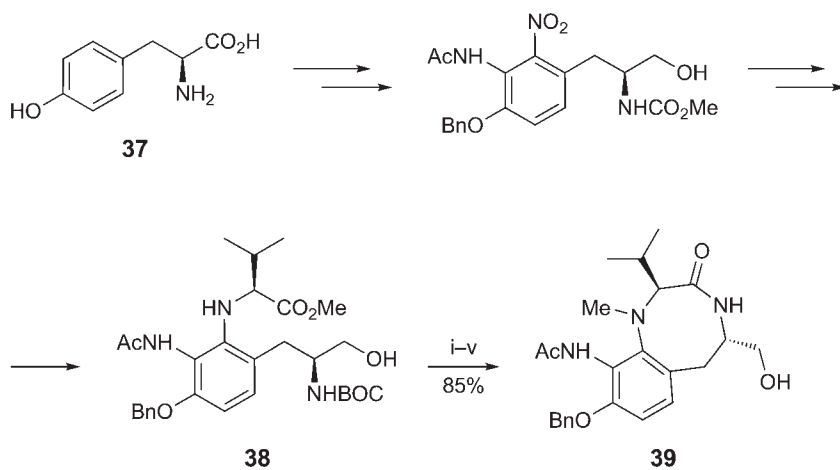
An alternative approach to precursor **35** was reported starting with 3-nitrophenol; one of the steps involved an asymmetric phase-transfer catalysis reaction, which resulted in enantiomeric mixture and required determination of the enantiomeric purity of the intermediates <2001BML99>.



Scheme 1

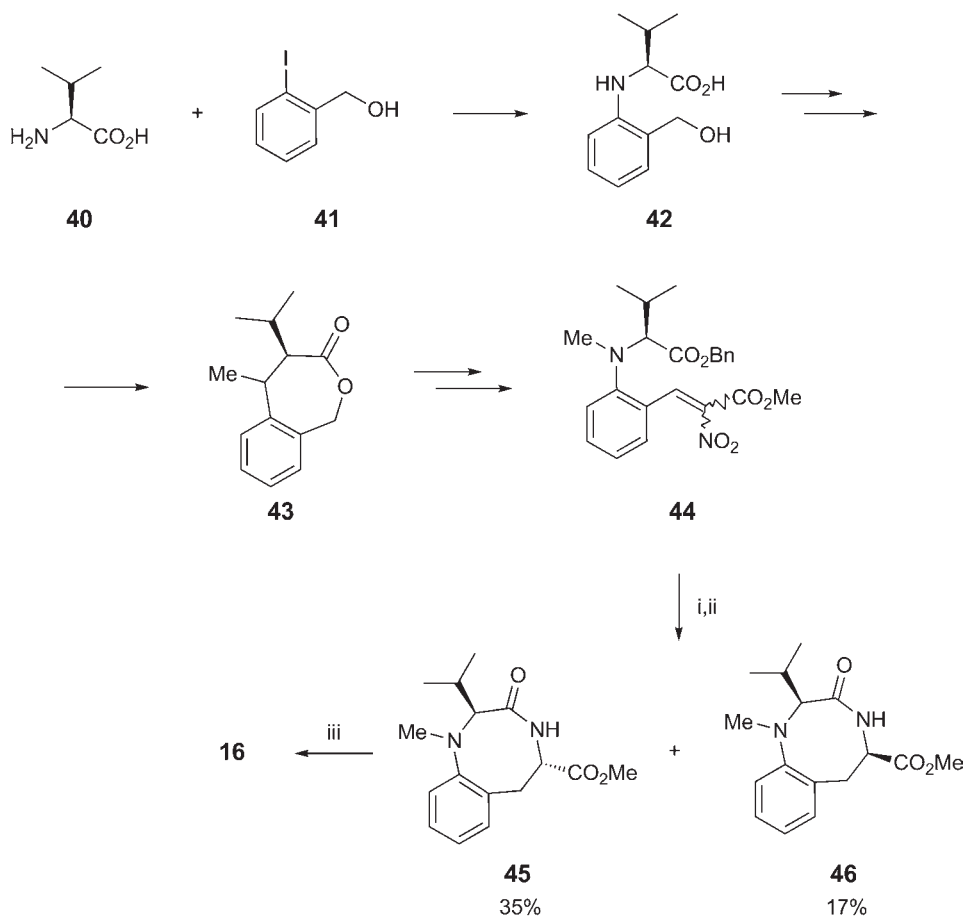
An approach to the key precursor **38** in the synthesis of 9,10-disubstituted analogs **39** implemented the introduction of chirality with the L-tyrosine derivative **37** (Scheme 2) <1999JOC6366>. A similar synthesis was reported for 9-substituted analogs of BL-V8 **16** <1998TL7369>.

Coupling of the optically pure L-valine **40** and iodide **41** produced the enantiopure **42**, which was transformed into the oxazepine **43** (Scheme 3) <1998JA12459>. No racemization was observed in this coupling reaction, which



i, aq. NaOH, MeOH; ii, *N*-hydroxysuccinimide, DCC; iii, TFA, CH₂Cl₂; iv, NaHCO₃; v, 3 N H₂SO₄, HCHO, NaBH₄

Scheme 2

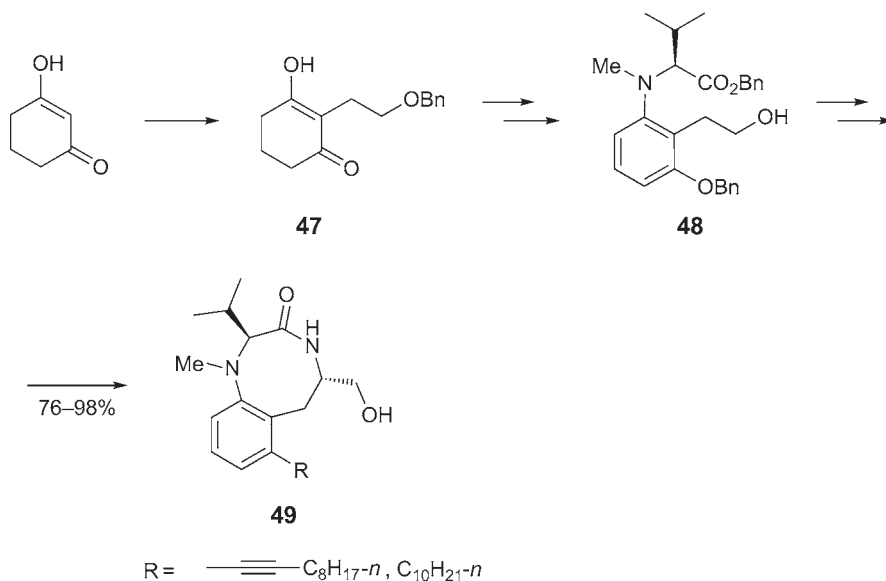


i, Pd/C, H₂, MeOH; ii, DPPA, DMF; iii, LiBH₄, THF

Scheme 3

proceeds at lower temperature than typical Ullmann condensation even for electron-rich aryl halides. This indicates that an accelerating effect induced by the structure of the α -amino acid exists in this reaction. The alkene **44** was cyclized to afford a separable mixture of diastereomers **45** and **46**, and, finally, reduction of **45** afforded BL-V8 **16** in 18% overall yield, the best yield reported in the literature.

N-Aryl-L-valine benzyl ester **48** was obtained by condensation of L-valine benzyl ester toluenesulfonic salt with cyclohexadione **47** (Scheme 4) <2002OL2377>. The intermediate **48** was converted into 7-substituted benzolactam **49** using asymmetric Strecker reaction as the key step.



Scheme 4

An efficient route to 6-hydroxylated benzolactam-V8 isomers **53** and **54** was reported via the intermediate aminodiols **51** and **52**, which were readily separated chromatographically upon hydrolysis of the inseparable diastereomeric mixture **50** (Scheme 5) <2002OL2169>.

A cyclization strategy was employed in the solid-support synthesis of the conformationally restrained peptidomimetic, 1,4-diazocine **55** although the final product was isolated in low yield (Scheme 6) <2004JME3131>.

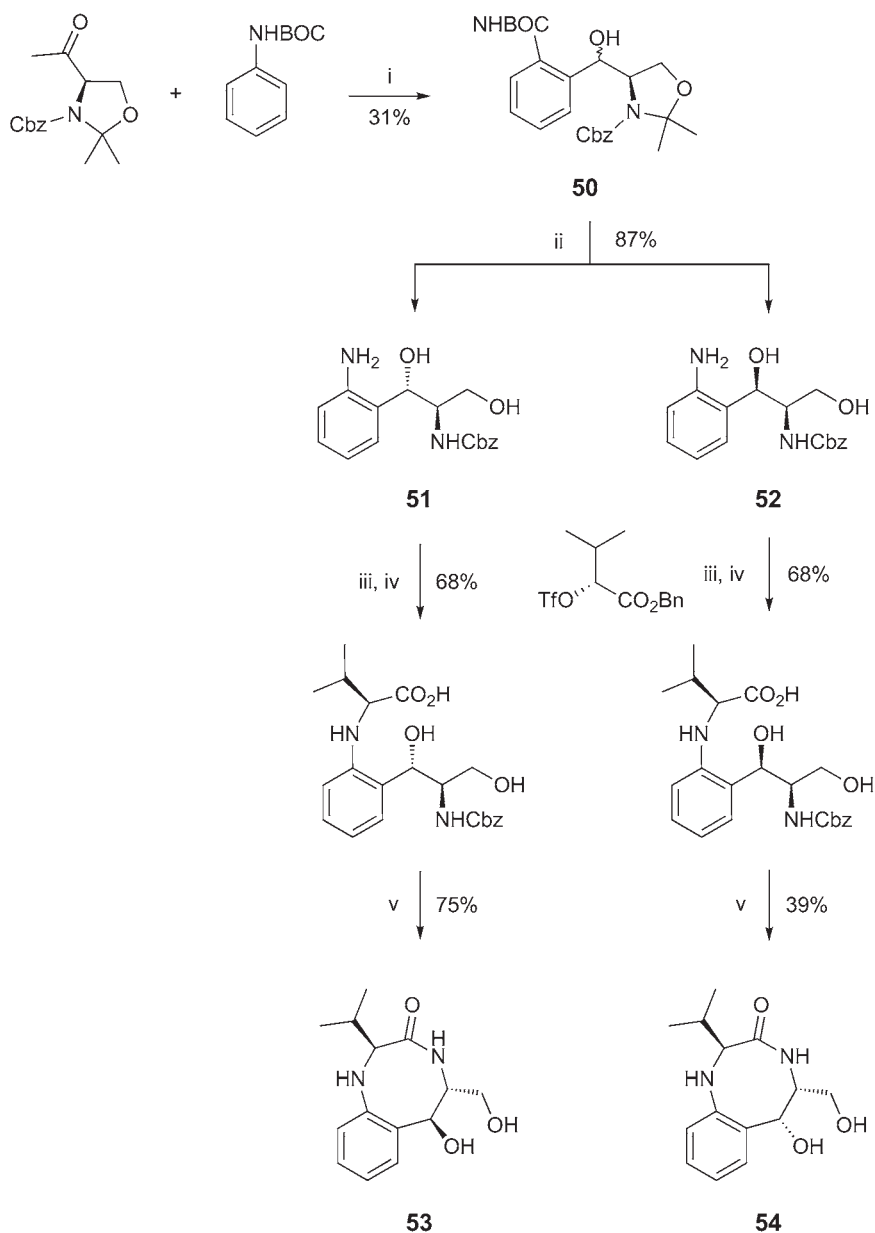
The multicomponent Ugi reaction was successfully applied to the synthesis of bisamides **56**, which on deprotection, followed by carbonylation and intramolecular amidation, afforded the macrolactams, 1,4-diazocines **57**, as racemic mixtures (Scheme 7) <2005TL1697>.

The perhydropyrrolo[1,2-*a*][1,4]diazocine **61** was obtained starting with *N*-*tert*-butoxycarbonyl glutamic acid **58** (Scheme 8) <1997BMC2029>. The α -carboxyl group in **58** was selectively blocked by conversion into *N*-benzhydrylglycolamide ester **59** using the substantial difference in the acidity of α - and γ -carboxyl moieties. In the final stage, the benzhydrylglycolamide ester **60** was readily converted into pyrrolodiazocine **61** (m.p. 232–234 °C).

A convenient intramolecular N-alkylation of the functionalized indole **62** produced the 1,4-diazocine **63** in high yield (Equation 8) <2004BML3925>.

Fusion of the acylamino precursors **64** resulted in the intramolecular amidation with the C=N bond formation, affording the new ring system, 11*H*-pyrazolo[3,4-*c*][1,6]benzodiazocine-11-ones **65**, (Equation 9) <2004ARK44>.

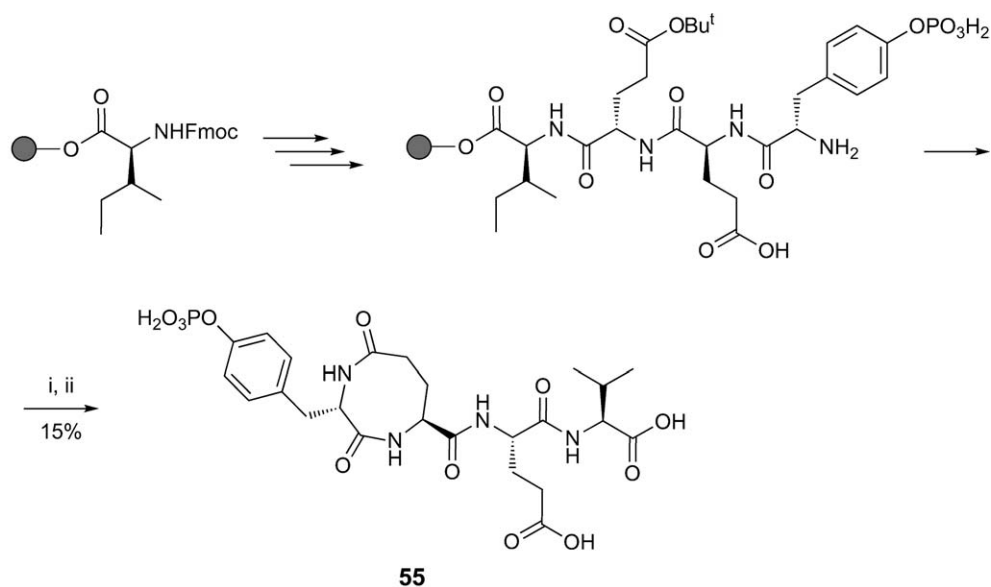
In an example of a C–C bond formation in the construction of a 1,4-diazocine ring, racemic [2,5]benzodiazocines **67** were synthesized from hydroxylactams **66** via an *N*-acyliminium ion–pyrrole cyclization reaction (Scheme 9) <2000H(52)273>.



i, Bu^tLi (2.2 equiv), THF, -78 °C → -20 °C, 5 h; ii, 1 M HCl, THF, 70 °C, 5 h; iii, 2,6-lutidine, ClCH₂CH₂Cl, 70 °C, 72 h; iv, Pd/C, H₂ (1 atm), EtOH, rt, 24 h; v, diphenylphosphonyl azide, Et₃N, DMF, rt, 48 h

Scheme 5

RCM has attracted much attention and has seen a tremendous increase in synthetic applications over the last decade <2000CR2963, 2006JOM(691)5129>. In this reaction, two C–C multiple bonds, such as double and double, or double and triple in the same molecule, are converted to unsaturated carbocycles or heterocycles in the presence of a metal carbene complex. The versatility of Schrock's molybdenum catalyst and Grubbs' ruthenium complexes **68** and **69** (Scheme 10) in carbo- and heterocyclizations, respectively, of very different ring sizes were demonstrated <2000CR2963, 2006JOM(691)5129>.

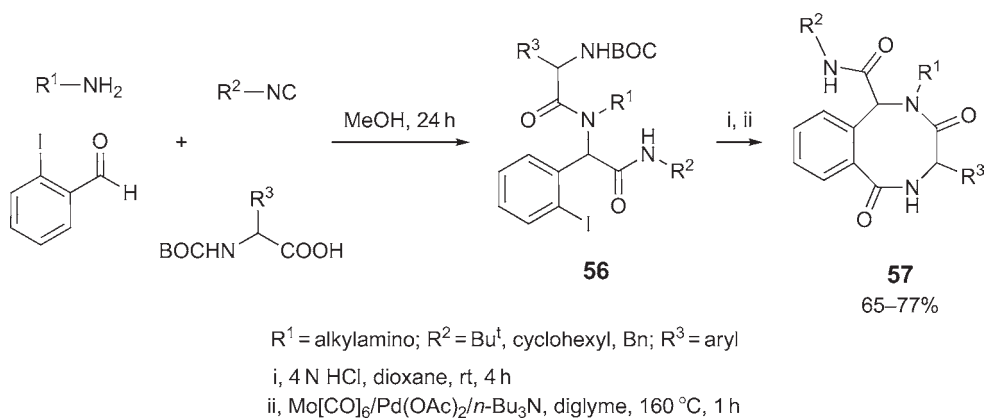


i, HBTU, NMM, DMF, 24 h; ii, TFA–anisole–H₂O, 90:5:5

HBTU = 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

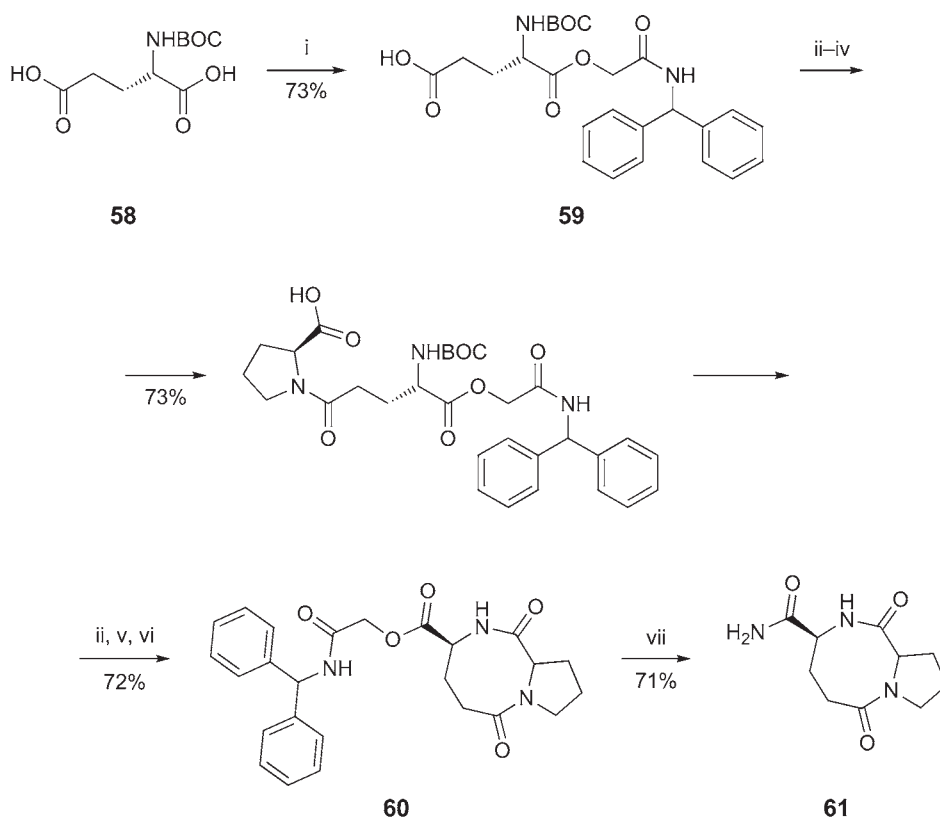
NMM = methylmaleimide

Scheme 6



Scheme 7

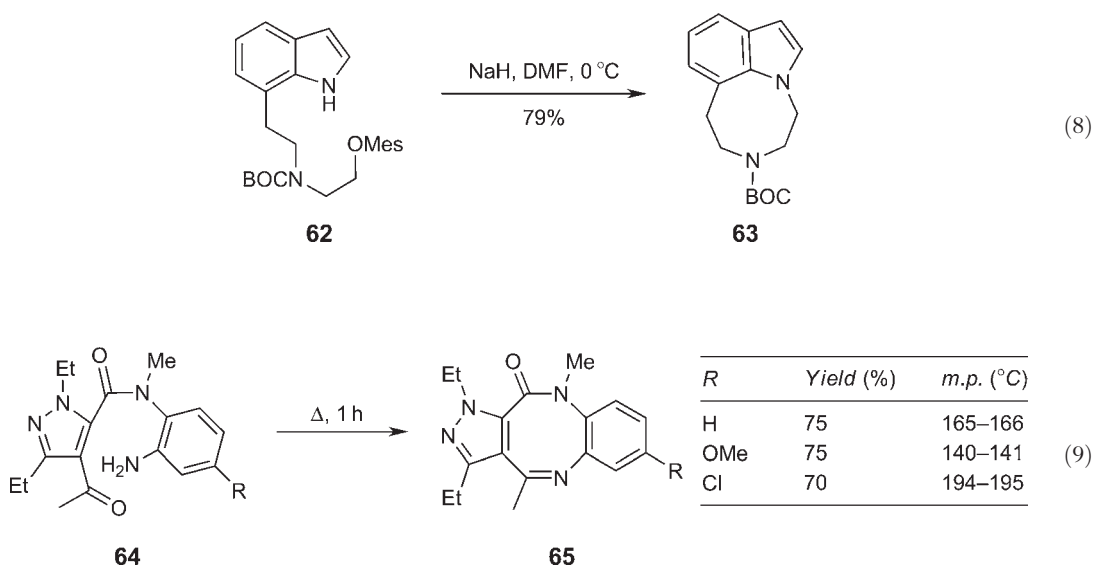
RCM of dialkenes using the Grubbs' ruthenium catalyst **68** has been reported earlier in the construction of the 1,4-diazocine ring via a C–C bond formation, although this approach failed in the synthesis of 1,4-oxazocines or -dioxocines <1995JA2108, 1996CHEC-II(9)527, 1996JA9606>. RCM with the use of the Grubbs' ruthenium catalyst **69** resulted in the 1,4-diazocines **71**, **73**, and **75** in good to high yields (**Scheme 10**) <2000OL543>. The tosyl group on the nitrogen atoms in the enynes **70**, **72**, and **74** accelerated the reaction rate in the formation of the 1,4-diazocines. Formation of the *cis*-bicyclooctene **73** proceeded easier than that of the corresponding *trans*-fused bicyclooctene, which was isolated after reflux for 15 h in 42% yield <2000OL543> (cf. Section 14.06.2). In contrast to **68**, the catalyst **69** was effective in the synthesis of 1,4-oxazocines and -dioxocines (see Sections 14.06.4.4 and 14.06.6.5).

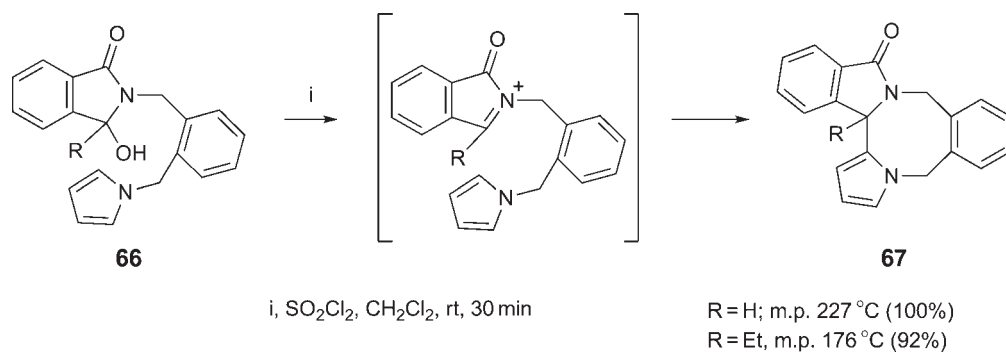


i, MeONa, 15-crown-5, BrCH₂CONHCHPh₂, EtOAc; ii, DCC, SuOH, THF; iii, H-Pro-ONa, 15-crown-5, DNF; iv, AcOH;
 v, 4 N HCl, dioxane; vi, *i*-Pr₂NEt, MeCN; vii, NH₄OH

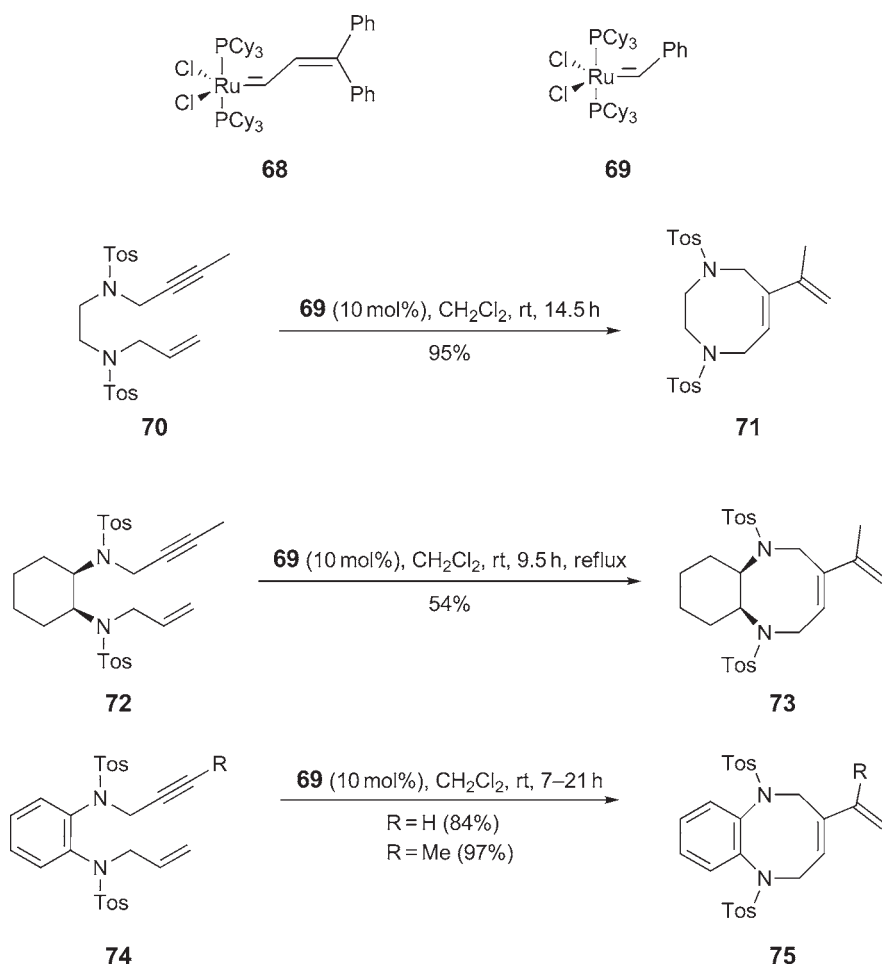
DCC = dicyclohexylcarbodiimide; SuOH = *N*-hydroxysuccinimide

Scheme 8



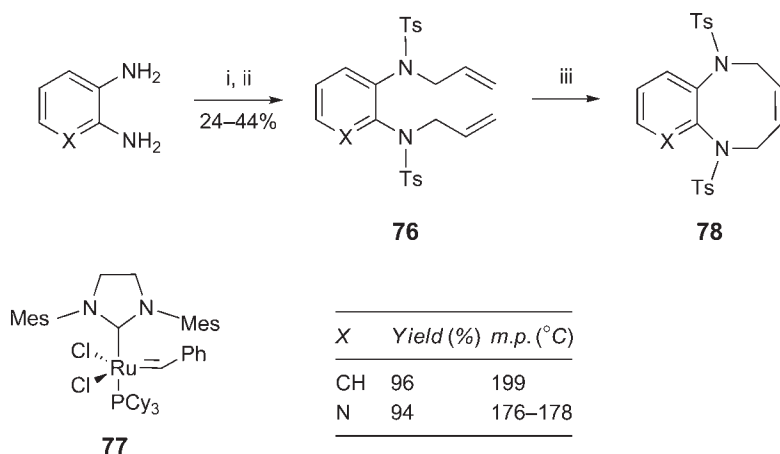


Scheme 9



Scheme 10

The [1,6]benzo- and [1,6]pyrido-diazocines **78** were obtained by one-pot procedure via isomerization–RCM of the diene **76** in the presence of the Grubbs' second-generation catalyst **77** (Scheme 11) <2004TL9171>. Although the number of literature examples describing isomerization–RCM is still limited, this concept has

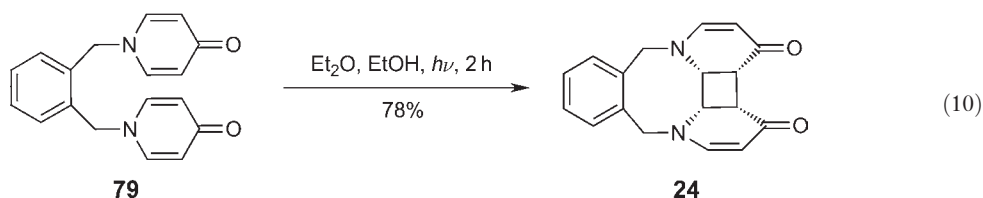


i, TsCl, pyridine, 60 °C, N₂, 20–23 h; ii, K₂CO₃, allyl bromide, acetone, N₂, 20–23 h; iii, **77** (5%), toluene, N₂, rt, 5 h

Scheme 11

been included in recent in-depth reviews <2004EJO1865, 2006JOM(691)5129>. Isomerization–RCM strategy was successfully applied to the synthesis of benzoxazocines (cf. Section 14.06.4.4) and benzothiazocines (cf. Section 14.06.5.2).

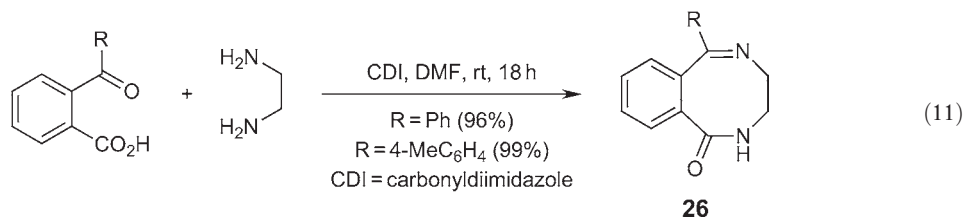
A novel [2+2] photocycloaddition reaction was reported for the bis-pyridone **79** to afford the diazocine **24** possessing the *cis,syn,cis*-configuration (Equation 10) (see Section 14.06.3.1) <1993TL5555>.



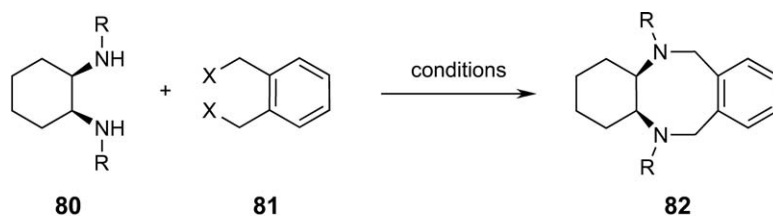
14.06.3.4.2 Intermolecular condensation reactions

Since 1995, a few examples of the 1,4-diazocine synthesis by condensation reactions with the formation of two C–N bonds have been described.

The coupling reactions of 2-carboxyl benzophenones with ethylenediamine resulted in 2,5-benzodiazocin-1-ones **26** (Equation 11) (see Section 14.06.3) <2003JOC92>.

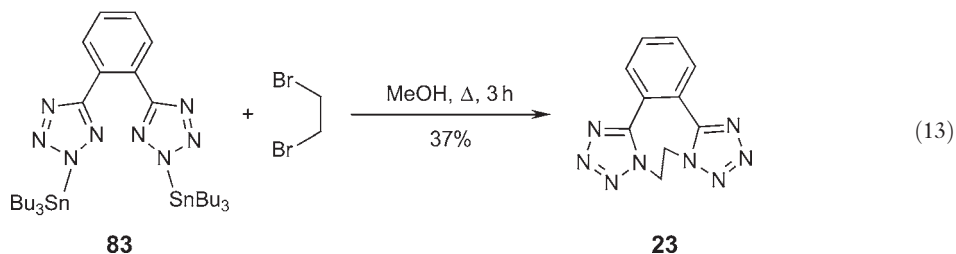


Cycloalkylation of the *N,N'*-disubstituted 1,2-diamines **80** with dihalides **81** produced the diazocines **82** in an optically active form (Equation 12) <2004TA2437, 2005TL3473>.



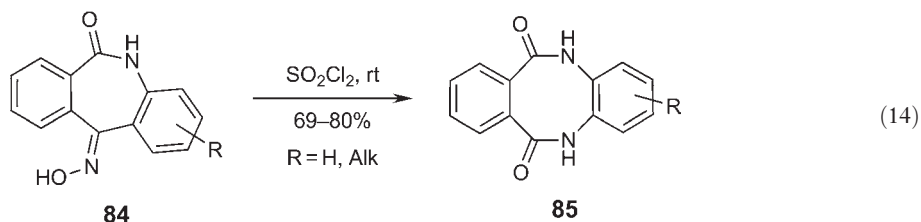
<i>R</i>	<i>X</i>	<i>Conditions</i>	<i>Yield of 82 (%)</i>	<i>Reference</i>	(12)
Pr ⁱ	Br	K ₂ CO ₃ , KI, MeCN, reflux, 12 h	80	2004TA2437	
Me	Cl	LiOH·H ₂ O, CH ₂ Cl ₂ , rt, 12 h	16	2005TL3473	
CH ₂ Ph	Cl	LiOH·H ₂ O, CH ₂ Cl ₂ , rt, 12 h	53	2005TL3473	
2-MeOC ₆ H ₄ CH ₂	Cl	LiOH·H ₂ O, CH ₂ Cl ₂ , rt, 12 h	33	2005TL3473	
2-NO ₂ C ₆ H ₄ CH ₂	Cl	LiOH·H ₂ O, CH ₂ Cl ₂ , rt, 12 h	59	2005TL3473	
2-Furyl	Cl	LiOH·H ₂ O, CH ₂ Cl ₂ , rt, 12 h	63	2005TL3473	
4-MeOC ₆ H ₄ CH ₂	Cl	LiOH·H ₂ O, CH ₂ Cl ₂ , rt, 12 h	85	2005TL3473	
4-NO ₂ C ₆ H ₄ CH ₂	Cl	LiOH·H ₂ O, CH ₂ Cl ₂ , rt, 12 h	34	2005TL3473	

Reaction of the bis-tetrazole **83** with dibromoethane led to the formation of the cyclophane **23** in moderate yield (Equation 13) (see Section 14.06.3.1) <1999J(P1)3507>.

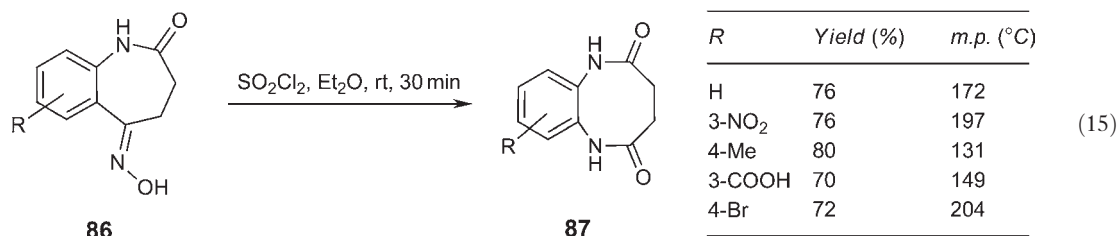


14.06.3.5 Ring Synthesis by Transformation of Another Ring

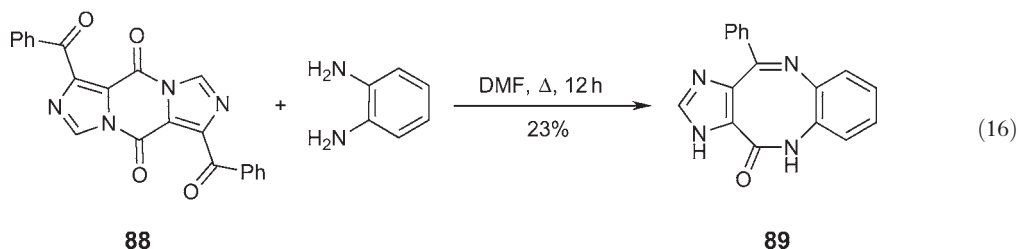
The novel heterocyclic system, 5,6,11,12-tetrahydridibenzo[*b,f*][1,4]diazocin-6,11-dione **85**, was synthesized via ring expansion by Beckmann rearrangement of the morphanthrindine oximes **84**, although the details on the substitution pattern *R* were not reported (Equation 14) <2002SC1929>.



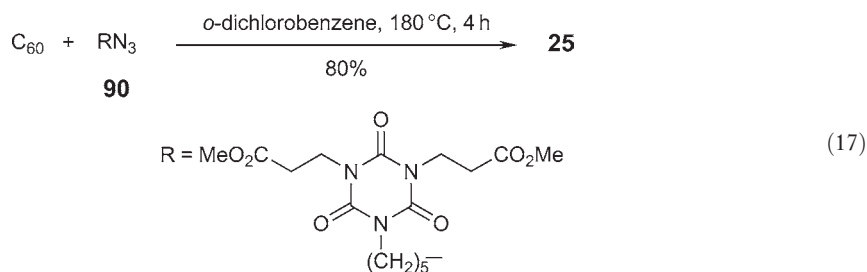
Similarly, Beckmann rearrangement of the seven-membered oximes **86** resulted in the diazocinones **87** (Equation 15) <2003BKC1377, 2004RJO575>.



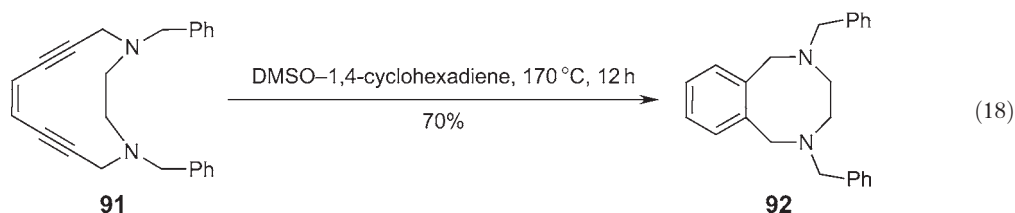
Pyrazine dione **88** reacted with *o*-phenylenediamine to give the imidazodiazocine **89** (m.p. 206–208 °C) in moderate yield (Equation 16) <2003CHE250>.



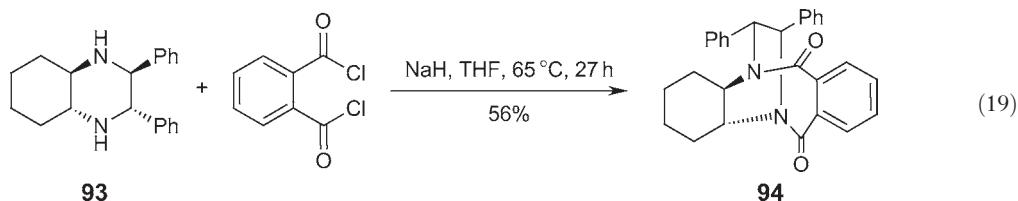
A single di(azahomo)[60]fullerene **25** (see Section 14.06.3.1) was prepared by the reaction between [60]fullerene and isocyanurato-substituted azide **90** (Equation 17) <2002RCB1491>.



Bergman cyclization of the enediyene **91** smoothly produced the benzodiazocine **92** (Equation 18) <2003CCC1156>.



Tetracyclic compound (*R,R,R,S,S,S*)-**94** (m.p. > 250 °C), which can be converted to a sort of chiral 1,4-diazabicyclo[2.2.2]octane (DABCO), was readily obtained by reaction of **93** with phthaloyl chloride (Equation 19) <2002TA2727>.



14.06.3.6 Comparison of Synthetic Routes

Intramolecular cyclization of the functionalized precursors is an efficient route to the analogs of BL-V8 **16** and NL-V8 **17** (Schemes 1–5), and to peptidomimetics (Schemes 6 and 8), although this method requires a multistep conventional construction of an appropriate precursor. RCM and isomerization–RCM (Schemes 10 and 11) are novel and promising strategies in the synthesis of both 1,4-diazocines and benzodiazocines although the substitution pattern remains limited and not all catalysts are commercially available. The coupling and cycloalkylation reactions (Equations 11 and 12) provide a route to the benzodiazocines substituted in the eight-membered ring either at C- or N-atoms. Application of Beckmann rearrangement to the oximes (Equations 14 and 15) offers a convenient approach to novel 1,4-diazocine diones. A simple and efficient post-Ugi carbonylation–intramolecular amidation (Scheme 7) outlines a flexible route toward the benzo[1,4]diazacinones with a variety of substitution in the eight-membered ring.

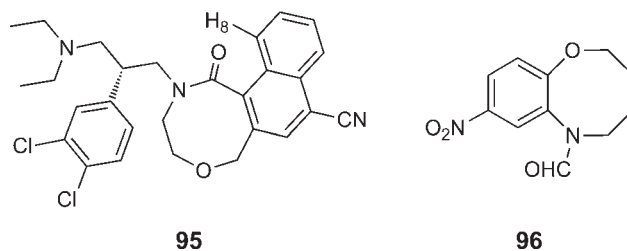
14.06.3.7 Important Compounds and Applications

BL-V8 **16** has been found to be a potent and isozyme-selective activator of PKC with activity similar to teleocidins <1998TL7369>. PKCs may play different roles in physiological and pathophysiological processes. Although several isozyme-selective inhibitors for PKCs have been developed in recent years, few isozyme-selective activators have been reported up to now. BL-V8 **16**, due to its comparative simplicity, was used as a good lead compound for developing isozyme-selective activators. 7,8-Disubstituted analogs of BL-V8 showed potent activity to three PKC isozymes <2001BML99>. 7-Substituted analogs of BL-V8 displayed a different isozyme selectivity pattern when compared to the 8-substituted analogs <2002OL2377>. Introduction of a substituent at either 8- or 10-position of the 9-substituted BL-V8 lowered binding affinity although these compounds still retained reasonably good potency for PKC <1999JOC6366>. Conformationally restrained diazocine **55** (Scheme 6) demonstrated a good binding affinity at the pp60 (Src) protein, which is a nonreceptor tyrosine kinase and has been implicated to play a role in both breast cancer and osteoporosis <2004JME3131>. 1,4-Diazocine dione **61** was effective *in vivo* as cognitive enhancer and antidepressant <1997BMC2029>. Aza-annulated diazocine **31** (Equation 6) was found to be a good proliferative agent in a human colon carcinoma cells <2004BML3925>.

14.06.4 Rings with One Nitrogen and One Oxygen (4*H*-1,4-Oxazocines)

14.06.4.1 Experimental Structural Methods

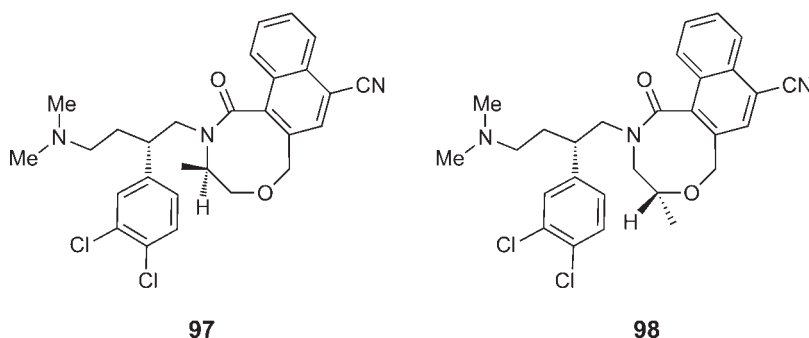
Surprisingly few reports appeared on the investigation of 1,4-oxazocines by experimental structural methods since 1995. The conformational features of 1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocines **20** were studied by molecular modeling and NMR spectroscopy of the model **95** to understand the factors responsible for the observed atropoisomeric properties <2004BML2653, 2004T4337> (cf. Sections 14.06.2 and 14.06.4.2). Proton NMR spectra indicated the presence of *exo*- and *endo*-isomers for 8-nitro-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazocine-6-carbaldehyde **96** <1996M305> with two approximate A₂X₂ spin systems observed at 300 MHz for the methylene protons of the 1,4-oxazocine ring (see discussion in Section 14.06.4.2).



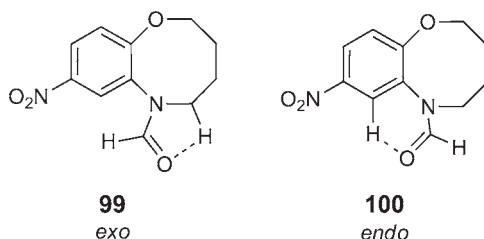
14.06.4.2 Thermodynamic Aspects

Melting points, where available, are given throughout this section for the individual compounds. During the last decade, scattered reports appeared on thermodynamic aspects of the 1,4-oxazocines. The reader is recommended the corresponding chapter in CHEC-II(1996) <1996CHEC-II(9)527> for comprehensive coverage of physical properties such as solubility, chromatographic behavior, and similar aspects.

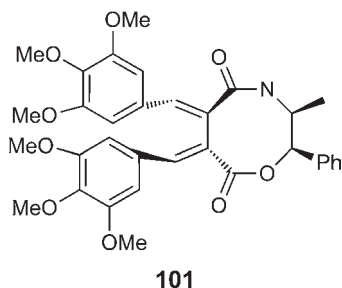
The conformational studies of a few novel 1,4-oxazocines have been reported by ^1H NMR spectroscopy and shown to correlate well with the theoretical calculations. Two atropoisomers were observed for **95** with a population distribution ca. 1:2 according to high-performance liquid chromatography (HPLC) and ^1H NMR spectroscopy <2004T4337>. Also, two discrete low energy conformations were identified for the naphthoxazocine **95** by MM calculations. In one conformation (A), the phenyl and naphthyl rings are oriented with an edge-to-face stacking interaction. Such a conformation would place the naphthalene H_8 in **95** into the shielding zone of the phenyl ring. In the second conformation (B), the orientation of the eight-membered ring positions the naphthalene away from the face of the phenyl ring that a stacking interaction is no longer possible. Modeling of **95** predicted that conformation A would be favored by 3 kcal mol^{-1} . For **95**, its NMR spectra showed that each of the two atropoisomers is resolved for many of the protons. The separation of the corresponding signals was particularly striking for the naphthalene H_8 signal. For the minor atropoisomer, the H_8 resonated in the expected region at ca. 7.4 ppm. For the major atropoisomer, the H_8 signal was shifted upfield to ca. 6.4 ppm. For the B conformation, the H_8 is distant from the phenyl ring, and no shift would be expected. Thus, the minor atropoisomer was suggested to have the conformation B, and this conclusion was in agreement with the results on energy calculations <2004BML2653, 2004T4337>. Rigidification of the eight-membered ring by additional substitution in **95** was investigated with the key goal to eliminate atropoisomeric properties completely. Indeed, **97** and **98** existed in predominantly single conformational form based upon HPLC and NMR spectral data <2004T4337>.



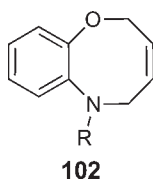
The existence of two isomers for the *N*-formyl oxazocine **96** was established by ^1H NMR spectral studies <1996M305> (Section 14.06.4.1). The relative amount of two isomers was solvent dependent, with the integral ratios ca. 5:1 in CDCl_3 and 1:3 in dimethyl sulfoxide ($\text{DMSO}-d_6$). The influence of the solvent on the population of different isomers suggested conformational isomerism that is, most probably, due to the hindered rotation around the $\text{C}(\text{O})\text{--N}$ bond with partial double-bond character as in the rotamers **99** and **100**, which can be stabilized by hydrogen bonding of the formyl oxygen. At elevated temperature (453 K) the signal of two rotamers collapsed.



The NMR spectrum of the 1,4-oxazocine dione **101** showed no evidence of two equilibrium diastereomers; thus, it was concluded that **101** exists in a single rotameric form <2004JOC4140>.

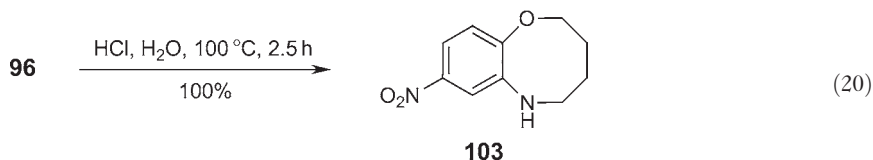


Benzoioxazocine **102** (R=Ts) was described as a mixture of (*E*)- and (*Z*)-isomers in 2:1 ratio <2002TL4207>, whereas another report identified **102** exclusively as the (*Z*)-isomer <2004TL9171> (cf. Equation (26), Section 14.06.4.4).

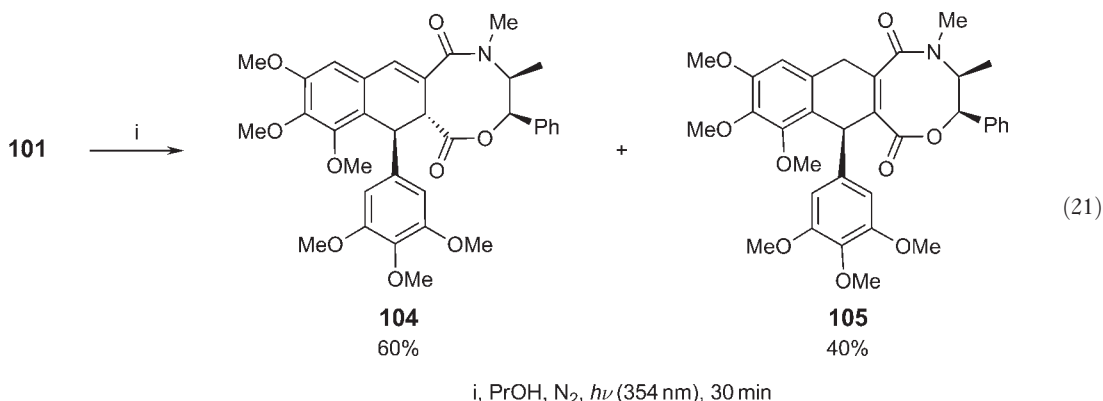


14.06.4.3 Reactivity of Nonconjugated Rings

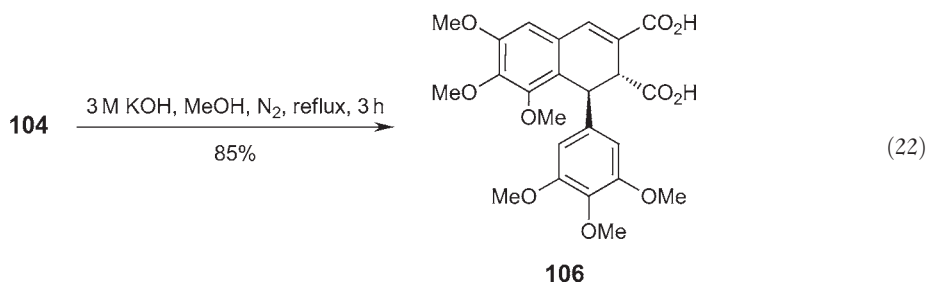
The *N*-formyl 1,4-oxazocine was readily hydrolyzed to the *N*-H derivative **103** (Equation 20) <1996M305>.



Irradiation of **101** produced a mixture of two cyclic isomers, the crystalline **104** and oily **105** (Equation 21) <2004JOC4140>. The regioselectivity of the photochemical ring closure in **101** to form **104** with the double bond next to the amido, and not the ester, fragment was established by NMR spectroscopy using heteronuclear multiple bond correlation (HMBC). Interestingly, **104** had a rotation of +476°, a very large optical rotation opposite to that of **101** (−342.9°) <2004JOC4140>. The absolute stereochemistry of the cyclic **105** was not determined but it was presumed to be the same as in **104**.



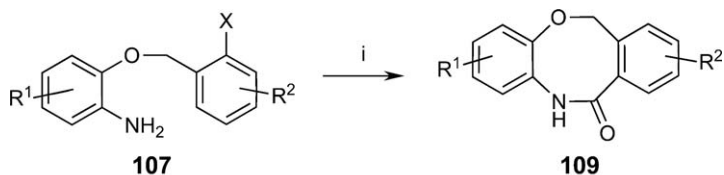
Removal of the chiral auxiliary from **104** was easily accomplished by hydrolytic cleavage with HCl into the diacid **106** (Equation 22) <2004JOC4140>.



14.06.4.4 Ring Syntheses

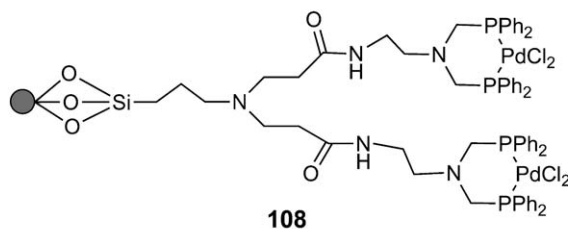
Earlier approaches to the 1,4-oxazocines have been discussed in CHEC(1984) <1984CHEC(5)653> and CHEC-II(1996) <1996CHEC-II(9)527>. Novel approaches and modifications of the previously known routes are discussed below.

In the evaluation of Pd-complexed dendrimers supported on silica as catalysts for intramolecular carbonylation reactions, the iodo- and bromoarenes **107**, substituted with either electron-withdrawing or electron-donating groups on the aromatic rings, in the presence of the catalyst **108** afforded the corresponding dibenzoxazocinones **109** in excellent yields (Equation 23) <2005JA14776>. The wide functional group compatibility is a significant advantage offered by this approach as the intramolecular carbonylation can encompass halide, ether, nitrile, oxo, and ester functionalities. Several examples of the dibenzo-1,4-oxazocinones, which were obtained by this method, are presented in Equation (23). The dendritic catalyst **108** can be recovered and reused at least five times.



i, **107** (1 mmol), CO (100 psi), **108** (15 mg), DIPEA (1.5 mmol), toluene
 X = I: 80 °C, 22 h; X = Br: 120 °C, 22 h

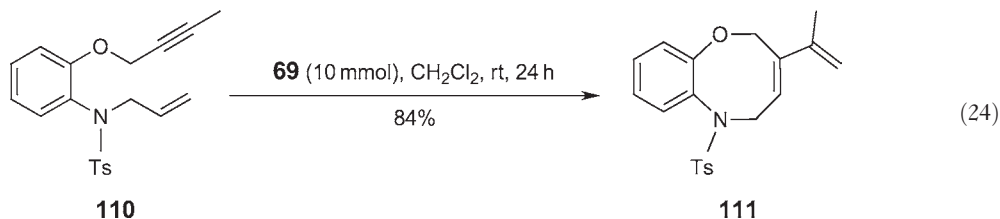
DIPEA = diisopropylethylamine



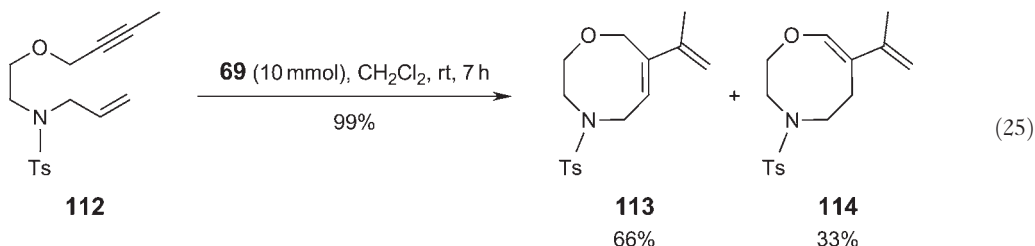
(23)

R^1	R^2	X	Yield (%)
H	H	I	98
5-Me	H	I	91
2,4-Me	H	I	96
4-F	H	I	95
4-Cl	H	I	94
3-Piperidyl	H	I	94
4-CO ₂ Me	H	I	95
2-Ph	H	Br	95
2-Me	8-F	Br	96
3-Me	8-F	Br	97

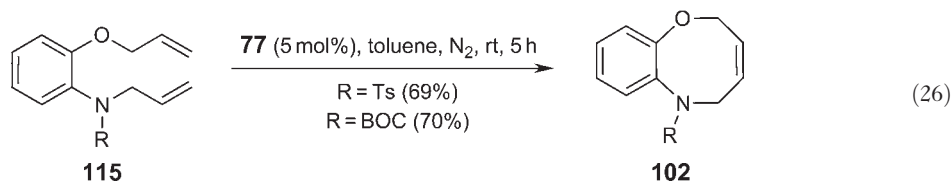
Application of the Grubbs' ruthenium catalyst **69** (see [Scheme 10](#), [Section 14.06.3.4.1](#)) in the enyne RCM of **110** smoothly produced the benzoxazocine **111** in high yield ([Equation 24](#)) <2000OL543> (cf. <1996CHEC-II(9)527> and [Section 14.06.3.4.1](#)).



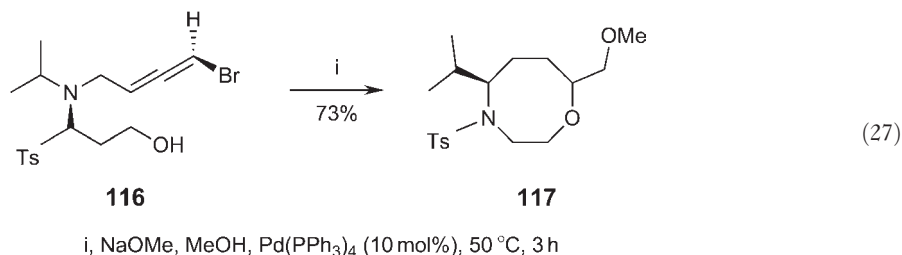
Under similar RCM conditions, the aliphatic enyne **112** gave the cyclized product **113** together with its alkene isomer **114** in overall high yield ([Equation 25](#)) <2000OL543>. The corresponding alkene isomer was not observed in the formation of 1,4-diazocine **71** (cf. [Scheme 10](#), [Section 14.06.3.4.1](#)).



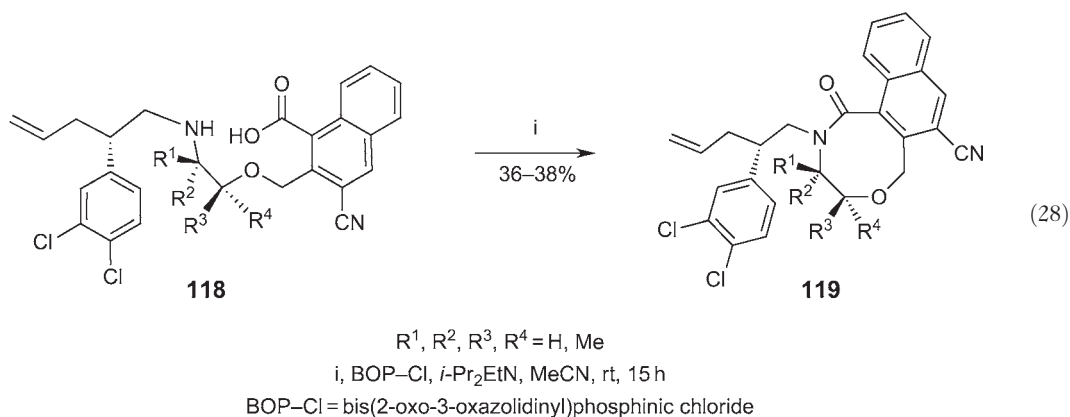
The isomerization–RCM strategy in the presence of the Grubbs' second-generation catalyst **77** was successfully applied to the synthesis of the benzoxazocines **102** isolated exclusively as the (*Z*)-isomer ([Equation 26](#)) <2004TL9171> (cf. [Scheme 11](#), [Section 14.06.3.4.1](#)). The use of Grubbs' catalyst **69** ([Scheme 10](#)) in the isomerization–RCM of **115** (R=Ts) resulted in **102** (R=Ts) as a mixture of (*E*)- and (*Z*)-isomers in 2:1 ratio <2002TL4207>.



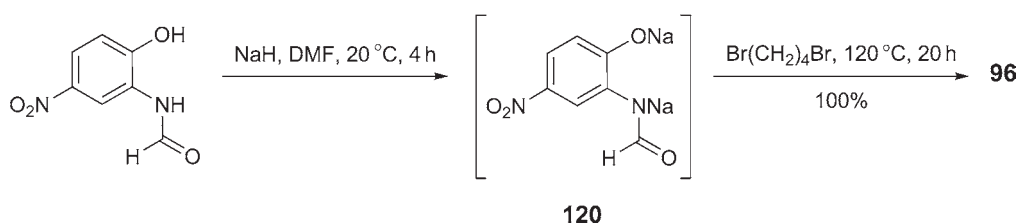
The first example of the synthesis of medium-sized rings via cyclization of the functionalized bromoallenes has been reported recently <2004JA8744>. In an approach to the eight-membered heterocines, **116** acts as an allyl dication equivalent, and the intramolecular nucleophilic attack takes place exclusively at the central carbon atom of the allene moiety to give the oxazocine **117** in high yield ([Equation 27](#)) <2004JA8744>.



The functionalized amino acid **118** underwent intramolecular cyclization to afford the naphthoxazinones **119** ([Equation 28](#)) <2004BML2653>. This synthesis is similar to the approach to the 1,4-diazocines via intramolecular cyclization (cf. [Equation 7](#), [Section 14.06.3.4.1](#)).

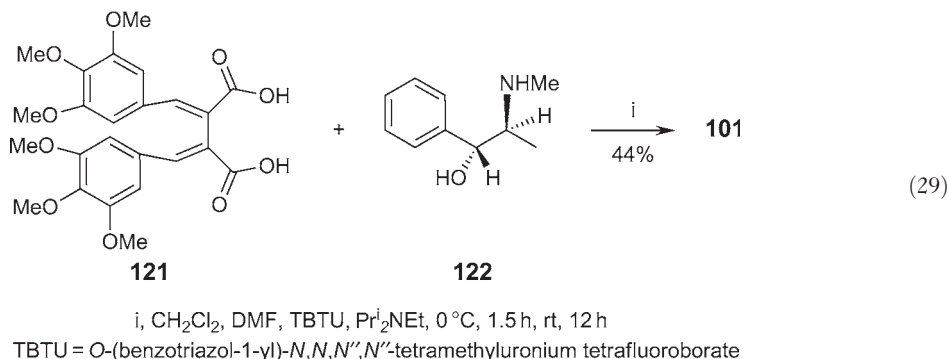


Alkylation of the disodium salt **120** with dibromobutane afforded the *N*-formyl benzoxazine **96** (m.p. 84–89 °C) in quantitative yield (Scheme 12) <1996M305>.



Scheme 12

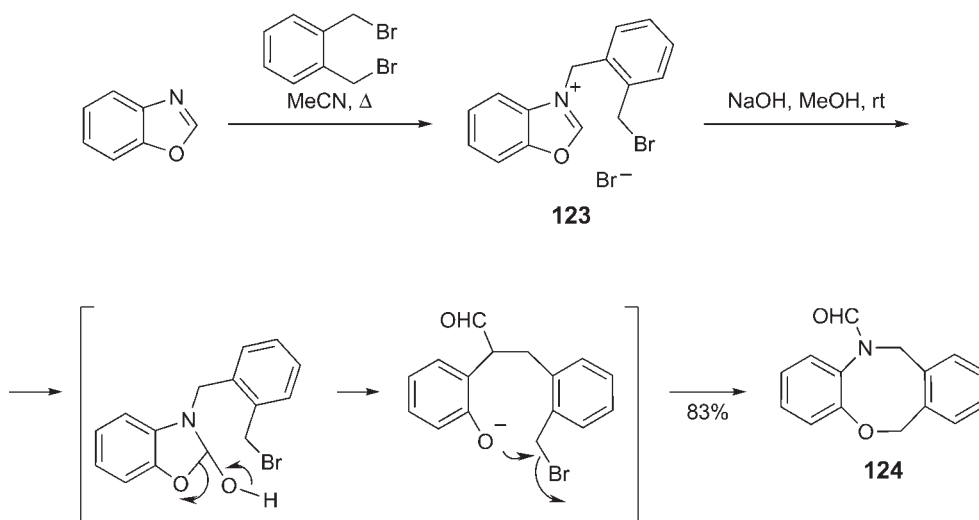
Condensation of the (*E,E*)-diarylsuccinic acid **121** with (1*R*,2*S*)-(–)-ephedrine **122** afforded the oxazocine dione **101**, as a single rotamer (Equation 29) <2004JOC4140>.



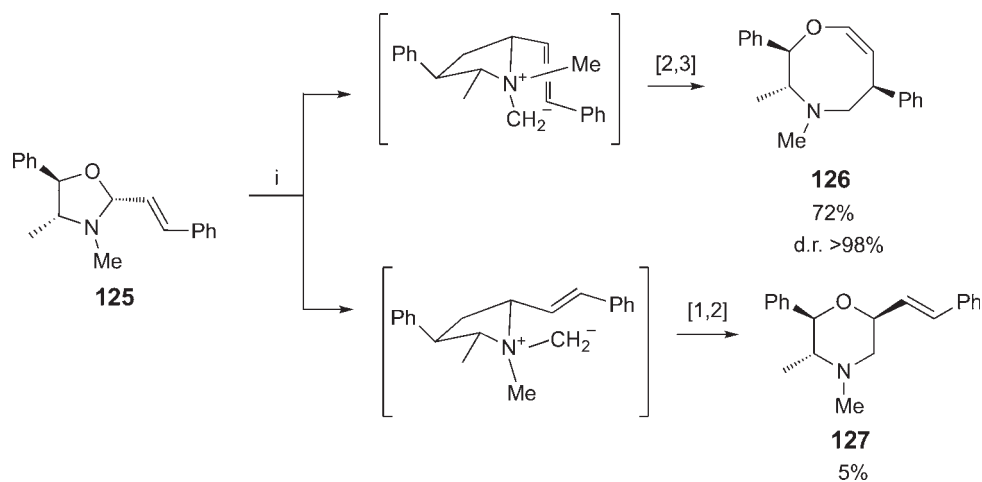
14.06.4.5 Ring Synthesis by Transformation of Another Ring

The two step conversion of the benzoxazole, first into the benzoxazolium bromide **123** followed by ring expansion afforded the *N*-formyl benzoxazocine **124** (Scheme 13) <1995JOC2597>. This approach was also successfully applied to the synthesis of *N*-formyl benzo[1,4]thiazocine from the benzothiazole (Scheme 16, Section 14.06.5.3).

Treatment of optically pure oxazolidine **125** with the Simmons–Smith reagent, generated from 1.1 equiv of ZnEt_2 and 2.2 equiv of CH_2I_2 , furnished the ring-expansion product, oxazocine **126** (m.p. 101–102 °C), as a single diastereoisomer. Formation of **126** was suggested via a [2,3]-sigmatropic rearrangement, whereas a small amount of the morpholine derivative **127** was presumably formed via a [1,2]-rearrangement (Scheme 14) <2003OL1757>. The structure of **126** was confirmed by X-ray crystallography.

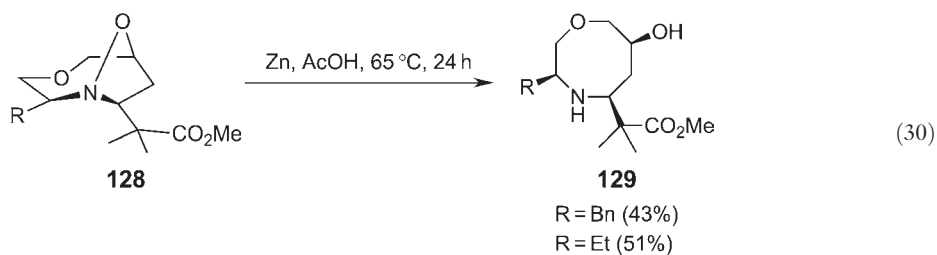


Scheme 13



Scheme 14

The chiral bicyclic β -amino acid esters **128** underwent reductive cleavage of the N–O bond to form oxazocanes **129** (Equation 30) <1999ZNB519>.



14.06.4.6 Comparison of Synthetic Routes

The flexible route to the substituted dibenzo[*b,f*][1,4]oxazocine-11(12*H*)-ones is offered by the carbonylation reaction catalyzed with recyclable Pd-complexed dendrimers on silica (Equation 23) <2005JA14776>. RCM and isomerization–RCM strategies are effective with the new generation of Grubbs' catalysts in the synthesis of oxazocines and benzoxazocines although the substitution pattern in the products remains limited (Equations 24–26) <2000OL543, 2002TL4207, 2004TL9171>. A few routes to the oxazocine ring system via ring-expansion (Equation 30, and Schemes 13 and 14) or other ring-construction approaches (Equations 29 and 30) represent rather special cases with limited applicability. A highly regio- and stereoselective synthesis of medium-sized heterocycles via cyclization of bromoallenes (Equation 27) offers a promise although it was illustrated by a single example in the construction of the 1,4-oxazocine ring. As for the synthesis of 1,4-diazocines, intramolecular cyclization of an appropriately functionalized precursor, when a precursor is constructed first, represents a multistep but reasonably effective route to the benzo- and naphtha-1,4-oxazocines with an orchestrated substitution pattern.

14.06.4.7 Important Compounds and Applications

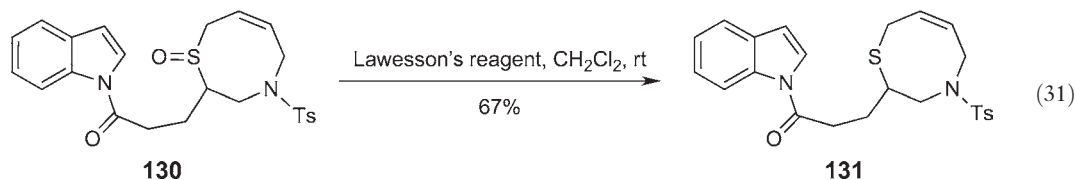
Naphtho-1,4-oxazocines have been investigated as antagonists for NK₁, one of three mammalian tachykinins which are thought to be involved in numerous physiological functions and are linked to the diseases and conditions such as asthma, inflammatory bowel disorders, inflammatory pain, cough, urinary disorders, and anxiety <2004BML2653, 2004T4337>. Dibenzoxazocines **109** and **124** might have the effects on the central nervous system and antihistaminic activity similarly to the earlier reported compounds with analogous structures <1995JOC2597> although no test results for novel compounds have been reported.

14.06.5 Rings with One Nitrogen and One Sulfur (4*H*-1,4-Thiazocines)

During the last decade, a few reports appeared on novel syntheses of the 1,4-thiazocine ring system, whereas no significant data were published on the experimental structural methods or thermodynamic aspects. The mass spectral data (molecular ions and fragmentation) and NMR spectra were reported as routine methods for the structure elucidation. Melting points, where available, are given throughout this section for the individual compounds. For comprehensive coverage of the experimental structural methods and thermodynamic aspects, the reader is recommended the corresponding section in CHEC-II(1996) <1996CHEC-II(9)527>. Novel routes to the 1,4-thiazocines and some other aspects are discussed in this section.

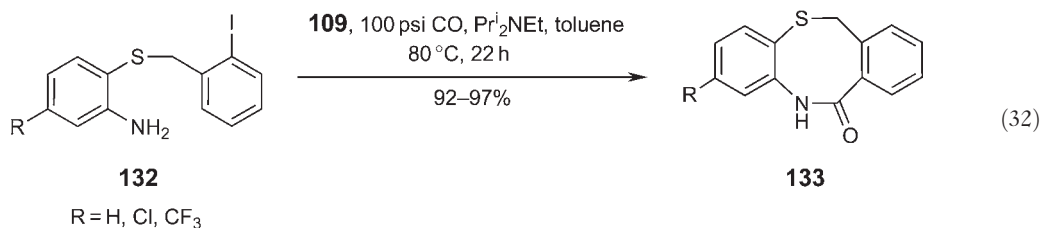
14.06.5.1 Reactivity of Nonconjugated Rings

A single example relevant to nonconjugated ring transformations has been found in the literature for the 1,4-thiazocine ring system. The sulfoxide **130** was reduced with Lawesson's reagent to form the sulfide **131** (m.p. 177–178.5 °C) (Equation 31) <2004JOC2750>. The 1,4-thiazocine **130** was synthesized via the RCM strategy (see Section 14.06.5.2), whereas the sulfide **131** could not be obtained by the same approach.

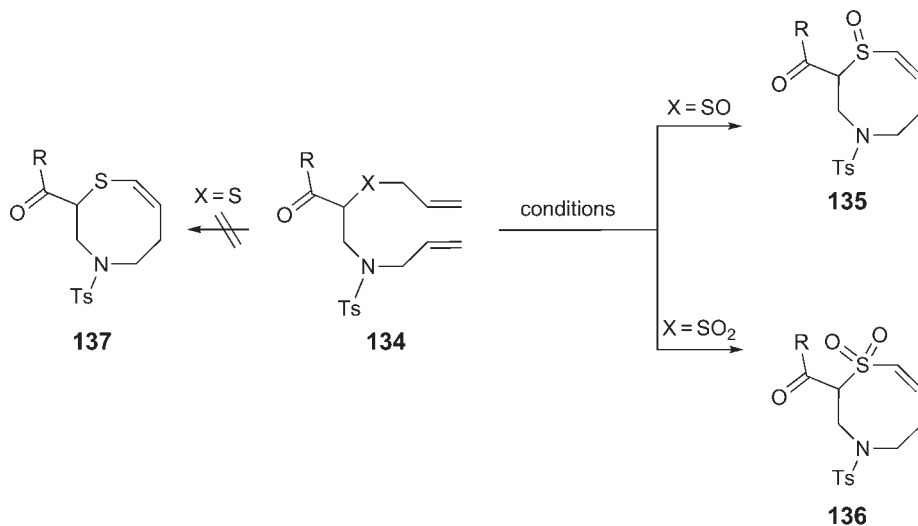


14.06.5.2 Ring Syntheses

As for the synthesis of dibenzo[*b,f*][1,4]oxazocine-11-ones (cf. Equation (23), Section 14.06.4.4), Pd-catalyzed carbonylation offers a convenient route to the dibenzo[*b,f*][1,4]thiazocine-11-ones **133** (Equation 32) <2005JA14776>.



The sulfone and sulfoxide alkenes **134** underwent the RCM reaction in the presence of Grubbs' second-generation catalyst **77** (see [Scheme 11](#), [Section 14.06.3.4.1](#)) to form the corresponding 1,4-thiazocines **135** and **136** ([Scheme 15](#)) [<2004JOC2750>](#). Sulfanyl derivatives **134** (X = S) were inactive in this transformation and did not produce the

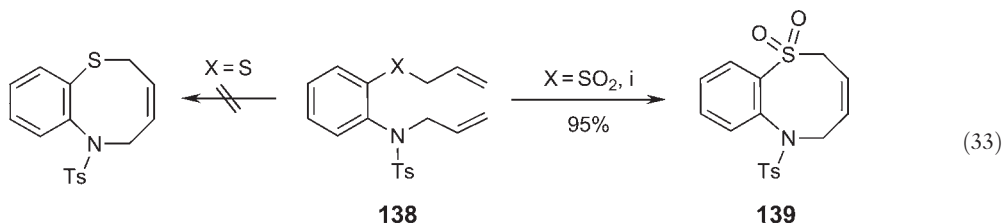


Compound	R	Conditions	Yield (%)
135	MeO	77 (5 mol%), DCM, reflux, 6 h	95
135		77 (10 mol%), DCM, reflux, 2.5 h	43
135		77 (10 mol%), DCM, reflux, 24 h	40
136	Me	77 (5 mol%), DCM, reflux	100
136		77 (5 mol%), DCM, reflux	89
136		77 (5 mol%), DCM, reflux	91

Scheme 15

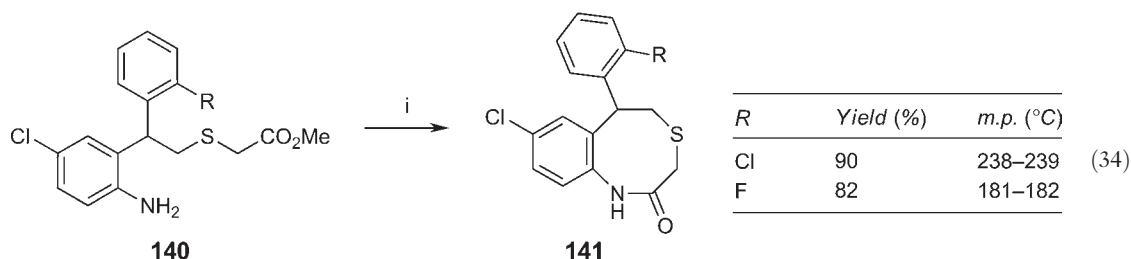
expected thiazocines **137**. The sulfides **137** can be obtained by reduction of the sulfoxides **135** as exemplified for **131** (Equation (31), Section 14.06.5.1).

Isomerization–RCM strategy, which was successfully applied to the synthesis of 1,4-diazocines and 1,4-oxazocines on catalysis with **77** (see Sections 14.06.3.4.1 and 14.06.4.4), afforded the benzothiazocine dioxide **139** from the sulfone **138** in high yield (Equation 33) <2004TL9171>. As for the sulfanyl compounds **134** (X = S) (Scheme 15), the substrate **138** (X = S) was inert under isomerization–RCM conditions.



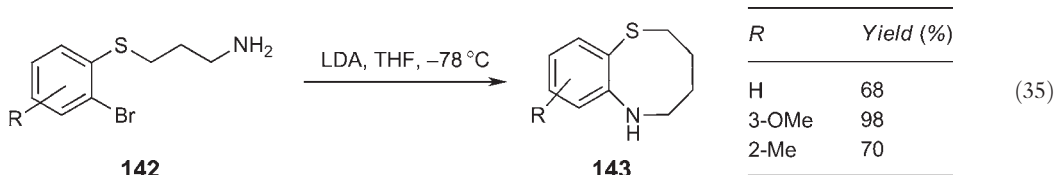
i, **77** (5 mol%), CHCl₃, rt, 24 h, then 45 °C, 24 h

Intramolecular cyclization of the thioethers **140** smoothly produced the benzo-1,4-thiazocines **141** in high yield (Equation 34) <2003JOC92>.



i, LiHMDS, THF, –78 °C → rt, 12 h

Bromosulfanyl arenes **142** were reported to cyclize in the presence of a strong base into the 2,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]thiazocines **143** in high yield (Equation 35) <2004H(63)2309>.

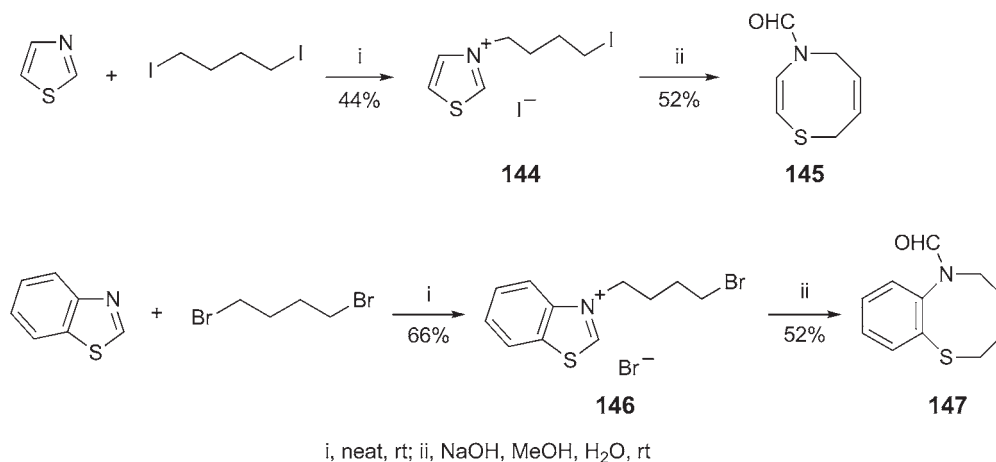


14.06.5.3 Ring Synthesis by Transformation of Another Ring

The two-step conversion of the thiazole and benzothiazole into the corresponding thiazolium salts **144** and **146** followed by ring expansion resulted in *N*-formyl thiazocine **145** and benzothiazocine **147** (Scheme 16) <1995JOC2597>. The mechanism of this ring expansion is similar to that described for the transformation of the benzoxazolium salt **123** into the *N*-formyl oxazocine **124** (Scheme 13, Section 14.06.4.5).

14.06.5.4 Comparison of Synthetic Routes

The 1,4-thiazocines represent a still rare class of the heterocycles although novel cyclization routes via RCM and isomerization–RCM strategies might result in a fast-growing number of newly synthesized compounds. The ring expansion of the thiazolium salts offered a route to nonbenzannelated thiazocines, which are difficult to prepare (cf. <1996CHEC-II(9)527>), although no developments of this approach have been reported so far.



Scheme 16

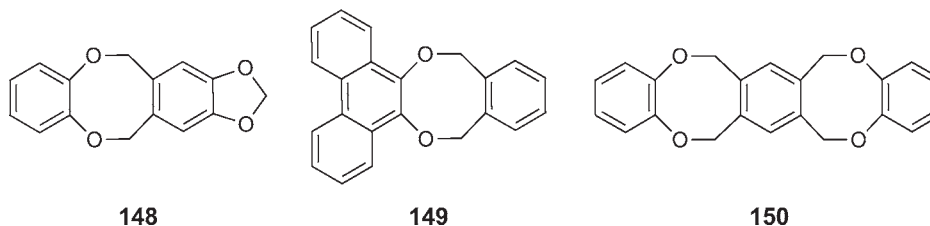
14.06.5.5 Important Compounds and Applications

The 1,4-thiazocines have a structural similarity with the thiazepine system, which is a core structure in a number of pharmacological agents, such as diltiazem and CGP37157, and thus might possess some physiological effects. The benzothiazocinones **141** were evaluated as antagonists for the mitochondrial sodium–calcium exchanger for potential treatment of type II diabetes and showed a moderate type of *in vitro* activity [\[2003JOC92\]](#).

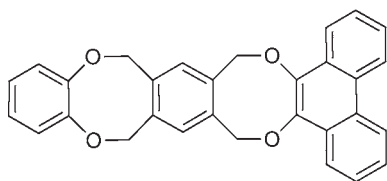
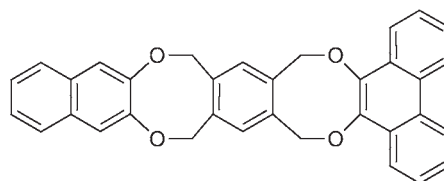
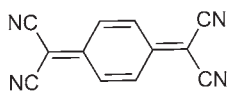
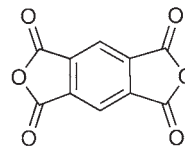
14.06.6 Rings with Two Oxygens (1,4-Dioxocines)

14.06.6.1 Experimental Structural Methods

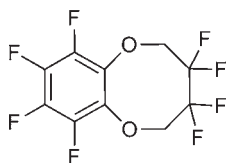
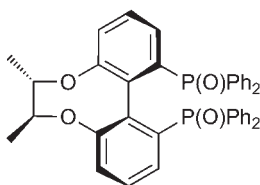
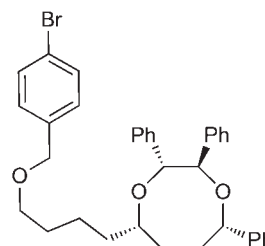
Single crystal X-ray diffraction analyses of 1,4-dioxocines **148–150** have been reported [\[1998T13495\]](#). The structure found in the crystalline state for **148** and **149** is the twist boat as was predicted by theoretical calculations (see [Section 14.06.2](#)). The eight-membered dihydrodioxocine ring in **150** adopts the screw form. The dihedral angles between atomic rings (center-terminal) within the molecule are 48.7°. This is the first example described in the literature in which a compound adopted the screw conformation in the crystalline state.



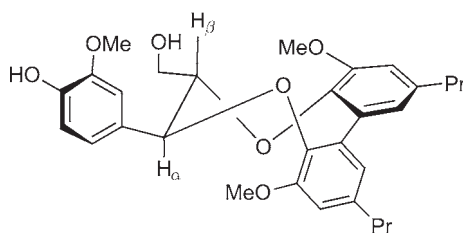
In the X-ray crystallographic study of the host–guest tweezers complexes, the single crystal structures of the complexes **151·153**, **151·154**, **152·153**, and **152·154** have been reported [\[2001T8667\]](#). It was found that the host has a tweezers-type conformation with a face-to-face *syn*-arrangement of the two terminal aromatic rings in **152·153** (cf. [Section 14.06.2](#)). A quite similar stacking mode was observed in **152·154**, although the relative special arrangement of the two terminal aromatic rings is different with no rotation of the central durene moiety. Unexpectedly, the 1:1 complex formation was not observed in the crystalline state for **151** and **153**, and the **151**₂·**153** complex was formed in the L-type conformation. The same host **151** holds guest **154** in 1:2 fashion in the crystalline state, and the complex **151·154**₂ accepted the Z-type form.

**151****152****153****154**

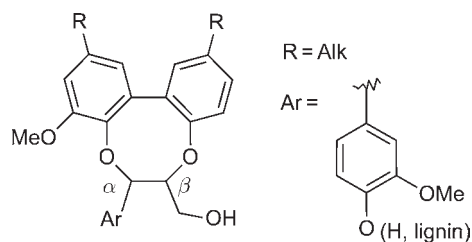
The crystal structure of **155** showed an almost planar C_6F_4 ring attached to a highly puckered eight-membered dioxocine ring [<1994IC415>](#). The molecular biaryl structure **156** was reported in the (R_{ax})-form [<2004PNA5815>](#); the stereochemistry of the dioxocane **157** was determined by single crystal X-ray diffraction [<1996TL2245>](#).

**155****156****157**

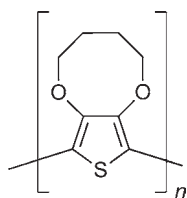
The dioxocine **158** was discovered as a novel structural type of the naturally occurring ‘neolignans’ [<1995TL4501, 2001T365, 2002JFA658>](#). The proton NMR spectrum of **158** exhibited signals at 4.15 and 4.85 ppm (H_α and H_β) with a coupling constant of 9.7 Hz. This implies a dihedral angle close to 180° with H_α and H_β in *trans*-position.

**158**

The structure of an acetylated ^{13}C -enriched poplar wood lignin was studied using three-dimensional heteronuclear multiple quantum correlation homonuclear Hartmann–Itahn (3-D HMQC-HOHAHA) NMR spectroscopy. This method takes advantage of the large dispersion of ^{13}C chemical shifts to resolve individual ^1H chemical shifts. The whole spin system of an ^1H - ^{13}C correlation observed in an HMQC spectrum, even for minor components and unknown structural units, can be traced. Using this method, it was shown that **159**, which belongs to recently discovered linkage in softwood lignins [<1995TL4501>](#) (cf. **158**), is a part of the lignin mixture and exists in both *trans*- and *cis*-isomeric forms [<1998JFA5113>](#).

**159**

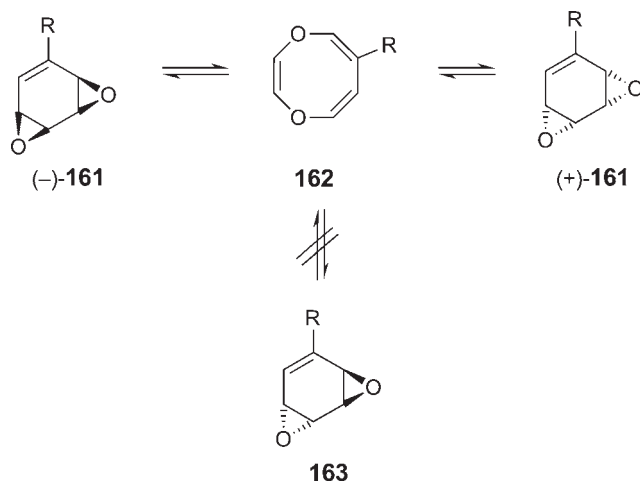
Using electron spin resonance (ESR) spectroelectrochemistry, the effects of overoxidation on the properties of the polymer **160** were studied [\[2006MI2135\]](#). Upon traversing of the potential boundary of electrochemical stability, a sharp drop in the number of free spins in the polymer was observed together with the changes in spectroscopic properties.

**160**

14.06.6.2 Thermodynamic Aspects

Thermodynamic aspects of numerous 1,4-dioxocines were comprehensively covered in CHEC-II(1996) [\[1996CHEC-II\(9\)527\]](#). The overview of the data, which appeared in the literature since 1995, is presented below.

It is known that 1,4-dioxocines **4** are paratropic and exist in the equilibrium with *syn*-benzene dioxides **5** (see [Equation \(1\)](#), [Section 14.06.2](#)). NMR analysis showed that the equilibrium mixture contained both the residual *syn*-benzene dioxide **161** (R = I) as a minor component (12%), and the corresponding 1,4-dioxocine isomer **162** (R = I) as a major component (88%) ([Scheme 17](#)) [\[2000CC2151\]](#). Chromatographic separation of **161** and **162** followed by heating either component yielded the same equilibrium mixture as before separation. This unusual example of a concerted racemization of four chiral centers in one enantiomer was not observed for the *anti*-benzene dioxide **163**.

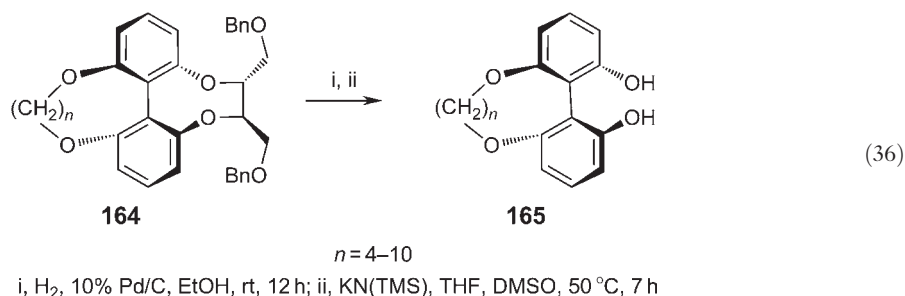
**Scheme 17**

The stoichiometry of the host (**151** or **152**) and guest (**153** or **154**) complexes (Section 14.06.6.1) was further supported by ^1H NMR measurements in CHCl_3 <2001T8667>. By titrating a solution of guest with that of a host using the complexation-induced shift for the guest, standard hyperbolic curves were constructed. The association constants were determined by the direct fitting using a nonlinear squares procedure with damping Gauss–Newton algorithm. The association constants for **152** were all larger than for **151**, reflecting the better donor–acceptor interactions between the host and the guest. It is known that the association constant of flexible molecular tweezers and electron-deficient guests is solvent dependent. ^1H NMR titration was conducted in acetone- d_6 , and neither **151** nor **152** showed any propensity for binding any guests. This result demonstrated the importance of the solvent polarity in the guest binding.

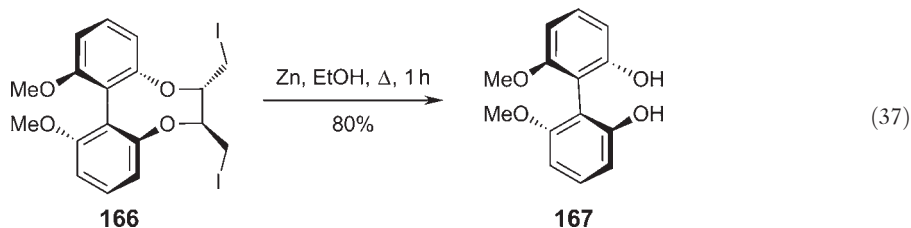
14.06.6.3 Reactivity of Nonconjugated Rings

Axially chiral diaryl compounds have become increasingly important as ligands for a variety of effective chiral catalysts <1992CR1007>. For this reason, much attention has been focused on their enantioselective synthesis. The 1,4-dioxocine motif, as a chiral 1,4-dioxy moiety, is frequently used in the construction of chiral 2,2',6,6'-tetrahydroxybiphenyls.

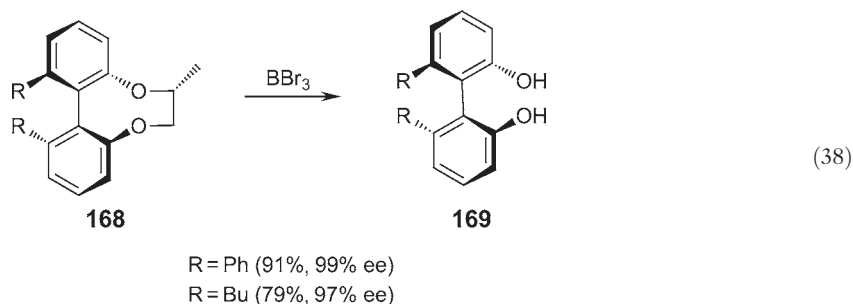
The chiral auxiliary in the diaryls **164** can be selectively removed to give (*S*)-biphenyldiols **165** in high enantiomeric purities and high yield (Equation 36) <2000JOC1335>.



In a similar reaction, the iodide **166** was reductively cleaved with activated Zn to form the diol **167** (m.p. 134–136 °C) (Equation 37) <1998CC2713>.

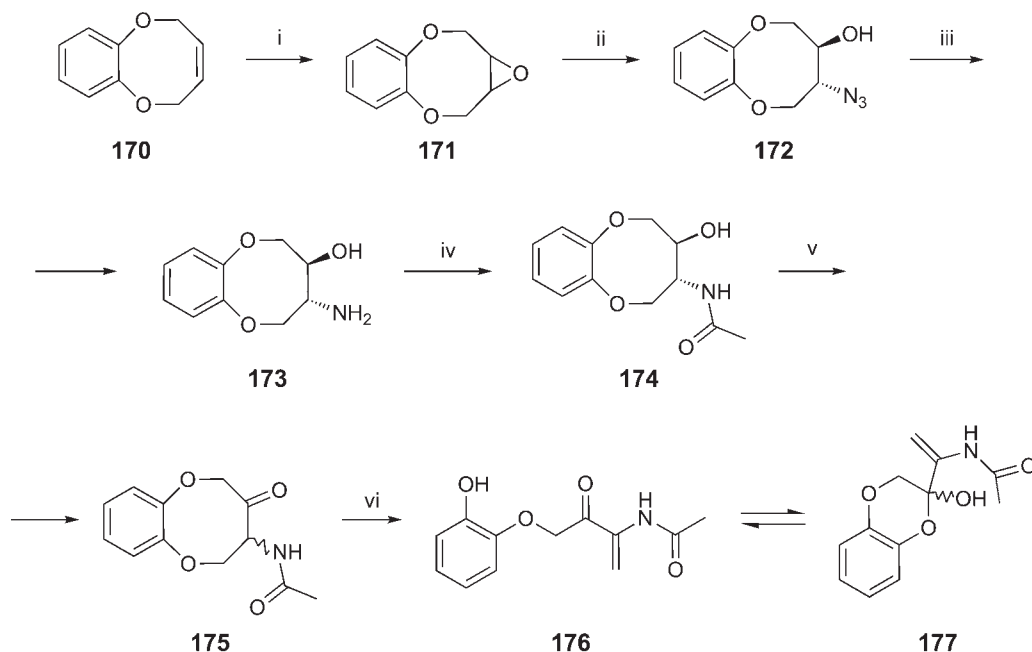


Removal of the chiral auxiliary in the diaryls **168** furnished enantiometrically pure diols (*S*)-**169** (Equation 38) <2000OL1319>.



In the study of novel classes of cathepsin K cysteine protease inhibitors, the benzodioxocin-3-one system **175** was investigated in terms of stability and reactivity (Scheme 18) <2004MI265> (see Section 14.06.6.4). It was found that

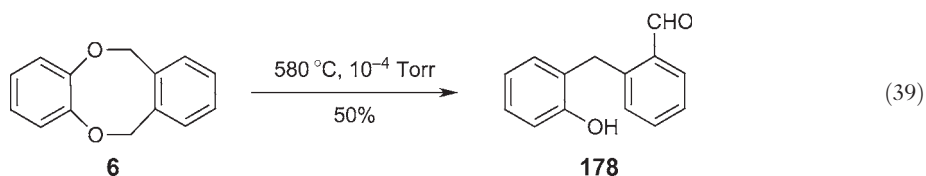
the benzodioxocinone **175** is chemically unstable and formed a mixture of *N*-acyl-3-amino-3-butene-2-one **176** and hemiketals **177** as determined by ^1H NMR spectroscopy.



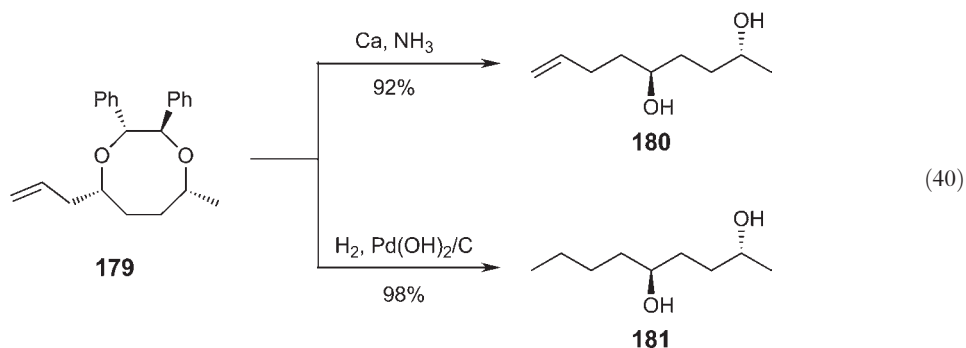
i, MeReO_3 , $\text{H}_2\text{NCONH}_2 \cdot \text{H}_2\text{O}_2$; ii, NaN_3 , NH_4Cl , MeOH ; iii, H_2 , Pd/C , CH_2Cl_2 ; iv, Ac_2O , Et_3N , DMF ; v, Dess–Martin periodinane; vi, silica gel chromatography

Scheme 18

Flash vacuum pyrolysis of the dibenzodioxocine **6** was reported to give the 2-(2'-hydroxybenzyl)benzaldehyde **178** (Equation 39), presumably via the intermediate diradical formation <1995JOC8410>.



In a new asymmetric synthesis of chiral 1,4-diols, the dioxocane **179** was transformed into diols **180** and **181** by either the Birch reduction or catalytic hydrogenolysis, respectively (Equation 40) <1996TL2245> (cf. Equation (46), Section 14.06.6.6).

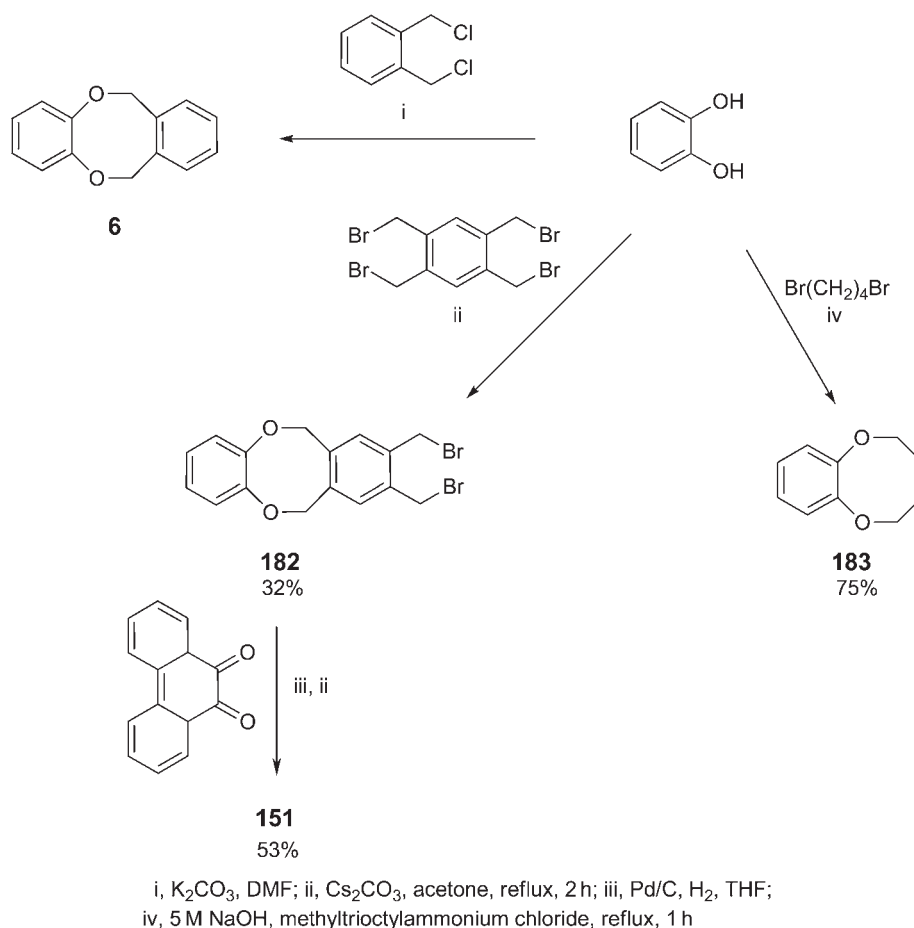


14.06.6.4 Reactivity of Substituents Attached to Ring Carbon Atoms

Reaction of the benzodioxocine **170** with the epoxidation reagent resulted in the epoxide **171**, which was then opened with sodium azide *in situ* to provide *trans*-racemic azide **172** (Scheme 18) <2004MI265>. Reduction of the azide **172** by hydrogenolysis using Pd on carbon gave *trans*-racemic amine **173** in 70% yield over three steps. On acylation of the amine with acetic anhydride, the *trans*-racemic alcohol **174** was formed, which was then oxidized with Dess–Martin periodinane into the unstable dioxocinone **175**.

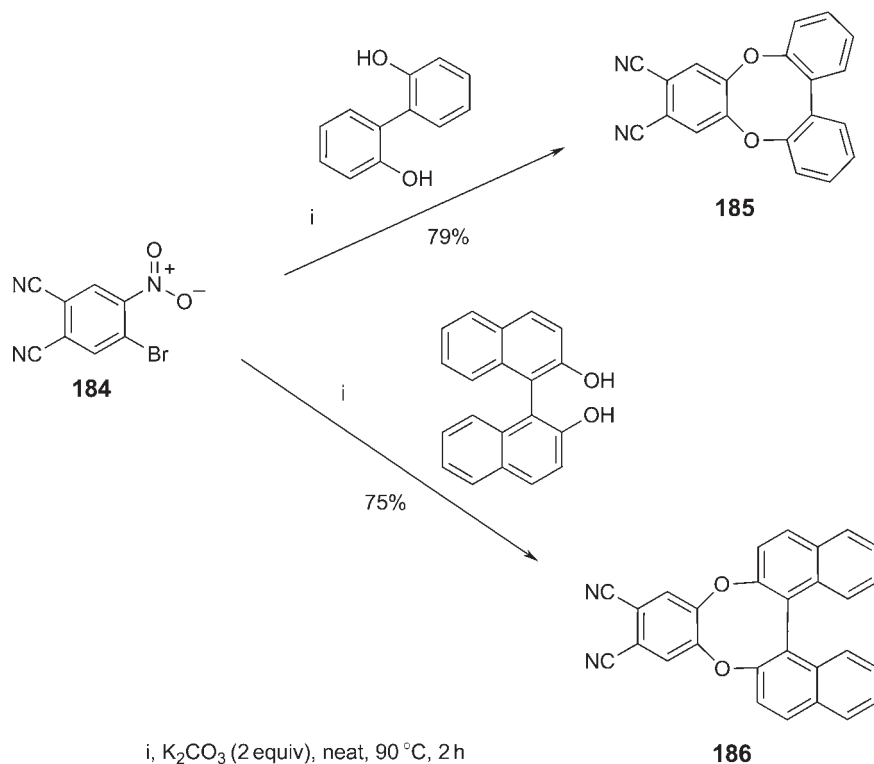
14.06.6.5 Ring Syntheses

Intermolecular condensation with the formation of two C–O bonds is a viable approach to the benzo-annulated dioxocines (cf. 1996CHEC-II(9)527). Treatment of catechol with α,α' -xylene dichloride afforded dihydrodi-benzo[*b,f*][1,4]dioxocine **6** (an oil) in excellent yield (Scheme 19) <1995JOC8410>. Similarly, catechol reacted with 1,2,4,5-tetrakis(bromomethyl)benzene to form the dibenzodioxocine **182** (m.p. 87–89°C) in moderate yield <2001H(54)849, 2001T8667>. The dibromide **182** was further treated with phenanthrenequinone under reductive conditions to afford 9,13,18,22-tetraoxa-9,10,12,13,18,19,21,22-octahydrobenzo-9',10'-phenanthro[*e,e'*]benzo[1,2- α :4,5- α']dicyclooctene **151** <2001T8667>. Catechol reacted with dibromoethane under phase-transfer catalysis conditions to form tetrahydro-1,6-benzodioxocine **183** in high yield <2001SC1>.



Scheme 19

4-Bromo-5-nitrophthalonitrile **184** is activated toward the reactions of aromatic nucleophilic substitution for the bromine and the nitro group, and on interaction with bifunctional hydroxy aryls afforded the tri- and tetrabenzodioxocines **185** (m.p. 205–206 °C) and **186** (m.p. > 300 °C), respectively (Scheme 20) <2001MC80>.



Scheme 20

In the asymmetric synthesis of axially chiral biaryls, the formation of two C–O bonds is the key step in the etherification of 2,2',6,6'-tetrahydroxybiphenyl **187** (Scheme 21). Sequential etherification of the biaryl **187** with 1,4-di-*O*-benzyl-L-threitol **188** under the Mitsunobu conditions afforded the monoether **189**. After deprotection of the *t*-butyldimethylsilyl (TBDMS) group with Bu₄NF, the intermediate alcohol was again subjected to the Mitsunobu reaction *in situ*. The intramolecular cyclization proceeded smoothly to give **190** in high yield (for R = Bn, m.p. 138–139 °C) <2000JOC1335>.

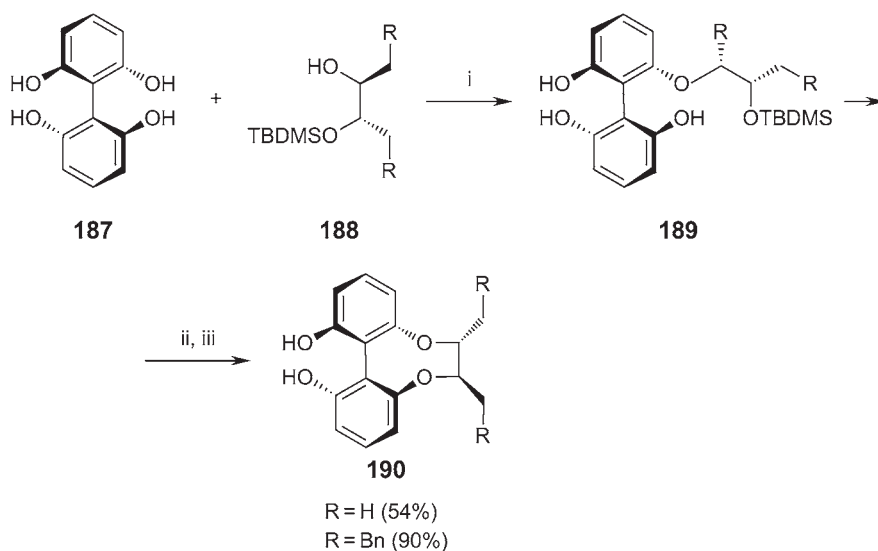
The biphenyl **187** underwent a facile annulation reaction with bis(mesylate) **191** to give the asymmetric desymmetrization product **192** (m.p. 230–231 °C) with exclusive stereoselectivity, which was readily separated from the by-products **193** (Equation 41) <2000OL1319>.

The formation of two C–O bonds occurred on condensation of the aryl halides **194** with tetrafluorodisiloxane **195** resulting in the dioxocines **196** or **197**, depending upon the positions in **194** susceptible toward the nucleophilic displacement (Scheme 22) <1994IC415, 1994IC5463>.

The formation of one C–C bond as the key step represents an alternative strategy to the dioxocine ring and is discussed below.

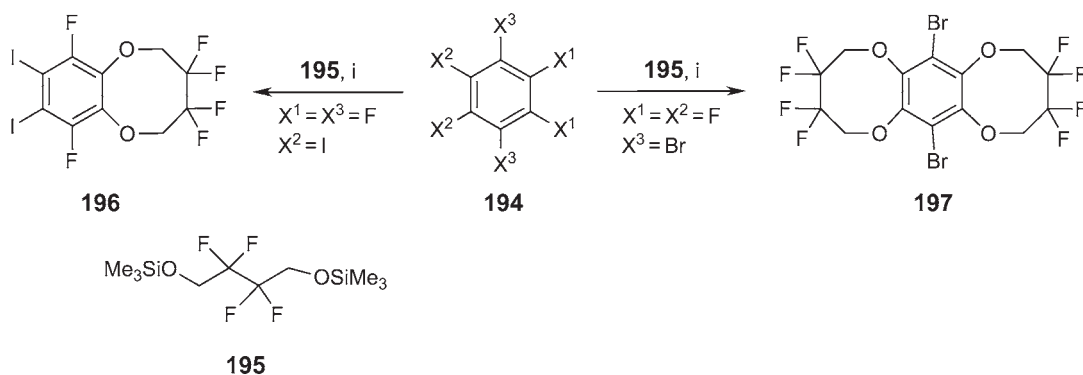
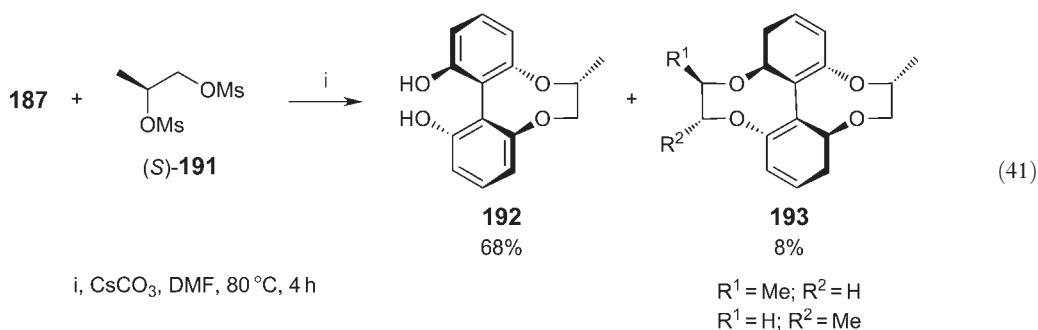
A highly stereoselective intramolecular couplings of **196**, where two aryl units are connected through a chiral 1,4-dioxy moiety, afforded the chiral **197** (Equation 42) <1997TL1087, 1998CC2713, 2004PNA5815>.

RCM of the enynes **198** in the presence of the Grubbs' catalyst **69** resulted in the benzodioxocines **199** via a C–C bond formation (Equation 43) <2000OL543> (see Scheme 10, Section 14.06.3.4.1).



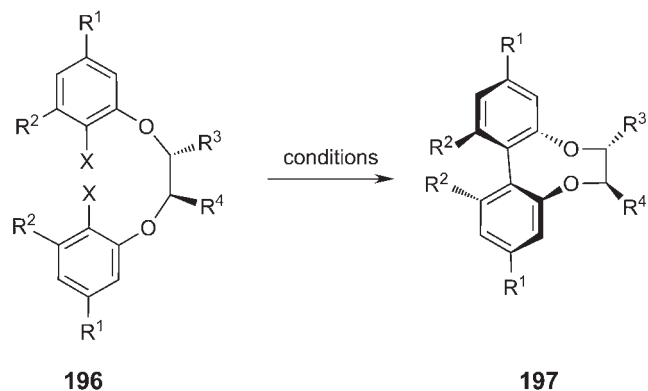
i, DEAD, PPh₃, THF, 0 °C, 3 h, 0 °C $\rightarrow$ 40 °C, 14 h; ii, Bu₄NF, THF, 0 °C $\rightarrow$ rt, 4 h; iii, DMAD, PPh₃, THF, 0 °C $\rightarrow$ rt, 14 h

Scheme 21



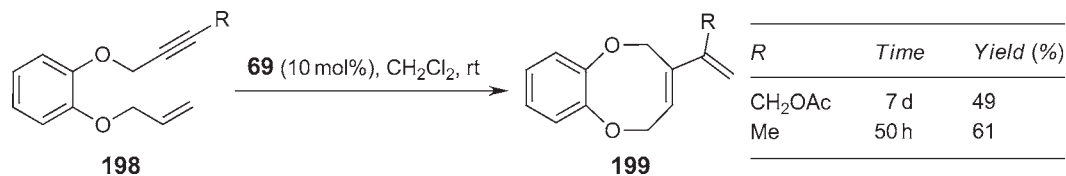
i, CaF (cat.), -196 °C, -196 °C $\rightarrow$ 25 °C, 60–70 °C, 12 h

Scheme 22



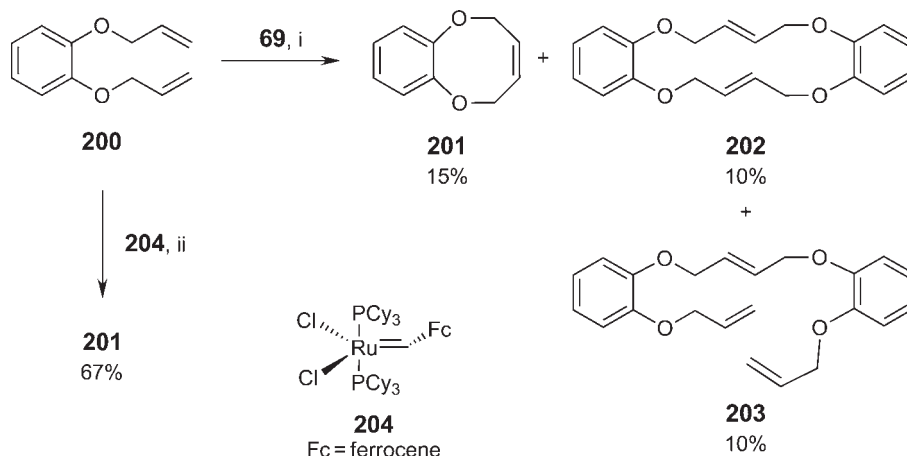
(42)

R^1	R^2	R^3	R^4	X	Conditions	Yield (%)	Reference
OMe	OMe	Bn	Bn	I	n -BuLi, THF, -78°C , 1 h; CuCN-TMEDA, 1:3, -78°C $\rightarrow -40^\circ\text{C}$, 1 h; dry O_2 , -78°C , 4 h	75	1997TL1087
OMe	Me	Bn	Bn	Br	n -BuLi, THF, -78°C , 1 h; CuCN; TMEDA, $-78^\circ\text{C} \rightarrow -40^\circ\text{C}$, 15 min; O_2 , -78°C , 3 h	40	1998CC2713
H	OP(O)Ph ₂	Me	Me	I	Cu, DMF, 140°C , 12 h	91	2004PNA5815



(43)

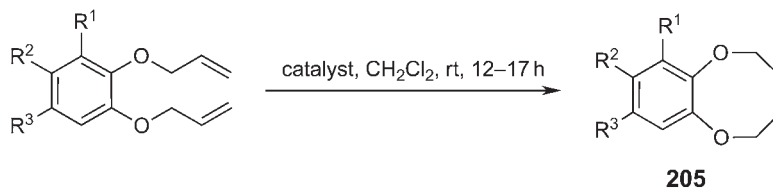
Isomerization–RCM of the diene **200** was catalyzed by **69** and resulted in a mixture of cyclic and acyclic products **201–203**, with the benzodioxocine **201** being formed in only 15% yield (Scheme 23) <1996SL1013>. The use of air-stable and recyclable Grubbs' catalyst **204** in the same transformation afforded **201** in 67% yield <2002SL1925>.



i, **69** (10 mol%), CH₂Cl₂, rt, 4 h; ii, **204** (2.5 mol%), CH₂Cl₂, rt, 1.5 h

Scheme 23

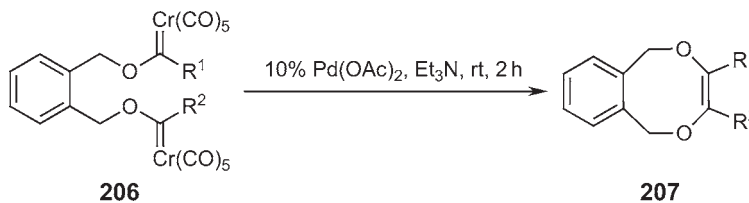
Benzo[*b,f*][1,4]dioxocines **205**, substituted in the benzene ring, were synthesized via isomerization–RCM approach in the presence of Grubbs' catalysts **69** or **77** in optimized good yields (Equation 44) <2004TL2631> (see Scheme 11, Section 14.06.3.4.1). The amount of a catalyst affected the yield of **205**. The catalyst **77** was also used in the construction of model benzo-substituted dioxocines in the synthesis of nakadomarin A <2003SL1207>.



R^1	R^2	R^3	Catalyst	Yield (%)
H	H	H	69 (20 mol%)	50
H	H	H	77 (10 mol%)	60
OMe	H	H	69 (8 mol%)	68
H	NO ₂	H	69 (8 mol%)	71
H	Br	H	69 (15 mol%)	69
H	CHO	H	69 (15 mol%)	62
F	H	H	69 (8 mol%)	70
H	–CH=CH–CH=CH–		69 (20 mol%)	56

(44)

The intramolecular carbene ligand dimerization of chromium bis-carbene complex **206** furnished the benzo [b,f][1,4]dioxocines **207** substituted in the dioxocine ring (Equation 45) <2001JA851>.

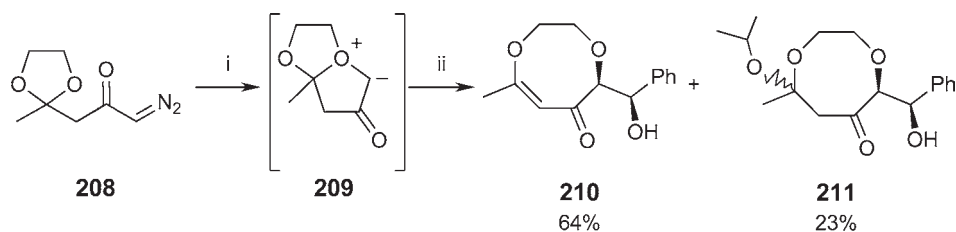


R^1	R^2	Yield (%)	<i>m.p.</i> (°C)
Ph	Ph	54	89–90
Me	Me	52	58–60
Me	Ph	53	Oil

(45)

14.06.6.6 Ring Synthesis by Transformation of Another Ring

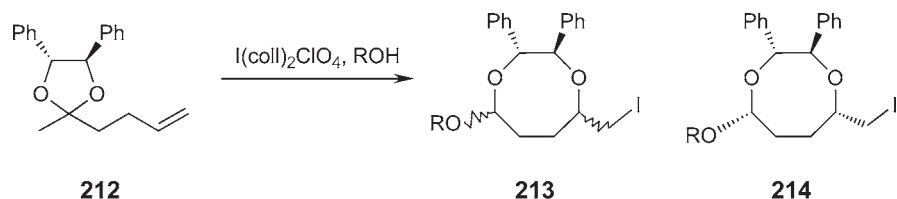
The ring expansion of the carbene dioxolane **208** occurred in the presence of Rh(II) catalyst. The reaction proceeded presumably via the intermediate ylide **209**, which was subjected to the reaction with benzaldehyde in the presence of Lewis acid to give a mixture of the dioxocine **210**, as the major product, as well as dioxocane **211** (Scheme 24) <2003JOC10040>. Compounds **210** and **211** were separated and the *syn*-conformation of **210** was determined by X-ray crystallographic analysis. The stereochemistry of **211** was also established by X-ray crystallography.



i, $\text{Rh}_2(\text{OAc})_4$ (1 mol%), CH_2Cl_2 , 15 min; ii, PhCHO (1 equiv), $\text{ClTi}(i\text{-PrO})_3$, -40°C , 2 h

Scheme 24

The electrophilic addition to the double bond in the dioxolane **212**, followed by five-membered ring expansion, resulted in the dioxocanes **213**, as a mixture of four inseparable stereoisomers (Equation 46) <1996TL2245>. The relative stereochemistry of the major product **214** was determined by ^1H NMR, nuclear Overhauser effect (NOE), and by converting **214** into the known **157** (cf. Section 14.06.6.1 and Equation (40)).



$\text{I}(\text{coll})_2\text{ClO}_4 = \text{bis}(\text{syn-collidine})\text{iodine(I) perchlorate}$

(46)

<i>R</i>	Yield (%)	Ratio of stereoisomers for 213
Me	86	85 (214):3:12:0
Bn	74	90 (214):10
$\text{MeO}(\text{CH}_2)_2$	90	86 (214):2:11:1

14.06.6.7 Comparison of Synthetic Routes

Approaches to the 1,4-dioxocines have been greatly improved during the last decade. Intermolecular condensation with the formation of two C–O bonds is an efficient route to 1,4-dioxocine ring system, particularly in the synthesis of numerous axially chiral biaryls. Intramolecular cyclization with the formation of a C–C bond, particularly by means of the RCM strategy, opened a new avenue in the synthesis of eight-membered 1,4-diheterocines with demonstrated success in the approaches to 1,4-dioxocines with a variable substitution pattern.

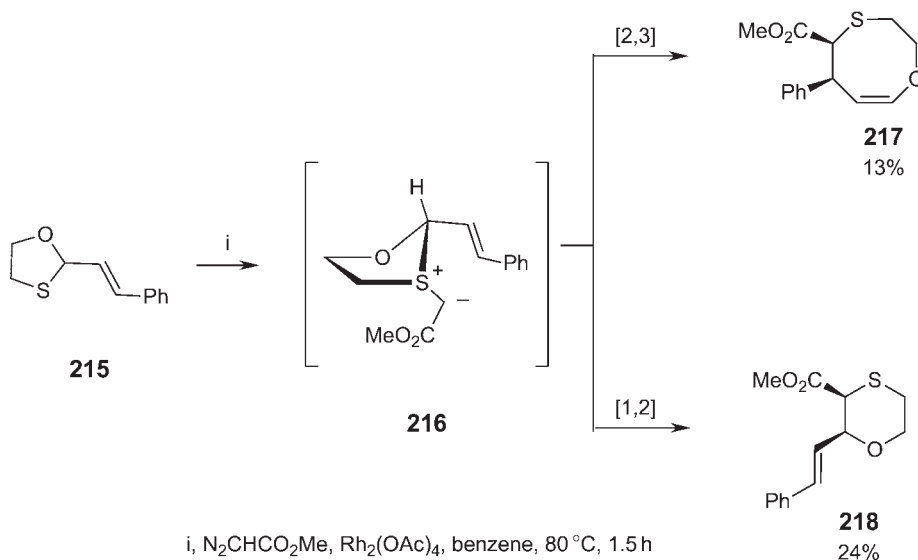
14.06.6.8 Important Compounds and Applications

Axially chiral biaryls, which are accessed via desymmetrization strategy involving a 1,4-dioxocine ring formation, are the catalysts in asymmetric synthesis, one of the most powerful methods for approaching a wide range of enantio-merically enriched compounds <1997TL1087, 2000JOC1335, 2000OL1319, 2002OL4495, 2003CC2210, 2004PNA5815>. 1,4-Dioxocines have been found to be reactive species in the degradation of lignin, an aromatic

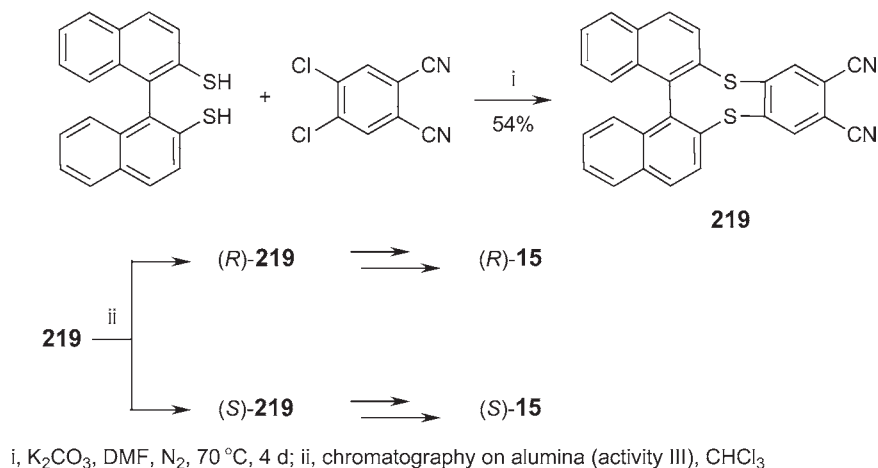
biopolymer <1995TL4501, 2001T365, 2002JFA658>. Poly(3,4-butylenedioxythiophene) **160** was a subject for investigation as a highly conductive polymer with interesting electrical and spectrochemical properties associated with low band gap, electrochromic, and antistatic properties, as well as a good stability <2006MI2135>.

14.06.7 Rings with One Oxygen and One Sulfur (1,4-Oxathiocines)

A single report on 1,4-oxathiocines has been found in the literature published since 1995. The 2-styryl-1,3-oxathilane **215** with the methyl diazoacetate, catalyzed by $\text{Rh}_2(\text{OAc})_4$, produced a complex mixture of products. 1,4-Oxathiocine **217** and 1,3-oxathiolane **218** were isolated from the mixture in low yield and their stereochemistry was assigned by NMR analysis (Scheme 25) <2006T3610>. The proposed mechanism of this transformation may involve formation of the ylide **216**, which presumably underwent [2,3]-sigmatropic rearrangement into **217**, or Stevens rearrangement into **218** (cf. Scheme 24 (Section 14.06.6.6) and Scheme 26 (Section 14.06.8)).



Scheme 25



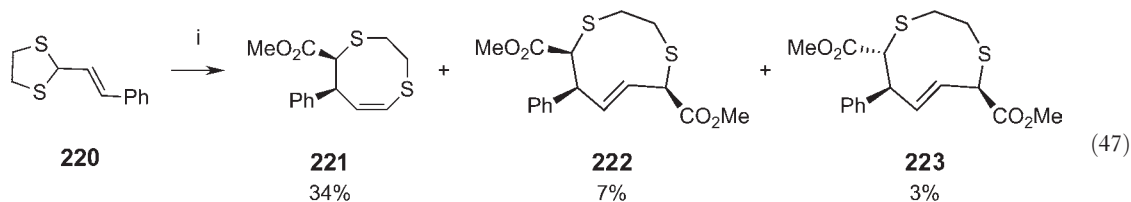
Scheme 26

No reports on practical applications of the 1,4-oxathiocines have been found in the literature.

14.06.8 Rings with Two Sulfurs (1,4-Dithiocines)

Phthalocyanines **15** with four optically active binaphthyl units were synthesized and characterized by electronic absorption, circular dichroism (CD) and magnetic circular dichroism (MCD) spectroscopy (Scheme 26) <1999JA12018> (see Section 14.06.2). The (*R*)- and (*S*)-**15** were each obtained independently from (*R*)- and (*S*)-**219**, respectively, which were isolated by separation of the racemate **219**. Phthalocyanines **15** with (*R*)- and (*S*)-binaphthyls showed positive and negative induced CD, respectively, in the characteristic planar absorptions of the phthalocyanine chromophore. The observed dichroism results from the interplay of two induction paths, which are both strongly geometry dependent. CD studies thus offered a sensitive tool for studying the ligand environment of these chromophores and may have implications for the design of magnetooptic materials and for the interpretation of fluorescence-detected circular dichroism (FDCD) in proteins.

Treatment of 2-styryl-1,3-dithiolane **220** with methyl diazoacetate, as a source of carbene by the previously discussed mechanism (1996CHEC-II(9)527), resulted in a mixture, which was separated chromatographically to give 1,4-dithiocine **221** (m.p. 82–83 °C) in moderate yield together with the minor dithionines **222** and **223** (Equation 47) <2006T3610>. The formation of **221** presumably proceeded similar to that of the 1,4-oxathiocine **217** from the oxathiolane **215** (see Scheme 25) although **221** was formed in higher yield. Formation of **222** and **223** was explained by rearrangement of the thia analog of **218** (Scheme 25), which was not detected in the transformation of the dithiolane **220**. The structures of **221** and **222** were established by X-ray diffraction analysis.



i, N₂CHCO₂Me, Rh₂(OAc)₄, benzene, 80 °C, 2 h

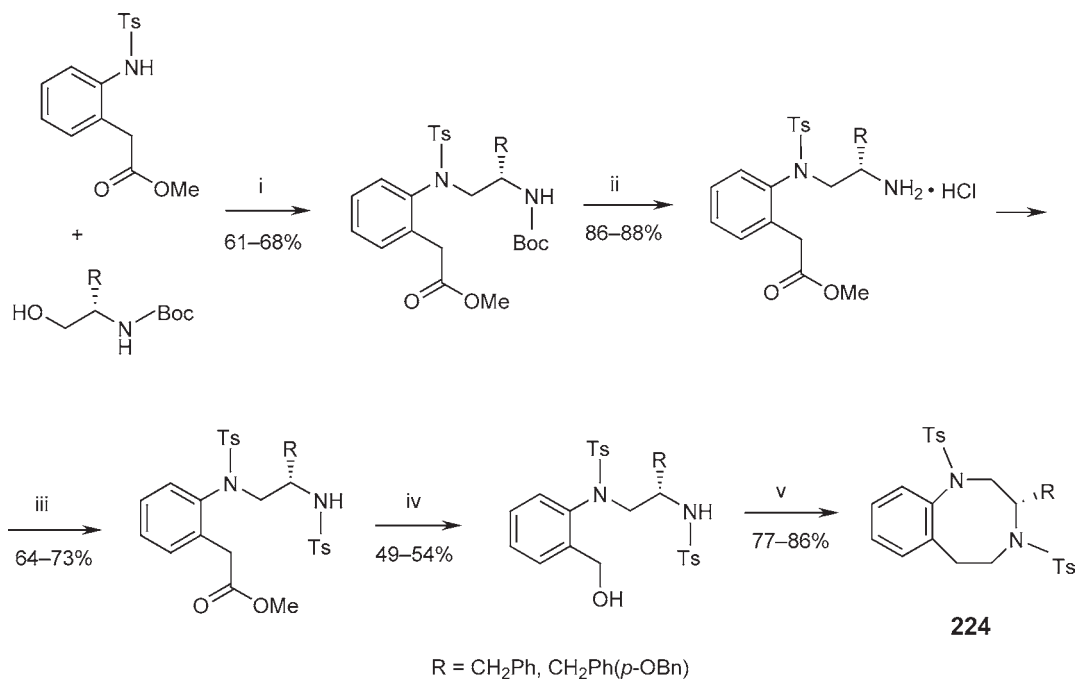
14.06.9 Further Developments

Recently, novel syntheses of 1,4-diazocines, 1,4-oxazocines and 1,4-oxazocanes have been reported via intramolecular cyclization of the appropriately functionalized compounds and formation of a single C–N or C–O bond.

The diversity-oriented synthesis of enantiomerically pure seven- and eight-membered ring systems was reported from easily accessible naturally occurring *S*-amino acids and their readily prepared derivatives as chiral synthons <2007JCO321>. Intramolecular Mitsunobu reaction was used as a key transformation to construct the 1,4-diazocines **224** (Scheme 27) and 1,4-oxazocines **225** (Scheme 28) <2007JCO321>.

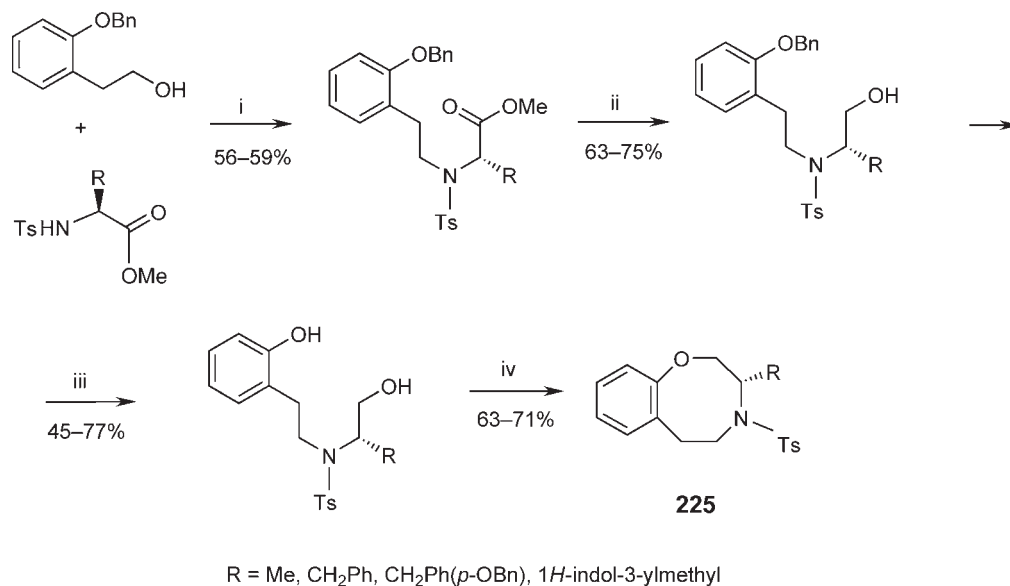
The multi-component Ugi reaction was applied to the synthesis of bisamide **226** (Scheme 29) <2007JOC2151> (cf. Scheme 7, Section 14.06.3.4), which under Mitsunobu conditions produced a mixture of 5-oxo-1,4-oxazocane **227** and acyclic **228**. The latter compound was partially decomposed during the separation by chromatography.

The Ugi reaction followed by Mitsunobu condensation was applied to the synthesis of the pyrrolidine-fused 1,4-oxazocane **230** (Scheme 30) <2007JOC2151>. It was expected that the pyrrolidine ring in the precursor **229** could furnish a steric bias favoring the cyclization. Indeed, the compound **230** was formed in 70% yield (cf. Scheme 29).



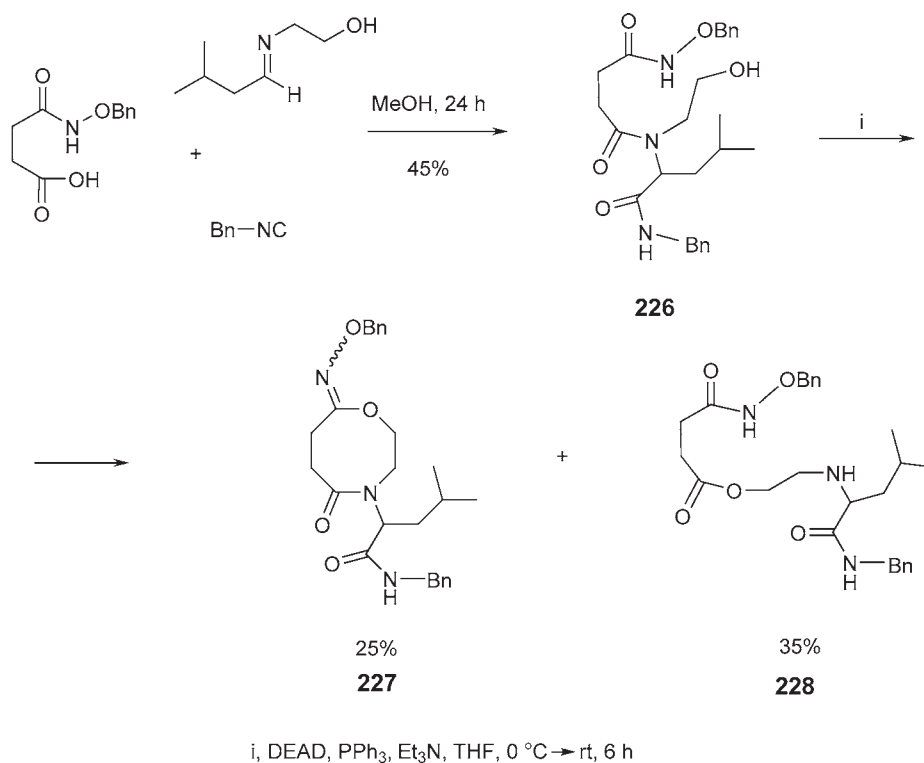
i, DEAD, PPh₃, THF, N₂, 0 °C → rt, 12 h; ii, 6 N HCl, MeOH, 0 °C → rt, 45 min; iii, *p*-TsCl, TEA, DCM, N₂, 0 °C → rt, 1 h; iv, LAH, THF, 0 °C, 1 h; v, DEAD, PPh₃, THF, N₂, 0 °C → rt, 14 h

Scheme 27

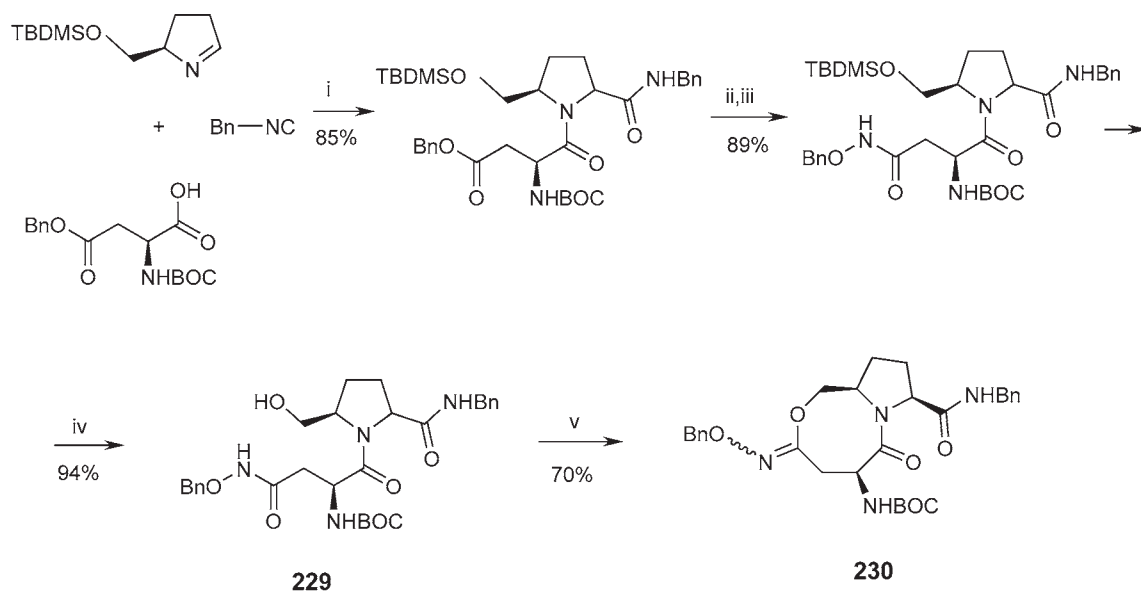


i, DEAD, PPh₃, THF, N₂, 0 °C, 2 h, 0 °C → rt, 10 h; ii, LAH, THF, 0 °C, 1 h; iii, 10% Pd/C, MeOH, rt, 2 h; iv, DEAD, PPh₃, THF, N₂, 0 °C → rt, 14 h

Scheme 28



Scheme 29



i, MeOH, 24 h; ii, H₂, Pd/C, EtOH, rt, 3.5 h; iii, BnNH₂·HCl, Et₃N, DCM, DMF, PyBOP, rt, 1 h;
iv, HF, MeCN, 0 °C, 1.5 h; v, DEAD, PPh₃, THF, rt, 1.5 h

PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

Scheme 30

References

- 1965RRC1059 A. T. Balaban and Z. Simon, *Rev. Roum. Chim.*, 1965, **10**, 1059.
- 1975AGE348 H. Prinzbach, M. Breuninger, B. Gallenkamp, R. Schwesinger, and D. Hunkler, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 348.
- 1984CHEC(5)653 J. A. Moore; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 5, p. 653.
- 1992CR1007 H. B. Kagan and H. B. Riant, *Chem. Rev.*, 1992, **92**, 1007.
- 1993TL5555 B. L. Johnson, Y. Kitahara, T. J. R. Weakley, and J. F. W. Keana, *Tetrahedron Lett.*, 1993, **34**, 5555.
- 1994IC415 N. R. Patel, J. Chen, Y. F. Zhang, R. L. Kirchmeier, and J. M. Shreeve, *Inorg. Chem.*, 1994, **33**, 5463.
- 1994IC5463 A. J. Elias, H. Hope, R. L. Kirchmeier, and J. M. Shreeve, *Inorg. Chem.*, 1994, **33**, 415.
- 1995JA2108 S. J. Miller, S.-H. Kim, Z.-R. Chen, and R. H. Grubbs, *J. Am. Chem. Soc.*, 1995, **117**, 2108.
- 1995JOC2597 H. J. Federsel, G. Glassare, K. Höglström, J. Wiestål, B. Zinko, and C. Odman, *J. Org. Chem.*, 1995, **60**, 2597.
- 1995JOC8410 W. S. Trahanovsky, S.-K. Lee, and J. F. Fennel, *J. Org. Chem.*, 1995, **60**, 8410.
- 1995TL4501 P. Karhunen, P. Rummakko, J. Sipilä, and G. Brunow, *Tetrahedron Lett.*, 1995, **36**, 4501.
- 1996CHEC-II(9)527 K. M. Doxsee; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 527.
- 1996JA9606 S. J. Miller, H. E. Blackwell, and R. H. Grubbs, *J. Am. Chem. Soc.*, 1996, **118**, 9606.
- 1996M305 R. Földényi, G. Szalontai, N. Szebényi, P. Kvintovics, and T. Bartik, *Monatsh. Chem.*, 1996, **127**, 305.
- 1996SL1013 B. König and C. Horn, *Synlett*, 1996, 1013.
- 1996TL2245 H. Fujioka, H. Kitagawa, N. Matsunaga, Y. Nagatomi, and Y. Kita, *Tetrahedron Lett.*, 1996, **37**, 2245.
- 1997BMC2029 A. A. Mazurov, S. A. Andronati, T. I. Korotenko, N. I. Sokolenko, A. I. Dyadenko, Y. E. Shapiro, V. Ya. Gorbatiyuk, and T. A. Voronina, *Bioorg. Med. Chem.*, 1997, **5**, 2029.
- 1997TL1087 G.-Q. Lin and M. Zhong, *Tetrahedron Lett.*, 1997, **38**, 1087.
- 1998CC2713 R. V. Kyasnoor and M. V. Sargent, *Chem. Commun.*, 1998, 2713.
- 1998JA12459 D. Ma, Y. Zhang, J. Yao, S. Wu, and F. Tao, *J. Am. Chem. Soc.*, 1998, **120**, 12459.
- 1998JFA5113 E. Ämmälähti, G. Brunow, M. Bardet, D. Robert, and I. Kilpeläinen, *J. Agric. Food Chem.*, 1998, **46**, 5113.
- 1998T13495 H. Kurebayashi, T. Mine, K. Harada, S. Usui, T. Okajima, and Y. Fukazawa, *Tetrahedron*, 1998, **54**, 13495.
- 1998TL7369 D. Ma and W. Tang, *Tetrahedron Lett.*, 1998, **39**, 7369.
- 1999JA12018 N. Kobayashi, R. Higashi, B. C. Titeca, F. Lamote, and A. Ceulemans, *J. Am. Chem. Soc.*, 1999, **121**, 12018.
- 1999JOC6366 D. Ma, W. Tang, A. P. Kozikowski, N. E. Lewin, and P. M. Blumberg, *J. Org. Chem.*, 1999, **64**, 6366.
- 1999JP13507 P. A. Bethel, M. S. Hill, M. F. Mayhon, and K. C. Molloy, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3507.
- 1999ZNB519 H. G. Aurich, C. Gentes, and U. Sievers, *Z. Naturforsch., B*, 1999, **54**, 519.
- 2000CC2151 D. R. Boyd, N. D. Sharma, C. R. O'Dowd, and F. Hempenstall, *Chem. Commun.*, 2000, 2151.
- 2000CR2963 L. Yet, *Chem. Rev.*, 2000, **100**, 2963.
- 2000H(52)273 M. Othman, P. Pigeon, P. Netchitaïlo, A. Daïch, and B. Decroix, *Heterocycles*, 2000, **52**, 273.
- 2000JOC1335 T. M. T. Tuyet, T. Harada, K. Hashimoto, M. Hatsuda, and A. Oku, *J. Org. Chem.*, 2000, **65**, 1335.
- 2000OL543 M. Mori, T. Kitamura, N. Sakakibara, and Y. Sato, *Org. Lett.*, 2000, **2**, 543.
- 2000OL1319 T. Harada, T. M. T. Tuyet, and A. Oku, *Org. Lett.*, 2000, **2**, 1319.
- 2001BML99 D. Ma, T. Zhang, G. Wang, A. P. Kozikowski, N. E. Lewin, and P. M. Blumberg, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 99.
- 2001CC475 S. Sakamuri and A. Kozikowski, *Chem. Commun.*, 2001, 475.
- 2001H(54)849 H. Kurebayashi and Y. Fukasawa, *Heterocycles*, 2001, **54**, 849.
- 2001JA851 M. A. Sierra, J. C. del Amo, M. J. Mancheño, and M. Gómez-Gallego, *J. Am. Chem. Soc.*, 2001, **123**, 851.
- 2001MC80 I. A. Abramov, A. V. Smirnov, S. A. Ivanovskii, M. B. Abramova, V. V. Plakhtinskii, and M. S. Belysheva, *Mendeleev Commun.*, 2001, 80.
- 2001SC1 J. J. V. Eynde and I. Mailleux, *Synth. Commun.*, 2001, **31**, 1.
- 2001T365 K. Syrjänen and G. Brunow, *Tetrahedron*, 2001, **57**, 365.
- 2001T8667 H. Kurebayashi, T. Haino, S. Usui, and Y. Fukazawa, *Tetrahedron*, 2001, **57**, 8667.
- 2002JFA658 D. S. Argyropoulos, L. Jurasek, L. Kríštofova, Z. Xia, Y. Sun, and E. Pauluš, *J. Agric. Food Chem.*, 2002, **50**, 658.
- 2002OL2169 Z.-L. Wei, S. Sakamuri, P. A. Petukhov, C. George, N. E. Lewin, P. M. Blumberg, and A. P. Kozikowski, *Org. Lett.*, 2002, **4**, 2169.
- 2002OL2377 D. Ma, G. Tang, and A. P. Kozikowski, *Org. Lett.*, 2002, **4**, 2377.
- 2002OL4495 S. Wu, W. Wang, W. Tang, M. Lin, and X. Zhang, *Org. Lett.*, 2002, **4**, 4495.
- 2002RCB1491 I. P. Romanova, G. G. Yusupova, A. A. Nafikova, V. I. Kovalenko, and O. G. Sinyashin, *Russ. Chem. Bull.*, 2002, **51**, 1491.
- 2002SC1929 V. G. Pawar, S. R. Bhusare, R. P. Pawar, and B. M. Bhawal, *Synth. Commun.*, 2002, **32**, 1929.
- 2002SL1925 T. K. Maishal and A. Sarkar, *Synlett*, 2002, 1925.
- 2002TA2727 R. Annunziata, M. Benaglia, M. Caporale, and L. Raimondi, *Tetrahedron Asymmetry*, 2002, **13**, 2727.
- 2002TL4207 Y. A. Ibrahim, H. Behbehani, and M. R. Ibrahim, *Tetrahedron Lett.*, 2002, **43**, 4207.
- 2003BKC1377 S. R. Bhusare, D. V. Jarikote, R. R. Deshmukh, W. N. Jadhav, R. P. Pawar, and Y. B. Vibhute, *Bull. Korean Chem. Soc.*, 2003, **24**, 1377.
- 2003CC1156 S. Bhattacharyya, A. E. Clark, M. Pink, and J. M. Zaleski, *Chem. Commun.*, 2003, 1156.
- 2003CC2210 P. Hannen, H.-C. Militzer, E. M. Vogl, and F. A. Rampf, *Chem. Commun.*, 2003, 2210.
- 2003CHE250 Yu. E. Ivanov, A. A. Yavolovsky, A. V. Mazepa, and S. P. Krasnoshchekaya, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 250.
- 2003JME364 A. P. Kozikowski, I. Nowak, P. A. Petukhov, R. Etcheberrigaray, A. Mohamed, M. Tan, N. Lewin, H. Hennings, L. L. Pearce, and P. M. Blumberg, *J. Med. Chem.*, 2003, **46**, 364.
- 2003JME4196 J. Sridhar, Z. L. Wei, I. Nowak, N. E. Lewin, J. A. Ayres, L. V. Pearce, P. M. Blumberg, and A. P. Kozikowski, *J. Med. Chem.*, 2003, **46**, 4196.
- 2003JOC92 Y. Pei, M. J. Lilly, D. J. Owen, L. J. D'Souza, X.-Q. Tang, J. Yu, R. Nazarbahi, A. Hunter, C. M. Anderson, S. Glasco, N. J. Ede, I. W. James, U. Maitra, S. Chandrasekaran, W. H. Moos, and S. S. Ghosh, *J. Org. Chem.*, 2003, **68**, 92.

- 2003JOC10040 Y. Sawada, T. Mori, and A. Oku, *J. Org. Chem.*, 2003, **68**, 10040.
2003OL1757 V. K. Aggarwal, G. Y. Fang, J. P. H. Charmant, and G. Meek, *Org. Lett.*, 2003, **5**, 1757.
2003SL1207 K. Ono, T. Nagata, and A. Nishida, *Synlett*, 2003, 1207.
2004ARK44 O. Migliara, S. Plescia, P. Diana, V. Di Stefano, L. Camarada, and R. Dall'Olio, *ARKIVOC*, 2004, v, 44.
2004BML2653 C. J. Ohnmacht, J. S. Albert, P. R. Bernstein, W. L. Rumsey, B. B. Masek, B. T. Dembofsky, G. M. Koether, D. W. Andisik, and D. Aharony, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2653.
2004BML3925 R. S. Al-awar, J. E. Ray, K. A. Hecker, S. Joseph, J. Huang, C. Shih, H. B. Brooks, C. D. Spencer, S. A. Watkins, R. M. Schultz, E. L. Considine, M. M. Faul, K. A. Sullivan, S. P. Kolis, M. A. Carr, and F. Zhang, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3925.
2004CR2777 A. T. Balaban, D. C. Oniciu, and A. R. Katritzky, *Chem. Rev.*, 2004, **104**, 2777.
2004EJO1865 B. Schmidt, *Eur. J. Org. Chem.*, 2004, 1865.
2004H(63)2309 C. Mukherjee and E. Biehl, *Heterocycles*, 2004, **63**, 2309.
2004JA8744 H. Ohno, H. Hamaguchi, M. Ohata, S. Kosaka, and T. Tanaka, *J. Am. Chem. Soc.*, 2004, **126**, 8744.
2004JME3131 N.-H. Nam, G. Ye, G. Sun, and K. Parang, *J. Med. Chem.*, 2004, **47**, 3131.
2004JOC2750 D. K. Bates, X. Li, and P. V. Jog, *J. Org. Chem.*, 2004, **69**, 2750.
2004JOC4140 T. Assoumatine, P. K. Datta, T. S. Hooper, B. L. Yvon, and J. L. Charlton, *J. Org. Chem.*, 2004, **69**, 4140.
2004MI265 D. S. Yamashita, R. Xie, H. Lin, B. Wang, S. D.-H. Shi, C. J. Quinn, M. E. Hemling, C. Hissong, T. A. Tomaszek, and D. F. Veber, *J. Peptide Res.*, 2004, **63**, 265.
2004PNA5815 L. Qiu, J. Wu, S. Chan, T. T.-L. Au-Yeung, J.-X. Li, R. Guo, C.-C. Pai, Z. Zhou, X. Li, Q.-H. Fan, and A. S. C. Chan, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 5815.
2004RJO575 D. V. Jarikote, V. G. Pawar, S. R. Bhusare, R. V. Hangarge, Y. B. Vibhute, and R. P. Pawar, *Russ. J. Org. Chem. (Engl. Transl.)*, 2004, **40**, 575.
2004T4337 J. S. Albert, C. Ohnmacht, P. R. Bernstein, W. L. Rumsey, D. Aharony, B. B. Masek, B. T. Dembofsky, G. M. Koether, W. Potts, and J. L. Evenden, *Tetrahedron*, 2004, **60**, 4337.
2004TA2437 M. Padmaja and M. Periasamy, *Tetrahedron Asymmetry*, 2004, **15**, 2437.
2004TL2631 R. Mamouni, M. Soukri, S. Lazar, M. Akssira, and G. G. Guillaumet, *Tetrahedron Lett.*, 2004, **45**, 2631.
2004TL9171 W. A. L. van Otterlo, G. L. Morgans, S. D. Khanye, B. A. A. Aderibigbe, J. P. Michael, and D. G. Billing, *Tetrahedron Lett.*, 2004, **45**, 9171.
2005JA5746 Y. Nakagawa, K. Irie, R. C. Yanagita, H. Ohigashi, and K.-I. Tsuda, *J. Am. Chem. Soc.*, 2005, **127**, 5746.
2005JA14776 S. M. Lu and H. Alper, *J. Am. Chem. Soc.*, 2005, **127**, 14776.
B-2005MI457 D. J. Abraham; in 'Cheminformatics in Drug Discovery', T. I. Opera, Ed.; Wiley-VCH Verlag GmbH&Co. KGaA, Weinheim, 2005, p. 457.
2005TL1697 A. Vasudevan and M. K. Verzal, *Tetrahedron Lett.*, 2005, **46**, 1697.
2005TL3473 E. Boyd, G. S. Coumbarides, J. Eames, R. V. H. Jones, M. Motevalli, R. A. Stenson, and M. J. Suggate, *Tetrahedron Lett.*, 2005, **46**, 3473.
2006JOM(691)5129 V. Dragutan and I. Dragutan, *J. Organomet. Chem.*, 2006, **691**, 5129.
2006MI2135 A. Zykwiniska, W. Domagala, A. Czardybon, B. Pilawa, and M. Lapkowski, *Electrochim. Acta*, 2006, **51**, 2135.
2006T3610 A. V. Stepanov, A. P. Molchanov, J. Magull, D. Vidović, G. L. Starova, J. Kopf, and R. R. Kostikov, *Tetrahedron*, 2006, **62**, 3610.
2007JCO321 J. K. Mishra and G. Panda, *J. Comb. Chem.*, 2007, **9**, 321.
2007JOC2151 L. Banfi, A. Basso, G. Guanti, N. Kielland, C. Repetto, and R. Riva, *J. Org. Chem.*, 2007, **72**, 2151.

Biographical Sketch



Irina Shcherbakova was born in Rostov on Don, Russia; she graduated from Rostov on Don University with M.Sc. in Chemistry of Natural Compounds and joined Research Institute of Physical and Organic Chemistry (RIPOC) at Rostov University as a junior research scientist. She conducted research on heterocyclic cations in the laboratory of Professor G. N. Dorofeenko and obtained her Ph.D. in organic chemistry in 1980. She spent 1985 in the laboratory of Professor A. T. Balaban (Bucharest, Romania) and 1990–92 in the laboratory of Professor A. R. Katritzky (University of Florida, USA) as a research fellow, while keeping her position as senior research scientist at RIPOC. She moved permanently to the USA and in 1997 took position as senior scientist at NPS Pharmaceuticals, Inc. (Salt Lake City, UT), where she led medicinal chemistry and preclinical development on therapeutic agents targeting calcium receptors. Currently, she is Chief Scientific Officer at MediProPharma, Inc., a startup biopharmaceutical company. Her scientific interests include all aspects of heterocyclic chemistry, in particular, functionally substituted biologically active heterocycles and their application in drug discovery.

14.07

Eight-membered Rings with Two Heteroatoms 1,5

G. Cirrincione and P. Diana

Università degli Studi di Palermo, Palermo, Italy

© 2008 Elsevier Ltd. All rights reserved.

14.07.1	Introduction	305
14.07.2	Rings with Two Nitrogens (1,5-Diazocines)	306
14.07.2.1	Theoretical Methods	306
14.07.2.2	Experimental Structural Methods	309
14.07.2.3	Thermodynamic Aspects	324
14.07.2.4	Reactivity of Nonconjugated Rings	329
14.07.2.5	Reactivity of Substituents Attached to Ring Carbon Atoms	334
14.07.2.6	Reactivity of Substituents Attached to Ring Heteroatoms	350
14.07.2.7	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	356
14.07.2.7.1	Natural products	356
14.07.2.7.2	Ring syntheses from C_6N_2 units	357
14.07.2.7.3	Ring syntheses from $C_6N + N$ units	364
14.07.2.7.4	Ring syntheses from $C_5N_2 + C$ units	364
14.07.2.7.5	Ring syntheses from $C_4N_2 + C_2$ units	366
14.07.2.7.6	Ring syntheses from $C_4N + 2C + N$ units	366
14.07.2.7.7	Ring syntheses from $C_3N_2 + C_3$ units	367
14.07.2.7.8	Ring syntheses from $C_3N + C_3N$ units	369
14.07.2.7.9	Ring syntheses from $C_2N + C_2N + 2C$ units	377
14.07.2.7.10	Ring syntheses from $C_2 + 4C + 2N$ units	382
14.07.2.8	Ring Syntheses by Transformation of Another Ring	382
14.07.2.9	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	385
14.07.2.10	Important Compounds and Applications	385
14.07.3	Rings with One Nitrogen and One Oxygen (1,5-Oxazocines)	386
14.07.3.1	Theoretical Methods	386
14.07.3.2	Experimental Structural Methods	387
14.07.3.3	Thermodynamic Aspects	391
14.07.3.4	Reactivity of Nonconjugated Rings	391
14.07.3.5	Reactivity of Substituent Attached to Ring Carbon Atoms	392
14.07.3.6	Reactivity of Substituent Attached to Ring Heteroatoms	394
14.07.3.7	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	398
14.07.3.7.1	Natural products	398
14.07.3.7.2	Ring syntheses from C_6NO units	399
14.07.3.7.3	Ring syntheses from $C_6O + N$ units	405
14.07.3.7.4	Ring syntheses from $C_5NO + C$ units	406
14.07.3.7.5	Ring syntheses from $C_4N + C_2O$ units	406
14.07.3.7.6	Ring syntheses from $C_4O + C_2N$ units	407
14.07.3.7.7	Ring syntheses from $C_4O + N + C_2$ units	408
14.07.3.7.8	Ring syntheses from $C_3NO + C_3$ units	408

14.07.3.8	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	408
14.07.3.9	Important Compounds and Applications	409
14.07.4	Rings with One Nitrogen and One Sulfur (1,5-Thiazocines)	409
14.07.4.1	Theoretical Methods	409
14.07.4.2	Experimental Structural Methods	410
14.07.4.3	Thermodynamic Aspects	412
14.07.4.4	Reactivity of Nonconjugated Rings	412
14.07.4.5	Reactivity of Substituent Attached to Ring Carbon Atoms	413
14.07.4.6	Reactivity of Substituent Attached to Ring Heteroatoms	413
14.07.4.7	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	413
14.07.4.7.1	Ring syntheses from C ₆ NS units	413
14.07.4.7.2	Ring syntheses from C ₅ S + CN units	416
14.07.4.8	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	417
14.07.4.9	Important Compounds and Applications	417
14.07.5	Rings with Two Oxygens (1,5-Dioxocins)	417
14.07.5.1	Theoretical Methods	417
14.07.5.2	Experimental Structural Methods	419
14.07.5.3	Thermodynamic Aspects	421
14.07.5.4	Reactivity of Nonconjugated Rings	423
14.07.5.5	Reactivity of Substituents Attached to Ring Carbon Atoms	429
14.07.5.6	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	432
14.07.5.6.1	Natural products	432
14.07.5.6.2	Ring syntheses from C ₆ O ₂ units	433
14.07.5.6.3	Ring syntheses from C ₄ O ₂ + C ₂ units	438
14.07.5.6.4	Ring syntheses from C ₃ O ₂ + C ₃ units	438
14.07.5.6.5	Ring syntheses from C ₃ O + C ₃ O units	441
14.07.5.6.6	Ring syntheses from C ₃ + C ₂ O + CO units	441
14.07.5.7	Ring Syntheses by Transformation of Another Ring	442
14.07.5.8	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	443
14.07.5.9	Important Compounds and Applications	443
14.07.6	Rings with One Oxygen and One Sulfur (1,5-Oxathiocins)	443
14.07.6.1	Theoretical Methods	443
14.07.6.2	Experimental Structural Methods	443
14.07.6.3	Thermodynamic Aspects	445
14.07.6.4	Reactivity of Nonconjugated Rings	446
14.07.6.5	Reactivity of Substituent Attached to Ring Carbon Atoms	447
14.07.6.6	Reactivity of Substituent Attached to Ring Heteroatoms	447
14.07.6.7	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	447
14.07.6.7.1	Ring syntheses from C ₆ OS units	447
14.07.6.7.2	Ring syntheses from C ₆ O + S units	450
14.07.6.8	Ring Syntheses by Transformation of Another Ring	450

14.07.6.9	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	451
14.07.6.10	Important Compounds and Applications	451
14.07.7	Rings with Two Sulfurs (1,5-Dithiocins)	451
14.07.7.1	Theoretical Methods	451
14.07.7.2	Experimental Structural Methods	456
14.07.7.3	Thermodynamic Aspects	457
14.07.7.4	Reactivity of Nonconjugated Rings	458
14.07.7.5	Reactivity of Substituent Attached to Ring Carbon Atoms	459
14.07.7.6	Reactivity of Substituent Attached to Ring Heteroatoms	460
14.07.7.7	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	460
14.07.7.7.1	Ring syntheses from C_6S_2 units	460
14.07.7.7.2	Ring syntheses from $C_3S_2 + C_3$ units	461
14.07.7.7.3	Ring syntheses from $C_3S + C_3S$ units	461
14.07.7.8	Ring Syntheses by Transformation of Another Ring	464
14.07.7.9	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	466
14.07.7.10	Important Compounds and Applications	467
	References	467

14.07.1 Introduction

Diheterocines in a 1,5-relationship were treated in CHEC(1984), which covered the literature through 1982, within a single chapter (5.19) in Volume 7 dealing with all eight-membered heterocycles with one or more heteroatoms. Within that chapter, relatively little attention was given to eight-membered rings with two heteroatoms in a 1,5-relationship. In fact, in Section 5.19.4, the 1,5-diazocine system, the largest class of 1,5-diheterocines (to which were dedicated nearly four pages) was only mentioned briefly. In a separate section dedicated to oxazocines (5.19.5), the scheme of the synthesis of one 1,5-oxazocine was only reported. In the section dedicated to rings with two or more oxygen atoms (5.19.7), the synthesis and reactivity of a 1,5-dioxocin derivative as well as the preparation of two benzo- and dibenzo-1,5-dioxocin derivatives were reported in few lines. In the dithiocane section (5.19.8.3) more than one page was dedicated to the perhydro-1,5-dithiocins and in the 'saturated rings with S and O or S and N', the synthesis of one thiazocine derivative and some data on its reactivity were reported. In Section 5.19.5 dedicated to 'conformations of heterocyclic eight-membered rings' the conformational behavior of all dibenzo-fused 1,5-diheterocines with the exception of dioxocins was reported.

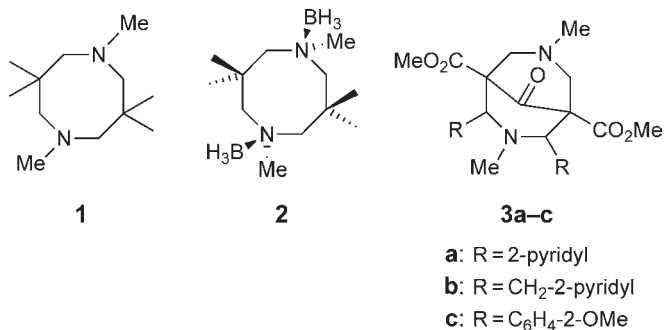
In CHEC-II(1996), which covered the literature from 1983 to 1995, the eight-membered rings with two heteroatoms in a 1,5 relationship were treated in Volume 9 in the dedicated Chapter 24 of 60 pages. This chapter covered those compounds with nitrogen, oxygen, and sulfur as heteroatoms and did not cover compounds in which the ring heteroatoms were members of another fused ring and bridged polycyclic compounds. The most important sections regarded the diazocines and the dithiocins. This chapter covers the literature from 1996 to 2006 and also reports those articles published in 1995 which were not reported in CHEC-II(1996). In this edition, in addition to the uncondensed derivatives, 1,5-diheterocines fused to five-, six-, and seven-membered carbocycles or heterocycles are covered. Bridged 1,5-heterocines, which actually constitute the majority of the compounds reported, were covered as well. Also in this edition, as in the previous one, the interest in this class of compounds has been driven by their pharmacological activity and some industrial applications found in different fields. The 1,5-diazocine ring is capable of imposing coordination constraints on metals so important in constructing some interesting models of hydrogenase enzymes. Sparteine and related compounds influence enantioselective formation of carbon-carbon bonds. In particular, Tröger's base analogues were used for various purposes in the area of supramolecular chemistry, such as the design of molecular receptors, clathrate hosts, chiral solvating agents, and DNA intercalators. Bispindines showed antiarrhythmic activity. Chitosan-polymer analogues showed good adsorption capacity and high selectivity for Ag^+ in

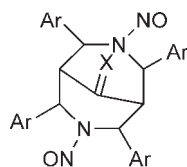
the presence of Pb^{2+} , Cd^{2+} , and Cr^{3+} . Some pyridooxazocines showed tachykinin receptor neurokinin 1 (NK1) antagonist activity at nanomolar level. Oxathiocins were used to produce polymers, copolymers, or block polymer to manufacture adhesive, dental compositions and optical lenses. Chiral phosphoramidate ligands embodying thiazocine framework and binaphthyl phosphoramidite were successfully employed for enantioselective Cu-catalyzed conjugated addition reactions. The methylene-1,5-dithiocins are polymerizable compounds that are typically used for optical and ophthalmologic applications. As in CHEC-II(1996), nomenclature for the eight-membered rings with two heteroatoms in a 1,5 relationship follows the usual standard system, with the exceptions introduced for the completely reduced derivatives. The six parent unsaturated systems are 1,5-diazocine, 1,5-oxazocine, 1,5-thiazocine, 1,5-dioxocin, 1,5-oxathiocin, and 1,5-dithiocin. No ‘fully conjugated’ 1,5-heterocines have been prepared and the section ‘Reactivity of Fully Conjugated Rings’ is absent from all six system subchapters. Hydrogenated analogues are generally named as di-, tetra-, hexa-, or in the case of diazocines octa- or perhydro derivatives. The completely saturated derivatives are generally referred to as diazocane, oxazocane, thiazocane, dioxocane, oxathiocane, and dithiocane in the literature. The main change in this chapter, with respect to CHEC-II(1996), is related to the ‘Theoretical Methods’ section. Such a section in CHEC-II(1996) was a unique section, placed immediately after the introduction, dealing with all the classes of eight-membered heterocycles with two heteroatoms. In this edition, each section dealing with a single class of heterocycles has its own theoretical methods section. The ‘Experimental Structural Methods’ section has received a strong impulse as, with some exceptions, the great majority of the reported derivatives have been adequately characterized. As already done in CHEC-II(1996), all six reported systems are discussed separately with each discussion following the same general format. In case particular sections are not mentioned, it means that no chemistry has been reported. In the last decade, comprehensive reviews on 1,3-heterocines did not appear due to their complete coverage received in CHEC-II(1996).

14.07.2 Rings with Two Nitrogens (1,5-Diazocines)

14.07.2.1 Theoretical Methods

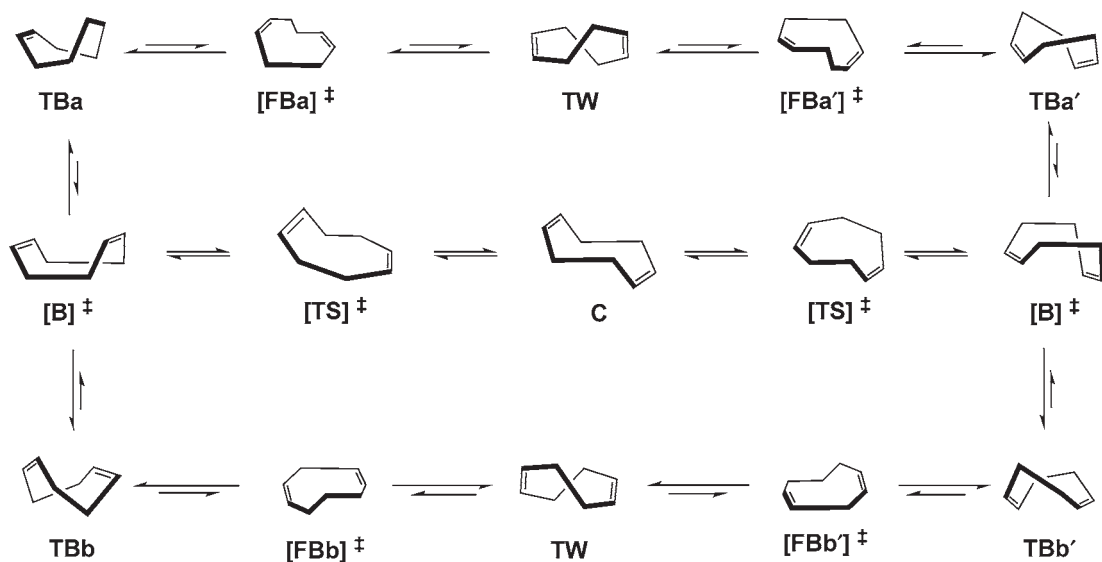
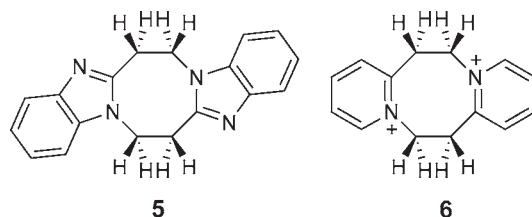
Molecular mechanics calculations were performed to understand the conformational equilibrium of the 1,5-diazocine **1**. Minimizations using the MM2 force field were conducted first and these structures were reoptimized using the MM3 force field as implemented in the SPARTAN suite of programs. Such calculations indicated that **1** exists in equilibrium of two forms in a ratio 2.7:1. The major form is a set of twist-chair-chair rapidly interconverting *via* the chair-chair; the minor form is most likely a set of twist-boat interconverting rapidly *via* the boat-boat (see Section 14.07.2.3, Scheme 6). The same calculations indicated that the bis- BH_3 adduct **2** has a twist-boat conformation with *cis* BH_3 s <1996JOC3061>, and were also utilized to compute the structural properties of a very rigid tetradentate ligand for tetrahedral coordination geometries. The calculations indicated that the pendant arms of the bridged 1,5-diazocines **3a–c** backbone needed to form six-membered chelate rings with the metal to allow a distorted tetrahedral geometry. Smaller rings led to five- (trigonal bipyramidal) or six-coordinate (octahedral) transition-metal compounds. The quality of these predictions was supported by the experimentally determined structure of a cobalt(II) complex of **3a** <1997JCD347>. The MM2 calculations performed on *N*-nitroso diazocines **4a–d** predicted two energy minima. One for the chair-boat conformer and one for a chair-chair conformer, with two phenyls occupying the equatorial positions and the remaining two in the axial locations. The latter is preferred by 6.7 and 4.7 kcal mol^{−1} in the case of **4a** and **4d**, respectively. A primary reason for this large energy difference between the conformers is the strong allylic strain in the chair-boat form, which prevails over the axial-axial steric interaction of the phenyl rings in the chair-chair form <1997JOC5619>.



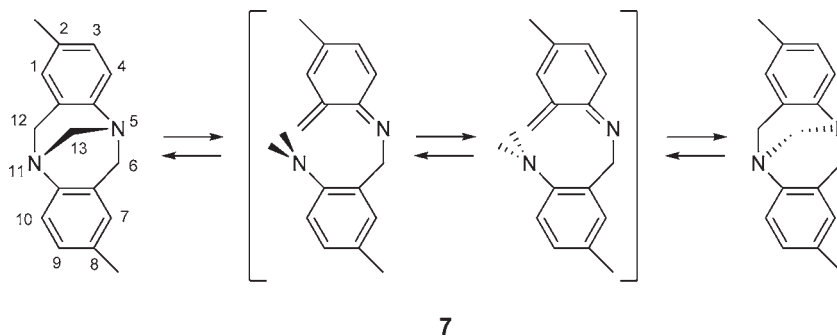
**4a–d**

- a:** Ar = Ph, X = O
b: Ar = C₆H₄-4-Me, X = O
c: Ar = C₆H₄-4-F, X = O
d: Ar = Ph, X = H₂

The differences in the dynamic behavior of condensed diazocines **5** and **6** were analyzed using different semiempirical calculations (MNDO, AM1, PM3) of the ground state and transition states. Such calculations indicated that there are three minima in the potential hypersurface: the chair **C** which is a rigid, almost-perfect, 'chair'; the twist-boat **TB** which is a mixture of deformed 'boat' conformations with a quite flat potential hypersurface, and the twist **TW**. There are three transition states connecting these conformations (and their enantiomers): $[\text{TS}]^\ddagger$ between **TB** and **C**; $[\text{FB}]^\ddagger$ between twist-boats (**TBa** and its enantiomer **TBa'** through **TW**) and $[\text{B}]^\ddagger$ between **TBa** and **TBb** (pseudorotation). The chair is slightly more stable than the twist-boat and the three transition states range in the order $[\text{TS}]^\ddagger$ ($\sim 10 \text{ kcal mol}^{-1}$) > $[\text{FB}]^\ddagger$ ($\sim 7 \text{ kcal mol}^{-1}$) > $[\text{B}]^\ddagger$ ($\sim 2 \text{ kcal mol}^{-1}$) (Scheme 1). A comparison of the calculations and experimental results obtained from NMR measurements revealed, concerning the ground states, that the AM1 calculations, the preferred theoretical method, overestimated the stability of the chair form, a fact that might be related to the dipole moments of the **C** and **TB** conformers. Concerning the transition states, it was pointed out that it was the charge that determined the barrier between the chair and boat conformations <1998T9569>.

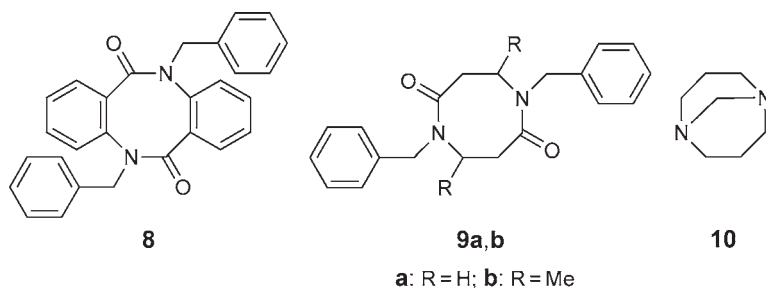
**Scheme 1**

Tröger's base **7** underwent enantiomerization in the gas and liquid phase. The enantiomerization pathway proceeding via a degenerated retro-hetero-Diels–Alder ring opening was confirmed by calculating an optimized structure of **7** with the HyperChem Package rel.4.0 using the MM+ force field followed by the AM1 method, which showed that the two six-membered rings of the methanodiazocine system formed an extended envelope facilitating ring opening and closure. In the second step, the bonds N(11)–C(12) and N(5)–C(13) of **7** were broken and double bonds were formed, respectively. The structures were optimized by the MM+ force field followed by the AM1 method. The energies and front orbital MO coefficients from the AM1 method confirmed the possibility of an intramolecular rearrangement via a hetero-Diels–Alder reaction (Scheme 2) <2000JA1424>.

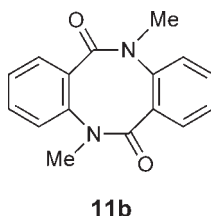


Scheme 2

Molecular-modeling studies attributed the remarkable multi-drug resistance (MDR) reversal activity, shown by **8**, to a rotamer as to be the preferred one for the best fitting with verapamil, used as reference drug, due to their structural resemblance. However, MM calculations pointed out that such a conformer has a thermodynamically limited concentration (5%). Therefore, the high MDR reversal activity has to be ascribed to a mode of action different from that of verapamil <2000JST(522)263>. Semiempirical (AM1, MNDO, PM3) and *ab initio* (HF/3-21G) calculations conducted on **9a**, reproduced with great accuracy the solid state conformation evidenced by X-ray crystallographic analysis (see Section 14.07.2.2). The same kind of calculations revealed that the conformation of **9b** having both methyl substituents in the pseudo-equatorial orientation was 3.6 kcal mol^{−1} more stable than the conformer having one methyl group in a pseudo-axial orientation <2001T1883>. The ¹³C NMR chemical shifts of **10**, which have an unambiguous conformational structure, were compared to predicted ¹³C NMR chemical shifts obtained via empirically scaled 'gauge including atomic orbitals' (GIAO) shielding for geometries from MM3 molecular-mechanics calculations. A deviation of 0.4 ppm for C-2/C-4/C-6/C-8 resonance was found; whereas, a difference of 1.5 and 1.8 ppm was observed for C-9 and C-3/C-7, respectively <2001JOC7967>.

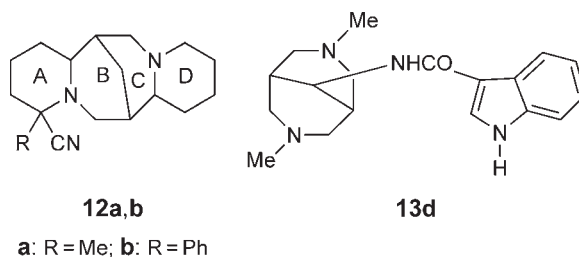


Theoretical calculations using Gaussian 98 with the B3LYP hybrid functional using 6-31G(d) basis set were performed to find transition structures for the formation of dibenzodiazocine **11b** from *N*-methylisatoic anhydride. A total of five different transition structures leading, through an overall [4+4] cycloaddition, to the eight-membered ring were located (see Section 14.07.2.8) <2004JOC86>. Density functional theory (DFT) absolute-energy calculations conducted on 3-fluoro-perhydrodiazocine dication comparing the fluorine atom in the axial and equatorial orientations indicated a preference for the axial conformational isomer of 9.2 kcal mol^{−1} <2006CC3190>.

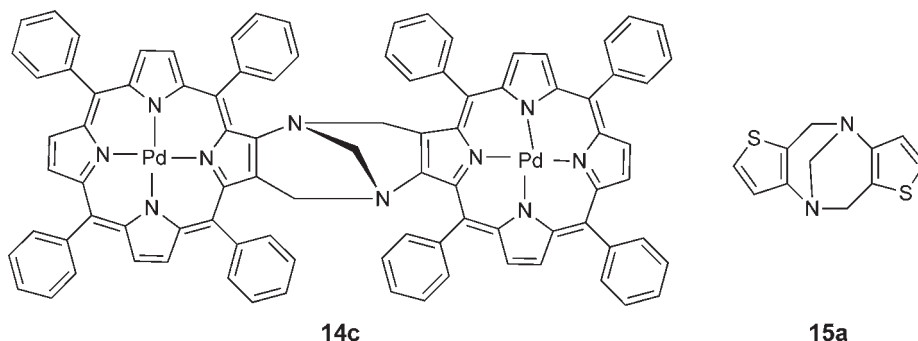


14.07.2.2 Experimental Structural Methods

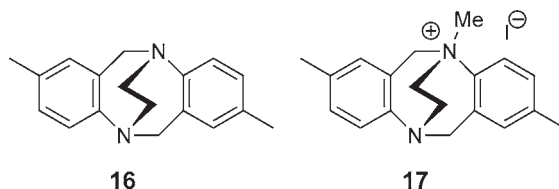
X-Ray crystallography established that **2**, in the solid state, has the BH_3 moieties in a *cis* relationship and adopts precisely the twist-boat conformation as supported by molecular-mechanics calculations (see Section 14.07.2.1) and deduced from the NMR spectra (*vide infra*) <1996JOC3061>. X-Ray diffraction analysis, conducted on **3c** and on the cobalt(II) nitrate complex of **3a**, showed that, upon coordination to cobalt(II), obtained by addition of $\text{Co}(\text{NO}_3)_2$ to a refluxing EtOH solution of **3a**, the keto group reacted to give an acetal. The bite distance $\text{N-3} \cdots \text{N-7}$ is almost identical for **3c** and the complex supporting the predicted rigidity of the system. The methoxy moieties of **3c** are, as expected, exposed to the periphery of the molecule, indicating that the only reorganization of this type of compounds, required prior to coordination, is one rotation about each of two single bonds <1997JCD347>. A single-crystal X-ray crystallographic analysis of **4a** revealed two molecules (assigned as A and B) in the asymmetric unit. Their geometric features were very similar: the diazocine skeleton adopted the chair–chair conformation, one nitrosamine group was significantly deviated from planarity (the N-3 atom is displaced by 0.335(3) and 0.307(4) Å in the molecule A and B, respectively, from the plane containing three neighboring atoms); on the other hand, the second was essentially planar (the N-7 atom was less than 0.05 Å out of the plane) <1997JOC5619>. The ORTEP plot of **8** showed that the main molecular skeleton consisted of one-folded eight-membered diazocine and two planar border aromatic rings. This ring system possessed a saddle arrangement with boat conformed diazocine heteroring at the bottom of the saddle. Both nitrogen atoms exhibited non-planar hybridization. This was reflected in the ring deformation and torsion angle values at the proximity of N-atoms, which were larger in one case ($\sim 74^\circ$) than in the other ($\sim 59^\circ$). The benzyl substituents branched on N-5 and N-11 were oriented differently with respect to the central molecular skeleton and were almost perpendicular to each other with a dihedral angle value of about 87° <2000JST(522)263>. A similar crystallographic structure was exhibited by the analogue of **8**, the uncondensed diazocine **9a**, having a slightly twisted boat conformation of the eight-membered ring and a close proximity between the basic amide nitrogen and the carbonyl carbon situated across the ring allowing for intramolecular electrostatic stabilization of the boat conformation <2001T1883>. X-Ray structural analysis of 2-methyl- and 2-phenyl-2-cyano-sparteine **12a** and **12b** confirmed that substituents in position 2 did not alter the conformation of the sparteine skeleton. Thus, the piperidine rings A, B, and D adopted chair conformations with ring C having a boat conformation. The A/B junction as well as the C/D junction had a *trans* configuration. The methyl and phenyl substituents had an equatorial orientation and the cyano group was axial <1995AXC1158, 1995AXC2716>. Similar conformation was shown by 17 β -isopropylsparteine diperchlorate with the sole difference of the distorted boat conformation of the C ring due to the presence of the isopropyl moiety. In the 17 β -isopropylpupanine perchlorate, instead, the A/B and C/D junctions were quasi-*trans* and *trans*, respectively, and the ring conformations were between sofa and half chair for the ring A; chair, distorted boat and chair for B, C and D rings, respectively <1996AXC2822>. X-Ray diffraction of the bridged diazocine **13d**, which crystallized as a hydrate hydrochloride, adopted an almost perfect chair–chair conformation with the N-methyl groups in the equatorial positions <1995JST(355)229>.



The X-ray crystal structure of the porphyrin analogue of Tröger's base **14c** revealed a concave chiral cavity with two metal ion binding sites suitable for ditopic interactions with guest molecules. The unit cell contained two crystallographically independent bis-porphyrins with Pd–Pd distances of 8.38 and 8.99 Å, respectively. The lengths and angles of the bridgehead portion of the molecule are very similar to those of Tröger's base itself, but the angles between the pyrrole rings connected to the diazocine bridge are smaller than the other Tröger's base analogues <1995CC1077>. Similarly, the thiophene analogue of Tröger's base **15a** exhibited a concave space with no significant differences in bond lengths and angles of the thiophene rings compared to those of thiophene or thiophene-fused derivatives. The dihedral angle between the two thiophene rings was 100.73(7)°, which is slightly larger than that observed in Tröger's base <2003AXEo745>. Similar concave cavity was exhibited by 2,8- and 4,10-disubstituted, and 2,4,8,10-tetrasubstituted Tröger's base analogues <2003EJO3179, 2006AXEo3479, 2006AXEo3674, 2006AXEo3893, 2006AXEo4887>, steroidal Tröger's base analogues <1995J(P1)2049>, or Tröger's base analogues derived from 5-substituted 3-amino-1-methylpyrroles <2005TA1969>, 3-aminoacridine, 10-aminobenzo[*b*][1,7]phenanthroline <1995TL1271>, and 2-naphthylamine <1998TA4151>. When a methanolic solution of the Tröger's base **7** was treated with phosphoric acid, colorless crystals were obtained whose structure involved alternating layers of Tröger's base cations (protonated at N-5) and layers containing phosphoric acid, dihydrogen phosphates, and MeOH connected by an extensive system of O–H···O hydrogen bonds. These hydrophilic layers and Tröger's bases are connected by N–H···O hydrogen bonds <2005AXEo3941>. Treatment of a solution of **7** in acetone with (–)-*O,O'*-dibenzoyl-L-tartaric acid yielded a crystalline precipitate whose X-ray analysis indicated that the asymmetric unit of the crystal structure contained one molecule of Tröger's base and one molecule of (–)-DBTA (1:1). The carboxylic acid moieties of the (–)-DBTA donated the protons to the nitrogen acceptors of the Tröger's base, making two separate strong O–H···N interactions. The bond lengths of the carboxylic acid groups in the (–)-DBTA-Tröger's base complex indicated that the diastereomeric precipitate formed was not a salt but a hydrogen-bonded aggregate <2006TA1116>.

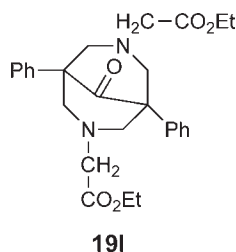
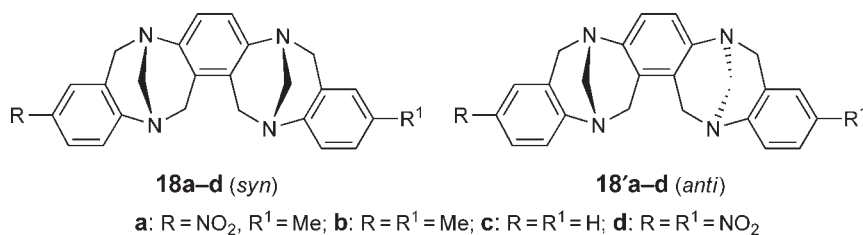


In the crystal structure of the ethano-Tröger's base **16**, the molecule had a noncrystallographic C_2 -symmetry with the twin-twist chair conformation. A peculiarity of the molecular structure is the larger angle between the axes of the lone electron pairs of the nitrogen atoms in comparison with the parent **7** (106° in **7** and 151° in **16**). The dihedral angle between the planes of the aromatic rings was equal to 89°, while the dihedral angle N(1)–C(19)–C(20)–N(10) in the ethylene bridge was 38°. The crystal structure of methiodide **17** (an inclusion compound with benzene) is characterized by two independent molecules of the salt and of the solvent. The conformation of the molecules is similar to that of **16**, with dihedral angles between the planes of the aromatic rings equal to 75° and 72° and the dihedral angle N(1)–C(19)–C(20)–N(9) in the ethylene bridge equal to –49.7° <2006TA2191>.

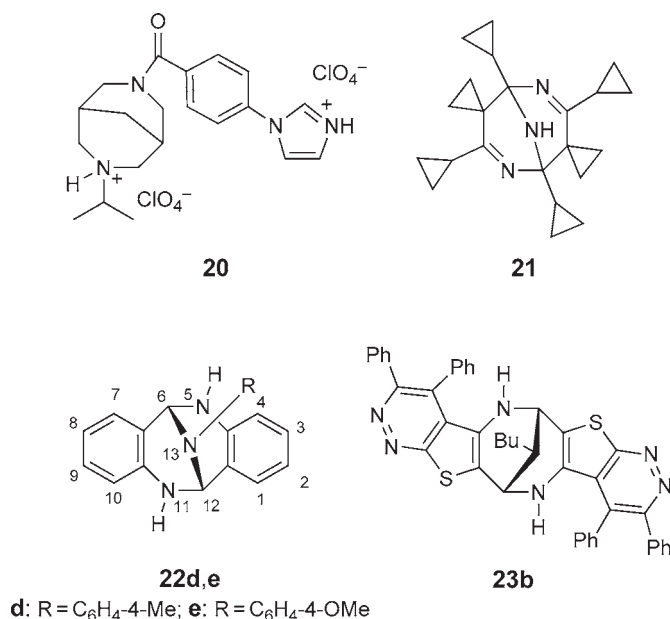


Instead, a tweezer shape was shown by the bis-Tröger base skeleton of **18** with the aromatic arms lying almost parallel with each other (23.1°), with a distance between its centroids of 4.368(5) Å. The central phenyl ring is almost orthogonal to the external aromatic arms (a, 79.3°; b, 88.6°). The molecular packing showed that in the *c*-direction every two molecules are intercalated each other in such a way that, in the case of **18a**, the nitro arm of one molecule is

located between the two arms of the front molecule with the nitro group pointed to the central aromatic ring in an edge-to-face interaction. In the case of the anti isomers **18'**, the central aromatic ring is also orthogonal to both external aromatic rings (a, 75.6°; b, 83.4°) and the planes defined by the external rings form an angle of 23.4°, similar to **18a**. The molecular packing showed that the molecules were stacked along the *c*-direction. At variance with **18a**, in **18'b** π -stacking interactions were absent and the lateral phenyl rings were identically polarized <2001JOC1607>. In the case of unsubstituted external phenyl groups, regioisomers with *anti* conformation **18'c** were obtained <2002CCCC609>, and in the case of the dinitro derivative, a mixture of *anti* (20%) and *syn* (17%) isomers **18'd** and **18d**, respectively, were obtained. The configuration of **18d** was consistent with other tweezer-shaped bis-Tröger bases <2004EJO1097>. The crystal structure of **19i** revealed that, in the solid state, this molecule existed equally in two forms. Both forms exhibited the chair–boat configuration with an *exo* orientation of the glycine moiety in the chair ring and an *endo* orientation of the glycine moiety in the boat ring. The glycine fragment of the chair ring was in the plane of the *N,N*-axis, while the glycine fragment of the boat ring was rotated by 47° on either side of the *N,N*-axis giving two equivalent conformations <1995T2055>.

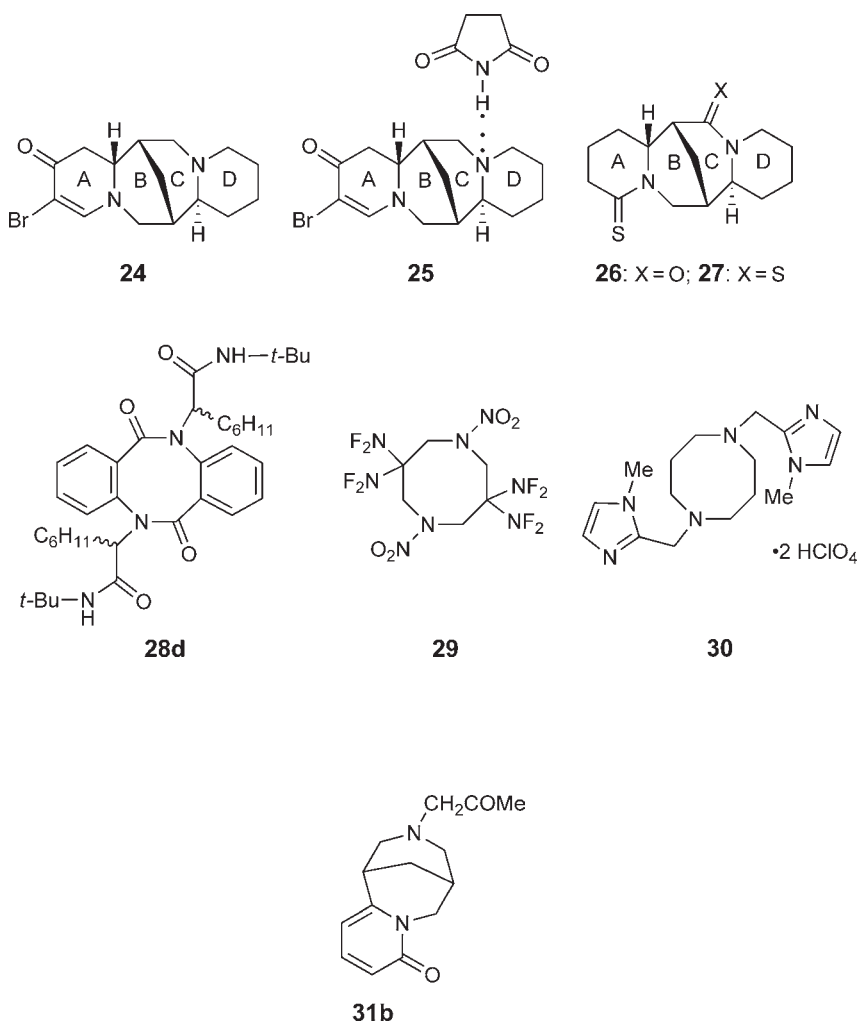


Replacement of the glycine moieties with a CH₂–(CH₂–O–CH₂)₃–CH₂ chain forming a flexible macrocycle maintained the chair–boat configuration <1996CC2093>. The ORTEP plot of the di-cation **20** revealed that the two hydrogen atoms were bound to N-3 and N-22. The geometry of N-3 is near tetrahedral (the average of the three C–N–C angles was 112.8°). The configuration of N-7 was nearly planar. Despite the large groups attached to the nitrogen atoms, the bridged diazocine system assumed a chair–chair conformation in the solid state. However, both chairs were significantly flattened due to the repulsion of the two nitrogen atoms and the large substituents <1996JME2559>. The crystal structure of **21** showed that the molecule did not contain any symmetry elements. The bridge nitrogen is pyramidal with the hydrogen pointing towards C-3 making this nitrogen chiral. Both enantiomers are present in the unit cell. In each enantiomer, the eight-membered ring is asymmetric, as indicated by the different bond lengths of the transannular bonds, for example, C(3)–C(4) (1.5082 (14) Å) and C(7)–C(8) (1.4959 (13) Å) <1998ACS790>. The most significant differences in the crystal structure of **22d** and **22e** were related to the conformation of the substituent at N-13 and the bond distances and angles around it. The intermolecular N(5)–H(5)···N(13) hydrogen bond interaction in **22e**, can be responsible for the distortion of the N-13 sp³ hybridization ($\sum \alpha N(13) = 339.0(2)$ and $343.1(5)$ in **22d** and **22e**, respectively). In **22d** where no hydrogen bonds were present, both pairs N(13)–C(6)/C(12) and C(6)–C(6a)/C(12a)–C(12) distances were alike; while in **22e**, a shortening of the N(13)–C(12), C(6a)–C(6) and a lengthening of the C(12a)–C(12) distances were observed together with a significant opening of the C(12)–N(3)–C(12) angle. The angle of the two benzene rings fused to the eight-membered system was quite constant (77.9(1) and 76.6(1)°) <1998T997>. Instead, the angle between the two thienopyridazino rings fused to the diazocine moiety in **23b** was 99.0°. The CH–N⁺Bu–CH angle was 107.8°; on the other hand, the N–CH₂–N angle in Tröger's base compounds ranged from 110.2° to 112.6° <1998J(P1)3557>.



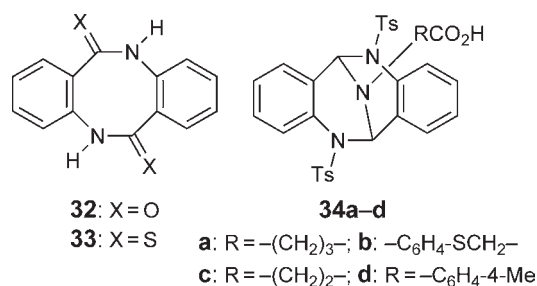
The structure, configuration, and conformation of 3-bromomultiflorine **24** are similar to the molecular structure of naturally occurring sparteine derivatives. The four-ring skeleton of **24** had a *trans-trans* orientation at the A/B and C/D ring junctions. Ring A was in a half-chair conformation, ring B adopted a distorted chair form, ring C was in a boat form, and D in a chair form. A characteristic feature of **24** as well as of all multiflorine derivatives was the electronic structure of ring A. In this γ -oxo- α,β -enamine system, a noticeable conjugation N(1)–C(2)–C(3)–C(4)–O(4) was present and visualized by a bond length pattern and also by a planarity of the N-1, C-2, C-3, C-4 fragment of the ring. The O-4 and Br-3 atoms were only slightly displaced out-of-the-plane. The lone pair of the nitrogen atom N-1 is also involved in the conjugation and as result; N-1 is devoid of basic properties. As a consequence, only N-16 is accessible in a protonation reaction. In fact, in the unexpected complex **25**, 3-bromoflorine and succinimide are connected by an intermolecular hydrogen bond N(suc)–H $\cdots$ N(16). The skeleton of **25** had a *trans/cis* configuration of A/B and C/D ring junctions. The C/D *cis* configuration is accompanied by the chair conformation of the ring C. The rings B and D had the same type of conformation as those observed in **24**. Ring A differed slightly from the corresponding ring in **24** and adopted a distorted sofa form. This deformation has been caused by the steric effect of the succinimide involved in molecular complex. The γ -oxo- α,β -enamine system is puckered and deviations from planarity were as high as $-0.043(3)$ and $0.041(3)$ Å for C-2 and C-3, respectively. The chair conformation of ring C was obviously a consequence of a configurational inversion of the N-16 atom, caused by intermolecular hydrogen bond formation <1998JST(442)103>. Similar behavior was shown by N-16 upon protonation of sparteine, and similar changes in the conformational structure of sparteinium salts and substituted sparteinium cations were observed <1999AXC1710, 2004JST(688)111>. The X-ray analysis of (+)-2-thiono-17-oxosparteine **26** and (+)-2,17-dithionosparteine **27** clearly indicated their conformationally rigid structure. The lactam and thiolactam groups are close to planarity, only the lactam group in molecule **26** is markedly nonplanar. The lactam and thiolactam moieties of **26** and **27** showed short C–N bonds and long C–O/S bonds caused by resonances between the lone electron pair of N-1 and N-16 and the π electrons of the carbonyl/thionocarbonyl groups that typify this class of compounds. Due to a higher polarizability of sulfur, the contribution of a dipolar structure of thiolactam to a hybrid is much higher than that of the lactam group; therefore the C–N bond lengths in the thiolactam group were shorter than those in the lactam group. The bond angles in the thiolactam and lactam groups are highly diverse but this feature is characteristic for all tertiary thiolactams. The rings A and C adopted a distorted sofa conformation in both compounds <2005JST(737)75>. The monoclinic crystals of **28d** showed that the dibenzodiazocine backbone had a boat shape, the two aromatic rings facing one level. On the opposite side, there are the bulky substituents, one MeOH and 1 equiv of interstitial water trapped by two carbonylic groups. The asymmetric unit consisted of additional 2 equiv of methanol. All acidic protons are involved in a complex hydrogen bonding system <1998T11887>. The X-ray crystallographic analysis of **29** recrystallized from a variety of solvents showed an

interesting unpredicted feature: empty channels with a three-fold axis of symmetry surrounded by molecules of **29**, passing through each unit cell. Analysis had sometimes shown the presence of disordered mass due to recrystallization solvent(s). Also solvent-free crystals retained these channels. The crystal density of the form produced is 1.807 g cm^{-3} if a vacuum is assumed in the channels [\[1999JOC960\]](#). The crystal structure of the dication diazocine **30** revealed that the eight-membered ring is folded up into a chair–boat conformation and the folding angles $\text{C}(2)\text{--N}(1)\text{--C}(8)$ and $\text{C}(4)\text{--N}(5)\text{--C}(6)$ were $112.6(7)$ versus $114.2(7)^\circ$, respectively. The two imidazole pendant arms departed from the parent eight-membered ring in *cis*-position with the angles $\text{N}(1)\text{--C}(9)\text{--C}(10)$ and $\text{N}(5)\text{--C}(9')\text{--C}(10')$ of $109.0(7)$ versus $110.3(6)^\circ$, respectively. The dihedral angle between the two planes of the imidazole rings was $16.0(4)^\circ$. Two nitrogen atoms of the parent ring and two nitrogen donors of the pendant arms were a mutual plane, forming a dihedral of $16.1(6)$ versus $15.0(4)^\circ$ with two imidazole rings, respectively [\[2000JCX531\]](#). The crystallographic analysis of *N*-acetylcytisine **31b** showed bond lengths and bond angles close to the cytosine itself except the C–O bond of the dihydropyridine moiety, which was $1.243(3) \text{ \AA}$, longer than the standard values. The configuration of the nitrogen bound to the acetyl group was pyramidal.

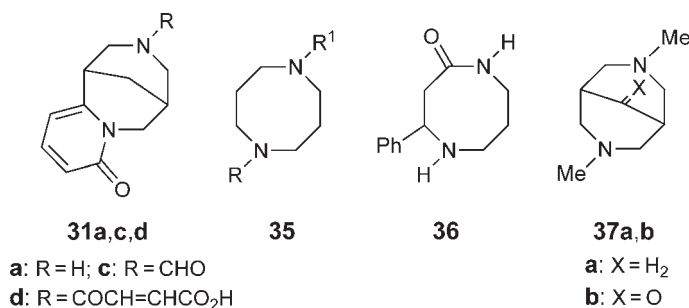


The dihydropyridine ring was planar within $\pm 0.005 \text{ \AA}$, and the carbonyl oxygen practically resided in the plane deviating by as little as $0.0029 \text{ \AA}$. The conformation of the tetrahydropyridine ring was a slightly distorted sofa and the bridging methylene carbon deviated from the mean plane defined by the other ring atoms by $0.75 \text{ \AA}$. The piperidine ring had an almost ideal chair conformation. The acetyl group was equatorial to piperidine ring

<2003RJC961>. Also *N*-acryloyl-, *N*-benzyl-, *N*-propynyl- and *N*-(β -morpholinopropionyl)-cytisine crystal structures furnished values related to the cytisine system very close to **31b** <2004RJO719, 2005OL4459, 2006RJC129>. The absolute configuration of (+)-**32** was unambiguously determined from the X-ray structure of the *N,N*-dicamphanoyl derivative and was assigned to be *S*. The solid-state structure of the complex, obtained from enantiomerically pure **33** and (*R,R*)-1,2-diaminocyclohexane, revealed that it was composed of one conjugated anion of **33** and the conjugated cation of (*R,R*)-1,2-diaminocyclohexane per two neutral amine guest molecules. The thioamide groups of **33** interacted solely with the amino groups of (*R,R*)-1,2-diaminocyclohexane and there were no hydrogen bonds between the thioamide functions <2004JOC1248>. The crystal structures of **34a–c**, established by X-ray, showed that both heterocycles in the bicyclic system adopted a sofa conformation. In all three structures, the central bridge nitrogen atom had a pyramidal configuration. The sum of the bond angles at N-13 atom was 339.7°, in **34a**, 347.7° in **34b**, and 334.7° in **34c**. The bond configuration of the N-5 and N-12 atoms are significantly more flattened. The sum of the bond angles at these atoms was 355.7° and 359.9° in **34a**, and 360.0° and 358.0° in **34c**. The geometry of **34b** was slightly different. The sum of the bond angles at the N-5 atom was 357.7°, which corresponded to a virtually planar bond configuration (as in **34a** and **34c**). The analogous sum of the bond angles at the N-11 atom (349.3°) suggested a noticeable pyramidal character of its bond configuration <2004RCB2262>. Crystal structure of 3-fluoro-perhydropyridazocine dihydrobromide revealed, as predicted by DFT calculations (see Section 14.07.2.1), revealed that the C–F bond occupied an axial orientation. There was no evidence of any disorder in the structure and particularly of any molecules with the C–F bond lying in an equatorial conformation <2006CC3190>. Other X-ray analyses in order to corroborate the assignment of diazocine structures were reported <1996TL2679, 1997RCB1931, 1998J(P1)1257, 1999JST(424)245, 2001EJM375, 2001JAPI793, 2001TL2621, 2002JOC2619, 2002MI249, 2002MI450, 2002CCL27, 2002JAP530, 2002PPS237, 2002S2168, 2002T55, 2003S2518, 2003TL2083, 2004ARK86, 2004JCO828, 2004TL6733, 2005OL4721>.



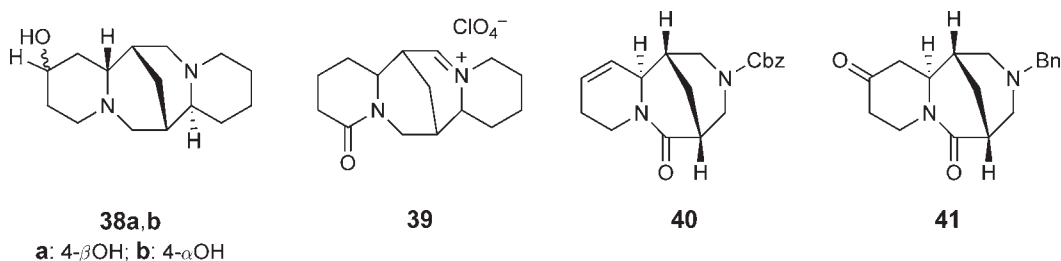
Nearly the totality of the 1,5-diazocines reported were characterized by ¹H NMR spectroscopy. However, considering the large number of compounds reported in more than 250 papers and the great variety of structures assigned, only general ¹H NMR spectroscopic features of some representatives will be described in this section to avoid a long, tedious list of chemical shifts. Successively, additional detailed studies that significantly contributed to the assignment of the structure will be reported. No conjugated uncondensed 1,5-diazocine have been reported, whereas for many perhydro-1,5-diazocines, variously substituted ¹H NMR data were provided. Thus, *N*-alkyl substituted 1,5-diazocines **35** (R, R¹ = alkyl) showed their methylene protons next to nitrogen in the range 2.53–3.79 ppm and the other methylene protons in the range 1.53–1.78 ppm <2001CCL769, 2001IC5060, 2002CCL115>. Introduction of a carbonyl group into the 1,5-diazocine system produces a lactam that experienced no changes in the chemical shifts of the ring protons <1995BCJ3121>. On the other hand, contemporaneous introduction of a phenyl group, as in **36**, shifted downfield both the protons next to nitrogen (3.16–4.04 ppm) and the other ring protons (1.52–2.92 ppm); a broad absorption at 5.76 ppm was attributed to the amine NH proton, whereas the amide proton was not observed <1995BCJ3121, 2002T7177>. The methylene bridged 1,5-diazocine **37a** in its ¹H NMR spectrum showed the N-CH₂ protons at slightly higher field than the unbridged derivatives (2.19–3.40 ppm); the methylenes bound to the bridge resonated at 1.82–1.91 ppm and the bridge signals at 1.42–2.30 ppm. When a carbonyl bridge is present as in **37b**, the signals remained within the same ranges except the methylenes bound to the carbonyl were shifted downfield (2.36–2.61 ppm) <2000EJO391>.

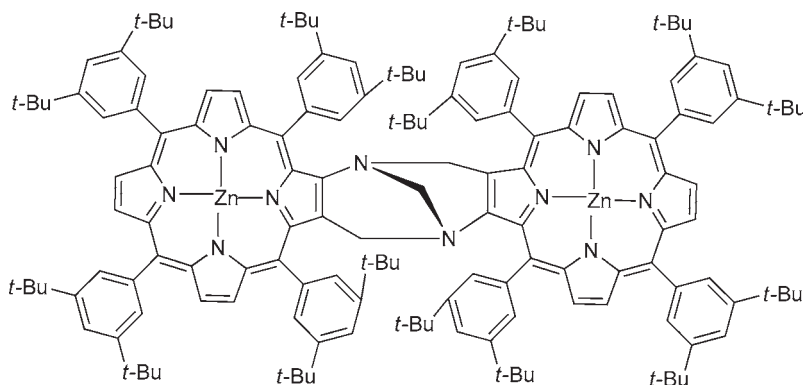


A variable-temperature ^1H and ^{13}C NMR study revealed a conformational equilibrium for **1** having $\Delta G^\ddagger = 8.8 \pm 0.6 \text{ kcal mol}^{-1}$ at 184 K. Such an activation barrier connects a major and a minor form of **1**. This finding was in agreement with the mechanics calculation conducted on this compound (see Section 14.07.2.1) <1996JOC3061>. The 90 MHz ^1H NMR spectrum of **2** exhibited no peaks corresponding to the methylene protons. Such a problem was solved when a 400 MHz ^1H NMR spectrum of **2** was obtained. This spectrum revealed the CH_2 signals as a series of four doublets at 2.56, 2.65, 3.12, and 4.00 ppm. The explanation for the difference between the 90 and 400 MHz spectra is that the ring is not completely conformationally averaged at 25 °C. When the conformational equilibrium at an NMR frequency of 90 MHz is observed, the exchange rate is such as to fortuitously produce coalescence at 25 °C, and the CH_2 signals broaden into the baseline and are not observed. However, at this same temperature of 25 °C, the conformational exchange rate appears sufficiently slow at an observation frequency of 400 MHz that individual multiplets may be seen <1996JOC3061>. Beside the above-mentioned doublets, the ^1H NMR spectrum of **2** exhibited a singlet at 2.78 ppm for the *N*-Me, and two singlets at 1.33 and 1.12 ppm for the geminal methyl groups. The ^{13}C NMR spectrum showed two broad singlets at 66.6 and 64.9 ppm for the methylene carbons, a singlet at 57.3 ppm for the *N*-Ms, a singlet at 36.3 ppm for the quaternary carbon, and two singlets at 31.3 and 29.0 ppm for the geminal methyls. This pattern of signals is compatible with a twist-boat conformation with the *cis* BH_3 groups <1996JOC3061>. The ^1H NMR spectra afforded additional evidence of the chair–chair geometry of the skeleton of diazocines **4**. Thus, in the spectrum of **4a**, the benzylic proton signals observed at 6.19 and 6.61 ppm were assigned to the ring with the axial phenyl groups, and those at 5.52 and 5.57 ppm to the ring with equatorial substituents. Moreover, in the case of **4d**, a close proximity of the axial phenyl groups to one of the methylene hydrogens at C-9 resulted in its significant downfield shift to 3.05 ppm. The NOE experiment showed that a selective irradiation of this proton produced a 12% enhancement of the signal at 6.57 ppm arising from the *ortho*-hydrogens in the axial phenyl groups. The observed nonequivalence of the benzylic protons in **4a–d** is solely due to a slow, on the NMR time scale, N–N rotation in the planar nitrosamine moiety, whereas the second NO group bound to the pyramidal N-3 amino nitrogen is expected to rotate relatively fast at 25 °C and thus it cannot cause splitting of these signals <1997JOC5619>. The ^1H NMR spectra of **5** were recorded at different temperatures and in different solvents: between –65 °C and +75 °C in CDCl_3 , $\text{DMF}-d_7$, acetone- d_6 and mixtures of these solvents. The spectra, save changes in the chemical shifts, remained identical; in particular, the CH_2CH_2 multiplets were always formed by narrow lines. The ^1H NMR spectrum of the double quaternary salt **6** was measured at 25 °C in DMSO and showed to be very broad – pointing to a dynamic process within the range of phenomena that can be studied by DNMR. Thus, it was measured in acetone/ D_2O at –30 °C. It exhibited two components, one was still broad and the other was well resolved, although overlapping in some parts. From the well-resolved spectrum, considering the prediction of the calculations, the **C** conformation was assigned, whereas to the broad spectrum, which remained above the coalescence, the family of the interconverting TBs was assigned <1998T9569>. ^1H and ^{13}C NMR spectra of sparteine, 13 α -hydroxysparteine and their *epi* *N*-oxides were fully assigned using two-dimensional techniques. It was found that sparteine, and 13 α -hydroxysparteine were conformationally homogeneous and their *epi* *N*-oxides retained the same conformation with a boat ring C. The *N*-oxidation effect as well as hydroxyl group and lactam effects were also determined <2003JST(647)247>. The ^1H and ^{13}C NMR spectra of the *N*-substituted cytosine derivatives **31c** and **31d** revealed two sets of signals indicating the existence of a 3:2 mixture of *Z* and *E* isomers. The two-dimensional COSY-45 and COSYLR-45 spectra assigned to the major isomer of **31c** the *Z*-conformation, whereas in the case of **31d** the *Z*-conformation was assigned to the minor isomer <2001MI356>. Also in the case of **31** (R = methyl[1-phenyl-5-(2,4-dimethoxybenzyl) barbituric acid]), the ^1H NMR spectrum exhibited two sets of signals compatible with a 2:1 mixture of diastereomers owing to the presence of the chiral C-5 <2000MI192>. The structure of the 5,6-dihydro derivative of cytosine **31a** was confirmed by the analysis of its ^1H NMR spectrum, by which the 6*R*,7*R*,9*R* stereochemistry was deduced. In fact, an almost negligible coupling (ca. 0.5 Hz) was observed between H-6 (at 3.57 ppm) and H-7

(at 1.80 ppm). Besides, diagnostic NOE interactions between H-6 and H-5ax (at 2.30 ppm) and between H-6 and H-13eq (at 4.09 ppm) were detected, compatible only with an absolute *R* configuration of C(6) <2004OL493>.

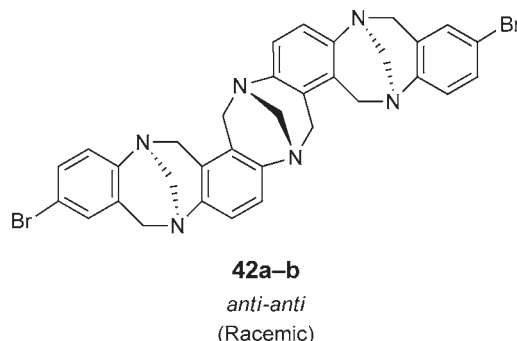
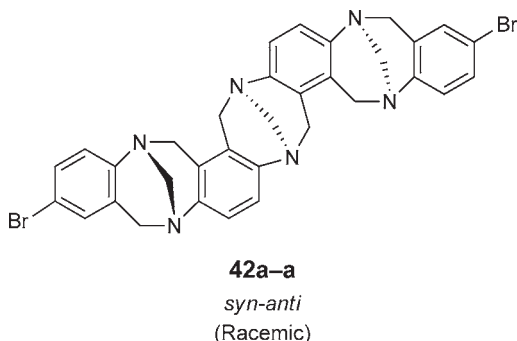
A complete assignment of the ^1H NMR spectra of 4- β - and 4- α -hydroxysparteine **38a** and **38b** as well as the determination of coupling constants was achieved by the analysis of HMQC and DQF-COSY spectra. Large coupling constants of H-4 (twice 11.0 Hz) and a large value of the coupling constants sum ($\sum J = 31.2 \text{ Hz}$) and the coupling of H-4 with axial protons at C-3 and C-5 proved the axial position of the H-4 and were in agreement with the equatorial position of the hydroxyl group on C-4 in **38b**. On the other hand, the low values of the vicinal coupling constants (four times 2.9 Hz) and a low coupling constants sum ($\sum J = 11.7 \text{ Hz}$) of the relatively narrow signal of H-4 in **38a** proved that the axial position of the C-4 hydroxyl group <2001M973>. The analysis of the NOESY spectrum of the anhydronium perchlorate of 17-hydroxylupanine **39** gave indications on the conformation of the four rings. The diaxial interactions between protons at C-6, C-10, and C-8 suggested the chair conformation of ring B. Instead, an NOE between the axial H-5 and H-3 is not indicative of a chair form of the ring A. However, the $^3J_{\text{HH}}$ value for C(6)H–C(5)H (10.2 Hz) is compatible with an nearly planar position of the C-5, C-6, N-1, C-2, and C-3 whereas, C-4 was above this plane towards the C(7)–C(8)–C(9) bridge. Thus, such an envelope conformer seemed to be the dominant form of ring A. Formation of the double bond between C-17 and N-16 induced a flattening into ring C, comprising C-7, C-17, N-16, and C-11. The C-9 might also participate in this flattening, since no vicinal coupling of H(9) and H(11) is observed; whereas, an NOE occurred between them. Moreover, H-11 showed the usual 1,3-diaxial Overhauser enhancement with H-15ax. These protons appearing in such a form belong to the planar H-C(17)=N-16<C-15,C-11 fragment which participated in the ring C together with the chair ring B, generating a rather rigid infrastructure for **39**. As a consequence, the sp^2 nitrogen N-16 from ring C introduced a strain onto the C(11)–N(16)–C(15) bond angle producing a destabilization of ring D. Analysis of the DQF-COSY spectrum and a decoupling experiment led to the conclusion that within ring D, there was a conformational equilibrium between a chair and twisted chair forms <2000M1073>. The structure of **40** was established by ^1H NMR analysis demonstrating that only a single (6*S*) stereoisomer was formed. The protons were assigned by COSY experiments. The stereochemistry was supported by NOE interaction between H-6 at 4.02 ppm, H-13e at 4.16 ppm, and H-2a at 2.56 ppm, and was confirmed by the negligible $J_{6,7}$ value which is indicative of the orthogonal nature of the C-6 (*S*) and C-7 (*S*) protons. The stereochemistry of **41** was deduced from the observation of a nearly negligible coupling ($\sim 0.5 \text{ Hz}$) between H-6 at 3.39 ppm and H-7 at 1.74 ppm. It was then confirmed by NOE interactions between H-6 and H-2a at 2.84 ppm and H-13e at 2.77 ppm, and by long-range coupling between H-6 and H-8a, observed in the COSY spectrum <2001EJO1377>. The rigidity, chirality, and asymmetric magnetic field generated by the very large ring current effects of the porphyrin rings of **14d** provided a binding site with very large dispersion of the resonances of protons within the cavity. As a consequence, resonances of diastereotopic geminally coupled protons are so well dispersed that ^1H NMR spectra of tightly bound ligands can be analyzed by first-order methods. This facilitated the study of the enantioselective recognition properties of the diZn host **14d** with amino acid derivatives, which can exploit the cavity's two metal binding sites. The ^1H NMR monitoring of the binding of L-histidine methyl ester to racemic ($\pm$)-**14d**, revealed that NH_2 , $\alpha\text{-CH}$ and $\beta\text{-CH}_2$ proton resonances of the guest lay between -0.1 and -5.3 ppm ; such large upfield shifts of the resonances of these protons are only consistent with the amino acid ester being bound within the bisporphyrin cavity. The system is clearly in slow exchange, indicating strong binding within the cavity. Although both diastereoisomeric complexes were observed, there was a strong preference for binding to (+)-**14d**. The amount of the minor diastereoisomer increased upon addition of the ligand. The ratio of the two sets of signals corresponded to the enantioselectivity observed with this ligand; the 93:7 ratio of the two diastereoisomers complexes corresponded to an enantiomeric excess of 86%. Full assignment of the complexes' spectra was now possible, when the experiment was repeated with pure (+)-**14d** and (–)-**14d**. L-Lysine benzyl ester was bound less tightly to (+)-**14d** and (–)-**14d** (48% ee) than the histidine benzyl ester. The two nitrogen binding sites present in this ligand are linked by a chain, which was more flexible than the one comprised of histidine derivatives, and thus the enantioselective recognition of a ligand of this type is more difficult <1995CC1925>.





14d

To assign the correct structure to **42a-a** and **42a-b**, their NOESY spectra were measured. The absence of a NOESY correlation from the methylene protons H-6(18) in **42a-a** and **42a-b** to protons in the inner aromatic rings, H-21(9) and H-22(10), strongly indicated that the nonlinear symmetric regioisomer structure. The NOESY spectra of **42a-a** also showed a correlation between H-7x(19x) and H-26, and between H-7n(19n) and the aromatic H-9(21), a doublet coupled to H-10(22) with a coupling constant of 8.7 Hz. The latter observation further established the proposed nonlinear symmetric regioisomer. The expected NOESY correlation between H-24n(12n) and H-22(10) was also observed.

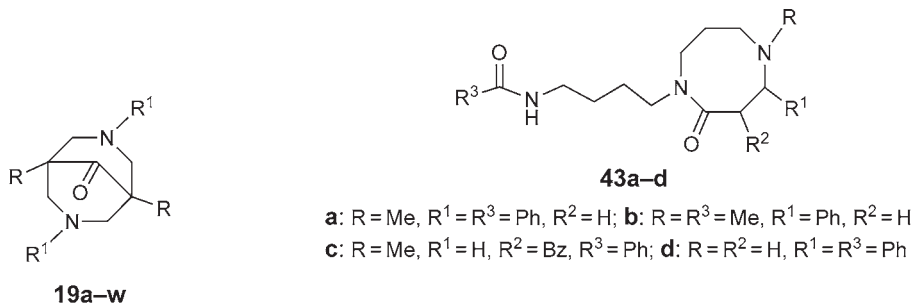


The diastereomer **42a-a** must be *syn-anti*, which is the only C_1 -symmetric diastereomer of a nonlinear symmetric regioisomer of a fused tris-Tröger's base analogue.

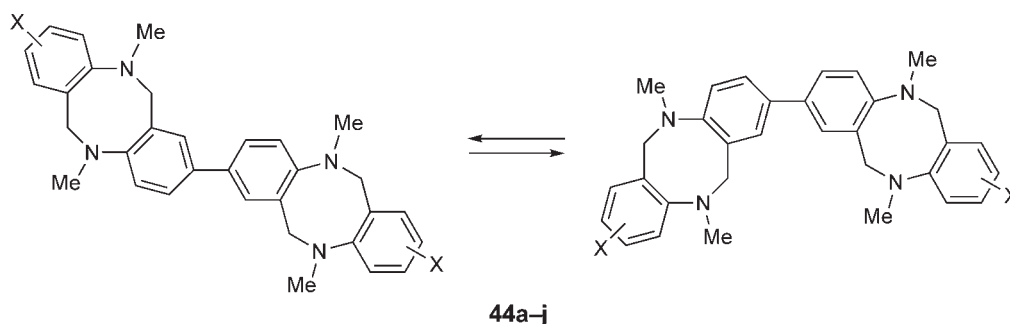
The diastereomer of the C_2 -symmetric **42a-b** could have been either *syn-syn* or *anti-anti*, but was proven to be *anti-anti* from the NOESY correlation between H-6x(18x) and H-7n(19n) and between H-7x(19x) and H-6n(18n) <2005OL2019>.

The ring protons of the carbonyl-bridged 1,5-diazocines **19a-o** were identified as an AB quartet. This pattern derived from the geminal couplings between the isolated axial and equatorial protons and can be interpreted in two ways. One interpretation is that these protons are fixed in a symmetrical configuration, the other in which is an average representation of the axial and equatorial protons of the eight-membered ring system in different conformations that are in rapid equilibrium on the NMR timescale. Axial protons are more strongly shielded than equatorial protons and the lower field doublet of the AB pattern was assigned accordingly. The chemical shifts of the axial protons ranged between 2.26–3.17 ppm and the equatorial protons ranged between 3.03 and 3.88 ppm. Coupling constants for the axial and equatorial protons ranged between 10.65 and 11.93 Hz <1995T2055>. In the case of **19p-v**, the unequivocal assignment of the geminal protons was based on the heteronuclear vicinal coupling constant ($^3J_{CH}$) between the methylene protons, that is, H_{ax} or H_{eq} and the keto or the ester carbonyl carbons and on the heteronuclear Overhauser effect from these protons to the *ipso* carbons. For these derivatives, the chemical shift order of axial and equatorial methylene protons may be altered by substituents in the 1,5-positions <1997MRC13>. When R^1-R^1 was a $CH_2-(CH_2-O-C_6H_4-O-CH_2)_2-CH_2$ chain instilling a flexible macrocycle, the pattern of the eight-membered ring protons remained unchanged and the ranges of the chemical shifts and coupling constants were very close to those reported above <1995T4819>. Analogues of compounds **19** bearing four aryl moieties in

2,4,6,8-positions maintained the chair–boat conformation with all the aryl groups equatorially oriented and the aryl groups of the boat lying in the shielding zone of the aryl groups of the chair <2000MRC883>. The structure of the spermidine alkaloids **43a–d** were established by two-dimensional COSY, NOESY, HSQC, and HMBC NMR experiments <2003OL2793, 2006JNP1300>. A characteristic of the ^1H NMR spectra of bisdibenzodiazocines **44a–j** is that the methylene protons of the diazocine ring appeared as very broad peaks at ~ 4.5 ppm at 25°C , which indicated a slow conformational flexion of the eight-membered ring. These broad peaks sharpened to a singlet, when the temperature increased to 40°C <2003S2839>.



a: R = Ph, R¹ = Me; **b:** R = Ph, R¹ = Bn; **c:** R = SPh, R¹ = Me; **d:** R = SPh, R¹ = Bn; **e:** R = R¹ = Me; **f:** R = Me, R¹ = Bn
g: R = Ph, R¹ = 2-MeO-Bn; **h:** R = Ph, R¹ = CH(Ph)₂; **i:** R = Ph, R¹ = CH₂CHCH₂; **j:** R = Ph, R¹ = (CH₂)₂OH
k: R = Ph, R¹ = CH₂CO₂H; **l:** R = Ph, R¹ = CH₂CO₂Et; **m:** R = SPh; R¹ = CH₂CO₂Et; **n:** R = Ph, R¹ = CH₂(2-pyridine)
o: R = Ph, R¹ = (CH₂)₂-NH-C₆H-2,3,5,6-tetra-F; **p:** R = CO₂Me, R¹ = Bn; **q:** R = CO₂Me, R¹ = Ph
r: R = CO₂Me, R¹ = -CH₂-; **s:** R = Me, R¹ = Ph; **t:** R = Me, R¹ = H; **u:** R = Ph, R¹ = Bn; **v:** R = Ph, R¹ = H; **w:** R = Me, R¹ = H



a: X = 2-OMe; **b:** X = 2-Me; **c:** X = 2-OEt; **d:** X = 2-Et; **e:** X = 2-F; **f:** X = 2-Cl; **g:** X = 2-Br; **h:** X = 4-OMe; **i:** X = 4-Me;
j: X = 4-Cl

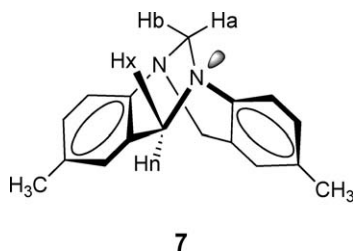
In their ^{13}C NMR spectra, the *N*-alkyl-1,5-diazocines **35** exhibited the resonances for the carbons adjacent to nitrogens at 43.2–64.2 ppm and the other ring carbons at 26.7–31.2 ppm <2001IC5060>. The introduction of a carbonyl experienced a slight upfield shift of the CH₂-N carbon resonances (39.4–51.9 ppm) and made wider the range of the resonances of the other ring carbons (25.2–45.3 ppm). The carbonyl carbon resonances were found at 173.0–176.6 ppm <1995BCJ3121>.

The methylene-bridged 1,5-diazocine **37a** showed the resonances of CH₂-N carbons at 32.2–32.8 ppm and the methylenes bound to the bridge at ca. 31 ppm. In **37b**, the presence of the carbonyl group in the bridge brought about a downfield shift of the methyne carbons bound to it (46.58–48.67 ppm) and the carbonyl carbon resonated at a very low field, 214.2–214.8 ppm <2000EJO391>.

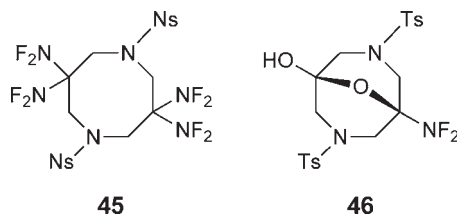
At -30°C , the ^{13}C NMR spectrum of **6** showed the same phenomenon already observed in the ^1H NMR spectrum: two components were in a 55:45 ratio. A ^1H - ^{13}C two-dimensional spectrum related the ^{13}C signals of the less abundant conformer to the TB form (^1H broad) and the most abundant to the C form (^1H well-resolved) <1998T9569>. The ^{13}C NMR spectra of 26 and 27 and other lactams and thiolactams of sparteine showed that most of the effects of thiolactam are greater than those of the lactam group in the oxo analogues. A good linear correlation between the ^{13}C chemical shifts of C=S and those of C=O was found <2003T5531>. The ^{13}C NMR of **38** revealed the existence of a mixture of two epimers: two signals assigned to C-4 bearing the hydroxyl group were

observed (64.55 and 69.33 ppm). The ^{13}C NMR spectra of 4 β - and 4 α -hydroxysparteine **38a,b** were assigned by comparison with the spectra of similar structures (13 α -hydroxysparteine (*vide infra*) and 13 α - and 13 β -hydroxylupanine). The correctness of these assignments was verified by molecular model considerations of **38a,b** and on the basis of the chemical shifts of the C-2 and C-6. The ^{13}C NMR spectrum of the isomer with the hydroxyl group in the axial position **38a** revealed upfield shifts of 1.23 (C-2), 4.68 (C-4), and 4.61 (C-6) ppm relative to the positions of these signals in the spectrum of **38b**. The upfield shift of C-2 and C-6 is a result of a γ -*gauche* substituent effect. In the case of C-4, the upfield shift was similar to related compounds <2001M973>. The C-17 resonance of the anhydronium perchlorate of 17-hydroxylupanine **39** appeared at 177.62 ppm confirming the presence of the $\text{HC}=\text{N}^+<$ moiety. The sp^2 hybridization of N-16 increased the ^{13}C chemical shift of its α -carbons. In particular, this concerned C-11 and C-15; their $\Delta\delta_{\text{C}}$ values relative to the free base were 8.96 and 6.01, respectively <2000M1073>. The chemical shifts of the eight-membered ring carbons of **19** and related compounds ranged between 53 and 69 ppm and it was observed that the carbonyl group behaved as ketones and the ^{13}C resonances were observed in the region 199–215 ppm <1995T2055, 1995T4819, 1997MRC13, 2000MRC883, 2001MRC101, 2005MRC479>.

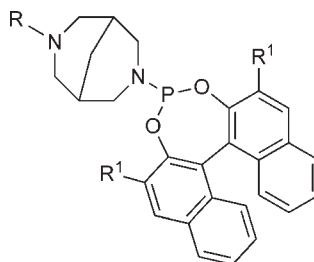
The ^{15}N signal of the Tröger's base **7** (arbitrarily, the labeled nitrogen was at position 5 and the unlabeled nitrogen was at position 11) appeared at -340.4 ppm, which was very similar to *N,N*-dimethylaniline (-338.2 ppm). Concerning the ^1H - ^{15}N coupling constants, it was possible to measure only those between N-5 and both protons Ha and Hb, at position 13, which were identical since the nitrogen's lone pair formed angles of $\sim 60^\circ$ with Ha and Hb. Concerning sp^3 atoms, the HMBC experiments showed strong correlation peaks for H-4 (^3J), H-6x (^2J), and H-13 (^2J) but no peak was observed for H-6n. The dihedral angles between the lone pair on N-5 and H-6x (30°) and H-6n (90°), together with data about the dependence of $^2J_{\text{HN}}$ on the dihedral angle, were compatible with this observation. Regarding sp^2 atoms, the fact that the correlation was strong with H-4 (*ortho*, ^3J), weak with H-3 (*meta*, ^4J), and absent with H-1 (*meta*, ^4J) was consistent with the couplings reported for aniline ($^3J=1.8$ Hz, $^4J=0.5$ Hz). The isotope effects on carbon atoms directly bound to ^{15}N -5 with regard to the corresponding carbon atoms linked to ^{14}N -11: C-6 and C-4a, were similar, both in sign and absolute value, to those observed for aniline. The ^{13}C - ^{15}N couplings of **7** differed from those measured in aniline; that is, ^2J with C-4 (6.3 Hz) is higher than the equivalent coupling in aniline (2.7 Hz). However, considering that the coupling is null with C-12a, the average for both *ortho* positions (3.2 Hz) was comparable. The most interesting result was the relatively low value of ^1J [$^{13}\text{C}(4a)$ - $^{15}\text{N}(5)$] (6.0 Hz) compared with that of aniline (11 Hz) <2002MRC743>.



The N–N rotation in both NNO moieties of **4a–d** could be observed with the aid of variable temperature ^1H and ^{19}F NMR spectra of **4c** <1997JOC5619>. The structural nature of difluoroamino-diazocines **45** and **46** could be diagnosed by ^{19}F NMR. The chemical shift of the fluorine signal for **45** was at 20.71 ppm, which is within the typical range (18–25 ppm) of internal mono(difluoroamino)alkanes; whereas, **46** showed an absorption at 29.4 ppm compatible with an internal *gem*-bis(difluoroamino) derivatives, which generally resonated at 27–33 ppm <1998JOC1566>.



The ^{31}P resonances of phosphites **47a–c** were found in the range 145.2–147.8 ppm <2002CEJ4767>.

**47a–c****a:** R = Ts, R¹ = H**b:** R = Ts, R¹ = Me**c:** R = Piv, R¹ = Me

Studies on fragmentation patterns of 1,5-diazocines were limited to a couple of cases reported below. A noticeable number of papers dealing with 1,5-diazocines reporting mass spectral data in their experimental sections only mentioned the molecular or quasimolecular ions. Thus were reported EI spectra <1995BCJ3121, 1995H(41)1709, 1995J(P1)2049, 1995JHC835, 1995JST(355)229, 1995M233, 1995T2055, 1995T4819, 1996JME2559, 1996JOC5581, 1996TL2679, 1996TL5791, 1997JHC375, 1997OM1167, 1998ACS790, 1998J(P1)1257, 1999J(P1)3623, 1998T997, 1998T11887, 1999JOC960, 1999TL1289, 2000EJO391, 2000EJO2367, 2000M1073, 2000OL1121, 2000OL4201, 2000T9641, 2000TL3475, 2000TL6161, 2001EJM375, 2001M973, 2001RCB753, 2001S1873, 2001TL4963, 2002CCC609, 2002EJO947, 2002JA11870, 2002J(P1)1963, 2002JHC727, 2002JOC2619, 2002JOC6008, 2002CCL115, 2002S906, 2002S2168, 2002T55, 2002TA1299, 2003ARK1, 2003JNP119, 2003S2518, 2003S2839, 2003T391, 2003T5531, 2003TA233, 2003TL2133, 2004EJO2375, 2004JOC86, 2004JCO828, 2004JOC5627, 2004MC235, 2004MI1368, 2004OL493, 2005BMC5717, 2006T12051>; FAB spectra <1995J(P1)2049, 1995JME2946, 1995TL1271, 1996JOC8897, 1998J(P1)3557, 1999AGE3713, 1999SL1875, 2000CEJ671, 2000JOC1207, 2000T7947, 2001EJO1377, 2001T1883, 2002CEJ3629, 2002CEJ4767, 2002EJM315, 2002T9567, 2003EJO3179, 2003JCO375, 2004EJO1097, 2004S1687, 2004TL1377, 2005BML4291, 2005CPB444, 2005OL67, 2005OL2019, 2005TA1969, 2006T8591>; CI spectra <1995J(P1)2049, 1995JOC1959, 1996JOC8897, 1999J(P1)3623, 2000JOC655, 2000TL6161, 2002HCA1659, 2002OL2577, 2003TL2083, 2004JOC5789, 2005OL4459, 2005T941>; ESI spectra <2002HCA1659, 2003HCA233, 2003OL2793, 2004JA14475, 2005OL4721, 2006JNP1300>, DCI spectra <2001JOC8222>; IC spectra <1995JOC2922>; LC/MS spectra <2004TL6733>; MALDI-TOF <1998T9569>; APCI spectra <2000OL4205, 2004TL5601>. All of the 1,5-diazocines, with one exception (*vide infra*), show the parent ions in their mass spectra.

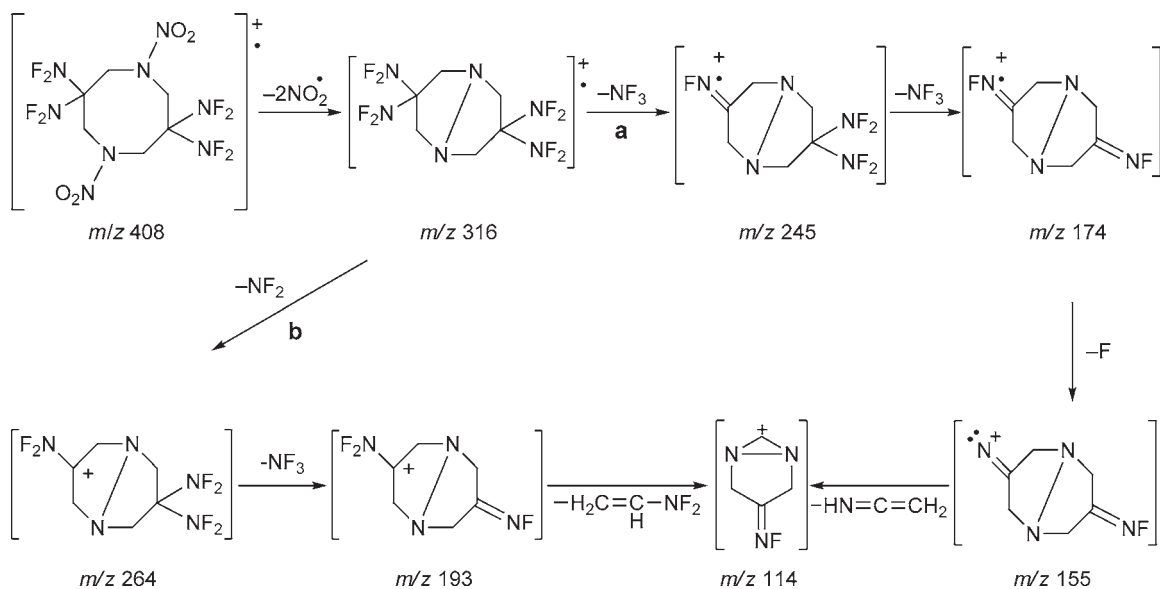
The mass spectrum of **29** was studied using electron ionization (EI) mass spectrometry. Collision-induced dissociation (CID) spectra were obtained for the major fragment ions of this compound using tandem mass spectrometric (MS/MS) techniques. The products from CID were used to elucidate the ion structures and origins of the fragments. Thus, in the EI mass spectrum of **29**, a molecular ion was not observed. The base peak was $[M - 2NO_2 - 2NF_3]^+$ at m/z 174. The major fragment ions were $[M - 2NO_2]^+$ at m/z 316 and $[M - 2NO_2 - NF_3]^+$ at m/z 245. The ion at m/z 316 was also the highest discernable mass. The CID spectrum of the fragment with m/z 316 made it clear that there were two separate pathways as outlined in **Scheme 3**. The major one goes through a fragment of m/z 245 (path a) and the minor one via a fragment of m/z 264 (path b).

Although the ion with m/z 316 may be assigned as $[M - 2NO_2]^+$ or $[M - NF_2 - 2HF]^+$, the assignment of the two fragment ions is more straightforward if the ion of m/z 316 is the result of loss of both nitramine NO_2 groups <2000JMP841>.

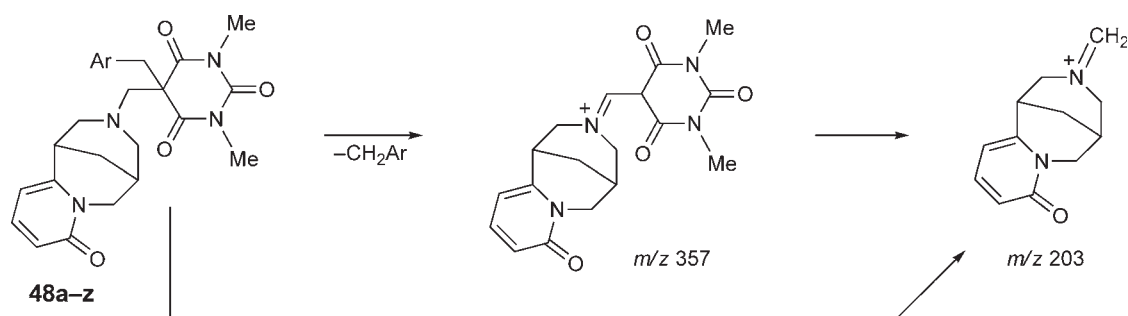
The mass spectra of cytosine derivatives **48a–z** showed peaks corresponding to the molecular ions with characteristic fragmentation into $[M - ArCH_2]^+$ ions with m/z 357 and the methylenecytisinium ion of m/z 203.

A general pattern of primary fragmentation of **48a–z** by electron impact shown in the **Scheme 4** has been proposed <2000MI192>.

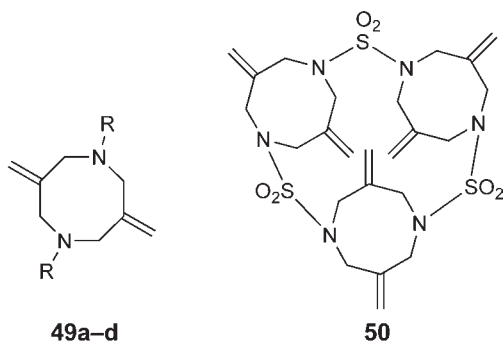
The matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectra of **49a–d** and macrocycle **50**, using α -cyano-4-hydroxycinnamic acid (CCA) as a matrix, exhibited, besides $[M + Na]^+$ as the main peak, $[M + K]^+$ adducts and ions corresponding to protonated molecules $[M + H]^+$ <1999RCM2359>.



Scheme 3



Scheme 4



a: R = 2,4,6-*i*-Pr-C₆H₂SO₂-

b: R = 4-Me-C₆H₄SO₂-

c: R = 2-NO₂-C₆H₄SO₂-

d: R = 2,3,4,5,6-Me-C₆SO₂-

The resolved enantiomers (+)-**14d** and (–)-**14d** showed mirror-image circular dichroism spectra and a split Cotton effect in the Soret region of the electronic spectrum and very high molar ellipticities were observed. This splitting is due to the chiral exciton coupling of the two identical chromophores and can be used to assign the absolute stereochemistry of the separated enantiomers of **14d**; (–)-**14d** showed a negative first Cotton effect and therefore the two porphyrin rings constituted a left-handed screw <1995CC1925>.

The CD spectra of **32** and **33**, measured in MeOH are reported in figures 1 and 2, respectively. The CD of **32** was characterized by three positive Cotton effects at 288, 240, and 206 nm. The first one was very weak and could be unequivocally assigned to the aromatic ^1L_b transition. The more intense second one occurred in the region of the forbidden amide $n-\pi^*$ excitation. The carboxamide group conjugated with an aryl ring constituted a chromophore of which the helicity determined the Cotton effect sign. Analogous to other α,β -unsaturated carbonyl compounds, the P helicity of the system should lead to the positive $n-\pi^*$ Cotton effects, whereas the M helicity leads to the negative

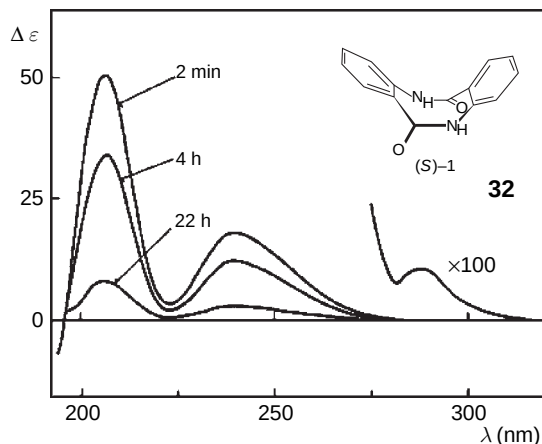


Figure 1

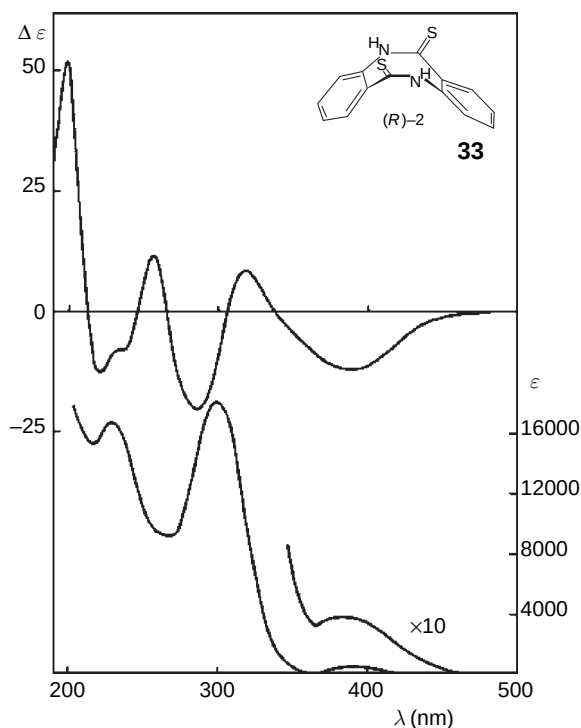
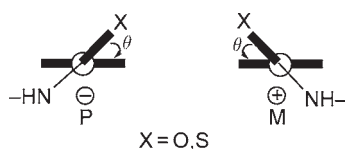


Figure 2

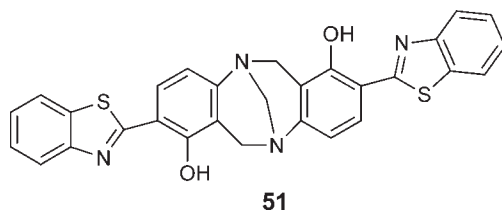
one. The fact that both amide groups were severely twisted with respect to the phenyl rings in the P sense (X-ray) explained the positive sign at 240 nm. The nature of the extremely strong CD band at 206 nm is less clear. Since the molecule contained two rigidly oriented amide units, the exciton coupling between these chromophores, leading to two intense and oppositely signed Cotton effects, is expected in the region of the allowed $\pi-\pi^*$ transition. However, only one positive CD band was observed in this region. On the other hand, the non-Gaussian shape of the neighboring $n-\pi^*$ band and a minimum near 220 nm pointed to a contribution from an additional band that might be due to a missing negative branch of the exciton couplet. The CD spectrum of **33** showed at least seven bands with alternating signs in the visible and near UV regions. Due to a similarity of the electronic structures of the amide and thioamide chromophores, there is a close correspondence between their lowest-energy transitions and the direction of the electronic transition moments. Furthermore, replacement of the carbonyl oxygen with a sulfur resulted in bathochromic shifts of the absorption maxima and a better resolution of the $n-\pi^*$ and $\pi-\pi^*$ electronic transitions. Therefore, the spectra of thiocarbonyl compounds may be useful in the analysis of amide spectra. Thus, the UV-Vis spectrum of **33** revealed three well-resolved absorption bands at 384, 300, and 230 nm corresponding to the thioamide $n-\pi^*$, $\pi-\pi^*$, and $\sigma_{C-S}-\pi^*$ excitations, respectively. Thus, a broad negative CD band near 390 nm should be assigned to the $n-\pi^*$ transition. Analogous to its carbonyl analogue, the Cotton effect sign is determined by the helicity of the thiobenzamide unit.

The twisted form in the M sense of (–)-**33** (X-ray) accounted for the observed negative $n-\pi^*$ Cotton effect sign. In the region of the thioamide $\pi-\pi^*$ transition, there were two CD bands: a positive one at 320 nm and a negative one near 290 nm. They could be attributed to the exciton coupling of the allowed $\pi-\pi^*$ transition of the thioamide units. In this case, the observed sequence of bands pointed to a positive exciton coupling and right-handed screw for the thioamide $\pi-\pi^*$ transition moments (Scheme 5) <2004JOC1248>.



Scheme 5

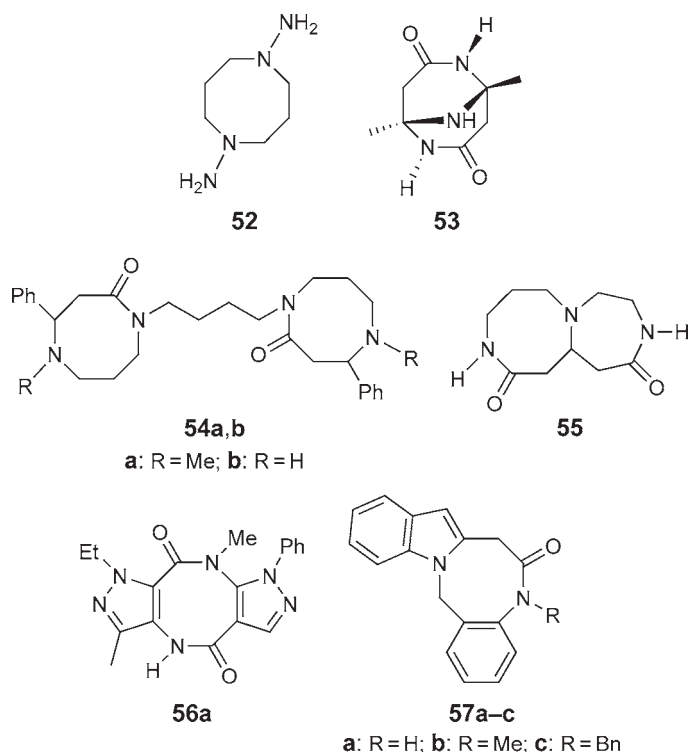
UV-Vis absorption and fluorescence emission of Tröger base analogue **51** and its precursor 2-(4-amino-2-hydroxyphenyl)benzothiazole were measured. In the UV-Vis spectra, all molar extinction coefficient values were in the order of $10^4 \text{ l mol}^{-1} \text{ cm}^{-1}$, as expected for $\pi-\pi^*$ transitions.



In its UV-Vis spectrum, **51** showed a bathochromic shift band (362 nm) with respect to the precursor (351 nm). This is due to the effect of the amino substituent in the benzothiazole precursor. A single fluorescence emission band was observed in **51** at 500 nm, while the precursor showed a maximum located at 499 nm. A Stokes shift ($\Delta\lambda$) of 138 and 148 nm could be detected for **51** and the precursor, respectively. Small blue-shifted bands at 386 and 373 nm could be observed for **51** and the precursor, respectively, with Stokes shift ($\Delta\lambda$) of 121 and 135, respectively <2004TL5601>.

IR spectra of diazocinones **9a,b** showed strong CO stretching bands at $1742\text{--}1747 \text{ cm}^{-1}$ <2001T1883>. The stretching of the carbonyl bridge of **19a-w** and related compounds was found at $1720\text{--}1755 \text{ cm}^{-1}$ <1995T2055, 1995T4819, 1997JCD347, 1997MRC13, 2000MRC883, 2001MRC101, 2005MRC479>. The IR spectrum of the amino-bridged cyclopropyl substituted diazocine **21** showed the NH stretching at 3247 cm^{-1} and the $C=N$ band at 1637 cm^{-1} <1998ACS790>. The carbonyl stretchings of the pyridine moiety of the *N*-substituted cytisines **31c-e** and related compounds were observed at $1620\text{--}1670 \text{ cm}^{-1}$ <2000MI192, 2001MI356, 2003RJC961, 2004JOC5789, 2004MI582, 2004RJC1133>. For dibenzodiazocine, **32** different values of wavelengths for the CO stretchings were reported in CHBr_3 , 1751 and 1788 cm^{-1} <2004JOC1248, 2004MI1368>, while the NH stretching was reported to be at 3450 cm^{-1} <2004MI1368>. For 2,8 disubstituted derivatives of the same ring system, broad absorptions due to the

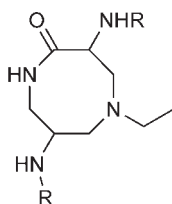
NH functionality were reported at $3440\text{--}3455\text{ cm}^{-1}$, while the carbonyl stretchings were exhibited at lower frequencies ($1621\text{--}1681\text{ cm}^{-1}$) <2006T12051>. The lactam carbonyl group of **40** and related compounds absorbed at $1715\text{--}1725\text{ cm}^{-1}$. In **41** and related derivatives, the amide carbonyl absorbed at slightly lower frequencies, $1702\text{--}1705\text{ cm}^{-1}$; while the ketone carbonyl stretching was found at 1640 cm^{-1} <2001EJO1377>. Perhydro-1,5-diamino-1,5-diazocine **52** exhibited the NH stretchings at 3300 and 3140 cm^{-1} <1998EJO1431>. The IR spectrum of **36**, recorded in CHCl_3 , showed the two different kind of NH stretchings at 3650 and 3380 cm^{-1} , while the carbonyl absorption was found at 1655 cm^{-1} <2002T7177>. Instead, the amino-bridged diazocinone **53** showed the lactam and amine stretchings at 3198 and 3282 cm^{-1} and the carbonyl band at 1662 cm^{-1} <2002T55>. The homaline **54a** exhibited the carbonyl stretching at 1630 cm^{-1} , while its demethyl derivative **54b** showed the CO band at 1621 cm^{-1} and the lactam NH at 3300 cm^{-1} <1995BCJ3121>. The hopromine and *t*-butyl-diphenylsilyl-hoprominol showed their carbonyl stretchings at 1725 cm^{-1} <2002HCA1659, 2003HCA233>. The diazepino-diazocine **55** showed the NH stretchings at 3370 and 3310 cm^{-1} and the carbonyl band at 1660 and 1620 cm^{-1} due to the different ring sizes <1995H(41)1709>. The dipyrazolo-diazocine **56a** and related derivatives showed the NH stretchings and carbonyl bands at $3200\text{--}3100$ and $1660\text{--}1670\text{ cm}^{-1}$, respectively <1995JHC835, 1995JHC1589>. The indolo-fused benzodiazocine **57a** exhibited the lactam NH at 3415 cm^{-1} and the carbonyl stretching at 1655 cm^{-1} . The *N*-substituted derivatives **57b,c** showed their carbonyl bands at slightly higher frequencies ($1660\text{--}1661\text{ cm}^{-1}$) <2005T941>.



14.07.2.3 Thermodynamic Aspects

Due to the wide arrays of substituents as well as different fused rings, 1,5-diazocines showed a large variety of phase behavior. In fact, the melting points of derivatives of the same ring system, can differ by more than 250°C . For instance, **47b** melted at $261\text{--}263^\circ\text{C}$ while the corresponding methylene-bridged diazocine having *N*-benzyl and BOC moieties was an oil <2002CEJ4767>. Simple uncondensed and unbridged 1,5-diazocines having substituted nitrogens are generally oils <2001IC5060, 2001CCL769, 2002CCL115, 2002JHC727>. Other 1,5-diazocines that generally exist as oils are sparteine, isosparteine, multiflorine, and analogues although such derivatives are polycyclic and often bear functionalities capable of good intermolecular interactions <1996JOC5581, 2001M973, 2002OL2577, 2005OBC1557>. When uncondensed and 1,5-diazocines possess unsubstituted NH and possibly carbonyl or other functionalities capable of increasing intermolecular interactions their melting points rose remarkably. Thus, the

amino-bridged cyclopropyl 1,5-diazocine **21** melted at 110–111 °C <1998ACS790>, **46** and **29** melted at 182–184 and at 216–218 °C, respectively <1998JOC1566, 1999JOC960>, **36** and other 4-substituted derivatives had melting points in the range 172–199 °C <2002HCA1659>, and diazocines **58** melted at 218–220 °C <1999SL1875>. Cytisine, **31a**, melted at 156–157 °C <2002JA11870> and its derivatives showed a very large range of phase behaviors: many *N*-substituted derivatives were isolated as oils <2000OL1121, 2001EJM375, 2001RJC650, 2002JA11870, 2004JCO828, 2004JOC5789, 2004OL493, 2005OL4459>, as gum or foam <2001EJO1377, 2002JA11870> or as solid melting in the ranges 50–120 °C <2001EJM375, 2001RJC650, 2003RJC961, 2004JCO828, 2004RJA1321>, 120–250 °C <2000OL1121, 2000OL4205, 2001MI356, 2001RJC151, 2002MI249, 2002TA1299, 2004MI582, 2004PCJ311, 2004RJA1321, 2004RJO719, 2004JOC5789, 2004RJC1133, 2005OL4459> or >250 °C <2002MI249>. Benzo- or dibenzo-condensation of 1,5-diazocines led to compounds with high melting points. Thus, 5-ethyl-2-methylene-1-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-1,5-diazocin-6-one melted at 180–183 °C <2004JOC5627> and dibenzodiazocine, analogue of **8** with unsubstituted NH melted at 166 °C <2004MI1368>, while substitution on the benzene moieties led to compounds melting at 248–250 °C <2004TL1377>. Dibenzodiazocinone **32** and the corresponding thio derivative **33** melted at 333–335 °C <2004JOC1248>. Amino-bridged dibenzodiazocines **22** melted at 158–211 °C <1998T997> and, in the case in which R was a sulfonamide moiety, the melting points rose to 258–300 °C <1997RCB1931>. Bis-dibenzodiazocines **44a–j** melted in the range 199–288 °C <2003S2839>. Tröger's base analogues showed a very wide range of melting points depending on the aryl substituents or the carbocyclic or heterocyclic systems that replaced them. The Tröger's base with two nitro groups replacing the two methyl groups melted at 258–260 °C <2003TL2133>. Different series of Tröger's base analogues with substituted benzenes were synthesized reporting melting points in the range 178–300 °C <1996TL5791>; 124–310 °C <2003EJO3179> or 66–300 °C <2004S1687>. Naphthodiazocine Tröger's base analogue melted at 213–215 °C <1998TA4151>. Further condensation of a Tröger's base with quinoline moieties increased the melting points to 350–360 °C <1995TL1271>. Also condensation of diazocines with heterocycles maintained high melting points: dipyrazolo-diazocines **56** melted in the range 230–303 °C <1995JHC1589> and indolo-diazocines **57a–c** melted at 269–271 °C <2005T941>.



58a,b

a: R = 2-imidazolyl

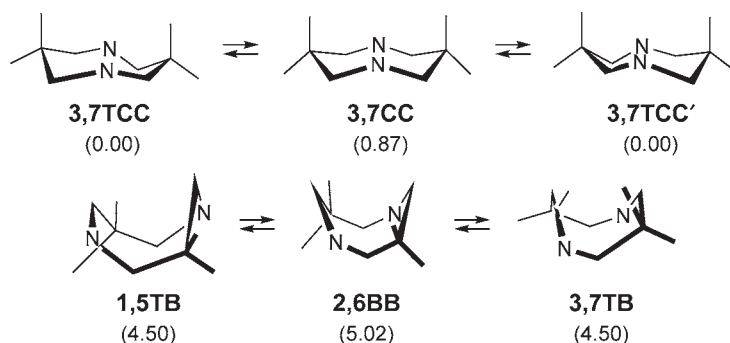
b: R = BOC

The solubility of 1,5-diazocines in most common organic solvents, with the exception reported below, is verified by the large selection of eluants used in their chromatographic separations. Actually it is impossible to give indication about typical solubility behavior of 1,5-diazocines even within the same series due to extraordinarily high number of derivatives synthesized with a large variety of substituents that heavily affect their solubility. Purification of 1,5-diazocines is very often achieved by column chromatography of silica gel with the eluants having very different polarity: EtOAc <1997T11859, 1998J(P1)1257, 2000S640, 2004ARK86, 2005BMC5717, 2005CPB444>; EtOAc/hexane <1995JME2946, 1998T14885, 2000JOC655, 2001EJO1377, 2000EJO391, 2001JOC1607, 2001T1883, 2002EJO947, 2002J(P1)1963, 2003T391, 2004JCO828, 2004S1687, 2005BMC5717>; EtOAc/petroleum ether <1998J(P1)1257, 2004JIB2231, 2005OL4459>; EtOAc/CHCl₃ <1995J(P1)2049>; EtOAc/MeOH <2000OL1121, 2002OL2577>; EtOAc/*n*-hexane <2002CEJ4767>; EtOAc/heptane <2002JOC6008, 2002S2761, 2003EJO3179>; EtOAc/toluene <2004S1687>; EtOAc/DCM <1998T997, 2001JOC1607>; EtOAc/MeOH/DCM <2001EJO1377>; MeOH <1998JCM196>; MeOH/CHCl₃ <1995BCJ3121, 1999J(P1)3623, 2000S640, 2000T7947, 2000T9641, 2001MI356, 2001EJM375, 2000EJO391, 2002JHC727, 2002T7177>; MeOH/DCM <2000OL1121, 2002EJM315, 2002HCA1659, 2002JA11870, 2003HCA233, 2004JOC5789>; MeOH/benzene <2001MI356>; MeOH/THF <2004JCO828>; MeOH/DCM/NH₄OH <1996JOC5581, 2000OL4205, 2000OL1121, 2000OL4201, 2002HCA1659, 2003OL2793, 2005OL4459>; MeOH/CHCl₃/NEt₃ <2000EJO391>; CHCl₃ <1995BCJ3121, 2001JOC8222>; CHCl₃/acetone <1998JOC1566>; CHCl₃/THF <2004JCO828>; DCM/Et₂O <2002CCC609, 2002MRC743>; DCM/*n*-hexane <2002CEJ4767>; DCM/hexane <2004TL5601>; DCM/THF <2004JCO828>.

EtOH/hexane <2000EJO2367>; benzene <2001RJC151>; benzene/petroleum ether <2004MI1368>; toluene <2004S1687>; Me *t*-Bu ether <2000EJO2367>. Less common was the purification in alumina using CHCl₃ <2003JNP119, 2004RCB2262>; DCM <2001MI356>; DCM/hexane <2000CEJ671>; petroleum ether <2002S2168>; as eluants. Purification was also achieved by recrystallization, generally from EtOH or MeOH <1995JHC1589, 1995T2055, 1995T4819, 1996JOC8897, 1997OM1167, 1998TA4151, 2001M973, 2001RCB753, 2002MI182, 2002MI450, 2002JOC2619, 2002S906, 2004PCJ311, 2004RCB2262>. In some occasion oils were purified by classical distillation <1996JME2559> or Kugelrohr distillation <1999J(P1)3623, 2001IC5060>.

All the bis-dibenzodiazocines **4a–j** were insoluble in water and almost insoluble in most organic solvents, such as: EtOAc, acetone, EtOH, and DMSO. They were only slightly soluble in CHCl₃ and formed a yellow solution. The alkyl or alkoxy substituted derivatives showed the better solubility in CHCl₃ as compared to their halogen substituted analogues, and the 4-substituted one were more soluble than their 2-substituted analogues <2003S2839>.

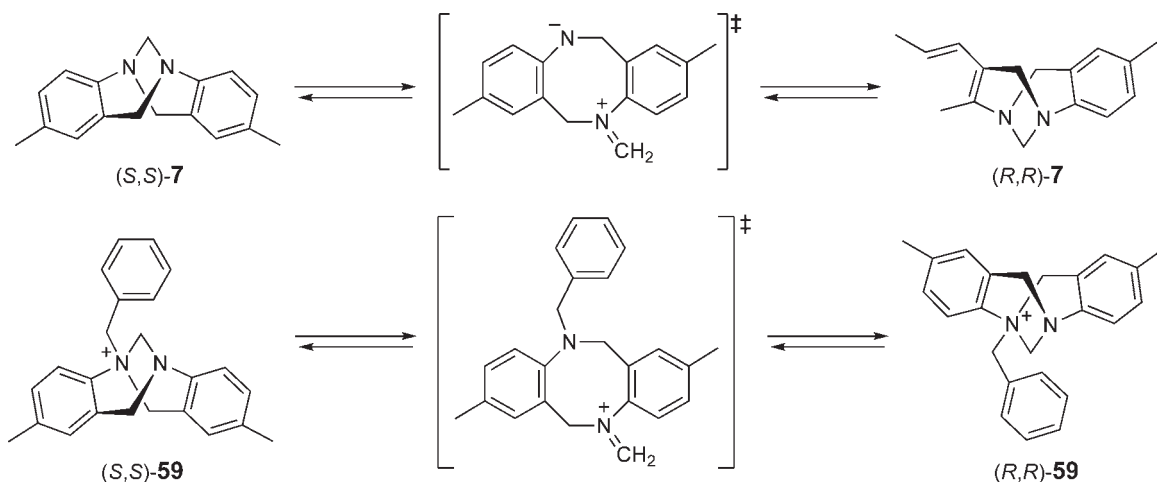
As predicted by calculations and confirmed by NMR studies, **1** exists in a conformational equilibrium of two forms. A set of rapidly equilibrating conformers was consistent with the ¹³C NMR of the major form. The lowest strain energy was calculated for the 3,7 twist–chair–chair (3,7TCC), which is connected with its mirror image (3,7TCC') through the 'static' conformation 3,7 chair–chair (3,7CC). The interconversion energy barrier is only 870 cal mol^{−1} and is consistent with the rapid equilibration even at 136 K, the lowest temperature at which an NMR spectrum was measured. The minor form was assigned to a rapid equilibrating set of 1,5TB–3,7TB conformers through the 2,6BB form with an energy barrier of 520 cal mol^{−1} (Scheme 6) <1996JOC3061>. Both the experimental structures **3c** and the cobalt(II) complex of **3a** showed the predicted chair–chair conformation of the diazocine backbone; the pendant arms were in an equatorial configurations. The overall structural features of the ligand backbone were very similar and in excellent agreement with the prediction obtained by mechanics calculations (see Section 14.07.2.1). The torsional barrier for a rotation around the single bond between the C-2 or C-4 carbon and the aromatic substituents was found to be 70 kJ mol^{−1} <1997JCD347>. In the chair–chair conformation of **4a–d**, the planar nitrosamine group was characterized by a relatively high energy barrier to the N–N rotation (~23 kcal mol^{−1}) owing to partial double bond character between two adjacent nitrogen atoms. The nitrosamine deviated from planarity showing a barrier height of ~21 kcal mol^{−1} due to a decreased π conjugation <1997JOC5619>. The Eyring activation parameters of the enantiomerization barrier of the Tröger base **7** were determined in an inert mobile gas, by enantioselective stopped-flow multidimensional gas chromatography: $\Delta G^\ddagger_{\text{gas}}(298.15\text{ K}) = 112.8 \pm 0.5\text{ kJ mol}^{-1}$; $\Delta H^\ddagger_{\text{gas}} = 62.7 \pm 0.3\text{ kJ mol}^{-1}$; $\Delta S^\ddagger_{\text{gas}} = -168 \pm 6\text{ J (K mol)}^{-1}$. Surprisingly, in the presence of the chiral stationary phase (CPS) Chirasil- β -Dex required for enantiomer separation of **7**, the enantiomerization barrier is higher than in the gas phase <2000JA1424>. However, in a triphosphate buffer at pH 2.2, the barrier was lower than in the gas phase being $\Delta G^\ddagger(298\text{ K}) = 100.9 \pm 0.5\text{ kJ mol}^{-1}$; $\Delta H^\ddagger = 89.5 \pm 2\text{ kJ mol}^{-1}$; $\Delta S^\ddagger = -42 \pm 10\text{ J (K mol)}^{-1}$.



Scheme 6

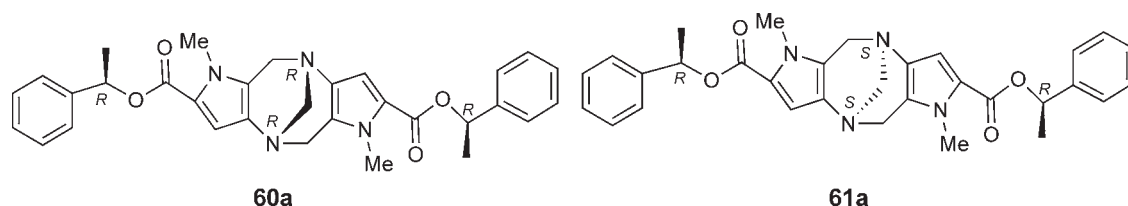
Introduction of a permanent positive charge attribute to quaternization of Tröger base **59** led to a significant decrease of the enantiomerization barrier [$\Delta G^\ddagger(298\text{ K}) = 90.2 \pm 0.5\text{ kJ mol}^{-1}$; $\Delta H^\ddagger = 91.4 \pm 2\text{ kJ mol}^{-1}$; $\Delta S^\ddagger = 9.8 \pm 10\text{ J (K mol)}^{-1}$] <2002CEJ3629>. In addition to the mechanism proposed for the enantiomerization of **7** shown in Scheme 2 whose validity was confirmed by theoretical calculation, an unproven mechanism was proposed via an iminium intermediate shown in Scheme 7. Such a mechanism involved a charge separation requiring a high activation energy, whereas a charge shift requiring less activation energy would apply for the *N*-monobenzylated derivative **59** (Scheme 7) <2002CEJ3629>. A convenient resolution of the Tröger's base involved the treatment of

racemic **7**, dissolved in acetone, with (–)-*O,O'*-dibenzoyl-L-tartaric acid in a 1:3 ratio. From the precipitate, the (*R,R*)-isomer of **7** was obtained in 91% ee (98% ee after recrystallization from acetone/hexane) while from the filtrate, the (*S,S*)-isomer was obtained in 41% ee. The (*R,R*)-isomer was obtained. The (*S,S*)-isomer was enriched <2006TA1116>. A naphthyl analogue of Tröger's base, 8*H*,16*H*,-7,15-methanodinaphtho[2,1-*b*][2',1'-*f*]-1,5-diazocine, was successfully resolved using (–)- and (+)-di-*p*-toluoyl-tartaric acid. Enantiomers obtained showed extremely high specific rotations related to the rigid 1,5-diazocine skeleton with molecular asymmetry and the presence of condensed aromatic rings, similar to helicenes <1998TA4151>.



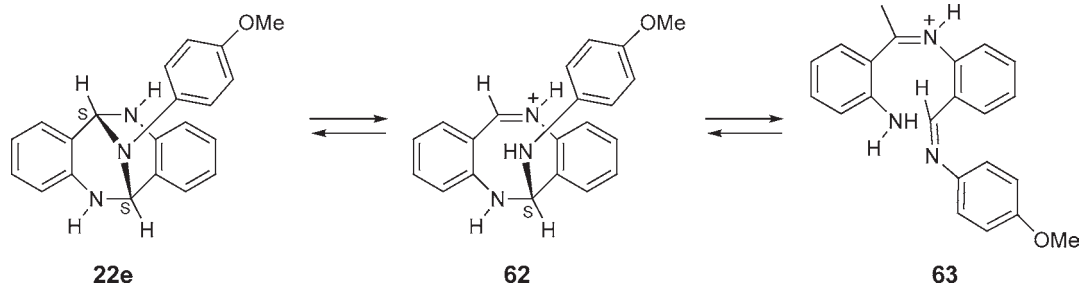
Scheme 7

The pyrrole analogue of Tröger's base was obtained as a 1:1 mixture of the two diastereoisomers **60a** and **61a**. The crude product was crystallized from Et₂O to afford pure crystals of **60a**. Subsequent separation of the mother liquor by chromatography gave an additional portion of **60a** and impure **61a** which by crystallization was obtained with de 90%. Transformation of **61a** into **60a** was achieved by crystallization-induced asymmetric transformation (CIAT), treating the former with MeOH containing catalytic amount of HCl. Crystalline **60a** was obtained in nearly quantitative yield (de ~95% and after crystallization from MeOH/DCM de >99%) <2005TA1969>. The enantiomers of the dizinc(II) bis-porphyrin Tröger's base analogue (+)-**14d** and (–)-**14d** displayed extremely high specific rotation, consistent with their helicity. Each enantiomer possessed a C₂ axis of symmetry, showed strong exciton coupling between the identical porphyrin chromophores, and showed a split Cotton effect in its CD spectrum. This allowed assignment of the (–)-**14d** enantiomer as having the two porphyrins in a M-configuration (left-handed screw arrangement). Resolution of **14d** was achieved by chromatography over silica that had been presaturated with L-histidine benzyl ester, taking advantage of the fact that binding of (+)-**14d** with L-histidine benzyl ester in toluene stronger than the enantiomer (–)-**14d**. The separation was very sensitive to the solvent used: a 9:1 pentane:CHCl₃ mixture gave complete separation, while 10:1 or 8:1 mixtures resulted in a poorly resolved separation. Interestingly, the (+)-**14d** enantiomer, which had a stronger binding interaction with L-histidine benzyl ester, was eluted from the column first indicating that it had a lessened interaction with the solid phase and was chromatographed as (+)-**14d** histidine complex; whereas, (–)-**14d** was eluted as mainly free compound <1997TA1161>. The reaction of cyclization leading to the tweezer-shaped bis-Tröger's base **18a** was stereo- and regioselective and only one of the two possible regioisomers, as a 4:1 mixture of the *syn/anti* stereoisomers **18a** and **18'a** was obtained. The *syn* configuration of the major isomer was determined by X-ray crystallography (see Section 14.07.2.2). When the minor isomer **18'a** was subjected to cyclization conditions (acid medium), an identical 4:2 mixture of **18a** and **18'a** was obtained. Therefore, the *syn* isomer was thermodynamically more stable than the *anti* isomer, either because of π -stacking interaction between the lateral aromatic rings, which are parallel, or due to differences in solvation between the two isomers <2001JOC1607>. Optically pure **42** racemized under moderately acidic conditions. Thus, stirring **42a-a** and **42a-b** separately in TFA for several days at 25°C gave in the first case a mixture of **42a-a** and **42a-b** in approximately 4:1 ratio and, in the second case, only **42a-b**. This proved, as expected that the *anti,anti* diastereomer **42a-b** is the thermodynamically more stable of the two isomers <2005OL2019>. The racemization process was also observed in **42** bearing a methoxy moiety instead of bromine <2005OL67>.



The unit cell of the pseudo-Tröger's base **22e** contained only one enantiomer whose absolute configuration was determined (*R,R*); however, a DCM solution of **22e** showed no rotary power. The most reasonable explanation is that **22e** is probably a racemate consisting in *R,R* and *S,S* crystals.

The molecular structure has been determined to be *R,R*. These enantiomers quickly racemized in solution by a mechanism showed in [Scheme 7](#) in which and *S,S* derivative could racemize by two successive ring opening; in **62**, the first *S* center lost its stereogenicity and in **63** the same happened for the second one ([Scheme 8](#) [<1998T997>](#)). In order to get information on the binding capabilities of the carbonyl-bridged diazocines **19**, called bispidinones, pK_a values in DMSO for **19f** ($R = \text{Me}$, $R^1 = \text{Bn}$), **19p** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{Bn}$), **19q** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{Ph}$), **19s** ($R = \text{Me}$, $R^1 = \text{Ph}$) and **19w** ($R = \text{Me}$, $R^1 = \text{H}$) along with NEt_3 , pyridine, bipyridyl, and *N,N*-dimethylbispidine, for comparison, were determined. Thus, the *N,N*-dibenzyl derivative **19f** showed a pK_a (7.7) comparable to aliphatic amines; whereas, the corresponding *N,N*-diphenyl derivative **19s** had a value (4.5) close to heteroaromatics. The keto function had a strong lowering effect on the pK_a , which changed by nearly four orders of magnitude from *N,N*-dimethylbispidine ($pK_a = 11.88$) to **19f** ($pK_a = 7.7$) and **19w** ($pK_a = 7.0$). Such an effect has been related to interactions between the nitrogen lone pairs and the keto function through σ bonds. An approximately equally large further decrease by 3.2 pK_a units is observed upon introduction of a phenyl substituent, that is, comparing **19f** with **19s**. A smaller decrease by only 0.9 units is observed for **19p** (5.3) and **19q** (4.4), since the pK_a of **19p** is already low. In a similar way, the carbomethoxy substituent lowered the pK_a , that is, comparing **19q** with **19s** and **19p** with **19f**. In conclusion, due to similar pK_a values, the *N*-phenyl-substituted bispidinones are expected to have σ -donor properties comparable to the bipyridyl ligands but more weakly bound, since they are not π -acceptors [<1997OM1167>](#). The magnitude of the observed Cotton effects in the CD spectrum of **32** in MeOH gradually decreased at 25 °C due to its slow racemization in solution. Thus, the measured rate constants k for the ring boat-boat interconversion were 1.43×10^{-5} , 1.43×10^{-5} , and 5.17×10^{-4} at 25, 40, and 50 °C, respectively. Racemic ($\pm$)-**32** easily formed inclusion complexes with a wide variety of organic substances. This was due to the geometric ('roof-shaped') features of **32** that made its close packing in the crystal difficult. Therefore, inclusion complexation of **32** with optically active guests, such as (*R,R*)-1,2-diaminocyclohexane, as an alternative method of the optical resolution, was attempted. Unfortunately, the dibenzodiazocine **32** liberated from the complex did not show any optical activity. Instead, treatment of the racemate ($\pm$)-**33** with excess (*R,R*)-1,2-diaminocyclohexane in toluene formed a crystalline complex between the enantiomerically pure **33** and the diamine. The enantiomerically pure ($-$)-**33** appeared to be optically stable at 25 °C since its optical rotation in EtOH remained unchanged after a week in the dark [<2004JOC1248>](#). The 4-hydroxysparteine **38**, as revealed by its ^{13}C NMR spectrum, exists as a mixture of two epimers: 4 β -hydroxy **38a** and 4 α -hydroxy **38b**. The ratio of these epimers varies from 1:1 to 1:99 depending on the reaction conditions used in the reduction of the multiflorine from which **38a,b** were derived. Analytical separation of the two epimers was possible by GC-MS after their conversion into the corresponding 4-*O*-acetyl derivatives. Preparative separation of the 4-*O*-acetyl derivatives

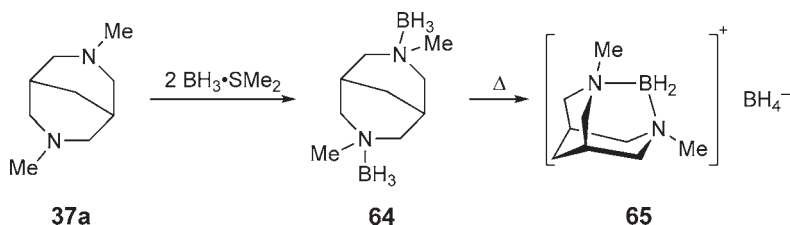


Scheme 8

was achieved by short column chromatography on Al_2O_3 with EtOAc/MeOH , as eluant [\[2001M973\]](#). The conformation of the anhydronium perchlorate of 17-hydroxylupanine **39**, confirmed by X-ray diffraction data, involved a distorted half chair, chair, distorted sofa, and chair conformations for the rings A, B, C, and D, respectively; no short electrostatic interaction between the immonium group and perchlorate anion was observed [\[1999JST\(424\)245\]](#). The NMR analysis of **39** in DMSO revealed a conformational equilibrium within rings A and D, whereas rings B and C remained rigid [\[2000M1073\]](#).

14.07.2.4 Reactivity of Nonconjugated Rings

The *N,N*-dimethyl-1,5-diazocine **37a** reacted completely with 2 equiv of $\text{BH}_3\cdot\text{SMe}_2$ to give the high-melting solid **64**, which upon heating at 100°C *in vacuo* for 20 h led to the salt **65**. Actually, the cation of **65** was previously reported but the fact that **64** was isolable and the transformation of **64** into **65** occurred in the solid state led to innovative aspects. Similarly, **1** with $\text{BH}_3\cdot\text{SMe}_2$ produced the bis- BH_3 adduct **2**, which during vacuum sublimation (0.5 Torr, 100°C , 3 h) yielded a solid, which was the corresponding mono- BH_3 adduct of **1**. In this case, only one of the two nitrogen donors interacted with BH_3 ([Scheme 9](#)) [\[1996JOC3061\]](#).

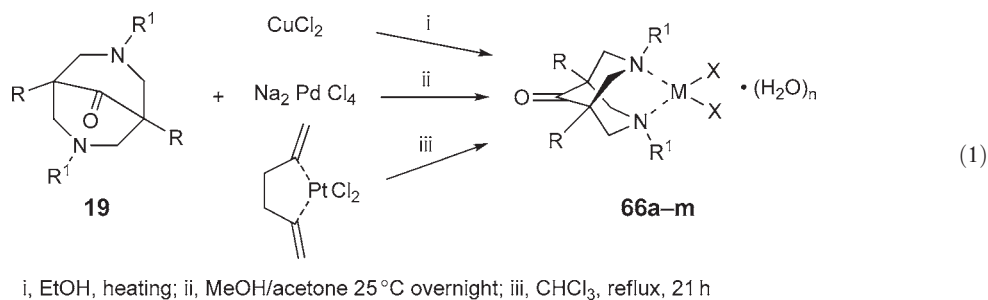


Scheme 9

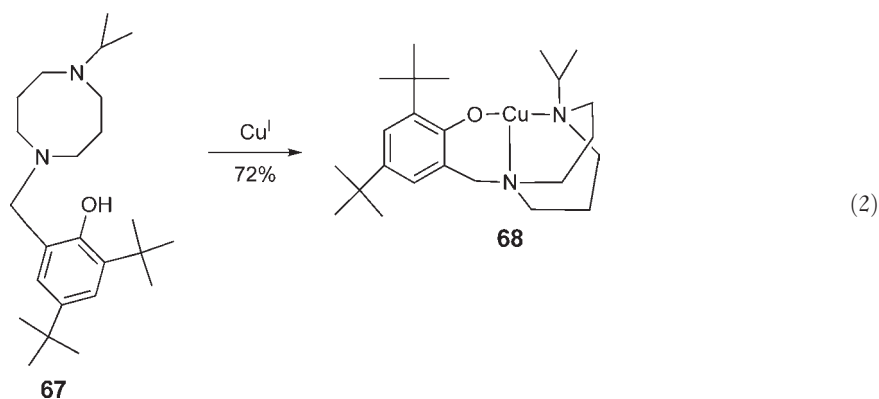
Bispidinones **19** readily formed metal complexes with transition metals of Cu(II), Pd(II), and Pt(II) in an alcoholic solution. Alternative solvents, such as MeCN, acetone, and water, could be used for Cu(II). This approach was not suitable for the preparation of Pt(II) complexes due to the reducing effect of alcohols. A general ligand displacement reaction of hexadiene from the dichloro platinum hexadiene was effective for the generation of *cis*-dichloro platinum bispidinones **66c,g** and an anion exchange reaction with NaI gave the *cis*-iodo complexes **66d,h**. In [Table 1](#), the bispidinone complexes synthesized are reported and depicted in [Equation \(1\)](#) [\[1995T2055\]](#). Similar complexes obtained from derivatives **19** and (1,3- η^3 -propenyl)Pd were obtained [\[1997OM1167\]](#).

Table 1 Bidentate transition metal complexes of bispidinones **19**

Complex	R	R ¹	M	X	N	Yield (%)
66a	Ph	H	Cu	Cl	0	76
66b	Ph	H	Pd	Cl	0	56
66c	Ph	H	Pt	Cl	0	46
66d	Ph	H	Pt	I	2	42
66e	Ph	Me	Cu	Cl	0	83
66f	Ph	Me	Pd	Cl	1	63
66g	Ph	Me	Pt	Cl	0	40
66h	Ph	Me	Pt	I	3	10
66i	SPh	Me	Cu	Cl	1	70
66j	Me	Me	Cu	Cl	0	63
66k	Ph	Bn	Cu	Cl	0	45
66l	Ph	Bn	Pd	Cl	1	72
66m	Ph	$\text{CH}_2\text{CH}=\text{CH}_2$	Cu	Cl	0.5	58



Attempts to generate a Cu(I) complex by reacting the sterically hindered potentially tridentate 1,5-diazocine **67** with one phenolate and two amine donors, with CuCl or [Cu(MeCN)₄]X (X = ClO₄[−] or SbF₆[−]) under an inert atmosphere in a variety of solvents only led to green mixtures indicative of disproportionation. However, treatment of **67** with Cu_xMes_x (X = 2 and 5) in THF under stringent anaerobic conditions, followed by precipitation with pentane yielded the complex **68**, as a white powder (Equation 2) <1998CC2521>.



The analogue of Tröger's base iminodibenzodiazocine **69** when refluxed in toluene with PdCl₂, yielded red crystals **70**, which precipitated at 25 °C and revealed (X-ray) the presence of the tridentate complex with Pd(II). The metal atom coordinated the pyridine moiety and the apical amino group of **69**; the resulting chelate **71** enhanced the acidity of the apical NH group, which was in an antiperiplanar arrangement with respect to one aminal bond. This arrangement favored ketimine formation and opening of the eight-membered ring with concomitant formation of the free aniline **72**. The diminished strain allowed for coordination of the second pyridine nitrogen atom to the Pd atom to afford the monovalent chloropalladium(II) complex cation **70** (Scheme 10) <2006EJO2987>. Treatment of 1,5-diazocines with acids gave different results. Thus, iminodibenzodiazocine **69** reacted with camphorsulfonic and methanesulfonic acid to give the corresponding ammonium salts <2006EJO2987>.

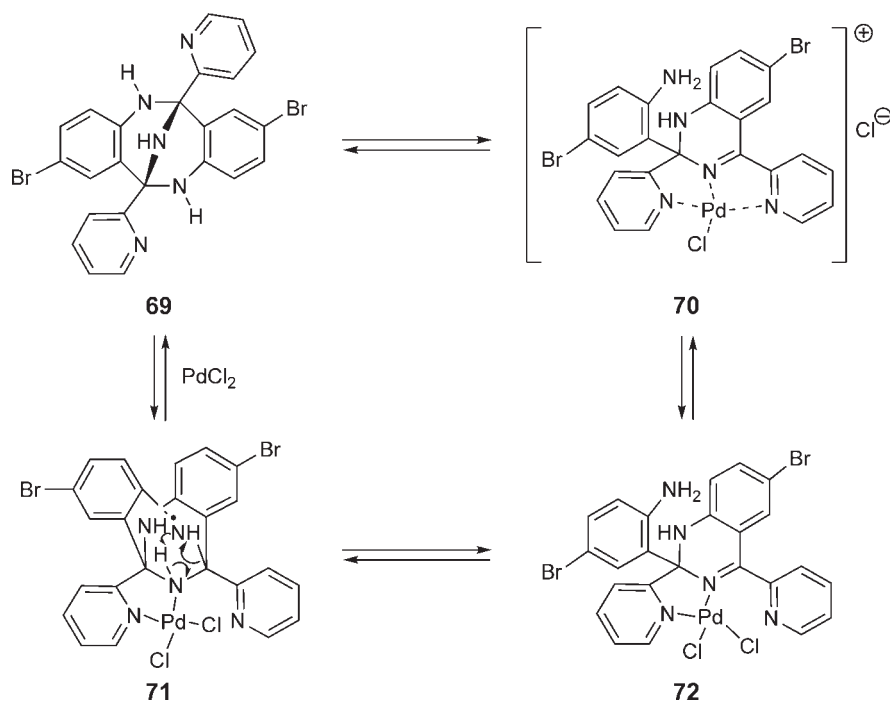
The *N,N*-dialkyl-1,5-diazocine analogues of **37a** reacted with perchloric acid to give the corresponding alkylammonium perchlorate <1996JME2559>. In other cases, the reaction with acid brought about transformation of the ring or further reaction with nucleophiles.

Treatment of the thiophene congener of Tröger's base **15a** with HCl in refluxing MeOH furnished the dithienopyridine **73**. Although the mechanism of such a rearrangement was not clarified, the intervention of a quinone-imine-methide intermediate was suggested (Equation 3) <2002J(P1)1963>.

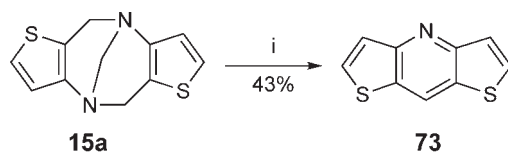
When the alkaloid caracurine V **74**, was treated with TFA instead of the expected bisnortoxiferine furnished in good yield the *iso*-caracurine V **75**, as a result of the cleavage of one of the oxepine rings (Scheme 11) <2003JNP119>.

Protonation with HClO₄ of 2-(*p*-tolyl)-2,3-didehydrosparteine **76** resulted in the formation of an immonium bond gave **77** which, upon reaction with cyanide ion, led to the introduction of the cyano group in position 2 of the sparteine system affording **78** (Scheme 12) <2004JST(688)111>.

Subjecting the diazepinodiazocinedione **79** to acid hydrolysis with dilute HCl gave the 13-membered triazacycloundecanetrione **80**, as the only product. Catalytic hydrogenation of **79** produced the perhydridiazepinodiazocinedione **55** in moderate yield (Scheme 13) <1995H(41)1709>.

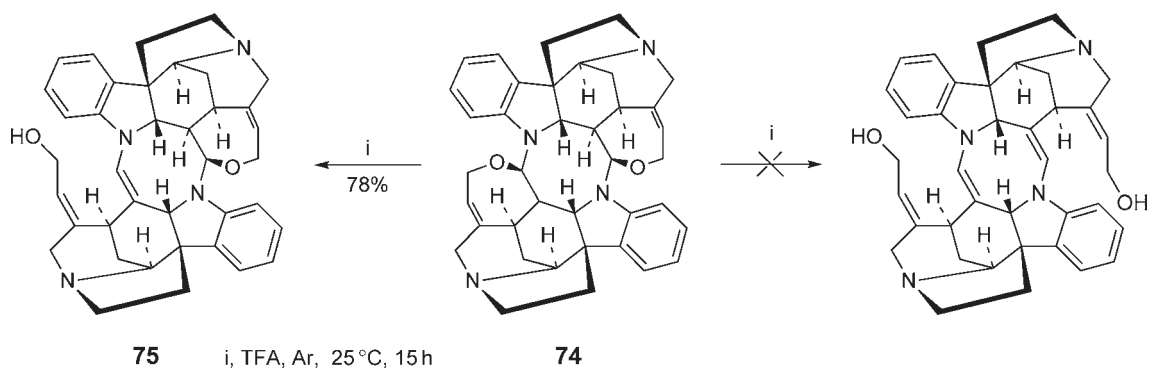


Scheme 10

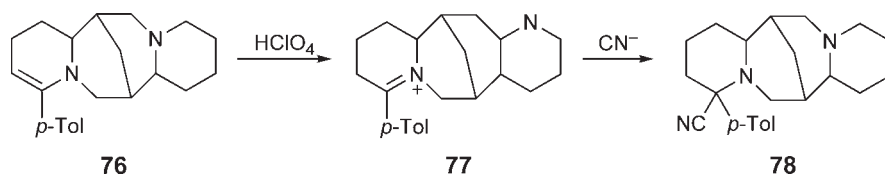


i, HCl (35%), MeOH, reflux, N₂; 19 h

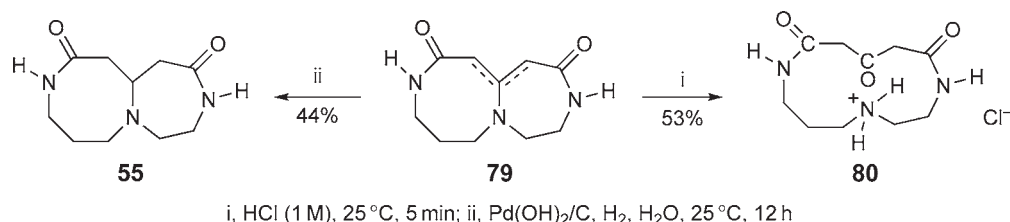
(3)



Scheme 11

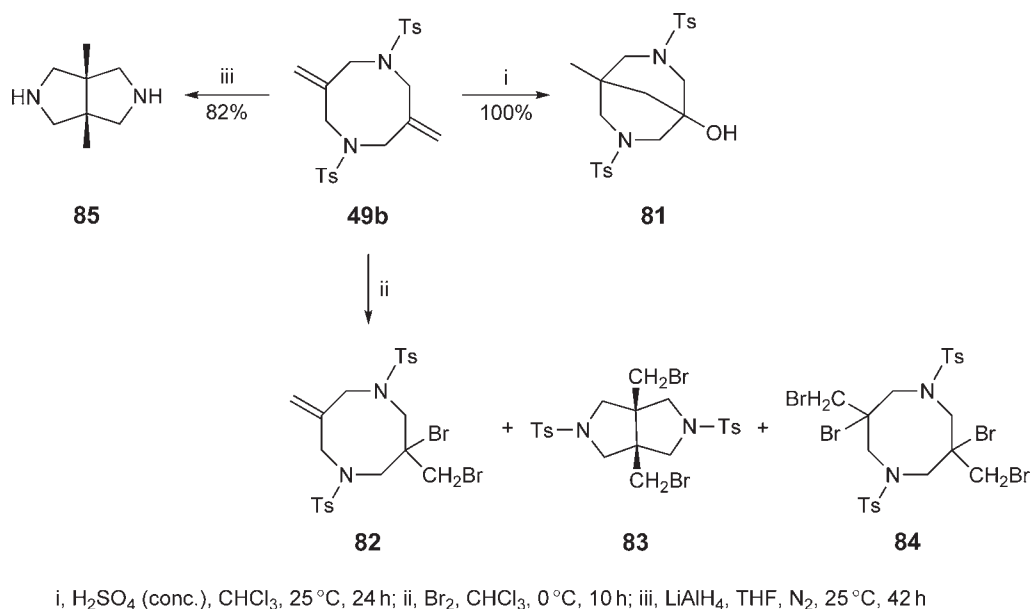


Scheme 12



Scheme 13

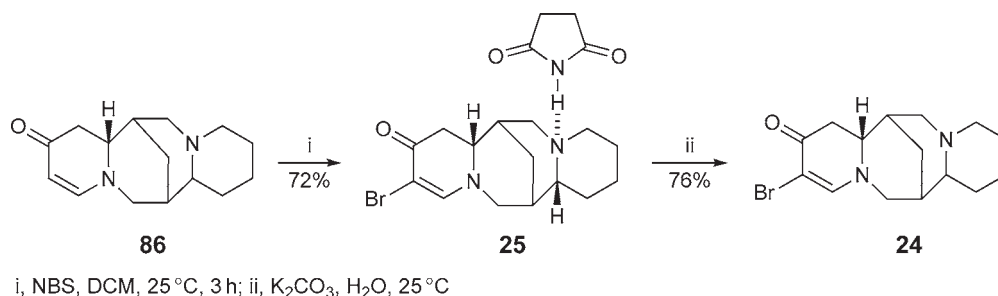
Treatment of **49b** with sulfuric acid quantitatively gave the methylene-bridged diazocine **81**, which was derived from protonation of the exocyclic methylene, nucleophilic attack of the other methylene forming the bridge and lastly addition of water. Reaction of **49b** with Br₂ produced an unexpected mixture of the 1,2- **82** and 1,4-dibromo **83** addition products together with very small quantities of the tetrabromide **84**. The relative amounts of **82** and **83** were sensitive to the reaction conditions. The rapid dropwise addition of a solution of a molar equivalent of Br₂ to **49b** afforded mainly **82** (ratio **82**:**83** = 88:12), whereas slow addition of the bromine reverses the situation leading to **83**, as the major product (68%), and **82** (30%). Attempts to convert **82** into **83** by heating in DMSO at 110 °C were unsuccessful, and the starting material was recovered [\[1996JOC8897, 1998USP5831099\]](#). Treatment of **49b** with LiAlH₄, in an attempted reductive detosylation to prepare the *N*-unsubstituted diazocine, furnished in good yield the 1,5-dimethyl-3,7-diazabicyclo[3.3.0]octane **85** upon a transannular bond formation (Scheme 14) [\[1996JOC8897, 1998USP5831099, 2002WO44168\]](#).



Scheme 14

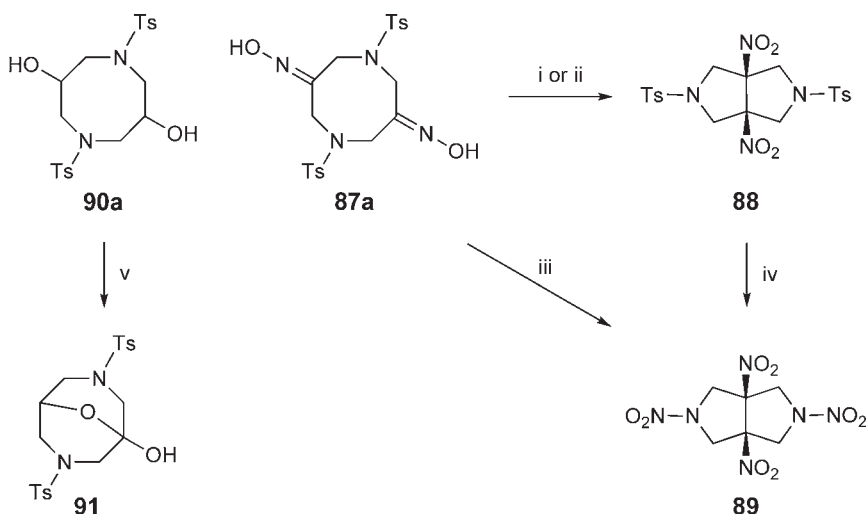
In the bromination of multiflorine **86** with NBS, a regiospecific C-3 bromination took place and unexpectedly the formation of the complex of 3-bromofluorine with succinimide **25** was observed. The free 3-bromomultiflorine **24** was obtained upon action of base (Scheme 15) [\[1998JST\(442\)103\]](#).

Treatment of the stereoisomeric mixture of dioximes **87a** with either NBS in aqueous dioxane or with MCPBA in a buffered medium led to the formation of a transannular bond to give **88** in 48 and 24% yields, respectively. Nitrolysis with 100% HNO₃ of **87a** led to the tetranitro derivative **89** in 25% yield.



Scheme 15

In this reaction, considerable nitration of the tosyl groups was observed. The bicycle **89** was obtained in better yield (36%) from **88** by reaction with trifluoroacetyl nitrate in DCM [\[1996JOC8897, 1998USP5831099\]](#). Swern oxidation of the dihydroxy diazocine **90a** led to the oxygen-bridged hydroxyl diazocine **91** by transannular hemiketalization ([Scheme 16](#)) [\[1996JOC8897\]](#).



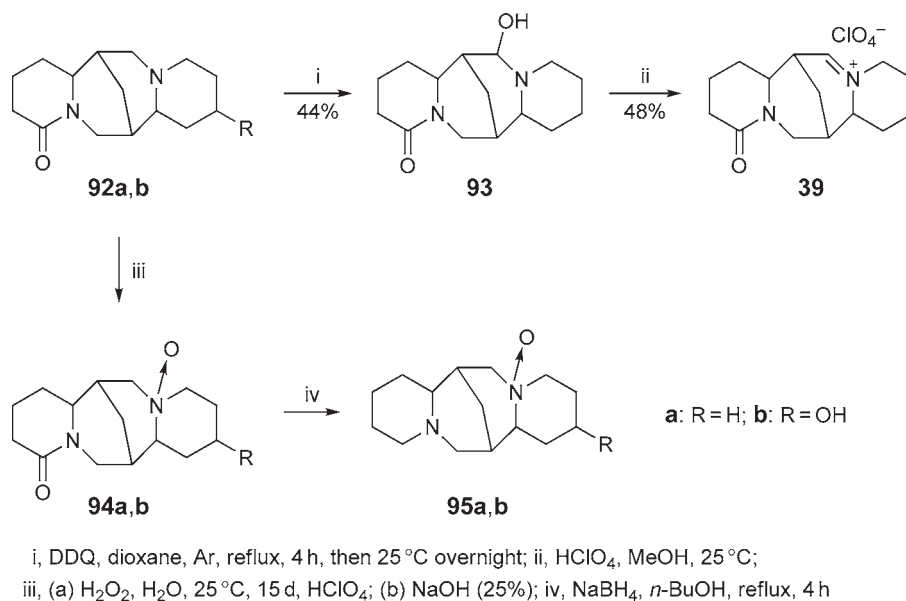
i, NBS, NaHCO₃, dioxane/H₂O (95:5), 25 °C, 4 h; ii, urea, Na₂HPO₄, MeCN (anhydrous), reflux, 10 min then MCPBA, reflux, 2 h; iii, HNO₃ (98%), DCM, reflux, 1 h; iv, HNO₃ (100%), TFAA, DCM –10 °C, 3 h; v, oxalylchloride, DMSO, NEt₃, –78 °C

Scheme 16

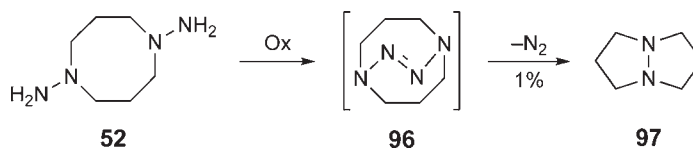
Action of DDQ on lupanine **92a** produced the 13-hydroxylupanine **93** in moderate yield. The free base **93**, upon action of HClO₄ gave the 13-dehydrolupaninium perchlorate **39** [\[2000M1073\]](#). Oxidation of lupanine **92a** and its 13-hydroxy derivate **92b** with H₂O₂ led to the corresponding *epi* *N*-oxides **94a,b**. Sparteine *epi* *N*-oxide **95a** and 13-hydroxysparteine *epi* *N*-oxide **95b** could be prepared by reduction with NaBH₄ of the 2-carbonyl group of the corresponding lupanine derivatives **94a,b**.

This route has to be preferred over the oxidation of sparteine with H₂O₂ since in this latter synthesis the expected *epi* *N*(16)-oxide was isolated along with the *epi* *N*(1)-oxide in ratio 3:1 ([Scheme 17](#)) [\[2003JST\(647\)275\]](#).

The 1,5-diazabicyclo[3.3.0]octane **97** was obtained, in very poor yield, by the oxidation of *N,N*-diamino-1,5-diazocine **52** through the probable intermediacy of tetrazene **96**. The oxidation was performed with different reagents: K₃Fe(CN)₆ in aqueous KOH; HgO (red) in DCM; Pb(OAc)₄ in DCM. The formation of nitrogen-rich polymeric products, which might indicate intermolecular 2-tetrazene formation, was observed ([Scheme 18](#)) [\[1998EJO1431\]](#).



Scheme 17



Scheme 18

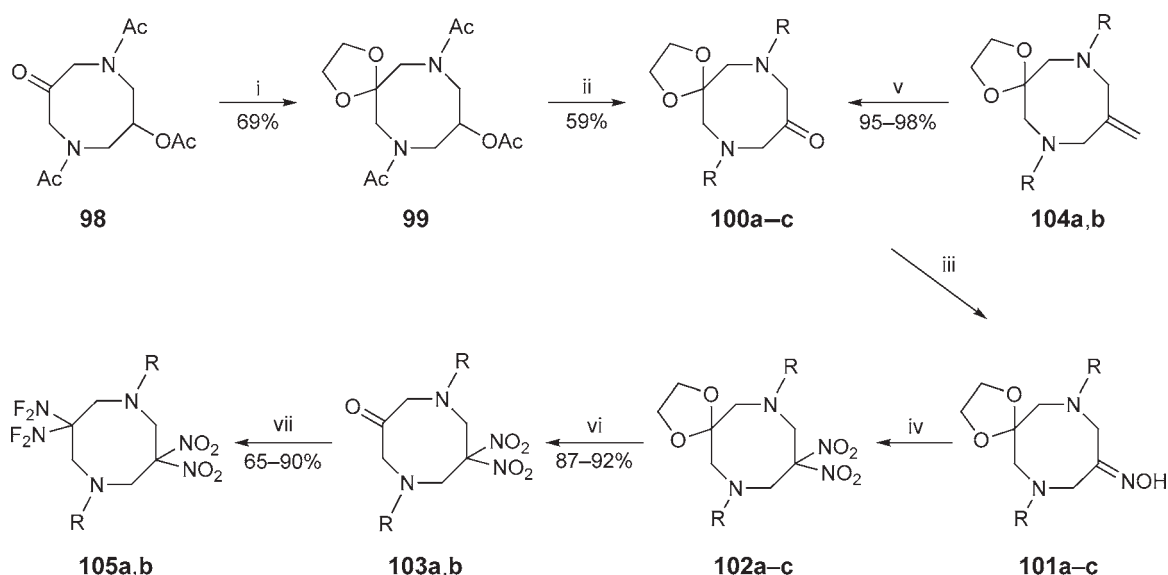
14.07.2.5 Reactivity of Substituents Attached to Ring Carbon Atoms

The synthetic approaches to *gem*-dinitro-*gem*-bis(difluoroamino)octahydrodiazocines **105**, key intermediates for the synthesis of explosives and solid propellant oxidizers, are outlined in [Scheme 19](#). In the first approach, ketone **98** was subjected to a sequence of transformations to give oxime **101c** in 40% overall yield. The 1,3-dioxolane protection of the keto functionality in the latter oxime was employed to avoid transannular reactions and, under these conditions, smooth conversion of oxime **101c** to the corresponding *gem*-dinitro derivative **102c** took place in moderate yield (36%).

However, under various conditions, deprotection of **102c** to the corresponding ketone **103** proved impossible. Alternatively, ozonolysis of the *exo*-methylene-1,5-diazocines **104a,b** led to monoprotected 1,5-diazocines **100a,b** in excellent yields. Oximation followed by HNO₃ oxidation of **101a,b** afforded the *gem*-dinitro derivatives **102a,b** in 30–45% yields; hydrolysis of the latter produced the desired 1,5-diazocinones **103a,b**. The *gem*-bis(difluoroamino) diazocines **105a,b** were obtained by a modified difluoroamination of **103a,b** with difluoroamine-difluoro-sulfamic acid in sulfuric acid <2001TL2621, 2002USP6417355>. The intermediate **100a** was obtained in 85% yield from the corresponding alcohol by oxidation with CrO₃ in H₂SO₄ at 25 °C in acetone/water medium <2006JHC519>.

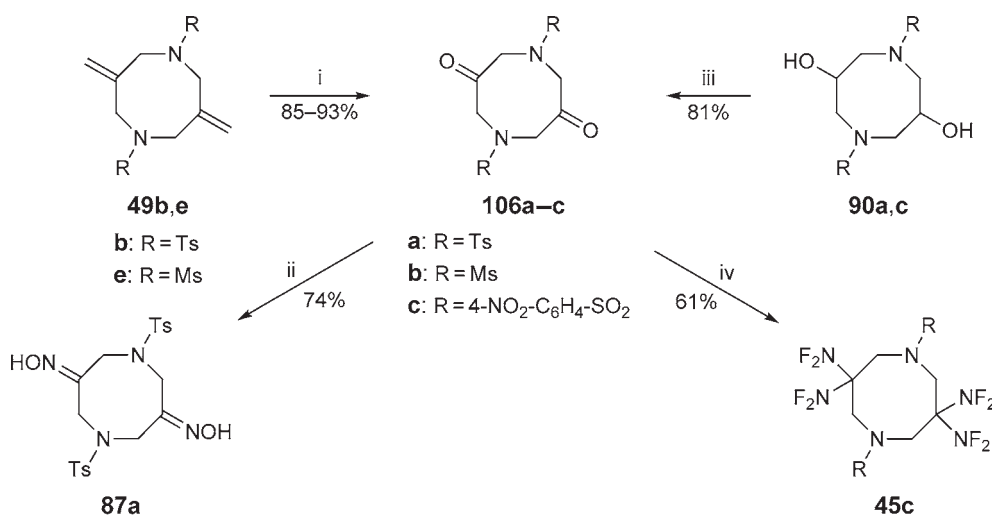
Under similar reaction conditions, bis-methylene-1,5-diazocines **49b,e** underwent ozonolysis to give the corresponding 1,5-diazocinediones **106a,b** in excellent yields. One of these, **106a**, was converted into the dioxime **87a** in good yield <1996JOC8897, 1998USP5831099>. Diazocinedione **106c** was efficiently obtained from the corresponding diol by oxidation with 100% HNO₃/TFAA. Diazocinedione **106c** was transformed into the 3,3,7,7-tetrakis(difluoroamino)diazocine **45c**, another key intermediate for the synthesis of solid fuel propellant oxidizers. The reaction

was conducted with $\text{HNF}_2/\text{oleum}$ and represented a method to reduce the time to produce **45c** to 1–3 days and the need to use relative large quantities of FREON[®] 11 (Scheme 20) <2006USP7145003>. Diazocinediones **106a,c** were obtained from a Swern oxidation of the corresponding diol **90a,c** in excellent yield (75% for **106a**, isolated as hemiacetal, and 94% for **106c**) <1998JOC1566>.



i, ethylene glycol, TsOH, benzene; ii, (a) K_2CO_3 , MeOH, 25 °C, (b) Jones reagent, 0 °C; iii, $\text{NH}_2\text{OH} \cdot \text{HCl}$, NaOAc, MeOH (**a**) or EtOH (**b–c**) reflux; iv, HNO_3 , NH_4NO_3 , urea; v, (a) O_3 , DCM, –78 °C, (b) Me_2S ; vi, H_2SO_4 (conc), 25 °C; vii, $\text{HNF}_2/\text{F}_2\text{NSO}_3\text{H}/\text{H}_2\text{SO}_4$, CFCI_3 , –15 °C

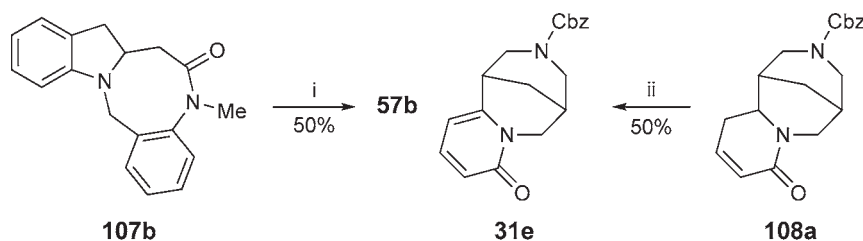
Scheme 19



i, O_3/O_2 , DCM, –78 °C, 1 h; ii, $\text{NH}_2\text{OH} \cdot \text{HCl}$, NaOAc, MeOH, reflux 5 d; iii, HNO_3 (100%) TFAA, DCM, –10 °C, 2 h, then 0 °C, 8 d; iv, $\text{HNF}_2/\text{oleum}$, pentane, –5 to 10 °C, 3 d

Scheme 20

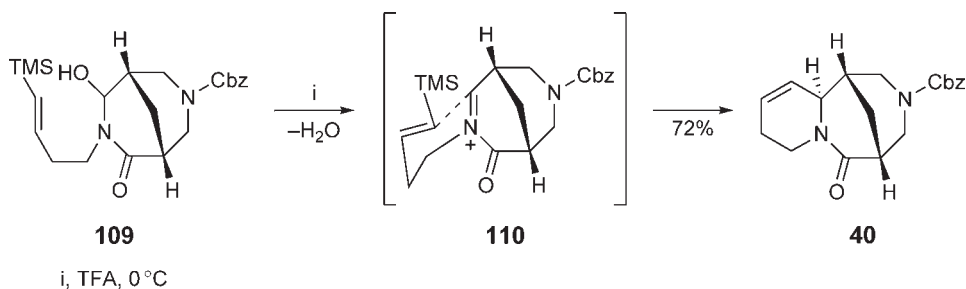
Other examples of oxidation of substituents attached to ring carbon atoms of 1,5-diazocine were observed in the aromatization of the indole moiety of **107b** to give in moderate yield the corresponding indolobenzodiazocine **57b** <2005T941> and the dehydrogenation of the C(5)–C(6) positions of *N*-Cbz dihydrocytisine **108a**, conducted with DDQ in refluxing dioxane to give the *N*-Cbz-cytisine **31e** in 50% yield. Attempts to improve this moderate yield by increasing the reagent and reaction time were unsuccessful (Scheme 21) <2004OL493>. Also changing the *N*-substituents did not help. In fact, under the same reaction conditions *N*-benzyl-dihydrocytisine gave no *N*-benzylcytisine and oxidation with MnO_2 in refluxing benzene yielded only 6% of *N*-benzylcytisine. Instead, oxidation with 10% Pd/C in dioxane-cyclohexene at 100 °C furnished *N*-benzylcytisine in 41% yield <2005OL4459>.



i, Pd/C, toluene (dry), reflux, 8 h; ii, DDQ, dioxane, N_2 , reflux, 4 h

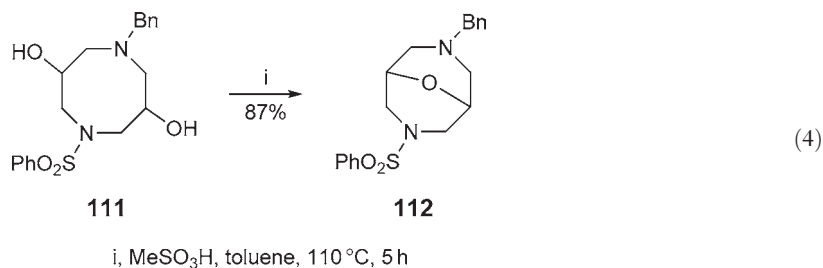
Scheme 21

Treatment of the hydroxylactam **109** with TFA provided tricyclic derivative **40** as the sole product in good yield, isolated as single (6*S*) stereoisomer. The formation of such a stereoisomer was consistent with *N*-acyliminium ion **110** undergoing cyclization only from the convex, sterically less hindered face of this intermediate through a chair-like transition state (Scheme 22). The same sort of cyclization was observed when the $\text{CH}=\text{CH}\text{-TMS}$ portion of **109** was replaced by a terminal alkyne. The cyclic analogue of **40**, possesses a carbonyl group instead of a double bond in γ position with respect to the N of the six-membered ring. <2001EJO1377>.



Scheme 22

A further cyclization brought about by a protonation of a hydroxyl group was furnished by the conversion of the 3,7-dihydroxydiazocine **111** into the oxygen-bridged diazocine **112** by transannular nucleophilic attack of the 3-hydroxyl group of **111** on the C-7 carbon bound to a hydroxyl protonated by the methanesulfonic acid (Equation 4) <2002WO083690, 2002WO083691>. Treatment of 1,5-diazocine bearing an amino group protected with a BOC moiety with TFA, as expected, gave the eight-membered rings bearing the free amino group in excellent yields <1999SL1875, 2005BML4291>.



Nitration of cytosine **31a** led to 3-nitrocytosine **113a** in 77% yield and to 5-nitrocytosine **114a** as a minor product (11%). Treatment of **113a** with Ac₂O quantitatively led to the corresponding acetyl derivative **113f**, which was nitrated to afford **115f** in 70% yield. Catalytic hydrogenation of *N*-acetyl-3-nitrocytosine **113f** quantitatively gave the corresponding amine **116f**, which was diazotized to obtain the diazonium fluoborate salt **117f** in 71% yield <2000OL1121>. Halogenation of cytosine and its *N*-substituted derivatives led to a mixture of 3- and 5-monohalo- and 3,5-dihalocytosine derivatives depending on the substrate, on the molar ratio of the halogenating agent, and on solvent. Thus, halogenation of cytosinium acetate **118**, prepared *in situ* using aqueous AcOH (60%), as the solvent, was conducted using NCS, NBS and ICl as halogen transfer reagents.

Using an excess of the halogenating agent, a twofold substitution of the 3- and 5-positions occurred, leading, nearly quantitatively, to the dihalocytosine **119a–c**. When only one molar equivalent of the halogen transfer reagent was employed, a mixture of the three halogenated products was obtained with the monosubstituted species **120** and **121** predominating. In particular, chlorination led to **119a** (5%), **120a** (26%), and **121a** (40%). Bromination led to **119b**, **120b**, and **121b** in 5%, 27%, and 27% yields, respectively. Iodination led to **119c**, **120c**, and **121c** in 1%, 35%, and 19%, respectively. All three series were converted into the stable hydrogen fumaric salts **122–124** <2001EJM375>. Bromination of *N*-carbamoylcytosine **31g** with NBS in DMF gave the 3-bromo **125g**, as the major (57%) product and 5-bromo **126g** (17%). The ratio of the 3- and 5-regioisomers was shown to be strongly dependent on the solvent [relative ratio **125c/126c/127c**: 73/23/2 (DMF), 72/19/9 (MeCN), 65/31/4 (DCM), 75/18/5 (H₂O, H⁺), 85/15/0 (THF)]. Similar results were obtained when *N*-nitrosocytosine **31h** was treated with NBS. *N*-Nitrosocytosine **31h** when reacted with iodine in the presence of CF₃CO₂Ag gave *N*-nitroso-3-iodocytosine **128h** in 50% yield. The palladium-mediated coupling reactions of **125h** and **128h** with tetramethyltin, tri-*n*-butylallyltin, tri-*n*-butylvinyltin or tetravinyltin were conducted at different temperatures (60–120 °C), times (0.25–48 h) and solvents (HMPA, DMF, dioxane) using ClPdBn(PPh₃)₂, PdCl₂(MeCN)₂, or PdCl₂(PPh₃)₂, as catalyst. Thus, *N*-nitroso-3-methylcytosine **130h** was obtained in 81% yield when the cross-coupling reaction of tetramethylstannane with the bromo derivative **125h** was conducted at 120 °C using a short time (15 min). Under the same conditions, the coupling of tri-*n*-butylallylstannane with **125h** to give **132h** was less efficient (55%). The use of PdCl₂(PPh₃)₂ led to *N*-nitroso-3-vinylcytosine **133h** in 70% yield. Reaction of *N*-nitroso-3-iodocytosine **128h** with hexamethylditin in dioxane in the presence of Pd(PPh₃)₄ yielded *N*-nitroso-3-stannylcytosine **129h** in 70% yield, which with 4-fluorobromobenzene afforded *N*-nitroso-3-(4'-fluorophenyl)cytosine **131h** in yields up to 65–70%. Such a strategy allowed the preparation of the radioligand *N*-nitroso-3-(4'-¹⁸F-fluorophenyl)cytosine (Scheme 23) <2000OL1121>.

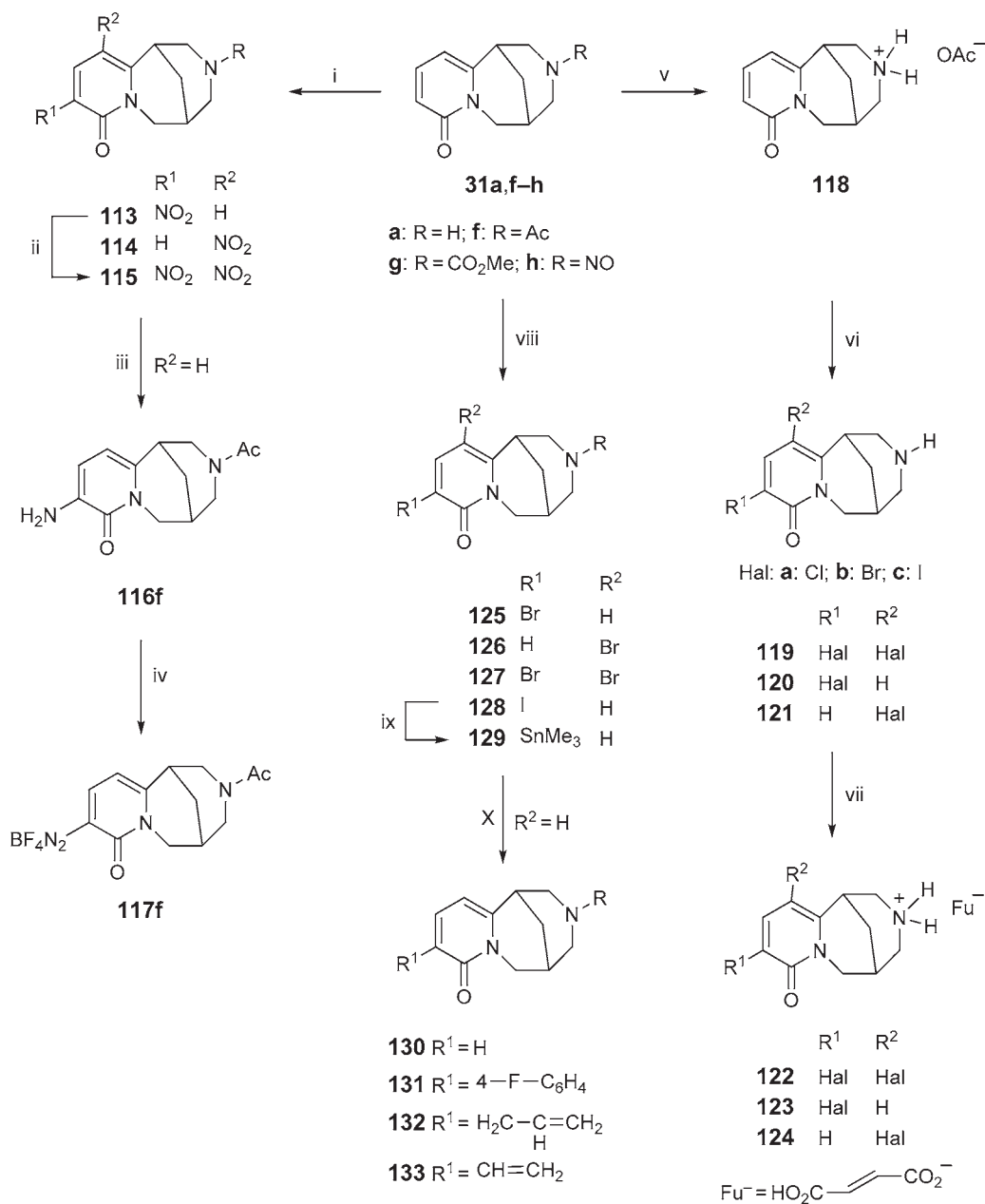
Another example of palladium-mediated coupling is provided by the Suzuki reaction of the pyrimidodiazocine **134**, which gave the arylated derivative **135** in nearly quantitative yield (Equation 5) <2005BMC5717>.

The macrocycles **138a–c** containing a Tröger's base unit were obtained in 20–32% yields by reacting the 2,8-dihydroxyethoxy analogue **136** with ditosylates **137a–c**. Addition of Cs₂CO₃ improved the yields but minimally (25–41%) (Equation 6) <1997T11859>.

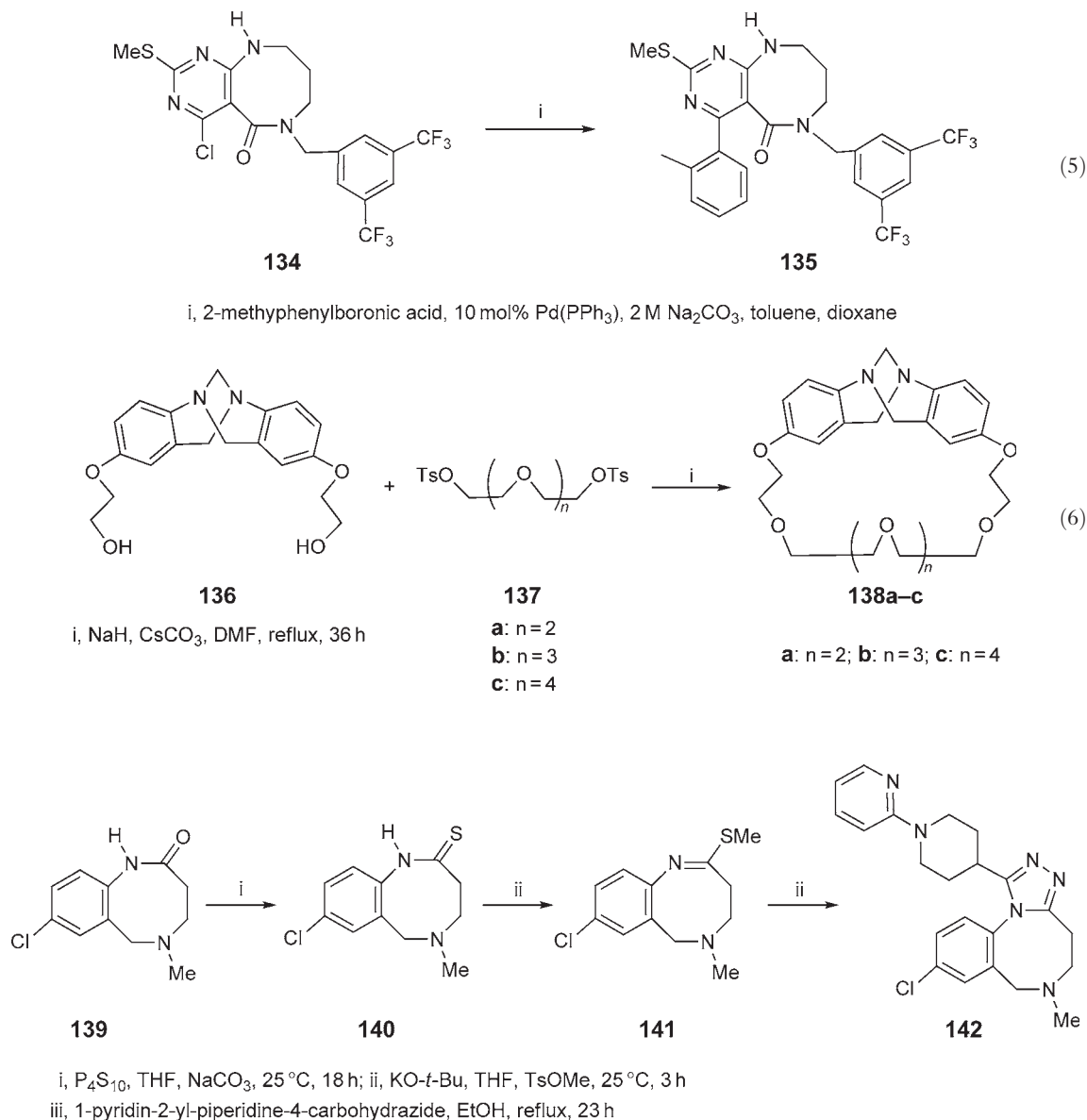
The benzodiazocinone **139** reacted with P₄S₁₀ to give in 40% yield the corresponding thiocarbonyl derivative **140**, which was converted quantitatively into the thiomethyl derivative **141** by action of *t*-butoxide and methyl tosylate. The thioether underwent annelation of the triazole ring on the 1,2-positions of the diazocine moiety by reaction with 1-pyridin-2-yl-piperidine-4-carbohydrazide to give the tricyclic diazocine **142** in low yield (25%) (Scheme 24) <2004WO074291>.

In another case, instead of methyl tosylate, for the methylation of a hydroxyl group diazomethane was used <2003S2518>.

Another example of conversion of a carbonyl into a thiocarbonyl is provided by dibenzodiazocinone **32** which, upon reaction with Lawesson's reagent, furnished the dithiocarbonyldiazocine **33** in 91% yield <2004JOC1248>.



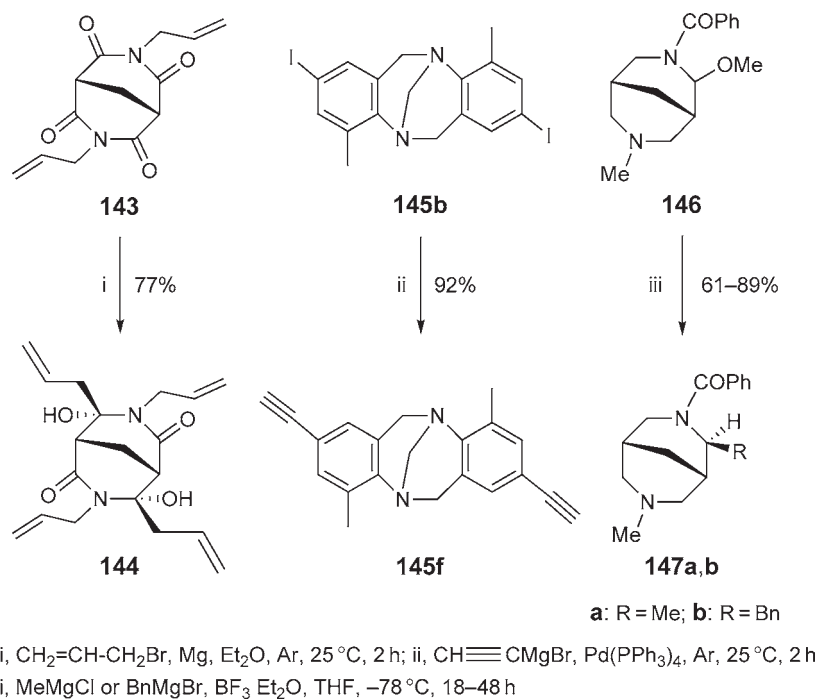
Corriu–Kumada cross coupling gave the diethynyl derivative **145f** in excellent yield <2001S1873>. Reaction of the α -methoxy bispidine amide **146** with MeMgCl or benzylmagnesium bromide, in the presence of Et₂O·BF₃, resulted in the replacement of the methoxy group by the methyl and benzyl groups to give **147a,b** in good yields (Scheme 25) <2000TL6167>.



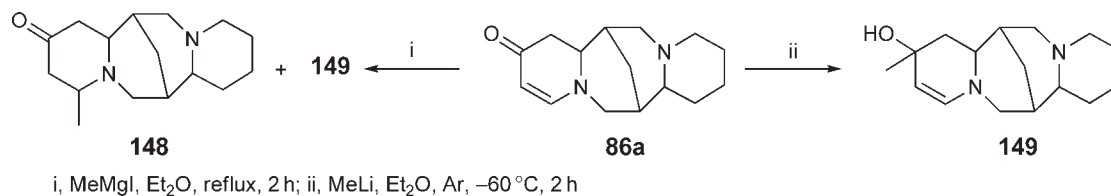
Scheme 24

Reaction of multiflorine **86a** with MeMgI gave the (2*S*)-2-methyl-4-oxosparteine **148** as major product (47%) as a result of a 1,4-addition and (4*S*)-4-hydroxy-4-methyl-2,3-didehydrosparteine **149**, as minor product (15%) following a 1,2-addition. Instead, reaction of **86a** with MeLi gave exclusively the 1,4-addition product in 77% yield (Scheme 26) <1995M233>.

Reaction of *N*-propionylcytisine **150** with LDA, in THF at –78 °C, followed by addition of benzyl bromide led mainly to the recovery of the starting material (78%) along with **150a** (20%). The mechanism proposed for the formation of **150a** involved the initial formation of the pyramidal carbanion at the position α to the pyridone ring **154**. Such a carbanion might attach the carbon atom of the amide function to give a strained five-membered ring, **155**.



Scheme 25



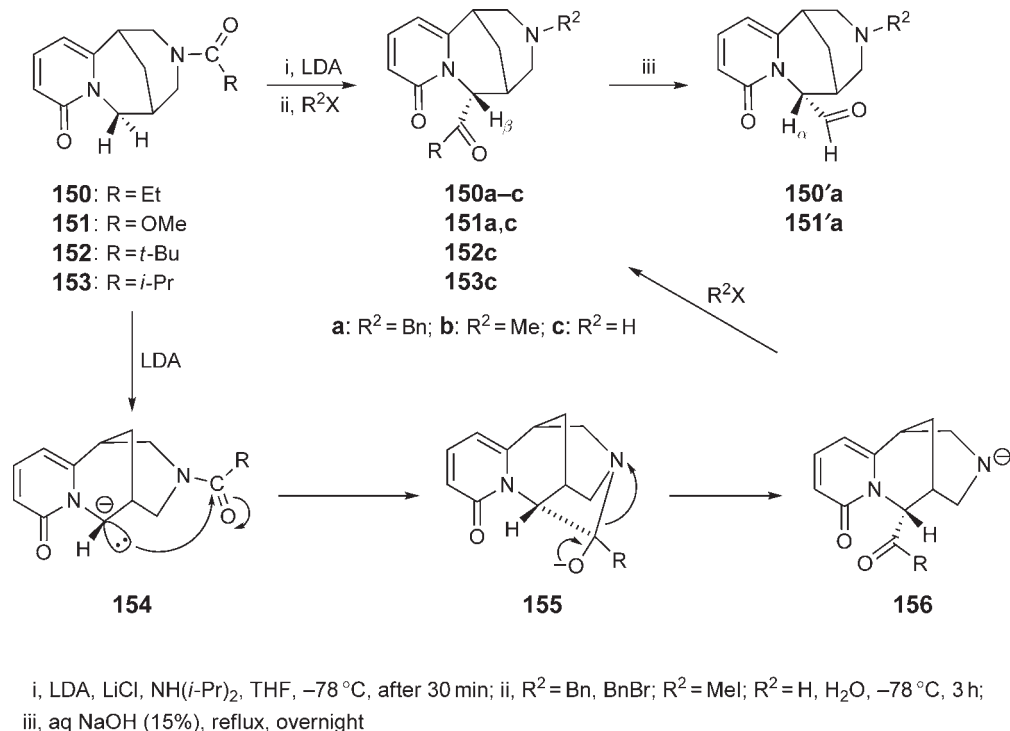
Scheme 26

This intermediate would then be stabilized by transferring the acyl group to the 10-position to give **156**. The lithiated amine would then be alkylated by benzyl bromide to afford the *N*-benzyl-10-propionylcytisine **150a**.

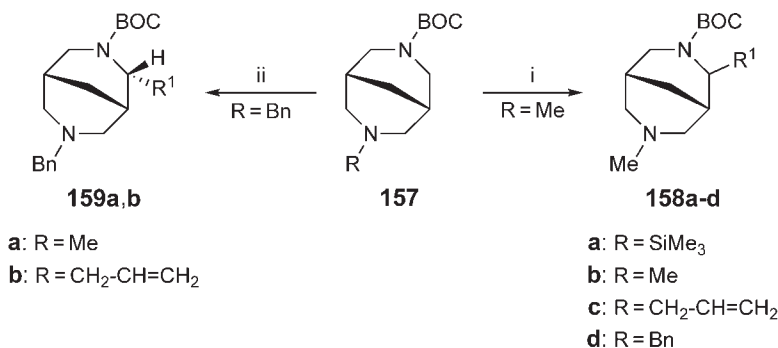
Optimization of the reaction by increasing the amount of LDA or adding a co-solvent failed. However, the addition of 5–6 molar equivalents of LiCl to the reaction mixture before deprotonation led to a complete conversion and a 75% isolated yield of the rearranged **150a**. The acyl migration of various amides and different electrophiles was examined and it was observed that **150** upon quenching with MeI or water afforded **150b,c** in 51–70% yield. Also branched alkylcarbonyl groups were transferred with good yields and **152** and **153** furnished **152c** and **153c**, respectively, in 57–65% yield.

Surprisingly, *N*-acetyl- and *N*-benzoyl-cytisine gave no rearranged product but only an inseparable mixture of compounds. Also a methoxycarbonyl group migrated efficiently and **151**, upon quenching with benzyl bromide or water, gave the rearranged products **151a,c** in 65–79% yield. The *N*-benzylcytisine **150a** and *N*-methyleytisine **151a** were completely epimerized to their thermodynamically more stable 10 β -derivatives **150'a** and **151'a**, under basic nonhydrolytic conditions in 85% and 57% yields, respectively (Scheme 27) <2002TA1299>.

The lithiation of *N*-BOC bispidine **157** and subsequent reaction with electrophiles were studied using different solvents, lithiation times, and solvents. The best yields of derivatives **158** were obtained using cyclopentane as solvent, using 1.3 equiv of *s*-BuLi, and 7 h as lithiation time. This procedure generated **158a–d** as single diastereoisomers and afforded **158a,b** in good yields (61–71%) but, when more hindered electrophiles were employed, low yields of adducts were obtained (**158c,d**: 20–24%) (Scheme 28) <2000TL6161>. In the case of **157** (R = Bn) the best conditions to obtain the methyl adduct **159a** involved Et_2O as solvent, 1.6 equiv of *s*-BuLi/TMEDA.



Scheme 27

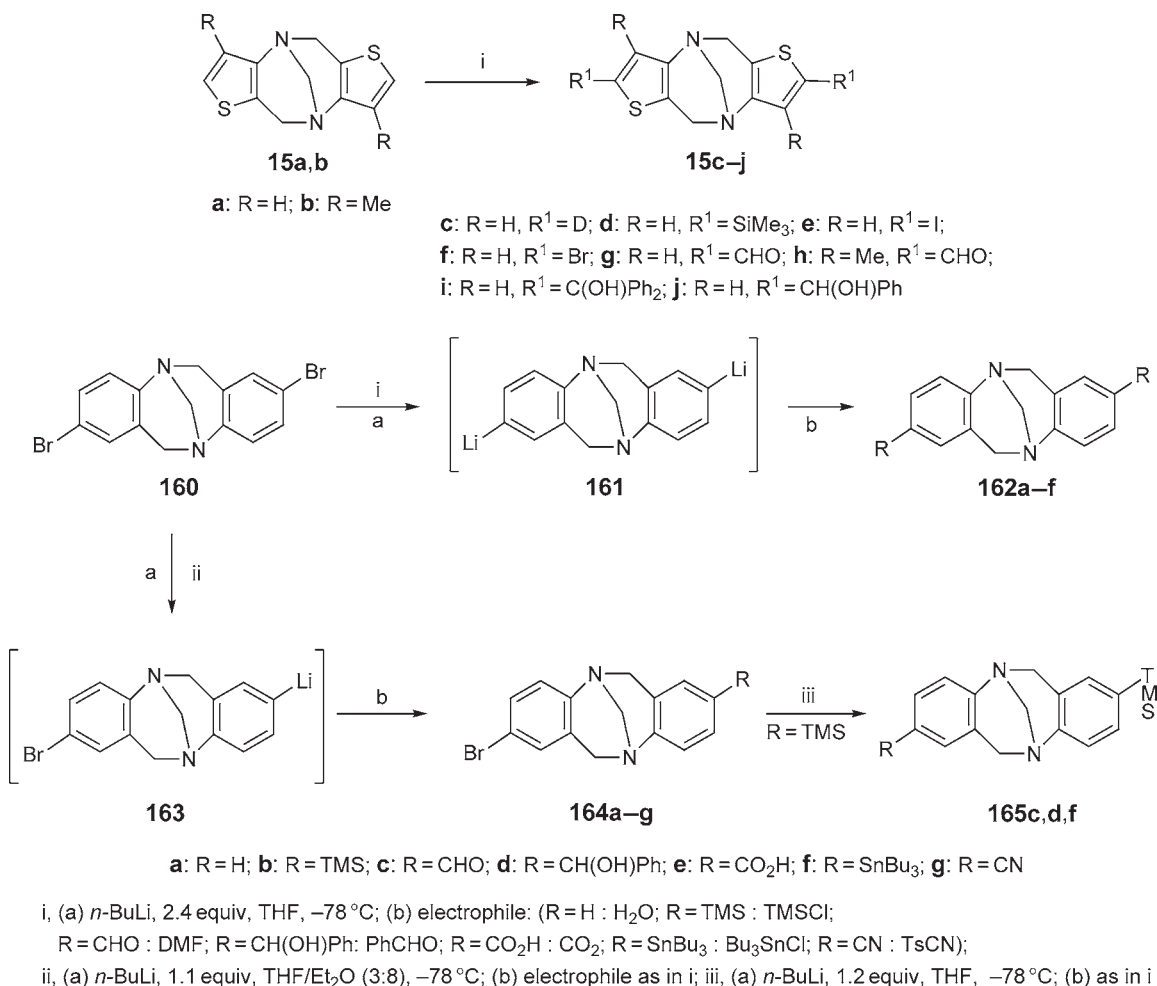


Scheme 28

When the lithiation time was 5 h, the yield of **159a** was 47% along with 43% of unreacted starting material; while with 7 h of lithiation time, the yield of the adduct was 58% along with starting material (24%). Direct allylation of the organolithium reagent generated from **157** (R = Bn) with allyl bromide afforded only 5% of **159b**. The yield was increased to 60% when a transmetalation from lithium to copper was performed using either 0.5 or 1.0 equiv of CuCN·2LiCl, and allyl diphenyl phosphate, as electrophile (Scheme 28) <2005OL4459>.

Reaction of the thiophene analogue of the Tröger's base **15a** with 3 molar equivalents of BuLi, followed by quenching with D₂O, resulted in the regioselective formation of 2,7-dideuterio derivative **15c** in 53% yield.

Under similar conditions, treatment of **15a** with Me_3SiCl , I_2 or NBS provided the 2,7-disubstituted derivatives **15d**, **15e**, and **15f**, respectively in 24–31% yield. The formylation of **15a** with DMF seemed to be more effective and the 2,7-dicarbaldehyde **15g** was obtained in 59% yield. Similarly, **15b** afforded **15h** in 53% yield, suggesting that the presence of the methyl groups did not affect the formation of the dianion. Treatment of **15a** with benzophenone produced **15i** in 51% yield and when benzaldehyde was used as an electrophilic reagent, two diastereoisomers were formed: one with C_2 symmetry and the other without a symmetrical axis (**Scheme 29**) <2002J(P1)1963>.

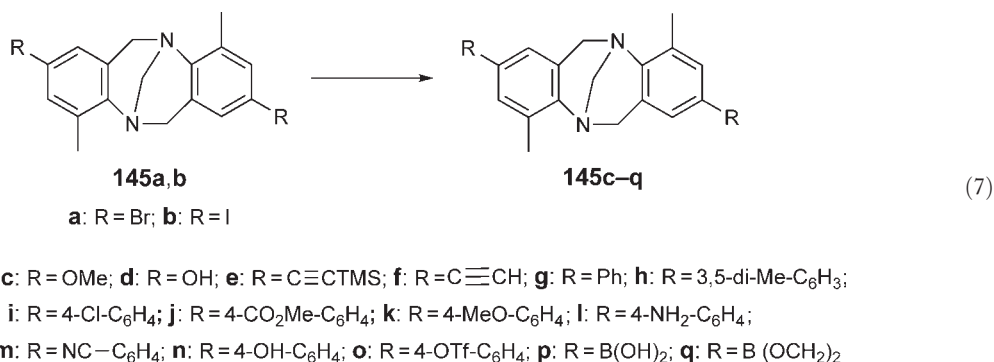


Scheme 29

When the 2,8-dibromo-dibenzodiazocine analogue of the Tröger's base **160** was treated with 2.4 equiv of BuLi in 5 min, the double bromine–lithium exchange giving **161** was complete and quenching with several electrophiles led to the C_2 -symmetric 2,8-disubstituted analogues **162a–f** in 54–89% yields. When **160** was reacted with 1.1 equiv of BuLi, a single bromine–lithium exchange occurred giving intermediate **163** which by quenching by electrophiles gave the unsymmetrical analogues **164a–g** in good yields (60–82%). Further bromine–lithium exchange quenching with electrophiles was conducted on **164b** and **165c,d,f** permitted the introduction of two different substituents, not bromine, into the Tröger's base core (**Scheme 29**) <2002JOC6008>. Single bromine–lithium exchange performed on **160**, followed by quenching with TsN_3 produced the azido derivative **164** (R = N₃), which was reduced to the corresponding amino group and isolated as hydrochloride <2005OL2019>. When the 2,8-dimethyl-dibenzodiazocine

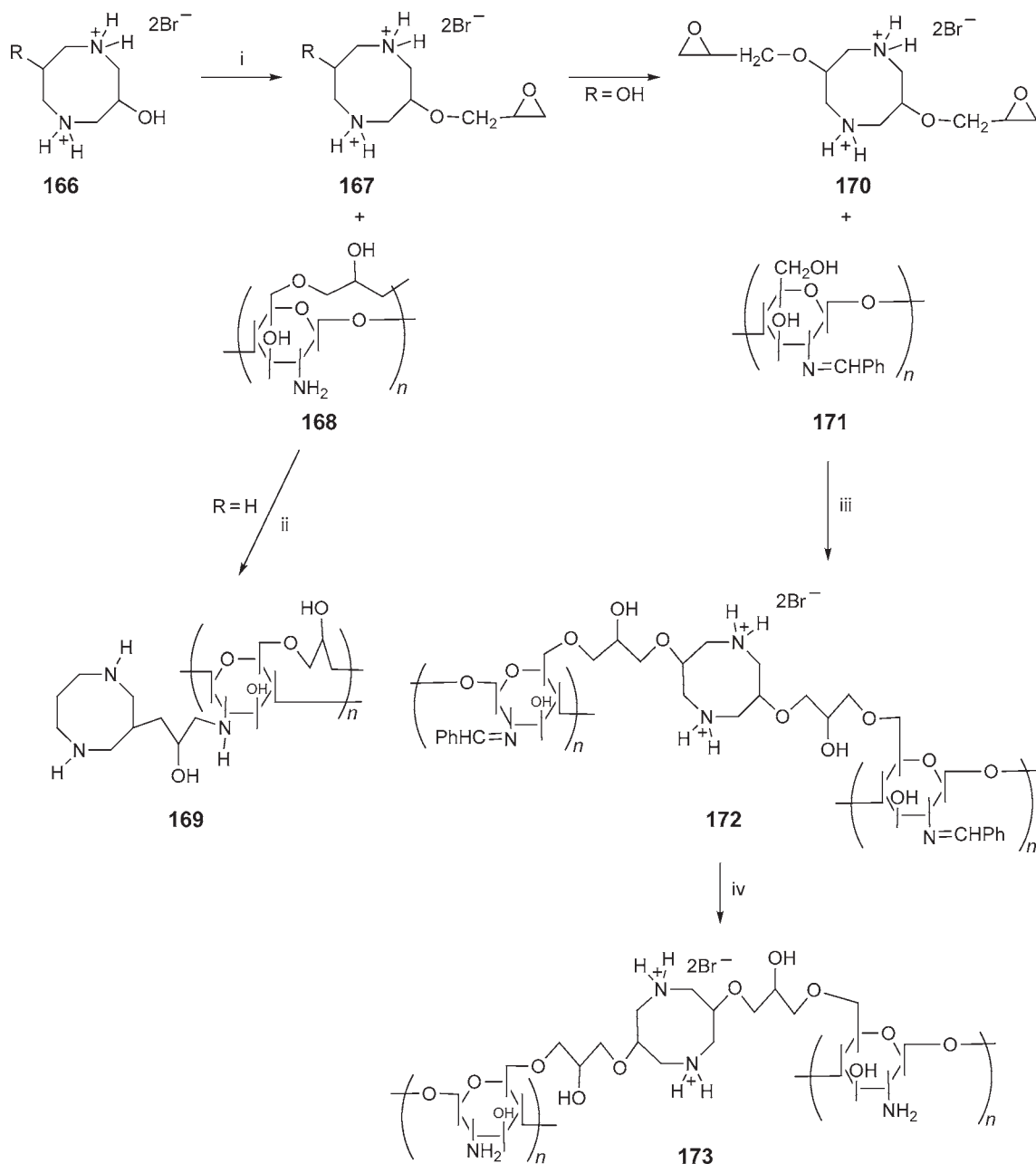
analogue of **160** was treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at 0°C followed by treatment of *n*-BuLi gave an intermediate which reacted with electrophiles, such as benzophenone or 1,1-diphenylethylene oxide to furnish the corresponding 6-substituted derivatives <2000TA2875>.

Dibromo and diiodo derivatives **145a,b** were versatile starting materials for the preparation of elaborated derivatives of Tröger's base using cross-coupling conditions like Ullmann, Sonogashira or Suzuki reactions. Thus, treatment of **145b** with NaOMe under Ullmann conditions gave **145c** in nearly quantitative yield. Subsequent deprotection of **145c** with BBr_3 gave the 2,8-dihydroxy derivative **145d** (93%). The dialkyne **145f** was obtained from **145a** or **145b** by a Sonogashira reaction with trimethylsilylacetylene, followed by deprotection of the TMS group (73% overall yield). Diaryls **145g,h** were obtained from both halogen derivatives **145** under Suzuki conditions in the presence of $[\text{Pd}(\text{Pt-Bu}_3)_2]$ and KF as the base in 65–91% yield. Under the same conditions **145b** reacted with 4-substituted phenylboronic acids in the presence of CsF to give **145i–k** in 85–97% yields. Derivative **145n** was synthesized in a similar way to **145d** and could be obtained from **145k** in quantitative yield. Reaction of **145n** with Trf_2O gave the triflate **145o** in moderate yield (45%). Since the above-described Suzuki reaction did not give access to **145l**, a different approach through a double bromine–lithium exchange of **145a**, formation of the diboronic acid derivative **145p** *in situ* by adding trimethyl borate and lastly treatment with 4-iodoaniline was undertaken. Through such protocol, **145l** was obtained in 88% yield. Similarly, the isolation of **145m** from 4-iodobenzonitrile was possible in 70% yield. Heating to reflux **145p** in a toluene/glycol mixture, the diboronic acid ester **145q** was obtained in 87% yield (Equation 7) <2004S1687>. The substitution of the iodo groups of **145b** by aryl-substituted acetylene moieties under Sonogashira conditions, in 46–91% yields, was reported <2002S2761>.



Perhydro-1,5-diazocines **166**, regarded as azacrown ethers, were reacted with chitosan, poly(D-glucosamine), for the synthesis of crosslinked chitosan, azacrown ethers, useful for their selectivity for metal ions. Thus, **166** both monohydroxy (R = H) and dihydroxy (R = OH) derivative reacted with 1 or 2 equiv of epichlorohydrin to give the mono- or diepoxide **167** and **170**, respectively. Monoepoxide **167** reacted with the chitosan derivative **168**, previously treated with epichlorohydrin to give in 82% yield the polymer **169**, by nucleophilic attack of the amino group at the epoxide ring of **167** <1999JAP3053>. The diepoxide **170** reacted with a chitosan **171** having the amino functionality protected with benzaldehyde, to avoid competitive nucleophilic attack by the amino group at the epoxide functionality of **170**. Thus, the hydroxymethyl group of two molecules of **171** reacted with the two epoxide moieties of **170** to give in 85% the polymer **172** which, upon acidic hydrolysis, restored the free amine group to afford **173** (Scheme 30) <2002JAP530>.

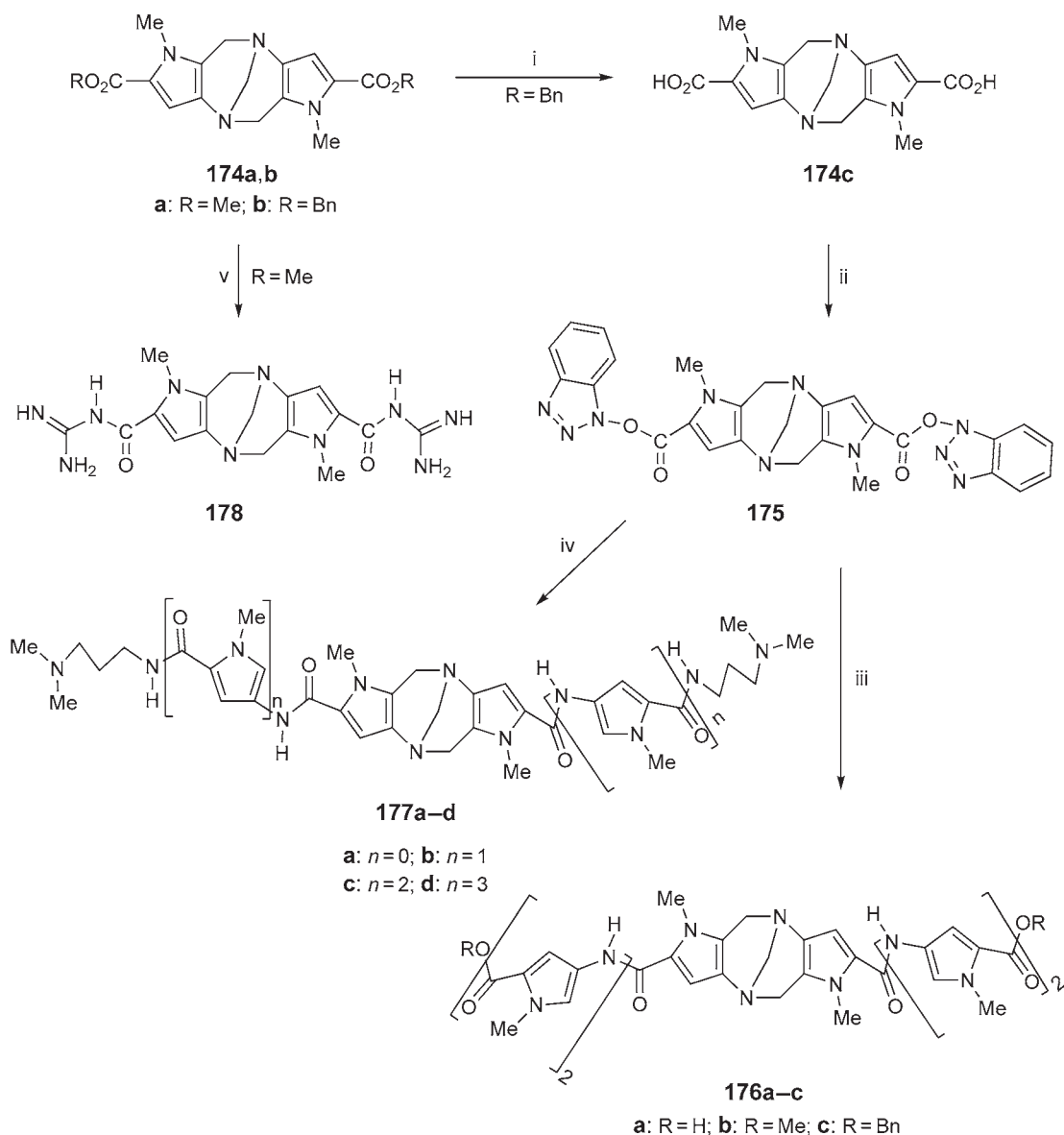
The dicarboxylic acid pyrrole analogue of the **174c** was obtained in 88% yield by the catalytic hydrogenation of the corresponding benzyl ester **174b**, while basic hydrolysis of the methyl ester **174a** led to partial degradation of the free dicarboxylic acid **174c**. However, acid **174c** was reacted with hydroxybenzotriazole to give the active ester **175** in 62% yield, which reacted with oligo-*N*-methylpyrrole peptide dimers bearing a carboxylate to give, in 30–60% yields, the bisdistamycin analogues containing a Tröger's base scaffold **176b,c**. The free acid **176a** was obtained by catalytic hydrogenation of **176c** in excellent yield (95%). Reaction of the active ester **175** with *N,N*-dimethylpropane-1,3-diamine gave in 91% yield, the bisdistamycin analogue **177a** while reaction of **175** with oligo-*N*-methylpyrroles with 1–3 units bearing a 3-dimethylamino-propylamide end gave **177b–d** in 39–72%. Reaction of the methyl ester **174a** with an excess of guanidine in the presence of methoxide gave the bisacylguanidine **178** in moderate yield (Scheme 31) <2003TL2083, 2006T8591>.



- i, TFA (60 ml), NaOH 5 ml (40%), epichlorohydrin (1 equiv for **167** and 2 equiv for **170**), MeOH, N₂, 45 °C, 48 h;
 ii, **168** in toluene, 25 °C, 8 h, then **167** in EtOH, reflux, 24 h; iii, **171** in DCE, 40 °C, 5 h, then **170** in EtOH, N₂,
 reflux, 14 h; iv, EtOH saturated with gaseous HCl

Scheme 30

The pyridinone moiety of cytosine **31a** was catalytically reduced with PtO₂ in water to give in nearly quantitative yield **179** (R = H) <2004JCO828>. The *N*-isopropylcytosine **31i** was reduced with the same reducing agent but in AcOH, as the solvent to give in 87% yield the tetrahydrocytosine **179** (R = *i*-Pr), which underwent further reduction with LiAlH₄ to give **180**, in excellent yield (94%) <2004EJO1894>. Similar reduction of the pyridinone moiety of *N*-alkylcytosine was reported <2004WO103991>.

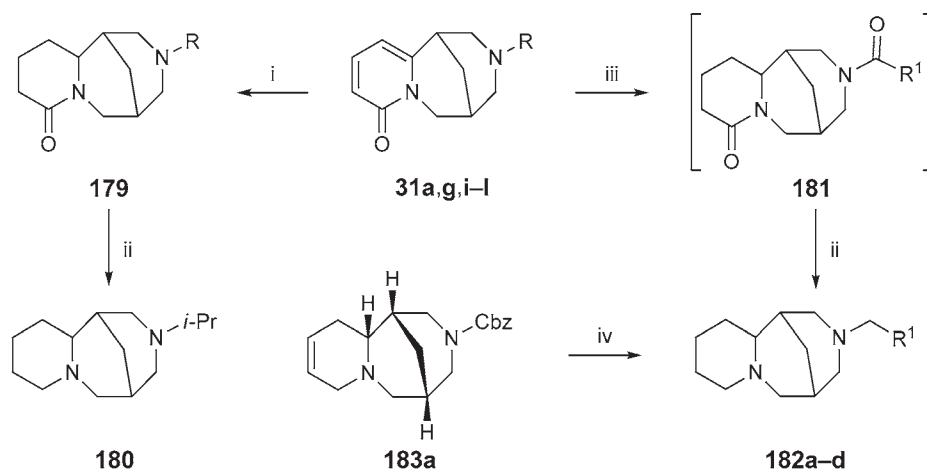


i, H_2 , Pd/C DMF; ii, DCC, HOBT, DMF, DCM, 50 °C; iii, corresponding amine 2 d; iv, corresponding amine, 60 °C, 12 h; v, guanidine, MeOH, MeONa, reflux, 2 d

Scheme 31

Cytosine methyl carbamate **31g** underwent a sequence of two reductions to give **182a** in 52% overall yield. The first catalytic reduction produced the nonisolated intermediate **181**, which was treated with LiAlH_4 to reduce the two carbonyl moieties <2002JA11870, 2006OS141>. Similar reactivity was shown by the *N*-carbonyl derivatives **31j–l**, which with the same reduction sequence afforded **182b–d** through the intermediacy of **181** <2004JOC5789>. The pyridine-fused diazocine **183**, upon catalytic reduction with Pd/C followed by a reductive methylation gave **182a** in 63% yield (Scheme 32) <2005TL7121>.

Catalytic hydrogenation and complex hydride reduction of multiflorine **86** produced a variety of products whose distribution depended on the reducing agent and reaction conditions. However, in all experiments the diastereomeric 4-hydroxysparteine derivatives **38a** and **38b** were formed as main products. In the resulting posthydrogenation mixture



31: **a:** R = H; **g:** R = CO₂Me; **i:** R = *i*-Pr; **j:** R = COMe; **k:** R = CO *i*-Pr; **l:** R = CO-*t*-Bu
185: **a:** R¹ = H; **b:** R¹ = Me; **c:** R¹ = *i*-Pr; **d:** R¹ = *t*-Bu

i, H₂/PtO₂, H₂O, 50 °C, 5 atm, 24 h; ii, LiAlH₄, THF, reflux; iii, H₂/PtO₂, MeOH, 25 °C, 5 h; iv, (a) H₂, Pd/C (10%), AcOEt; (b) NaCNBH₃, CH₂O (aq), THF

Scheme 32

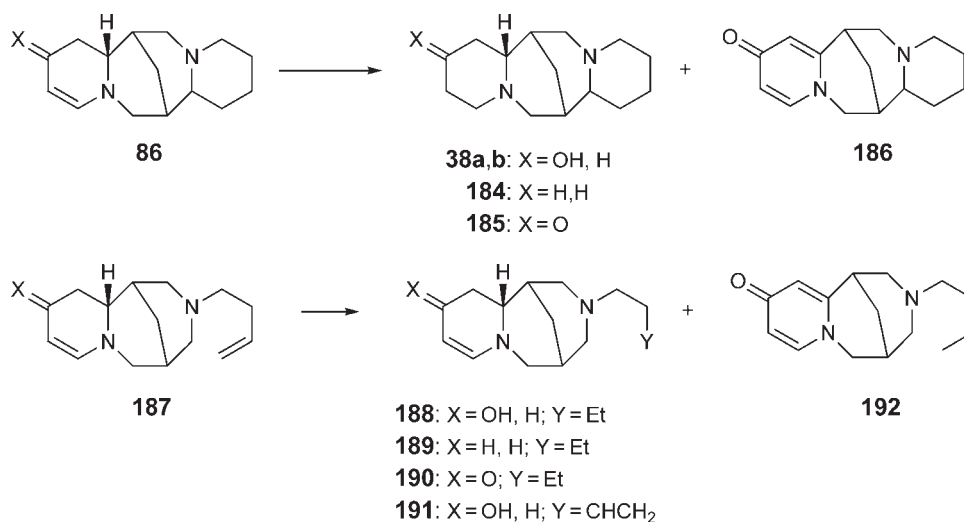
conducted with PtO₂ both in aqueous solution and absolute EtOH the didehydro compound **186** was formed in 78% and 27% yield, respectively, and the hydroxyl derivatives **38a** and **38b** were obtained in 22% (ratio 1:1) and 73% (ratio 1:1.2) yields. Hydrogenation with PtO₂ in HCl or glacial AcOH resulted in the formation of **38** in 48% (ratio 1:15) and 79% (ratio 1:3.6) yields, respectively, and sparteine **184**, a product of hydrogenolysis, in 52% and 21% yields, respectively. The hydrogenation rate in the presence of Pd/CaCO₃, Pd/BaSO₄, and Pd/C, all conducted in absolute EtOH, was very low. However, under such conditions in 7–27 d, the hydroxyl derivatives **38** were exclusively obtained in quantitative yields in ratio 7:93, 3:97, and 1:99, respectively. Analysis of the reaction mixture after 48 and 24 h of the reductions performed in the presence of Pd/CaCO₃ and Pd/C revealed the presence of the 4-oxosparteine **185** in 70% and 85%, respectively, indicating that this product is a precursor to **38**. The complex hydride reductions were efficient. Reduction with NaBH₄ in MeOH and DCM were complete in 0.5–1 h with a quantitative conversion of **86** in **38** (ratio 10:90 and 12:88, respectively). Reduction with LiAlH₄ in Et₂O or THF needed 24–43 h for a total conversion to **38**. Also with such a reducing agent, the presence of the precursor **185** was observed during the reaction. Reduction of the *seco*-(11,12)-12,13-didehydromultiflorine **187** gave different results.

Reduction with PtO₂ in H₂O and EtOH gave the hydroxyl compounds **188**, as main products, along with **190** and **192** that are analogues of **185** and **186**. In acid medium (HCl), the main product was **189**, an analogue of sparteine. With Pd/C, the hydroxyl derivatives **188** were obtained in 95% yield along with 5% of **190**. The reduction with NaBH₄ produced exclusively **191** in a β : α ratio 6:94. With LiAlH₄ beside **191**, the formation of **188** (6%) was also observed (Scheme 33) <2001M973>. Reduction of the carbonyl group of the piperidone moiety of **193** with tosyl hydrazide, followed by hydride reduction, and subsequent reductive methylation at the N-12 produced **194**, as a mixture of diastereoisomers <2002TL7155>. Reduction of (+)-17-oxosparteine **195** with LiAlH₄ produced a nearly quantitative yield of (+)-sparteine **184** <2002OL2577>.

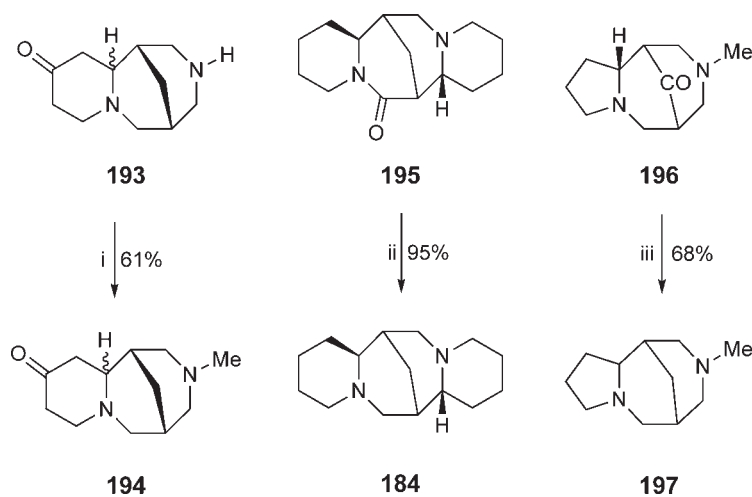
The carbonyl-bridged pyrrolo-diazocine **196** was converted, in good yield, into the corresponding methylene-bridged system **197** by Wolff-Kishner reduction (Scheme 34) <1999J(P1)3623>.

The Wolff-Kishner reduction of the carbonyl-bridged diazocines **198a–c** gave in good yields the corresponding methylene-bridged diazocine **199a–c**, which could be easily transformed into the perchlorate salts **200a–c** by adding perchloric acid to an ethereal solution of the free bases (Scheme 35). Perchlorate salts were also obtained from diazocines **198** (R = R¹ = *i*-Pr, Bn) bearing a thioketal moiety obtained from the reaction of the carbonyl bridge with 1,2-ethanediol (71–72%) <1996JME2559>. The *N*-BOC protected diazocine **199d**, under the same reaction conditions, gave **200d** in lower yield (60%) but was isolated as the free base <2005OL4459>. The Wolff-Kishner

reduction of another carbonyl into a methylene bridge has been reported [\[2000EJO391\]](#). Diazocine derivatives bearing one or more carbonyl group in the eight-membered ring were efficiently reduced with LiAlH_4 [\[1998JME318, 2002JHC727\]](#). Bispidinone **198d** was the precursor for the synthesis of a bispidinone-phosphoramidite library. Thus, **198d** was subjected to a Wittig to give the alkene **201**, which by a sequence of reduction of the double bond, exchange of the *N*-benzyl group for a Fmoc urethane, and coupling with the solid support, hydroxymethylpolystyrene, gave **202**. Removal of the F-moc group from **202**, and introduction of 28 substituents followed by the exchange of the BOC moiety with phosphoramidite portion to produce the library **203**_{1–28} (Scheme 35) [\[2002CCC673, 2002CEJ4767\]](#).

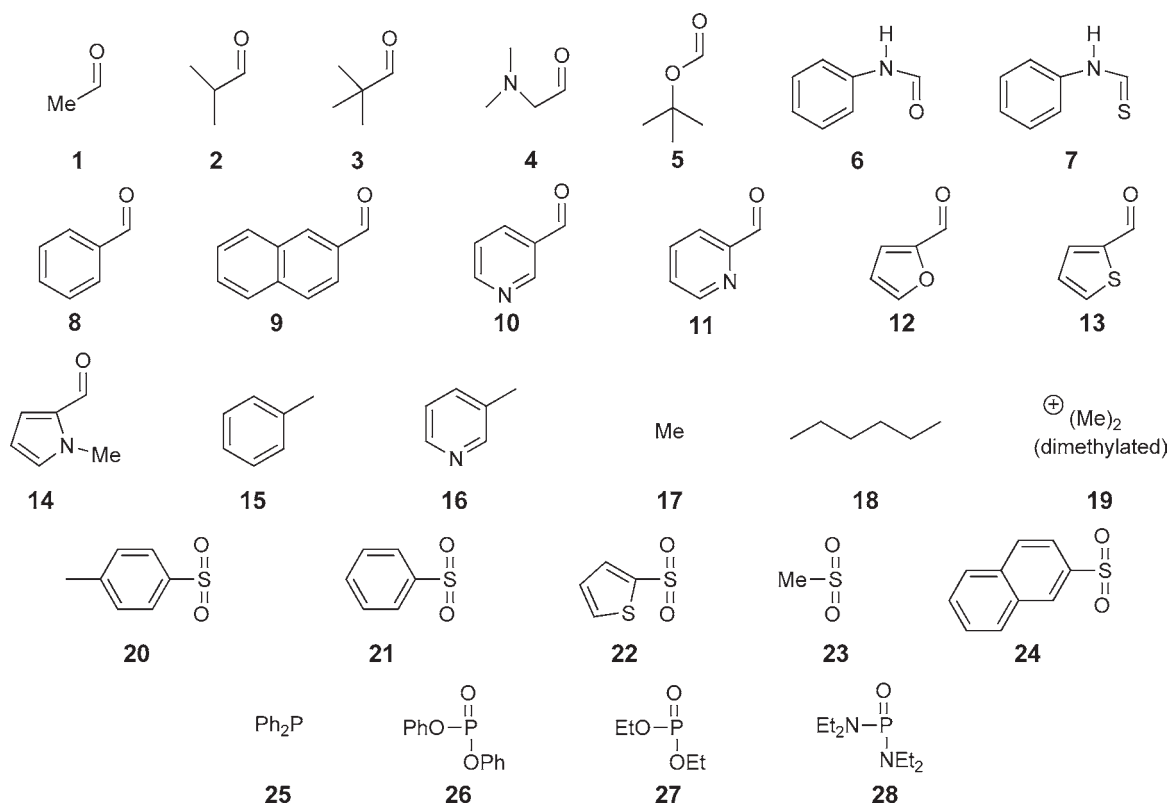


Scheme 33

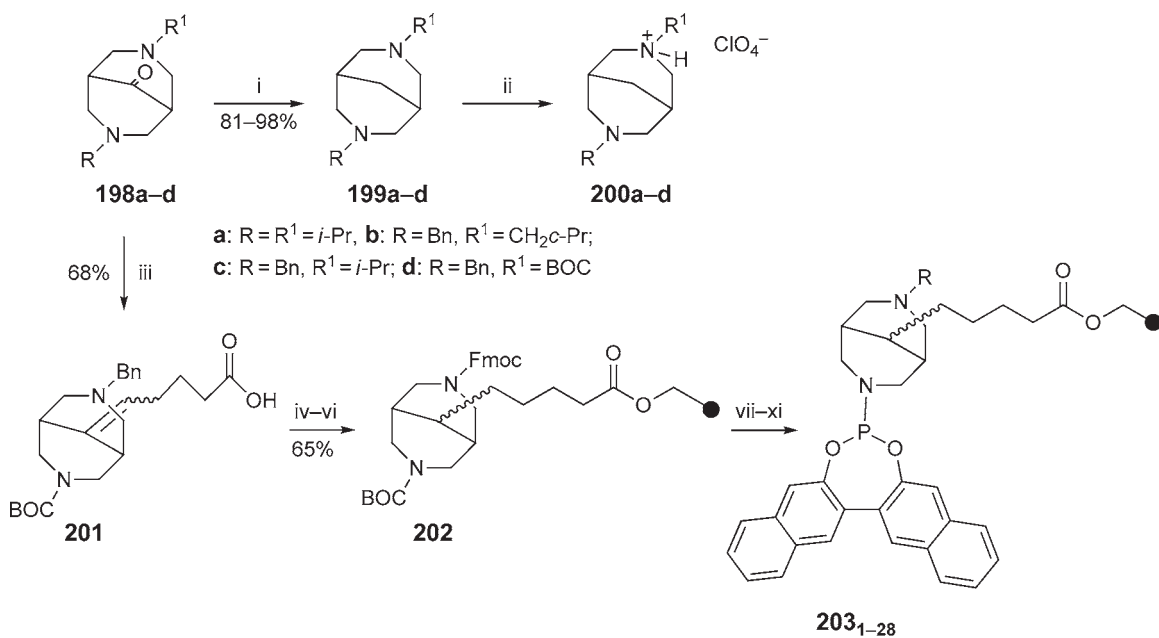


i, (a) TsNHNH_2 , EtOH, reflux, then NaBH_4 , THF, reflux; (b) CH_2O (aq), NaBH_3CN , THF;
 ii, LiAlH_4 , THF, reflux, 2 h; iii, $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, KOH, diethyleneglycol, reflux, 2 h

Scheme 34



Scheme 35



i, NH₂NH₂, KOH, TEG, 170 °C, 4 h; ii, HClO₄, Et₂O, 5 °C, 15 min;

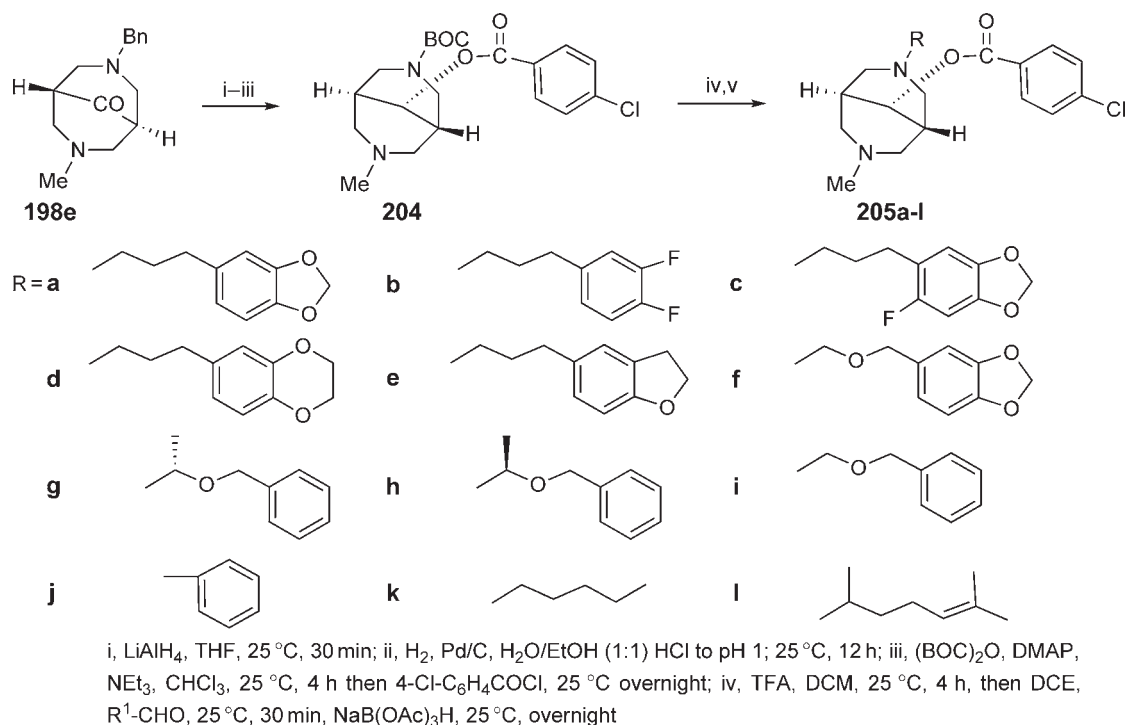
iii, Br⁻Ph₃P⁺(CH₂)₄CO₂H, KOt-Bu, THF, 0 to 25 °C, 12 h; vi, hydroxymethyl-polystyrene, DIC, DMAP,

DCM, 25 °C, 12 h (0.61 mmol g⁻¹), then Ac₂O, pyridine, DCM; vii, piperidine, DCM; viii, introduction of the *N*-substituent **1-28**; ix, TFA, DCM; x, NEt₃, DCM; xi, CIP(R₂BINOL), DCM

DIC = N,N'-diisopropylcarbodiimide, BINOL = 2,2'-dihydroxy[1,1']binaphthyl

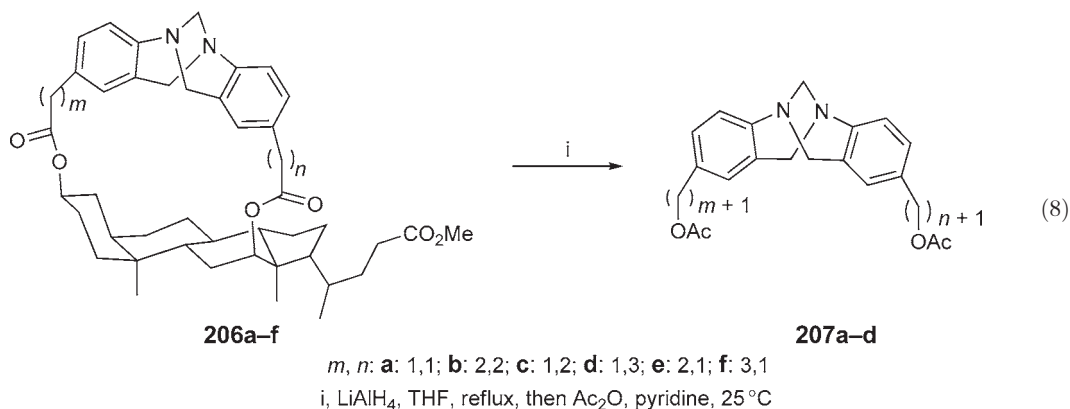
Partial reduction of the carbonyl bridge of the *N,N*-asymmetrically disubstituted benzodiazocine **198e** gave an hydroxyl group, which was reacted with 4-chlorobenzoyl chloride to afford the corresponding ester.

Successive catalytic removal of the benzyl moiety and introduction of the BOC protecting group gave **204**. This latter, upon action of TFA and reductive alkylation afforded 12 biologically active compounds **205a-l** (Scheme 36) <1999WO32487>.

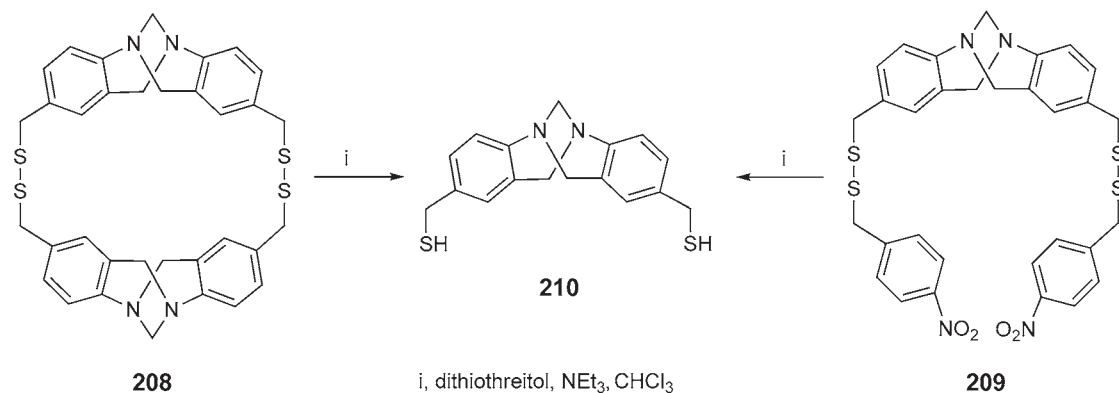


Scheme 36

Reduction with LiAlH_4 of the ester functionalities at the side chains of the diastereoisomeric mixtures of unsymmetrical Tröger's bases **206a-f** brought about the detachment of the steroidal component and the pendant hydroxyl group were *in situ* acetylated to give **207a-d** as a diastereoisomeric mixture whose ratio was dependent on the starting material (Equation 8) <1995J(P1)2049>. Nitro and oxime functionalities, attached to carbon atoms of 1,5-diazocine, showed the expected reactivity being reduced to amino derivatives, which were directly acylated with acyl chloride or anhydrides <1995JST(355)229, 2001JOC1607, 2004MC235>.



The 2,8-bis(mercaptomethyl)-analogue of Tröger's base **210** was obtained by reductive cleavage by dithiothreitol of the disulfide linkages of the macrocyclic dimeric Tröger's base **208** and of the bis-(4-nitrophenylmethyl)disulfide moiety of **209** (Scheme 37) <1999AGE3713, 1999TL1289>.



Scheme 37

14.07.2.6 Reactivity of Substituents Attached to Ring Heteroatoms

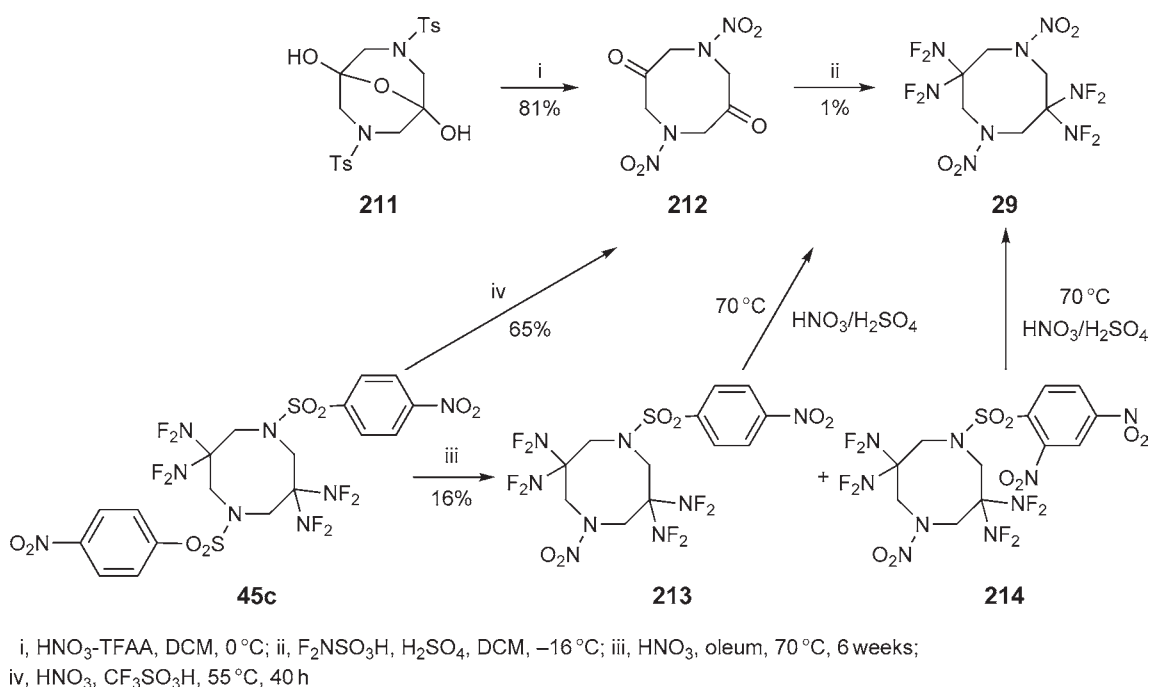
The first synthetic approach to the tetrakis(difluoroamino)diazocine **29** involved the nitrolysis of **211** to give **212** in good yield. Unfortunately, difluoroamination of **212**, under various anhydrous conditions, produced **29** in only ~1% yield. It was therefore necessary to convert nosylamide **45c** into nitramide **29** after the difluoroamination. However, **45c** proved inert toward the relatively powerful nitrating system HNO₃/TFAA. Nitrolysis with a mixture of HNO₃ and H₂SO₄ at elevated temperature (~70 °C) produced **29** in 16% yield and required 6 weeks to consume starting material and mononitrodiazocine intermediates **213** and **214**. There was crystallographic evidence that these conditions caused competitive *C*-nitration of the nosyl protecting groups. The resultant 2,4-dinitrobenzenesulfonyl substituent would be even more difficult to remove from the nitrogen by electrophilic substitution.

Better results were obtained when a mixture of HNO₃ and triflic acid, involving protonitronium (NO₂H²⁺) as the reactive nitrating species, was used and **29** was obtained in good yield at 55 °C in 40 h. The use of a strong Lewis acid, which generally increases the amount of the nitrating species in the mixture, did not improve the yields (Scheme 38) <1999JOC960, 2006USP7145003>. Using the same nitrating system but at 25 °C, nitrolysis of **105a** led, in good yield, to the corresponding nitramide (**105**, R = NO₂) <2001TL2621, 2002USP6417355>.

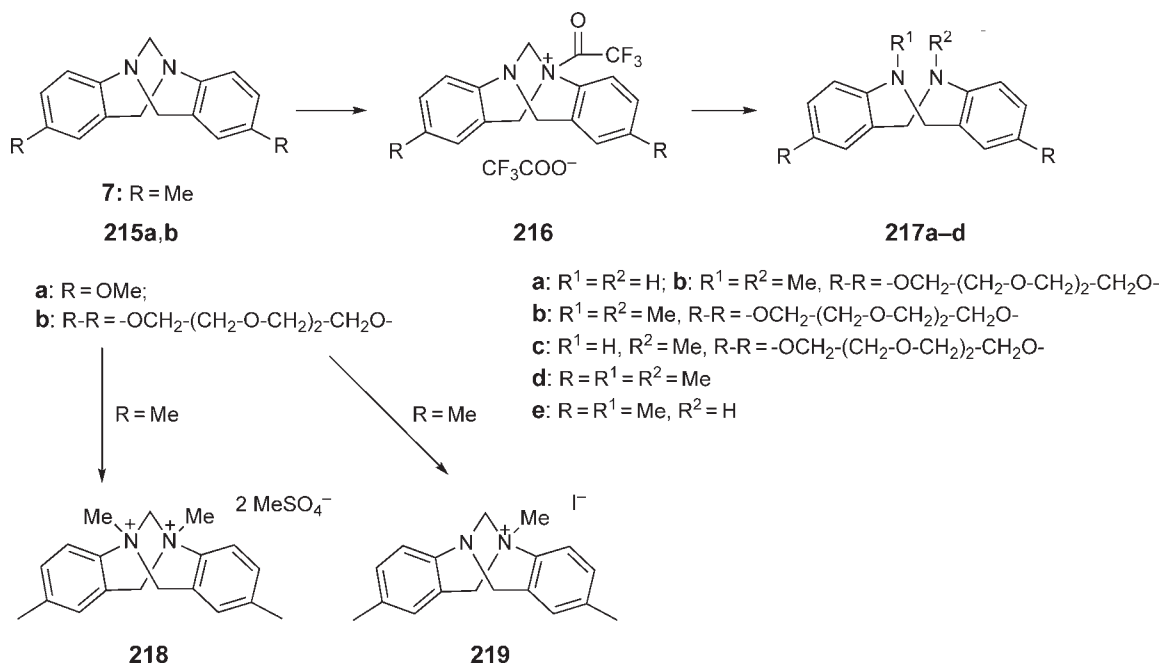
Unsubstituted perhydro-1,5-diazocine underwent classical acylation with α,α-dimethylglycine sulfonamides to give the corresponding glycinamides <2006JME3602>. Similarly, 1-benzyl-perhydro-1,5-diazocine was treated with 2-(2-tolyl)pyrrolidine carbamoyl chloride in a sealed tube to give the corresponding amide <2004WO110996>; dibenzodiazocinone **32** was also acylated with acyl chlorides in the presence of pyridine <2004JOC1248>. Acylative dealkylation of 1,5-di-*n*-butyl-3-acetoxy-7-methylidene-1,5-diazacyclooctane and the corresponding 3-benzyloxy compound, with Ac₂O in the presence of Et₂O·BF₃ gave the corresponding *N,N*-diacetyl derivatives in low yields <2000JOC1207>.

Removal of the endo methylene bridge of Tröger's bases could be achieved with or without concomitant methylation of the nitrogen(s). Thus, trifluoroacetylation of **215b** with trifluoroacetic anhydride did not give the expected bis(trifluoroacetamide) **217** (R¹ = R² = CF₃CO) but rather the trifluoroacetamide trifluoroacetate salt **216** in 79% yield.

The latter was readily hydrolyzed in refluxing MeOH in the presence of K₂CO₃ to give **217a** (Scheme 39) in 79% yield. Acetylation and benzylation of **215b** proceeded smoothly providing the corresponding diamides, but the subsequent hydrolysis was very sluggish. When **215b** in dioxane was treated with dimethyl sulfate in the presence of sodium hydroxide at 25 °C, **217b** was obtained in 92% yield. If the intermediate *N*-methylated ammonium salt of the above reaction, the analogue of **216**, was isolated and hydrolyzed in alkaline medium, the *N*-methyl derivative **217c** was obtained in 96% yield. The nitrosation-CuCl reductive sequence conducted on **215b** and its open-chain analogue **215a** gave intractable products due to the presence of the electron-rich ether groups <1999TL1705>. Bis-methylation of the parent Tröger's base **7** went smoothly in Me₂SO₄ and gave the *N,N'*-dimethyl bis-methylsulfate **218**. A parallel behavior was exhibited by the ethylene-bridged **16**, which upon treatment with Me₂SO₄ gave the *N,N'*-dimethyl bis-methylsulfate analogue of **218** and upon reaction with MeI gave **17** <2006TA2191>. Also **74**, the alkaloid caracurine V, upon reaction with alkyl halides produced bis-ammonium salts with the alkyl groups bound to the two piperidine rings <2004JME3561>.



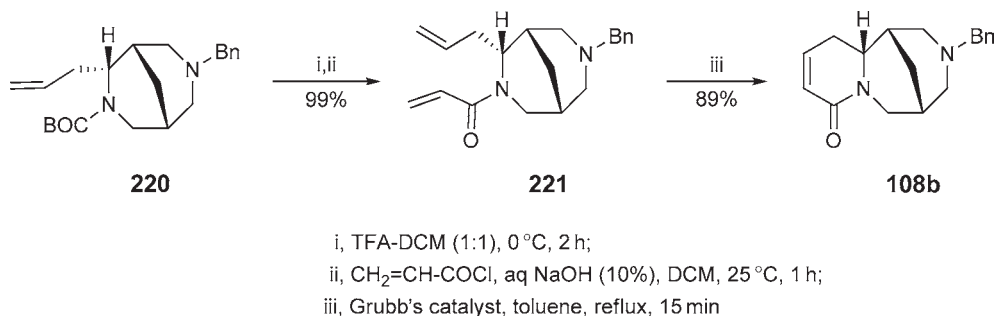
Scheme 38



Scheme 39

N-Benzilyldihydrocystisine **108b** was obtained from bispidine **220** (Scheme 40), in 88% overall yield, through a sequence involving deprotection of the BOC group and acylation of the *N*-unsubstituted bispidine with acryloyl chloride to give the diene **221**, which was subjected to ring-closing metathesis using the first generation Grubb's catalyst. This reaction is particularly efficient, presumably due to the equatorially disposed allyl group and the conformational rigidity of the bispidine <2005OL4459>. Another ring closure leading to tetrahydrocystisine was observed when a

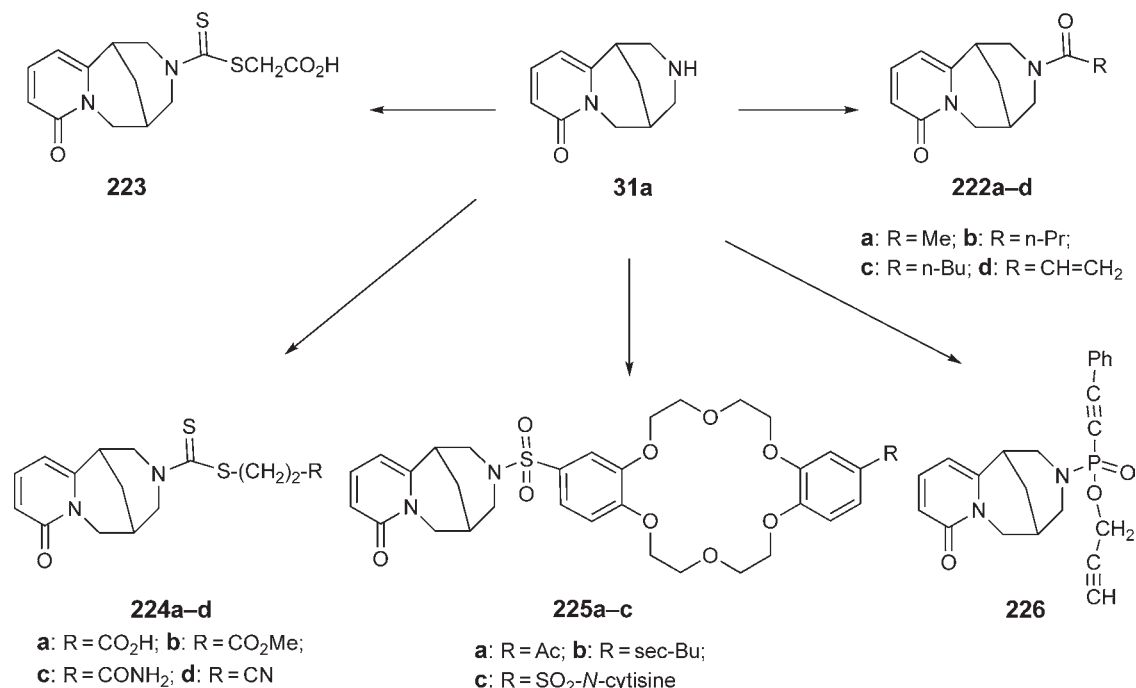
N-BOC-bispidine derivative **157** (R = BOC) bearing a butyric acid moiety in position 2 was treated with carbonyldiimidazole, as the condensing agent <2004TL6733>. Other *N*-acylations of bispidine or bispidone were reported <1996JME2559, 2000WO44755, 2003USP0225268, 2005WO103054>. Bispidine also reacted with two moles of (*R*)-1,1'-binaphthyl-2,2'-dioxaphosphorochloridite to give the corresponding *N,N*-diphosphoramidites <2000CEJ671>.



Scheme 40

Reaction of cytosine with acyl chlorides is straightforward and occurs with high yield, producing acylcytosine, with the acyl groups bound to N-12. In the preceding sections, the spectroscopic and chemical properties of several *N*-acylcytosine derivatives have been discussed. They have been numbered differently but were prepared through the same method. Thus, referring to the general formula **222** below, the acylcytosine derivatives mentioned already and their synthesis will be reported: R = H (from cytosine and formic acid), and R = CH=CH-CO₂H were numbered **31c** and **31d** <2001MI356>; R = Et, OMe, *t*-Bu, and *i*-Pr were numbered **150–153** respectively <2002TA1299>.

Further acylcytosines **222a–d** were analogously prepared <2001EJM375, 2004JOC5789, 2004RJO719>. To the *N*-carbonyl of **222** more complex structures were also attached such as the glycyrrhetic residue <2002MI249>, benzocrown-ether fragments <2002MI344>, and benzothiadiazolyl sulfanilides (Scheme 41) <2004USP0224983>.



Scheme 41

Cytisine with CS₂ and monochloroacetic acid gave *N*-cytisyl thiocarbonylmercaptoacetic acid **223** in 75% yield. The reaction can proceed either by attack of the cytisyl-carbamodithioic acid, prepared *in situ* from CS₂ and cytisine, to the monochloroacetic acid or by reaction of this latter with an authentic sample of the salts of carbamodithioic acid. However, in this case the reaction was slower and the yield lower <2002RJC324>. The cytisyl-carbamodithioic acid reacted with alkenes activated with electron-withdrawing groups such as acrylic acid, methyl acrylate, acrylamide or acrylonitrile to give the β -(cytisinothiocarbamoylthio)propionic acid and its ester, amide, and nitrile derivatives in 65–89% yields **224a–d** <2004RJA1321>. Cytisine reacted with dibenzo-18-crown-6-sulfonyl chlorides or disulfonylchlorides to give the sulfonylcytisine derivatives **225a,b** or **225c**, respectively <2002MI182>. Cytisine reacted with 2-propynyl-2-chloro-2-phenylethenephosphonochloridate to give propargyl 2-chloro-2-phenylethenephosphonocytisinidate which, in ethanolic KOH, readily eliminated HCl to form propargyl phenylethynephosphonocytisinidate **226** (Scheme 41) <2004RJGC1225>.

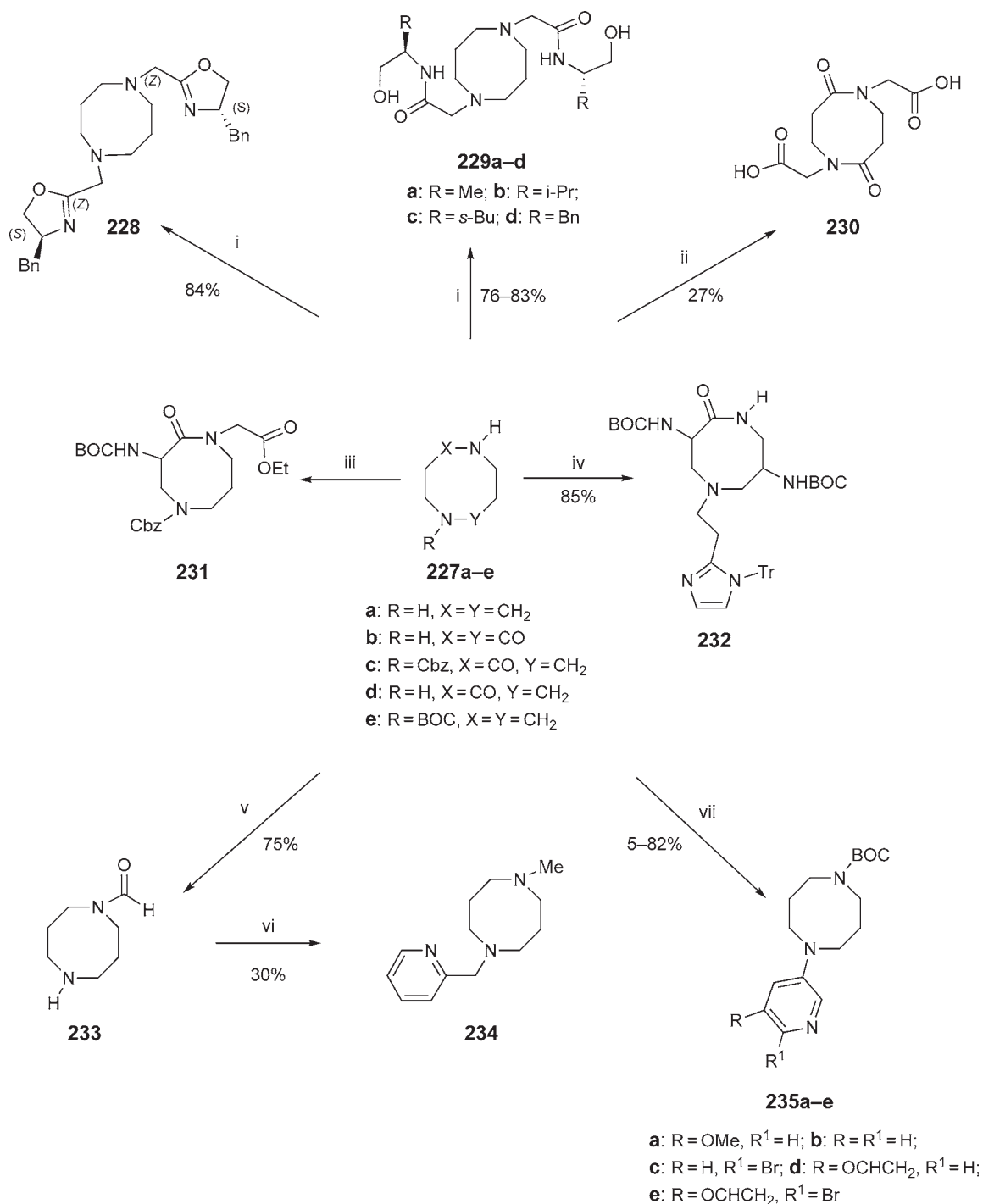
Perhydro-1,5-diazocine, 1,5-diazocinedione, and 1,5-diazocinone **227a–e** were easily alkylated at the nitrogen by nucleophilic substitution on the halo derivatives or by reductive alkylation. Thus, **227a** reacted with 4-benzyloxy-2-chloromethyloxazoline to give the bis-alkylated diazocine **228** <2002CCL115>. Unsubstituted diazocine **227a** also reacted with *N*-chloroacetamido alcohols to give the corresponding *N,N*-bis-acetamido derivatives **229a–d** <2001CCL769>. Diazocinedione **227b**, upon reaction with *t*-butyl bromoacetate and subsequent removal of the *t*-butyl group afforded **230** in 27% overall yield <2001WO10848, 2002WO060895>. A derivative of diazocinone **227c**, bearing at the N-5 a Cbz protecting group and a substituent (NHBOC) at 3-position, with ethyl bromoacetate produced corresponding *N*-substituted derivative **231** <2005BML4291>. A derivative of diazocinone **227d** bearing two NHBOC moieties in 3- and 7-position underwent reductive alkylation upon reaction with 2-(1-tritylimidazolyl)acetaldehyde and successive reduction to give **232** in good yield <1999SL1875>. Diazocine **227a** was dialkylated by formylation with ethyl formate to give **233**, subsequent alkylation of the second nitrogen with picolyl chloride and final reduction of the *N*-formyl group with LiAlH₄ produced the *N,N*-dialkyldiazocine **234** <2001IC5060>.

The *N*-BOC protected diazocine **227e** underwent arylation, in very variable yields when treated with substituted 3-halopyridines in the presence of Pd(PPh₃)₄ to give the *N*-pyridyldiazocines **235a–e** (Scheme 42) <2006JME3159>. Perhydro-diazocine **227a** was bisheteroarylated by reaction of substituted 2-chloroquinazolines <1999USP5874438>.

Spermine alkaloids homaline, hopromine and a *N*- and *O*-protected precursor of hoprominol were obtained through alkylation involving the nitrogens of 1,5-diazocines. Thus, nucleophilic substitution of the bromobutyl side chain of **236** (see Scheme 43), on the anion of the lactams **237a,b** led to the bis-diazocine derivatives **238a,b**. The yields were good in the case of **238a** (71%) and very poor (8%) for **238b**, the precursor of hoprominol, although the starting materials could be partially recycled <2002HCA1659, 2003HCA233>. The tosyl protecting group of **238a** was removed electrolytically and the resulting NH derivative was methylated, by treatment with formaldehyde and subsequent reduction, to give hopromine **239** in 64% yield <2002HCA1659>. Homaline could be obtained, in 35% overall yield, by a bis alkylation of **237c** with 1,4-dibromobutane producing **54c**, which was transformed into homaline **54a**, through the same sequence that led to **239** <2002HCA1659>.

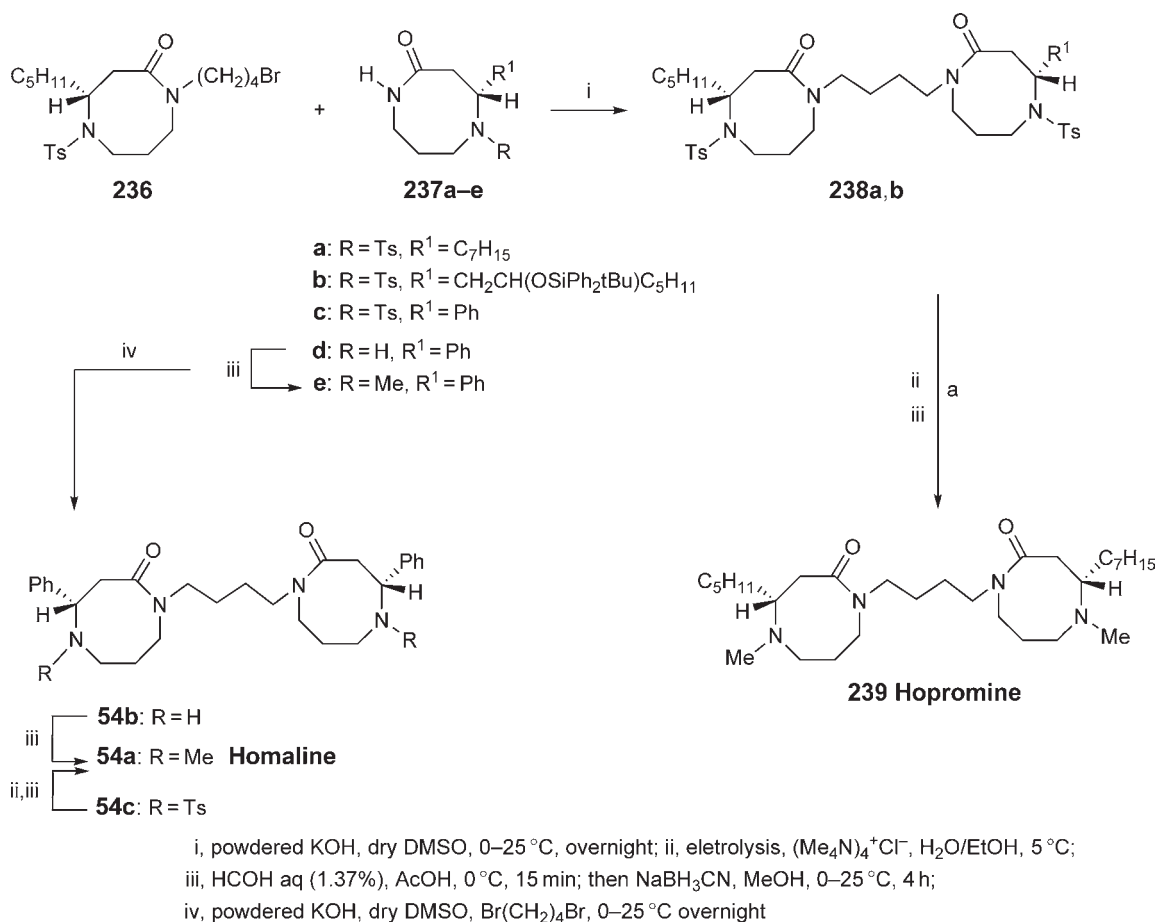
Alternatively, homaline was obtained by bis-alkylation of **237d** to give **54b**, which by reductive methylation gave the alkaloid **54a** in an overall yield of 20%. A better overall yield, 37%, was obtained by methylation of **237d** to give **237e** followed by bisalkylation with 1,4-dibromobutane to give **54a** <1995BCJ3121>. Chitosans bearing epoxide moieties reacted with 3-hydroxydiazocine **166** (R = H) or 3,7-dihydroxydiazocine **166** (R = OH) alkylating the two nitrogens of the eight-membered ring producing polymeric analogues of **173** <2001JAP1793, 2002CCL27, 2002JAP2677>.

Double ring-closing metathesis of the tetraene **144** conducted with Grubbs' first generation ruthenium alkylidene catalyst was sluggish, requiring over 24 h but eventually delivered the sparteine derivative **240** in 81% yield <2005OL4721>. The benzamide protection of diazocines **146** was converted into the BOC protecting group by reaction with MeMgCl in refluxing THF and subsequent action of (BOC)₂O to give **241**. The methyl substituent was replaced with the ethoxycarbonyl moiety upon reaction with ethyl chloroformate in toluene <2000TL6167>. For the derivatives related to **157** (R = Me), BOC protection was converted into a benzyl substituent by action of TFA, acylation with benzoyl chloride, and subsequent reduction with LiAlH₄ <2000TL6161>. Bispidines **242a,b** reacted with a chiral epoxide, generated *in situ* from 2-chloro-3-methylbutanol by treatment with NaOMe in MeOH, to give the bispidine aminoalcohols **243a,b** <2000EJO391>. Bispidine **242b** reacted with pyrazolyl- or triazolylmethylalcohols to give quantitatively **244a–d** <2003JCO375>. Bispidine **245** underwent *N,N*-bismethylation by action of formaldehyde and successive reduction with formic acid to give **246**.



i, K₂CO₃, MeCN; ii, (a) NaH, DMF, 0 °C, 15 min, then BrCH₂COO*t*-Bu, 0–25 °C, 45 min; (b) TFA, DCM, 25 °C overnight;
 iii, BrCH₂CO₂Et, KHMDS, THF; iv, CHCl₃:EtOH (3:1), then NaBH₃CN, AcOH; v, HCO₂Et, MeOH, reflux, overnight;
 vi, (a) PyCH₂Cl, Na₂CO₃, MeCN, reflux, 18 h; (b) LiAlH₄, THF, N₂, reflux, 3 h; vii, Pd(PPh₃)₄, KO*t*-Bu, DHE, reflux, 3 h

Scheme 42



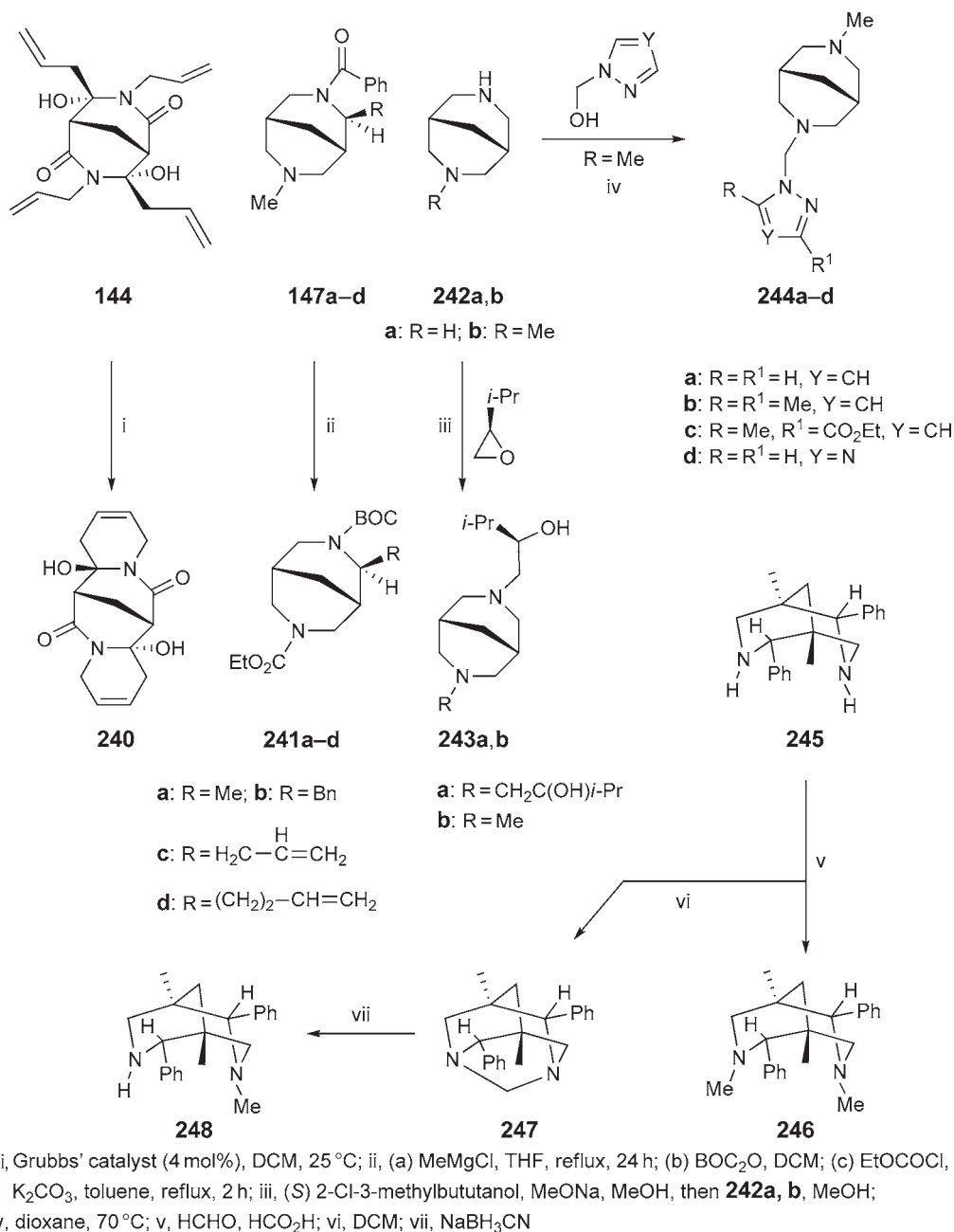
Scheme 43

The same **245** was converted, by reaction with DCM, into a Tröger's base analogue **247** which, upon reduction gave the *N*-methylidiazocine **248** (Scheme 44) <2006TL2581>. Cases of alkylation of bispidinones have been reported <2001WO28992, 2004WO035592, 2005WO103054>.

Cytisine **31a** was *N*-alkylated, arylalkylated, or arylated using different approaches. Thus, reaction of **31a** with ethylene oxide gave in 96% yield *N*-(2-hydroxyethyl) derivative **249** <2004PCJ311> The *N*-*i*-propyl derivative **250** was obtained from the reaction of cytosine with acetone, followed by reduction of the resultant hydroxyl group <2004EJO1894>. Treatment of **31a** with 1,3-dimethyl-5-arylbarbituric acids in aqueous formaldehyde gave the 5-cytisylmethyl barbituric acids **48a–z** in 65–93% yields <2000MI192, 2002MI450>.

Reaction of cytosine with aromatic aldehydes and acetone cyanohydrin produced the *N*-acetonitrile derivatives of cytosine **251a–d** (Scheme 45) in 71–85% yields <2001RJC151>. Beside the above-mentioned alkylations, the nucleophilic attack of cytosine on halo derivatives has to be mentioned: <1999FA438, 2001MI356, 2001RJC650, 2002FA469, 2003RJC961, 2003TA233, 2004JCO828, 2004MI582, 2006RJC129, 2006MI470>. Methylene-bridged pyrido[1,2-*a*]-1,5-diazocine underwent arylation upon treatment with 1-cyano-4-fluoronaphthalene <2005WO115361>.

The *N*-nitrosodiazocines **4a–d** were obtained from the corresponding unsubstituted derivatives upon action of nitrous acid <1997JOC5619>. Bispidine derivatives bearing a benzyl group at one or both nitrogens are easily debenzylated by Pd-catalyzed hydrogenolysis <1996JME2559, 2000EJO391, 2000WO76997, 2001WO28992, 2004TL6733, 2005WO103054>. Bispidinones are also easily debenzylated. For example, **19b** and **19d** in EtOAc gave in good yields the corresponding NH derivatives but in EtOH it was necessary to add catalytic amounts of HClO₄ <1995T2055, 1995T4819, 1997OM1167>. 3-Methoxy-*N*-benzyleytisine and indolodiazocine **57c** were easily debenzylated by Pd-catalyzed hydrogenolysis <2000OL4201, 2005T941>; whereas, the Cbz protection of **31e** could be removed upon refluxing in concentrated HCl <2004OL493>.

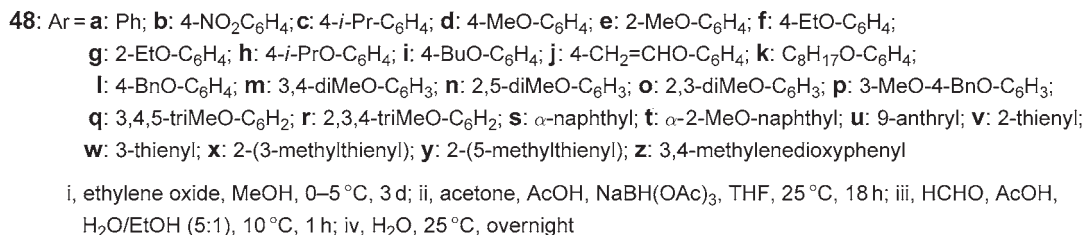


Scheme 44

14.07.2.7 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

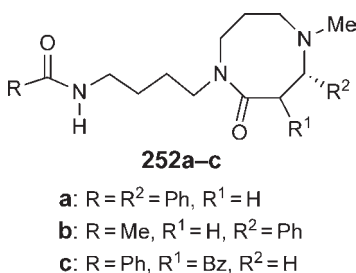
14.07.2.7.1 Natural products

The lupine alkaloid (–)-cytisine **31a** was obtained from the basic fraction of the 75% methanolic extraction of the dry branches of *Maackia hupehensis* collected in Jiang Xi province of China, along with hupeol, a oxazocine derivative, and eight other lupine alkaloids <1998JCM196>. (–)-Cytisine was also extracted with MeOH/DCM from *Laburnum anagyroides cytisus* seeds <2000OL1121, 2002JA11870, 2006OS141>.



Scheme 45

Spermine alkaloids **252a–c** were extracted from the leaves of *Dovyalis macrocalyx*, a plant belonging to a genus of small trees and shrubs found in Africa and Asia (family Flacourtiaceae) <2003OL2793>.

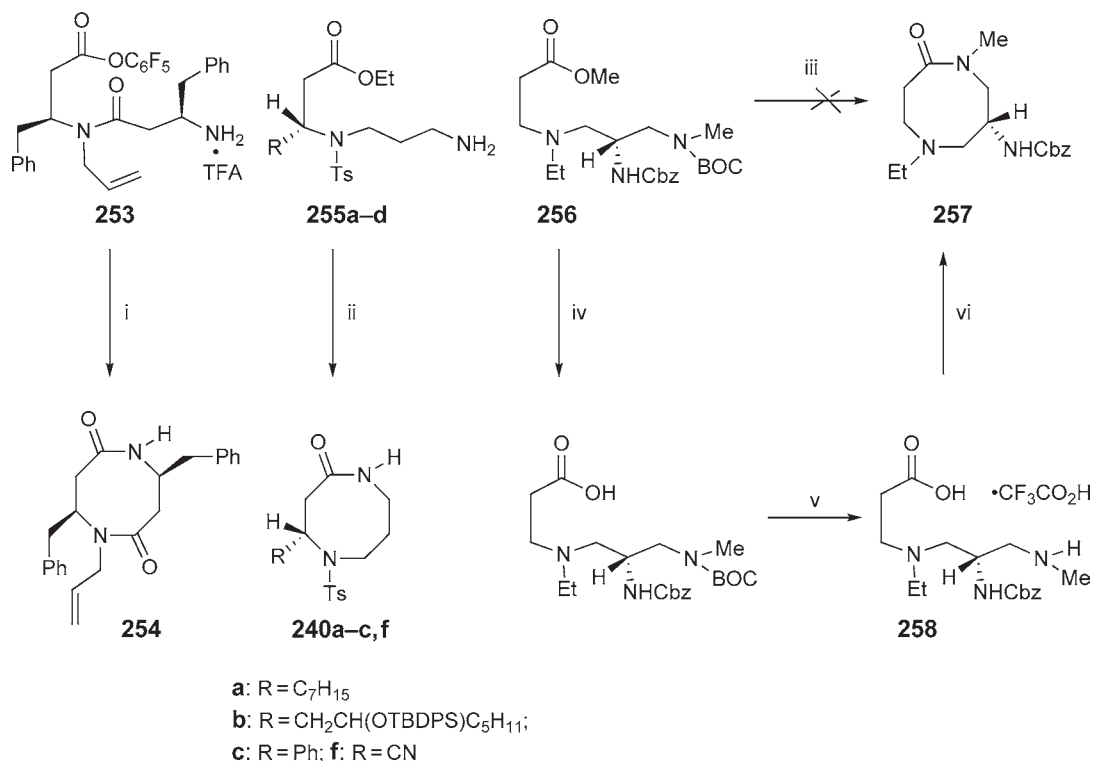


14.07.2.7.2 Ring syntheses from C₆N₂ units

Diazocinedione **254** was obtained in 74% yield by the cyclization of the amino ester **253** under dilute conditions (0.002 M); however, at higher concentrations (0.1–2.0 M), the yields decreased to 20–30% and **254** was obtained along with a 16-membered macrocycle via dimerization of **253** <2000T7947>. The diazocinones **240a–c,f**, units of the spermine alkaloids homaline, hopromine and hoprominol, were smoothly prepared, in excellent yields (83–95%), by the cyclization of the aminoesters **255a–d** by cycloamidation under high dilution conditions <2002HCA1659, 2003HCA233>. The attempt to obtain **257** from **256** through removal of the BOC group and intramolecular amidation of the resulting aminoester with NaOMe was unsuccessful.

However, **257** could be obtained by alkaline hydrolysis of **256** followed by removal of the BOC moiety with TFA and intramolecular amidation of **258** to give the final product in 89% overall yield (**Scheme 46**) <2002JHC727>. The same

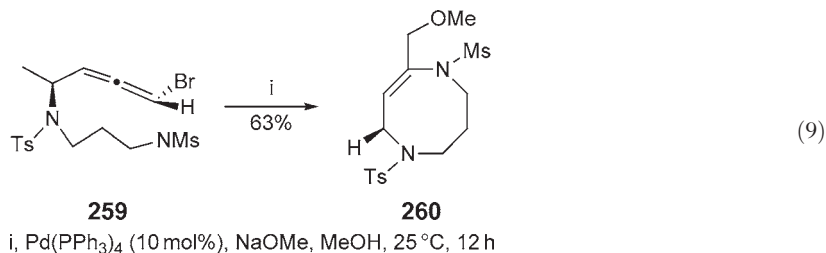
sort of intramolecular cyclization observed in the case of **258** occurred when 3-[(2-amino-5-chlorobenzyl)methylamino]propionic acid was reacted with a condensing agent to give the benzodiazocine **139** <2004WO074291>.



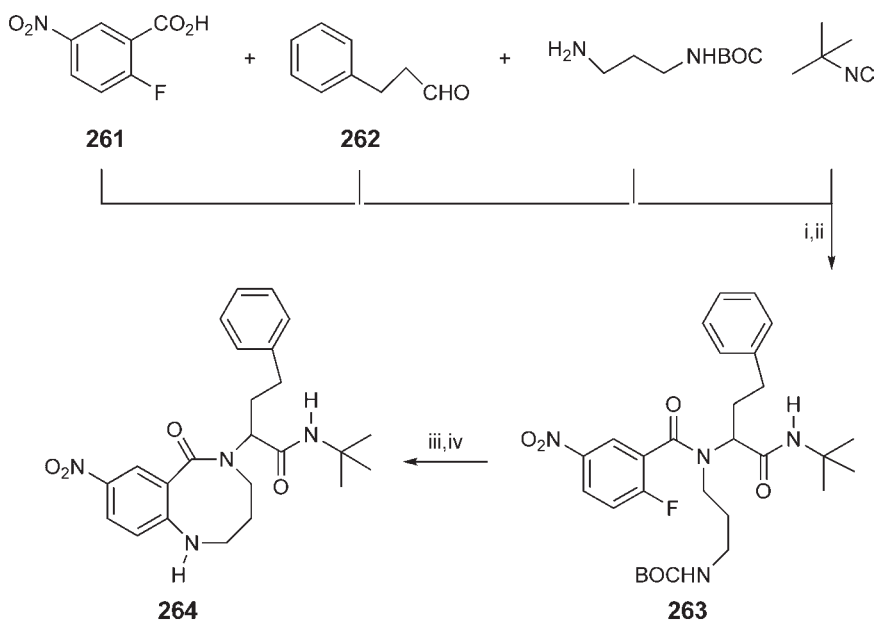
i, Ni-(Pr)₂Et, MeCN, 70 °C, 15 h; Sb(OEt)₃, dry benzene, 4-Å mol sieves, reflux, 16 h; iii, TFA, then NaOMe
 iv, aq NaOH (8%), reflux, 2 h; v, TFA, DCM, 25 °C, 3 h; vi, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, DCM, NEt₃, 25 °C, 16 h

Scheme 46

The hexahydro-1,5-diazocine **260** was obtained, as a single isomer, from the Pd-catalyzed cyclization of the allene **259** conducted in the presence of methoxide ion. The intramolecular nucleophilic attack, by the mesylated amino group, occurred at the central position of the allenic moiety and the regioselectivity of the attack of the methoxide is extremely high (Equation 9) <2004JA8744>.



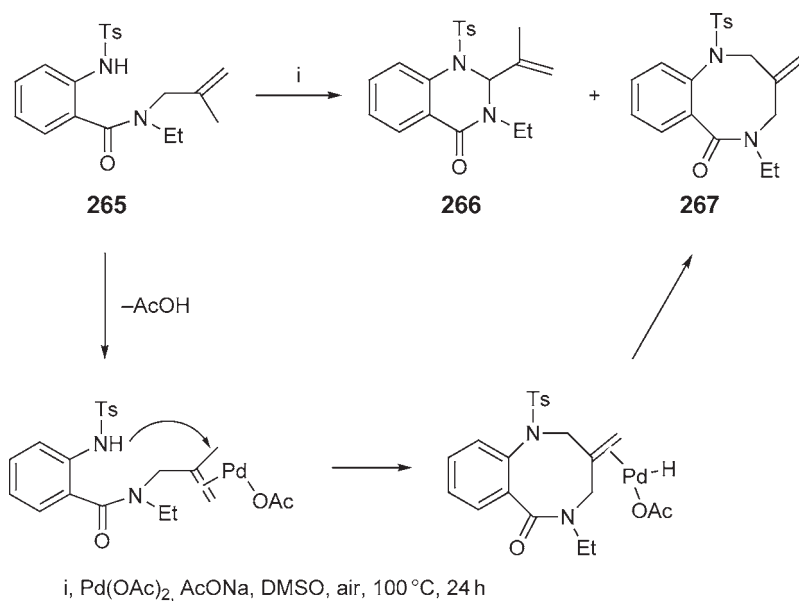
Benzodiazocine **264** was prepared through a 4-component Ugi reaction including a primary amine tethered to a BOC-protected internal amino nucleophile, followed by a postcondensation base-catalyzed cyclization. Thus, 2 equiv of aldehyde **262** were employed to promote Schiff base formation and a one-pot, double scavenging protocol with immobilized tosylhydrazine and di-isopropylethylamine removed both the excess aldehyde and any unreacted acid **261**. The intermediate **263** was then subjected to treatment with TFA, followed by proton scavenging with resin bound morpholine, to promote cyclization to afford the eight-membered ring (Scheme 47) <2001TL4963>.



i, **262** (0.2 M, 200 μ l, MeOH), N-BOC-(CH₂)₃NH₂ (0.1 M, 200 μ l, MeOH), **261** (0.1 M, 200 μ l, MeOH), *t*-BuNC (0.1 M, 200 μ l, MeOH), 25 °C, 48 h; ii, PS-tosylhydrazine (3 equiv), PS-diisopropylethylamine (3 equiv), THF:DCM (600 μ l, 1:1), 24 h; iii, TFA/DCM (600 μ l), 4 h; iv, PS-morpholine (3 equiv), DMF (600 μ l), 36 h

Scheme 47

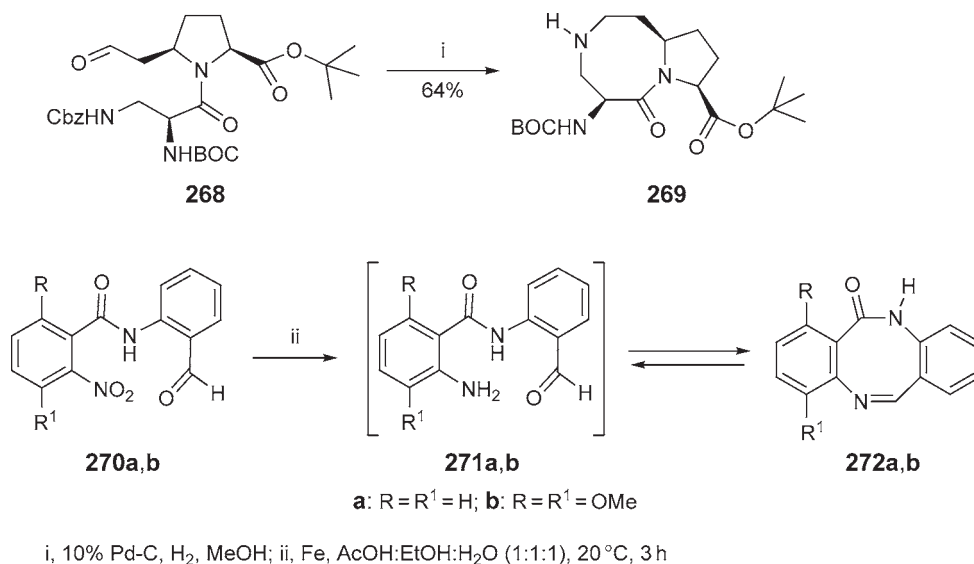
Intramolecular Pd-catalyzed amination of *N*-allyl-anthranilamide **265** gave the quinazoline **266**, as the main product (62%), and the benzodiazocine **267**, as minor product (20%). The formation of **267** was explained by the formation of an η^3 -allyl-Pd complex, as outlined in Scheme 48 <2004JOC5627>.



Scheme 48

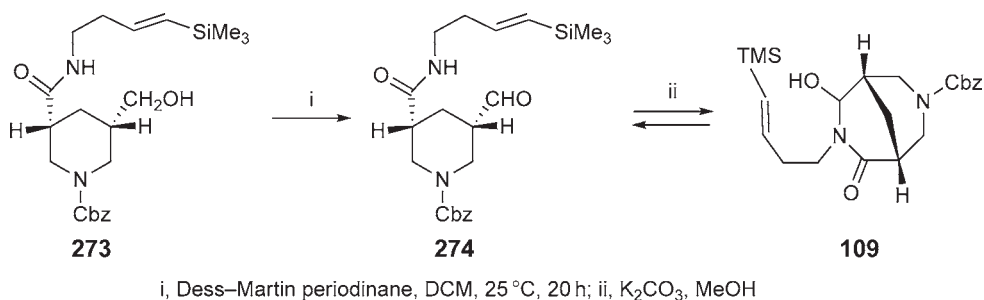
The Pd-catalyzed hydrogenation of the pyrrolidine **268** removed the Cbz protecting group, intramolecular condensation with the aldehyde and subsequent reduction of the resulted enamine gave in good yield the pyrrolidiazocine **269** <2006TL4769>. Reduction of the nitro-aldehydes **269a,b** with Fe^0 in acid medium afforded the dibenzodiazocinones **272a,b** in 32–36% yields.

In the case of **269a** along with **272a**, the reduction produced the intermediate amine **271a**, as main product (56%). The presence of the intermediate was independent on the reduction time but rather resulted by an imine hydrolysis promoted by the aqueous acidic medium (Scheme 49) <2005SC1493>.



Scheme 49

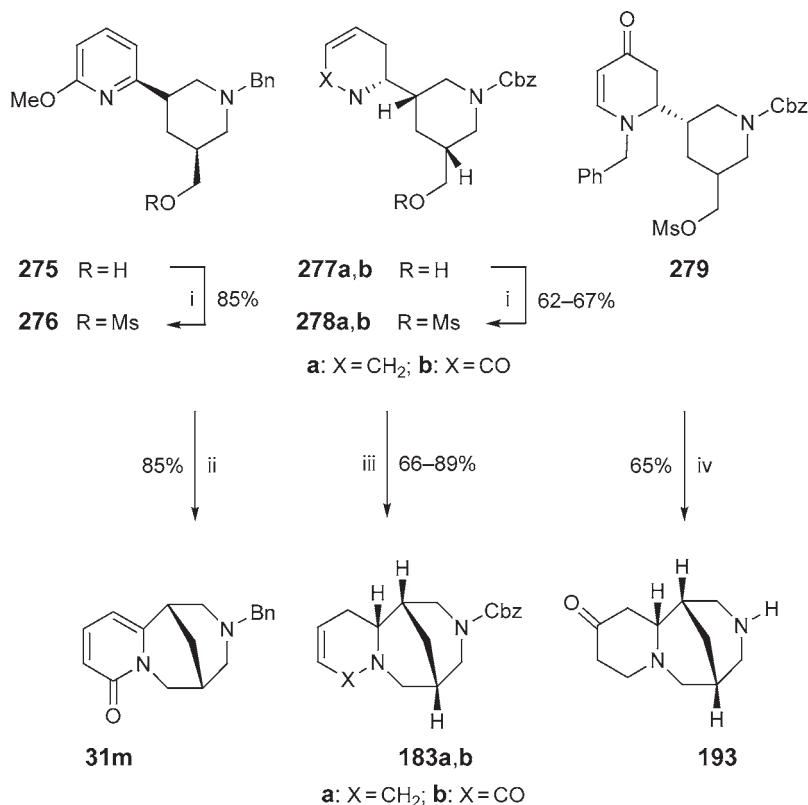
Oxidation of alcohol **273** with Dess–Martin periodinane afforded in 88% yield a 2.3:1 mixture of aldehyde **274** and methylene-bridged diazocinone **109**, which was obtained as a single stereoisomer, and the sole product in 76% yield when the unseparated mixture was treated with $\text{K}_2\text{CO}_3/\text{MeOH}$ (Scheme 50) <2001EJO1377>.



Scheme 50

The *N*-benzyleytisine **31m** was conveniently prepared from piperidinyl-pyridine **275**, which underwent standard mesylation, followed intramolecular nucleophilic attack of the pyridine nitrogen on the methylene carbon becoming the mesyl leaving group. The same procedure led to the *N*-benzyl-3-methoxycytisine starting from the suitable dimethoxypyridine <2000OL4201>. The above intramolecular cyclization worked efficiently in the synthesis of cytisine analogues **183a,b** and **193**, which were obtained from tetrahydropyridine and dihydropyridone derivatives respectively. Thus, the mesyl derivatives **278a,b**, derived from **277a,b**, respectively, were cyclized in the presence of

NEt₃ or NaH to give, in good yield, **183a** or **183b**, respectively <2004OL493, 2005TL7121>. The benzylpyridone **279**, prior to cyclization, had to be deprotected under catalytic hydrogenation conditions. The cyclized cytosine analogue **193** was obtained upon refluxing in aqueous HCl (Scheme 51) <2002TL7155>.

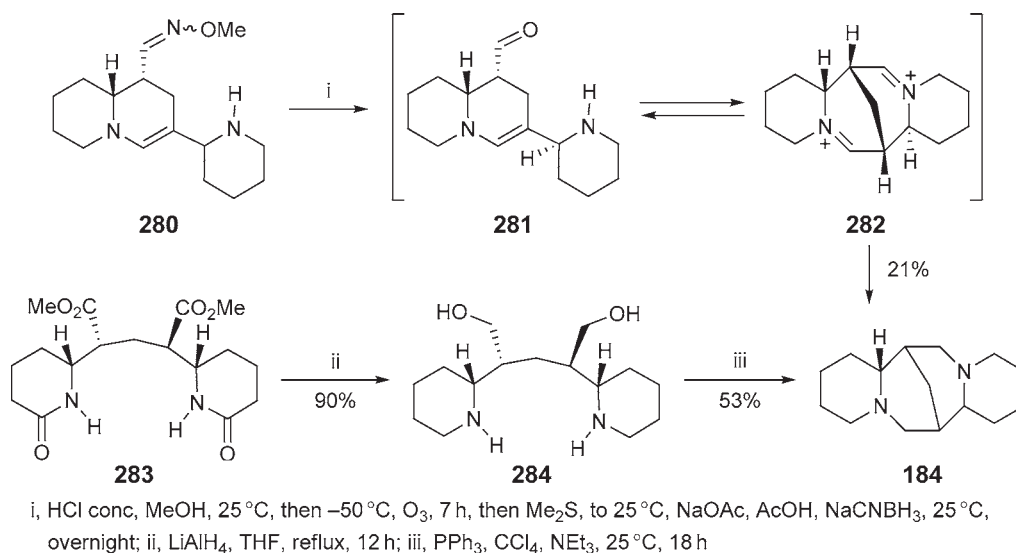


i, MsCl, NEt₃, DCM; ii, a toluene, reflux, b Pd/C, NH₄⁺HCOO[−], MeOH; iii, for **278a**: NEt₃, DCM, reflux for **278b**: NaH, THF, 25 °C; iv, Pd/C, H₂; EtOH, HCl aq (2 equiv), then NEt₃

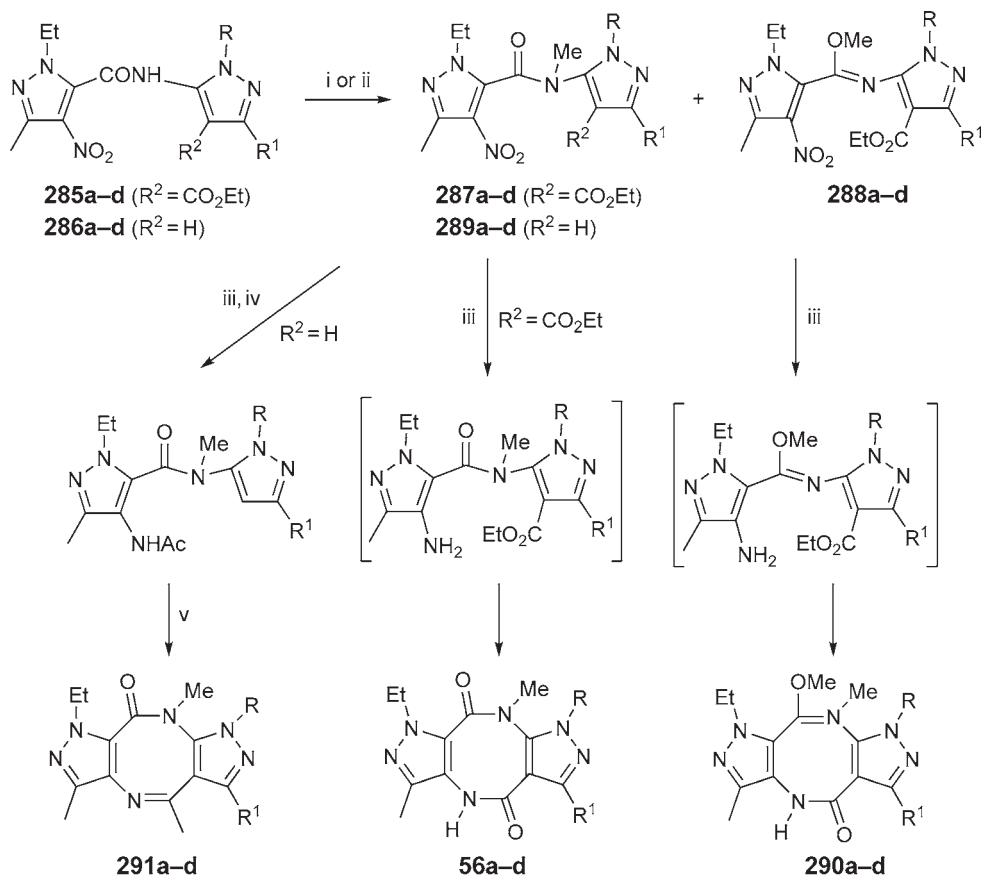
Scheme 51

Sparteine **184** was obtained by two different approaches. In the first, the starting material was oxime **280** which underwent oxidative removal of the oxime using ozone and acid. The reaction proceeded very slowly and incompletely, probably because ozone had to react with a species that was protonated at the two nitrogen atoms. During the ring closure of **281** to **282** with AcOH/NaOAc an imine–enamine equilibrium occurred, enabling the formation of an intermediate with diaxial substituents at C-1 and C-3, which are required for cyclization. Reduction of the dication **282** led to (+)-sparteine **184**, as the only isomer in 21% yield <1996JOC5581>. The second approach involved the reduction of **283** resulting in the transformation of the bis-piperidin-2-one portion to the corresponding piperidine rings and in the conversion of the methoxycarbonyl moieties to the corresponding hydroxyl groups to give **284**, which upon treatment with PPh₃ and CCl₄ afforded sparteine (Scheme 52) <2005OBC1557>.

Methylation of amides **285a–d** (R² = CO₂Et) with an ethereal solution of diazomethane afforded both the *N*-methylated **287a–d** and the *O*-methylated derivatives **288a–d** in 27–73 and 19–46% yields, respectively. Both **287a–d** and **288a–d**, upon catalytic hydrogenation with Raney-nickel, directly afforded the dipyrazolodiazocines **56a–d** and **290a–d** in 38–50% and 39–66% yields, respectively. Evidently, the intermediate amino group spontaneously underwent ring closure with the ester group to give the eight-membered ring <1995JHC1589>. When **286a–d** (R² = H) were methylated with Me₂SO₄, only the *N*-methylated derivatives **289a–d** (R² = H) were obtained in 64–68%. Reduction of the nitro group of these latter with Raney-nickel followed by treatment with Ac₂O produced, in 60–80% yields, the corresponding acetyl amino compounds, which were then subjected to a Bischler–Napieralski cyclization to give the dipyrazolo-diazocines **291a–d** in good yields (65–75%) (Scheme 53) <1995JHC835>.



Scheme 52



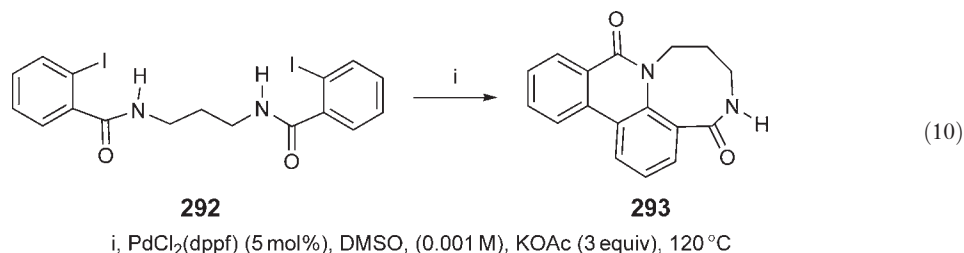
a: R = Ph, R¹ = H; **b:** R = Ph, R¹ = Me; **c:** R = Me, R¹ = H; **d:** R = R¹ = Me

i, CH₂N₂, Et₂O, 25 °C, overnight; ii, Me₂SO₄, KOH aq (10%), 25 °C, 3 h; iii, Raney-nickel, H₂, 25 °C, 24 h; iv, Ac₂O, 25 °C, 24 h; v, POCl₃, reflux, 2 h

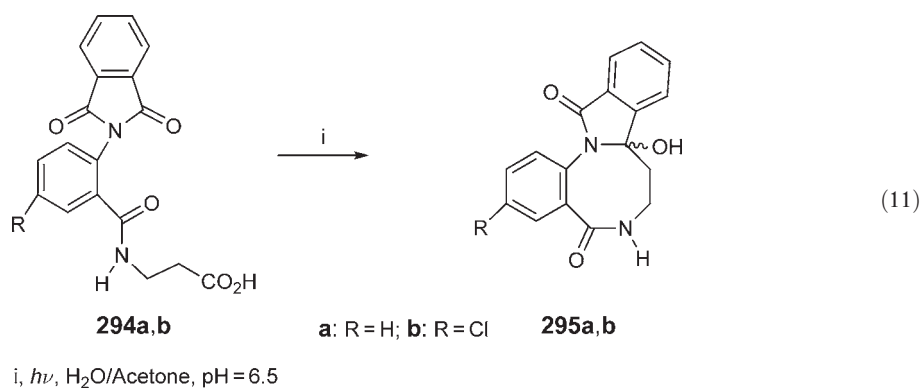
Scheme 53

Linear amide **292**, upon catalysis of $\text{PdCl}_2(\text{dppf})$, prepared *in situ* from $\text{Pd}(\text{OAc})_2$ and BINAP in a molar ratio of 1:2, produced, in moderate yield, the azaphenanthrene-fused diazocine **293**.

The formation of **293** was explained considering that Pd triggered initially an intramolecular amination, followed by C–H activation, and then aryl–aryl bond formation. Such a process is dramatically temperature dependent and higher yields were obtained when the reaction was performed at higher temperature (Equation 10) <2003AGE4774, 2004JA14475, 2006CRV4644>.



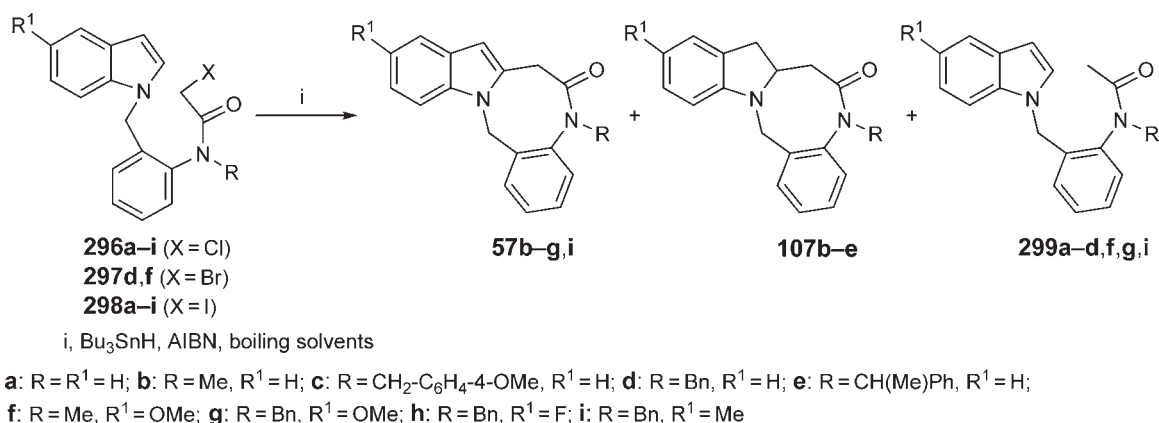
Coupling of phthaloylanthranilic amides with β -alanine originated amidoacids **294a,b** that contained an electronically excited acceptor (phthalic carbonyl), a linker (ethylene chain), and an electron donor (carboxylic group) capable of undergoing a photoelectron transfer (PET)-induced decarboxylation–cyclization to eight-membered cycles. Thus, irradiation of **294a** produced the isoindolo-benzodiazocine **295a** in 75% yield along with the ‘simple’ decarboxylation product (10%). A lower yield was observed in the case of the chloro derivative **295b** (Equation 11) <2002PPS237>.



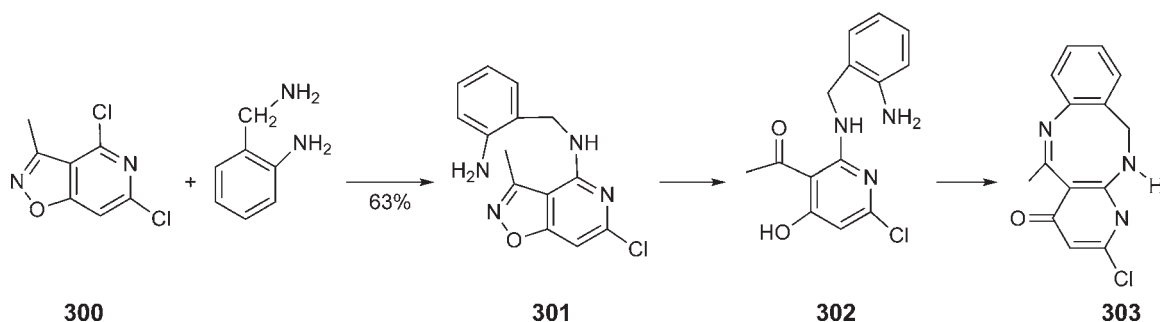
A free-radical cyclization of 1-substituted indole derivatives with appropriately positioned haloacetamide functionalities, such as **296a–i**, **297d,f**, and **298a–i**, was a versatile route to indolo[2,1-*d*]-1,5-benzodiazocines **57**. Thus, slow addition of tributyltin hydride to a boiling toluene solution of the haloacetamides, in the presence of azobisisobutyronitrile (AIBN), gave the indole-fused diazocines **57** and **107**, in fair yields, along with the reduced **299**. Aromatization of **107** was achieved in a separate aromatization reaction (see Section 14.07.2.5, Scheme 21). An increase in the cyclization product yields was generally observed as the steric bulk of the substituent R^1 on the haloacetamide nitrogen was increased. When the haloacetamides **296a** and **298a** with $\text{R}^1 = \text{H}$ were reacted, only the reduction product **299a** was obtained. A temperature-dependence study of the cyclization revealed increasing yields with higher boiling solvents. Cyclization in boiling xylenes and mesitylene increased the yields of **57** and neither the dihydroindole-fused products **107** nor the acetamides **299** were isolated when **298b** or **298d** was the substrate (Scheme 54) <2005T941>.

4,6-Dichloro-3-methylisoxazolo[4,5-*c*]pyridine **300** underwent nucleophilic substitution with 2-(aminomethyl)aniline to give the corresponding aminopyridine intermediate **301** in good yield.

Reaction of this latter with $\text{Mo}(\text{CO})_6$ in MeOH released the masked acetyl group of the isoxazole ring by ring opening at the level of N–O bond to give the acetylpyridine, **302**, which upon prolonged reflux in xylene gave the benzopyridodiazocine **303** in 46% yield (Scheme 55) <2003S2518>.



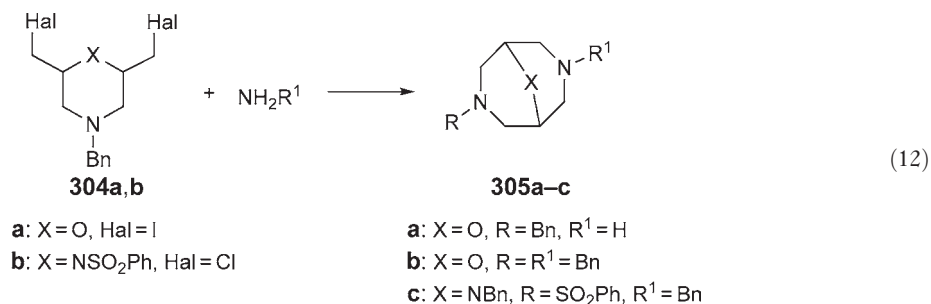
Scheme 54



Scheme 55

14.07.2.7.3 Ring syntheses from $\text{C}_6\text{N} + \text{N}$ units

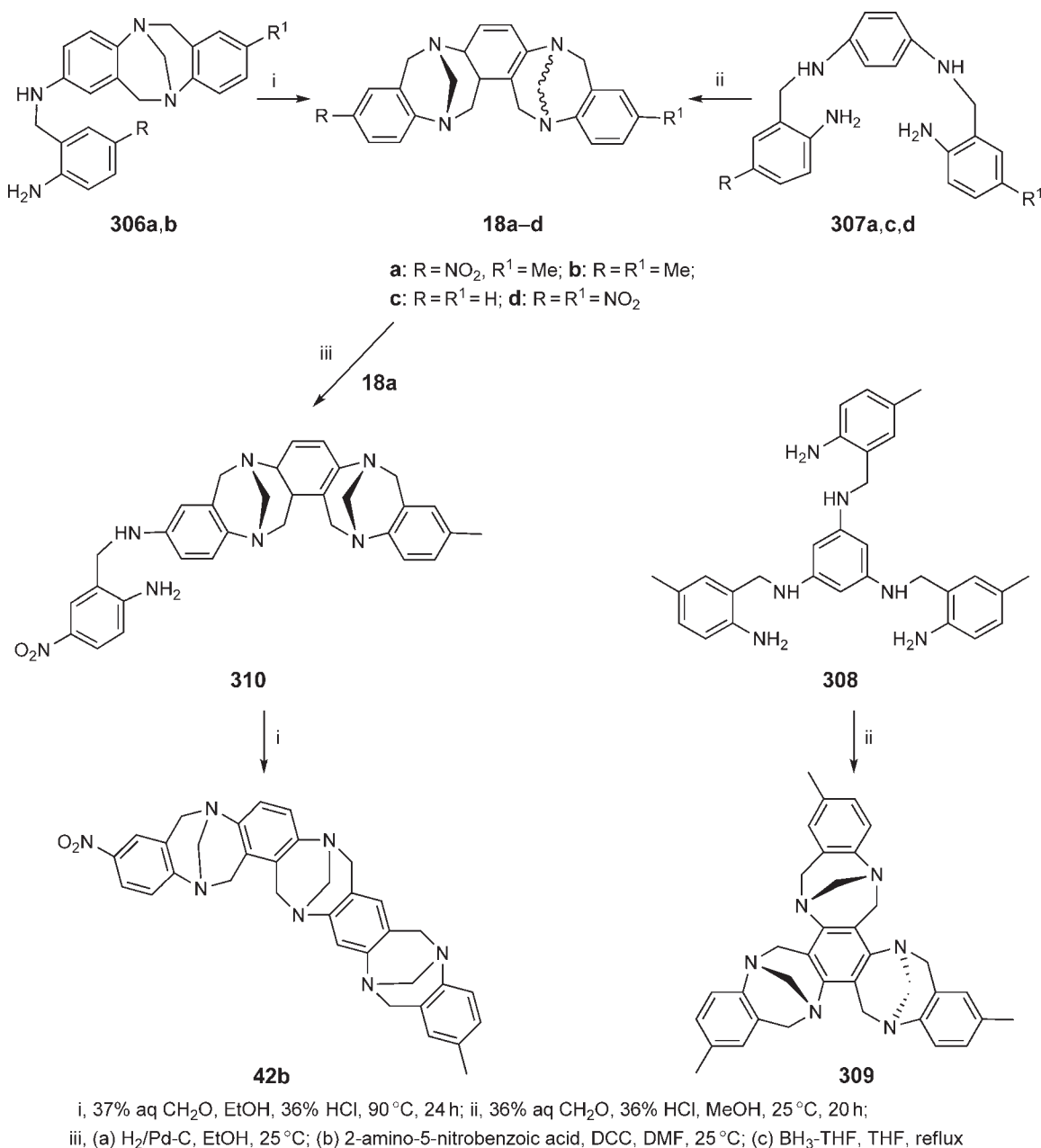
Oxygen-bridged diazocines **305a,b** were prepared by nucleophilic substitution of ammonia or benzylamine on the bis-iodomethyl substituted morpholine derivative **304a** in high yield. Diazocines **305a,b** represent the key intermediate for the synthesis of numerous N,N' -disubstituted oxabispindines, having antiarrhythmic activity, in which one of the N -substituents is an (alkoxycarbonylamino)alkyl group <2006WO137769, 2006WO137770>. Refluxing piperazine derivative **304b** in xylene with 3 equiv of benzylamine resulted in a clean conversion to the sulfonamide-bridged diazocine **305c** (75%) (Equation 12) <2005TL5577>.

14.07.2.7.4 Ring syntheses from $\text{C}_5\text{N}_2 + \text{C}$ units

The tweezer-shaped Tröger's bases **18a,b** were prepared by cyclization of the amines **306a,b**, which were heated with formaldehyde in the presence of concentrated HCl . Amine **306a** afforded, in a 63% yield, a 4:1 mixture of stereoisomers *syn* and *anti* of **18a**. Amine **306b**, instead, under the same reaction conditions, afforded a complex mixture from which a significant quantity of **306b** was recovered and the *anti* stereoisomer of **18b** was obtained in very low yield (6%)

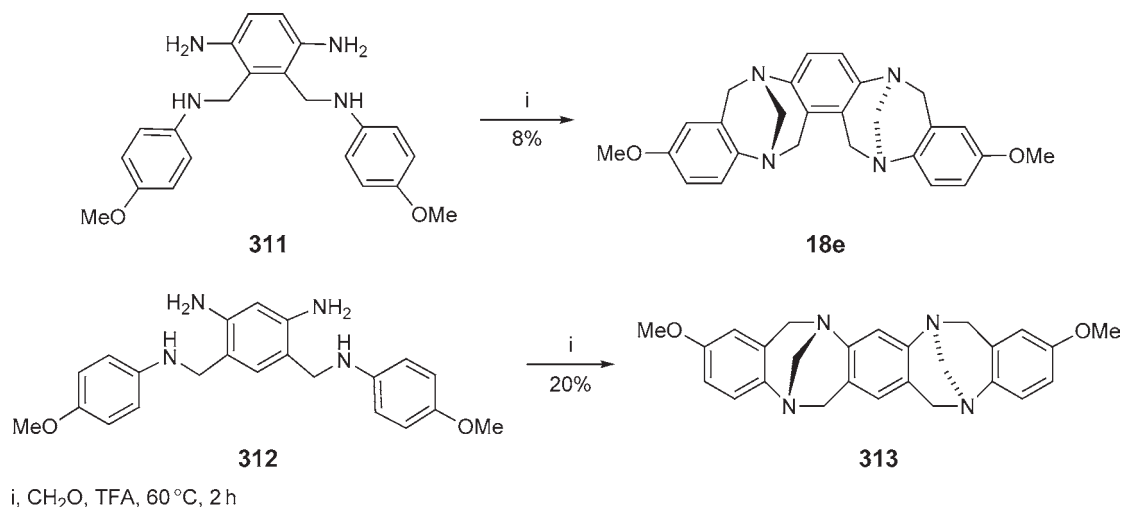
<2001JOC1607>. The Tröger's bases **18a,c,d** were alternatively obtained, although in low yield, from the tetraamine derivative **307a,c,d** by reaction with formaldehyde and concentrated HCl, through a simultaneous formation of the two eight-membered rings. That both cyclizations led to the angular **18a-d** and no formation of linear derivatives was observed were somewhat surprising facts since these latter would be preferred due to steric effects. However, the formation of **18a-d** might be explained by higher reactivity of the central benzene meso position of **307** towards electrophilic substitution <2002CCC609, 2004ARK86, 2004EJO1097>. The same simultaneous ring-closure approach was used for the preparation of the tris-Tröger's base derivative **309** from the amino derivative **308** <2002CCC609>.

The tris-Tröger's base derivative **42b** was obtained from **18a** by reduction of the nitro group, successive condensation with 2-amino-5-nitrobenzoic acid and reduction of carbonyl group to give **310**, which underwent the final cyclization to give **42b**, as a 11:8:7 mixture of *anti-syn*, *syn-anti*, and *syn-syn* isomers (Scheme 56) <2004MC235>.



Scheme 56

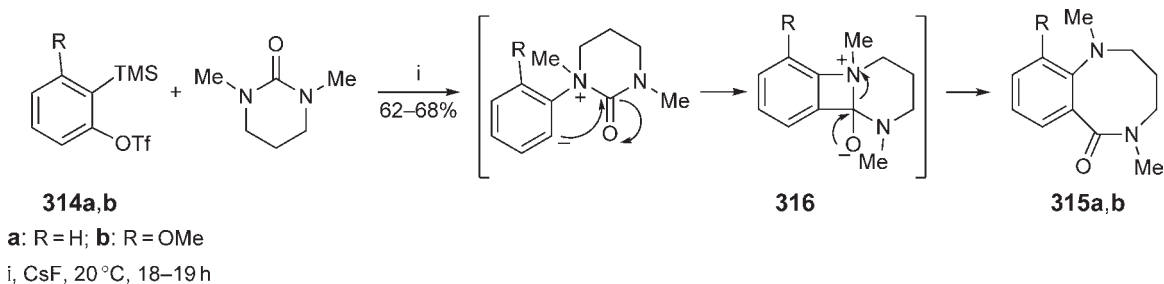
The angular isomer **18e** was obtained, in low yield, as a 1:1 mixture of the *syn* and *anti* diastereoisomers, from the tetraamine **311** with paraformaldehyde in TFA. The corresponding linear isomer was obtained instead, also as a 1:1 mixture of the *syn* and *anti* diastereoisomers, under the same reaction condition, from the tetraamine **312**. A lower yield was observed when, instead of the methoxyaniline moiety, in the starting tetraamine there was a 2-amino-naphthalene moiety (**Scheme 57**) <2006OL4867>.



Scheme 57

14.07.2.7.5 Ring syntheses from C₄N₂ + C₂ units

Addition of *N,N'*-dimethylpropyleneurea to arynes generated from 2-(trimethylsilyl)aryl triflates **314a,b** provided a smooth and straightforward synthesis of benzodiazocines **315a,b**. A plausible mechanism involved the addition of a urea nitrogen to generate a zwitterion **316**, which by the intramolecular nucleophilic substitution at the carbonyl carbon atom furnished the product. The perfect regioselectivity observed in the reaction could be rationally explained by steric considerations: urea attacked the aryne carbon atom *meta* to the substituent. Good yields were also observed when *N,N'*-dimethylpropyleneurea was reacted with 1-(trimethylsilyl)-2-naphthyl triflate to give the naphthodiazocine (**Scheme 58**) <2002AGE3247>.

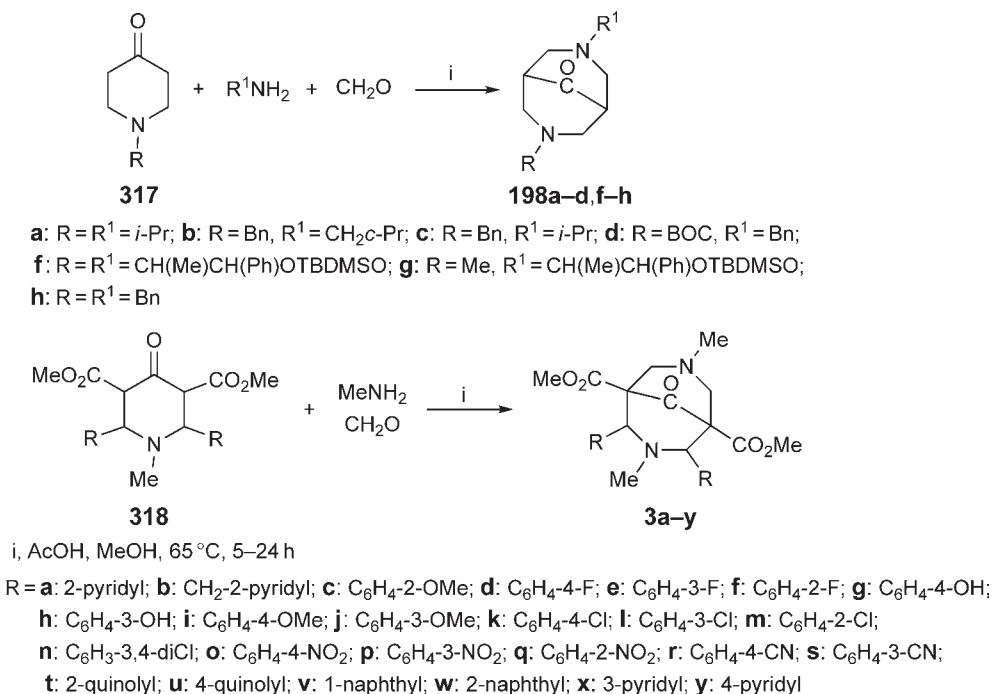


Scheme 58

14.07.2.7.6 Ring syntheses from C₄N + 2C + N units

Treatment of the *N*-substituted piperidinones **317** with primary amines and formaldehyde gave bispidinones **198**. This double Mannich reaction provided a valuable and versatile approach to a large number of bispidinone derivatives. The reaction took place with a wide variety of primary amines and provided both symmetric and asymmetric bispidinones depending on whether the primary amine and the piperidinone nitrogen bore the same or different substituents.

Thus, piperidone **317** gave 1,5-substituted bispidinones **198a–d,f–h** generally in good yield <1996JME2559, 2000EJO391, 2002CEJ4767, 2005OL4459>. Starting from 2,3,5,6-tetrasubstituted 1-methylpiperidinones **318**, the tetrasubstituted 1,5-dimethylbispidinines **3a–y** were obtained (Scheme 59) <1997JCD347, 2000JME3746>.



Scheme 59

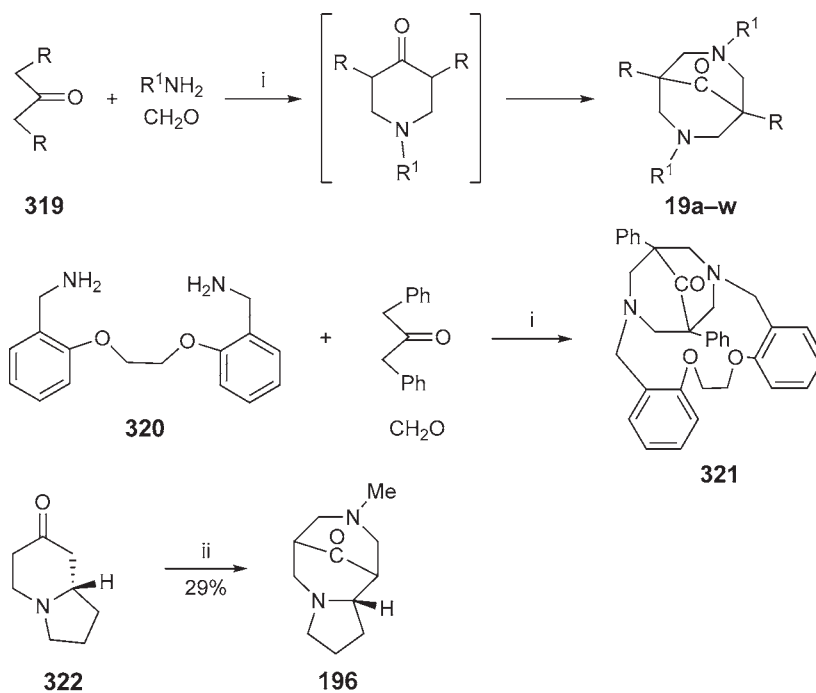
A closely related synthesis of symmetrically substituted bispidinones **19a–w** is provided by the Mannich reaction with acetone derivatives **319**, paraformaldehyde, and the acetate salts of various amines. Such a reaction is formally a $C_2N + C_2N + 2C$ synthesis but is reported here because of its relationship to the above bispidinone synthesis. In this case the intermediate piperidinone cannot be isolated but once formed, it reacted with the primary amine and formaldehyde to give the eight-membered ring <1995T2055, 1997OM1167>. Similarly, the diamine **320** reacted with dibenzyl ketone and formaldehyde to give the macrocycle **321** in 48% yield <1995T4819>.

Such a Mannich cyclization worked for fused piperidines, as demonstrated by the isolation of pyrrolo-diazocine **196** derived from **322** with methylamine and formaldehyde <1999J(P1)3623> (Scheme 60). Good results were also obtained when arylaldehydes were reacted with ethyl acetoacetate in the presence of NH₄OAc in refluxing EtOH to produce carbonyl-bridged diazocines <2005MRC479>.

Nucleophilic substitution of benzylamine on 4-benzenesulfonyl-1-benzyl-2,6-bis-chloromethylpiperazine **323** led, in good yield, to the *N*-benzyl-bridged diazocine **305c**, an anti-inflammatory agent <2005WO103054>. The *N*-acetyldiallylamine **324**, under Rh^I-catalyzed hydroformylation conditions in the presence of primary amines produced, in low yields (15–33%), the diazocines **325a,b**, which was obtained in a 1:1 mixture of diastereoisomers, along with the pyrrole derivatives **326a,b**, as minor products (6–7%) (Scheme 61) <2000EJO2367>.

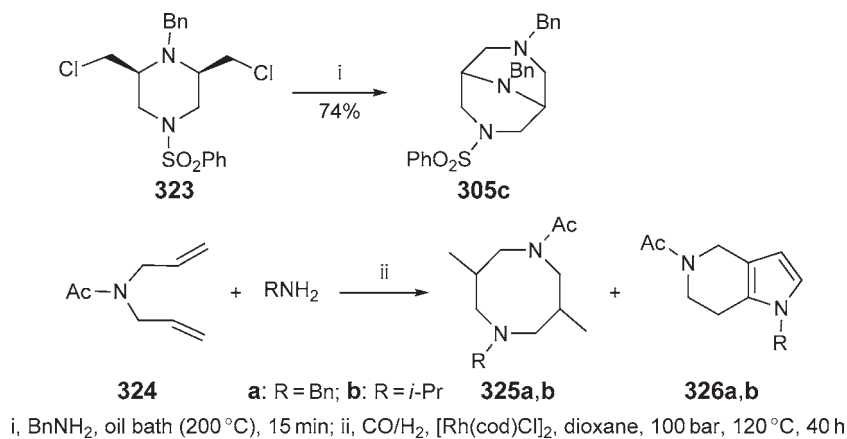
14.07.2.7.7 Ring syntheses from C₃N₂ + C₃ units

Diazocines **104a,b**, intermediates for the production of solid propellant oxidizers, were efficiently prepared (76–86%) from the reaction of **327a,b**, 1,3-diaminopropan-2-one, and methallyl dibromide <2001TL2621, 2002USP6417355>. Reaction of **327a** with 1,3-dibromopropan-2-ol produced the 3-hydroxy-*N,N*-protected diazocine **328a** (Scheme 62) <2006JHC519>.



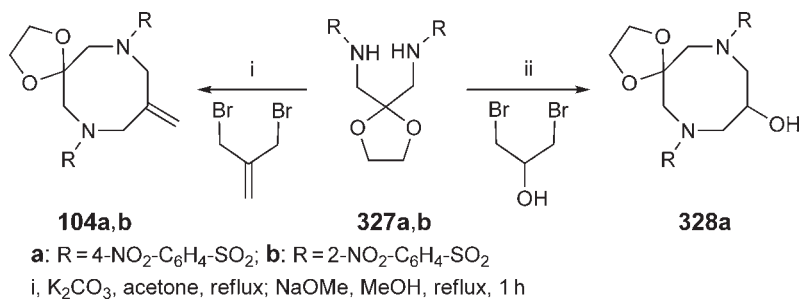
i, AcOH, EtOH, reflux, 4–5 h; ii, $MeNH_2$, $(HCHO)_n$, AcOH, MeOH, reflux, 16 h

Scheme 60



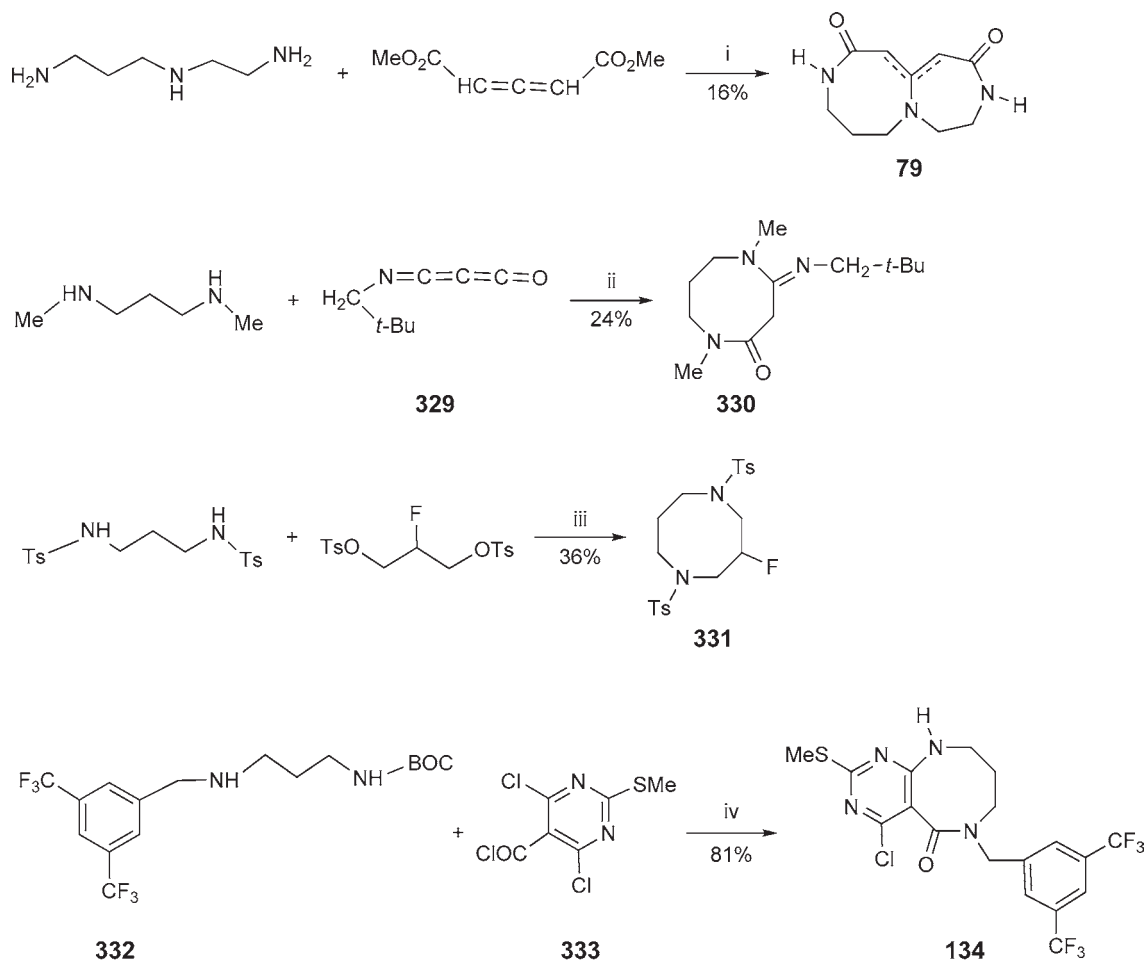
i, $BnNH_2$, oil bath (200 °C), 15 min; ii, CO/H_2 , $[Rh(cod)Cl]_2$, dioxane, 100 bar, 120 °C, 40 h

Scheme 61



Scheme 62

In **Scheme 63**, four further examples of 1,5-diazocines obtained from 1,3-propanediamine derivatives are outlined, although only one was reported in good yields. Thus, *N*-(2-aminoethyl)-1,3-propanediamine reacted with methyl allene dicarboxylate to give the diazepinodiazocine **79** in which the double bond can be located either on the diazocine ring or in the diazepine nucleus <1995H(41)1709>.



i, CHCl_3 , 0–25 °C, 12 h; ii, (neopentylimino) propadienone in dry, DCM, *N,N*-dimethylpropylenediamine in dry, Et_2O , (slow addition), 21 h; iii, NaH, DMF, 100 °C, 17 h; iv, **a**: NEt_3 , THF, 0–25 °C, 3 h; **b**: HCl/EtOH, 25 °C, 2 h; **c**: K_2CO_3 , DMF, 80 °C, 1 h

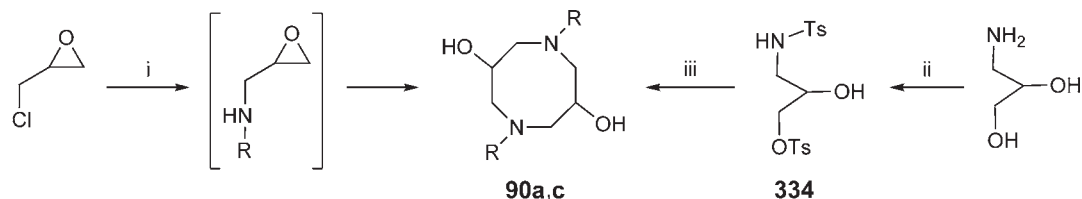
Scheme 63

N,N-Dimethylpropylenediamine reacted with (neopentylimino)propadienone **329**, generated by flash vacuum thermolysis from the suitable Meldrum's acid derivative, to give diazocinone **330** <2002JOC2619>. Reaction of *N,N'*-propane-1,3-diyl-ditosylamide with *N,N'*-(2-fluoropropane-1,3-diyl)ditosylamide produced the monofluoro substituted *N,N'*-ditosyl diazocine **331** <2006CCC3190>. The *N,N*-disubstituted diaminopropane **332** reacted with the acyl chloride **333** to give the corresponding amide, which was not isolated but underwent BOC deprotection with HCl and intramolecular cyclization with K_2CO_3 to give the pyrimidodiazocine **134** in good yield <2005BMC5717>.

14.07.2.7.8 Ring syntheses from $\text{C}_3\text{N} + \text{C}_3\text{N}$ units

Reaction of epichlorohydrine with aryl sulfonamides afforded a mixture of the cyclodimerization products, *cis* and *trans* 1,5-bis(arylsulfonyl)-3,7-dihydroxyoctahydro-1,5-diazocines **90a,c** <1995JOC1959, 1998JOC1566, 2006USP7145003>.

Alternatively, **90a** could be prepared from 3-amino-1,2-propanediol with tosyl chloride and subsequent cyclodimerization of **334** <1995JOC1959> (Scheme 64). The *N,N*-disubstituted diazocines **49a,b,d-f** were obtained through such a cyclodimerization. Thus, 3-chloro-2-(chloromethyl)-1-propene reacted with tosylamide or mesylamide to give, probably through the intermediates **335**, the cyclodimeric products **49b,e** in 50% yield <1996JOC8897>. The *N,N*-ditosyl derivative **49b** could be also obtained, in 60% yield, from the reaction of 3-chloro-2-(chloromethyl)-1-propene with tosylamide <2002WO44168>. The Pd-catalyzed reaction of arylsulfonamides or cyanamide with the bis-carbonate **336** furnished the eight-membered rings **49a,b,d,f** in 30–51% yields, along with minor quantities of other macrocycles <1998T14885>.



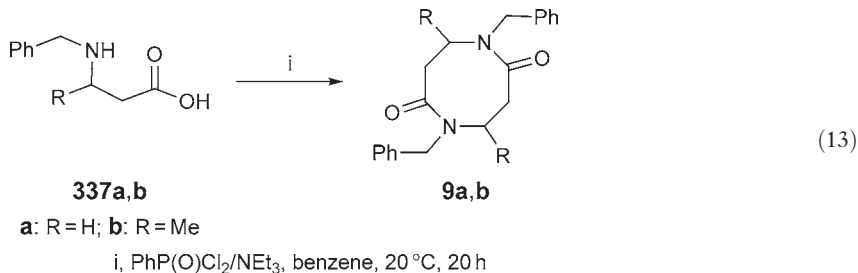
a: R = Ts; **c:** R = 4-NO₂-C₆H₄SO₂

a: R = 2,4,6-*i*-Pr-C₆H₂SO₂; **b:** R = Ts; **d:** R = 2,3,4,5,6-Me-C₆SO₂; **e:** R = Ms; **f:** R = CN

i, R-NH₂, NaOH, 95% EtOH, reflux, overnight; ii, TsCl, pyridine, 25 °C overnight; iii, LiH, THF, N₂, reflux, 12 h
iv, RNH₂, K₂CO₃, MeCN, reflux, 4 h; v, Pd(dba)₂/dppf, THF, 25 °C, 14 h

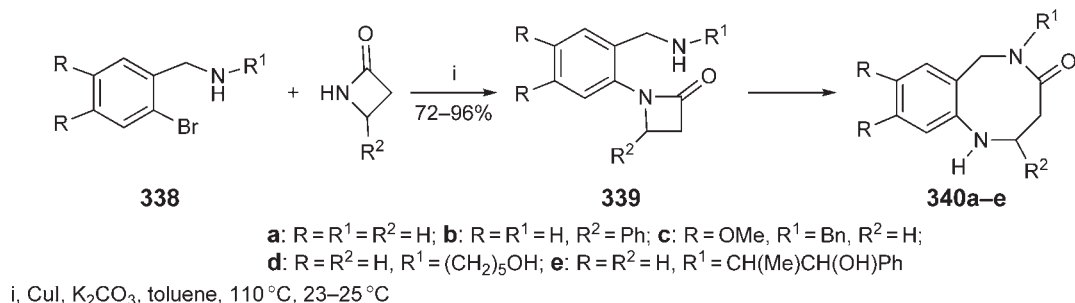
Scheme 64

Reaction of (*N*-benzyl-amino) propionic acid **337a** and its 3-methyl derivative **337b** with phenylphosphonic dichloride in the presence of excess of NEt₃ gave the diazocinediones **9a,b**, which have a cyclo-β-dipeptide structure (Equation 13). The reaction was performed under different reaction conditions, that is, changing solvents, temperature, reaction time, and reactant concentration. The best results (54–68% yields) were obtained in benzene at 80 °C for 20 h. The diazocinediones **9a,b** were formed in similar yields at high and low concentrations of the reactant <2001T1883>.



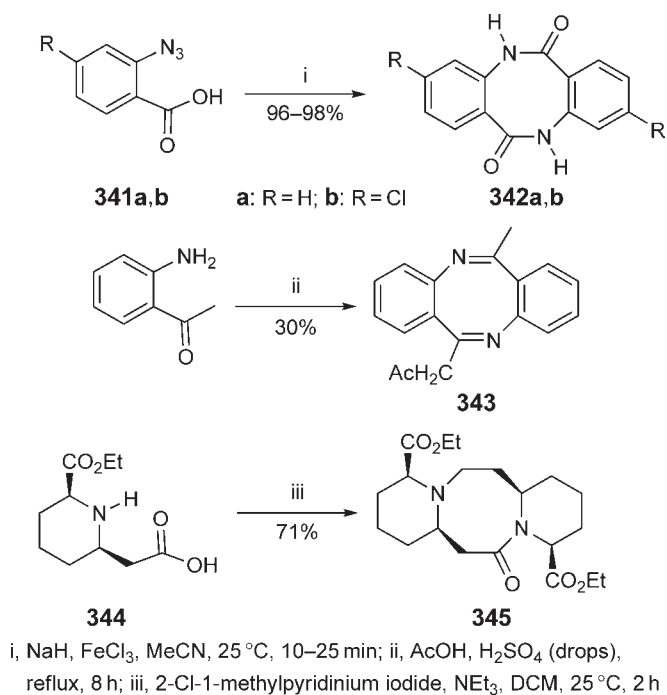
Reaction of 2-bromobenzylamines **338** with 2-azetidinones in the presence of CuI produced benzodiazocines **340a-e** in excellent yields through a facile domino process involving the C–N coupling to give the intermediates **339** and subsequent ring expansion. Presumably the amino group in **338** bound the copper catalyst, activating the aryl bromide toward oxidative addition. The reaction tolerated substituents on the β-lactam ring, electron-donating groups in the aryl bromide, and an aliphatic OH group. If a norephedrine-derived aryl bromide containing a relatively

bulky *N*-substituent **338e** was used, a mixture of the desired diazocine **340e** and the β -lactam intermediate **339e** was obtained. To catalyze the ring expansion, which is essentially a transamidation Lewis acid catalysts were used but AcOH was the most effective (Scheme 65) <2004JA3529>.



Scheme 65

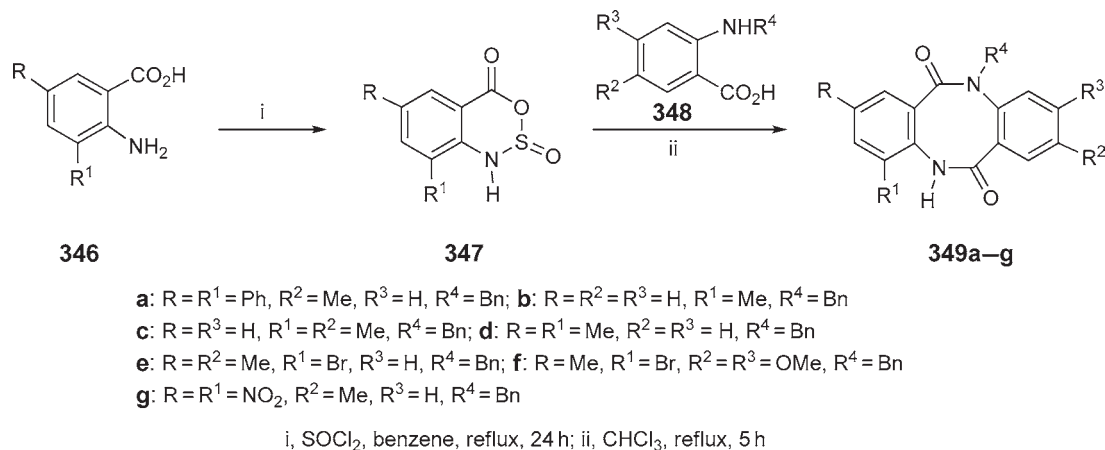
Dibenzodiazocinediones **342a,b** were obtained in nearly quantitative yields by reduction of the azido group of the 2-azidobenzoic acid derivatives **341a,b**. The reduction was performed with NaI/ $FeCl_3$ and was selective in the presence of a nitro group <2002TL6861>. Dibenzodiazocinediones **342b** could be also obtained in 78% yield by Pd-catalyzed carbonylation dimerization of 2-iodo-4-chloroaniline <2006T12051>. In the reaction of 2-aminoacetophenone with 1-oxocyclopentylindoles in AcOH and in the presence of H_2SO_4 , the formation of the dibenzodiazocine **343** in 30% yield was always observed as a result of a cyclodimerization followed by acetylation of one of the diazocine methyl group with the excess of AcOH <2004IJB2231>. Diazocine **345** was obtained in good yield by cyclodimerization of the aminoacid **344**, upon treatment with Mukaiyama's reagent (Scheme 66) <1995JOC2922>.



Scheme 66

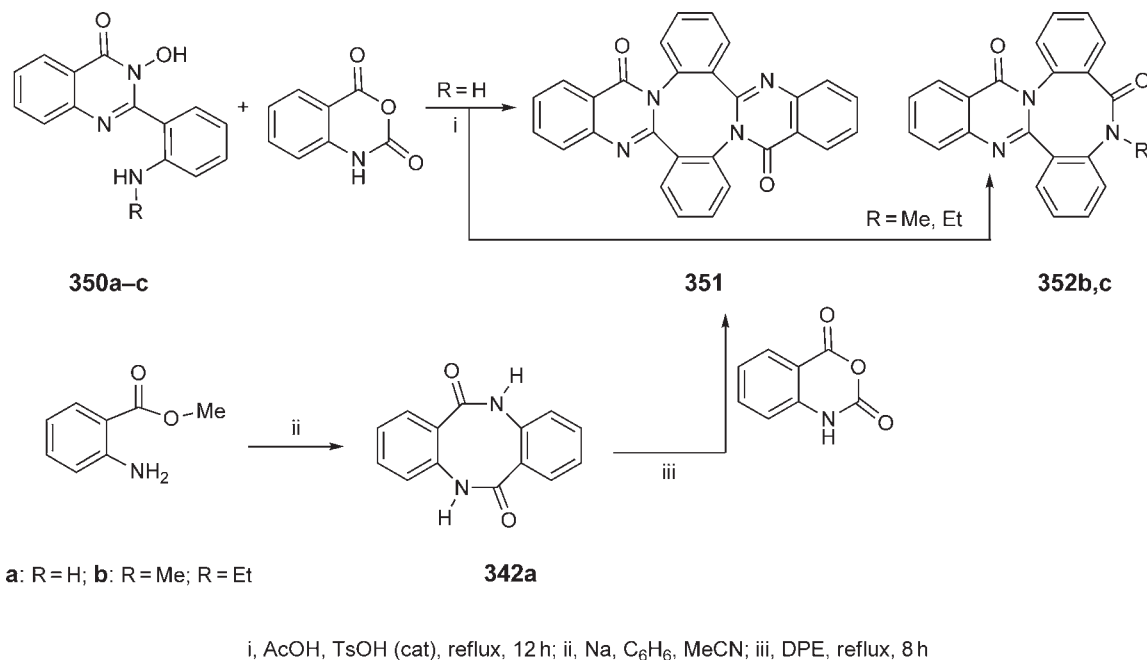
When substituted anthranilic acids **346** were reacted with thionyl chloride **347** was produced, the thio analogues of isatoic anhydride, which readily underwent reaction with differently substituted *N*-alkylantranilic acids **348** to

furnish the nonsymmetrically substituted dibenzodiazocinediones **349a–g** in 58–88% yields. The aromatic substituents were both electron-withdrawing or -donating. In some cases, a symmetrical dibenzodiazocinedione, derived by self-condensation-decomposition of **347**, was isolated as side product in low yield (**Scheme 67** <2004TL1377>).



Scheme 67

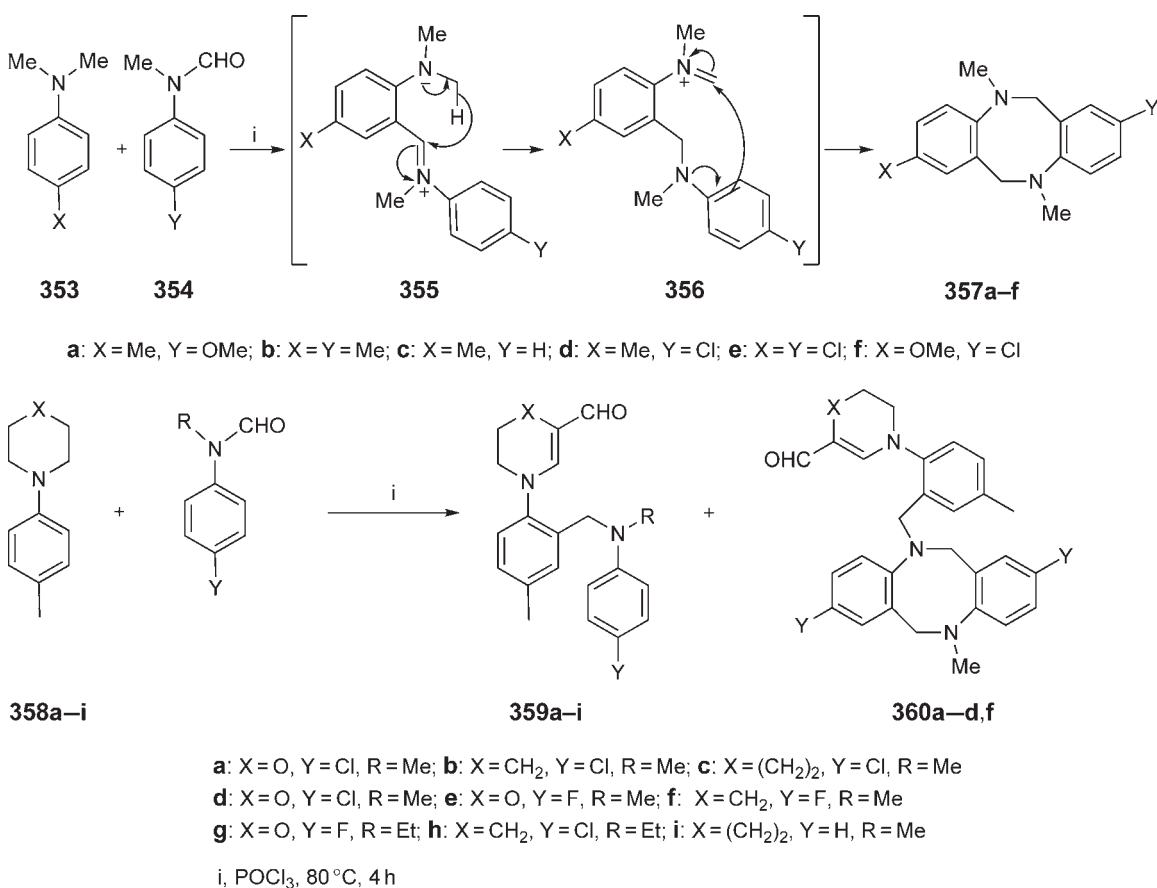
Attempt to aroylate the amino group of **350a** surprisingly produced the dibenzodiazocinodiquinazolinone **351** in 62% yield. In the case instead of **350b,c**, the dibenzodiazocinoquinazolines **352b,c** were isolated in 72–73% yields. In an alternative synthesis, **351** was obtained in 60% yield by refluxing a mixture of methyl anthranilate and isatoic anhydride in diphenyl ether. A plausible mechanism involved the initial cyclodimerization of the anthranilate to give **342a**, followed by condensation with iminoketene, generated by the decomposition of isatoic anhydride. This route was proven by the isolation of **342a** and by reaction of the latter with isatoic anhydride to give **351**. It was also discovered that isatoic anhydride alone, under microwave (and pyrolysis) conditions yielded **351** by an initial cyclodimerization of the iminoketene to give **342a**, followed by double annelation of two additional molecules of iminoketene (**Scheme 68** <2002S2168>).



Scheme 68

A cyclodimerization, analogous to that of methyl anthranilate, was exhibited by 2-aminothiophenes bearing a carboxylic portion in position 3 to give the dithienodiazocines. In that patent, the procedures for the synthesis of unsymmetrical dithienodiazocines, thienobenzodiazocines and tetracyclic diazocines were also described <2004WO010136>.

Reaction of 4-substituted *N,N*-dimethylanilines **353** with *N*-methylformanilides **354** in POCl₃ did not give the expected *ortho*-formylated products but rather dibenzodiazocines **357a–f** in generally fair yields. This transformation was explained in terms of attack of the Vilsmeier reagent, derived from **354** and POCl₃, at the *ortho* position to the dimethylamino group of the anilines **353** forming the iminium ion **355**. A 1,5-sigmatropic shift of hydride from the α -position of a tertiary amine to the unsaturated iminium group gave the new iminium intermediate **356**, which underwent an electrophilic cyclization by attacking the adjacent activated aromatic ring to yield diazocines **357** <1995CC1463, 1996TL2679, 1998J(P1)1257>. When 4-tolyl-pyrrolidines **358 a,e,g**, -piperidines **358b,f,h**, -perhydroazepines **358c,i** and -morpholine **358d** were formylated, under similar conditions, the enamino aldehydes **359a–i** were obtained, as the major products (12–60%) instead of the expected pyrrolidino-, piperidino-, azepino-, and morpholino-annelated dibenzodiazocines. A diazocine **360** bearing a substituted benzyl group was found in most cases, albeit in low yields (1–13%) (Scheme 69).

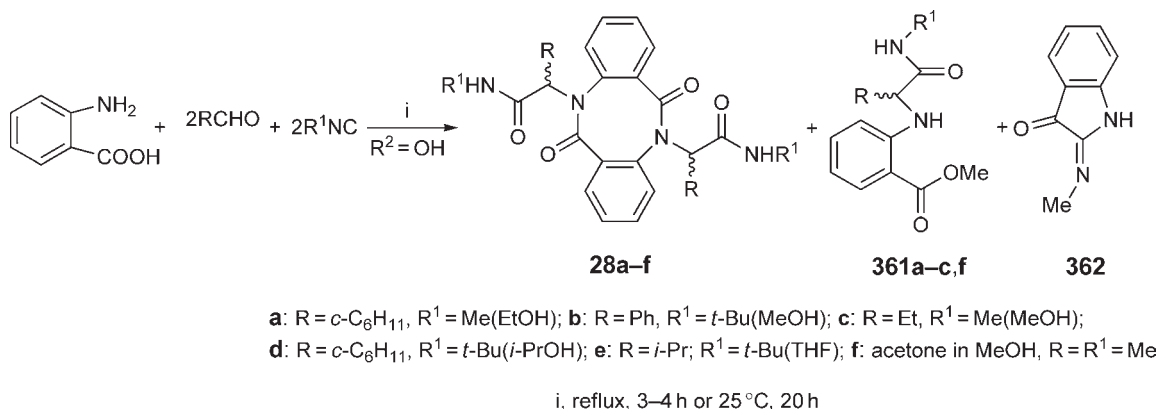


Scheme 69

An *N*-formylated dibenzodiazocine was isolated in some cases in very poor yield <1998J(P1)1257>. Using the same synthetic approach, a series of fused diazocines were obtained. Thus, the action of bis-Vilsmeier reagents derived from *N,N*-dimethyl-*N,N'*-diformyl-4-phenylenediamine with 4-substituted *N,N*-dimethylanilines, the dibenzo[*b,b'*]benzo[1,2-*f*:4,5-*f'*]bis-1,5-diazocines were obtained <2000S640>. Benzo[2,3]pyrido[6,7-*b*]-1,5-diazocines were synthesized from a Vilsmeier reagent derived from 4-*N*-(methylformamido)pyridine reacting with 4-substituted

dimethylanilines <2000TL3475>. Benzo[*b*]naphtho[1,2-*f*]-1,5-diazocine and benzo[*b*]naphtho[2,1-*f*]-1,5-diazocine were obtained from either 1- or 2-dimethylaminonaphthalene, respectively, by Vilsmeier formylation with *N*-methylformanilides <2002S906>. Bis-dibenzodiazocines **44a–j** were obtained from Vilsmeier reagent derived from *N*-methylformanilides with *N,N,N',N'*-tetramethylbiphenyldiamine <2003S2839>.

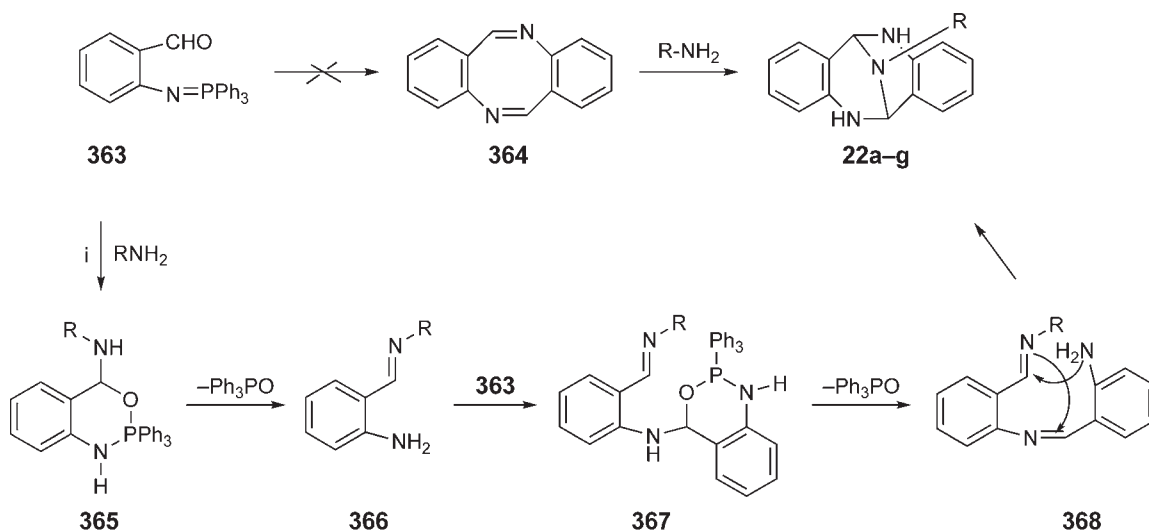
Anthranilic acid reacting with carbonyl compounds, isocyanides and alcohols through a double four-component Ugi reaction provided dibenzodiazocines **28a–f** in 16–80% yields. Sterically hindered aldehydes gave diazocines **28** along with *N*-(carbamoylmethyl)anthranilic esters **361**. When acetone was used as a carbonyl compound and MeOH, as a solvent, the reaction produced the 2-iminoindolin-3-one **362**, as the main product, along with diazocine **28f** and the anthranilic ester **361f** in 16% and 18% yield, respectively. Diazocine **28e** was obtained in 69% yield using THF as a solvent (Scheme 70) <1998T11887>.



Scheme 70

Reaction of iminophosphorane **363** with primary amines in EtOH and in the presence of catalytic quantities of AcOH gave the dibenzodiazocines **22a–g** in 40–80% yield. When the reaction was conducted in absence of the amine, the iminophosphorane was recovered unchanged. Similar results were obtained when **363** was heated in refluxing toluene and even at 220 °C in a sealed tube. Therefore, the conversion of **363** to **22** involving the initial formation of the dibenzodiazocine **364** via a double aza Wittig reaction, followed by cross-addition of the amino group on the two aldimine groups of **364** was ruled out. A reasonable mechanism could involve the initial reaction with the primary amine to give the intermediate **365**, which by loss of Ph₃PO provided the aniline derivative **366**, which reacted with a second equivalent of **363** to give **367** that on the loss of Ph₃PO formed **368**.

Such compounds underwent cyclization by attack of the amine on the adjacent aldimine bond with concomitant attack of the resulting amine on the other aldimine bond (Scheme 71) <1998T997>. Many other iminodibenzodiazocine derivatives, usually referred to as ‘anhydrous dimers’ of the corresponding aminobenzaldehyde, were prepared by methods based on the cyclization of synthetic equivalents of 2-aminobenzaldehydes. Masking one or both amines and the aldehyde functionalities resulted in increased yields of the final products. Thus, 2-tosylaminobenzaldehyde reacted with amino acids or with sulfanilamides to give the dibenzodiazocines **34** <2004RCB2262> or 4-aminosulfonylphenyl-bridged dibenzodiazocines, respectively <1997RCB1931>. Lewis-acid-mediated cyclization of the alkenyl imines of the BOC-protected 2-aminobenzaldehydes produced alkenylimino-bridged dibenzodiazocines in good yields <1998TL7239, 2000JOC655>. Also the ketimine functionality adjacent to the amino group gave good yields of iminodibenzodiazocines, as in the case of **69** <2006EJO2987>. Analogously, substituted 5-aminothieno[2,3-*c*]pyridazine-6-carbaldehydes reacted with primary amines to give the corresponding bis-thienopyridazinodiazocines in 39–87% yields <1998J(P1)3557>. When 2-aminobenzaldehyde was dissolved in acid in the absence of primary amines, a tetramerization process to give the dication 4b,5,15b,16-tetrahydrodibenzo[3,4:7,8]1,5-diazocino[2,1-*b*:6,5-*b'*]diquinazoline-11,22-dium, often abbreviated as H₂TAAB²⁺, occurred. A better yield and easier work-up was achieved if 2-aminobenzaldehyde is generated *in situ* from reduction of 2-nitrobenzaldehyde with Fe or Sn in HCl <1998JOC4515>.



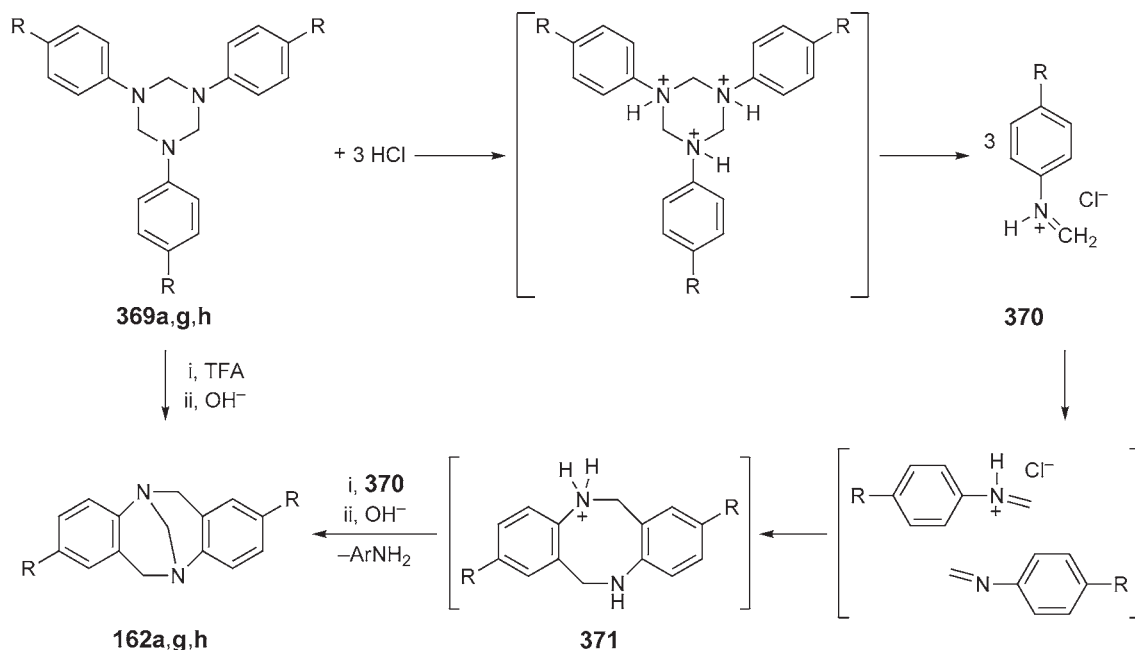
a: R = Bn; **b:** R = CH₂-ferrocenyl; **c:** R = CH₂-3-Pyridyl; **d:** R = C₆H₄-4-Me; **e:** R = C₆H₄-4-OMe;

f: R = C₆H₄-4-Cl; **g:** R = C₆H₄-4-Br

i, EtOH (dry), AcOH (cat.), 25 °C, 16 h

Scheme 71

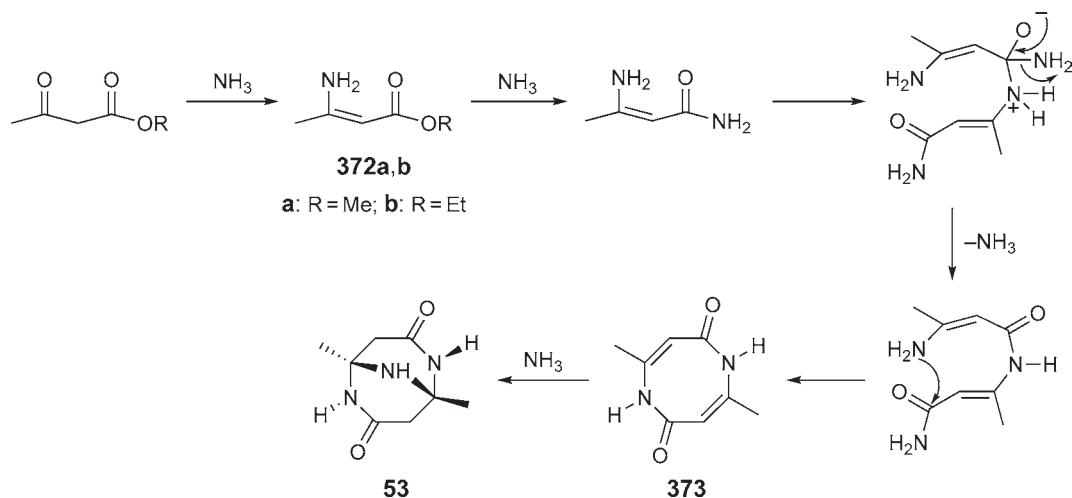
Hexahydro-1,3,5-triazines **369a,g,h** cyclodeverted upon exposure to gaseous HCl to give solid arylmethylen iminium chlorides **370**, which upon treatment with the weak gaseous nucleophiles, such as water vapor, underwent deprotonation and formed, by cyclodimerization with **370**, the intermediate **371**, which, with an additional equivalent of **370**, quantitatively produced the Tröger's bases **162a,g,h** and the corresponding arylamine. This sort of reaction worked equally well in solution. Thus, **369** dissolved in TFA at 25 °C produced **162a,g,h** in 87–90% yields (**Scheme 72**) <2000JPR269>.



a: R = H; **g:** R = Me; **h:** R = OMe

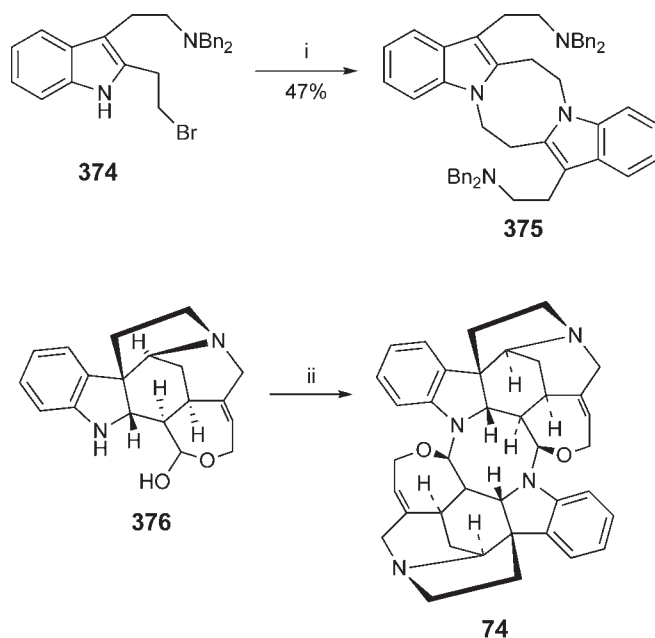
Scheme 72

Ammonolysis of alkyl acetoacetates with 15% aqueous ammonia at 25 °C initially led to the formation of alkyl β -aminocrotonates **372a,b**, which slowly converted into the iminodiazocine **53**, as the main product. A plausible mechanism is depicted in **Scheme 73**. Once formed, the aminocrotonates underwent further ammonolysis to give β -aminocrotonamide, which cyclodimerized to give the diazocinedione **373**, which, in the presence of ammonia, finally underwent a transannular Michael addition to give **53** <2002T55>.



Scheme 73

The diindolodiazocine **375**, a precursor of alkaloid caracurine V, was obtained by cyclodimerization of the indole derivative **374** upon treatment with hydride in DMF <2003T391>. Instead caracurine V **74** was obtained, albeit in low yield, by the dimerization of the polycondensed indole derivative **376** by action of pivalic acid (**Scheme 74**)



i, NaH, dry DMF, 0–25 °C, 35 min; ii, pivalic acid, 120 °C, 14 h

Scheme 74

<2004JME3561>. A further example of cyclodimerization is provided by 2-(benzimidazo-2-yl)-3-dimethylamino-acrylonitrile, which in refluxing AcOH afforded the corresponding dibenzimidazodiazocine ring system in 85% yield <2005JCM440>.

14.07.2.7.9 Ring syntheses from $C_2N + C_2N + 2C$ units

This synthetic approach was widely used for the preparation of numerous Tröger's base analogues. This class of compounds has recently attracted a great deal of attention due to their usage for various purposes in the area of supramolecular chemistry, such as the design of molecular receptors, clathrate hosts, chiral solvating agents, and DNA intercalators. The synthesis generally involved the reaction of substituted anilines with paraformaldehyde in TFA at 25 °C <2001S1873, 2003EJO3179, 2006AXEo3479, 2006AXEo3674, 2006AXEo4887>. Equation 14 variations to this protocol have also been proposed. For instance, urotropine <1996TL5791, 2004TL5601> or aqueous formaldehyde (37%) <1997T11859, 1999TL1289> were used as the carbonyl compound. Lewis acids ($TiCl_4$, $AlCl_3$, $SnCl_4$, $ZnCl_2$, $ZrCl_4$) in DCM were used instead of TFA <2006TA1116> as well as HCl in EtOH or THF <1997T11859, 1999TL1289>. The temperature is generally 25 °C, although higher (50–60 °C) <1999TL1289, 2001S1873> or lower (0 to –15 °C) <2003JHC373> temperatures were used. Comparison of different reaction conditions and related yields were also reported <2001S1873, 2003JHC373>. The yields were from moderate to good and the best results were verified with electron-donating substituents. In Table 2, all the results of synthesis in the past decade are reported. Many of the compounds listed have already been mentioned and numbered in several previous sections of this chapter. Table 2 reports the Tröger's base analogues that were directly synthesized but there are many other derivatives obtained by conversion or replacement of substituents attached to the Tröger's base skeleton as reported in Section 14.07.2.5 (Schemes 25 and 29 and Equation 7). Furthermore, Tröger's base analogues being part of macrocycles, systems containing two or more Tröger's base units and heterocycles fused to the diazocine core of the Tröger's base were also reported. Thus, Tröger's bases **138** ($n = 0$ and $n = 1$) (Equation 6) and **206a–f** (Equation 8) were prepared from the two aniline units connecting each through the *para* positions by the suitable chains <1997T11859, 1995J(P1)2049>. The macrocycle **208** (Scheme 37) containing two Tröger's base units was prepared from the dinitro derivative **209** by reduction and subsequent 'trögerization' of the corresponding diamine derivative <1999AGE3713>.

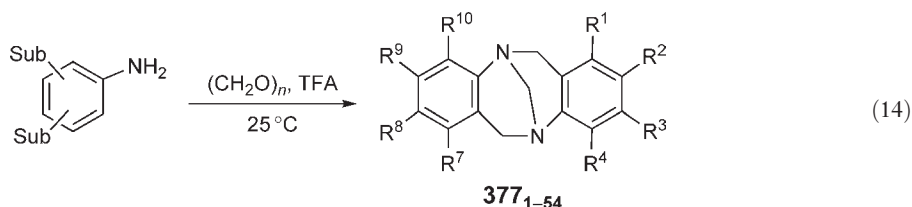


Table 2

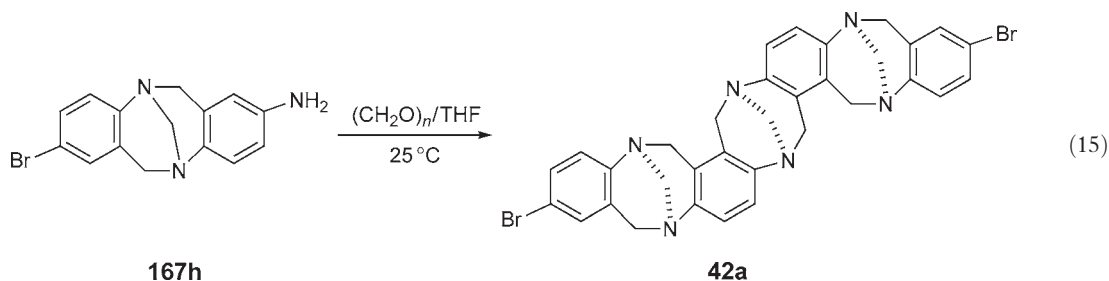
Cpd	R ¹	R ²	R ³	R ⁴	R ⁷	R ⁸	R ⁹	R ¹⁰	References
1	H	Me	H	H	H	Me	H	H	2006TA1116
2	H	Br	H	H	H	Br	H	H	2003JOC373 2006AXEo3674
3	H	CO ₂ Me	H	H	H	CO ₂ Me	H	H	2006AXEo3479
4	H	I	H	H	H	I	H	H	2003JHC373
5	H	Cl	H	H	H	F	H	H	2003JHC373
6	H	F	H	H	H	F	H	H	2003JHC373
7	H	O(CH ₂) ₂ OH	H	H	H	O(CH ₂) ₂ OH	H	H	1997T11859
8	H	CH ₂ SSBn-4-NO ₂	H	H	H	CH ₂ SSBn-4-NO ₂	H	H	1999TL1289
9	H	Bn-4-CO ₂ H	H	H	H	Bn-4-CO ₂ H	H	H	1996TL5791
10	H	Bn-4-CO ₂ Me	H	H	H	Bn-4-CO ₂ Me	H	H	1996TL5791
11	H	Bn-4-CH ₂ -CO ₂ H	H	H	H	Bn-4-CH ₂ -CO ₂ H	H	H	1996TL5791
12	H	CO ₂ Et	H	Br	H	CO ₂ Et	H	Br	2006AXEo4887
13	OH	Benzothiazole-2-yl	H	H	OH	Benzothiazole-2-yl	H	H	2004TL5601
14	OH	Benzoxazole-2-yl	H	H	OH	Benzoxazole-2-yl	H	H	2004TL5601
15	H	Me	H	Br	H	Me	H	Br	2003EJO3179
16	H	Me	H	Cl	H	Me	H	Cl	2003EJO3179

(Continued)

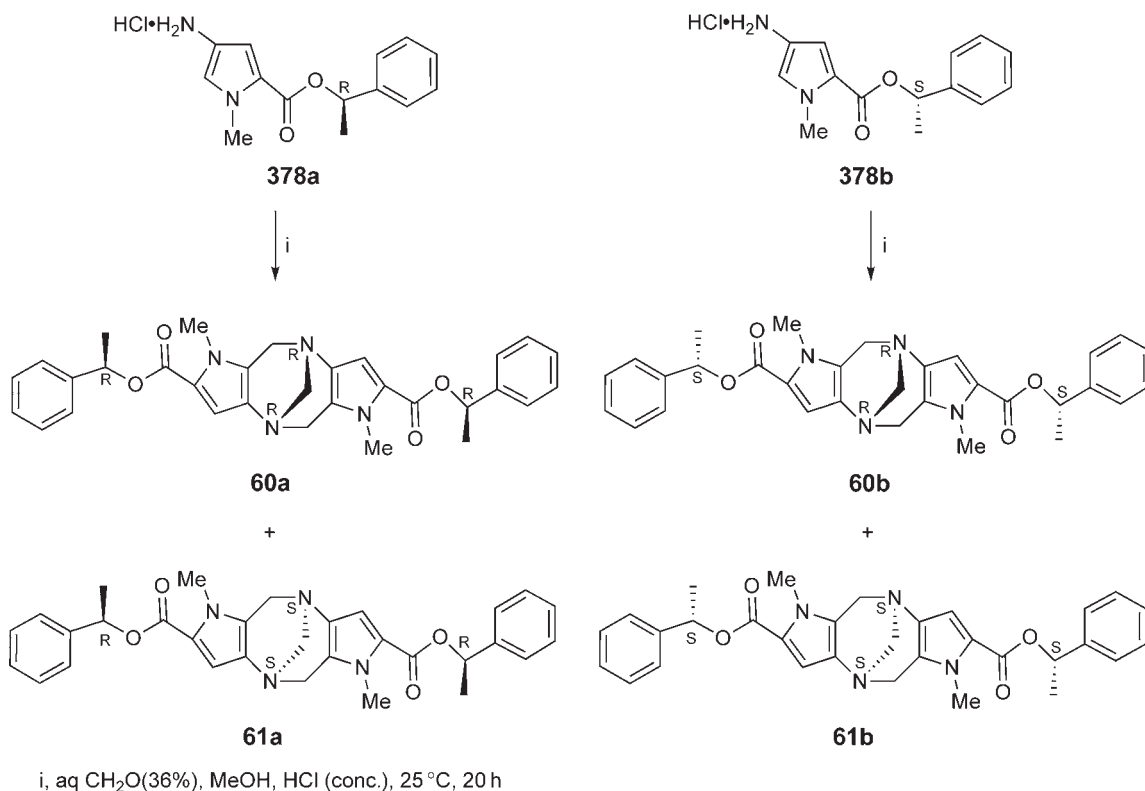
Table 2 (Continued)

<i>Cpd</i>	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	<i>R</i> ⁷	<i>R</i> ⁸	<i>R</i> ⁹	<i>R</i> ¹⁰	<i>References</i>
17	H	Me	H	F	H	Me	H	F	2003EJO3179
18	H	Me	H	I	H	Me	H	I	2003EJO3179
19	H	Me	H	I	H	Me	H	H	2003EJO3179
20	H	H	H	I	H	H	H	I	2003EJO3179
21	H	H	H	Br	H	H	H	Br	2003EJO3179
22	H	H	H	Cl	H	H	H	Cl	2003EJO3179
23	H	H	H	F	H	H	H	F	2003EJO3179
24	I	Me	H	H	I	Me	H	H	2003EJO3179
25	Br	Me	H	H	Br	Me	H	H	2003EJO3179
26	Cl	Me	H	H	Cl	Me	H	H	2003EJO3179
27	I	H	H	H	I	H	H	H	2003EJO3179
28	Br	H	H	H	Br	H	H	H	2003EJO3179
29	Cl	H	H	H	Cl	H	H	H	2003EJO3179
30	H	Me	I	H	H	Me	I	H	2003EJO3179
31	H	Me	Br	H	H	Me	Br	I	2003EJO3179
32	H	Me	Cl	H	H	Me	Cl	H	2003EJO3179
33	H	H	I	H	H	H	I	H	2003EJO3179
34	H	H	Br	H	H	H	Br	H	2003EJO3179
35	H	H	Cl	H	H	H	Cl	H	2003EJO3179
36	H	H	I	H	H	H	I	H	2003EJO3179
37	I	Me	H	H	H	Me	I	H	2003EJO3179
38	Br	Me	H	H	H	Me	Br	H	2003EJO3179
39	Cl	Me	H	H	H	Me	Cl	H	2003EJO3179
40	I	H	H	H	H	H	I	H	2003EJO3179
41	Br	H	H	H	H	H	Br	H	2003EJO3179
42	Cl	H	H	H	H	H	Cl	H	2003EJO3179
43	H	H	I	Me	H	H	I	Me	2003EJO3179
44	H	H	Br	Me	H	H	Br	Me	2003EJO3179
45	H	H	Cl	Me	H	H	Cl	Me	2003EJO3179
46	H	H	F	Me	H	H	F	Me	2003EJO3179
47	H	I	H	Me	H	I	H	H	2001S1873
48	H	Br	H	Me	H	Br	H	H	2001S1873
49	H	Cl	H	Me	H	Cl	H	H	2001S1873
50	H	F	H	Me	H	F	H	H	2001S1873
51	H	I	H	H	H	I	H	H	2001S1873
52	H	Br	H	H	H	Br	H	H	2001S1873
53	H	Cl	H	H	H	Cl	H	H	2001S1873
54	H	F	H	H	H	F	H	H	2001S1873

The fused tris-Tröger's base analogue **42a** was obtained, in 40% yield, as a separable 1:2 mixture of the *syn-anti* and *anti-anti* diastereoisomers **167h** under the classical reaction conditions (Equation 15) <2005OL2019>. Similarly, a tris-Tröger's base analogue in which the bromine groups were replaced by methoxy moieties was obtained from the 2-amino-8-methoxy substituted monomer <2005OL67>.



The two enantiomers of 1-phenylethyl 4-amino-1*H*-pyrrole-2-carboxylate **378a** and **378b** were separately reacted with aqueous formaldehyde in the presence of HCl to give the corresponding pyrrole analogues of Tröger's base as a 1:1 mixture of diastereoisomers **60a/61a** and **60b/61b**, respectively, in 82% yield (Scheme 75) <2005TA1969>. Under the same reaction conditions, the 2-methyl and 2-benzyl esters gave in 52–63% yields the corresponding pyrrole analogues of the Tröger's base <2003TL2083>.



Scheme 75

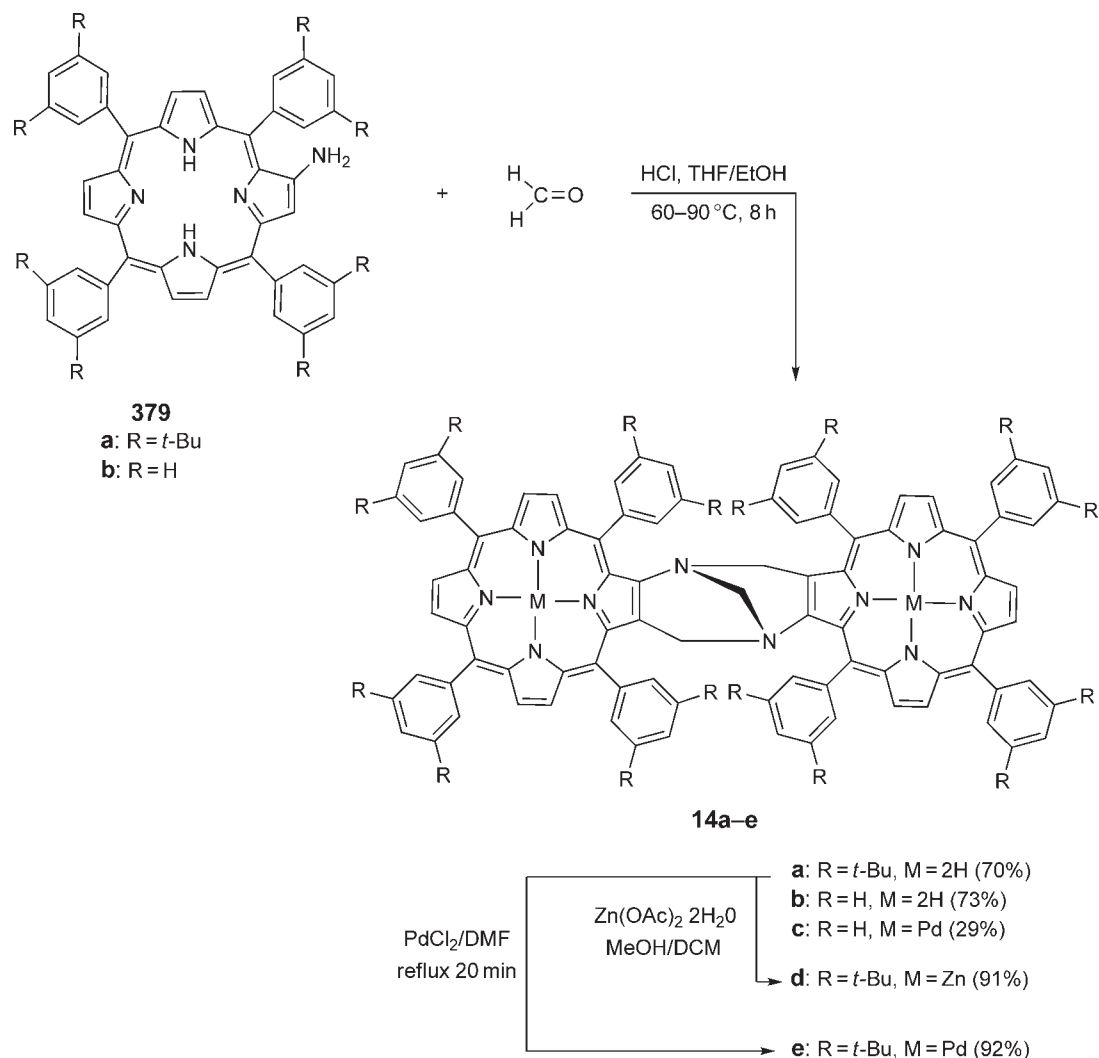
Analogously, thiophene congeners of **15a,b** (Scheme 29) were obtained from 3-aminothiophenes by the usual protocol (Scheme 75) <2002J(P1)1963>.

The porphyrin analogues **14a,b** were prepared by acid-catalyzed reaction of the porphyrin **379a,b** and formaldehyde in good yields. Condensation of the palladium(II) chelate of **379b** with formaldehyde gave the corresponding **14c** in 29% yield. A better method to get metallo-derivatives of **14** involved metallation of **14a**. Thus, **14d,e** were obtained in 91–92% yields by reacting under standard conditions **14a** with PdCl₂ or ZnCl₂.

It was also possible to obtain the mono zinc or palladium derivatives using equimolecular amounts of the metal salt (Scheme 76) <1995CC1077>.

Reaction of 3-aminoacridine **380a** and 11-aminobenzo[*b*][1,7]phenanthroline **380b** with formaldehyde in acidic conditions gave three types of products: the Tröger's base derivatives **381a** and **381b**, the 'dimeric' compounds **382a** and **382b**, and the dihydrooxazines **383a** and **383b**, respectively.

Both aminoheterocycles reacted quite similarly. For both compounds, the relative yields of the different compounds were highly dependent upon the nature and concentration of the acid used. In 6N HCl, no Tröger's base derivative was formed. The 'dimeric' **382a,b** and the dihydrooxazines **383** were isolated in relatively low yields. In more acidic conditions (12N HCl), the formation of **382a,b** was not observed. The Tröger's bases **381a,b** were obtained in 52% and 70% yields, respectively; the dihydrooxazines were formed as minor products.



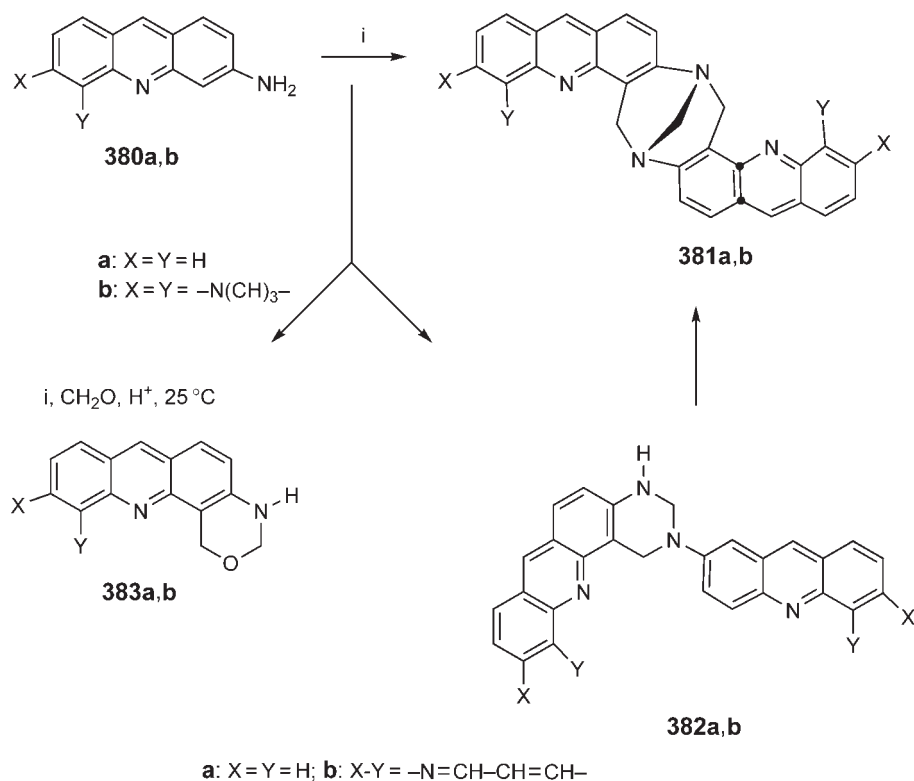
Scheme 76

Using TFA increased dramatically the reaction's selectivity. The Tröger's bases were obtained almost exclusively in more than 90% yields; the dihydrooxazines were the only by-products. The formation of the 'dimeric' structure **382a,b** and of the Tröger's bases **381a,b** is closely related, since **382a,b** are intermediates in the synthesis of **381a,b**. Actually, by adding formaldehyde to **382a** dissolved in 12 N HCl, **381a** was formed quantitatively. On the contrary, formation of the dihydrooxazines and Tröger's bases appeared to be competitive. The yields in Tröger's bases were optimized by using the exact required stoichiometry (1.5 equiv of paraformaldehyde) and TFA, as a solvent (Scheme 77) <1995TL1271>.

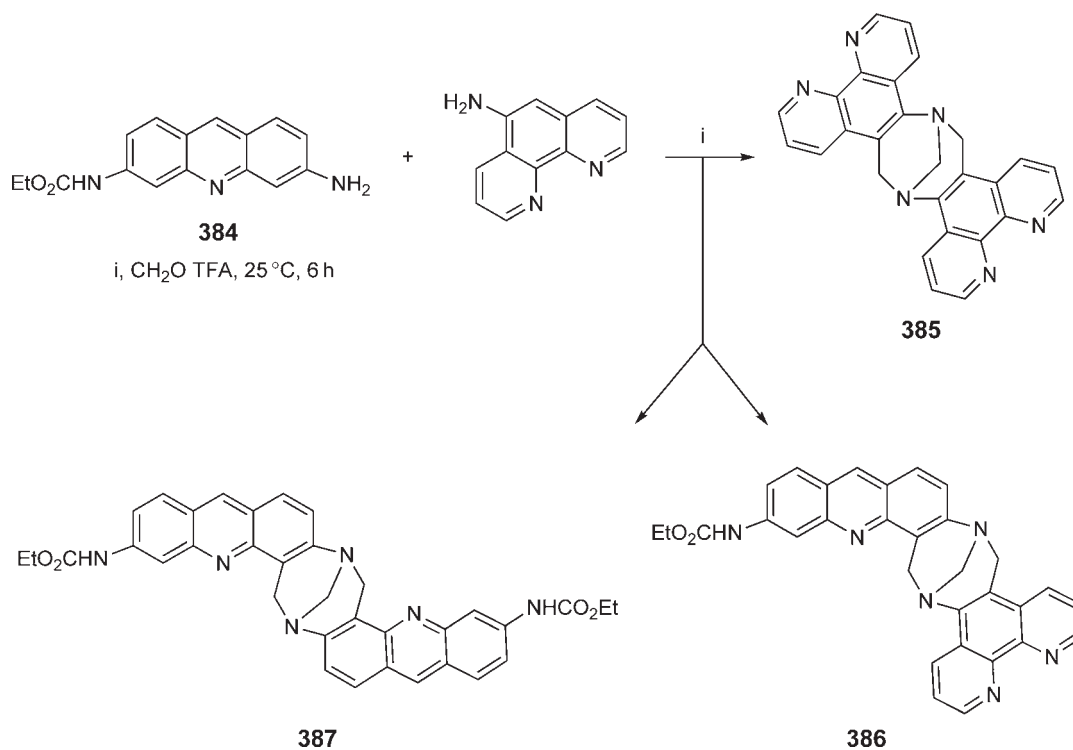
When 3-ethoxycarbonylaminoacridine was subjected to 'trögerization' conditions, the analogue of **381a** with the two nitrogen atoms of the diazocine ring substituted with an ethoxycarbonyl moiety was obtained in 68% yield along with the *N*-ethoxycarbonyl substituted dihydrooxazine, analogue of **383**, as minor product (38%) <2001JOC8222>. In the case of 2-aminoacridine, reaction with TFA and paraformaldehyde led to the isomer of **381** with the diazocine ring annelated onto the 1–2 positions of the acridine system, in 45% yield <2003ARK1>.

Reaction of the mono-protected proflavine **384** with 5-amino-[1,10]phenanthroline in the presence of paraformaldehyde in TFA produced a mixture mainly formed by the symmetrical phenanthroline **385** and the acridine-phenanthroline **386** while the acridine **387** was obtained, as traces (Scheme 78) <2002EJM315>.

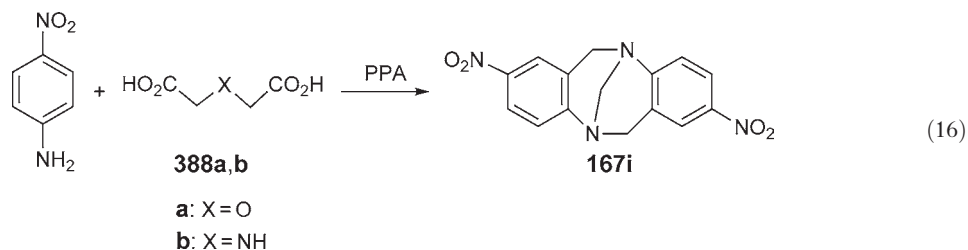
A synthetic approach alternative to the classical 'trögerization' conditions involved the reaction of 4-nitroaniline with diglycolic acid **388a** or iminodiacetic acid **388b** in the presence of PPA and the dinitro substituted Tröger's base **167i** was obtained in 10–56% yields depending on the diacid used (Equation 16) <2003TL2133>.



Scheme 77

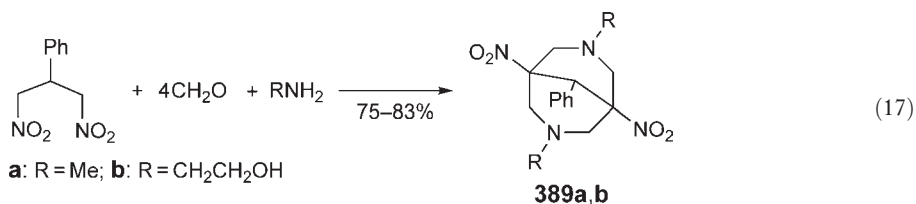


Scheme 78



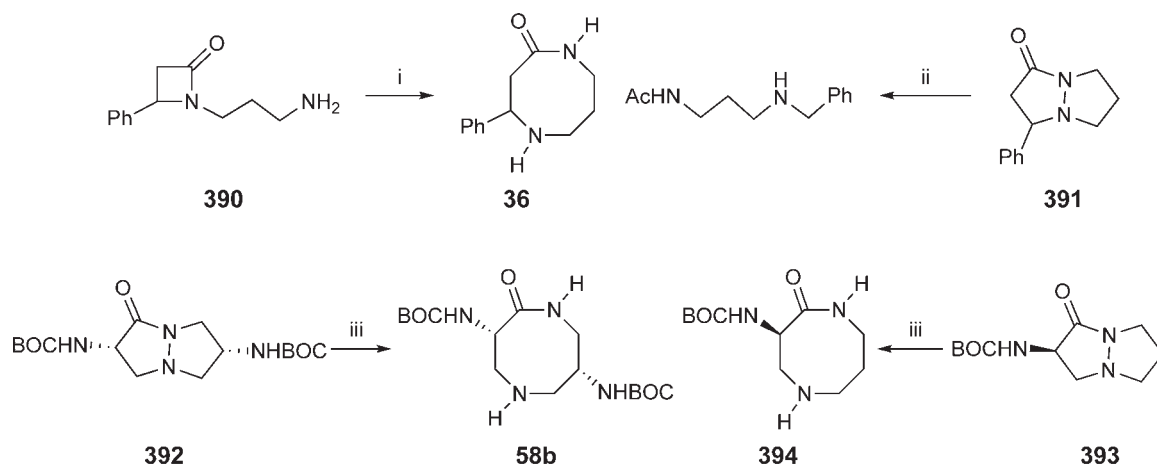
14.07.2.7.10 Ring syntheses from C₂ + 4C + 2N units

The 3,7-dinitrodiazocines **389a,b** were obtained by one-pot synthesis in good yields from the reaction of 1,3-dinitro-2-phenylpropane with formaldehyde and methylamine or 2-aminoethanol with a considerable excess of both formaldehyde and the amine (1:7:9) (Equation 17) <2001RCB753>.



14.07.2.8 Ring Syntheses by Transformation of Another Ring

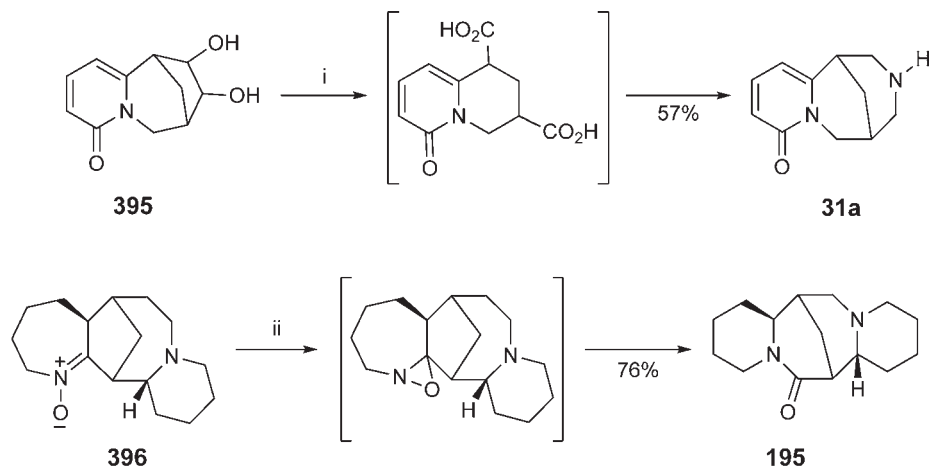
The amino β -lactam **390** underwent a facile ring enlargement under mild conditions to give the diazocinone **36** in 50% yield <2002T7177>. Diazocinone **36** was prepared by reductive cleavage of N–N bond of optically active bicyclic lactam **391** with Na in liquid NH₃. First, using a large excess of Na (15 molar amounts), a further cleavage of the eight-membered ring took place to give *N*-(3-benzylaminopropyl)acetamide (65%); **36** was obtained in 27% yield. When reductive cleavage of the N–N bond of (*S*)-(–)-**391** (87% ee) was performed with 3 molar amounts of Na, diazocine (*S*)-(–)-**36** (87% ee) was obtained in 99% yield and the asymmetric carbon of (*S*)-(–)-**391** could be retained during the reduction process. Similarly (*R*)-(+)-**36** (82% ee) was obtained in 79% yield from the reductive-cleavage of (*R*)-(+)-**391** (82% ee) <1995BCJ3121>. Similar reductive cleavage of N–N with consequent ring enlargement was observed for bicyclic lactam **392** and **393**, which produced the diazocine derivatives **58b** and **394**, respectively, by reduction with Raney nickel (Scheme 79) <1999SL1875, 2005BML4291>.



i, NaOH (1M), 55 °C, 12 h; ii, NH₃, Na, THF, –78 °C, 1 h; iii, Raney nickel, *i*-PrOH, 50 °C, 1 h

Scheme 79

Direct conversion of diol **395** to cytisine **31a** was accomplished by a one-pot procedure. Oxidative cleavage to give the dicarboxylic acid, followed by treatment with aqueous ammonia and catalytic reduction provided racemic cytisine **31a** in good yield <2000OL4205>. Photolysis in benzene at 254 nm of the nitron **396** afforded smooth rearrangement to 17-oxosparteine **195** likely through the intermediacy of an oxaziridine derivative (Scheme 80) <2002OL2577>.



i, NaIO_4 (1 equiv), EtOH, 30 min, then NH_4OH , H_2 , $\text{Pd}(\text{OH})_2$, 48 h; ii, $h\nu$, (254 nm), benzene, 25 °C, 2 h

Scheme 80

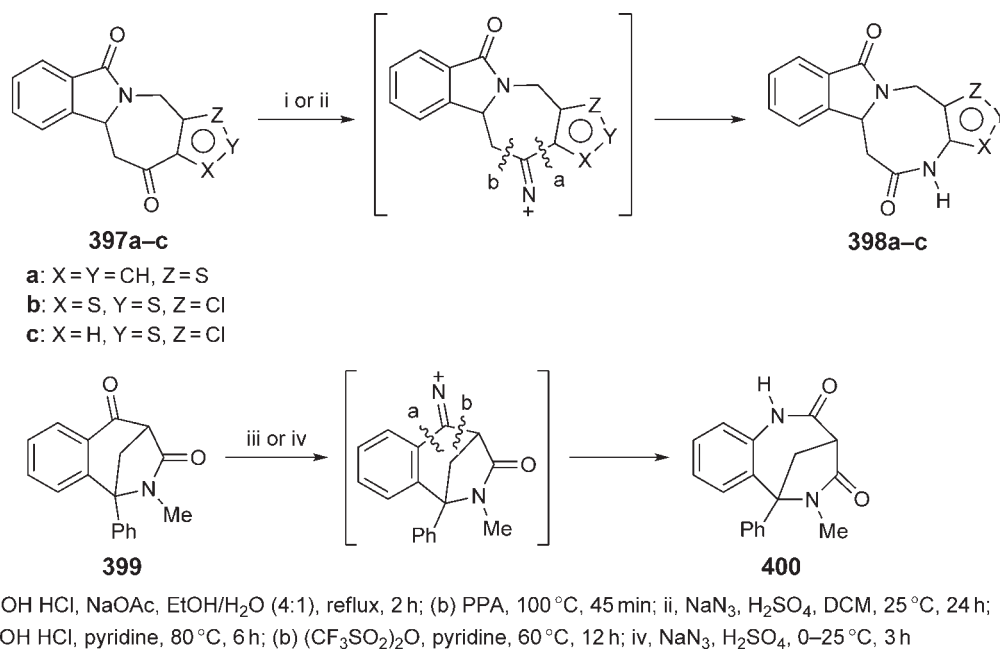
Diazocines **398a–c** were prepared from the suitable thienoazepinoisindolediones **397a–c** via a Beckman rearrangement of the corresponding oximes or via the Schmidt rearrangement. Thus, ketones **397a–c** heated with hydroxylamine hydrochloride gave the corresponding oximes in a mixture of *syn* and *anti* forms.

The *anti* isomer is the major product in all cases. When the mixtures of the oximes obtained from **397a,c** were heated in PPA, 1,5-diazocines **398a,c**, as the result of the a cleavage were only obtained in 95–96% yield. In the case of the oximes obtained from **397b**, the Beckmann rearrangement led to the 1,5-diazocine **398b**, in 74% yield, along with the product of the b cleavage, the corresponding 1,4-diazocine (24%).

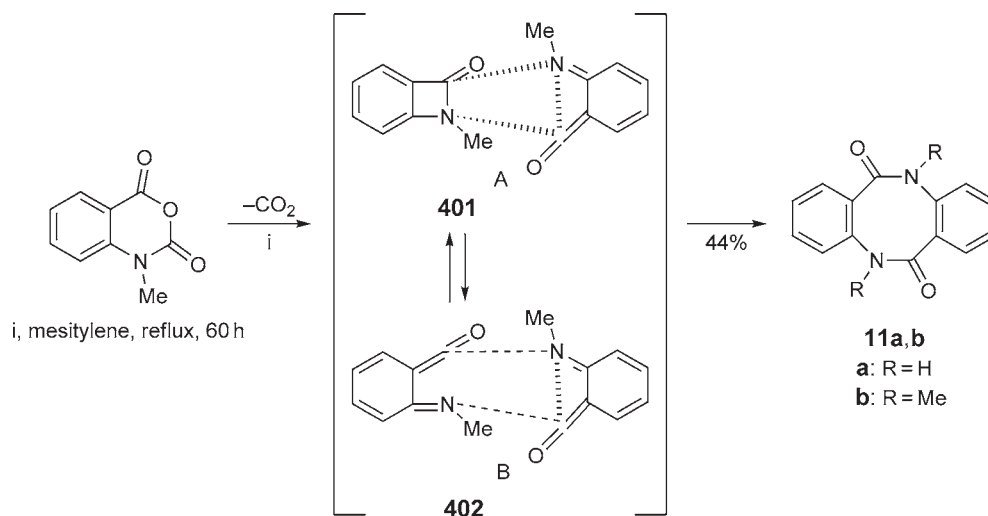
Ketones **397a–c** showed parallel behavior when undergoing the Schmidt rearrangement and **397a,c** gave only the 1,5-diazocines **398a,c** in 76–81% yields, while **397b** afforded **398b** in 42% yield along with the corresponding 1,4-diazocine (32%) <1997JHC375>. Benzazepinedione **399**, subjected both to Beckmann and Schmidt rearrangements, exhibited a reactivity similar to that already described for **397b**. Thus, treatment of **399** with NH_2OH gave, in 83% yield, the *E*-configured oxime, which reacted with TiF_2O in pyridine to give the corresponding trifluoromethanesulfonate. Addition of H_2O and heating afforded the 1,5-diazocine **400** as the sole rearrangement product (a cleavage). The use of TiF_2O is essential, since the reaction failed if other activating agents, such as TsCl or MsCl , were used. The Schmidt rearrangement of **399** with NaN_3 and H_2SO_4 gave **400** (a cleavage) in 48% yield along with the corresponding 1,4-isomer (b cleavage) (37%) (Scheme 81) <1995JME2946>.

Refluxing *N*-methylisatoic anhydride in mesitylene resulted in a slow liberation of CO_2 and the isolation of the dibenzodiazocine **11b**. The formation of **11b**, as confirmed by theoretical calculations (see Section 14.07.2.1), was explained in terms of an overall [4+4] cycloaddition through the formation of the *N*-substituted benzoazetidinone **401**, which is in equilibrium with the less stable benzoimidoylketene **402**.

For this cycloaddition, five transition structures were found. Three of them are true [4+4] pseudopericyclic dimerization of **402** and one of these, **B**, with an orthogonal [4+4] geometry, had a barrier of only 700 cal mol^{-1} . However, the overall lowest energy pathway involved concerted addition of **402** across a σ bond in **401** via **A** <2004JOC86> (Scheme 82). Analogously, isatoic anhydride, under microwave conditions, afforded **11a**. Sulfinamide anhydride, instead, in absence of dienophile, in dry benzene at 25 °C decomposed to iminoketene that gave **11a** in 81% yield <2004MI1368>.

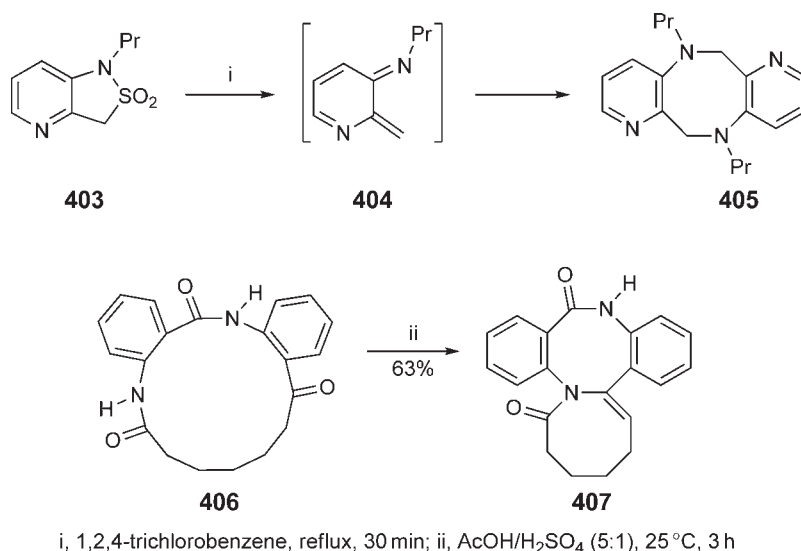


Scheme 81



Scheme 82

Thermal expulsion of SO_2 from the pyridosultam **403** generated a pyridine analogue of aza-*o*-xylylene **404**, which produced the cyclodimerization product dipyridodiazocine **405** in 25% yield [\[2002EJO947\]](#). The dibenzozazocinodiazocinone **407** was obtained in good yield from an acid-catalyzed transannular cyclization due to a nucleophilic attack of the amide nitrogen at the carbonyl carbon of the macrocycle **406** (Scheme 83) [\[2000T9641\]](#).



Scheme 83

14.07.2.9 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Due to the large number of 1,5-diazocine derivatives reported in the past decade, the 10 different types of synthetic approaches to such ring systems beside the natural sources have appeared. Among the unimolecular reactions, the best reliable and efficient method resulted in the preparation of the spermine alkaloids precursor from aminoesters. Other cyclizations of aminoesters took place with satisfactory yields (Scheme 46). Also the cyclization of piperidinyl-pyridine derivatives to *N*-substituted analogues of cytosine appeared of general application with good overall yields (Scheme 52). Other unimolecular cyclizations worthy to be mentioned are the synthesis of sparteine from bispiperidin-2-one derivative with 48% overall yield (Scheme 52). The rest of the reported unimolecular cyclizations provided the diazocines in low yields or with other products. The synthesis of bispiridine derivatives from nucleophilic substitution of primary amines on bis-iodomethyl morpholine or piperazine derivative and certainly applicable to piperidine derivatives gave the entry to a very large number of variously bridged bispidine with very interesting yields (Equation 12). The replication of the Tröger's base unit through the reaction of suitable substituted amines with formaldehyde often provided the 'Tweezers'-shaped Tröger's bases in low yield and as a mixture of stereoisomers. The double Mannich reaction of *N*-substituted piperidinones with primary amines and formaldehydes proved to be a very important and versatile approach to the synthesis of symmetrically and asymmetrically substituted bispidinones (Scheme 59). The dibenzodiazocines were generally and efficiently prepared by the cyclodimerization of benzene or cycloalkanes or heterocycles bearing in adjacent positions an amino and carboxy acid moieties (Scheme 66). Instead, the four-component Ugi reaction leading to dibenzodiazocines was not always convenient in terms of yields. Another valuable synthesis was the reaction of substituted anilines, with formaldehyde in acid medium leading to the Tröger's base analogues. By this method many compounds (see Table 2) were prepared generally in moderate to good yields. Among the synthesis of 1,5-diazocines by transformation of another ring, the enlargement of fused azepinoximes upon Beckmann or Schmidt rearrangement that furnished the polycondensed diazocines in excellent yields seems to be the only approach worthy to mention.

14.07.2.10 Important Compounds and Applications

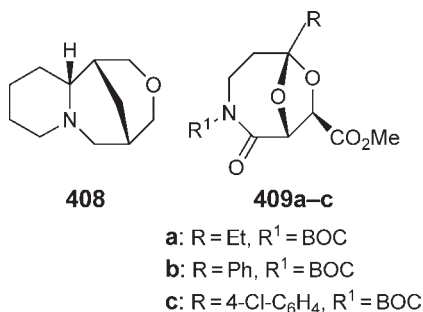
Bispidine derivatives of general formula 305 bearing alkyl or cycloalkyl R and X moieties and arylsulfonyl, alkyl, cycloalkyl, or benzyl substituents in R¹ showed antiarrhythmic activity <1995EPP0665014, 1995EPP0665228, 2000WO76997, 2004WO045591, 2005WO011690, 2005USP0054667> and were used even for the prophylaxis of the Brugada syndrome <2005WO030207>. Such antiarrhythmic activity was maintained in oxygen-bridged bispidines

bearing an (alkoxycarbonylamino)alkyl group <2001WO28992, 2006WO137769, 2006WO137770> and in *N*-hydroxyethylcytisine <2004PCJ311>. Also dication **20** exhibited predominately class III antiarrhythmic activity via prolongation of the ventricular effective refractory period in the models <1996JME2559>. Methylene-bridged diazocine-2-one derivatives with one unsubstituted nitrogen and the other substituted with a carboxamido moiety bound to 74 different aryl or heteroaryl groups showed a nicotinic cholinergic effect and a dopamine-releasing effect, and are usable as a remedy for dementia, such as Alzheimer's disease, memory disorders, central nerve degeneration diseases, and cerebral function disorders <1996WO30372>. Nicotinic cholinergic activity was also exhibited by fumaric acid salts of 1-pyridyl or pyridazinyl or other five- and six-membered heterocycle-substituted perhydrodiazocines <1999WO21834, 2000WO64885> and from bispidine derivatives having one ring nitrogen bound to five- and six-membered heterocycles, related benzo-fused derivatives, and the other ring nitrogen bound to hydrogen, alkyl, amino, aminoalkyl, and aminocarbonylalkyl groups <2000WO44755, 2003USP0225268>. However, the best nicotinic cholinergic activity was shown by 3-bromocytisine **120b**, which inhibited the $(\alpha_4)_2(\beta_2)_3$ nAChR subtype in membranes from rat forebrain at the concentration of 10 pM <2001EJM375>. Diazocine **228** and related compounds were used as tryptase inhibitors <2002WO060895>. Diazocines related to **231** were shown to inhibit the interleukin-1 β synthesis <2005BML4291>. Both *N*-methylenepyrimidine-substituted perhydrodiazocines and benzodiazocine **139** bearing, instead of a methyl group, a substituted methylenepyrimidine moiety were used in the treatment of cancer due to their action as mitotic kinesin inhibitors <2003WO049527, 2003WO049678, 2003WO049679, 2003WO099211>. Diazocines **205** were patented as antagonist of the delayed rectifier potassium channel Kv2.1 and for treatment of non-insulin dependent diabetes mellitus <1999WO32487>. Carbonyl-bridged diazocines **3d–y** showed considerable affinity, ranging from micromolar to nanomolar concentrations, for the k-opioid receptor <2000JME3746>. Both enantiomers of the benzodiazocine **400** showed a pharmacological *in vitro* profile comprising a positive inotropic effect based on Ca²⁺ sensitization and a negative chronotropic effect in the low micromolar range <1995JME2946>. *N*-Acyl citysines were inhibitors of factor Xa and are useful, as anticoagulants, in the treatment of cardiovascular diseases associated with thromboses <2004USP0186134>. Sparteine **184** produced a dose-dependent reduction in heart rate and blood pressure over the dose range 1–64 $\mu\text{M kg}^{-1} \text{ min}^{-1}$ <1995EPH319>. The Tröger's base **386**, containing proflavine and phenanthroline moieties, two well-known characterized DNA-binding chromophores, interacted with DNA with the proflavine portion which intercalated between DNA base pairs and the while the phenanthroline system occupied the DNA groove <2002EJM315>. Also the bis-distamycin Tröger's base **177a–d** interacted with DNA showing a clear sequence selectivity for A–T rich sequences of DNA, although a nonspecific binding mode with low affinity was also observed for G–C rich sequences <2006TA1049>. It was observed that (4*R*,9*R*) configuration of methanodiazocine bridge was better suited for interaction with ct-DNA than (4*S*,9*S*) configuration <2006T8591>. Chitosan-polymer analogues of **173** showed good adsorption capacity and high selectivity for Ag⁺ in the presence of Pb²⁺, Cd²⁺, and Cr³⁺ as well as its adsorption selectivity is better than that shown by chitosan <2002JAP2677>. Bis-quaternary salts of caracurine V, **74**, the related tetrahydro derivative and iso-caracurine V, **75**, inhibited dissociation of the orthosteric antagonist [³H]N-methylscopolamine (NMS) from porcine cardiac M₂ receptors with EC_{0.5 diss} values 4–3270 nM <2004JME3561>. The triazolobenzodiazocine **142** and related compounds have found application in the treatment of dysmenorrhoea <2004WO074291>. The tosylate salt of bisbenzimidazodiazocines has found an application as a hair dye <2005EPP1634575>.

14.07.3 Rings with One Nitrogen and One Oxygen (1,5-Oxazocines)

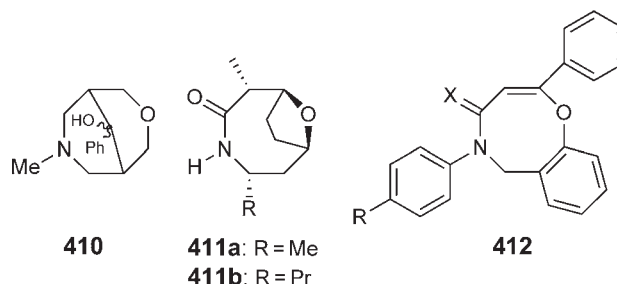
14.07.3.1 Theoretical Methods

The enantioselective lithiation of *N*-BOC-pyrrolidine using isopropyllithium in presence of 1,5-oxazocine **408** has been studied computationally at various theoretical levels through to HF/3-21G and B3P86/6-31G*. Geometry optimizations were initially calculated for the four optimized structures which had difference in energy (*H*_{rel} and *G*_{rel}) quite small. These results indicated that the enantioselectivity generated using 1,5-oxazocine **408** would be small and in a sense opposite to that obtained with sparteine-like derivative in which the oxygen was replaced by *N*Me group <2004JA15480>. Conformation analysis using MM2* force field, was performed on the oxygen bridged oxazocines **409a–c** and the corresponding 7- and 9-membered-ring derivatives in order to evaluate how the enlargement of the rigid ring of **409** affected the conformational freedom. Molecular-modeling calculations revealed that 1,5-oxazocines **409a–c** were less rigid than their seven-membered counterparts and were prone to take different conformations. The distance between the aromatic ring and the carbomethoxy group decreased as the ring enlarged (**409b** = 3.4 Å, whereas the corresponding distance in seven- and nine-membered rings were 3.8 and 3.0 Å, respectively). This observation was confirmed by the experimental ¹H NMR data (see Section 14.07.3.2) <2004T2583>.

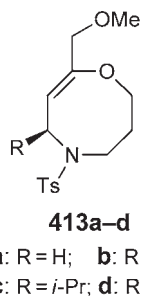


14.07.3.2 Experimental Structural Methods

X-Ray single-crystal investigation were limited to only very few derivatives. X-Ray structure of *cis*-oxazocine **410** was determined in order to refine the spatial structure of the *cis*- and *trans*-isomers. The basic geometric parameters of the molecule were normal and the piperidine and the tetrahydropyran rings exhibited chair conformation. The OH group forms an intermolecular hydrogen bond O–H···N with the nitrogen atom of neighboring molecules, forming a chain along the *c*-axis <2004CHE641>. X-Ray crystallography studies performed on lactams **411a** and **411b** established the relative configuration and revealed that no epimerization was observed during their formation <2002T4451>. The structure of 5-(4-methoxyphenyl)-2-phenyl-5,6-dihydrobenzo[*b*][1,5]oxazocin-4-one **412a** (X = O, R = OMe) was unambiguously established by single-crystal X-ray diffraction analysis. The crystal cohesion was due to the H-bond between the carbonyl oxygen atom and the *ortho*-hydrogen of the phenyl in position 2 and van der Waals forces <2003H(60)1793>.

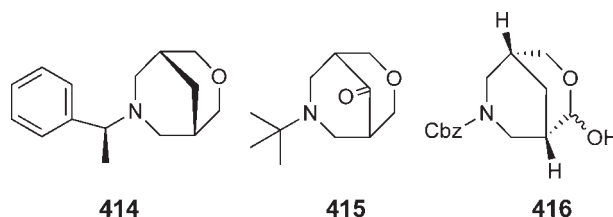


The NMR techniques were widely used to establish the structure of 1,5-oxazocines, which are generally part of condensed and/or bridged systems. The only unbridged, and uncondensed 1,5-oxazocines **413a–d** reported, showed in their ¹H NMR spectra the signals of methyne and methylene protons next to nitrogen at 3.82–4.63 and 3.28–3.76 ppm respectively; the methylene protons were adjacent to oxygen at 3.40–4.90 ppm, while the other ring methylene protons resonated at 1.88–2.13 ppm <2004JA8744>.

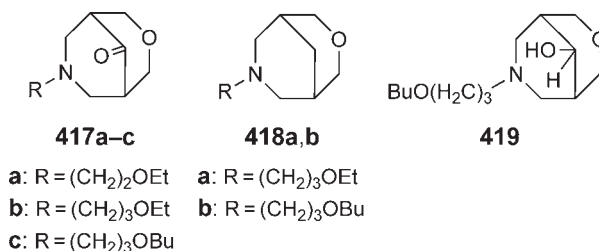


The methylene bridged *N*-(1'-phenylethyl)-1,5-oxazocine **414** exhibited in its ¹H NMR spectrum an upfield shift for all the eight-membered ring protons (CHN and CH₂N at 3.34 and 2.26–3.13 ppm, respectively, the CH₂O protons at 3.76–3.98 ppm, whereas the other ring CH and CH₂ protons were found at 1.54–1.83 ppm) <1995JOC8148>. The ¹H NMR spectrum of the carbonyl-bridge-*N*-*t*-butyl substituted 1,5-oxazocine **415** showed the CH₂N protons at

3.83–4.10 ppm, the CH₂O protons were reported at 2.94–3.09 ppm and the CH protons at 2.47 ppm <2006OL3399>. Proton NMR spectra of bridged oxazocine **416** revealed that both C-2 epimers exist in CDCl₃ solution as an equilibrium of two conformations about the CO–N bond, slowly interconverting on the NMR timescale. Assignment of the methyne and methylene protons of the four isomers, facilitated by COSY spectra, showed the ring proton resonances within the ranges previously described for the other oxazocines <1998JOC3492>.

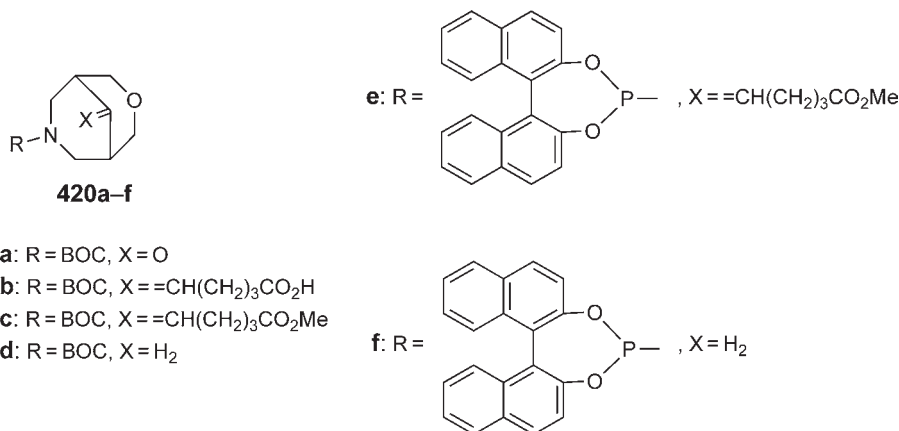


The carbonyl-bridged oxazocines **417a–c**, showed in their ¹H NMR spectra, the signals of the methylene protons next to nitrogen at 3.87–4.21 ppm, the methylene hydrogens adjacent to the oxygen at 2.91–3.13 ppm and the methyne protons resonated at 2.53 ppm, while the oxazocines **418a,b** exhibited an additional signal for the CH₂ bridge at 1.59–1.79 ppm. The ¹H NMR spectrum of **419** showed a 1:1 mixture of two stereoisomers the values found for the vicinal constants indicated that one of them showed a double-chair conformation, whereas the other isomer occurred in a chair–boat conformation (see Section 14.07.3.3) <2003CHE1376>.

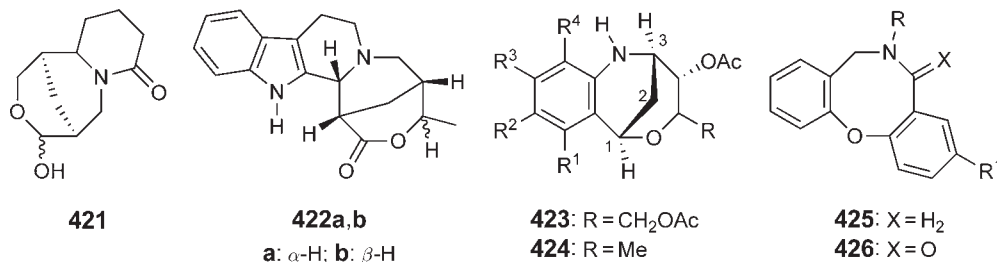


The signals for the CH₂–O and CH₂–N protons in the *N*-BOC-1,5-oxazocines **420a–d** were found at 3.58–4.41 and 2.98–4.83 ppm, respectively, while the corresponding protons of *N*-binaphthylphosphites **420e,f** resonated at 3.62–3.97 and 2.66–3.73 ppm <2000CEJ671, 2002CEJ4767>. The *N*-BOC bridged oxazocines **409a–c** exhibited in their ¹H NMR spectra the CH₂–N protons at 3.25–4.43 ppm, the CH–O signal at 4.71–4.96 ppm, the other ring CH and CH₂ protons resonated at 4.48–5.17 and 1.82–2.49 ppm, respectively. The *N*-unsubstituted derivatives **409** (R¹ = H) showed a similar pattern of signals with the addition of the NH proton that was found at 6.26–6.75 ppm. A comparison analysis of the ¹H NMR data of the oxygen-bridged oxazocines **409a–c** and the corresponding seven- and nine-membered-ring derivatives showed that the shielding effect of the aromatic ring increased with the enlargement of the ring; the OMe groups resonated at 3.75 ppm (seven-membered-ring), 3.70 ppm (eight-membered-ring) and 3.37 ppm (nine-membered-ring) (see Section 14.07.3.1) <2004T2583>. The isomers *trans*-**410** and *cis*-**410** were identified on the basis of magneto-anisotropic influence of the phenyl substituent on the chemical shifts of the protons of methylene group. The CH₂–O protons in the *cis* isomer of **410** resonated at 2.75–3.64 ppm, while in the *trans* isomer **410** appeared at downfield shift (4.02–4.54 ppm). The CH₂–N protons in the *cis* isomer of **410** were found at 2.42–3.00 ppm, whereas the analogue signals for the *trans* isomer **410** appeared at 2.84–3.25 ppm. The *N*-Me signal of **3** was exhibited at 2.12–2.38 ppm <2004CHE641>. The NH protons of bridged oxazocines **411a,b** were observed at 5.17–5.21 ppm <2002T4451>. Benzo-oxazocines **412a–d** (a, X = O, R = OMe; b, X = O, R = Br; c, X = O, R = I; d, X = O, R = C(NH)NH₂) showed in their ¹H NMR spectra, the signals of the methylene next to nitrogen at 5.06–5.26 ppm and the CH=Ph proton resonated at 6.45–6.78 ppm, instead oxazocine **412e** (X = H₂, R = Br) exhibited the CH₂–N signal at 4.57 ppm, the CH=Ph proton at 5.81 ppm, whereas the allyl CH₂ was found at 3.93 ppm with a *J* = 6.2 Hz <2003H(60)1793>. Hupeol **421**, a nonbasic metabolite of cytosine in its ¹H NMR spectrum showed two sets of signals in a 3:1 ratio indicating that **421** was a 3:1 mixture of two structurally related compounds. ¹H–¹H and ¹H–¹³C COSY spectra established that in the major isomer the orientation of the hydroxyl group was axial and in the minor was equatorial <1998JCM196>. The ¹H NMR spectra of oxazocine **422a,b** exhibited the CHN and CH₂N signals at 3.59 and 2.59–3.27 ppm, respectively, the OCH proton at 4.70 ppm, the CH and CH₂ bridge protons were found at 2.00–3.13 and 2.08–2.28 ppm, respectively while the Me group protons appeared at 1.42–1.49 ppm. Irradiation of C(1') Me group at 1.42 ppm of lactone **422a** led to an NOE of 2% for the

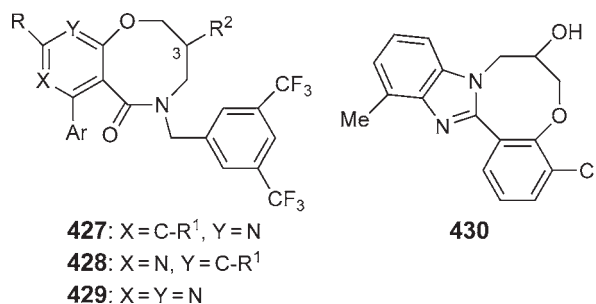
C(2 α)-H, of 3% for the C(3)-H, and of 6% for the C(1')-H, whereas irradiation at C(1')-H at 4.73 ppm resulted in NOEs at C(4 α)-H (5%), C(3)-H (3.5%), and C(1') Me group (6%) evidence for (1'*S*)-configuration. Irradiation of lactone **422b** at C(1')-H at 4.73 ppm resulted in NOEs at C(2 α)-H (3%), C(3)-H (8%), and C(1') Me group (4%), whereas irradiation of C(1') Me group at 1.49 ppm led to a NOE of 1% for the C(3)-H, of 3% for the C(4 α)-H, and of 5.5% for the C(1')-H, indicating the (1'*R*)-configuration (see [Section 14.07.3.3](#) <1997H(45)361>).



The ¹H NMR spectra of benzo-1,5-oxazocines **423** and **424** showed the CH–N signal at 3.76–3.84 ppm, the OCH protons at 3.47–4.81 ppm, while the bridge methylene protons and the methyne proton resonated at 1.96–2.29 ppm and 4.60 ppm, respectively; the NH proton was instead found at 4.41–4.44 ppm. The heteronuclear single quantum correlation (HSQC) confirmed the location of the methylene group in the bridge by the presence of small coupling constants between the bridge protons H-2 and the bridgehead protons H-1 and H-3 ($J_{\text{H-2H}} = 1.8, 3.7$ Hz; $J_{\text{H-2H-3}} = 2.4, 4.6$ Hz) and indicate a half-chair conformation. The large coupling constant ($J_{\text{H-4H-5}}$ ca. 10 Hz) as well as the NOESY cross-peak for H-2/H-4 further supported the chair form <2003AGE5198, 2004S405, 2004T3261, 2004TL1543>. Dibenzooxazocines **425** and **426** exhibited in their ¹H NMR spectra CH₂–N protons at 3.50–4.70 ppm and the *N*-Me group at 1.80–2.20 ppm. *N*-Unsubstituted oxazocines **426** showed their NH proton at 8.56–10.47 ppm <1999T8295, 1999TL5827, 2000T2369>.



In the ¹H NMR spectra of pyrido- and pyrimido-1,5-oxazocines **427**, **428**, and **429** the eight-membered ring protons appeared as an AB pattern ($J \sim 15$ Hz). The ¹H NMR spectra of **427a,b** (**a**, R = H, R¹ = R² = Me; **b**, R = R¹ = H, R² = Me) showed signals due to two diastereomers in a ratio of nearly 98:2 as determined by the peak area of Me group at C-3. The NOE observed between the C(3)–H and benzylic methylene proton indicated that the axial chirality is *aR*, and the chemical shifts and coupling constants together with long-range coupling between the C(4b)–H and benzylic methylene proton ($J = 1.4$ Hz) supported an (*aR*, 3*S*) structure. In the NOESY spectrum of (3*S*)-**427a** (R = H, R¹ = R² = Me), intersite exchange peaks were observed between the two isomers at the position of C(3)–Me, C(8)–Me, C(4b)–H, C(2a)–H, and C(2b)–H, demonstrating that these isomers were interconverted in solution (see [Section 14.07.3.2](#) <2004T4481>). The AB pattern for the benzylic methylene protons of **429** deteriorated to very broad peak at 100 °C and collapsed to singlet peaks at 150 °C. In addition, each pair of oxazocine ring methylene protons showed one peak with distinct fission patterns at 150 °C. From these results it could be predicted that the barrier for inversion is too low to allow the isolation of the enantiomers since rapid interconversion occurred at 25 °C <2005BML1485>. Benzimidazooxazocine **430** exhibited the sp³ ring protons at 3.90–4.30 ppm while the OH group appeared at 5.49 ppm <2003OL4795>.



¹³C NMR data were not provided for all the 1,5-oxazocines reported. The bridged oxazocines **411a,b** showed in their ¹³C NMR spectra the CH-N carbon resonance at 41.5 ppm, the CH-O carbon signal was found downfield (76.7–82.6 ppm), instead the CH₂ bridge carbons resonated in the range 27.0–32.0 ppm; moreover, the Me, *N*-CH-Me, and CO groups were observed at 13.4, 22.8, and 175.3 ppm, respectively <2002T4451>. Benzooxazocines **412a–d** (a, X = O, R = OMe; b, X = O, R = Br; c, X = O, R = I; d, X = O, R = C=(NH)NH₂) showed in their ¹³C NMR spectra the signals of the methylene next to nitrogen at 52.1–55.0 ppm, the CH=Ph carbon resonated at 110.8–112.6 ppm, and the carbonyl carbons at 167.5–168.0 ppm, instead oxazocine **412e** (X = H₂, R = Br) exhibited the two CH₂-N signals at 44.9 and 52.0 ppm, the CH=Ph proton at 109 ppm <2003H(60)1793>. The ¹³C NMR spectrum of methylene bridged *N*-phenylethyl-1,5-oxazocine **414** showed the CH₂N carbon signals at 54.5–56.0 ppm, the CH₂-O carbon resonance at 70.9–71.2 ppm, while the CH and CH₂ bridge carbon resonated at 30.3–30.5 ppm <1995JOC8148>. Carbon spectra of the carbonyl-bridged *N*-*t*-butyl-1,5-oxazocine **415** exhibited the resonances for all the eight-membered carbons within the range previously described, while the carbonyl resonance was found at 213.0 ppm <2006OL3399>. The assignment of the methyne and methylene carbons of the four isomers of 1,5-oxazocine **416** was facilitated by HETCOR spectra and showed that both C-2 epimers exist in CDCl₃ solution as an equilibrium of two conformations about the CO-N bond, slowly interconverting on the NMR timescale <1998JOC3492>. The signals for the CH₂-O and CH₂-N carbons in the 1,5-oxazocines **420** were found at 71.1–74.3 and 47.2–51.1 ppm, respectively. Compound **420a** exhibited the bridge carbonyl carbon signal at 210.9 ppm, whereas *N*-BOC carbonyl carbon, as well as **420a–d** at ca. 155 ppm <2000CEJ671, 2002CEJ4767>. The ¹³C NMR spectra of oxazocine **422a,b** exhibited the CHN and CH₂N signals at 62.9 and 55.3–61.3 ppm, respectively, the OCH carbon was found at 18.6–22.2 ppm, the CH and CH₂ bridge carbons resonated at 32.0–39.9 ppm and 29.4–29.9 ppm, respectively, the Me and CO group carbons appeared at 18.6–22.2 ppm and 170.4–170.7 ppm, respectively <1997H(45)361>. Dibenzooxazocine **425** exhibited in their ¹³C NMR spectrum the CH₂-N carbons at 42.8–59.8 ppm and the *N*-Me group at 37.6 ppm <1999TL5827>. Benzoimidazooxazocine **430** exhibited the methylene carbon next to nitrogen at 47.4 ppm, the methylene adjacent to the oxygen at 75.7 ppm while the methyne carbon, bearing the OH group, experienced a downfield (65.6 ppm) <2003OL4795>.

³¹P NMR spectra of *N*-binaphthylphosphites **420e,f** showed the phosphorus signal in the range 145.8–148.4 ppm <2000CEJ671, 2002CEJ4767>.

No studies on fragmentation patterns of 1,5-oxazocines have been reported in the past decade. In some cases, the molecular or quasimolecular ion spectra have been reported; EI spectra <2002CEJ4767, 2004JCO54, 2004T2583, 2004WO58767, 2005BML1479, 2005BML1485, 2006JOC3291>; ESI spectra <2003OL4795, 2004CPB675, 2006OL3399>; IS spectra <2003H(60)1793>; and FAB spectra <1999JOC1074, 1999T8295, 1999TL5827, 2000CEJ671, 2000T2369, 2002CEJ4767, 2003AGE5198, 2004CPB675, 2004JA8744, 2004S405, 2004T3261, 2004TL1543>. In the GS/MS spectrum of the lactams **411a** and **411b**, beside the parent ion (*m/z* 183 and *m/z* 211), were also reported the fragmentation peaks at *m/z* 168 (**411a** = M⁺-Me and **411b** = M⁺-*i*-Pr), and *m/z* 196 (**411b** = M⁺-Me), due to the loss of the Me and *i*-Pr groups from the eight-membered rings <2002T4451>.

IR data for the reported 1,5-oxazocines were highly fragmentary, in several occasions, these were not reported at all. The benzooxazocines **412** showed, in their IR the carbonyl stretching in the range 1676–1644 cm⁻¹ <2003H(60)1793>, while the lactams **411a,b** exhibited the CO peak at 1662–1660 cm⁻¹ and the NH stretching at 3299–3087 cm⁻¹ <2002T4451, 1997EJM241, 2003JOC92, 2003JOC3315>. The carbonyl stretching of 1,5-oxazocine **415**, **422a,b**, and **430** could be found at 1770–1720 cm⁻¹ <2006OL3399, 1997H(45)361, 2001EJO1511>. The bridged 1,5-oxazocine **416** showed the OH stretching at 3690–3450 cm⁻¹ <1998JOC3492>. The IR spectrum of **421** showed an absorption band at 3300 cm⁻¹ due to the hydroxyl group and the carbonyl stretching at 1650 cm⁻¹ <1998JCM196>.

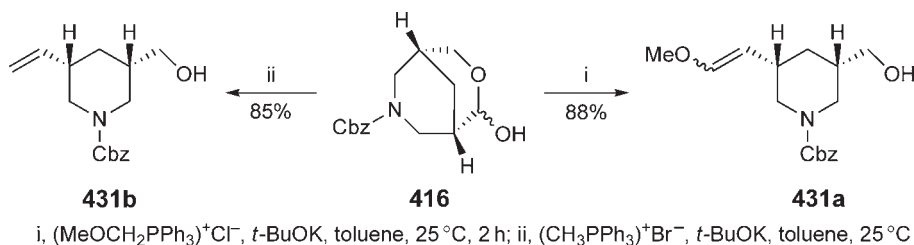
14.07.3.3 Thermodynamic Aspects

The phase behavior of 1,5-oxazocine is characterized by relatively high melting points. There are some exceptions as in the case of **413**, **415**, and **416** which are oils <2004JA8744, 1995JOC8148, 1998JOC3492> or compounds **425** ($R^1 = \text{NHAc}$), **417**, **418**, and **419** which melted in the range 57–67 °C <2002JOC4086>. Uncondensed 1,5-oxazocines **410**, **411a,b**, and **420a–f** showed melting points at 176–180, 110–180, and 86–249 °C, respectively. Annellation of the eight-membered ring with one or two benzene originated compounds melting in the range 99–280 °C <1999TL5827, 1999T8295, 2000T2369, 2003AGE5198, 2004T3261>. Condensation with one or more heterocycles generally, with the exception of benzimidazooxazocine **430**, which is an oil <2001EJO1511>, produced compounds that melted in the range 142–293 °C <1997FA751, 2003OL4795, 2004T4481>.

Soluble in most common solvents, oxazocines were purified by recrystallization from DCM or diethyl ether <2004CHE641>, AcOEt/IPE or AcOEt/hexane <2004T4481>, DCM/hexane <2005WO084296>, and EtOAc/EtOH <2004WO058767>. Some 1,5-oxazocines were also purified by chromatography on silica gel using as eluant DCM, DCM/EtOAc, or petroleum ether/EtOAc <2003OL4795, 2003H(60)1793, 2004T2583, 2006JOC3291>, EtOAc/hexane <2000CEJ671, 2000T2369, 2003AGE5198, 2004JCO54, 2004S405, 2004T3261, 2004TL8475>, DCM/MeOH <1997H(45)361, 2000T2369, 2002T4451>, $\text{CHCl}_3/\text{MeOH}$ <1999T8295, 2002CEJ4767>. The *cis*- and *trans*- mixtures (2:1) of bridged oxazocines **410** were isolated by crystallization from DCM. In CDCl_3 solution, the piperidine ring of *cis*-**410** was in a boat conformation stabilized by an intramolecular hydrogen bond <2004CHE641>. Using the ^1H NMR spectroscopic method (see Section 14.07.3.2) was showed that carbonyl-bridged oxazocines **417a–c** and methylene-bridged oxazocines **418a–c** existed in CDCl_3 solution in a double-chair (CC) conformation. Instead **419** was a 1:1 mixture of the two stereoisomeric alcohols; one of them existed in a double-chair (CC) conformation having an equatorial OH group relative to the piperidine ring and the other in a chair–boat (CB) conformation having an axial OH group which was involved in an intramolecular hydrogen bond with the unshared electron pair of nitrogen atom <2003CHE1376>. The configuration at the C(1') on lactones **422a** (*R*) and **422b** (*S*) was unambiguously provided by NOE difference spectroscopy. The virtual lack of coupling between the C(1')–H and C(3)–H (torsion angle $\sim 90^\circ$) further provided evidence for the stereochemistry (see Section 14.07.3.2) <1997H(45)361>. The two different conformations of benzo-1,5-oxazocines **423** and **424** were assigned by using various NMR studies (see Section 14.07.4.2). The oxygen-containing ring was in a chair form, whereas the other ring with nitrogen and fused to the benzene moiety existed in the half-chair form <2003AGE5198, 2004S405, 2004T3261, 2004TL1543>. The stereochemistry of (3*S*)-isomer of pyrido[2,3-*b*][1,5]oxazocin-6-one **422a** ($R = \text{H}$; $R^1 = R^2 = \text{Me}$; $\text{Ar} = \text{C}_6\text{H}_5$), deduced by detailed NMR spectroscopic analysis, could reasonably be explained as (*aR*,3*S*) in the solid state and in equilibrium state between (*aR*,3*S*)- and (*aS*,3*S*)-forms in a ratio of nearly 98:2 in solution. The corresponding enantiomer (3*R*)- **422a** should have an (*aS*,3*R*) stereochemistry. Analogously, the stereochemistry determined for (3*S*)-isomer of 1,5-oxazocine **422b** ($R = R^1 = \text{H}$; $R^2 = \text{Me}$; $\text{Ar} = \text{C}_6\text{H}_5$) established the same conformation (see Section 14.07.3.1) <2004T4481>.

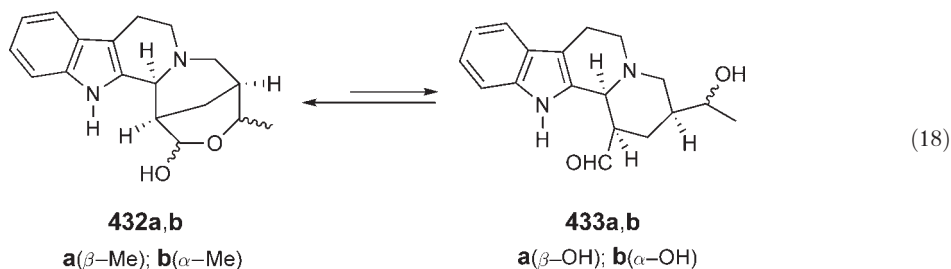
14.07.3.4 Reactivity of Nonconjugated Rings

The Wittig olefination of 1,5-oxazocine **416** with [(methoxy)methylene]triphenylphosphorane led to the formation of the enol ether **431a** (88% yield) as an inseparable mixture of *E* and *Z* isomers (2.5:1 ratio). Instead, when the reaction was carried out using methyltriphenylphosphorane as Wittig reagent, the *cis* 3,5-disubstituted diastereoisomer **431b** was exclusively formed in 85% yield (Scheme 84) <1998JOC3492>.

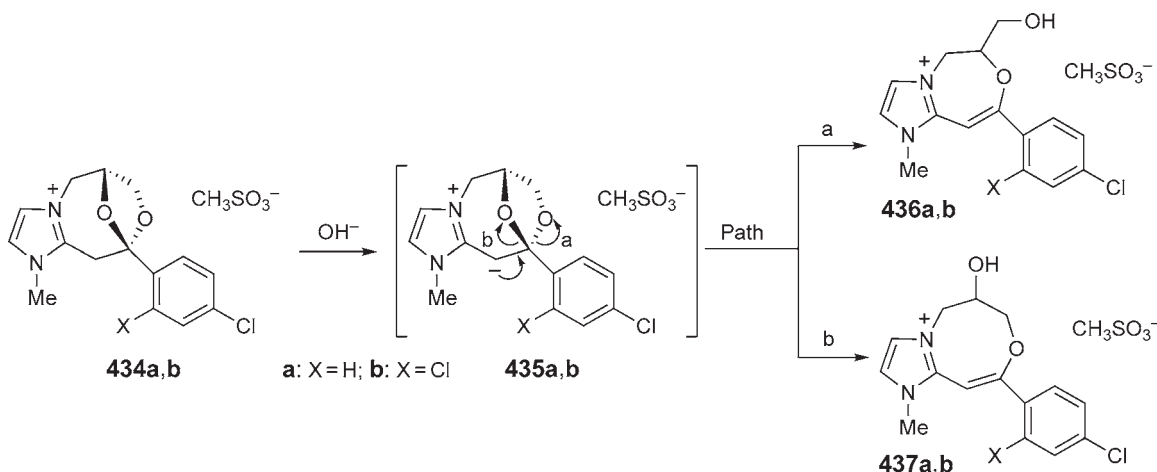


Scheme 84

The bridge 1,5-oxazocines **432a,b** were in equilibrium with the open aldehydes **433a,b** and thus it could not be isolated in pure state (Equation 18) (see Section 14.07.3.7.1.) <1998T4673>.



Treatment of the imidazo-1,5-oxazocines methanesulfonates **434a,b** with NaOD in D₂O or K₂CO₃ upon neutralization of the active methylene protons (H-10) generated the methylene anions **435a,b** which collapsed with ring opening of the ketal, via path a or b, to form either the seven- or the eight-membered rings **436a,b** and **437a,b**, respectively (Scheme 85) <1997JHC1607>.



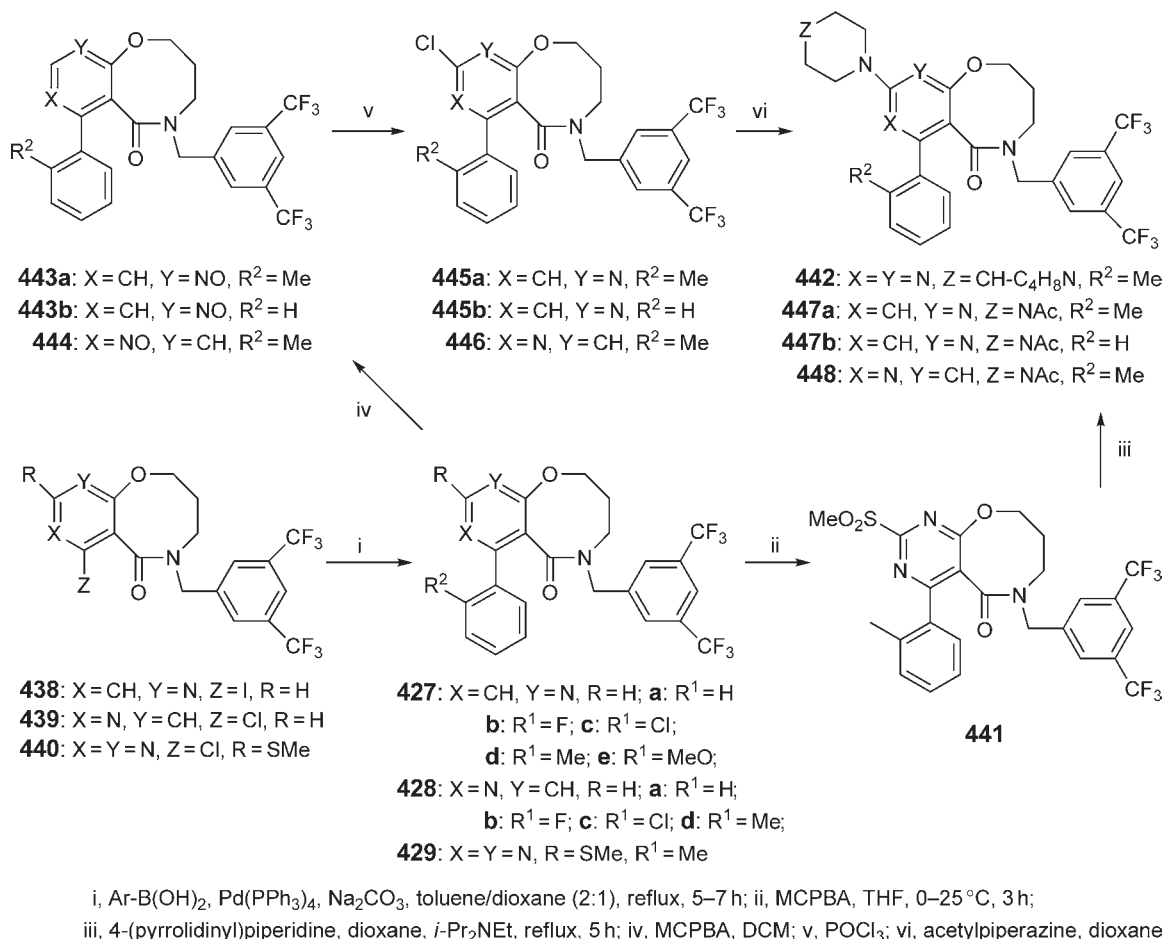
Scheme 85

14.07.3.5 Reactivity of Substituent Attached to Ring Carbon Atoms

Treatment of 5-(4-bromophenyl)-2-phenyl-5,6-dihydrobenzo[*b*][1,5]oxazocin-4-one **412b** (X = O, R = Br) with LiAlH₄ in THF at 0°C for 1 h gave the 5-(4-bromophenyl)-2-phenyl-5,6-dihydro-4H-benzo[*b*][1,5]oxazocine **412e** (X = H₂, R = Br) in 39 % yield <2003H(60)1793>. Reduction of the carbonyl-bridged oxazocines **417b,c** under Wolff-Kishner conditions gave the corresponding methylene-bridged oxazocines **418a,b**. When the reduction of 1,5-oxazocine **417c** was conducted using NaBH₄ in *i*-PrOH at 20°C for 20 h, **419** was obtained as a mixture of two isomers in 89% yield as result of partial reduction of carbonyl-bridge <2003CHE1376>. 7-Aryl-3,4,5,6-tetrahydropyrido[2,3-*b*] **427** and -pyrido[4,3-*b*]-1,5-oxazocines **428** were synthesized from the corresponding iodide **438** or chloride **439** derivatives by Suzuki coupling reaction with arylboronic acids, using Pd(PPh₃)₄ in 77–99% and 60–98% yield, respectively. The coupling reaction proceeded equally well using iodide **438** or chloride **439** derivative <2004TL8475>. Analogously, Suzuki coupling reactions of pyrimido[4,5][1,5]oxazocin-5-one **440** afforded the corresponding aryl substituted 1,5-oxazocine **429** in 95 % yield after reflux for 6 h. Oxidation of sulfide **429** using MCPBA in THF gave the corresponding sulfone **441** (99% yield). Subsequent nucleophilic amination of this latter with 4-(pyrrolidinyl)piperidine furnished the amine derivative **442** (64%) <2005BML1485, 2005WO019225>.

Formation of chlorides **445a,b** and **446**, in nearly quantitative yields, via the Meisenheimer reaction was accomplished by treatment of the corresponding 1,5-oxazocines **427a,d** and **428d** with MCPBA to give **443a,b** and **444**

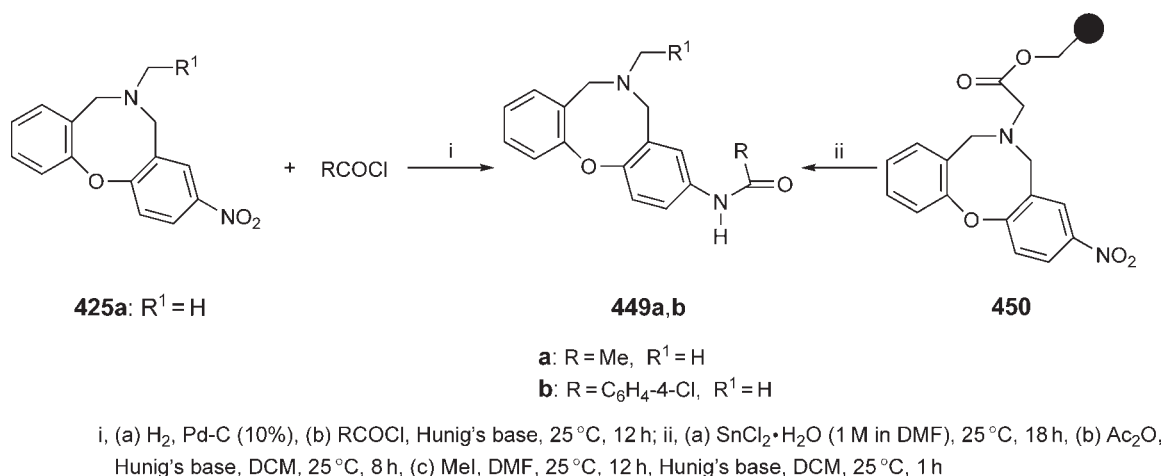
(54–83% and 75% yield, respectively) which were subsequently rearrangement with POCl₃. Coupling of 1,5-oxazocines **445a,b** and **446**, with 1-acetylpiperazine, provided the eight-membered rings **447a,b** and **448** in 38–57% and 55% yield, respectively (Scheme 86) <2005BMC5717, 2005BML1479>.



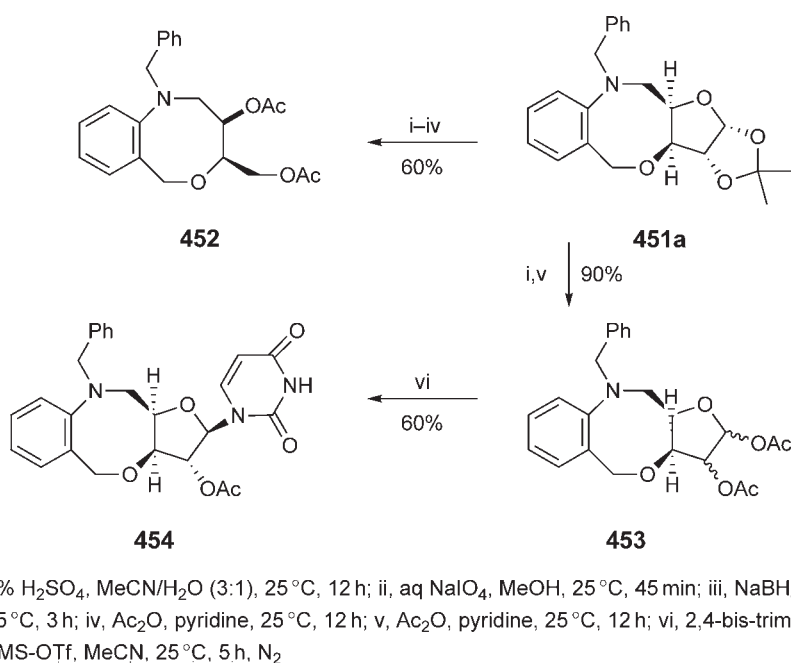
Scheme 86

Catalytic reduction of nitro group of dibenzooxazocine **425a**, followed by acylation of the resulting amine with MeCOCl or 4-ClC₆H₄Cl, proceeded smoothly to afford the acylaminooxazocines **449a,b** <2000T2369> (Scheme 87). *N*-(6-Methyl-5*H*,7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocine-3-yl)acetamide **449a** was also obtained starting from resin 1,5-oxazocine **450**, by reduction to the corresponding amine and subsequent acylation with Ac₂O. Treatment of acethylamino intermediate with MeI followed by Hunig's base afforded the oxazocine **449a** in 78% yield (Scheme 4) <1999TL5827>. Wittig reaction of *N*-BOC-1,5-oxazocine **420a** with Br[−] Ph₃P⁺(CH₂)₄COOH, in the presence of *t*-BuOK yielded the oxazocine **420b** in 54% yield. Treatment of the carboxy acid moiety of **420b** with MeOH in presence of EEDQ as activating reagent furnished the methyl ester **420c** in 82% yield; instead, when **420b** was reacted with hydroxymethylpolystyrene in presence of DIC and DMAP the corresponding polymer was obtained in 71% yield <2002CC673, 2002CEJ4767>.

Furanose-annulated benzoxazocine **451a** was converted into (3*R*,4*R*)-3-acetoxy-4-acetoxymethyl-1-benzyl-1,3,4,6-tetrahydro-2*H*-benzo[*c*][1,5]oxazocine **452** through a sequence of reactions involving the removal of the 1,2-*O*-isopropylidene group, NaIO₄ cleavage of diol, NaBH₄ reduction of the carbonyl group, and acetylation. Cleavage of the acetonide group of oxazocine **451a** followed by acetylation using Ac₂O furnished the anomeric mixture of diacetates **453** which was reacted with 2,4-bis(trimethylsilyloxy)uracil to give the nucleoside 1,5-oxazocine **454** (Scheme 88) <2006JOC3291>.



Scheme 87

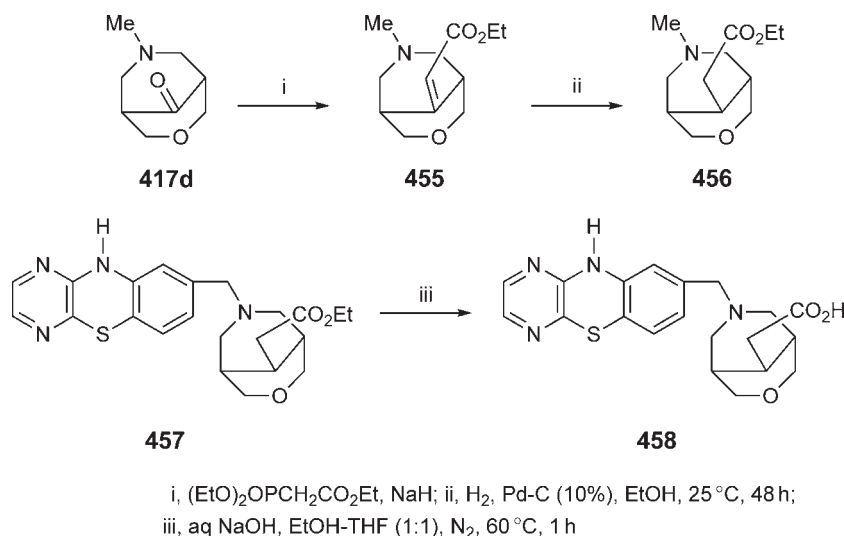


Scheme 88

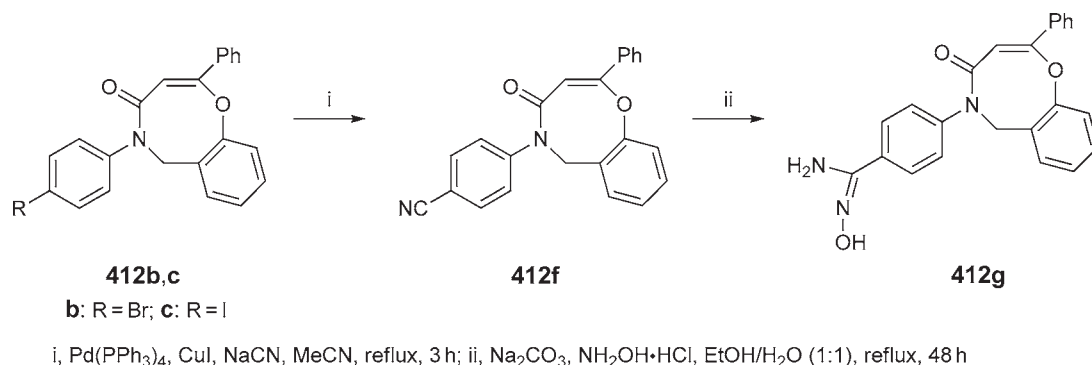
The unsaturated ester 1,5-oxazocine **455** was obtained by treatment of bridged oxazocine **417d** with triethyl phosphonoacetate (59% yield). Catalytic hydrogenation of **455** afforded the saturated ester **456** in 77% yield. Alkaline hydrolysis of ester moiety of 1,5-oxazocine **457** gave the corresponding acid **458** in 85% yield (Scheme 89) <2004CPB675>.

14.07.3.6 Reactivity of Substituent Attached to Ring Heteroatoms

Reaction of bromo-benzoxazocine **412b** with NaCN, in the presence of catalytic amount of Pd(0), gave the cyano derivative **412f** in 87% yield. When iodo-benzoxazocine **412c** was used, under the same reaction conditions, the 1,5-oxazocine **412f** was obtained in better yield (99%). Treatment of this latter with $NH_2OH \cdot HCl$ in basic medium afforded the *N*-hydroxy-4-(4-oxo-2-phenyl-4*H*,6*H*-benzo[*b*][1,5]oxazocin-5-yl)benzamidine **412g** in 51% yield (Scheme 90) <2003H(60)1793>.



Scheme 89

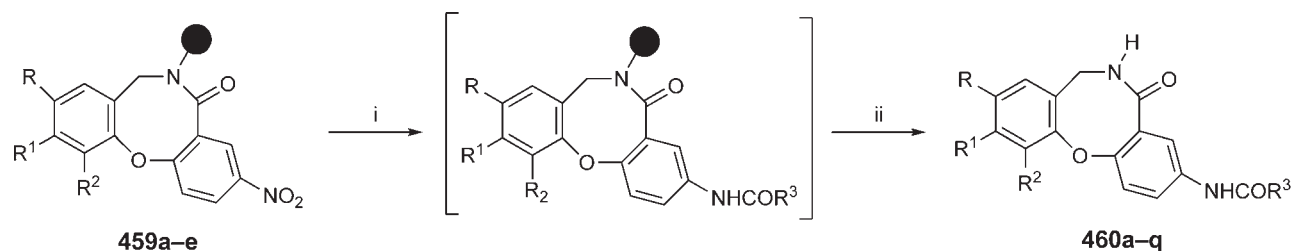


Scheme 90

Reduction of nitro dibenz[*b,f*]oxazocines **459a–e** afforded the corresponding amino derivatives. Acylation of these latter using furoyl chloride, 4-methoxybenzoyl chloride and 4-chlorobenzoyl chloride furnished the corresponding amides, which were cleaved by treatment with TFA to provide a 15-member library of dibenzoxazocines **460a–q** (31–76% yield) (Scheme 91) <1999T8295, 2002BMC2415>. Treatment of 1,5-oxazocine on solid support **450** with alkyl iodides in DMF followed by addition of Hunig's base to the resulting quaternized amines afforded the eight-membered heterocycles **461a–e** in 38–53% yield (Scheme 91) <1999TL5827>.

N-Phosphoramidite 1,5-oxazocines **420e,f,i,j** were easily obtained from the reaction of (*R*)-3,3'-substituted-1,1'-binaphthyl-2,2'-dioxaphosphorochloridites **463a** or **463b**, prepared *in situ* from the corresponding derivatives **462a** and **462b** with oxazocines **420c,d,g,h**. The BOC group was first removed from the oxazocines **420c**, and **420g** using TFA then phosphitylation with chlorophosphite **463a** in the presence of Et_3N furnished derivatives **420ej** (41–71% yield). *N*-Phosphoramidite substituted oxazocine **420f** was obtained from 1,5-oxazocine **420d**, which was BOC-deprotected using the above-mentioned reaction conditions, and phosphitylated with **463b**. The direct phosphitylation of 1,5-oxazocine **420h** with **463a** at elevated temperature (80 °C) afforded the corresponding phosphoramidite oxazocine **420j** in 53% yield (Scheme 92) <2000CEJ671, 2002CC673, 2002CEJ4767>.

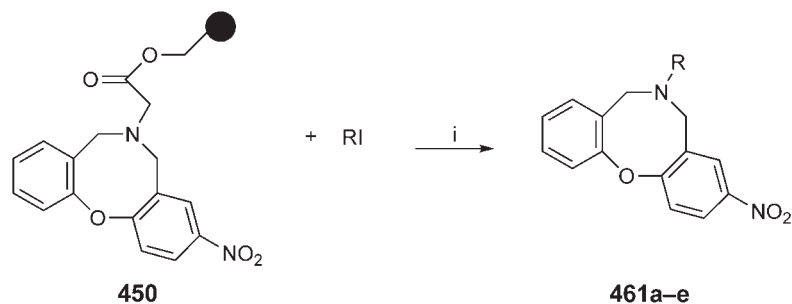
Deprotection of the amino group of the *N*-methyl 1,5-oxazocine **456** using 1-chloroethyl chloroformate (ACE-Cl) in EtOH afforded the corresponding *N*-substituted oxazocines <2004CPB675>. *N*-BOC 1,5-oxazocines **409a–c** were obtained by treatment of the corresponding NH 1,5-oxazocines **409d–f** (d: R = Et; e: R = Ph; f: R = C_6H_4 -4-Cl) with BOC_2O and Et_3N in the presence of a catalytic amount of DMAP (60–76%) <2004T2583>.



459: **a:** $R=R^1=R^2=H$; **b:** $R=R^1=H, R^2=OMe$; **c:** $R^1=R^2=H, R=OMe$; **d:** $R=R^2=H, R^1=OMe$; **e:** $R^1=R^2=H, R=Me$

460: **a:** $R=R^1=R^2=H, R^3=C_4H_3O$; **b:** $R=R^1=H, R^2=OMe, R^3=C_4H_3O$; **c:** $R^1=R^2=H, R=OMe, R^3=C_4H_3O$;
d: $R=R^2=H, R^1=OMe, R^3=C_4H_3O$; **e:** $R^1=R^2=H, R=Me, R^3=C_4H_3O$; **f:** $R=R^1=R^2=H, R^3=C_6H_4-4-OMe$;
g: $R=R^1=H, R^2=OMe, R^3=C_6H_4-4-OMe$; **h:** $R^1=R^2=H, R=OMe, R^3=C_6H_4-4-OMe$; **i:** $R=R^2=H, R^1=OMe, R^3=C_6H_4-4-OMe$;
l: $R^1=R^2=H, R=Me, R^3=C_6H_4-4-OMe$; **m:** $R=R^1=R^2=H, R^3=C_6H_4-4-Cl$; **n:** $R=R^1=H, R^2=OMe, R^3=C_6H_4-4-Cl$;
o: $R^1=R^2=H, R=OMe, R^3=C_6H_4-4-Cl$; **p:** $R=R^2=H, R^1=OMe, R^3=C_6H_4-4-Cl$; **q:** $R^1=R^2=H, R=Me, R^3=C_6H_4-4-Cl$

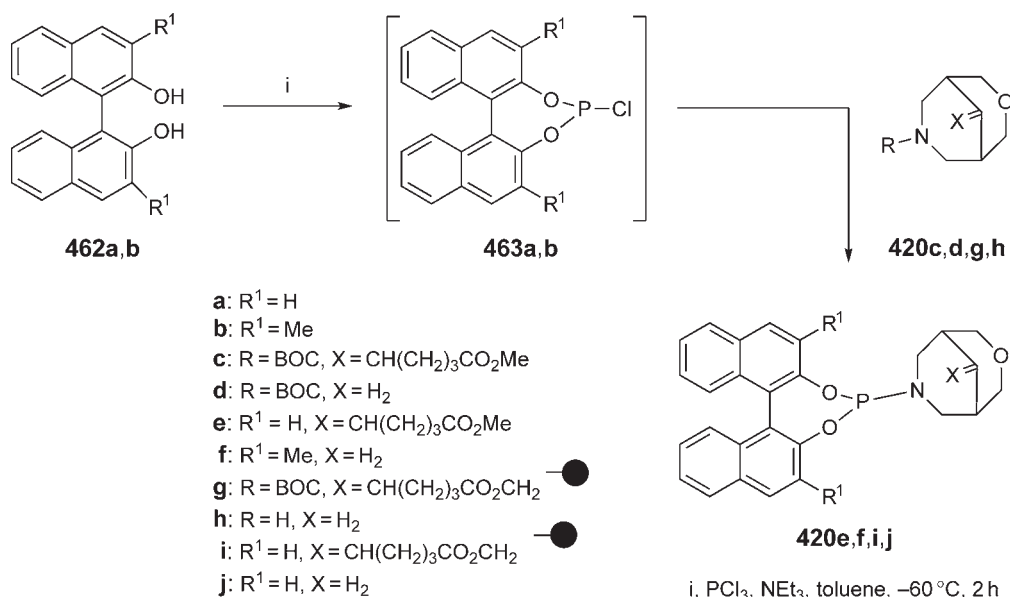
i, **a:** $SnCl_2 \cdot 2H_2O$, DMF, 25 °C, 24 h; **b:** R^3COCl , DMF, Hunig's base, 25 °C, 8 h; ii, TFA (20%), DCM, 40 min



i, **a:** DMF, 25 °C, 24 h; **b:** Hunig's base, 25 °C, 12 h

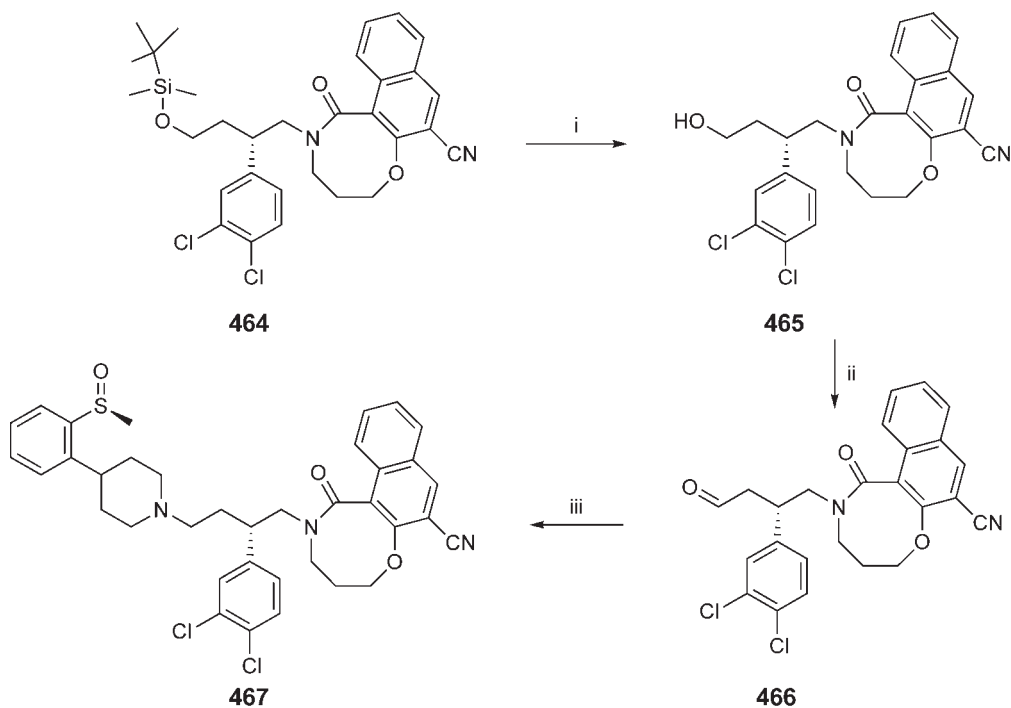
a: $R=Me$
b: $R=CH_2-CH=CH_2$
c: $R=Bn$
d: $R=4-Cl-Bn$
e: $R=4-Me-Bn$

Scheme 91



Scheme 92

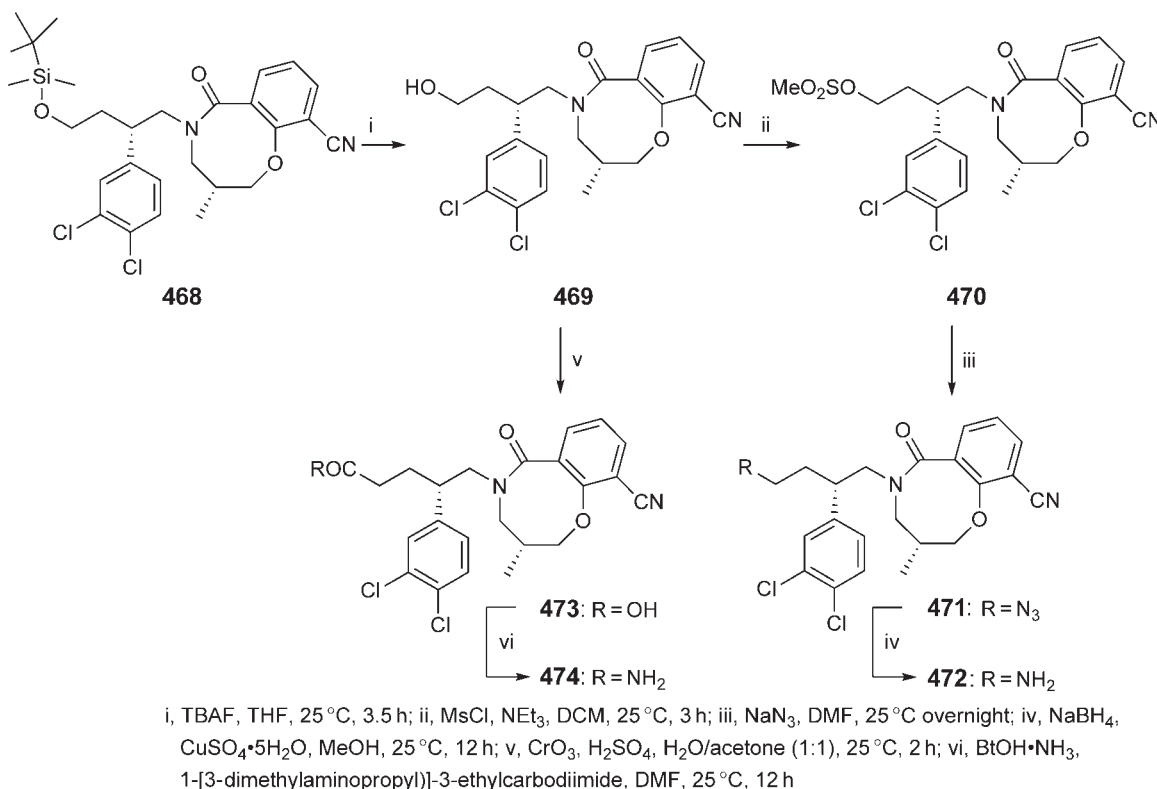
Treatment of naphtho[2,1-*b*][1,5]oxazine **464** with HF yielded the deprotected alcohol **465** (95%), which was subsequently oxidized under Swern conditions to give the oxo-butyl 1,5-oxazine **466** (96%). Reaction of the latter with 4-[(*S*)-2-methylsulfinylphenyl]piperidine in presence of NaBH_4 under standard reductive amination, afforded the oxazine **467** (72%) ([Scheme 93](#) <2004BMC2653>).



i, 5% HF, MeCN, 25°C , 40 min; ii, oxalyl chloride, DMSO, NEt_3 , DCM, -68°C , 30 min, then 25°C , 2 h;
 iii, 4-[(*S*)-2-methylsulfinylphenyl]piperine, NaBH_4 , AcOH, MeOH

Scheme 93

The *t*-butyldimethylsilyloxy group was removed from the benzo[*b*][1,5]oxazocine **468** using tetrabutylammonium fluoride (TBAF) in THF to give the corresponding alcohol **469** (96%). Reaction of the latter with MsCl in the presence of Et₃N afforded the mesyl **470** in quantitative yield. Subsequent nucleophilic substitution of **470** with NaN₃ furnished 1,5-oxazocine **471** in quantitative yield. Reduction of the azide moiety of **471** with NaBH₄ gave the amino derivative **472** (69%). Oxidation of OH group of 1,5-oxazocine **469** by Jones reagent gave the carboxylic acid derivative **473** in 96% yield. Treatment of this latter with HOBu^t.NH₃ and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, as coupling agent, afforded the amide **474** in 78% yield (Scheme 94) <2002WO26724>.



Scheme 94

The phenylsulfonamide-protecting group in 1,5-oxazocine **475** was removed by reduction with Red-Al[®] (84%) and replaced by the BOC-group using BOC₂O (90%). Subsequent catalytic hydrogenation to remove the benzyl group afforded the 1,5-oxazocine **476** in quantitative yield.

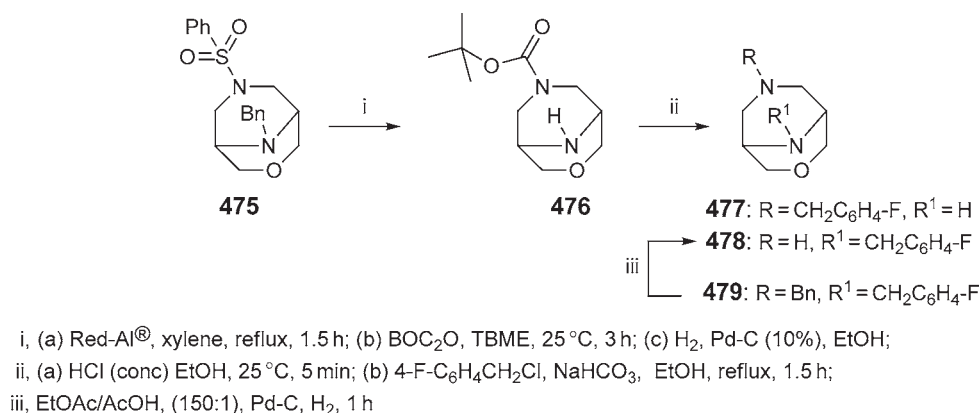
Removing the BOC-group of **476** with HCl in EtOH and selective benzylation at the less hindered *N*-atom with 4-fluorobenzyl chloride in EtOH delivered the 1,5-oxazocine **477** in 74% yield. The regioisomer **478** was obtained by benzylation first, followed by removal of the BOC group (84%). Selective debenylation of **479** with H₂ and Pd/C yielded 1,5-oxazocine **478** (82%) (Scheme 95) <2005TL5577>.

Treatment 1,5-oxazocine **480** with Ac₂O in presence of DMAP afforded in 55% yield the *N*-acetyl-dibenzo-1,5-oxazocine **481** which underwent Suzuki coupling reaction with phenylboronic acid to give the phenyl substituted 1,5-dibenzoxazocine **482** (13%) (Scheme 96) <2005WO084296>.

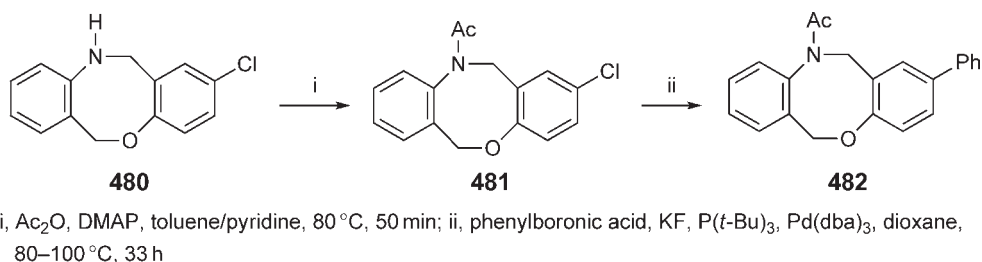
14.07.3.7 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.07.3.7.1 Natural products

Hupeol **421** was obtained from the dry branches of *M. hupehensis* collected in Jiang Xi province, China <1998JCM196>.



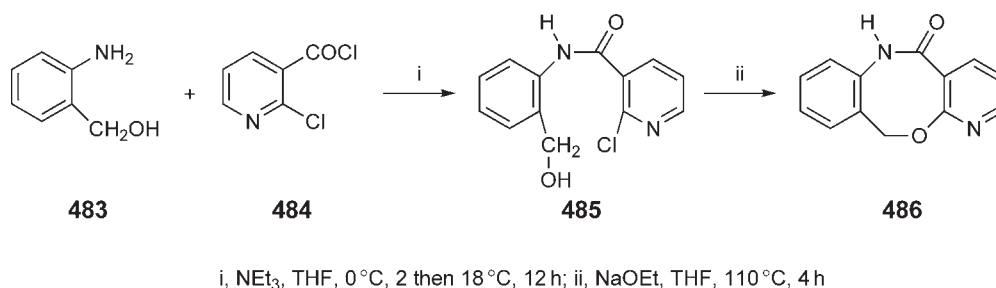
Scheme 95



Scheme 96

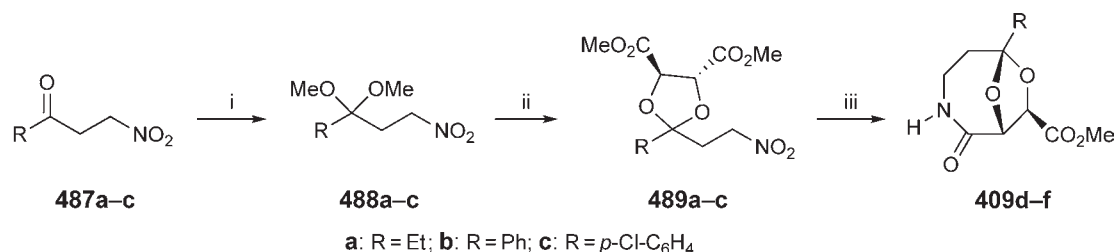
14.07.3.7.2 Ring syntheses from C₆NO units

Reaction of 2-aminobenzyl alcohol **483** with 2-chloronicotinoyl chloride **484** in the presence of Et₃N yielded the 2-hydroxymethylphenylamide-2'-chloronicotinic acid **485** (32%). Such an intermediate underwent a base promoted to give the pyridobenzo[*b,f*][1,5]oxazocin-6-one **486** in 36% yield (Scheme 97) <1997FA751>.



Scheme 97

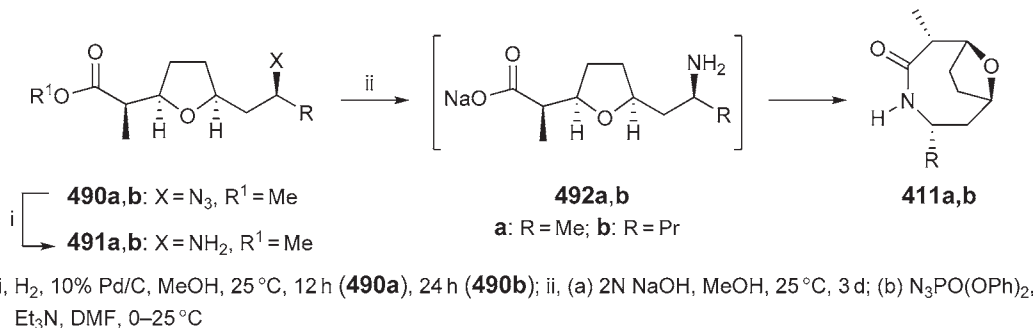
Ketones **487a–c** were converted into their corresponding dimethyl ketals **488a–c** by treatment with an excess of HC(OMe)₃ in MeOH under *p*-TsOH catalysis. Depending on the substrate, the reaction was left 72 h at 25 °C **487a** or refluxed for 5 h (**487b,c**) affording **488a–c** in very good yields (75% to quantitative). *Trans*-ketalization of **488a–c** performed using dimethyl (*R,R*)-tartrate and BF₃·Et₂O furnished **489a–c** (42–63%). Reduction of the nitro group of **489a–c** led to the corresponding amine, which spontaneously cyclized to give the 1,5-oxazocine **409d–f** (76–99%) (Scheme 98) <2004T2583>.



i, HC(OMe)₃, *p*-TsOH cat., MeOH, reflux to 25 °C, 5 h; ii, (*R,R*)-dimethyl tartrate, BF₃/Et₂O, EtOAc, 0 °C, 4 h; iii, Raney-Ni, H₂, MeOH, 25 °C, 16 h

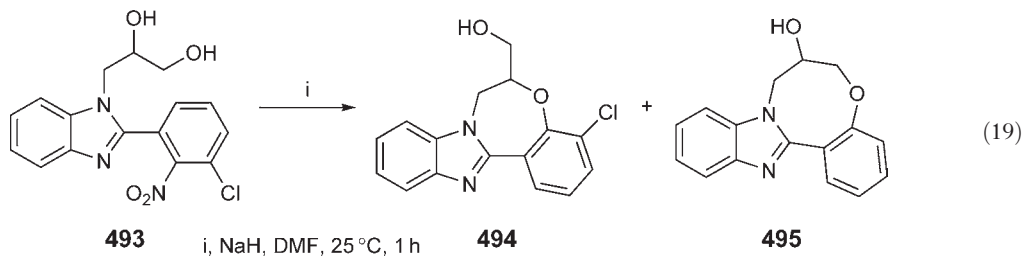
Scheme 98

Hydrogenation of the racemic azides **490a** and **490b** afforded the corresponding amino esters **491a** and **491b** in 98% and 96% yield, respectively. Saponification of the latter gave the sodium carboxylates **492a,b** which treated with diphenylphosphoryl azide (DPPA) induced a smooth ring closure to give the lactams **411a,b** in 53% and 61% yield, respectively (Scheme 99) <2002T4451>.

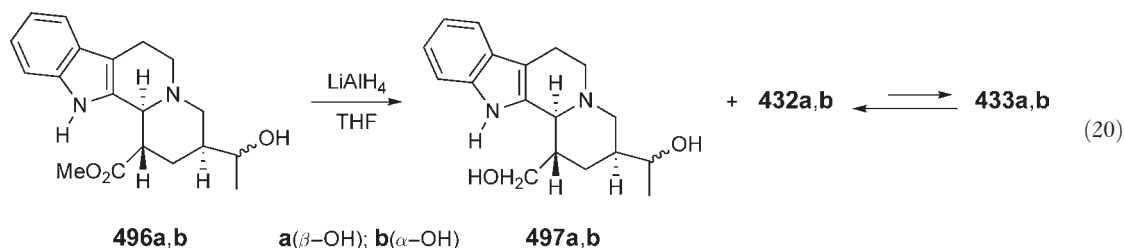


Scheme 99

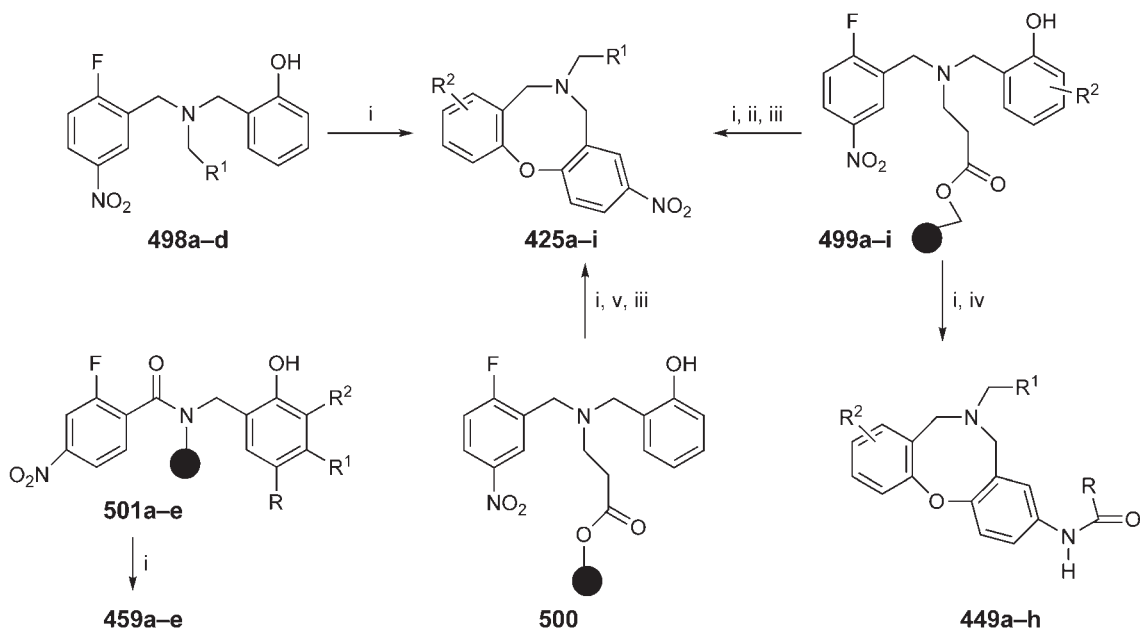
The diol **493** cyclized by intramolecular S_NAr of the sterically hindered benzimidazole-activated nitro group by the primary or the secondary alkoxide in the presence of NaH to give the 1,5-oxazocine **495** (8%) and the thermodynamically more favored 1,4-oxazepine **494** (70%) (Equation 19) <2003OL4795, 2005USP0239767>.



Reduction of the hydroxyl esters **496a,b** with LiAlH₄ at 25 °C afforded the corresponding alcohols **497a,b** together the bridged 1,5-oxazocines **432a,b** as a result of the epimerization and ring closure of the aldehyde intermediates **433a,b**. It was impossible to isolate in pure state the eight-membered ring **432a,b** due to its equilibrium with the open aldehydes **433a,b** (Equation 20) (see Section 14.07.3.4) (Equation 18) <1998T4673>.



Intramolecular nucleophilic substitution of fluorine with the phenolic hydroxide of tertiary amines **498a–d** in presence of an excess of DBU in DMF afforded the 1,5-oxazocines **425a–d** in 12–77% yield. The use of other bases (K_2CO_3 , Cs_2CO_3 , t -BuOK, Bu_4NF , and CsF) yielded the eight-membered ring in lower yields. Analogously, treatment of the immobilized intermediate **499a–i**, on Wang resin, with DBU in DMF afforded the immobilized 1,5-oxazocines which were subsequently reacted with the alkylating agent (R^1CH_2Br) followed by Hunig's base to give the 9-nitro-dibenzo[*b,f*][1,5]-oxazocines **425a–i** (12–75%). Alternatively, cyclization of **499a–i** with DBU was followed by reduction of the nitro group with $SnCl_2 \cdot H_2O$ in DMF, subsequent treatment with $MeCOCl$ or $pCl-C_6H_4COCl$, alkylation with R^1CH_2Br and cleavage with Hunig's base afforded the 1,5-oxazocines **449a–h** in 20–78% yield (Scheme 100) <2000T2369>. Oxazocines **425a–i** could also be obtained in 38–55% yield when the resin **500** was subjected to the same reaction sequence described for **499a–i** <1999TL5827>. Substituted 6*H*,7*H*-dibenzo[*b,g*][1,5]oxazocin-5-ones on solid support **459a–e** were obtained by intramolecular ring closure of the intermediates **501a–e** promoted by DBU (Scheme 100) <1999T8295, 2002BMC2415>.



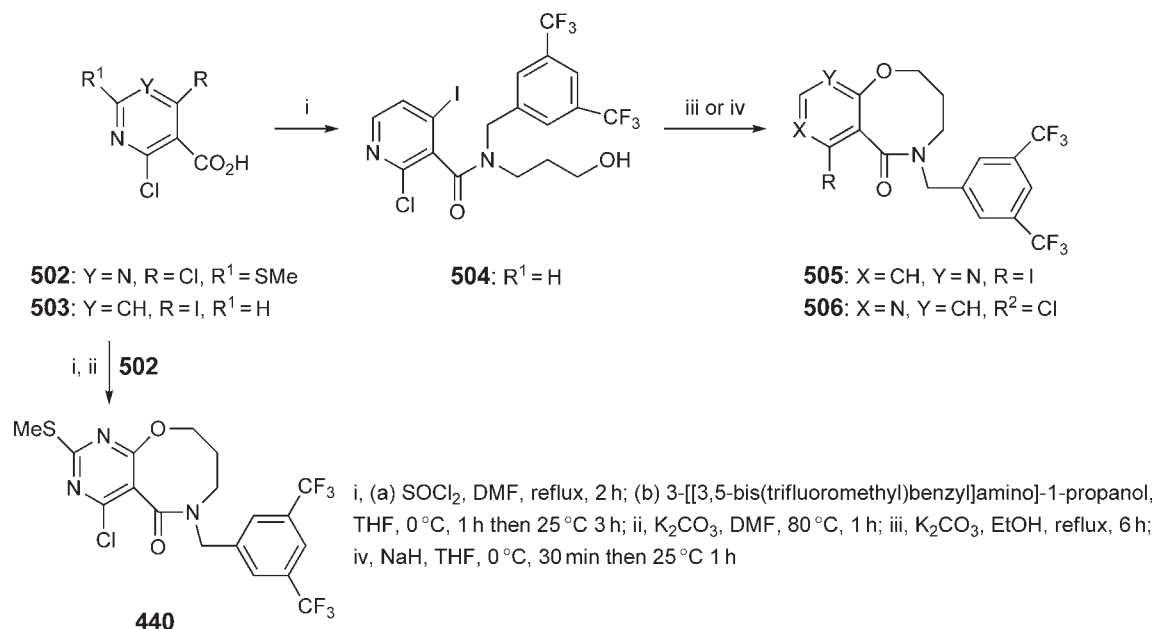
i, DBU, DMF, 25 °C, 6 h; ii, $SnCl_2 \cdot H_2O$, DMF, 25 °C, 12 h; iii, R^1COCl , Hunig's base, DCM, 25 °C, 4 h;
iv, $R^1CH_2Cl_2$, 25 °C, 2 h; v, alkyl halides, DMF

425: **a**: $R^1 = R^2 = H$; **b**: $R^1 = CH=CH_2$, $R^2 = H$; **c**: $R^1 = Ph$, $R^2 = H$; **d**: $R^1 = C_6H_4-4-Cl$, $R^2 = H$; **e**: $R^1 = CH=CH_2$, $R^2 = 6-OMe$; **f**: $R^1 = CH=CH_2$, $R^2 = 5-OMe$; **g**: $R^1 = CH=CH_2$, $R^2 = 4-OMe$; **h**: $R^1 = CH=CH_2$, $R^2 = -CH=CH-CH=CH-$; **i**: $R^1 = CH=CH_2$, $R^2 = 5-Br$

449: **a**: $R = Me$, $R^1 = R^2 = H$; **b**: $R = C_6H_4-4-Cl$, $R^1 = R^2 = H$; **c**: $R = C_6H_4-4-Cl$, $R^1 = CH=CH_2$, $R^2 = 6-OMe$; **d**: $R = C_6H_4-4-Cl$, $R^1 = CH=CH_2$, $R^2 = 5-OMe$; **e**: $R = C_6H_4-4-Cl$, $R^1 = CH=CH_2$, $R^2 = 4-OMe$; **f**: $R = C_6H_4-4-Cl$, $R^1 = CH=CH_2$, $R^2 = -CH=CH-CH=CH-$; **g**: $R = Me$, $R^1 = Ph$, $R^2 = 5-Br$; **h**: $R = Me$, $R^1 = Ph$, $R^2 = 6-F$

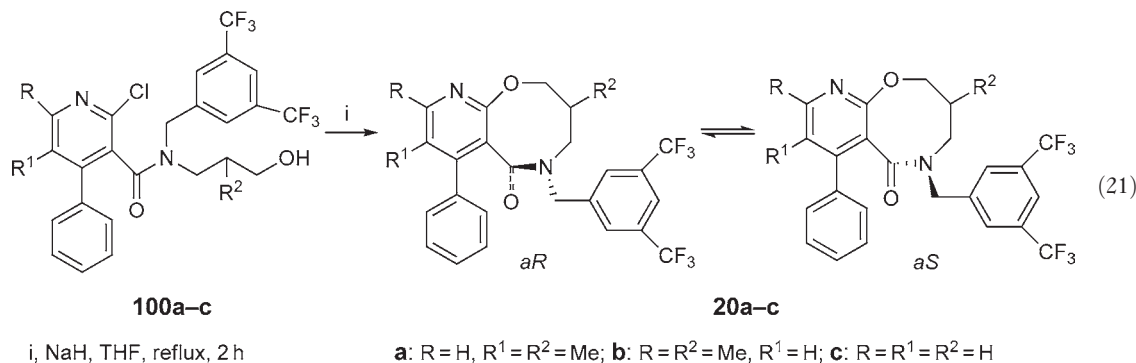
Scheme 100

Treatment of the 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylic acid **502**, with SOCl_2 gave the corresponding acyl chloride, which upon condensation with 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-propanol and subsequent intramolecular base promoted cyclization afforded the pyrimido[4,5-*b*][1,5]oxazocin-5-one **440** in 63% yield <2005BML1485, 2005WO019225>. The 2-chloro-4-iodopyridine-3-carboxylic acid **503** was analogously treated with SOCl_2 and condensed with 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-propanol to give the alcohol **504** (92%), which was converted to the pyrido[2,3-*b*]-1,5-oxazocine **505** and its regioisomer pyrido[4,3-*b*]-1,5-oxazocine **506** (42% and 71% yield, respectively) (Scheme 101) <2005BMC5717, 2004TL8475>.

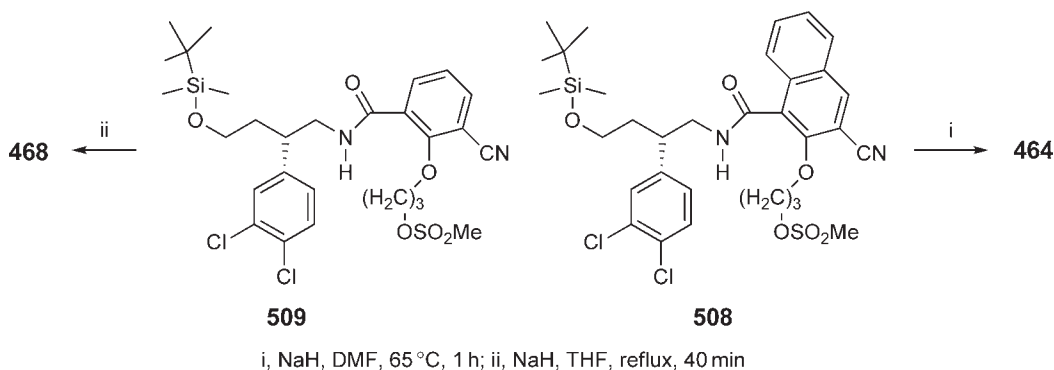


Scheme 101

Intramolecular cyclization of *N*-[3,5-bis(trifluoromethyl)benzyl]-2-chloro-*N*-(3-hydroxypropyl)-substituted phenyl-nicotinamides **507a–c** using NaH in THF under reflux yielded the pyrido[2,3-*b*]-1,5-oxazocines **427a–c** (64–86%). The intermediates **507a,b** with the (*S*)-methyl group gave the cyclized (*3S*)-**427a** and (*3S*)-**427b**, while the enantiomeric intermediates **507Ra** and **507Rb** afforded (*3R*)-**427a** and (*3R*)-**427b**, respectively (Equation 21) (see Sections 14.07.3.2 and 14.07.3.3) <2004T4481>.

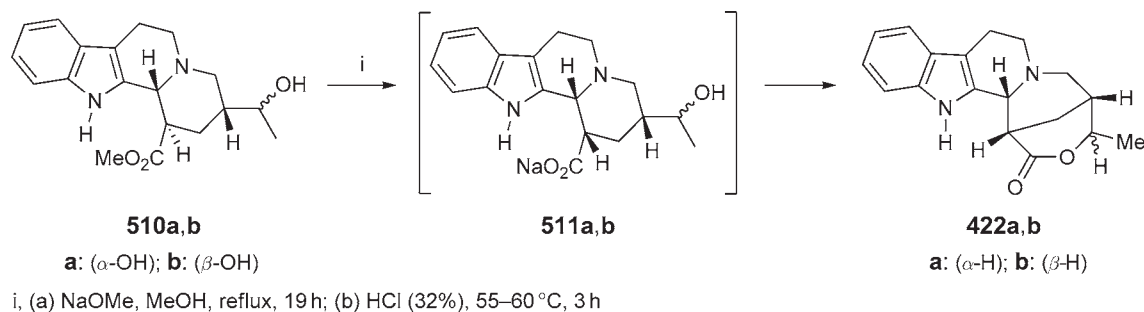


The naphtho[2,1-*b*]1,5-oxazocine **464** and benzo[*b*]1,5-oxazocine **468** were obtained by action of NaH on the corresponding mesylates **508** and **509** in 54% and 23% yield, respectively (Scheme 102) <2002WO26724, 2004BMC2653>.



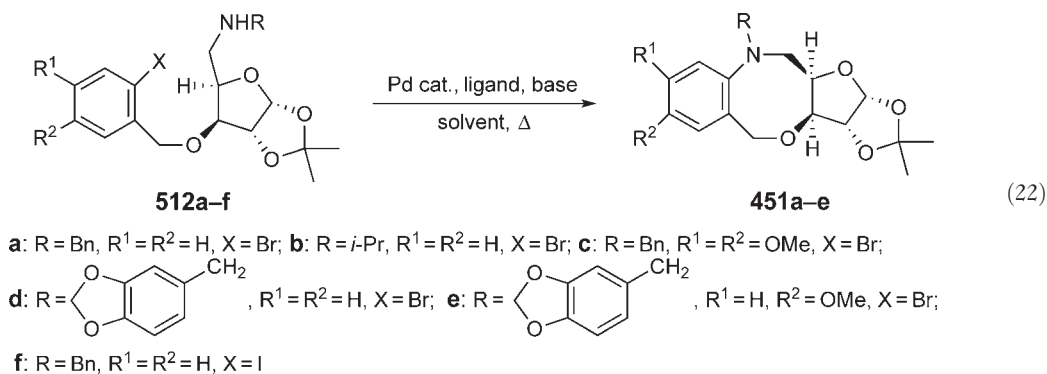
Scheme 102

Lactones **422a,b** were obtained by epimerization of the esters **510a,b**. Saponification of these latter using NaOMe in MeOH afforded the intermediates **511a,b**, which upon treatment with 32% HCl yielded the 1,5-oxazocine **422a,b** (10%) (Scheme 103) <1997H(45)361>.

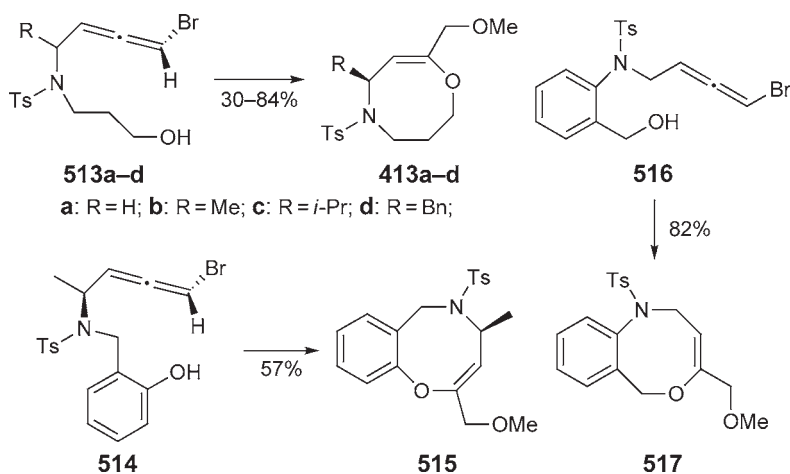


Scheme 103

The furo[3,2-*c*][1,5]benzoxazocines **451a–e** were synthesized from halobenzylated furanose-amines **512a–f** through Pd-catalyzed intramolecular cycloamination reactions in the presence of bases and ligands. The best conditions for this reaction were 10 mol% Pd₂(dba)₃ as the catalyst, 7 mol% $\pm$ BINAP, as ligand, and combination of K₂CO₃ and *t*-BuOK, as the base (68–77%) (Equation 22) <2006JOC3291>. The 1,5-oxazocine **416** was obtained, as a 1.6:1 inseparable mixture of C-2 epimers, from the epimeric 2.3:1 mixture of (3*R*,5*S*) and (3*S*,5*S*)-benzyl 3-formyl-5-acetoxymethyl-1-piperidinecarboxylate by alkaline hydrolysis (NaOH in THF), followed by acid work-up (5% H₃PO₄) in 95% yield <1998JOC3492>.

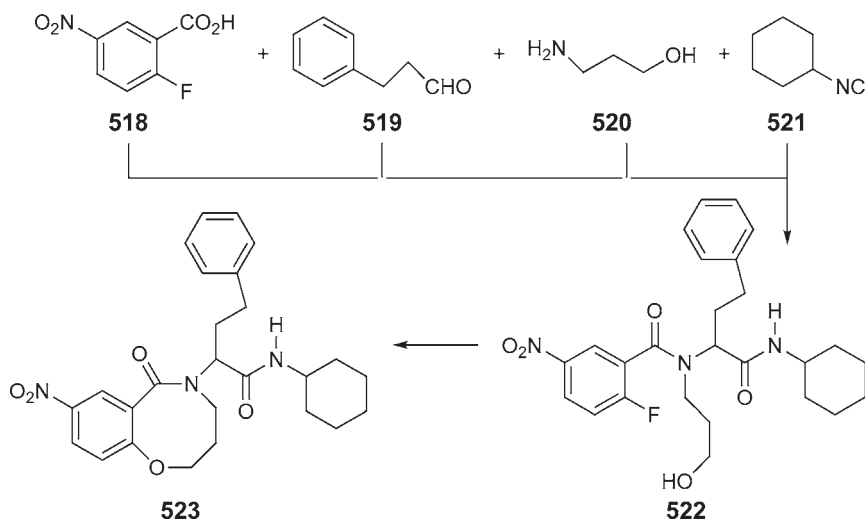


The 8-methoxymethyl-5-(4-methylphenylsulfonyl)-3,4,5,6-tetrahydro-2*H*-1,5-oxazocines **413a–d** were synthesized via cyclization of bromoallenes **513a–d**, by treatment with NaOMe in MeOH in the presence of Pd(PPh₃)₄. The bromoallene **513c** with a bulkier substituent at C-4 gave the eight-membered ring **413c** in low yield (14%) under identical reaction conditions reported above, while using fresh NaOMe, prepared *in situ* from NaH and MeOH, yielded 1,5-oxazocine **413c** in 30% yield. The palladium(0)-catalyzed cyclization of bromoallene **514** in MeOH gave benzo[*b*]-1,5-oxazocine **515** in low yield (15%), whereas the use of fresh MeONa slightly improved the yield (33%). The eight-membered ring **515** was obtained in 57% yield using NaH in MeOH-THF (1:1). Similarly, the reaction of bromoallene **516** under the same reaction conditions gave benzo[*b*]-1,5-oxazocine **517** (82%) (Scheme 104) <2004JA8744>.



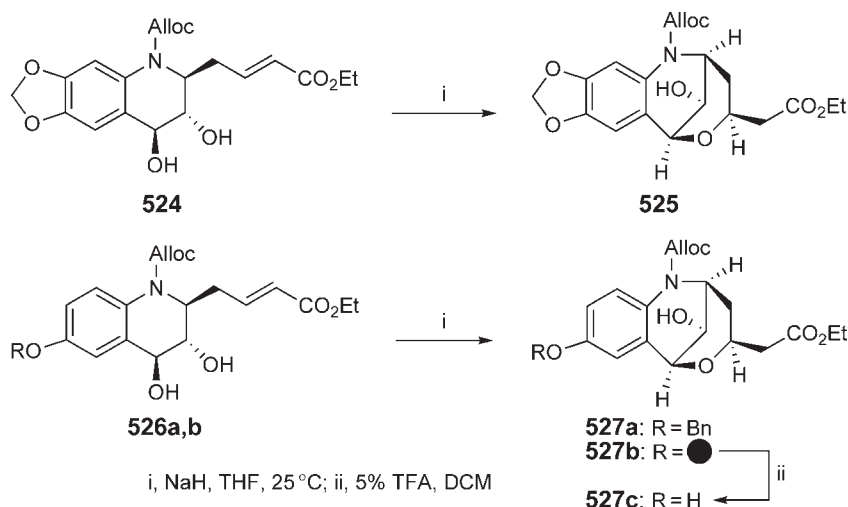
Scheme 104

The benzo-1,5-oxazocine **523** was obtained utilizing the Ugi-4-component reaction (U-4CR). Reaction of 2-fluoro-5-nitrobenzoic acid **518** with 3-phenylpropionaldehyde **519**, cyclohexyl isocyanide **521**, and the aminopropanol **520** afforded the Ugi-product **522** which was subjected to treatment with TFA followed by proton scavenging with resin, to promote cyclization to give 1,5-oxazocine **523** (60% yield) (Scheme 105) <2001TL4963>.



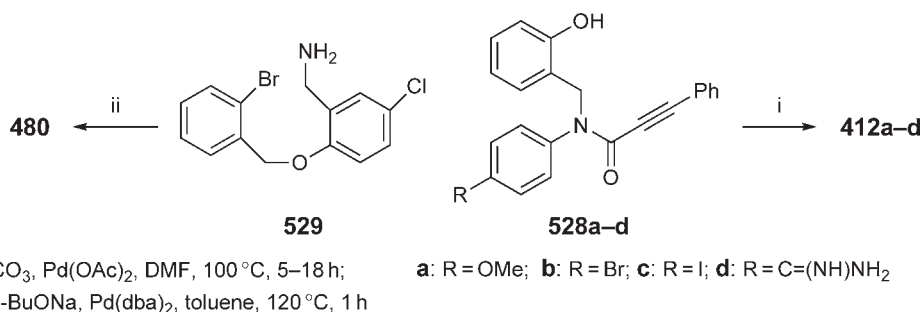
Scheme 105

Asymmetric hetero-Michael reaction of dihydroxyl derivative **524** using NaH as base gave the 1,5-oxazocine **525** in 84% yield. Similarly eight-membered ring **527a** was obtained using the same reaction condition from **526a**. Solid-phase synthesis of **527c** was achieved starting from the immobilized **526b**, which was subjected to hetero-Michael reaction to give **527b**, and subsequent cleavage from the support using TFA in DCM gave the 1,5-oxazocine **527c** (Scheme 106) <2004JCO54>.



Scheme 106

Cyclization of *N*-aryl-*N*-(2-hydroxybenzyl)-3-phenylpropynamide **528a–d** in basic medium (LiCl and K₂CO₃) under the influence of a catalytic amount of Pd(OAc)₂ afforded the 5-(4-aryl)-2-phenyl-5,6-dihydrobenzo[*b*][1,5]oxazocin-4-ones **412a–d** (32–62%) (Scheme 107) <2003H(60)1793>. Treatment of 2-(2-bromobenzoyloxy)-5-chlorobenzylamine **529** with BINAP and *t*-BuONa in presence of Pd(dba)₃ provided the dibenzoxazocine **480** 51% yield (Scheme 107) <2005WO084296>.

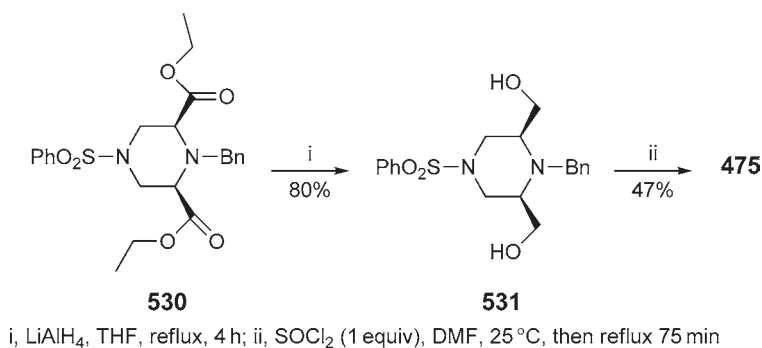


Scheme 107

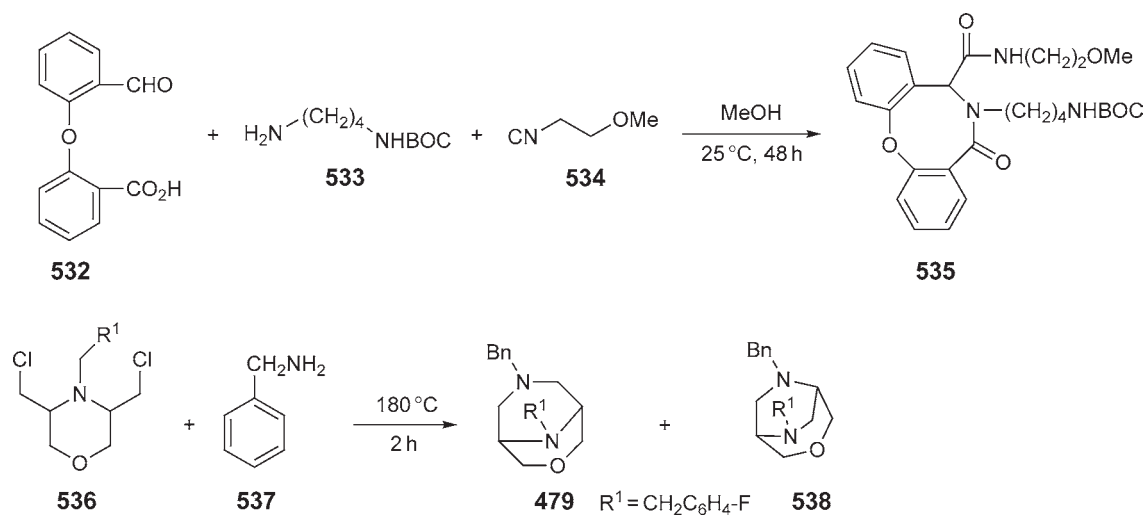
Selective reduction of diester **530**, generated the *cis*-diol **531**, which, treated with 1 equiv of SOCl₂, furnished the 1,5-oxazocine **475** (Scheme 108) <2005TL5577>.

14.07.3.7.3 Ring syntheses from C₆O + N units

The dibenzoxazocine **535** was obtained in 33% yield through a three-component condensation (3CC) reaction of 2'-formylphenoxy-2-benzoic acid **532**. Reaction of this latter with 4-(-*t*-butoxycarbonylamino)butylamine **533** and methoxyethylisocyanide **534** (Scheme 109) <1999JOC1074>.



Scheme 108

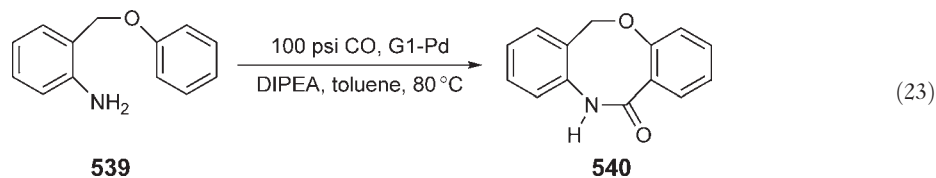


Scheme 109

Heating a *cis/trans* mixture (1:1) of dichloride **536** with benzylamine **537** gave rise to the 1,5-oxazocine **479** in 35% yield along with a small amount of the seven-membered ring **538** (5%) (Scheme 109) <2005TL5577>.

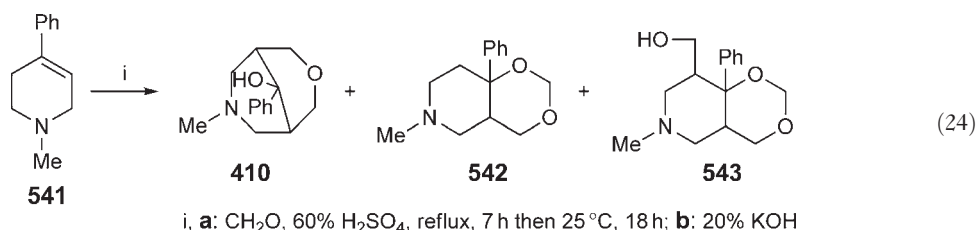
14.07.3.7.4 Ring syntheses from $\text{C}_5\text{NO} + \text{C}$ units

The dibenzo-1,5-oxazocine **540** was obtained, in nearly quantitative yield, via intramolecular carbonylation of *ortho*-substituted aniline **539** with 100 psi CO in the presence of recyclable palladium-complexed dendrimer on silica (G1-Pd) as catalyst and diisopropylethylamine (DIPEA) (Equation 23) <2005JA14776>.



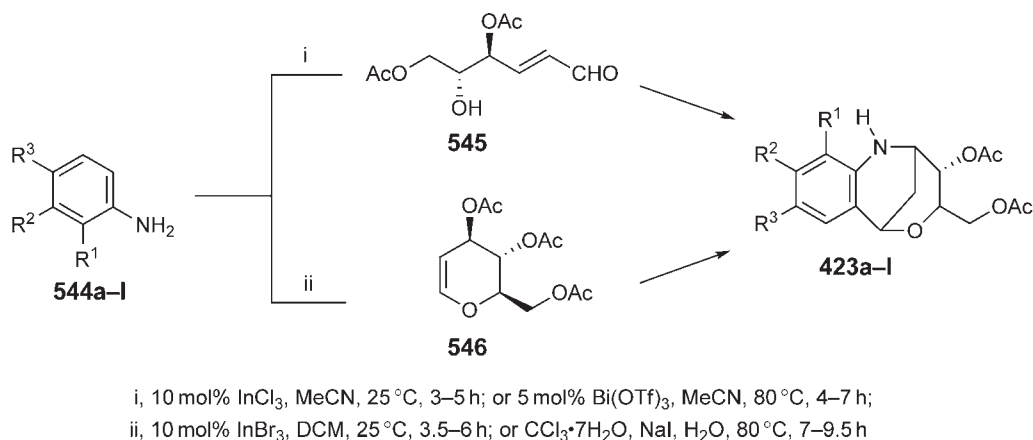
14.07.3.7.5 Ring syntheses from $\text{C}_4\text{N} + \text{C}_2\text{O}$ units

The isomers *cis*- and *trans*- bridged 1,5-oxazocines **410** were obtained by the oxidatively catalyzed condensation of tetrahydropyridine **541** with formaldehyde in 21% yield. From the reaction mixture were also isolated the phenyl-piperidino[4,5-*d*]dioxanes **542** and **543** (6% and 15% yield, respectively) (Equation 24) <2004CHE641>.



14.07.3.7.6 Ring syntheses from C₄O + C₂N units

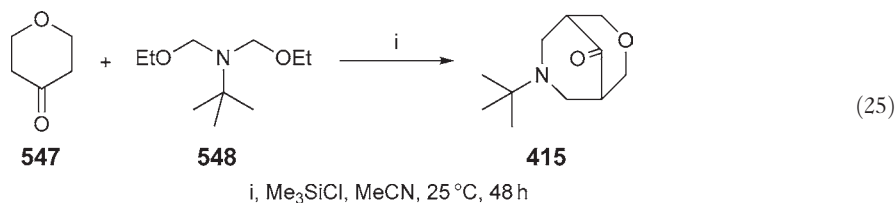
The optically active 4,6-di-*O*-acetyl-2,3-dideoxyaldehyde-D-erythro-*trans*-hex-2-enose **545** underwent a tandem Michael and intramolecular Friedel–Crafts type cyclization with arylamines **544** (mono-, di-, and trisubstituted anilines) in the presence of InCl₃ or Bi(OTf)₃ under mild conditions to give the benzofused-1,5-oxazocines **423a–l** in good yield with high stereoselectivity. The *ortho* positions of the anilines should be free from substitution for the success of the reactions. Other substituted δ -hydroxy- α,β -unsaturated aldehydes such as methoxy- and benzyloxy derivatives also gave similar results <2004TL1543, 2004S405>. The eight-membered ring derivatives **423a–l** were also obtained in good yields by treatment of 3,4,6-tri-*O*-acetyl-D-glucal **546** with substituted anilines **544** in the presence of CeCl₃·7H₂O and InBr₃, as catalyst (Scheme 110) <2004T3261>. Similarly, L-rhamnal and D-xylal underwent cyclization with arylamines to afford the corresponding 1,5-oxazocine <2003AGE5198>.



a: R¹ = R² = R³ = H; **b**: R¹ = R² = H, R³ = Cl; **c**: R¹ = R² = H, R³ = Me; **d**: R¹ = R² = H, R³ = F; **e**: R¹ = R² = H, R³ = Br;
f: R¹ = R³ = H, R² = Me; **g**: R¹ = R² = H, R³ = OMe; **h**: R¹ = R³ = H, R² = Cl; **i**: R¹ = Cl, R² = Me, R³ = H; **j**: R¹ = Cl, R² = R³ = H;
k: R¹ = Me, R² = R³ = H; **l**: R¹ = Br, R² = H, R³ = Me

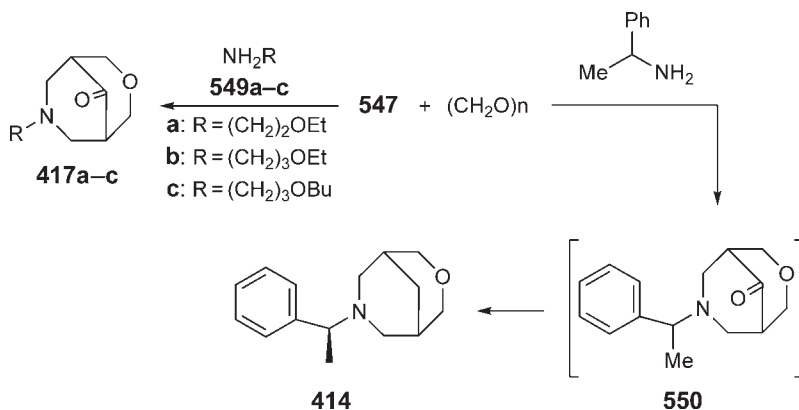
Scheme 110

Treatment of *N,N*-bis(ethoxymethyl)isopropylamine **548** with pyran-4-one **547** through a double-Mannich reaction, Lewis acid promoted, yielded the 1,5-oxazocine **415** in 75% yield (Equation 25) <2006OL3399>.



14.07.3.7.7 Ring syntheses from $C_4O + N + C_2$ units

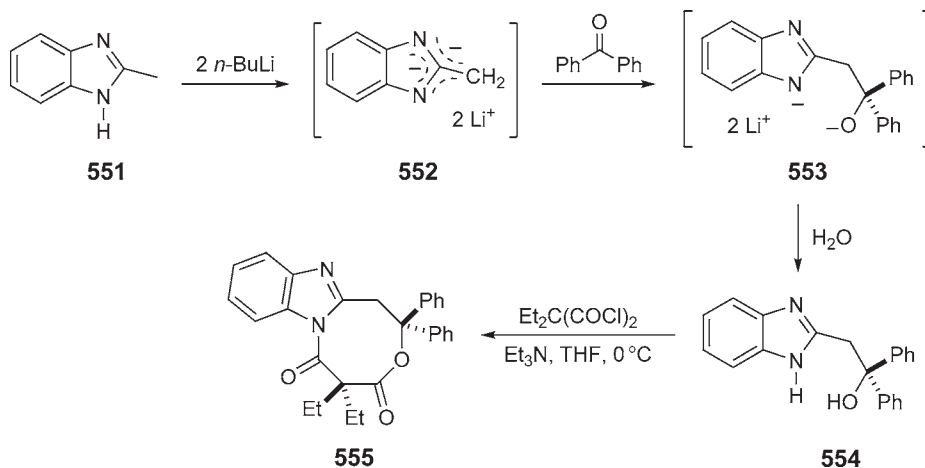
The carbonyl-bridged oxazocines **417a–c** were obtained from the reaction of tetrahydro-4*H*-pyran-4-one **547** with paraformaldehyde and ethoxyethyl-, ethoxypropyl-, and butoxypropylamines **549a–c** (Scheme 28) <2003CHE1376>. Treatment of pyran-4-one **547** with $(CH_2O)_n$ and α -methylbenzylamine in AcOH gave the intermediate **550**, which was subsequently reduced to give the 1,5-oxazocine **414** in 18% yield (Scheme 111) <1995JOC8148>.



Scheme 111

14.07.3.7.8 Ring syntheses from $C_3NO + C_3$ units

The dianion of 2-methylbenzimidazole **552** was generated and condensed *in situ* with benzophenone and subsequently treated with H_2O to give the alcohol **554** (85%). Reaction of the latter with diethylmalonyl chloride afforded the benzoimidazooxazocine **555** (15%) (Scheme 112) <1999SL135, 2001EJO1511>.



Scheme 112

14.07.3.8 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

The majority of the synthetic approaches to 1,5-oxazocines involved unimolecular cyclizations. Among them the most reliable terms of yields seemed the synthesis of oxygen-bridged oxazocines from nitroketones through ketal intermediates. Another efficient cycloamidation appeared to be the reaction between the side chains on 2 and 5 positions of tetrahydrofuranes, containing an amino and an ester group. The approach involving the nucleophilic replacement

of fluorine by phenolic hydroxyl group is certainly of wide application and showed to be suitable for a solid phase synthesis although the yield resulted quite variable. The Ugi-4-component approach to oxazocines appears to be interesting for good yields. High yields were observed in the asymmetric hetero-Michael addition of hydroxyl group to an α - β -unsaturated ester bound in position 3 and 2, respectively, of a tetrahydroquinoline system. Out of the unimolecular cyclization the only synthesis worthy to be mentioned is the double-Mannich reaction of pyran-4-one with a tertiary amine that produced oxygen-bridged oxazocine in good yield.

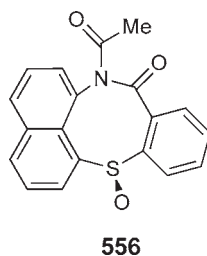
14.07.3.9 Important Compounds and Applications

Pyridobenzoxazocinone hydrochloride **486** inhibited HIV-1 reverse transcriptase activity; at 0.35 μ M the enzyme activity decreased by 64%, while higher concentrations (17.5 and 35 μ M) of this compound completely abolished the enzyme activity expressed as radioactivity of acid insoluble products <1997FA751>. The series of *N*-benzyl carboxamide derivatives of 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*]- and pyrido[4,3-*b*][1,5]oxazocines **427** and **428** showed excellent NK₁-antagonistic activity; the (3*S*)-isomers which had a predominantly *aR* stereochemistry showed nearly 50–200-fold higher than the (3*R*)-enantiomers, indicating that axial chirality is recognized by the NK₁ receptor <2004T4481, 2005BML1479>. The 2-substituted-4-aryl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocines showed *in vitro* activity similar to that of pyrido-oxazocines, although an higher *in vivo* activity on the effective bladder capacity of guinea pigs. In particular, one derivative of this series namely **KRP-510** (bearing the acetylpi-peraziny group and a 2-methylphenyl group) showed antagonist activity with a *K_b* value of 0.105 nM <2005BML1485, 2005BMC5717, 2005WO019225>. The naphtho[2,1-*b*]- and benzo[*b*][1,5]oxazocines **467** and **473** also exhibited NK₁ antagonist activity. (*R*)-1-(3-(11,12-dihydro-10*H*-dibenzo[*b,g*][1,5]oxazocin-11-yl)-3-piperidinecarboxylic acid was patented for the treatment, prevention, alleviation or amelioration of conditions related to angiogenesis <2000WO32193>. Moreover, the benzo-oxazocines are useful for treatment of various CNS disorders, movement disorders, obesity, emesis, rheumatoid arthritis, Alzheimer's disease, cancer, edema, allergic rhinitis, inflammation, pain, gastrointestinal hypermotility, Huntington's disease, COPD, hypertension, migraine, bladder hypermotility, and urticaria <2004BMC2653, 2002WO26724>. Other 1,5-oxazocine derivatives were patented for the use as tachykinin receptor antagonist <1996EPP0733632, 1998USP5770590> or as antagonist against CRF receptors <2004WO058767> or for the treatment of hormone sensitive diseases such as prostate cancer <2005WO084296>. Chiral phosphoramidate ligands embodying 1,5-oxazocine framework and binaphthyl phosphoramidite of type **420** were successfully employed for enantioselective Cu-catalyzed conjugated addition reactions <2000CEJ671, 2002CC673, 2002CEJ4767>.

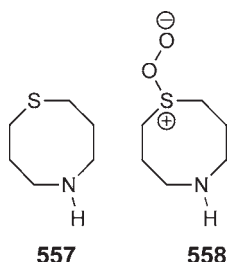
14.07.4 Rings with One Nitrogen and One Sulfur (1,5-Thiazocines)

14.07.4.1 Theoretical Methods

The conformational properties of the 7-acetyl-benzo[*b*]naphtho[1,8-*fg*]thiazocin-8(7*H*)-one **556** were studied by a semiempirical MO method (AM1). The ring structure of **556** was predetermined by a combination of three independent variables (equatorial/axial, *endo*-amide *cis/trans*, *exo*-amide *cis/trans*) leading to eight independent energy-minimum structures located from a to h. Structures **556a**, **556b**, **556c**, and **556d** had a boat-like conformation, **556e** and **556f** assumed a chair-like shape, whereas **556g** and **556h** were distorted to a twist-chair form. The sulfur atom exhibited a sulfurane-like configuration with a relatively short transannular S···N nonbonded distance (2.85 Å). The change in the sulfur configuration (equatorial → axial) caused an increase in energy ($\Delta E = 3.8$ – 9.3 kcal mol^{−1}) and the disappearance of the sulfurane-like geometry with elongation of the S···N distance (3.15–3.16 Å). The *cis-trans* change in the endocyclic amide moiety was associated with a boat to chair transformation causing energy increase ($\Delta E = 11.5$ – 14.1 kcal mol^{−1}) <1996JST(365)93>. The stereoisomers of **556** were also studied by *ab initio* MO method at the HF/3-21G level and the results were compared with those obtained at the semiempirical MO (AM1) level of theory. Of eight energy-minimum structures optimized by the semiempirical methods, two were rather distorted in their molecular geometries. These two structures were annihilated at the *ab initio* level of theory. The relative order of stability obtained by the two methods was qualitatively the same, whereas, quantitatively, the corresponding structures differed somewhat from each other both in their geometry data and relative energy values. Bader-Type density analysis suggested that some of the stereoisomers of **556** exhibited a transannular S···N interaction. Such interaction can be regarded to be as 10% of a single bond. In addition to the N···S interactions, the stereoisomer **556a** showed similar O···H interactions between the sulfoxide oxygen and H-1 and H-12 hydrogens <1997JST(418)155>.

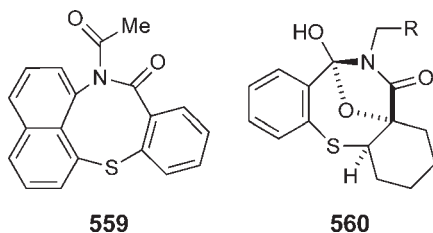


The conformationally induced electrostatic stabilization (CIES) photo-oxygenation mechanism of sulfide **557** was computationally examined using the MP2/6-31G(d) method and extended to the study of the homologous persulfide **558** containing a lone-pair donor group, a nitrogen ideally situated for through-space electrostatic stabilization. The calculated geometries and a natural population analysis of natural lone-pair orbitals on the donor atoms revealed that the nitrogen in thiazocine **558** is more stabilizing than sulfur in the corresponding 1,5-dithiocin <2006JOC1247>.



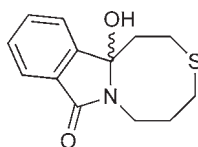
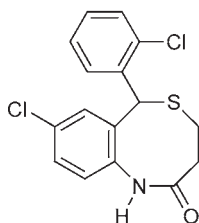
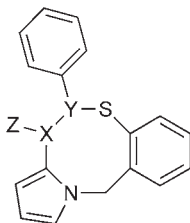
14.07.4.2 Experimental Structural Methods

X-Ray single-crystal investigations were limited to only very few derivatives. Since 7-acetylbenzo[*b*]naphtho[1,8-*fg*]thiazocin-8(7*H*)-one 13-oxide **556** exhibited polymorphism, both **556a** and **556b** were investigated. The *cis*-amide adopted a boat-like conformation with trans-annular sulfur-nitrogen close contact $r(\text{S} \cdots \text{N}) = 2.75\text{--}2.83 \text{ \AA}$ for **556a** and **556b**, values close to that predicted by theoretical calculations (see Section 14.07.4.1); instead, for 7-acetylbenzo[*b*]naphtho[1,8-*fg*]thiazocin-8(7*H*)-one **559** such distance was $2.97 \text{ \AA}$. In these compounds the *peri*-(1,8) and *ortho*-(1,2) positions, of the planar naphthalene and benzene rings, respectively, are connected by a nonrigid amide (-NAc-CO-) and sulfur (-S-) bridge resulting in the formation of eight-membered thiazocine ring. The out-of-ring position of the sulfinyl oxygen led to a sulfurane-like trigonal bipyramidal geometry about sulfur in **556** $\theta(\text{O}=\text{S} \cdots \text{N}) = 175.8\text{--}178.7^\circ$. The interatomic distances $r(\text{S}=\text{O}) = 1.48 \text{ \AA}$ and $r(\text{O}=\text{S} \cdots \text{N}) = 4.25\text{--}4.31 \text{ \AA}$ are in agreement with an $\text{S}=\text{O}$ double bond and $\text{S} \cdots \text{N}$ close contact rather than with an O-S-N type molecular structure observed in spiro-sulfurane <1996JST(382)1>. X-Ray diffraction studies were also conducted on the thiazabicyclo[4.2.1]nonanes **560** ($\text{R} = \text{C}_6\text{H}_4\text{-4-NO}_2$) to corroborate the structure assignment <2003JOC3315>.

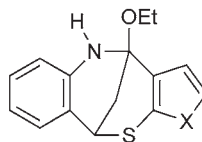


Nearly all reports dealing with 1,5-thiazocines provided ^1H NMR data. The tricyclic bridged thiazocines **560** ($\text{R} = \text{C}_6\text{H}_4\text{-4-NO}_2$; $\text{R} = n\text{-Bu}$; *c*-hexyl) showed, in their ^1H NMR spectra, the methylene protons next to sulfur at 3.32–3.39 ppm, the $\text{CH}_2\text{-N}$ at 4.21–4.29 ppm, and a broad signal for the OH group at 4.00 ppm <2003JOC3315>. The isoindolo-1,5-thiazocine **561** showed in its ^1H NMR spectrum, the signals of the methylene next to nitrogen at 3.52–3.63 ppm, the methylene hydrogens adjacent to the sulfur at 2.47–2.83 ppm, the other ring methylene protons

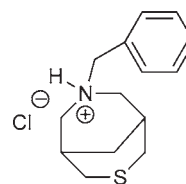
resonated at 1.66–2.42 ppm and the OH group at 5.19 ppm <2001EJO1831>. 1,5-Benzothiazocine **562** showed a downfield shift for the methyne and methylene protons next to sulfur (2.87–5.33 ppm) and the CH₂ adjacent to carbonyl at 2.38–2.80 ppm; the NHCO proton instead resonated at 8.68 ppm <2003JOC92>. Pyrrolo[2,1-*d*][1,5]benzothiazocine **563a** showed a further downfield shift for the methyne adjacent to the sulfur resonating at 6.15 ppm, whereas the CH₂–N protons appeared at 5.45–6.10 ppm with a coupling constant of $J = 15$ Hz. Similar chemical shifts were shown in the ¹H NMR spectrum of **563b** <1997EJM241>. The ¹H NMR spectrum of the dibenzothiazocine **564a** and thienobenzothiazocine **564b** showed the CH–S methyne at 3.79–3.85 ppm, the CH–N proton at 4.40–4.57 ppm, the NH proton at 4.30–4.53 ppm, whereas the bridge methylene protons resonated at 2.63–2.78 ppm <2002JOC8662>. 7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane chloride **565** exhibited an upfield shift for all eight-membered ring protons (CH₂–N at 3.13–3.60 ppm; CH₂–S at 2.71–3.36 ppm; bridge methylene and the methyne protons at 1.84 and 2.34 ppm; respectively), while the *N*-benzyl and the NH protons were found at 4.29 and 9.25 ppm, respectively <1996JME2559>.

**561****562**

563a: X–Y = CH–C, Z = O
563b: X–Y = C=C, Z = OCONMe₂



564a: X = CH=CH
564b: X = S

**565**

The ¹³C NMR data were not provided for all the 1,5-thiazocine reported. In some cases, the ¹³C signals were not assigned and the signal multiplicities were missing. 7-Acetylbenzo[*b*]naphto[1,8-*fg*]thiazocin-8(7*H*)-one 13-oxide **556** having an acetyl group as substituent on nitrogen showed, in its ¹³C NMR spectrum, the Me of the acetyl moiety at 34.7 ppm, whereas the carbonyl signal could be found at 170.6 ppm <1996JST(382)1>. The ¹³C NMR spectra of **561** showed the CH₂–S signals at 30.4–37.5 ppm, the CH₂–N resonance at 38.3 ppm, and the other CH₂ at 27.7–27.8 ppm while the isindolinone carbonyl carbon resonated at 168.0 ppm <2001EJO1831>. The benzothiazocine **562** in the ¹³C NMR spectrum showed the CH₂–S and CH–S signals at 35.6 and 43.5 ppm, respectively, the CH₂ next to the carbonyl at 28.4 ppm and the lactam carbonyl at 174.6 ppm <2003JOC92>. The ¹³C NMR spectra of the dibenzothiazocine **564a** and thienobenzothiazocine **564b** showed the CH–S methyne at 57.9–58.0 ppm, the CH–N carbon at 81.5 ppm, whereas the bridge methylene carbon carbons resonated at 31.8 ppm <2002JOC8662>. 1,5-Thiazocine hydrochloride **565** exhibited the CH₂–N carbons at 56.4 ppm, the CH₂–S at 30.9 ppm, and the bridge methylene and the methyne carbons at 28.7 and 26.0 ppm, respectively <1996JME2559>.

No detailed fragmentation studies were performed on 1,5-thiazocines reported in the past decade. Mass data on five thiazocine derivatives, limited to the molecular ions <1996JME2559, 2002JOC8662, 2003JOC3315> or quasi-molecular ions <2003JOC92>, were reported.

The benzonaphthothiazocine **556**, thiazabicyclo[4.2.1]nonanes **560** benzothiazocine **562**, dibenzothiazocine **564**, and thienobenzothiazocine **565** showed, in their IR, the eight-membered ring carbonyl stretching in the range 1694–1656 cm^{–1} <1996JST(382)1, 1997EJM241, 2003JOC92, 2003JOC3315>. The S=O stretching of **556** was exhibited at 1027 cm^{–1} <1996JST(382)1>. The bridged thiazocines **564** and **565** showed the NH stretching at 3361–3354 cm^{–1} <2002JOC8662>. Derivatives **560** showed the OH stretching at 3427–3290 cm^{–1} <2003JOC3315>.

14.07.4.3 Thermodynamic Aspects

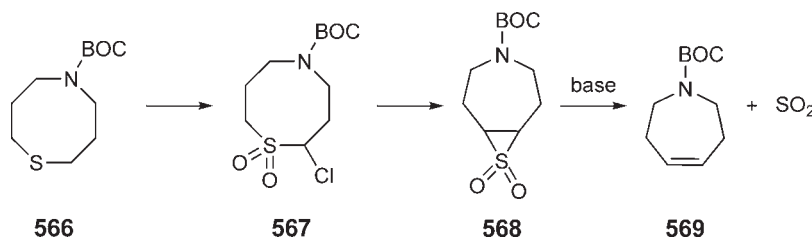
The phase behavior of 1,5-thiazocines is characterized by relatively high melting points. There are some exceptions as in the case of **561**, which is an oil <2001EJO1831>, or the methylene bridged thiazocines **564** and **565**, which are liquids <2002JOC8662>. Annulation of the eight-membered ring with one or more benzene units resulted in compounds melting in the range 134–242 °C <1996JST(382)1, 2003JOC3315>. Condensation with one or more heterocycles generally produced compounds with melting points >200 °C. <1997EJM241>.

Soluble in most common solvents, 1,5-thiazocines were purified by recrystallization from MeOH <2003JOC3315>, EtOH or EtOAc/hexane <1997EJM241>, MeOH/Et₂O <1996JME2559> and H₂O–acetone <1996JST(382)1>. Purification of 1,5-thiazocines was also performed by chromatography in silica gel with EtOAc/hexane <2002JOC8662> or petroleum ether/EtOAc <2003JOC92> as eluants.

The 7-acetylbenzo[*b*]naphtho[1,8-*fg*]thiazocin-8(*7H*)-one **556**, as predicted by theoretical calculations (see Section 14.07.4.1) and confirmed by X-ray investigation (see Section 14.07.4.2), adopted a boat-like conformation <1996JST(365)93>.

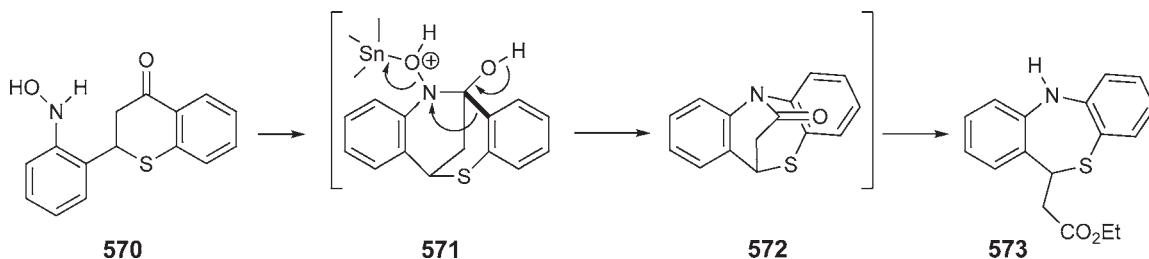
14.07.4.4 Reactivity of Nonconjugated Rings

The 1,5-thiazocine **566** was oxidized to chlorosulfone **457** by treatment with *N*-chlorosuccinimide in CCl₄ and *m*-MCPBA. The Ramberg–Bäcklund rearrangement involved conversion of the α -chlorosulfone **567** into the azepine **569** under basic conditions through the formation of episulfone **568** followed by extrusion of SO₂. The reaction was conducted using different bases, such as KO^{*t*}Bu (66% yield), aqueous KOH (43% yield), and alumina-supported KOH (63% yield) (Scheme 113) <2000JOC8367>.



Scheme 113

1,5-Thiazocine **571**, obtained from **570** through a nucleophilic addition of the hydroxylamine moiety to the ketone carbonyl functionality, as soon as formed, readily undergo a tin-mediated pinacol-type rearrangement with preferred migration of the phenyl substituent to give amide **572**. Ethanolysis of the amide generated 1,4-thiazepine **573** (97% yield) (Scheme 114) <2002JOC8662>. 7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane hydrochloride **565** was obtained, by treatment of the corresponding amine with HCl gaseous in Et₂O for 15 min, in 61% yield <1996JME2559>.



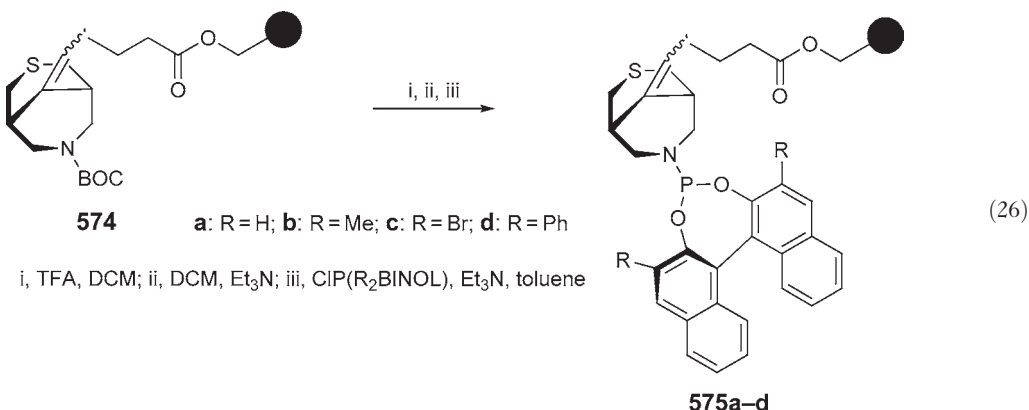
Scheme 114

14.07.4.5 Reactivity of Substituent Attached to Ring Carbon Atoms

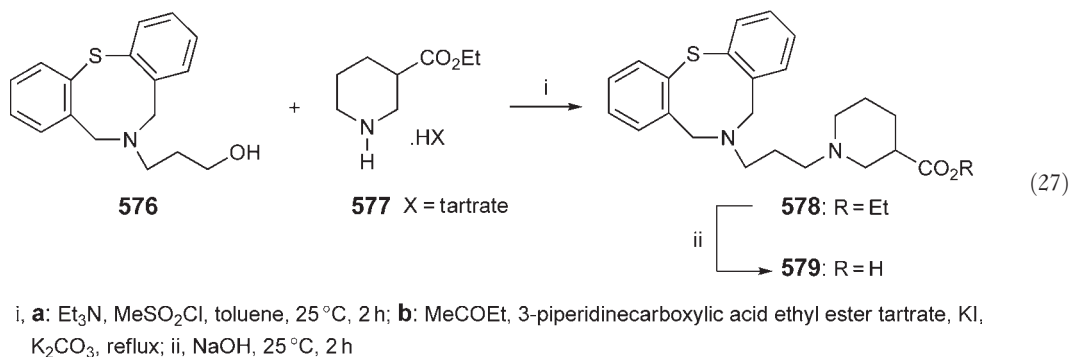
Enolization of pyrrolobenzothiazocine **563a** at 25 °C using KH in THF and subsequent acylation with dimethylcarbamoyl chloride furnished the corresponding derivative **563b** (20% yield) <1997EJM241>.

14.07.4.6 Reactivity of Substituent Attached to Ring Heteroatoms

Polymer-bound ligands **575a–d** were obtained from the BOC-protected derivative **574**. Removal of the BOC group under acid conditions afforded the free secondary amine, which was treated with Et₃N and subsequent coupling with *ortho*-substituted (*R*)-[binaphthyl-2,2'-diyl]chlorophosphite CIP(BINOL) gave phosphoramidites **575a–d** (Equation 26) <2002CEJ4767>.



1-(3-(11,12-Dihydro-10*H*-dibenzo[*b,g*][1,5]thiazocin-11-yl)-1-propyl)-3-piperidinecarboxylic acid **579** was prepared from **576** in 29% overall yield. Halogenation of the *N*-propanol side chain followed by nucleophilic substitution with 3-piperidinecarboxylic acid ethyl ester tartrate **577** afforded the ester **578**, which was hydrolyzed using NaOH to give the corresponding carboxylic acid **579** (Equation 27) <1996WO31497>. Sulfoxide **556** was obtained in 47% yield by oxidation of **559** using 30% aqueous H₂O₂ in AcOH at 100 °C for 1 h <1996JST(382)1>.

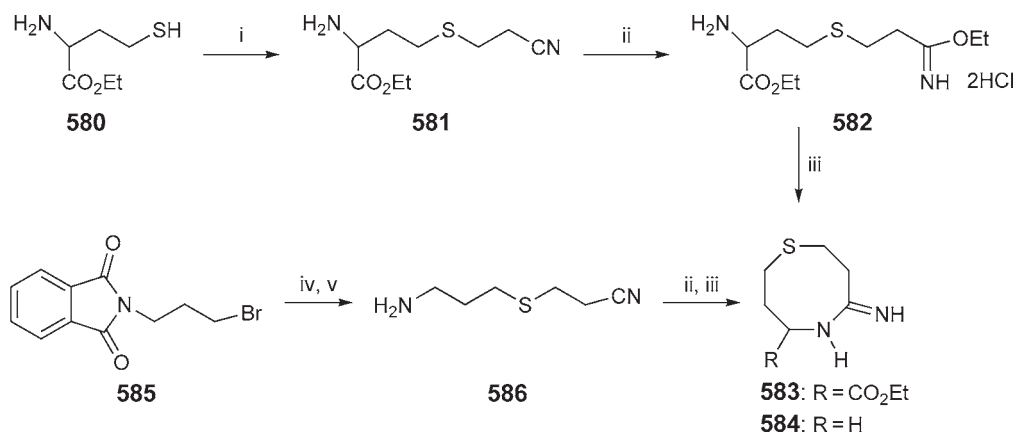


14.07.4.7 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.07.4.7.1 Ring syntheses from C₆NS units

The iminothiazocine **583** was synthesized from the ethyl ester **580** by Michael addition to acrylonitrile in DMF to give the nitrile **581** which, treated with EtOH saturated with HCl, gave the iminoether **582**. Cyclization of **582** upon treatment with Amberlyst A-21 ion exchange resin gave the 1,5-thiazocine **583** (Scheme 115).

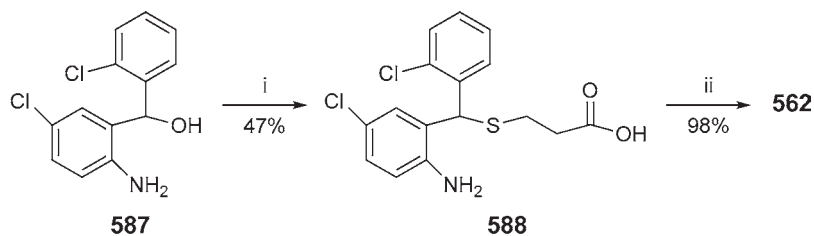
The thiazocine **584** was synthesized from bromide **585**, which was alkylated with the sodium salt of 3-thiopropionitrile then refluxed with NH₂NH₂·H₂O in EtOH to produce the aminonitrile **586**, which was converted into the iminoether and cyclized by treatment Amberlyst to afford **584** (Scheme 115) <2001BML2651>.



i, acrylonitrile, K₂CO₃, DMF; ii, EtOH saturated with HCl, 0–25 °C; iii, Amberlyst A-21, EtOH;
iv, sodium-3-thiopropionitrile, EtOH; v, hydrazine hydrate (1.1 equiv), EtOH, reflux

Scheme 115

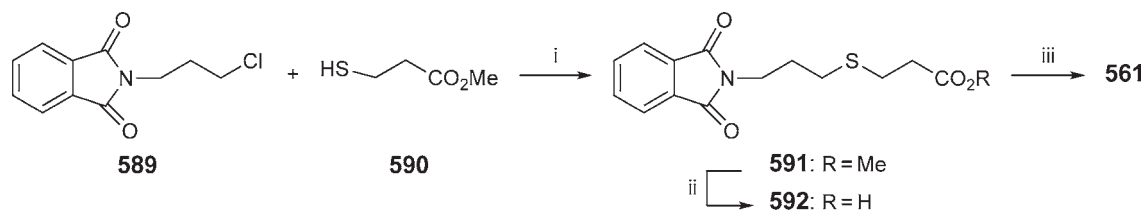
S-Alkylation of 3-mercaptopropionic acid with benzhydryl **587** in neat TFA gave acid **588**, which underwent EDC-facilitated lactam formation and furnished benzothiazocine **562**, in nearly quantitative yield (Scheme 116) <2003JOC92>.



i, 3-mercaptopropionic acid, TFA, 25 °C, 96 h; ii, EDC, DIEA, DMAP, THF, 25 °C, 48 h

Scheme 116

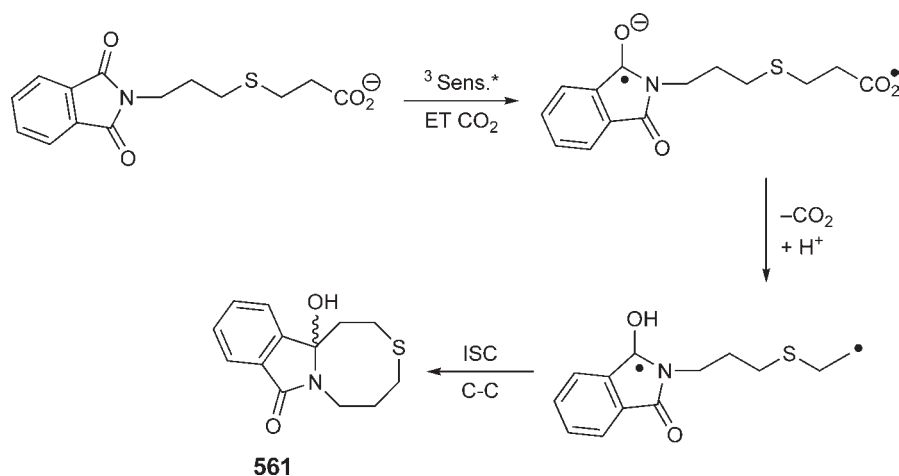
The phthalimidoalkylsulfanylcarboxylic acid **592** was easily available from the corresponding chloro-*N*-(propyl)phthalimide **589** and methyl mercaptopropionate ester **590** and subsequent hydrolysis of ester **591** were obtained. Under standard irradiation conditions at 300 nm in acetone/water, the potassium salt of **592** cyclized with concomitant extrusion of CO₂ to give the isindolothiazocine **561** in low yield (15 %) (Scheme 117).



i, (a) K₂CO₃, DMF, 25 °C, 12 h; ii, HCl, acetone, reflux, 2 h; iii, (a) K₂CO₃, acetone, 20% H₂O; (b) *hν*, 300 nm

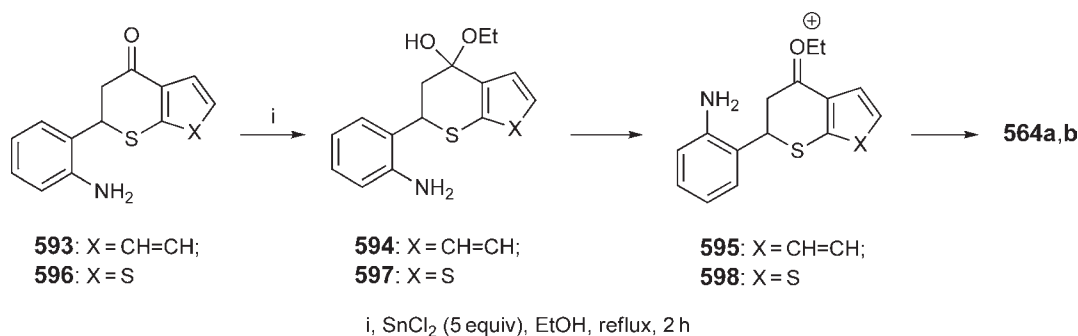
Scheme 117

The cyclization can be explained mechanistically by direct electron transfer involving the carboxylate anion, extrusion of CO₂, and intersystem crossing allowing the C–C bond formation (Scheme 118) <2001EJO1831>.



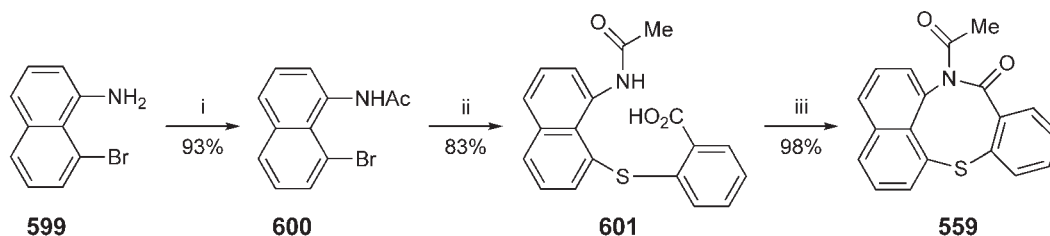
Scheme 118

Treatment of **593** with SnCl_2 in refluxing EtOH gave **564a** in nearly quantitative yield. The reaction pathway proceeded with the initial formation of the hemiacetal **594**, by attack of EtOH at the thiopyran carbonyl. Under Sn catalysis, **594** formed an oxenium ion **595**, which underwent nucleophilic intramolecular attack by the amino group to give dibenzothiazocine **564a**. Thienobenzothiazocine **564b** was analogously obtained in excellent yield from **596** (Scheme 119) <2002JOC8662>.



Scheme 119

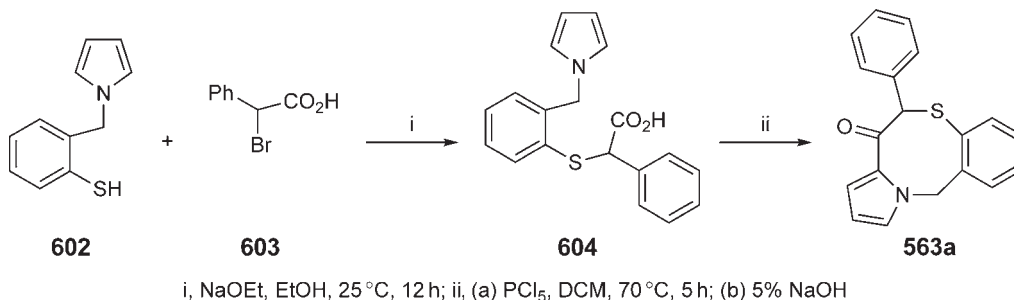
The benzonaphthothiazocine **559** was obtained from 1-amino-8-bromonaphthalene **599**, which by acetylation with Ac_2O furnished the corresponding acetyl derivative **600**. This latter compound was coupled with thiosalicylic acid to give thioether **601** that was converted into the polycondensed thiazocine **559** by initial formation of acyl chloride and subsequent cyclization to the lactam (Scheme 120) <1996JST(382)1>.



i, Ac_2O , pyridine, 100°C , 3 h; ii, thiosalicylic acid, Cu_2O , pyridine-DMF, reflux, 7 h; iii, TsCl , pyridine, 100°C , 4 h

Scheme 120

Pyrrolo[2,1-*d*][1,5]benzothiazocine **563a** was prepared by alkylation of thiophenol **602** with α -bromophenylacetic acid **603** that furnished the carboxylic acid **604** (73% yield) which, by an intramolecular cyclization in presence of PCl_5 , yielded **563a** (41% yield) (Scheme 121) <1997EJM241>.

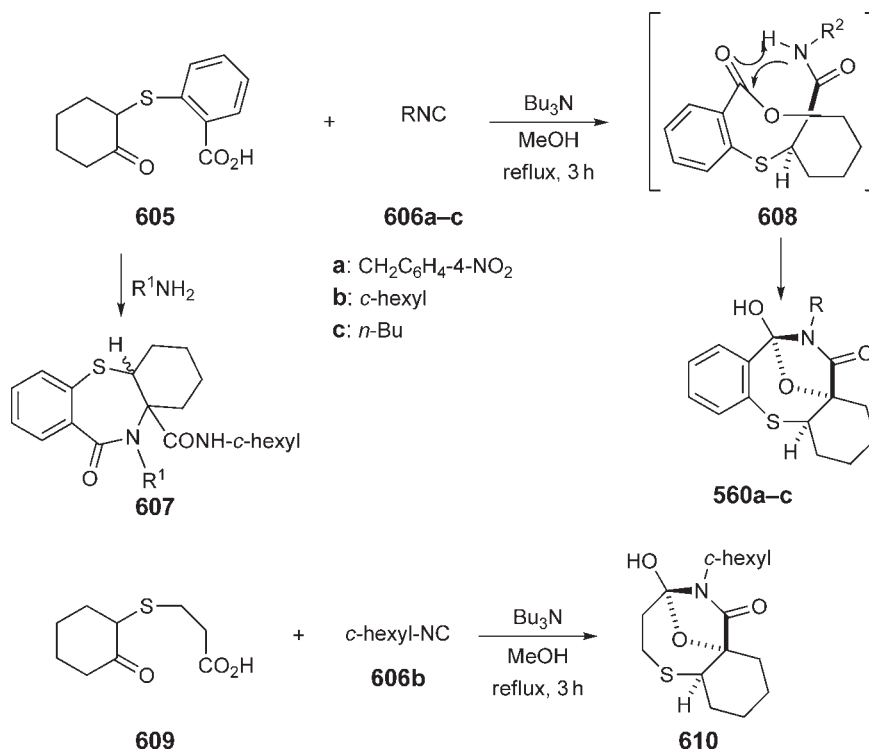


Scheme 121

14.07.4.7.2 Ring syntheses from $\text{C}_5\text{S} + \text{CN}$ units

The synthesis of 1,4-benzothiazepine-5-one ring system **607** was achieved, in excellent yields by intramolecular Ugi reaction between bifunctional oxoacid **605**, amines, and *c*-hexyl isocyanide **606b**. However, when ammonia was used as the amine the benzothiazepine **607** ($\text{R} = \text{H}$) was obtained in low yield, in addition to the thiazocine **560b** isolated in 40% yield. The formation of **560b** was rationalized in terms of formation of the intermediate **608** originated by a three-component Passerini-like reaction (the oxyacid and isocyanide), which evolved to the final product by a nucleophilic attack of the amine nitrogen to the lactone carbonyl group catalyzed by ammonia with formation of a rare orthoamide group. The thiazocine **560b** was obtained as the only product in 91% yield, by performing the reaction in absence of ammonia, but in presence of a catalytic amount of Bu_3N . Actually, **560b** was also obtained at 25 °C in the absence of base in 88% yield.

Analogously, **560a,c** were prepared from the isocyanides **606a,c** in 73% and 87% yield, respectively. Under the same Passerini-like reaction conditions, the acid **609** and isocyanide **606b** gave the corresponding thiazocine **610** in low yield (14%) (Scheme 122) <2003JOC3315>.



Scheme 122

14.07.4.8 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

The reported synthesis of 1,5-thiazocines, with two exceptions, described the isolation of one derivative. Thus, a comparison among the synthetic approaches is not easy and might be misleading. However, for the series of 1,5-diheterocines, the unimolecular cyclizations represent the most important route to get the thiazocines. No doubt that the most convenient synthesis is the stannous chloride mediated reductive cyclization rearrangement of nitroarenyl ketones leading to **564a,b** with nearly quantitative overall yields. Less efficient, but still good, level is for the synthesis of the naphthobenzothiazocine **559** obtained in 76% overall yield. The other reported unimolecular cyclization gave the final products in moderate or low yields. The unexpected benzothiazocines **560** obtained by a Passerini-like reaction were isolated in high yield and the synthetic approach seems interesting, although with substrates different from **605** the yield dramatically dropped.

14.07.4.9 Important Compounds and Applications

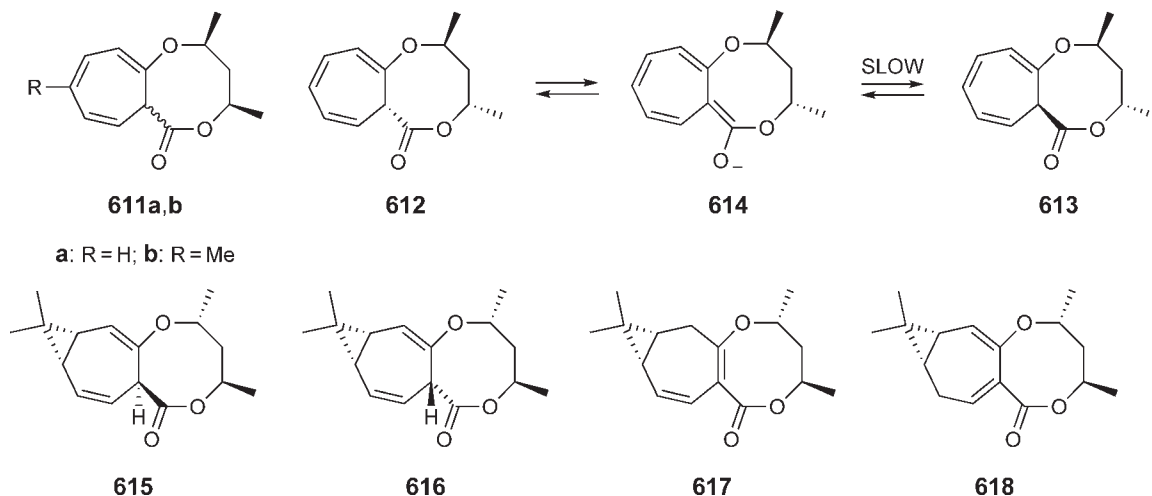
1-(3-(11,12-Dihydro-10*H*-dibenzo[*b,g*][1,5]thiazocin-11-yl)-1-propyl)-3-piperidinecarboxylic acid **579** was patented for the clinical treatment of painful, hyperalgesic and/or inflammatory conditions in which C-fibers play a pathophysiological role by eliciting neurogenic pain or inflammation <1996WO31497>. The 1,5-benzothiazocinone **562** inhibited the mitochondrial sodium-calcium exchanger (mNCE) at IC₅₀ value of 12.6 μM <2003JOC92>. 7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane hydrochloride, called BRB **584**, a novel type of Ib antiarrhythmic agent, investigated in male and female mice, showed LD₅₀ of 12 mg kg⁻¹ (male mice) and 131 mg kg⁻¹ (female mice). This limited toxic potential was coupled with low proarrhythmic and other cardiovascular effects <2000MI817>. The 1,5-thiazocine **584** inhibited the human inducible nitric oxide synthase (i-NOS) at the concentration of 13.1 μM <2001BML2651>. Chiral phosphoramidate ligands embodying thiazocine framework and binaphthylphosphoramidite were successfully employed for enantioselective Cu-catalyzed conjugated addition reactions <2002CCC673, 2002CEJ4767>. 10*H*,12*H*-Dibenzo[*c,f*][1,5]thiazocine, also called chalcogenide, was used as catalyst in the Chalcogeno-Baylis-Hillman reaction. The reaction was applied to activated cyclohex-2-en-1-one which reacted with *p*-nitrobenzaldehyde in the presence of TiCl₄ to give the corresponding coupling product in good yield (76%) <1998CC197>.

14.07.5 Rings with Two Oxygens (1,5-Dioxocins)

14.07.5.1 Theoretical Methods

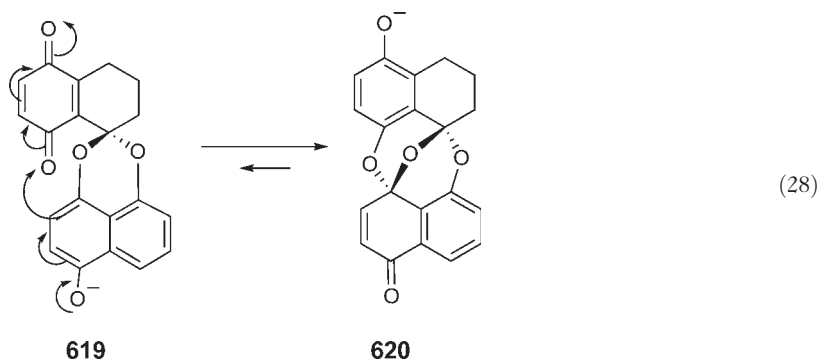
The conformation of dioxocin **611a**, calculated by the PM3 method consisted of a relatively planar tropilidene ring, an axial ester group and closely placed H-7 and H-2' at 1.847 Å distance which agreed with the observed strong NOE <1998CL45>. In a successive report, the same authors compared the structural difference between **611a** and 7-methoxycarbonyl-1,3,5-cycloheptatriene, estimated by calculations using the MOPAC93-PM3 method, and stated that, in both compounds, the most stable conformers have the ester group at the equatorial positions. The calculated heat of formation for the equatorial conformation of **611a** was -319.02 kJ mol⁻¹ and for the axial one was -316.08 kJ mol⁻¹. The dihedral angle of H(7)-C(7)-C=O was ~120°. Thus, the conjugation between the carbonyl and H-7 made weaker the C(7)-H(7) bond reducing the *E_a* in the isomerization of **611** (see Section 14.07.5.3) <1999CL1143>. The enolate ion **614**, derived from **612** or **613**, had only a single stable conformation located by *ab initio* MO calculations at the HF/6-31G level. This common enolate had a bent seven-membered ring and could be protonated from the less hindered side to give the epimer **613**. Such a protonation was found experimentally to be a high-energy process. A remarkable difference in conformation is found between the lactone forms **612** and **613**: the dihedral angles of the carbonyl and the α C-H bonds are 115° and 4.4° for **612** and **613**, respectively. In the conformation of **613**, the enolate conjugation should be negligible on deprotonation, and this conformational strain might be reflected in the transition state for the enolization of **613** or deprotonation of **614** leading to **613**. Such a conformational restriction is smaller for the enolization of **612** <2002OL2059>. PM3 calculations showed that dioxocins **615**, **616**, and **618** have similar thermochemical stability while **617** was more stable by ~8 kcal mol⁻¹. The stereochemical instability of **615** was governed by its kinetic acidity, and the acidity is due to conjugation of a developing carbanion with the C=O and C=C double bonds on deprotonation. The calculated dihedral angles between the C(8)-H bond and the unsaturated bonds of **615** and **616** suggested that the effects of the carbonyl substituent on the acidity were similar between **615** and **616**, whereas those by the vinyl groups were larger in **616**

than in **615**. Thus, kinetic acidity of **615** is expected to be lower than **616**. Conversely, protonation of a common enolate (or enol) of **615** and **616** should give **616** preferentially under kinetically controlled conditions (Scheme 123) <2003CL128>.

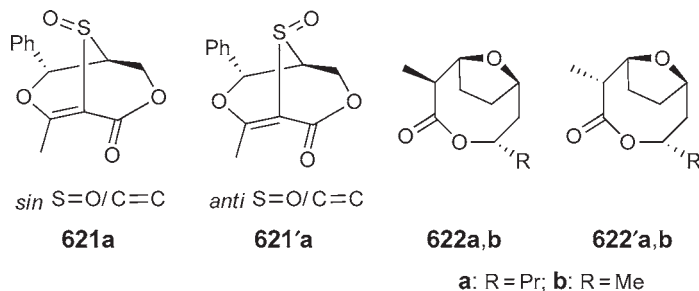


Scheme 123

In the rearrangement of quinone **619** to the polycondensed dioxocin **620**, the resonance energy gained from the formation of two isolated benzene rings in **610** provided a strong driving force for this transformation. Thermodynamic analysis using bond strength energies qualitatively suggested that this rearrangement is exothermic by approximately 5 kcal mol⁻¹. *Ab initio* (HF/6-31G*) calculations indicated this energy difference to be about 7.9 kcal mol⁻¹ in favor of **610** (Equation 28) <1999OL3>.

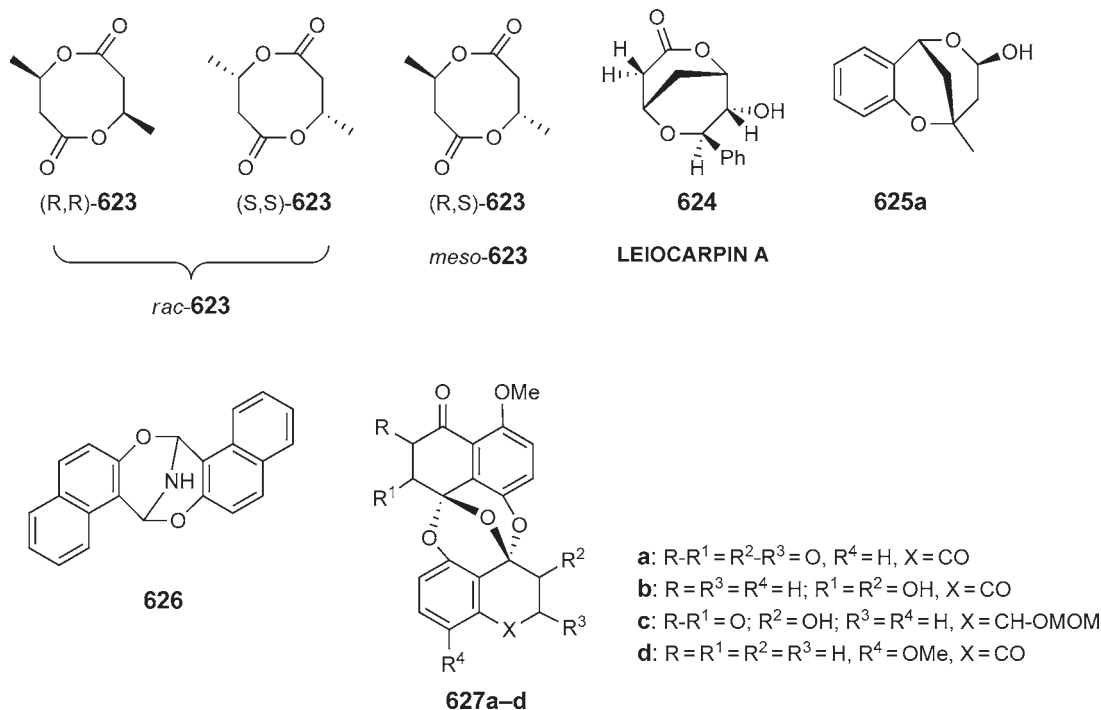


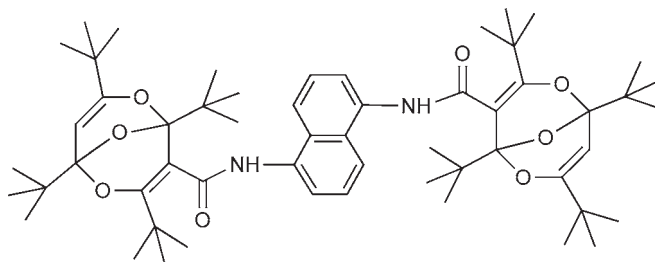
Evidence for explaining the stereochemistry at the sulfoxide stereogenic center of **621a** and **621a'** was provided by molecular-mechanics calculations, which showed that the *anti*-isomer **621a'** was about 8 kcal mol⁻¹ more stable than **621a** <2000EJO3721>. The PM3 semi-empirical calculations conducted on both epimers **622a** and **622a'** indicated that **622a'** is more stable than **622a** by ~3 kcal mol⁻¹ <2001TL5377>.



14.07.5.2 Experimental Structural Methods

The X-ray crystal structure analysis *rac*-diolide **623** revealed that the almost perfectly C_2 -symmetric structure could be described as an eight-membered ring built from two planar halves, which were two *s-cis*-ester groups. They were connected head to tail by two C–C bonds and were tilted from each other such that the conformation could be designated as boat form. In the structure of the *meso*-diolide **623** the molecule had a typical boat–chair conformation, which is the lowest-energy conformation for an eight-membered ring. However, both C=O groups occupied the positions which were subjected to the strongest trans-annular interaction within the eight-membered ring, and while one ester bond was *s-cis*, the other, which had a torsion angle of 49° , adopted a conformation almost half way to that of the transition state of the ester-bond rotation. The diolides *rac*-**623** and *meso*-**623** differed only by one stereocenter, but X-ray structures of the molecules showed completely different conformations. The most striking common structural feature was the equatorial position of the methyl substituents. An axial methyl group on these eight-membered rings would have caused such unbearable strain that even *s-cis*-ester bond torsion angles were tolerated to avoid it <1995HCA1525>. X-Ray diffraction unambiguously proved that *rac*-**622b** epimerized at C-2 <2001TL5377>. The relative configuration of leiocarpin A **624** was determined from the crystallographic data as $1S^*$, $5S^*$, $7R^*$, and $8R^*$ <1999H(51)2969>. Analysis of a single crystal revealed the relative configuration of **625a**. Both the methyl and hydroxyl group take up equatorial positions. Within the crystal, the compound formed dimers, which are stabilized by two intermolecular hydrogen bonds <2005S1888>. Dinaphthodioxocine **626**, as revealed from the crystallographic data existed in a folded conformation with a dihedral (folding) angle of 92° <1996H(43)977>. The structural identities of **627a** and **627b** were confirmed by X-ray crystallographic analysis. The ORTEP representations showed that both structures were exactly in accordance with those reported for the natural products. Also **627c** in its ORTEP representation, as in the previous compounds, showed that the two quasiplanar subunits are almost perpendicular to each other <2004TL4877, 2004OBC2483>. The same general shape was observed in the case of the anhydro dimers of 5-substituted 2-hydroxybenzaldehydes, which had four of the six rings present in the natural products <2000OL1613>. X-ray analysis provided unambiguous evidence that **628** was an *anti*-isomer. In the crystal, **628** was situated on a center of symmetry which related the two halves of the molecule. Furthermore, the structure made evident the presence of an *R,S*-diastereoisomer. One of the four independent *t*-butyl groups was found to be disordered over two orientations in each bisdioxin unit. The amide group is not coplanar with the naphthalene ring but is rotated out of the ring plane by ca. 50° <2004T2857>.

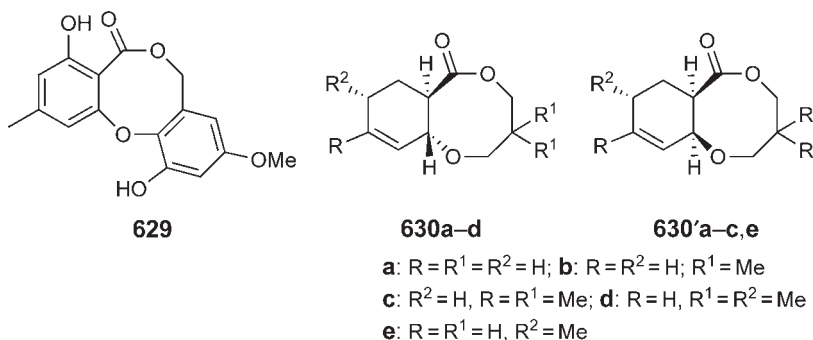




628

Nearly all the papers appeared in the past decade reported ^1H NMR data to support the structure of the synthesized compounds. The simple dioxocinedione **623**, in its ^1H NMR spectrum, exhibited the oxygen adjacent proton resonances at 5.21–5.34 ppm, the methylene ring protons in the range 2.55–2.91 ppm and the methyl groups at 1.45 ppm <1995HCA1525>. The introduction of a methylene bridge as in the case of **624** and related compounds, experienced an upfield shift of the resonances of the protons adjacent to the heteroatoms, 3.94–5.02 ppm, whereas the other ring protons resonated downfield, 2.78–3.16 ppm; the methylene bridge were found at 2.10–2.99 ppm <1995AJC199, 1995JOC3121, 1997JOC6619>. The ^1H NMR spectrum of **629** showed the four benzene proton resonances at 6.27–6.73 ppm, the dioxocin methylene protons at 5.14 ppm, and the methyl and methoxy signals at 2.28 and 3.74 ppm, respectively.

The structure of **629** was established on the basis of HMQC and HMBC NMR experiments. For instance, the HMBC correlations of methylene adjacent to the oxygen to the ring carbonyl established the lactone ring <1995JNP986>. Using the same techniques as well as COSY-45, NOESY, and *J*-resolved experiments, the structures of the steroidal lactones withametelinol, withametelinone <1999AJC905>, and luisol A <1999JNP608> were assigned. The stereochemistry of the cyclohexene-fused dioxocins **630a–c** and **630'a–c** was assigned on the basis of the patterns of the bridgehead protons H-1 and H-8. In the case of *trans* ring junctions **630a–c** both connecting atoms of the lactone ring adopted a (pseudo) equatorial orientation. Therefore, both H-1 and H-8 were axial and the H-8 coupling pattern displayed a large triplet in all cases. In the *cis* ring junction situation, two conformations, whether it was the carbonyl or the oxygen that was in an axial orientation, had to be considered. The first was the case, **630'b**, H-8 is equatorial, no large coupling constant was measured and its signal appeared as a multiplet, even at 500 MHz. In the second case, **630'a** and **630'c**, H-8 was axial and presented a relatively large axial–axial coupling constant <1996JOC7597>. Using the same approach, cyclohexene-fused diazocines **630d** and **630e** were assigned the *trans* ring junction and the *cis* ring-junction, respectively <1998J(P1)881>.



Nearly all the reports that described ^1H NMR spectra also provided ^{13}C NMR data. Thus, the dioxocindiones **623** showed the carbonyl resonance at 173–174 ppm, the methyl groups were found at 21.0–21.2 ppm; the carbon next to oxygen had chemical shift at 73.8–74.7 ppm and the other ring carbon atoms resonated at 43.9–44.7 ppm <1995HCA1525>. In dioxocin **624** and analogues, the presence of the methylene bridge in the eight-membered ring, which was found at 29.4–36 ppm, brought about a slight upfield shift of the carbonyl singlet (169.0–169.4 ppm) and a wider range for the resonances of the carbon atoms adjacent to oxygen 64.9–75.0 ppm, while the other ring carbon atoms were found at 24.0–36.2 ppm <1995AJC199, 1995JOC3121, 1997JOC6619, 1998CJC94>. Changing the bridge from methylene to an imino group did not affect the chemical shift of the sp^3 carbon signals in dioxocin **626**

<1996H(43)977>, whereas an oxygen bridge in polycondensed dioxocins **627** and related compounds experienced a remarkable downfield shift of the carbon atoms bound to two oxygen atoms (90.1–97.6 ppm) <1999OL3, 2000OL1613, 2004OBC2483>.

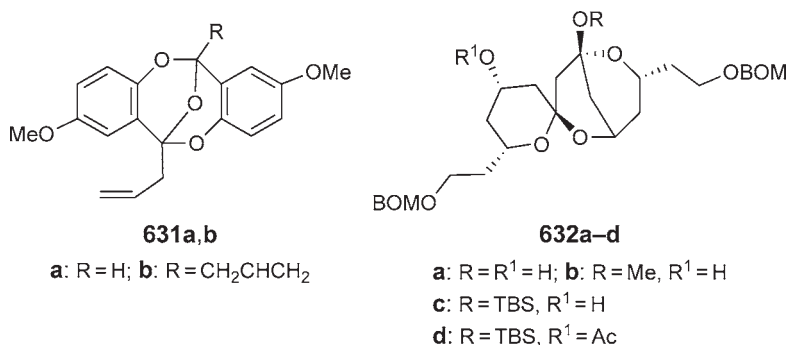
No ^{17}O NMR spectra were reported for 1,5-dioxocins synthesized in the past decade.

Also for the 1,5-dioxocins, no studies on fragmentation patterns were reported although nearly all the papers reported mass data in their experimental sections mentioning only the molecular or quasi-molecular ions utilizing different MS techniques. Spectra reported were: CI spectra <2004EJO5040, 2004HCA1493>; EI spectra <1995JOC3121, 1996JOC7597, 1997JOC6619, 1998JS(P1)881, 1999T2493, 2001EJO1511, 2004OL2965>; ESI spectra <2001AP143, 2003STE361, 2004OL127, 2004HCA1493, 2005MI1228>; FAB spectra <1999JNP608, 1999TL2149, 2003OL1959, 2004OBC2483, 2004T2857, 2003STE361>; LSI spectra <1995HCA1525>; and MALDI spectra <2004EJO5040>.

The carbonyl stretching of dioxocindiones **623** was found at 1746–1750 cm^{-1} . The IR spectra of **624** and isomers showed broad absorption at 3360–3542 cm^{-1} due to the hydroxyl group and the carbonyl stretching at 1720–1736 cm^{-1} <1995AJC199, 1999H(51)2969>. The carbonyl absorption of dibenzodioxocin **629** needed lower frequencies (1717 cm^{-1}) due to the conjugation with the benzene ring <1995JNP986>. The amino bridge absorption of the dinaphthodioxocin **626** appeared at 3342 cm^{-1} <1996H(43)977>.

14.07.5.3 Thermodynamic Aspects

Very few dioxocin derivatives were isolated as oils: the polycondensed dioxocin **627d** and the related oxygen-bridged dibenzodioxocins **631a,b** <2000OL1613>. The cyclohexene dioxocins **630** (*trans* ring junction) were oils, while the *cis* ring-junction products **630'****a,c,e** were solids melting at 99–116 °C and **630'a** was an oil <1996JOC7597>. Also the spirodioxocins **632a–d** are oils <2004EJO5040>. Although leiocarpin A **624** is a solid melting at 132–134 °C <1999H(51)2969>, several isomers were isolated as oils, and when the methylene bridge was replaced by an hydroxyl group the melting point increased to 174–177 °C <1999T2493>. Many other dioxocin derivatives were solid as in the case of **623**: *rac*-**623** melted at 125–126 °C, while *meso*-**623** melted at quite a lower temperature (76–78 °C) <1995HCA1525>. Annellation, as usual, increased the melting point; thus, dibenzodioxocin **629** melted at 195 °C <1995JNP986>. Additional annellation further increased the melting point and dinaphthodioxocin **626** melted at 240–242 °C; however, replacement of the NH bridge of **626** with an oxygen bridge made the compound become an oil <1996H(43)977>.

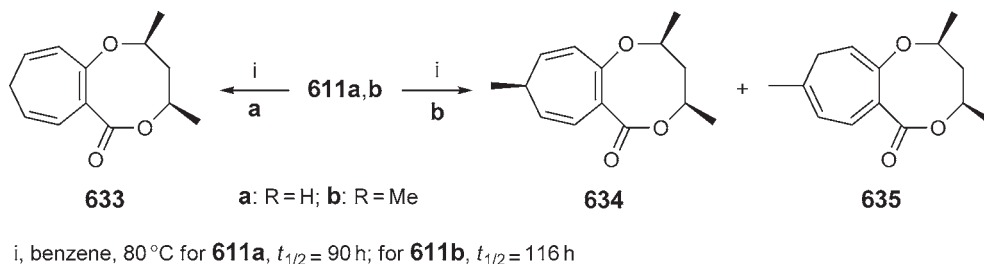


Soluble in most common solvents, dioxocins were purified by recrystallization from MeOH <1999AJC905, 2004OBC2483, 2004T2857>, Et₂O/pentane <1995HCA1525>, Et₂O <2004OBC2483>, MeCN <1998H(48)1841, 2004T2857>, and AcOEt/MeCN <2004T2857>. They were generally purified in silica gel using as eluant: AcOEt/hexane <1995JOC3121, 1997JOC6619, 1999T13011, 1999T2493, 2003OL1959, 2003TA881, 2006JOC413>, AcOEt/petroleum ether <1999T13011, 2000OL1613, 2004EJO5040, 2004OBC2483, 2005ASC555>, Et₂O/petroleum ether <1996JOC7597, 1998J(P1)881>, Et₂O/pentane <1995HCA1525, 2004EJO5040, 2005ASC555>, toluene/EtOAc <1998CJC94>, DCM/EtOH <2003STE361>; DCM/MeOH <2004EJO5040, 2004HCA1493, 2004OL2965>, and hexane/acetone <2004OL2965>.

Dioxocin **612**, in CD₃OD-D₂O underwent fast H/D exchange, but no detectable amount of the epimer **613** was formed during the exchange. Since protonation of the enolate **614** could lead to either of the epimers, the protonation should have been stereoselective by at least 100 times (detection limit <1%). The H/D exchange of **613** was actually very slow, and the solvolysis to give a methyl ester was much faster than the exchange. The rate of enolization of **612**

is over 1000-fold greater than that of the epimer **613**. The thermodynamic stability could be evaluated from mutual isomerization. The isomerization between **612** and **613** was observed in the presence of alumina in an aprotic solvent like hexane giving a mixture of 1:0.7 from either side of the isomer. The stability of **612** and **613** is essentially the same, the difference being less than 1 kJ mol^{-1} <2002OL2059>. Dioxocin **615** was relatively stable under basic conditions, and isomerization occurred to give a conjugated regioisomer **617** only when **615** was heated with DBU (50°C , 86.1% yield). Stereoisomer **616** was accidentally obtained. In fact, when **615** was heated to 110°C in toluene with 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione and CuI catalyst aiming at cycloaddition, **616** was produced in a ratio of **616**:**615** = 1.5:2.5, while formation of **617** was negligible. Conversion of **616** to **617** was easily performed by treatment with either acid or base <2003CL128>. Exposing the epimer **622a** to a thermodynamically controlled base catalyzed equilibrium in DBU at 100°C , a 19:81 mixture of lactones favoring the thermodynamically more stable epimer **622'a** was isolated in 74% combined yield, confirming the prediction of the calculations that indicated **622'a** more stable than **622a** (see Section 14.07.5.1) <2001TL5377>.

The thermal stability of **611a** under neutral conditions was studied in $[d]_6$ -benzene monitored by ^1H NMR. At 80°C , a first-order rate, regiospecific and quantitative [1,5]-hydrogen shift to give **633** was observed in 90 h half-life ($k = 2.29 \times 10^{-6} \text{ s}^{-1}$). The thermal [1,5]-shift of **611b** at 80°C occurred quantitatively at a similar rate ($k = 1.62 \times 10^{-6} \text{ s}^{-1}$) affording **634** with its regioisomer **635** in a ratio 3:1. Both **611a** and **611b** were stable below 80°C (Scheme 124) <1998CL45>. When the same experiment was conducted on the 2,4-dimethyl derivative of the cycloheptatriene-fused dioxocin the result was parallel to that observed in the case of **611a** and the [1,5]-hydrogen shift gave quantitatively the dimethyl analogue of **633** with a faster reaction ($k = 1.3 \times 10^{-5} \text{ s}^{-1}$) <1999CL1143>.



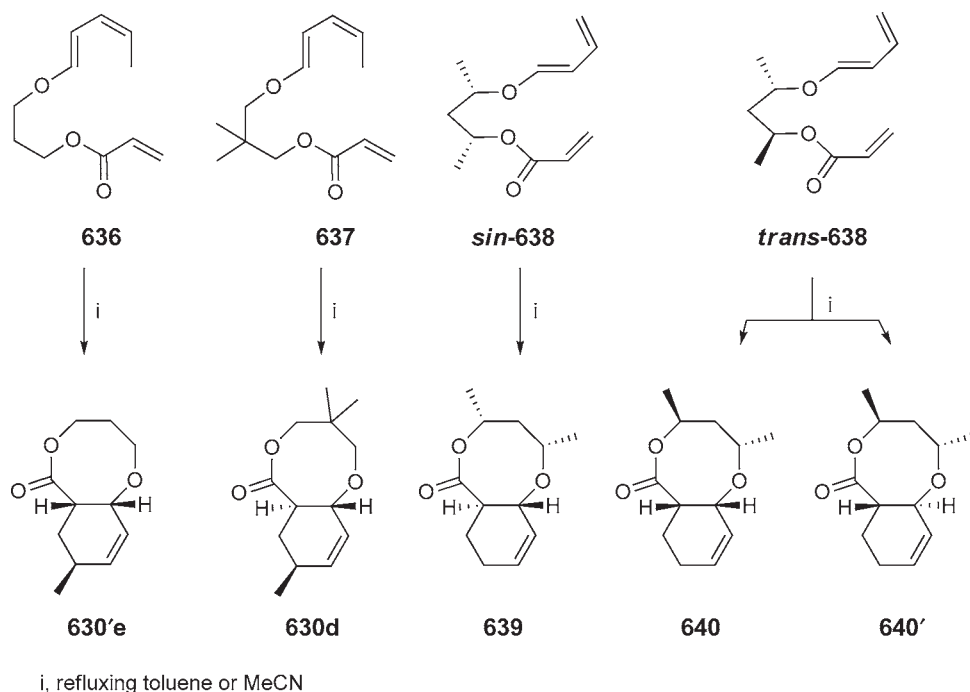
Scheme 124

The stereochemistry of the products of the intramolecular cycloaddition of trienes **636–638** was studied on the basis of the pattern of the ^1H NMR signals of the bridgehead protons H-1 and H-8 (see Section 14.07.5.2). In the case of trienes **636** and **637**, the cycloaddition led to cyclohexene-fused dioxocins **630'e** and **630d**, respectively. These cycloadducts exhibited completely opposite stereochemistry at the junction. In particular, **636** selectively afforded the *endo* addition product **630'e** (deduced from the *cis* pattern of the H-1 and H-8 signals). Triene **637**, instead, afforded the *exo* adduct **630d**, exhibiting a clear *trans* junction pattern. The *endo/exo* selectivity could be tentatively rationalized by considering that, in the case of **636**, a flexible tether connected dienic and dienophilic moieties, allowing the formation of two relatively loose near attack conformations (NACs) that showed comparable weak steric interactions. Such a situation might favor the *endo* approach on the basis of orbital factors similar to those that control the intermolecular cycloaddition. On the contrary, in the case of **637** the *gem*-dimethyl substitution led to more compact NACs in which the orbital factors cannot cope with the unfavorable pseudo-axial orientation of the ester vinyl group, occurring in the *endo* transition structure.

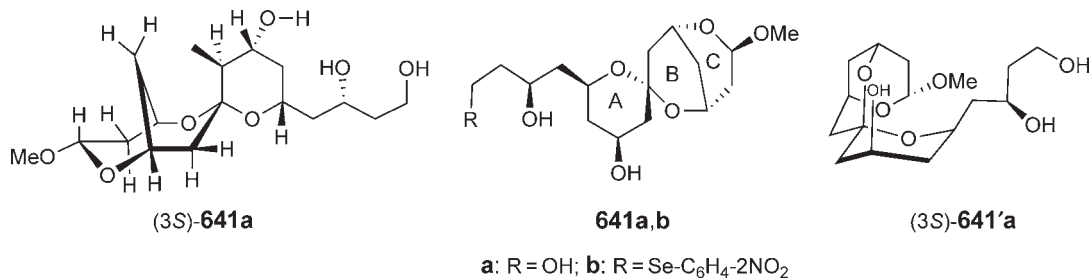
Following the NAC-type analysis mode, it was predicted that the more rigid *sin*-**638** produced the *trans* junction product **639**. In the case of *trans*-**638**, instead, many conformers had to be considered, and all showed unfavorable axial–axial steric interactions. Consequently cycloaddition afforded a mixture of two diastereoisomers **640** (*endo*) and **640'** (*exo*) (Scheme 125) <1998J(P1)881>.

The 2D-NMR NOESY correlations determined the absolute configuration (3*S*) for spirodioxocin **641a**, which could adopt different conformations whose relative populations depended on steric factors, anomeric, and related effects and intramolecular *H*-bonding. In the preferred conformation of **641a**, both endocyclic oxygen atoms were disposed in equatorial position relative to the other cycle and, therefore, such a structure was not stabilized by a conformational anomeric effect. The conformation (3*S*)-**641'a** that disposed both endocyclic oxygen atoms in an axial position, which was stabilized by a double conformational anomeric effect, would imply chair–chair conformation for

its *AB* bicyclic moiety. This conformation was impeded by steric factors that overrode the stabilized anomeric effect, as both substituents on cycle *A* were disposed in unfavorable axial positions, and, additionally, the side chain of cycle *A* was subjected to severe steric interaction with the *BC* moiety. The same configuration (*3S*) and similar conformation were observed for **641b** <2004HCA1493> and for **632d** <2004EJO5040>, respectively.

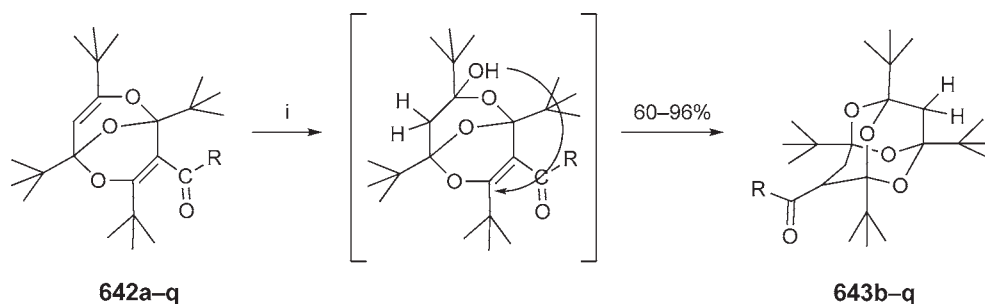


Scheme 125



14.07.5.4 Reactivity of Nonconjugated Rings

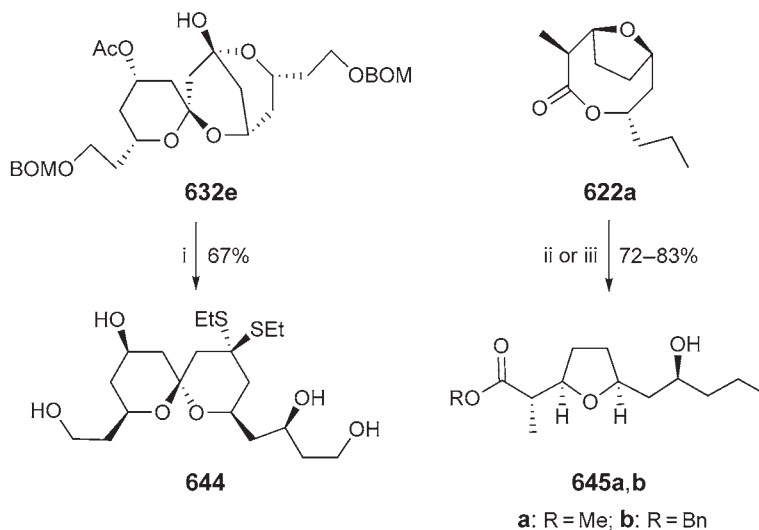
Treatment of oxygen-bridged dioxocins **642a–q** with AcOH and HCl produced the tetraoxaadamanthanes **643b–q**. The reaction took place under very mild conditions and would appear to have wide application in view of reported good to excellent yields. Such a cyclization could precede either by addition of one mole of H₂O to the electron rich double bond via a subsequent Michael addition reaction, as outlined in Scheme 126 or, by addition of two moles of H₂O to the two double bonds, followed by a cyclocondensation. When **642a** bearing a carboxy acid (R = OH) underwent acid treatment, the adamantane formation was accompanied by spontaneous decarboxylation to yield the unsubstituted tetraoxaadamantane <1995CC797, 1998H(48)1841>. This reaction was also successful with the naphthyl derivative **638** (77%), or its isomers with the dioxocin portions bound to 2,6-diaminonaphthalene (85%), 2,7-diaminonaphthalene (80%), or with 1,3-diaminobenzene (86%), 1,3,5-triaminobenzene (81%) and 4,4',4''-triamino-triphenylmethane (75%) <2004T2857>.



642, 643 R: **a**: OH; **b**: OEt; **c**: NHPh; **d**: NH-C₆H₄-4-OMe; **e**: O-N=C(Ph)Me; **f**: O-N=C(Ph)H; **g**: O-N=C(Ph)Et; **h**: O-N=C(Ph)Pr; **i**: O-N=C(Me)₂; **j**: O-N=C=(CH₂)₅; **k**: NNNHPh; **l**: NNNHSO₂Ph; **m**: NNNHCOPh; **n**: NNNHCOC₆H₄-3-NO₂; **o**: NNNHCOC₆H₄-4-Cl; **p**: NNNHCOMe; **q**: NNNHCOPYRIDIN-4-yl
 i, AcOH, HCl (drops), DCM, 20 °C, 24 h

Scheme 126

Spirodioxocin **632e**, upon treatment with BBr₃, cleaved the eight-membered ring to give the dioxaspiroundecane derivative **644** in good yield <2004EJO5040>. Another case of cleavage of the eight-membered ring brought about by Lewis acid was observed in the case of treatment of **622a** with ethereal BF₃ in MeOH, which originated in a good yield of methyl ester **645a** <2001TL5377>. The same ring cleavage but with better yield was obtained when **622a** was reacted with lithium alkoxide of benzyl alcohol to give the benzyl ester **645b** (Scheme 127) <2001TL7801>. When the ring cleavage was performed with LiAlH₄ a tetrahydrofuran with two hydroxyalkyl chains in 2- and 5-position was obtained <1997JOC2975>.

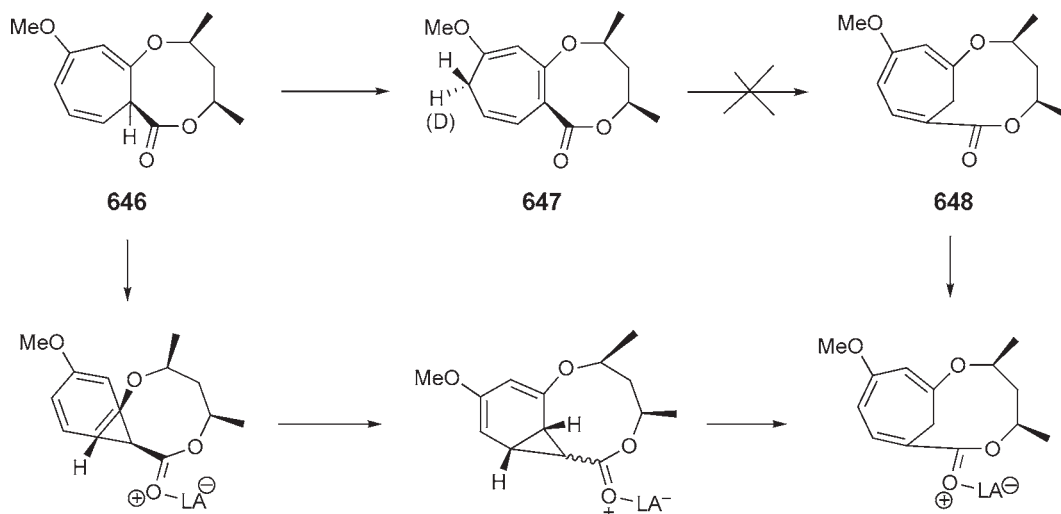


i, BBr₃, EtSH, DCM, 0 °C, 15 min; ii, BF₃·Et₂O, MeOH, 25 °C; iii, BnOLi, BnOH, THF, 25 °C

Scheme 127

The cycloheptatriene-fused dioxocin **646** underwent two different types of acid-catalyzed rearrangements depending on the acid employed. When **646** was treated with catalytic or stoichiometric amounts of TsOH in ether, **647** was obtained regioselectively in a quantitative yield. By using deuterated acid TsOD, a deuterium was incorporated stereoselectively at the 9-position to give (9*S*)-9-²H-**647**. When Lewis acids were used, the mode of rearrangement changed completely. The reaction with BF₃ (in ether at 25 °C, 0.5 h), SnCl₄ (in DCM, 0.5 h) or ZnI₂ (in ether 25 °C, 13.5 h) resulted in skeletal rearrangement and irrespective of the Lewis acid used **648** was quantitatively obtained.

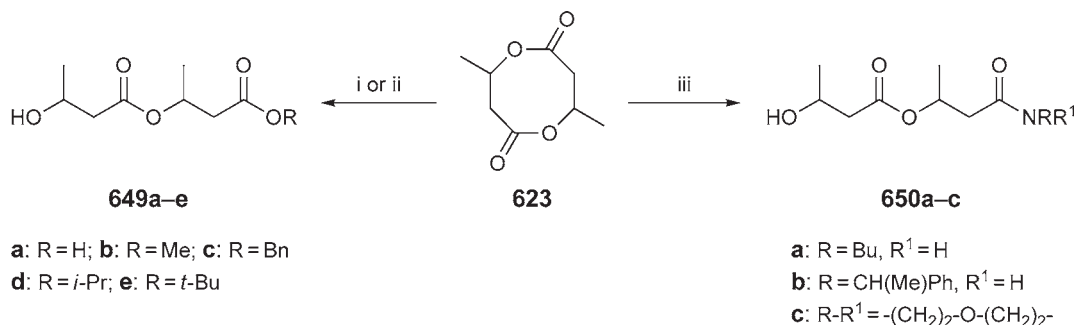
Formation of **648** from **647** was experimentally discarded. Since the most basic site of **646** is the carbonyl group, both Brønsted and Lewis acids should first coordinate to this position. In the case of Brønsted acid, protonation could occur at the electron-rich 9-position, and this was followed by deprotonation at the 11a-position, which is promoted by the carbonyl protonation. In contrast, the Lewis acid cannot add to the 9-position and thus the skeletal rearrangement to give **648** took place. This kind of rearrangement through norcaradiene tautomers, shown in **Scheme 128**, is called ‘walk rearrangement’ in thermal reaction of cycloheptatrienes <2002CL260>.



Scheme 128

Stirring *rac*-**623** or *meso*-**623** with H₂O in the presence of silica gel afforded the dimeric hydroxy acid **649a**. The same ring opening could also be performed by dissolving **623** in aqueous THF and catalytic amounts of TFA or AcOH. Primary alcohols such as MeOH or BnOH reacted completely with **623** to produce the corresponding hydroxy esters **649b** and **649c**, respectively.

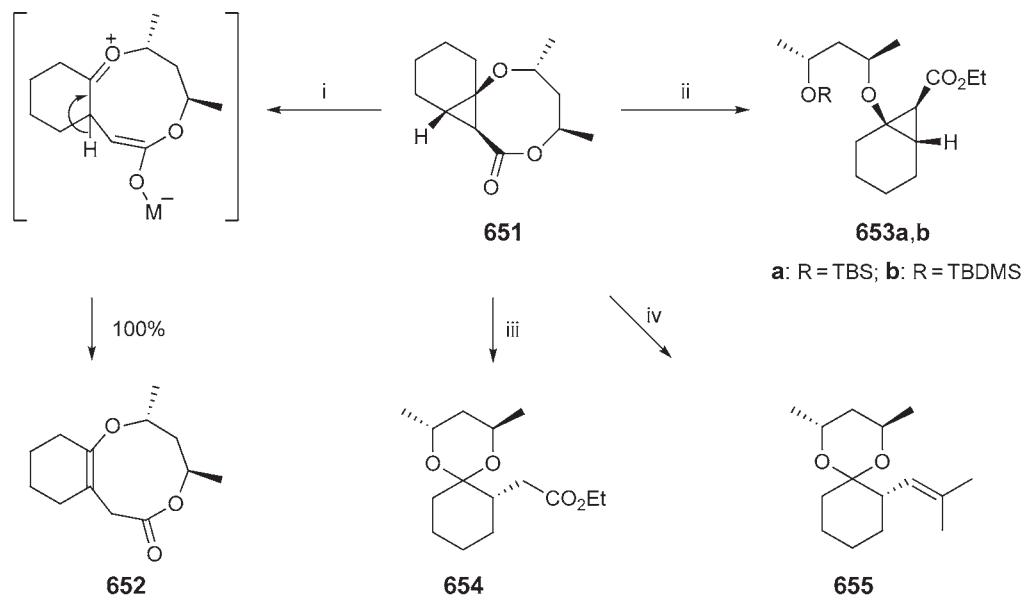
TFA catalysis accelerated the reaction, which reached 90% conversion after 15 min. Secondary alcohols were considerably less reactive (with *i*-PrOH 92% of **623** remained after 1 h) and tertiary alcohols showed the lowest reactivity (with *t*-BuOH 98% of **623** remained after 1 h). Dioxocindione **623** reacted with BuNH₂ to give **650a** in 70% yield after 24 h. More sterically hindered amines such as 1-phenethylamine furnished **650b** after 10 d in 50% yield. The secondary amine morpholine converted **623** into **650c** after 6 d in 94% yield (**Scheme 129**) <1995HCA1525>.



i, H₂O/SiO₂, 25 °C, 3 h or THF/H₂O (99:1), AcOH or TFA (cat.), 25 °C
 ii, R-OH, TFA (cat.), 25 °C; iii, RR₁NH, 25 °C

Scheme 129

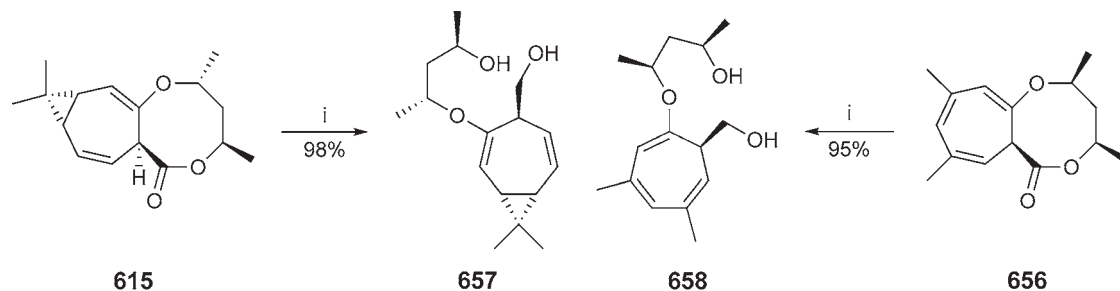
Treatment of dioxocinone **651** with $\text{Cu}(\text{OTf})_2$ in refluxing benzene produced quantitatively, by ring enlargement, the hexahydrobenzodioxonin-6-one **652**. When **651** was subjected to a two-step reaction, initial treatment with ethoxide followed by action of TBSCl or TBDMSCl produced **653a** or **653b**, as single isomers. When the reaction of **651** (>99% de) with ethoxide was followed by treatment with AcOH in pyridine, the spiro compounds **654**, in 69% overall yield and 79.1% de, were isolated. Treatment of **651** with excess of MeLi in ether and successive dehydration in HMPA at 180 °C furnished the spiro derivative **655** in 61% overall yield and 97.6% de (**Scheme 130**) <1997TA661, 2003TA881>.



i, $\text{Cu}(\text{OTf})_2$, benzene, reflux; ii, **a**: NaOEt, EtOH, 25 °C, 1.3 h; **b**: TBSCl, imidazole, DMAP, DMF, 25 °C, 15.5 h for **651a**, TBDMSCl for **651b**; iii, **a**: NaOEt, EtOH; **b**: AcOH-Pyridine, benzene; iv, **a**: MeLi (2 equiv), ether, **b**: HMPA, 180 °C

Scheme 130

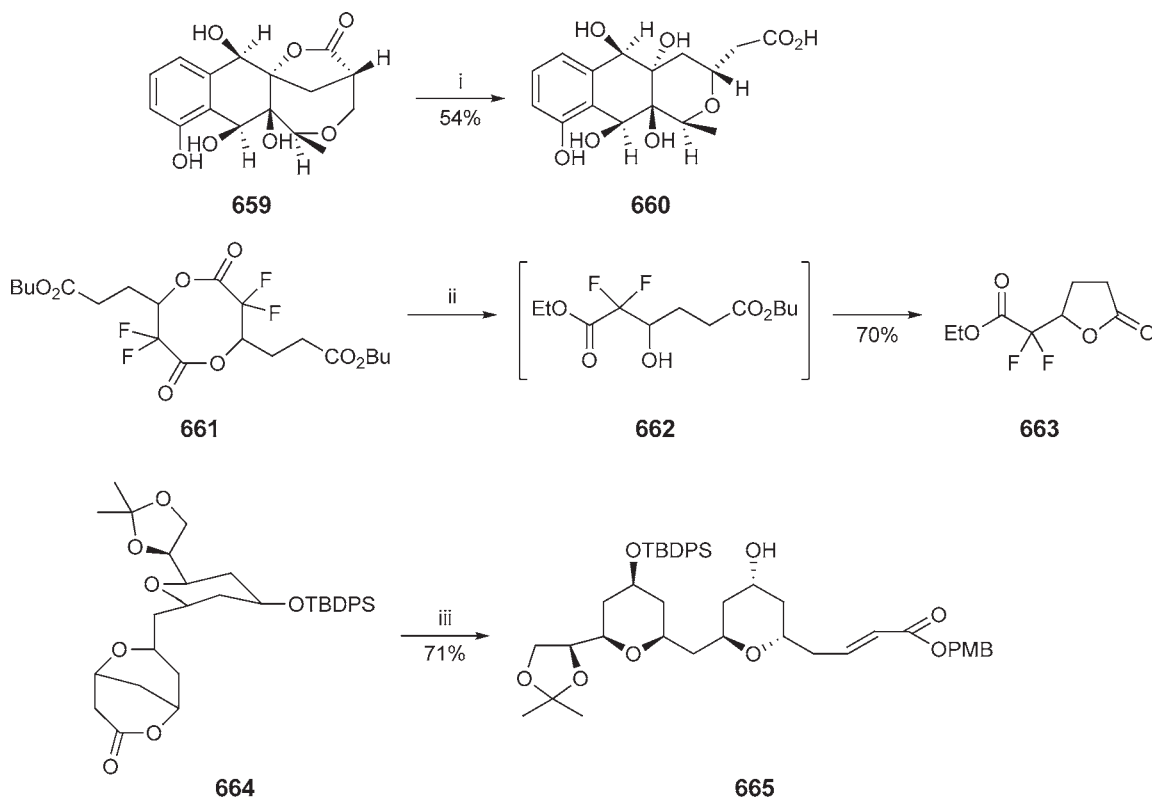
Reductive cleavage of the eight-membered ring of the cycloheptatriene-fused dioxocins **615** and **656** was achieved by treatment of the substrates with LiAlH_4 in ether at low temperature to give in nearly quantitative yields the pentanediol derivatives **657** and **658**, respectively (**Scheme 131**) <2003CL128, 2004OL4439>.



i, LiAlH_4 , Et_2O , 0 °C, 2 h

Scheme 131

In **Scheme 132**, three examples of cleavage of the dioxocin ring under basic conditions are reported. Thus, treatment of the fused dioxocin **659** with alcoholic KOH produced in moderate yield the hexahydrobenzo[*g*]isochromene **660** <1999JNP608>. Action of ethoxide on the dioxocindione **661** brought about a retro-cyclodimerization producing the hydroxy ester **662**, which, due to the basic conditions, underwent transesterification to give the 5-substituted dihydrofuran-2-one **663** <1997H(46)275>. Methylene-bridged dioxocinone **664** underwent ring opening by Dibal-H/Still–Gennari olefination sequence to give in good yield derivative **665** <2004OL2965>.

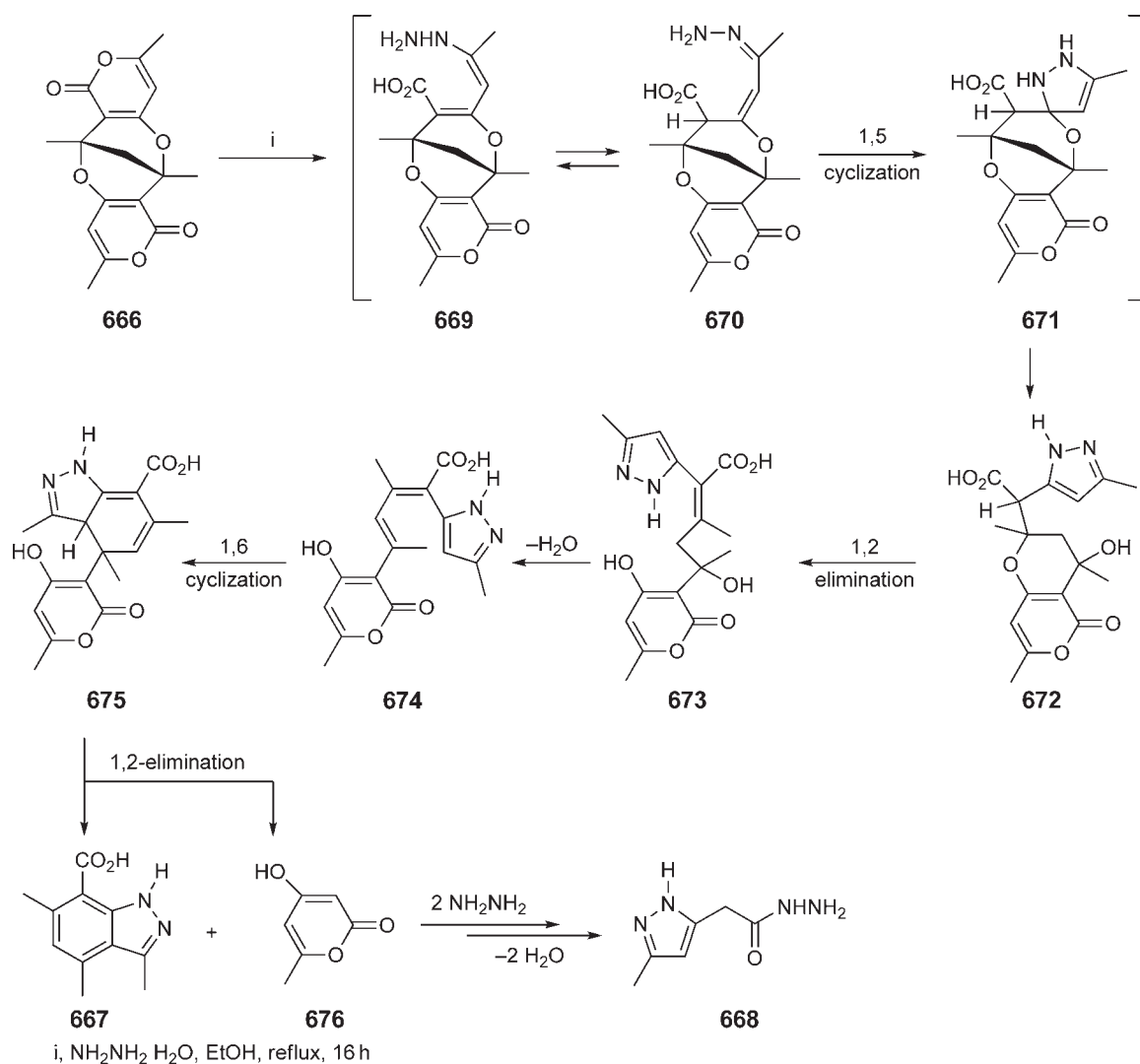


i, KOH, MeOH, 25 °C, 20 min; ii, **a**: NaOEt (cat.), EtOH, **b**: TsOH (cat.), benzene; iii **a**: DIBAL-H, DCM, -78 °C, **b**: (CF₃CH₂O)₂POCH₂CO₂PMB, KHMDS, 18-C-6, 30 °C, 12 h

Scheme 132

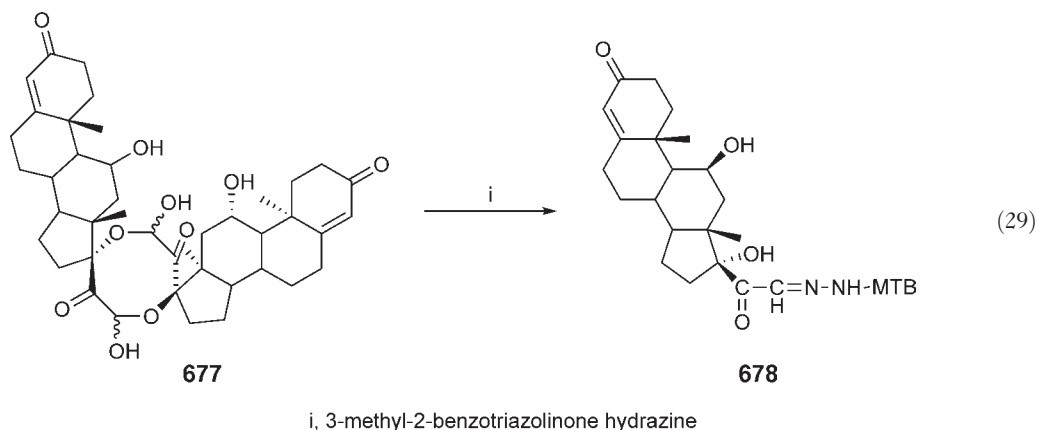
Treatment of **666** with an excess of hydrazine in refluxing EtOH produced **667** and **668** in 61% and 57% yields, respectively. A tentative mechanism to rationalize the conversion of dioxocin **666** into **667** and **668** presumed the initial attack of the hydrazine at C-3 of **666** inducing the cleavage of one pyranone ring. The resulting ω -hydrazino-dienoic acid **669** was considered to equilibrate with tautomer **670**; the α,β -unsaturated hydrazone moiety of the latter underwent 1,5-electrocyclic ring closure forming the 2,3-dihydropyrazole ring of intermediate **671** with both spiro rings participating in a hydrazinoaminal function. Intermediate **671** was anticipated to undergo elimination and formation of the functional components, the pyrazole ring and the hydroxyl group of intermediate **672**. Two subsequent elimination steps were conceivably driven by the extension of the conjugation range: 1,2-elimination of the 4-hydroxypyranone moiety forming the α,β -unsaturated acid **673** was followed by elimination of water affording the dienoid acid derivative **674**. Electrocyclization involving the diene π -bonds and the 4,5- π -bonds of the pyrazole ring of **674** afforded the 3*a*,4-dihydroindazole intermediate **675**.

Elimination of 4-hydroxy-6-methyl-2*H*-pyran-2-one **676** provided **667**, one of the final products; however, **676** was not found; instead, (3-methyl-1*H*-pyrazol-5-yl)acetic acid hydrazide was isolated presumably as a result of the reaction of **676** with hydrazine (**Scheme 133**) <1997H(45)1833>.



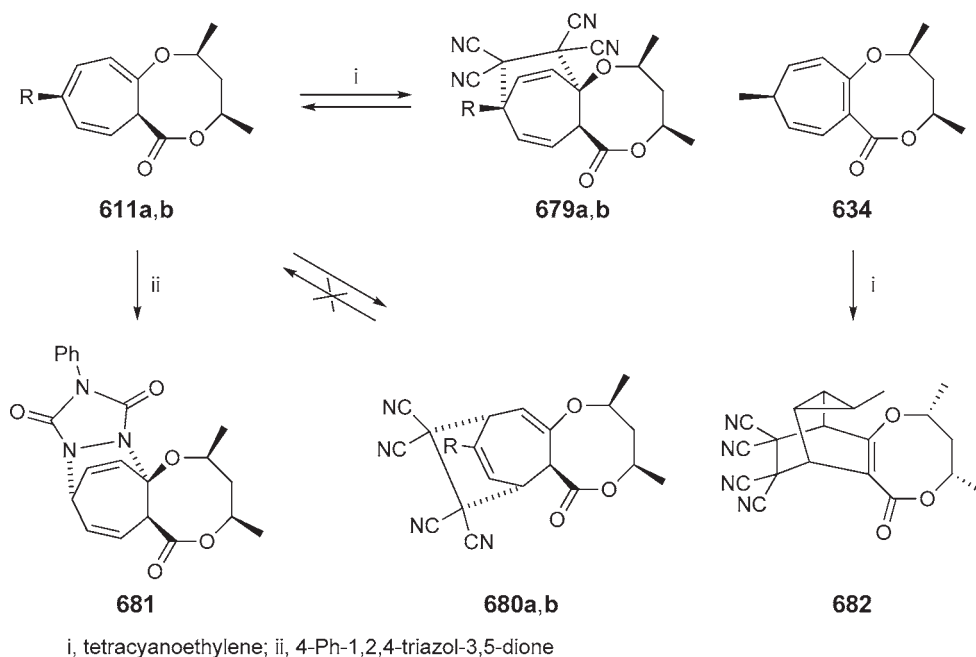
Scheme 133

The hemiacetal character of the dioxocin **677** was confirmed by reaction with 2 equiv of 3-methyl-2-benzotriazolinone hydrazine (MTBH) in DCM or EtOH giving quantitatively 2 equiv of the 3-methyl-2-benzotriazolinone hydrazone of 21-dehydrohydrocortisone **678** (Equation 29) <2003STE361>.



14.07.5.5 Reactivity of Substituents Attached to Ring Carbon Atoms

Cycloaddition of dioxocins **611a,b** to tetracyanoethylene (TCNE) in MeCN at 50 °C afforded the 1,4-adducts **679a,b** in quantitative yields, but prolonged reaction time resulted in the formation of the 3,6-adduct **680a,b**. Cycloadducts **579a,b**, stable crystals, in solution (MeCN) gradually became mixtures of the 1,4-adducts **679a,b** and the 3,6-adducts **680a,b**. Thus, heating **679a,b** in CD₃CN and CDCl₃ at 50 °C, by NMR, both the equilibration constants were determined. Heating **611a,b** with TCNE at 80 °C in MeCN for 48 h, the predominant formation of the 3,6-adducts **680a,b** was achieved. The same reaction in THF also produced **680** but the conversion rate was much slower. The reaction in benzene and CHCl₃ did not give **680** but afforded **679** in good yield. Thus, the 1,4-addition was the kinetically predominant process in both polar and nonpolar solvents and was reversible at the same temperature as the addition. The 3,6-addition was a slower process than 1,4-addition, occurred only in polar solvents and was irreversible so that such adducts could be obtained as sole products at the higher temperature. Such highly regio- and diastereo-differentiating 1,4-addition was also possible using 4-phenyl-1,2,4-triazol-3,5-dione, as the dienophile. The addition of **611a** was faster than that with TCNE and predominantly resulted in the 1,4-adduct **681** <1999CL179>. Addition of **634** to TCNE occurred through the norcaradiene form to give the adduct **682** (Scheme 134) <1998CL45>.

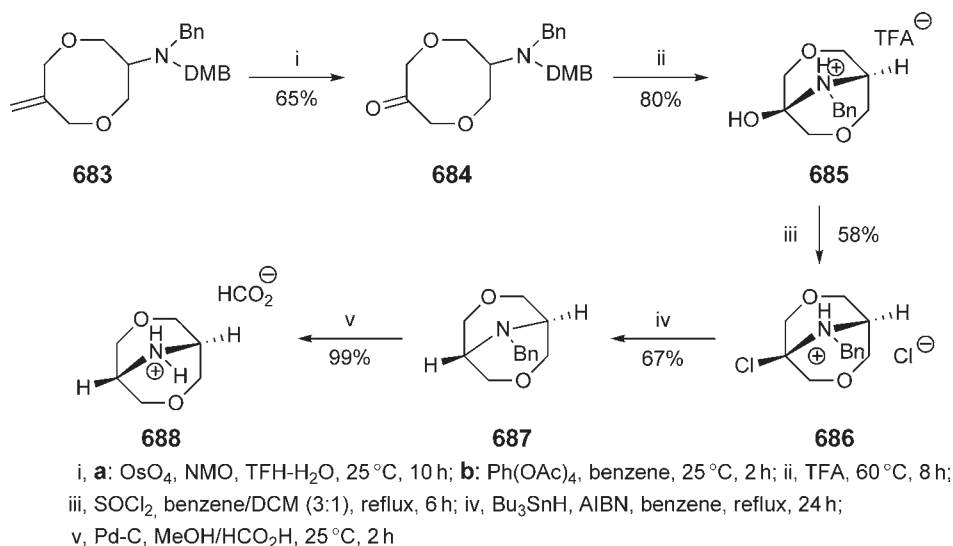


Scheme 134

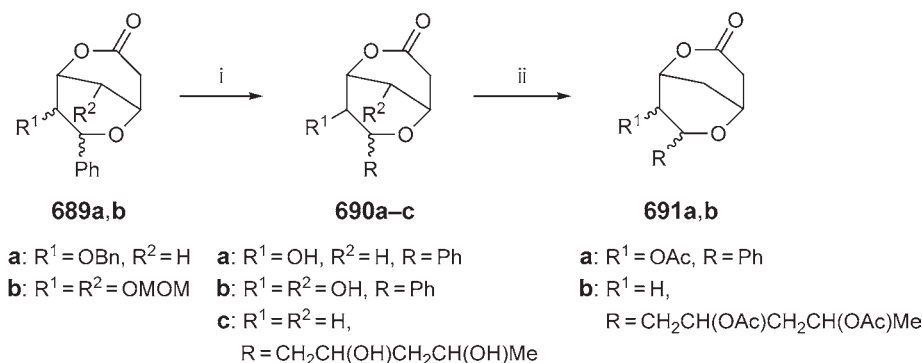
The imino-bridged dioxocin **688** was prepared from the 3-amino derivative **683** through a sequence of reaction of substituents attached to ring carbon atoms. The oxidation of the exocyclic olefin moiety of **683** to a carbonyl group was performed in two steps by initial oxidation with OsO₄ to give the corresponding diol, which was not isolated and subjected to conversion to **684** by reaction with Pb(OAc)₄. Selective deprotection of the dimethoxybenzyl group under acidic conditions led to the spontaneous formation of the hemiaminal **685**. The hydroxyl group was converted to the hydrochloride **686** using SOCl₂, and Bu₃SnH-mediated reduction of hydrochloride **686** smoothly provided the benzyl-protected amine **687**. The final deprotection was performed under Pd black-HCO₂H conditions (Scheme 135) <2006JOC413>.

Deprotection of the benzyl group of **689a** was performed in nearly quantitative yield by treatment TiCl₄ to give (+)-9-deoxygoniopyrpyrone or its 8-epimer **690a** <1997JOC6619, 1998TL9681, 1999T13011, 2003JA3793>. Removal of the methoxymethyl group from **689b** was, instead, achieved by treatment with TFA at 25 °C to give **690b** and the yield was excellent as well <1999T2493>. The stereoisomers **690a** were efficiently acetylated by treatment with

Ac₂O in pyridine or in DCM in the presence of DMAP to give **691a** in excellent yields <1995AJC199, 1998TL9681>. The same acetylating agent was efficient in producing **691c** from the corresponding diol derivative **690c** (Scheme 136) <2003OL1959>. A further example of acetylation of a dioxocin derivative is provided by the steroidal lactone with ametelinol, which furnished the corresponding monoacetyl derivative <1999AJC905>.



Scheme 135

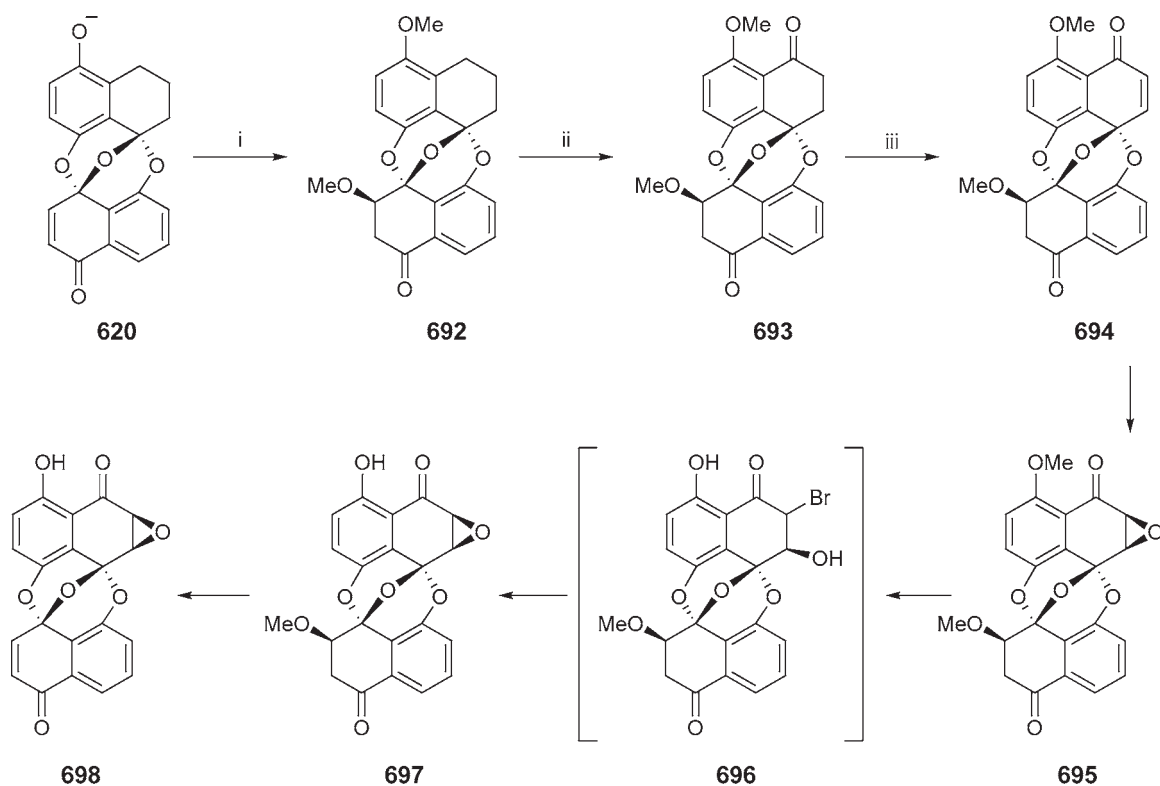


i, for **689a**: TiCl₄, DCM, 25 °C, 30 min for **689b** (TFA, DCM, 25 °C, 6 h); ii, Ac₂O, pyridine, 25 °C, 24 h or Ac₂O, DMAP DCM, 25 °C, 1 h

Scheme 136

(±)-Preussomerin I **697** and (±)-preussomerin G **698** were obtained from **620** with a five- and six-steps sequence in 15% and 12% overall yield, respectively, through modifications of substituents of the dioxocin ring. Thus, attack of lithium methoxide from the less hindered face of the enone **620**, followed by protection of the phenolic oxygen as its methyl ether provided the methoxy adduct **692**. The ketone **693** was obtained through a benzylic bromination–solvolysis–oxidation protocol, which required only a single purification. The C(2)–C(3) olefin was introduced by selective silylation of the C-1 carbonyl of diketone **693** and oxidation of the silyl enol ether with Pd(OAc)₂. Enone **694** was then epoxidized under basic conditions using H₂O₂ and NaHCO₃ to give **695**. Deprotection of methyl ether **695** with BBr₃ provided the demethylated product **696** in which bromide addition to the epoxide had occurred.

However, the epoxide was easily reformed under basic conditions to complete the synthesis of (±)-Preussomerin I **697**. Elimination of MeOH from **697** under Lewis acid conditions yielded (±)-preussomerin G **698** (Scheme 137) <1999OL3>.

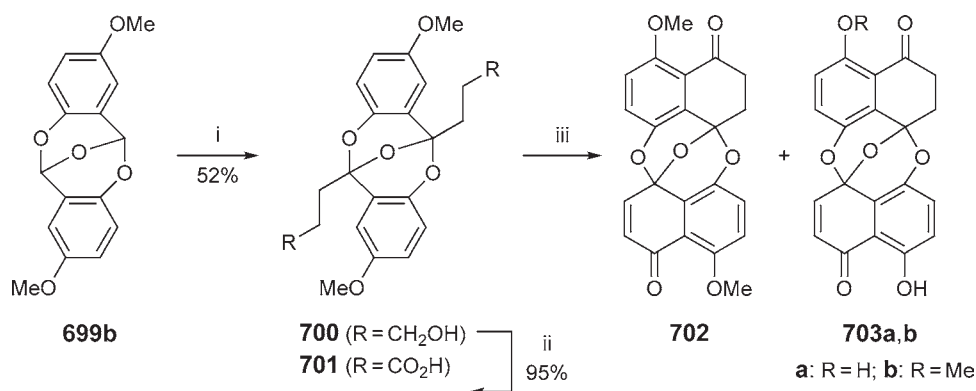


i, **a**: LiOMe, MeOH, 25 °C, 1 h; **b**: CH₂N₂, Et₂O, MeOH, 25 °C, 15 h; ii, **a**: NBS, AIBN, CCl₄, reflux, 1 h; **b**: THF-H₂O₂; **c**: Dess–Martin periodinane; iii, **a**: TMSOTf, NEt₃, DCM, –12 °C, 45 min; **b**: Pd(OAc)₂, MeCN, 25 °C, overnight; iv, H₂O₂ (aq 30%), NaHCO₃, MeOH, 0 °C, 5 h; v, **a**: BBr₃, DCM, –78 °C, 10 min; **b**: LiOMe, MeOH, 25 °C, 10 min; vi, TMSOTf (2 equiv), NEt₃ (2 equiv), DCM, 25 °C, 15 min

Scheme 137

Alkylation of the dibenzodioxocin **699b** gave the entry to compounds that contained the full preussomerin hydrocarbon skeleton. Thus, the bisalkylation product **700** (R=CH₂OH) was obtained with a one-pot deprotonation–alkylation sequence using an excess of oxetane as the electrophile in the presence of a Lewis acid. Oxidation of the diol with Jones' reagent produced, in excellent yield, the dicarboxy acid **701** (R=CO₂H), which after the activation as the acyl chloride, underwent Friedel–Craft cyclization to give **702** in 95% yield. However, if the reaction was allowed to stand for longer times, **703a** and **703b** were formed in 33% and 44% yields, respectively, due to the cleavage of one or both the methoxy groups by the remaining Lewis acid (Scheme 138) <2000OL1613, 2004TL4877>. Compound **703b** resulted an ideal advanced intermediate for the synthesis of preussomerins K and L through reaction sequences similar to those described in Scheme 137 <2004OBC2483, 2004TL4877>.

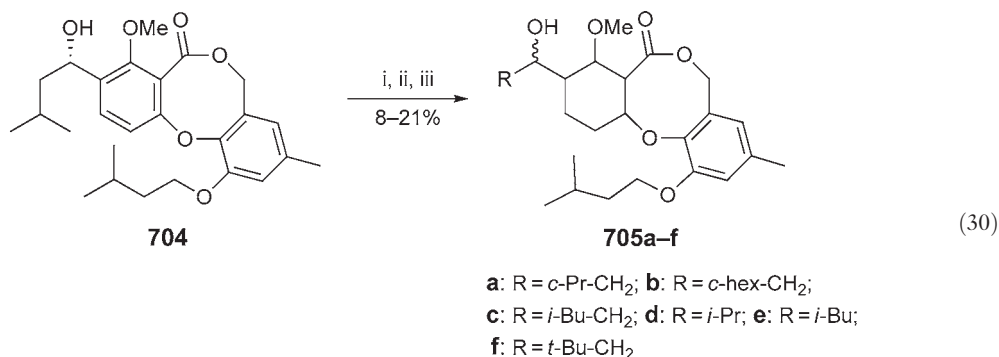
Dibenzodioxocin **704** underwent a transalkylation to give the series of substituted secondary alcohols **705a–f**. Thus, refluxing **704** in toluene in the presence of TsOH produced an alkene, which by treatment with OsO₄ originated an aldehyde group. The latter reacted with Grignard reagents to give the alcohols **705a–f** in low overall yields (Equation 30) <2005BML3611>.



i, **a:** s-BuLi, THF; **b:** oxetane/BF₃ Et₂O (excess), -100 to -40 °C; ii, Jones' reagent, 25 °C, 10 min;

iii, **a:** (COCl)₂, DMF (cat.), DCM, 0–25 °C, 1 h; **b:** AlCl₃ (7.2 equiv), MeNO₂, DCM, 25 °C, 20 h

Scheme 138



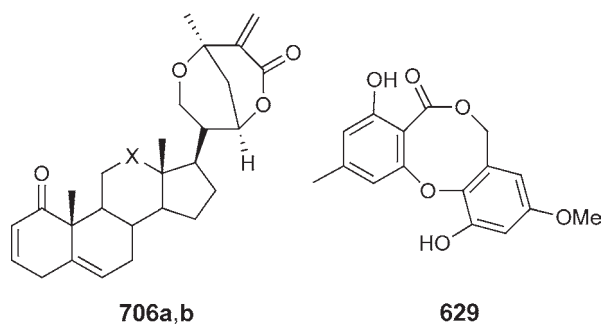
i, TsOH, toluene, reflux, 2 h; ii, OsO₄ (0.1 equiv), NaIO₄ (5 equiv), dioxane/H₂O(1.6:1), 1.5 h;
 iii, RMgBr, THF -78 to 25 °C, 3 h

(30)

14.07.5.6 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.07.5.6.1 Natural products

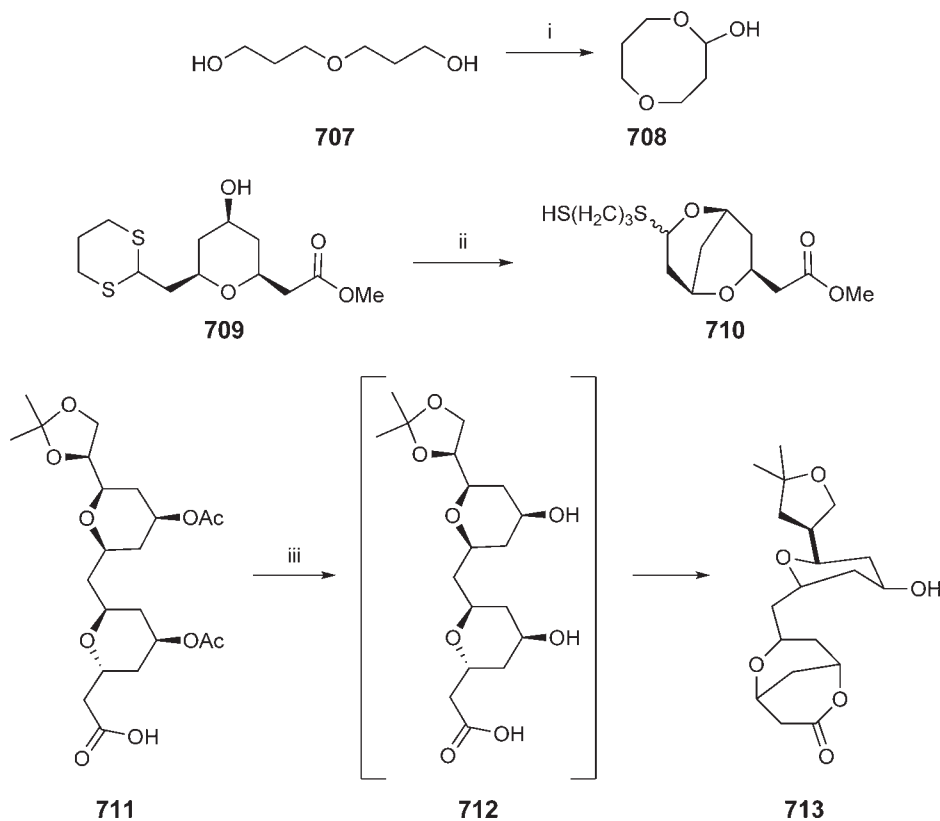
Cyclononactic acid **622b** and cyclohomononactic acid **622c** (R = Et) were isolated from an endophyte *Streptomyces* sp. Is9131 of the plant *Maytenus hookeri* <2005MI1228>. Leiocarpin A **624** was isolated from the ethanolic extracts of the stem barks of *Goniothalamus leiocarpus*, a tropical plant distributed in the south of Yunnan province in China <1999H(51)2969>. From *Goniothalamus cheliensis*, grown in the same province of China, were isolated iso-goniopyrpyrone and 8-acetyl-9-deoxypyrpyrone <2003CCL487>. Instead, from the ethyl acetate extracts of the stem barks of *Goniothalamus dolichocarpus* an endemic plant in Sarawak, Malaysia, was isolated (–)-iso-5-deoxygoniopyrpyrone a stereoisomer of leiocarpin A <1995AJC199>. Luisol A **659** was isolated from cultivation broth of an estuarine marine actinomycete of the genus *Streptomyces* (strain CNH-370) <1999JNP608>. From *Datura innoxia* syn. *D. metel*, grown in Pakistan, were isolated two steroidal lactones of the withanolide group which were named withametelinol **706a** and withametelinone **706b** <1999AJC905>. Barceloneic lactone **629** was isolated from a fermentation extract of a fungus of the genus *Phoma* <1995JNP986>.



a: X = CH-OH; **b:** X = CO

14.07.5.6.2 Ring syntheses from C₆O₂ units

In **Scheme 139**, three examples of unimolecular cyclization leading to uncondensed dioxocins by nucleophilic attack of an hydroxyl group at a carbonyl, a masked carbonyl or a carboxy acid are reported. 2-Hydroxy-1,5-dioxocin **708** was accidentally obtained in the attempt to oxidize the ether diol **707** to the corresponding dialdehyde derivative. Rather, oxidation occurred at one end of the molecule followed by intramolecular hemiacetal formation to yield **708** <2003JOC9166>.

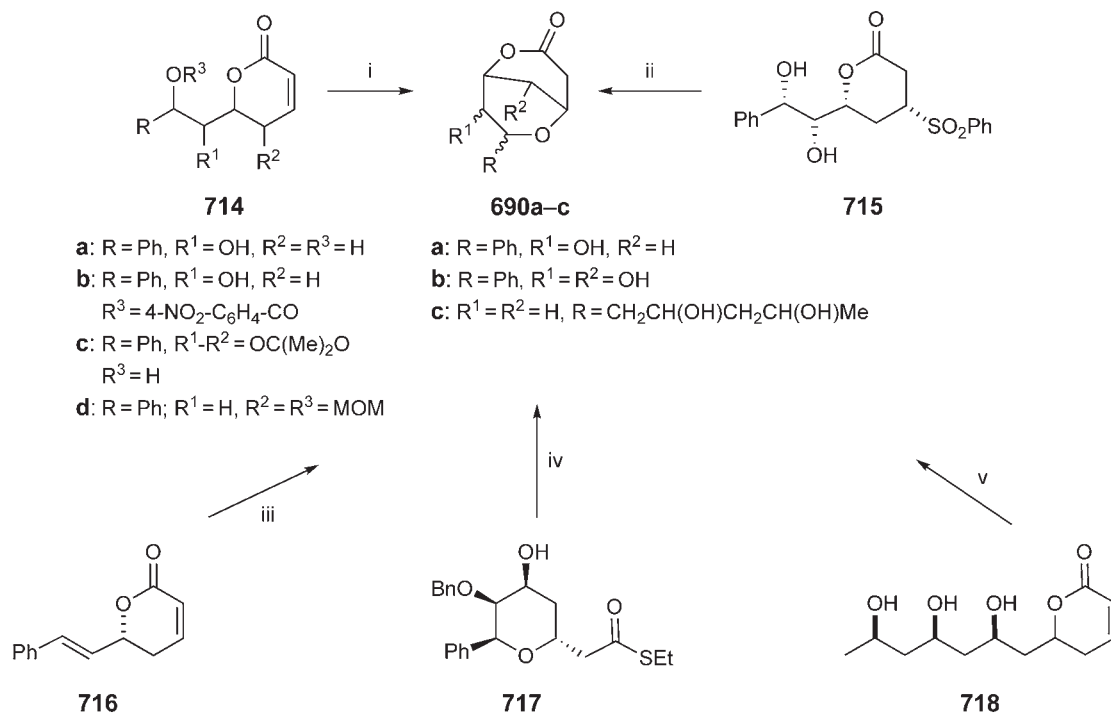


i, iodoxybenzoic acid, EtOAc, 80 °C to 23 °C, 2 h; ii, 4-NO₂-C₆H₄-CO₂H, PPh₃, DEAD, toluene, 25 °C, 4 h;
iii, **a:** NaOH, MeOH, 25 °C, 1 h, then Dowex CCR-3; **b:** DIAD, PPh₃, THF, 25 °C, 1 h

Scheme 139

Also the methylene-bridged dioxocin **710** was the undesired product of the attempted Mitsunobu inversion of alcohol *cis*-**709**. In this case the excess of PPh_3 suppressed nucleophilic attack of dithiane on DEAD and, instead, a nucleophilic attack of the hydroxyl group at the dithioacetal carbon took place originating **710**. However, dioxocin **710** was obtained along with the 4-methoxybenzoyl ester *trans*-**709** <2001OL177>. After deprotection of the hydroxyl groups, **711**, under Mitsunobu conditions, produced the methylene bridged dioxocin **713** in good yield <2004OL2965>. A further example of dioxocins obtained from cyclization of a hydroxyl group with a carboxy acid moiety was provided by the hydroxy acid **645** ($\text{R} = \text{H}$), which was first activated by reaction with 2,4,6-trichlorobenzoyl chloride to give the corresponding ester and then cyclized with DMAP in refluxing toluene to give **622a**. The same procedure, starting from the suitable hydroxy acid, gave **622b** <2001TL5377>.

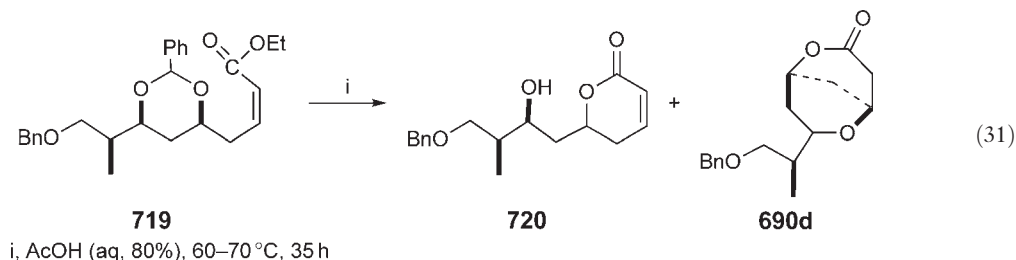
The remarkable cytotoxic activity of the natural occurring (+)-9-deoxygoniopypyrone **690a** prompted many research groups to propose syntheses of this dioxocin derivative. The early synthesis involved the intramolecular cyclization of 8-epigonodiol **714a** by nucleophilic attack of the hydroxyl group adjacent to the phenyl moiety to the double bond and the final product was obtained in 60–82% yield <1998CJC94, 1999T2493>. Starting from the 6-epigonodiol, the leiocarpin A **624**, a stereoisomer of **690a** <2004TL8111> was obtained in 94% yield. (+)-9-Deoxygoniopypyrone was also obtained, in 84% yield, from **714b** if the cyclization step was preceded by the hydrolysis of the ester with LiOH in THF <1997JOC6619>. Lactone **715** furnished **690a** in 80% yield; in this case the nucleophilic attack of the hydroxyl group was facilitated by the electron-withdrawing ability of the phenylsulfonyl group <1999T13011>. Dihydroxylation of goniothalamine **716** with AD-mix- α reaction directly gave the natural product **690a**, likely through the intermediacy of **714a**, in 84% yield and 94:6 de <2002SL1265>. A further synthesis of **690a** in excellent yield was achieved by cyclization of the alcohol **717** in the presence of $\text{Cu}(\text{OTf})_2$ and successive debenzoylation with TiCl_4 <2003JA3793>. Goniopypyrone **690b**, another pharmacologically interesting dioxocin, was obtained, in 70% yield, from the acetonide **714c** by initial hydrolysis to the corresponding triol derivative and successive intramolecular Michael addition catalyzed by DBU in THF <1995JOC3121>. Goniopypyrone could also be prepared from **714d**, in 88 overall yield, by the classic DBU-mediated intramolecular Michael addition of the hydroxyl group and successive MOM deprotection with TFA (Scheme 140) <1999T2493>.



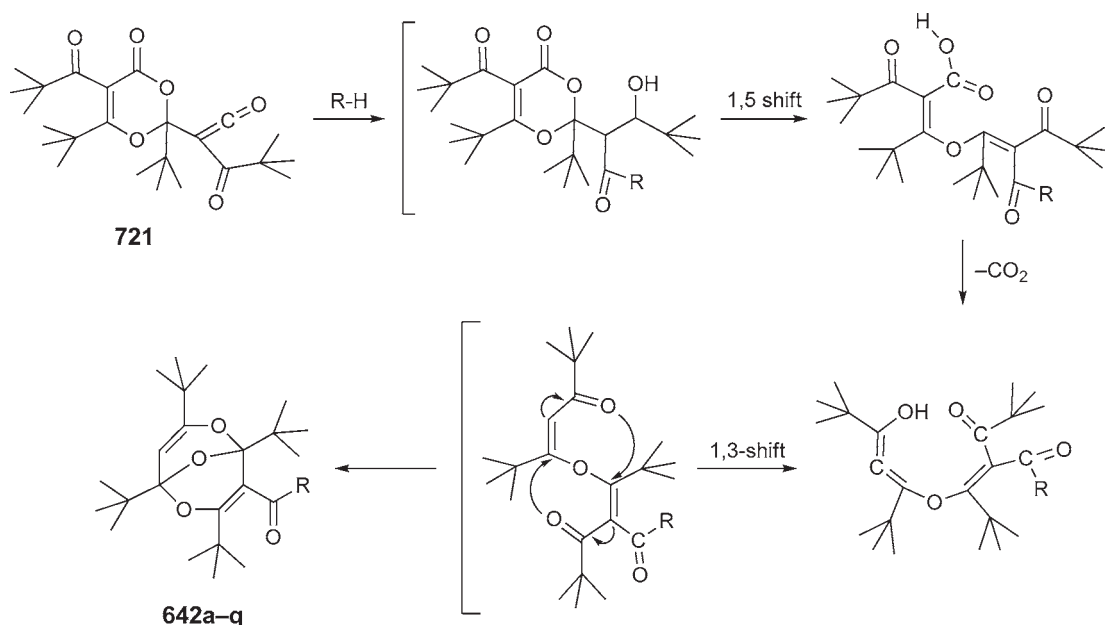
i, DBU, 25°C , 15 h; ii, DBU excess, 25°C ; iii, AD-mix- α reaction; iv, **a:** $\text{Cu}(\text{OTf})_2$; MeCN, 60°C , 18 h; **b:** TiCl_4 , DCM, 25°C , 30 min; v, TsOH, benzene, 25°C , 12 h

Scheme 140

Cryptocaryolone **690c** was prepared, in 44% yield, from the triol **718** by cyclization in benzene in the presence of TsOH <2003OL1959>. The lactonization of **719**, under normal hydrolytic conditions, afforded the expected pyranone **720** along with the dioxocin **690d** by way of the intramolecular conjugate addition of the hydroxyl group. The reaction was found to be susceptible to hydrolytic conditions and the dioxocin was obtained in >90% yield with 80% AcOH at 100 °C for 12 h (Equation 31) <2000TL707>.

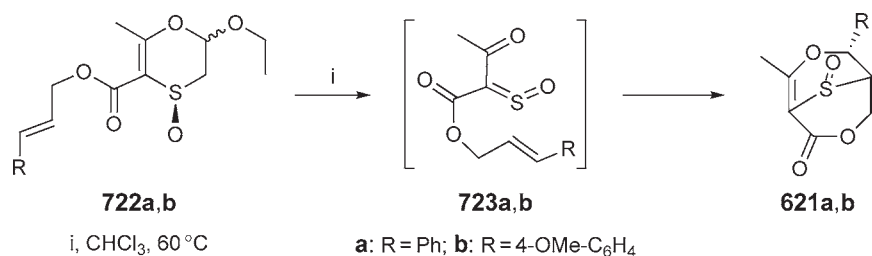


Dipivaloylketene dimer **721** added H₂O, amines, oximes, or hydrazines to give the oxygen-bridged dioxocins **642a–q** in yields from moderate to excellent (40–90%). A plausible mechanism proposed the addition of the nucleophile (R-H) to the ketene moiety of **721**, which underwent 1,5 H-shift, followed by decarboxylation. The resulting intermediate tautomerized to an oxygen-bridged double 1,3-oxadiene, which cyclized to the final dioxocin **642** via a pseudopericyclic [4+4] tandem cyclization (Scheme 141) <1995CC797, 1998H(48)1841, 2004T2857>.



Scheme 141

Heating sulfoxide **722a** at 60 °C in CHCl₃ directly furnished the sulfine-bridged dioxocin **621a** in 43% yield. The formation of **621a** was explained by an intramolecular hetero Diels–Alder reaction by the intermediate oxosulfine **723**. An appreciable increase in the rate of cycloaddition was observed on going from sulfine **723a** to **723b** as a result of the introduction of a 4-methoxy group causing a decrease in the energy gap between the molecular orbitals involved in the cycloaddition (Scheme 142) <2000EJO3721>.



Scheme 142

When dihemiacetal **724** was subjected to acidic treatment, a mixture of the spirodioxocin **632a** and β -hydroxyenone **725** was formed. When this mixture was treated with a catalytic amount of camphorsulfonic acid in MeOH at 0°C , the spirodioxocin (–)-**632b** was obtained in 69% yield. Treatment of the mixture under the same catalytic conditions in DCM provided pure (+)-**632a** in 72% yield <2004EJO5040>. Spiroketalization of (+)-**726** or (–)-**726** was performed in DCM/MeOH under acidic catalysis (TsOH).

The reactions were complete after a few minutes at 25°C and no change in products was observed even after heating to 60°C . The crude reaction mixtures contained a mixture of anomeric methyl acetals **641a**, and their proportions varying slightly with the concentration of the acid catalyst and the reaction temperature (Scheme 143) <2004HCA1493>.

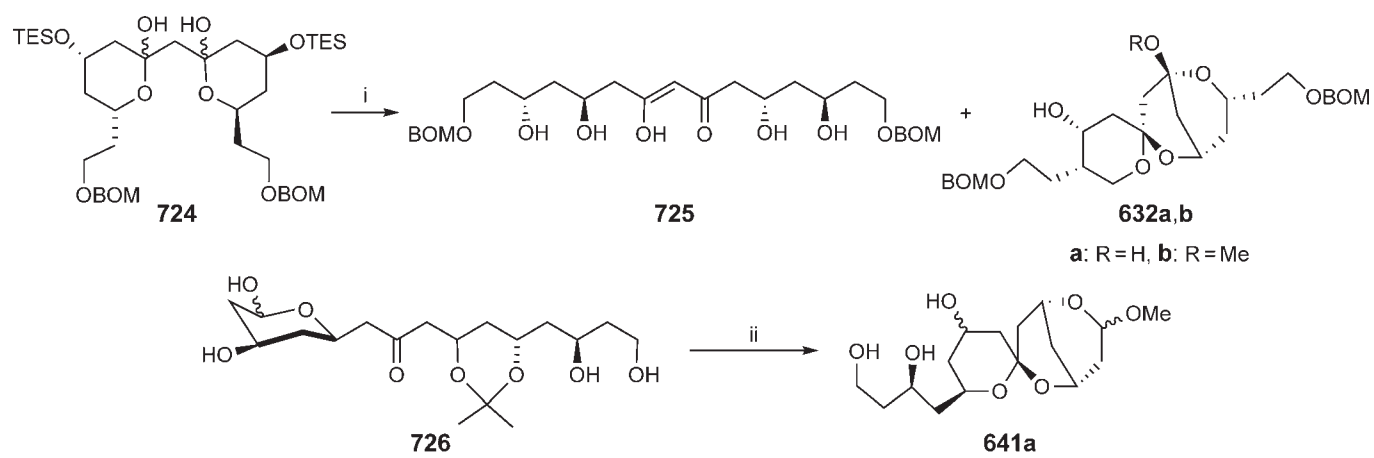
Esters **727a–c** in which a diene and a dienophile moieties are connected through a six-atom tether underwent intramolecular Diels–Alder reaction, which occurred in a regioselective way in toluene and only fused lactones **630a–c** and **630'a–c** were produced. In lower-boiling solvent, the reaction remained under kinetic control, determined by the interactions between HOMO and LUMO coefficients that prevented the formation of the bridged lactone **728**, which was formed from **727a** in benzonitrile (bp 191°C) (Scheme 144). In Scheme 125, other dioxocin derivatives obtained from the same sort of intramolecular cyclization are reported <1996JOC7597, 1998J(P1)881>.

Benzodioxocin **730** was obtained in 90% yield from the alcohol **729** upon DDQ oxidation. Presumably the benzylic cation, formed *in situ*, could be trapped by the hydroxyl group, which completely ruled out the potentially competitive elimination to afford the corresponding chromen <2004JA11966>. Treatment of the *trans*-dihydropyran **731** with AcOH in the presence of $\text{BF}_3\cdot\text{OEt}_2$ unexpectedly gave benzodioxocin **732**, as minor product, along with the *trans*-diaxial tetrahydropyran **733**, as main product, and its *trans*-diequatorial diastereoisomer **734** (Scheme 145) <1999J(P1)2627>.

Intramolecular cyclopropanation of **735** in refluxing benzene smoothly gave dioxocin **651** in 92% yield, as a single diastereoisomer with *de* >99%. The reaction was also performed in the presence of typical catalyst for generation of metal carbenoids. The isolated yield of **651** depended much on the catalyst employed; CuSO_4 was the best catalyst in terms of the product yield (92%). Use of $\text{Rh}_2(\text{OAc})_4$ was also advantageous in that its high catalytic activity allowed the reaction to be performed at 25°C , though the isolated yield of **651** was not excellent (77%). When the reaction was performed at high temperature in refluxing solvents in the presence of CuSO_4 , the *de*'s of the **651** decreased to 98% (80°C refluxing benzene), 92% (110°C refluxing toluene), 88% (138°C refluxing xylene) <1997TA661, 2003TA881>. The same sort of cyclization on the same substrates was also performed under flash vacuum pyrolysis conditions <2003TL3115>. Cyclopropanation was successfully performed on the substrates **736** bearing a phenyl group.

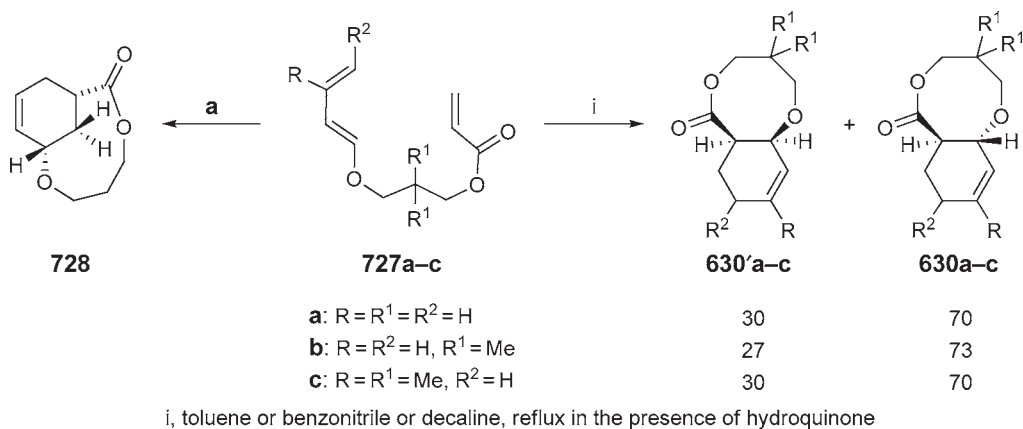
The reaction was performed with $\text{Rh}_2(\text{OAc})_4$, as catalyst, at 25°C and gave (6*aS*)-**611a,b** in quantitative yield as a single diastereoisomer <1998CL45>. Successively, the reaction was also conducted on **736c–f**. In substrates **736c–e**, having a different tether, the reaction selectivities were moderate to very high and the major products had the same (6*aS*) stereochemistry as that of **611a,b**. The reaction of **736a,c** was faster than those of **736d,e** having a singly methylated tether, which was faster than that of the achiral **736f** possessing no methyl group. Thus, each methyl substitution on the tether enhanced the reaction rate by one order of magnitude <2001OL37>. The $\text{Rh}_2(\text{OAc})_4$ catalyzed cyclization on **737** gave dioxocin (8*S*)-**615** in 70% yield, as a single diastereoisomer, by the usual intramolecular cycloaddition to give **738** and successive rearrangement of this latter (Scheme 146) <2003CL128>.

Hydrolysis of trichloroacetate ester **739** provided the dioxocin **740** as the only observable product in a remarkable 97% yield. This unusual reaction was viewed as a ‘ring–chain tautomerization’ or as a nucleophilic 1,6-addition of a phenoxide to the oxygen end of the quinone carbonyl group (Equation 32) <1999OL3>.

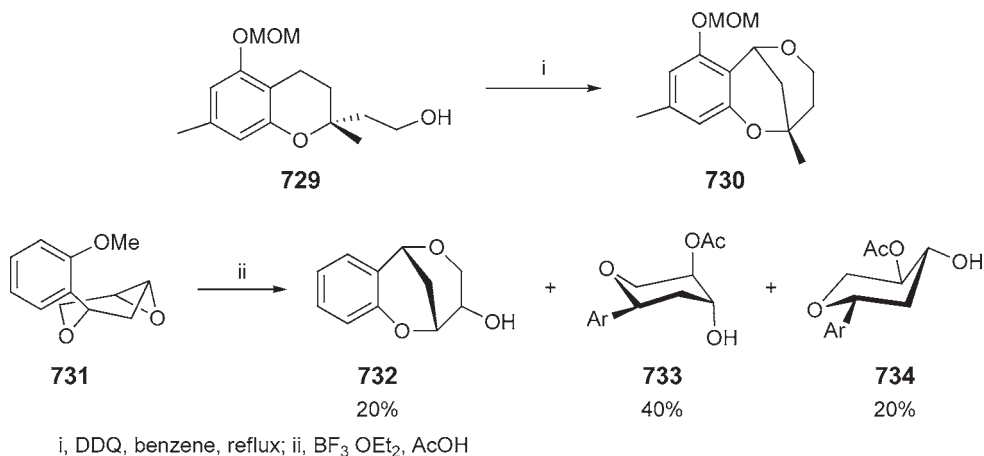


i, HF (aq, 40%), MeCN, -50°C , 20 min; ii, TsOH, DCM/MeOH, 20°C , 1 h

Scheme 143



Scheme 144



Scheme 145

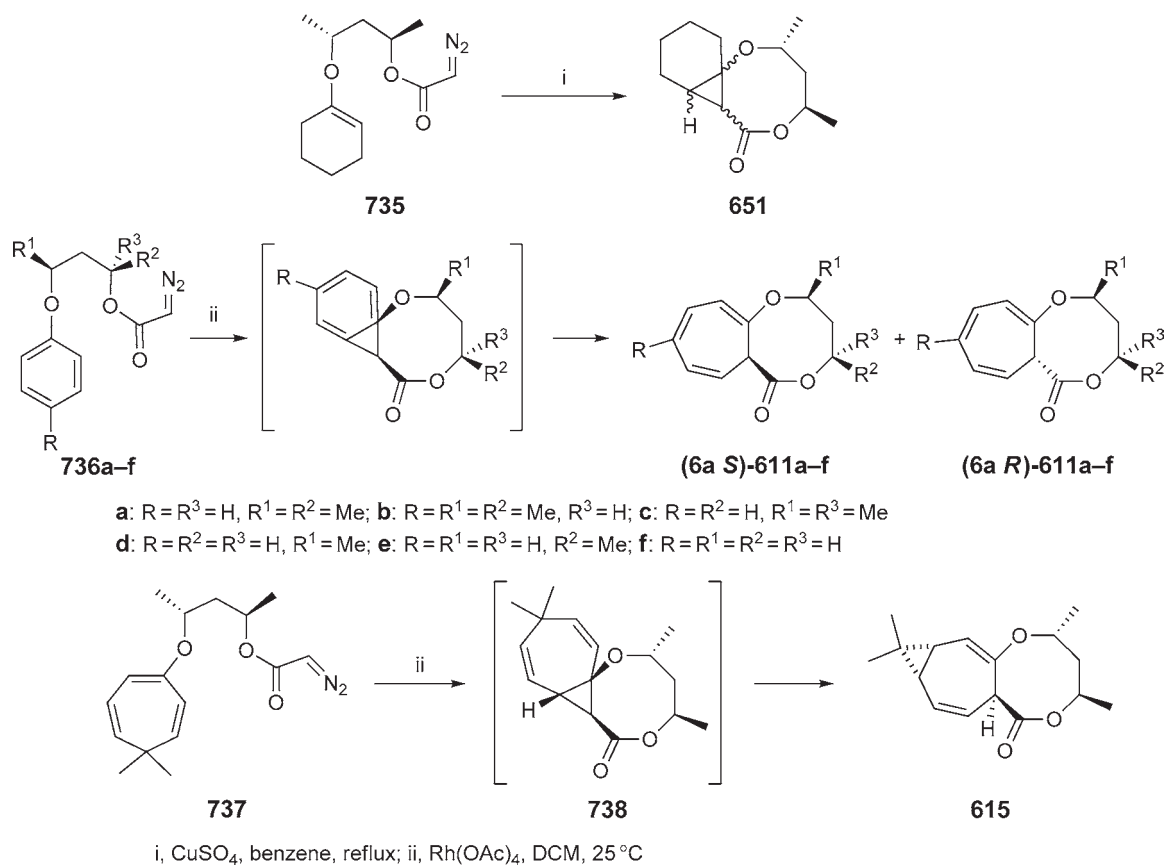
14.07.5.6.3 Ring syntheses from C₄O₂ + C₂ units

The methylene bridged dioxocin **689a**, the immediate precursor of (–)-8-*epi*-9-deoxygoniopyrpyrone, was prepared by addition of the lithium salt of methyl 3-phenylsulfonyl orthopropionate to the epoxide **741**, in the presence of BF₃·Et₂O, followed by acid treatment, which effected cleavage of the silyl protecting group and lactone formation. Exposure of the crude mixture to an excess of DBU led to the bicyclic lactone via PhSO₂H elimination and concomitant intramolecular Michael addition of the benzylic hydroxyl function to the resulting α,β-unsaturated-γ-lactone <1998TL9681>. Reaction of trichloroacetyl chloride and Zn–Cu couple with 1,3-dioxane **742a** afforded the dichlorodioxocinone **743** in 63% yield <1996AGE1970>. Dioxocin **744** was instead obtained by an intermolecular aldol-type condensation from 1,3-dioxane **742b** with acetone in the presence of an amine, followed a rapid addition of Bu₂BOTf (Scheme 147) <2004OL127>.

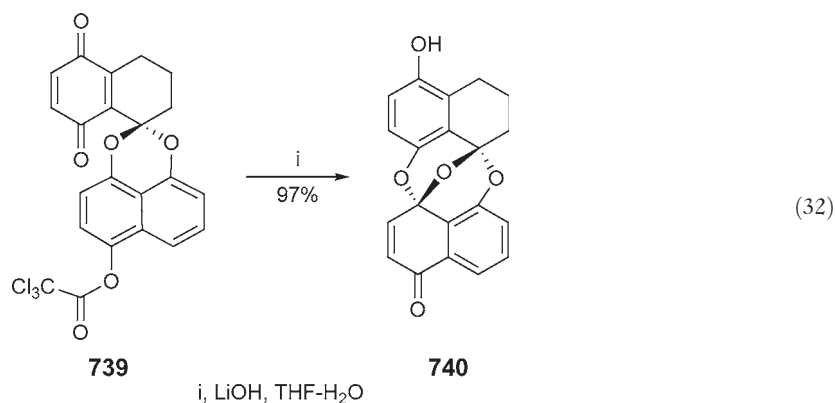
14.07.5.6.4 Ring syntheses from C₃O₂ + C₃ units

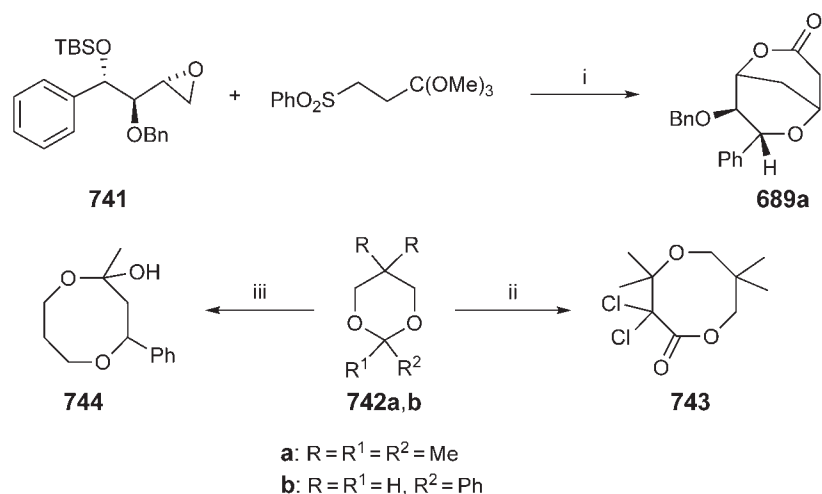
The aminodiols **745**, obtained from 2-amino-1,3-propanediol by two sequential reductive alkylations with 2,4-dimethoxybenzaldehyde and benzaldehyde, reacted with 3-chloro-2-(chloromethyl)prop-1-ene to give dioxocin **683** in 46% yield <2006JOC413>. Similar formation of dioxocins was observed when 3-chloro-2-(chloromethyl)prop-1-ene

was reacted with 2-methylidene-1,3-dihydroxypropanediol <1999USP5874573>. Reaction of substituted 2-hydroxybenzaldehydes **746a–j** with senecialdehyde produced benzodioxocins **625a–j** along with chromenes **747a–j**. The formation of **625** involved the vinylogous addition of the dienolate, present basic conditions, to the 2-hydroxybenzaldehyde to give **748**. The phenolic hydroxyl group of the α,β -unsaturated aldehyde **748** underwent a base-promoted intramolecular stereoselective 1,4-addition to form the aldehyde **749**, which cyclized stereoselectively to give the dioxocin **625**. Optimization of the reaction revealed that Na_2CO_3 favored the formation of **747a–j**, while NEt_3 favored the formation of **625a–j** (Scheme 148) <2005ASC555, 2005S1888>.



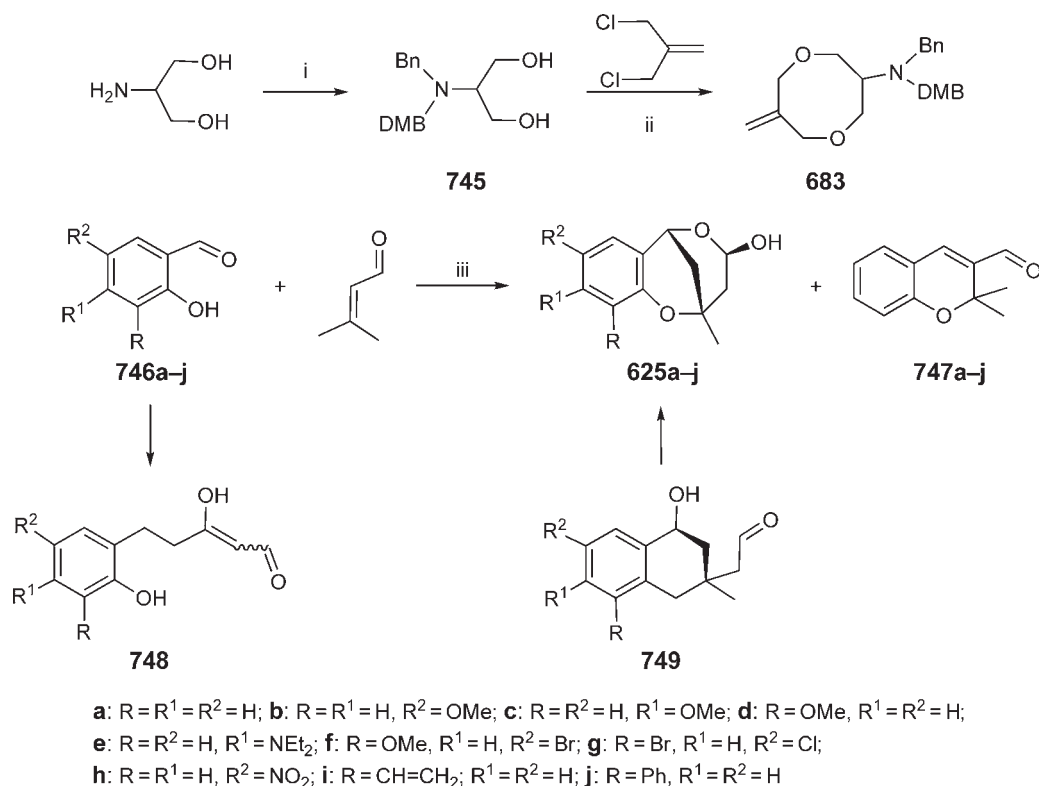
Scheme 146





i, **a:** $n\text{-BuLi}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, THF , -78°C , 1 h; **b:** $\text{TFA}-\text{H}_2\text{O}$ (9:1), 25°C , 3 h; **c:** DBU , DCM , 0°C , 1 h; ii, Cl_3CCOCl , Et_2O , 25°C , 1 h, then $\text{Zn}-\text{Cu}$, Et_2O , reflux, 1 h; iii, acetone, $i\text{-PrNEt}_2$, DCM , -78°C , then Bu_2BOTf

Scheme 147

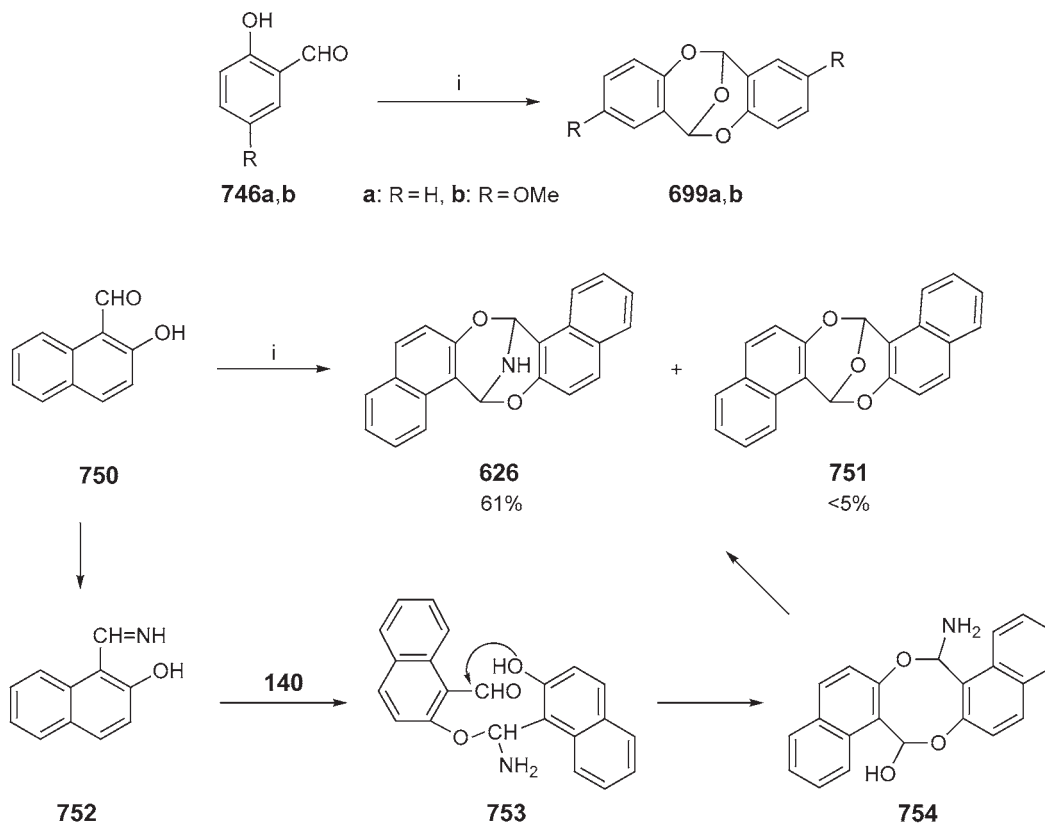


i, **a:** $2,4\text{-diMeO}-\text{C}_6\text{H}_3-\text{CHO}$, $\text{Na}(\text{OAc})_3\text{BH}$, MeOH , 25°C , 1 h; **b:** PhCHO , $\text{Na}(\text{OAc})_3\text{BH}$, $\text{AcOH}-\text{MeOH}$, 25°C , 2 d; ii, TBAI , NaH , DMF , 50°C , 1 h; iii, DABCO , H_2O , sonification, 25°C , 2.5 d

Scheme 148

14.07.5.6.5 Ring syntheses from $C_3O + C_3O$ units

Cyclodimerization of hydroxyaldehydes **746a,b** furnished in good yields the dibenzodioxocins **699a,b**. Generally, the preferred method of dimerization employed acetic anhydride, as the dehydrating agent, and a catalytic amount of H_2SO_4 giving **699a,b** in 40–65% yields. The yield of **699b** was improved (96%) using pivalic anhydride in place of acetic anhydride <2000OL1613, 2004TL4877, 2004OBC2483>. Refluxing 2-hydroxy-1-naphthaldehyde **750** in ethanol with NH_4OAc provided the imine bridged-dinaphthodioxocin **626** in 61% yield. The reaction also produced small quantities of **751** (<5%). A reasonable mechanism leading to **626** involved the initial formation of the aldimine **752**, which reacting with a further molecule of **750** gave the adduct **753**. The latter cyclized to the amino alcohol **754**, which by a transannular nucleophilic substitution afforded **626** (Scheme 149) <1996H(43)977>. Other examples of dioxocins obtained by cyclodimerization of β -hydroxyaldehydes were provided by a taxinine derivative <1999TL2149> and air oxidation of hydrocortisone that gave dioxocin **677** <2003STE361>.

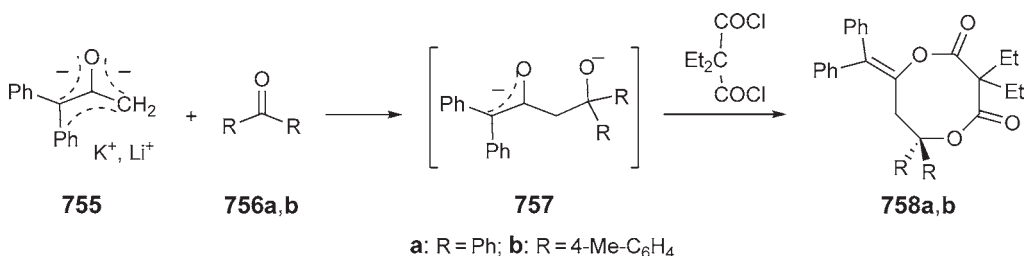


Scheme 149

In this section, the cyclodimerization reaction leading to dioxocinone **661** from the reaction of 4-pentenoic acid with ethyl bromodifluoroacetate in Zn-THF, likely through the intermediate **662**, will be reported. The retro-cyclodimerization **661** was reported in Section 14.07.5.4 (Scheme 132) <1997H(46)275>.

14.07.5.6.6 Ring syntheses from $C_3 + C_2O + CO$ units

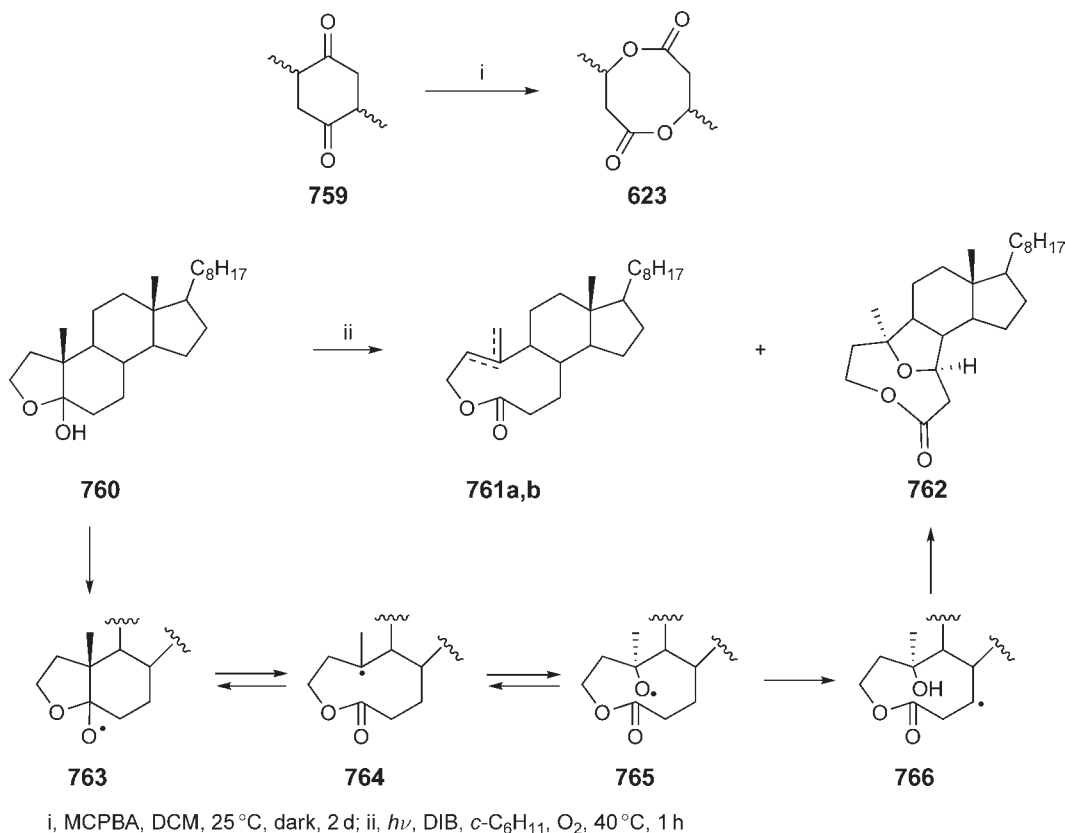
The dianion of 1,1-diphenylacetone **755** (Scheme 150), generated by treatment of the ketone with KH and *n*-BuLi, reacted with benzophenones **756a,b** and diethyl malonic dichloride to give, in good yield, the dioxocins **758a,b**. The anion **755** reacted first with **756** to give the intermediate dianion **757**, which in turn reacted with the acyl chloride to give the eight-membered ring (Scheme 50) <2001EJO1511>.



Scheme 150

14.07.5.7 Ring Syntheses by Transformation of Another Ring

Treatment of *rac*-**759** or *meso*-**759** with 3 equiv of MCPBA in the dark for 2 d gave the corresponding dilactones *rac*-**623** or *meso*-**623**, respectively, in ca. 70% yields. The rearrangement occurred with complete regio- and stereoselectivity, following the rules of sextet rearrangements [<1995HCA1525>](#). When the steroidal hemiacetal **760** was irradiated with visible light in the presence of (diacetoxyiodo)benzene and I_2 under argon with rigorous exclusion of air, only lactones **761a,b** were obtained in 85% yield. Irradiation of **760** in the presence of oxygen, in addition to **761a,b**, produced the dioxocinone **762** in moderate yield (35%). A plausible mechanism leading to **762** involved the initial formation of the alkoxy radical **763**, which underwent β -fragmentation through C(5)–C(10), to provide a C-10 radical **764**. The latter, under oxygen atmosphere, was stereoselectively peroxidated with inversion of configuration and successive homolysis of the O–O bond led to the alkoxy radical **765**, which underwent hydrogen abstraction from C-7 to give **766** that furnished the final eight-membered ring ([Scheme 151](#)) [<1997JOC2975>](#).



Scheme 151

14.07.5.8 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

As already observed for the other 1,5-heterocines, the unimolecular cyclizations were the most convenient syntheses of dioxocins. Among them, the most important was the 'biomimetic approach' to the preussomerin family in nearly quantitative yields. Excellent yields were also reported for the intramolecular cyclopropanation leading to heptatriene-fused dioxocins. Such a reaction allowed substituents both at the dioxocin and heptatriene moieties. Lower, but still good yields were observed in the synthesis of cyclohexene-fused dioxocins obtained from an intramolecular Diels–Alder reaction of suitable trienes. Another synthesis that allowed the preparation, in moderate to excellent yields, of 15 dioxocin derivatives was the addition of nucleophiles, such as water, amines, oximes, and hydrazines, to dipivaloylketene. Also efficient is the 'nonbiomimetic approach' to preussomerin derivatives involving the cyclodimerization of substituted 2-hydroxyaldehydes in acid medium. The only synthesis of a dioxocin by transformation of another ring reporting good yield, was the ring enlargement of 2,5-dimethylcyclohexene-1,4-dione.

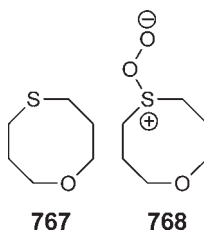
14.07.5.9 Important Compounds and Applications

(+)-9-Deoxygoniopyrpyrone **690a** and (+)-goniopyrpyrone **690b** showed cytotoxicity against P388 murine leukemia cells with IC_{50} values 13.63 and $5.33 \mu\text{g ml}^{-1}$, respectively <1999T2493>. Compounds belonging to the same series also showed larvicidal activity (*Aedes aegypti*) with LC_{50} values of $15\text{--}20 \mu\text{g ml}^{-1}$ <1995AJC199>. Cyclononactic acid **622b** and cyclohomononactic acid **622c** showed activity against *Saccharomyces cerevisiae* ScAL 141, *S. cerevisiae* ScAL 143 and *Candida albicans* with MIC $2\text{--}10 \mu\text{g ml}^{-1}$ <2001AP143>. Compounds belonging to the series **705** were inhibitors of the cholesterol ester transfer protein with IC_{50} $0.2\text{--}0.015 \mu\text{M}$ <2004WO039364, 2005BML3611>. Triazacyclononane bearing three 3-hydroxy substituted dioxocin moieties and related compounds showed chelation affinity and selectivity for first transition series elements. Administration of the free or conjugated compounds resulted in a decrease in the *in vivo* bioavailability of first transition series elements and/or removal from the body of first transition series elements and elements with similar chemical properties <1999USP5874573>.

14.07.6 Rings with One Oxygen and One Sulfur (1,5-Oxathiocins)

14.07.6.1 Theoretical Methods

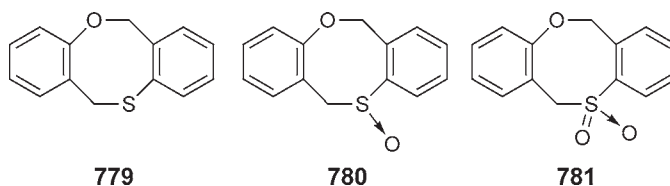
The study of the conformationally induced electrostatic stabilization (CIES) photooxygenation mechanism of sulfide **767** was computationally examined using an *ab initio* model and extended to the homologous persulfoxide **768**. The MP2/6-31G(d) geometries and a natural population analysis of persulfoxides **768**, containing lone-pair donor atoms, supported the mechanism and demonstrated that oxygen donor group, in the 1,5-oxathiocin **767**, was more effective than sulfur in the corresponding 1,5-dithiocin in promoting oxygenation <2006JOC1247>.



14.07.6.2 Experimental Structural Methods

Single-crystal X-ray investigations of fused 1,5-oxathiocin derivative **769** (Ar = *p*-NO₂-C₆H₄) and 5*H*,7*H*-dibenzo[*c,f*]-1,5-oxathiocin-7-one 12-oxide **770** were performed to confirm their structure and stereochemistry. The C–C bond lengths of the oxathiocin ring in **769** ranged from 1.508 Å for C(3)–C(4) and up to 1.547 Å for C(6a)–C(10a). The bond distances C(6)–S, S–O, and S–C(4) (1.804, 1.505, and 1.786 Å, respectively) were in agreement with the corresponding values reported for analogous sulfoxides. Compound **769** co-crystallized equimolecularly with the solvent EtOAc. Besides the normal van der Waals interactions, the crystal packing was mainly stabilized by intermolecular hydrogen

The sulfone **781** exhibited the methylene adjacent to the oxygen signal at 5.97 ppm and the SO₂-methylene resonance at 4.81 ppm. In **780** and **781**, the benzene protons *ortho* to the sulfoxide or sulfone group resonated at 8.00–8.30 ppm. The downfield shift relative to the other aromatic protons is a direct consequence of its projection into the molecule where the deshielding anisotropies of the sulfoxide or sulfone group are exerting the effect <1995HAC145>.



The ¹³C NMR data were not provided for all the 1,5-oxathiocins reported. The ¹³C NMR spectrum of **771** showed the CH₂-S signals at 32.7–38.8 ppm, the CH₂-O resonance at 69.5 ppm, the C-7 signal at 31.7 ppm, the exocyclic CH₂ at 120.8 ppm, and the carbonyl carbon resonated at 169.9 ppm, while the 1,5-oxathiocin **772** in the ¹³C NMR spectra exhibited the CH₂-S resonance at an upfield shifts (27.5–32.7 ppm), CH₂-O resonance at 64.5 ppm, the C-7 signal at 31.8 ppm, and the carbonyl singlet at 175.4 ppm <2005ASC1811>. The ¹³C NMR spectra of diastereoisomers of **773** showed the CH₂-S carbon signals at 31.5–31.7 ppm, the CH-S carbon resonance at 54.9–56.1 ppm, while CH₂-O carbon resonated at 64.4–65.3 ppm, the C-7 absorption at 28.3–29.7 ppm, and the Me and CO groups resonances were found at 15.9–17.3 and 175.6–175.9 ppm, respectively <1997T7165>. The bridged 1,5-oxathiocin **774** exhibited in the ¹³C NMR spectrum the CH₂-S resonances at 27.2–29.7 ppm, the CH₂-O signals at 65.5–69.3 ppm, the CH₂-N at 53.0 ppm and the methynes bound to nitrogen bridge at 34.0 ppm <2006JOC4678>. The ¹³C NMR spectra of fused 1,5-oxathiocane derivatives **769**, **776–781** showed all the signals at downfield shifts; the CH₂-S could be found in the range at 53.2–53.9 ppm, the CH-O signals at 81.2–82.5 ppm, and other ring protons resonated at 35.8–38.6 ppm <1997J(P2)273>.

No studies on fragmentation patterns of 1,5-oxathiocins have been reported in the past decade. In some cases, only the molecular or quasi-molecular ions of their EI spectra were provided <1997T7165, 2005ASC1811, 2005OL1181> and FAB spectra <1997J(P2)273>.

The 1,5-dibenzo-oxathiocin **770** as well as **771–773** derivatives, showed in their IR spectra the eight-membered ring carbonyl stretching in the range 1728–1740 cm⁻¹ <1997TA2411, 2005ASC1811, 1997T7165>. Compounds **770**, **776–778**, **780**, and **781** exhibited the S=O stretching at 1075–1020 cm⁻¹ <1997TA2411, 1995HAC145>. Derivatives **773** and **775** showed the OH stretchings at 3535–3204 cm⁻¹ <1997T7165, 2005OL1181>.

14.07.6.3 Thermodynamic Aspects

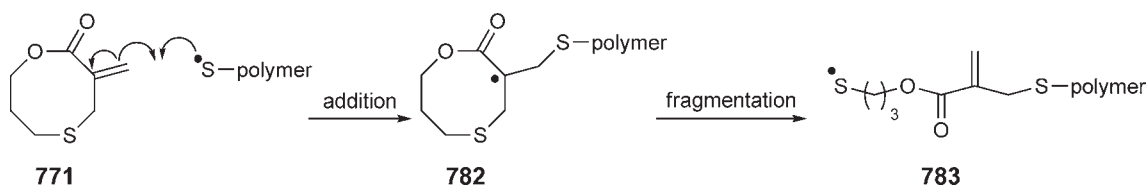
Uncondensed 1,5-oxathiocins were generally oils <1997T7165, 2005OL1181> or characterized by low melting points (18–48 °C) <2005ASC1811, 2006JOC4678>, whereas the fused oxathiocine sulfoxide **769** melted at 176 °C <1997J(P2)273>. Annulation of two benzene units to the eight-membered ring gave compounds melting in the range 99–185 °C <1995HAC145, 1997TA2411>.

Soluble in most common solvents, oxathiocins were purified by recrystallization from EtOH <2006JOC4678>, hexane/Et₂O or DCM/hexane <1995HAC145>, and EtOAc <1997J(P2)273>. Some 1,5-oxathiocins were also purified by chromatography on silica gel with DCM, DCM/ petroleum ether or petroleum ether/EtOAc <2005ASC1811, 1997J(P2)273>, EtOAc/hexane <1997T7165, 2005OL1181>.

X-Ray structural study of derivative **769** (see Section 14.07.6.2) gave evidences for a boat–chair (BC) conformation of the heterocycles and showed five chiral centers. It was enantiomerically pure in the crystal packing owing to the polar space group *P*₂₁. The recovery of only one C-Ar epimer of the fused oxathiocine *S*-oxide **769** was a consequence of conformational control during the eight-membered ring closure, which led to the formation of the thermodynamically favored isomer <1997J(P2)273>. The direct chiral chromatographic resolution of 5*H*,7*H*-dibenzo[*c,f*]-1,5-oxathiocin-7-one 12-oxide **770** was achieved, although with very poor resolution, by Kromasil-based chiral sorbent (*O,O'*-bis(3,5-dimethylbenzoyl)-*N,N'*-diallyl-L-tartardiamide silica CSP) using hexane as mobile phase <1999MI 1224-02>. Dibenzo-1,5-oxathiocins **779–781**, in CDCl₃ solution, as demonstrated by their ¹H NMR spectra, existed as single conformers in the BC form in which the sulfoxide oxygen should be close to the *ortho* hydrogen of benzene moiety <1995HAC145>.

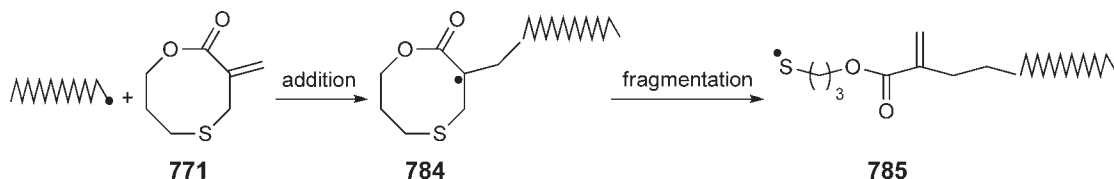
14.07.6.4 Reactivity of Nonconjugated Rings

Polymerization of the oxathiocinone **771** proceeded, in benzene at 40–70 °C, with complete ring-opening up to ca. 25% conversion. A two-step mechanism was involved: addition of sulfanyl radical onto monomer exocyclic double bond to form the intermediate carbon centered radical **782** fragmentation of this latter yielding a new propagating sulfanyl radical and polymer backbone double bond (Scheme 152) <2005ASC1811>.



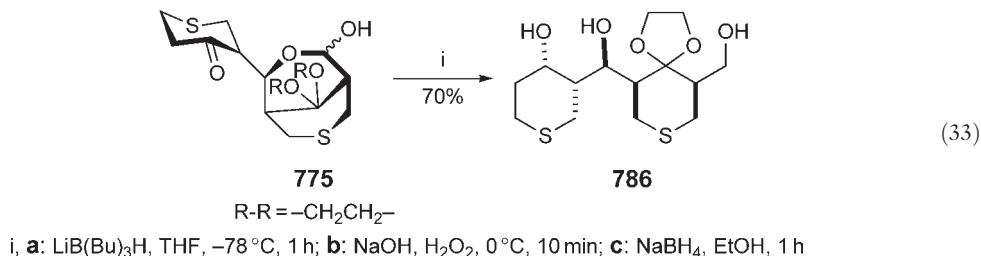
Scheme 152

A similar mechanism was proposed when 1,5-oxathiocinone **771** underwent polymerizations with methyl methacrylate (MMA) and styrene (STY). The activated double bond of **771** was found to have a profound effect on reactivity. In fact, copolymerization of **771** with MMA at 70 °C the 5-terminated sulfanyl radicals preferred to undergo homopropagation, while cross-propagation is favored for MMA-terminated radicals. Both monomers possessed an electron-deficient acrylate double bond with similar possibilities for conjugative stabilization of the adduct radical by the ester functionality, which would explain the apparent equal reactivity of the MMA radical to either monomer. In copolymerization of **771** with STY at 80 °C, the cross-propagation is favored, consistent with electrophilic sulfanyl radicals adding rapidly to electron-rich STY, and nucleophilic styryl radicals adding rapidly to electron-deficient acrylate **771** double bonds (Scheme 153) <2006MI2475>.

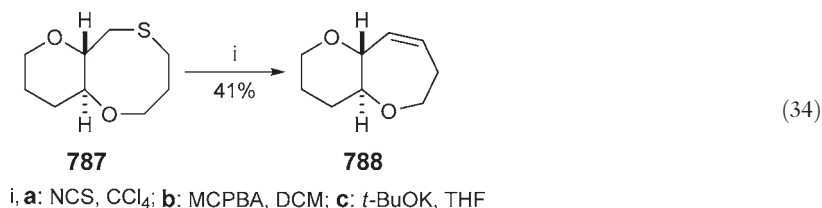


Scheme 153

The ketone and hemiacetal groups in spiro-1,5-oxathiocin **775** were sequentially reduced to give **786** a useful synthon for tetrapropionate obtainable by desulfurization with Raney–Nickel (Equation 33) <2005OL1181>.

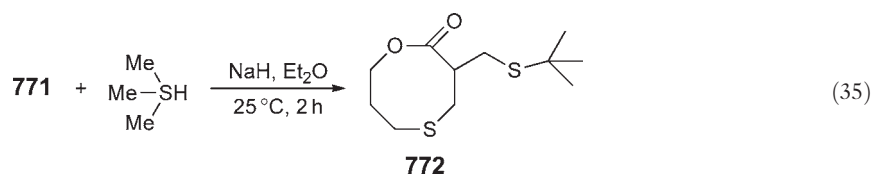


The unsaturated *trans*-oxabicyclo **788** was formed from the 1,5-oxathiocin **787**, via the Ramberg–Backlund olefination process, whose mechanism is parallel to that observed in the thiazocine series, involving an α -halogenation and oxidation at sulfur, followed by SO₂ extrusion (Equation 34) <1996TL2865>.



14.07.6.5 Reactivity of Substituent Attached to Ring Carbon Atoms

Michael additions of 2-methyl-2-propanethiol onto 1,5-oxathiocinone **771** gave the 3-[(*t*-butylthio)methyl]-1,5-oxathiocan-2-one **772** in 82% yield. The reaction was performed in order to obtain model for chain-transfer products of hydrogen abstraction by carbon-centered radicals (see Section 14.07.6.4) (Equation 35) <2005ASC1811>.



Condensation of fused 1,5-oxathiocane derivative **777** with 2,4-dinitrophenylhydrazine (2,4-DNP) afforded the corresponding 2,4-dinitrophenylhydrazone **769** (Ar = *p*-NO₂-C₆H₄) in quantitative yield <1997J(P2)273>.

14.07.6.6 Reactivity of Substituent Attached to Ring Heteroatoms

Oxidation of 5*H*,7*H*-dibenzo[*c,f*][1,5]oxathiocin **779** with MCPBA in DCM at 25 °C for 25 h furnished a mixture of the sulfoxide **780** and sulfone **781** in 71% and 16% yield, respectively <1995HAC145>.

14.07.6.7 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

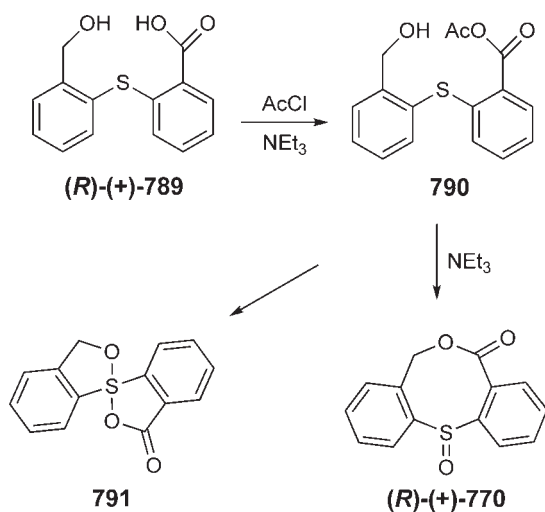
14.07.6.7.1 Ring syntheses from C₆OS units

Dibenzooxathiocin **770** was obtained in 36% yield, from diphenyl sulfoxide **789**, bearing a 2-hydroxymethyl and 2'-carboxy acid substituents. The reaction was performed at -70 °C using acetyl chloride, as dehydrating agent, in the presence of 2 equiv of Et₃N. When the reaction was conducted at the same temperature with the same dehydrating agent but in the presence of 1 equiv of Et₃N the mixed anhydride **790** was isolated in 85% yield. Refluxing **790** in DCE gave the spiro **791** in 61% yield, whereas when **790** was heated in DCE in the presence of 1 equiv of Et₃N, the dibenzooxazocin was isolated in 70% yield.

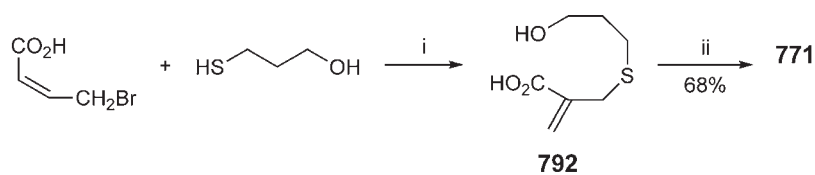
Probably the presence of Et₃N originated a harder nucleophile, which then attacks the less polarizable carbonyl of the mixed anhydride instead of the sulfur (Scheme 154) <1997TA2411>.

The oxathiocin **771** was synthesized from α-(bromomethyl)acrylic acid and 3-mercapto-1-propanol in the presence of NEt₃ to give α-[(3-hydroxypropyl)thio]methyl]acrylic acid **792**, which by an intramolecular cyclization in presence of NEt₃ and 2-chloro-1-methylpyridinium iodide yielded the eight-membered ring in good yield (Scheme 155) <2005ASC1811>.

Regioselective photocyclization of ethylthiopropyl phenylglyoxalate **793**, by an electron-transfer process, produced the 1,5-oxathiocin **773** in 96% yield. The mechanism proposed for such a photocyclization involved excitation of the keto ester **793** to its triplet state (**T**) upon irradiation (350 nm), and electron transfer between the donor and acceptor occurred in **T** producing the ketyl radical anion (**A**). This was deactivated to ground state **793** by back electron transfer or was converted to biradical (**B**) by proton transfer process. Cyclization occurred between the excited carbonyl group and the carbon α to the sulfur on the remote side (Scheme 156) <1997T7165>.

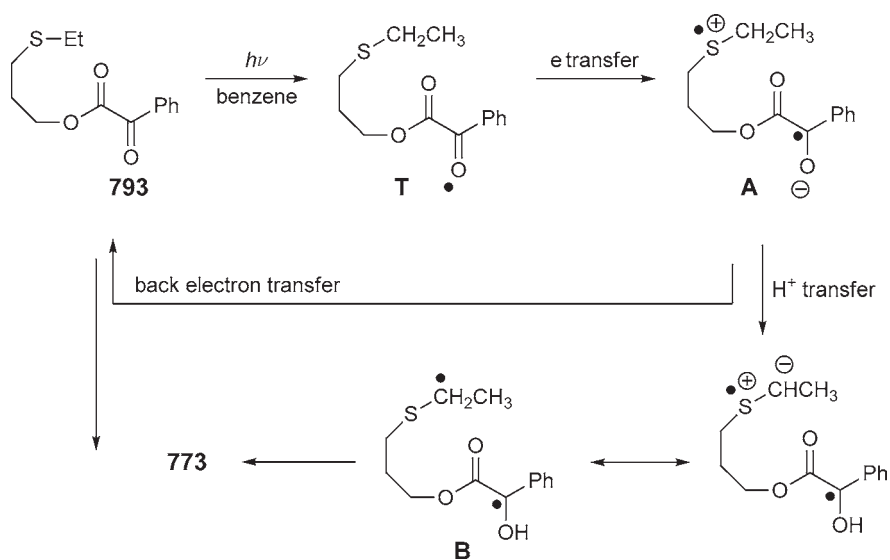


Scheme 154



i, DCM, NEt₃, 0–25 °C, 18 h; ii, 2-Cl-1-Me-pyridinium iodide, NEt₃, DCM, 25 °C, 8 h; then reflux, 2 h

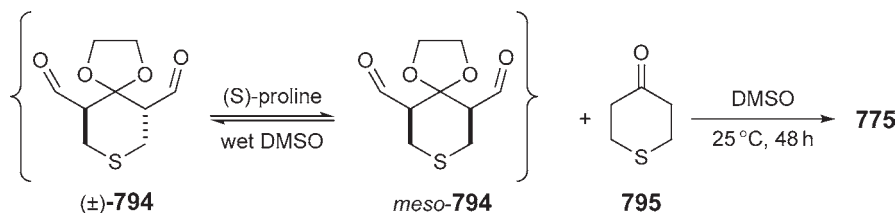
Scheme 155



Scheme 156

Reaction of tetrahydro-4*H*-thiopyranone **795** with *meso*-**794** gave the bridged oxathiocins **775** in 68% yield and 92% ee, respectively. Oxazocine **775** existed exclusively in the hemiacetal form, suggesting that the stereocenter originating from C-6 in **794** could be set under thermodynamic control. Reaction of **795** with the readily available 3.5:1 mixture of ($\pm$)-**794** and *meso*-**794**, respectively, produced **775** in the same yield and ee.

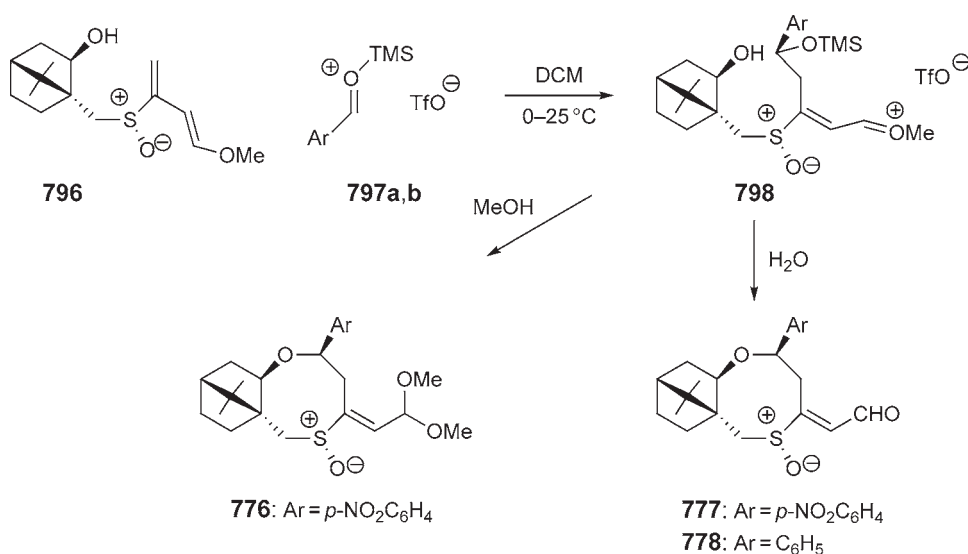
Rapid proline-catalyzed isomerization of *meso*-**794** to give a 3.5:1 equilibrium mixture of ($\pm$)-**794** and *meso*-**794**, respectively, was established by ^1H NMR. The selective formation of **775** from *meso*-**794** is readily explained by preferential aldol reaction of **795** with the (α *S*)-aldehyde group of *meso*-**794** (Scheme 157) <2005OL1181>.



Scheme 157

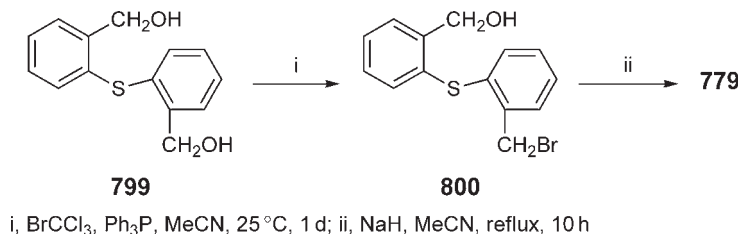
Reaction of benzaldehyde and its 4-nitro derivative with the enantiopure diene **796** in DCM and in presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) afforded the condensed enantiopure oxathiocanes **777** and **778** (50% yield). The reaction path began with the ionic addition of the diene **796** onto the carbon atom of the aldehyde function in **797a,b** activated by trimethylsilyl cation attack to the carbonyl oxygen.

The acid-catalyzed closure to eight-membered ring **777** and **778** occurred by way of the isoborneol hydroxyl group and the carbocation, which was easily formed from **798** due the aryl group, which had an increased activating effect when *p*-nitro group was present. Hydrolytic loss of the methoxy moiety took place during the aqueous work-up of the crude reaction mixture giving the α,β -unsaturated formyl group in **777** and **778**. When the work-up was carried out in presence of MeOH, instead of H_2O , the α,β -unsaturated dimethyl acetal **776** was obtained (55% yield) adding substantial support to the hypothesis that **798** is the reactive intermediate in the path from **796** and benzaldehyde towards enantiopure oxathiocin **778** (Scheme 158) <1997J(P2)273>.



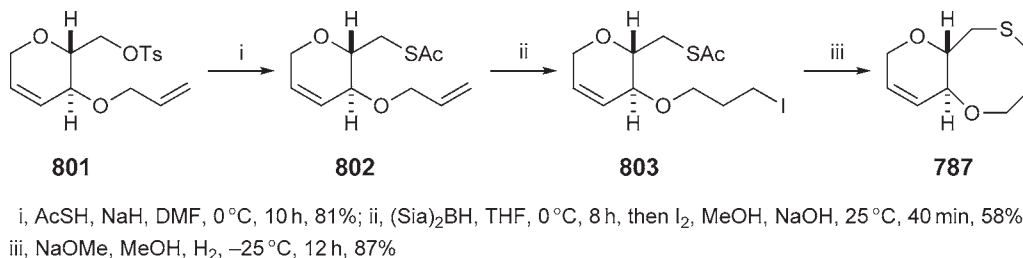
Scheme 158

5*H*,7*H*-Dibenzo[*c,f*][1,5]oxathiocin **779** was prepared from diol **799** by monobromination with BrCCl_3 and Ph_3P in MeCN to give **800**, which, on treatment with NaH, gave 1,5-oxathiocin **779** in 76% yield (Scheme 159) <1995HAC145>.



Scheme 159

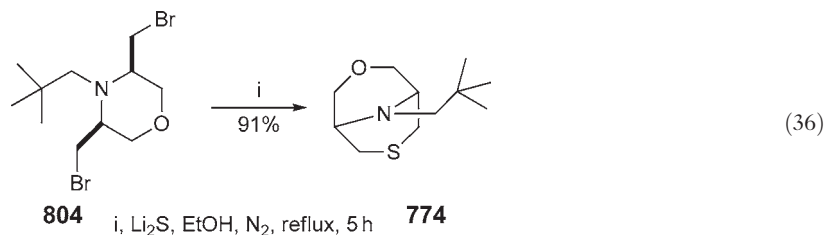
Compound **787** was synthesized in 41% overall yield via treatment of tosyl derivative **801** with NaH/AcSH to give **802**, which was further iodinated using $(\text{Sia})_2\text{BH}$ followed by I_2/NaOH oxidation to yield iodide **803**. Thioannulation to **787** proceeded smoothly by treatment of **803** with MeONa in MeOH at -25°C under H_2 atmosphere (Scheme 160) <1996TL2865>.



Scheme 160

14.07.6.7.2 Ring syntheses from $\text{C}_6\text{O} + \text{S}$ units

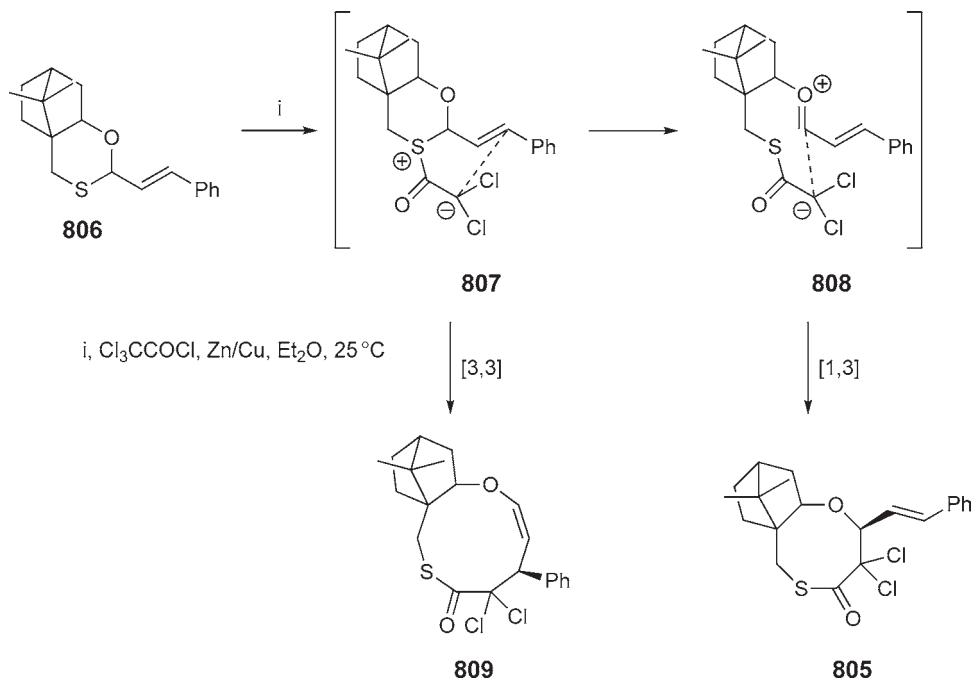
The treatment of morpholine **804** with 5 equiv of Li_2S in EtOH furnished the bridged 1,5-oxathiocin **774** in 91% yield (Equation 36) <2006JOC4678>.



14.07.6.8 Ring Syntheses by Transformation of Another Ring

Treatment of **806** with trichloroacetyl chloride in Et_2O in presence of activated zinc gave oxathiocin **805** (21–40% yield) instead of the expected 1,3-oxathiane obtainable from a [3,3]rearrangement. When the reaction was carried out using a bidentate ligand, DME, to sequester ZnCl_2 , the 1,3-oxathiane **809** was obtained in moderate yield (48%), together with a small amount of **805** (8% yield). The formation of the two products **805** and **809** could be rationalized considering the structure of the intermediate betaine **807**, which in absence of naked ZnCl_2 , rapidly rearranged via a chair transition state to give **809**. Formation of **805** presumably was a result of stabilization of the enolate by ZnCl_2 .

This slowed down the rate of the [3,3]-sigmatropic rearrangement and likely allowed time for thioacetal to ring-open and form the oxonium ion **808**. Subsequent reaction of the Zn enolate with **808** furnished **805** (Scheme 161) <2002CC2534>.



Scheme 161

14.07.6.9 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Out of nine syntheses of oxathiocin derivatives described in the previous two sections, seven involved unimolecular cyclizations, one went through the introduction of sulfur into a C₆O unit, and the last one described the transformation of a thiopyran nucleus into the oxathiocin ring system. Also, in this case, as for thiazocines, each synthesis (with one exception) described the obtaining of one derivative only, making the comparison among the different methods more difficult. However, the most popular approach to get oxathiocins, as usual, is the unimolecular cyclization. The most advantageous route appeared to be the photocyclization of a phenyl glyoxalate, which furnished the oxathiocin in nearly quantitative yield. The other unimolecular processes did not present any particular feature worthy of mention. The thioannulation of Li₂S to morpholine, although it accomplished only on one derivative, it is potentially capable of wide application. The transformation of thiopyran ring into oxathiocins took place in low yield thus of poor synthetic value but nevertheless of interesting mechanistic aspects.

14.07.6.10 Important Compounds and Applications

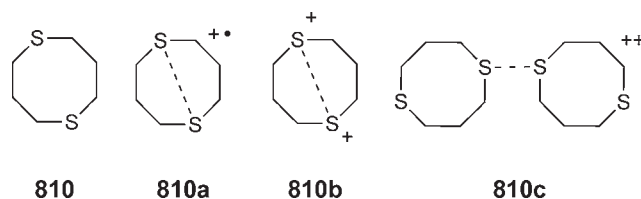
Oxathiocin **771** and related compounds were used to produce polymers, co-polymers, or block polymer to manufacture adhesive, dental compositions, and optical lenses <1996WO19471>.

14.07.7 Rings with Two Sulfurs (1,5-Dithiocins)

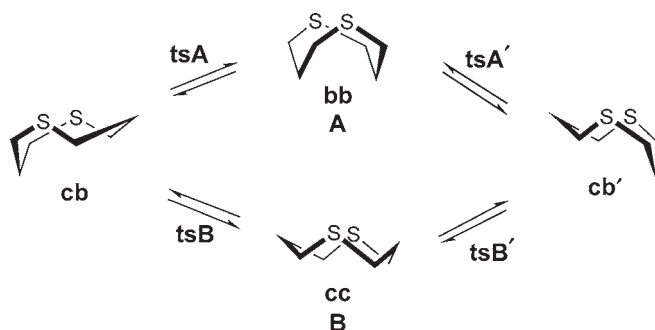
14.07.7.1 Theoretical Methods

Nine energy-minimum structures of 1,5-dithiacyclooctane **810** (DTCO) were obtained by the *ab initio* molecular orbital method (6-31G^{*}); the most stable was a twist-boat-chair structure (TBC) while the BC conformer, in which

the two sulfur atoms faced each other, had the highest HOMO energy. The energy barriers between TBC and BC conformers of **810** were calculated to be relatively low. Therefore, a conformational change from TBC to the BC was predicted to occur before these compounds were oxidized in solution <1999HAC159>. A theoretical conformational analysis of the dithiacyclooctane radical cation **810a** (DTCO^{•+}) suggested that the lowest-energy conformer is a chair-boat, with a partial but significant S-S δ bond (2.78 Å).



The calculated interconversion barrier for the ring-flip process was nearly 40 kJ mol⁻¹ with two possible pathways; one involved a boat-boat conformer and an untwisted transition structure (**A**), the other a chair-chair conformer and twisted transition structure (**B**) (Scheme 162) <1999J(P2)1559>. The molecular and electronic structures of the dications **810b** were investigated by *ab initio* molecular-orbital calculations. Four energy-minimum structures were obtained, three of those (boat-chair, boat-boat, chair-chair) had *cis* configuration with respect the sulfur lone pairs and the remaining one had *trans* configuration. The *cis* isomers were found to be much more stable than the *trans* isomer.

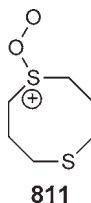


Scheme 162

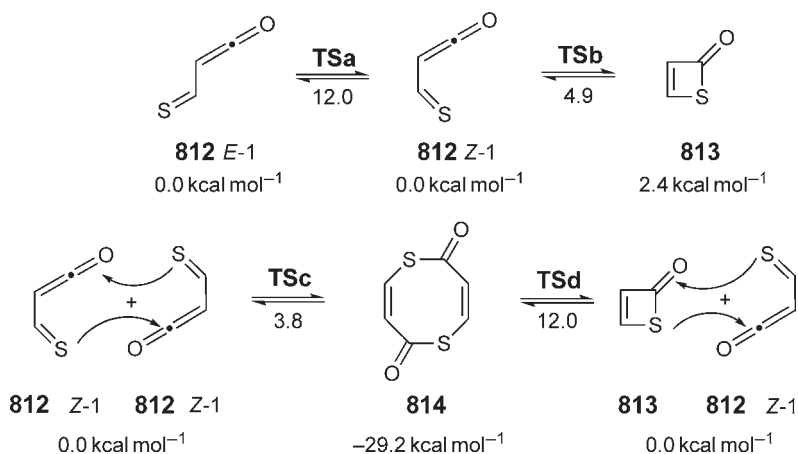
Among the *cis* structures, the stability is in the order of boat-chair > boat-boat > chair-chair. In the crystalline state, the dication **810b** adopted a distorted C₂ chair-chair conformation <2000HAC31>. The reactivity of S-S dication **810b** and alkenes was studied at MP2/6-31G* level of theory. The results obtained indicated a stepwise electrophilic addition of dication moiety to the double C=C bond to be the preferable mechanism <2003RCB1667>. *Ab initio* computational studies on the dimer of 1,5-DTCO **810c** using RHF/6-31G* and 3-21G* exhibited three structures: BC-BC and TBC-TBC with C₂ symmetry and BC-TBC with C₁ symmetry. In all the structures, the lone pairs of the sulfur atoms of the intermolecular bond are *trans* with respect to each other. The most stable was BC-BC. In this structure, the distance of the intramolecular S-S bond is longer (0.1–0.2 Å) than that in the monomer. The distance of the intermolecular S-S bond is ca. 0.1 Å longer than the S-S distance in the monomer dication <2001JST(542)215>. The *ab initio* quantum-chemical methods were used to explore the reactivity of the 1,5-dithiacyclooctane **810**, which exhibited an enhanced ability to removed singlet oxygen from solution, and a remarkable proclivity to chemically react rather than physically quench singlet oxygen. Its oxidation was extremely easy and exhibited electrochemically reversible behavior. The transannular interactions led to the formation of a S-S bond in both the radical cation **810a** and dication **810b** <2005JA11819>.

The study of the CIES photooxygenation mechanism of sulfide **810** was computationally examined using an *ab initio* model and extended to a series of homologous persulfides, containing a long-pair donor group or atom

ideally situated for through-space electrostatic stabilization. The MP2/6-31G(d) geometries and a natural population analysis of the occupancies of the natural lone-pair orbital ion showed a depletion of electron density with their donor function of persulfoxides **811**, and demonstrated that the sulfur donor group in the 1,5-dithiocin **810** was less effective than oxygen and nitrogen donor groups, in the corresponding 1,5-oxathiocin and 1,5-oxazocine, respectively, in promoting oxygenation <2006JOC1247>. An extensive search of persulfoxide **811** conformational space with MP2/6-31G(d) computational method located two low-energy conformations, one adopted a BC (0.0 kcal mol⁻¹) and the other adopted a boat–boat conformation (2.3 kcal mol⁻¹). Both conformations have hydrogen atoms removed by the persulfoxide terminal oxygen atom <2006T10724>.

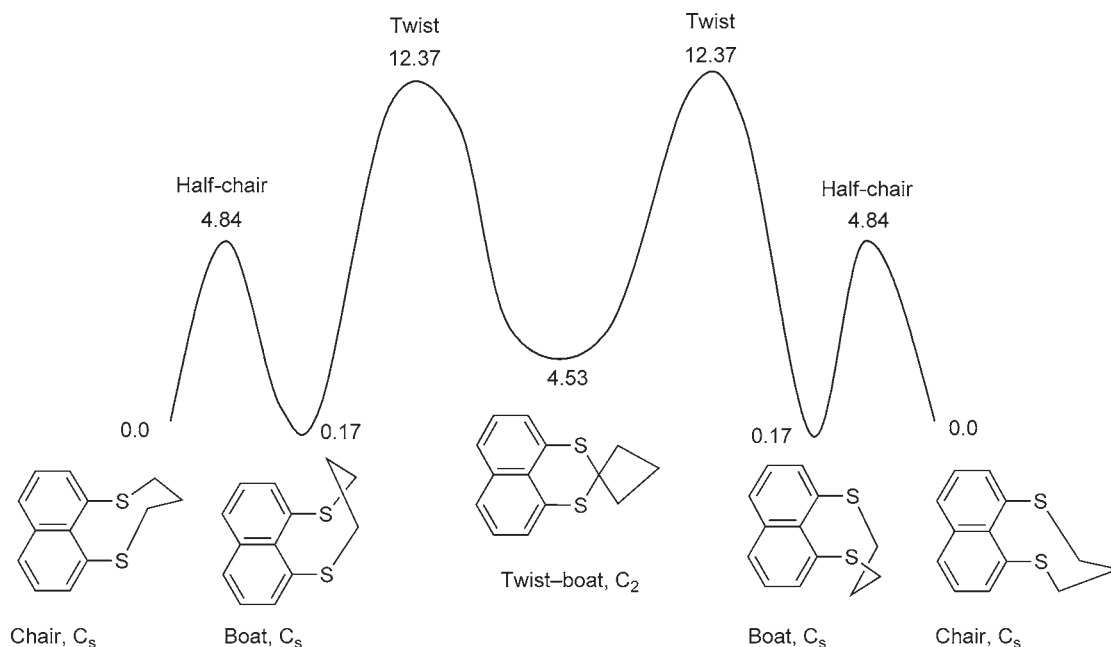


A theoretical study of dimerization of the thioformylketene **812** was performed at the B3LYP/6-31G-(d,p) and G3MP2B3 levels. The two conformations of ketene **812** (*E*-1 and *Z*-1) were very close in energy and, indeed, were equal at G3MP2B3 level, while **813** is 2.4 kcal mol⁻¹ higher in energy. Four pathways were considered: two [4+2] pathways with thioformyl ketene **812**, one [4+4] pathway with **813** and one [4+2] pathway involving **812** and thietone **813**. The [4+4] pathway (TSc) with **812** had lowest barrier (3.8 kcal mol⁻¹), while the dimerization of **812** and **813** gave the 1,5-dithiocin **814** by a [4+2] pathway (TSd) has higher barrier of 12.0 kcal mol⁻¹. The low-energy barriers for the alternative [4+2] dimerizations of **812** (4.6 kcal mol⁻¹ across C=C and 4.8 kcal mol⁻¹ across C=O) suggested that [4+4] cycloaddition (TSc) was the favored pathway for the formation of 1,5-dithiocin via a pseudo-pericyclic reaction mechanism (Scheme 163) <2005OL5817>.



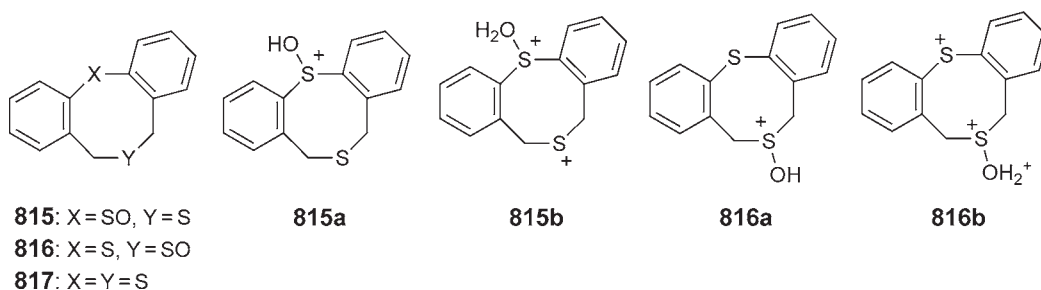
Scheme 163

The conformational properties of the naphtho[1,8-*b,c*]1,5-dithiocin were studied by the MNDO semiempirical SCF MO method. The most stable conformation was the chair conformation. The plane-symmetrical boat, which has C_s symmetry, was calculated to be 0.17 kcal mol⁻¹ was less stable than chair conformation. Both were separated by a low-energy barrier (4.84 kcal mol⁻¹). The twist–boat conformation is 4.53 kcal mol⁻¹ higher than that of the boat conformation. The barrier for chair-to-chair ring inversion in this compound was 12.37 kcal mol⁻¹ (Scheme 164) <1999JST(489)67>.



Scheme 164

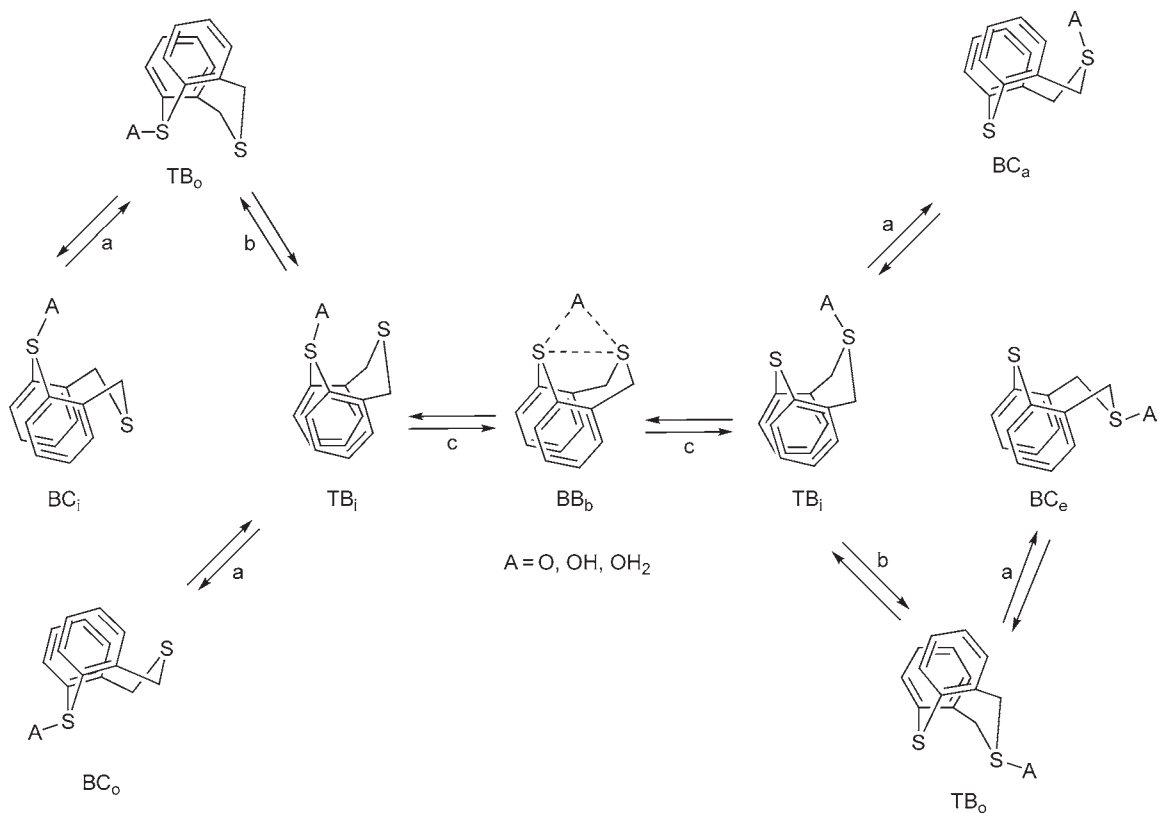
The total energies of various conformers of dibenzo-1,5-dithiocin oxides **815** and **816** obtained by *ab initio* MO calculations indicated that the BC forms were the more stable than the TB forms (0.0 and 28.0 kJ mol^{-1} for **815**, respectively, while -5.2 and 7.6 kJ mol^{-1} for **816**, respectively). The calculated interatomic distance between two sulfur atoms in the TB form of **815** was almost the same as that in dibenzodithiocin **817**. The *ab initio* MO calculations were performed also on the mono-protonated and the di-protonated 1,5-dithiocin **815a**, **816a** and **815b**, **816b**, respectively.



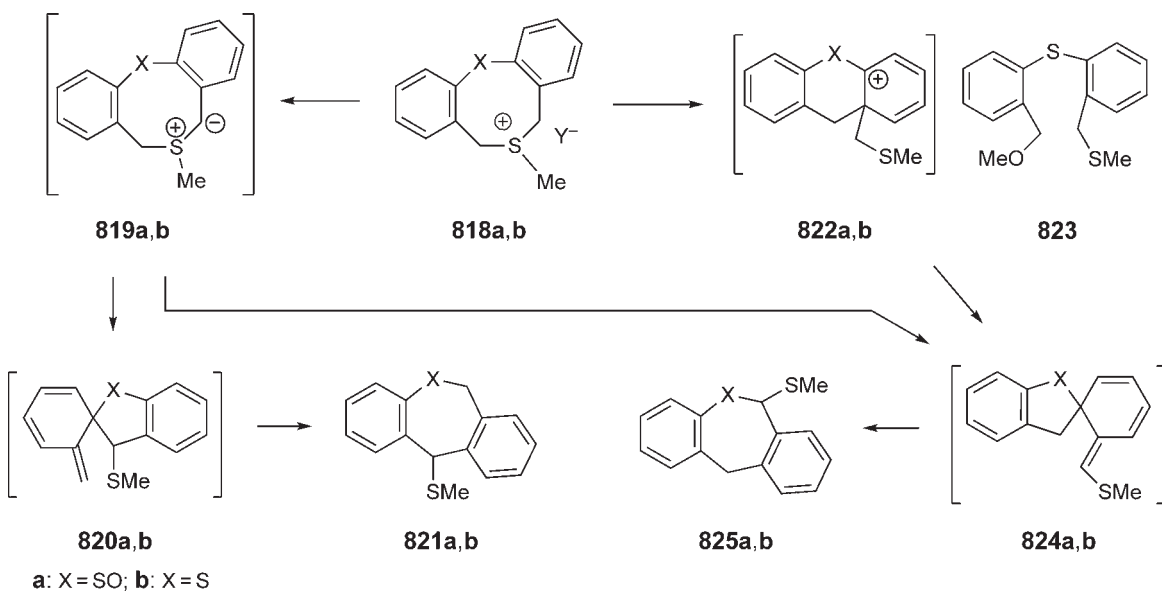
The calculations indicated that the protonation was very important process for the 1,5-oxygen shift and the oxygen atom approaches another sulfur by protonation. The inside oxygen conformation (TB or BB) was important for the intramolecular oxygen shift to form the oxygen-bridged intermediate in **815b**-BB and the outside oxygen conformation (TB or BB) is the most probable conformation to form sulfurane intermediate in **815b**-BB and **816b**-BB, respectively (Scheme 165) <2004H(62)235>.

Reaction of 6-methyl-12-oxo-5*H*,7*H*-dibenzo[*b,g*][1,5]dithiocininium salts **818** with MeOH/KOH afforded a mixture of dibenzothiepins **821**. In order to clarify the mechanism of the rearrangement, *ab initio* MO calculations with HF/6-31G* basis set were performed on the reaction intermediates, the transition states, and related compounds. The rearrangement was explained in terms of the usual [2,3]-sigmatropic shift via spirocyclic intermediate, followed by 1,3-shift of the sulfonyl group. A similar calculation was carried out for the rearrangement of the 1,5-dithiocininium salts **818b**. The formation of **823** and **825b** was understandable by the assumption of a cationic intermediate resulting

from heterolytic cleavage at benzyl position. Moreover, an alternative [2,3]-sigmatropic shift from **819b** into **824b** and direct formation of **824b** via heterolytic cleavage of S-CH₂ bond in **818b** also gave **825b**, as final product (see Section 14.07.7.4) (Scheme 166) <2002J(P1)2704, 2003JPO271>.



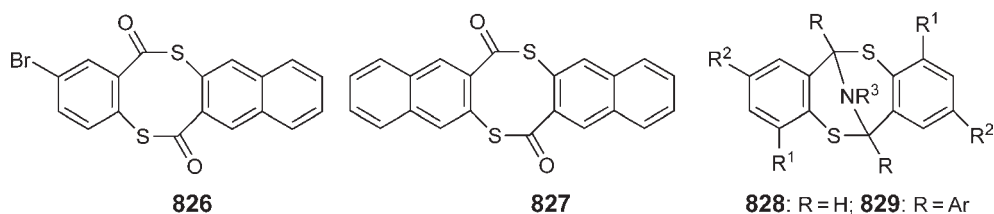
Scheme 165



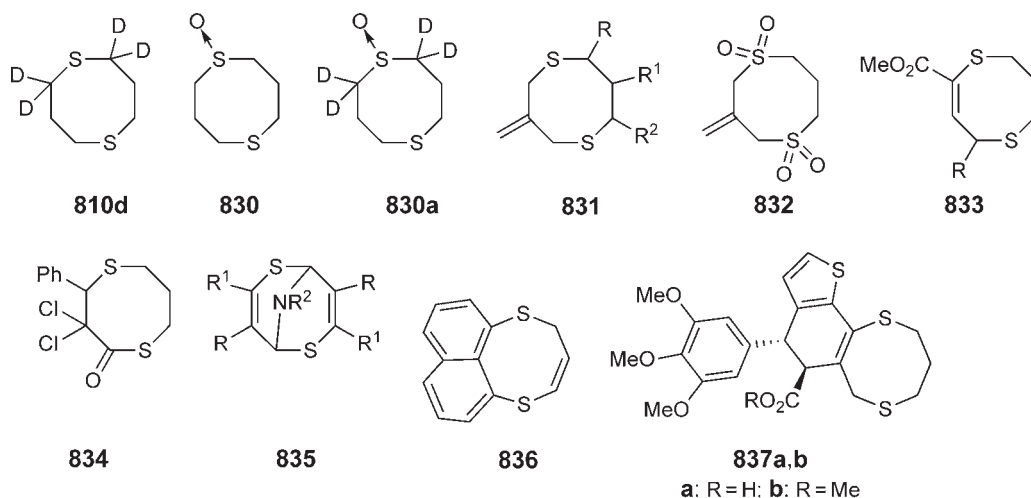
Scheme 166

14.07.7.2 Experimental Structural Methods

X-Ray single-crystal investigations were limited to only very few derivatives. X-Ray crystallography studies performed on 2-bromo-6*H*,12*H*-naphthobenzothio[*b,f*][1,5]dithiocin-6,12-dione **826** and dinaphtho[2,3-*c*:2',3'-*g*][1,5]dithiocin-7,15-dione **827** established that each molecule contained a well-defined V-shaped pocket with dihedral angles between the planes of their aromatic units of 62.2° **826** and 56.6° **827**. Both molecules assemble such that they form self-included dimers held together by offset face-to-face (plane-to-plane distances: 3.48 and 3.60 Å for **826** and 3.62 and 3.67 Å for **827**) and tilted T edge-to-face π - π interactions (ring center-ring center: 5.37 Å). The self-inclusion exhibited by the unsymmetric cleft **826** displayed selectivity, with the naphthyl rather than the bromo, residing within the cleft. Neighboring dimers in both structures interact via offset face-to-face π - π interactions, which rise to infinite supramolecular layered arrays <1997JOC9361>. The structure of *cis*-6,12-diphenyl-6*H*,12*H*-dibenzo[*b,f*][1,5]dithiocin-6,12-imine **828** (a R = Ph, R¹ = R² = R³ = H) was determined by X-ray analysis. The compound **828** crystallized in space group P1, with two independent molecules in the asymmetric unit <1995JHC1683>. X-Ray diffraction studies were also performed on the dibenzo-1,5-dithiocin **829** (a R = R¹ = R² = R³ = H) to corroborate the structure assignment <1995TL6619>.



Nearly all reports dealing with 1,5-dithiocins provided ¹H NMR data. The 1,5-dithiacyclooctane **810** showed, in its ¹H NMR spectrum, the methylene protons next to sulfur at 2.82 ppm; while the other ring methylene protons resonated at 2.06 ppm <1997T7461>. The 2,2,8,8-tetradeuterio-1,5-dithiacyclooctane **810d** exhibited the four methylene protons adjacent to sulfur at 2.63–3.00 ppm, while the other ring protons resonated at 1.87–2.22 ppm. Dithiacyclooctane 1-oxide **830** showed a downfield shift for the CH₂–SO protons (3.12–3.17 ppm) while the CH₂–S and the other CH₂ signals were found at 2.58–2.67 ppm and 2.19–2.31 ppm, respectively. Similar chemical shifts were shown in the ¹H NMR spectrum of 2,2,8,8-tetradeuterio-1,5-dithiacyclooctane 1-oxide **830a** <2006T10724>. 3-Methylene-1,5-dithiocins **831** showed, in their ¹H NMR spectra, methylene protons next to sulfur at 2.70–3.40 ppm, the CH₂ signals resonated at 1.40–2.00 ppm, while the exocyclic methylene protons were found at 4.98–5.20 ppm <1996MM6983, 2000MM6722, 2000MM9553, 2001PSA202>. The ¹H NMR spectrum of the 3-methylene-1,5-dithiocane 1,1,5,5-tetraoxide **832** exhibited a downfield shift for the methylene protons next to the sulfur (3.48–4.13 ppm) and for the =CH₂ protons (5.67 ppm), while the other methylene signals resonated at 2.11 ppm <2006MI1934>. The 1,5-dithiocin **833** (R = C₆H₄-4-NO₂) showed, in its ¹H NMR spectrum, the CH₂–S and the CH₂ protons at 2.16–3.03 ppm, while the CH–S and the vinylic protons appeared at 5.82 and 7.49 ppm, respectively <1998TL7113>. The ¹H NMR spectrum of the 3,3-dichloro-4-phenyl-1,5-dithiocin-2-one **834** showed the CH–S methyne at 4.91 ppm, the CH₂–S protons at 2.61–3.26 ppm, whereas the other methylene protons resonated at 2.01–2.42 ppm <1998S653>. The 2,6-imino-2*H*,6*H*-1,5-dithiocins **835** showed, in their ¹H NMR spectra, the signals of the methyne next to sulfur at 5.00–7.00 ppm <1999S787>. The ¹H NMR spectra of the 1,5-naphthodithiocin **836** besides the signals of the CH₂–S protons at 3.20–3.70 ppm, showed the CH=CH–S proton at 6.05–6.12 ppm and CH=CH–S signal at 6.55–6.60 ppm <1995T12239>. The 1,5-dithiocins **837a** and **837b** showed the CH₂–S and CH₂ protons at 1.90–2.80 ppm, whereas the CH₂–S–C= signals experienced a downfield shift (3.28–4.45 ppm) <2001T3963>. The 6,12-iminodibenzo-1,5-dithiocins **828** (a R¹ = R² = R³ = H; b R² = Me, R¹ = R³ = H; c R² = Me, R¹ = S-*t*-Bu, R³ = H) exhibited in their ¹H NMR spectra the methyne next to sulfur at 5.65–5.74 ppm, while the NH proton resonated at 2.81–4.31 ppm <1995TL6619>. The ¹H NMR spectra of the dibenzo-1,5-dithiocins **828** (d R¹ = H, R² = Me, R³ = CO₂Me and m R¹ = R² = H, R³ = CH(CO₂*t*-Bu)CH₂CH(Me)₂) showed two nonequivalent methyne protons at 6.57, 6.74 ppm and 5.70, 5.78 ppm due to the restricted bond rotation in the N–R³ bond <1999CJC113>. The 6,12-diaryliminodibenzo-1,5-dithiocins **829** (a R¹ = R² = R³ = H, R = Ph; b R¹ = R² = R³ = H, R = C₆H₄-4-OMe; c R¹ = R² = R³ = H, R = C₆H₄-4-CF₃) showed relatively to **828** a downfield shift of the NH proton (4.37–5.25 ppm) <1995JHC1683>.



The ¹³C NMR data were not provided for all the 1,5-dithiins reported. In several cases, the ¹³C signals were not assigned and/or the signal multiplicities were missing. Dithiicin **810** showed, in its ¹³C NMR spectrum, two set of signals at 30.2 and 30.8 ppm attributable to the CH₂ and CH₂-S carbons, respectively <2003MI1224-05>. The 3,3-dichloro-4-phenyl-1,5-dithiocan-2-one **834** exhibited the CH₂ at 29.9 ppm and the CH₂-S signals at 31.6–33.9 ppm; the methyne carbon adjacent to the sulfur, bearing a phenyl group, resonated at 66.7 ppm, while the carbonyl signal could be found at 192.0 ppm <1998S653>. The 3-methylene-1,5-dithiins **831** showed, in their ¹³C NMR spectra, methylene carbons next to sulfur at 34.6–39.7 ppm, the other sp³ carbon atoms appeared at 29.4–30.6 ppm, while the exocyclic methylene carbon was found at 114.9–120.3 ppm <1996MM6983, 2000MM6722, 2000MM9553, 2001PSA202>. The 2,6-imino-2*H*,6*H*-1,5-dithiins **835**, showed in their ¹³C NMR spectra, the methyne carbons at 59.1–66.7 ppm <1999S787>. The 6,12-iminodibenzo-1,5-dithiins **831** (a R¹ = R² = R³ = H; b R¹ = Me, R² = R³ = H; c R¹ = Me, R² = S-*t*-Bu, R³ = H) exhibited in their ¹³C NMR spectra the methyne next to the sulfur at 56.1–57.5 ppm <1995TL6619>. The ¹³C NMR spectra of fused 1,5-dithiins **826** and **827** showed the carbonyl resonance at 194.7–198.3 ppm <1995TL1391, 1997JOC9361>.

No studies on fragmentation patterns of 1,5-dithiins have been reported in the past decade. In some cases, only the molecular or quasi-molecular ions of their EI spectra <1997JOC9361, 1998S653, 2001PSA202, 2003MI1224-05> or CI spectra were provided <1995JHC1683, 1996MM6983, 2000MM6722>.

The 3,3-dichloro-4-phenyl-1,5-dithiocan-2-one **834** showed, in its IR spectrum, the carbonyl stretching at 1716 cm⁻¹ <1998S653>. The 6,12-diaryliminedibenzo-1,5-dithiins **829** (a R¹ = R² = R³ = H, Ar = Ph; b R¹ = R² = R³ = H, Ar = C₆H₄-4-OMe; c R¹ = R² = R³ = H, Ar = C₆H₄-4-CF₃) exhibited the imine moiety at 3336 cm⁻¹ <1995JHC1683>. The IR spectrum of the 3-methylene-1,5-dithiocane 1,1,5,5-tetroxide **832** showed the SO₂ stretching at 1288–1119 cm⁻¹ <2006MI1934>. The 3-methylene-1,5-dithiins **831** (R = R² = H, R¹ = OH) showed in their IR spectra the OH stretchings at 3248 cm⁻¹. <2000MM6722>.

14.07.7.3 Thermodynamic Aspects

Uncondensed 1,5-dithiins were generally oils <1996MM6983, 2000MM9553, 2001PSA202, 2003MI1224-05> or characterized by low melting points (54–64 °C) <2000MM6722, 2006T10724>, whereas 3,3-dichloro-4-phenyl-1,5-dithiocan-2-one **834** and 2,6-imino-2*H*,6*H*-1,5-dithiins **835** melted at 89–90 and 122–249 °C, respectively <1998S653, 1999S787>.

Annulation of naphtho or two benzene units to the eight-membered ring originated compounds melting in the range 110–324 °C <1995JHC1683, 1995T12239, 1995TL1391, 1997JOC9361, 1999CJC113> with the exception of dibenzo-1,5-dithiins **828c** (R³ = H, R¹ = Me, R² = S-*t*-Bu) and **828h** (R¹ = R² = H, R³ = Ph), which melted at 44–70 °C, while the 1,5-dithiicin **828j** (R¹ = H, R² = Me, R³ = CH₂CH(Me)₂) was an oil <1995TL6619, 1999CJC113>.

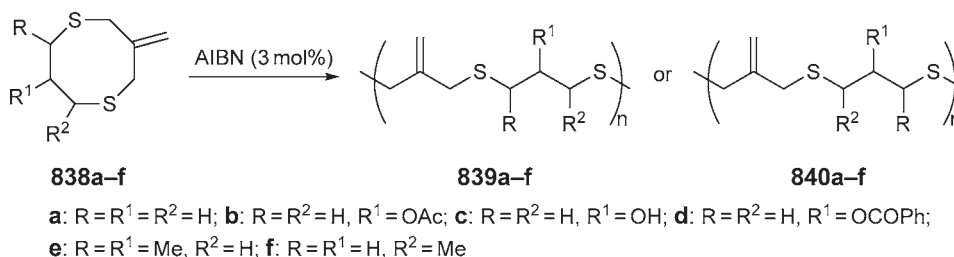
Soluble in most common solvents, dithiins were purified by recrystallization from EtOH or MeOH <1995JHC1683, 1999S787, 1999CJC113>, DCM/hexane <1995JHC1683, 1995TL6619, 1997JOC9361, 1999CJC113>, MeCN <1999S787>, EtOH/hexane, EtOH/CHCl₃, or CHCl₃/hexane <1997JOC9361>. Some 1,5-dithiins were also purified by chromatography on silica gel using as eluant CCl₄ <1995T12239>, DCM/hexane

<1999CJC113>, EtOAc/hexane or EtOAc <1995JHC1683, 1997JOC9361, 1998S653, 1999CJC113, 2003MI1224-05, 2006T10724>, Et₂O/hexane <2000MM6722>, and EtOAc/MeOH <2006T10724>.

14.07.7.4 Reactivity of Nonconjugated Rings

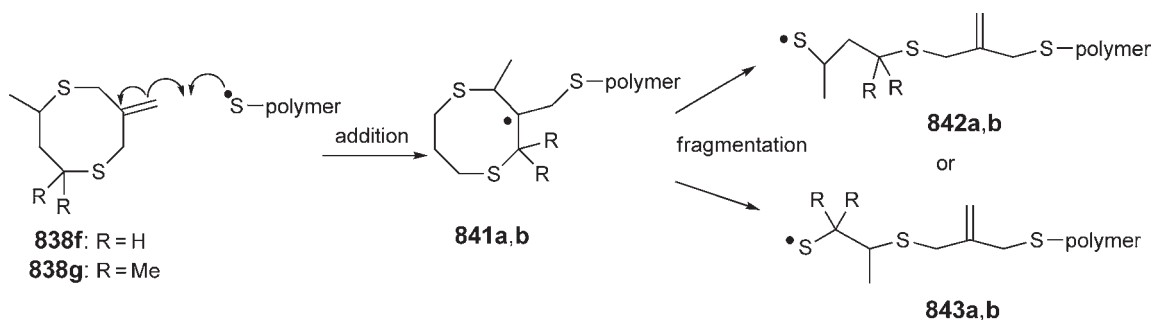
Treatment of 6-methyl-12-oxo-5*H*,7*H*-dibenzo[*b,g*][1,5]dithiocinium salt **819a** with MeOH/KOH at 25 °C afforded a mixture of dibenzothiepin derivative **821a** in 66% yield. However, 6-methyl-5*H*,7*H*-dibenzo[*b,g*][1,5]dithiocinium salt **822b** under the same reaction conditions unexpectedly gave dibenzothiepin derivative **825b** in 29% yield along with a small amount of a ring-opening product **823** in 5% yield (see Section 14.07.7.1) <2002J(P1)2704>.

The 1,5-dithiocins **838a–f** polymerized in bulk using thermal azoisobutyronitrile (AIBN) and photochemical initiators in benzene solution (60–70 °C) to give lightly cross-linked materials such as **839a–f** and **840a–f** (Scheme 167) <1996WO19471, 1996MM6983, 2000MM6722, 2001PSA202, 2006MI1934>.



Scheme 167

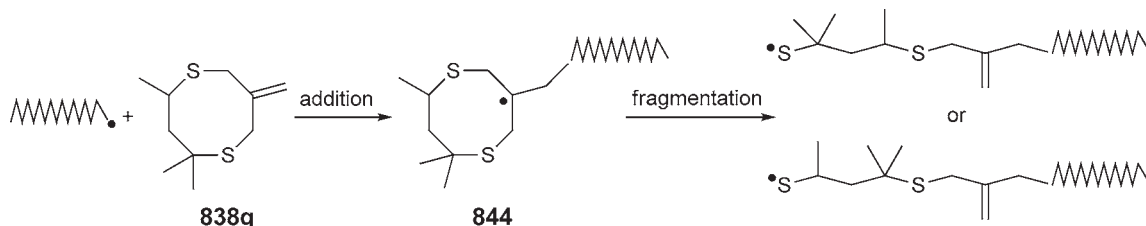
Polymerization of the dithiocins **838f,g** proceeded, in benzene at 40–70 °C, with complete ring opening. A two-step mechanism was involved: in the first step, addition of sulfanyl radical onto monomer exocyclic double bond formed the intermediate carbon-centered radicals **841**, which do not propagate; in the second step, a rapid fragmentation of **841** yielded new propagating sulfanyl radicals **842** and **843** and polymer backbone double bonds (Scheme 168) <2005MM2143>.



Scheme 168

A similar mechanism was proposed when 1,5-dithiocin **838g** underwent polymerizations with methyl methacrylate (MMA) and styrene (STY). The activated double bond of **838g** was found to have a profound affect on reactivity. In fact, co-polymerization of **838g** with MMA at 70 °C the 5-terminated sulfanyl radicals preferred to undergo homo-propagation, while cross-propagation is favored for MMA-terminated radicals. Both monomers possessed an electron-deficient acrylate double bond with similar possibilities for conjugative stabilization of the adduct radical by the ester functionality, which would explain the apparent equal reactivity of the MMA radical to either monomer.

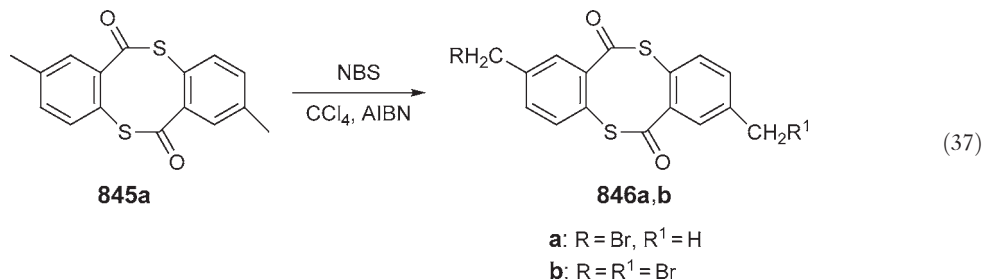
In co-polymerization of **838g** with STY at 80°C, the cross-propagation is favored, consistent with electrophilic sulfanyl radicals adding rapidly to electron-rich STY, and nucleophilic styryl radicals adding rapidly to electron-deficient acrylate double bond (**Scheme 169**) <2006MI2475>.



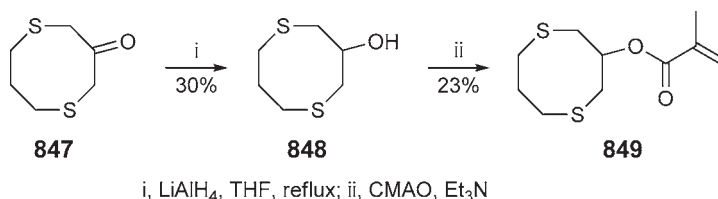
Scheme 169

14.07.7.5 Reactivity of Substituent Attached to Ring Carbon Atoms

Treatment of 2,8-dimethyldibenzo-1,5-dithiocin **845a** with NBS in CCl₄ yielded a mixture of monobrominated **846a** and dibrominated **846b** analogues in 30% and 27% yields, respectively (**Equation 37**) <1997JOC9361>. *N*-(Methoxycarbonyl)-2,8-dimethyl-6,12-imino-6*H*,12*H*-dibenzo[*b,f*]-1,5-dithiocin **828d** was obtained by refluxing the 1,5-dithiocin **828b** in chloroformate, using K₂CO₃ or Cs₂CO₃ as base, in 89% yield <1999CJC113>. Reaction of 1,5-dithiocin **837a** with CH₂N₂ afforded the (±)methyl (7*S*,8*R*)-8-(3,4,5-trimethoxyphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-1,5-dithiocyclooctan[2,3-*g*]benzothiophene-7-carboxylate **837b** <2001T3963>. The 7-methylene-1,5-dithia-cyclooctan-3-yl acetate **838b** was prepared from the alcohol **838c** and acetyl chloride (51% yield) <2000MM6722, 2006WO122074>. Analogously, the 7-methylene-1,5-dithiacyclooctan-3-yl benzoate was obtained by reaction of **838c** with benzoyl chloride (53% yield) <2000MM6722>. When **838c** was reacted with 2,4,4-trimethyl-1,6-diido-cyanohexane, the 1,6-bis(7-methyl-1,5-dithiacyclooctan-3-yl)2,4,4-trimethylhexane dicarbamate in THF under reflux was obtained in 96% yield <2006WO122074>. Treatment of dithiocin **838c** with mono-2-methacryloyloxyethyl phthalate in DCC and DMAP furnished the 1-(2-methacryloyloxyethyl)-2-(7-methylene-1,5-dithiaoctan-3-yl) phthalate in 84% yield. Analogously, **838c** by treatment of mono-2-methacryloyloxyethyl succinate yielded the corresponding 1-(2-methacryloyloxyethyl)-2-(7-methylene-1,5-dithiaoctan-3-yl) succinate <2006WO122081>.



Reduction of the 1,5-dithiocin **847** with LiAlH₄ gave the 1,5-dithiacyclooctan-7-ol **848** (30%). Condensation of alcohol **848** with methacryloyl chloride (CMAO) in presence of NEt₃ afforded the 1,5-dithiocin **849** in low yield (**Scheme 170**) <1998WO35955>.

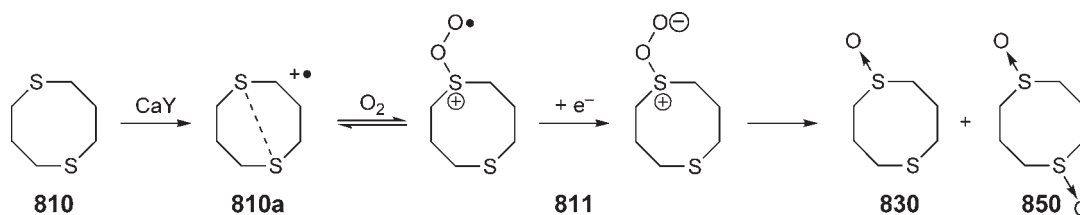


Scheme 170

14.07.7.6 Reactivity of Substituent Attached to Ring Heteroatoms

Treatment of 1,5-dithiacyclooctane **810** with NaIO_4 in MeOH at 25°C for 24 h furnished the corresponding 1-oxide **833** in 76% yield. Reaction of **833** with NaOD in D_2O at 100°C afforded the tetradeuterio-1,5-dithiacyclooctane 1-oxide **833a**, which reduced with NaI in HClO_4 and subsequently treated with $\text{Na}_2\text{S}_2\text{O}_3$ to give the tetradeuterio-1,5-dithiacyclooctane **810d** (74%). An intramolecular isotope effect has been measured for the reaction of singlet oxygen with **810a**. The magnitude of the isotope effect provides verification of removal of an α -hydrogen during the product determining step to form a hydroperoxysulfonium ylide and ultimately the sulfoxide product <2006T10724>.

Addition of 1,5-dithiacyclooctane **810** to zeolite CaY resulted in electron-transfer formation of the corresponding radical cation **810a**, which undergoes a reaction with molecular oxygen to give mono- and bis-sulfoxide products **830** and **850** in 7% and 90% yields, respectively (Scheme 171) <1999CC2261>. Oxidation of 1,5-dithiocin **838a** ($\text{R}=\text{R}^1=\text{R}^2=\text{H}$) with H_2O_2 gave the 3-methylene-1,5-dithiocane 1,1,5,5-tetraoxide **832** in 62% yield <2006MI1934>.

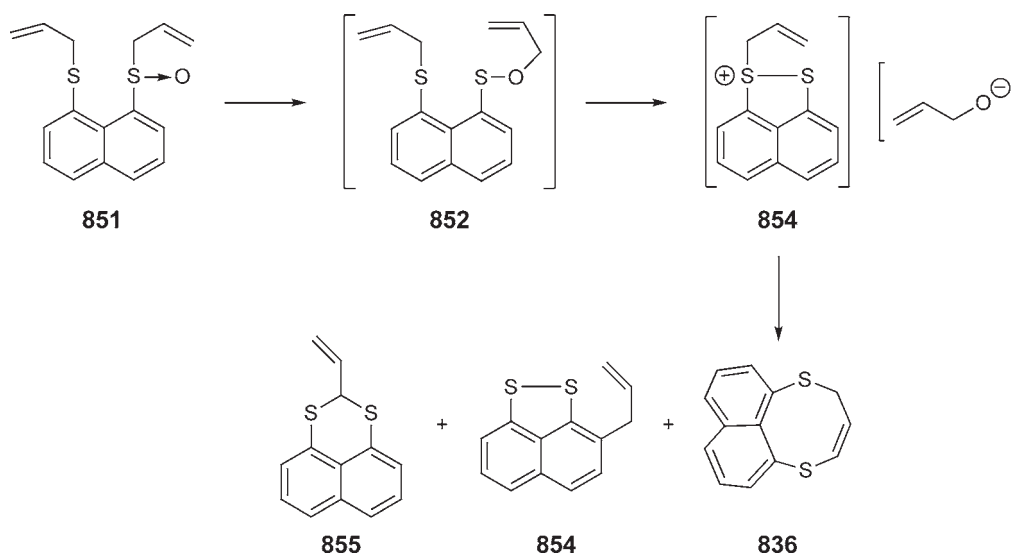


Scheme 171

14.07.7.7 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

14.07.7.7.1 Ring syntheses from C_6S_2 units

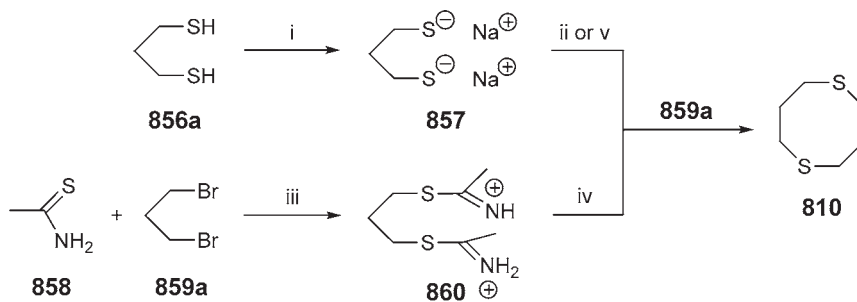
Thermolysis of the monosulfoxide **851** by heating in CCl_4 at 80°C for 2 h gave a mixture of three products **836**, **854**, and **855** in 26%, 23%, and 30% yields, respectively. The reaction proceeded initially via [2,3]sigmatropic allylic rearrangement of sulfoxide **851** to sulfenate **852**, which underwent facile intramolecular substitution by the remote sulfenyl sulfur atom at the 8-position of naphthalene ring to give thiasulfonium salt **853** and allyl alcoholate anion. From this salt **853**, finally naphtho-1,5-dithiocin **836** along with **854** and **855** were formed (Scheme 172) <1995T12239>.



Scheme 172

14.07.7.7.2 Ring syntheses from $C_3S_2 + C_3$ units

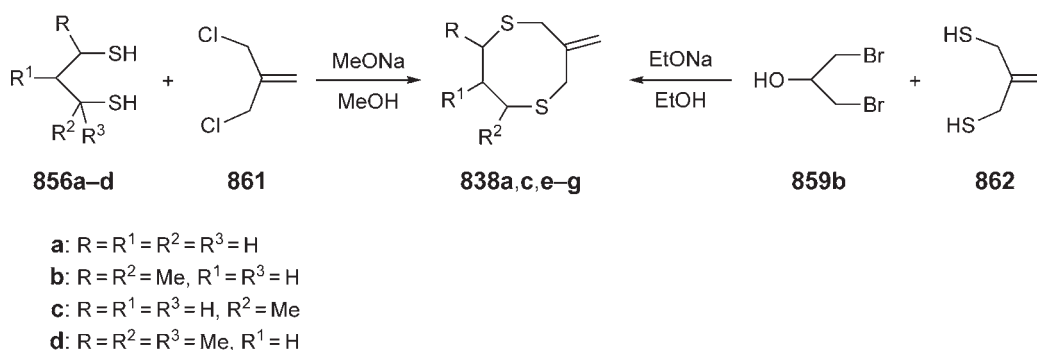
The 1,5-dithiocin **810** was obtained from the reaction of sodium salt of 1,3-propanedithiol **857** and 1,3-dibromopropane **859a** (26% yield) <2006T10724>. However, the reaction of dibromopropane **859a** with twofold excess of thioacetamide **858** afforded 1,1'-(dithiopropyl)diethaniminium salt **860**, which was treated with dibromopropane **859a** in a two-phase system consisting of benzene and an aqueous solution of NaOH in the presence of TBAB as a phase-transfer catalyst to give 1,5-dithiocin **810** in 37% yield <2003MI1224-05>. Treatment of 1,3-propanedithiol **856a** with the dibromopropane **859a** in presence of the ionic liquid 1-pentyl-3-methylimidazolium bromide ([pmIm]Br) at 60 °C for 7 min gave the 1,5-dithiocin **810** in 80% yield (Scheme 173) <2005MI1224-05>.



i, Na, EtOH; ii, EtOH, 50 °C; iii, $CHCl_3$ 70–80 °C for 2 h; iv, TBAB, benzene– H_2O , NaOH, 60–65 °C, 6 h; v, [pmIm]Br, 60 °C, 7 h

Scheme 173

Reaction of 2-(chloromethyl)-3-chloro-1-propene **861** and the 1,3-propanedithiols **856a–d** using MeONa in MeOH yielded the corresponding 3-methyl-7-methylene-1,5-dithiocins **838a,e–g** (39–58% yield) (Scheme 174) <1996MM6983, 2001PSA202>. The 7-methylene-1,5-dithiacyclooctan-3-ol **838c** was synthesized by reaction of 3-mercapto-2-(mercaptomethyl)-1-propene **862** with the 1,3-dibromo-2-propanol **859b** in presence of EtONa in EtOH, in 50% yield (Scheme 174) <2000MM6722>.

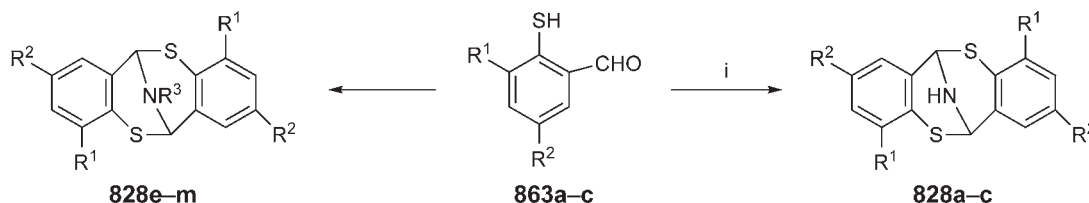


Scheme 174

14.07.7.7.3 Ring syntheses from $C_3S + C_3S$ units

Treatment of the thiosalicylaldehydes **863a–c** with NH_4OAc in refluxing $MeNO_2$ gave the 6,12-imino-6*H*,12*H*-dibenzo[*b,f*]-1,5-dithiocins **828a–c** in excellent yields (71–99%) (Scheme 175) <1995TL6619>. When the same reaction was conducted in refluxing EtOH, **828a–c** were obtained in 89–91% yield <1999CJC113>. By modifying

the reaction of **863a** or **863b** and replacing the NH_4OAc with a mixture of primary amine and AcOH (1:4), a series of *N*-alkyl 1,5-dithiocin analogues **828e–j** were isolated in excellent yields (83–91%). The 1,5-dithiocins **828k–m** were prepared by reaction of **863a** with α -amino acids (L-leucine, L-phenylalanine) or their methyl esters (L-leucine methyl ester and L-leucine *t*-butyl ester) in refluxing EtOH (68–88%). However, the formation of the *N*-substituted 1,5-dithiocins **828k–m** was accompanied by loss of the carboxylate moiety. The naphtho-fused 1,5-dithiocins **864**, **865**, and **866** were synthesized under the same reaction conditions from the corresponding aldehydes **867**, **868**, and **869**, respectively (92–96%) (Scheme 175) <1999CJC113>.

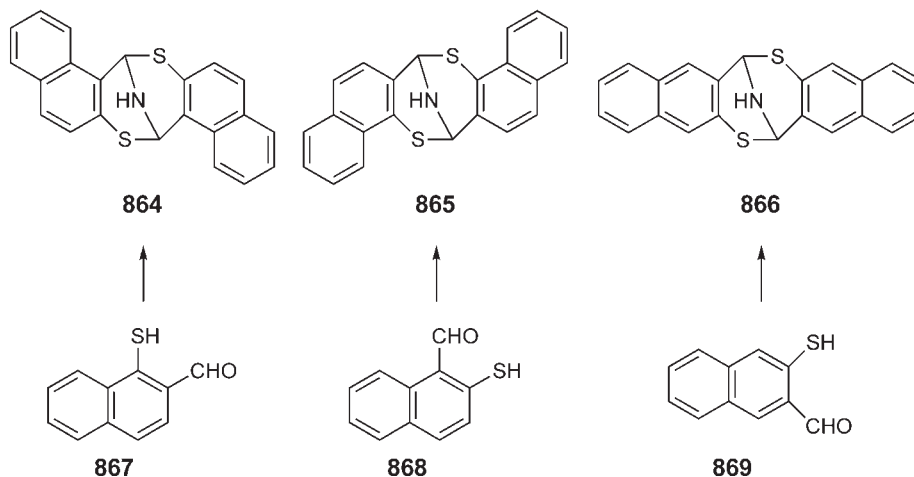


863: **a**: $\text{R}^1 = \text{R}^2 = \text{H}$; **b**: $\text{R}^2 = \text{Me}$, $\text{R}^1 = \text{H}$; **c**: $\text{R}^2 = \text{Me}$, $\text{R}^1 = \text{S-}t\text{-Bu}$

828: **a**: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$; **b**: $\text{R}^2 = \text{Me}$, $\text{R}^1 = \text{R}^3 = \text{H}$; **c**: $\text{R}^2 = \text{Me}$, $\text{R}^1 = \text{S-}t\text{-Bu}$, $\text{R}^3 = \text{H}$; **e**: $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{CH}_2\text{CH}_2\text{Ph}$
f: $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{CH}_2\text{CH}(\text{Me})_2$; **g**: $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = i\text{-Pr}$; **h**: $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$; **i**: $\text{R}^2 = \text{Me}$, $\text{R}^1 = \text{H}$,
 $\text{R}^3 = \text{CH}_2\text{CH}_2\text{Ph}$;

j: $\text{R}^2 = \text{Me}$, $\text{R}^1 = \text{H}$, $\text{R}^3 = \text{CH}_2\text{CH}(\text{Me})_2$; **k**: $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{CH}_2\text{CH}_2\text{CH}(\text{Me})_2$; **l**: $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{CH}_2\text{CH}_2\text{OH}$; **m**:
 $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{CH}(\text{CO}_2\text{-}t\text{Bu})\text{CH}_2\text{CH}(\text{Me})_2$

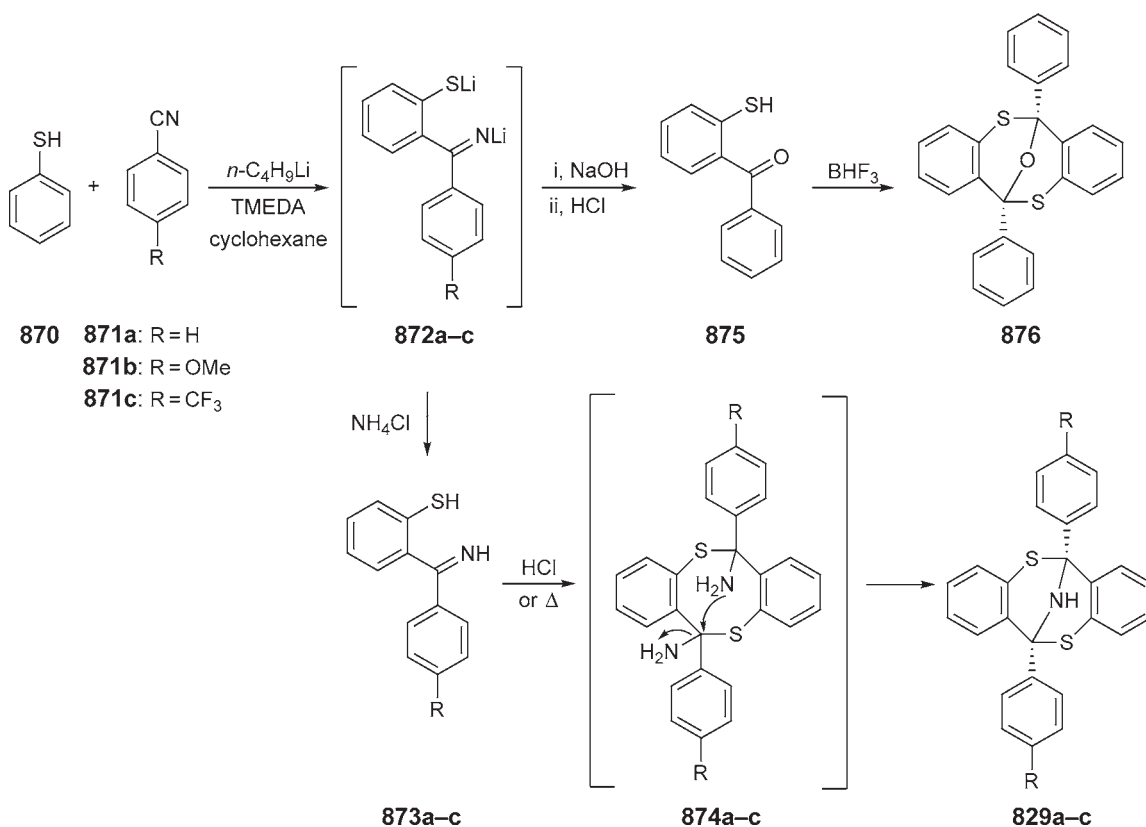
i, NH_4OAc (1.1 equiv) MeNO_2 , reflux, 5 h



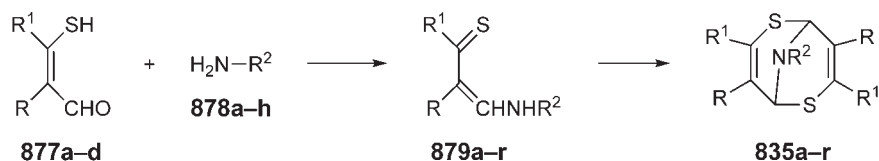
Scheme 175

Treatment of dilithio salt of thiophenol **870** with benzonitriles **871a–c** gave the intermediates **872a–c**, which were converted in presence of NH_4Cl into the corresponding thioimine **873a–c**. Such intermediates revealed to be capable of undergoing a bimolecular reaction with themselves under either strong acid conditions or thermally to give 1,5-dibenzodithiocins **829a–c** (33–80%). When the intermediate **872a** was treated first with NaOH and subsequently with HCl , the thiobenzophenone **875** was isolated in 81% yield. Reaction of the latter with boron trifluoride yielded the oxygen bridged 1,5-dithiocin **876** (27%) (Scheme 176) <1995JHC1683>.

The substituted secondary β -enaminothioketones **879a–r**, obtained from the reaction of β -mercaptovinylaldehydes **877a–d** with primary amines **878a–h**, were reacted in AcOH to give the 2,6-imino-2*H*,6*H*-1,5-dithiocins **835a–r** (32–93%) (Scheme 177) <1999S787>. The 1,5-dithiacyclooctan-3-one **845** was synthesized from 1,3-propanedithiol **856a** and 1,3-dichloropropen-2-one in the presence of MeONa in Et_2O in 31% yield <1998WO35955>.



Scheme 176



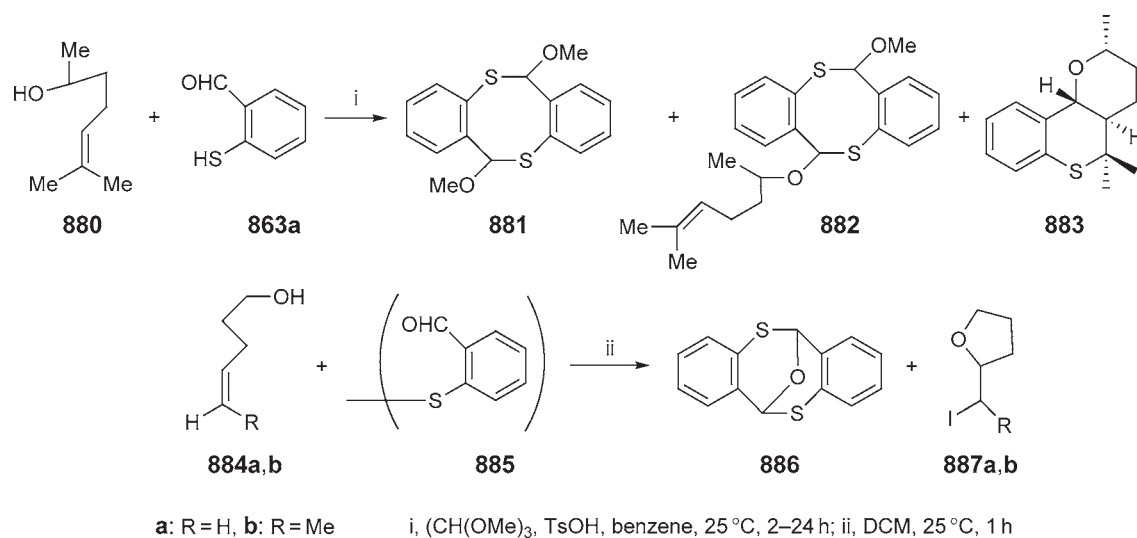
877: **a:** R = Me, R¹ = Ph; **b:** R = Ph, R¹ = CF₃; **c:** R = C₆H₄-4-Cl, R¹ = CF₃; **d:** R = R¹ = Ph

878: **a:** R² = Ph; **b:** R² = C₆H₄-4-OMe; **c:** R² = CH₂CF₃; **d:** R² = Et; **e:** R² = CH₂CO₂Et; **f:** CH(Me)CO₂Et

879 and **835:** **a:** R = Me, R¹ = R² = Ph; **b:** R = Me, R¹ = Ph, R² = C₆H₄-4-OMe; **c:** R = Me, R¹ = Ph, R² = CF₃
d: R = Ph, R¹ = CF₃, R² = C₆H₄-4-OMe; **e:** R = C₆H₄-4-Cl, R¹ = CF₃, R² = C₆H₄-4-OMe; **f:** R = R¹ = Ph, R² = Et
g: R = R¹ = Ph, R² = CH₂CF₃; **h:** R = R¹ = Ph, R² = CH₂CO₂Et; **i:** R = R¹ = Ph, R² = CH(Me)CO₂Et; **k:** R = R¹ = Ph, R² = CH₂(Bn)CO₂Et; **l:** R = R¹ = R² = Ph; **m:** R = R¹ = Ph, R² = C₆H₄-4-Me; **n:** R = R¹ = Ph, R² = C₆H₄-4-Cl;
o: R = R¹ = Ph, R² = C₆H₄-4-NMe₂; **p:** R = R¹ = Ph, R² = C₆H₄-4-NO₂; **q:** R = R¹ = Ph, R² = C₆H₄-4-OMe;
r: R = R¹ = Ph, R² = 6-pyridyl-(2-Me)

Scheme 177

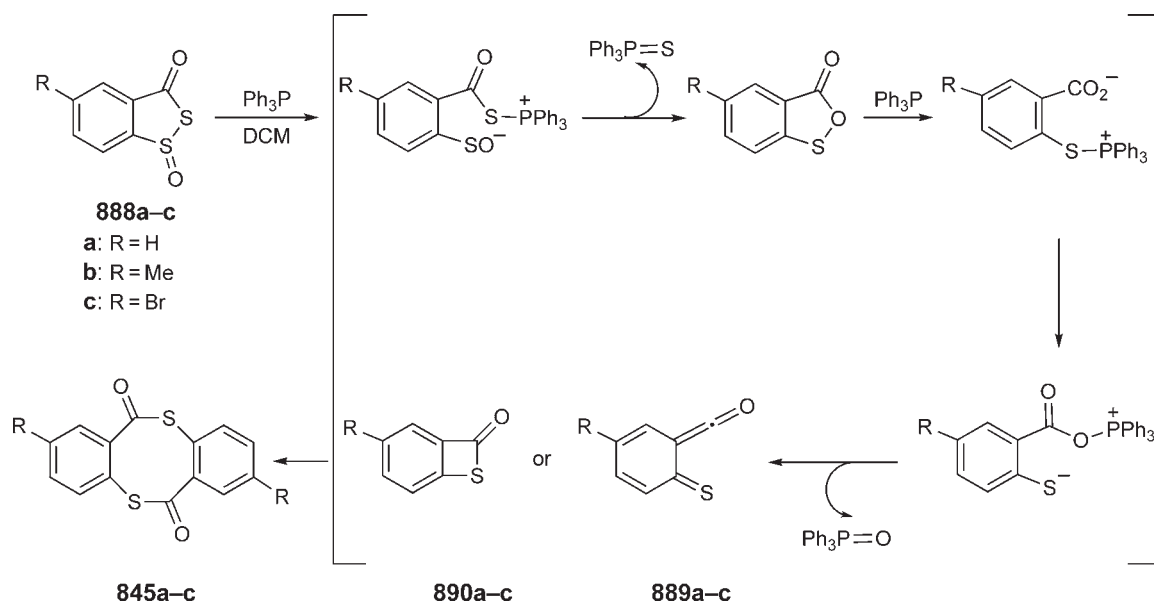
Treatment of *o*-mercaptobenzaldehyde **863a** with the alkenol **880** under Inoue's protocol conditions afforded the dibenzo-1,5-dithiacyclopentanes **881** and **882**, as major products, with a trace amount of fused pyranobenzothiopyran **883**. Reaction of 4-penten-1-ol **884a** or hex-4-en-1-ol **884b** with disulfide **885** gave the 1,5-dithiacyclopentane **886** together the corresponding iodocyclization products **887a,b** (Scheme 178) <2003TL6513>.



Scheme 178

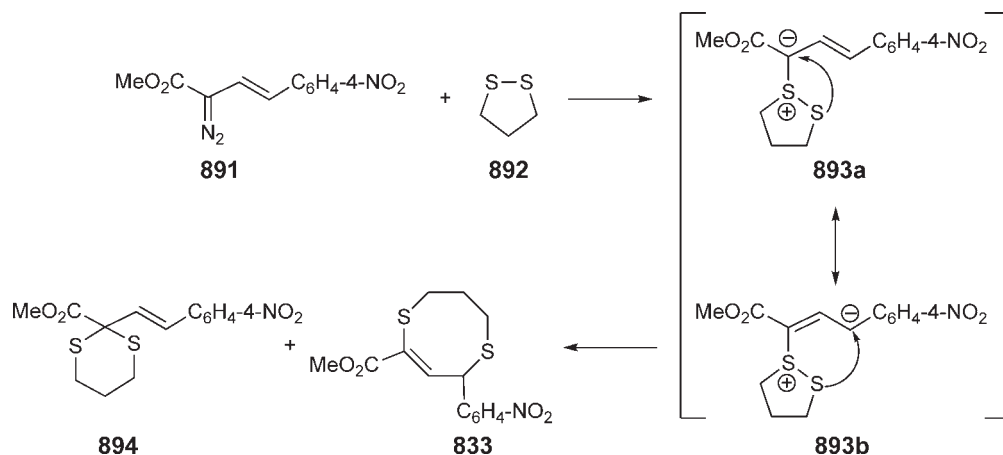
14.07.7.8 Ring Syntheses by Transformation of Another Ring

Treatment of 3*H*-1,2-benzodithiol-3-ones with PPh₃ (1 equiv) in DCM at 25 °C afforded the corresponding dibenzo-1,5-dithiins **845a** in good yields (62%). Also 3*H*-1,2-benzodithiol-3-ones 1-oxide **888a–c** rapidly reacted with 2 equiv of PPh₃ to give **845a–c** in 72–74% yield. The reaction of **888** with PPh₃ is complete within 15 min, whereas under identical conditions, the reaction of benzodithiol-3-one remained incomplete even after 7 d. A reasonable mechanism presumably went through dimerization of the ketenes **889a–c** or benzothietan-2-ones **890a–c** intermediates (Scheme 179) <1995TL1391, 1997JOC9361>. Analogously, the dinaphtho[2,3-*c*:2',3'-*g*][1,5]dithiocin-7,15-dione **827** was obtained from 3*H*-1,2-naphthodithiolan-3-one under the same reaction conditions in 48% yield. Reaction of a 1:1 mixture of 3*H*-1,2-naphthodithiolan-3-one and **888c** with Ph₃P (2 equiv) in DCM at 25 °C yielded the asymmetrical naphthobenzo-1,5-dithiocin **826** (22%) together the 1,5-dithiins **846c** and **827** (33% and 30%, respectively) <1997JOC9361>.



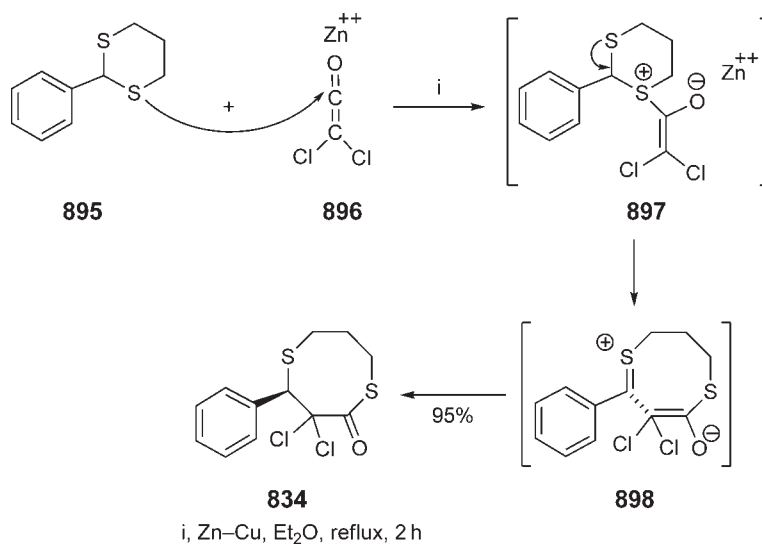
Scheme 179

Reaction of methyl 2-diazo-4-nitrophenyl-3-butenate **891** with 1,2-dithiapentane **892** in the presence of $\text{Rh}_2(\text{OAc})_4$ afforded the 1,5-dithiocin **833** (27%) together with the derivative **894** (44%). The intermediate sulfonium ylide **893**, which had a resonance contribution of formula **893a** and **893b** could give the 1,1-insertion adduct **894** through a 1,2-migration of thio group to the ylide carbon, or forming a 1,3-insertion adduct **833** from a 1,4-migration (Scheme 180) <1998TL7113>.



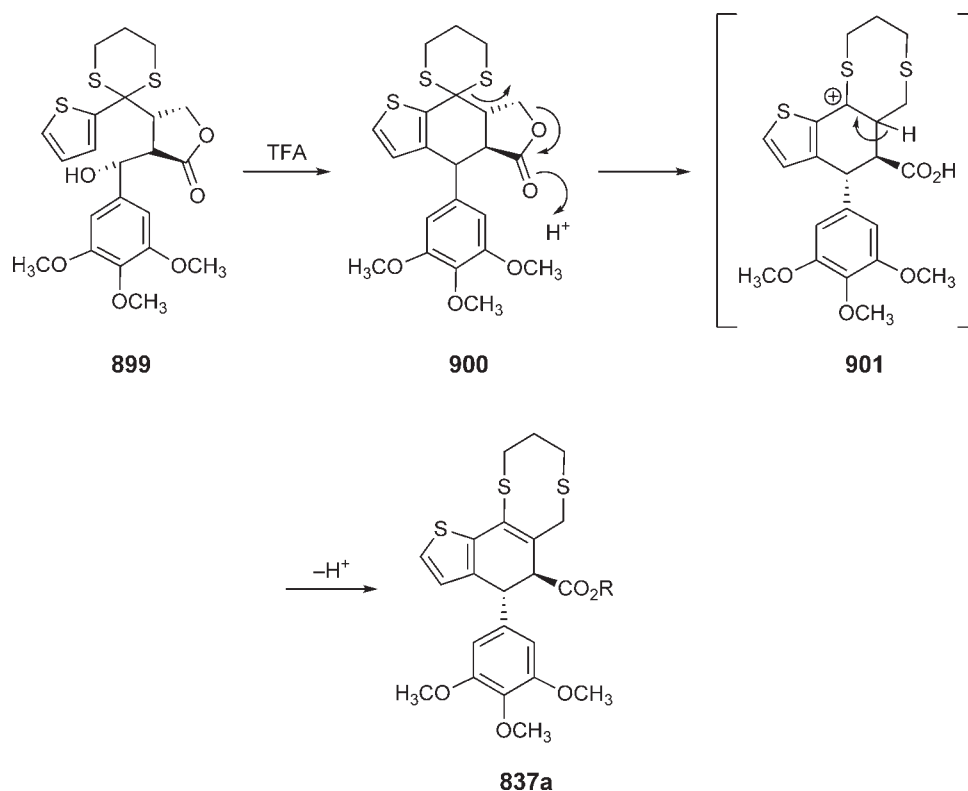
Scheme 180

The dichloroketene **896**, generated *in situ* by reduction of Cl_3CCOCl with Zn–Cu couple, was reacted with the 2-phenyl-1,3-dithiane **895** to give the 3,3-dichloro-4-phenyl-1,5-dithiocan-2-one **834** in nearly quantitative yield (95%). The mechanism of formation of the eight-membered ring involved the nucleophilic attack of sulfur on the ketene **896**, which is activated by ZnCl_2 . The resulting zwitterion **897** underwent C,S-bond cleavage and rearranged under C,C-bond formation via transition state **898** to afford the 1,5-dithiocin **834** (Scheme 181) <1998S653>.



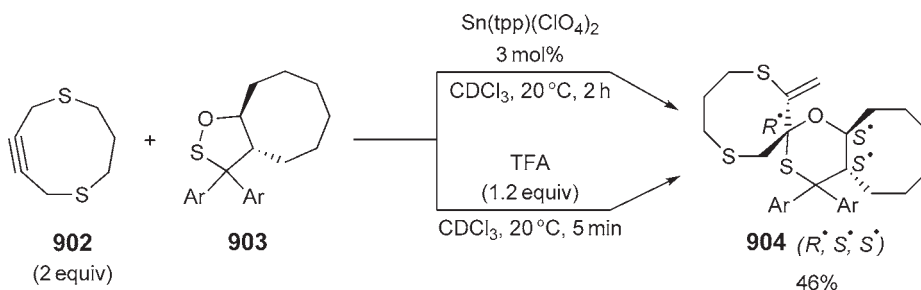
Scheme 181

Treatment hydroxylactone **899** with TFA yielded the cyclized product **900** (69%) and the eight-membered ring **837a** in moderate yield (18%). The mechanism for such transformation can be explained by considering that the lactone moiety was a potential leaving group that generated the unstable intermediate cation **901**, which was transformed into the 1,5-dithiocin **837a** (Scheme 182) <2001T3963>.



Scheme 182

The eight-membered ring **904** was obtained in 46% yield from the reaction of dithiacyclononyne **902** and sultene **903** with 3 mol% of Lewis acid, while using TFA. The sultene **903** was fully converted within 5 min into the corresponding 1,5-dithiocin **904** (Scheme 183) <2002JA8316>.



Scheme 183

14.07.7.9 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

This class of 1,5-diheterocines is the only one which is inconvenient to synthesize by a unimolecular cyclization. In fact, the only example of unimolecular cyclization leading to dithiocins reported low yields and the eight-membered ring was isolated along with other products. The cyclodimerization of substituted thiosalicylaldehydes leading to imino-bridged dibenzodithiocins is by far the most convenient synthetic approach both from yield and functionalization points of view. Another synthesis that allows the preparation of a wide range of substituted imino-bridged dithiocins involves the reaction of mercaptovinylaldehydes and primary amines and successive cyclization of the

β -enaminothioketones. In this case the yields were variable, from moderate to excellent. The only synthesis of 1,5-dithiocins by transformation of another ring worth mentioning is the nearly quantitative ring enlargement of a 1,3-dithiane upon reaction with dichloroketene.

14.07.7.10 Important Compounds and Applications

The 2*H*,6*H*-[1,5]-dithiocino[3,2-*b*]pyridines are useful as calcium-channel antagonist with cardiovascular, antiasthmatic, and antibroncho-constriction activity. Such derivatives showed the nitrendipine binding values at IC₅₀ in the range 40–1337 nM <2001WO92267>. The methylene-1,5-dithiocins are polymerizable compounds that are typically used for optical and ophthalmologic applications <1996WO19471, 1998WO35955, 2006WO122081>. The 1,5-dithiocins are widely used as toning agents for the silver halide photographic films <1998WO02779, 1999USP5922527, 2004USP0224267, 2005USP0106513>. 10*H*,12*H*-Dibenzo[*c,f*][1,5]dithiocin, also called Chalcogenide, was used as catalyst in the Chalcogeno–Baylis–Hillman reaction. The reaction was applied to activated cyclohex-2-en-1-one which reacted with *p*-nitrobenzaldehyde in the presence of TiCl₄ to give the corresponding coupling product in good yield (78%) <1998CC197, 1998T11813>.

References

- 1995AJC199 S. H. Goh, G. C. L. Ee, C. H. Chuah, and C. Wei, *Aust. J. Chem.*, 1995, **48**, 199.
 1995AXC1158 I. Wolska and T. Borowiak, *Acta Crystallogr., Sect. C*, 1995, **51**, 1158.
 1995AXC2716 I. Wolska and T. Borowiak, *Acta Crystallogr., Sect. C*, 1995, **51**, 2716.
 1995BCJ3121 N. Itoh, H. Matsuyama, M. Yoshida, N. Kamigata, and M. Iyoda, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 3121.
 1995CC797 W. Heilmayer, T. S. Dalvi, C. O. Kappe, C. Wentrup, K. Gruber, H. Sterk, and G. Kollenz, *J. Chem. Soc., Chem. Commun.*, 1995, 797.
 1995CC1077 M. J. Crossley, T. W. Hambley, L. G. Mackay, A. C. Try, and R. Walton, *J. Chem. Soc., Chem. Commun.*, 1995, 1077.
 1995CC1463 O. Meth-Cohn and D. L. Taylor, *J. Chem. Soc., Chem. Commun.*, 1995, 1463.
 1995CC1925 M. J. Crossley, L. G. Mackay, and A. C. Try, *J. Chem. Soc., Chem. Commun.*, 1995, 1925.
 1995EPH319 M. K. Pugsley, D. A. Saint, E. Hayes, K. D. Berlin, and M. J. A. Walker, *Eur. J. Pharm.*, 1995, **294**, 319 (*Chem. Abstr.*, 1996, **124**, 106023).
 1995EPP0665014 U. Schön, R. Brücker, J. Meil, and D. Thormählen, *Eur. Pat.* 0 665 014 (1995) (*Chem. Abstr.*, 1995, **123**, 188602).
 1995EPP0665228 U. Schön, A. Farjam, R. Brückner, and D. Ziegler, *Eur. Pat.* 0 665 228 (1995) (*Chem. Abstr.*, 1995, **123**, 188601).
 1995H(41)1709 T. Okawara, S. Ehara, A. Takenaka, T. Hiwatashi, and M. Furukawa, *Heterocycles*, 1995, **41**, 1709.
 1995HAC145 K. Ohkata, K. Okada, and K. Akiba, *Heteroatom Chem.*, 1995, **6**, 145.
 1995HCA1525 N. Seebach, T. Hoffmann, F. N. M. Kühnle, J. N. Kinkel, and M. Schulte, *Helv. Chim. Acta*, 1995, **78**, 1525.
 1995JHC835 O. Migliara, L. Lamartina, M. Timonieri, and S. Plescia, *J. Heterocycl. Chem.*, 1995, **32**, 835.
 1995JHC1589 O. Migliara, L. Lamartina, and R. Raineri, *J. Heterocycl. Chem.*, 1995, **32**, 1589.
 1995JHC1683 L. E. Bricaddy and K. H. Donaldson, *J. Heterocycl. Chem.*, 1995, **32**, 1683.
 1995JME2946 P. Herold, J. W. Herzig, P. Wenk, T. Leutert, P. Zbinden, W. Fuhrer, S. Stutz, K. Schenker, M. Meier, and G. Rihs, *J. Med. Chem.*, 1995, **38**, 2946.
 1995JNP986 H. Jayasuriya, R. G. Ball, D. L. Zink, J. L. Smith, M. A. Goetz, R. G. Jenkins, M. Nallin-Omstead, K. C. Silverman, G. F. Bills, R. B. Lingham, S. B. Singh, F. Pelaez, and C. Cascales, *J. Nat. Prod.*, 1995, **58**, 986.
 1995JOC1959 T. Axenrod, C. Watnick, and H. Yazdekhashti, *J. Org. Chem.*, 1995, **60**, 1959.
 1995JOC2922 J. F. Berrein, M. A. Billion, H. P. Husson, and J. Royer, *J. Org. Chem.*, 1995, **60**, 2922.
 1995JOC3121 T. K. M. Shing, H.-C. Tsui, and Z.-H. Zhou, *J. Org. Chem.*, 1995, **60**, 3121.
 1995JOC8148 D. J. Gallagher, S. Wu, N. A. Nikolic, and P. Beak, *J. Org. Chem.*, 1995, **60**, 8148.
 1995J(P1)2049 U. Maitra, B. G. Bag, P. Rao, and D. Powell, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2049.
 1995JST(355)229 M. J. Fernández, R. M. Huertas, E. Gálvez, J. Server-Carrió, M. Martínez-Ripoll, and J. Bellanato, *J. Mol. Struct.*, 1995, **355**, 229.
 1995M233 J. Thiel, W. Wysocka, and W. Boczoń, *Monatsh. Chem.*, 1995, **126**, 233.
 1995T2055 D. St. C. Black, G. B. Deacon, and M. Rose, *Tetrahedron*, 1995, **51**, 2055.
 1995T4819 D. St. C. Black, M. A. Horsham, and M. Rose, *Tetrahedron*, 1995, **51**, 4819.
 1995T12239 H. Shima and N. Furukawa, *Tetrahedron*, 1995, **51**, 12239.
 1995TL1271 H. Salez, A. Wardani, M. Demeunynck, A. Tatibouet, and J. Lhomme, *Tetrahedron Lett.*, 1995, **36**, 1271.
 1995TL1391 K. Mitra and K. S. Gates, *Tetrahedron Lett.*, 1995, **36**, 1391.
 1995TL6619 F. D. Toste, A. J. Lough, and I. W. J. Still, *Tetrahedron Lett.*, 1995, **36**, 6619.
 1996AGE1970 J. Mulzer, D. Trauner, and J. W. Bats, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1970.
 1996AXC2822 I. Wolska, T. Borowiak, and W. Boczoń, *Acta Crystallogr., Sect. C*, 1996, **52**, 2822.
 1996CC2093 D. St. C. Black, K. C. Craig, M. A. Horsham, and M. Rose, *J. Chem. Soc., Chem. Commun.*, 1996, 2093.
 1996EPP0733632 N. Hideaki, I. Takenori, D. Takayuki, I. Yoshinori, and K. Chiharu, *Eur. Pat.* 0 733 632 (1996) (*Chem. Abstr.*, 1996, **125**, 301003).
 1996H(43)977 H. M. Refat, A. A. Fadda, Y. Lu, and E. R. Biehl, *Heterocycles*, 1996, **43**, 977.
 1996JME2559 G. L. Garrison, K. D. Berlin, B. J. Scherlag, R. Lazzara, E. Patterson, T. Fazekas, S. Sangiah, C.-L. Chen, F. D. Schubot, and D. Van der Helm, *J. Med. Chem.*, 1996, **39**, 2559.

- 1996JOC3061 P. Livant, A. W. Majors, and T. R. Webb, *J. Org. Chem.*, 1996, **61**, 3061.
- 1996JOC5581 M. J. Wanner and G.-J. Koomen, *J. Org. Chem.*, 1996, **61**, 5581.
- 1996JOC7597 A. Deagostino, J. Maddaluno, C. Prandi, and P. Venturello, *J. Org. Chem.*, 1996, **61**, 7597.
- 1996JOC8897 P. R. Dave, F. Forohar, T. Axenrod, K. K. Das, L. Qi, C. Watnick, and H. Yazdekhashti, *J. Org. Chem.*, 1996, **61**, 8897.
- 1996JST(365)93 I. Jalsovszky, Ö. Farkas, J. Rábai, and Á. Kucsman, *J. Mol. Struct.*, 1996, **365**, 93.
- 1996JST(382)1 M. Kuti, J. Rábai, I. Kapovits, I. Jalsovszky, G. Argay, A. Kálmán, and L. Párkányi, *J. Mol. Struct.*, 1996, **382**, 1.
- 1996MM6983 R. A. Evans and E. Rizzardo, *Macromolecules*, 1996, **29**, 6983.
- 1996TL2679 O. Meth-Cohn and Y. Cheng, *Tetrahedron Lett.*, 1996, **37**, 2679.
- 1996TL2865 E. Alvarez, M. Delgado, M. T. Diaz, L. Hanxing, R. Pérez, and J. D. Martin, *Tetrahedron Lett.*, 1996, **37**, 2865.
- 1996TL5791 P. Rao and U. Maitra, *Tetrahedron Lett.*, 1996, **37**, 5791.
- 1996WO19471 R. Evans, E. Rizzardo, and G. Moad, *PCT Int. Appl. WO 19471* (1996) (*Chem. Abstr.*, 1996, **125**, 143546).
- 1996WO30372 K. Orita, A. Hamada, T. Inaba, H. Abe, and S. Miyazaki, *PCT Int. Appl. WO 30372* (1996) (*Chem. Abstr.*, 1997, **126**, 8107).
- 1996WO31497 T. Jorgensen, K. E. Andersen, H. S. Andersen, R. Hohlweg, P. Madsen, and U. B. Olsen, *PCT Int. Appl. WO 31497* (1996) (*Chem. Abstr.*, 1997, **126**, 8146).
- 1997EJM241 G. Campiani, V. Nacci, I. Fiorini, M. P. De Filippis, A. Garofano, S. M. Ciani, G. Greco, E. Novellino, C. Manzoni, and T. Pennini, *Eur. J. Med. Chem.*, 1997, **32**, 241.
- 1997FA751 D. Nowak, R. Glinka, T. Pietras, M. Cieslinski, P. Mazerant, P. Idowski, M. Leder, and M. Sidorkiewicz, *Farmaco*, 1997, **52**, 751.
- 1997H(45)361 M. Lounasmaa, K. Karinen, D. D. Belle, and A. Tolvanen, *Heterocycles*, 1997, **45**, 361.
- 1997H(45)1833 J. Svetlik, V. Hanus, I. M. Lagoja, and J. G. Schantl, *Heterocycles*, 1997, **45**, 1833.
- 1997H(46)275 H. Fukuda and T. Kitazume, *Heterocycles*, 1997, **46**, 275.
- 1997JCD347 P. Comba, B. Nuber, and A. Ramlow, *J. Chem. Soc., Dalton Trans.*, 1997, 347.
- 1997JHC375 P. Pigeon and B. Decroix, *J. Heterocycl. Chem.*, 1997, **34**, 375.
- 1997JHC1607 S. P. Upadhyaya, F. S. Davis, J. J. Lee, K. Zaw, and L. Bauer, *J. Heterocycl. Chem.*, 1997, **34**, 1607.
- 1997JOC2975 A. Boto, R. Freire, R. Hernández, E. Suárez, and M. S. Rodriguez, *J. Org. Chem.*, 1997, **62**, 2975.
- 1997JOC5619 M. Gdaniec, M. Pham, and T. Poloński, *J. Org. Chem.*, 1997, **62**, 5619.
- 1997JOC6619 C. Mukai, S. Hirai, and M. Hanaoka, *J. Org. Chem.*, 1997, **62**, 6619.
- 1997JOC9361 K. Mitra, M. E. Pohl, L. R. MacGillivray, C. L. Barnes, and K. S. Gates, *J. Org. Chem.*, 1997, **62**, 9361.
- 1997J(P2)273 M. C. Aversa, A. Barattucci, P. Bonaccorsi, G. Bruno, P. Giannetto, and F. Nicolò, *J. Chem. Soc., Perkin Trans. 2*, 1997, 273.
- 1997JST(418)155 I. Jalsovszky, Ö. Farkas, J. Rábai, and Á. Kucsman, *J. Mol. Struct.*, 1997, **418**, 155.
- 1997MRC13 A. Gogoll, H. Grennberg, and A. Axén, *Magn. Reson. Chem.*, 1997, **35**, 13.
- 1997OM1167 A. Gogoll, H. Grennberg, and A. Axén, *Organometallics*, 1997, **16**, 1167.
- 1997RCB1931 L. Y. Ukhin, Z. I. Orlova, and V. N. Khrustalev, *Russ. Chem. Bull.*, 1997, **46**, 1931.
- 1997T7165 S. Hu and D. C. Neckers, *Tetrahedron*, 1997, **53**, 7165.
- 1997T7461 C. P. Nash, S. D. Toto, and W. K. Musker, *Tetrahedron*, 1997, **53**, 7461.
- 1997T11859 A. Manjula and M. Nagarajan, *Tetrahedron*, 1997, **53**, 11859.
- 1997TA661 A. Mori, T. Sugimura, and A. Tai, *Tetrahedron Asymmetry*, 1997, **8**, 661.
- 1997TA1161 P. R. Allen, J. N. H. Reek, A. C. Try, and M. J. Crossley, *Tetrahedron Asymmetry*, 1997, **8**, 1161.
- 1997TA2411 D. Szabó, S. Szendeffy, I. Kapovits, Á. Kucsman, M. Czugler, A. Kálmán, and P. Nagy, *Tetrahedron Asymmetry*, 1997, **8**, 2411.
- 1998ACS790 P. Songe, P. Kolsaker, and C. Rømming, *Acta Chem. Scand.*, 1998, **52**, 790.
- 1998CC197 T. Kataoka, T. Iwama, and S. I. Tsujiyama, *J. Chem. Soc., Chem. Commun.*, 1998, 197.
- 1998CC2521 B. A. Jazdzewski, V. G. Young, Jr., and W. B. Tolman, *J. Chem. Soc., Chem. Commun.*, 1998, 2521.
- 1998CJC94 R. W. Friesen and S. Bissada, *Can. J. Chem.*, 1998, **76**, 94.
- 1998CL45 T. Sugimura, S. Nagano, and A. Tai, *Chem. Lett.*, 1998, 45.
- 1998EJO1431 B. Porath, R. Münzenberg, P. Heymanns, P. Rademacher, R. Boese, D. Bläser, and R. Latz, *Eur. J. Org. Chem.*, 1998, 1431.
- 1998HL(48)1841 T. S. Dalvi, C. O. Kappe, C. Wentrup, and G. Kollenz, *Heterocycles*, 1998, **48**, 1841.
- 1998JCM196 Y. Wang, H. Kubo, K. Higashiyama, H. Komiya, J. Li, and S. Ohmiya, *J. Chem. Res. (S)*, 1998, 196.
- 1998JME318 U. Schön, J. Antel, R. Brückner, and J. Messinger, *J. Med. Chem.*, 1998, **41**, 318.
- 1998JOC1566 R. D. Chapman, M. F. Welker, and C. B. Kreutzberger, *J. Org. Chem.*, 1998, **63**, 1566.
- 1998JOC3492 B. Danieli, G. Lesma, D. Passarella, and A. Silvani, *J. Org. Chem.*, 1998, **63**, 3492.
- 1998JOC4515 A. G. Kolchinski and N. W. Alcock, *J. Org. Chem.*, 1998, **63**, 4515.
- 1998J(P1)881 A. Deagostino, J. Maddaluno, M. Mella, C. Prandi, and P. Venturello, *J. Chem. Soc., Perkin Trans. 1*, 1998, 881.
- 1998J(P1)1257 Y. Cheng, O. Meth-Cohn, and D. Taylor, *J. Chem. Soc. Perkin Trans. 1*, 1998, 1257.
- 1998J(P1)3557 J. M. Quintela, R. Alvarez-Sarandés, C. Peinador, and M. Maestro, *J. Chem. Soc. Perkin Trans. 1*, 1998, 3557.
- 1998JST(442)103 T. Borowiak, M. Kubicki, W. Wysocka, and A. Przybyl, *J. Mol. Struct.*, 1998, **442**, 103.
- 1998S653 D. Trauner, S. Porth, T. Opatz, J. W. Bats, G. Giester, and J. Mulzer, *Synthesis*, 1998, 653.
- 1998T997 P. Molina, A. Arques, A. Tàrraga, M. del Rosario Ob, òn, C. Foces-Foces, N. Jagerovic, and J. Eiguero, *Tetrahedron*, 1998, **54**, 997.
- 1998T4673 M. Lounasmaa, D. D. Belle, and A. Tolvanen, *Tetrahedron*, 1998, **54**, 4673.
- 1998T9569 R. M. Claramunt, J. L. Lavandera, D. Sanz, J. Elguero, and M. L. Jimeno, *Tetrahedron*, 1998, **54**, 9569.
- 1998T11813 T. Kataoka, T. Iwama, S. Tsujiyama, T. Iwamura, and S. Watanabe, *Tetrahedron*, 1998, **54**, 11813.
- 1998T11887 B. M. Ebert, I. K. Ugi, M. Grosche, E. Herdtweck, and W. A. Hermann, *Tetrahedron*, 1998, **54**, 11887.
- 1998T14885 S. Cerezo, J. Cortés, J.-M. López-Romero, M. Moreno-Mañás, T. Parella, R. Pleixats, and A. Røglans, *Tetrahedron*, 1998, **54**, 14885.
- 1998TA4151 E. Tàlas, J. Margitfalvi, D. Machytka, and M. Czugler, *Tetrahedron Asymmetry*, 1998, **9**, 4151.
- 1998TL7113 M. Hamaguchi, T. Misumi, and T. Oshima, *Tetrahedron Lett.*, 1998, **39**, 7113.
- 1998TL7239 K. E. Frank and J. Aubé, *Tetrahedron Lett.*, 1998, **39**, 7239.
- 1998TL9681 J.-P. Surivet and J.-M. Vattè, *Tetrahedron Lett.*, 1998, **39**, 9681.
- 1998USP5770590 H. Natsugari, T. Ishimaru, T. Doi, Y. Ikeura, C. Rimura, and N. Tarui, *US Pat. 5 770 590* (1998) (*Chem. Abstr.*, 1998, **129**, 95515).

- 1998USP5831099 P. R. Dave, T. Axenrod, and F. Forohar, *US Pat.* 5 831 099 (1998) (*Chem. Abstr.*, 1998, **129**, 330747).
- 1998WO02779 C. G. Barlow, R. R. Ollmann, A. S. Warner, R. J. D. Nairne, A. L. Beck, and A. Mott, *PCT Int. Appl.* WO 02779 (1998) (*Chem. Abstr.*, 1998, **128**, 160933).
- 1998WO35955 F. Caye, D. Paquer, D. Jury, M. Schneider, and J. L. Mieloszynski, *PCT Int. Appl.* WO 35955 (1998) (*Chem. Abstr.*, 1998, **129**, 203381).
- 1999AGE3713 B. G. Bag and G. Von Kiedrowski, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 3713.
- 1999AJC905 B. S. Siddiqui, S. Afreen, and S. Begum, *Aust. J. Chem.*, 1999, **52**, 905.
- 1999AXC1710 A. Farina, S. V. Mille, M. T. Messina, P. Metrangolo, and G. Resnati, *Acta Crystallogr., Sect. C*, 1999, **55**, 1710.
- 1999CC2261 W. Zhou and E. L. Clennan, *J. Chem. Soc., Chem. Commun.*, 1999, 2261.
- 1999CJC113 I. W. J. Still, R. Natividad-Preyra, and F. D. Toste, *Can. J. Chem.*, 1999, **77**, 113.
- 1999CL179 T. Sugimura, S. Nagano, H. Kohno, M. Fujita, and A. Tai, *Chem. Lett.*, 1999, 179.
- 1999CL1143 T. Sugimura, H. Kohno, S. Nagano, F. Nishida, and A. Tai, *Chem. Lett.*, 1999, 1143.
- 1999FA438 C. Canu Boido and F. Sparatore, *Farmaco*, 1999, **54**, 438.
- 1999H(51)2969 Q. Mu, W. Tang, C. Li, Y. Lu, H. Sun, H. Zheng, X. Hao, Q. Zheng, N. Wu, L. Lou, and B. Xu, *Heterocycles*, 1999, **51**, 2969.
- 1999HAC159 N. Nakayama, O. Takahashi, O. Kikuchi, and N. Furukawa, *Heteroatom Chem.*, 1999, **10**, 159.
- 1999JAP3053 Z. Yang, Y. Wang, and Y. Tang, *J. Appl. Polym. Sci.*, 1999, **74**, 3053 (*Chem. Abstr.*, 2000, **132**, 55458).
- 1999JCL993 G. Szökán, S. Szarvas, Z. Majer, D. Szabó, I. Kapovits, and M. Hollösi, *J. Liq. Chrom. Relat. Technol.*, 1999, **22**, 993 (*Chem. Abstr.*, 1999, **130**, 332018).
- 1999JNP608 X. C. Cheng, P. R. Jensen, and W. Fenical, *J. Nat. Prod.*, 1999, **62**, 608.
- 1999JOC960 R. D. Chapman, R. D. Gilardi, M. F. Welker, and C. B. Kreutzberger, *J. Org. Chem.*, 1999, **64**, 960.
- 1999JOC1074 J. Zhang, A. Jacobson, J. R. Rusche, and W. Herlihy, *J. Org. Chem.*, 1999, **64**, 1074.
- 1999J(P1)2627 B. Schmidt, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2627.
- 1999J(P1)3623 J. R. Harrison, P. O'Brien, D. W. Porter, and N. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3623.
- 1999J(P2)1559 R. Stowasser, R. S. Glass, and R. Hoffmann, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1559.
- 1999JST(424)245 A. Katrusiak, A. Kowalski, D. Kucharczyk, and H. P. Weber, *J. Mol. Struct.*, 1999, **424**, 245.
- 1999JST(489)67 I. Yavari, D. Tahmassebi, K. Madidi, D. Nori-Shargh, and S. Balalaie, *J. Mol. Struct.*, 1999, **489**, 67.
- 1999OL3 S. Chi and C. H. Heathcock, *Org. Lett.*, 1999, **1**, 3.
- 1999RCM2359 S. Cerezo, J. Cortés, D. Galvan, J.-M. López-Romero, M. Moreno-Mañas, R. Pleixats, F. X. Avilés, F. Canals, and A. Roglans, *Rapid Commun. Mass Spectrom.*, 1999, **13**, 2359.
- 1999S787 M. Pulst, M. Weeks, U. Eilitz, and D. Greif, *Synthesis*, 1999, 787.
- 1999SL1875 J. A. Martinez-Perez, M. A. Pickel, E. Caroff, and W.-D. Woggon, *Synlett*, 1999, 1875.
- 1999T2493 M. Tsubuki, K. Kanai, H. Nagase, and T. Honda, *Tetrahedron*, 1999, **55**, 2493.
- 1999T8295 X. Ouyang and A. S. Kiselyov, *Tetrahedron*, 1999, **55**, 8295.
- 1999T13011 J.-P. Surivet and J.-M. Vatele, *Tetrahedron*, 1999, **55**, 13011.
- 1999TL1289 B. G. Bag and G. Von Kiedrowski, *Tetrahedron Lett.*, 1999, **40**, 1289.
- 1999TL1705 Y. Miyahara, K. Izumi, A. A. Ibrahim, and T. Inazu, *Tetrahedron Lett.*, 1999, **40**, 1705.
- 1999TL2149 H. Hosoyama, H. Shigemori, and J. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 2149.
- 1999TL5827 X. Ouyang and A. S. Kiselyov, *Tetrahedron Lett.*, 1999, **40**, 5827.
- 1999USP5874438 R. Schohe-Loop, P. R. Seidel, W. Bullock, W. Hübsch, A. Feuer, H. G. Lerchen, G. Terstappen, J. Schuhmacher, F. J. Van der Staay, B. Schmidt, R. J. Fanelli, J. C. Chisholm, and R. T. McCarthy, *US Pat.* 5 874 438 (1999) (*Chem. Abstr.*, 1999, **130**, 196662).
- 1999USP5874573 H. S. Winchell, J. Y. Klein, E. D. Simhon, R. L. Cyjon, O. Klein, and H. Zaklad, *US Pat.* 5 874 573 (1999) (*Chem. Abstr.*, 1999, **130**, 196676).
- 1999USP5922527 C. G. Barlow, R. R. Ollmann, A. S. Zinn-Warner, R. J. D. Nairne, A. L. Beck, and A. Mott, *US Pat.* 5 922 527 (1999) (*Chem. Abstr.*, 1999, **131**, 94801).
- 1999WO21834 D. Peters, G. Gunnar, S. Nielsen, and E. Nielsen, *PCT Int. Appl.* WO 21834 (1999) (*Chem. Abstr.*, 1999, **130**, 325154).
- 1999WO32487 G. Dulce, I. D. Dukes, E. W. McLean, R. A. Noe, A. J. Peat, J. R. Szweczyk, S. A. Thomson, and J. F. Worley, *PCT Int. Appl.* WO 32487 (1999) (*Chem. Abstr.*, 1999, **131**, 58813).
- 2000CEJ671 O. Huttenloch, J. Spieler, and H. Waldmann, *Chem. Eur. J.*, 2000, **6**, 671.
- 2000EJO391 J. Spieler, O. Huttenloch, and H. Waldmann, *Eur. J. Org. Chem.*, 2000, 391.
- 2000EJO2367 C. L. Kranemann and P. Eilbracht, *Eur. J. Org. Chem.*, 2000, 2367.
- 2000EJO3721 G. Capozzi, S. Menichetti, C. Nativi, and A. Provenzani, *Eur. J. Org. Chem.*, 2000, 3721.
- 2000HAC31 N. Nakayama, O. Takahashi, O. Kikuchi, and N. Furukawa, *Heteroatom Chem.*, 2000, **11**, 31.
- 2000JA1424 O. Trapp and V. Schurig, *J. Am. Chem. Soc.*, 2000, **122**, 1424.
- 2000JCX531 M. Du, X.-H. Bu, Q. Xu, Z.-L. Shang, and R.-H. Zhang, *J. Chem. Crystallogr.*, 2000, **30**, 531.
- 2000JME3746 T. Siener, A. Cambareri, U. Kuhl, W. Englberger, M. Haurand, B. Kögel, and U. Holzgrabe, *J. Med. Chem.*, 2000, **43**, 3746.
- 2000JMP841 J. Zhang, J. Oxley, J. Smith, C. Bedford, and R. Chapman, *J. Mass Spectrom.*, 2000, **35**, 841.
- 2000JOC655 K. E. Frank and J. Aubé, *J. Org. Chem.*, 2000, **65**, 655.
- 2000JOC1207 P. R. Dave, K. A. Kumar, and R. Duddu, *J. Org. Chem.*, 2000, **65**, 1207.
- 2000JOC8367 D. I. MaGee and E. J. Beck, *J. Org. Chem.*, 2000, **65**, 8367.
- 2000JPR269 G. Kaupp, J. Schmeyer, and J. Boy, *J. Prakt. Chem.*, 2000, **342**, 269.
- 2000JST(522)263 E. Nonnenmacher, P. Brouant, A. Mrozek, J. Karolak-Wojciechowska, and J. Barbe, *J. Mol. Struct.*, 2000, **522**, 263.
- 2000M1073 J. Thiel, W. Boczoń, and W. Wysocka, *Monatsh. Chem.*, 2000, **131**, 1073.
- 2000MI192 K. A. Krasnov, V. G. Kartsev, and A. S. Gorovoi, *Chem. Nat. Comp.*, 2000, **36**, 192 (*Chem. Abstr.*, 2001, **134**, 131699).
- 2000MI817 C. L. Chen, A. M. S. Chandra, S. Kim, S. Sangiah, H. Chen, J. D. Roder, C. W. Qualls, G. L. Garrison, R. L. Cowell, K. D. Berlin, B. J. Scherlag, and R. Lazzara, *Food Chem. Toxicol.*, 2000, **38**, 817 (*Chem. Abstr.*, 2002, **133**, 290884).
- 2000MM6722 R. A. Evans and E. Rizzardo, *Macromolecules*, 2000, **33**, 6722.
- 2000MM9553 S. Harrison, T. P. Davis, R. A. Evans, and E. Rizzardo, *Macromolecules*, 2000, **33**, 9553.
- 2000MRC883 V. Vijayakumar, M. Sundaravadeivel, S. Perumal, and M. J. E. Hewlins, *Magn. Reson. Chem.*, 2000, **38**, 883.

- 2000OL1121 E. Marrière, J. Rouden, V. Tadino, and M.-C. Lasne, *Org. Lett.*, 2000, **2**, 1121.
- 2000OL1613 J. P. Ragot, M. E. Prime, S. J. Archibald, and R. J. K. Taylor, *Org. Lett.*, 2000, **2**, 1613.
- 2000OL4201 B. T. O'Neill, D. Yohannes, M. W. Bundesmann, and E. P. Arnold, *Org. Lett.*, 2000, **2**, 4201.
- 2000OL4205 J. W. Coe, *Org. Lett.*, 2000, **2**, 4205.
- 2000S640 Y. Cheng, Q.-X. Liu, and O. Meth-Cohn, *Synthesis*, 2000, 640.
- 2000T2369 X. Ouyang, Z. Chen, L. Liu, C. Dominguez, and A. S. Kiselyov, *Tetrahedron*, 2000, **56**, 2369.
- 2000T7947 P. W. Sutton, A. Bradley, J. Farràs, P. Romea, F. Urpi, and J. Vilarrasa, *Tetrahedron*, 2000, **56**, 7947.
- 2000T9641 F. Sigaut, B. Didierdefresse, and J. Lévy, *Tetrahedron*, 2000, **56**, 9641.
- 2000TA2875 M. Harmata and M. Kahraman, *Tetrahedron Asymmetry*, 2000, **11**, 2875.
- 2000TL707 H. Hayakawa and M. Miyashita, *Tetrahedron Lett.*, 2000, **41**, 707.
- 2000TL3475 Y. Cheng, Q.-X. Liu, and O. Meth-Cohn, *Tetrahedron Lett.*, 2000, **41**, 3475.
- 2000TL6161 J. R. Harrison and P. O'Brien, *Tetrahedron Lett.*, 2000, **41**, 6161.
- 2000TL6167 J. R. Harrison and P. O'Brien, *Tetrahedron Lett.*, 2000, **41**, 6167.
- 2000WO44755 W. Bunnelle, D. B. Cristina, J. Daanen, M. D. Dart, K. Ryther, M. Schrimpf, K. Sippy, and R. Toupençe, *PCT Int. Appl.* WO 44755 (2000) (*Chem. Abstr.*, 2000, **133**, 135332).
- 2000WO64885 S. Nielsen, D. Peters, E. Nielsen, and G. Olsen, *PCT Int. Appl.* WO 64885 (2000) (*Chem. Abstr.*, 2000, **133**, 321908).
- 2000WO76997 M. Frantsi, K. J. Hoffmann, and G. Strandlund, *PCT Int. Appl.* WO 76997 (2000) (*Chem. Abstr.*, 2001, **134**, 42149).
- 2001AP143 M. Stadler, F. Bauch, T. Henkel, A. Mühlbauer, H. Müller, F. Spaltmann, and K. Weber, *Arch. Pharm. Pharm. Med. Chem.*, 2001, **334**, 143 (*Chem. Abstr.*, 2001, **135**, 177889).
- 2001BML2651 A. E. Moormann, S. Metz, M. V. Toth, W. M. Moore, G. Jerome, C. Kormeier, P. Manning, D. W. Hansen, B. S. Pitzele, and R. K. Webber, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2651.
- 2001CCL769 Z. L. Shang, Z. C. Shang, and Q. S. Yu, *Chin. Chem. Lett.*, 2001, **12**, 769 (*Chem. Abstr.*, 2002, **136**, 118437).
- 2001EJM375 P. Imming, P. Klaparski, M. T. Stubbs, G. Seitz, and D. Gündisch, *Eur. J. Med. Chem.*, 2001, **36**, 375.
- 2001EJO1377 A. Consonni, B. Danieli, G. Lesma, D. Passarella, P. Piacenti, and A. Silvani, *Eur. J. Org. Chem.*, 2001, 1377.
- 2001EJO1511 P. Langer, M. Döring, and H. Görls, *Eur. J. Org. Chem.*, 2001, 1511.
- 2001EJO1831 A. G. Griesbeck, M. Oelgemöller, J. Lex, A. Hacuser, and M. Schmitt, *Eur. J. Org. Chem.*, 2001, 1831.
- 2001IC5060 J. A. Halfen, D. C. Fox, M. P. Mehn, and L. Que, Jr., *Inorg. Chem.*, 2001, **40**, 5060.
- 2001JAP1793 Z. Yang and Y. Yang, *J. Appl. Polym. Sci.*, 2001, **81**, 1793 (*Chem. Abstr.*, 2001, **135**, 182267).
- 2001JOC1607 C. Pardo, E. Sesmiño, E. Gutiérrez-Puebla, A. Monge, J. Elguero, and A. Fruchier, *J. Org. Chem.*, 2001, **66**, 1607.
- 2001JOC7967 A. B. Sebag, D. A. Forsyth, and M. A. Plante, *J. Org. Chem.*, 2001, **66**, 7967.
- 2001JOC8222 F. Charmantray, M. Demeunynck, J. Lhomme, and A. Duflos, *J. Org. Chem.*, 2001, **66**, 8222.
- 2001JST(542)215 N. Nakayama, O. Takahashi, O. Kikushi, and N. Furukawa, *J. Mol. Struct.*, 2001, **542**, 215.
- 2001M973 W. Wysocka and A. Przybyl, *Monatsh. Chem.*, 2001, **132**, 973.
- 2001MI356 T. V. Khakimova, O. A. Pukhlyakova, G. A. Shavaleeva, A. A. Fatykhov, E. V. Vasil'eva, and L. V. Spirikhin, *Chem. Nat. Comp.*, 2001, **37**, 356 (*Chem. Abstr.*, 2002, **137**, 93883).
- 2001MRC101 V. Vijayakumar, M. Sundaravadivelu, and S. Perumal, *Magn. Reson. Chem.*, 2001, **39**, 101.
- 2001OL37 T. Sugimura, K. Hagiya, Y. Sato, T. Tei, A. Tai, and T. Okuyama, *Org. Lett.*, 2001, **3**, 37.
- 2001OL177 A. Vakalopoulos and H. M. R. Hoffmann, *Org. Lett.*, 2001, **3**, 177.
- 2001PSA202 R. A. Evans and E. Rizzardo, *J. Polym. Sci., Polym. Chem., Part A*, 2001, **39**, 202.
- 2001RCB753 N. N. Yarmukhamedov, N. Z. Baibulatova, V. A. Dokichev, Y. V. Tomilov, and M. S. Yunusov, *Russ. Chem. Bull.*, 2001, **50**, 753.
- 2001RJC151 A. Zh. Aubakirova, O. A. Nurkenov, A. M. Gazaliev, G. G. Baikenova, and M. Zh. Zhurinov, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2001, **71**, 151.
- 2001RJC650 A. Zh. Aubakirova, A. M. Gazaliev, S. D. Fazylov, O. A. Nurkenov, S. Zh. Kudaibergenova, and G. G. Baikenova, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2001, **71**, 650.
- 2001S1873 J. Jensen and K. Wärnmark, *Synthesis*, 2001, 1873.
- 2001T1883 J. Escalante, M. A. González-Tototzin, J. Aviña, O. Muñoz-Muñoz, and E. Juaristi, *Tetrahedron*, 2001, **57**, 1883.
- 2001T3963 A. C. Ramos, R. Peláez, J. L. López, E. Caballero, M. Medarde, and A. San Feliciano, *Tetrahedron*, 2001, **57**, 3963.
- 2001TL2621 T. Axenrod, X.-P. Guan, J. Sun, L. Qi, R. D. Chapman, and R. D. Gilardi, *Tetrahedron Lett.*, 2001, **42**, 2621.
- 2001TL4963 P. Tempest, V. Ma, M. G. Kelly, W. Jones, and C. Hulme, *Tetrahedron Lett.*, 2001, **42**, 4963.
- 2001TL5377 H. Bernsmann, M. Gruner, R. Fröhlich, and P. Metz, *Tetrahedron Lett.*, 2001, **42**, 5377.
- 2001TL7801 Y. Wang, H. Bernsmann, M. Gruner, and P. Metz, *Tetrahedron Lett.*, 2001, **42**, 7801.
- 2001WO10848 T. Baer, T. Martin, J. Stadlwieser, A. Dominik, D. Bundschuh, K. Zech, and C. Sommerhoff, *PCT Int. Appl.* WO 10848 (2001) (*Chem. Abstr.*, 2001, **134**, 163070).
- 2001WO28992 A. Björe, M. Björns, D. Clandig-Boel, K.-J. Hoffman, J. Pavey, F. Pontén, G. Strandlund, P. Svensson, C. Thomson, and M. Wilstermann, *PCT Int. Appl.* WO 28992 (2001) (*Chem. Abstr.*, 2001, **134**, 326548).
- 2001WO92267 J. H. Dodd, J. L. Bullington, D. A. Hall, J. R. Henry, and K. C. Rupert, *PCT Int. Appl.* WO 92267 (2001) (*Chem. Abstr.*, 2002, **136**, 20094).
- 2002AGE3247 H. Yoshida, E. Shirakawa, Y. Honda, and T. Hiyama, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 3247.
- 2002BMC2415 S. Bräse, C. Gil, and K. Knepper, *Bioorg. Med. Chem.*, 2002, **10**, 2415.
- 2002CC673 O. Huttenloch, E. Laxman, and H. Waldmann, *J. Chem. Soc., Chem. Commun.*, 2002, 673.
- 2002CC2534 V. K. Aggarwal, A. Lattanti, and D. Fuentes, *J. Chem. Soc., Chem. Commun.*, 2002, 2534.
- 2002CCC609 M. Valik, B. Dolensky, H. Petříčková, and V. Král, *Collect. Czech. Chem. Commun.*, 2002, **67**, 609.
- 2002CCL27 Z. K. Yang, L. Zhuang, and Y. Yuan, *Chin. Chem. Lett.*, 2002, **137**, 27 (*Chem. Abstr.*, 2002, **13**, 342464).
- 2002CCL115 Z. L. Shang, Z. C. Shang, C. Y. Wang, and Q. S. Yu, *Chin. Chem. Lett.*, 2002, **13**, 115 (*Chem. Abstr.*, 2002, **137**, 33284).
- 2002CEJ3629 O. Trapp, G. Trapp, J. Kong, U. Hahn, F. Vögtle, and V. Schurig, *Chem. Eur. J.*, 2002, **8**, 3629.
- 2002CEJ4767 O. Huttenloch, E. Laxman, and H. Waldmann, *Chem. Eur. J.*, 2002, **8**, 4767.
- 2002CL260 T. Sugimura, M. Kagawa, K. Hagiya, and T. Okuyama, *Chem. Lett.*, 2002, 260.
- 2002EJM315 B. Baldeyrou, C. Tardy, C. Bailly, P. Colson, C. Houssier, F. Charmantray, and M. Demeunynck, *Eur. J. Med. Chem.*, 2002, **37**, 315.

- 2002EJO947 K. Wojciechowski and S. Kosiński, *Eur. J. Org. Chem.*, 2002, 947.
- 2002FA469 O. Nicolotti, C. Canu Boido, F. Sparatore, and A. Carotti, *Farmaco*, 2002, **57**, 469.
- 2002HCA1659 C. Ensich and M. Hesse, *Helv. Chim. Acta*, 2002, **85**, 1659.
- 2002JA8316 W. Adam, S. G. Bosio, B. Fröhling, D. Leusser, and D. Stalke, *J. Am. Chem. Soc.*, 2002, **124**, 8316.
- 2002JA11870 M. J. Dearden, C. R. Firkin, J. P. R. Hermet, and P. O'Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870.
- 2002JAP530 Z. Yang, L. Zhuang, and G. Tan, *J. Appl. Polym. Sci.*, 2002, **85**, 530 (*Chem. Abstr.*, 2002, **137**, 186321).
- 2002JAP2677 Z. Yang and J. Li, *J. Appl. Polym. Sci.*, 2002, **86**, 2677 (*Chem. Abstr.*, 2003, **138**, 57712).
- 2002JHC727 Y. Hirokawa, H. Yamazaki, and S. Kato, *J. Heterocycl. Chem.*, 2002, **39**, 727.
- 2002JOC2619 H. Bibas, D. W. J. Moloney, R. Neumann, M. Shtaiwi, P. V. Bernhardt, and C. Wentrup, *J. Org. Chem.*, 2002, **67**, 2619.
- 2002JOC6008 J. Jensen, J. Tejler, and K. Wärnmark, *J. Org. Chem.*, 2002, **67**, 6008.
- 2002JOC8662 D. K. Bates and K. Li, *J. Org. Chem.*, 2002, **67**, 8662.
- 2002J(P1)1963 T. Kobayashi, T. Moriwaki, M. Tsubakiyama, and S. Yoshida, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1963.
- 2002J(P1)2704 K. Okada and M. Tanaka, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2704.
- 2002MI182 A. D. Grebenyuk, V. I. Vinogradova, and A. K. Tashmukhamedova, *Chem. Nat. Compd.*, 2002, **38**, 182 (*Chem. Abstr.*, 2003, **138**, 187944).
- 2002MI249 B. A. Salakhutdinov, D. N. Dalimov, T. F. Aripov, I. I. Tukfatullina, R. Kh. Ziyatdinova, A. Zh. Dzhuraev, F. G. Kamaev, L. Yu. Izotova, B. T. Ibragimov, I. Mavridis, and P. Giastas, *Chem. Nat. Compd.*, 2002, **38**, 249 (*Chem. Abstr.*, 2003, **138**, 271827).
- 2002MI344 A. A. Rakhimov, V. I. Vinogradova, and A. K. Tashmukhamedova, *Chem. Nat. Compd.*, 2002, **38**, 344 (*Chem. Abstr.*, 2003, **138**, 401940).
- 2002MI450 K. A. Krasnov, V. G. Kartsev, A. S. Gorovoi, and V. N. Khrustalev, *Chem. Nat. Compd.*, 2002, **38**, 450 (*Chem. Abstr.*, 2003, **139**, 53190).
- 2002MRC743 F. Salort, C. Pardo, and J. Elguero, *Magn. Reson. Chem.*, 2002, **40**, 743.
- 2002OL2059 T. Sugimura, W. H. Kim, M. Kagawa, and T. Okuyama, *Org. Lett.*, 2002, **4**, 2059.
- 2002OL2577 B. T. Smith, J. A. Wendt, and J. Aubé, *Org. Lett.*, 2002, **4**, 2577.
- 2002PPS237 A. G. Griesbeck, W. Kramer, T. Heinrich, and J. Lex, *Photochem. Photobiol. Sci.*, 2002, **1**, 237 (*Chem. Abstr.*, 2002, **137**, 294942).
- 2002RJC324 S. D. Fazylov, A. M. Gazaliev, S. Kudaibergenova, M. Zhukonov, and M. Ibraev, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2002, **72**, 324.
- 2002S906 Y. Cheng, H. B. Yang, B. Liu, O. Meth-Cohn, D. Watkin, and S. Humphries, *Synthesis*, 2002, 906.
- 2002S2168 K. S. Deethi and P. S. N. Reddy, *Synthesis*, 2002, 2168.
- 2002S2761 J. Jensen, M. Strozyk, and K. Wärnmark, *Synthesis*, 2002, 2761.
- 2002SL1265 J. Chen, G. Q. Lin, Z. M. Wang, and H. Q. Liu, *Synlett*, 2002, 1265.
- 2002T55 R. Paredes, R. Abonia, J. Cadavid, R. Moreno-Fuquen, A. Jaramillo, A. Hormaza, A. Ramirez, and A. Kennedy, *Tetrahedron*, 2002, **58**, 55.
- 2002T4451 H. Bernsmann, Y. Wang, R. Fröhlich, and P. Metz, *Tetrahedron*, 2002, **58**, 4451.
- 2002T7177 H. H. Wasserman, H. Matsuyama, and R. P. Robinson, *Tetrahedron*, 2002, **58**, 7177.
- 2002T9567 F. N. Burnett and R. S. Hosmane, *Tetrahedron*, 2002, **58**, 9567.
- 2002TA1299 J. Rouden, A. Ragot, S. Gouault, D. Cahard, J. C. Plaquevent, and M. C. Lasne, *Tetrahedron Asymmetry*, 2002, **13**, 1299.
- 2002TL6861 A. Kamal, K. V. Ramana, H. B. Ankati, and A. V. Ramana, *Tetrahedron Lett.*, 2002, **43**, 6861.
- 2002TL7155 B. Danieli, G. Lesma, D. Passarella, P. Piacenti, A. Sacchetti, A. Silvani, and A. Virdis, *Tetrahedron Lett.*, 2002, **43**, 7155.
- 2002USP6417355 R. D. Chapman, T. Axenrod, J. Sun, X. P. Guan, and L. Qi, *US Pat. 6 417 355* (2002) (*Chem. Abstr.*, 2002, **137**, 78873).
- 2002WO26724 P. Bernstein, *PCT Int. Appl. WO 26724* (2002) (*Chem. Abstr.*, 2002, **136**, 294860).
- 2002WO44168 S. Dugar, B. J. Mavunkel, G. R. Luedtke, and G. Mcenroe, *PCT Int. Appl. WO 44168* (2002) (*Chem. Abstr.*, 2002, **137**, 6088).
- 2002WO060895 T. Bär, T. Martin, J. Stadlwieser, S. L. Wollin, K. Zech, and C. P. Hoff, *PCT Int. Appl. WO 060895* (2002) (*Chem. Abstr.*, 2002, **137**, 154955).
- 2002WO083690 L. Cheema, D. Cladingboel, and R. Sinclair, *PCT Int. Appl. WO 083690* (2002) (*Chem. Abstr.*, 2002, **137**, 325449).
- 2002WO083691 L. Cheema and D. Cladingboel, *PCT Int. Appl. WO 083691* (2002) (*Chem. Abstr.*, 2002, **137**, 325445).
- 2002WO085838 S. Buchwald, A. K. Lapars, J. Cantilla, G. E. Job, M. Wolter, F. Y. Kwong, G. Nordmann, and E. J. Hennessy, *PCT Int. Appl. WO 085838* (2002) (*Chem. Abstr.*, 2002, **137**, 352492).
- 2003AGE4774 G. Cuny, M. Bois-Choussy, and J. Zhu, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 4774.
- 2003AGE5198 J. S. Yadav, B. V. S. Reddy, K. V. Rao, K. S. Raj, A. R. Prasad, S. K. Kumar, A. C. Kunwar, P. Jayaprakash, and B. Jagannath, *Angew. Chem., Int. Ed.*, 2003, **42**, 5198.
- 2003ARK1 F. Carrée, C. Pardo, J. P. Galy, G. Boyer, M. Robin, and J. Elguero, *ARKIVOC*, 2003, i, 1.
- 2003AXEO745 T. Kobayashi, T. Moriwaki, and M. Shiro, *Acta Crystallogr. Sect. E*, 2003, **59**, o745.
- 2003CCL487 S. Wang, S. J. Dai, Y. Chen, S. S. Yu, and D. Q. Yu, *Chin. Chem. Lett.*, 2003, **14**, 487 (*Chem. Abstr.*, 2004, **140**, 2799).
- 2003CHE1376 S. G. Klepikova, V. K. Yu, E. E. Fomicheva, R. D. Mukhasheva, K. D. Praliev, V. A. Solomin, and K. D. Berlin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 1376.
- 2003CCL128 T. Sugimura, T. Tei, and T. Okuyama, *Chem. Lett.*, 2003, 128.
- 2003EJO3179 A. Hansson, J. Jensen, O. F. Wendt, and K. Wärnmark, *Eur. J. Org. Chem.*, 2003, 3179.
- 2003EPH85 E. Carbonnelle, F. Sparatore, C. Canu-Boido, C. Salvano, B. Baldani-Guerra, G. Terstappen, R. Zwart, H. Vijverberg, F. Clementi, and C. Gotti, *Eur. J. Pharmacol.*, 2003, **471**, 85 (*Chem. Abstr.*, 2003, **139**, 286461).
- 2003EPP1283439 T. Tanaka, N. Kagawa, Y. Iwai, and T. Oshiyama, *Eur. Pat. 1 283 439* (2002) (*Chem. Abstr.*, 2003, **138**, 161027).
- 2003FA265 C. Canu Boido, B. Tasso, V. Boido, and F. Sparatore, *Farmaco*, 2003, **58**, 265.
- 2003H(60)1793 Y. Davion, G. Guillaumont, J. M. Lèger, C. Jarry, B. Lesur, and J. Y. Mèroux, *Heterocycles*, 2003, **60**, 1793.
- 2003HCA233 C. Ensich and M. Hesse, *Helv. Chim. Acta*, 2003, **86**, 233.
- 2003JA3793 Y. Yamashita, S. Saito, H. Ishitani, and S. Kobayashi, *J. Am. Chem. Soc.*, 2003, **125**, 3793.
- 2003JCO375 R. Touzani, S. Garbacia, O. Lavastre, V. K. Yadav, and B. Carboni, *J. Comb. Chem.*, 2003, **5**, 375.
- 2003JHC373 J. Jensen, M. Strozyk, and K. Wärnmark, *J. Heterocycl. Chem.*, 2003, **40**, 373.
- 2003JNP119 D. P. Zlotos, *J. Nat. Prod.*, 2003, **66**, 119.

- 2003JOC92 Y. Pei, M. J. Lilly, D. J. Owen, L. J. D'Souza, X. Q. Tang, J. Yu, R. Nazarbarghi, A. Hunter, C. M. Anderson, S. Glasco, N. J. Ede, I. W. James, U. Maitra, S. Chandrasekaran, W. H. Moos, and S. S. Ghosh, *J. Org. Chem.*, 2003, **68**, 92.
- 2003JOC3315 S. Maraccini, D. Miguel, T. Torroba, and M. Garcia-Valverde, *J. Org. Chem.*, 2003, **68**, 3315.
- 2003JOC9166 E. C. Knuf, J. K. Jiang, and M. S. Gin, *J. Org. Chem.*, 2003, **68**, 9166.
- 2003JPO271 K. Okada, M. Tanaka, and R. Takagi, *J. Phys. Org. Chem.*, 2003, **16**, 271.
- 2003JST(647)275 T. Brukwichi and W. Wysocka, *J. Mol. Struct.*, 2003, **647**, 275.
- 2003OL1959 C. M. Smith and G. A. O'Doherty, *Org. Lett.*, 2003, **5**, 1959.
- 2003OL2793 D. Stärk, M. Witt, H. A. Oketch-Rabah, and J. W. Jaroszewski, *Org. Lett.*, 2003, **5**, 2793.
- 2003OL4795 T. Fekner, J. Gallucci, and M. K. Chan, *Org. Lett.*, 2003, **5**, 4795.
- 2003PS(178)1295 T. Takido, M. Toriyama, K. Ogura, H. Kamijo, S. Motohashi, and M. Seno, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 1295 (*Chem. Abstr.*, 2003, **139**, 323878).
- 2003RCB1667 S. A. Pissarev, N. E. Shevchenko, V. G. Nenaidenko, and E. S. Balenkova, *Russ. Chem. Bull.*, 2003, **52**, 1667.
- 2003RJC961 O. A. Nurkenov, A. M. Gazaliev, K. M. Turdybekov, A. B. Bukeeva, and I. V. Kulakov, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2003, **73**, 961.
- 2003S2518 D. Donati, S. Ferrini, S. Fusi, and F. Ponticelli, *Synthesis*, 2003, 2518.
- 2003S2839 Y. Cheng, B. Wang, and O. Meth-Cohn, *Synthesis*, 2003, 2839.
- 2003STE361 C. Arbez-Gindre, V. Berl, and J. P. Lepoittevin, *Steroids*, 2003, **68**, 361 (*Chem. Abstr.*, 2003, **140**, 42335).
- 2003T391 K. Sripha and D. P. Zlotos, *Tetrahedron*, 2003, **59**, 391.
- 2003T5531 R. Kolanoś, W. Wysocka, and T. Brukwicki, *Tetrahedron*, 2003, **59**, 5531.
- 2003TA233 S. A. Popov, Y. V. Gatilov, T. V. Rybalova, and A. V. Tkachev, *Tetrahedron Asymmetry*, 2003, **14**, 233.
- 2003TA881 T. Sugimura, A. Mori, A. Tai, T. Tei, Y. Sakamoto, and T. Okuyama, *Tetrahedron Asymmetry*, 2003, **14**, 881.
- 2003TL2083 M. Valik, B. Dolensky, H. Petříčková, P. Vašek, and V. Král, *Tetrahedron Lett.*, 2003, **44**, 2083.
- 2003TL2133 W. W. K. R. Mederski, M. Baumgarth, M. Germann, D. Kux, and T. Weitzel, *Tetrahedron Lett.*, 2003, **44**, 2133.
- 2003TL3115 T. Sugimura, T. Tei, and T. Okuyama, *Tetrahedron Lett.*, 2003, **44**, 3115.
- 2003TL6513 T. Saito, T. Horikoshi, T. Otani, Y. Matsuda, and T. Karakasa, *Tetrahedron Lett.*, 2003, **44**, 6513.
- 2003USP0225268 W. H. Bunnelle, D. C. Barlocco, J. F. Daanen, M. J. Dart, M. D. Meyer, K. B. Ryther, M. R. Schrimpf, K. B. Sippy, and R. B. Toupençe, *US Pat.* 0 225 268 (2003) (*Chem. Abstr.*, 2004, **140**, 16752).
- 2003WO049527 M. E. Fraley, G. D. Hartman, and W. F. Man, *PCT Int. Appl.* WO 049527 (2003) (*Chem. Abstr.*, 2003, **139**, 47130).
- 2003WO049678 M. E. Fraley and R. M. Garbaccio, *PCT Int. Appl.* WO 049678 (2003) (*Chem. Abstr.*, 2003, **139**, 53029).
- 2003WO049679 M. E. Fraley, G. D. Hartman, and W. F. Hoffman, *PCT Int. Appl.* WO 049679 (2003) (*Chem. Abstr.*, 2003, **139**, 69275).
- 2003WO099211 P. Coleman, G. D. Hartman, and L. A. Neilson, *PCT Int. Appl.* WO 099211 (2003) (*Chem. Abstr.*, 2004, **140**, 16735).
- 2004ARK86 T. Mas, C. Pardo, and J. Elguero, *ARKIVOC*, 2004, iv, 86.
- 2004BMC2653 C. J. Ohnmacht, J. S. Albert, P. R. Bernstein, W. L. Rumsey, B. B. Masek, B. T. Dembofsky, G. M. Koether, D. W. Andisik, and D. Aharony, *Bioorg. Med. Chem.*, 2004, **12**, 2653.
- 2004CHE641 A. T. Soldatenkov, K. B. Polyanskii, A. V. Temesgen, N. D. Sergeeva, V. V. Vysotskaya, B. B. Averkiev, M. Y. Antipin, and N. N. Lobanov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 641.
- 2004CPB675 T. Kaneko, R. S. J. Clark, N. Ohi, F. Ozaki, T. Kawahara, A. Kamada, K. Okano, H. Yokohama, M. Ohkuro, K. Muramoto, O. Takenaka, and S. Kobayashi, *Chem. Pharm. Bull.*, 2004, **52**, 675.
- 2004EJO1097 T. Mas, C. Pardo, F. Salort, J. Elguero, and M. R. Torres, *Eur. J. Org. Chem.*, 2004, 1097.
- 2004EJO1894 M. J. Johansson, L. O. Schwartz, M. Amedjkouh, and N. C. Kann, *Eur. J. Org. Chem.*, 2004, 1894.
- 2004EJO2375 D. P. Zlotos, *Eur. J. Org. Chem.*, 2004, 2375.
- 2004EJO5040 S. Gerber-Lemaire and P. Vogel, *Eur. J. Org. Chem.*, 2004, 5040.
- 2004H(62)235 K. Okada, M. Tanaka, and K. Ohkata, *Heterocycles*, 2004, **62**, 235.
- 2004HCA1493 K. Meilert, G. R. Pettit, and P. Vogel, *Helv. Chim. Acta*, 2004, **87**, 1493.
- 2004IJB2231 V. Sangeetha and K. J. R. Prasad, *Indian J. Chem., Sect. B*, 2004, **43**, 2231.
- 2004JA3529 A. Klapars, S. Parris, K. W. Anderson, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 3529.
- 2004JA8744 H. Ohno, H. Hamaguchi, M. Ohata, S. Kosaka, and T. Tanaka, *J. Am. Chem. Soc.*, 2004, **126**, 8744.
- 2004JA11966 B. M. Trost, H. C. Shen, L. Dong, J. P. Surivet, and C. Sylvain, *J. Am. Chem. Soc.*, 2004, **126**, 11966.
- 2004JA14475 G. Cuny, M. Bois-Choussy, and J. Zhu, *J. Am. Chem. Soc.*, 2004, **126**, 14475.
- 2004JA15480 P. O'Brien, K. B. Wiberg, W. F. Bailey, J.-P. R. Hermet, and M. J. McGrath, *J. Am. Chem. Soc.*, 2004, **126**, 15480.
- 2004JCO54 P. Arya, P. Durieux, Z.-X. Chen, R. Joseph, and D. M. Leek, *J. Comb. Chem.*, 2004, **6**, 54.
- 2004JCO828 A. V. Ivachtchenko, S. E. Tkachenko, Y. B. Sandulenko, V. Y. Vvdensky, and A. V. Khvat, *J. Comb. Chem.*, 2004, **6**, 828.
- 2004JME3561 D. P. Zlotos, S. Buller, N. Stiefl, K. Baumann, and K. Mohr, *J. Med. Chem.*, 2004, **47**, 3561.
- 2004JOC86 C. Zhou and D. M. Birney, *J. Org. Chem.*, 2004, **69**, 86.
- 2004JOC1248 T. Olszewska, M. Gdaniec, and T. Poloński, *J. Org. Chem.*, 2004, **69**, 1248.
- 2004JOC5627 E. M. Beccalli, G. Brogini, G. Paladino, A. Penoni, and C. Zoni, *J. Org. Chem.*, 2004, **69**, 5627.
- 2004JOC5789 M. J. Dearden, M. J. McGrath, and P. O'Brien, *J. Org. Chem.*, 2004, **69**, 5789.
- 2004JST(688)111 B. Jasiewicz, W. Boczoń, B. Warżajtis, and U. Rychlewska, *J. Mol. Struct.*, 2004, **688**, 111.
- 2004MCC235 T. Mas, C. Pardo, and J. Elguero, *Mendeleev Commun.*, 2004, **14**, 235.
- 2004MI582 V. A. Saprykina, V. I. Vinogradova, R. F. Ambartsumova, T. F. Ibragimov, A. Sultankulov, and Kh. M. Shakhidoyatov, *Chem. Nat. Compd.*, 2004, **40**, 582 (*Chem. Abstr.*, 2005, **143**, 440601).
- 2004MI1368 E. D. Jacob and L. Mathew, *Curr. Sci.*, 2004, **86**, 1368 (*Chem. Abstr.*, 2005, **142**, 261518).
- 2004OBC2483 E. Quesada, M. Stockley, J. P. Ragot, M. E. Prime, A. C. Whitwood, and R. J. K. Taylor, *Org. Biomol. Chem.*, 2004, **2**, 2483.
- 2004OL127 L. S. Li, S. Das, and S. C. Sinha, *Org. Lett.*, 2004, **6**, 127.
- 2004OL493 B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, A. Silvani, and A. Virdis, *Org. Lett.*, 2004, **6**, 493.
- 2004OL2965 B. S. Lucas, L. M. Luther, and S. D. Burke, *Org. Lett.*, 2004, **6**, 2965.
- 2004OL4439 T. Sugimura, Y. Sato, C. Y. Im, and T. Okuyama, *Org. Lett.*, 2004, **6**, 4439.
- 2004PCJ311 R. Yu. Khisamutdinova, N. N. Yarmukhamedov, S. F. Gabdrakhmanova, L. T. Karachurina, T. A. Sapozhnikova, N. Z. Baibulatova, N. Z. Baschenko, and F. S. Zarudii, *Pharm. Chem. J.*, 2004, **38**, 311 (*Chem. Abstr.*, 2005, **142**, 411207).

- 2004RCB2262 L. Y. Ukhin and L. G. Kuz'mina, *Russ. Chem. Bull.*, 2004, **53**, 2262.
- 2004RJA1321 T. S. Zhivotova, A. M. Gazaliev, M. K. Ibraev, S. D. Fazylov, and R. Z. Kasenov, *Russ. J. Appl. Chem.*, 2004, **77**, 1321 (*Chem. Abstr.*, 2005, **142**, 392554).
- 2004RJC1133 S. D. Fazylov, A. M. Gazaliev, A. B. Karimova, and S. Zh. Kudaibergenova, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2004, **74**, 1133.
- 2004RJO719 M. K. Ibraev, D. M. Turdybekov, S. D. Fazylov, K. M. Turdybekov, A. M. Gazaliev, and T. S. Zhivotova, *Russ. J. Org. Chem. (Engl. Transl.)*, 2004, **40**, 719.
- 2004S405 J. S. Yadav, B. V. S. Reddy, and B. Padmavani, *Synthesis*, 2004, 405.
- 2004S1687 U. Kiehne and A. Lützen, *Synthesis*, 2004, 1687.
- 2004T2583 D. Scarpi, D. Stranges, L. Cecchi, and A. Guarna, *Tetrahedron*, 2004, **60**, 2583.
- 2004T2857 W. Heilmayer, R. Smounig, K. Gruber, W. M. F. Fabian, C. Reidlinger, C. O. Kappe, C. Wentrup, and G. Kollenz, *Tetrahedron*, 2004, **60**, 2857.
- 2004T3261 J. S. Yadav, B. V. S. Reddy, M. Srinivas, and B. Padmavani, *Tetrahedron*, 2004, **60**, 3261.
- 2004T4481 Y. Ishichi, Y. Ikeura, and H. Natsugari, *Tetrahedron*, 2004, **60**, 4481.
- 2004TL1377 A. Hassner, B. Sun, G. Gellermann, and S. Meir, *Tetrahedron Lett.*, 2004, **45**, 1377.
- 2004TL1543 J. S. Yadav, B. V. S. Reddy, G. Parimala, and A. K. Raju, *Tetrahedron Lett.*, 2004, **45**, 1543.
- 2004TL4877 E. Quesada, M. Stockley, and R. J. K. Taylor, *Tetrahedron Lett.*, 2004, **45**, 4877.
- 2004TL5601 S. K. Abella, F. S. Rodembucsh, and V. Stefani, *Tetrahedron Lett.*, 2004, **45**, 5601.
- 2004TL6733 A. V. Ivachtchenko, A. Khvat, S. E. Tkachenko, Y. B. Sandulenko, and V. Y. Vvedensky, *Tetrahedron Lett.*, 2004, **45**, 6733.
- 2004TL8111 J. Chen, G. Q. Lin, and H. Q. Liu, *Tetrahedron Lett.*, 2004, **45**, 8111.
- 2004TL8475 S. Seto, *Tetrahedron Lett.*, 2004, **45**, 8475.
- 2004USP0186134 S. P. O'Connor, M. Lawrence, Y. Shi, and P. D. Stein, *US Pat.* 0 186 134 (2004) (*Chem. Abstr.*, 2004, **141**, 295864).
- 2004USP0224267 H. Itoh, *US Pat.* 0 224 267 (2004) (*Chem. Abstr.*, 2004, **141**, 417852).
- 2004USP0224983 B. Allison, L. C. McAtee, V. K. Phuong, M. H. Rabinowitz, and N. P. Shankley, *US Pat.* 0 224 983 (2004) (*Chem. Abstr.*, 2004, **141**, 410932).
- 2004WO010136 D. Ofer, *PCT Int. Appl.* WO 010136 (2004) (*Chem. Abstr.*, 2004, **140**, 139446).
- 2004WO035592 D. Cladingboel, *PCT Int. Appl.* WO 035592 (2004) (*Chem. Abstr.*, 2004, **140**, 357385).
- 2004WO039364 H. Bischoff, C. Schmeck, D. Schmidt, A. Vakalopoulos, and G. Wirtz, *PCT Int. Appl.* WO 039364 (2004) (*Chem. Abstr.*, 2004, **140**, 400081).
- 2004WO045591 M. Straub, J. W. C. M. Jansen, M. H. De Vries, C. R. Steinborn, and W. Cautreels, *PCT Int. Appl.* WO 045591 (2004) (*Chem. Abstr.*, 2004, **141**, 12308).
- 2004WO058767 A. Nakazato, T. Okubo, D. Nozawa, M. Yamaguchi, T. Tamita, L. E. J. Kennis, M. F. L. Bruyn, J.-P. A. Bongartz, F. M. A. Van De Keybus, Y. E. M. Van Roosbroeck, M. G. M. Luyckx, and R. J. M. Hendrickx, *PCT Int. Appl.* WO 058767 (2004) (*Chem. Abstr.*, 2004, **141**, 123649).
- 2004WO074291 J. S. Bryans, P. S. Johnson, T. Ryckmans, and A. Stobie, *PCT Int. Appl.* WO 074291 (2004) (*Chem. Abstr.*, 2004, **141**, 225517).
- 2004WO103991 A. V. Ivashchenko, V. Y. Vvedensky, A. Y. Agarkov, Y. B. Sandulenko, S. V. Shkavrov, D. V. Kravchenko, S. Y. Tkachenko, A. V. Khvat, and I. M. Okun, *PCT Int. Appl.* WO 103991 (2004) (*Chem. Abstr.*, 2005, **142**, 6567).
- 2004WO110996 T. Wager, W. M. J. Welch, and B. T. O'Neill, *PCT Int. Appl.* WO 110996 (2004) (*Chem. Abstr.*, 2005, **142**, 93683).
- 2005ASC555 B. Lesch, J. Torång, S. Vanderheiden, and S. Bräse, *Adv. Synth. Catal.*, 2005, **347**, 555 (*Chem. Abstr.*, 2006, **144**, 88265).
- 2005ASC1811 B. C. Ranu and R. Jana, *Adv. Synth. Catal.*, 2005, **347**, 1811 (*Chem. Abstr.*, 2006, **145**, 210976).
- 2005AXE03941 I. Matulková, K. Teubner, I. Němec, J. Rohovec, and Z. Mička, *Acta Crystallogr. Sect. E*, 2005, **61**, o3941.
- 2005BMC5717 S. Seto, A. Tanioka, M. Ikeda, and S. Izawa, *Bioorg. Med. Chem.*, 2005, **13**, 5717.
- 2005BML1479 S. Seto, A. Tanioka, M. Ikeda, and S. Izawa, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1479.
- 2005BML1485 S. Seto, A. Tanioka, M. Ikeda, and S. Izawa, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1485.
- 2005BML3611 D. Brückner, F. T. Hafner, V. Li, C. Schmeck, J. Telser, A. Vakalopoulos, and G. Wirtz, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3611.
- 2005BML4291 K. A. Oppong, C. D. Ellis, M. C. Lauferweiler, S. V. O'Neil, Y. Wang, D. L. Soper, M. W. Baize, J. A. Wos, B. De, G. K. Bosch, A. N. Fancher, W. Lu, M. K. Suchanek, R. L. Wang, and T. P. Demuth, Jr., *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4291.
- 2005CPB444 T. Masuko, K. Metori, Y. Kizawa, T. Kusama, and M. Miyake, *Chem. Pharm. Bull.*, 2005, **53**, 444.
- 2005EPP1634575 A. Lagrange, *Eur. Pat.* 1 634 575 (2005) (*Chem. Abstr.*, 2006, **144**, 298824).
- 2005JA11819 E. L. Clennan, S. E. Hightower, and A. Greer, *J. Am. Chem. Soc.*, 2005, **127**, 11819.
- 2005JA14776 S.-M. Lu and H. Alper, *J. Am. Chem. Soc.*, 2005, **127**, 14776.
- 2005JCM440 A. Z. A. Hassanien, M. H. Mohamed, and S. A. S. Gohzlan, *J. Chem. Res.*, 2005, 440.
- 2005JST(737)75 R. Kolanoś, W. Wysocka, T. Borowiak, G. Dutkiewicz, and T. Brukwicki, *J. Mol. Struct.*, 2005, **737**, 75.
- 2005MI1228 P. J. Zhao, L. M. Fan, G. H. Li, N. Zhu, and Y. M. Shen, *Arch. Pharm. Res.*, 2005, **28**, 1228 (*Chem. Abstr.*, 2006, **144**, 124666).
- 2005MM2143 M. Phelan, F. Aldabbagh, P. B. Zetterlund, and B. Yamada, *Macromolecules*, 2005, **38**, 2143.
- 2005MRC479 V. Vijayakumar and M. Sundaravadivelu, *Magn. Reson. Chem.*, 2005, **43**, 479.
- 2005OBC1557 T. Buttler, I. Fleming, S. Gonsior, B.-H. Kim, A. Y. Sung, and H.-G. Woo, *Org. Biomol. Chem.*, 2005, **3**, 1557.
- 2005OL167 B. Dolenský, M. Valík, D. Šýkora, and V. Král, *Org. Lett.*, 2005, **7**, 67.
- 2005OL1181 D. E. Ward, V. Jheengut, and O. T. Akinnusi, *Org. Lett.*, 2005, **7**, 1181.
- 2005OL2019 A. Hansson, T. Wixe, K.-E. Bergquist, and K. Wärnmark, *Org. Lett.*, 2005, **7**, 2019.
- 2005OL4459 D. Stead, P. O'Brien, and A. J. Sanderson, *Org. Lett.*, 2005, **7**, 4459.
- 2005OL4721 P. R. Blakemore, C. Kilner, N. R. Norcross, and P. C. Astles, *Org. Lett.*, 2005, **7**, 4721.
- 2005OL5817 D. V. Sadasivam and D. M. Birney, *Org. Lett.*, 2005, **7**, 5817.
- 2005PLMI12046 M. Phelan, F. Aldabbagh, P. B. Zetterlund, and B. Yamada, *Polymer*, 2005, **46**, 12046 (*Chem. Abstr.*, 2006, **144**, 213128).
- 2005S1888 B. Lesch, J. Torång, M. Nieger, and S. Bräse, *Synthesis*, 2005, 1888.
- 2005SC1493 H. Pessoa-Mahana, K. G. M. Aranguiz, R. Araya-Maturana, and C. D. Pessoa-Mahana, *Synth. Commun.*, 2005, **35**, 1493.
- 2005T941 J. B. Bremner and W. Sengpracha, *Tetrahedron*, 2005, **61**, 941.
- 2005TA1969 M. Valík, B. Dolenský, E. Herdtweck, and V. Král, *Tetrahedron Asymmetry*, 2005, **16**, 1969.
- 2005TL5577 L. Revesz, E. Blum, and R. Wicki, *Tetrahedron Lett.*, 2005, **46**, 5577.
- 2005TL7121 B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, and A. Silvani, *Tetrahedron Lett.*, 2005, **46**, 7121.

- 2005USP0054667 W. Cautreels, C. Steinborn, M. Straub, K. Beckman, and J. W. C. M. Jansen, *US Pat.* 0 054 667 (2005) (*Chem. Abstr.*, 2005, **142**, 291382).
- 2005USP0106513 A. Matsunaga, M. Kikuchi, K. Morimoto, M. Taniguchi, and N. Hanaki, *US Pat.* 0 106 513 (2005) (*Chem. Abstr.*, 2005, **142**, 472558).
- 2005USP0239767 M. K. Chan and T. Fekner, *US Pat.* 0 239 767 (2005) (*Chem. Abstr.*, 2005, **143**, 422352).
- 2005WO011690 W. Cautreels, C. Steinborn, M. Straub, K. Beckmann, and J. W. C. M. Jansen, *PCT Int. Appl.* WO 011690 (2005) (*Chem. Abstr.*, 2005, **142**, 191265).
- 2005WO019225 I. Araya and S. Kanazawa, *PCT Int. Appl.* WO 019225 (2005) (*Chem. Abstr.*, 2005, **142**, 280235).
- 2005WO030207 D. Thormaehlen, M. Straub, J. Jansen, and C. Antzelevitch, *PCT Int. Appl.* WO 030207 (2005) (*Chem. Abstr.*, 2005, **142**, 349064).
- 2005WO084296 B. E. Fink, A. V. Gavai, G. D. Vite, W.-C. Han, R. N. Misra, H.-Y. Xiao, D. J. Norris, and J. S. Tokarski, *PCT Int. Appl.* WO 084296 (2005) (*Chem. Abstr.*, 2005, **143**, 306202).
- 2005WO103054 R. Heng, L. Révész, A. Schlapbach, and R. Wächli, *PCT Int. Appl.* WO 103054 (2005) (*Chem. Abstr.*, 2005, **143**, 440438).
- 2005WO115361 N. Schlienger, J. Pawlas, A. Fejzic, R. Olsson, B. W. Lund, F. Badalassi, R. Lewinsky, and M. B. Thygesen, *PCT Int. Appl.* WO 115361 (2005) (*Chem. Abstr.*, 2006, **144**, 36358).
- 2006AXEo3479 M. Faroughi, A. C. Try, and P. Turner, *Acta Crystallogr. Sect. E*, 2006, **62**, o3479.
- 2006AXEo3674 M. Faroughi, A. C. Try, and P. Turner, *Acta Crystallogr. Sect. E*, 2006, **62**, o3674.
- 2006AXEo3893 M. Faroughi, A. C. Try, and P. Turner, *Acta Crystallogr. Sect. E*, 2006, **62**, o3893.
- 2006AXEo4887 M. D. H. Bhuiyan, A. C. Try, J. Klepetko, and P. Turner, *Acta Crystallogr. Sect. E*, 2006, **62**, o4887.
- 2006CC3190 N. E. J. Gooseman, D. O'Hagan, A. M. Z. Slawin, A. M. Teale, D. J. Tozer, and R. J. Young, *J. Chem. Soc., Chem. Commun.*, 2006, 3190.
- 2006CRV4644 G. Zeni and R. C. Larock, *Chem. Rev.*, 2006, **106**, 4644.
- 2006EJO2987 A. Leganza, C. Bezze, C. Zonta, F. Fabris, O. De Lucchi, and A. Linden, *Eur. J. Org. Chem.*, 2006, 2987.
- 2006JHC519 Y.-D. Park, S.-D. Cho, J.-J. Kim, H.-K. Kim, D.-H. Kweon, S.-G. Lee, and Y.-J. Yoon, *J. Heterocycl. Chem.*, 2006, **43**, 519.
- 2006JME3159 K. Audouze, E. Ø. Nielsen, G. M. Olsen, P. Ahring, T. D. Jørgensen, D. Peters, T. Liljefors, and T. Balle, *J. Med. Chem.*, 2006, **49**, 3159.
- 2006JME3602 D. Fattori, C. Rossi, C. I. Fincham, M. Berettoni, F. Calvani, F. Catrambone, P. Felicetti, M. Gensini, R. Terracciano, M. Altamura, A. Bressan, S. Giuliani, C. A. Maggi, S. Meini, C. Valenti, and L. Quartara, *J. Med. Chem.*, 2006, **49**, 3602.
- 2006JNP1300 B. Rasmussen, A.-J. Nkurunziza, M. Witt, H. A. Oketch-Rabah, J. W. Jaroszewski, and D. Stærk, *J. Nat. Prod.*, 2006, **69**, 1300.
- 2006JOC413 C. M. Park, *J. Org. Chem.*, 2006, **71**, 413.
- 2006JOC1247 E. L. Clennan and S. E. Hightower, *J. Org. Chem.*, 2006, **71**, 1247.
- 2006JOC3291 A. Neogi, T. P. Majhi, R. Mukhopadhyay, and P. Chattopadhyay, *J. Org. Chem.*, 2006, **71**, 3291.
- 2006JOC4678 M. D'hooghe, T. Vanlangendonck, K. W. Törnroos, and N. De Kimpe, *J. Org. Chem.*, 2006, **71**, 4678.
- 2006MI470 V. A. Saprykina, V. I. Vinogradova, R. F. Ambartsumova, T. F. Ibragimov, and Kh. M. Shakhidoyatov, *Chem. Nat. Compd.*, 2006, **42**, 470 (*Chem. Abstr.*, 2007, **146**, 45630).
- 2006MI2475 M. Phelan, F. Aldabbagh, P. B. Zetterlund, and B. Yamada, *Eur. Polym. J.*, 2006, **42**, 2475 (*Chem. Abstr.*, 2007, **146**, 8382).
- 2006MI1934 M. Ochiai, K. Kuwabara, D. Nagai, T. Miyagawa, and T. Endo, *Eur. Polym. J.*, 2006, **42**, 1934 (*Chem. Abstr.*, 2006, **145**, 315344).
- 2006OL3399 J. I. Halliday, M. Chebib, P. Turner, and M. D. McLeod, *Org. Lett.*, 2006, **8**, 3399.
- 2006OL4867 M. Havlík, V. Král, and B. Dolenský, *Org. Lett.*, 2006, **8**, 4867.
- 2006OS141 A. J. Dixon, M. J. McGrath, and P. O'Brien, *Org. Synth.*, 2006, **83**, 141.
- 2006RJC129 O. A. Nurkenov, G. G. Baikenova, D. M. Turdybekov, M. K. Ibraev, A. M. Gazaliev, and K. M. Turdybekov, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2006, **76**, 129.
- 2006T8591 M. Valík, J. Malina, L. Palivec, J. Foltýnová, M. Tkadlecová, M. Urbanová, V. Brabec, and V. Král, *Tetrahedron*, 2006, **62**, 8591.
- 2006T10724 E. L. Clennan and C. Liao, *Tetrahedron*, 2006, **62**, 10724.
- 2006T12051 P. Ács, E. Müller, G. Rangits, T. Löränd, and L. Kollár, *Tetrahedron*, 2006, **62**, 12051.
- 2006TA1049 L. Palivec, M. Valík, V. Král, and M. Urbanová, *Tetrahedron Asymmetry*, 2006, **17**, 1049.
- 2006TA1116 S. Satishkumar and M. Periasamy, *Tetrahedron Asymmetry*, 2006, **17**, 1116.
- 2006TA2191 D. A. Lenev, D. G. Golonavov, K. A. Lyssenko, and R. G. Kostyanovsky, *Tetrahedron Asymmetry*, 2006, **17**, 2191.
- 2006TL2581 F. H. V. Chau and E. J. Corey, *Tetrahedron Lett.*, 2006, **47**, 2581.
- 2006TL4769 Y. Peng, H. Sun, and S. Wang, *Tetrahedron Lett.*, 2006, **47**, 4769.
- 2006USP7145003 H. G. Adolph and A. G. Stern, *US Pat.* 7 145 003 (2006) (*Chem. Abstr.*, 2007, **146**, 29528).
- 2006WO122074 A. S. Abuelyaman, S. B. Mitra, K. M. Lewandowski, D. J. Plaut, and T. D. Jones, *PCT Int. Appl.* WO 122074 (2006) (*Chem. Abstr.*, 2006, **145**, 495785).
- 2006WO122081 A. S. Abuelyaman, S. B. Mitra, K. M. Lewandowski, and D. J. Plaut, *PCT Int. Appl.* WO 122081 (2006) (*Chem. Abstr.*, 2006, **145**, 506648).
- 2006WO137769 E. Anderson, D. Cladingboel, G. Ensor, D. Holmes, and M. Purdie, *PCT Int. Appl.* WO 137769 (2006) (*Chem. Abstr.*, 2007, **146**, 100734).
- 2006WO137770 D. Cladingboel and G. Ensor, *PCT Int. Appl.* WO 137770 (2006) (*Chem. Abstr.*, 2007, **146**, 100735).

14.08

Eight-membered Rings with Three Heteroatoms

D. O. Tymoshenko

Albany Molecular Research, Inc., Albany, NY, USA

© 2008 Elsevier Ltd. All rights reserved.

14.08.1	Introduction	476
14.08.1.1	Scope of the Chapter	476
14.08.1.2	Structural Types	477
14.08.2	Theoretical Methods	477
14.08.2.1	Semi-empirical Methods	477
14.08.2.2	Molecular Mechanics	477
14.08.2.2.1	Trioxocines	477
14.08.2.2.2	Dioxazacines	478
14.08.3	Experimental Structural Methods	478
14.08.3.1	X-Ray Crystallography	478
14.08.3.1.1	Triazocines	478
14.08.3.1.2	Trioxocine	479
14.08.3.1.3	Trithiocines	479
14.08.3.1.4	Oxadiazocines	479
14.08.3.1.5	Thiodiazocines	479
14.08.3.1.6	Dioxazocines	480
14.08.3.1.7	Dioxathiocines	480
14.08.3.2	NMR Spectroscopy	480
14.08.3.3	Mass Spectrometry	482
14.08.3.4	UV Spectroscopy	482
14.08.3.5	IR and Raman Spectroscopy	483
14.08.4	Thermodynamic Aspects	483
14.08.4.1	Intermolecular Forces	483
14.08.4.2	Conformational Studies	483
14.08.4.3	Kinetics	484
14.08.5	Reactivity of Nonconjugated Rings	484
14.08.5.1	Intramolecular Thermal and Photochemical Reactions	484
14.08.5.2	Electrophilic Attack on Ring Heteroatoms	485
14.08.5.2.1	Electrophilic attack on ring nitrogen	485
14.08.5.2.2	Electrophilic attack on ring oxygen	487
14.08.5.3	Reactions with Nucleophiles	487
14.08.5.4	Oxidation and Reduction	488
14.08.5.5	Intramolecular Ring-transformation Reactions	489
14.08.6	Reactivity of Substituents Attached to Ring Carbon Atoms	489
14.08.6.1	Alkyl Groups and Further Carbon Functional Groups	489
14.08.6.2	O-Linked Groups	489
14.08.6.3	S-Linked Groups	490
14.08.7	Ring Syntheses from Acyclic Compounds	490
14.08.7.1	Ring Formation by Intramolecular Cyclization	490
14.08.7.1.1	C–C bond formation	490

14.08.7.1.2	C–N bond formation	491
14.08.7.1.3	C–O bond formation	493
14.08.7.1.4	C–S bond formation	495
14.08.7.1.5	S–S bond formation	496
14.08.7.2	Ring Formation by [7+1] Cyclization	496
14.08.7.2.1	C–C bond formation	496
14.08.7.2.2	C–N bond formation	497
14.08.7.2.3	C–O bond formation	499
14.08.7.2.4	C–S bond formation	500
14.08.7.2.5	N–S bond formation	502
14.08.7.2.6	O–S bond formation	502
14.08.7.3	Ring Formation by [6+2] Cyclization	502
14.08.7.3.1	C–N bond formation	502
14.08.7.3.2	C–O bond formation	503
14.08.7.4	Ring Formation by [5+3] Cyclization	503
14.08.7.4.1	C–C bond formation	503
14.08.7.4.2	C–N bond formation	503
14.08.7.4.3	C–O bond formation	504
14.08.7.4.4	C–S bond formation	505
14.08.7.5	Miscellaneous Methods	505
14.08.8	Ring Syntheses by Transformation of Another Ring	506
14.08.8.1	Ring Expansion by Ionic Ring Openings	506
14.08.8.1.1	Trithiocines	506
14.08.8.1.2	Dioxazonines	508
14.08.8.2	Miscellaneous Ring Expansion Methods	509
14.08.8.2.1	Triazocines	509
14.08.8.2.2	Thiodiazocines	509
14.08.8.2.3	Dioxathiocines	510
14.08.8.2.4	Dithiazocines	511
14.08.8.2.5	Oxadithiacines	511
14.08.8.2.6	Oxathiazocines	511
14.08.9	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	512
14.08.10	Important Compounds and Applications	512
14.08.11	Further Developments	513
References		514

14.08.1 Introduction

14.08.1.1 Scope of the Chapter

Eight-membered rings with three heteroatoms were reviewed in CHEC(1984), where they were treated in the single chapter with eight-membered heterocycles with other numbers of heteroatoms. CHEC-II(1996) covered the developments of this class of heterocycles up to 1994, and included data on nitrogen, sulfur, and/or oxygen heterocycles, as well as particular examples of phosphorus- and boron-containing ring systems. Synthesis of eight-membered heterocycles and heteroannulenes with one or more heteroatoms, including systems with three heteroatoms, was a part of reviews published recently <1999RCC(4)1, 2004SOS(17)979>.

Numerous reviews cover the synthesis, structures, reactivity, and applications of eight-membered heterocycles as a part of the general medium-size ring discussion <2005PHC(17)418, 2004PHC(16)451, 2003PHC(15)431, 2002PHC(14)356, 2001PHC(13)378, 2000PHC(12)352, 1999PHC(11)338, 1998PHC(10)335, 1996PHC(8)320>.

14.08.1.2 Structural Types

A large number of eight-membered heterocyclic systems containing three heteroatoms is known. Only those rings with nitrogen, oxygen, and/or sulfur heteroatoms, and their fused derivatives, are covered in this chapter. Ring systems with phosphorus, boron, and other heteroatoms as well as bridged systems are discussed in the corresponding chapters of this volume. Particular types of rings and their fused derivatives discussed in this chapter are reviewed in the order of nitrogen-, oxygen-, and sulfur-containing heterocycles, beginning with rings containing three identical heteroatoms, that is, triazocines, trioxocines, and trithiocines. All six possible combinations of eight-membered systems with three heteroatoms are surveyed in the order oxadiazocines, thiodiazocines, dioxazocines, dithiazocines, oxadithiocines, and dioxathiocines, followed by N,O,S-containing oxathiazocines.

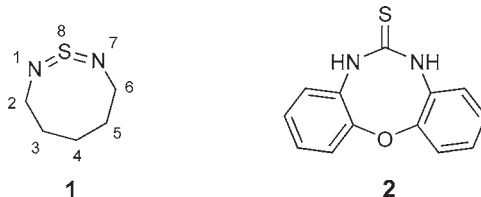
14.08.2 Theoretical Methods

Semi-empirical and molecular mechanics calculations have been widely used in the study of eight-membered heterocycles with three heteroatoms. Theoretical studies have centered on conformations of this class of heterocines, which usually belong to four low-energy conformational families classified as boat-chair, crown, boat, and chair forms (see Section 14.08.4.2).

14.08.2.1 Semi-empirical Methods

Modified neglect of diatomic overlap (MNDO) semi-empirical self-consistent field molecular orbital (SCF MO) calculations were used to investigate the conformational properties of eight-membered ring sulfur diimide **1** <1996JMT79>. Structure **1** is of a particular interest since the sulfur diimide moiety places considerable restraint on internal movements and, in contrast to most eight-membered rings, conformational inversion takes place at only one part of the ring. Five geometries were found to be important for a description of the conformational features of **1**. Three of these geometries correspond to energy minima, and two are one-dimensional (1-D) energy maxima (saddle points or transition states). Chair and boat conformations are most important because they are expected to be significantly populated at room temperature. The most stable conformation of **1** and the starting geometry for semi-empirical calculations is the chair, which has C_s symmetry. By changing ϕ_{3456} and ϕ_{4567} , a smooth conformational change occurred, leading to a transition state. Upon further changing of the same torsional angles, another energy minimum conformation, the boat, was obtained, which is 4.5 kJ mol⁻¹ higher than 4-C. The calculated strain energy for the transition state is 29.6 kJ mol⁻¹ higher than that for the chair conformation. By changing ϕ_{2345} in the boat conformation from 44° to -2°, another transition state was obtained which had a calculated strain energy of 21.7 kJ mol⁻¹ above that of the chair. Further changing of this torsion to +51° leads to yet another minimum-energy conformation, the twisted boat. As this conformation is 11.4 kJ mol⁻¹ less stable than chair, it is not expected to be populated at room temperature.

Geometry and electronic structure of 5*H*-dibenzo[*b,g*][1,4,6]oxadiazocine-6(7*H*)-thione **2** were studied using semi-empirical AM1 method <2002APH379>. The molecule forms in the space a characteristic butterfly shape with the angle of 119.3° between planes formed by phenyl rings.

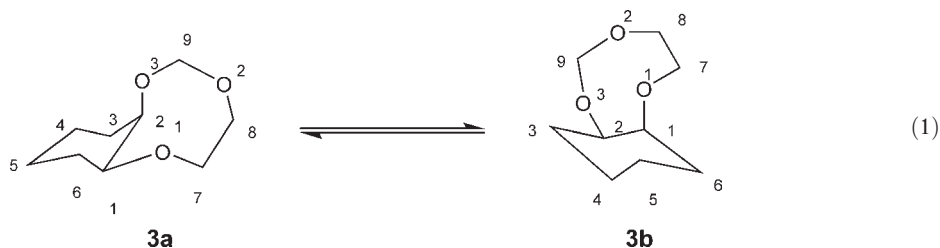


14.08.2.2 Molecular Mechanics

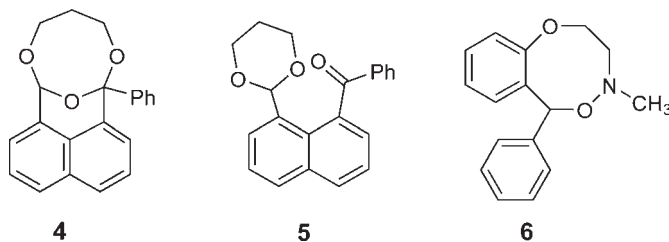
14.08.2.2.1 Trioxocines

Merck molecular force field (MMFF) calculations were performed for octahydrobenzo[*d*][1,3,6]trioxocine (Equation 1; <1999MRC401>). They indicated a preference of ca. 1.8 kJ mol⁻¹ for the most populated conformation **3b**, which is in reasonable agreement with ¹³C NMR experimental value of 4.4 kJ mol⁻¹. In the preferred conformer, the

geometry of the heterocyclic ring is a boat-chair, which is in agreement with one of the two populated conformations of 1,3,6-trioxocane itself. The conformations in the C(8)–O(2)–C(9)–O(3) and O(2)–C(9)–O(3)–C(2) units are both *gauchoid* because of the anomeric effect. In the less favored conformer **3a**, the preferred calculated conformation is a twist boat-chair. Such a form has been postulated to exist in 1,3,6-trioxocane itself due to transannular repulsions between oxygen atoms. For **3a**, the O(2)–C(9)–O(3)–C(2) moiety has a *gauche*-type geometry in accord with the anomeric effect, but the C(8)–O(2)–C(9)–O(3) unit has a torsion angle of -14.6° .



Structural modeling of the bicyclic acetal **4** using molecular mechanics (MM2) combined with a Monte Carlo conformational search procedure indicates that the 1,3,5-trioxocane ring adopts three well-defined, recognizable conformations: a boat-chair, a twist-chair-chair, and a crown with MM2 strain energies 18.058, 22.000, and 22.691 kcal mol⁻¹, respectively <1998J(P1)2353>. The structure of molecule **4** in the solid state corresponds to a boat-chair conformation, essentially the same as the global minimum identified by molecular mechanics. Comparison of the calculated and solid-state molecular structures of the isomeric keto acetal **5** reveals marked differences in the orientations of the 1,3-dioxanyl and benzoyl groups. From heats of formation calculated for minimized structures (MOPAC-PM3), the bicyclic acetal **4** is more stable than the keto acetal **5** by about 1.7 kcal mol⁻¹.



14.08.2.2.2 Dioxazacines

Molecular mechanics calculations using MMX-93 field were performed for four conformations of 4-methyl-6-phenyl-2,3,4,6-tetrahydrobenzo[*l*][1,5,2]dioxazocine **6** to predict its conformational behavior in solid state and solution <1995NJC1099>. Conformations of **6** are determined by vicinal lone pair electrostatic interactions. Two twist-chair-flattened-chair conformations (TCfC) are characterized by two *antidinal* lone pair (LP) arrangements (conformer A) and one *synperiplanar* and one *antidinal* LP–LP arrangement (conformer B). Their energies were compared to two boat–boat (BB) conformers C and D, with one *antiperiplanar* and one *synclinal* LP–LP, and two *synclinal* vicinal LP–LP arrangements, respectively. The ordering of energies was B > D > C > A which was in good correspondence with X-ray and ¹H nuclear magnetic resonance (NMR) data (see Sections 14.08.3.1.6 and 14.08.3.2).

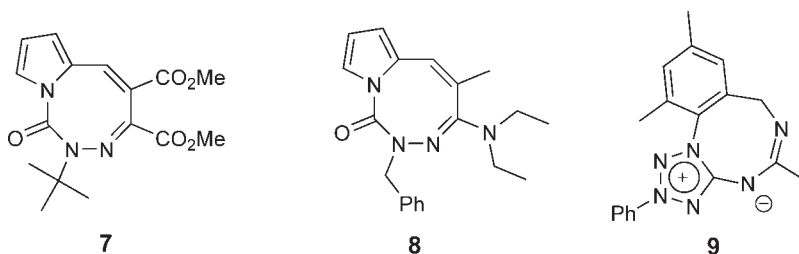
14.08.3 Experimental Structural Methods

14.08.3.1 X-Ray Crystallography

14.08.3.1.1 Triazocines

X-Ray study of two 5,6-dihydropyrrolo[1,2-*d*][1,2,4]triazocin-6-ones **7** and **8** showed boat conformation of the triazocine ring. Pyrrole ring and triazocinone skeleton are not coplanar and bend to avoid steric strain <1999T13703>.

Boat conformation of the triazocine ring was observed in tricyclic mesoionic tetrazolium derivative of 1,3,5-triazocine **9**. Bond lengths in the tetrazolium ring were in good correspondence with those of the similar 1,3-diphenyltetrazolium mesoionic systems <2000JHC1129>.



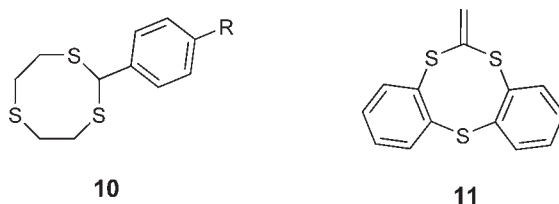
14.08.3.1.2 Trioxocine

Solid-state structure of bicyclic 1,3,5-trioxocane **4** was studied and supported with molecular mechanics computational data to determine its ring-chain tautomerism with keto acetal **5** (see Section 14.08.2.2.1; <1998J(P1)2353>).

14.08.3.1.3 Trithiocines

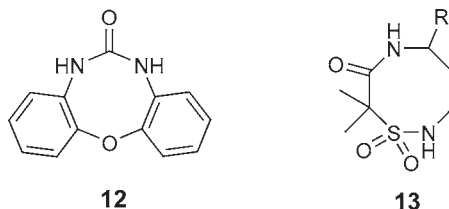
Structure and crystallographic data for *para*-substituted 2-phenyl-1,3,6-trithiocanes **10** have been reported <1994J(P1)707>. The structures of eight-membered rings (R=H, Cl, NO₂) have a remarkable similarity of conformations with minor differences in some bond lengths and bond angles, induced by the *para*-substituents on the aryl ring.

The *exo*-methylene structure of the 6-methylenedibenzo[*d,g*][1,3,6]trithiocine **11** was determined by X-ray crystallographic analysis. Any axis, plane, or point of symmetry does not exist in the molecule in the crystalline state, although the two benzene rings and two *exo*-methylene hydrogen atoms are equivalent in solution as is evident from the ¹H NMR spectrum <1999T10057>.



14.08.3.1.4 Oxadiazocines

Crystalline structure of 5*H*-dibenzo[*b,g*][1,4,6]oxadiazocin-6(7*H*)-one **12** was studied regarding its possible applications as a building block for supramolecular structures assembled via hydrogen bonding <2004AXCo136>. The asymmetric crystal unit contains two almost identical molecules. The conformation of the eight-membered heterocycle may be described as an envelope consisting of two nearly planar moieties formed by aromatic rings and attached nitrogen and oxygen atoms. The two N–C_{ar} bonds are of equal length, but the N–C_{carbonyl} bonds differ markedly.



14.08.3.1.5 Thiodiazocines

Structure of 8,8-dimethyl-1,2,6-thiadiazocan-7-one 1,1-dioxides **13** in the solid state significantly depends on substitution on position 5 <1999HCA354>. The eight-membered ring of unsubstituted compound (R=H) contains a *trans*-configured amide bond (H and O *trans*). Intermolecular H-bonds between the amide NH and a sulfonyl O-atom of a neighboring molecule, as well as between the sulfonamide NH and the amide O-atom of a different neighboring molecule, link the molecules into an infinite two-dimensional network. Independently, each type of H-bond links the

molecules into infinite one-dimensional chains. The additional substituent in the α -position to the amide group ($R = \text{Me}$) has a remarkable influence on the conformation of the eight-membered ring. In this case, the amide bond has a *cis*-configuration (H and O *cis*). Each NH group of methyl-substituted compound acts as a donor for intermolecular H -bonds. The amide NH interacts with one of the sulfonyl O -atoms of a neighboring molecule, while the other NH interacts with the amide O -atom of a different neighboring molecule. Independently, the two H -bonds link the molecules into infinite one-dimensional chains. The combination of both interactions links the molecules into a three-dimensional network.

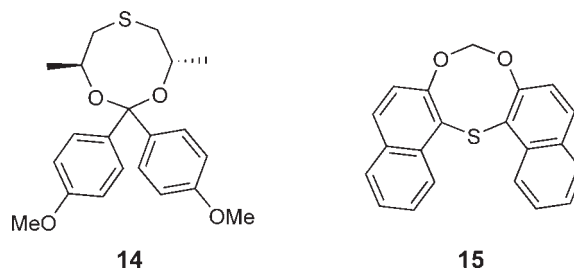
14.08.3.1.6 Dioxazocines

4-Methyl-6-phenyl-2,3,4,6-tetrahydrobenzo[*f*][1,5,2]dioxazocine **6** gives crystals belonging to the monoclinic space group $P2_1/n$, and at 293 K: $a = 13.309(1) \text{ \AA}$, $b = 6.1615(6) \text{ \AA}$, $c = 16.753(1) \text{ \AA}$; $\beta = 100.522(5)^\circ$, $V = 1350.6(2) \text{ \AA}^3$; $Z = 4$, $R(F) = 0.045$, and $R_w(F) = 0.049$. The solid-state structure was found to be a twist-chair–flattened-chair conformation in which the benzo ring is located in the flattened-chair portion of the molecule, the $N\text{-Me}$ group occupies an equatorial orientation vis-à-vis the $-\text{CH}_2\text{CH}_2\text{N}-$ fragment, and the phenyl ring resides in an *exo*-quasi-equatorial position relative to the $-\text{CH}(\text{Ph})-\text{O}-\text{N}-$ fragment <1995NJC1099>.

14.08.3.1.7 Dioxathiocines

Structure of (4*S*,8*S*)-2,2-bis(4-methoxyphenyl)-4,8-dimethyl-1,3,6-dioxathiocane **14** was confirmed by X-ray analysis, which showed boat conformation of the substrate <2001HCA3319>.

The molecular structure of 8*H*-dinaphtho[2,1-*d*;1',2'-*g*][1,3,6]dioxathiocine **15** containing two planar fragments in the ring has been studied by X-ray single crystal diffraction. Steric interactions were found to determine the conformation realized in the crystalline phase. Comparison with eight other, mainly dioxocine, structures showed that depending on the type of planar fragments in the cycle and the group bridging them, boat-chair, distorted boat, twist, or twist boat conformations exist. Distorted boat conformation is the major one for compound **15** <1995JST95>.



14.08.3.2 NMR Spectroscopy

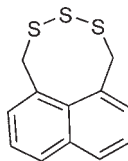
NMR methods were used extensively in structure elucidation of triheterocines and their conformations (see also Section 14.08.4.2).

Two conformations of octahydrobenzo[*d*][1,3,6]trioxocine **3a** and **3b** were detected at 185 K (Equation 1; Section 14.08.2.2.1). From relative ^{13}C NMR peak area measurements, the conformation with the equatorial $\text{O}-\text{CH}_2-\text{O}$ unit was found to be favored by 4.4 kJ mol^{-1} . In the spectrum of the minor conformer at low temperature, a 9.6 ppm ^{13}C chemical shift difference is present between the two methine carbons. Transannular 1,4- $\text{H}-\text{H}$ interactions are believed to be partly responsible for this effect <1999MRC401>.

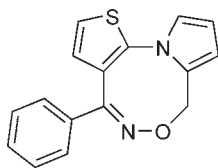
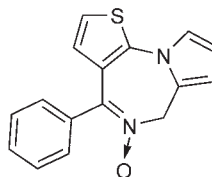
The structural difference between 6-methylenedibenzo[*d,g*][1,3,6]trithiocine **11** with 18-membered by-product **134** <1999T10057> is most clearly reflected in the ^{13}C NMR spectra. The 18-membered product **134** showed seven sp^2 carbon peaks (one alkenic + six aromatic carbons), whereas dibenzo[*d,g*][1,3,6]trithiocine **11** eight sp^2 carbon peaks (two alkenic + six aromatic carbons). In the ^1H NMR spectra, the *exo*-methylene hydrogens of **11** appeared at 5.98 ppm, as compared with 6.48 ppm of alkenic hydrogens of the compound **134**. Further, the structure of these compounds was confirmed by X-ray crystallographic analyses (Section 14.08.3.1.3).

Intramolecular dynamics of 1,5-dihydronaphtho[1,8-*ef*][1,2,3]trithiocine **16** in solutions was studied by 2-D nuclear Overhauser enhancement spectroscopy (NOESY) technique <2003AMR97> and interpreted based on the

variable-temperature analysis of integral intensities of cross-peaks. Compound **16** exists in solutions in boat and chair conformations. The differences of the boat-chair equilibrium enthalpy were 13.4 ± 0.4 and 7.1 ± 0.4 kJ mol⁻¹ in toluene-*d*₈ and acetone-*d*₆, respectively. The rate constants of the boat-boat inversion in toluene and acetone were determined, and the activation enthalpies of the process were 57.9 ± 2.0 kJ mol⁻¹ and 74.2 ± 2.0 kJ mol⁻¹, correspondingly.

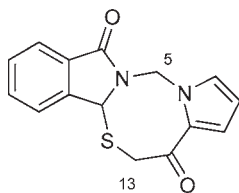
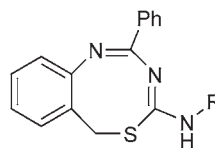
**16**

¹H NMR of 7*H*-pyrrolo[1,2-*f*]thieno[3,2-*d*][1,2,6]oxadiazocine **17** demonstrates singlet at 5.49 ppm, while the by-product, diazepine *N*-oxide **18**, shows a peak at 5.08 ppm. This assignment was confirmed by mass spectra of **18** with loss of 16 Da characteristic for *N*-oxides <1996JHC75>.

**17****18**

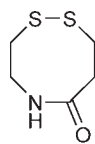
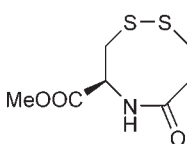
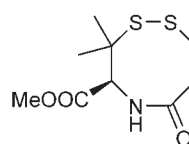
¹H NMR spectrum of 5,11b-dihydro-13*H*-pyrrolo[1',2':5,6][1,3,5]thiadiazocino[2,3-*a*]isoidole-7,14-dione **19** <1998JHC9> demonstrates two AB systems. Protons at position 13 appear as two well-resolved doublets at 2.30 and 2.85 ppm ($J = 15.1$ Hz), as well as protons at position 5 (5.40 and 6.05 ppm, $J = 14.1$ Hz).

4-Amino-substituted 2-phenyl-6*H*-5,1,3-benzothiadiazocines **20** demonstrate in their ¹H NMR spectra two doublets at 4.5 and 3.5 ppm with coupling constant $J(A,B) = 12$ Hz, belonging to two protons of the methylene group incorporated in the rigid skeleton of the nonplanar eight-membered ring <1996CCC1681>. The ¹³C NMR spectrum of the 4-aminophenyl compound **20** ($R = Ph$) displays characteristic C-6 signal at 32.59 ppm aromatic carbon signals grouped in quasi-doublets at 119.12 and 120.64 ppm (2C), 122.92 and 123.62 ppm (2C), 127.78 and 127.89 ppm (2C), 128.54 (2C), 128.77 (2C), 129.53 and 130.99 ppm (2C), 135.73 and 140.12 ppm (2C), in addition to the single-bonded carbon signals at 146.46, 150.04, 156.94, and 157.14 ppm.

**19****20**

The magnitudes of the ¹H NMR vicinal coupling constants in the -OCH₂CH₂NO- fragment of 4-methyl-6-phenyl-2,3,4,6-tetrahydrobenzo[*f*][1,5,2]dioxazocine **6** <1995NJC1099> are consistent with the TCfC conformation and N-configuration as found in the crystalline structure, in which the vicinal nitrogen lone pair of electrons is as far away from each of the two oxygen lone pairs as possible (see Section 14.08.2.2.2). Two anticlinal LP-N-O-LP arrangements minimize unfavorable electrostatic interactions.

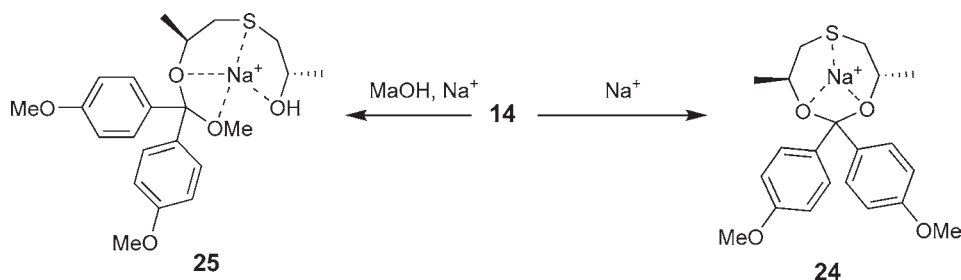
1,2-Dithia-5-azacyclooctan-6-one **21** was found by nuclear Overhauser effect (NOE) experiments to exist in a conformation with a *trans*-amide bond. The substituted derivative **22** was also found to possess a *trans*-amide bond while for compound **23** three conformations were identified with the major conformer possessing a *cis*-amide bond <1997T16859>.

**21****22****23**

14.08.3.3 Mass Spectrometry

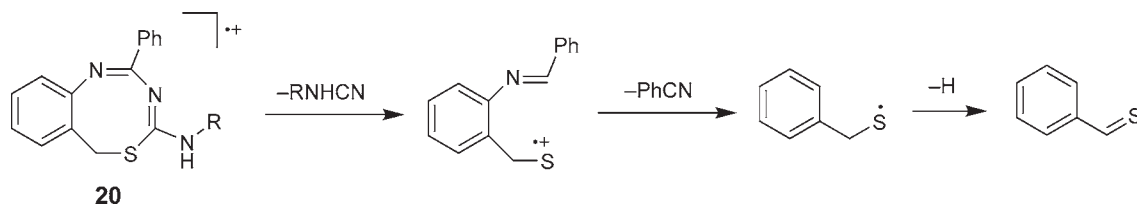
Mass spectrometric techniques are very important in gaining structural information on heterocyclic medium-sized rings. Most of the systems described in this chapter have been subjected to mass spectral analysis and the reader is referred to the individual references for this information.

Mass spectrometry of (4*S*,8*S*)-2,2-bis-(4-methoxyphenyl)-4,8-dimethyl-1,3,6-dioxathiocane **14** by electrospray ionization mass spectrometry (ESI-MS) method indicates $[M+K]^+$, $[M+Na]^+$, and $[M+MeOH+Na]^+$ as the most important peaks [<2001HCA3319>](#). This phenomena was explained by formation of crown ether-type complexes **24** and **25** (Scheme 1).

**Scheme 1**

A similar fragmentation pattern was observed for 2-methyl-3,6-di(tosyl)-1-oxa-3,6-diazacyclooctane [<2001EJO4233>](#).

The principal path of molecular fragmentation in the mass spectra of 4-amino-substituted 2-phenyl-6*H*-5,1,3-benzothiadiazocines **20** is similar to that of benzothiazepines, and includes the loss of an aryl- or alkylcyanamide ion followed by elimination of benzonitrile (Scheme 2; [<1996CCC1681>](#)).

**Scheme 2**

14.08.3.4 UV Spectroscopy

The nonaromatic eight-membered rings absorb little in accessible regions of the ultraviolet (UV) spectrum. [Table 1](#) represents structures and data on reported spectra of triheterocines, whose absorptions are due to fused aromatic rings, aromatic substituents, or carbonyl groups.

Table 1 UV spectral maxima of eight-membered heterocycles with three heteroatoms

Heterocycle	$\lambda_{\max}$ (nm) (log ϵ)	Solvent	References
9	250 (4.36) 275 (4.30) 402 (3.25)	Acetonitrile	2000JHC1129
63 : R = Me; R ¹ = H	263	DMSO	2002ZPK1309
100	224 (4.45) 285 (3.52)	Ethanol	2003KGS485
159	340 (4.22)	CH ₂ Cl ₂	1996CC205, 1996BCJ2349
183	258 (3.24) 205 (1.05)	Ethanol	2002EJO2400
184	257 (2.78)	Ethanol	2002EJO2400

Table 2 IR absorptions of eight-membered heterocycles with three heteroatoms

Heterocycle	Stretching frequencies (cm ⁻¹)	Reference
8	1680 (C=O), 1558 (C=N)	1999T13703
9	1604, 1594, 1526, 1466	2000JHC1129
13 : R = Ph	3400, 3250, 2940, 1650, 1530, 1475, 1450, 1420, 1395, 1315, 1290, 1270, 1200, 1160, 1130, 1110, 1080, 1060, 995, 870, 820, 775, 705, 655, 610	1999HCA354
14	2965, 2925, 2835, 1610, 1585, 1508s, 1465, 1440, 1410, 1375, 1334, 1312, 1301, 1245s, 1205, 1172, 1128, 1080, 1030, 1010, 975, 829	2001HCA3319
19	1730, 1686 (C=O)	1998JHC9
52	3417, 1738, 1666	1999EJO2709
31	1318 (SO ₂), 1153 (SO ₂)	1999TL9363
102	1755 (C=O)	1999TL2117
103	1725 (C=O)	1999TL2117
109 : R = Ph, Nu = CH(COOEt) ₂	1026, 1047 (C–O–C), 1713 (C=O), 3063 (C–H _{arom})	2000CPA36
136	1201	1998MAC1785
183	3550, 1705	2002EJO2400
184	3480, 1655	2002EJO2400

14.08.3.5 IR and Raman Spectroscopy

Usually, the infrared (IR) absorption frequencies for eight-membered rings with three heteroatoms are poorly defined. The characteristic absorption bands for the selected triheterocines are listed in [Table 2](#).

14.08.4 Thermodynamic Aspects

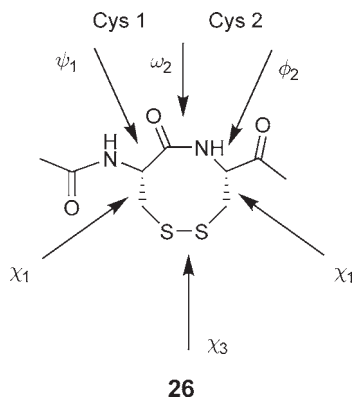
14.08.4.1 Intermolecular Forces

Heterocines with three heteroatoms are usually solids with variable melting points. Their saturated counterparts, heterocanes, are as a rule relatively low-melting solids or liquids. For example, unsubstituted 1,3,6-trioxocane is a liquid with boiling point of 56–70 °C at 2666 Pa, while its 2-methyl derivative melts at 14 °C [<1995MI790>](#). 1,3,6-Heterocanes with *C*-phenyl and *N*-tosyl substitution do not have considerably increased melting points [<1994J\(P1\)707, 2001HCA3319, 2001H\(54\)151, 2001EJO4233>](#). Substitution at the *para*-position in 2-(4-*R*-phenyl)-[1,3,6]trithiocanes with chloro and, in particular, nitro group increases melting points [<1994J\(P1\)707>](#). Heterocycles bearing groups capable of H-bonding are high melting [<1999HCA354, 2002APH379, 2003SL1591, 2004AXCo136>](#).

14.08.4.2 Conformational Studies

Four main low-energy conformational families of eight-membered ring systems, consisting of the boat-chair, crown, boat, and chair forms, were surveyed in CHEC-II(1996). They are discussed in the foregoing sections of this chapter in conjunction with the theoretical and experimental structural studies of triheterocines (see [sections 14.08.2 and 14.08.3](#)).

A complete conformational analysis of a model compound Ac-*ox*-[Cys-Cys]-NH₂ **26** in water was performed <2001JA12664>. Structure **26** models an unusual oxidized eight-membered ring disulfide *ox*-[Cys-Cys] which is found in the N-terminal extracellular domain of most nAChR protein subtypes. It adopts in water four distinct low-energy conformers. Two populations are dependent on the peptide ω_2 dihedral angle, with the *trans*-amide to the *cis*-amide ratio of ca. 3:2. Two conformers with a *cis*-amide bond differ from each other primarily by variation of the χ_3 dihedral angle, which defines the orientation of the helicity about the S-S bond. Two *trans*-amide conformers have the same χ_3 value of ca. 90°, but are distinguished by a backbone rotation about ϕ_2 and ψ_1 . The ratio of the four conformers was established. These conformational preferences are also observed in tetrapeptide and undecapeptide fragments of the human R7 subtype of the nAChR that contains the *ox*-[Cys-Cys] unit.



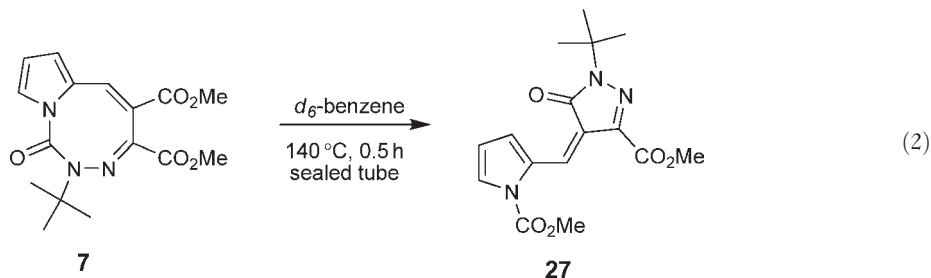
14.08.4.3 Kinetics

A kinetics study has been performed on the formation of 1,3,6-trioxocane in the interaction of formaldehyde with diethylene glycol in the presence of 0–0.5 mol l⁻¹ of sulfuric acid <1998ZFK1031>. The rate of the reaction was found to be determined by the equilibrium of cyclization of half-acetal into eight-membered ring and of reverse process of hydrolysis. Rate constants demonstrated linear dependence on Hammett acidity function. Activation energies were 20.9 and 14.0 kcal mol⁻¹ for the formation of cyclic acetal and its hydrolysis, correspondingly.

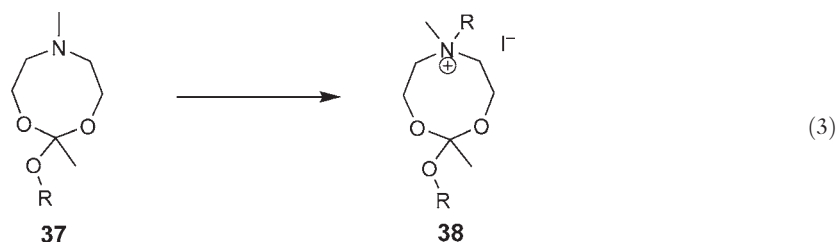
14.08.5 Reactivity of Nonconjugated Rings

14.08.5.1 Intramolecular Thermal and Photochemical Reactions

2-*tert*-Butyl-2,3-bis(methoxycarbonyl)-5,6-dihydropyrrolo[1,2-*d*][1,2,4]triazocin-6-one **7** undergoes thermal ring opening to afford structural isomer, 1-*tert*-butyl-4-(1'-ethoxycarbonyl-2'-pyrrolylmethylene)-3-methoxycarbonyl-2-pyrazolin-5-one **27** in 21% yield (Equation 2, <1999T13703>).

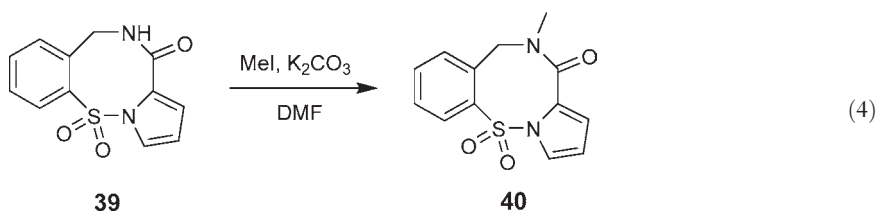


1,2,4-Oxadithiocines **29** are unstable, acid-sensitive compounds, obtained by photolysis of 4,8,10-trithiadibenzo[*cd,i*]azulene 8-oxides **28** (see Section 14.08.8.2.5). Their additional photolysis results in the corresponding aldehydes or ketones and 4,8,9-trithiacyclopenta[*def*]phenanthrene **30** as a major rearrangement product (Scheme 3; <1996CL655>).

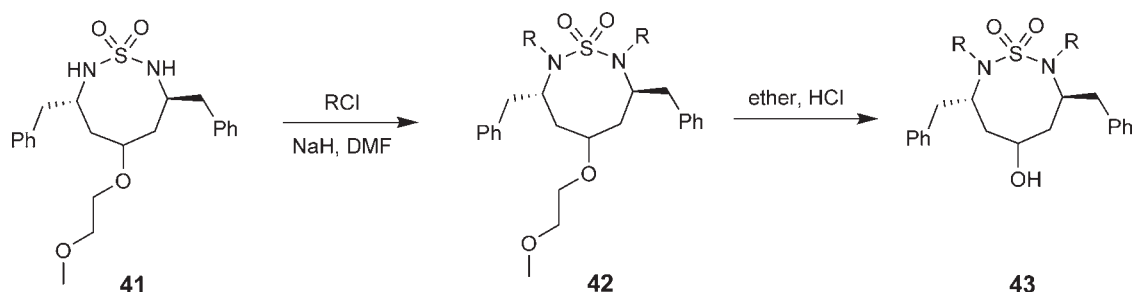


Similarly, alkylation of 6-methyl-2-methylene-1,3,6-dioxazocane with methyl iodide cleanly affords the corresponding quaternary ammonium salt [\(<2004AGE1117>\)](#).

10*H*-Pyrolo[1,2-*b*][1,2,5]benzothiadiazocine-12(11*H*)-one 5,5-dioxide **39** was methylated with methyl iodide in the presence of potassium carbonate to afford the corresponding 5-methyl derivative **40** in 25% yield ([Equation 4](#); [\(<1995JHC1779>\)](#)).

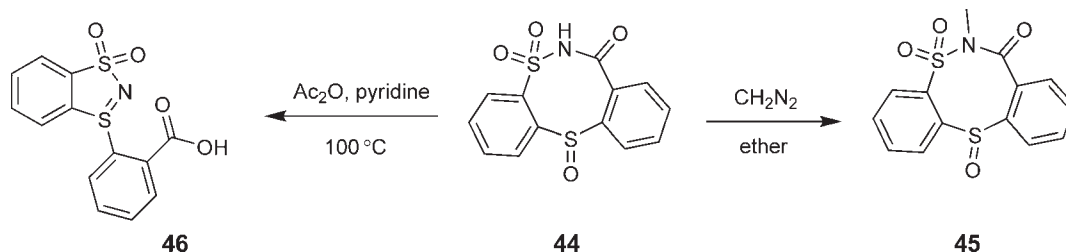


Cyclic sulfamide **41** was alkylated with various alkylating agents using sodium hydride as a base in dimethylformamide (DMF) ([Scheme 6](#); [\(<1995TL6383>\)](#)).



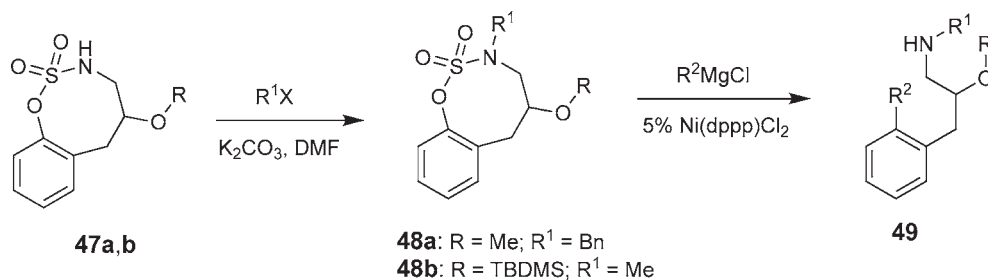
Scheme 6

Compound **44** can be transformed into the cyclic imide **45** by *N*-methylation with diazomethane. Reaction with acetic anhydride leads to sulfilimine **46**, as a product of intramolecular attack of sulfone on imide nitrogen followed by ring opening ([Scheme 7](#); [\(<1995CC1069>\)](#)).



Scheme 7

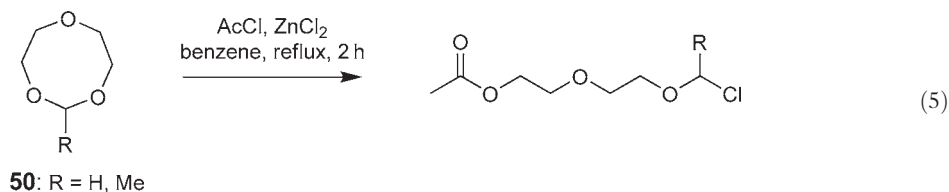
Cyclic sulfamates **47** can be smoothly transferred into the corresponding *N*-substituted derivatives **48a** and **48b** in the presence of potassium carbonate in DMF ([Scheme 8](#); [\(<2005OL4685>\)](#)).



Scheme 8

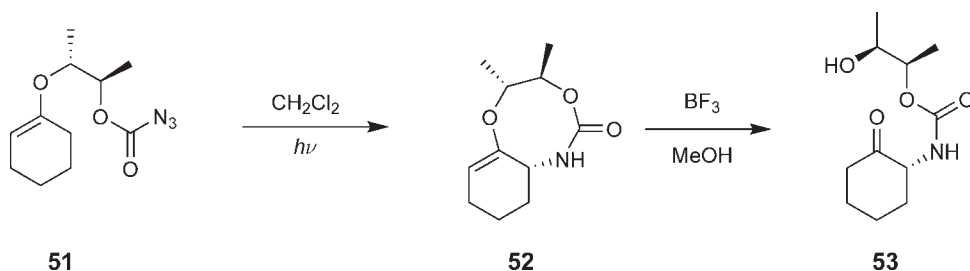
14.08.5.2.2 Electrophilic attack on ring oxygen

1,3,6-Trioxocanes **50** undergo ring opening with acetyl chloride to afford the corresponding chloromethyl ethers (Equation 5; <1995MI790>).



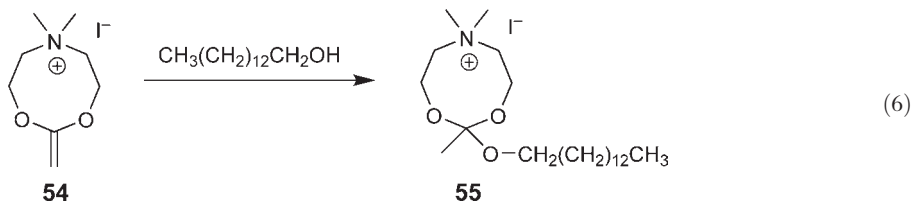
14.08.5.3 Reactions with Nucleophiles

The enol ether moiety of 3,6-dioxazocan-2-one **52** undergoes hydrolysis and ring opening with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in aqueous methanol to give the N-substituted 2-aminocyclohexanone **53** in 95% yield as a single stereoisomer (Scheme 9; <1999EJO2709>).



Scheme 9

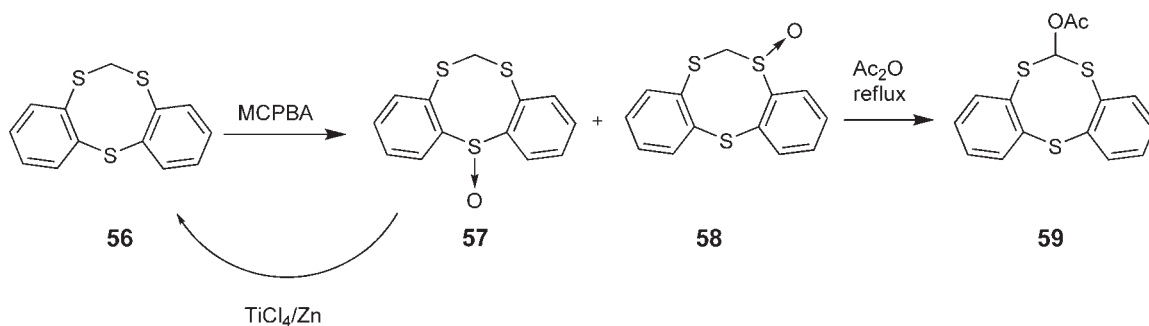
Quarternary ammonium salt **54** can be readily converted into orthoesters (Equation 6). Under HBF_4 catalysis reaction undergoes smoothly and provides derivative of myristyl alcohol **55**. Other catalysts examined included trifluoromethanesulfonic acid, methanesulfonic acid, and anhydrous HCl in diethyl ether, but none were as effective as HBF_4 . Reaction of **54** with 1,2- or 1,3-disubstituted glycerol gives the lipid-type orthoesters in good to moderate yields depending on the degree of substitution of the alcohol <2004AGE1117>.



Cyclic sulfamates **48a** and **48b** (Scheme 8, section 14.08.5.2.1) function as electrophilic partners with Ni-catalyzed cross-coupling reaction of Grignard reagents. This transformation thus offers an easy access to the variety of aryl-substituted amines **49** <2005OL4685>.

14.08.5.4 Oxidation and Reduction

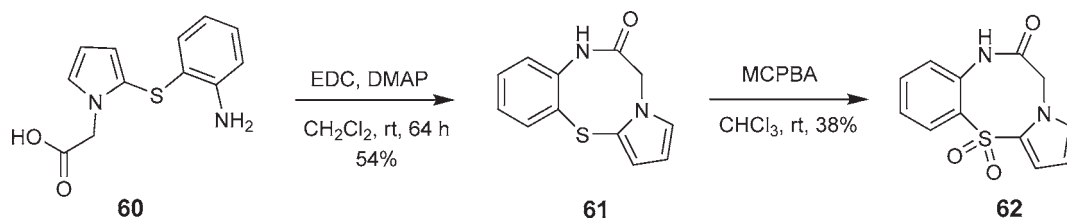
Dibenzo[*d,g*][1,3,6]trithiocine **56** was oxidized with *m*-chloroperbenzoic acid (MCPBA) to give a mixture of sulfoxides **57** and **58** in 5% and 77% yields, respectively (Scheme 10). Further Pummerer rearrangement of **58** in refluxing acetic anhydride gave the expected product **59** in 97% yield <1998BCJ1187>.



Scheme 10

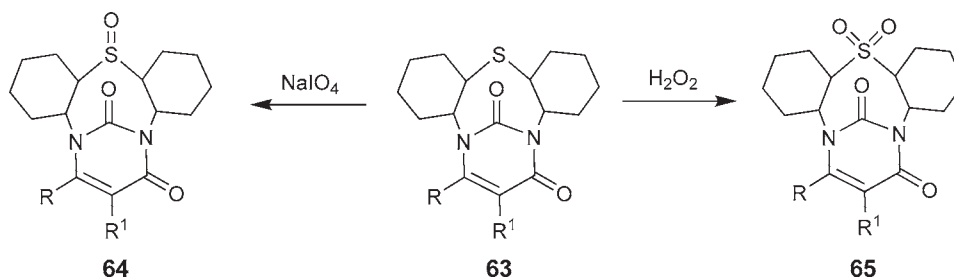
The minor isomer **57**, which can be prepared in high yield using alternative pathway <1998BCJ1187> (see Scheme 40, Section 14.08.8.1.1), was converted back to unsubstituted dibenzo[*d,g*][1,3,6]trithiocine **56** by reduction with a low-valent titanium reagent in 95% yield <1996CC205, 1996BCJ2349>.

9*H*-Pyrrolo[2,1-*b*][1,3,6]benzothiadiazocine-10(11*H*)-one 4,4-dioxide **62** is the sole product of the oxidation of the starting benzothiadiazocinone **61** with MCPBA (Scheme 11; <1995JHC683>).



Scheme 11

Treatment of pyrimidine derivatives **63** with NaIO_4 afforded corresponding sulfoxides **64**, while oxidation with hydrogen peroxide led to sulfones **65** (Scheme 12; <2002ZPK1309>).

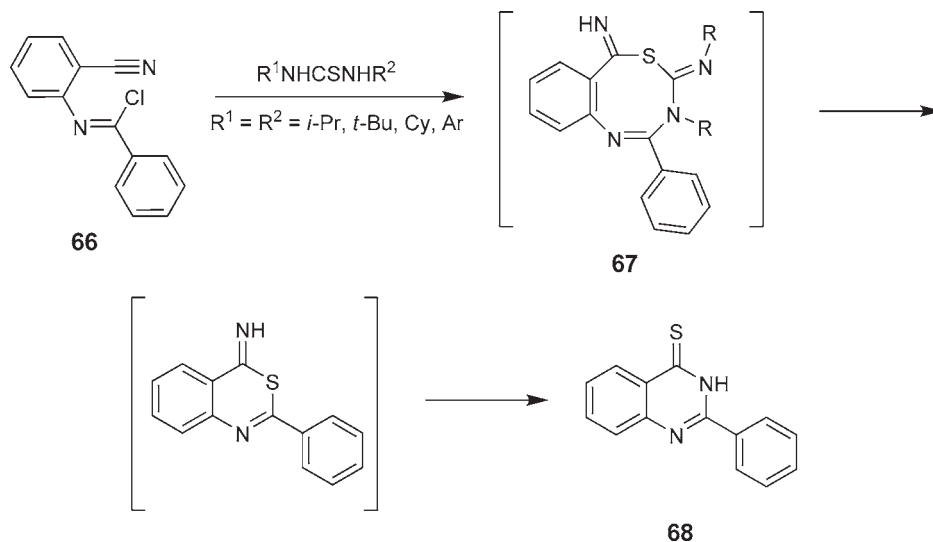


Scheme 12

14.08.5.5 Intramolecular Ring-transformation Reactions

There are only few known ring-contraction reactions of heterocines with three heteroatoms. They lead to more favorable smaller ring systems or to bicyclic or bridged products of transannular transformations. Examples of analogous photo- and thermal intramolecular transformations are discussed in [Section 14.08.5.1](#).

Reaction of *N*-(2-cyanophenyl)benzimidoyl chloride **66** with sterically hindered thioureas gives intermediate 1-[(2-cyanophenylimino)phenylmethyl]thioureas **67** (see also [Section 14.08.7.4.2](#)), which are prone to intramolecular S-attack and give 2-phenylquinazoline-4(3*H*)-thione **68** as a final elimination/rearrangement product ([Scheme 13](#); <2002MOL96>).



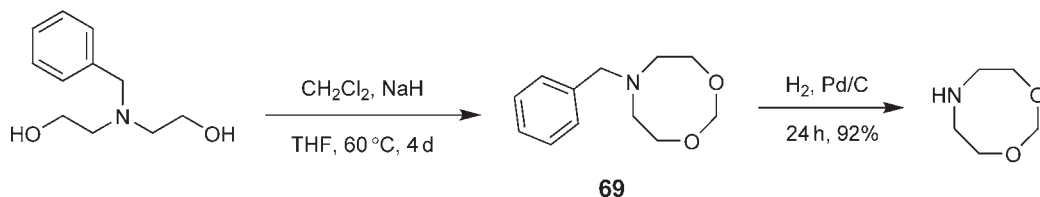
Scheme 13

Reaction of compound **44** with acetic anhydride leads to sulfilimine **46**, as a product of intramolecular attack of sulfone on imide nitrogen followed by ring opening ([Scheme 7](#); [Section 14.08.5.2.1](#); <1995CC1069>).

14.08.6 Reactivity of Substituents Attached to Ring Carbon Atoms

14.08.6.1 Alkyl Groups and Further Carbon Functional Groups

6-Benzyl-1,3,6-dioxazocane **69** was smoothly deprotected under standard hydrogenation procedure ([Scheme 14](#); <2001H(54)151>).

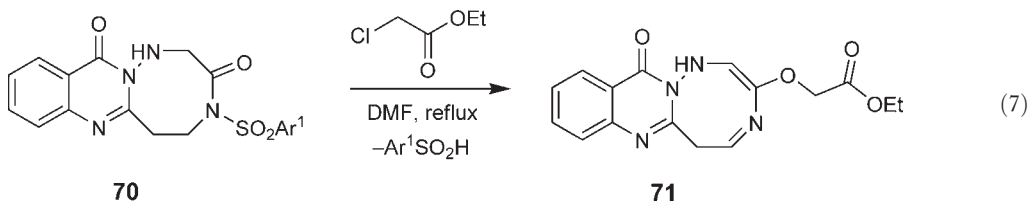


Scheme 14

14.08.6.2 O-Linked Groups

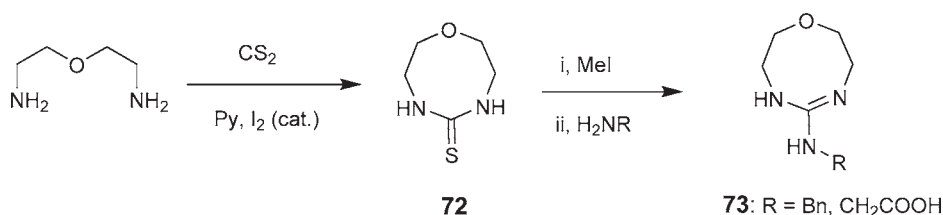
Deprotection of the MEM group in substrate **42** with anhydrous 2 M hydrogen chloride in 1:1 methanol–dioxane mixture provided target molecules **43** as potential inhibitors of HIV-1 protease ([Scheme 6](#); [Section 14.08.5.2.1](#); <1995TL6383>).

Arylsulfonyl triazocine **70**, bearing a fused benzoquinazolinone ring, was reacted with ethyl 2-chloroacetate in refluxing DMF to give, after elimination of arylsulfinyl group and sequential alkylation, derivative of 3-hydroxy-1*H*-[1,2,5]triazocino[8,1-*b*]quinazolin-12(6*H*)-one **71** in 63% yield (Equation 7; <2001MOL267>).



14.08.6.3 S-Linked Groups

1,4,6-Oxaiazocane-5-thione **72** can be S-methylated and subsequently reacted with benzylamine or glycine in the presence of yellow HgO to afford 3,4,7,8-tetrahydro-2*H*-1,4,6-oxadiazocin-5-amines **73** in low to moderate yields (Scheme 15; <1988APH400>).



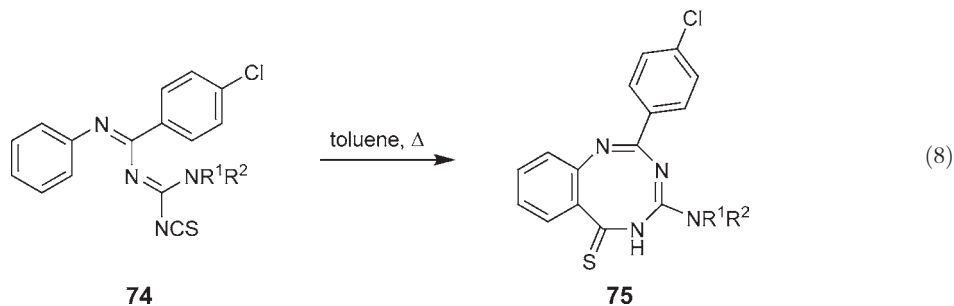
Scheme 15

14.08.7 Ring Syntheses from Acyclic Compounds

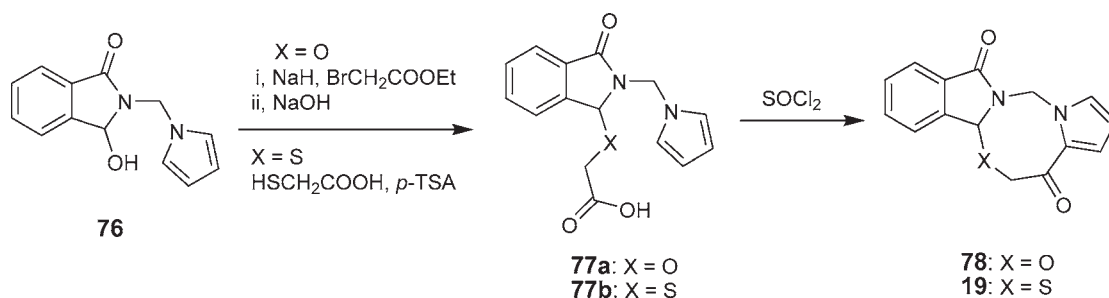
14.08.7.1 Ring Formation by Intramolecular Cyclization

14.08.7.1.1 C–C bond formation

Imidoyl isothiocyanates **74** are readily available through stepwise nucleophilic substitution of *N*-phenyl(phenylimino)methylchloromethanimidoyl chloride with secondary amines and potassium thiocyanate. Subsequent thermal intramolecular cyclization of intermediates **74** affords substituted 1,3,5-benzotriazocine derivatives **75** (Equation 8; <2005ARK96>).

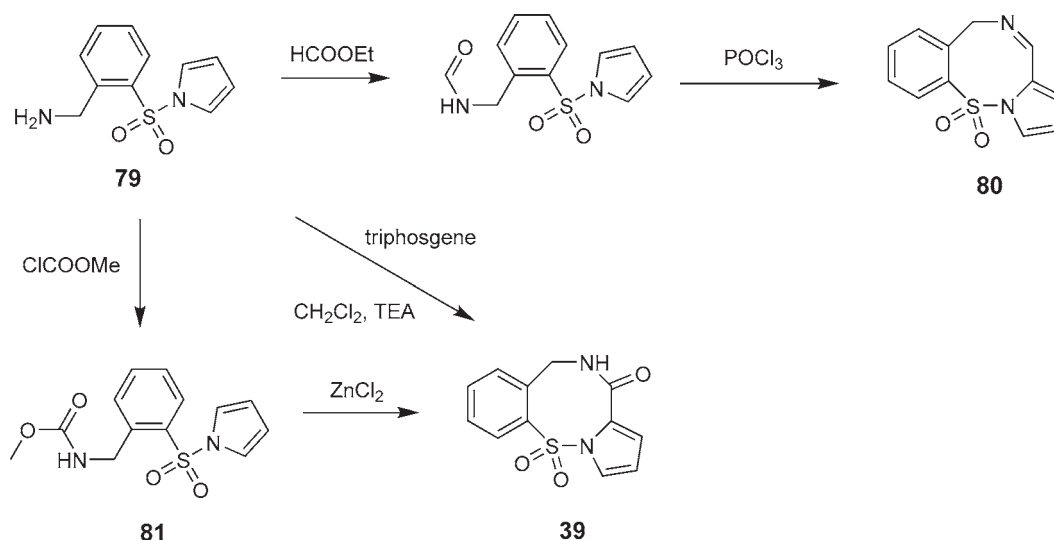


2,3-Dihydro-1*H*-pyrrolo[1,2-*e*][1,3,5]oxadiazocin-6(5*H*)-one ring system **78** can be obtained from 2,3-dihydro-3-hydroxy-2-(pyrrol-1-ylmethyl)-1*H*-isoindol-1-one **76**. No intermediate acyl chloride was observed during the cyclization of **77a**, and product **78** (X = O) was isolated in low 15% yield. Yields were not improved after addition of Lewis acids or use of polyphosphoric acid as a condensation reagent (Scheme 16; <1998JHC9>). Similarly, 2,3-dihydro-1*H*-pyrrolo[1,2-*e*][1,3,5]thiadiazocin-6(5*H*)-one ring system **19** (X = S) was obtained in low yield. Key intermediate **77b** was prepared from **76** in one step under acidic catalysis.



Scheme 16

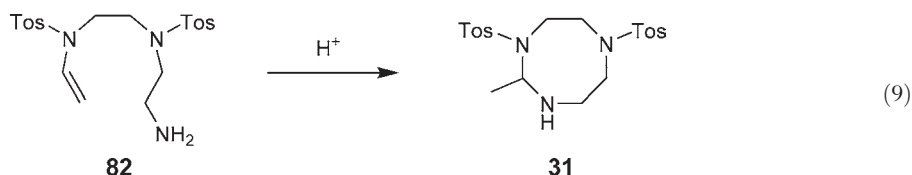
Synthesis of 10H-pyrrolo[1,2-*b*][1,2,5]benzothiadiazocine 5,5-dioxide was reported by intramolecular cyclization of 1-(2-formylamidomethylphenylsulfonyl)-1H-pyrrole **80**. Treatment of the key intermediate **79** with triphosgene affords 10H-pyrrolo[1,2-*b*][1,2,5]benzothiadiazocine-12(11H)-one 5,5-dioxide **39**, which can be also prepared by cyclization of the corresponding methylcarbamate **81** (Scheme 17; <1995JHC1779>).



Scheme 17

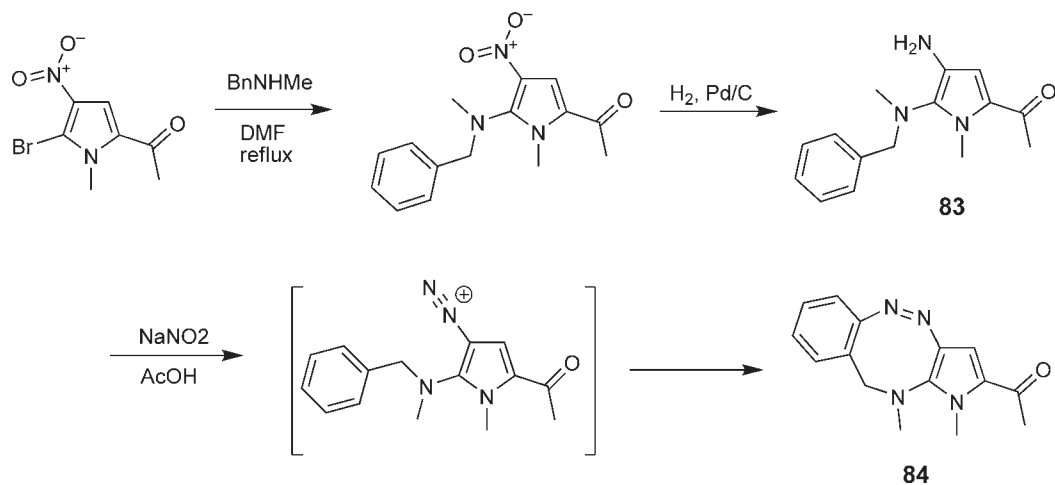
14.08.7.1.2 C–N bond formation

Open-chain vinylamine is an identifiable side product during synthesis of 1,4,7-triazacyclononanes, resulting from the side *E2*-elimination process. Intermediate **82** can be isolated by column chromatography on neutral alumina and subsequently converted to 2-methyl-1,6-ditosyl-1,3,6-triazocane **31** by the addition of either silica gel or HBF₄. The reaction also proceeds smoothly under Lewis acid catalysis using BF₃ etherate (Equation 9; <1999TL9363>).



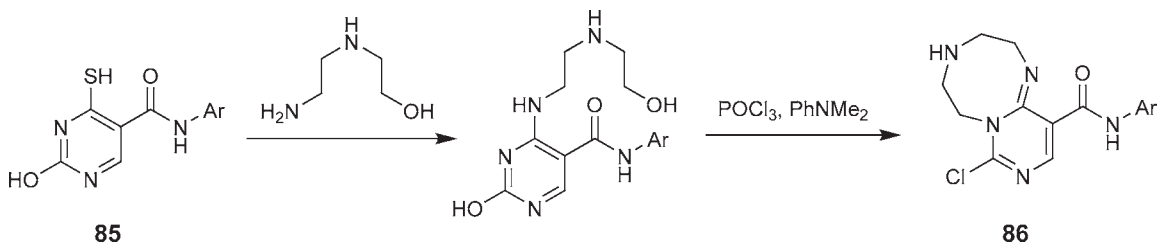
An alternative mechanism for this transformation, resulting in formation of oxadiazocanes rather than triazocanes, was proposed recently <2001EJO4233>.

A novel ring system, pyrrolo[3,2-*c*][1,2,5]benzotriazocine **84**, was synthesized using a three-step sequence (Scheme 18; <1998JHC1535>). Diazotization of amino pyrrole derivative **83** in acetic acid afforded 1,2,5-triazocine ring in 75% yield by intramolecular coupling of diazonium group with *ortho*-position of benzyl substituent.



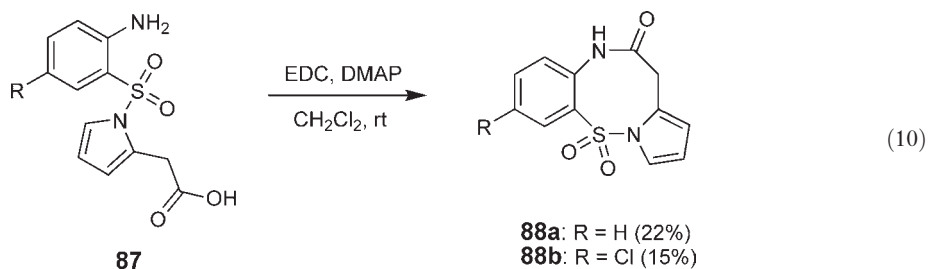
Scheme 18

Reaction of amides **85** with 2-hydroxyethyl-1,2-diaminoethane in pyridine and subsequent treatment of the intermediate hydroxyl compound with POCl₃ yielded the corresponding pyrimidinotriazocines **86** (Scheme 19; <1993APH253>).

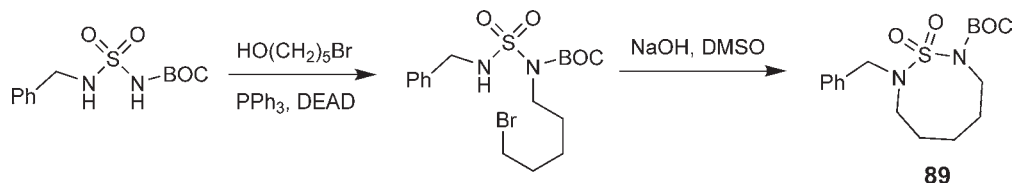


Scheme 19

Intramolecular cyclization of 1-(2-aminophenylsulfonyl)-1*H*-pyrrole-2-acetic acid **87** gave 10*H*-pyrrolo[1,2-*b*]-[1,2,6]benzothiadiazocin-11(12*H*)-one 5,5-dioxides **88**. Intermediate **87** was prepared in four steps starting from the corresponding *ortho*-nitrobenzenesulfonyl chlorides and ethyl 1*H*-pyrrole-2-(α -oxo)acetate (Equation 10; <1996JHC2019>).

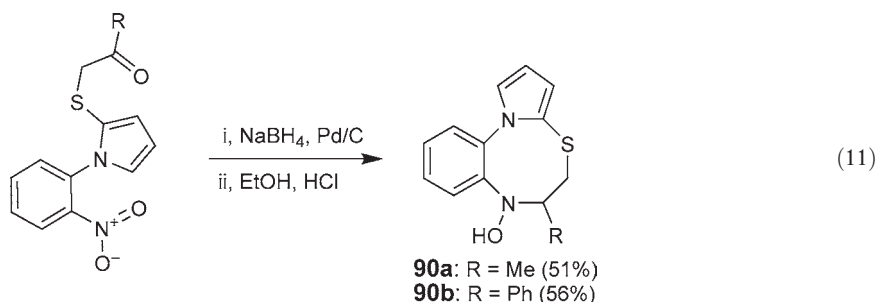


Eight-membered *N,N'*-protected cyclic sulfonamide **89**, bearing two different protecting groups, was demonstrated as useful intermediate for preparation of pseudopeptides. Synthesis of **89** was carried out in two steps by an intermolecular Mitsunobu reaction followed by intramolecular N-alkylation (**Scheme 20**; <2003T6051>).



Scheme 20

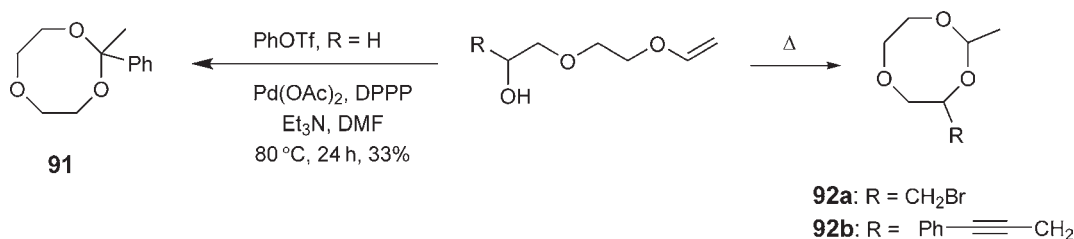
Reduction of 1-[[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl]-acetone or -1-phenylethan-1-one with sodium borohydride and 5% palladium on carbon, a reagent known to convert aromatic nitro compounds to hydroxylamines, triggers intramolecular interaction and gives pyrrolo[1,2-*a*][3,1,6]benzothiadiazocine derivatives **90** (**Equation 11**; <2001MI1405, 2004T8807>). This method was further successfully applied to the reductive cyclization of 2-[[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl]acetonitrile.



Starting from 2-(2-(2-aminophenylthio)-1*H*-pyrrol-1-yl)acetic acid **60**, available through two synthetic steps from *o*-aminothiophenol, 9*H*-pyrrolo[2,1-*b*][1,3,6]benzothiadiazocine-10(11*H*)-one **61** was obtained in 54% yield (**Scheme 11**, Section 14.08.5.4; <1995JHC683>). Azidoformate **51** derived from chiral enol ether, when irradiated, gives 3,6-dioxazocan-2-one derivative **52** by a highly diastereoselective intramolecular cycloaddition (**Scheme 9**, Section 14.08.5.3; <1999EJO2709>).

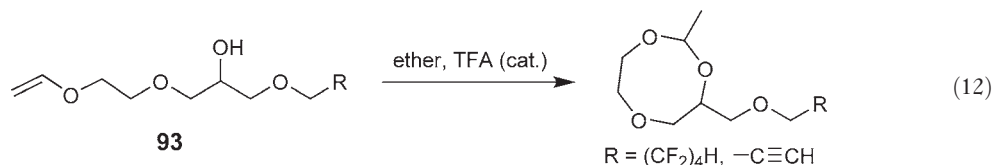
14.08.7.1.3 C–O bond formation

Reaction of di(ethylene glycol) vinyl ether with phenyl triflate in presence of a catalytic amount of palladium acetate and 1,3-bis(diphenylphosphino)propane (DPPP), as a ligand, provides a direct route to cyclic ketal of acetophenone **91** (**Scheme 21**). It is postulated that the reaction proceeds via an initial arylation of the vinyl ethers to give labile aryl vinyl ether intermediates, which undergo subsequent ketalization <1997JOC7858>. Similarly, substituted vinyl ethers undergo thermal transformation to afford corresponding functionalized 1,3,6-trioxicanes **92a** and **92b** <2005RJO1583>.

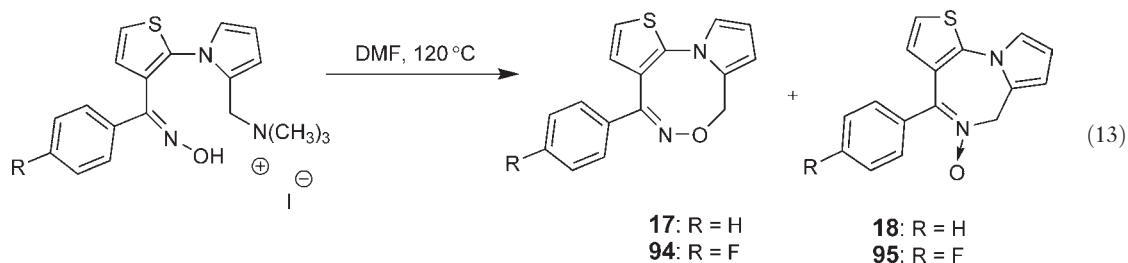


Scheme 21

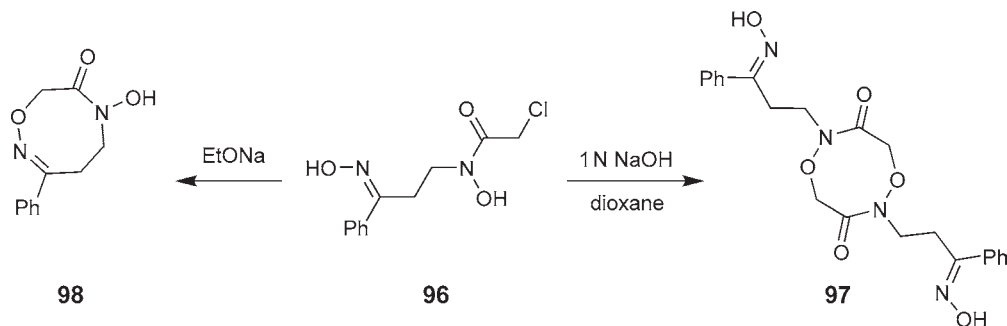
In the same way, substituted vinyl alcohols **93** are readily converted into 2-methyl-1,3,6-trioxocan propynyl-[2003RJO1384](#) or polyfluoroalkyl-[2002KGS1419](#) ethers (Equation 12), difficultly accessible by other methods. The cyclization is promoted by trifluoroacetic acid in boiling dry diethyl ether and affords high yields of the products.



7*H*-Pyrrolo[1,2-*f*]thieno[3,2-*d*][1,2,6]oxadiazocines **17** and **94** can be synthesized from the oxime precursors (Equation 13; [1996JHC75](#)). Product mixture consists of oxadiazocine derived from *syn*-oxime ((*Z*)-form), and diazepine *N*-oxide, as a cyclization product of *anti*-oxime ((*E*)-form). The ratio of the products **17**:**18** was 4:1, while in the case of *p*-fluorophenyl-substituted compound oxadiazocine **94** was formed as the sole product.

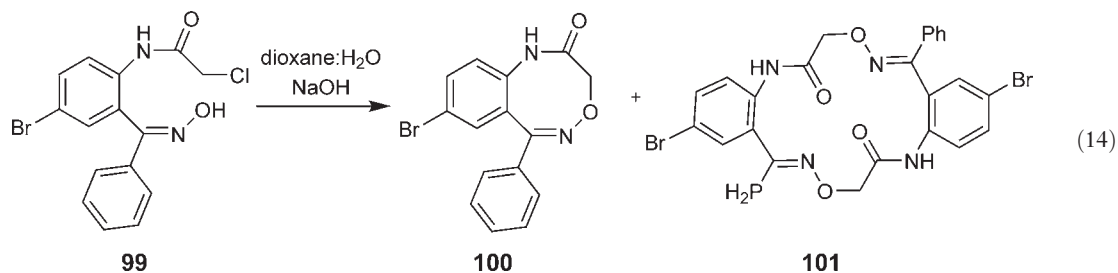


The relative reactivity of two O-nucleophilic sites of 2-chloro-*N*-hydroxy-*N*-(3-(hydroxyimino)-3-phenylpropyl)-acetamide **96** and the direction of its intramolecular cyclization appeared to be sensitive to the nature of base. Reaction can be tuned up to provide either dimerization product, 1,5,2,6-dioxadiazocane-3,7-dione **97**, or 5,6-dihydro-4*H*-1,2,6-oxadiazocin-7(8*H*)-one ring system **98**, obtained through intramolecular cyclization ([Scheme 22](#); [1993MI97](#)).

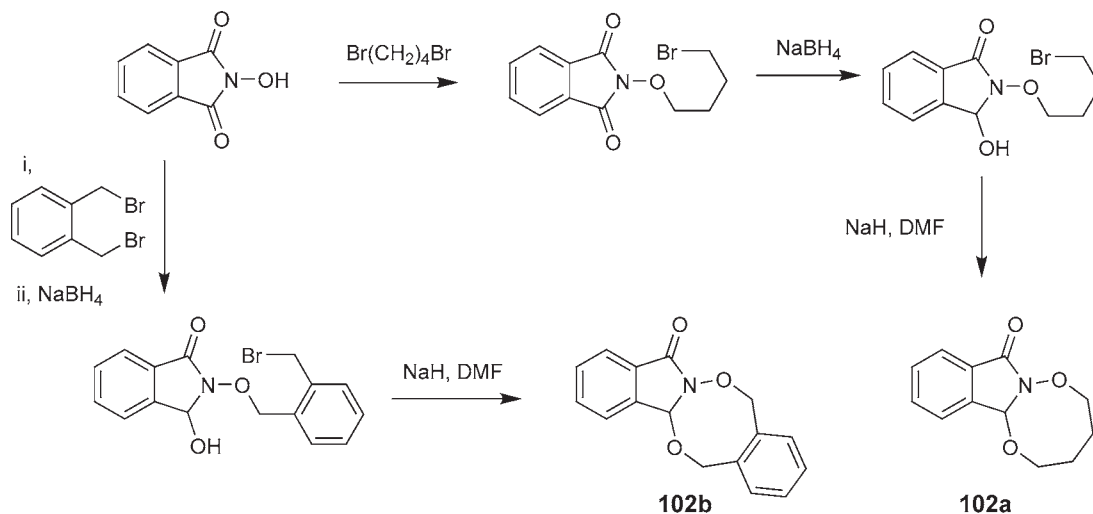


Scheme 22

Intramolecular cyclization of the *syn*-isomer of *N*-chloroacetyl oxime **99** produced 1*H*-benzo[*d*][1,2,6]oxadiazocin-2(3*H*)-one **100** only in 3% yield, while the major intermolecular macrocyclic product **101** was obtained in 41% yield (Equation 14; [2001MI140](#)).

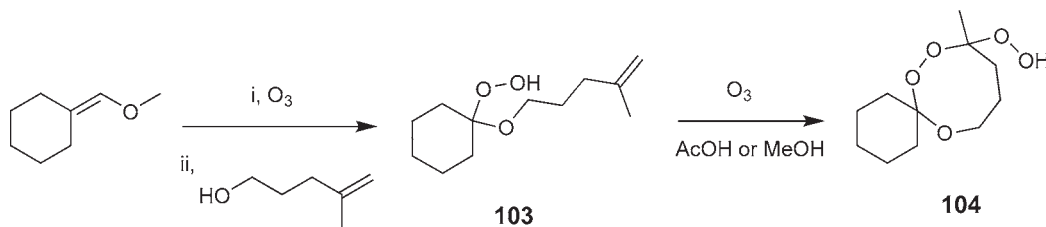


Dioxazocinoisindolone **102a** and isoindolobenzodioxazocine **102b** were synthesized from *N*-hydroxyphthalimide by intramolecular nucleophilic substitution of intermediate 2-(bromoalkoxy)-3-hydroxyisindolones (Scheme 23; <1999TL2117>).



Scheme 23

Entropically disfavored eight-membered cyclic peroxide, 1,2,4-trioxocanes **104**, can be produced by intramolecular cyclization of the intermediate hydroperoxide **103**. Thus, treatment of **103** with ozone in acetic acid–methylene chloride affords trioxocane **104** in 33% yield (Scheme 24; <1997JOC4949>).

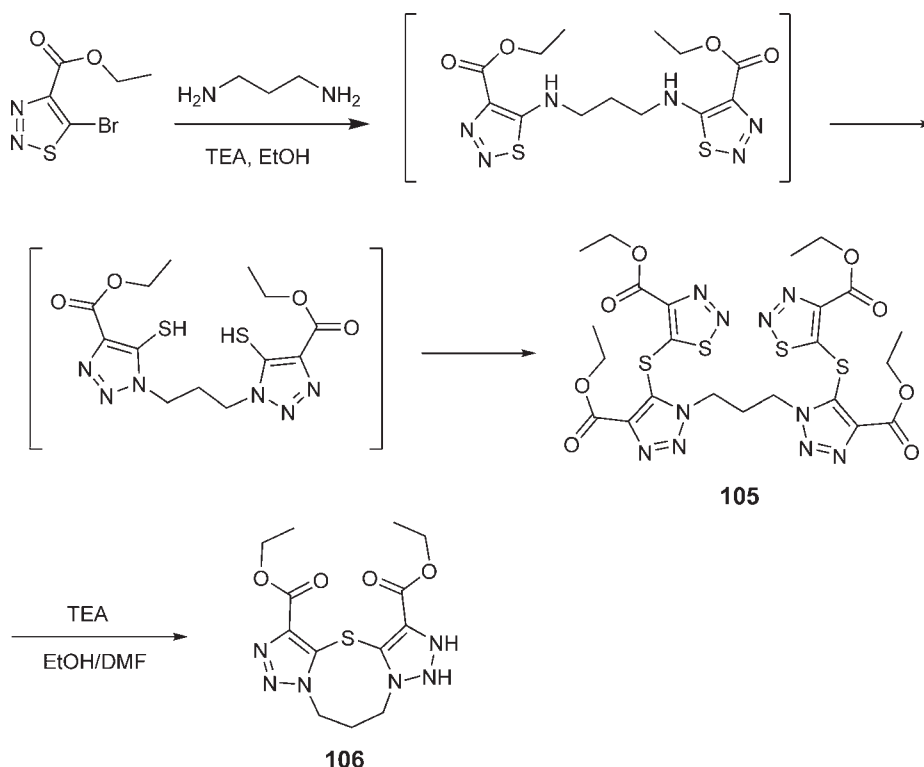


Scheme 24

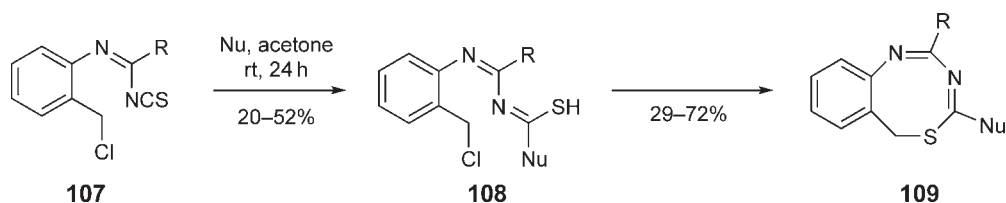
14.08.7.1.4 C–S bond formation

Reaction of 5-halo-1,2,3-thiadiazoles with 1,3-diaminopropane leads to bis(1,2,3-triazolyl-1,2,3-thiadiazolyl)sulfide **105**. Further intramolecular cyclization affords bis-[1,2,3]triazolo[1,3,7]thiadiazocine ring system **106** in 79% yield (Scheme 25; <2003OBC4030>). The role of the ester groups on both the 1,2,3-triazole and 1,2,3-thiadiazole rings in the formation of the final product is essential.

Benzimidoyl ($\text{R} = \text{Ph}$) or amidinoyl ($\text{R} = \text{piperidino}$ or morpholino) isothiocyanates **107** react with a variety of N-, O-, or C-nucleophiles to yield addition products **108** (Scheme 26). Intermediate thioureas **108**, formed from N-nucleophiles, were isolated and characterized. They further undergo cyclization under mild thermal conditions to afford corresponding thiadiazocines, for example, **20** <1996CCC1681, 1996CPA28>. Contrary, intermediates **108**, derived from O- and C-nucleophiles, as well as heterocyclic derivatives ($\text{Nu} = 1,2,4\text{-triazole}$, benzimidazole, benzotriazole), are prone to spontaneous cyclization into 6*H*-benzo[*f*][1,3,5]thiadiazocines **109** <1995CCC1415, 2000CPA36>.



Scheme 25



Scheme 26

14.08.7.1.5 S–S bond formation

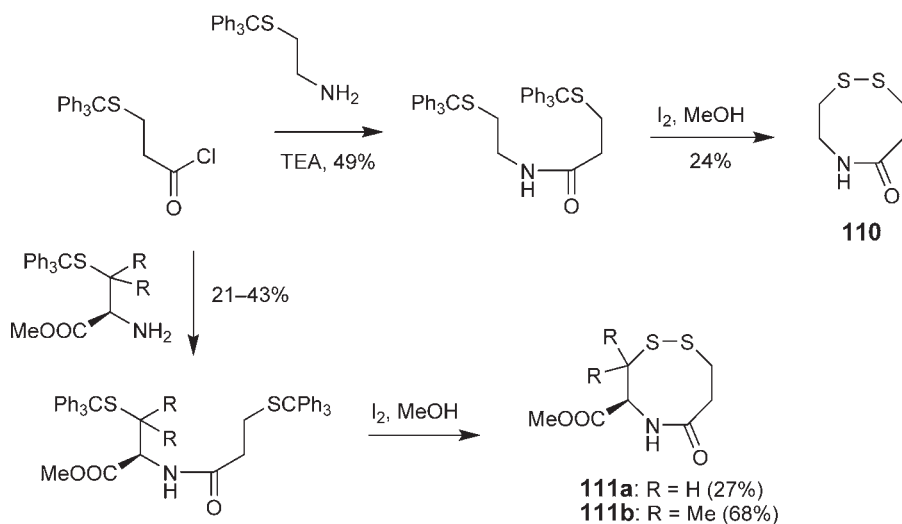
The first synthesis of 1,2-dithia-5-azacyclooctan-6-one **110**, the parent member of a dithiazocane family, has been reported (Scheme 27; <1997T16859>). Starting from the corresponding amino esters, substituted derivatives **111a** (R = H) and **111b** (R = Me) were also prepared using similar strategy.

14.08.7.2 Ring Formation by [7+1] Cyclization

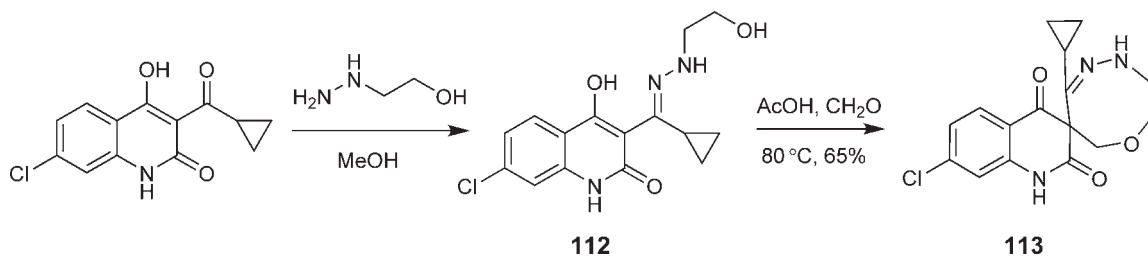
14.08.7.2.1 C–C bond formation

A new method for the synthesis of 1,4,5-oxadiazocines starting from β -diketones with acidic α -hydrogens has been described (Scheme 28). The method involves formation of 2-hydroxyethylhydrazone **112** and sequential reaction with an aldehyde in the presence of acetic acid providing from moderate to good yields of 1,4,5-oxadiazocines **113** <2005TL8009>.

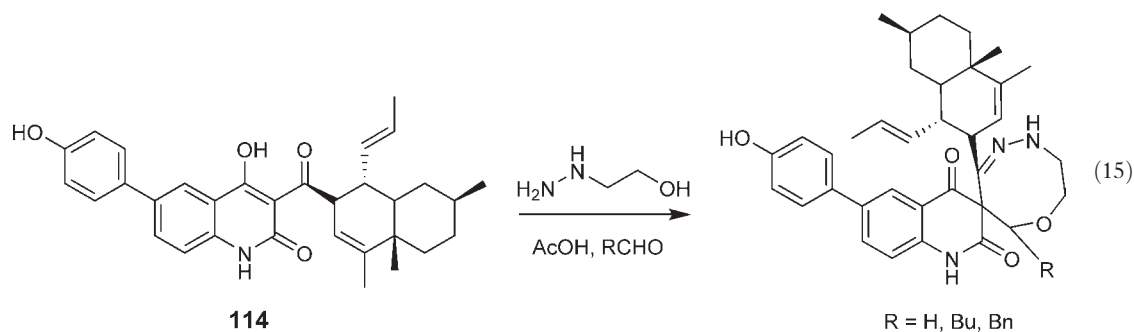
This method was further applied in the structure modification of Illicicolin H, polyketide isolated from the *Cylindrocladium iliciola* MFC-870 (Equation 15).



Scheme 27

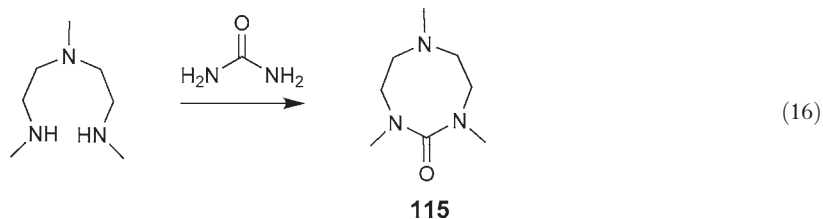


Scheme 28



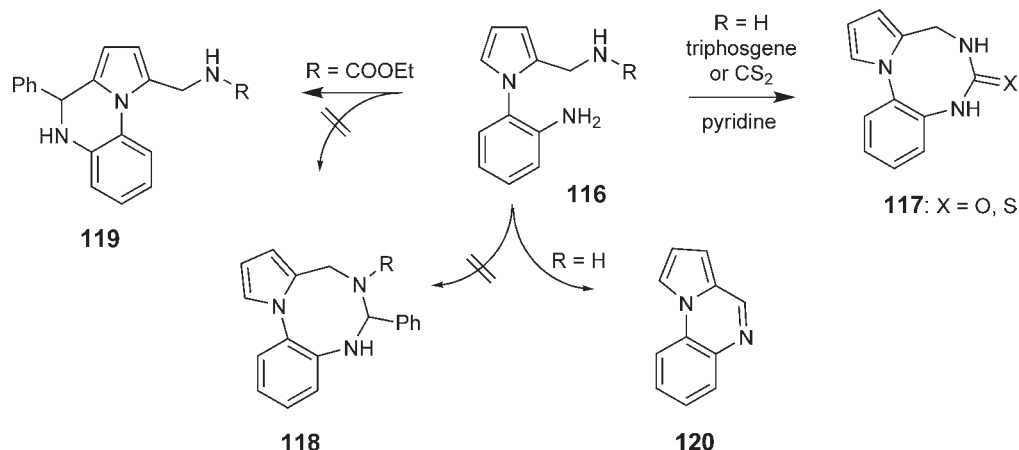
14.08.7.2.2 C–N bond formation

1,3,6-Trialkylhexahydro-1,3,6-triazocin-2-ones were prepared by the cyclocondensation of *N,N,N'*-trialkyldiethylenetriamines with urea, phosgene, or carbon dioxide. Thus, trimethyldiethylenetriamine was reacted with urea, producing 1,3,6-trimethylhexahydro-1,3,6-triazocin-2-one **115** in 80% yield (Equation 16; <1995EPP670316>).



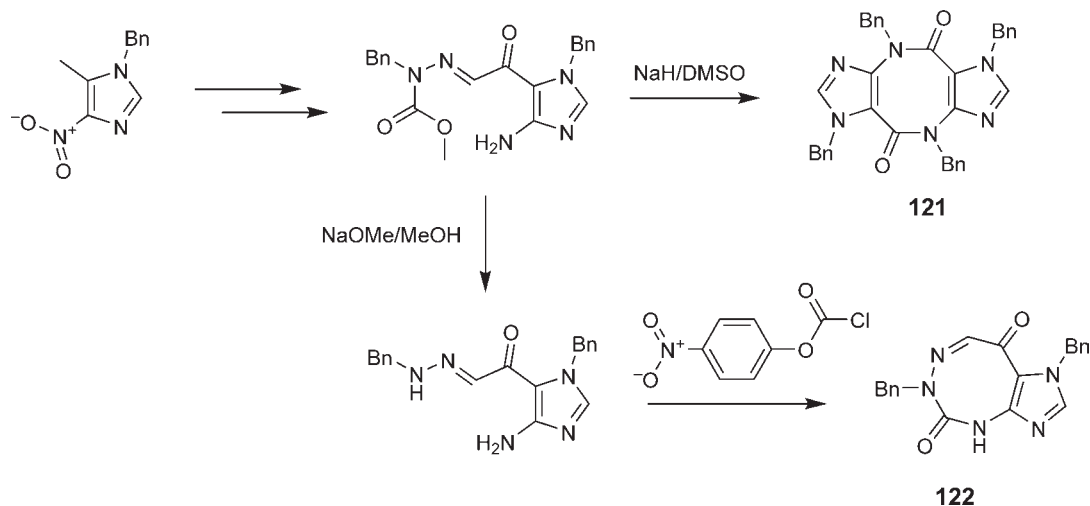
1,4,6-Oxadiazocane-5-thione **72** is readily available from 2,2'-oxydiethanamine and carbon disulfide (Scheme 15, Section 14.08.6.3; <1988APH400>).

Intramolecular coupling of diamine **116** with triphosgene or carbon disulfide yields pyrrolo[2,1-*e*][1,3,6]benzotriazocinones **117** (Scheme 29; <1996T10751>). Attempted synthesis of the pyrrolobenzotriazocine **118**, by reacting diamine **116** with benzaldehyde in a refluxing mixture of tetrahydrofuran (THF) and pyridine, gave instead pyrrolo[1,2-*a*]quinoxaline **120**, probably due to prototropic transamination rearrangement and sequential intramolecular cyclization with loss of aniline. Similar treatment of the *N*-substituted species with benzaldehyde in pyridine afforded 4,5-dihydropyrroloquinoxaline **119** instead of pyrrolobenzotriazocine **118**.



Scheme 29

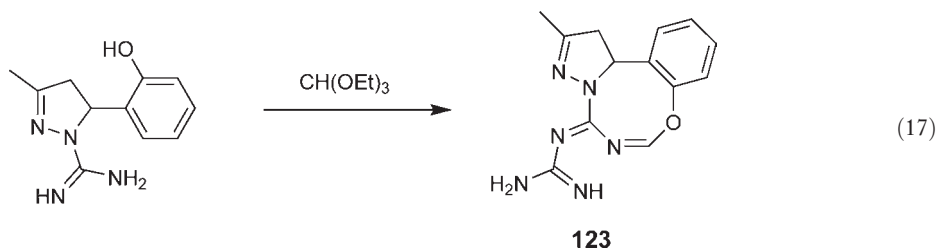
A novel 5:8-fused heterocycle containing the imidazo[4,5-*e*][1,2,4]triazocine ring system **122** has been synthesized in seven steps commencing from 1-benzyl-5-methyl-4-nitroimidazole (Scheme 30; <2001MI1558, 2002T9567>). Preliminary cyclization attempts using sodium hydride in dimethyl sulfoxide (DMSO) led only to dimerization at 0 °C or to tetrabenzyl diimidazodiazocinone **121** at elevated temperatures <2001MI1558, 1997H(45)857>. Stepwise deprotection and cyclization, and use of *p*-nitrophenylchloroformate as one-carbon synthon, afforded desired imidazo-triazocine ring system **122**.



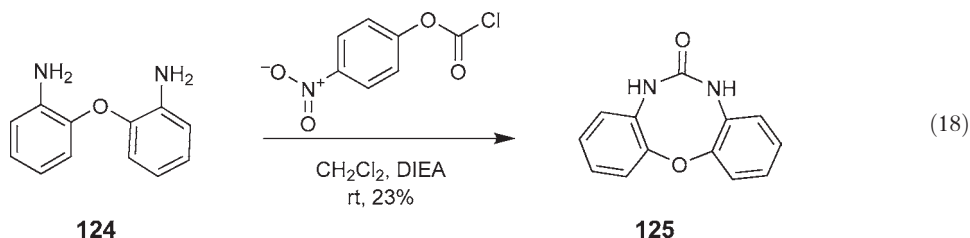
Scheme 30

A novel tricyclic mesoionic tetrazolium derivative of 1,3,5-triazocine **9** was the major product of photochemical conversion of 5-azido-1-mesityl-3-phenyltetrazolium tetrafluoroborate **32** (Scheme 4, Section 14.08.5.2.1; <2000JHC1129>). The proposed mechanism of the transformation included benzylic hydrogen abstraction by the triplet nitrene intermediate to produce biradical species, which captures the solvent acetonitrile to afford **9**.

The new pyrazolo[1,5-*e*][1,3,5]benzoxadiazocine heterocyclic ring system **123** was prepared by cyclization of 4,5-dihydro-3-methyl-5-(2-hydroxyphenyl)-1*H*-pyrazole-1-carboximidamide with triethyl orthoformate. A reaction mechanism involving re-esterification of triethyl orthoformate with phenolic hydroxyl of the additional equivalent of hydroxyphenyl pyrazoline was proposed to explain the formation of the product with an additional guanidine moiety (Equation 17; <2002JP11260>).

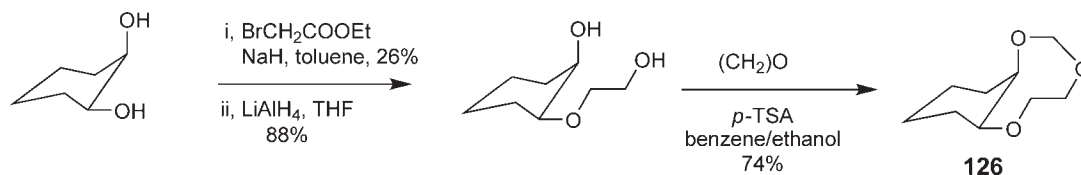


5*H*-Dibenzo[*b,g*][1,4,6]oxadiazocin-6(7*H*)-one **125** has been reported as the only product of reaction of diamine **124** with *p*-nitrophenyl chloroformate (Equation 18; <2004AXCo136>).



14.08.7.2.3 C–O bond formation

Synthesis of *cis*-cyclohexano-8-crown-3 **126** as a representative of 1,3,6-trioxacane family was reported starting from 1,2-*cis*-dihydroxycyclohexane (Scheme 31; <1999MRC401>).

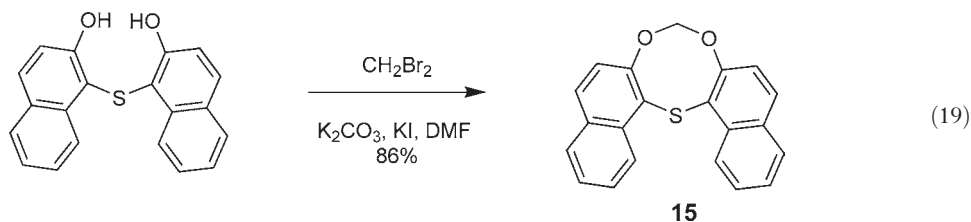


Scheme 31

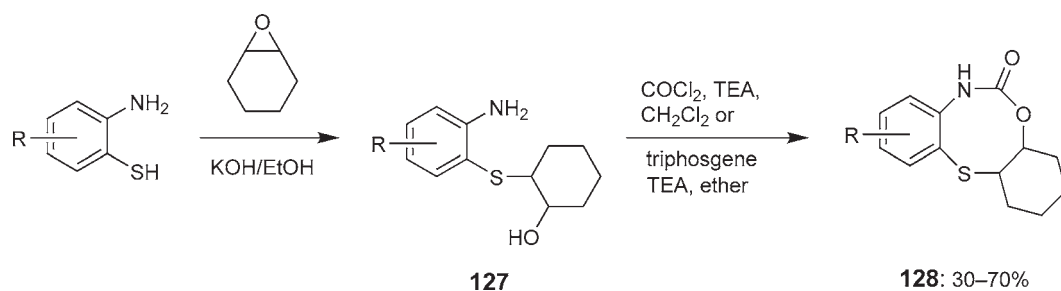
2,2'-Oxydiethanol, when reacted with formaldehyde in polyphosphoric acid, affords 1,3,6-trioxacane in 81% yield (<2000MI1069>). Similar reaction with acetaldehyde requires milder conditions, and 2-methyl-1,3,6-trioxacane was synthesized in 20% yield after 5 h reflux in toluene in the presence of Dowex 50 × 8 resin (<1995MI790>).

Reaction of 2,2'-(benzylazanediyloxy)diethanol with methylene chloride in THF in the presence of sodium hydride leads to 24% yield of 6-benzyl-1,3,6-dioxazocane **69** (Scheme 14, Section 14.08.6.1; <2001H(54)151>), accompanied with 35% of dimeric 6,14-dibenzyl-1,3,9,11-tetraoxa-6,14-diazacyclohexadecane (not shown in the scheme).

8*H*-Dinaphtho[2,1-*d*:1',2'-*g*][1,3,6]dioxathiocine **15** was synthesized from the corresponding bis-phenol and methylene bromide in 86% yield (Equation 19; <1995JST95>).



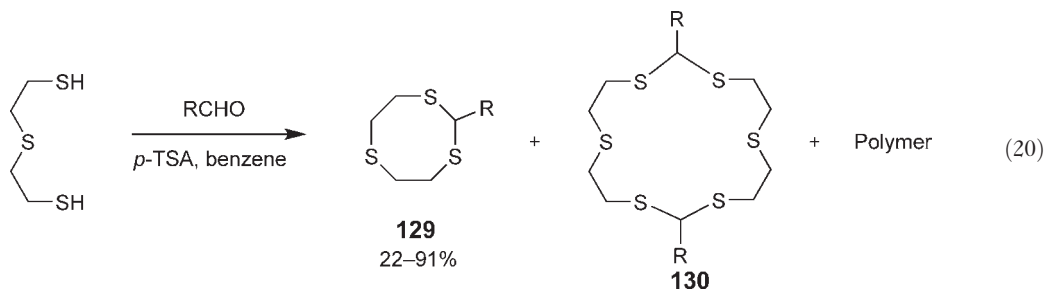
Amino alcohols **127** are readily available from *o*-aminothiophenols and oxirane. They were further cyclized with phosgene or triphosgene to afford dibenzo[*d,g*][1,6,3]oxathiazocin-6(7*H*)-ones **128** in moderate to good yields (Scheme 32; <1997USP5621153>).



Scheme 32

14.08.7.2.4 C–S bond formation

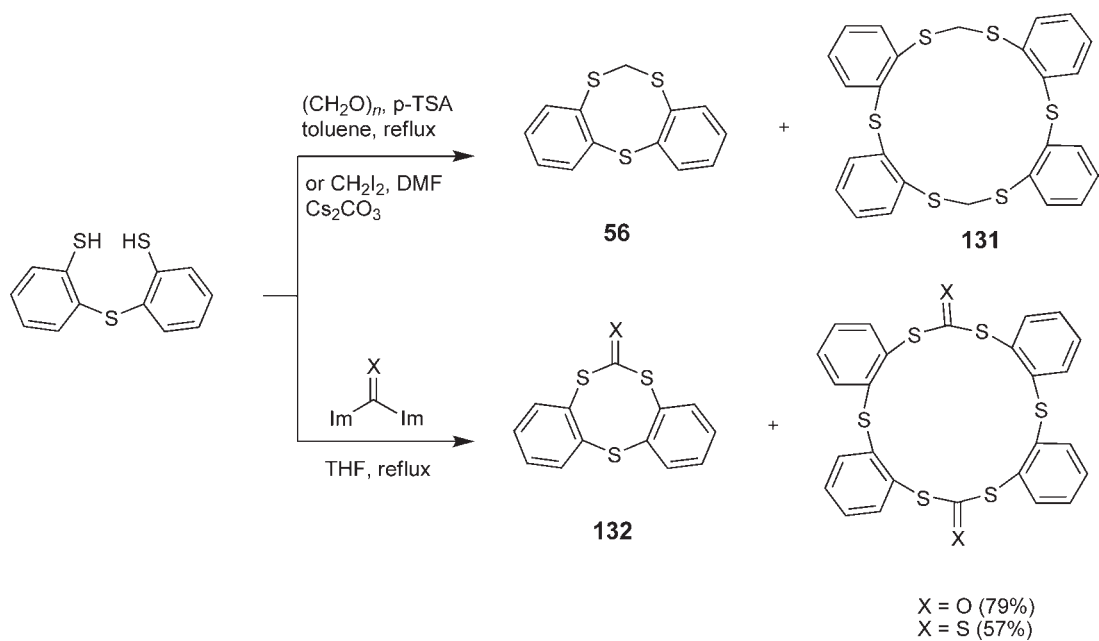
The acid-catalyzed condensation of 2,2'-thiodiethanethiol with carbonyl compounds under properly chosen conditions leads in good yield to thiocrown ethers containing thioacetal units. The reaction with benzaldehyde has been examined in detail, and the monomer **129**, dimer **130**, and polymer products have been characterized. The reaction was driven in good yield to any of these products by a proper choice of conditions (Equation 20; <1994J(P1)707>).



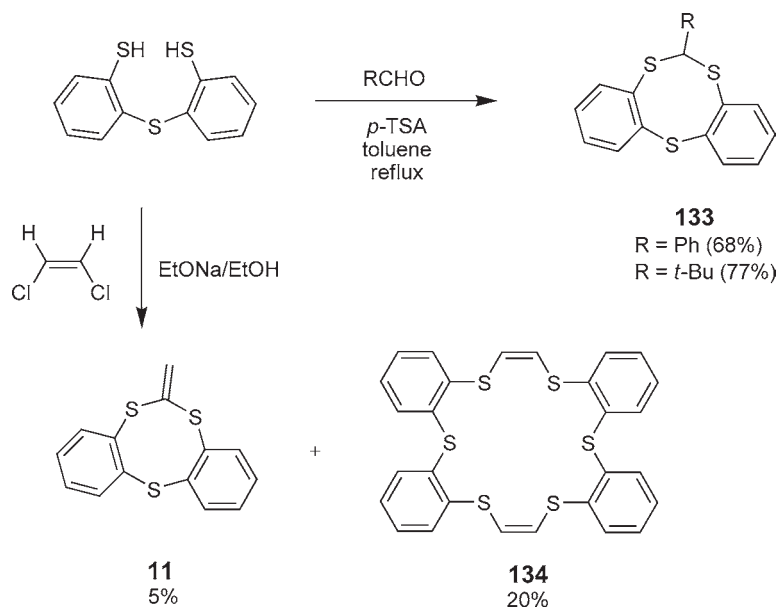
Condensations of bis(*o*-mercapto)phenyl sulfide with paraformaldehyde or diiodomethane in moderately concentrated solutions gave dibenzo[*d,g*][1,3,6]trithiine **56** in 28–49% yields, accompanied with 6–10% yields of the product of 2:2 condensation, hexathiacyclohexadecine **131** (Scheme 33). Condensation with diiodomethane in diluted solution afforded trithiine **56** as a sole product in 90% yield. Interestingly, when carbonyl or thiocarbonyl diimidazoles were used as dielectrophile, formation of a 16-membered ring was predominant and the eight-membered product **132** was not observed <1999H(50)103>.

Similar reaction with benzaldehyde or pivalaldehyde led to 6-phenyl- and 6-*t*-butyl-dibenzo[*d,g*][1,3,6]trithiins **133** in good yields (Scheme 34; <1998BCJ1187>). Reaction of bis(*o*-mercapto)phenyl sulfide with 1,2-*cis*-dichloroethylene produced 6-methylenedibenzo[*d,g*][1,3,6]trithiine **11** as a mixture with 18-membered product **134** instead of an expected nine-membered dibenzo[*b,e*][1,4,7]trithionine <1999T10057>.

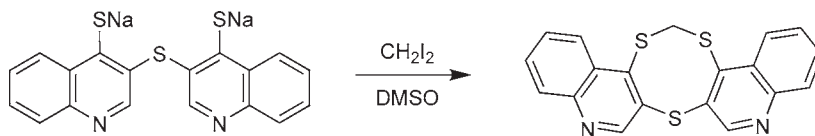
Disodium salt of 3,3'-thiodiquinoline-4-thiol when reacted with diiodomethane gives the corresponding 1,3,6-trithiine ring system with two annulated quinoline rings (Equation 21; <1999H(51)2861>).



Scheme 33



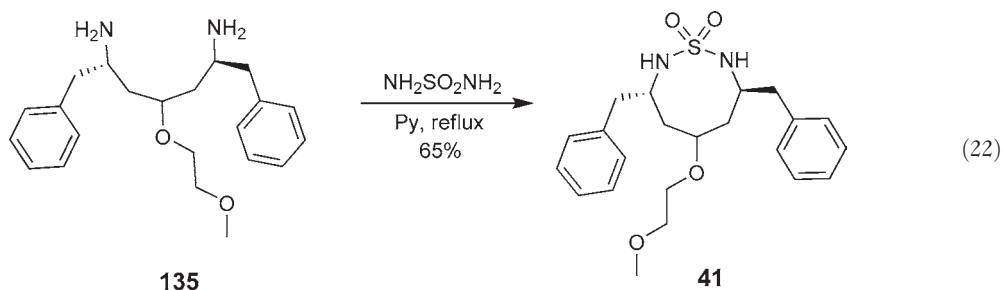
Scheme 34



(21)

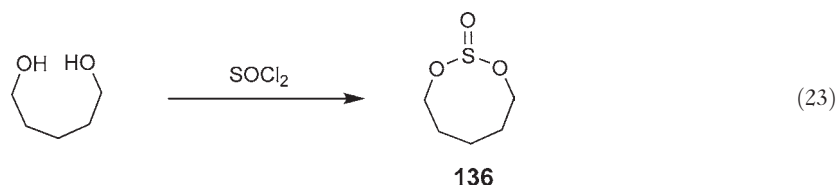
14.08.7.2.5 N–S bond formation

Enantiomerically pure diamine **135** can be reacted with sulfamide to provide eight-membered cyclic sulfamide **41** as a representative of 1,2,8-thiadiazocane ring system (Equation 22; <1995TL6383>).



14.08.7.2.6 O–S bond formation

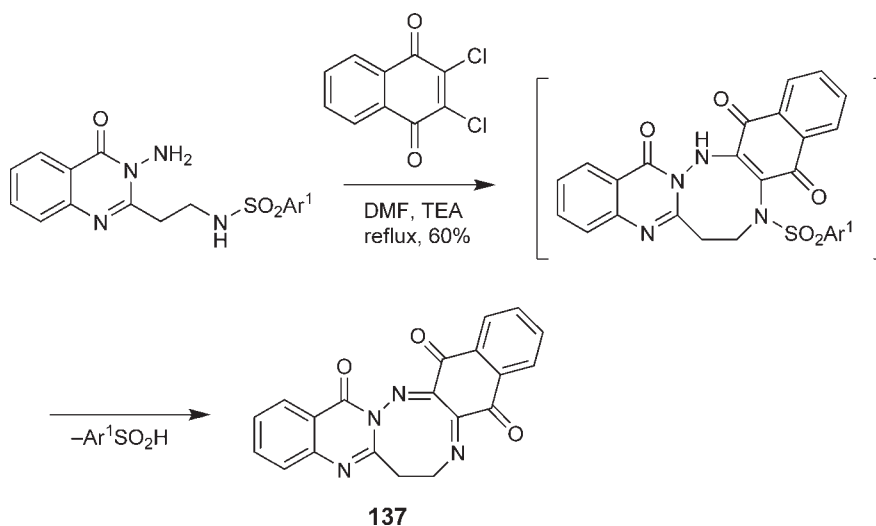
1,7,8-Dioxathiocane **136** was synthesized from 1,5-pentanediol and thionyl chloride in 16% yield (Equation 23). This compound is prone to further cationic polymerization when TfOH, TfOMe, BF₃NOEt₂, TsOMe, and MeI were used as initiators <1998MAC1785>.



14.08.7.3 Ring Formation by [6+2] Cyclization

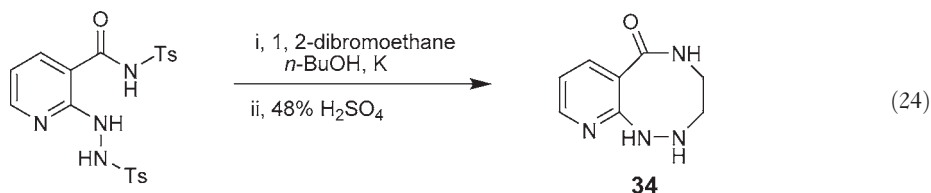
14.08.7.3.1 C–N bond formation

Naphtho[2',3':3,4]-[1,2,5]triazocino[8,1-*b*]quinazolinone **137** was obtained by refluxing of 2-substituted 3-aminoquinoxalin-4-one with 2,3-dichloro-1,4-naphthoquinone in DMF (Scheme 35; <2001MOL267>). Initial formation of 5,6-dihydrotriazocine derivative was followed by elimination of arylsulfonic acid and formation of ring system **137**.



Scheme 35

Ditosyl derivative of 2-hydrazinonicotinic acid is a convenient starting material for synthesis of pyrido[3,2-*g*]-[1,2,5]triazocine **34** (Equation 24; <1986PJC1115>).



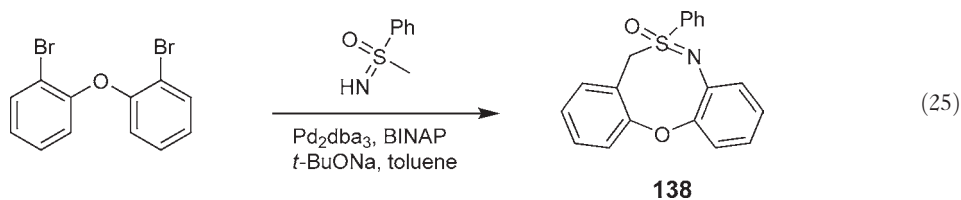
14.08.7.3.2 C–O bond formation

When reaction of *syn*-isomer of substituted *o*-aminobenzophenone oxime with chloroacetyl chloride was performed under Shotten–Baumann conditions, it failed to stop on the formation of 2-chloroacetamide intermediate **99** (see Equation (14), Section 14.08.7.1.3; <2001MI140>) and spontaneously formed 1*H*-benzo[*d*][1,2,6]oxadiazocin-2(3*H*)-one **100** <2003KGS485>.

14.08.7.4 Ring Formation by [5+3] Cyclization

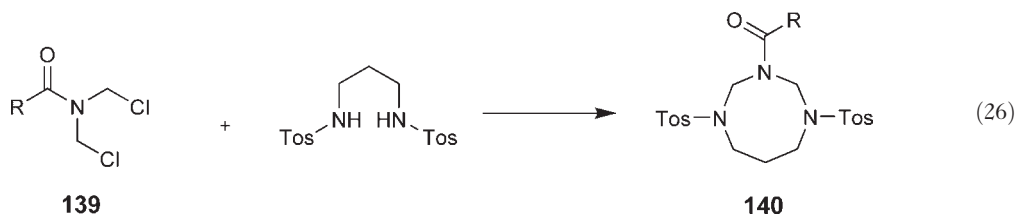
14.08.7.4.1 C–C bond formation

Palladium-catalyzed coupling of dibromoarene and sulfoximine gives 1,5,6-oxithiazocine **138** ring system in 69% yield (Equation 25; <2002SL832>). The reaction sequence involves an intramolecular N-arylation followed by intramolecular ring closure.



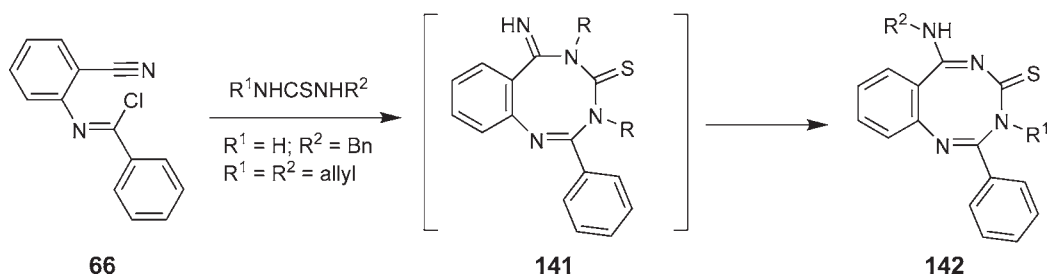
14.08.7.4.2 C–N bond formation

Reactions of *N,N*-bis(chloromethyl)amides **139** (R = Me, H) with *N,N'*-ditosylated 1,3-diaminopropane result in formation of the corresponding 1,3,5-trisubstituted 1,3,5-triazocanes **140** (Equation 26; <1998RCB2201>).

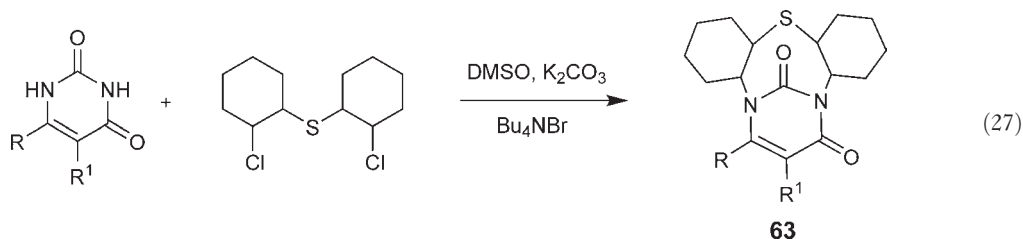


N-(2-Cyanophenyl)benzimidoyl chloride **66** can be reacted with thioureas to give 1-[(2-cyanophenylimino)phenylmethyl]thioureas containing two nucleophilic active sites (nitrogen and the sulfur atoms) capable of attacking the cyano group. In the case of derivatives of benzylthiourea or symmetrical diallylthiourea they spontaneously cyclizes into benzotriazocines via nitrogen attack. The resultant benzotriazocines **141** were not the final products, as they further underwent Dimroth rearrangement to finally give the triazocine derivatives **142** (Scheme 36; <2002MOL96>). When more sterically hindered thioureas were used, intramolecular S-attack is preferable to give 2-phenylquinazoline-4(3*H*)-thione as a final elimination/rearrangement product (see Scheme 13, Section 14.08.5.5).

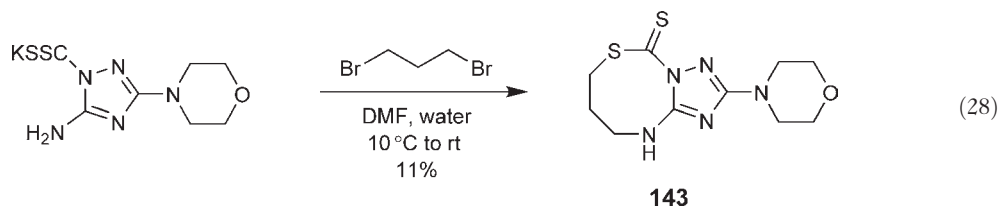
An eight-membered ring was annulated to pyrimidines by reaction of *trans*-2,2'-dichlorodicyclohexylsulfide with uracil derivatives in DMSO in the presence of phase-transfer catalyst (Equation 27; <2002ZPK1309, 2004MI1213>).



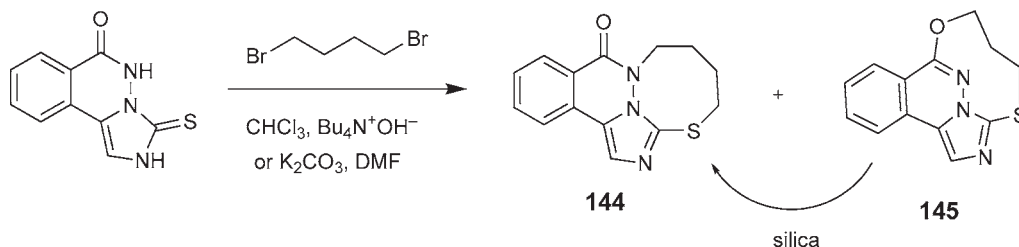
Scheme 36



Reaction of potassium triazolyldithiocarbonate with dibromopropane leads to substituted [1,2,4]triazolo[1,5-*c*]-[1,3,5]thiadiazocine-5-thione **143** in poor yield (Equation 28; <1994JHC997>). The major products of this transformation were uncyclized 3-bromopropyldithiocarbonate (20%) and bis-substituted propylene derivative (16%).



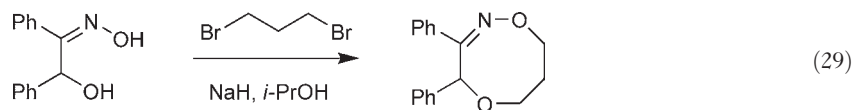
Cyclization of 2,3-dihydro-3-thioxoimidazo[5,1-*a*]phthalazin-6(5*H*)-one (and the corresponding pyrido[3,2-*d*]pyridazin-5(6*H*)-ones not depicted in the scheme) with 1,4-dibromobutane afforded a novel annulated 1,3,4-thiadiazocine ring system **144**. Product of O-intramolecular alkylation 1,6,3,4-oxathiadiazonane **145** was also detectable when reaction was performed in chloroform. Compound **145** underwent ring contraction during attempted chromatographic separation on silica gel yielding 1,3,4-thiadiazocine **144**, which was a sole product when reaction was performed in DMF (Scheme 37; <2002T8963>).



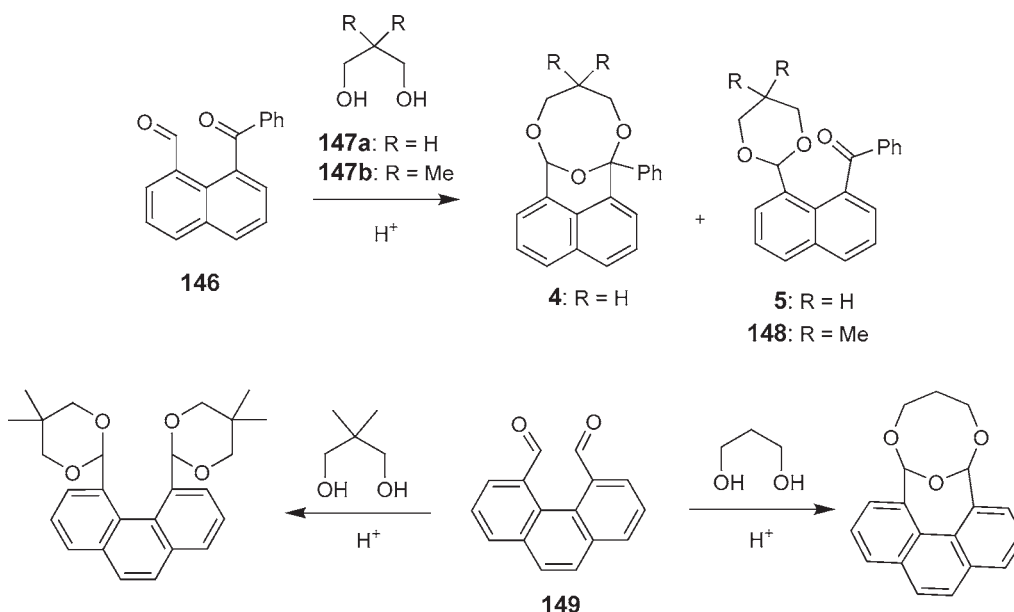
Scheme 37

14.08.7.4.3 C–O bond formation

Reaction of benzoin- α -oxime with sodium hydride in propan-2-ol produces 1,5-dianion which is further cyclized into 1,5,6-dioxazocine ring system with 1,3-dibromopropane (Equation 29; <2004S837>).



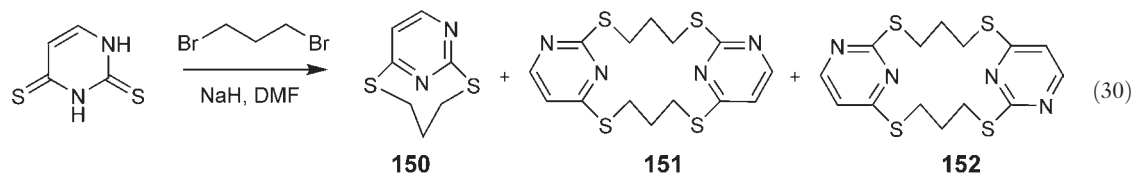
Acid-catalyzed condensations of 1,5- or 1,6-dicarbonyl compounds with 1,3-dihydroxypropane give 1,3,5-trioxocane derivatives as a result of neighboring participation by the adjacent carbonyl group during the acetalization process (Scheme 38; <1998J(P1)2353>). When a mixture of the keto aldehyde **146** and 1,3-dihydroxypropane **147a** (R = H) was treated with chlorosulfonic acid in dichloromethane, the corresponding 1,3,5-trioxocane **4** was obtained in 34% yield along with 30% amount of the keto acetal **5**. With 2,2-dimethylpropane-1,3-diol **147b** (R = Me), however, only the keto acetal **148** was isolated. The corresponding condensation reactions involving the structurally rigid 1,6-dialdehyde **149** yielded the analogous products.



Scheme 38

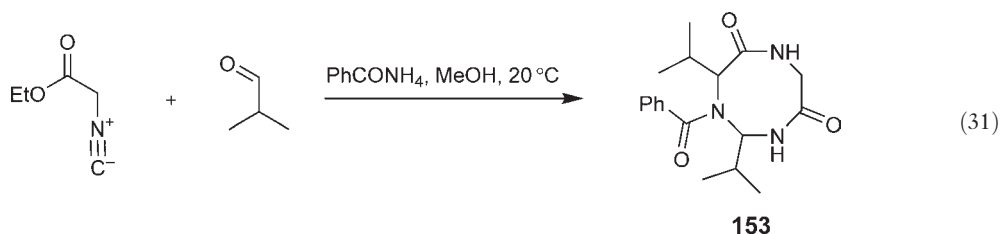
14.08.7.4.4 C–S bond formation

Thiapyrimidinophane **150** was prepared from 2,4-dithiouracil and 1,3-dibromopropane in 8% yield. Two 16-membered thiapyrimidinophanes **151** and **152** were the major products of the reaction, which were isolated as inseparable mixture in 56% yield (Equation 30; <1997JHC687>).

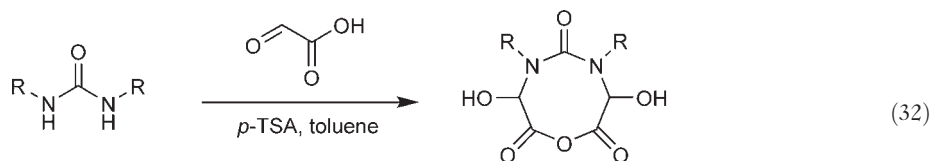


14.08.7.5 Miscellaneous Methods

A three-component cyclization approach toward 1-benzoyl-2,8-diisopropyl-[1,3,6]triazocane-4,7-dione **153** has been reported (Equation 31; <2003SL1591>).

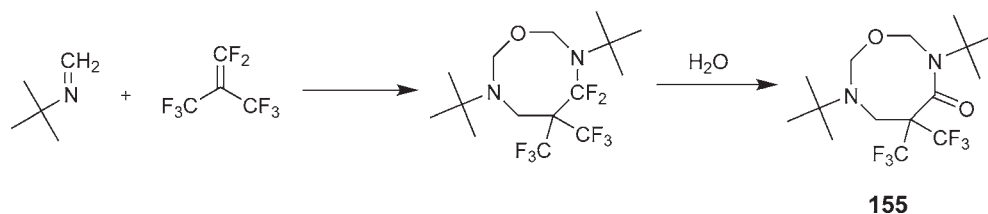


A novel 1,4,6-oxadiazocine-2,5,8-trione **154** was obtained by the condensation of glyoxylic acid with urea derivatives under acidic catalysis conditions (Equation 32; <1997JHC829>).



154: R = Ph, 1-CH₂-Naphth

Reaction of *N*-methylene-*tert*-butylamine with octafluoroisobutylene in diethyl ether in the presence of water leads to unexpected 1,3,7-oxadiazocan-4-one ring system **155** as a result of the complex sequence of reactions (Scheme 39; <1996ZOB344>). It is believed to include steps of imine hydration, cyclization accompanied by elimination of *tert*-butylamine, and final hydrolysis of difluoromethyl moiety into carbonyl group.



Scheme 39

14.08.8 Ring Syntheses by Transformation of Another Ring

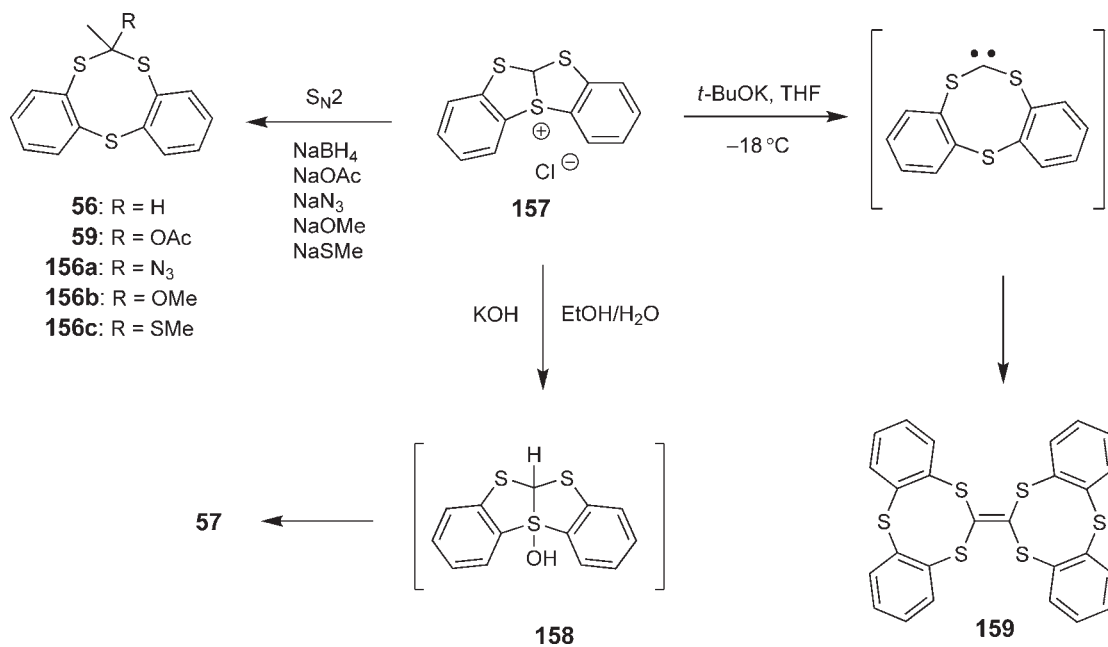
Many heterocines with three heteroatoms are synthesized using expansion reactions of the other ring systems, while contractions of the larger rings into eight-membered heterocyclic systems are rare and were not reported during review period. General methods for ring expansions were categorized in CHEC-II(1996), and this classification is followed in this section.

14.08.8.1 Ring Expansion by Ionic Ring Openings

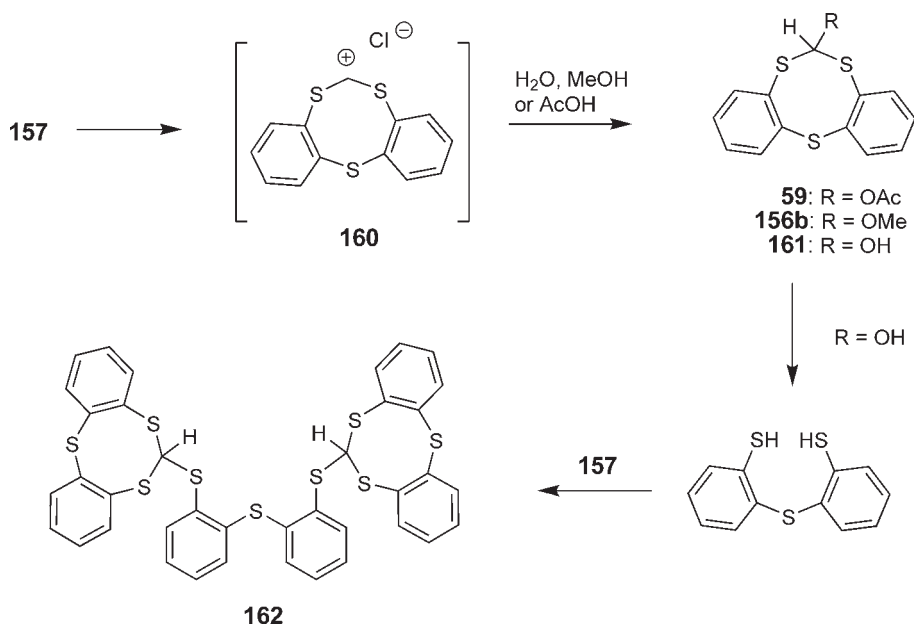
14.08.8.1.1 Trithiocines

6-Substituted dibenzo[*d,g*][1,3,6]trithiocines **59** and **156a–c**, as well as 6-unsubstituted compound **56**, were synthesized by reactions of 9a*H*-9,10-dithia-4*b*-thioniaindono[1,2-*a*]indene chloride **157** with appropriate nucleophiles in THF or acetonitrile in good yields (Scheme 40; <1998BCJ1187>). A usual S_N2 mechanism was suggested for these transformations, where the sulfonium sulfur serves as a leaving group. In the case of alkaline solvolysis addition of OH[−] to the sulfonium sulfur yields intermediate sulfurane **158**. It is prone to C–S bond cleavage followed by proton transfer to afford final product **57** <1996BCJ2349>. In the case of stronger and bulky *t*-BuOK, the dimeric product **159** was formed through carbene intermediate <1996BCJ2349, 1996CC205>.

Solvolysis products **59**, **156b**, and **161** were explained (Scheme 41; <1998BCJ1187>) as a result of solvent addition to carbenium ion **160**. Addition of water leads to arene thiol as a final product. Its reaction with two



Scheme 40



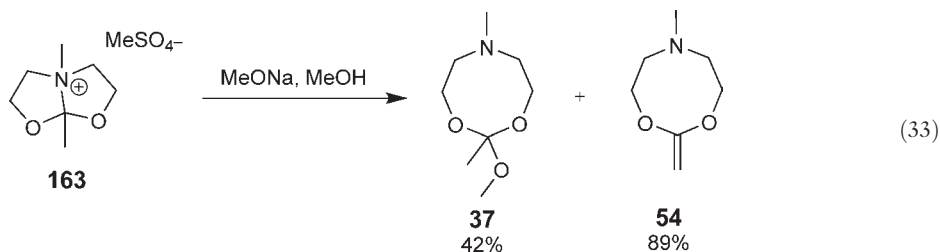
Scheme 41

molecules of **157** produces bis-dibenzo[*d,g*][1,3,6]trithiocine **162** as a by-product, which was observed in most of cases of solvolysis in protic solvents.

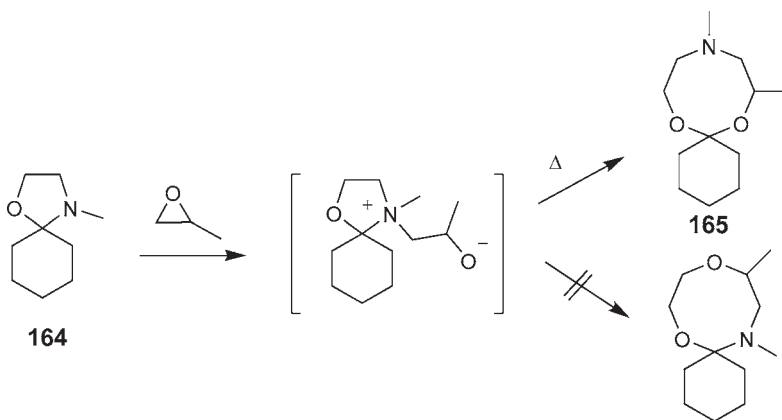
Interestingly, reaction of **157** with other nucleophiles (ammonia, amines, Grignard reagents, alkylolithiums, KCN, triphenylphosphine, and trimethylphosphite) did not give any expected products and trimer **162** was the only identifiable compound.

14.08.8.1.2 Dioxazonines

Exposure of quaternary ammonium salt **163** to NaOMe gives methyl orthoester **37** and ketene acetal **54** as the consequence of a competing Hofmann-type elimination (Equation 33). Elution of **163** as a methanol solution through an anion-exchange resin (Dowex-550-OH, MeOH) leads exclusively to ketene acetal **54** in 89% yield <2004AGE1117>.

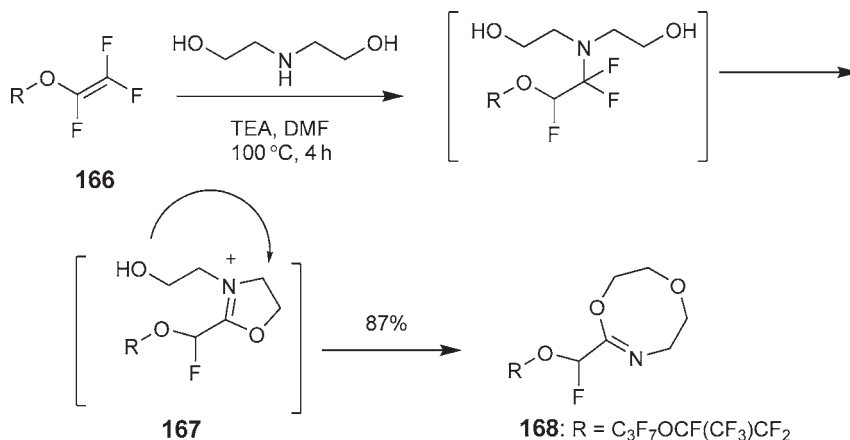


Initial addition reaction of methyloxirane to 4-methyl-1-oxa-4-azaspiro[4.5]decane **164** is followed by ring expansion under thermal conditions. O-Nucleophilic attack is directed on quaternary carbon of the spiro system rather than on C-4 carbon of the oxazolidine ring, and 8,10-dimethyl-7,13-dioxa-10-azaspiro[5.7]tridecane **165** is a major product of the transformation (Scheme 42; <1995IZV1838>).



Scheme 42

Reaction of 1,1,2-trifluorovinyl ether **166** with 2,2'-iminodiethanol leads to 1,4,7-dioxazocane system **168** (Scheme 43; <1999ZPK1345, 2000JFC13>). The proposed mechanism involves addition of amine to substrate, formation of oxazolinium intermediate **167** via intramolecular nucleophilic cyclization and fluoride α -elimination, and final intramolecular O-alkylation/ring expansion.

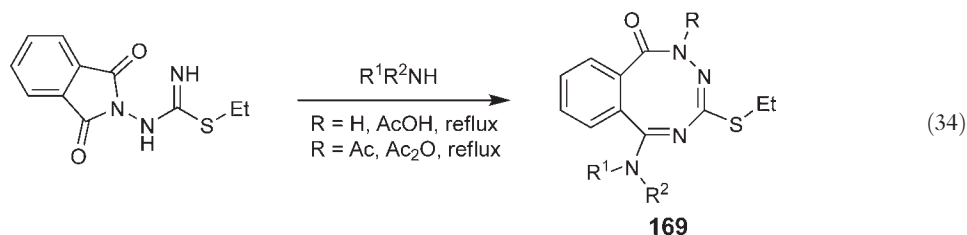


Scheme 43

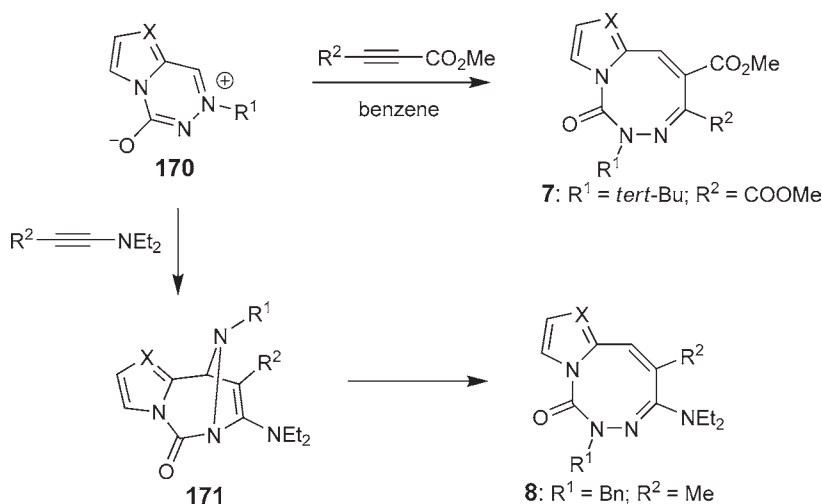
14.08.8.2 Miscellaneous Ring Expansion Methods

14.08.8.2.1 Triazocines

Phthaloylisothiosemicarbazide was refluxed in AcOH with secondary amines to yield 59–95% of substituted 6-amino-4-ethylthiobenzo[*f*][1,2,4]triazocin-1(2*H*)-ones **169**. Corresponding acetyl derivatives were produced if reaction was performed in acetic anhydride (Equation 34, <1994APH77>).



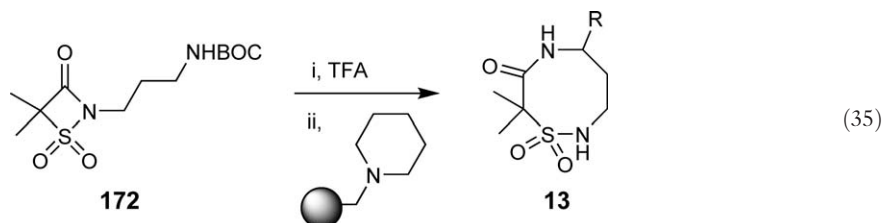
The mesomeric betaines **170** were found to act as cyclic azomethine imines in the presence of acetylenic dipolarophiles. They give unusual ring-expanded adducts **7** and **8** containing bicyclic triazocinone structure in good to high yields (Scheme 44; <1999T13703>). In the case of electron-rich dipolarophiles such as ynamines, the formation of the initial 1:1 adducts **171** was observed. In particular, imidazobetaines (X = N) reacted with an ynamine at room temperature to provide only the initial cycloadducts. The reactivity and regioselectivity of the cycloaddition were in agreement with the results of MO calculations.



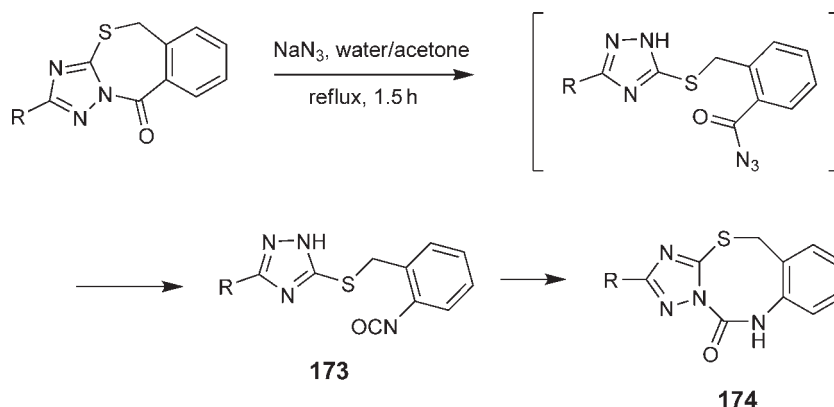
Scheme 44

14.08.8.2.2 Thiodiazocines

The transamidation-like reactions of the 2-(aminoalkyl)-1,2-thiazetidin-3-one 1,1-dioxides **172** in the presence of (piperidinomethyl)-polystyrene give the ring-enlarged eight-membered products **13** in 42–87% yields (Equation 35; <1999HCA354>). To prove the exclusive attack of the amine at the carbonyl rather than at the sulfonyl group, compound **13** ($R = \text{Me}$) and its structure with an asymmetrically situated methyl substituent was then established by X-ray crystallography (see Section 14.08.3.1.5).

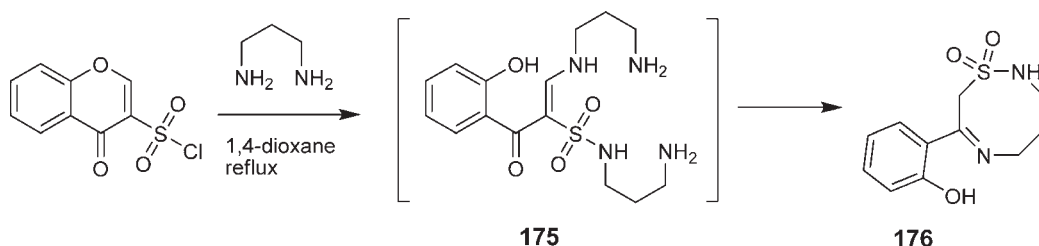


Several [1,2,4]triazolobenzothiadiazocin-11-ones **174** were prepared via ring expansion of [1,2,4]triazolo[3,2-*b*]-[2,4]benzothiazepin-10(5*H*)-ones in presence of sodium azide. The intermediate aryl isocyanate **173**, formed as a result of Curtius rearrangement, was isolated and characterized by elemental analysis, IR, ^1H NMR, and mass spectroscopies (Scheme 45; <2002PS2303>).



Scheme 45

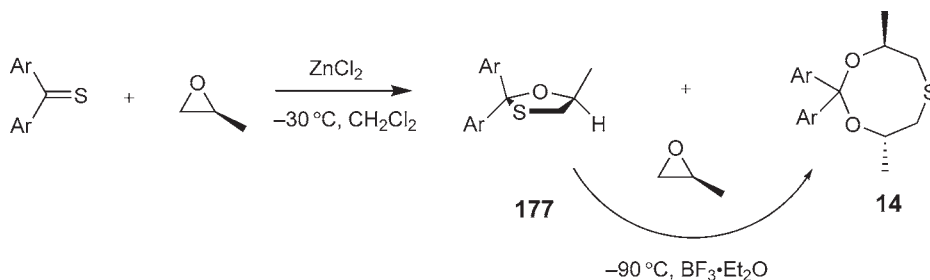
Reaction of 4-oxo-4*H*-chromene-3-sulfonyl chloride with an excess of 1,3-diaminopropane believed to proceed through acylation/ring-opening sequence. Open-chain intermediate **175** undergoes intramolecular cyclization accompanied by elimination of amine and formic acid to afford 1,2,6-thiadiazocine ring system **176** (Scheme 46; <1994AP819>).



Scheme 46

14.08.8.2.3 Dioxathiocines

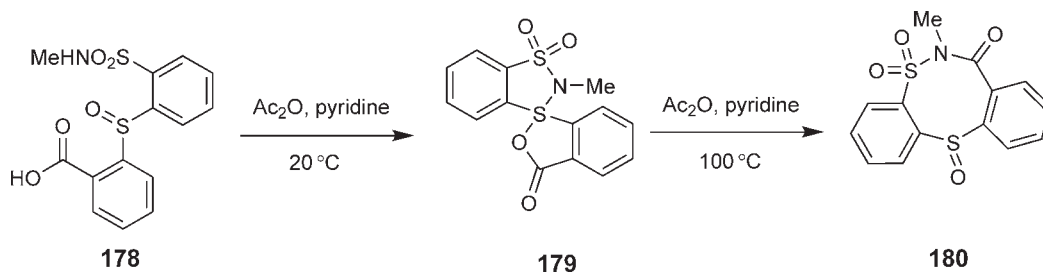
The reaction of 4,4'-dimethoxythiobenzophenone with (*S*)-2-methyloxirane in the presence of ZnCl_2 leads to the corresponding 1:1 adduct, that is, 1,3-oxathiolane **177**. A 1:2 adduct, (4*S*,8*S*)-1,3,6-dioxathiocane **14**, was formed as a minor product. Treatment of the mixture of 1:1 adduct and (*S*)-2-methyloxirane with BF_3 etherate gives the 1:2 adduct **14** in low yield (Scheme 47; <2001HCA3319, 2003HCA2833>).



Scheme 47

14.08.8.2.4 Dithiazocines

Spiro(3*H*-2,1-benzoxathio1-3-one)-1,1'-3*H*-2-methyl-1,3,2-benzodithiazole 3,3-dioxide **179** is readily available from sulfoxide **178** under mild reaction conditions, and optimal 86% yield of spiro- λ^4 -sulfane **179** was achieved after 10–15 min at room temperature. Harsher reaction conditions, that is, 3 h at reflux, lead to ring-enlargement product, dibenzodithiazocine **180**, in 89% yield (Scheme 48; <1995CC1069>).



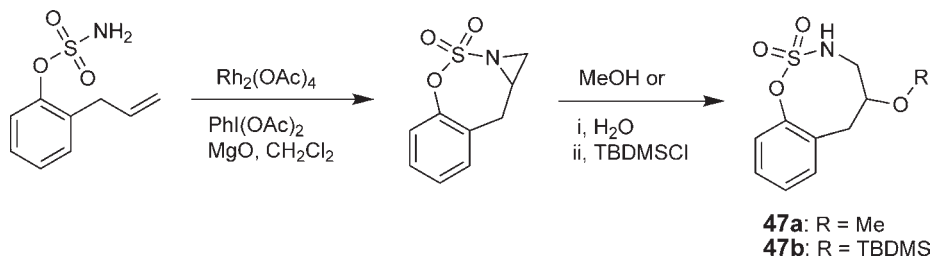
Scheme 48

14.08.8.2.5 Oxadithiacines

Photolysis of 4,8,10-trithiadibenzo[*cd,i*]azulene 8-oxides **28** under irradiation with high-pressure Hg lamp (500 W, $\lambda = 313\text{ nm}$) afforded an unstable, acid-sensitive 1,2,4-oxadithiocine ring system **29**, which was characterized by ^1H NMR and mass spectrometry (Scheme 3, Section 14.08.5.1; <1996CL655>).

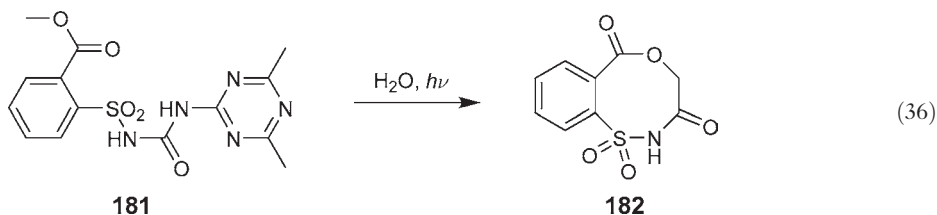
14.08.8.2.6 Oxathiazocines

2-Allylphenyl sulfamate cyclizes under oxidizing conditions to furnish bicyclic aziridine. Subsequent nucleophilic addition of alcohols or H_2O occurs selectively to afford 1,2,3-oxathiazocine structures **47a** and **47b** (Scheme 49; <2005OL4685>). Similarly, Rh-catalyzed oxidative transformation of hex-5-enyl sulfamate leads to 1,2,3-oxathiazocane with annulated aziridine ring <2004AGE4349>.



Scheme 49

Benzo[*f*][1,5,4]oxathiazocine-3,6(2*H*,4*H*)-dione 5,5-dioxide **182** was isolated and characterized as the major product of photodegradation of **181**, a commercial sulfonylurea herbicide, in aqueous solution (Equation 36; <1999MI873>).



14.08.9 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

There has been a significant increase in the methodology available to assemble medium-size ring systems, including eight-membered ones bearing three heteroatoms, during the last decade. Development of efficient routes toward various biologically valuable targets was a primary goal of numerous studies.

In spite of the apparent problems with cyclizing medium-size ring systems, most classes of triheterocines are accessible through flexible synthetic routes. Numerous high-yielding processes for heterocines have been developed starting with acyclic precursors.

Unimolecular cyclizations involving C–N bond formation include intramolecular alkylations and acylations were applied for a variety of azocines, while macrocyclic O-alkylations and ketalizations are the most reliable methods for oxocine core synthesis through C–O bond formation. Other types of unimolecular cyclizations are scarce and erratic, and they usually depend on stereochemistry of the open-chain precursors and require tuning of the functional groups involved.

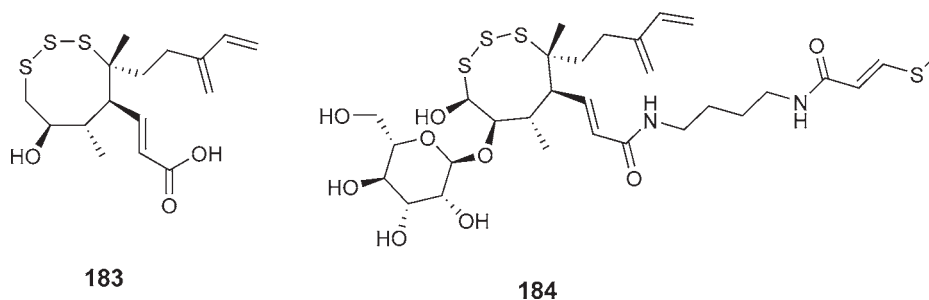
Bimolecular triheterocine syntheses remain the most important way of ring assembly. Utility of readily available 1,1-dielectrophilic reagents, for example, phosgene and its analogues, orthocarboxylates, 1,1'-carbonyldiimidazole (CDI), and 1,7-dinucleophiles, usually derived from 2,2'-disubstituted diethyl ethers, predominates in [7+1] syntheses, while cyclization of 1,2-diamines (or their protected counterparts), 1,2-diols, or 1,2-thiols with dielectrophiles remains the primary means of entry to the 1,4-heterocine ring system.

Syntheses from other heterocyclic systems via ring expansion are well developed (Section 14.08.8.1). Each of the approaches reported thus far for this type of ring construction appears rather promising, although ionic strategy is the most advanced.

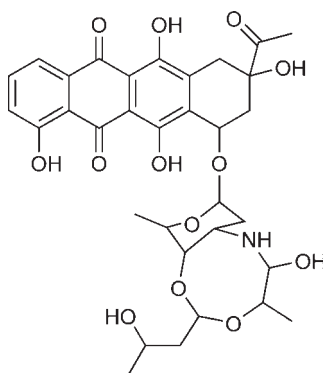
Data on transformations of side chains are limited to the reactivity of substituents attached to ring carbons. Reactivity of the rings typically includes electrophilic substitution on heteroatoms and oxidative/reductive sequences involving variety of thiocines.

14.08.10 Important Compounds and Applications

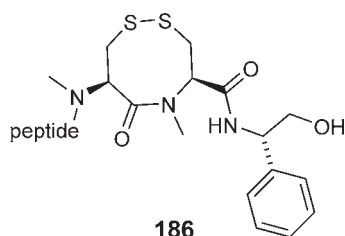
Eight-membered heterocyclic rings with three heteroatoms rarely occur as structural blocks of natural products and their synthetic analogues. The first example of natural 1,2,3-trithiocanes has been reported recently <2002EJO2400>. Two novel sulfur derivatives **183** and **184**, one of which is a glycoside, containing substituted 1,2,3-trithiocane cycles were isolated from *Perophora viridis* which was collected off the Atlantic coast of North Carolina.



Barminomycin **185**, known also as SN-07 chromophore, is an active chromophore isolated from *Actinomadura roseoviolacea* var. *miuraensis* nov. var. <1999NAR1781>. It is highly potent cytotoxic agent, bearing both anthracycline and 1,3,6-dioxazocane moieties. It is active against cancer and leukemia cells, and it believed to exist in *gem*-aminoalcohol form. Synthesis of barminomycin family N-substituted prodrugs has been reported <2005WO2005086951>.

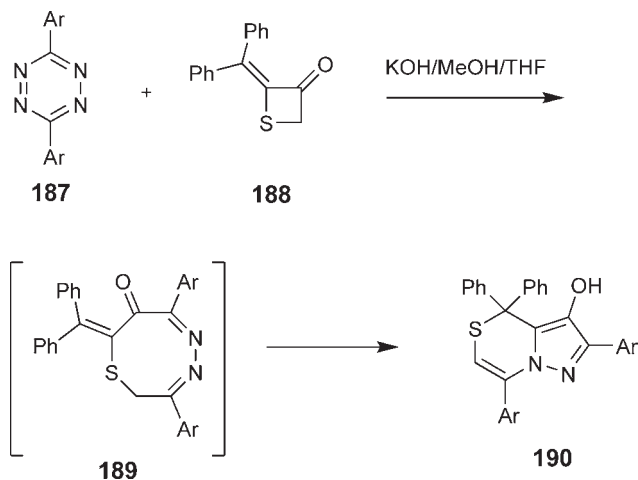
**185**

Kendarimide A **186**, a novel modulator of P-glycoprotein-mediated multidrug resistance, was isolated from a marine sponge of *Haliclona* sp. (see other chapters of Volume 12) <2005H(65)563>.

**186**

14.08.11 Further Developments

Few novel examples of the heterocines with three hetero atoms have been reported recently. Reaction of 1,2,4,5-tetrazines **187** with 2-(diphenylmethylene)thietan-3-one **188** in KOH/MeOH/THF proceeds through the intermediate 8-(diphenylmethylene)-2*H*-1,4,5-thiadiazocin-7(8*H*)-ones **189** which spontaneously transform into 4*H*-pyrazolo[5,1-*c*]thiazines **190** by multi-step rearrangement including a rare anti-Michael addition (Scheme 50, <2006TL7893>).



Scheme 50

- 1999PHC(11)338 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 1999, vol. 11, p. 338.
- 1999RCC(4)1 E. J. Grayson, P. M. Kelly, and J. A. H. MacBride; in 'Rodd's Chemistry of Carbon Compounds II', M. Sainsbury, Ed.; Elsevier, Amsterdam, 1999, vol. 4, p. 1.
- 1999T10057 J. Nakayama, A. Kaneko, Y. Sugihara, and A. Ishii, *Tetrahedron*, 1999, **55**, 10057.
- 1999T13703 N. Sakai, M. Funabashi, T. Hamada, S. Minakata, I. Ryu, and M. Komatsu, *Tetrahedron*, 1999, **55**, 13703.
- 1999TL2117 A. Bartovic, P. Netchitailo, A. Daich, and B. Decroix, *Tetrahedron Lett.*, 1999, **40**, 2117.
- 1999TL9363 S. Pulacchini and M. Watkinson, *Tetrahedron Lett.*, 1999, **40**, 9363.
- 1999ZPK1345 G. G. Furin, I. A. Salmanov, and V. G. Kiriyanov, *Zh. Prikl. Khim.*, 1999, **72**, 1345.
- 2000CPA36 S. Stankovsky and K. Spirkova, *Chem. Pap.*, 2000, **54**, 36.
- 2000FC13 G. G. Furin, L. S. Pressman, L. M. Pokrovsky, A. P. Krysin, and K.-W. Chi, *J. Fluorine Chem.*, 2000, **106**, 13.
- 2000JHC1129 S. Araki, H. Hattori, H. Yamamura, and M. Kawai, *J. Heterocycl. Chem.*, 2000, **37**, 1129.
- 2000MI1069 N. Yamasaki, J. Masamoto, and K. Kanaori, *Appl. Spectrosc.*, 2000, **54**, 1069.
- 2000PHC(12)352 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 2000, vol. 12, p. 352.
- 2001EJO4233 S. Pulacchini and M. Watkinson, *Eur. J. Org. Chem.*, 2001, **22**, 4233.
- 2001H(54)151 A. P. Marchand, H. K. Hariprakash, H.-S. Chong, and M. Takhi, *Heterocycles*, 2001, **54**, 151.
- 2001HCA3319 C. Fu, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2001, **84**, 3319.
- 2001JA12664 C. J. Creighton, C. H. Reynolds, D. H. S. Lee, G. C. Leo, and A. B. Reitz, *J. Am. Chem. Soc.*, 2001, **123**, 12664.
- 2001MI140 Yu. A. Simonov, K. Suwinska, V. I. Pavlovskii, O. V. Kulikov, E. V. Ganin, and S. A. Andronati, *Dopov. Natl. Akad. Nauk Ukr.*, 2001, **6**, 140.
- 2001MI1405 A. Kimbaris, J. Cobb, and G. Varvounis, Eds.; in 'International Electronic Conference on Synthetic Organic Chemistry', J. A. Seijas, Ed.; 5th (1–30 Sep. 2001), 6th (1–30 Sep. 2002), 7th (1–30 Nov. 2003), 8th (1–30 Nov. 2004), p. 1405.
- 2001MI1558 F. N. Burnett, R. S. Hosmane, Eds.; in 'International Electronic Conference on Synthetic Organic Chemistry', J. A. Seijas, Ed.; 5th (1–30 Sep. 2001), 6th (1–30 Sep. 2002), 7th (1–30 Nov. 2003), 8th (1–30 Nov. 2004), p. 1558.
- 2001MOL267 A. M. S. El-Sharief, Y. A. Ammar, M. A. Zahran, A. H. Ali, and M. S. A. El-Gaby, *Molecules*, 2001, **6**, 267.
- 2001PHC(13)378 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 2002, vol. 13, p. 378.
- 2002APH379 E. Brzezinska and R. Glinka, *Acta Polon. Pharm.*, 2002, **59**, 379.
- 2002AXEo1323 M. M. Olmstead, K. By, and M. H. Nantz, *Acta Crystallogr. Sect. E*, 2002, **58**, o1323.
- 2002EJO2400 T. Rezanka and V. M. Dembitsky, *Eur. J. Org. Chem.*, 2002, 2400.
- 2002J(P1)1260 J. Svetlik and T. Liptaj, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1260.
- 2002KGS1419 N. A. Nedolya, V. P. Zinov'eva, N. I. Shlyakhtina, A. I. Albanov, and L. Brandsma, *Khim. Geterotsikl. Soedin.*, 2002, **38**, 1419.
- 2002MOL96 W. M. Fathalla and P. Pazdera, *Molecules*, 2002, **7**, 96.
- 2002PHC(14)356 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and T. L. Gilchrist, Eds.; Elsevier, 2002; vol. 14, p. 356.
- 2002PS2303 M. Bakavoli, A. Davoodnia, M. Rahimizadeh, and M. M. Heravi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 2303.
- 2002SL832 C. Bolm, M. Martin, and L. Gibson, *Synlett*, 2002, 832.
- 2002T8963 A. Csampai, M. Simo, Z. Szlavik, A. Kotschy, G. Magyarfalvi, and G. Turos, *Tetrahedron*, 2002, **58**, 8963.
- 2002T9567 F. N. Burnett and R. S. Hosmane, *Tetrahedron*, 2002, **58**, 9567.
- 2002ZPK1309 V. P. Krivonogov, N. G. Afzaletdinova, G. A. Sivkova, G. G. Kozlova, Yu. I. Murinov, and I. B. Abdrakhmanov, *Zh. Prikl. Khim.*, 2002, **75**, 1309.
- 2003AMR97 V. V. Klochkov, R. A. Shaikhutdinov, B. I. Khairutdinov, E. N. Klimovitskii, M. Findeisen, and S. Berger, *Appl. Magn. Reson.*, 2003, **24**, 97.
- 2003HCA2833 C. Fu, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2003, **86**, 2833.
- 2003KGS485 O. V. Kulikov, V. I. Pavlovsky, A. V. Mazepa, and S. A. Andronati, *Khim. Geterotsikl. Soedin.*, 2003, **39**, 485.
- 2003OBC4030 N. N. Volkova, E. V. Tarasov, M. I. Kodess, L. Van Meervelt, W. Dehaen, and V. A. Bakulev, *Org. Biomol. Chem.*, 2003, **1**, 4030.
- 2003PHC(15)431 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2003, vol. 15, p. 431.
- 2003RJO1384 L. P. Nikitina, L. L. Dmitrieva, A. I. Albanov, N. A. Nedolya, and L. Brandsma, *Russ. J. Org. Chem.*, 2003, **39**, 1384.
- 2003SL1591 U. Kzmaier and C. Hebach, *Synlett*, 2003, 1591.
- 2003SOS(17)979 R. M. Borzilleri; in 'Science of Synthesis', S. M. Weinreb, Ed.; Thieme, Teningen, 2003, vol. 17, p. 979.
- 2003T6051 Z. Regainia, J.-Y. Winum, F.-Z. Smaïne, L. Toupet, N.-E. Aouf, and J.-L. Montero, *Tetrahedron*, 2003, **59**, 6051.
- 2004AGE1117 K. By and M. H. Nantz, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 1117.
- 2004AGE4349 K. W. Fiori, J. J. Fleming, and J. Du Bois, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 4349.
- 2004AXCo136 V. Boehmer, D. Meshcheryakov, I. Thondorf, and M. Bolte, *Acta Crystallogr., Sect. C*, 2004, **60**, o136.
- 2004MI1213 N. G. Afzaletdinova, Yu. I. Murinov, and V. P. Krivonogov, *Zh. Neorg. Khim.*, 2004, **49**, 1213.
- 2004PHC(16)451 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2005, vol. 16, p. 451.
- 2004S837 M. S. Singh and A. K. Singh, *Synthesis*, 2004, **6**, 837.
- 2004T8807 A. Kimbaris, J. Cobb, G. Tsakonas, and G. Varvounis, *Tetrahedron*, 2004, **60**, 8807.
- 2005ARK96 K. Spirkova, M. Bucko, and S. Stankovsky, *ARKIVOC*, 2005, **5**, 96.
- 2005H(65)563 N. Kotoku, L. Cao, S. Aoki, and M. Kobayashi, *Heterocycles*, 2005, **65**, 563.
- 2005OL4685 P. M. Wehn and J. Du Bois, *Org. Lett.*, 2005, **7**, 4685.
- 2005PHC(17)418 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2005, vol. 17, p. 451.
- 2005RJO1583 L. L. Dmitrieva, L. P. Nikitina, A. I. Albanov, and N. A. Nedolya, *Russ. J. Org. Chem.*, 2005, **41**, 1583.
- 2005TL8009 W. Liu, Z. Guan, and S. B. Singh, *Tetrahedron Lett.*, 2005, **46**, 8009.
- 2005WO2005086951 M. Matteucci and J.-X. Duan, (Threshold Pharmaceuticals), *PCT Int. Appl.*, 2005086951 (2005).
- 2006JHC593 A. A. Hassan and D. Döpp, *J. Heterocycl. Chem.*, 2006, **43**, 593.
- 2006TL7893 Y. F. Suen, H. Hope, M. H. Nantz, M. J. Haddadin, and M. J. Kurth, *Tetrahedron*, 2006, **47**, 7893.

Biographical Sketch



Dmytro O. Tymoshenko received his M.S. (Chemical Engineering) from the Ukrainian University of Chemical Engineering (UUCE) of Dnepropetrovsk, Ukraine. Later on, as a scientist at the Department of Macromolecular Compounds of the UUCE, he received his Ph.D. in 1986, with a thesis focused on synthesis and properties of water-soluble polymer carriers for drug immobilization and transport. His tenure at UUCE included positions of Assistant Professor and Associate Professor, while his research was focused on various aspects of heterocyclic synthesis and synthesis on polymer supports. His postdoctoral experience was gained with Volodymyr Syromyatnikov at the National Taras Shevchenko University of Kiev, Ukraine, and Alan Katritzky at the University of Florida. In 2000, he joined Albany Molecular Research, Inc., at Albany, New York, as senior research scientist, leading the parallel synthetic chemistry research program and working in the area of medicinal chemistry. His research interests include synthesis and reactivity of heterocycles, polymer-supported reagents, and their application in organic synthesis.

14.09

Eight-membered Rings with Four or More Heteroatoms

I. Shcherbakova

MediProPharma, Inc., Midvale, UT, USA

© 2008 Elsevier Ltd. All rights reserved.

14.09.1	Introduction	517
14.09.2	Theoretical Methods	518
14.09.3	Experimental Structural Methods	520
14.09.3.1	NMR Spectroscopy	520
14.09.3.2	Mass Spectroscopy	521
14.09.3.3	X-Ray Crystallography	521
14.09.3.4	Other Spectroscopic Methods	522
14.09.4	Thermodynamic Aspects	522
14.09.5	Reactivity of Fully Conjugated Rings	523
14.09.6	Reactivity of Nonconjugated Rings	526
14.09.7	Reactivity of Substituents Attached to Ring Carbon Atoms	526
14.09.8	Reactivity of Substituents Attached to Ring Heteroatoms	527
14.09.9	Ring Syntheses from Acyclic Compounds	528
14.09.9.1	Synthesis of Rings Containing Four Heteroatoms	528
14.09.9.1.1	1,3,5,7-Substitution	528
14.09.9.1.2	1,2,5,6-Substitution	532
14.09.9.1.3	Other substitution patterns	533
14.09.9.2	Synthesis of Rings Containing Five or More Heteroatoms	535
14.09.10	Ring Synthesis by Transformation of Another Ring	537
14.09.11	Important Compounds and Applications	542
14.09.12	Further Developments	543
	References	544

14.09.1 Introduction

This chapter focuses on eight-membered rings with four or more heteroatoms, nitrogen, oxygen, and/or sulfur, and concentrates on the publications from 1995 and later, thus chronologically extending coverage of the topic in CHEC(1984) <1984CHEC(9)653> and CHEC-II(1996) <1996CHEC-II(9)705>. For comprehensive coverage of the subject, the reader is recommended to treat this chapter in conjunction with the corresponding publications in CHEC(1984) and CHEC-II(1996). The former, where all eight-membered ring heterocycles with one or more heteroatoms were treated in a single chapter, did not cover eight-membered rings with five or more heteroatoms; the latter publication, however, discussed the topic comprehensively through the mid-1990s.

As in CHEC-II(1996), this chapter is organized into 11 sections. The deviation from the standard 12-section format of CHEC-III involves the merger of [Section 14.09.11](#) 'Synthesis of particular compounds and critical comparison of various routes available' with two [sections](#), [14.09.9](#) 'Ring synthesis from acyclic compounds' and [14.09.10](#) 'Ring synthesis by transformations of another ring'. Thus, the syntheses of these different heterocycles, most of which are accessible only by a limited number of synthetic routes, are discussed and compared where appropriate in [Sections 14.09.9 and 14.09.10](#). In turn, each section is organized by the type of the compounds: (1) the heterocyclic systems are arranged in an order determined by the molecular weight of the total number of the heteroatoms in the ring; (2) rings

containing four like heteroatoms are discussed first in the order of nitrogen, oxygen, and sulfur; (3) unsaturated ring systems appear before those of lower oxidation level; (4) then, rings containing four heteroatoms of two or more types are discussed; (5) finally, all eight-membered rings with five or more heteroatoms are covered.

Nomenclature is consistent with IUPAC rules and the names are generated with the ACD Labs software. The parent unsaturated systems are referred to as the corresponding *-cines*, whereas the fully saturated rings are recognized as *-canes*. Benzo and dibenzo derivatives follow the standard IUPAC nomenclature. In some cases, specific nomenclature appears where appropriate for the individual compounds.

Compounds in which ring heteroatoms are members of another fused ring and bridged polycyclic compounds are, with few exceptions, not covered in this chapter.

Among eight-membered rings containing four or more heteroatoms, 1,3,5,7-tetrazocanes are the largest class based on the number of publications due mainly to their properties and applications, particularly for cucurbituril and its derivatives. 1,3,5,7-Tetraoxocanes have been marked as the second largest class among the eight-membered heterocycles with four heteroatoms <1996CHEC-II(9)705>; the latest literature survey moved this class of heterocycles by a number of publications behind 1,2,5,6- and 1,2,3,4-tetrathiocanes. A few rare eight-membered rings containing four or more heteroatoms were mentioned in CHEC-II(1996) <1996CHEC-II(9)705>; missing information on these heterocycles in this chapter corresponds to those cases in which no relevant chemistry has been reported since 1995.

14.09.2 Theoretical Methods

Cucurbit[6]uril (CB[6]) is a macrocycle, which consists of six 1,3,5,7-tetrazocane units fusing six glycourils and has outstanding molecular recognition properties (1996CHEC-II(9)705; Section 14.09.11). Studies of the mechanism of formation of CB[6] and its homologs might provide insights to allow the tailor-made synthesis of CB[n] homologs and derivatives. By reducing the complexity to the formation of the methylene-bridged glycouril dimers, S-shaped **1** and C-shaped **2** diastereomers have been evaluated by AM1 calculations for a thermodynamic preference (Table 1) <2002JA8297>. These computations suggest a small (0.5 kcal mol⁻¹) to a quite large (−10.2 kcal mol⁻¹) difference in the heat of formation between S- and C-shaped diastereomers. The experimental determinations of differences in free energy between the dimers **1** and **2** have been obtained <2002JA8297> (see Section 14.09.4).

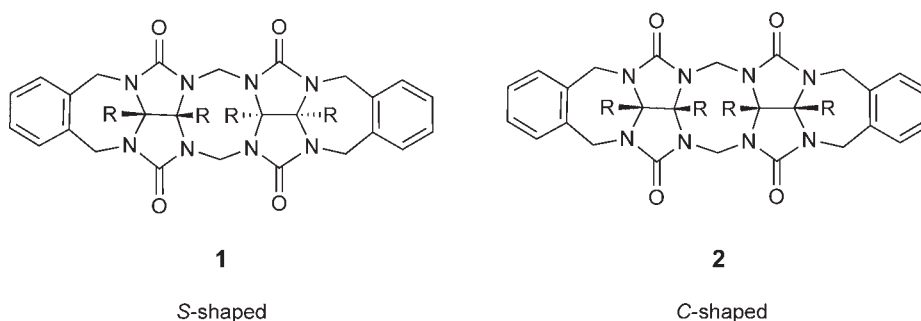


Table 1 AM1 Heats of formation (kcal mol⁻¹) for **1** and **2**

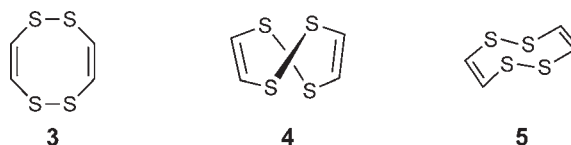
<i>R</i>	ΔH_f°		$\Delta\Delta H_f^\circ$
	1	2	
CO ₂ Et ^a	−237.7 to −243.8	−246.9 to −250.1	−6.3 to −10.2
(CH ₂) ₂ ^b	47.6/47.3	45.3/45.2	−2.3 to −2.2
Ph	216.9	211.5	−5.4
H	58.2	58.7	0.5

^aThere are many different relative orientations for the four CO₂Et groups.

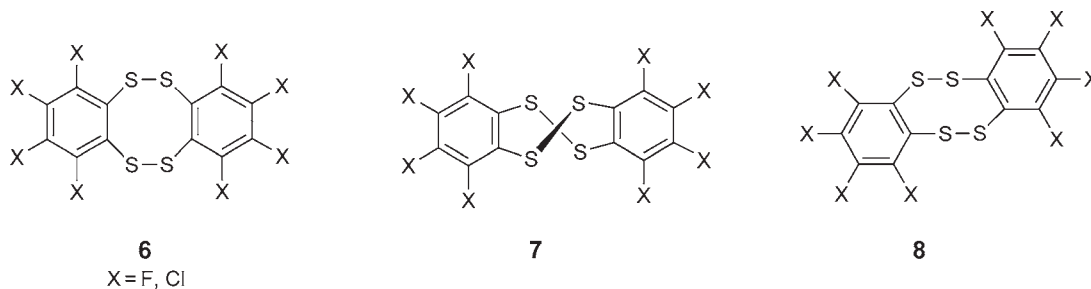
^bTwo different relative orientations of the boat-shaped six-membered rings are possible.

1,2,5,6-Tetrathiocine **3** was first synthesized in 1996 <1996AGE2357> (see Equation (28) in Section 14.09.9.1.2). Among several conformers optimized for **3** at local minima by *ab initio* (MP2/D95*), the twist boat form **4** was calculated to lie on the lowest potential level. The calculations indicate that the energy difference between the two

conformers **4** and **5** is 22.2 kJ mol^{-1} . In contrast, the chair form of type **5** was optimized as a global minimum for the carbocyclic analog of the tetrathiocine **3**, cycloocta-1,5-diene <1994JCM436>. The existence of the tetrathiocine **3** as the twisted structure **4** with nearly D_2 symmetry in a crystal has been confirmed by X-ray crystallography <1996AGE2357>.



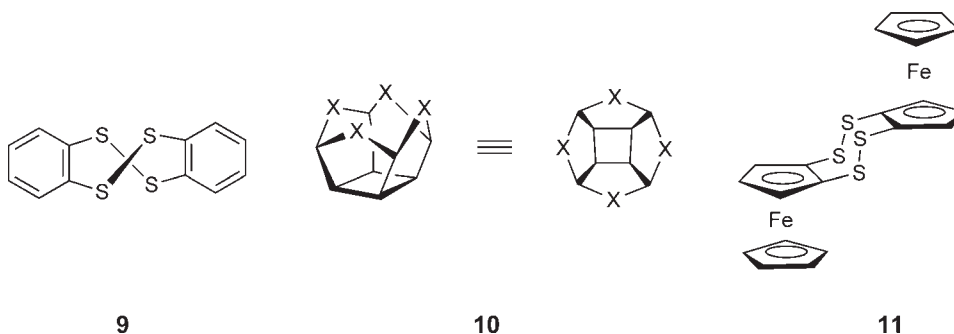
The difference of total energies of the two conformations **7** and **8** with symmetry D_2 and C_{2h} , respectively, for the dibenzotetrathiocine **6** ($X = \text{F}$) was calculated by density functional theory (DFT) to be only 4.6 kJ mol^{-1} in favor of the twist boat **7** <1998CJC1093>. Indeed, **6** ($X = \text{F}$) undergoes a slow conformational isomerization in solution (Section 14.09.3.1) but adopts the chair conformation **8** in crystalline form (cf. Section 14.09.4).



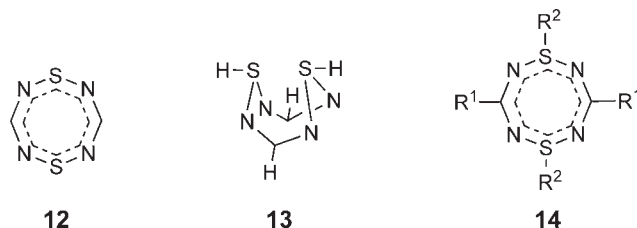
The DFT B3LYP/6-31G(d) study of the cyclic sulfuration of *o*-benzyne has been reported on the relative energies and geometries of the polysulfur rings <2004JOC5483>. An 'odd-even' alteration, which is guided by a number of the sulfur atoms in the products formed, was found in the stability of the *o*- $\text{C}_6\text{H}_4\text{S}_x$ compounds ($x = 1-8$). The low yield of tetrathiocine **9**, which belongs to the 'even' compounds, was explained by higher energy and strain of the twisted thiocine ring comparing to the 'odd' polysulfur compounds.

A new class of molecular entities of type **10** is named 'heterobowls', derived through the replacement of methylene groups by heteroatoms, nitrogen, oxygen, or sulfur, and belongs to the family of homologous polycyclic hydrocarbons known as 'peristylenes'. Besides having high C_{nv} symmetry, these heterobowls are endowed with two chemically distinct surfaces composed of a hydrophobic base and a hydrophilic rim, and are expected to exhibit many interesting properties such as selective avidity for metal ions. The heterobowls **10** are discussed in the appropriate sections throughout this chapter. The synthesis of oxa- and thia[4]peristylenes has been reported (see Section 14.09.9.1 <1999TL2417; 2003TL9313>); the aza analogs **10** still remain illusive. The geometry of the thiabowl **10** ($X = \text{S}$) was fully optimized by DFT B3LYP method in 6-311G(d) basis set with the Gaussian 98 program resulting in a C_{4v} symmetry <2003TL9313>. The calculated ^1H NMR chemical shifts for the C_{4v} optimized structure **10** ($X = \text{S}$) correlate well with the experimental data, while the carbon chemical shifts exhibit significant differences, perhaps due to the limitations of the computational methods.

The geometry of a novel sulfur-containing compound fused to two ferrocene units, tetrathiocine **11**, has been optimized by DFT at B3PW91/3-21G* level <2002TL5825>. Among two possible orientations for the ferrocene rings, *syn* and *anti*, the *anti* oriented chair form is 26.7 kJ mol^{-1} lower than the *syn* oriented twist form. These results are in a good agreement with the X-ray crystallography data (Section 14.09.4).



Since discovery of dithiotetrazocines in 1981, heterocycles based on carbon–nitrogen–sulfur frameworks have been the subject of numerous investigations <B-1992MI1, B-1992MI2, 1996CHEC-II(9)705>. Most of these studies have involved ring systems containing two-coordinate sulfur atoms, some of which form stable radicals. A series of calculations has been performed on 1,5-dithia-2,4,6,8-tetrazocines in an attempt to explain the structural dichotomy, and a planar conformation has been assigned to 10 π -electron monocycle **12** <1996CHEC-II(9)705>. DFT calculations have been carried out on the model system **13** in order to explain the structural features of dithiotetrazocines. The calculations reveal that the observed C_{2v} geometry for the substituted 1,5-dithia-2,4,6,8-tetrazocine **14** (R^1 , $R^2 = \text{Ar}$) is the result of a second-order Jahn–Teller distortion of the planar D_{2h} structure. The structure **13** was optimized on the basis of the C_{2v} structure determined for the dithiatetrazocine **14** ($R^1 = 4\text{-BrC}_6\text{H}_4$, $R^2 = \text{Ph}$) by X-ray crystallography <1997IC1669> (see Section 14.09.3). The boat conformer **13** is only *c.* 10 kJ mol^{−1} lower in energy than the chair conformer (C_{2h}) <1997IC1669>.

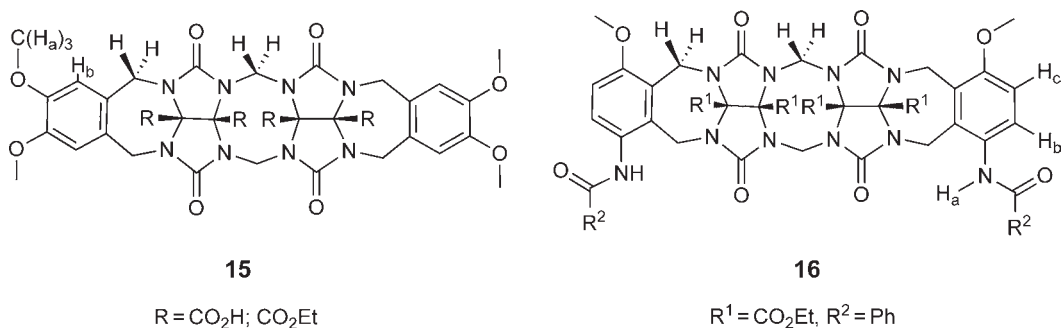


14.09.3 Experimental Structural Methods

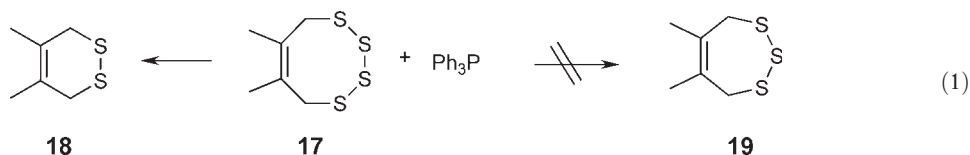
14.09.3.1 NMR Spectroscopy

Diastereoselective formation of numerous glycouril functionalized dimers has been reported in the study of the cucurbituril homologs <2001OL3221; 2002JA8297; 2003OL3745>. Proton NMR spectroscopy has been applied to the structural analysis of the recognition properties of the CB[n] homologs <2003OL3745>. In studies of self-association of the cucurbituril compounds, it is challenging to unambiguously establish the degree-of-association. The hydrophobically formed dimers **15**·**15** have been used as a model in the temperature-dependent ¹H NMR studies with the goal to determine directional preferences governing the self-association of **15** and its derivatives <2001OL3221>. As the temperature is decreased from 324 to 294 K, the time-averaged C_{2v} symmetry observed at higher temperature is reduced and two resonances are observed for the methoxy (H_a) and aromatic (H_b) protons. It was suggested that coalescence at higher temperatures resulted from an exchange process between protons on the inside of the aggregate **15**·**15**, H_a and H_b , although the precise structural details of the dimers could not be described.

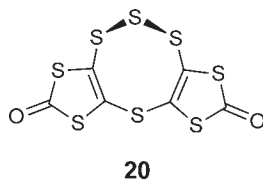
Significant anisotropic effects are observed in the ¹H NMR spectra recorded for **16** in CDCl₃ (for H_a , H_b , and H_c) relative to DMSO-*d*₆, where **16** is monomeric <2004JA10035>. These data indicate the presence of hydrogen-bonding interactions depending on the solvent. The solid-state geometry of the dimer **16**·**16** (Section 14.09.3.3) is fully consistent with the ¹H NMR spectral data; thus, it was suggested that the dimer **16**·**16** is isostructural in solution and the solid state.



The kinetics of desulfurization of the tetrasulfide **17** to disulfide **18** has been monitored by ^1H NMR spectroscopy and showed no evidence for the formation of the alternative trisulfide **19** (Equation 1) <1991TL7651>.



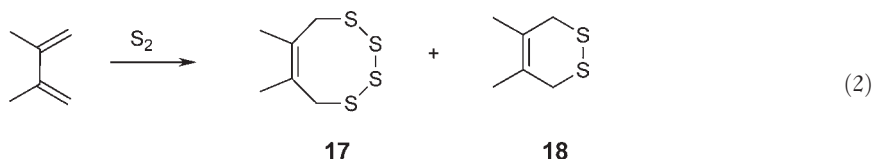
The chair-folded structure of the 1,4,5,6-tetrathiocine ring in **20** was first suggested from the ^{13}C NMR spectrum, which showed three resonance signals, and then confirmed by single crystal X-ray diffraction <1994IC4537> (Section 14.09.3.3).



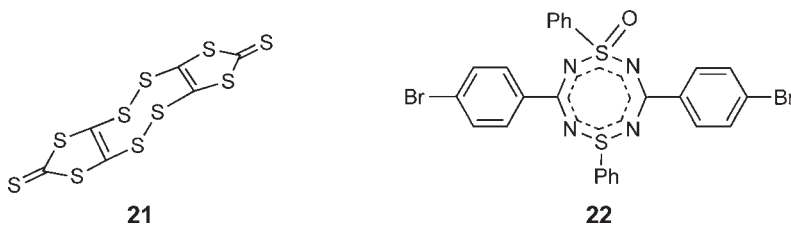
The ^{19}F NMR spectral studies reported the existence of two conformers **7** and **8** ($\text{X} = \text{F}$) in solutions and slow conformational isomerization <1998CJC1093> (see Section 14.09.2).

14.09.3.2 Mass Spectroscopy

The mass spectral data (molecular ion and fragmentation) are frequently reported for the medium-sized rings and along with NMR spectroscopy represent a routine method for the structure elucidation. In some examples, the mass spectral fragmentation is discussed as a confirmation for the reaction pathway and the products formed. Thus, in the study of trapping diatomic sulfur by the reaction with dienes, the 1,2,3,4-tetrathiocine **17** was isolated together with the expected disulfide **18** (Equation (2); see Section 14.09.9) <1991TL7651>. In the electron impact spectrum, the octamer **17** showed the fragmentation pattern of two consequent losses of S_2 and the fragment of tetramethylethene.



A weak S_8^+ peak was observed in the electron impact mass spectrum of the 1,2,5,6-tetrathiocine **21** indicating the absence of polysulfide linkages (see Scheme 4 in Section 14.09.10) <1994IC4537>. Formation of the mixed oxidation state $[\text{S(IV)}]$ and $[\text{S(VI)}]$ heterocycle **22** has been confirmed by a strong molecular ion in the electron impact mass spectrum <2000IC1697>.



14.09.3.3 X-Ray Crystallography

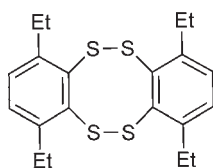
Single-crystal X-ray diffraction analyses have provided evidence for the solid-state structures and conformational preferences of the substituted S- and C-shaped methylene-bridged glycouril dimers with the 1,3,5,7-tetrazocine core unit <2000OL755, 2002JA8297, 2002JOC5817, 2004JA10035>, cucurbituril supramolecular adducts <2004EJI63>,

cucurbituril hexamers <2004OL1225>, and cucurbituril analogs and homologs, CB[5], CB[7], CB[8], and CB[10] <2000JA540; 2001JOC8094>. The solid-state architectures of the heterobowls, tetraoxa- and tetrathia[4]peristylenes **10** (Section 14.09.2) have been investigated by X-ray structural analysis <1995JOC7558; 1999TL2417; 2003TL9313>. X-Ray crystallography has been used in the structure elucidation and conformational studies for the following general compound classes: 1,2,5,6-tetrathiocines <1994IC4537, 1996AGE2357, 1998CJC1093, 1999TL9101, 2000TL1801, 2002BCJ2647, 2002TL5825, 2003CC2226>, 1,2,3,4-tetrathiocines <2002J(P1)330, 2002JOC6220, 2002TL5825>, 1,2,3,4,5,7-pentathiazocanes <2002CL90>, dithiotetrazocines <1997IC1669, 2000IC1697, 2003CC2774>, and the rare heptathiocane ring <2003OL1939>.

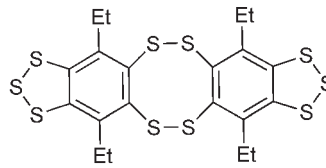
14.09.3.4 Other Spectroscopic Methods

Raman spectrum of **21** (Section 14.09.3.2) was used to confirm the formation of the 1,2,5,6-tetrathiocine ring <1994IC4537>. An infrared study of the tetrathiocines **20** (Section 14.09.3.1) and **21** (Section 14.09.3.2) was applied to the structure elucidation <1994IC4537>.

The ultraviolet spectra of 1,2,5,6-tetrathiocines **23** ($\lambda_{\max}$ 350 nm, ϵ 7500) and **24** ($\lambda_{\max}$ 361 nm, ϵ 36 000) were helpful in the comparison of their photochemical reactivity (see Section 14.09.5) <2002BCJ2647>.



23



24

14.09.4 Thermodynamic Aspects

Melting points, where available, are given throughout this chapter for the individual compounds.

The mechanism of synthesis of cucurbituril homologs (CB[n]) is a challenging subject for investigation <2001JOC8094, 2001OL3221, 2002JA8297>. The kinetic formation of a mixture of S- and C-shaped glycouril dimers (**1** and **2**; see Section 14.09.2) was investigated in search of evidence that the mechanism of CB[n] synthesis involves the intermediacy of both diastereomers. The first experimental determination of the relative free energies of the S- and C-shaped dimers indicates a thermodynamic preference (1.55–3.25 kcal mol⁻¹) for the C-shaped diastereomer **2** <2002JA8297> (see Section 14.09.2, and Scheme 3 in Section 14.09.9.1.1). The labeling experiments were used in the interpretation of the mechanism of acid-catalyzed equilibrium between S- and C-shaped diastereomers. The equilibrium is an intramolecular process that proceeds with high diastereoselectivity and retention of configuration <2002JA8297>. The elucidation of the mechanism of the isomerization reaction has broad implications for the improved synthesis of functionalized CB[n].

Isothermal titration calorimetry (ITC) dilution experiments were used to measure association constants and thermodynamic parameters for the formation of dimers **15–15** (cf. Section 14.09.3.1) <2001OL3221>. Aggregates **15–15** are highly associated at 298 K and entropically driven. The change in heat capacity (ΔC_p) for the formation of dimer **15–15** was determined by ITC measurements from 288 to 328 K yielding the negative value ($\Delta C_p = -185 \pm 6$ cal mol⁻¹ K⁻¹). It was concluded that the dimerization process is driven by hydrophobic effect.

Electrochemical studies of a novel tetrathiocine **11** (Section 14.09.2) was performed by cyclic voltammetry and showed two reversible redox waves <2002TL5825>.

The conformational studies of the methylene-bridged glycouril dimers of type **1**, **2**, **15**, and **16** (Sections 14.09.2 and 14.09.3.1) and cucurbituril analogs and homologs have been reported by X-ray and NMR analyses <2000JA540, 2000OL755, 2001OL3221, 2002JA8297, 2002JOC5817, 2003OL3745, 2004JA10035>.

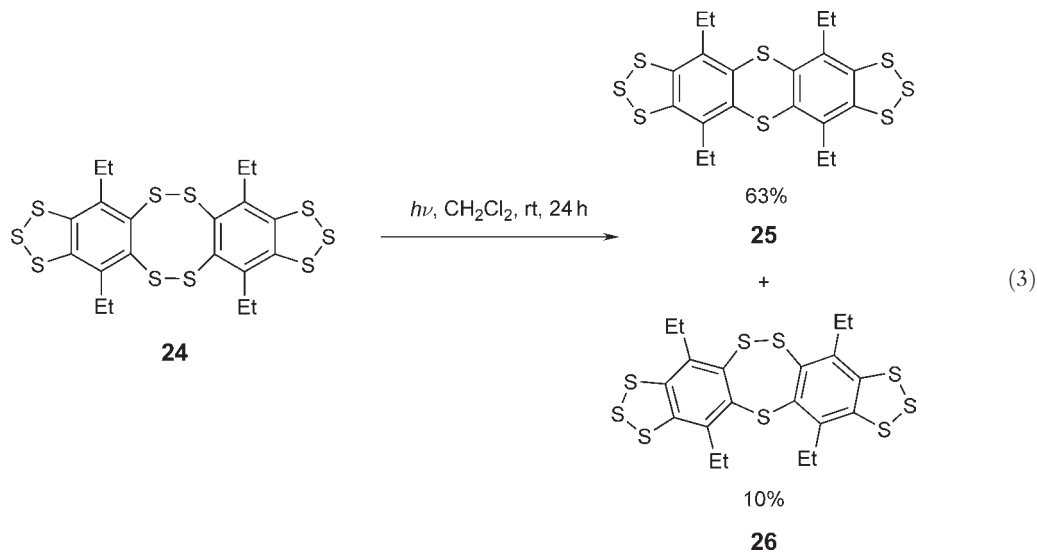
X-Ray crystallography has confirmed the existence of 1,2,5,6-tetrathiocine **3** as the twisted conformer **4** (see Section 14.09.2) <1996AGE2357>. The fluoro-substituted dibenzo-1,2,5,6-tetrathiocine **6** (X = F) adopts the chair conformation **8** in the crystalline state, while the chloro compound **6** (X = Cl) was found in the twist boat conformation **7** in solid state (see Section 14.09.2) <1998CJC1093>. The calculated difference in the energies of the two conformers **7** and **8** for the fluoro-substituted derivative **6** is very small (<5 kJ mol⁻¹), and its slow conformational isomerization in solution was

studied by ^{19}F NMR spectroscopy (Section 14.09.3.1). The tetrathiocine **11** (Section 14.09.2) exists in *ant*-oriented chair form as was found by X-ray analysis <2002TL5825>. X-Ray crystallography data demonstrated that the 1,2,5,6-tetrathiocine **21** (Section 14.09.3.2) adopts a chair conformation with two planar C_3S_3 subunits <1994IC4535>.

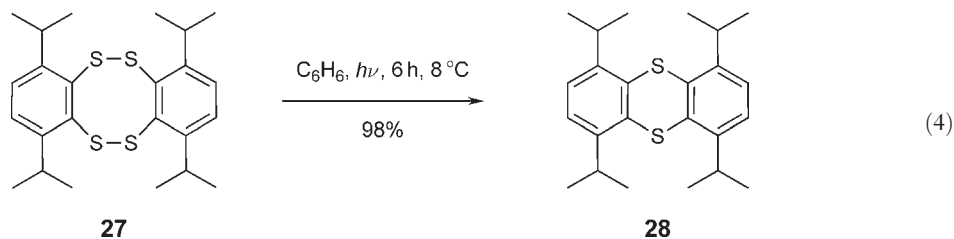
The dithiatetrazocine ring **14** (Section 14.09.2) has a long boat conformation with the aryl groups attached to sulfur atoms in equatorial positions <1997IC1669>.

14.09.5 Reactivity of Fully Conjugated Rings

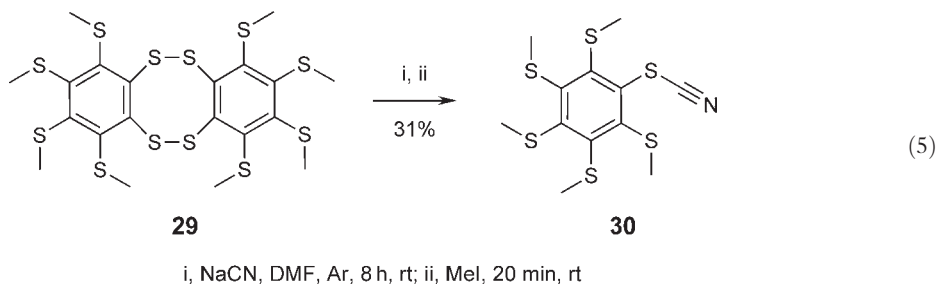
Irradiation of the 1,2,5,6-tetrathiocine **24** in CH_2Cl_2 at room temperature resulted in the mixture of two products, the dithianthrene **25** and trithiepine **26** (Equation 3) <2000TL1801, 2002BCJ2647>. In turn, the trithiepine **26** can be further desulfurized on irradiation to give the dithianthrene **25**.



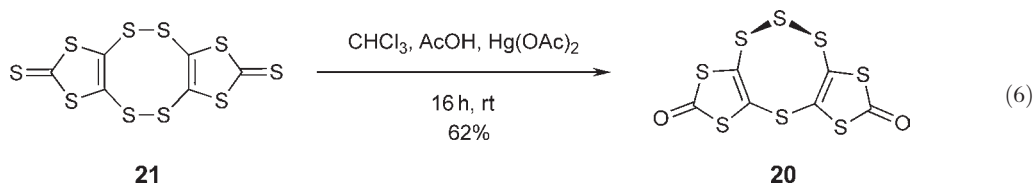
Photolytic desulfurization of the tetrathiocine **27** bearing the sterically hindered substituents resulted in the dithianthrene **28** in high yield (Equation 4) <1999TL9101>.



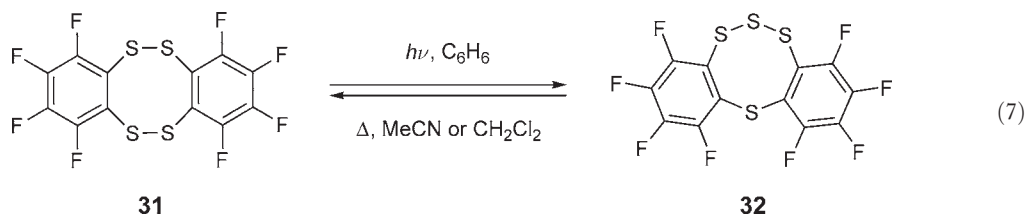
In the nucleophilic elimination of sulfur, the tetrathiocine **29** underwent transformation into a mixture of which the isolated benzocyanate **30** was the major product (Equation 5) <1995T2533>.



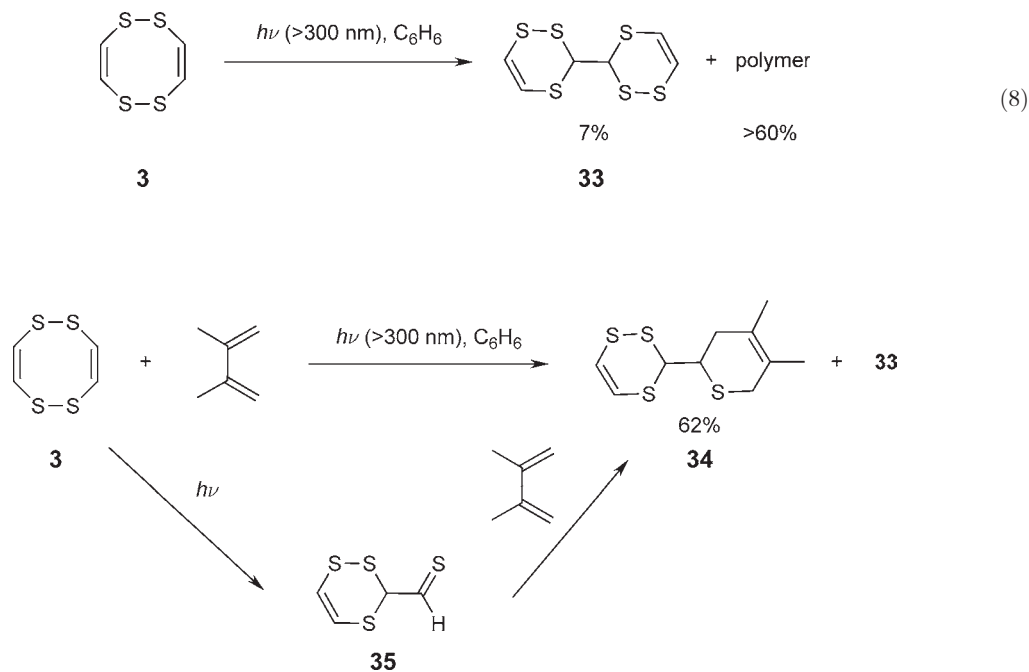
The Hg^{2+} -promoted hydrolysis of the thiocarbonyl groups was accompanied with an unexpected ring rearrangement in the 1,2,5,6-tetrathiocine **21** (Section 14.09.3.2) and produced the 1,2,3,6-tetrathiocine **20** (Section 14.09.3.1) (Equation 6) <1994IC4537>.



Photolysis of the 1,2,5,6-tetrathiocine **31** promoted a reversible, transannular sulfur migration to give 1,2,3,6-tetrathiocine **32** (Equation 7) <1998CJC1093>. The photoisomerized product **32** was readily distinguished by the ^{19}F NMR spectrum, which exhibits an AMXY pattern.

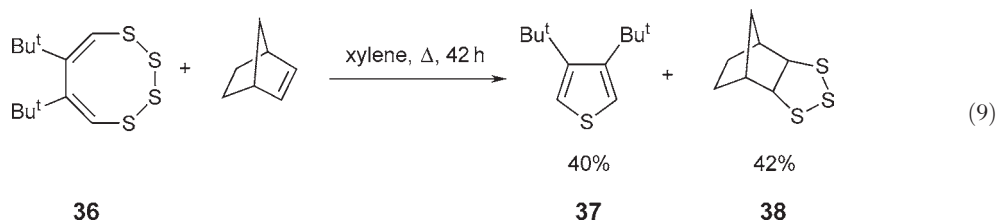


Since 1,2,5,6-tetrathiocine **3** (see Sections 14.09.2 and 14.09.9.1.2) is unstable toward irradiation and even room light, upon irradiation in a benzene solution, the thiocine **3** formed the bicyclic compound **33** in low yield together with a polymer, as the main product (Equation 8) <1996AGE2357>. Irradiation of **3** in the presence of a large excess of 2,3-dimethylbutadiene hindered the formation of the polymer, and the bicyclic product **34** was obtained together with a small amount of the symmetrical bicycle **33** (Scheme 1) <1996AGE2357>. This indicates the formation of the intermediate thioaldehyde **35** by photochemical rearrangement of thiocine **3**, while several mechanisms are plausible for the formation of the symmetrical **33**.

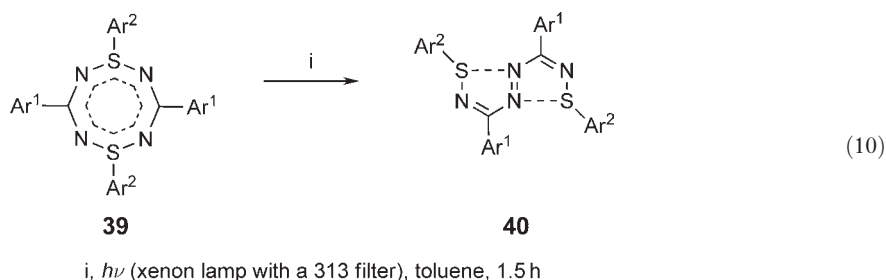


Scheme 1

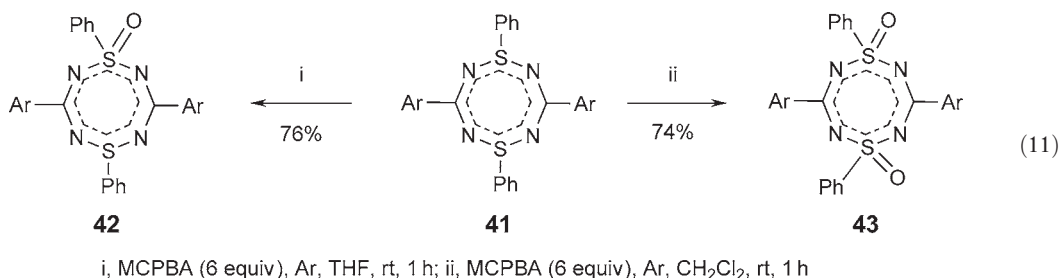
In the study of S_3 sources, the interaction of the tetrathiocine **36** with norbornene yielded a mixture of the thiophene **37** and 3,4,5-trithiatricyclodecane **38**; the products were derived from sulfur extrusion by the retro-Diels–Alder reaction and sulfur trapping, respectively (Equation 9) <2004JA9085>.



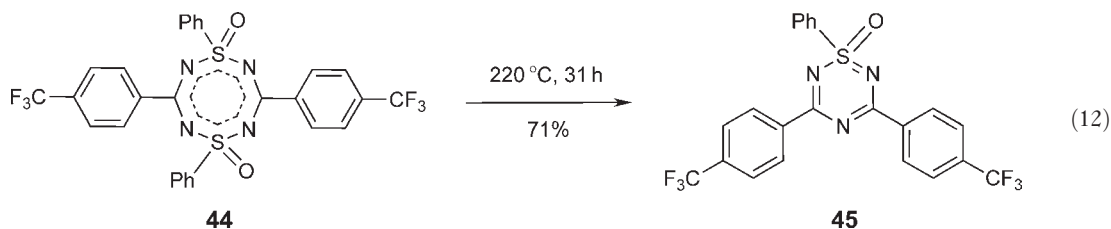
Although dithiatetrazocines are quite stable due to their aromatic character <1996CHEC-II(9)705>, a study reported an unusual intramolecular isomerization of **39** on photolysis or thermolysis to give the intensely colored diazenes **40** (Equation 10) <1996CC949>. The driving force for this transformation is the formation of a very stable $N=N$ bond at the expense of elongation of two $S-N$ bonds in the azenes **40**. A recent X-ray structural determination of **40** ($Ar^1 = Ar^2 = 4\text{-MeC}_6\text{H}_4$) has revealed a closed *cis, trans, cis* structure with weak intramolecular $S \cdots N$ interactions <1996CC949> (cf. 1996CHEC-II(9)705).

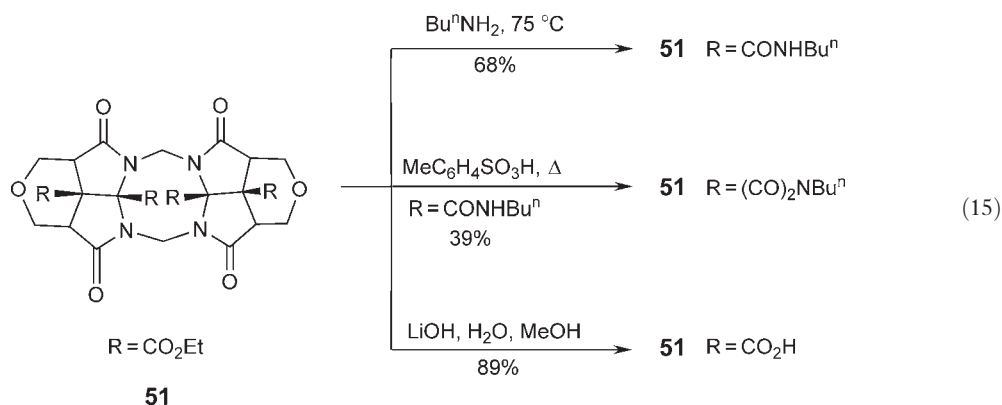


Dithiatetrazocines **41** were oxidized in different solvents via either the mixed or fully oxidation state to yield the corresponding oxides **42** and **43** (Equation 11) <2000IC1697>.



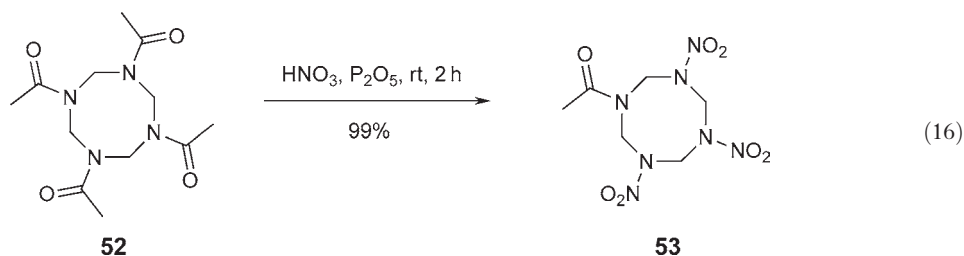
The thermal decomposition of the dithiatetrazocine **44** produced the thiatriazine-1-oxide **45** in good yield (Equation 12) <2000IC1697>. It was found that photolysis of **44** also engendered the ring contraction, but thermolysis provides a cleaner route to the cyanuric–sulfanuric heterocycle **45**.



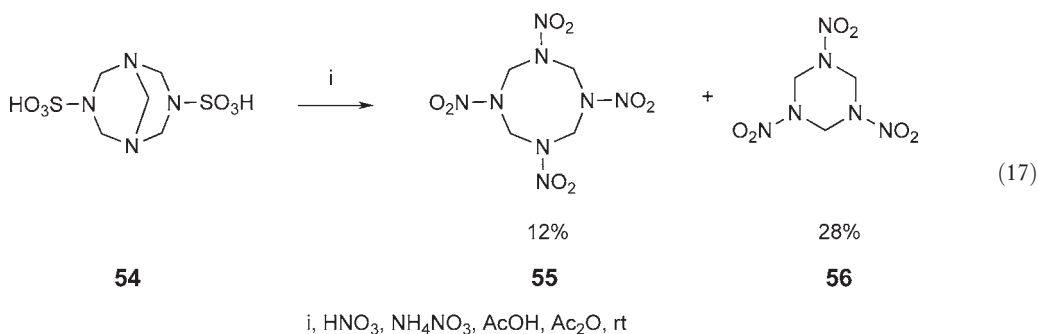


14.09.8 Reactivity of Substituents Attached to Ring Heteroatoms

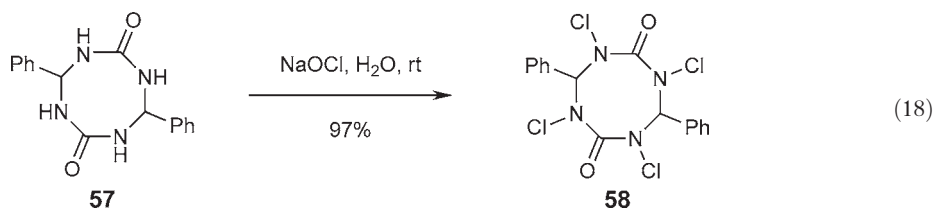
There are a few examples of reactions involving substituents on the nitrogen atoms of the 1,3,5,7-tetrazocanes. The reaction of tetraacetyltetrazocane **52** with nitric acid was reported as a clean and convenient approach to 1-acetyl-3,5,7-trinitro-1,3,5,7-tetrazocane **53** (SOLEX) (Equation 16) <1992USP5120887>.



The reaction of tetraazobicyclononane **54** with nitric acid resulted in the mixture of two heterocycles, the tetrazocane **55** (mp 279.5–280 °C) and triazinane **56** (Equation 17) <2001RJO1030>.



Convenient chlorination of the tetrazocane **57** produced the tetrachlorotetrazocane **58** in nearly quantitative yield (Equation 18) <1993MI38>.

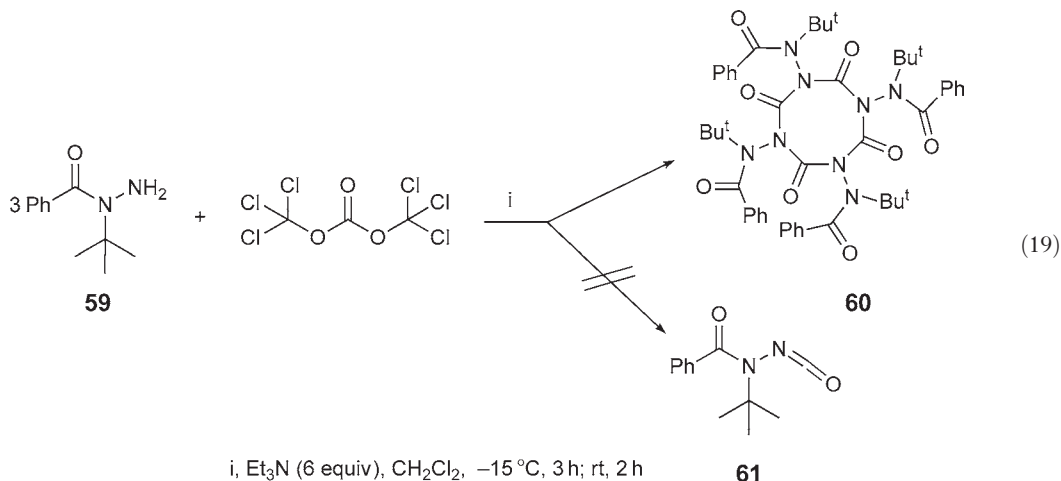


14.09.9 Ring Syntheses from Acyclic Compounds

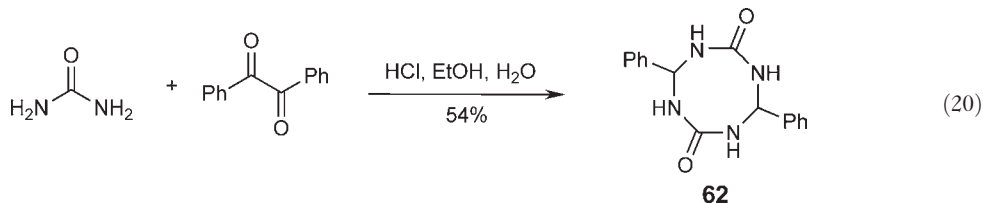
14.09.9.1 Synthesis of Rings Containing Four Heteroatoms

14.09.9.1.1 1,3,5,7-Substitution

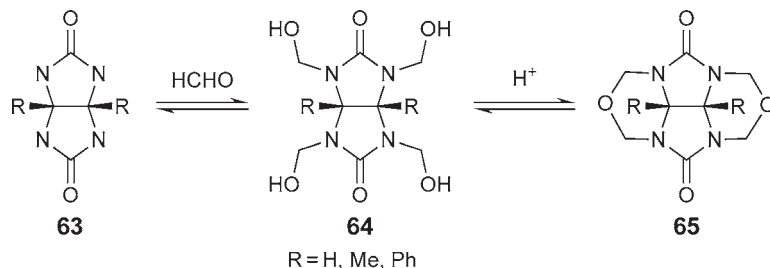
N-Benzoylhydrazine **59** reacted with triphosgene to form the tetrazocane **60** (mp 160–162 °C) instead of the expected isocyanate **61** (Equation 19) <2003JHC195>. The octaamide **60** was reported to be the first cyclic tetramer of isocyanate **61**. The reaction proceeded in the presence of an excess amount of triethylamine, as an acid scavenger.



A convenient approach to diaryl C-substituted tetrazocanes **62** involved an acid-catalyzed condensation of urea and 1,2-diphenylethane-1,2-dione (Equation 20) <1993MI38>.

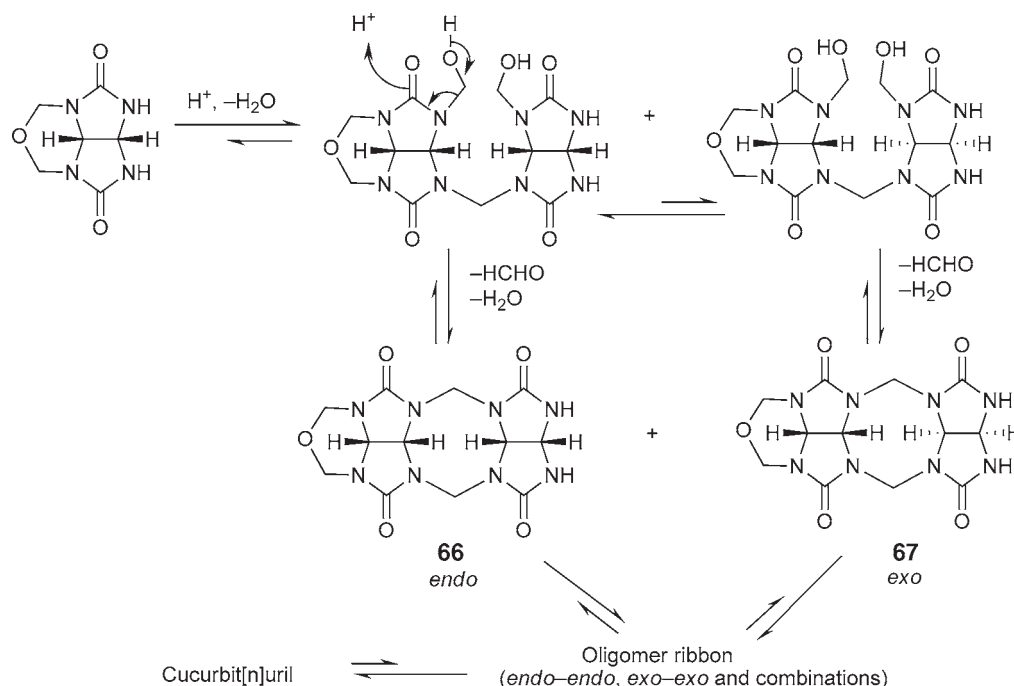


Cucurbit[6]uril is a remarkably robust macrocyclic host that has a rigid cavity that is capable of binding small guests under a variety of conditions (1996CHEC-II(9)705; Sections 14.09.2 and 14.09.11). It was synthesized from glycouril and formaldehyde under acidic conditions <1996CHEC-II(9)705>. A wide range of reactions that include the effects of acid type and concentration, reactant concentrations, and temperature to both probe the mechanism and optimize the yields of isolated cucurbit[n]urils (*n* = 5–10) have been studied <2001JOC8094, 2002JA8297, 2002JOC5817, 2003OL3745, 2003T1961, 2004OL1225>. The primary stage of the reaction is an acid-catalyzed condensation of glycouril **63** and formaldehyde, which is rapid and facile (Scheme 2). No intermediates of type **64** or **65** have been observed under acidic conditions as they react rapidly, even at room temperature <2001JOC8094>.



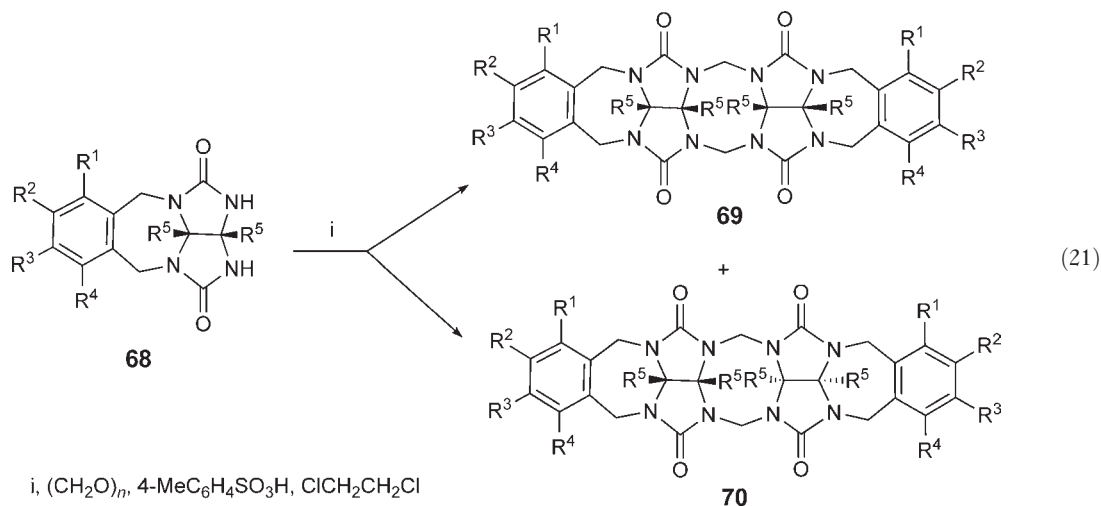
Scheme 2

The proposed mechanism for the cucurbit[n]uril synthesis is presented in **Scheme 3** and involves the kinetic formation of a mixture of 1,3,5,6-tetrazocane derivatives, *endo* and *exo* glycouril dimers **66** and **67** <2001JOC8094> (cf. Section 14.09.1 for S- and C-shaped glycouril dimers **1** and **2**). Manipulation of the acid concentration, acid type, temperature, and reactant concentrations allows a degree-of-selectivity in the cucurbit[n]uril synthesis to be achieved. It is expected that the number of repeat glycouril units in cucurbit[n]uril significantly impacts the properties of these macrocyclic molecules.



Scheme 3

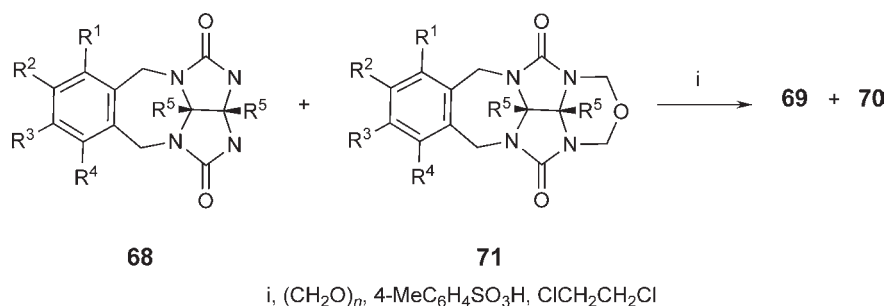
There are three general approaches to the synthesis of S- and C-shaped methylene-bridged glycouril dimers of type **1** and **2** (Section 14.09.2) as precursors in the cucurbit[n]uril synthesis, and those involve (1) dimerization of glucouril derivatives **68** bearing the ureidyl NH groups (Equation 21); (2) dimerization reactions of ureidyl NH **68** and cyclic ether **71** compounds (Equation 22); and (3) dimerization of glycouril-derived cyclic ethers **71** (Equation (35), Section 14.09.10) <2000OL755, 2002JA8297, 2002JOC5817>. In most cases, the C- and S-shaped methylene-bridged glycourils **69** and **70**, respectively, are obtained in good-to-excellent yields. In many cases, the C-shaped **69** are formed preferentially with high diastereoselectivity. Cyclic ethers **71** undergo highly diastereoselective dimerization reactions to yield methylene-bridged glycouril dimers with the formal extrusion of formaldehyde.



R^1	R^2	R^3	R^4	R^5	Yield (%)		
					69	70	Side products
H	H	H	H	CO ₂ Et	88	nd	
H	H	H	H	Ph	19	nd	38
H	H	H	H	2-Pyridyl	nd ^a	nd	
H	H	H	H	(CH ₂) ₄	57	nd	14
H	OMe	OMe	H	CO ₂ Et	87	nd	
OMe	H	H	OMe	CO ₂ Et	nd	nd	
H	Me	Me	H	CO ₂ Et	75 ^b	6 ^c	
OMe	H	H	Br	CO ₂ Et	46 (<i>cis</i>)	nd	
					48 (<i>trans</i>)	nd	
OMe	H	H	NO ₂	CO ₂ Et	28 (<i>cis</i>)	21 (<i>cis</i>)	
					24 (<i>trans</i>)	22 (<i>trans</i>)	
Br	H	H	Br	CO ₂ Et	47	10	
F	F	F	F	CO ₂ Et	44	3	

^aNot detected; ^bmp > 300 °C; ^cmp 297–299 °C.

It is possible to perform selective heterodimerization reactions using both cyclic ethers **71** and glycouril derivatives **68** bearing ureidyl NH groups (Equation 22) <2002JOC5817>. These reactions delivered the desired C- and S-shaped heterodimer **69** and **70** with low-to-moderate diastereoselectivities. This heterodimerization route is the method of choice in cases where the homodimerization reactions fail.



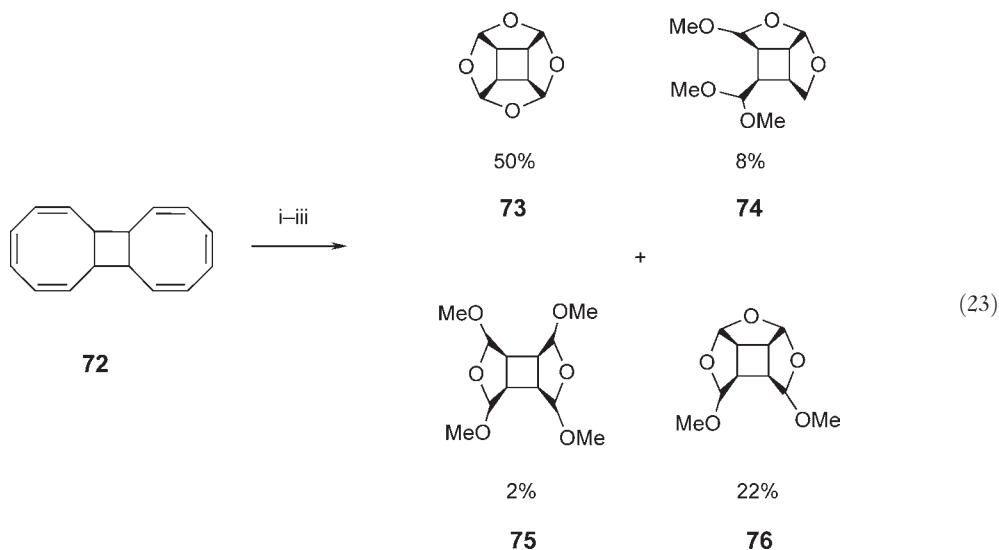
R^1	R^2	R^3	R^4	R^5	Yield (%)		
					69	70	Side products
H	H	H	H	CO ₂ Et	89	2	
H	H	H	H	Ph	16 ^a	nd	70 ^c
H	H	H	H	2-Pyridyl	nd ^b	nd	
H	H	H	H	(CH ₂) ₄	30	nd	22
H	OMe	OMe	H	CO ₂ Et	91	2	
OMe	H	H	OMe	CO ₂ Et	56	nd	
H	Me	Me	H	CO ₂ Et	90	3	

^amp 384 °C (decomp); ^bnot detected; ^cmp 310–312 °C (decomp).

(22)

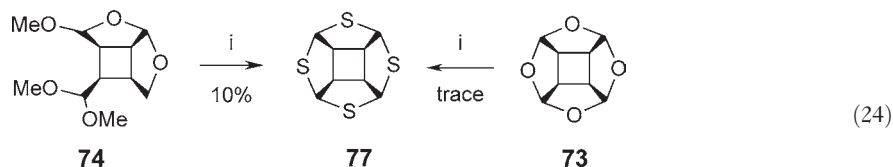
A practical method for the separation and purification of cucurbituril hexamers was developed on the basis of affinity chromatography using aminopentylaminomethylated polystyrene beads <2004OL1225>.

The [2+2] dimer **72** of cyclooctatetraene was subjected to ozonolysis and further stirring with Amberlyst 15 resin to furnish the tetraoxaperistylane **73** (see Section 14.09.2) and cyclic acetals **74–76** (Equation 23) <1999TL2417, 2003TL9313>.



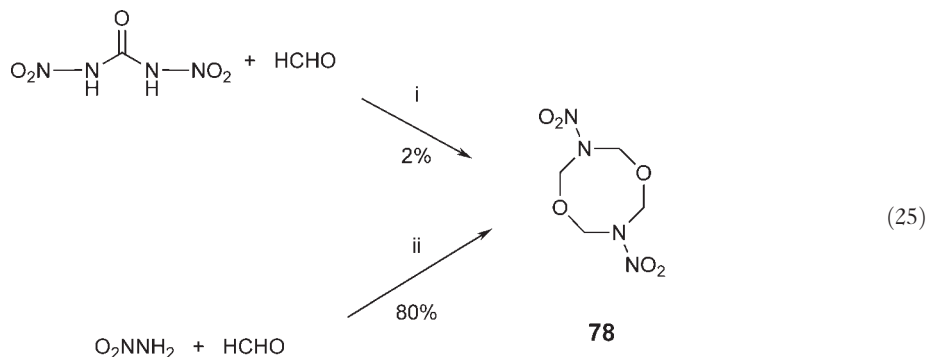
i, O₃, CH₂Cl₂–MeOH, 2:1, –78 °C; ii, Me₂S, –78 °C to rt; iii, Amberlyst 15, rt, 12 h

The proposed oxygen–sulfur exchange in the oxabowl **73** was based on the synthetic equivalency of the acetal and carbonyl groups. Thus, the use of Lawesson's reagent in the reaction with **73** was expected to produce the thia analog **77** (Equation 24) <2003TL9313>; however, the best but still low yield of the thiaperistylane **77** was obtained by a one-pot procedure from cyclic acetal **74**.



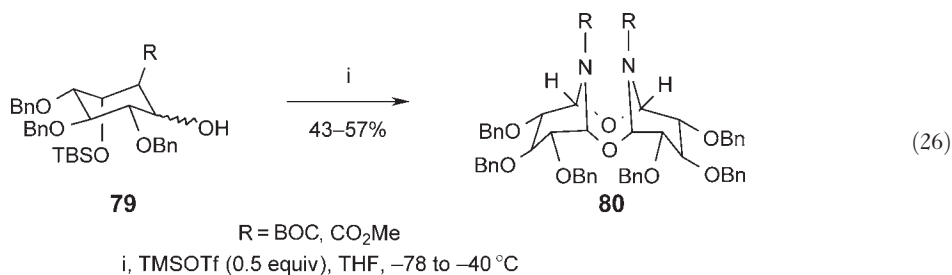
i, Lawesson's reagent, toluene, sonication, rt, 12 h

Dioxadiazocane **78** (mp 260 °C) was formed in low yield on interaction of *N,N'*-dinitrourea with formaldehyde (Equation 25) <2002RJO1739>. Alternatively, the cyclic diether **78** can be prepared by a one-pot procedure from *N*-nitroamine and formaldehyde in high yield <2002RJO1>.



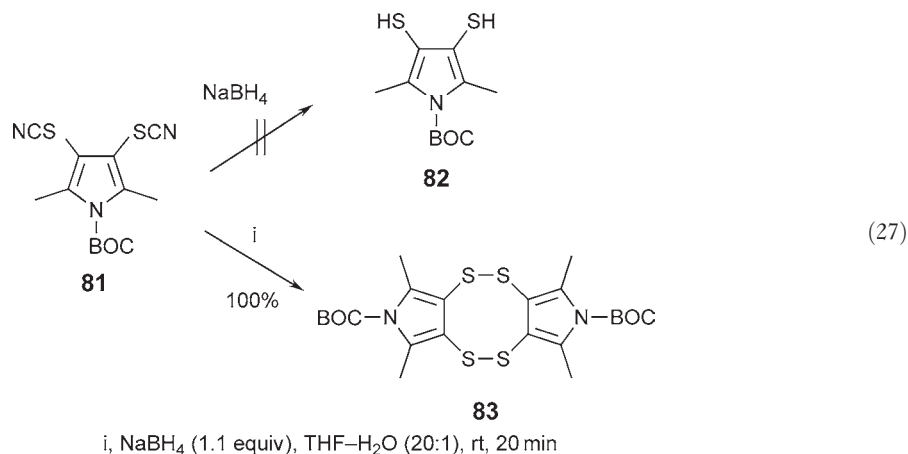
i, H₂SO₄, H₂O, rt to 65–70 °C, 20 min; ii, H₂SO₄, AcOEt, H₂O, rt

The aza sugar derivatives **79** are dimerized in the presence of a promoter to form the dioxadiazocanes **80** (Equation 26) <2005TL2399>.

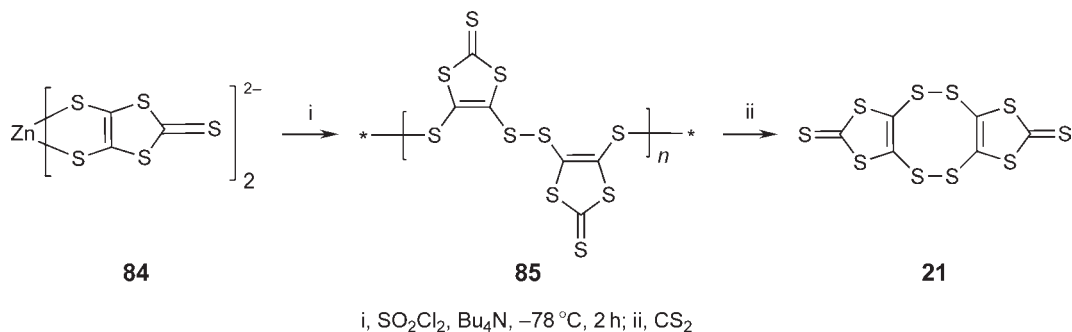


14.09.9.1.2 1,2,5,6-Substitution

Attempts to reduce the dithiocyanate **81** to dithiol **82** using NaBH_4 resulted in the tetrathiocine **83** (mp > 250 °C) (Equation 27) <1996JOC8117>. Reductive dimerization of organic thiocyanates to disulfides has been reported using a number of reagents <B-2005MI186>. Compound **83** was also formed in high yield by the reaction of dithiocyanate **81** with nucleophiles, such as sodium methoxide or hydrazine <1988SC575>.

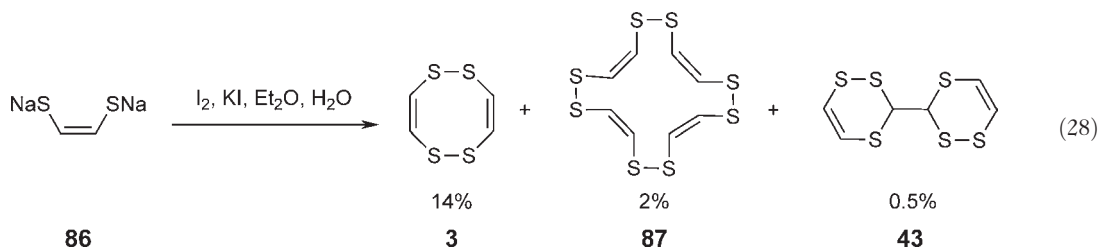


Sulfuryl chloride readily converted the zinc complex **84** to a yellow-orange solid **85** (Scheme 4) <1994IC4537; cf. CHEC-II(9)705>. The polymer **85** is transparent in the IR spectrum in the range 2500–3500 cm^{-1} demonstrating the absence of hydrocarbons. Upon treatment of the polymer **85** with carbon disulfide, the 1,2,5,6-tetraazocine **21** was isolated see (Section 14.09.3.2; 1994IC4537).

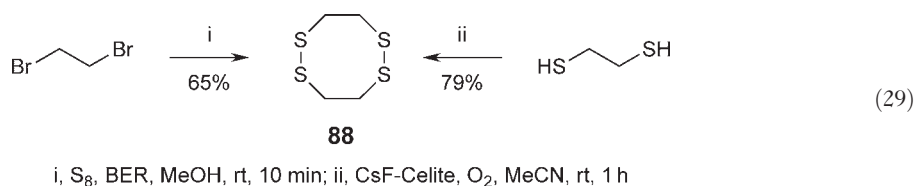


Scheme 4

In the first preparation of 1,2,5,6-tetrathiocane, oxidation of *cis*-disodium ethene-1,2-dithiolate **86** with iodine and KI led to the formation of **3** (mp 97.5–98.5 °C), as the main product (Equation 28; see Sections 14.09.2 and 14.09.6) <1996AGE2357>. The structures of **3** and **87** have been proved by X-ray crystallography.

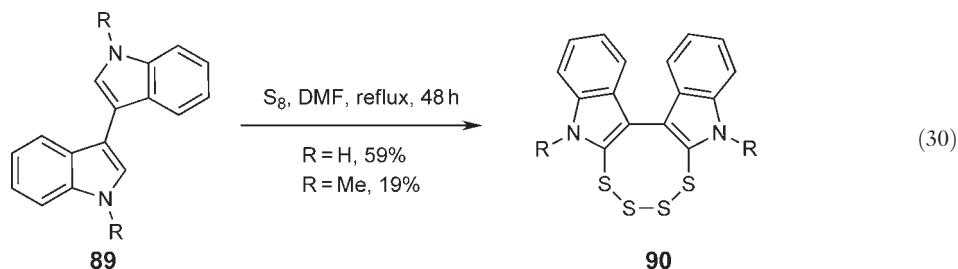


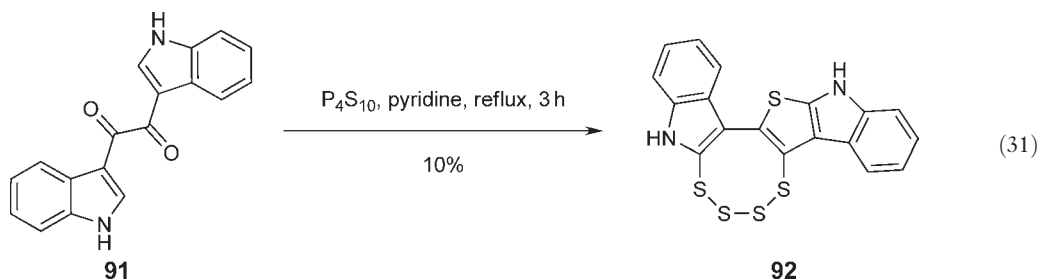
Two efficient syntheses have been reported for the parent 1,2,5,6-tetrathiocane **88** (Equation 29). Treatment of dibromoethane with a borohydride exchange resin (BER) and elemental sulfur resulted in the formation of tetrathiocane **88** in good yield <2001TL6741>. Alternatively, oxidative coupling of ethane-1,2-dithiol using cesium fluoride-Celite produced **88** in high yield <2003TL6789>. Additionally, the tetrathiocane **88** was reported by the Rh-catalyzed oxidation of ethane-1,2-dithiol in 29% yield <1997JA9309>, oxidative coupling of ethane-1,2-dithiol with metal nitrates on a bentonite clay (TAFB) in 6% yield <2003HAC262>, and catalytic transformation of the thiirane (see Equation (42) in Section 14.09.10) <1996JA10674>.



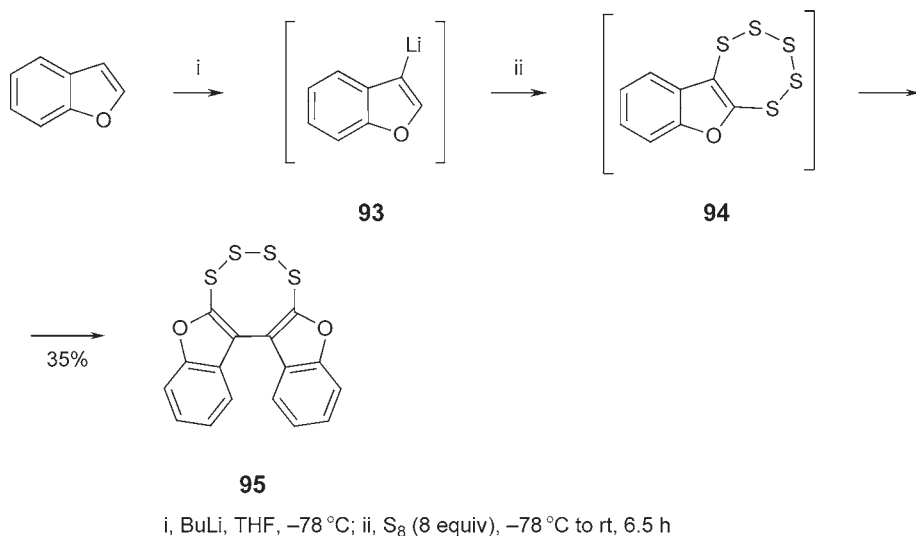
14.09.9.1.3 Other substitution patterns

Thionation of 3,3'-biindole **89** with elemental sulfur in hot DMF produced the 1,2,3,4-tetrathiocines **90** (Equation 30) <2002JP1330>. The dione **91** was thionated with P_4S_{10} to form the thienoindole derivative **92** in low yield (Equation 31) <2002JP1330>. The tetrathiocines **90** and **92** were studied by X-ray crystallography (Section 14.09.3.3); it was established that **90** ($\text{R}=\text{H}$, mp 301–302 °C) is chiral in the crystalline state <2002JP1330>. Alternatively, the *N,N'*-dimethyl tetrathiocine **90** ($\text{R}=\text{Me}$) can be obtained from *N*-methylindolopentathiepine in 87% yield (see Scheme 9 in Section 14.09.10) <2001T7185>.



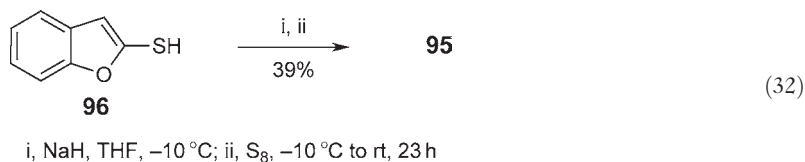


The reaction of lithiated benzo[*b*]furan **93** with sulfur resulted in a novel heterocyclic system, bis(benzo[4,5]-furo)[2,3-*e*:3'.2'-*g*][1,2,3,4]tetrathiocine **95**, possibly formed via intermediate pentathiepine **94** (Scheme 5) <2002JOC6220>. The assumed mechanism was based on the reported transformation of a pentathiepine into a tetrathiocine induced by Et₃N <2001T7185> (cf. Section 14.09.10).



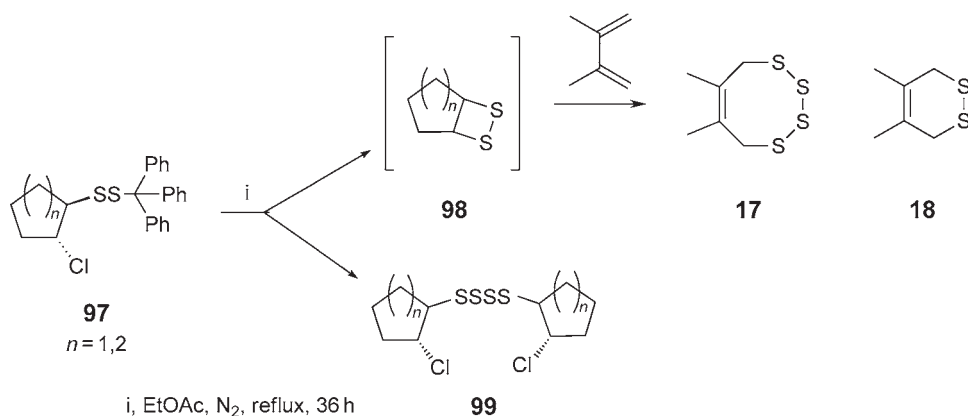
Scheme 5

The preference for formation of the tetrathiocine structure was also demonstrated by the conversion of thiol **96** into **95** (Equation 32) <2002JOC6220>.



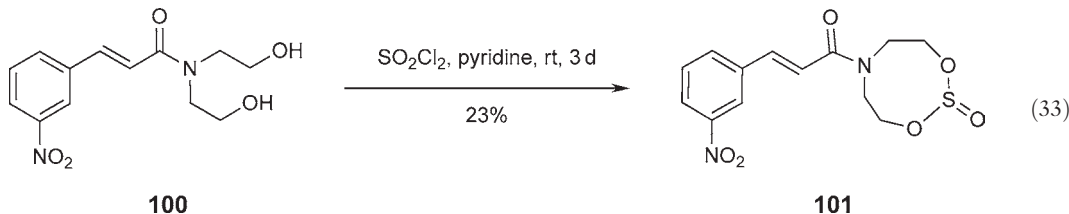
In the studies on novel precursors for diatomic sulfur, the formation of 6,7-dimethyl- and 6,7-diphenyl-5,8-dihydrotetrathiocines together with the corresponding 4,5-substituted 3,6-dihydro[1,2]dithiines has been reported by the reaction of 2,3-dimethyl- or 2,3-diphenyl-1,3-butadiene with the following sulfur-transfer agents: dialkoxy disulfides <1995JA9067, 2002TL8781>, 6-*tert*-butyl-6-phenylpentathiane-3-oxide <2001TL3117>,

diselenatetrasulfides [<2004TL9181>](#), elemental sulfur and sodium hydride in the presence of phase-transfer catalysts, 15-crown-5 or tris[2-(2-methoxyethoxy)ethyl]amine [<1998H\(48\)1519>](#), and cyclodecasulfur [<1999TL7961>](#) (cf. [1996CHEC-II\(9\)705](#)). Harpp and Leste-Lesserre reported novel precursors for diatomic sulfur, the sulfenyl chlorides **97**, which on thermolysis in the presence of 2,3-dimethyl-1,3-butadiene formed a mixture of the disulfide **18** and tetrathiocine **17** (**Scheme 6**; see [Equation \(1\)](#) in Section 14.09.9.3.1) [<1998JOC8654>](#). The product distribution in the mixture depended upon ratio of reagents, as well as the time and temperature of the reaction and varies from 7% to 58% for the tetrathiocine **17**. By-products, the acyclic tetrasulfide adducts **99**, were formed in low yield. The formation of **17** and **18** was proposed via the dithietanes **98**, as potentially stable intermediates and/or diatomic sulfur precursors.



Scheme 6

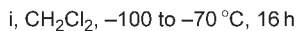
Diol **100** reacted with thionyl chloride to form sulfoxide **101** ([Equation 33](#)) [<2002EJM607>](#). A similar approach to dioxathiocanes with substituents at the carbon atoms on the eight-membered ring has been reported earlier [<1996CHEC-II\(9\)705>](#).



14.09.9.2 Synthesis of Rings Containing Five or More Heteroatoms

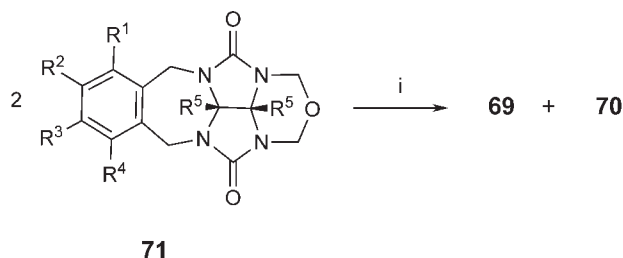
An unusual transformation occurred when triethylamine reacted with disulfur dichloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) to form heptathiocane **103** (mp 72–73 °C) and thienopentathiepine **104** (**Scheme 7**) [<2003OL1939>](#). The proposed mechanism involved the adduct **102** and oxidation of the intermediate complex **105**, followed by the formation of enamines **106** and **107**. The intermediate **106** outlined a pathway to the extended polysulfur chain, such as in **107**, which cyclized into heptathiocane **103**. Incorporation of only one carbon into the heterocyclic ring from the ethyl group rather than both was presumably controlled by the reactivity of the enamine **107**. For the mechanism of formation of thienopentathiepine **104**, Chapter 13.17, CHEC-3 should be consulted. The rare heptathiocane ring structure was proved by X-ray crystallography ([Section 14.09.3.3](#)).

Treatment of the guanidine derivatives **108** with PhSCl resulted in the formation of dithiatetrazocines **109** together with the dimer **110** and the 16-membered ring **111** ([Equation \(34\)](#); cf. [Equation \(9\)](#) in [Section 14.09.5](#)) [<1997IC1669>](#).

^amp 199 °C (decomp.); ^bmp 178 °C (decomp.).

14.09.10 Ring Synthesis by Transformation of Another Ring

Dimerization of glycouril-derived cyclic esters **71** is one of three general approaches to the precursor **69** and **70** in the synthesis of cucurbituril homologs and analogs (Equation (35); see Section 14.09.9.1.1 and Equations (21) and (22)) <2002JA8297, 2002JOC5817>. It was suggested that the use of two different glycouril derivatives **71** in the dimerization reaction might result in a selective heterodimerization; an example of the C-shaped heterodimer has been reported <2000OL755>.



i, (CH₂O)_n, 4-MeC₆H₄SO₃H, ClCH₂CH₂Cl, Δ

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	<i>R</i> ⁵	Yield (%)		
					69	70	Side products
H	H	H	H	CO ₂ Et	92	nd	
H	H	H	H	Ph	nd ^a	nd	42
H	H	H	H	2-pyridyl	nd	nd	28
H	H	H	H	(CH ₂) ₄	34	nd	
H	H	H	H	CONH(CH ₂) ₃ NMe ₂	85	nd	
H	H	H	H	CO ₂ Li	85	nd	
H	OMe	OMe	H	CO ₂ Et	93	nd	
OMe	H	H	OMe	CO ₂ Et	nd	nd	
H	Me	Me	H	CO ₂ Et	87	nd	

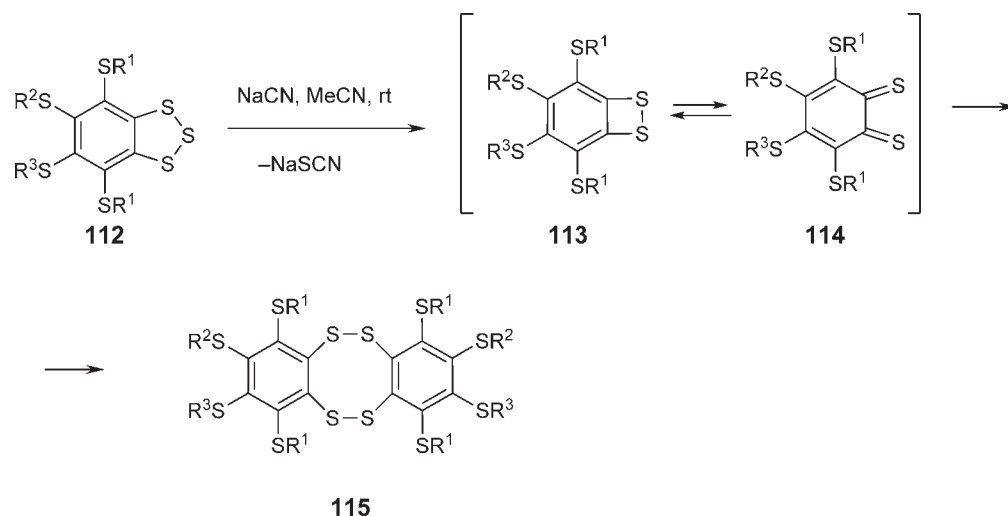
^aNot detected.

(35)

In the study of the controlled elimination of one sulfur atom from the trithiols **112** to generate the benzo-dithietes **113**, the 1,2,5,6-tetrathiocenes **115** were isolated in high yield (Scheme 8) <1995T2533>. It was suggested that the equilibrium between the benzothiete **113** and *o*-dithiobenzoquinone **114** should favor dimerization to form **115**.

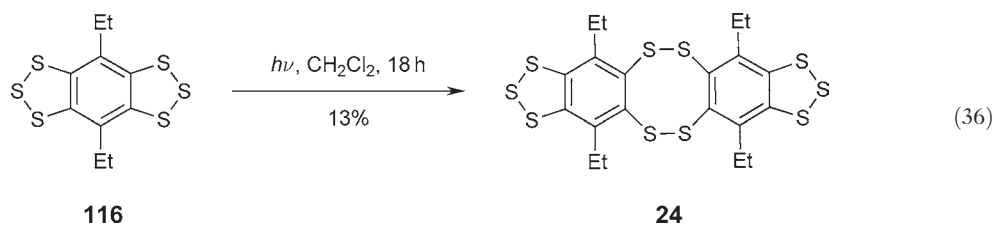
Photolysis of the trithiole **116** produced 1,2,5,6-tetrathiocene **24** (mp 239.5–241.5 °C) in low yield (Equation (36); see Section 14.09.3.4) <2002BCJ2647>.

1,2,3,6-Tetrathiocene **32** was obtained by photolysis of the 1,2,5,6-tetrathiocene **31** (see Equation (7) in Section 14.09.5) <1998CJC1093>.

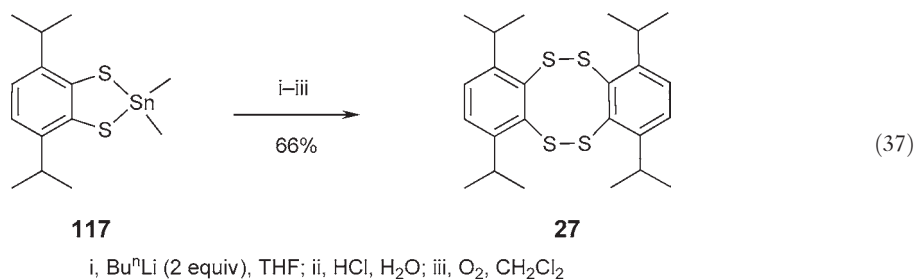


R^1	R^2	R^3	Yield (%)	mp ($^{\circ}\text{C}$)
Me	Me	Me	95	260
$(\text{CH}_2)_3\text{CNMe}_2$			92	248

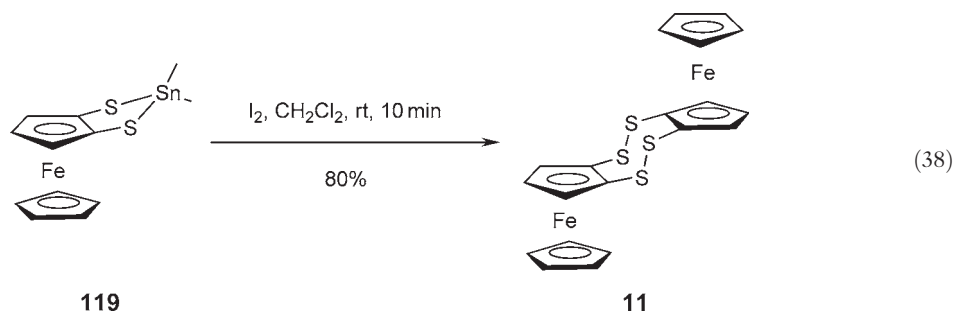
Scheme 8



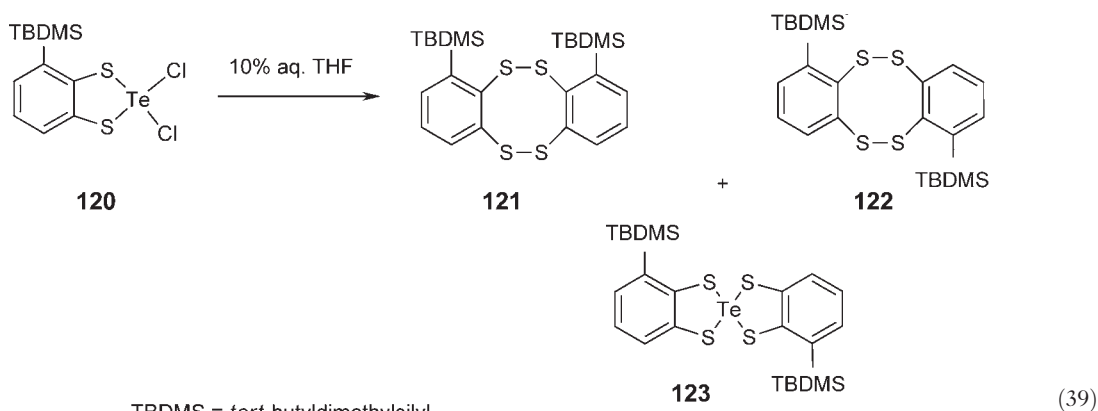
Dithiastannole **117** was coupled oxidatively into the sterically hindered 1,2,5,6-tetrathiocine **27** in good yield (Equation (37); see Equation (4) in Section 14.09.5) <1999TL9101>.



Ferrocene dithiastannole **119**, a synthetic equivalent of an unstable ferrocene 1,2-dithiol, reacted with iodine under conditions of deprotection to give the tetrathiocine **11** (mp $> 300\text{ }^{\circ}\text{C}$), as a single diastereomer (Equation (38); see Sections 14.09.2 and 14.09.4) <2002TL5825>.



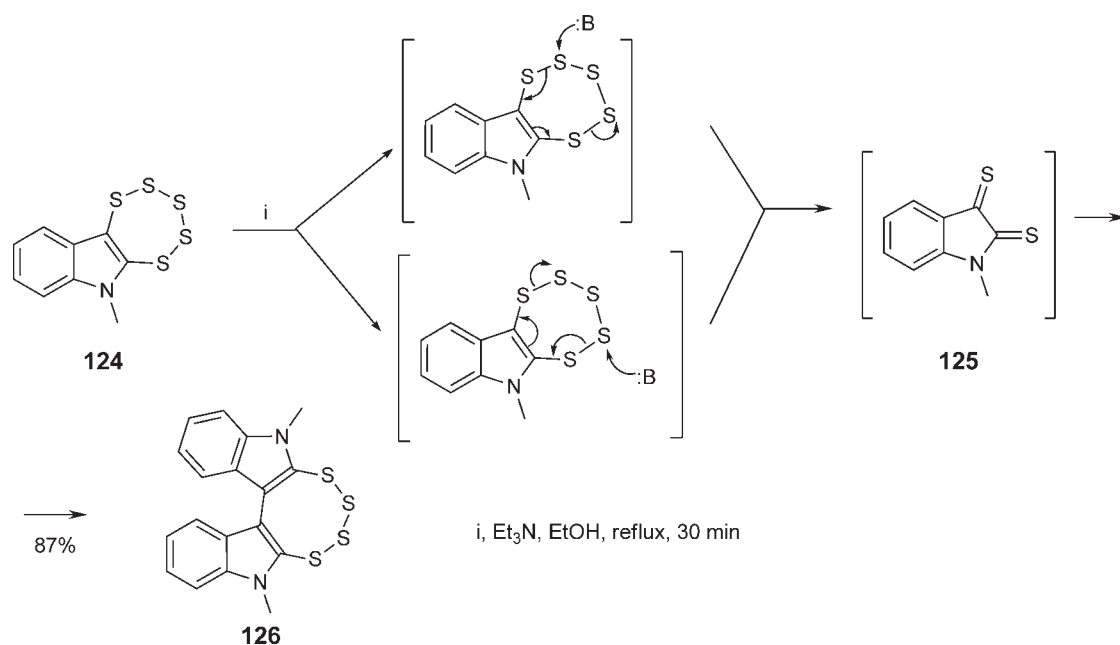
When dithiatellurole **120** was treated with aqueous tetrahydrofuran, the dibenzotetrathiocines **121** (mp 189–190.5 °C) and **122** (mp 246–246.5 °C) were produced along with spirotellurane **123** (Equation 39) <1995TL587>. The isomer **121** and **122** ratio was affected by reaction time, and the reaction conditions. On heating, the isolated spirotellurane **123** was converted into a **121** and **122** mixture in 1:6.1 ratio in 80% yield.



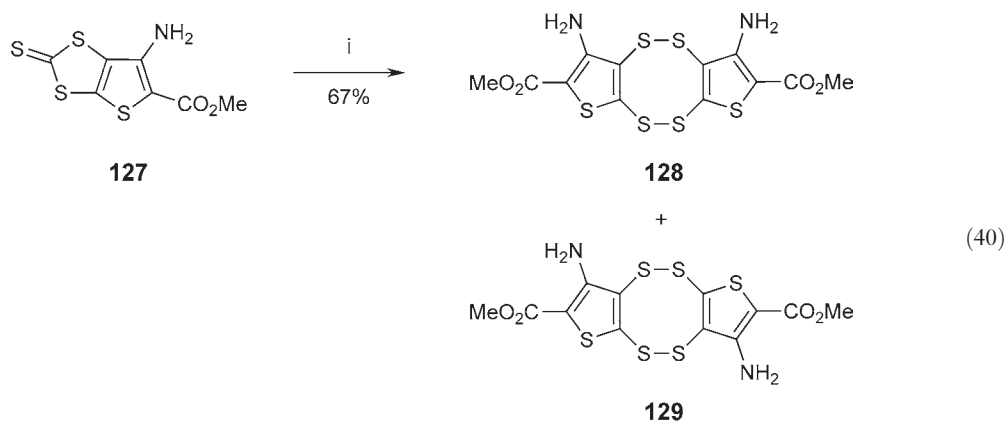
Conditions	Yield (%)		Ratio
	121+122	123	121:122
Reflux, 1 h	34	64	2.3:1.0
Reflux, 8 h	39	60	1.8:1.0
Reflux, 20 h	76	24	1.3:1.0
Reflux, 40 h	84	16	1.0:1.8
rt, 20 h	18	74	1.4:1.0
–15 °C, 1 h	Trace	88	

Transformation of pentathiepine **124** to 1,2,3,4-tetrathiocine **126** (mp 250–255 °C) proceeded in the presence of triethylamine in EtOH in high yield (Scheme 9) <2001T7185>. The proposed mechanism involves the intermediate formation of the dithioisatine **125** (cf. Scheme 6). Alternatively, the octameric **126** was isolated on sulfurization of 3,3'-biindole **89** in 19% yield <2002JP1330> (see Equation (30) in Section 14.09.9.1.3).

The first example of an enzymatic cleavage of trithiocarbonate **127** followed by oxidative dimerization was reported to give an inseparable mixture of 1,2,5,6-tetrathiocines **128** and **129** (Equation 40) <2002TL2589>, whose structure assignments were based on mass spectrometry data.



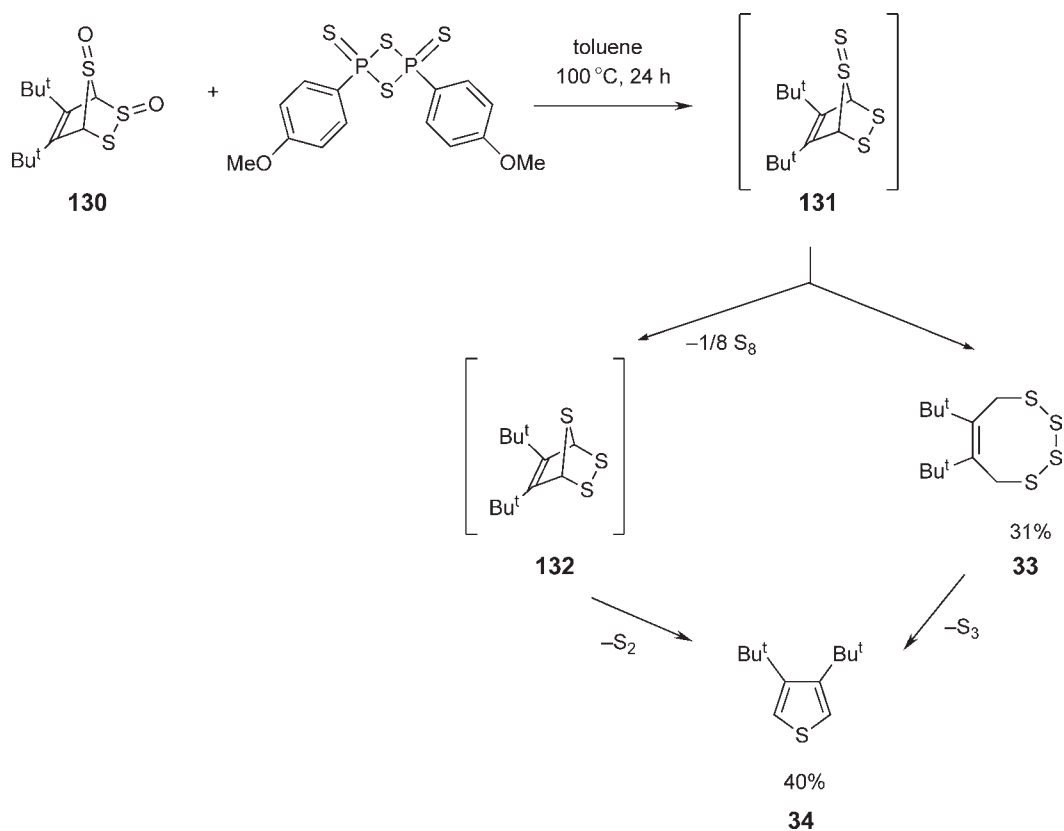
Scheme 9



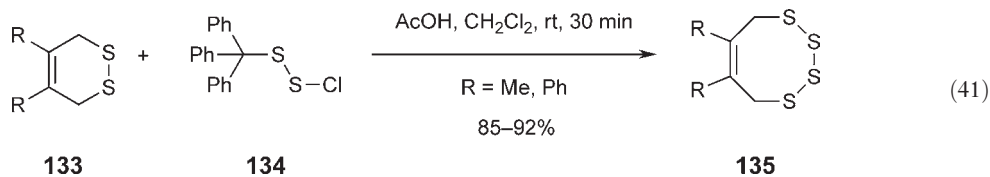
i, *Pseudomonas chloraphis* ATCC9447 whole lypophylized cells or fermenting cells

Heating the disulfoxide **130** with Lawesson's reagent, a reagent that reduces sulfoxides to the corresponding sulfides [<1999CL695, 2003JOC1555>](#), provided the 1,2,3,4-tetrathiocine **33** and thiophene **34** (Scheme 10; see Equation (8) in Section 14.09.5) [<2004JA9085>](#). The formation of the tetrathiocine **33** was explained by skeletal rearrangement of the intermediate thiosulfoxide **131**. Thiophene **34** can be produced by extrusion of S₂ from the intermediate **132**. Competitively, the compound **34** can be formed by extrusion of S₃ from the tetrathiocine **33** (cf. Section 14.09.5).

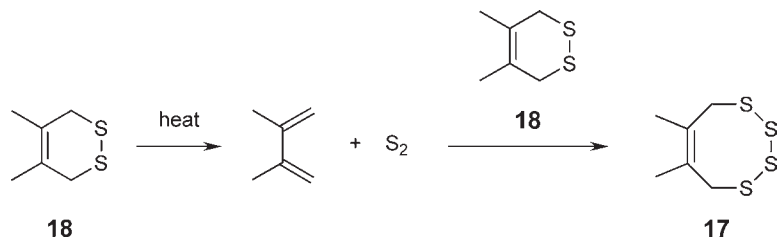
Insertion of a two-sulfur unit into the S–S bond of the tailor-made polysulfides was studied by Harpp and Rys [<2000TL7169>](#). Triphenylthiosulphenyl chloride **134** was used as a source of diatomic sulfur to produce the tetrathiocines **135** from the disulfides **118** in high yield (Equation 41).



Scheme 10

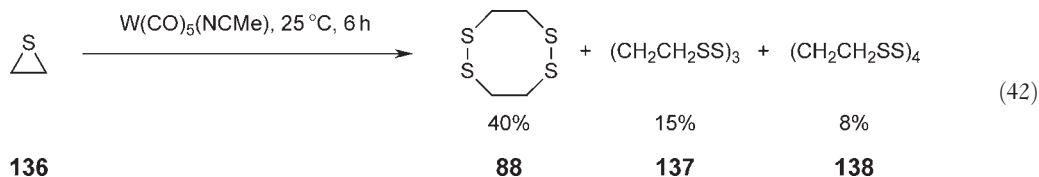


It was reported that on heating in various solvents (in toluene at 100 °C or in chlorobenzene at 135–140 °C) the disulfide **18** is slowly converted to the tetrathiocine **17** by the mechanism proposed in (Scheme 11) <1995JA9067> (cf. Equation (2) in Section 14.09.3.2).

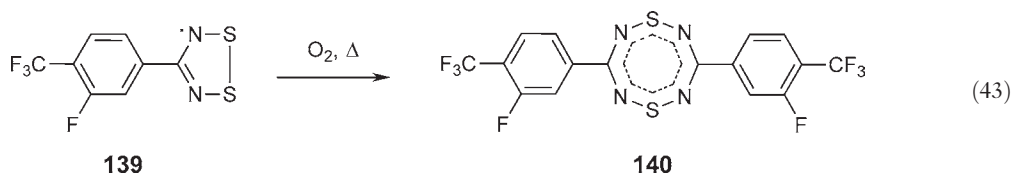


Scheme 11

A new route to cyclic polysulfides was reported by catalytic transformation of an excess of thiirane **136** with a $W(CO)_5$ complex to give the tetrathiocine **88**, as the main product, together with cyclic polysulfides **137** and **138** (Equation 42) <1996JA10674>. The possible mechanism of this transformation involved a thiirane- $W(CO)_5$ ligand complex, followed by the formation of a SCH_2CH_2S tungsten complex. Alternatively, **88** can be efficiently prepared from dibromoethane on borohydride resin <2001TL6741> or by oxidative coupling of ethane-1,2-diol using cesium fluoride-Celite <2003TL6789> in high yield (see Equation (29) in Section 14.09.9.1.2).



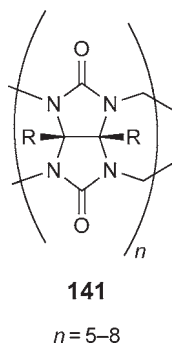
Sublimation of the dithiadiazolyl radical **139** in a partial atmosphere of oxygen resulted in the formation of dithiatetrazocine **140**, as a yellow solid (Equation 43) <2003CC2774, 2004PS981>. Earlier, it was shown that dithiadiazolyl radicals reacted with dioxygen in MeCN to generate dithiatetrazocines <1996CHEC-II(9)705>.



14.09.11 Important Compounds and Applications

N-Nitro and acetyl-substituted 1,3,5,7-tetrazocanes are important compounds as explosives and propellants <1996CHEC-II(9)705>. In the syntheses of the nitro-substituted 1,3,5,7-tetrazocanes, their processing, and application, it is possible that they come into contact with ammonium nitrate, or they are directly mixed with this oxidant. Thermal reactivity of the nitro-substituted 1,3,5,7-tetrazocanes has been examined by means of nonisothermal differential thermal analysis <2005MI11>. It has been established that impurities of ammonium nitrate can destabilize some *N*-substituted 1,3,5,7-tetrazocanes and that this effect is due to acidolytic attack of nitric acid.

Cucurbituril (cucurbit[6]uril or CB[6]), a hexameric macrocycle **141** ($R = H$, $n = 6$) with a 1,3,5,6-tetraazocane core unit, is self-assembled from an acid-catalyzed condensation reaction of glycouril and formaldehyde (see Section 14.09.9.1.1 and 1996CHEC-II(9)705). Although its synthesis first appeared in 1905, its chemical nature and structure remained unknown until 1981, when full characterization was reported by Mock and co-workers <1981JA7367>.



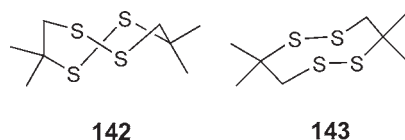
The pumpkin-shaped molecule CB[6] has a cavity of $\sim 5.5 \text{ \AA}$ diameter, accessible from the exterior by two carbonyl-laced portals of $\sim 4 \text{ \AA}$ diameter. Although it resembles α -cyclodextrin (α -CD) in terms of cavity size, the highly symmetrical structure with two identical openings distinguishes it from α -CD. CB[6] is potentially as useful as crown ethers, CDs and calixarenes in many applications <B-1996MI477>. Despite the range of useful properties of CB[6], several drawbacks prevent its more widespread use, such as: (1) its small cavity volume which limits the range of molecular guests that can be incorporated, (2) its poor solubility in water and common organic solvents, and (3) a

lack of easily manipulated functional groups that would allow derivatization. During the last decade, several groups have been involved to alleviate each of these problems reflected in the growing number of publications appearing on this subject each year. The recent advances on synthesis and applications of the cucurbit[*n*]uril family include: preparation of glycouril monomers for expanded cucurbit[*n*]uril synthesis <2001JOC8094, 2001OL3221, 2003T1961>, synthesis and characterization of cucurbit[*n*]uril homologs **141** (*n* = 5, 7, 8) <2000JA540, 2003ACR621>, synthesis of the functionalized cucurbit[*n*]urils <2003JA10186, 2003JOC9040>, mechanically interlocked molecules incorporating cucurbituril and their supramolecular assemblies, for example rotaxanes and molecular necklaces <2002BKC1347, 2002CC496, 2002CSR96, 2002JA2140, 2002MI147, 2003AGE2293, 2004EJI63>, and catalysis of 1,3-dipolar cycloadditions between suitably substituted aliphatic azides and terminal alkynes in a regioselective fashion <1995TCC1, 2002CC22, 2003CC2176>.

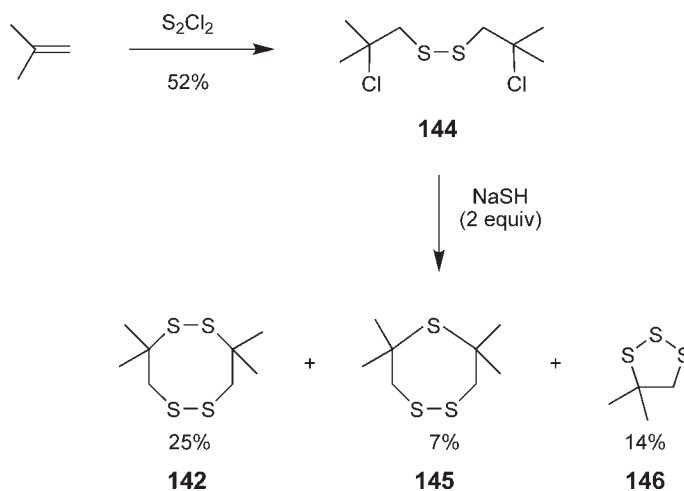
Design and synthesis of polycyclic molecules with unusual shape, symmetry, and chemically distinct surfaces resulted in a novel class of heterobowls such as **10** (see Section 14.09.2). Although no utilitarian applications of these compounds have been reported yet, this is perhaps because of their recent discovery, the heterobowls might display many interesting properties, such as selective activity for metal ions, face-selective chemical reactivity, surfactant chemistry, and enzyme mimicry <1997TL4173, 2001JOC6905>.

14.09.12 Further Developments

A few novel polycyclic sulfides were identified in extracts of two bacterial *Cytophaga* strains, and among those were the tetramethyl 1,2,5,6-tetrathiacanes **142** and **143** <2007JOC3776>. The structures of the isolated sulfides were deduced by analysis of their mass spectra and confirmed by synthesis. The favored 'twisted chair' and 'chair' conformations for **142** and **143** respectively were proposed from the data of dynamic NMR spectroscopy and a series of DFT (density functional theory) gas-phase calculations.

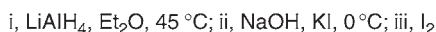
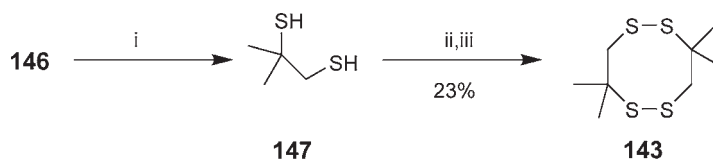


The tetrathiacane **142** (mp 71 °C) and the trisulfides **145** and **146** were isolated from the mixture when disulfide **144** reacted with sodium sulfide (Scheme 12) <2007JOC3776> (cf. Equation (29), Section 14.09.9.1.2).



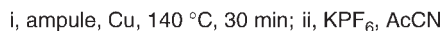
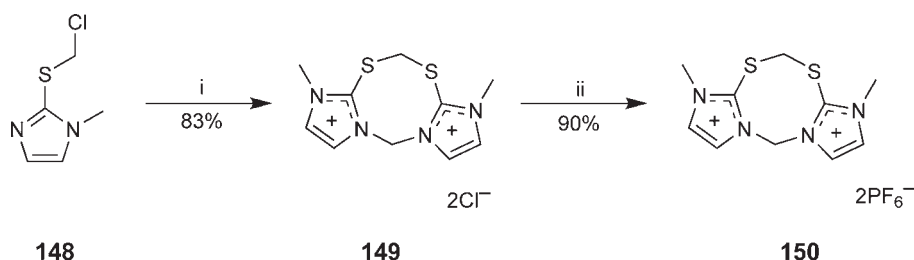
Scheme 12

Reduction of the trisulfide **146** furnished the diol **147** which was oxidatively coupled with NaOH and iodine to form the tetrathiacane **143** (mp 106 °C) (Scheme 13) <2007JOC3776> (cf. Equation (28), Section 14.09.9.1.2).



Scheme 13

The studies of the linkage isomers of the bis(thioimidazolyl)methane family reported the cyclization of the chloromethylthioimidazole **148** into the unstable ionic dithiadiazocine chloride **149** (mp 224°C , dec.) which was converted into the stable hexafluorophosphate **150** (mp 234°C , dec.) (Scheme 14) <2005JOC8755>. The dication **150** was characterized by single-crystal X-ray diffraction and was shown to have a chair conformation. Electrochemical studies of the salt **150** in acetonitrile showed an irreversible reduction wave centered at -1.09 V <2005JOC8755>.



Scheme 14

References

- 1981JA7367 W. A. Freeman, W. L. Mock, and N.-Y. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 7367.
 1984CHEC(9)653 J. A. Moore, in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky, C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol.5, p. 653.
 1988SC575 S. N. Maiti, P. Spevak, M. P. Singh, and N. Reddy, *Synth. Commun.*, 1988, **18**, 575.
 1991TL7651 C. R. Williams, and D. N. Harpp, *Tetrahedron Lett.*, 1991, **32**, 7651.
 1992USP5120887 W. Lukasavage, S. Nicolich, and J. Alster, *US Pat.* 5120887 (1992) (*Chem. Abstr.*, 1992, **117**, 111657).
 B-1992MI1 A. W. Cordes, R. C. Haddon, and R. T. Oakley, in 'The Chemistry of Inorganic Ring Systems', R. Steudel, Ed.; Elsevier, Amsterdam, 1992, Chapter 16.
 B-1992MI2 A. J. Banister, and J. M. Rawson, in 'The Chemistry of Inorganic Ring Systems', R. Steudel, Ed.; Elsevier, Amsterdam, 1992, Chapter 17.
 1993MI38 J. Wang, and S. Tian, *Tongweisu*, 1993, **6**, 38 (*Chem. Abstr.*, 1993, **119**, 180704).
 1994IC4537 C. P. Galloway, D. D. Doxsee, D. Fenske, T. B. Rauchfuss, S. R. Wilson, and X. Yang, *Inorg. Chem.*, 1994, **33**, 4537.
 1994JCM436 T. Shimizu, K. Iwata, N. Kamigata, and S. Ikuta, *J. Chem. Res. (S)*, 1994, 436.
 1995JA9067 S. L. Tardif, C. R. Williams, and D. N. Harpp, *J. Am. Chem. Soc.*, 1995, **117**, 9067.
 1995JOC7558 H.-J. Wu, and C.-C. Lin, *J. Org. Chem.*, 1995, **60**, 7558.
 1995T2533 E. Fanghanel, R. Herrmann, and H. Naarmann, *Tetrahedron*, 1995, **51**, 2533.
 1995TCC1 W. L. Mock, *Top. Curr. Chem.*, 1995, **175**, 1.
 1995TL587 S. Ogawa, M. Yamashita, and R. Sato, *Tetrahedron Lett.*, 1995, **36**, 587.
 1996AGE2357 T. Shimizu, K. Iwata, and N. Kamigata, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2357.
 1996CC949 T. Chivers, I. Vargas-Basa, T. Ziegler, and P. Zoricak, *J. Chem. Soc., Chem. Commun.*, 1996, 949.
 1996CHEC-II(9)705 R. R. Ollmann, Jr., in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 705.
 1996JA10674 R. D. Adams, J. A. Queisser, and J. H. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 10674.
 1996JOC8117 K. Zong, W. Chen, M. P. Cava, and R. D. Rogers, *J. Org. Chem.*, 1996, **61**, 8117.
 B-1996MI477 W. L. Mock, in 'Comprehensive Supramolecular Chemistry', V. Vögtle, Ed.; Pergamon, Oxford, 1996, 2, p. 477.
 1997IC1669 T. Chivers, M. Parvez, I. Vargas-Baca, T. Ziegler, and P. Zoricak, *Inorg. Chem.*, 1997, **36**, 1669.
 1997JA9309 J. B. Arterburn, M. C. Perry, S. L. Nelson, B. R. Dible, and M. S. Holguin, *J. Am. Chem. Soc.*, 1997, **119**, 9309.
 1997TL4173 G. Mehta, and R. Vidya, *Tetrahedron Lett.*, 1997, **38**, 4173.
 1998CJC1093 T. Chivers, M. Parvez, I. Vargas-Baca, and G. Schatte, *Can. J. Chem.*, 1998, **76**, 1093.
 1998H(48)1519 K. Okuma, S. Kuge, Y. Koga, K. Shioji, H. Wakita, and T. Machiguchi, *Heterocycles*, 1998, **48**, 1519.
 1998JOC8654 I. A. Abu-Yousef, and D. N. Harpp, *J. Org. Chem.*, 1998, **63**, 8654.

- 1999CL695 K. Shimada, K. Kodaki, S. Aoyagi, Y. Takikawa, and C. Kabuto, *Chem. Lett.*, 1999, 695.
- 1999TL2417 G. Mehta, R. Vidya, and K. Venkatesan, *Tetrahedron Lett.*, 1999, **40**, 2417.
- 1999TL7961 P. Lesté-Lasserre, and D. N. Harpp, *Tetrahedron Lett.*, 1999, **40**, 7961.
- 1999TL9101 S. Ogawa, M. Sugawara, Y. Kawai, S. Niizuma, T. Kimura, and R. Sato, *Tetrahedron Lett.*, 1999, **40**, 9101.
- 2000IC1697 T. Chivers, M. P. Gibson, M. Parvez, and I. Vargas-Baca, *Inorg. Chem.*, 2000, **39**, 1697.
- 2000JA540 J. Kim, I.-S. Jung, S.-Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi, and K. Kim, *J. Am. Chem. Soc.*, 2000, **122**, 540.
- 2000OL755 D. Witt, J. Lagona, F. Damkaci, J. C. Fetting, and L. Isaacs, *Org. Lett.*, 2000, **2**, 755.
- 2000TL1801 T. Kimura, K. Tsujimura, S. Mizusawa, S. Ito, Y. Kawai, S. Ogawa, and R. Sato, *Tetrahedron Lett.*, 2000, **41**, 1801.
- 2000TL7169 A. Z. Rys, and D. N. Harpp, *Tetrahedron Lett.*, 2000, **41**, 7169.
- 2001JOC6905 G. Mehta, and R. Vidya, *J. Org. Chem.*, 2001, **66**, 6905.
- 2001JOC8094 A. Day, A. P. Arnold, R. J. Blanch, and B. Snushall, *J. Org. Chem.*, 2001, **66**, 8094.
- 2001OL3221 L. Isaacs, D. Witt, and J. Lagona, *Org. Lett.*, 2001, **3**, 3221.
- 2001RJO1030 G. A. Lyushnina, A. Yu. Bryukhanov, M. Turkina, K. V. Malakhov, and E. L. Golod, *Russ. J. Org. Chem.*, 2001, **37**, 1030.
- 2001T7185 G. W. Rewcastle, T. Janosik, and J. Bergman, *Tetrahedron*, 2001, **57**, 7185.
- 2001TL3117 A. Ishii, H. Oshida, and J. Nakayama, *Tetrahedron Lett.*, 2001, **42**, 3117.
- 2001TL6741 B. P. Bandgar, L. S. Uppalla, and V. S. Sadavarte, *Tetrahedron Lett.*, 2001, **42**, 6741.
- 2002BCJ2647 T. Kimura, S. Mizusawa, A. Yoneshima, S. Ito, K. Tsujimura, T. Yamashita, Y. Kawai, S. Ogawa, and R. Sato, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 2647.
- 2002BKC1347 J. W. Lee, S. W. Choi, Y. H. Ko, S.-Y. Kim, and K. Kim, *Bull. Korean Chem. Soc.*, 2002, **23**, 1347.
- 2002CC22 T. C. Kraisa, and J. H. G. Steinke, *J. Chem. Soc., Chem. Commun.*, 2002, 22.
- 2002CC496 D. Tuncel, and J. H. G. Steinke, *J. Chem. Soc., Chem. Commun.*, 2002, 496.
- 2002CL90 K. Shimada, T. Yoshida, K. Makino, T. Otsuka, Y. Onuma, A. Aoyagi, Y. Takikawa, and C. Kabuto, *Chem. Lett.*, 2002, 90.
- 2002CSR96 K. Kim, *Chem. Soc. Rev.*, 2002, **31**, 96.
- 2002EJM607 L. Hedvati, A. Nudelman, E. Falb, B. Kraiz, R. Zhuk, and M. Sprecher, *Eur. J. Med. Chem.*, 2002, **37**, 607.
- 2002JA2140 K.-M. Park, S.-Y. Kim, J. Heo, D. Whang, S. Sakamoto, K. Yamaguchi, and K. Kim, *J. Am. Chem. Soc.*, 2002, **124**, 2140.
- 2002JA8297 A. Chakraborty, A. Wu, D. Witt, J. Lagona, J. C. Fetting, and L. Isaacs, *J. Am. Chem. Soc.*, 2002, **124**, 8297.
- 2002JP1330 T. Janosik, J. Bergman, B. Stensland, and C. Stålhandske, *J. Chem. Soc., Perkin Trans. 1*, 2002, 330.
- 2002JOC5817 A. Wu, A. Chakraborty, D. Witt, J. Lagona, F. Damkaci, M. A. Ofori, J. K. Chiles, J. C. Fetting, and L. Isaacs, *J. Org. Chem.*, 2002, **67**, 5817.
- 2002JOC6220 T. Janosik, B. Stensland, and J. Bergman, *J. Org. Chem.*, 2002, **67**, 6220.
- 2002MI147 R. J. Blanch, A. J. Sleeman, T. J. White, A. P. Arnold, and A. I. Day, *Nanoletters*, 2002, **2**, 147.
- 2002RJO1 A. A. Lobanova, S. G. Il'yasov, N. I. Popov, and R. R. Sataev, *Russ. J. Org. Chem.*, 2002, **38**, 1.
- 2002RJO1739 S. G. Il'yasov, A. A. Lobanova, N. I. Popov, and R. R. Sataev, *Russ. J. Org. Chem.*, 2002, **38**, 1739.
- 2002T2589 W. Kroutil, A. A. Stämpfli, R. Dahinden, M. Jörg, U. Müller, and J. P. Pachlatko, *Tetrahedron*, 2002, **58**, 2589.
- 2002TL5825 N. Nagahora, S. Ogawa, Y. Kawai, and R. Sato, *Tetrahedron Lett.*, 2002, **43**, 5825.
- 2002TL8781 R. Priefer, P. G. Farrell, and D. N. Harpp, *Tetrahedron Lett.*, 2002, **43**, 8781.
- 2003ACR621 J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, and K. Kim, *Acc. Chem. Res.*, 2003, **36**, 621.
- 2003AGE2293 K. Kim, W. S. Jeon, J.-K. Kang, J. W. Lee, S. Y. Jon, T. Kim, and K. Kim, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 2293.
- 2003CC2176 S. Choi, S. H. Park, A. Y. Ziganshina, Y. H. Ko, J. W. Lee, and K. Kim, *J. Chem. Soc., Chem. Commun.*, 2003, 2176.
- 2003CC2226 M. C. Aragoni, M. Arca, F. D. Devillanova, F. Isaia, V. Lippolis, A. Mancini, L. Pala, A. M. Z. Slawin, and J. D. Woollins, *J. Chem. Soc. Chem. Commun.*, 2003, 2226.
- 2003CC2774 C. S. Clarke, D. A. Haynes, J. M. Rawson, and A. D. Bond, *J. Chem. Soc., Chem. Commun.*, 2003, 2774.
- 2003HAC262 G. Arroyo, R. Osnaya, T. Cruz, A. Londoño, C. Álvarez, F. Delgado, R. Santiago, and R. Miranda, *Heteroatom Chem.*, 2003, **14**, 262.
- 2003JA10186 S. Y. Jon, N. Selvapalam, D. H. Oh, J.-K. Kang, S.-Y. Kim, Y. I. Jeon, J. W. Lee, and K. Kim, *J. Am. Chem. Soc.*, 2003, **125**, 10186.
- 2003JHC195 W. Qing-Min, C. Jun-Ran, and H. Run-Qiu, *J. Heterocycl. Chem.*, 2003, **40**, 195.
- 2003JOC1555 A. Ishii, R. Yamashita, M. Saito, and J. Nakayama, *J. Org. Chem.*, 2003, **68**, 1555.
- 2003JOC9040 J. A. W. Elemans, R. R. J. Slagen, A. E. Rowan, and R. J. M. Nolte, *J. Org. Chem.*, 2003, **68**, 9040.
- 2003OL1939 L. S. Konstantinova, O. A. Rakitin, C. W. Rees, L. I. Souvorova, D. G. Golovanov, and K. A. Lyssenko, *Org. Lett.*, 2003, **5**, 1939.
- 2003OL3745 J. Lagona, J. C. Fetting, and L. Isaacs, *Org. Lett.*, 2003, **5**, 3745.
- 2003T1961 C. A. Burnett, J. Lagona, A. Wu, J. A. Shaw, D. Coady, J. C. Fetting, A. I. Day, and L. Isaacs, *Tetrahedron*, 2003, **59**, 1961.
- 2003TL6789 S. T. A. Shah, K. M. Khan, M. Fecker, and W. Voelter, *Tetrahedron Lett.*, 2003, **44**, 6789.
- 2003TL9313 G. Mehta, V. Gagliardini, C. Schaefer, and R. Gleiter, *Tetrahedron Lett.*, 2003, **44**, 9313.
- 2004EJI63 M. N. Sokolov, O. A. Gerasko, D. N. Dybtsev, E. V. Chubarova, A. V. Virovets, C. Vicent, R. Llusar, D. Fenske, and V. P. Fedin, *Eur. J. Inorg. Chem.*, 2004, 63.
- 2004JA9085 J. Nakayama, S. Aoki, J. Takayama, A. Sakamoto, Y. Sugihara, and A. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 9085.
- 2004JA10035 A. Wu, P. Mukhopadhyay, A. Chakraborty, J. C. Fetting, and L. Isaacs, *J. Am. Chem. Soc.*, 2004, **126**, 10035.
- 2004JOC5483 E. M. Brzostowska, and A. Greer, *J. Org. Chem.*, 2004, **69**, 5483.
- 2004OL1225 S. Sasmal, M. K. Sinha, and E. Keinan, *Org. Lett.*, 2004, **6**, 1225.
- 2004PS981 A. D. Bond, C. S. Clarke, D. A. Haynes, S. I. Pascu, and J. M. Rawson, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 981.
- 2004TL9181 A. Z. Rys, Y. Hou, I. A. Abu-Yousef, and D. N. Harpp, *Tetrahedron Lett.*, 2004, **45**, 9181.
- 2005JOC8755 R. M. Silva, M. D. Smith, and J. B. Gardiner, *J. Org. Chem.*, 2005, **70**, 8755.
- B-2005MI186 I. Shcherbakova, and A. F. Pozharskii, in 'Comprehensive Organic Functional Group Transformations II', A. R. Katritzky, R. J. K. Taylor, Eds.; Elsevier, Oxford, 2005, Vol. 2, p. 186.
- 2005MI11 S. Zeman, Y. Shu, Z. Friedl, and J. Vágenknecht, *J. Hazardous Materials*, 2005, **A121**, 11.
- 2005TL2399 D. Sawada, H. Takahashi, M. Shiro, and S. Ikegami, *Tetrahedron Lett.*, 2005, **46**, 2399.
- 2007JOC3776 P. Sobik, J. Grunenberg, K. Böröczky, H. Laatsch, I. Wagner-Döbler, and S. Schulz, *J. Org. Chem.*, 2007, **72**, 3776.

Biographical Sketch



Irina Shcherbakova was born in Rostov on Don, Russia, graduated from Rostov on Don University with an M.Sc. in chemistry of natural compounds and joined the Research Institute of Physical and Organic Chemistry (RIPOC) at Rostov University as a junior research scientist. She conducted research on heterocyclic cations in the laboratory of Professor G. N. Dorofeenko and obtained her Ph.D. in organic chemistry in 1980. She spent 1985 in the laboratory of Professor A. T. Balaban (Bucharest, Romania) and 1990–92 in the laboratory of Professor A. R. Katritzky (University of Florida, USA) as a research fellow, while keeping her position as senior research scientist at RIPOC. She moved permanently to the USA and in 1997 took a position as senior scientist at NPS Pharmaceuticals, Inc. (Salt Lake City, UT), where she led medicinal chemistry and preclinical development on therapeutic agents targeting calcium receptors. Currently, she is chief scientific officer at MediProPharma, Inc., a startup biopharmaceutical company. Her scientific interests include all aspects of heterocyclic chemistry, in particular, functionally substituted biologically active heterocycles and their application in drug discovery.

14.10

Nine-membered Rings

D. O. Tymoshenko

Albany Molecular Research, Inc., Albany, NY, USA

© 2008 Elsevier Ltd. All rights reserved.

14.10.1	Introduction	548
14.10.1.1	Scope of the Chapter	548
14.10.1.2	Structural Types	549
14.10.2	Theoretical Methods	549
14.10.2.1	<i>Ab Initio</i> and Semi-Empirical Methods	549
14.10.2.2	Molecular Mechanics	551
14.10.3	Experimental Structural Methods	552
14.10.3.1	X-Ray Crystallography	552
14.10.3.2	NMR Spectroscopy	556
14.10.3.3	Mass Spectrometry	558
14.10.3.4	UV Spectroscopy	559
14.10.3.5	IR and Raman Spectroscopy	560
14.10.3.6	Other Spectroscopic Methods	560
14.10.4	Thermodynamic Aspects	560
14.10.4.1	Intermolecular Forces	560
14.10.4.2	Protonation, Basicity, and Complexation	560
14.10.4.3	Conformational Studies	561
14.10.4.4	Kinetics	562
14.10.5	Reactivity of Nonconjugated Rings	562
14.10.5.1	Intramolecular Thermal and Photochemical Reactions	562
14.10.5.2	Electrophilic Attack on Ring Heteroatoms	563
14.10.5.2.1	Electrophilic attack on ring nitrogen	563
14.10.5.2.2	Electrophilic attack on ring sulfur	566
14.10.5.3	Electrophilic Attack on Ring Carbon	567
14.10.5.4	Reactions with Nucleophiles	567
14.10.5.5	Oxidation and Reduction	568
14.10.5.5.1	Reactions at surfaces	568
14.10.5.5.2	Chemical reduction	569
14.10.5.5.3	Oxidations and oxidation/reduction sequences	569
14.10.5.6	Intramolecular Ring-Transformation Reactions	570
14.10.5.6.1	Ring contractions	571
14.10.5.6.2	Formation of bridged systems and ring expansions	571
14.10.5.6.3	Transannular transformations	573
14.10.5.7	Reactivity of Transition Metal Complexes	574
14.10.6	Reactivity of Substituents Attached to Ring Carbon Atoms	575
14.10.6.1	Alkyl Groups and Further Carbon Functional Groups	575
14.10.6.2	Amino and Imino Groups	577
14.10.6.3	Hydroxy and Oxo Groups	578
14.10.6.4	Other O-Linked Groups	580

14.10.6.5	Halogen Atoms	581
14.10.7	Reactivity of Substituents Attached to Ring Heteroatoms	581
14.10.7.1	Alkyl Groups	581
14.10.7.2	Further Carbon Functional Groups	581
14.10.7.3	Amino Groups and Other N-linked Substituents	582
14.10.7.4	Hydroxy and Oxo Groups	583
14.10.7.5	S-Linked Substituents	583
14.10.7.6	Halogen Atoms	585
14.10.8	Ring Syntheses from Acyclic Compounds	585
14.10.8.1	Bond Formation by Intramolecular Cyclization	585
14.10.8.1.1	C–C Bond formation	585
14.10.8.1.2	C–N bond formation	586
14.10.8.1.3	C–O bond formation	588
14.10.8.1.4	C–S bond formation	588
14.10.8.1.5	S–S bond formation	588
14.10.8.2	Ring Formation by [8+1] Cyclization	588
14.10.8.3	Ring Formation by [7+2] Cyclization	589
14.10.8.4	Ring Formation by [6+3] Cyclization	590
14.10.8.5	Ring Formation by [5+4] Cyclization	590
14.10.8.6	RCM Syntheses	591
14.10.8.7	Miscellaneous Methods	594
14.10.9	Ring Syntheses by Transformation of Another Ring	595
14.10.9.1	Ring Expansion by Ionic Ring Openings	595
14.10.9.2	Reductive Ring Openings	597
14.10.9.3	Oxidative Ring Openings	597
14.10.9.4	Beckmann and Related Rearrangements	599
14.10.9.5	Sigmatropic Rearrangements	599
14.10.9.6	Miscellaneous Ring-Expansion Methods	601
14.10.9.7	Ring Contractions	601
14.10.10	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	602
14.10.11	Important Compounds and Applications	602
14.10.12	Further Developments	603
References		604

14.10.1 Introduction

14.10.1.1 Scope of the Chapter

Nine-membered rings were reviewed in CHEC(1984), where they were treated in the single chapter with other heterocycles with ring systems larger than eight membered. CHEC-II(1996) covered the developments of this class of heterocycles up to 1994, and included data on nitrogen, sulfur, and/or oxygen heterocycles, as well as particular examples of fused and bridged ring systems. Synthesis of nine-membered hetarenes and heteroannulenes was a part of a review published recently <2004SOS(17)979> (Chapters 14.01–14.09).

Numerous reviews cover the synthesis, structures, reactivity, and applications of nine-membered heterocycles as a part of the general medium-size ring discussion <2005PHC(17)418, 2004PHC(16)451, 2003PHC(15)431, 2002PHC(14)356, 2001PHC(13)378, 2000PHC(12)352, 1999PHC(11)338, 1998PHC(10)335, 1996PHC(8)320>. Metal-mediated synthesis of medium-sized rings <2000CRV2963>, synthesis of oxygen- and nitrogen-containing

heterocycles by ring-closing metathesis (RCM) <2004CRV2199>, and synthesis of sulfur and phosphorus heterocycles via ring-closing olefin metathesis <2004CRV2239> were reviewed. Synthetic aspects of various nine-membered heterocyclic systems were surveyed as related to total synthesis of natural products <2004CRV3371, 2005CRV4314, 2005CRV4379, 2006CRV911> (see other chapters in Volume 12). Conformational studies of saturated nine-membered rings and nine-membered rings containing one torsional constraint were the subject of the review <1999MI(5)89>.

Syntheses and macrocyclic complexes of 1,4,7-triazacyclononane and related crown-type systems were reviewed <B-2005MI67, 2001ARA331, 2002ARA321>.

14.10.1.2 Structural Types

A large number of nine-membered heterocyclic systems are known. Only those rings with nitrogen, oxygen, and/or sulfur heteroatoms, and their fused derivatives are covered in this chapter. Ring systems with phosphorus, boron, and other heteroatoms, as well as bridged systems, are discussed in the corresponding chapters of this volume. Structural types and nomenclature of nine-membered heterocycles were outlined in CHEC-II(1996). Particular types of rings and their fused derivatives are reviewed in this chapter in the order of nitrogen-, oxygen-, and sulfur-containing heterocycles, beginning with rings containing one heteroatom, that is, azonines, oxonines, and thionines. Systems with two heteroatoms are discussed in the order diazonines, dioxonines, and dithionines, followed by oxazonines, thiazonines, and oxathionines.

The number of possible nine-membered rings with three or more heteroatoms is enormous, and the reviewed structures are listed in Table 1 and surveyed in the heteroatom order of mono- and diheteronines.

Table 1 Structural types of heteronines and their nomenclature

Name	Total number of heteroatoms	Number of heteroatoms		
		N	O	S
Triazonine	3	3	0	0
Trioxonine	3	0	3	0
Trithionine	3	0	0	3
Oxadiazonine	3	2	1	0
Dioxazonine	3	1	2	0
Thiadiazonine	3	2	0	1
Dithiazonine	3	1	0	2
Oxadithionine	3	0	1	2
Oxathiazonine	3	1	1	1
Tetraoxonane	4	0	4	0
Dioxadiazonine	4	2	2	0
Hexaoxonane	6	0	6	0
Octathionane	8	0	0	8

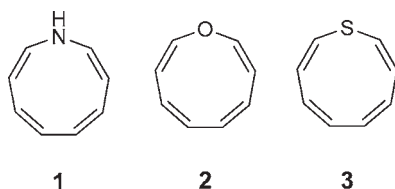
14.10.2 Theoretical Methods

Ab initio, semi-empirical, and molecular mechanics calculations have been used extensively in the study of nine-membered heterocycles. Theoretical studies of heteronines have centered on the question of their aromaticity, which was surveyed as a part of general heterocycles aromaticity study <2004CRV2777>. Another important aspect is the conformation of the nonconjugated compounds (see Section 14.10.4.3). Computational aspects of conformational behavior of saturated nine-membered rings and nine-membered rings containing one torsional constraint were the part of the review <1999MI(5)89>.

14.10.2.1 *Ab Initio* and Semi-Empirical Methods

Full geometry optimization for 1*H*-azonine **1**, oxonine **2**, and thionine **3** was carried out at the B3LYP/6-311G(2d,p) level without symmetry constraints using the Gaussian 94 code <2001T8759>. Azonine has planar aromatic structure, while electronegativity of the oxygen atom in oxonine leads to localized electron pairs and distorted

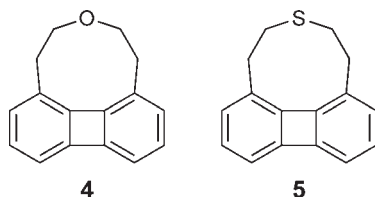
nonplanar polyenic structure. Thionine, in spite of having the same number of valence electrons as oxonine, is partially aromatic, as sulfur atom is less electronegative than oxygen, and sulfur π -electrons are more delocalized.



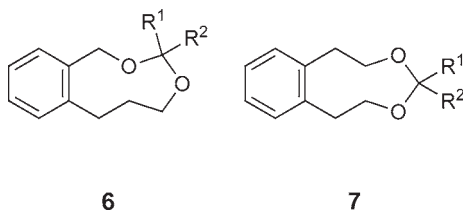
The aromaticity of heteronines was quantified with the help of nucleus-independent chemical shifts (NICSs) criteria [<2005PCA11870>](#). NICS(0) values, which are defined as the amount of absolute magnetic shielding calculated at the ring center, for azonine, thionine, and oxonine were -13.6 , -0.5 , and 4.2 ppm, respectively, thus confirming fully aromatic structure of **1** and antiaromatic character of **2**. A set of N-substituted azonines with Me, Et, CHO, COMe, COOMe, COOEt, CN, CONMe₂, and SO₂Ph substituents was studied. With the exception of *N*-Et and *N*-Me, the lone pair on nitrogen atom in these structures is not completely available for the cyclic delocalization. As a result, the optimized molecular structures show that planarity is lost in all the molecules and the NICS(0) value for all these species indicated that they are all nonaromatic.

The *ab initio* study showed that the interaction of azonine with surrounding H₂O molecules, with alkali ions in *N*-azonides and substitution of the azonine *N*-H hydrogen, distorts the planarity of the ring [<2004PCA4059>](#). This distortion is such that the aromaticity remains, and the global minimum structures of the alkali salts have the metal residing on top of the distorted ring (cation- π -interaction). These findings explain the experimental ¹H nuclear magnetic resonance (NMR) spectra, ultraviolet-visible (UV-Vis) spectra, and thermal stability results.

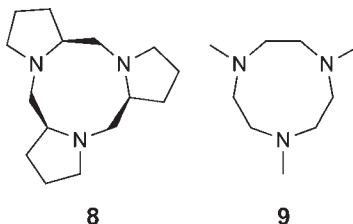
The conformational properties of bridged biphenylenes, 1,2,4,5-tetrahydrobiphenyleno[1,8-*def*]oxonine **4** and 1-thionine **5**, were studied using *ab initio* molecular orbital and density functional theory (DFT) methods. Studies on the Hartree-Fock (HF)/6-31G* level of theory revealed that for **5**, a plane symmetrical boat conformation was of the lowest energy. The twist, twist-boat, and chair conformations are less stable by 2.41, 5.02, and 2.62 kcal mol⁻¹, respectively. Contrary, the twist conformation was found to be the most stable form for **4** [<2003JMT\(637\)115>](#).



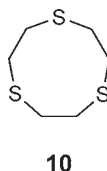
Conformations of the 2,4- and 3,5-benzodioxonine derivatives **6** and **7** (R¹, R² = H or/and alkyl) were examined using DFT calculations [<2006JOC5498>](#). The most stable conformations were TBC and TCB type 1 for the 2,4- and 3,5-benzodioxonine derivatives, respectively. In both of these conformations, the acetal moiety adopts the *g* $\pm$ *g* $\pm$ geometry. The natural bond orbital analysis yielded values of the stabilization energy associated with the stereoelectronic $n_O \rightarrow \sigma_{C-O^*}$ interactions that were highest for conformations other than the global minima. Conformers displaying the strongest interactions followed different patterns of atom arrangement within the acetal moiety, namely *g* + *g*−, and those in which one or both of the torsion angles within the C–O–C–O–C segment were close to 90°. Steric repulsion caused by alkyl substituents at the anomeric carbon was found to influence the strength of the $n_O \rightarrow \sigma_{C-O^*}$ stabilization through modification of bond lengths and torsion angles. The adopted ground-state conformations result from accommodation of steric repulsions and stabilizing stereoelectronic interactions.



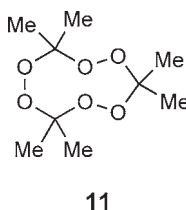
Quantum-chemical *ab initio* calculations have been conducted to determine the proton affinities of tripyrrolidinyl- and 1,4,7-trimethyl-1,4,7-triazacyclononane (**8** and **9**, respectively). Their proton affinities have been found to be up to 20 kcal mol⁻¹ higher than the values of noncyclic tertiary aliphatic amines due to an effective stabilization of the ammonium cations <2005T12371>.



Complete energy calculations using the AM1 method have been performed for three possible conformers of 1,4,7-trithionane **10** <1995JST(355)169>. The calculations indicated that the most stable conformer is that with *D*₃ symmetry, total energy of which is 24.2 kJ mol⁻¹ lower than that of *C*₃-symmetry crystalline structure and 5.2 kJ mol⁻¹ lower than the *C*₂-symmetry conformer predicted by molecular mechanics calculations. Calculated forms of the normal modes of vibration of the molecule allowed a complete assignment of the observed bands in the Raman and infrared (IR) spectra (see Section 14.10.3.5).



The calculations of geometry, binding energies, and vibrational frequencies of triacetone triperoxide **11** were conducted using the DFT-based method as implemented in the Gaussian 98 code package with an appropriate basis set. The geometry of **11** in the ground state obtained was compared to the X-ray crystallographic data (Section 14.10.3.1). A good agreement between the calculated and experimental results was observed, suggesting that the intermolecular forces in the solid phase are too weak to cause any significant alteration of the molecular geometry <2005JA1146>.



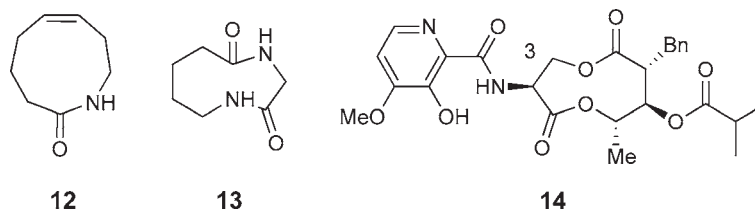
14.10.2.2 Molecular Mechanics

Conformational analysis of the *cis*-tetrahydroazoninone **12**, performed using MM2 method, revealed two pairs of major conformers with a comparable energy, which differs by position of NH group against double bond <2005OBC97>. The results obtained for this model structure were further used in the conformational analysis of azoninone amino acid derivatives (Section 14.10.4.3).

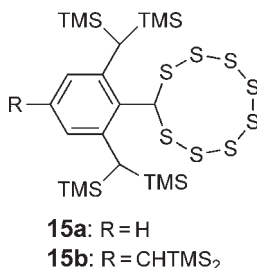
Steric energies for the three possible conformations of the two amide systems in macrocycle **13** were determined by MM+ method <2002J(P2)2078>. Depicted trans-trans-configuration with total force field energy 8.1–12.3 kcal mol⁻¹ is less stable when compared to trans-cis- and cis-cis-conformations (2.9–6.3 and 6.3 kcal mol⁻¹, respectively).

The conformations of substituted (3*S*,7*R*,8*R*,9*S*)-3-amino-7-benzyl-8-hydroxy-9-methyl-1,5-dioxonane-2,6-dione **14**, its (3*R*,7*R*,8*R*,9*S*)-isomer, and their common enol tautomer at the C-3 position were studied by molecular mechanics method. The enol form was supposed to be the initial transition state during the course of the

epimerization. The conformation of 3(*S*)-isomer is similar to that of the enol, which explains its tendency to rapid epimerization. 3(*R*)-Isomer with an axial array of the side chain at the C-3 position is an energetically unfavorable conformation, and it does not undergo epimerization even under harsh reaction conditions <1998T12745>.



Calculations of substituted octathionane **15a** using MMP2 force field were performed by replacement of one of sulfur atoms of cyclonanosulfur C₉ with 2,6-disubstituted phenyl substituent <1995BCJ2757>. Ground-state geometry of **15a** was almost identical with the crystal structure of **15b** and its differences with cycloninosulfur were explained by steric repulsion of bulky aryl group and the polysulfur linkage.

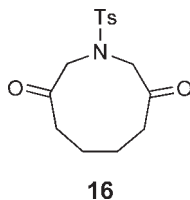


14.10.3 Experimental Structural Methods

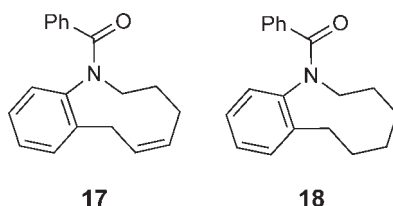
14.10.3.1 X-Ray Crystallography

Conformational families of saturated nine-membered rings and nine-membered rings containing one torsional constraint were illustrated by examples from Cambridge Crystallographic Data Base as the part of the review <1999MI(5)89>. In general, the structures of nine-membered heterocycles, as determined by X-ray crystallography, showed predictable bond lengths or angles when compared to acyclic analogues. Considerable deviations from the planarity are characteristic for systems with endocyclic trans C=C bonds, ester bonds, or amide bonds.

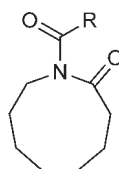
The structure of *N*-tosyl azonane-3,8-dione **16** was determined using X-ray crystallography <1995J(P1)1137>. The ring adopts conformation with *cis*-orientation of carbonyls.



Conformational features, transannular distances, and dynamic behavior of benzazonines **17** and **18** were studied using X-ray crystallography and variable-temperature NMR spectroscopy <2005JOC1552>. Both benzazonines **17** and **18** adopt boat-chair conformations in the solid state. Amide group distortion revealed ring strain of these medium-sized heterocyclic rings and led to a more stable structure. Thus, the unsaturated heterocycle **17** has an amide bond more distorted than that of **18**, displaying substantial *N*-pyramidization. This is accompanied by a lengthening of the amide bond (1.373(2) Å). Notably, there is a very close transannular distance in **17** between H-4 α and H-7 α of 2.07 Å, which could suggest the presence of a small repulsive interaction. When the endocyclic double bond is reduced, the transannular distance between H-4 α and H-7 α in **18** becomes greater (2.15 Å). The C–N bond length returns to a more expected value (1.354(2) Å), as the amide moiety becomes essentially planar.

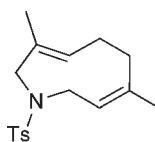


The most remarkable geometrical feature of *N*-acylcapyrolactams is that the amide linkage of *N*-Cbz lactam **19d** is trans, while *N*-acyl derivatives **19a–c** have a cis amide linkage in the lactam ring with a similar conformation <2002CC2656>. Compared with the geometry of unsubstituted caprylolactam, which is trans in the crystalline state due to intermolecular hydrogen bonding, *N*-acyl compounds **19a–d** have much larger twist angles, longer N–C(2) bonds, and smaller nitrogen atom pyramidization. These results clearly showed that the *N*-acyl and *N*-Cbz substituents are responsible for the ring conformation by reducing the double-bond character of the endocyclic amide linkage. It results in lengthening of the N–C(2) bond and twisting of the amide bond to diminish the ring strain originated from the planarity of the amide linkage. The conformational differences in *N*-acyl- or *N*-Cbz-substituted compounds are attributable to the differences in the electronic properties of the N-substituents. Due to electronic repulsion between the *N*-benzyloxycarbonyl group and the lactam carbonyl, trans-conformation is preferable for **19d**.



19a: R = Me
19b: R = *i*-Pr
19c: R = *t*-Bu
19d: R = OBn

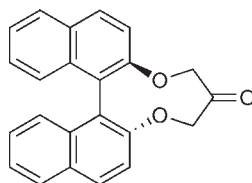
Structure of tosyl derivative **20** was determined by X-ray crystallography and revealed that the sum of the nitrogen's bond angles is 348.2°. This means that the nitrogen center of **20** is chiral and C(3)–C(4) and C(7)–C(8) olefinic moieties form chiral planes in the solid state <2006OL963>.



20

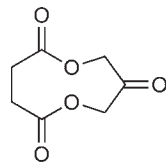
X-Ray crystallography was extensively used for experimental proof of absolute configuration of natural product-like nine-membered lactones <2000CC567> and ethers <2005T7456>.

The structure of dioxonine **21** was confirmed by single crystal X-ray structure analysis. Ketone **21** has a C_2 -symmetric structure with the keto group, which lies on C_2 -axis of the molecule and the dihedral angle of the two naphthalene rings is 71° <1997TA2921>. Later, another solid-state non- C_2 -symmetric conformation for **21** was reported by Yang *et al.* <1998JA5943>.

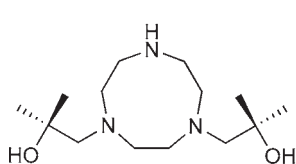
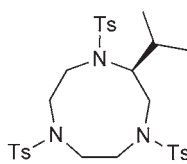
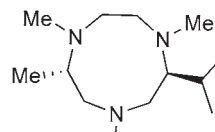
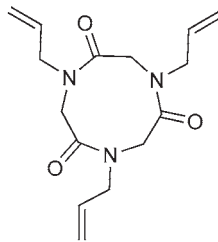


21

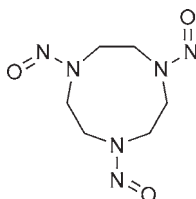
The X-ray structure of keto diester **22** has twofold symmetry with the keto group lying on the twofold axis and two ester groups with *s-trans*-geometry. The dihedral angle of the ester group (C–O–CO–C, 158°) deviated from its ideal 180° plane. The extent of ester bending, indicating ring strain in **22** and similar cyclic ketones, was attempted to correlate with the activity in catalyzing *in situ* epoxidation <1998JOC9888>.

**22**

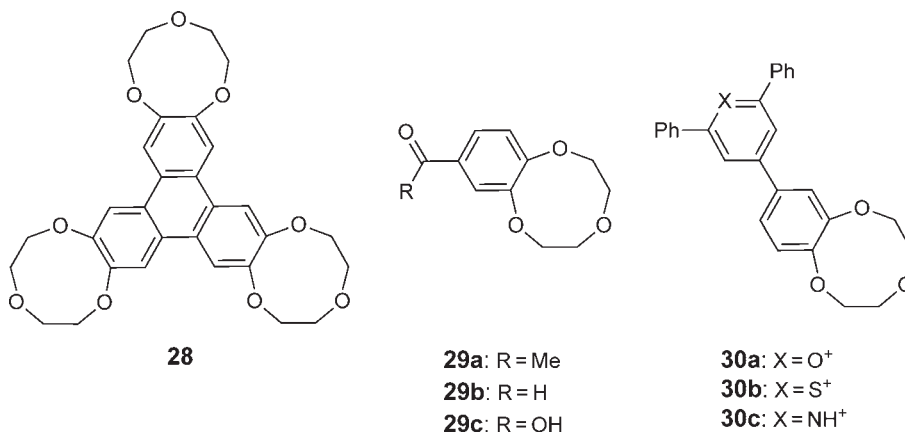
The single crystal X-ray structure of **23** confirmed that the macrocyclic ring adopts a [333] conformation <1994CC2467>. The solid-state structure of tritosyl derivative **24** <2003OBC2357> indicated that the isopropyl group adopts a pseudoequatorial position on the ring. The ring puckering is dominated by the three sp^2 N-centers. Two of them have the same directionality and hold their substituent tosyl groups on the face of the nine-membered ring opposite the isopropyl group. The third tosyl group, furthest from the isopropyl, is on the same face with it. All three N-centers showed considerable deviations from planarity (N-1, N-2, and N-3 lie -0.320 , 0.211 , and -0.104 Å, respectively, from the planes). The tosyl on the nitrogen adjacent to isopropyl is twisted so that the phenyl ring lies over one face of the nine-membered ring while the other tosyl groups point away from the main body of the molecule. The crystalline nature of hydrobromide salt of triazonine **25** allowed both the stereochemistry and absolute structure to be confirmed unequivocally by single crystal diffraction <2003OBC4408>. X-Ray analysis of cyclic tripeptide **26** confirmed its crown conformation <2004TL1091>.

**23****24****25****26**

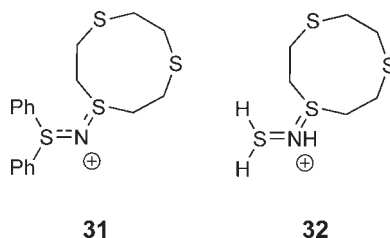
The ring conformation of trinitroso derivative **27** is very similar to that found in formyl and benzoyl 1,4,7-triazonanes <1996JCD31>. Among the three NO groups, one lies above and two below the average ring plane leading to minimal C–H bond eclipsing. All C–C–N–N–O moieties are essentially planar with maximum deviation of 0.090 Å. The N–N and N–O distances (1.318 and 1.239 Å, respectively) are all equal within experimental error and are typical for *N*-nitroso amines with partial π -electron delocalization over the N–NO fragments <2002TL771>.

**27**

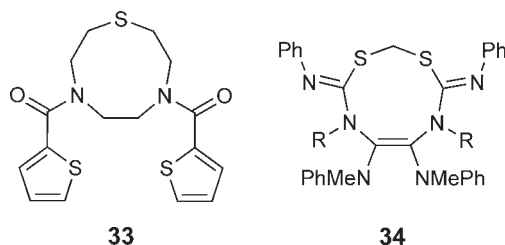
Tris-(9-crown-3)-triphenylene **28**, the product of trimerization of benzo-9-crown-3 ether, crystallized in the monoclinic $P2_1/c$ space group: $a = 13.759(2) \text{ \AA}$, $b = 13.318(2) \text{ \AA}$, $c = 13.399(2) \text{ \AA}$, $\beta = 96.883(2)^\circ$, with $Z = 4$. The three 9-crown-3 ether units of the trimer possess different geometries and there is substantial deviation from coplanarity in the three aromatic rings <2001CJC195>. The X-ray crystal structures for the 4-acetyl-, formyl-, and carboxy-benzo-9-crown-3 ethers **29a–c** showed remarkably similar geometries with gauche O–C–O networks normal for crown ethers <2001JST(561)43>. 9-Crown-3 ethers **30a–c** containing pyrilium, thiopyrilium, and pyridinium subunits were reported. The solid-phase structures of **30a** and **30c** showed small deviation from planarity for the four aromatic rings, whereas two phenyl rings in **30b** are out of heteroaromatic ring <2002JOC2065>.



The X-ray crystal structure of diphenyl *N*-sulfoniosulfimidium **31**, crystallized as tetraphenylborate salt, exhibited an S–N–S angle of 108.55° and S–N distances of $1.6433 \text{ \AA}$ and N–S (crown) $1.6559 \text{ \AA}$ <2004NJC959>. Interestingly, the latter distance is almost identical to the S–N distance in the unsubstituted cation **32** <2002CJC1410>.



The torsion angles C(ring)–N–C(carbonyl)–C(α -thiophene) of 7.2° and 9.8° for disubstituted 1,4,7-thiadiazonane **33** indicated that the amide units are almost planar due to the partial double-bond character of amide C–N. The (CO)–N and C=O bond lengths of $1.348/1.344 \text{ \AA}$ and $1.236/1.236 \text{ \AA}$, respectively, are typical for tertiary amides. Two rotational isomers were observed in the solid state: the major conformation (83%) is related to the minor (17%) by a rotation of 180° about the C(carbonyl)–C(α -thiophene) <1996AXC3062>. X-Ray analysis for dithiadiazonine **34** (R = 4-MeC₆H₄) was reported <1998EJO1803>.



Solid-state structure of hexaoxonane **11** can be studied by X-ray crystallography only at low temperatures, as crystals are unstable at room temperature under X-ray irradiation. The crystals of **11** are monoclinic with cell parameters a $13.788(6) \text{ \AA}$, b $10.664(5) \text{ \AA}$, c $7.894(4) \text{ \AA}$, β $91.77(5)^\circ$, V $1160.1(9) \text{ \AA}^3$, with four molecules in the unit cell and space group $P2_1/c$. The molecules have approximately D_3 symmetry with the nine-membered ring adopting a

twisted boat-chair conformation. The crystal packing consisted of stacks around the molecular threefold axis with no apparent C–H···O interactions <2005JA1146>.

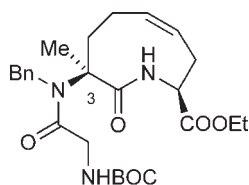
The octathionane ring of **15b** was of C_1 symmetry in contrast to cyclonanosulfur C_9 , which was concluded to be of C_1 or C_2 symmetry from Raman spectral data and C_2 symmetry in the ground state from theoretical calculations <1995BCJ2757>. The crystal structure of 3,3,6,6,9,9-hexamethyl-[1,2,4,5]-tetraoxonane has been reported <1995RCB105>.

14.10.3.2 NMR Spectroscopy

NMR spectroscopy has been used extensively for structure elucidation of nine-membered rings and their conformations. The latter is discussed further in Section 14.10.4.3.

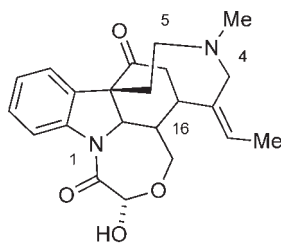
Nuclear Overhauser effect (NOE) experiments clarified the preference of the cis–trans-geometry in solution for cyclic lactams **19**. For **19a–c**, X-ray geometries (Section 14.10.3.1) retain in solution, and NOEs were observed between the methylene protons next to the ring carbonyl and the NCH_2 protons, whereas no such NOE was observed in **19d** <2002CC2656>.

The double-bond configuration in azoninone **35** was demonstrated to be (*Z*) by the $CH=CH$ vicinal coupling constants of 9–10 Hz <2005OBC97>. Only one set of signals was detected by NMR at room temperature, meaning that only one of the two possible rotamers around the ring amide bond is present. This rotamer in the case of (*S*)-**35** is the anti one, as demonstrated by the presence of a strong NOE between the NH and the ortho-hydrogens of the benzyl group. A very strong NOE between the NH and the CH_3 bonded at C-3 in was observed for (*R*)-counterpart of **35**, which also exists as anti-rotamer.



35

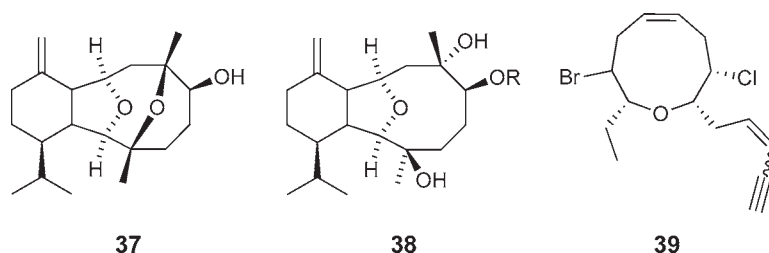
Structure of *Strychnos* alkaloid holstiine **36**, which contains a nine-membered azonine ring, was studied using long-range ^1H – ^{15}N heteronuclear shift correlation technique <2000JNP543>. The structural changes in holstiine relative to its congeners strychnine and brucine are not so large that the nitrogen chemical shifts would be substantially affected. Indeed, the N-1 and N-4 of holstiine resonate at 146.5 and 39.5 ppm, respectively, which compares very favorably with both strychnine and brucine. The sole coupling observed to N-1 in the long-range ^1H – ^{15}N spectrum of **36** is the coupling from H-16 α . The smaller number of long-range couplings to N-4 can likely be attributed to the greater flexibility of the aliphatic segment of the molecule in which N-4 is contained. Proton H-5 β strongly couples to N-4 when the C-5/H-5 β bond vector is oriented synclinally to the N-4 lone pair.



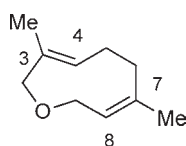
36

The structural connectivity derived from examination of the ^1H , ^{13}C /DEPT, DQF-COSY, HMQC, and HMBC data (DEPT = distortionless enhancement by polarization transfer; DQF = double quantum filtering; COSY = correlation spectroscopy; HMQC = heteronuclear multiple quantum correlation; HMBC = heteronuclear multiple bond correlation) resulted in global reevaluation of sclerophytin B structure and demonstrated that this compound and the related alcohol are not composed of two ether bridges as in the originally formulated structure **37**, but share the structural features depicted as **38** <2000OL1879>. Comparison of ^{13}C and ^1H NMR data of Norte's

obtusenyne isolated from *Laurencia pinnatifida* with that of two stereoselectively synthesized analogues confirmed their (12*R*,13*R*)-(–)-structure **39** <1999CL461>.

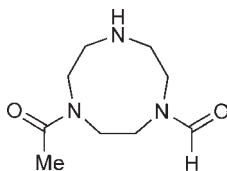


An NOE experiment of cyclic ether **40** with irradiation at the methyl group on C-3 showed 3% enhancement in the signal of the vinyl proton at C-8. This result along with the molecular modeling suggests that the C(3)–C(4) and C(7)–C(8) olefinic moieties of **40** form stereogenic planes in the most stable conformation, and proves its planar chiral nature <2005JA12182>.



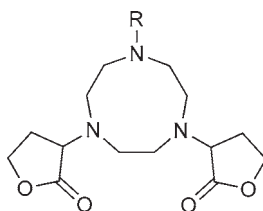
40

^{13}C and ^1H NMR spectra of disubstituted triazonane **41** revealed a mixture of isomeric forms <1999J(P1)1211>. The ^{13}C NMR spectrum in CDCl_3 showed 21 aliphatic resonances (3 methyl and 18 ring), three formyl $\text{C}=\text{O}$ resonances, and three acetamide $\text{C}=\text{O}$ resonances as the major spectral components. Similarly, the ^1H NMR spectrum showed three major methyl singlets and three major formyl singlets. An additional fourth methyl and fourth formyl singlet were also observable, but they are considerably lower in intensity, suggesting a fourth less stable isomer. This number of observed resonances is consistent with **41** existing in three major and one minor isomeric forms which interconvert slowly on the NMR timescale due to restricted rotation about the C–N amide bonds.



41

Structural properties of two macrocyclic derivatives **42** ($\text{R} = \text{H}$, Ts) have been studied by molecular mechanics and ^1H NMR spectroscopy, and new sets of Karplus parameters for calculation of the vicinal coupling constants of the butyrolactone moieties have been determined <2002EJO351>.

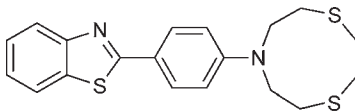


42

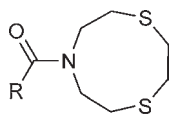
Solid-phase ^{13}C NMR chemical shift differences of ca. 8.5 ppm were observed between the two aryl–O–C carbons of benzo-9-crown-3 derivatives **29a–c**. This was explained using results of *ab initio* calculations performed on anisole,

which demonstrated dependence of the total shielding of the methyl group as a function of Ph–O–Me torsion angle <2001JST(561)43>. The recognition of Li^+ by the chiral diaza-9-crown-3 derivatives was investigated by ^1H NMR in CD_3CN <2004T5799>. The resonances for the crown ether moiety and α -methyl protons adjacent to the ring were shifted upfield and broadened upon Li^+ recognition.

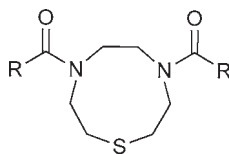
Complexation of Ag^+ ion with benzothiazole dithiazonine derivative **43** was examined by ^1H NMR titration <1999J(P2)1273>. The downfield shifts in the proton signals of the methylenes adjacent to the sulfur atoms were caused by the strong interaction of Ag^+ ion with the sulfur atoms of the polythiazaalkane moiety. On the other hand, the decrease in π -electron density of the aromatic group caused by the interaction between the nitrogen atom and the complexed Ag^+ ion results in a downfield shift in the chemical shifts of the aromatic signals.

**43**

In ^1H NMR spectra of acyl dithiazonines **44**, each of the methylene groups of the ring gives rise to a fairly broad multiplet due to the low symmetry of the molecule imposed by the amide group <2001JMC1011>. Analysis of the COSY ^1H NMR spectrum allowed the assignment of each methylene group to individual multiplets. The macrocyclic methylene group closest in space to the amide carbonyl is shifted toward higher frequency and appears at 3.98 ppm. This resonance couples to the adjacent macrocyclic methylene group, which appeared at 3.18 ppm. A second pair of NCH_2CH_2 protons can be assigned to the signals at 3.71 and 3.43 ppm, while resonances at 3.06 and 2.95 ppm are due to the protons of the methylene groups situated between sulfur atoms. The ^{13}C NMR spectrum of **44** revealed six signals corresponding to the methylene carbon atoms of the macrocyclic ring.

**44**

^1H NMR spectrum of diacyl thiadiazonine **45** showed three resonances at 3.93, 3.80, and 2.88 ppm corresponding to the protons of three distinct sets of macrocyclic methylene groups with an integration ratio of 4:4:4. The ^{13}C NMR spectrum of **45** showed the expected three signals for macrocyclic ring <2001JMC1011>.

**45**

^1H NMR spectra of 1,3,5,7-tetraoxonane <1998CC1809> demonstrated the 1:2:2 ratio of H_a (proton of formal linkage, δ 5.05 ppm) to H_b (proton of formal linkage, δ 4.93 ppm) and H_c (proton of ether linkage, δ 3.85 ppm). The ^{13}C NMR pattern of this compound showed three different types of carbon: C_a (formal carbon, δ 96.9 ppm), C_b (formal carbon, δ 97.1 ppm), and C_c (ether carbon, δ 70.5 ppm).

14.10.3.3 Mass Spectrometry

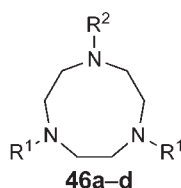
Mass spectrometric techniques are very important in gaining structural information on heterocyclic medium-sized rings. Most of the systems described in this chapter have been subjected to mass spectral analysis and the reader is referred to the individual references for this information. Selected data on published mass spectra of different classes of heteronines and ionization methods are summarized in Table 2.

Table 2 Mass spectrometry of heteronines

Name	Ionization method	References
Azonines	CI EI FAB	1996J(P1)123, 1997J(P1)447, 2002EJM379, 2001J(P1)2161 1996CEJ894, 1997JOC2544, 2003M1241, 2005JOC1552 1997J(P1)447
Oxonines	EI	1999T7471, 2004JA12432
Oxazonines	N/A	2003SL1043
Thiazonines	N/A	1995JOC2597
Oxathionines	N/A	2004S1696
Triazonine	EI FAB	1996JA11555, 2002TL771 2001EJO4233, 2004OBC2664
Tetraoxonane	EI	1998CC1809
Hexaoxonane	CI	2002AN1627

14.10.3.4 UV Spectroscopy

The nonaromatic nine-membered rings absorb little in accessible regions of the UV spectrum. **Figure 1** represents structures and data on reported spectra of trisubstituted 1,4,7-triazonanes whose absorptions are due to fused aromatic rings, aromatic substituents, or carbonyl groups. UV absorption data in dioxane–water for hydrazone derivative of 1,4,7-dithiazonane were published <1995BCJ3071>.



			$\lambda_{\max}$, nm (log ϵ)	Reference
46a	$R^1 = R^2 =$		217 (4.35) 239 (4.62) 285 (4.75) in CH_2Cl_2	1998S1339
46b	$R^1 = R^2 =$		220 (4.94) 260 (4.73) in MeOH	1998S1339
46c	$R^1 = R^2 =$		288 303 in H_2O	1996HCA789
46d	$R^1 = \text{CH}_2\text{CH}_2\text{COOH}; R^2 =$		240 (3.88) 292 (3.53) in acetonitrile	1996JCD4409

Figure 1

14.10.3.5 IR and Raman Spectroscopy

In general, the IR absorption frequencies for nine-membered heterocycles are ill defined, and detailed listings of the vibrational frequencies were reported only for few cyclic systems.

Fleming *et al.* reported a Fourier transform infrared (FTIR) study of 1,4,7-triaza- and 1,4,7-trithia-cyclononanes and their copper(II) complexes in the 120–4000 cm^{-1} region <1999SAA1827>. Raman and IR spectra of 1,4,7-trithia-cyclononane **10** in both the pure solid and liquid form, and its IR spectra in CCl_4 , have been studied. The IR spectrum of liquid **10** is very similar to that of the solution, but both the Raman and IR spectra of the liquid differ from the solid-state spectra. Changes in the spectra on heating through the melting point of the solid near 350 K are attributed to a change from the molecular conformation of symmetry C_3 in the solid state to D_3 structure in the liquid phase or in solution <1995JST(355)169, 1996JST(378)165>. As the temperature is lowered from room temperature to 10 K, splitting of many bands in the Raman and IR spectra of **10** is observed. This indicates that a further lowering of symmetry occurs at low temperatures. It is suggested that a structural phase change occurs in the crystalline solid near 225 K <1996JST(378)165>.

1,4,7-Triazonane N-trisubstituted with *d*₇-benzyl chloride was characterized <1996JA11555> using IR spectroscopy (KBr, 2277 cm^{-1} (C–D), 2165 cm^{-1} (C–D), and 2045 cm^{-1} (C–D)).

14.10.3.6 Other Spectroscopic Methods

Two chiral diaza-9-crown-3 derivatives with naphthalene moieties attached to macrocycle with $\text{CH}(\text{Me})\text{NHCOCH}_2$ linker were designed as luminescent chemosensors for lithium. The fluorescence emission from the naphthalene moieties was ‘switched on’ upon Li^+ recognition by the crown ether moiety in organic solvents, showing excellent selectivity over other group I and II cations. Even though the recognition of Li^+ was not achieved in water (pH 7.4) or aqueous alcohol solution, the fluorescence (which was switched on at pH 7.4) was substantially modulated by spherical anions, where the fluorescence emission was quenched in the presence of Br^- and I^- , but less by Cl^- and not by acetate <2004T5799>.

In the photoelectron spectrum of 1,4,7-trithia-cyclononane **10**, the ionizations in the region from 8 to 10 eV arise from ejection of an electron from sulfur 3p lone-pair orbitals, while those from about 10 to 12 eV corresponds to removal of an electron from S–C σ -bonding orbitals. Ionizations observed at lower energies correspond to removal of electrons from the C–C σ - and C–H σ -bonding orbitals <1997PCA9180>.

14.10.4 Thermodynamic Aspects

14.10.4.1 Intermolecular Forces

Heteronines are solids with variable melting points. Their saturated counterparts, heteronananes, are as a rule relatively low-melting solids. For example, unsubstituted 1,5-dithionane, 1,4,7-trithionane, and dithiazonane melt at 57, 81, and 71 °C, respectively, indicating the absence of significant intermolecular interactions <1996JST(378)165, 2003PS1295>. 1,4,7-Heteronananes with C- or N-phenyl substitution do not have considerably increased melting points <1995JOC3980, 1995BCJ2831>. N-Substitution with thiazole and benzoxazole increased intermolecular interactions and melting points <1995H(41)237>. Heterocycles bearing groups capable of H-bonding are high melting <2002S1398, 2005JOC3838>.

14.10.4.2 Protonation, Basicity, and Complexation

Thermodynamic properties of polyazacycloalkanes, including octahydro heteronines, have been carefully studied in regard of their protonation and complexation (usually with transition metals) reactions. This topic rapidly advances, for example, in areas of ternary complexes <2003JA3889> and relationships between changing of macrocycle basicity and increasing ligand denticity <2003AJC61>. It was extensively reviewed <B-2005MI67, 2001ARA331, 2002ARA321> and, hence, only a few points are discussed here.

[⁶Li,¹⁵N]-Lithium hexamethyldisilazide ([⁶Li,¹⁵N]-LiHMDS) coordination by 1,4,7-trimethyl azononane **9**, along with other polyamines and polyethers, was studied by ⁶Li, ¹⁵N, and ¹³C NMR spectroscopy <1996JA10707>. Samples of [⁶Li,¹⁵N]-LiHMDS with 1–10 equiv of **9** display exclusively ⁶Li doublets and ¹⁵N triplets characteristic of solvated monomers. The low-temperature ¹³C NMR spectra recorded for the monomer complex of [⁶Li,¹⁵N]-LiHMDS

and **9** showed numerous broad ^{13}C resonances. It was suggested that this behavior of macrocycle-bound LiHMDS is the result of the restricted rotation about Li–N bond.

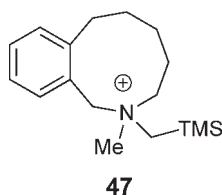
Coordination of $[\text{}^6\text{Li}]\text{-}\alpha\text{-(phenylthio)benzyl}^\text{+}\text{Li}$ with **9** was studied by $^1\text{H}, ^6\text{Li}$ -HOESY NMR technique (HOESY = heteronuclear Overhauser effect spectroscopy) <1998JOM(550)359>. This interaction results in the formation of contact ion pair and ligand and tetrahydrofuran (THF) solvent molecules compete for three coordination sites. The fourth site is occupied by the anionic benzylic carbon atom in an η^1 -like manner.

The charge-transfer complex of 1,4,7-trithiacyclononane **10** and I_2 has been prepared by slow evaporation of solutions containing I_2 and thioether macrocycle in CH_2Cl_2 . The structure of the complex showed two independent macrocycles in the asymmetric unit which are linked by a diiodine bridge. Asymmetric units are linked by iodine–iodine and sulfur–iodine interactions to form an extended array of linked macrocycles. The formation enthalpy ($\Delta H = 35.0 \text{ kJ mol}^{-1}$) and formation constant ($K = 169 \text{ dm}^3 \text{ mol}^{-1}$) of 1:1 adduct have been determined by electronic spectroscopy and compared to other polythia macrocycles of different sizes <1997JCD1337>.

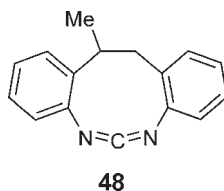
14.10.4.3 Conformational Studies

Nine-membered rings are strained in all of their conformations. Conformational studies of saturated heteronines and heteronines containing torsional constraint caused by double bonds, three-membered and benzo-annulated rings, lactams and lactones were the part of the survey <1999MI(5)89>.

The signals in the ^1H NMR spectra of 2-methyl-2-[(trimethylsilyl)methyl]-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonium iodide **47** were observed as doubled patterns of the expected proton signals <1997JOC2544>. This result suggested that it exists in solution as a mixture of two stable conformational isomers in the ratio 31:69 and with characteristic signals at 0.27 and 0.33 ppm (Me_3Si), 3.34 and 3.09 ppm (N–Me), and 2.64, 3.39 and 3.27, 3.40 ppm (NCH_2Si), respectively. The chemical shifts of the (trimethylsilyl)methyl groups at a higher field and of N–Me group at the lower field are assigned to the isomer with a methylene group located around phenyl ring due to the diamagnetic anisotropy effect of the benzene ring (trimethylsilyl = TMS).



Cyclic carbodiimide **48** theoretically exists as two conformational isomers. Comparison of the coupling constant values, calculated using AM1 Hamiltonian and Karplus relationship, with the experimental vicinal coupling constants of 8.33 and 1.05 Hz, undoubtedly prove its ‘methyl-out’ structure **48** <1996JOC4289>.



Analysis of the ^1H NMR coupling constants and NOEDIFF experiments gave an accurate idea of the preferred conformation of the nine-membered ring in (3*S*)-azoninone **35** and its (3*R*)-isomer <2005OBC97>; see also Sections 14.10.2.2 and 14.10.3.2. An examination of the NMR data indicated that for both isomers a conformation with COOEt in pseudoequatorial (β -) position is preferred. For (3*S*)-isomer **35**, there is a high coupling constant J_{1-9} of 9.3 Hz, which excludes conformation with the COOEt in pseudoaxial position. The J_{8-9} (3.9 and 7.2 Hz) and J_{7-8} (6.7 and 9.0 Hz) are perfectly compatible with conformations where amide NH is on the opposite side of double bond. Moreover, NOEs detected between the ring NH and one of the H-8 and one of the H-5, and an NOE between H-9 and H-7, are in agreement with the proposed conformation. Similar observations were made for (3*R*)-isomer.

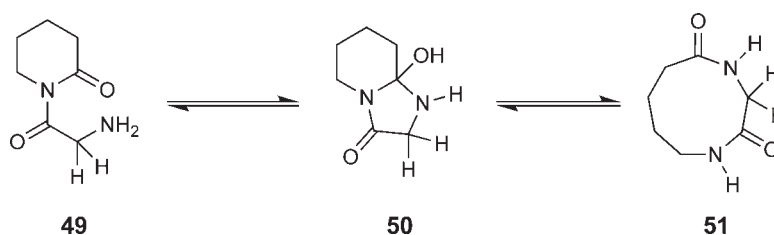
The solid-phase ^{13}C cross-polarization/magic angle spinning (CP/MAS) NMR, as a tool for conformation prediction, revealed that the solid-phase conformation of the nine-membered ring crown cavity in naphtho-9-crown-3 is different from benzo-9-crown-3. The two key C–O–CH₂ units are predicted to be out of naphthalene plane, and the two C–C–O–CH₂ torsion angle values are close to each other <2000JST(526)185>.

Conformational analysis of 1,4,7-trithiacyclononane **10** in the gas phase was done using *ab initio* molecular orbital calculations at the HF and MP2 levels as well as microwave and photoelectron spectroscopies. The photoelectron spectroscopic data showed evidence for at least two conformations with different ionization energies. Using the calculated photoelectron spectra, the observed sulfur 3p-ionization peaks can be assigned to C_1 and C_2 conformations. Forty of the observed microwave transitions can be assigned to a C_1 symmetry, while additional microwave lines are believed to be due to a nonrigid C_2 -symmetry conformation <1997PCA9180>.

14.10.4.4 Kinetics

The thermal decomposition reaction of cyclic triacetone triperoxide **11** in the temperature range of 130.0–166.0 °C and an initial concentration of 0.021 M has been studied in toluene solution. The thermolysis follows first-order kinetic laws up to at least ca. 78% acetone triperoxide conversion. The activation parameters corresponding to the unimolecular thermal decomposition reaction of the molecule ($\Delta H^\ddagger = 41.8 \pm 1.6 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = 18.5 \pm 3.8 \text{ cal mol}^{-1} \text{ K}^{-1}$) were determined <2000JOC2319>. Similarly, thermal decomposition reaction of hexaethyl analogue of **11** in chlorobenzene solution follows a first-order kinetic law. The activation parameter values for the initial O–O bond rupture in chlorobenzene ($\Delta H^\ddagger = 134.6 \pm 1.7 \text{ kJ mol}^{-1}$, $\Delta S^\ddagger = 4.2 \pm 3.8 \text{ J mol}^{-1} \text{ K}^{-1}$) and the observed reaction products supported a stepwise reaction mechanism. It includes as a first step the unimolecular homolytic cleavage of one peroxidic bond of the molecule giving rise to a biradical as intermediate. Additionally, the results obtained were compared with those obtained in toluene, toluene–styrene, and chlorobenzene–styrene solution, showing that the decomposition reaction is strongly solvent dependent <2004JPO215>. Three pathways for the decomposition of **11** were proposed based on theoretical studies <2005JA1146>.

When *N*-(2-aminoacetyl)-2-piperidone **49** was dissolved in aprotic or protic solvents, a fast equilibrium, ca. 1:1, between the cyclol form (tetrahedral intermediate) **50** and the bislactam **51** is established (Scheme 1). Dynamic ^1H NMR has been used to evaluate the exchange between the two forms at different pH. The rate law for the proposed exchange mechanism between the cyclol form and macrocycle was proposed. Both the macrocycle formation and cyclol formation constants are specific base catalyzed; however, the equilibrium constant is independent of pH <2002J(P)2078>.

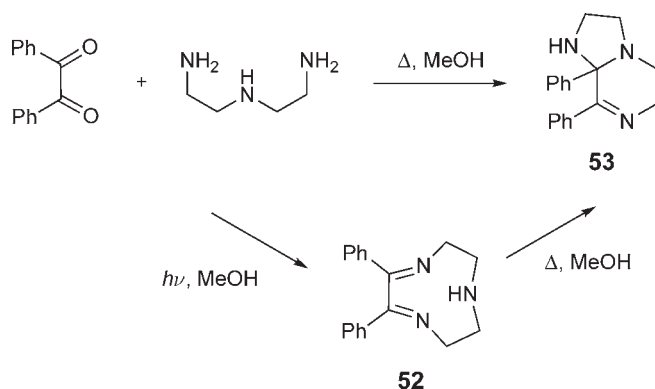


Scheme 1

14.10.5 Reactivity of Nonconjugated Rings

14.10.5.1 Intramolecular Thermal and Photochemical Reactions

Diphenyl triazonine **52** is a product of UV irradiation of benzyl and diethylenetriamine in the presence of oxygen. It can be thermally converted into bicyclic derivative **53** (Scheme 2), which is the major product of the thermal reaction between benzyl and triamine <2000NJC719>.



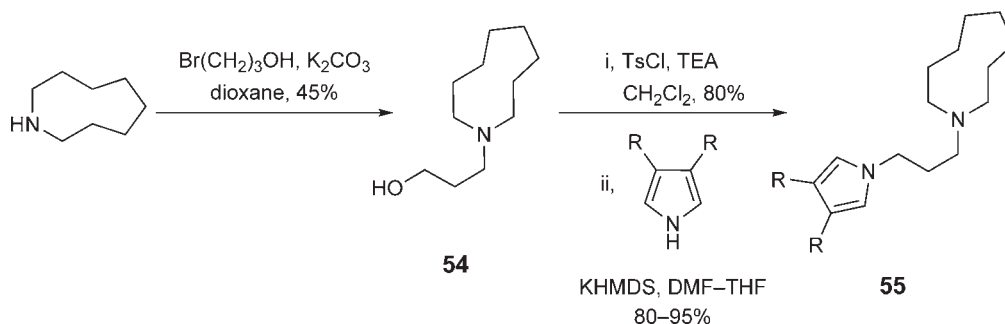
Scheme 2

14.10.5.2 Electrophilic Attack on Ring Heteroatoms

14.10.5.2.1 Electrophilic attack on ring nitrogen

Chapters 6.10.3.3.1 of CHEC(1984) and 9.27.6 of CHEC-II(1996) partially covered this class of transformations. Since that time, numerous syntheses of this type were reported and they have become a major method of synthetic modification of azonines and their poly-heteroatom analogues.

N-Ethyl azonan-2-one is readily available by alkylation with the ethyl iodide <1998BML1973>. Similarly, azonane was alkylated with 3-bromopropan-1-ol to afford intermediate alcohol 54 in 45% yield (Scheme 3) <2003T9239>.

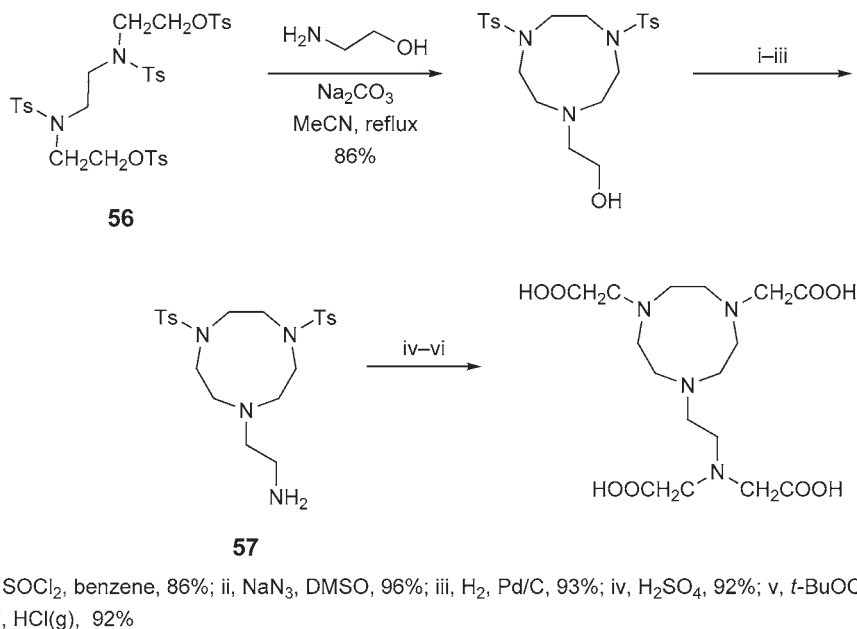


Scheme 3

1,4,7-Triazonanes were reacted with various alkylating agents to yield mono-, di-, and trisubstituted products. Expected compounds are often accompanied with by-products of higher degree of substitution. Trisubstitution of this heteronane system with substituted alkyl halides <1995S453, 2000JCD4607, 2000AJC791, 2002AJC655, 2001CJC888, 1997AGE2346, 1999TL4989>, and their activated substituted allyl <2002AJC655>, benzyl <2001CJC888, 2000JA9663, 1997AGE642, 1998CEJ93, 2000CC443, 1996JA11575>, heteroarene methyl <1996HCA789, 1998S1339, 2003JCM704, 2001JA2436, 2002JOC3933, 2000JOM(611)586, 2001PS85, 2001PS325, 2003JCD2428>, or α -carbonyl <2002EJO351> analogues are the most common. Selective mono- <1997AGE642> and bis- <1996JA4396> alkylation are quite rare, and protection/deprotection strategies are required if mono- or disubstituted 1,4,7-triazonanes are synthetic targets. Tosyl group is frequently used for monoprotection and sequential dialkylation <1999AGE980, 1996JCD353, 1997ACR227, 2002EJO351, 1995JA10745>. Alkylations of di-BOC <2001JA5030, 2001JA6025, 2003TL535> and di-Cbz <2000JOM(611)586> as well as dialkyl <1996JA10920, 2000JA9663, 2001CC637, 1995JA3983, 1996JA11575> triazonane derivatives are straightforward and high yielding (BOC = *t*-butoxycarbonyl; Cbz = carbobenzyloxy). Triazonane alkylation with tris-(3-chloropropyl)amine leads to 38% yield of a macrocyclic tetramino cage <1999J(P2)2701>. The new bis-triazonane bridged with pyrazole moiety was synthesized from 3,5-dichloromethylpyrazole and ditrityl-protected triazonane <1995HCA693>. Similarly, reactions of 1,4,7-dithiazonane and monoformyl 1,4,7-thiadiazonane afforded corresponding bis-derivatives <1997HCA2315>.

Electrophilic attack on 1,4,7-triazonane with oxiranes <2004JME5683, 2005BMC2389, 1997CC845, 2003AJC61, 1994CC2467, 1999J(P1)1211, 2004CEJ2022>, thiirane <1995JA10745>, and *N*-tosylaziridine <2001CC2582> proceeds smoothly and leads to the corresponding mono- <1999J(P1)1211, 2004CEJ2022, 1994CC2467>, di- <2003AJC61, 1994CC2467, 2001CC2582>, and trisubstituted <2004JME5683, 2005BMC2389, 1997CC845> products.

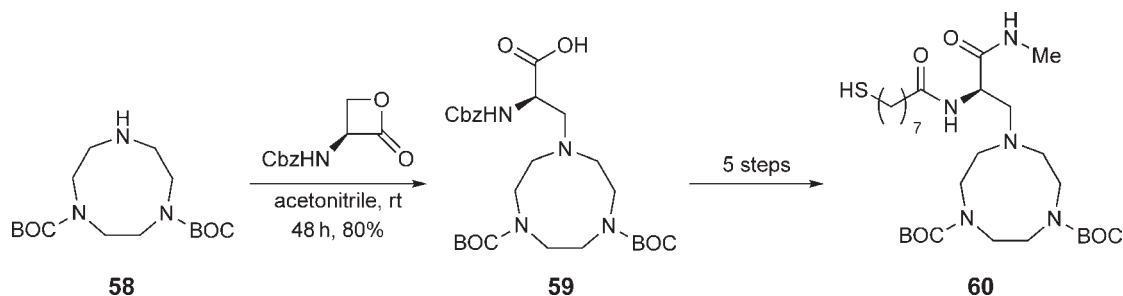
1,4,7-Oxadiazonane was alkylated with substituted 2-chloroacetamides in acetonitrile to give a mixture of disubstituted (yields of ca. 30%) and monosubstituted derivatives <2002TL4989, 2004T5799>. 2-Aminoethyltriazonane **57** underwent both ring and side-chain alkylations when reacted with *tert*-butyl 2-bromoacetate (Scheme 4), <2002JME3458>.



Scheme 4

Michael addition of methyl acrylate to azonane gave methyl 3-(azonan-1-yl)propanoate <2002JOC245>, while addition of acrylonitrile to 1,4-diisopropyl-1,4,7-triazonane resulted in 95% of a heterocyclic nitrile <2000NJC575>.

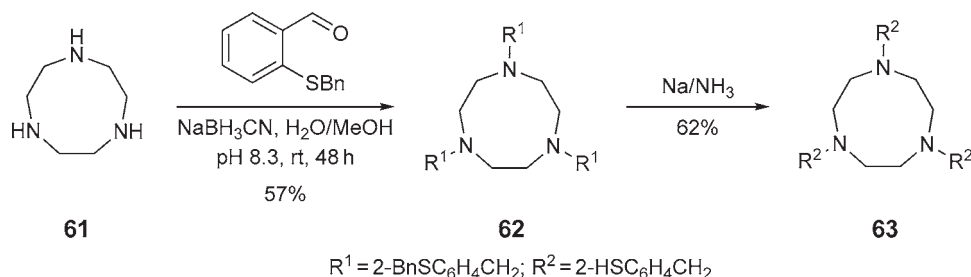
Protected (*S*)-2-amino-3-[1-(1,4,7-triazacyclononane)]propanoic acid **59** (Scheme 5) is a valuable building block in peptide synthesis <2002PNA5144> and in the preparation of functionalized amino acid **60** <2004AGE6165>. It was obtained by ring-opening reaction of di-BOC-protected 1,4,7-triazacyclononane **58** with (*S*)-2-Cbz-amino- β -lactone. This transformation is regiospecific and produces the functionalized amino acid **59**, as a sole product, without any traces of serine amide, an expected by-product corresponding to the attack of the amine on the β -carbon <1998TL7159, 2000CEJ4498>.



Scheme 5

1,4,7-Triazonanes react with formaldehyde or paraformaldehyde and further undergo Mannich reaction with a variety of phenols [<1997CEJ308, 1997JA8217, 1997JA8889, 1999CEJ2554>](#), trialkoxyphosphines [<1995S453>](#), or alkyl dialkoxyphosphines [<1995S453, 1996JA4396>](#) to form mono-, di-, and trisubstituted derivatives, which were obtained in good to excellent yields.

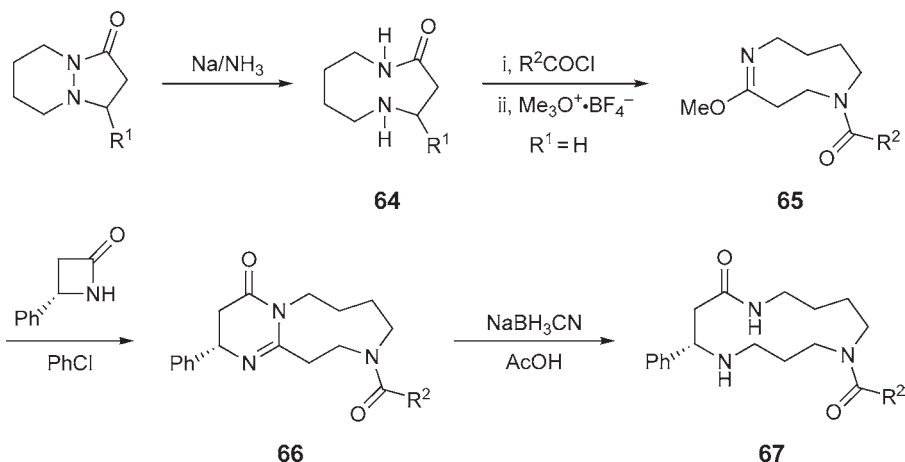
Reductive amination of triazonane **61** requires controlled pH conditions and affords good yield of *ortho*-*S*-benzyl derivative **62** (Scheme 6) [<1999T5733>](#).



Scheme 6

1,4-Di-(2-propyl)azonane was successfully transformed into product of reductive amination with *ortho*-diphenylphosphinobenzaldehyde and sodium triacetoxyborohydride [<1999JCD1539>](#).

Acylation of diazoninone **64** and subsequent treatment with Meerwein's reagent ($\text{Me}_3\text{O}^+\text{BF}_4^-$) resulted in the imino ether **65** ($\text{R}^2 = \text{PhCH}=\text{CH}$, Scheme 7). It further reacts with β -lactam to produce the corresponding bicyclic 4-oxotetrahydropyrimidine derivative **66**, as a product of addition–ring-annulation process [<2000CL1104>](#). Analogous sequence was used for the preparation of racemic precursor of dihydroperiphylline [<2002T7177>](#).

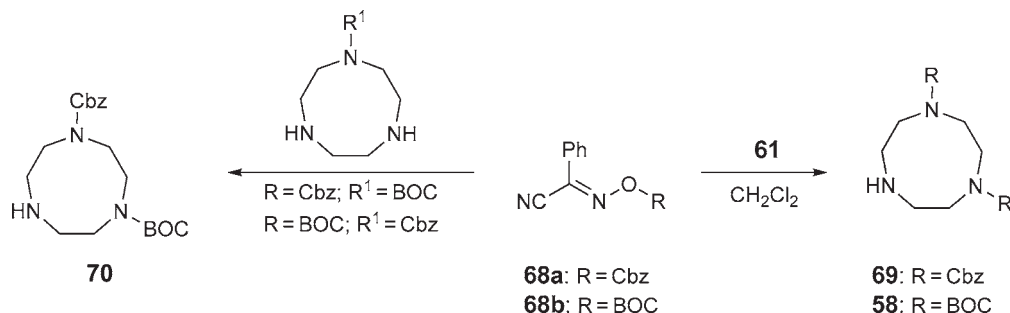


Scheme 7

Several acylation transformations of 1,4,7-triazonane were reported. Benzoylation of 1,4,7-triazonane under kinetic control, that is, through formation of dianion with 2 equiv of *n*-BuLi in THF, led to an 85% yield of mono- and disubstituted compounds in 20:1 ratio [<1999JOC7661>](#). Reaction of triazonane with ethyl trifluoroacetate is a facile method of incorporation of two protecting groups and results in 94% yield of the product when reaction is performed in methanol in the presence of triethylamine [<2003TL2481>](#).

1,4,7-Triazonane **61** when reacted with $(\text{BOC})_2\text{O}$ yielded di-BOC derivative in 67% yield [<2005JOC115>](#). Noteworthy, reaction with 2 equiv of 2-(benzyloxycarbonyloxyimino)-2-phenylacetonitrile (Z-ON) **68a** or 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON) **68b** in chloroform under anhydrous conditions gave high yields (>90%) of the diprotected derivatives **69** or **58**, respectively (Scheme 8) [<1995TL9269, 1996BML2673>](#).

2001JA5030, 2001JA6025, 2003TL5699>. The remarkable preference of BOC-ON and Z-ON for disubstitution was demonstrated by the reaction of the monoprotected derivatives with these reagents. Both reactions afforded **70** having two different protecting groups in nearly quantitative yields <1995TL9269>.

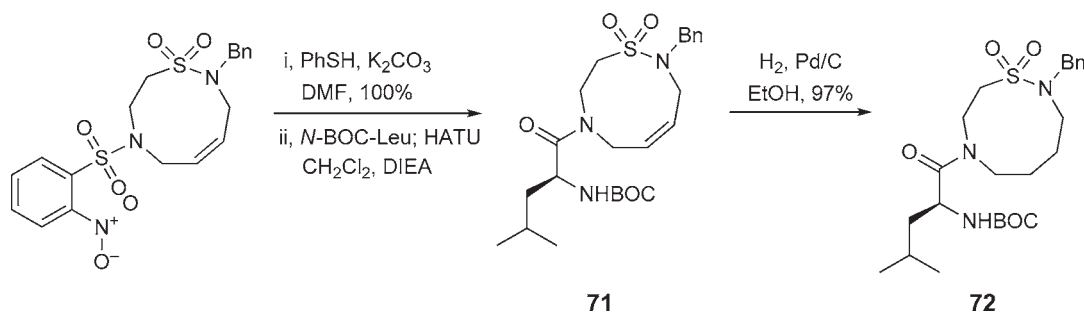


Scheme 8

Other reported examples of triazonane acylations included reactions with succinic anhydride <2002S1398>, carboxymethyl calixarene <1995CC929>, and *N*-BOC-sarcosine <2003TL5699>.

Acylation of 1-thia-4,7-diazonane with 2-chlorocarbonylthiophene in CH₂Cl₂ in the presence of triethylamine led to the corresponding bis-amide **33** <1996AXC3062>. 1,4,7-Dithiazonane and 1,4,7-thiadiazonane underwent smooth acylation with substituted benzoyl chlorides to afford correspondent products **44** and **45** <2001JMC1011>.

Synthesis of model cyclic peptidosulfonamides containing 1,2,7-thiadiazonine moiety was performed by the incorporation of an amino acid on the 7-position leading to **71** (Scheme 9) <2004JOC3662>.



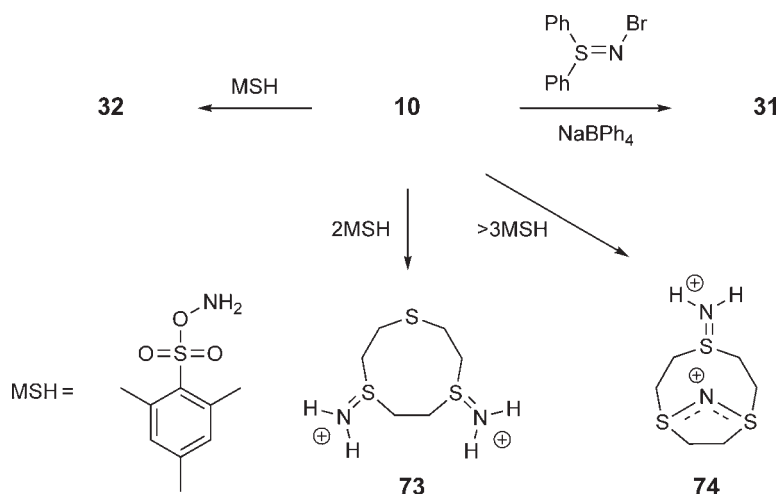
Scheme 9

N-Arylation of azonane with 2-chloro-5-nitrobenzoic acid was reported <1998JME5219>. Arylation of anion formed from 1,6-diazonane (PhLi, diethyl ether) with 4-chloropyridine resulted in mixture of mono- (38%) and disubstituted (13%) products <1998CC1625>. A novel 1,4,7-triazonanes bearing thiazol-2-yl and benzoxazol-2-yl substituents were synthesized by high-pressure S_NAr reactions <1995H(41)237>. Arylation of 1,4,7-triazonane with 5 equiv of 4,7-dichloroquinoline in dimethylformamide (DMF) at reflux in the presence of potassium carbonate afforded a mixture of mono- and disubstituted products, while formation of the trisubstituted derivative was not indicated <2001JME1658>.

Triazonane was converted into 1,4,7-trinitroso-1,4,7-triaacyclononane **27** in 84% yield by standard treatment with NaNO₂/HCl <2002TL771>.

14.10.5.2.2 Electrophilic attack on ring sulfur

Treatment of the 1,4,7-trithionane **10** with 1 equiv of *O*-mesitylsulfonylhydroxylamine (MSH) yielded the water-soluble protonated sulfimide **32** (Scheme 10) <2002CJC1410>. Two equivalents of MSH lead to the formation of bis-sulfimide **73**, while excess MSH generated cation **74**. Compounds **32**, **73**, and **74** formed mesitylsulfonate salts, structures of which were assigned based on X-ray crystallography (see Section 14.10.3.1).

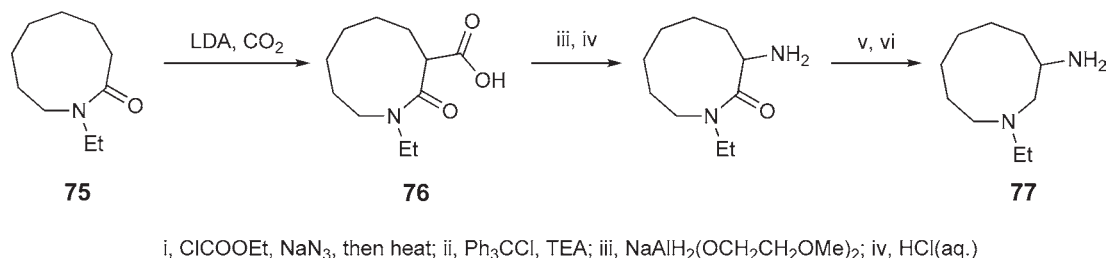


Scheme 10

Brominated sulfimide was reacted with trithionane to afford sulfimidium salt **31** <2004NJC959>, which was further crystallized as tetraphenyl borate derivative and studied by ^1H and ^{13}C NMR and X-ray crystallography (Section 14.10.3.1). Contrary to MSH derivatives **73**, and **74**, excess of diphenyl sulfimide did not lead to disubstituted product, which was attributed to bulkiness of phenyl groups.

14.10.5.3 Electrophilic Attack on Ring Carbon

N-Ethyl azonanone **75** can be lithiated on position 3, and further quenched with carbon dioxide to produce 3-carboxy derivative **76** (Scheme 11) <1998BML1973>.



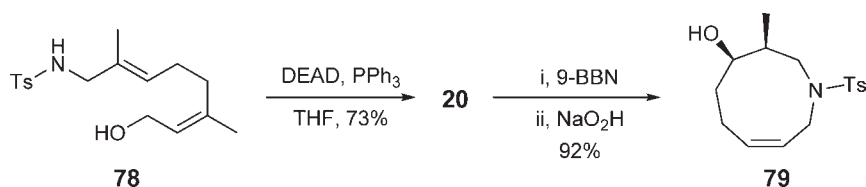
Scheme 11

Trinitroso derivative **27** underwent in $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ solution fast base-catalyzed H/D exchange on the whole set of methylene hydrogens, and nitroso groups can be subsequently removed by reduction with Ni/Al alloy <2002TL771>.

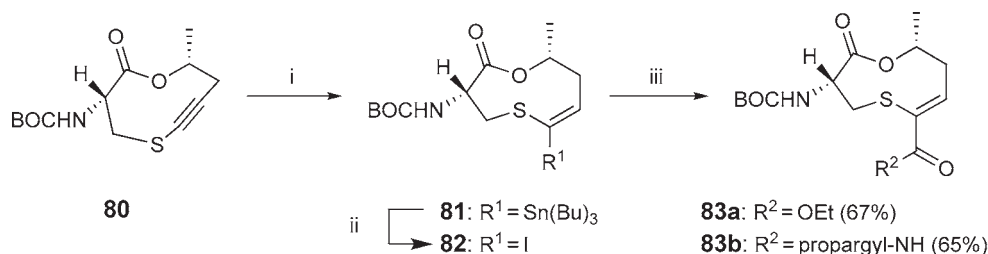
14.10.5.4 Reactions with Nucleophiles

Azonine **20** is a representative of cyclic diallylic amides with a remarkably stable planar chirality. When its (*S*)-isomer was hydroborated using 9-borabicyclo[3.3.1]nonane (9-BBN), the reaction went stereospecifically to give exclusively (3*S*,4*R*)-**79** in 92% yield (Scheme 12) <2006OL963>.

Oxonane-2,9-dione reacts with amines, producing monoanilide in 94% yield <2001OPP391>. Hydrostannylation of oxathionine **80** gave vinyl tin lactone **81** in 80% yield. Formation of the corresponding iodo lactone **82** was achieved in 87% yield by a Sn/I-exchange (Scheme 13) <2002JOC4565>.



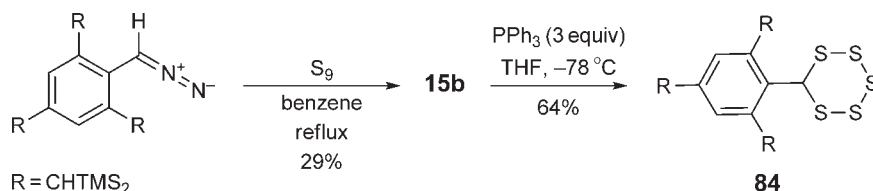
Scheme 12



i, Bu_3SnH , $\text{Pd}(\text{PPh}_3)_4$, toluene, 20°C , 80%; ii, I_2 , CH_2Cl_2 , 20°C , 30 min, 87%; iii, CO (8 bar), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, MeCN, amine or alcohol

Scheme 13

C-Substituted octathionane **15b**, when reacted with 7 equiv of triphenylphosphine, desulfurized to produce the corresponding 2,4,6-trisubstituted thiobenzaldehyde <1997CEJ62, 1994PS389>. Partial desulfurization to pentathiane **84** occurred when 3 equiv of PPh_3 was used (Scheme 14) <1994PS389> (Chapter 9.14).



Scheme 14

14.10.5.5 Oxidation and Reduction

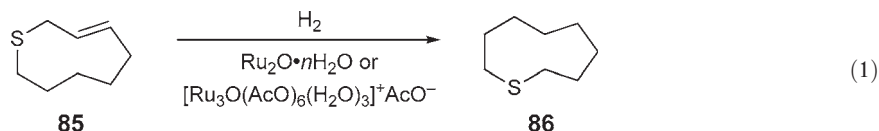
It is convenient to discuss oxidative attack on ring carbon in the same chapter with reduction of heteronines as many reported syntheses involved various oxidative/reductive sequences and reagent combinations. Examples of oxidative transformations involve radical as well as electrophilic oxidizing agents, while reductive syntheses include both chemical reduction and reactions on surfaces via catalytic hydrogenation.

14.10.5.5.1 Reactions at surfaces

Catalytic hydrogenation of hexahydroazonines with different substitution patterns afforded almost quantitative yields of azonane racemic amino acids <2002EJM379, 1999SL954, 1997CC637, 1997J(P1)447>. Asymmetric hydrogenation of methyl 4,5,6,7,8,9-hexahydro-1*H*-azonine-2-carboxylate in the presence of a catalytic amount of $[\text{Rh}(\text{COD})-(2)-(R,R)\text{-(Et-DuPHOS)}]\text{OTf}$ afforded the corresponding saturated cyclic amino acid in excellent yield and with high enantioselectivity (COD = cyclooctadiene) <1998CC1757>.

Hydrogenation of trans-isomer of 2,3,4,5,6,9-hexahydrothionine **85** (Equation 1) under heterogeneous Ru_2O catalysis led to only 7% yield of reduction product **86**. A major process is the isomerization into the *cis*-isomer (80% yield), which has a reduced ring strain, and, thus, is inert to reduction under conditions employed

<1996SC899>. Reduction under homogeneous catalysis conditions using $[\text{Ru}_3\text{O}(\text{AcO})_6(\text{H}_2\text{O})_3]\text{AcO}$ as a catalyst led to 67% yield of the thionine **86**.



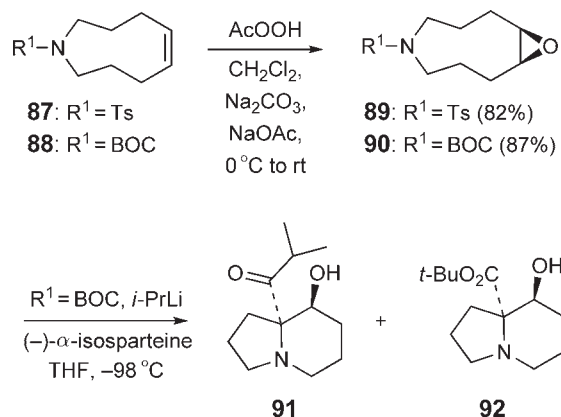
Hydrogenation of **71** led to 1,4,7-thiadiazonane **72** in 97% yield (Scheme 9, Section 14.10.5.2.1) <2004JOC3662>.

14.10.5.5.2 Chemical reduction

Synthesis of dihydroperiphylline **67** ($\text{R}^2 = \text{PhCH}=\text{CH}$, 81%) was accomplished in one step by treatment of intermediate **66** with sodium cyanoborohydride in acetic acid (Scheme 7, Section 14.10.5.2.1). The conditions are mild enough to leave the exocyclic double bond unaffected. The physical, optical, and NMR spectral data of ring expansion product **67**, thus prepared, were consistent with those reported for (+)-(*S*)-dihydroperiphylline <2000CL1104>. Analogous sequence was used for the preparation of racemic dihydroperiphylline <2002T7177>. Borane–THF reduction of 2,3,6,7-tetrahydro-1*H*-benzo[*f*][1,5]diazonin-4(5*H*)-one led to the corresponding hexahydrodiazonine in 88% yield <2004JA3529>. Reduction of substituted 1-acetyl-1,4,7-triazonane with lithium aluminium hydride (LAH) afforded 39% of the corresponding N-ethyl derivative <2004OBC2664>.

14.10.5.5.3 Oxidations and oxidation/reduction sequences

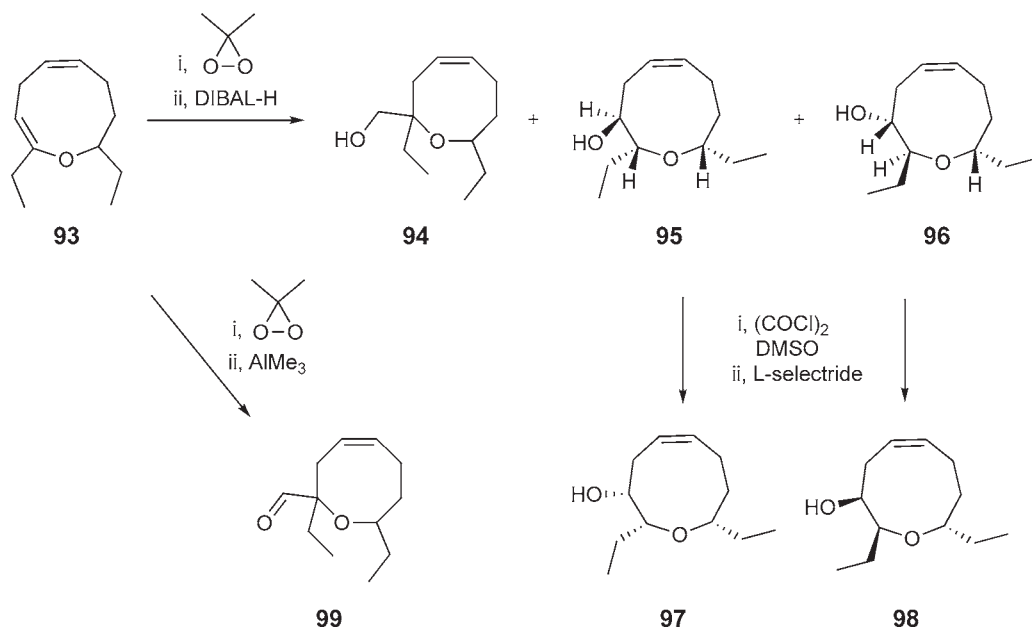
N-Protected azonines **87** and **88** are smoothly transformed into epoxides **89** and **90**, correspondingly, when reacted with peroxyacetic acid (Scheme 15) <1999CC309>.



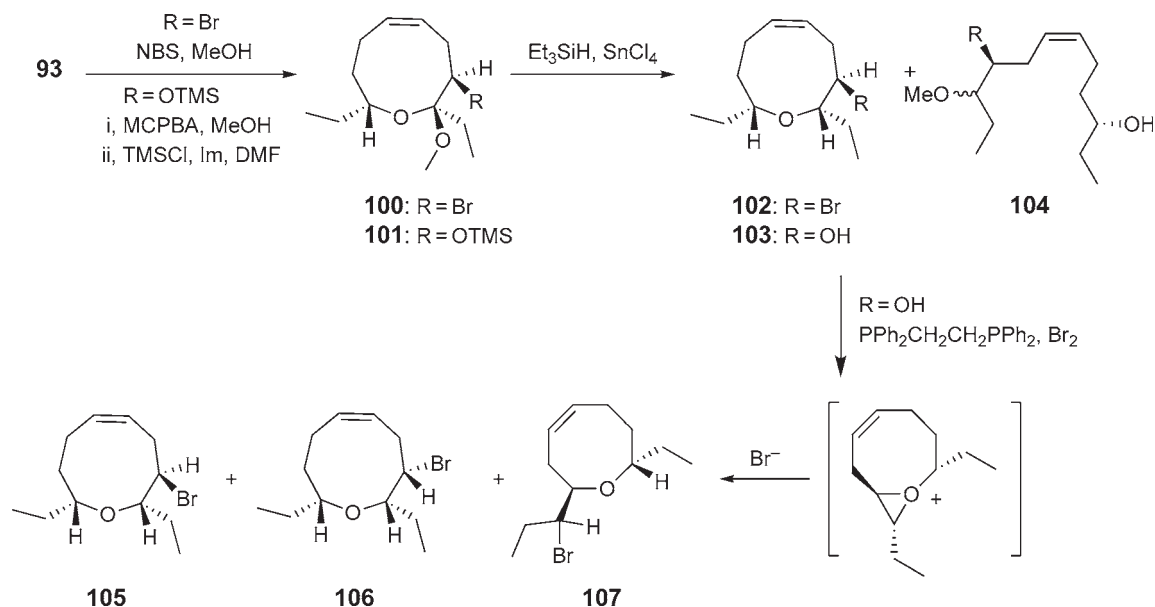
Scheme 15

2,3-Epoxidation of oxonine **93** with dimethyldioxirane, followed by reduction with diisobutylaluminium hydride (DIBAL-H), resulted in a separable mixture of alcohols **95** and **96**, and the side product **94** (Scheme 16). Each of the isomers was submitted to Swern oxidation and sequential stereoselective reduction with L-selectride to achieve desired stereochemistry of the products **97** and **98**. Formation of the side product **94** was explained by Lewis acidity of DIBAL-H and confirmed by treatment of oxirane derived from **93** with another Lewis acid, AlMe_3 , to produce oxocine aldehyde **99** in 35% isolated yield <1997CL665>. Similar oxidative synthetic sequence was utilized for the synthesis of functionalized oxonines as precursors of (+)-obtusenyne <1999JOC2616>.

Cyclic diene ether **93** underwent oxidative acetalization to produce corresponding 3-substituted acetals **100** and **101** (Scheme 17) <1995TL8263>. Further Lewis acid-catalyzed reduction with triethylsilane afforded corresponding 3-bromo- and 3-hydroxy-oxonenenes (**102**: $\text{R} = \text{Br}$ (68%); **103**: $\text{R} = \text{OH}$ (49%), respectively) together with 1:1 diastereomeric mixture of acyclic methyl ethers **104** ($\text{R} = \text{Br}$ (18%); $\text{R} = \text{OH}$ (13%)).



Scheme 16

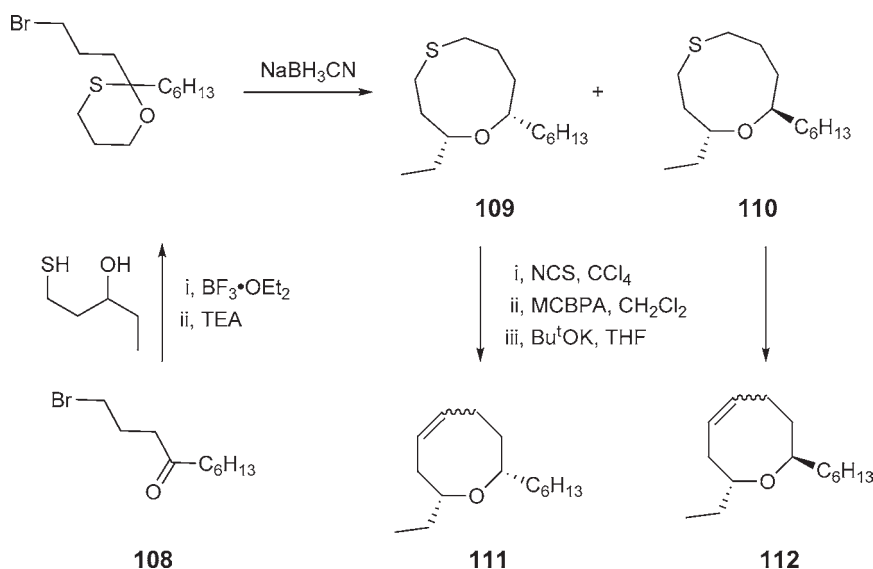


Scheme 17

S-Oxidation of oxathianes is an intermediate step in their transformation into the corresponding oxocines (Scheme 18, Section 14.10.5.6.1) <2002OL3047> (Chapter 14.02).

14.10.5.6 Intramolecular Ring-Transformation Reactions

Ring strain of heteronines resulted in various ring-contraction reactions to produce more favorable smaller ring systems, or, in some specific cases, bicyclic products of transannular transformations. Heteronines are prone to the formation of bridged systems or ring enlargement when their side chains contain reactive groups. This section covers intramolecular ring-contraction and ring-extension reactions other than photolytic and thermal ones (see Section 14.10.5.1).

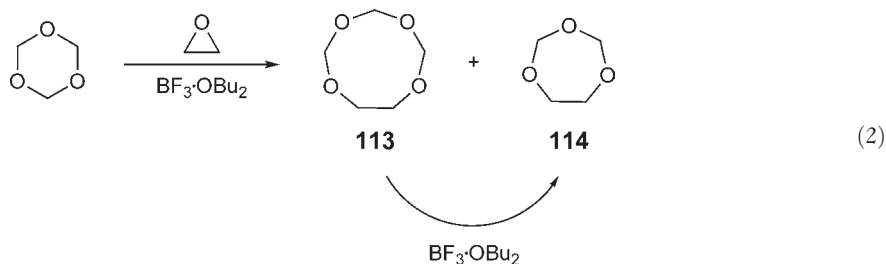


Scheme 18

14.10.5.6.1 Ring contractions

Oxathionanes **109** and **110** were transformed into the corresponding oxocines using a three-step procedure (Scheme 18) <2002OL3047>. Chlorination with *N*-chlorosuccinimide (NCS) followed by oxidation on sulfur with *m*-chloroperbenzoic acid (MCPBA) gave a mixture of four possible α -chloro sulfones (not shown in the scheme). Subsequent Ramberg–Bäcklund rearrangement with potassium *tert*-butoxide resulted in oxocines **111** and **112** (56 and 50%, respectively) as ca. 9:1 mixture of (*Z*)- and (*E*)-isomers.

1,3,5,7-Tetraoxonane **113** underwent a ring contraction to afford 1,3,5-trioxepane **114**, which is also observed as the main by-product of the tetraoxonane synthesis (Equation 2) <1998CC1809, 2001TL271> (Chapter 13.16).

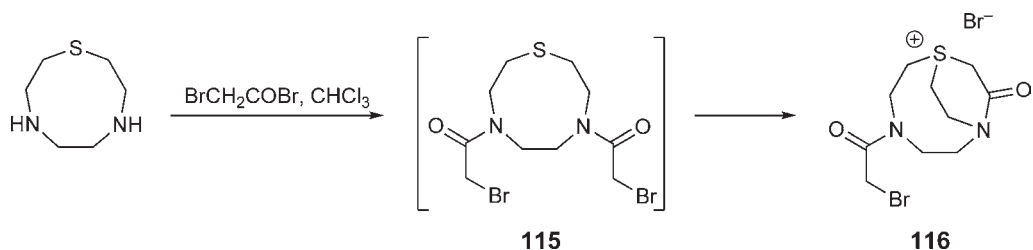


1,2,4,5,7,8-Hexaoxonane **11** underwent a slow ring narrowing in methylene chloride or chloroform in the presence of *p*-toluenesulfonic acid (PTSA) to yield 60% of diacetone diperoxide <2005JA1146>.

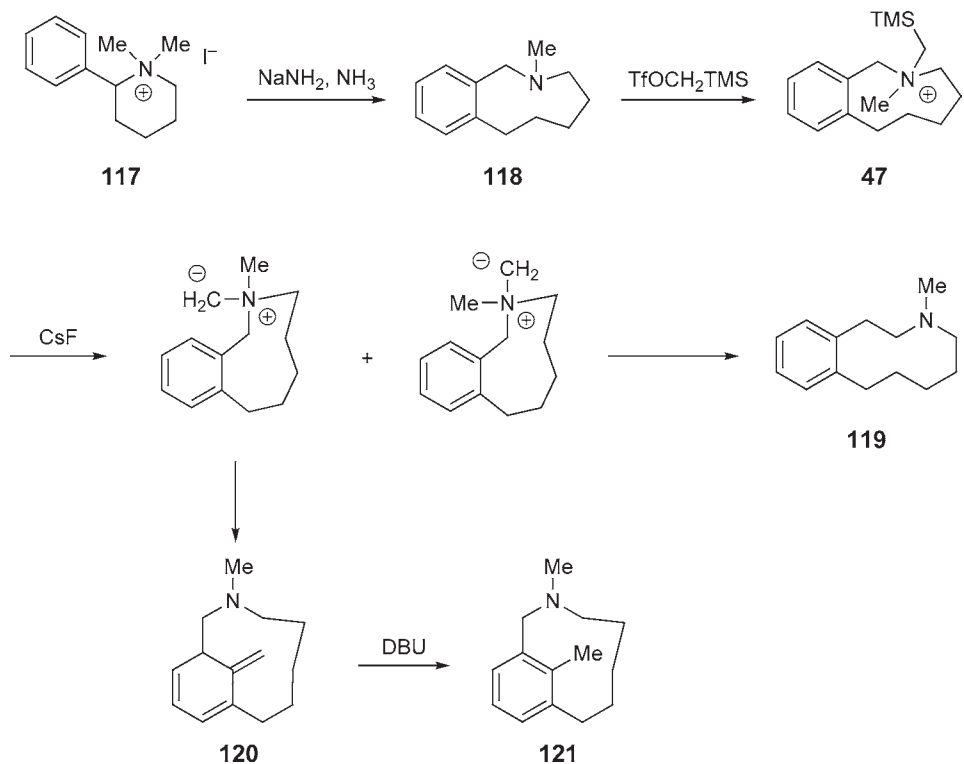
14.10.5.6.2 Formation of bridged systems and ring expansions

Reaction of 1,4,7-thiadiazonane with bromoacetyl bromide in CHCl_3 afforded, instead of expected 4,7-bis-(2-bromoacetyl)-1-thia-4,7-diazacyclononane **115**, derivative of 1-thionia-4,7-diazabicyclo[5.2.2]undecane **116** as a product of intramolecular cyclization (Scheme 19) <2004AXCo100>.

Reaction of 2-methyl-2-[(trimethylsilyl)methyl]-2,3,4,5,6,7-hexahydro-1*H*-2-benzazoninium iodide **47**, with cesium fluoride in DMF for 0.5 h at room temperature, gave a mixture of **119** and product of [2,3]-sigmatropic rearrangement **120** (Scheme 20). The structure of **120** was assigned based on a comparison of the ^1H NMR, ^{13}C NMR, and UV spectra of the product mixture with those of an authentic sample of **119**. The product ratio **119**:**120** did not change after 24 h. However, when the reaction was repeated in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 2.5 mol equiv), **121** was formed with decreasing yield of **120** <1997JOC2544>.

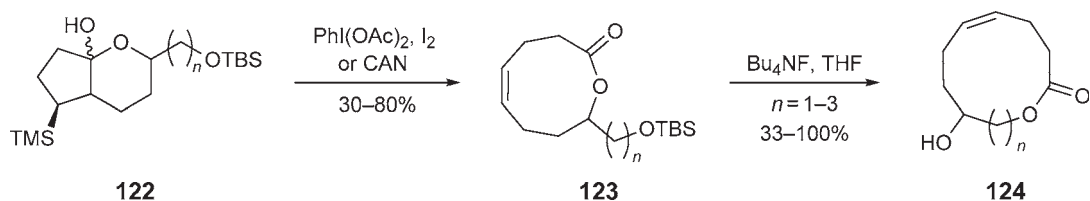


Scheme 19



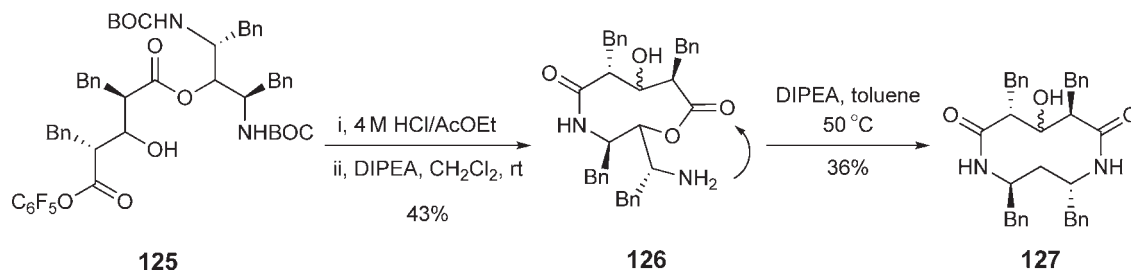
Scheme 20

Nine-membered lactones **123** underwent a ring expansion under mild desilylation conditions to produce 10–12-membered lactones **124** in moderate to excellent yields (Scheme 21) <2005OL4301> (Chapter 14.11).



Scheme 21

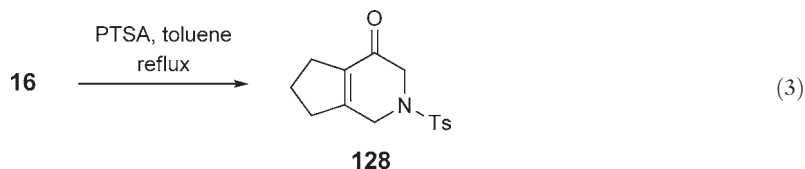
Ring expansion of oxazonine dione **126** (Scheme 22) occurred upon treatment with *N,N*-diisopropylethylamine (DIPEA) in toluene at 50 °C to form the corresponding 1,5-diazecane-6,10-dione ring system **127** in 36% yield <2002T2957> (Chapter 14.12).



Scheme 22

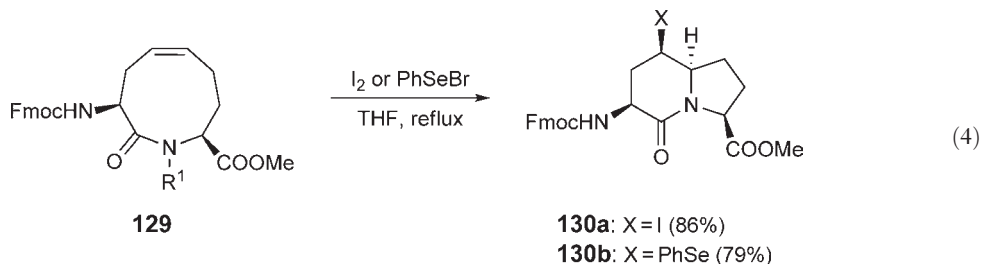
14.10.5.6.3 Transannular transformations

Treatment of *N*-tosyl azonane-3,8-dione **16** with PTSA resulted in an intramolecular aldol reaction giving tetrahydrocyclopenta[*c*]pyridinone ring system **128** (Equation 3) <1995J(P1)1137>.



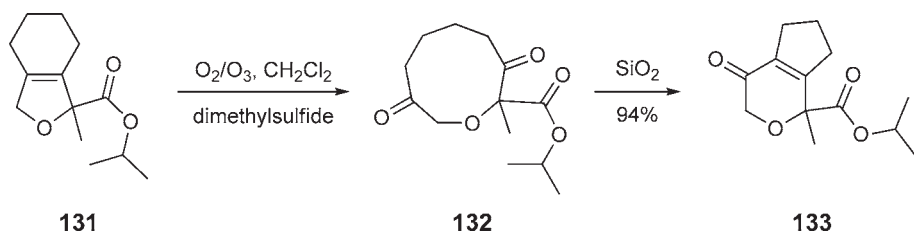
Lithiation of epoxide **89** ($R^1 = \text{Ts}$; Scheme 15, Section 14.10.5.5.3) under standard conditions (*sec*-BuLi in ether at -78°C for 5 h, followed by warming to 25°C) led to recovery of the starting material or, in the separate D_2O quench experiment, to ortho-deuterium incorporation into tosyl substituent <1999CC309>. Substrate with blocked ortho-positions ($R^1 = 2,4,6\text{-triisopropylbenzenesulfonyl}$) proved to be unreactive <2001J(P1)2161>. Contrary, BOC-protected **90** underwent a meso-epoxide α -deprotonation–transannular N–C-insertion reaction to produce mixture of ketone **91** and ester **92**. The optimized conditions, *i*-PrLi at -98°C <1999CC309>, or *sec*-BuLi at -90°C <2003OBC4293> in the presence of (–)- α -isopartene as an asymmetric inducing agent, resulted in 45–49% isolated yield of **92** with 89% ee and ratio of **91**:**92** = 1:10 <1999CC309>.

Electrophilic transannular cyclization of nine-membered ring lactam **129** led to formation of protected methyl 6-amino-8-iodo-5-oxooctahydroindolizine-3-carboxylates **130a** and **130b** in high yields (Equation 4) <2006OL2851>.

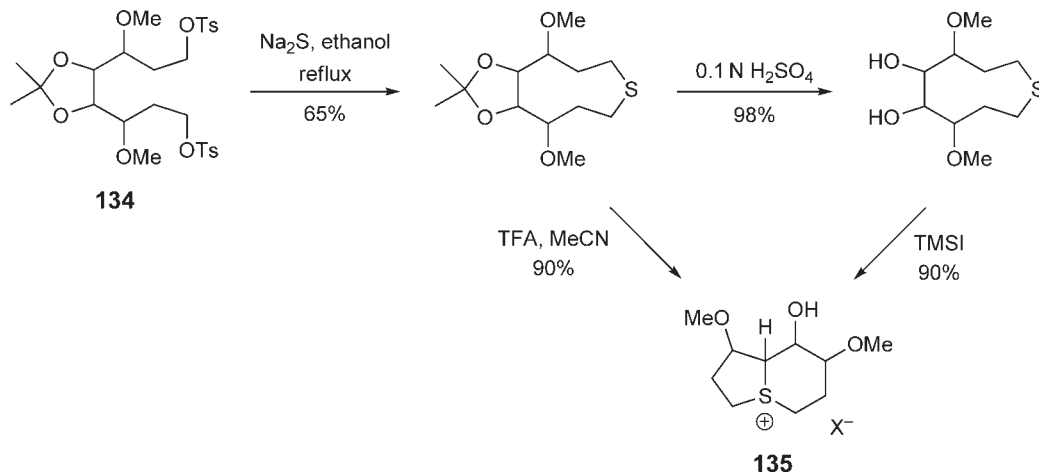


Oxonine diketone **132** (Scheme 23) is highly sensitive to acidic conditions and prone to intramolecular aldol condensation. The sole product of the process, 4-oxocyclopenta[*c*]pyran-1-carboxylate **133**, was isolated in 94% yield, and the regiochemistry of the process was assigned by X-ray crystal structure of the related amide aldol adduct <2002OL3059>.

The enantioselective synthesis of bicyclic sulfonium salts **135**, starting from thionane ring system, has been reported <2003JOC3311>. The synthetic strategy is based on a stereo- and regiospecific transannular cyclization of nine-membered cyclic sulfides, mediated by TMSI or carried out under acidic catalysis (Scheme 24, stereochemistry omitted). Each compound was prepared in two enantiomerically pure forms starting from the corresponding (*R,R*)- and (*S,S*)-intermediate.

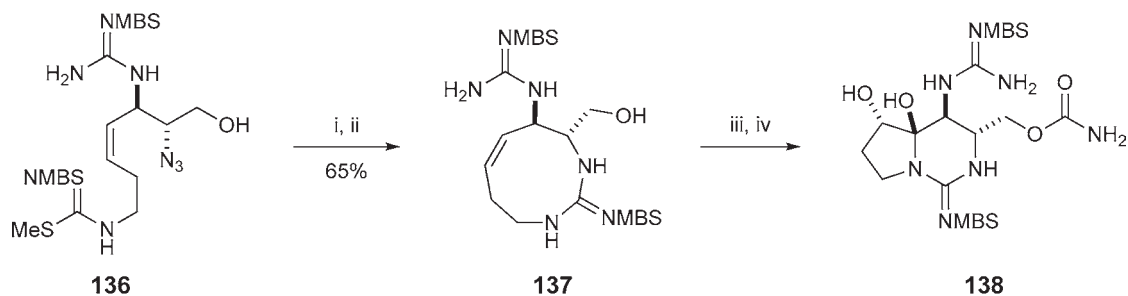


Scheme 23



Scheme 24

Nine-membered protected guanidine **137** can be readily transferred into corresponding carbamate, which was further oxidized into intermediate hydroxy ketone, which spontaneously forms the bicyclic dihydroxy compound **138** (Scheme 25) <2006JA3926>.

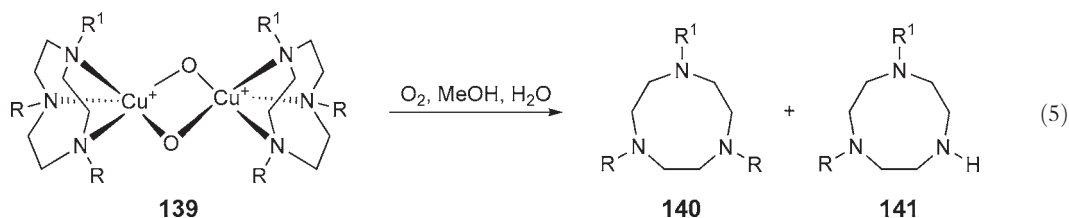


i, Me_3P , THF/ H_2O ; ii, $AgNO_3$, TEA, MeCN; iii, $Cl_3C(O)NCO$, 82%; iv, $OsCl_3$, Oxone, Na_2CO_3 , EtOAc/MeCN/ H_2O , 57%

Scheme 25

14.10.5.7 Reactivity of Transition Metal Complexes

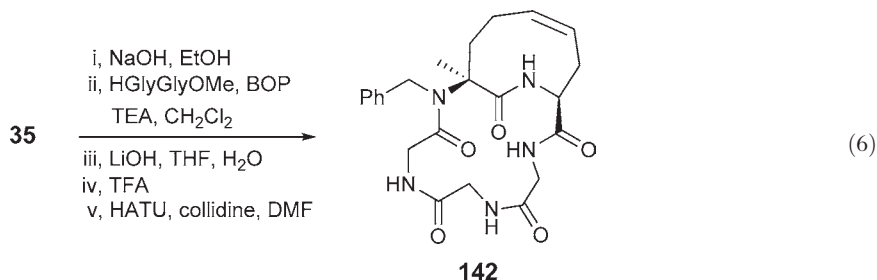
Oxidative decomposition of bis(μ -oxo)dicopper complexes of trisubstituted triazonanes **139** resulted in the dealylation products **141** along with recovered ligand **140** (Equation 5) <1996JA11575>. In the case of tribenzyl-substituted ligand ($R = R^1 = Bn$), equivalent amounts of benzaldehyde were formed and detected as side products of the oxidative process. Ligands with isopropyl moiety ($R = R^1 = i\text{-Pr}$; or $R = i\text{-Pr}$, $R = Bn$) produced acetone in the similar manner.



14.10.6 Reactivity of Substituents Attached to Ring Carbon Atoms

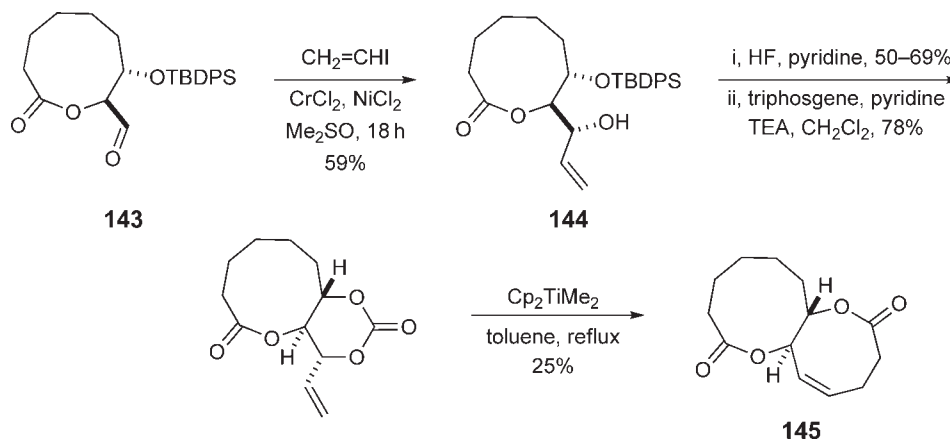
14.10.6.1 Alkyl Groups and Further Carbon Functional Groups

C-Carboxy-substituted heteronines and their protected counterparts underwent standard amide bond formation. 2,3,4,5,6,7-Hexahydro-1*H*-benzo[*e*]azonine-3-carboxylic acid underwent two sequential amide bond couplings through BOC-protected intermediate [<1997BML1289>](#). Removal of the terminal protecting groups from *cis*-azoninone **35**, followed by cyclization with *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU)/collidine, afforded the cyclopeptide **142** in 55% yield ([Equation 6](#)). Formation of the isomeric adduct (not shown) starting from *trans*-isomer of **35** was much more troublesome, giving only crude 13% yield [<2005OBC97>](#).



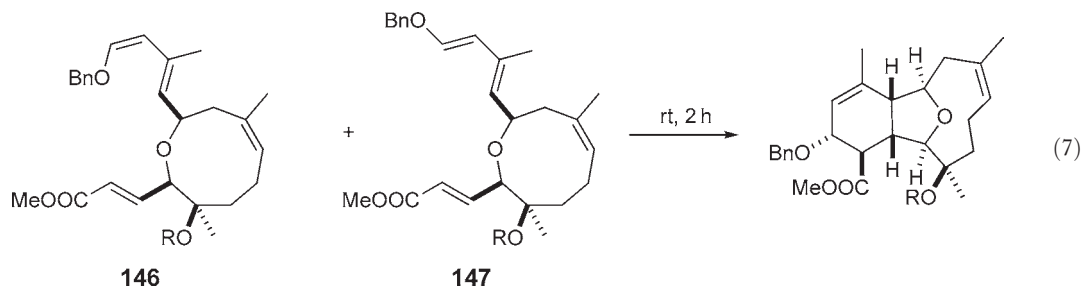
Azonanone-3-carboxylic acid **76** was converted into 3-amino-1-ethylazonine **77** by a Curtius rearrangement of intermediate azide, and final protection/reduction sequence ([Scheme 11](#), [Section 14.10.5.3](#)) [<1998BML1973>](#). Ester group of ethyl 2-oxo-1*H*-azonine-4-carboxylates was selectively reduced with NaBH₄ in *tert*-butyl alcohol and methanol to give the corresponding alcohol [<1995AGE1026>](#).

Lactone carbaldehyde **143** was treated with vinyl iodide in the presence of chromium(II) chloride and Me₂SO to provide allyl alcohol **144** in 59% yield as a 2:1 diastereomeric mixture ([Scheme 26](#); major isomer shown) [<2000CC631>](#). Further deprotection, conversion into cyclic carbonate, and final treatment with dimethyltitanocene provided *trans*-fused bicyclic lactone **145** in 25% yield.

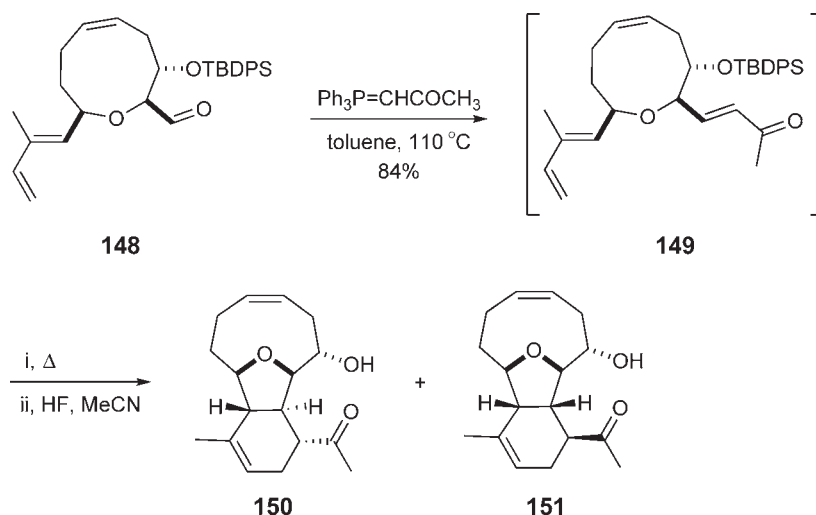


Scheme 26

Only diene **147** undergoes *exo*-Diels–Alder reaction when mixture of dienes **146** and **147** was allowed to stand at room temperature (Equation 7) <2004JA10264>. Unreactive isomer **146** was converted into **147** by irradiation, and overall 80% isolated yield was achieved when reaction mixture was submitted to several equilibration cycles.



Wittig reaction of aldehyde **148**, followed by *in situ* intramolecular Diels–Alder reaction of intermediate **149** and desilylation, afforded eunicellin analogues **150** and **151** as 3:1 mixture (Scheme 27) <2004SL1434>.

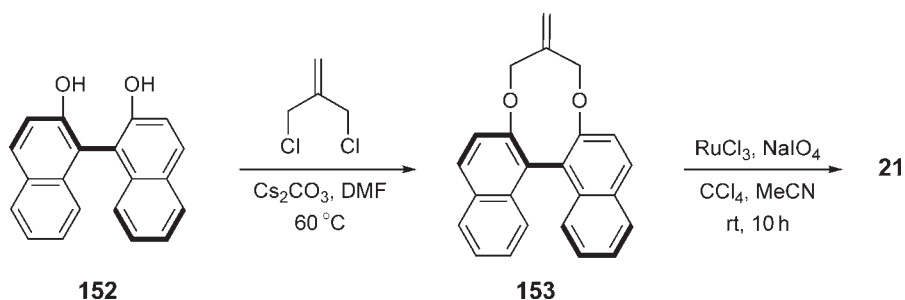


Scheme 27

Many synthetic transformations of carbon functional groups have been reported for a variety of oxonines as directed toward construction of carbon side chains of natural products (cf. Section 14.10.11). They usually involved synthesis of alcohol intermediates by DIBAL-H reduction <2001JA1533, 2004JA10264, 2006JA1371>, *p*-methoxybenzyl (PMB) deprotection <2004JA12432, 2002JA15196> or desilylation <1999JOC2616, 2003JA7592>, their Dess–Martin oxidation <1999JOC2616, 2003JA7592, 2004JA10264, 2004JA12432, 2002JA15196, 2006JA1371> into the corresponding aldehydes followed by Wittig olefination <2003JA7592, 2001JA1533, 2004JA10264, 2004SL1434, 2006JA1371>. Alternatively, aldehyde precursors can be obtained by oxidative cleavage of vicinal diols <2003JA7592, 2001JA1533> or Pummerer rearrangement, followed by cleavage <2004SL1434>. Synthetic pathways involving Peterson olefination <2004JA12432, 2002JA15196> and Sonogashira coupling <2003JA7592, 1999JOC2616> have been reported.

Oxidation of unsaturated intermediate **153** with $\text{RuCl}_3/\text{NaIO}_4$ <1998JA5943> or its ozonolysis <1997TA2921> resulted in the ketone dioxonine **21** (Scheme 28).

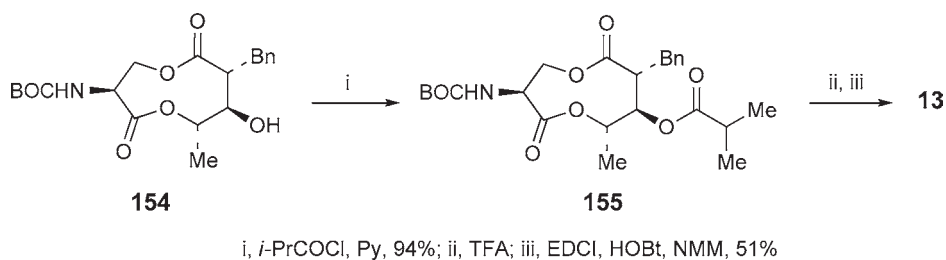
The pyrilium salt **30a** was obtained from benzo-9-crown-3 in 29% yield in two steps by formylation with hexamine in the presence of $\text{CF}_3\text{CO}_2\text{H}$, followed by reaction with 2 equiv of acetophenone in the presence of POCl_3 <2002JOC2065>. In the same manner, the Vilsmeier formylation of the *N*-phenyl dithiazonine and the subsequent condensation reaction with 2-aminobenzenethiol resulted in substituted benzothiazole **43** in 38% yield <1999J(P2)1273>. Benzo-9-crown-3 ether trimerizes in the presence of FeCl_3 and aqueous sulfuric acid to produce tris-(9-crown-3)-triphenylene **28** in 25% yield <2001CJC195>.



Scheme 28

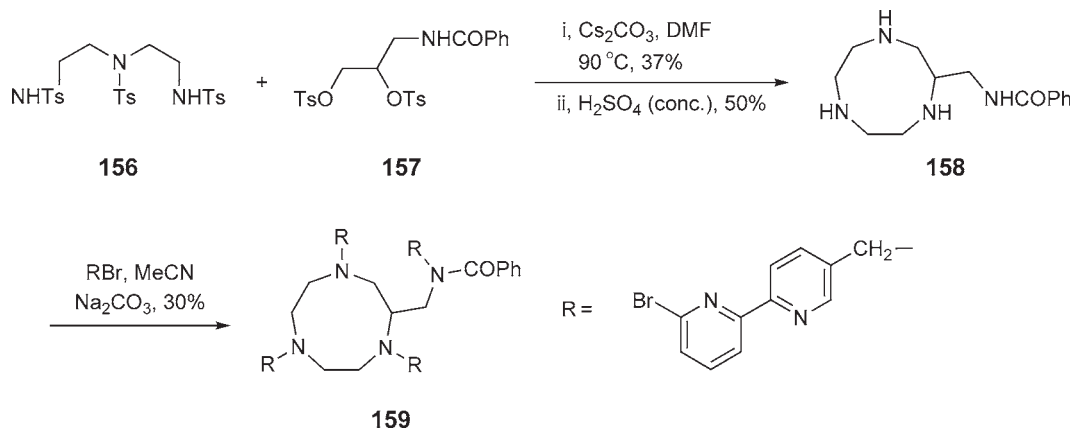
14.10.6.2 Amino and Imino Groups

Deprotection of dilactone **155** and sequential coupling with 3-hydroxy-4-methoxypyridine-2-carboxylic acid afforded (*S*)-dioxonine **13** in 51% yield (Scheme 29) <1998T12745, 1998TL4363>. Similar reaction sequence performed on (*R*)-isomer (not shown in the scheme) resulted in 61% yield of the product. Several structural analogues of amide **13**, containing heterocyclic moieties other than pyridine, were reported <2005BML2011>.



Scheme 29

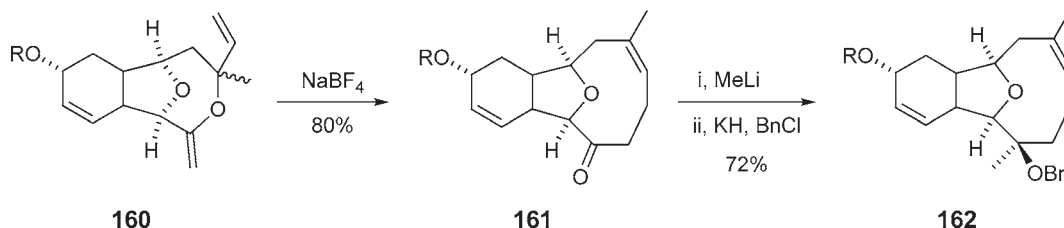
Alkylation of functionalized triazonane **158** involved both ring and side-chain amino groups and afforded tetra-substituted product **159** in 30% yield (Scheme 30) <2002JOC3933>.



Scheme 30

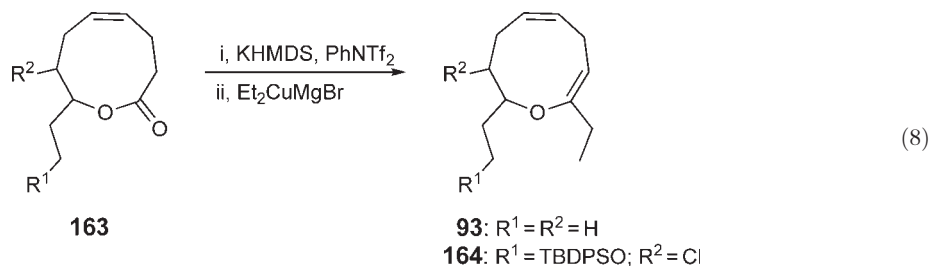
14.10.6.3 Hydroxy and Oxo Groups

C-Hydroxy heteronines underwent standard electrophilic attack to produce O-substituted derivatives. Thus, desilylation and acylation of intermediate cyclic dilactone afforded corresponding ester **155** in 94% yield (Scheme 29, Section 14.10.6.2). Similar reaction sequence performed on (*R*)-isomer (not shown in the scheme) resulted in 90% yield of the product <1998T12745, 1998TL4363>. Other examples of reactions with electrophiles include benzylation <2000OL1875, 2001JA9021> and reaction with carbon disulfide <1995J(P1)1137>. Starting hydroxy heteronines are readily available from the corresponding carbonyl compounds via reactions with nucleophiles. 3-Keto oxonine **161** (Scheme 31) was reacted with methyl lithium to give the corresponding α -methyl alcohol, which was further O-alkylated with benzyl chloride to give ether **162** <2000OL1875, 2001JA9021>.



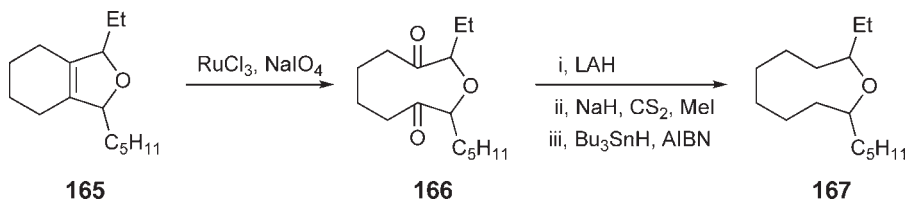
Scheme 31

Cyclic diene ether **93** was prepared in high yield starting from lactone **163** through the corresponding enol triflate (Equation 8) <1995TL8263, 1997CL665>.



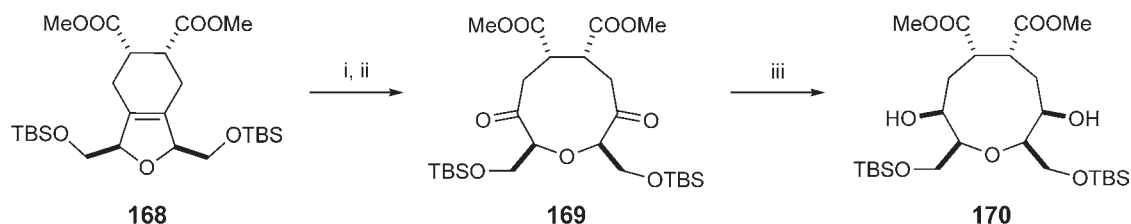
Similar synthetic strategy was applied for the preparation of functionalized cyclic ether **164** ($R^1=TBDPPO$, $R^2=Cl$, 83%) <1999JOC2616> (Chapter 14.02).

Chemical reductions of carbonyl compounds into hydroxy derivatives are more often and various reducing agents were used. Stepwise deoxygenation of diketone **166** included LAH reduction as a first step toward obtaining structure **167** (Scheme 32), which was obtained as a 2.5:1 mixture of *cis*- and *trans*-isomers <1995J(P1)1137>.



Scheme 32

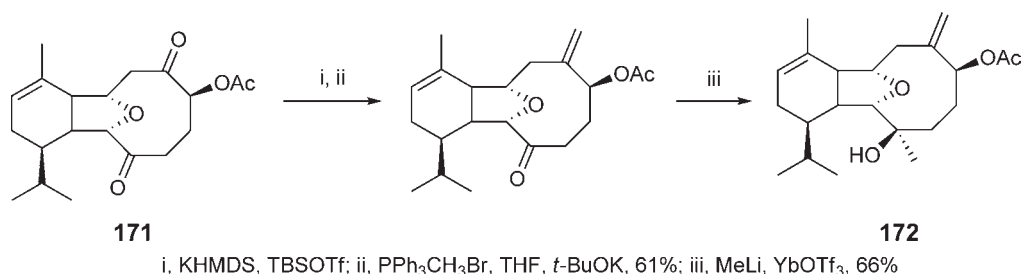
Reduction of diketone **169** with sodium borohydride proceeded stereoselectively to give diol **170**, as a single isomer in 83% yield (Scheme 33) <1999T7471>.



i, OsO₄, *N*-Me-morpholine-*N*-oxide, dioxane, H₂O, 75 °C, 94%; ii, Pb(OAc)₄, Py, 94%; iii, NaBH₄, MeOH, 0 °C, 94%

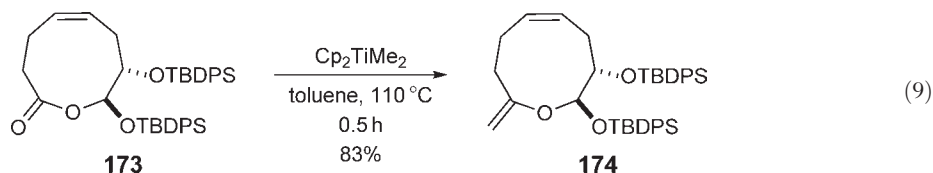
Scheme 33

A keto group was extensively used in olefinations, providing a convenient access to natural-type oxonine products. Chemoselective formation of silyl enol ether of oxonine **171** (Scheme 34) followed by Wittig olefination, deprotection, and diastereoselective methylation afforded acetate **172** in good yield <2004JA1642>.

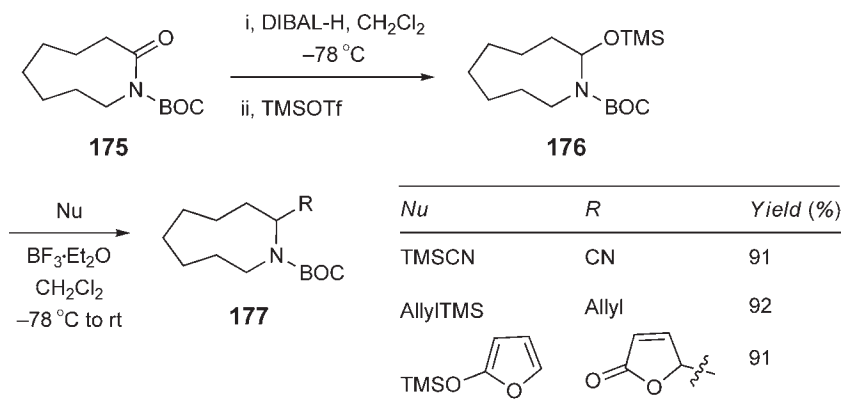


Scheme 34

Lactone precursor **173** was converted in 83% yield into enol ether **174** via Petasis methylation (Equation 9) <2004SL1434>.



The DIBAL-H reduction of lactam **175** and subsequent etherification of the resulting *N,O*-hemiacetal with TMSOTf resulted in **176** (Scheme 35). It was further reacted with a variety of nucleophiles in the presence of Lewis acid to afford corresponding α -substituted azonines **177** in high yields <2002TL3165>.



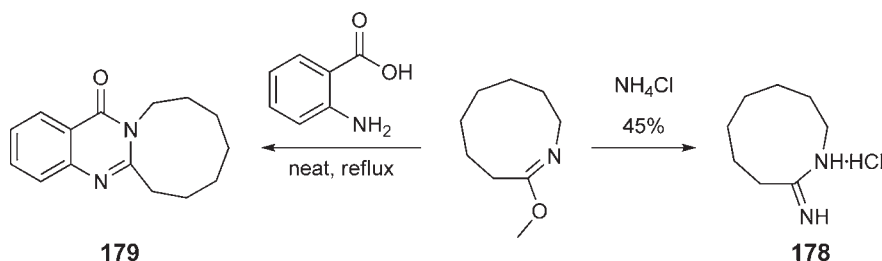
Scheme 35

Reduction of nine-membered lactam with $\text{BH}_3\text{--THF}$ afforded the corresponding reduced azonine in moderate yield [<1996T8063>](#).

Reaction of 3-hydroxy-oxonene **103** with the complex of bromine and 1,2-bis(diphenylphosphino)ethane resulted in an expected mixture of brominated compounds **105** and **106**, along with single stereoisomer of oxocene **107**, probably due to the formation of the bridged oxonium cation and its two different directions of the reaction with bromide anion ([Scheme 17](#), [Section 14.10.5.3](#)) [<1995TL8263>](#).

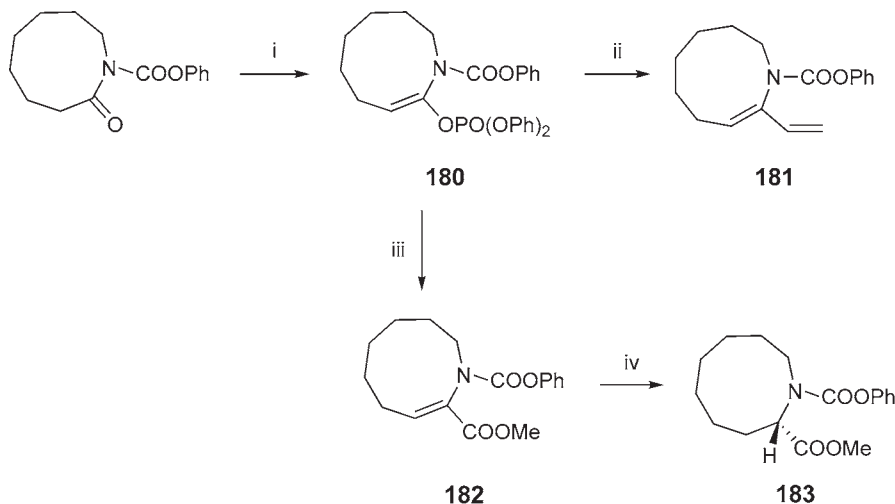
14.10.6.4 Other O-Linked Groups

Azonan-2-one easily forms cyclic imidate, which produced azonan-2-imine **178** ([Scheme 36](#)) [<1996JME669>](#). On the other hand, its reaction with anthranilic acid led to the corresponding quinazolinone-type 6,6,9-ring system **179** [<1996BML737>](#).



Scheme 36

N-Protected 2-oxoazonane formed ketene aminal diphenylphosphate **180** via potassium enolate. It underwent coupling reactions with appropriate partners under palladium(0)-catalyzed conditions ([Scheme 37](#)). Reactions proceeded smoothly in good to excellent yields furnishing diene **181** and ester **182** [<1998CC1757>](#).



i, $(\text{PhO})_2\text{POCl}$, KHMDS, THF, -78°C , 0.5 h, 41%; ii, $\text{Bu}_3\text{SnCH=CH}_2$, $\text{Pd}(\text{PPh}_3)_4$, LiCl, THF, 94%;
 iii, CO (1 atm), $\text{Pd}(\text{OAc})_2$, PPh_3 , MeOH, Et_3N , DMF, 60°C , 4 h, 74%; iv, H_2 (90 psi), cat., MeOH, rt, 97%, 94.5% ee

Scheme 37

Oxonine with homoallyl ether side chain was a suitable intermediate for RCM synthesis of oxonines with annulated oxepine ring <2004TL7567>.

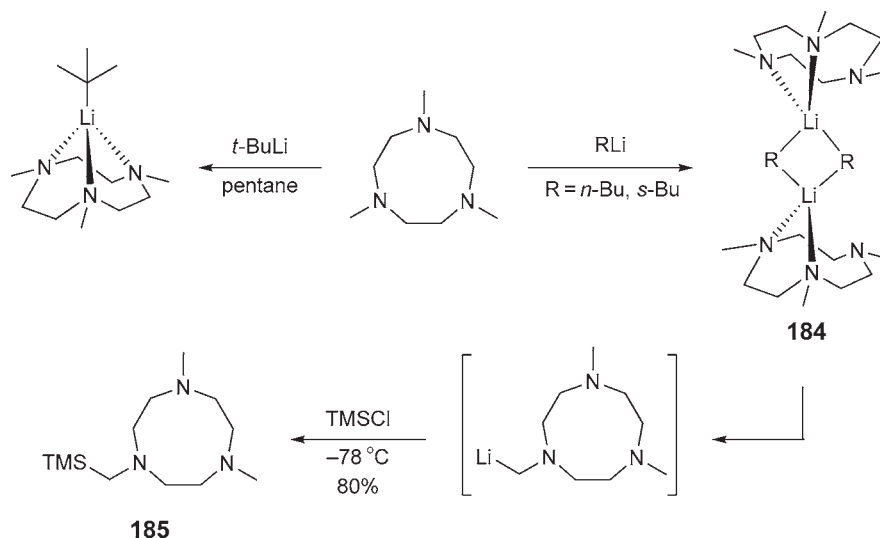
14.10.6.5 Halogen Atoms

Synthesis of ester **83a** and amide **83b** was performed by palladium-catalyzed carbonylation starting from iodo lactone **98** to afford products in good yields (Scheme 13, Section 14.10.5.4) <2002JOC4565>.

14.10.7 Reactivity of Substituents Attached to Ring Heteroatoms

14.10.7.1 Alkyl Groups

Monomer complex of *t*-BuLi with 1,4,7-trimethyl-1,4,7-triazacyclononone **9** is identified by ^{13}C NMR and it is stable in pentane at temperatures up to 20 °C and (Scheme 38) <1997T9977>. Conversely, lithiation of *N*-Me was the exclusive reaction with *n*-BuLi and *s*-BuLi, as indicated by the formation of TMS derivatives **185**, isolated after silylation of the reaction mixture. This result evidenced the existence of uncoordinated *N*-Me groups in complexes with *n*-BuLi and *s*-BuLi. Dimeric structure **184** was suggested based on decreasing tendency to form monomer complexes going from *t*-BuLi via *s*-BuLi to *n*-BuLi.

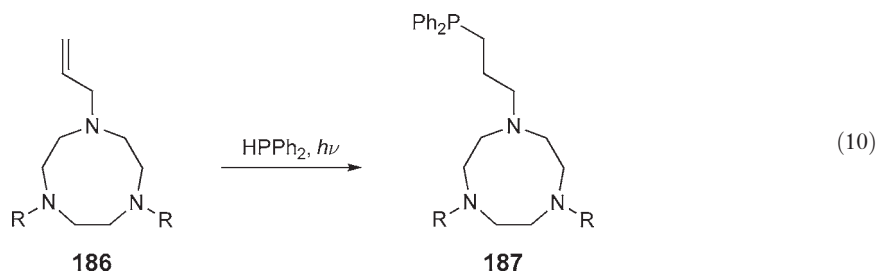


Scheme 38

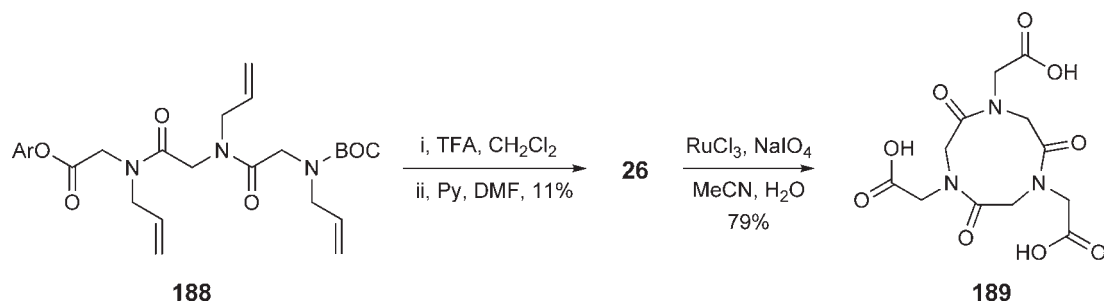
Trityl protecting groups are easily cleaved (MeOH, HCl) from substituted 1,4,7-triazonane <1995HCA693>. Reaction of 2-methyl-2-[(trimethylsilyl)methyl]-2,3,4,5,6,7-hexahydro-1*H*-2-benzazoninium iodide **47** with cesium fluoride in DMF for 0.5 h at room temperature led to formation of ylide, which spontaneously transforms into a mixture of ring-enlargement products **119** and **120** (Scheme 20, Section 14.10.5.6.2) <1997JOC2544> (Chapter 14.11).

14.10.7.2 Further Carbon Functional Groups

The key step in the synthesis of triazonines with pendant diphenylphosphine arms is the free radical addition of Ph_2PH across the alkene double bond (Equation 10) <1996CC1817>. This is accomplished in quantitative yield by photolysis under strictly anaerobic conditions using a mercury lamp. The method was not restricted to allyl substituents; longer-arm alkenes react in an identical manner, although more slowly, yielding phosphines with longer alkyl, for example C-5, chains.



Oxidative cleavage of triallyl cyclic tripeptide **26** resulted in 79% of tricarboxylic acid **189** (Scheme 39) <2004TL1091>.



Scheme 39

N-Acyl heteronines with more than two nitrogen atoms were of primary interest due to their synthetic utility through protection/deprotection sequences. *N*-Formyl 1,4,7-triazonanes are easily accessible from 1,4,7-triazatricyclo[5.2.1.0^{4,10}]-decane (see Section 14.10.9.1). This protecting group was readily cleaved in refluxing 3 M hydrobromic acid as it was demonstrated for 1-formyl-4,7-bis(2-hydroxyethyl)-1,4,7-triazacyclononane <2003AJC61>. Deprotection of 1-formylazonane and 1-formyl-4-benzylazonane was achieved under basic conditions with KOH in ethanol <1994CC2467> or Amberlite IRA400 resin <1999J(P1)1211>. Formyl-protected derivative of the bridged bis-thiadiazonine was successfully deprotected in 3N HCl to afford 46% of the product <1997HCA2315>.

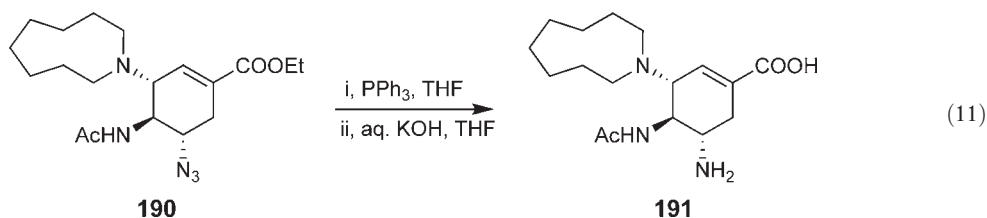
Di-BOC-1,4,7-triazonanes are smoothly deprotected with trifluoroacetic acid (TFA) in dichloromethane <2001JA5030, 2001JA6025>. Triazonines can be selectively cleaved from the trityl-type polymer support with 1% TFA in CH₂Cl₂, while BOC-protecting groups are not affected under these conditions <2004SL453>.

Synthesis of 1,4-di-Cbz-protected triazonane and further substitution on the position 7 and 1,4-deprotection were reported <2000JOM(611)586>. Methyl carbonate protecting group is easily removed in *p*-hydroxybenzoyl derivatives of thiadiazonane and dithiazonane by NH₄OH <2001JMC1011>. Their further O-acylation gave a variety of derivatives with ester substituents on benzoyl moiety.

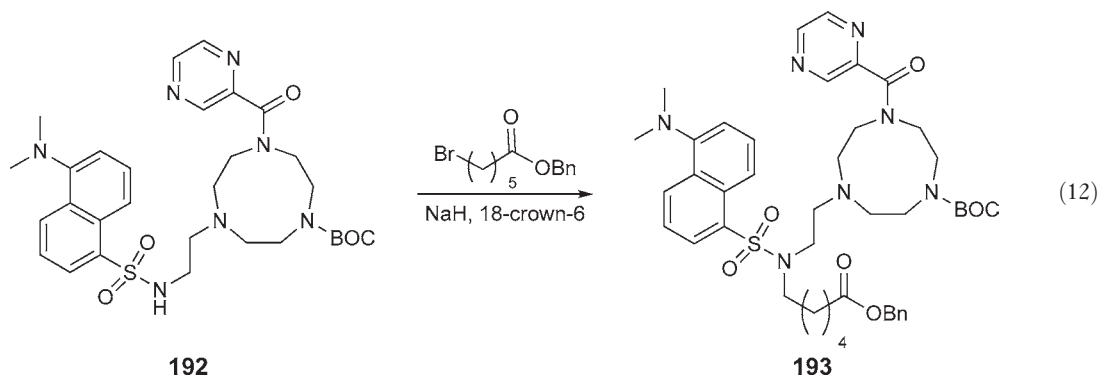
Reduction of *N*-acyl moieties in heteronines proceeded in a regular fashion. Thus, refluxing of quinazolinone **179** (Section 14.10.6.4) with zinc dust in acetic acid/hydrogen chloride afforded the corresponding quinazoline <1996BML737>. Both ring and side-chain BOC protecting groups of 1,4,7-triazonane afforded the corresponding methyl derivatives upon treatment with LAH in refluxing THF <2003TL5699>. Carboxy functional groups attached to heteronine ring with a spacer show usual reactivity, for example, amide coupling through preparation of activated pentafluorophenyl ester <2002S1398>.

14.10.7.3 Amino Groups and Other N-linked Substituents

Azide **190**, available through palladium-catalyzed amination of the corresponding cyclohex-2-enyl acetate with azonane, can be sequentially reduced and hydrolyzed to produce amino acid **191** (Equation 11) <2000BML1257>.



N-Alkylation of the sulfonamide **192** with benzyl 6-bromohexanoate yielded the highly functionalized **193** – a valuable synthon for fluorescent sensors synthesis (Equation 12) <2000TL9601>.



Amide group reduction of *N*-acyl-1,4,7-triazonanes with LAH proceeded smoothly to afford corresponding saturated alkyl chain derivatives <1995CC929, 2001CC637, 2003TL5699>. Reduction of side-chain nitrile group with borane–THF complex in refluxing THF led to the corresponding amine in 67% yield <2000NJC575>, while hydrogenation of azide affords 93% of amine **57** (Scheme 4, Section 14.10.5.2.1) <2002JME3458>.

1-(3,5-Di-*tert*-butyl-2-nitrobenzyl)-4,7-dimethyl-1,4,7-triazacyclononane can be easily reduced with LAH in THF to afford corresponding 2-aminobenzyl derivative <2000JA9663>. Reduction of side-chain aromatic nitro group in trisubstituted triazonanes with Raney-Ni has been reported <2000CC443>.

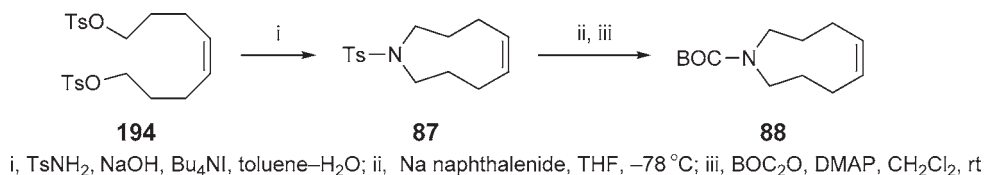
14.10.7.4 Hydroxy and Oxo Groups

N-2-Hydroxyethyl- and *N*-3-hydroxypropyl-1,4,7-azonanes were smoothly converted into corresponding chlorides with thionyl chloride in high to quantitative yields (Scheme 4, Section 14.10.5.2.1) <2002JME3458>; see also <2004JME5683> and <2005BMC2389>. 3-*N*-Hydroxypropylazonane was activated through tosylation and further reacted with 3,4-disubstituted pyrrole to afford derivative **55** in good yield (Scheme 3, Section 14.10.5.2.1) <2003T9239>.

14.10.7.5 S-Linked Substituents

Developments in the chemistry of *N*-tosyl heteronines and similar sulfonamides are connected with their easy accessibility through Richman–Atkins cyclization (Section 14.10.8.3) and synthetic utility through protection/deprotection sequences. Selective cleavage of sulfonamides was a primary goal of many studies.

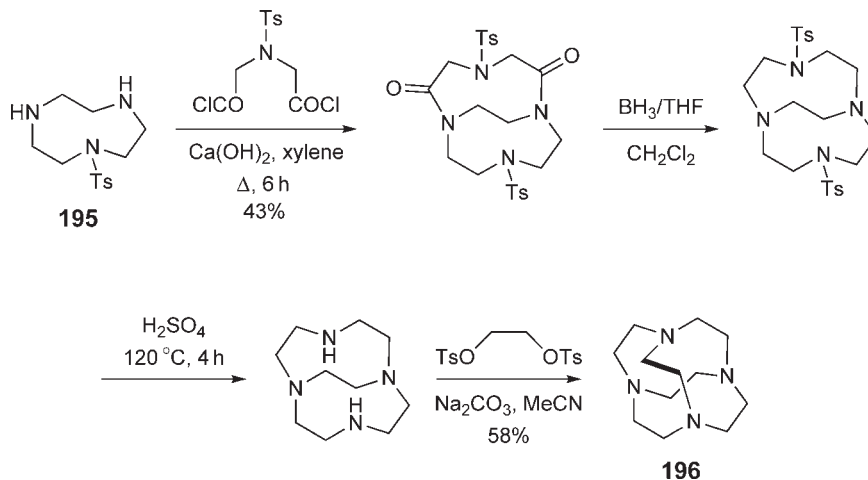
Exchange of protecting group for azonine was achieved in two steps (Scheme 40), including detosylation of intermediate **87** using sodium naphthalenide and immediate BOC reprotection of the amine hydrochloride salt to give the BOC-azonine **88** in 64% yield <1999CC309>.



Scheme 40

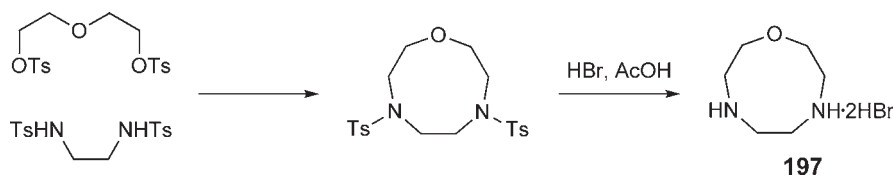
Mono- and ditosylated 1,4,7-triazacyclononanes were synthesized in 30% and 68% yields, correspondingly, by rapid partial deprotection of 1,4,7-tritosyl-1,4,7-triazacyclononane in vigorously stirred refluxing acetic acid–hydrobromic acid mixture [<2001SC3141>](#). Rapid full detosylation of tritosyl 1,4,7-triazonane was achieved in high yield by heating it in a 50% solution in concentrated sulfuric acid at 170–180 °C for 5–8 min [<1995SC3181>](#), or at milder conditions for a prolonged period of time [<2004OBC2664>](#). This process is accelerated by microwave irradiation [<2003PJC485>](#).

Similarly, two tosyl groups were selectively removed by heating under reflux in 47% water HBr solution and acetic acid in 2:1 ratio for 5 h to afford **195**, as a dihydrobromide salt in 69% yield [<1999AGE956>](#). The next sequence of four synthetic steps (**Scheme 41**), including second nine-membered ring annulation, reduction, full detosylation of bicyclic intermediate with sulfuric acid, and bridge formation, resulted in hexaethylene tetramine **196**.



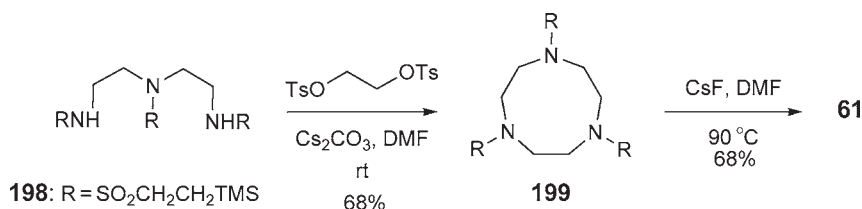
Scheme 41

The ditosyl derivative of 1,4,7-oxadiazonane was reacted with HBr in acetic acid to afford the deprotected **197**, as HBr salt in 87% yield (**Scheme 42**) [<2004T5799>](#).



Scheme 42

ortho-Nitrophenyl sulfonyl protecting group was easily removed from 1,2,7-thiadiazonine using potassium carbonate/thiophenol in DMF (**Scheme 9**, Section 14.10.5.2.1) [<2004JOC3662>](#). Removal of the β -trimethylsilylethane-sulfonamide (SES-sulfonamide) group from triazonane **199** smoothly occurred upon treatment of the macrocyclic tris-sulfonamide with CsF in DMF at 95 °C for 24 h (**Scheme 43**) [<2001JOC2722>](#).

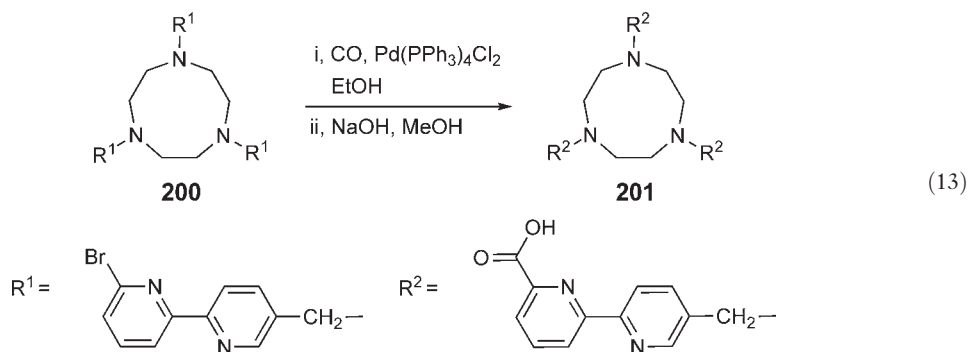


Scheme 43

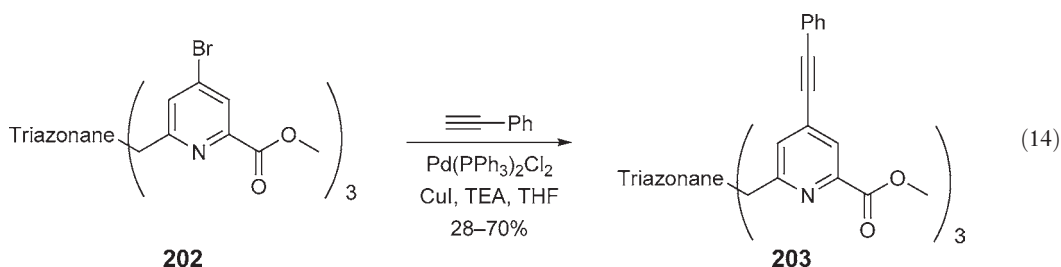
Triazonane thiobenzyl derivative **62** was smoothly transformed into corresponding thiol **63** using sodium in liquid ammonia (**Scheme 6**, Section 14.10.5.2.1) <1999T5733>.

14.10.7.6 Halogen Atoms

Triazonane bearing three ethyl carboxylate 2,2'-bipyridine units was synthesized in 83% yield from the corresponding 6-bromo derivative **200** by a carboalkoxylation reaction promoted by a catalytic amount of Pd(0) (**Equation 13**). Subsequent smooth saponification resulted in the tris-acid **201** in 80% yield <2001JA2436, 2002JOC3933>.



Trisubstituted 4-bromopyridine **202** was coupled with phenyl acetylene to produce corresponding alkyne **203** in 28–70% yield (**Equation 14**) <1996HCA789>.



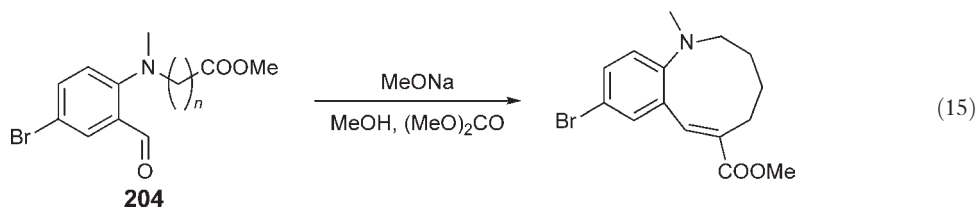
14.10.8 Ring Syntheses from Acyclic Compounds

14.10.8.1 Bond Formation by Intramolecular Cyclization

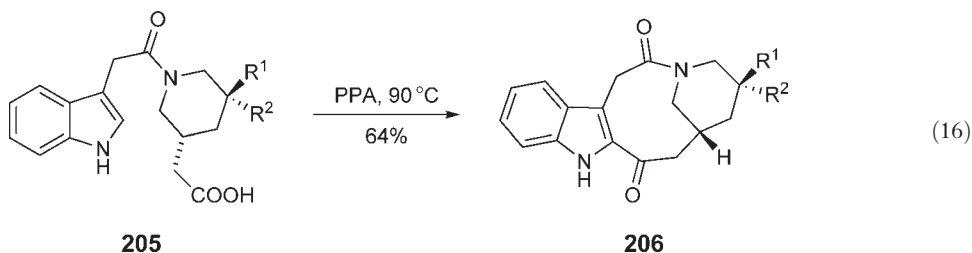
Unimolecular cyclization is an important method of heteronine ring system formation. It is reviewed in this section in the order of the bond types formed. Taking into account the synthetic value of the RCM strategy and its extensive development over recent years, it is excluded from general discussion of C–C bond-formation reactions in Section 14.10.8.1.1 and considered separately in Section 14.10.8.6.

14.10.8.1.1 C–C Bond formation

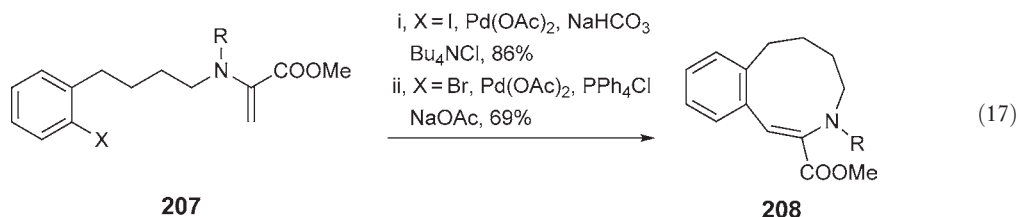
A convenient synthesis of 1-benzazonine, which can be performed in large scale, involved intramolecular cyclization of formyl derivative **204** to give the product in 18% yield (**Equation 15**) <2004TL9335>.



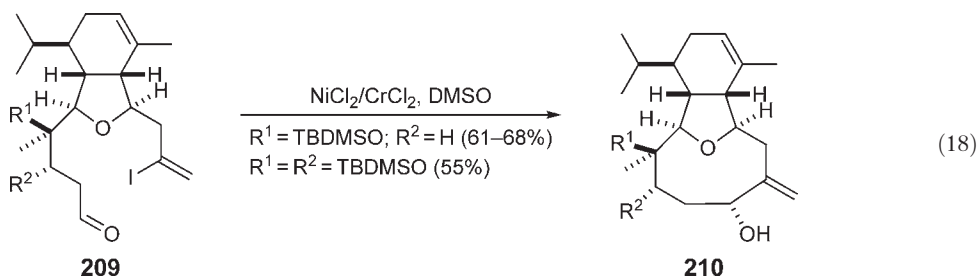
Closure of the nine-membered ring for the *trans*-isomer of the indole derivative **205** was carried out by heating with PPA for 30 min at 90 °C to give the desired tetracyclic keto lactam **206** in good yield (Equation 16) <2006JOC3804>.



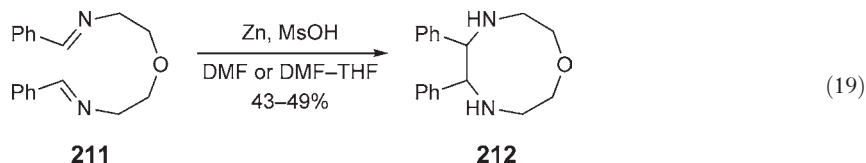
Heck-type cyclization of iodo ester **207** (X = I) with catalytic amounts of palladium acetate proceeded smoothly to generate **208** in 86% yield (Equation 17) <2002EJM379, 1999SL954, 1995CC1743, 1997CC637, 1997J(P1)447>. A catalytic system utilizing PPh₄Cl permitted the extension of this methodology to the corresponding aryl bromide (X = Br) <1999SL954>.



The oxonane ring was fashioned by treating aldehydes **209** with NiCl₂/CrCl₂ in dimethyl sulfoxide (DMSO) to provide tricyclic ether **210** in 65% yield (Equation 18) <1995JA10391, 2000OL2683, 2001JA9033, 2001OL135, 2003JA6650, 2003OL1543>.



Reductive coupling of aromatic diimine **211** with zinc in the presence of MsOH in DMF or DMF–THF led to the substituted dioxidiazonane **212** in 43–49% yield (Equation 19) <1995JOC3980>.

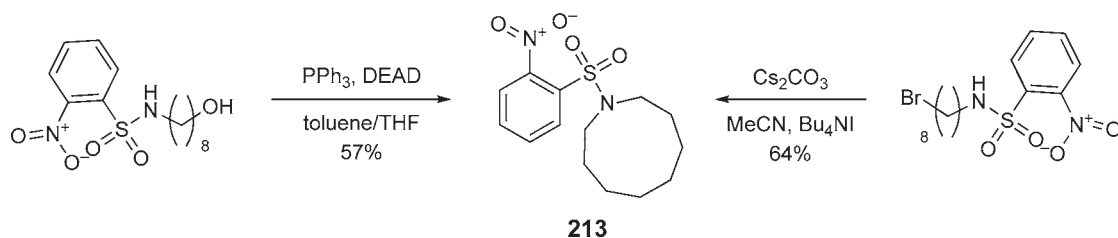


14.10.8.1.2 C–N bond formation

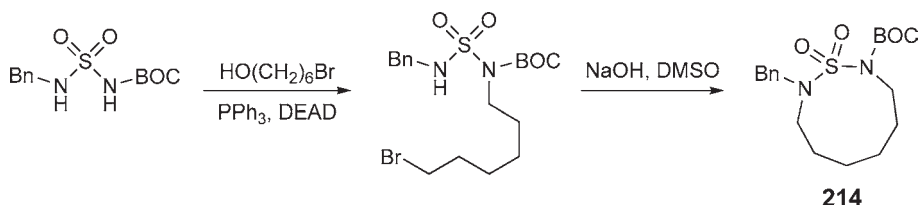
The most general methods of C–N bond formation used for heteronine formation are alkylation or Mitsunobu condensation. Azonine **213** was synthesized starting from 2-nitrobenzenesulfonamides and using conventional alkylation procedures or Mitsunobu conditions (Scheme 44) <2002SL697, 2002T6267>.

Facile formation of nine-membered N,N'-protected cyclic sulfamide **214** was carried out in two steps by an intermolecular Mitsunobu condensation and subsequent intramolecular N-alkylation (Scheme 45) <2003T6051>.

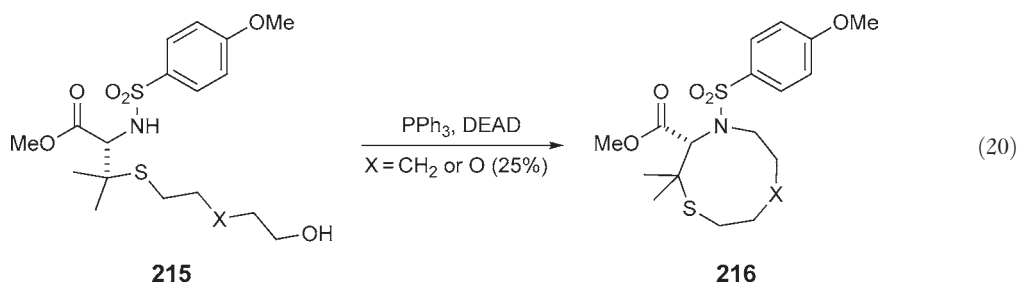
Mitsunobu cyclization of sulfonamides **215** produced substituted heteronines **216** in moderate yield (Equation 20) <1999JME4547>.



Scheme 44



Scheme 45

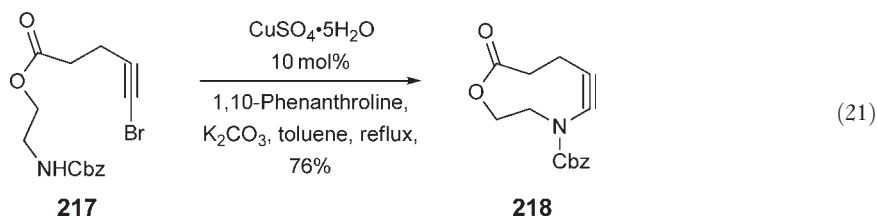


An intramolecular Mitsunobu reaction of alcohol **78** was performed under high-dilution conditions (0.01 M) providing cyclic tosyl derivative **20** in 73% yield (Scheme 12, Section 14.10.5.4) <2006OL963>.

Amide bond-formation cyclizations were reported. Deprotection of di-BOC derivative **125** (Scheme 22, Section 14.10.5.6.2) and subsequent treatment with DIPEA led to the oxazonine dione **126** in good yield <2002T2957>. Activated ester **188** after deprotection was converted in the mixture of pyridine and DMF under diluted conditions into cyclic tripeptide **26** in 11% yield along with 22% of *N,N'*-diallyldiketopiperazine (Scheme 39, Section 14.10.7.2) <2004TL1091>.

Unusual macrocyclization with the formation of guanidine moiety has been reported (Scheme 25, Section 14.10.5.6.3) <2006JA3926>. Reduction of azide **136** with Me_3P was followed by its immediate exposure to AgNO_3/TEA . The latter conditions presumably trigger formation of a reactive *N*-sulfonylcarbodiimide, which in turn is intercepted by the pendant C-6-amine to form the nine-membered guanidine **137** in 65% yield.

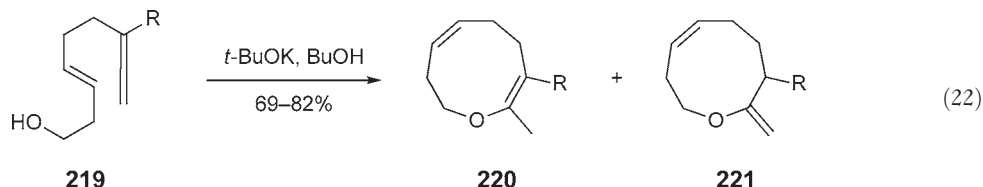
Copper(II)-catalyzed intramolecular amidation of alkynyl bromide **217** led to macrocyclic ynamide **218** in 76% yield (Equation 21) <2006JOC4170>.



14.10.8.1.3 C–O bond formation

The most general method of cyclization through C–O bond formation is lactonization, and its synthetic aspects, including alcohol or acid moiety activation, enantio- and diastereoselectivity, were reviewed recently [<2006CRV911>](#).

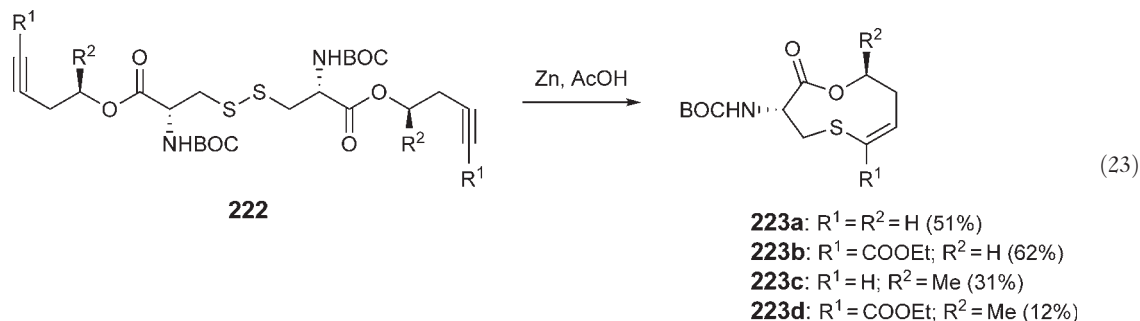
Synthesis of cyclic ethers is less common. Thus, basic conditions (*t*-BuOK in BuOH at 30 °C) effected the rapid *endo*-mode ring closure of the allene derivatives **219** to furnish 2,3,6,7-tetrahydro-9-methyloxonines **220** in good yields as single isomers (Equation 22) [<2004JOC6867>](#). In the case of sulfonyl derivative **220** (R = SO₂Ph), the *endo*-mode reaction proceeded as expected to give the ring-closed products in 66% yield as a mixture of **220** and its isomer **221** with an *exo*-methylene moiety in a ratio of ca. 2:1.



Oxonan-2-yl methanols are readily available from the corresponding hydroxy epoxides [<2003TL2709>](#). 1,4,7-Oxadithionane was isolated and characterized as a side product of hydrolysis of 1,2-bis(2-chloroethylthio)ethane [<2003AJC309>](#).

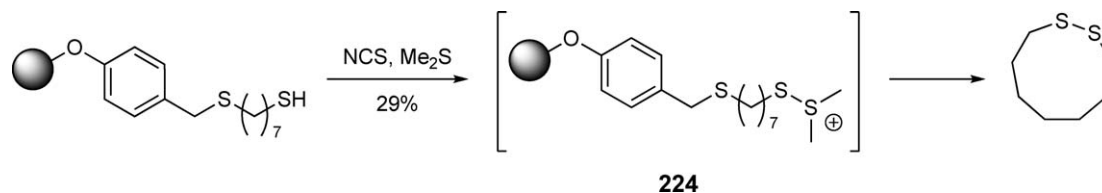
14.10.8.1.4 C–S bond formation

Treatment of cystine derivatives **222** with Zn/AcOH led to S–S bond cleavage and ring closure of intermediate thiols into lactones **223a–d** in moderate yields (Equation 23) [<2004S3029>](#).



14.10.8.1.5 S–S bond formation

Polymer-bound thiol was reacted with the complex of NCS and dimethylsulfide to afford 1,2-dithionane through spontaneous cyclization of the dimethyl(thio)sulfonium intermediate **224** (Scheme 46) [<2000TL9989>](#).



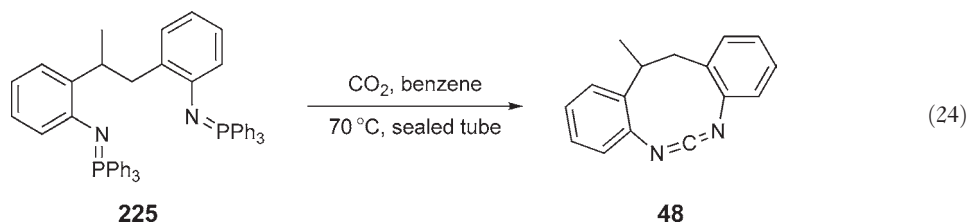
Scheme 46

14.10.8.2 Ring Formation by [8+1] Cyclization

Cyclization of the ditosylate **194** under dilute conditions gave *N*-tosyl azonine **87** in 62% yield (Scheme 40, Section 14.10.7.5) [<1999CC309, 2001J\(P1\)2161>](#). Similarly, monosubstituted ditosyl 1,4,7-triazonanes are readily available from the corresponding 1,8-ditosylate **56** and amine, for example, Scheme 4 (Section 14.10.5.2.1) [<2002JME3458>](#);

see also <2003SC1147>, <2001EJO4233>, and <1999TL9363>. Synthesis of thionane ring system from the corresponding 1,8-ditosylate **134** and sodium sulfide in 65% yield has been reported (Scheme 24, Section 14.10.5.6.3) <2003JOC3311>.

Bis(iminophosphorane) **225** was reacted with carbon dioxide in dry benzene at 70 °C in a sealed tube to afford the nine-membered cyclic carbodiimide **48** in 98% yield (Equation 24) <1996JOC4289>.



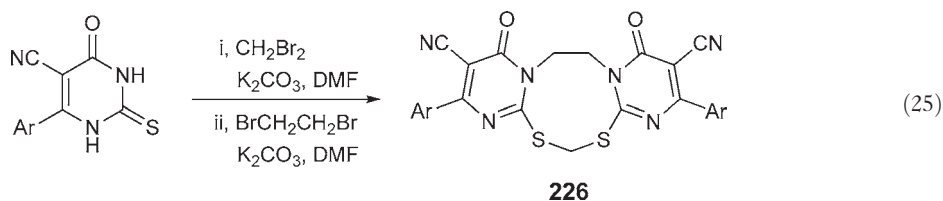
1,3-Dioxonines are readily available from corresponding 1,6-diols and geminal dielectrophiles. Therefore, *trans*-acetalization of substituted acrolein dimethyl acetals with 1,2-phenylenedimethanols has been reported <2004T415>. Reaction of substituted 1,1-difluoro alkene with 1,6-hexanediol led to the formation of dioxonane ring in 2% yield <1995H(41)641>.

14.10.8.3 Ring Formation by [7+2] Cyclization

Cyclizations of this type involved suitable 1,7-dinucleophilic species and 1,2-dielectrophile, which is typically a 1,2-dihaloethane or ethylene glycol ditosylate.

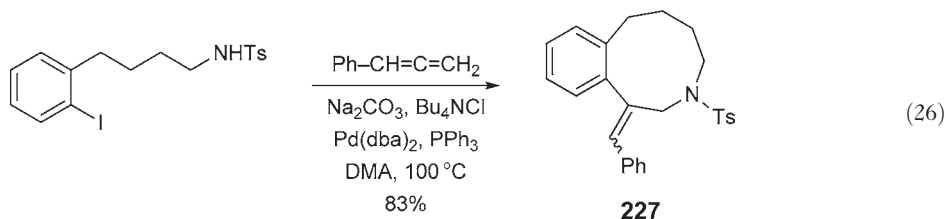
The Richman–Atkins cyclization of tritosyl-substituted ethylenetriamine with glycol ditosylate gave tritosyl 1,4,7-triazonane, for example, Scheme 30 (Section 14.10.6.2) <2002JOC3933>; see also <1998J(P2)83> and <2002IJB372>. Functionalized <2003OBC2357> and chiral <2002TL3795, 2002OL949, 2003OBC4408> derivatives of diethylenetriamine can also be used. Similar reaction of tri- β -trimethylsilylethanesulfonamide **198** afforded the protected triazonane **199** in 68% yield (Scheme 43, Section 14.10.7.5) <2001JOC2722>. Kuksa *et al.* reported Richman–Atkins-type cyclization of bis-hydroxylamine to produce dioxadiazonine ring system <1999S1034>.

Reaction of 2,2'-thiodiethanethiol with 1,2-dichloroethane yielded 37% of 1,4,7-trithionane <1995T4065>. A convenient synthesis of 2,3-pyrimidinophanes **226** has been described starting from 6-aryl-5-cyano-2-thiouracils (Equation 25) <2003JCM380>. A reaction of 2-thiouracil with dibromomethane and a sequential second S-alkylation with dibromoethane under basic conditions produced 2,3-pyrimidinophane **226** in 11% yield.



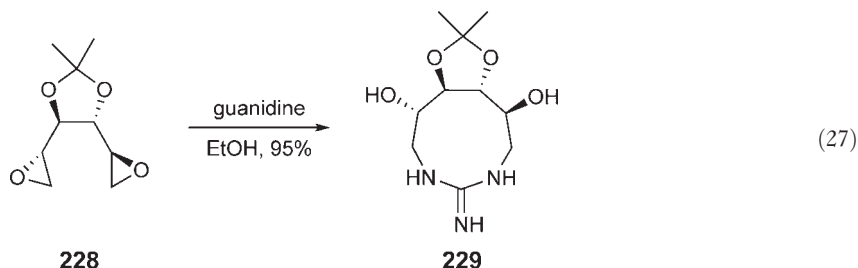
1,2-Diketone, for example, benzyl, can serve as a dielectrophile in its reaction with diethylenetriamine giving triazonine **52** as a product under UV irradiation in the presence of oxygen (Scheme 2, Section 14.10.5.1) <2000NJC719>).

Palladium-catalyzed heteroannulation is illustrated by synthesis of substituted 1*H*-benzo[*d*]azonine **227**, which was prepared from allene and tosylamide-containing aryl halide (Equation 26). The reaction was suggested to proceed by addition of an arylpalladium compound to the allene to generate a π -allylpalladium intermediate, which subsequently undergoes nucleophilic displacement of palladium at the less-hindered end of the π -allyl system <1998JOC6859>.

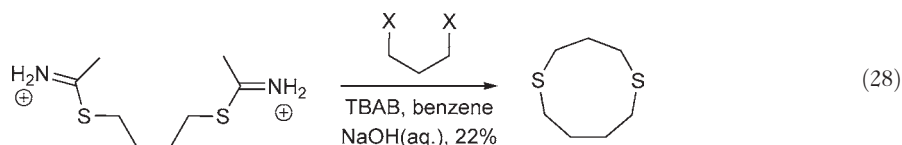


14.10.8.4 Ring Formation by [6+3] Cyclization

Guanidine serves in a regular manner as a 1,3-dinucleophile when reacted with suitable 1,6-dielectrophile. This approach resulted in an efficient method for the synthesis of symmetrical cyclic guanidino-sugars **229** from 1,2:5,6-dianhydro-3,4-*O*-methylethylidene-L-iditol **228** (Equation 27) <1998SL402, 2000BMC307>.



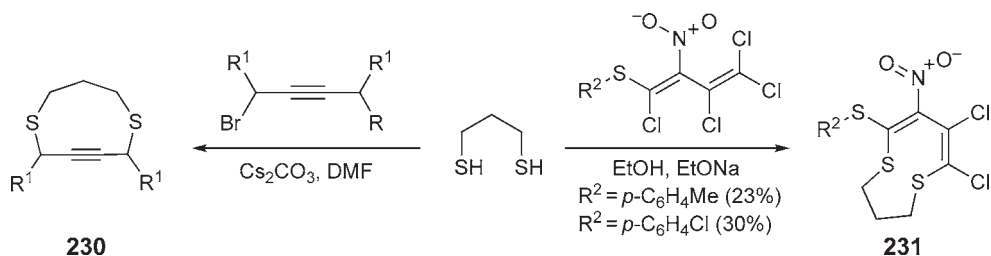
A useful route toward heteronines is an application of 1,3-dielectrophiles when they react with O- and S-nucleophiles. The chiral (*R*)-1,1'-bi-2-naphthol **152** was reacted with 3-chloro-2-(chloromethyl)prop-1-ene to afford dioxonine **153** (Scheme 28, Section 14.10.6.1) <1998JA5943, 1997TA2921>. A novel procedure for the preparation of cyclic polythioethers by the reaction of dithioiminium salt with 1,3-dihalopropane using phase-transfer catalyst has been reported (Equation 28) <2003PS1295>. This approach avoided the use of thiols, which are not only hard to handle, but also prone to oxidation.



Reaction of vicinal oximes with 1,3-dibromopropane in THF in the presence of 2 equiv of NaH resulted in 60% of 1,5,6,9-dioxadiazonines <2000H(53)851>.

14.10.8.5 Ring Formation by [5+4] Cyclization

1,5-Dinucleophilic reagents have a limited use in heteronine ring assemblies. 1,5-Dioxonane-3,6,9-trione **22** was readily available from succinic anhydride and 1,3-dihydroxy acetone <1998JOC9888>. Dithionine **230** has been prepared by the reaction of 1,4-dibromobut-2-yne ($\text{R}^1=\text{H}$) with dithiol in DMF in 75% yield (Scheme 47) <1996JOM(519)177>. The more-hindered dibromide ($\text{R}^1=i\text{-Pr}$) gave a mixture of the corresponding dithionine and dimeric 18-membered product. Reaction of 2-nitropentachlorobutadiene with 1,3-dithiopropane in ethanol under basic conditions led to dithionines **231** in moderate yields <1996BSB317, 1997PS79>.



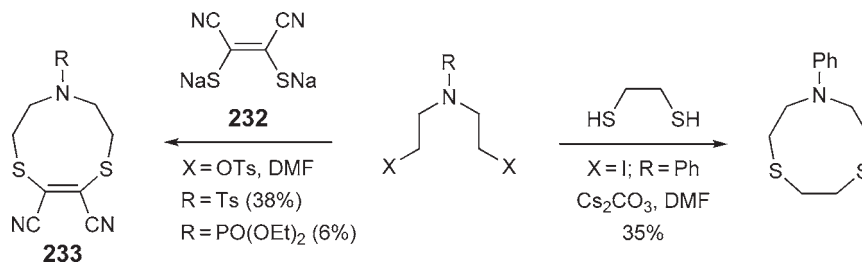
Scheme 47

The reaction of benzoin oxime with sodium hydride in propan-2-ol produced a 1,5-dianion which further cyclized with 1,4-dibromobutane into dioxazonine in 75% yield <2004S837>.

The use of 1,4-dinucleophiles is more common due to accessibility of 1,2-dihydroxy compounds, 1,2-diamines, and their derivatives. Benzo-9-crown-3 ether is easily available from pyrocatechol and 1-chloro-2-(2-chloroethoxy)ethane <1998ANC5259, 2002JOC2065>. Similar procedure for 2,3-dihydroxynaphthalene resulted in a 4.5% yield of naphtha-9-crown-3 <2000JST(526)185>.

Ditosyl derivative of 1,4,7-oxadiazonane was synthesized from *N,N'*-ditosyl diaminoethane and diethylene glycol ditosylate (see **Scheme 42**, Section 14.10.7.5) <2004T5799> or with 1-chloro-2-(2-chloroethoxy)ethane <1998JRM1448>. Similarly, Richman–Atkins cyclization of ditosyl-substituted ethylenediamine with ditosylate of *N,N*-bis(2-hydroxyethyl)-4-methylbenzenesulfonamide gave the functionalized triazonanes <2003OBC2357>.

Bis-heteronucleophilic Michael addition of symmetrical dibenzyl 1,2-diaminoethane to divinyl sulfone resulted in the quantitative yield of *S,S*-dioxo-1,4,7-thiadiazonane <2003EJO54>. Disodium derivative **232** gave moderate to poor yields of dithiazonines **233** (**Scheme 48**) <1995T8175>, while a moderate yield of *N*-phenyl dithiazonane was obtained from 1,2-ethanedithiol <1995BCJ2831, 1995BCJ3071>. The latter was used as a 1,4-dithio fragment for functionalized 1,4,7-oxadithionanes synthesis as well <1999SC3939>.



Scheme 48

14.10.8.6 RCM Syntheses

RCM strategies gained significant value over the last few years and were extensively developed for nine-membered heterocyclic systems. Although formally they belong to unimolecular C–C bond-formation reactions, discussed in Section 14.10.8.1.1, it is more convenient to discuss them separately in this section. This type of heteronines ring construction was reviewed as a part of more general medium-size ring surveys <2000CRV2963, 2004CRV2199, 2004CRV2239> (see other chapters in Volume 12). Usually the formation of medium-size rings, and nine-membered rings in particular, by RCM is a considerable challenge, since their ring strain prompts cyclic systems toward ring-opening metathesis or ring-opening metathesis polymerization.

Azonine **35** was synthesized in 53% yield when RCM is carried out with Grubbs' first-generation catalyst in refluxing CH_2Cl_2 ; while in refluxing benzene, dichloroethane, or THF, the catalyst was rapidly deactivated. When Grubbs' second-generation catalyst was employed the reaction was faster; however, the relative percentage of intermolecular products was increased. The reaction was completely stereoselective with regard to the double bond, giving only (*Z*), and **35** as well as its diastereomer were easily separated from each other <2003TL7655, 2005OBC97>. Further examples of azonine ring systems synthesized by RCM methodology are depicted in **Figure 2** and include 2-trifluoromethylazonine **234** <2003JOC8932>, 1*H*-benzo[*b*]azonine **235** <2005JOC1552>, azonine amino acids **236** <2005JOC3838, 2006OL2851> and **237** <2005JOC3838>, *N*-tosylazonine **238** <2001CEJ4811>, mono- <2005SL631> and di- <2004TL9607> carboxy derivatives, **239** and **240**, respectively.

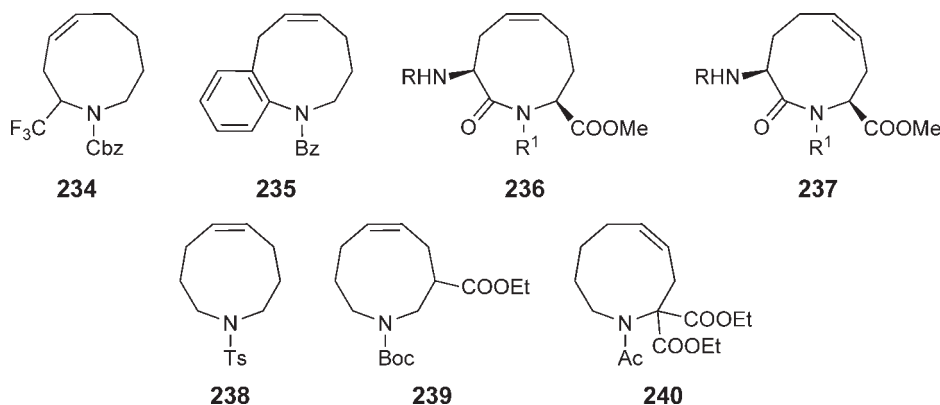


Figure 2

The RCM methodology was widely used for oxonine ring construction. Target compounds, which are depicted in **Figure 3**, included oxirane derivative **242** and its unsaturated precursor **241** <2003JA7592>, dibenzyloxy alcohol **243** <2004JA10264, 2006JA1371>, protected trialcohols **244** and **245** ($R^1 = \text{Bn}$, Et_3Si ; $R^2 = \text{H}$, TMS , Ac ; $R^3 = \text{Bn}$, 1,1,3,3-tetraisopropylidisiloxane (TIPS)) <2001JA1533, 2002T1817>, and oxirane **246** <2002T1817>. RCM strategy was successfully used for stereoselective synthesis of BCDE fragment of brevetoxin A <2005OL4033>.

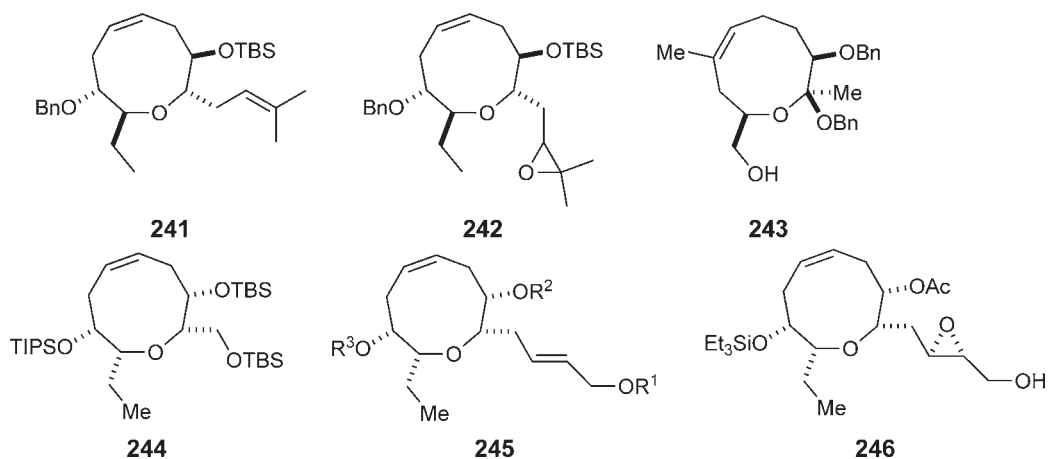
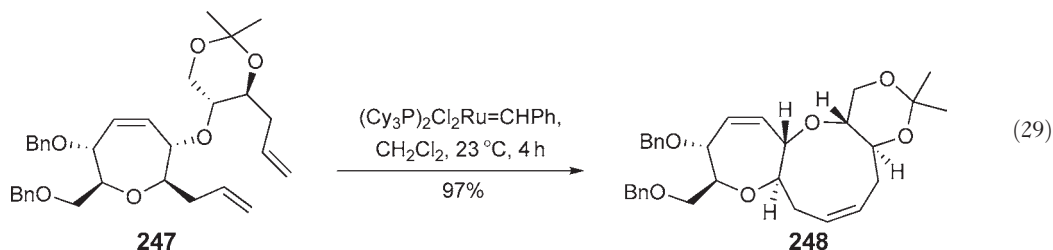


Figure 3

Besides oxonine single ring construction, RCM is an efficient tool in oxonine cycle annulation. Thus, intermediate **247** with Grubbs' first-generation catalyst in CH_2Cl_2 at room temperature produced annulated oxonine **248** in 97% yield (Equation 29) <2005T7392>.



The RCM syntheses of diazonine ring system (**Figure 4**) led to 61% of cyclic urea **249**, <2003JOC4876>, hydrazide **250** (42%) <2004OL4351>, ditosyl derivative **251** (85%) <2002TL4207>, diprotected 1,2-diazonine **252** (72%) <2004TL3757>, and [1,4]diazonino[1,2-*a*]indole **253** (62%) <2002T10181>.

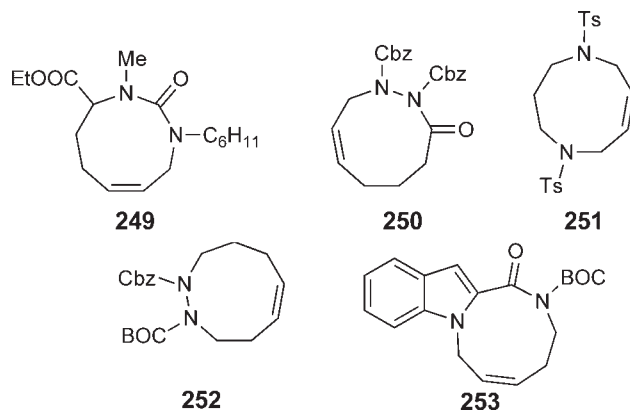
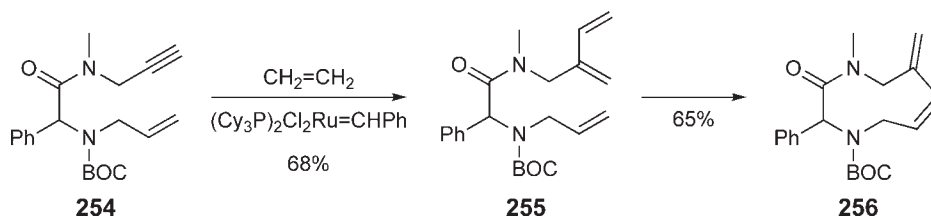


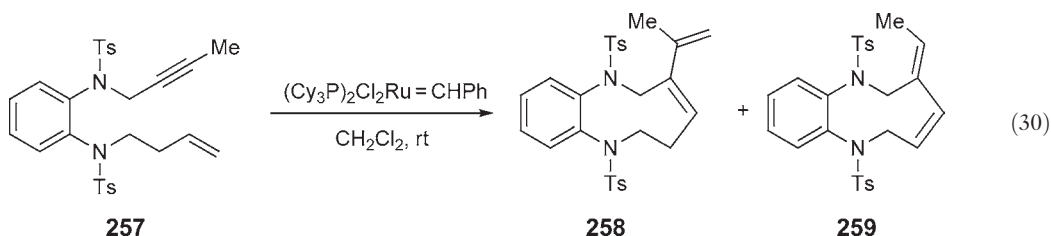
Figure 4

Contrary to foregoing examples, acyclic enyne substrate **254** was inert to direct ring-closure enyne metathesis, giving only recovery of the starting material. However, it underwent an efficient cross-metathesis with ethylene to form **255** and afforded **256** upon subsequent RCM in good overall yields (Scheme 49) <2004JA15074>. The formation of *endo*-product, observed in this case, is significant as the normal tendency for medium-sized rings is to give *exo*-products via direct enyne metathesis.

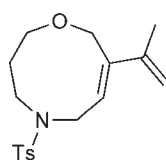


Scheme 49

Enyne derived from ditosyl *o*-phenylenediamine **257** formed in the presence of benzylidene ruthenium carbene complex a nine-membered ring **258** in 5% yield (Equation 30) <2000OL543, 2001S654>. Dimerization was a major by-process (22% yield) along with formation of a small amount of **259** (5% yield), which was explained by β -hydride elimination from the intermediary ruthenacyclobutane.

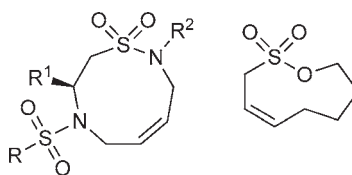


Ring-closure enyne metathesis was a convenient route toward tosyl oxazonine derivative **260** <2001S654>. Synthesis of 1,2-oxazonines from dienes tethered by hydroxylamine has been reported <2003SL1043>.



260

Further examples of RCM in heteronine synthesis include a variety of 1,2,7-thiadiazonines **261**, which can be incorporated into a peptide sequence <2004JOC3662>, and unsaturated nine-membered sultone **262** <2004S1696, 2002SL2019>.

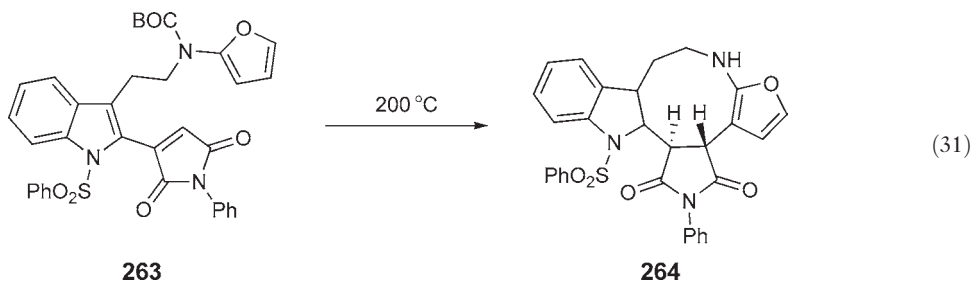


261

262

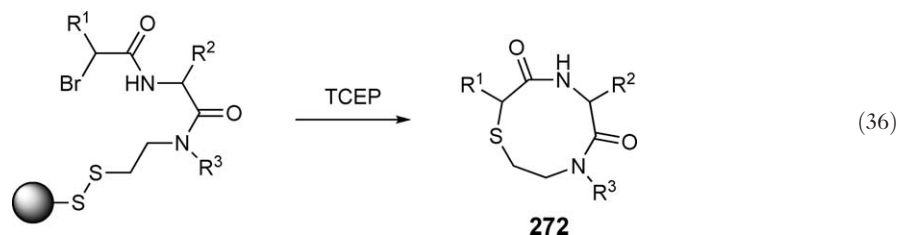
14.10.8.7 Miscellaneous Methods

Thermolysis of indole maleimide derivative **263** led to deprotection and cyclization to form substituted azonine system **264**, as a sole product, in 45% yield (Equation 31) <2005JOC2206>.



Mono-*O*-allyl derivative of 1,6-hexanediol undergoes $\text{RuCl}_2(\text{PPh}_3)_3$ -catalyzed isomerization to give 2-ethyl 1,3-dioxonane <2004SL1203>.

A library of thiadiazonines **272** were prepared when tris-(2-carboxyethyl)phosphine (TCEP) was used to reduce the disulfide in cleavage–cyclization strategy (Equation 36) <1996TL6961, 1999JA1817, 1999JME4380>. Both an excess of phosphine and phosphine oxide were scavenged by polymer-bound tetramethylguanidine to yield the crude **272** uncontaminated with reagent by-products. A similar synthetic approach was reported for the solution-phase thiadiazonine synthesis <2000BML2731>.



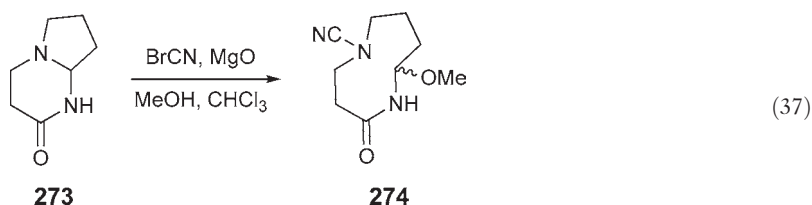
1,4,7-Trithionine was readily available from *cis*-1,2-dichloroethylene and sodium sulfide <2001JA11534>. 1,2,4,5,7,8-Hexaoxonane **11** was accessible in 65% yield by the reaction of acetone and 30% water solution of hydrogen peroxide at 0 °C <2005JA1146>.

14.10.9 Ring Syntheses by Transformation of Another Ring

Many heteronines are synthesized using another ring-expansion reactions, while contractions of the larger rings into nine-membered heterocyclic systems are less frequent. General methods for ring expansions were categorized in CHEC-II(1996), and this classification is followed in the current section.

14.10.9.1 Ring Expansion by Ionic Ring Openings

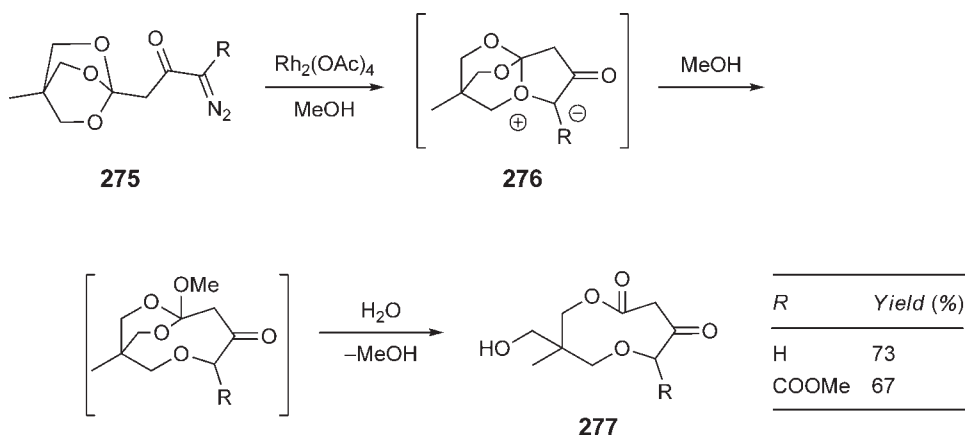
Reaction of bicyclic lactam **273** with BrCN and MgO in $\text{MeOH}/\text{CHCl}_3$ led to formation of the nine-membered amino compound **274** in 47% yield (Equation 37) <1999AJC1131>.



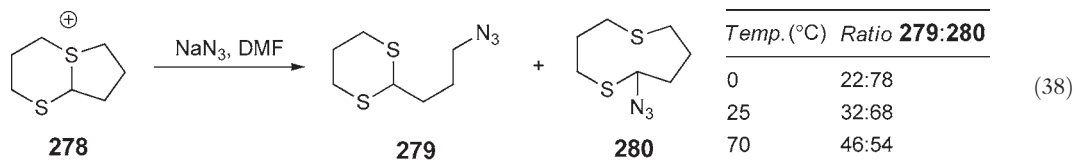
Bicyclic ortho esters **275**, which are tethered to a diazocarbonyl group by a methylene linkage, were prepared and catalytically decomposed by treatment with $\text{Rh}_2(\text{OAc})_4$ either in the presence or absence of a protic nucleophile (MeOH , PhOH , AcOH) to give ring-enlargement, functionalized lactones **277** (Scheme 50) <2000JOC1899>. A similar sequence led to unsubstituted rings, when cyclic acetals were used instead of orthoesters <1998J(P1)3623>.

The formation of the products can be explained by an intramolecular reaction between the alkylidenecarbene and a cyclic acetal or cyclic orthoester units and formation of bicyclooxonium ylides **276**. Analogous alkylidenecarbene species were generated using copper catalyst <1996TL5053>.

Nucleophilic attack by azide anion on bicyclic sulfonium salt **278** kinetically favors ring opening to give a nine-membered α -azidosulfide **280**, while 2-(3'-azidopropyl)-1,3-dithiane **279** is the thermodynamic product (Equation 38) <2003TL2841>.

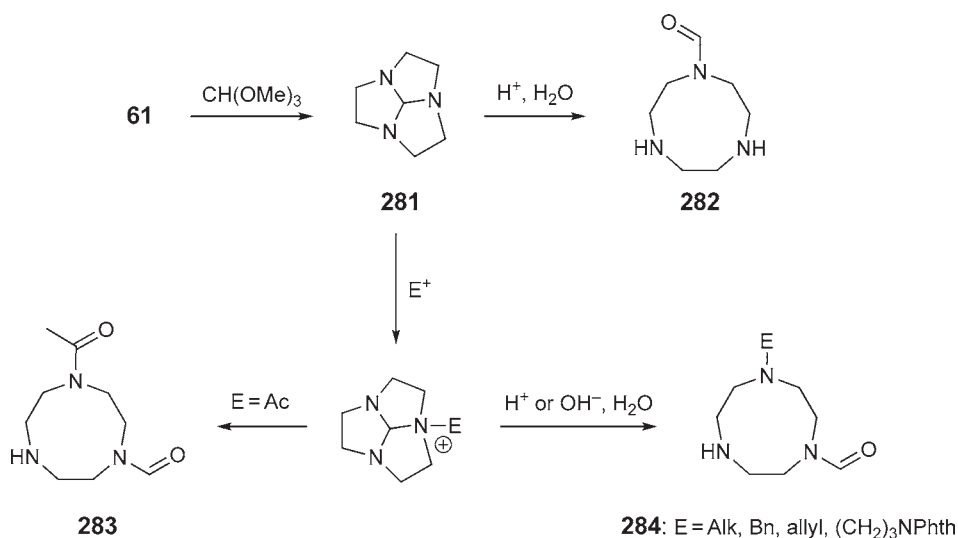


Scheme 50



Ring expansion of ω -bromoalkyl benzothiazolium salt into *N*-formyl derivative of benzo[*b*][1,4]thiazonine has been reported [<1995JOC2597>](#).

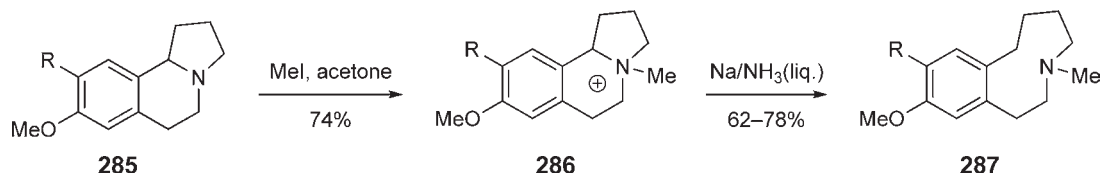
The general method for the synthesis of *N*-protected triazonines ([Scheme 51](#)) utilizes the synthesis of the bridged 1,4,7-triazatricyclo[5.2.1.0^{4,10}]decane **281**, followed by its acidic hydrolysis to afford *N*-formyl triazonane **282** [<2003AJC61>](#). Similar synthetic routes, which involved intermediate benzylation [<1994CC2467, 2001OL2855, 2005T7499>](#), allylation [<1996CC1817>](#), alkylation [<2005T7499>](#), or acetylation [<1999J\(P1\)1211>](#) steps followed by acidic or basic hydrolysis, were utilized for the synthesis of 1,4-diacyl triazonane **283** and formyl derivatives **284**. Bis-thiadiazonanes were prepared using the same methodology [<1997HCA2315>](#).



Scheme 51

14.10.9.2 Reductive Ring Openings

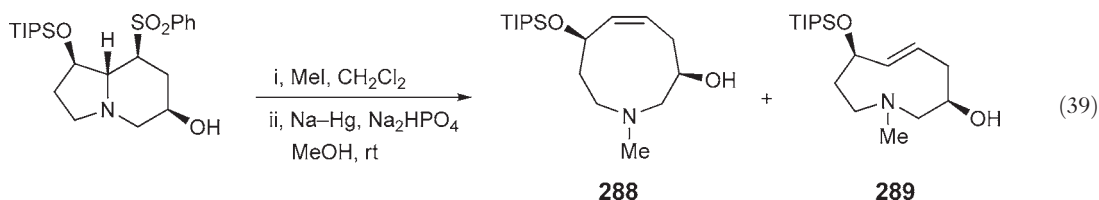
Ionic species described in Section 14.10.9.1 can be submitted to reactions with reducing agents rather than solvolysis to produce saturated azonane analogs. Thus, treatment of hexahydropyrrolo[2,1-*a*]isoquinolines **285** with MeI in acetone afforded quarternary salts **286**, which were subjected to ring opening using Na/NH₃ to produce hexahydro-1*H*-benzo[*d*]azonines **287** in good yields (Scheme 52) <2002AP443>. Similarly, dimethoxy intermediate **286** (R = MeO) was reacted with benzyl chloroformate and sodium cyanoborohydride to give N-unsubstituted analogue through a 3-Cbz benzazonine intermediate.



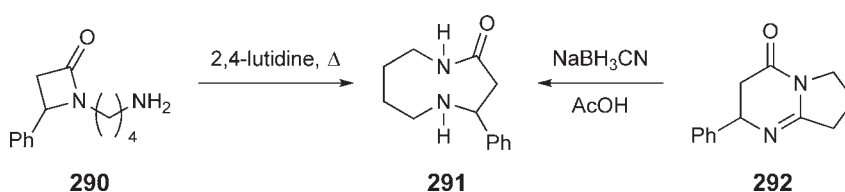
Scheme 52

An analogous sequence was used for the synthesis of indole-fused azonanes and benzoazonanes <2006JME760>.

Alkylation–reduction methodology was applied for the synthesis of monosubstituted dihydroxy azonine, which was obtained as a separable mixture of *cis*-**288** and *trans*-**289** isomers (44% and 38%, respectively; Equation 39) <2001OL2957>.



Diazoninones **64** were synthesized by reduction of hexahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-ones with sodium in liquid ammonia (Scheme 7, Section 14.10.5.2.1) <2000CL1104, 2002T7177>. One of the synthetic routes for the preparation of diazoninone **291** includes reduction of dihydropyrimidinone **292** (Scheme 53) <2002T7177>.

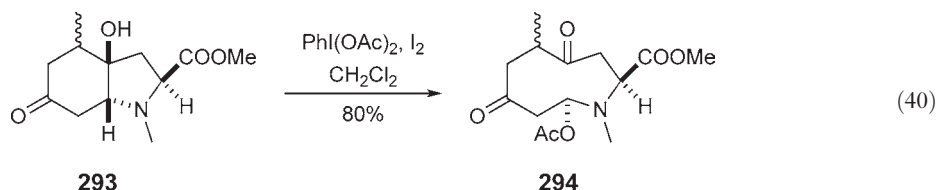


Scheme 53

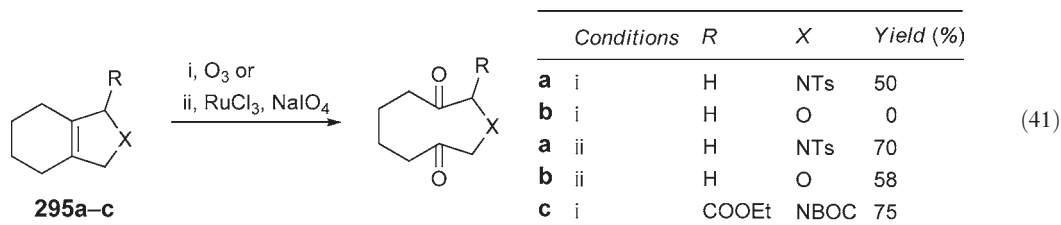
Synthesis of oxathionanes from ω -bromo ketone **108**, which is formally a [5+4]-type cyclization, requires Lewis acid-catalyzed cyclic acetal intermediate formation. It was further transformed into the corresponding oxathionanes **109** and **110** using a two-step reductive procedure (Scheme 18, Section 14.10.5.6.1) <2002OL3047>.

14.10.9.3 Oxidative Ring Openings

Tertiary alcohol **293**, when reacted with iodobenzene diacetate and iodine, underwent a formal alkoxy radical fragmentation and provided the nine-membered diketone **294** in 80% yield as a separable 1.2:1 mixture of epimers (Equation 40) <1999JOC4576>.



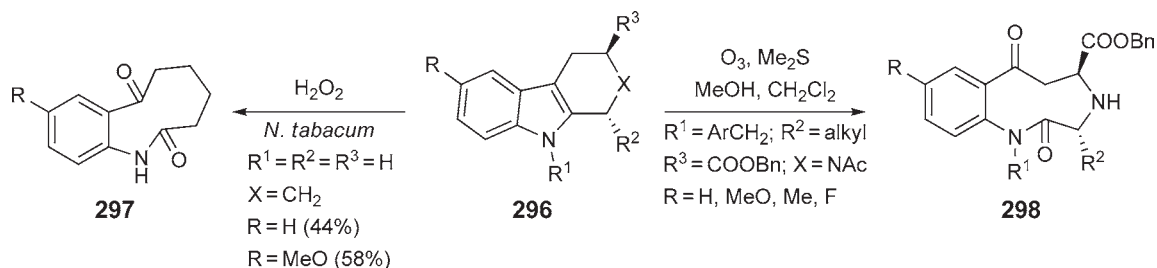
Ozonolysis of tosyl derivative **295a** led to the corresponding protected azonane-3,8-dione in 50% yield (Equation 41). Ruthenium-catalyzed oxidation was found to be more efficient, resulting in an increased 70% yield of the product, which is consistent with the result obtained for dialkyl-substituted systems (Scheme 32, Section 14.10.6.3) <1995J(P1)1137>. Similar ozonolysis of pyrrole ethyl carboxylate **295c** led to 75% of cyclic amino acid derivative <2001OL861>.



Oxidative ring expansion of hexahydroisobenzofuran derivatives was less straightforward. Thus, unlike pyrrole derivatives **295a** and **295c**, ozonolysis of **295b** did not lead to the corresponding oxonine-3,8-dione (Equation 41) <1995J(P1)1137>. Ruthenium-catalyzed oxidation was found to be more efficient, resulting in 58% yield of the product. Another example of ruthenium-catalyzed transformation, that is, the catalytic oxidative cleavage of octahydrobenzofuran-3*a*-ols, was reported <2003OL1337>. Catalytic amounts of ruthenium trichloride and an excess of sodium periodate, as a co-oxidant, led to the nine-membered ring keto lactones in moderate to good yields and high purity.

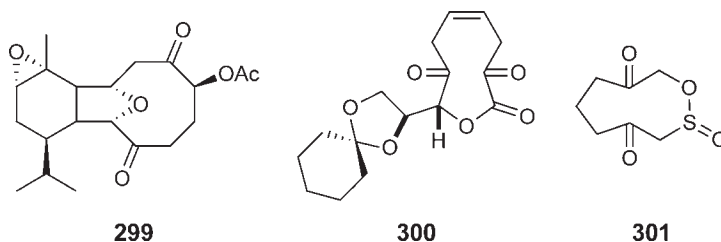
Oxidative cleavage of the double bond in **168** (Scheme 33, Section 14.10.6.3) by ozonolysis was unsuccessful, while its dihydroxylation and treatment of resulting diol with lead(IV) acetate gave diketone **169** <1999T7471>. Ozonolysis of isopropyl 1,3,4,5,6,7-hexahydro-1-methylisobenzofuran-1-carboxylate **131** (Scheme 23, Section 14.10.5.6.3) proceeded smoothly and led to the corresponding oxonine carboxylate **132** <2002OL3059>.

A novel procedure for the oxidative cleavage of indole carbon double bonds in the presence of H₂O₂ using plant cell cultures, as a catalytic system, led to benzazonine diones **297** (Scheme 54) <2004TL8061>. 1*H*-Benzo[*h*][1,4]diazonines **298** were obtained in a highly substituted form and in high yields by ozonolysis of 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole derivatives **296** (X = NAc) <2000JME3518>.

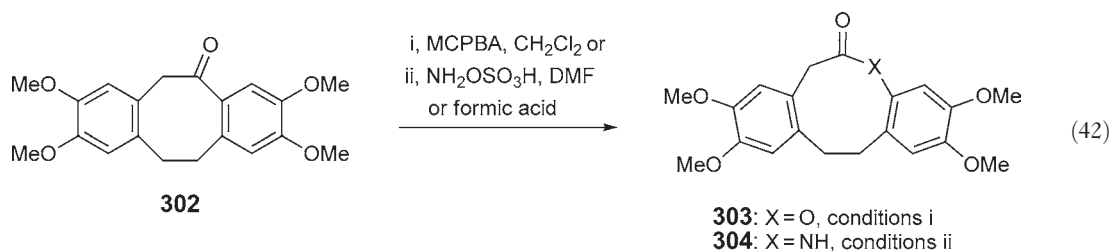


Scheme 54

Bicyclic semi-acetals **122**, when reacted with Dess–Martin periodate or ceric ammonium nitrate (CAN), underwent oxidative ring expansion to produce nine-membered unsaturated lactones **123** in moderate to good yields (Scheme 21, Section 14.10.5.6.2) <2005OL4301> (Chapters 10.06–10.08). Several other products of oxidative ring-expansion strategy have been reported, including epoxy dione **299** <2004JA1642>, diketone lactone **300** <2000CC567, 2002T1779>, and unstable diketone **301** <2002HCA712>.



Dibenzo[*a,e*]cycloocten-5-one **302** was transformed by Baeyer–Villiger oxidation into the substituted 6-oxodibenzo[*b,f*]oxonin **303** (Equation 42) <1996T8063>. The regiochemistry of the process and structure of the product was assigned based on ^1H NMR data and their comparison to theoretical chemical shifts of the product and of the hypothetical dihydridibenzo[*c,g*]oxonin-5(7*H*)-one isomer.



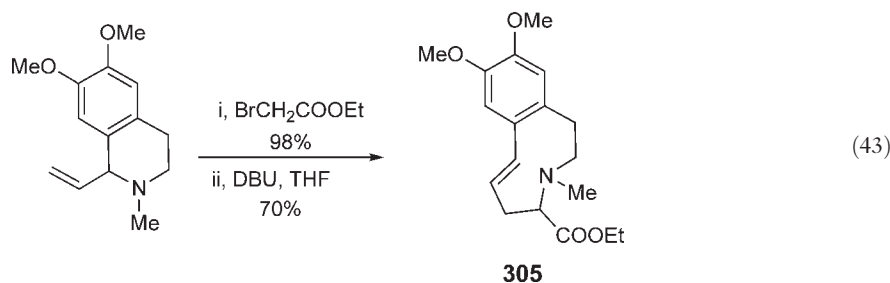
14.10.9.4 Beckmann and Related Rearrangements

2,3,8,9-Tetramethoxy-5,6,11,12-tetrahydridibenzo[*a,e*]cycloocten-5-one **302** was reacted with hydroxylamine-*O*-sulfonic acid and underwent a one-pot Beckmann (formic acid, reflux) or Schmidt (DMF, reflux) rearrangement to afford the 6-oxodibenzo[*b,f*]azonine **304** (Equation 42). Regioselectivity of the process was assigned based on ^1H NMR data and on model reactions to prove preferential migration of the 3,4-dimethoxyphenyl over the 3,4-dimethoxybenzyl group <1996T8063>.

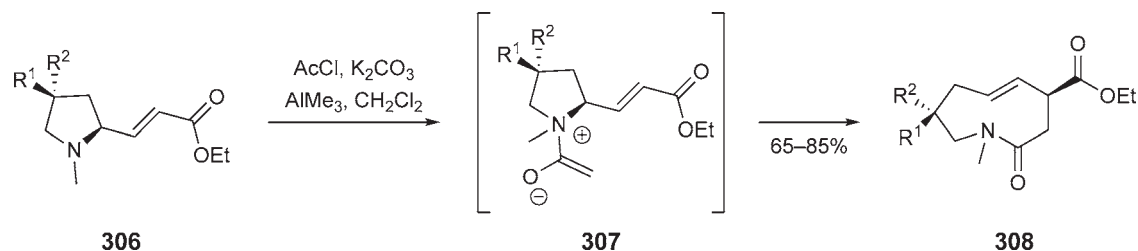
14.10.9.5 Sigmatropic Rearrangements

Sommelet–Hauser rearrangement of α -phenylcycloammonium *N*-methylides is useful for three-carbon ring enlargement of cyclic amines. Thus, 2-methyl-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonine **118** was obtained in high yield by the reaction of 1,1-dimethyl-2-phenylpiperidinium iodide **117** with sodium amide in liquid ammonia (Scheme 20, Section 14.10.5.6.2) <1997JOC2544>. Similar ylides derived from 3-aryl tetrahydroisoquinolines gave a complex mixture of azonine type [2,3]-sigmatropic rearrangement products, accompanied by benzazepine and open-chain products resulting from a Stevens rearrangement and Hofmann degradation, respectively <1995JOC4272>.

Alkylation of 1-vinyl tetrahydroisoquinoline with ethyl bromoacetate afforded the ammonium salt in high yield (Equation 43). Treatment of this compound with DBU in THF at room temperature gave the [2,3]-sigmatropic rearrangement product **305** in 70% yield. The product consisted of a mixture of isomers in an (*E*)/(*Z*)-ratio of 96:4 <2005JOC5519>.

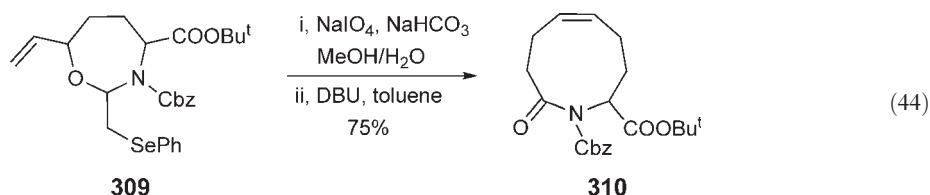


Two-phase conditions were developed for the Claisen rearrangement of amino esters **306** into azonines **308** (Scheme 55). A slurry of the amino ester and solid potassium carbonate in anhydrous chloroform at 0 °C was treated with acetyl chloride and trimethylaluminum to produce azoninones **308** in good yields. The reaction mechanism involves formation of zwitterionic intermediate **307** from acyl ammonium salt via deprotonation of the α -position of the activated carbonyl group. Further [3,3]-sigmatropic rearrangement resulted in azoninones **308** <1995AGE1026, 1999SL25>.

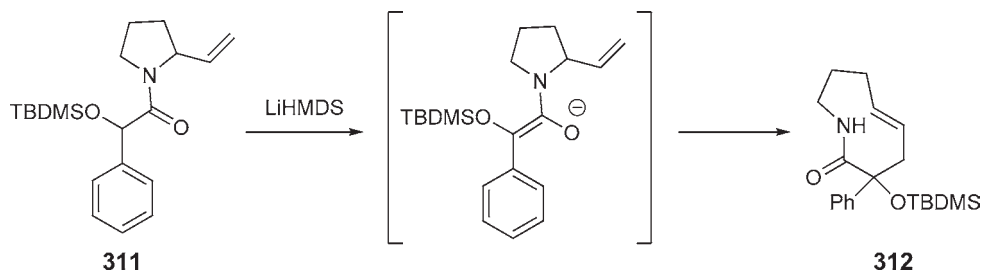


Scheme 55

Aminal **309** was oxidized to selenoxide, and then heated in refluxing toluene with DBU to give the protected 9-substituted azoninone **310** in 75% yield as a result of Claisen rearrangement of the vinyl-substituted intermediate (Equation 44) <1996J(P1)123>.



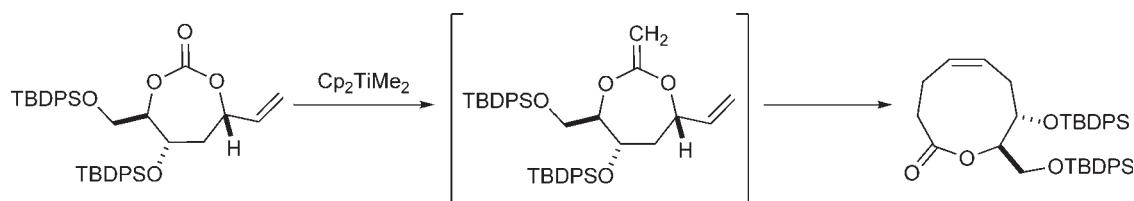
The base-induced aza-Claisen rearrangement (Scheme 56) of 2-vinylpyrrolidine intermediate **311** proceeded smoothly in refluxing toluene to give the nine-membered lactam **312** in good yield <2005T2659>.



Scheme 56

Substituted 3-keto oxonine **161** was accessible through a thermal Claisen rearrangement of the corresponding 2-methylene-7-vinyl-1,4-dioxepane **160** (Scheme 31, Section 14.10.6.3) <2000OL1875, 2001JA9021>. The conversion of vinyl-substituted seven-membered cyclic carbonates into nine-membered ring lactones has been achieved in good yields using dimethyltitanocene in toluene at reflux (Scheme 57) <2002T1943>. The reaction proceeds by initial formation of ketene acetal, which undergoes subsequent *in situ* Claisen rearrangement to provide corresponding lactones.

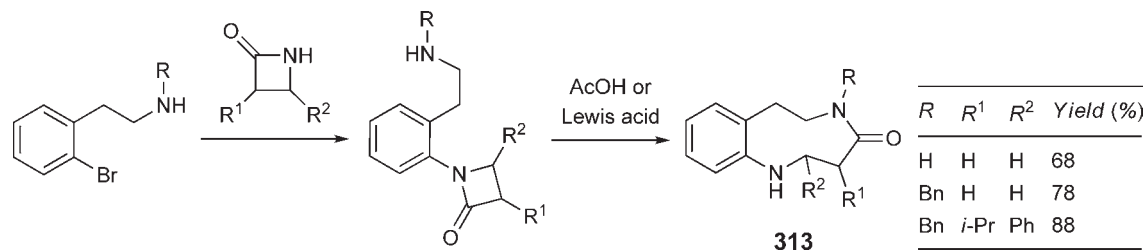
The anionic [3,3] sigmatropic rearrangement of cyclic diacyl pyrazolidines resulted in poor to good yields of 1,5-diazonane-6,9-diones <2000H(53)151>.



Scheme 57

14.10.9.6 Miscellaneous Ring-Expansion Methods

N-(2-Aminoacetyl)-2-valerolactam **49** underwent ring expansion into 1,4-diazonane-2,5-dione **51** in MeOH media (Scheme 1, Section 14.10.4.4) <2002J(P2)2078>. An alternative route for the preparation of diazoninones **291** includes thermal ring expansion of ω -aminoalkyl- β -lactam **290** (Scheme 53, Section 14.10.9.2) <2002T7177>. Tandem Cu-catalyzed coupling of a β -lactam with an aryl bromide followed by intramolecular attack of a pendant amino group led to diazonines **313**. In some instances, the intermediate β -lactam was observable and can be further converted to the aza-heterocycle by catalysis (Scheme 58) <2004JA3529>.

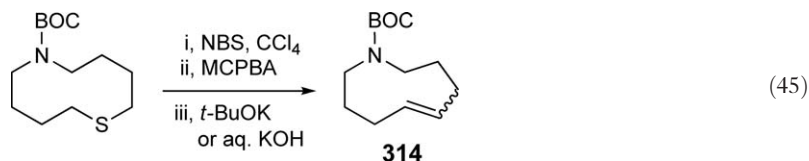


Scheme 58

Bicyclic 9-oxabicyclo[6.1.0]nonan-2-ol when treated with diethylaminosulfur trifluoride (DAST) gave a rearranged 2-fluoro-2,3,4,5,6,7-hexahydrooxonine by a ring expansion via C–C bond cleavage of the oxirane ring <2002OL451>. A novel 1,3,5,7-tetraoxonane was synthesized in 33% yield when ethylene oxide was bubbled through melted 1,3,5-trioxane at 70 °C in the presence of BF₃·OEt₂ (Equation 2, Section 14.10.5.6.1) <1998CC1809, 2001TL271>. Thermal reaction of the *C*-aryl diazomethane with cyclooctasulfur in benzene in the dark led to octathionane **15b** (Scheme 14, Section 14.10.5.4) <1995BCJ2757>.

14.10.9.7 Ring Contractions

tert-Butyl 1,6-thiazecane-6-carboxylate underwent a Ramberg–Bäcklund reaction to produce after treatment with base, the *N*-BOC-azonine **314** (Equation 45) <2000JOC8367>. When the reaction was conducted with potassium *tert*-butoxide, the *trans*-olefin was produced in quantitative yield with high stereoselectivity (96:4), while with aqueous KOH it gave only 59% of the product in a 65:35 *trans*:*cis* ratio.



(45)

14.10.10 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

There has been a tremendous increase in the methodology available to assemble nine-membered ring systems during the last decade. Development of efficient routes to prepare various natural products was a primary goal of numerous studies. Synthesis of different saturated structures relative to crown ethers, usually with 1,4,7-heteroatom pattern, were of great importance.

In spite of the apparent problems with cyclizing medium-size ring systems, most classes of heteronines are accessible through flexible synthetic routes. Numerous high-yield processes for heteronines have been developed starting with acyclic precursors. Advances in RCM methodology have had a remarkable impact on nine-membered heterocycles synthesis providing feasible routes toward azonine, oxonine, and diazonine ring systems (see Section 14.10.8.6). The RCM chemistry for other heteronines is less well developed, although it suggests a potentially versatile and general route particularly deserving of further study. Unimolecular cyclizations involving C–N bond formation include intramolecular alkylations and Mitsunobu condensations and were applied for a variety of azonines, while macrocyclic lactonization is the most reliable method for oxonine core synthesis through C–O bond formation. Other types of unimolecular cyclizations are scarce and erratic, and they usually depend on stereochemistry of the open-chain precursors and require tuning of the functional groups involved.

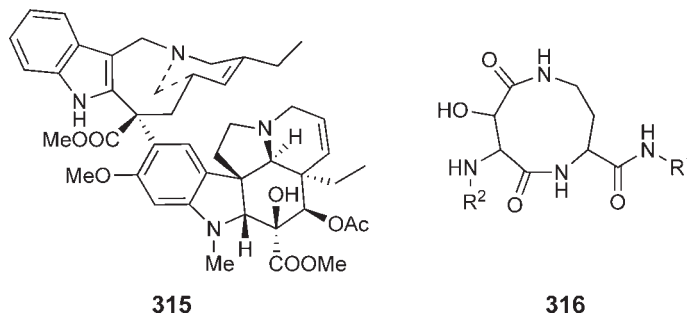
Bimolecular heteronine syntheses remain the most important way of ring assembly. Utility of 1,2- and 1,3-dielectrophilic reagents predominates in [7+2] and [6+3] syntheses, while cyclization of 1,2-diamines (or their protected counterparts), 1,2-diols, or 1,2-thiols with dielectrophiles remains the primary means of entry to the 1,4-diheteronine ring system.

Syntheses from other heterocyclic systems via ring expansion are well developed (Sections 12.17.9.1–14.10.9.6). Each of the approaches reported thus far for this type of ring construction appears rather promising, although ionic, reductive, and oxidative strategies are the most advanced. The ring-contraction approach is applicable, but limited in scope given the challenging accessibility of heterocyclic rings with 10 and more atoms.

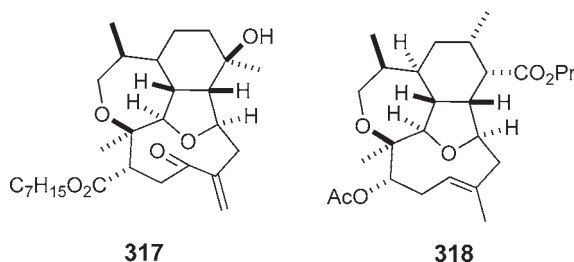
Transformations of side chains are largely explored including both reactivity of substituents attached to ring carbons and heteroatoms. Reactivity of the rings typically includes electrophilic substitution on heteroatoms and oxidative/reductive sequences involving C–C double bonds. Transformations of heteronines into other, usually bicyclic [6,5]-systems, are of significant value.

14.10.11 Important Compounds and Applications

Nine-membered heterocyclic rings are structural blocks of valuable natural products and their synthetic analogues. *Strychnos* alkaloid holstiine **36** is structurally related to strychnine and brucine <2000JNP543>. Navelbine **315**, synthetic azonine-bearing analog of natural alkaloids isolated from *Catharanthus roseus* (L.) G. Don (Apocynaceae) or *Vinca rosea* L., is used against non-small-cell lung and advanced breast cancers <2004JNP273>. Cyclic derivative of D-threo- β -OH-Asp and L-diaminobutyric acid **316** is a key structural fragment of marinobactins, a class of newly discovered marine bacterial siderophores, which are responsible for the acquisition of iron by heterotrophic bacteria <2002JA13408>.

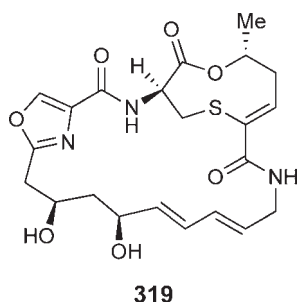


(–)-7-Deacetoxyalecyonin **210**, which contains oxonine cycle, was obtained as acetate from a *Cladiella* species of soft coral, and belongs to eunicellin diterpenes, a family of marine metabolites <1995JA10391, 2000OL2683, 2001JA9033, 2001OL135>. Other representatives of this diterpene family are briarellins **317** and asbestinins **318**, and they have in common a rare tricyclic oxonine containing ring system <2003JA6650>. Oxonine unit is a structural element of several marine organism metabolites, including brevetoxin A <2005OL4033> and topsentolides <2006JNP567>.



The dioxonine subunit is a core of UK-2A, dilactone which was isolated along with the structurally similar congeners, from the mycelial cake of *Streptomyces* sp. 517-02 <1998TL4363, 1998T12745>.

Griseoviridin **319**, a cyclic structure which encompasses the unsaturated sulfur-containing nine-membered lactone, is a representative member of streptogramin group A antibiotics, which was isolated from *Streptomyces griseus* <2002JOC4565, 2000AGE1664, 2000JOC4553, 2003JOC5346>.

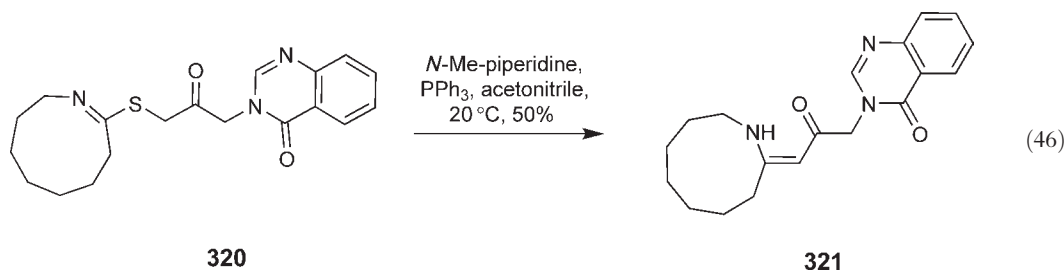


1,4,7-Triazacyclononane **61** and related crown-type systems are important ligands in inorganic chemistry and they have been extensively reviewed <B-2005MI67, 2001ARA331, 2002ARA321>. Manganese complexes of substituted 1,4,7-triazacyclononanes catalyze the selective epoxidation of a large number of olefins to epoxides with hydrogen peroxide <1996JOM(520)195, 1999T5345>.

1,4,7-Triazacyclononane-capped porphyrin models of myoglobin were synthesized and steric interactions of their gas binding were studied <1997JA3481, 1997JOC2308, 1998JOC8082, 2004OL1033, 2005OL975>. 1,4,7-Triazonane serves as a building block for the synthesis of novel conical peptides from the cyclooligomerization of functionalized thiazole amino acids <2001JA333>.

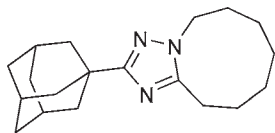
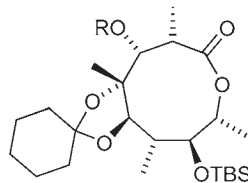
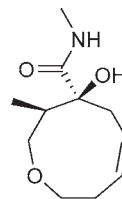
14.10.12 Further Developments

Few novel examples of the mono-heteronines have been reported recently. Azonane analogue **321** of antimalarial alkaloid ($\pm$)-deoxyfebrifugine is the product of an Eschenmoser sulfide contraction of intermediate thioimide **320** (Equation 46, <2006SL383>).

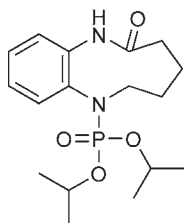
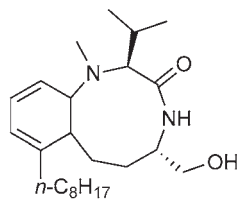
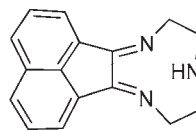


Synthesis of azonane-2-one from cyclooctanone by a Schmidt reaction <2006JCR(S)218> is advantageous when compared to the Beckmann rearrangement of the corresponding oxime <2005JA11240>, providing 92% and 27% yields of the product, respectively. Further reaction of azonane-2-one with trimethyloxonium tetrafluoroborate produces a cyclic imidate, which can be reacted with hydrazide adamantane-1-carbohydrazide to give triazole **322** <2005BMCL4359>.

Stereoselective synthesis of the *pseudo* 2-epibotcinolide **323**, which contains a nine-membered lactone has been reported <2006OL5279>. Functionalized oxonine **324** can be synthesized by RCM of the corresponding *spiro* morpholinone precursor <2006OL5897>.

**322****323****324**

Benzodiazonine **325**, which is readily available by an intramolecular copper-catalyzed *N*-arylation of the corresponding 2-bromoaniline phosphoramidate <2005OL4781>, induces apoptosis of human chronic myelogenous leukemia K562 cells <2006BMC3766>. 8-Octyl-benzolactam **326** has been synthesized by lactam bond formation starting from the corresponding *N*-aryl-valine benzyl ester <2006JMC2681>.

**325****326****327**

Similar to diphenyl triazonine **52** (Scheme 2, Section 14.10.5.1), the fused analog **327** with naphthalene motif has been reported <2005JMC7192>. 1,4,7-Triazonane has been studied as a multivalent scaffold for fully symmetrical functionalization on a solid support <2006T11670>. Its 2-aminomethyl derivative can be synthesized by LAH reduction of the corresponding nitrile <2006TL3673>. *N*-Alkylation of triazacyclononane with ethyl 6-chloromethyl-pyridine-2-carboxylate results in the mixture of mono-, di- and tri-substituted products <2006CEJ7133>. Other types of transformations for 1,4,7-triazonane include Buchwald–Hartwig coupling of di-BOC derivative with aryl bromides <2006MI1823>, coupling to *C*-terminus of glycine <2005JOC115>, and alkylation with tosylates <2006TL3541>, alkyl bromides, and functionalized propiolactone <2007JOC376>.

References

- 1994CC2467 A. J. Blake, I. A. Fallis, R. O. Gould, S. Parsons, S. A. Ross, and M. Schroeder, *J. Chem. Soc., Chem. Commun.*, 1994, 2467.
 1994PS389 N. Tokitoh, N. Takeda, and R. Okazaki, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1994, **96**, 389.
 1994T11709 J. Das and S. Chandrasekaran, *Tetrahedron*, 1994, **50**, 11709.
 1995AGE1026 M. Diederich and U. Nubbemeyer, *Angew. Chem., Int. Ed. Engl.*, 1995, **134**, 1026.
 1995BCJ2757 N. Takeda, N. Tokitoh, T. Imakubo, M. Goto, and R. Okazaki, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2757.
 1995BCJ2831 H. Sakamoto, J. Ishikawa, and M. Otomo, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2831.
 1995BCJ3071 J. Ishikawa, H. Sakamoto, T. Mizuno, and M. Otomo, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 3071.
 1995CC929 P. D. Beer, M. G. B. Drew, P. B. Leeson, K. Lyssenko, and M. I. Ogden, *J. Chem. Soc., Chem. Commun.*, 1995, 929.
 1995CC1743 S. E. Gibson and R. C. Middleton, *J. Chem. Soc., Chem. Commun.*, 1995, 1743.
 1995H(41)237 K. Matsumoto, K. Fukuyama, H. Iida, M. Toda, and J. W. Lown, *Heterocycles*, 1995, **41**, 237.
 1995H(41)641 B. T. Kim, Y. K. Min, N. K. Park, K. Y. Cho, and I. H. Jeong, *Heterocycles*, 1995, **41**, 641.
 1995HCA693 L. Behle, M. Neuburger, M. Zehnder, and T. A. Kaden, *Helv. Chim. Acta*, 1995, **78**, 693.
 1995JA3983 G. C. Silver and W. C. Troglor, *J. Am. Chem. Soc.*, 1995, **117**, 3983.
 1995JA10391 D. W. C. MacMillan and L. E. Overman, *J. Am. Chem. Soc.*, 1995, **117**, 10391.
 1995JA10745 R. P. Houser, J. A. Halfen, V. G. Young, N. J. Blackburn, and W. B. Tolman, *J. Am. Chem. Soc.*, 1995, **117**, 10745.
 1995JOC2597 H. J. Federsel, G. Glasare, C. Hoegstroem, J. Wiestal, B. Zinko, and C. Oedman, *J. Org. Chem.*, 1995, **60**, 2597.
 1995JOC3980 N. Kise, H. Oike, E. Okazaki, M. Yoshimoto, and T. Shono, *J. Org. Chem.*, 1995, **60**, 3980.
 1995JOC4272 N. Kawanishi, N. Shirai, Y. Sato, K. Hatano, and Y. Kurono, *J. Org. Chem.*, 1995, **60**, 4272.
 1995J(P1)1137 D. S. Brown, M. C. Elliott, C. J. Moody, and T. J. Mowlem, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1137.
 1995JST(355)169 Y. S. Park and H. F. Shurvell, *J. Mol. Struct.*, 1995, **355**, 169.

- 1995RCB105 V. L. Antonovsky, A. Yu. Kosnikov, I. L. Shamovskii, V. N. Khrustalev, S. V. Lindeman, and Yu. T. Struchkov, *Russ. Chem. Bull.*, 1995, **44**, 105.
- 1995S453 I. Lazar and A. D. Sherry, *Synthesis*, 1995, 453.
- 1995SC3181 I. Lazar, *Synth. Commun.*, 1995, **25**, 3181.
- 1995T4065 V. Guyon, A. Guy, J. Foos, M. Lemaire, and M. Draye, *Tetrahedron*, 1995, **51**, 4065.
- 1995T8175 S. J. Lange, J. W. Sibert, C. L. Stern, A. G. Barrett, and B. M. Hoffman, *Tetrahedron*, 1995, **51**, 8175.
- 1995TL8263 K. Fujiwara, M. Tsunashima, D. Awakura, and A. Murai, *Tetrahedron Lett.*, 1995, **36**, 8263.
- 1995TL9269 Z. Kovacs and A. D. Sherry, *Tetrahedron Lett.*, 1995, **36**, 9269.
- 1996AXC3062 A. J. Blake, J. P. Danks, S. Parsons, and M. Schroeder, *Acta Crystallogr., Sect. C*, 1996, **52**, 3062.
- 1996BML737 J. C. Jaen, V. E. Gregor, C. Lee, R. Davis, and M. Emmerling, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 737.
- 1996BML2673 E. J. Iorio and W. C. Still, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2673.
- 1996BSB317 C. Ibis, *Bull. Soc. Chim. Belg.*, 1996, **105**, 317.
- 1996CC1817 D. Ellis, L. J. Farrugia, D. T. Hickman, P. A. Lovatt, and R. D. Peacock, *J. Chem. Soc., Chem. Commun.*, 1996, 1817.
- 1996CEJ894 M. Diederich and U. Nubbemeyer, *Chem. Eur. J.*, 1996, **2**, 894.
- 1996HCA789 H. Takalo, I. Hemmilä, T. Sutela, and M. Latva, *Helv. Chim. Acta*, 1996, **79**, 789.
- 1996JA4396 J. Huskens and A. D. Sherry, *J. Am. Chem. Soc.*, 1996, **118**, 4396.
- 1996JA10707 B. L. Lucht, M. P. Bernstein, J. F. Remenar, and D. B. Collum, *J. Am. Chem. Soc.*, 1996, **118**, 10707.
- 1996JA10920 J. A. Halfen, V. G. Young, and W. B. Tolman, *J. Am. Chem. Soc.*, 1996, **118**, 10920.
- 1996JA11555 S. Mahapatra, J. A. Halfen, E. C. Wilkinson, G. Pan, X. Wang, V. G. Young, C. J. Cramer, L. Que, and W. B. Tolman, *J. Am. Chem. Soc.*, 1996, **118**, 11555.
- 1996JA11575 S. Mahapatra, J. A. Halfen, and W. B. Tolman, *J. Am. Chem. Soc.*, 1996, **118**, 11575.
- 1996JCD31 A. J. Blake, I. A. Fallis, A. Heppeler, S. Parsons, S. A. Ross, and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 1996, 31.
- 1996JCD353 J. H. Koek, S. W. Russell, L. van der Wolf, R. Hage, J. B. Warnaar, A. L. Spek, J. Kerschner, and L. DelPizzo, *J. Chem. Soc., Dalton Trans.*, 1996, 353.
- 1996JCD4409 C. Stockheim, L. Hoster, T. Weyhermueller, K. Wieghardt, and B. Nuber, *J. Chem. Soc., Dalton Trans.*, 1996, **23**, 4409.
- 1996JME669 W. M. Moore, R. K. Webber, K. F. Fok, G. M. Jerome, and J. R. Connor, *J. Med. Chem.*, 1996, **39**, 669.
- 1996JOC4289 P. Molina, M. Alajarin, P. Sanchez-Andrada, J. S. Carrio, and M. Martinez-Ripoll, *J. Org. Chem.*, 1996, **61**, 4289.
- 1996JOM(519)177 F. M. Kerton, G. F. Mohmand, A. Tersteegen, M. Thiel, and M. J. Went, *J. Organomet. Chem.*, 1996, **519**, 177.
- 1996JOM(520)195 D. E. De Vos and T. Bein, *J. Organomet. Chem.*, 1996, **520**, 195.
- 1996J(P1)123 P. A. Evans, A. B. Holmes, R. P. McGeary, A. Nadin, and K. Russell, *J. Chem. Soc. Perkin Trans. 1*, 1996, 123.
- 1996JST(378)165 Y. S. Park and H. F. Shurvell, *J. Mol. Struct.*, 1996, **378**, 165.
- 1996PHC(8)320 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', H. Suschitzky and G. W. Gribble, Eds.; Elsevier, Amsterdam, 1996, vol. 8, p. 320.
- 1996SC899 V. Cere, F. Massaccesi, S. Pollicino, and A. Ricci, *Synth. Commun.*, 1996, **26**, 899.
- 1996T8063 I. W. Elliott, M. J. Sloan, and E. Tate, *Tetrahedron*, 1996, **52**, 8063.
- 1996TL5053 J. B. Brogan, C. B. Bauer, R. D. Rogers, and C. K. Zercher, *Tetrahedron Lett.*, 1996, **37**, 5053.
- 1996TL6961 A. A. Virgilio, S. C. Schuerer, and J. A. Ellman, *Tetrahedron Lett.*, 1996, **37**, 6961.
- 1997ACR227 W. B. Tolman, *Acc. Chem. Res.*, 1997, **30**, 227.
- 1997AGE642 H. Chen, M. M. Olmstead, R. L. Albright, J. Devenyi, and R. H. Fish, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 642.
- 1997AGE2346 J. M. Vincent, A. Rabion, V. K. Yachandra, and R. H. Fish, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2346.
- 1997BML1289 S. E. Gibson, N. Guillo, S. B. Kalindjian, and M. J. Tozer, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1289.
- 1997CC637 S. E. Gibson, N. Guillo, and M. J. Tozer, *Chem. Commun.*, 1997, 637.
- 1997CC845 J. Huskens and A. D. Sherry, *Chem. Commun.*, 1997, 845.
- 1997CEJ62 N. Takeda, N. Tokitoh, and R. Okazaki, *Chem. Eur. J.*, 1997, **3**, 62.
- 1997CEJ308 B. Adam, E. Bill, E. Bothe, B. Goerdt, and G. Haselhorst, *Chem. Eur. J.*, 1997, **3**, 308.
- 1997CL665 K. Fujiwara, M. Tsunashima, D. Awakura, and A. Murai, *Chem. Lett.*, 1997, 665.
- 1997HCA2315 H. Weller, L. Siegfried, M. Neuburger, M. Zehnder, and T. A. Kaden, *Helv. Chim. Acta*, 1997, **80**, 2315.
- 1997JA3481 J. P. Collman, P. C. Herrmann, L. Fu, T. A. Eberspacher, and M. Eubanks, *J. Am. Chem. Soc.*, 1997, **119**, 3481.
- 1997JA8127 J. A. Halfen, B. A. Jazdzewski, S. Mahapatra, L. M. Berreau, and E. C. Wilkinson, *J. Am. Chem. Soc.*, 1997, **119**, 8217.
- 1997JA8889 A. Sokolowski, J. Mueller, T. Weyhermueller, R. Schnepf, and P. Holdebrandt, *J. Am. Chem. Soc.*, 1997, **119**, 8889.
- 1997JCD1337 A. J. Blake, F. Cristiani, F. A. Devillanova, A. Garau, L. M. Gilby, R. O. Gould, F. Isaia, V. Lippolis, S. Parsons, C. Radek, and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 1997, 1337.
- 1997JOC2308 J. P. Collman, B. Boitrel, L. Fu, J. Galanter, A. Straumanis, and M. Rapt, *J. Org. Chem.*, 1997, **62**, 2308.
- 1997JOC2544 K. Narita, N. Shirai, and Y. Sato, *J. Org. Chem.*, 1997, **62**, 2544.
- 1997J(P1)447 S. E. Gibson, N. Guillo, R. J. Middleton, A. Thuilliez, and M. J. Tozer, *J. Chem. Soc., Perkin Trans. 1*, 1997, 447.
- 1997PCA9180 B. J. Drouin, N. E. Gruhn, J. F. Madden, S. G. Kukolich, M. Barfield, and R. S. Glass, *J. Phys. Chem. A*, 1997, **101**, 9180.
- 1997PS79 C. Ibis, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1997, **130**, 79.
- 1997T9977 H. Luitjes, M. Schakel, M. P. Aarnts, R. F. Schmitz, F. J. J. De Kanter, and G. W. Klumpp, *Tetrahedron*, 1997, **53**, 9977.
- 1997TA2921 C. E. Song, Y. H. Kim, K. C. Lee, S. Lee, and B. W. Jin, *Tetrahedron Asymmetry*, 1997, **8**, 2921.
- 1998ANC5259 M. R. Ganjali, A. Moghimi, and M. Shamsipur, *Anal. Chem.*, 1998, **70**, 5259.
- 1998BML1973 Y. Hirokawa, H. Yamazaki, N. Yoshida, and S. Kato, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1973.
- 1998CC1625 R. Schneider, M. W. Hosseini, J. Planeix, A. De Cian, and J. Fischer, *Chem. Commun.*, 1998, 1625.
- 1998CC1757 K. C. Nicolaou, G. Shi, K. Namoto, and F. Bernal, *Chem. Commun.*, 1998, 1757.
- 1998CC1809 J. Masamoto, N. Yamasaki, W. Sakai, T. Itoh, N. Tsutsumi, and H. Nagahara, *Chem. Commun.*, 1998, 1809.
- 1998CEJ93 G. H. Walf, R. Benda, F. J. Litterst, U. Stebani, S. Schmidt, and G. Lattermann, *Chem. Eur. J.*, 1998, **4**, 93.
- 1998EJO1803 M. Wenzel, R. Beckert, W. Guenther, and H. Goerls, *Eur. J. Org. Chem.*, 1998, 1803.
- 1998JA5943 D. Yang, M. Wong, Y. Yip, X. Wang, and M. Tang, *J. Am. Chem. Soc.*, 1998, **120**, 5943.
- 1998JME5219 W. Grell, R. Hurnaus, G. Griss, R. Sauter, and E. Rupprecht, *J. Med. Chem.*, 1998, **41**, 5219.
- 1998JOC6859 R. C. Larock, C. Tu, and P. Pace, *J. Org. Chem.*, 1998, **63**, 6859.

- 1998JOC8082 J. P. Collman, M. Broering, L. Fu, M. Rapta, R. Schwenninger, and A. Straumanis, *J. Org. Chem.*, 1998, **63**, 8082.
1998JOC9888 D. Yang, Y. Yip, M. Tang, M. Wong, and K. Cheung, *J. Org. Chem.*, 1998, **63**, 9888.
1998JOM(550)359 S. Schade and G. Boche, *J. Organomet. Chem.*, 1998, **550**, 359.
1998J(P1)3623 T. Mori, M. Taniguchi, F. Suzuki, H. Doi, and A. Oku, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3623.
1998J(P2)83 S. A. Bourne, X. Y. Mbianda, T. A. Modro, L. R. Nassimbeni, and H. Wan, *J. Chem. Soc., Perkin Trans. 2*, 1998, 83.
1998JRM1448 A. M. Costero, C. Andreu, and E. Monrabal, *J. Chem. Res. (M)*, 1998, 1448.
1998PHC(10)335 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 1998, vol. 10, p. 335.
1998S1339 R. Ziessel, M. Hissler, and G. Ulrich, *Synthesis*, 1998, 1339.
1998SL402 L. Gauzy, Y. Le Merrer, and J. Depezay, *Syn lett.*, 1998, 402.
1998T12745 M. Shimano, N. Kamei, T. Shibata, K. Inoguchi, and N. Itoh, *Tetrahedron*, 1998, **54**, 12745.
1998TL4363 M. Shimano, T. Shibata, and N. Kamei, *Tetrahedron Lett.*, 1998, **39**, 4363.
1998TL7159 P. Rossi, F. Felluga, and P. Scrimin, *Tetrahedron Lett.*, 1998, **39**, 7159.
1999AGE956 Y. Miyahara, Y. Tanaka, K. Amimoto, T. Akazawa, T. Sakuragi, H. Kobayashi, K. Kubota, M. Suenaga, H. Koyama, and T. Inazu, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 956.
1999AGE980 D. E. De Vos, S. de Wildeman, B. F. Sels, P. J. Grobet, and P. A. Jacobs, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 980.
1999AJC1131 D. J. Bergmann, E. M. Campi, R. W. Jackson, and A. F. Patti, *Aust. J. Chem.*, 1999, **52**, 1131.
1999CC309 D. M. Hodgson and L. A. Robinson, *Chem. Commun.*, 1999, 309.
1999CEJ2554 M. D. Snodin, L. Ould-Moussa, U. Wallmann, S. Lecomte, V. Bachler, E. Bill, H. Hummel, T. Weyhermueller, P. Hildebrandt, and K. Wiegardt, *Chem. Eur. J.*, 1999, **5**, 2554.
1999CL461 D. Awakura, K. Fujiwara, and A. Murai, *Chem. Lett.*, 1999, 461.
1999JA1817 A. J. Souers, A. A. Virgilio, A. Rosenquist, W. Fenuik, and J. A. Ellman, *J. Am. Chem. Soc.*, 1999, **121**, 1817.
1999JCD1539 S. E. Watkins, X. Yang, D. C. Craig, and S. B. Colbran, *J. Chem. Soc., Dalton Trans.*, 1999, 1539.
1999JME4380 C. Haskell Luevano, A. Rosenquist, A. Souers, K. C. Khong, J. A. Ellman, and R. D. Cone, *J. Med. Chem.*, 1999, **42**, 4380.
1999JME4547 N. G. Almstead, R. S. Bradley, S. Pikul, B. De, M. G. Natchus, Y. O. Taiwo, L. E. Williams, B. A. Hynd, M. J. Janusz, C. M. Dunaway, and G. E. Mieling, *J. Med. Chem.*, 1999, **42**, 4547.
1999JOC2616 K. Fujiwara, D. Awakura, M. Tsunashima, A. Nakamura, T. Honma, and A. Murai, *J. Org. Chem.*, 1999, **64**, 2616.
1999JOC4576 P. Wipi and W. Li, *J. Org. Chem.*, 1999, **64**, 4576.
1999JOC7661 T. Wang, Z. Zhang, and N. A. Meanwell, *J. Org. Chem.*, 1999, **64**, 7661.
1999J(P1)1211 S. P. Creaser, S. F. Lincoln, and S. M. Pyke, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1211.
1999J(P2)1273 J. Ishikawa, H. Sakamoto, and H. Wada, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1273.
1999J(P2)2701 J. Springborg, B. Nielsen, C. E. Olsen, and I. Soetofte, *J. Chem. Soc., Perkin Trans. 2*, 1999, 2701.
1999MI(5)89 R. Glaser and D. Shiftan; in 'Advances in Molecular Structure Research', M. Hargittai and I. Hargittai, Eds.; JAI Press, Stamford, CT, 1999, vol. 5, p. 89.
1999PHC(11)338 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 1999, vol. 11, p. 338.
1999S1034 V. Kuksa, C. Marshall, S. Wardell, and P. K. Lin, *Synthesis*, 1999, 1034.
1999SAA1827 G. D. Fleming, M. M. C. Vallette, E. Clavijo, S. Diez, and M. Saavedra, *Spectrochim. Acta, Part A*, 1999, **55**, 1827.
1999SC3939 M. Romdhani and M. M. Chaabouni, *Synth. Commun.*, 1999, **29**, 3939.
1999SL25 S. Laabs, A. Scherrmann, A. Sudau, M. Diederich, C. Kierig, and U. Nubbemeyer, *Synlett*, 1999, 25.
1999SL954 S. E. Gibson, J. O. Jones, R. McCague, M. J. Tozer, and N. J. Whitcombe, *Synlett*, 1999, 954.
1999T5345 G. B. Shul'pin, G. Siiss-Fink, and J. R. L. Smith, *Tetrahedron*, 1999, **55**, 5345.
1999T5733 Y. Sun, C. S. Cutler, A. E. Martell, and M. J. Welch, *Tetrahedron*, 1999, **55**, 5733.
1999T7471 T. Oishi, M. Maruyama, M. Shoji, K. Maeda, N. Kumahara, S. Tanaka, and M. Hirama, *Tetrahedron*, 1999, **55**, 7471.
1999TL4989 S. Delagrangue and F. Nepveu, *Tetrahedron Lett.*, 1999, **40**, 4989.
1999TL9363 S. Pulacchini and M. Watkinson, *Tetrahedron Lett.*, 1999, **40**, 9363.
2000AGE1664 C. A. Dvorak, W. D. Schmitz, D. J. Poon, D. C. Pryde, J. P. Lawson, R. A. Amos, and A. I. Meyers, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 1664.
2000AJC791 M. V. Baker, D. H. Brown, B. W. Skelton, and A. H. White, *Aust. J. Chem.*, 2000, **53**, 791.
2000BMC307 Y. Le Merrer, L. Gauzy, C. Gravier-Pelletier, and J. Depezay, *Bioorg. Med. Chem.*, 2000, **8**, 307.
2000BML1257 W. Lew, H. Wu, X. Chen, B. J. Graves, P. A. Escarpe, H. L. MacArthur, D. B. Mendel, and C. U. Kim, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1257.
2000BML2731 A. J. Souers, A. Rosenquist, E. M. Jarvie, M. Ladlow, W. Feniuk, and J. A. Ellman, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2731.
2000CC443 P. D. Beer and D. Gao, *Chem. Commun.*, 2000, 443.
2000CC567 S. Bond and P. Perlmutter, *Chem. Commun.*, 2000, 567.
2000CC631 J. W. Burton, P. T. O'Sullivan, E. A. Andersen, I. Collins, and A. B. Holmes, *Chem. Commun.*, 2000, 631.
2000CEJ4498 F. Formaggio, M. Crisma, P. Rossi, P. Scrimin, B. Kaptein, Q. B. Broxterman, J. Kamphuis, and C. Toniolo, *Chem. Eur. J.*, 2000, **6**, 4498.
2000CL1104 H. Matsuyama, A. Kurosawa, T. Takei, N. Ohira, M. Yoshida, and M. Iyoda, *Chem. Lett.*, 2000, 1104.
2000CRV2963 L. Yet, *Chem. Rev.*, 2000, **100**, 2963.
2000H(53)151 Y. Endo, T. Uchida, and K. Yamaguchi, *Heterocycles*, 2000, **53**, 151.
2000H(53)851 M. S. Singh and A. K. Singh, *Heterocycles*, 2000, **53**, 851.
2000JA9663 F. N. Penkert, T. Weyhermueller, E. Bill, P. Hildebrandt, S. Lecomte, and K. Wiegardt, *J. Am. Chem. Soc.*, 2000, **122**, 9663.
2000JCD4607 M. V. Baker, D. H. Brown, B. W. Skelton, and A. H. White, *J. Chem. Soc., Dalton Trans.*, 2000, 4607.
2000JME3518 I. M. McDonald, D. J. Dunstone, S. B. Kalindjian, I. D. Linney, C. M. R. Low, M. J. Pether, K. I. M. Steel, M. J. Tozer, and J. G. Vinter, *J. Med. Chem.*, 2000, **43**, 3518.
2000JNP543 G. E. Martin and C. E. Hadden, *J. Nat. Prod.*, 2000, **63**, 543.
2000JOC1899 A. Oku and M. Numata, *J. Org. Chem.*, 2000, **65**, 1899.
2000JOC2319 G. N. Eyler, C. M. Mateo, E. E. Alvarez, and A. I. Canizo, *J. Org. Chem.*, 2000, **65**, 2319.

- 2000JOC4553 E. Marcantoni, M. Massaccesi, M. Petrini, G. Bartoli, M. C. Bellucci, M. Bosco, and L. Sambri, *J. Org. Chem.*, 2000, **65**, 4553.
- 2000JOC8367 D. I. MaGee and E. J. Beck, *J. Org. Chem.*, 2000, **65**, 8367.
- 2000JOM(611)586 M. Tamura, Y. Urano, K. Kikuchi, T. Higuchi, M. Hirobe, and T. Nagano, *J. Organomet. Chem.*, 2000, **611**, 586.
- 2000JST(526)185 A. Moghimi, M. F. Rastegar, M. Ghandi, G. W. Buchanan, and H. Rahbarnoohi, *J. Mol. Struct.*, 2000, **526**, 185.
- 2000NJC575 N. A. H. Male, M. E. G. Skinner, P. J. Wilson, P. Mountford, and M. Schroeder, *New J. Chem.*, 2000, **24**, 575.
- 2000NJC719 P. R. Bangal, G. K. Patra, and D. Datta, *New J. Chem.*, 2000, **24**, 719.
- 2000OL543 M. Mori, T. Kitamura, N. Sakakibara, and Y. Sato, *Org. Lett.*, 2000, **2**, 543.
- 2000OL1875 L. A. Paquette, O. M. Moradei, P. Bernardelli, and T. Lange, *Org. Lett.*, 2000, **2**, 1875.
- 2000OL1879 D. Friedrich, R. W. Doskotch, and L. A. Paquette, *Org. Lett.*, 2000, **3**, 1879.
- 2000OL2683 L. E. Overman and L. D. Pennington, *Org. Lett.*, 2000, **2**, 2683.
- 2000PHC(12)352 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 2000, vol. 12, p. 352.
- 2000TL9601 A. Singh, Q. Yao, L. Tong, W. C. Still, and D. Sames, *Tetrahedron Lett.*, 2000, **41**, 9601.
- 2000TL9989 T. Zoller, J. Ducep, C. Tahtaoui, and M. Hibert, *Tetrahedron Lett.*, 2000, **41**, 9989.
- 2001ARA331 I. A. Fallis, *Annu. Rep. Prog. Chem., Sect. A*, 2001, **97**, 331.
- 2001CC637 S. Bambirra, D. van Leusen, A. Meetsma, B. Hessen, and J. H. Teuben, *Chem. Commun.*, 2001, 637.
- 2001CC2582 L. Tei, A. J. Blake, F. A. Devillanova, A. Garau, V. Lippolis, C. Wilson, and M. Schroeder, *Chem. Commun.*, 2001, 2582.
- 2001CEJ4811 A. Fürstner, O. Guth, A. Dueffels, G. Seidel, M. Liebl, B. Gabor, and R. Mynott, *Chem. Eur. J.*, 2001, **7**, 4811.
- 2001CJC195 G. W. Buchanan, M. Rastegar, and G. P. A. Yap, *Can. J. Chem.*, 2001, **79**, 195.
- 2001CJC888 J. M. Vincent, A. Rabion, V. K. Yachandra, and R. H. Fish, *Can. J. Chem.*, 2001, **79**, 888.
- 2001EJO4233 S. Pulacchini and M. Watkinson, *Eur. J. Org. Chem.*, 2001, 4233.
- 2001JA333 Y. Singh, N. Sokolenko, M. J. Kelso, L. R. Gahan, G. Abbenante, and D. P. Fairlie, *J. Am. Chem. Soc.*, 2001, **123**, 333.
- 2001JA851 M. A. Sierra, J. C. del Amo, M. J. Mancheno, and M. Gomez-Gallego, *J. Am. Chem. Soc.*, 2001, **123**, 851.
- 2001JA1533 M. T. Crimmins and K. A. Emmitte, *J. Am. Chem. Soc.*, 2001, **123**, 1533.
- 2001JA2436 L. Charbonniere, R. Ziessel, M. Guardigli, A. Roda, N. Sabbatini, and M. Cesario, *J. Am. Chem. Soc.*, 2001, **123**, 2436.
- 2001JA5030 G. Lin, G. Reid, and T. D. H. Bugg, *J. Am. Chem. Soc.*, 2001, **123**, 5030.
- 2001JA6025 S. Kimura, E. Bill, E. Bothe, T. Weyhermueller, and K. Wieghardt, *J. Am. Chem. Soc.*, 2001, **123**, 6025.
- 2001JA9021 P. Bernardelli, O. M. Moradei, D. Friedrich, J. Yang, F. Gallou, B. P. Dyck, R. W. Doskotch, T. Lange, and L. A. Paquette, *J. Am. Chem. Soc.*, 2001, **123**, 9021.
- 2001JA9033 D. W. C. MacMillan, L. E. Overman, and L. D. Pennington, *J. Am. Chem. Soc.*, 2001, **123**, 9033.
- 2001JA11534 T. Tsuchiya, T. Shimizu, and N. Kamigata, *J. Am. Chem. Soc.*, 2001, **123**, 11534.
- 2001JMC1011 A. J. Blake, D. W. Bruce, J. P. Danks, I. A. Fallis, D. Guillon, S. A. Ross, and H. Richtzenhain, *J. Mater. Chem.*, 2001, **11**, 1011.
- 2001JME1658 S. Girault, P. Grellier, A. Berecibar, L. Maes, P. Lemiere, E. Mouray, E. Davioud-Charvet, and C. Sergheraert, *J. Med. Chem.*, 2001, **44**, 1658.
- 2001JOC2722 R. C. Hoye, J. E. Richman, G. A. Dantas, M. F. Lightbourne, and L. S. Shinneman, *J. Org. Chem.*, 2001, **66**, 2722.
- 2001JP12161 D. M. Hodgson, I. D. Cameron, M. Christlieb, R. Green, G. P. Lee, and L. A. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2161.
- 2001JST(561)43 G. W. Buchanan, M. F. Rastegar, and G. P. A. Yap, *J. Mol. Struct.*, 2001, **561**, 43.
- 2001OL135 F. Gallou, D. W. C. MacMillan, L. E. Overman, L. A. Paquette, L. D. Pennington, and J. Yang, *Org. Lett.*, 2001, **3**, 135.
- 2001OL861 T. J. Donohoe, A. Raoof, J. D. Linney, and M. Helliwell, *Org. Lett.*, 2001, **3**, 861.
- 2001OL2855 A. Warden, B. Graham, M. T. W. Hearn, and L. Spiccia, *Org. Lett.*, 2001, **3**, 2855.
- 2001OL2957 F. Iradier, G. Arrayas, and J. C. Carretero, *Org. Lett.*, 2001, **3**, 2957.
- 2001OPP391 A. Mai, M. Esposito, G. Sbardella, and S. Massa, *Org. Prep. Proced. Int.*, 2001, **33**, 391.
- 2001PHC(13)378 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 2002, vol. 13, p. 378.
- 2001PS85 L. Plasseraud and R. W. Saalfrank, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2001, **168**, 85.
- 2001PS325 L. Plasseraud and R. W. Saalfrank, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2001, **169**, 325.
- 2001S654 M. Mori, T. Kitamura, and Y. Sato, *Synthesis*, 2001, 654.
- 2001SC3141 I. Lazar and Z. Takacs, *Synth. Commun.*, 2001, **31**, 3141.
- 2001T8759 R. Salcedo, A. Martínez, and L. E. Sansores, *Tetrahedron*, 2001, **57**, 8759.
- 2001TL271 N. Yamasaki, H. Nagahara, and J. Masamoto, *Tetrahedron Lett.*, 2001, **42**, 271.
- 2002AJC655 M. V. Baker, D. H. Brown, B. W. Skelton, and A. H. White, *Aust. J. Chem.*, 2002, **55**, 655.
- 2002AN1627 L. Widmer, B. Watson, K. Schlatter, and A. Crowson, *Analyst*, 2002, **127**, 1627.
- 2002AP443 H. El Subbagh, T. Wittig, M. Decker, S. Elz, M. Nieger, and J. Lehmann, *Arch. Pharm. (Weinheim, Ger.)*, 2002, **335**, 443.
- 2002ARA321 I. A. Fallis, *Annu. Rep. Prog. Chem., Sect. A*, 2002, **98**, 321.
- 2002CC2656 S. Yamada and A. Homma, *Chem. Commun.*, 2002, 2656.
- 2002CJC1410 M. R. J. Elsegood, L. M. Gilby, K. E. Holmes, and P. F. Kelly, *Can. J. Chem.*, 2002, **80**, 1410.
- 2002EJM379 S. E. Gibson, N. Guillo, J. O. Jones, I. M. Buck, S. B. Kalindjian, S. Roberts, and M. J. Tozer, *Eur. J. Med. Chem.*, 2002, **37**, 379.
- 2002EJO351 I. Lazar, A. Egri, R. Kiraly, Z. Baranyai, T. Ivanyi, and E. Bruecher, *Eur. J. Org. Chem.*, 2002, 351.
- 2002HCA712 F. Monnat, P. Vogel, and J. A. Sordo, *Helv. Chim. Acta*, 2002, **85**, 712.
- 2002IJB372 J. Gao, H. He, X. Zhang, X. Lu, and J. Kang, *Indian J. Chem., Sect. B*, 2002, **41**, 372.
- 2002JA13408 G. Xu, J. S. Martinez, J. T. Groves, and A. Butler, *J. Am. Chem. Soc.*, 2002, **124**, 13408.
- 2002JA15196 S. E. Denmark and S. Yang, *J. Am. Chem. Soc.*, 2002, **124**, 15196.
- 2002JME3458 H. S. Chong, K. Garmestani, D. Ma, D. E. Milenic, T. Overstreet, and M. W. Brechbiel, *J. Med. Chem.*, 2002, **45**, 3458.
- 2002JOC245 D. E. Williams, K. S. Craig, B. Patrick, L. M. McHardy, R. Van Soest, M. Roberge, and R. J. Andersen, *J. Org. Chem.*, 2002, **67**, 245.
- 2002JOC2065 A. Moghimi, M. F. Rastegar, M. Ghandi, M. Taghizadeh, A. Yari, M. Shamsipur, G. P. A. Yap, and H. Rahbarnoohi, *J. Org. Chem.*, 2002, **67**, 2065.
- 2002JOC3933 L. J. Charbonniere, N. Weibel, and R. F. Ziessel, *J. Org. Chem.*, 2002, **67**, 3933.

- 2002JOC4565 C. Kuligowski, S. Bezzenine-Lafollee, G. Chaume, J. Mahuteau, J. Barriere, E. Bacque, A. Pancrazi, and J. Ardisson, *J. Org. Chem.*, 2002, **67**, 4565.
- 2002J(P2)2078 T. Guedez, A. Nunez, E. Tineo, and O. Nunez, *J. Chem. Soc., Perkin Trans. 2*, 2002, 2078.
- 2002OL451 P. Lakshminpathi, D. Gree, and R. Grec, *Org. Lett.*, 2002, **4**, 451.
- 2002OL949 B. M. Kim, S. M. So, and H. J. Choi, *Org. Lett.*, 2002, **4**, 949.
- 2002OL3047 M. J. Coster and J. J. De Voss, *Org. Lett.*, 2002, **4**, 3047.
- 2002OL3059 T. J. Donohoe, A. Raouf, G. C. Freestone, I. D. Linney, A. Cowley, and M. Helliwell, *Org. Lett.*, 2002, **4**, 3059.
- 2002PHC(14)356 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 2002, vol. 14, p. 356.
- 2002PNA5144 A. Scarso, U. Scheffer, M. Göbel, Q. B. Broxterman, B. Kaptein, F. Formaggio, C. Toniolo, and P. Scrimin, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 5144.
- 2002S1398 C. Liu, R. H. E. Hudson, and N. O. Petersen, *Synthesis*, 2002, 1398.
- 2002SL697 T. Kan, H. Kobayashi, and T. Fukuyama, *Synlett*, 2002, 697.
- 2002SL2019 S. Karsch, P. Schwab, and P. Metz, *Synlett*, 2002, 2019.
- 2002T1779 S. Bond and P. Perlmutter, *Tetrahedron*, 2002, **58**, 1779.
- 2002T1817 M. T. Crimmins, K. A. Emmitte, and A. L. Choy, *Tetrahedron*, 2002, **58**, 1817.
- 2002T1943 E. A. Anderson, J. E. P. Davidson, J. R. Harrison, P. T. O'Sullivan, J. W. Burton, I. Collins, and A. B. Holmes, *Tetrahedron*, 2002, **58**, 1943.
- 2002T2957 T. Doi, H. Nagamiya, M. Kokubo, K. Hirabayashi, and T. Takahashi, *Tetrahedron*, 2002, **58**, 2957.
- 2002T6267 T. Kan, A. Fujiwara, H. Kobayashi, and T. Fukuyama, *Tetrahedron*, 2002, **58**, 6267.
- 2002T7177 H. H. Wasserman, H. Matsuyama, and R. P. Robinson, *Tetrahedron*, 2002, **58**, 7177.
- 2002T10181 L. Chacun-Lefèvre, V. Bénétiau, B. Joseph, and J.-Y. Mèroux, *Tetrahedron*, 2002, **58**, 10181.
- 2002TL771 M. Pacchioni, A. Bega, A. C. Fabretti, D. Rovai, and A. Cornia, *Tetrahedron Lett.*, 2002, **43**, 771.
- 2002TL3165 Y. G. Suh, S. Kim, J. Jung, and D. Shin, *Tetrahedron Lett.*, 2002, **43**, 3165.
- 2002TL3795 G. Argouarch, C. L. Gibson, G. Stones, and D. C. Sherrington, *Tetrahedron Lett.*, 2002, **43**, 3795.
- 2002TL4207 Y. A. Ibrahim, H. Behbehani, and M. R. Ibrahim, *Tetrahedron Lett.*, 2002, **43**, 4207.
- 2002TL4989 T. Gunnlaugsson, B. Bichell, and C. Nolan, *Tetrahedron Lett.*, 2002, **43**, 4989.
- 2003AJC61 S. P. Creaser, S. M. Pyke, and S. F. Lincoln, *Aust. J. Chem.*, 2003, **56**, 61.
- 2003AJC309 M. T. S. Quintin, D. R. Leslie, and J. G. Collins, *Aust. J. Chem.*, 2003, **56**, 309.
- 2003EJO54 M. L. Teyssot, M. Fayolle, C. Philouze, and C. Dupuy, *Eur. J. Org. Chem.*, 2003, 54.
- 2003JA3889 K. M. Hendrickson, J. P. Geue, O. Wyness, S. F. Lincoln, and A. D. Ward, *J. Am. Chem. Soc.*, 2003, **125**, 3889.
- 2003JA6650 O. Corminboeuf, L. E. Overman, and L. D. Pennington, *J. Am. Chem. Soc.*, 2003, **125**, 6650.
- 2003JA7592 M. T. Crimmins and M. T. Powell, *J. Am. Chem. Soc.*, 2003, **125**, 7592.
- 2003JCD2428 C. Gateau, M. Mazzanti, J. Pecaut, F. A. Dunand, and L. Helm, *J. Chem. Soc., Dalton Trans.*, 2003, 2428.
- 2003JCM380 D. N. Upadhyay, N. Agarwal, A. Goel, and V. J. Ram, *J. Chem. Res. (S)*, 2003, 380.
- 2003JCM704 J. P. Cross and P. G. Sammes, *J. Chem. Res. (S)*, 2003, 704.
- 2003JOC3311 V. Cere, S. Pollicino, and A. Ricci, *J. Org. Chem.*, 2003, **68**, 3311.
- 2003JOC4876 R. V. Hoffman and S. Madan, *J. Org. Chem.*, 2003, **68**, 4876.
- 2003JOC5346 X. Moreau and J. Campagne, *J. Org. Chem.*, 2003, **68**, 5346.
- 2003JOC8932 S. Gille, A. Ferry, T. Billard, and B. R. Langlois, *J. Org. Chem.*, 2003, **68**, 8932.
- 2003JMT(637)115 D. Nori-Shargh and F. R. Ghanizadeh, *J. Mol. Struct. Theochem*, 2003, **637**, 115.
- 2003M1241 T. A. Salama, A. S. El-Ahl, A. M. Khalil, M. M. Girges, B. Lackner, C. Steindl, and S. S. Elmorsy, *Monatsh. Chem.*, 2003, **134**, 1241.
- 2003OBC2357 G. Stones, G. Argouarch, A. R. Kennedy, D. C. Sherrington, and C. L. Gibson, *Org. Biomol. Chem.*, 2003, **1**, 2357.
- 2003OBC4293 D. M. Hodgson, T. J. Buxton, I. D. Cameron, E. Gras, and E. H. M. Kirton, *Org. Biomol. Chem.*, 2003, **1**, 4293.
- 2003OBC4408 G. Argouarch, G. Stones, C. L. Gibson, A. R. Kennedy, and D. C. Sherrington, *Org. Biomol. Chem.*, 2003, **1**, 4408.
- 2003OL1337 H. M. C. Ferraz and L. S. Longo, *Org. Lett.*, 2003, **5**, 1337.
- 2003OL1543 O. Corminboeuf, L. E. Overman, and L. D. Pennington, *Org. Lett.*, 2003, **5**, 1543.
- 2003JOC3089 J. M. Schomaker, B. R. Travis, and B. Borhan, *Org. Lett.*, 2003, **5**, 3089.
- 2003PHC(15)431 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2003, vol. 15, p. 431.
- 2003PJC485 J. F. Wei, X. Y. Shi, D. P. He, and B. H. Ma, *Pol. J. Chem.*, 2003, **77**, 485.
- 2003PS1295 T. Takido, M. Toriyama, K. Ogura, H. Kamijo, S. Motohashi, and M. Seno, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 1295.
- 2003SC1147 H. S. Chong and M. W. Brechbiel, *Synth. Commun.*, 2003, **33**, 1147.
- 2003SL1043 Y. K. Yang and J. Tae, *Syn Lett*, 2003, 1043.
- 2003T6051 Z. Regania, J. Winum, F. Smaine, L. Toupet, N. Aouf, and J.-L. Montero, *Tetrahedron*, 2003, **59**, 6051.
- 2003T6759 F. Ek, L. Wistrand, and T. Frejd, *Tetrahedron*, 2003, **59**, 6759.
- 2003T9239 M. R. Heinrich, W. Steglich, M. G. Banwell, and Y. Kashman, *Tetrahedron*, 2003, **59**, 9239.
- 2003TL535 G. M. Bonora, S. Trioli, F. Felluga, F. Mancin, P. Rossi, P. Scrimin, and P. Tecilla, *Tetrahedron Lett.*, 2003, **44**, 535.
- 2003TL2481 W. Yang, C. M. Giandomenico, M. Sartori, and D. A. More, *Tetrahedron Lett.*, 2003, **44**, 2481.
- 2003TL2709 T. Saitoh, T. Suzuki, N. Onodera, H. Sekiguchi, H. Hagiwara, and T. Hoshi, *Tetrahedron Lett.*, 2003, **44**, 2709.
- 2003TL2841 M. Gibson, J. M. Goodman, L. J. Farrugia, and R. C. Hartley, *Tetrahedron Lett.*, 2003, **44**, 2841.
- 2003TL5699 M. A. Calter and R. K. Orr, *Tetrahedron Lett.*, 2003, **44**, 5699.
- 2003TL7655 L. Banfi, A. Basso, G. Guanti, and R. Riva, *Tetrahedron Lett.*, 2003, **44**, 7655.
- 2004AGE6165 F. Manea, F. B. Houillon, L. Pasquato, and P. Scrimin, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 6165.
- 2004AXCO100 A. J. Blake, V. Lippolis, and M. Schroeder, *Acta Crystallogr., Sect. C*, 2004, **60**, O100.
- 2004CEJ2022 P. C. Griffiths, I. A. Fallis, D. J. Willock, A. Paul, C. L. Barrie, P. M. Griffiths, G. M. Williams, S. M. King, R. K. Heenan, and R. Goergl, *Chem. Eur. J.*, 2004, **10**, 2022.

- 2004CRV2199 A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199.
2004CRV2239 M. D. McReynolds, J. M. Dougherty, and P. R. Hanson, *Chem. Rev.*, 2004, **104**, 2239.
2004CRV2777 A. T. Balaban, D. C. Oniciu, and A. R. Katritzky, *Chem. Rev.*, 2004, **104**, 2777.
2004CRV3371 D. J. Edmonds, D. Johnston, and D. J. Procter, *Chem. Rev.*, 2004, **104**, 3371.
2004JA1642 G. A. Molander, D. J. St. Jean, and J. Haas, *J. Am. Chem. Soc.*, 2004, **126**, 1642.
2004JA3529 A. Klapars, S. Parris, K. W. Anderson, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 3529.
2004JA10264 M. T. Crimmins and B. H. Brown, *J. Am. Chem. Soc.*, 2004, **126**, 10264.
2004JA12432 S. E. Denmark and S. Yang, *J. Am. Chem. Soc.*, 2004, **126**, 12432.
2004JA15074 E. C. Hansen and D. Lee, *J. Am. Chem. Soc.*, 2004, **126**, 15074.
2004JME5683 L. L. Parker, S. M. Lacy, L. J. Farrugia, C. Evans, D. J. Robins, C. C. O'Hare, J. A. Hartley, M. Jaffar, and I. J. Stratford, *J. Med. Chem.*, 2004, **47**, 5683.
2004JNP273 K.-H. Lee, *J. Nat. Prod.*, 2004, **67**, 273.
2004JOC3662 A. J. Brouwer and R. M. J. Liskamp, *J. Org. Chem.*, 2004, **69**, 3662.
2004JOC6867 C. Mukai, M. Ohta, H. Yamashita, and S. Kitagaki, *J. Org. Chem.*, 2004, **69**, 6867.
2004JPO215 A. Canizo, G. N. Eyler, G. Morales, and J. R. Cerna, *J. Phys. Org. Chem.*, 2004, **17**, 215.
2004PCA4059 K. R. F. Somers, E. S. Kryachko, and A. Ceulemans, *J. Phys. Chem. A*, 2004, **108**, 4059.
2004SOS(17)979 R. M. Borzilleri, in 'Science of Synthesis', S. M. Weinreb, Ed.; Georg Thieme Verlag, Stuttgart, 2004, vol. 17, p. 979.
2004NJC959 S. M. Aucott, M. R. Bailey, M. R. J. Elsegood, L. M. Gilby, K. E. Holmes, P. F. Kelly, M. J. Papageorgiou, and S. Pedron-Haba, *New J. Chem.*, 2004, **28**, 959.
2004OBC2664 J. E. W. Scheuermann, K. F. Sibbons, D. M. Benoit, M. Motevalli, and M. Watkinson, *Org. Biomol. Chem.*, 2004, **18**, 2664.
2004OL1033 J. P. Collman, R. A. Decreau, and S. Costanzo, *Org. Lett.*, 2004, **6**, 1033.
2004OL4351 Y. J. Kim and D. Lee, *Org. Lett.*, 2004, **6**, 4351.
2004PHC(16)451 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2005, vol. 16, p. 451.
2004S837 M. S. Singh and A. K. Singh, *Synthesis*, 2004, 837.
2004S1696 S. Karsch, D. Freitag, P. Schwab, and P. Metz, *Synthesis*, 2004, 1696.
2004S3029 G. Chaume, C. Kuligowski, S. Bezzenine-Laffolee, L. Ricard, A. Pancrazi, and J. Ardisson, *Synthesis*, 2004, 3029.
2004SL453 M. Oliver, M. R. Jorgensen, and A. D. Miller, *Synlett.*, 2004, 453.
2004SL1203 M. Urbala, N. Kuznik, S. Krompiec, and J. Rzepa, *Synlett.*, 2004, 1203.
2004SL1434 J. E. P. Davidson, R. Gilmour, S. Ducki, J. E. Davies, R. Green, J. W. Burton, and A. B. Holmes, *Synlett.*, 2004, 1434.
2004T415 L. Lemiegre, F. Lesetre, J. Combret, and J. Maddaluno, *Tetrahedron*, 2004, **60**, 415.
2004T5799 T. Gunnlaugsson, B. Bichell, and C. Nolan, *Tetrahedron*, 2004, **60**, 5799.
2004TL1091 H. Hioki, H. Kinami, A. Yoshida, A. Kojima, M. Kodama, S. Takaoka, K. Ueda, and T. Katsu, *Tetrahedron Lett.*, 2004, **45**, 1091.
2004TL3757 J. Tae and D. Hahn, *Tetrahedron Lett.*, 2004, **45**, 3757.
2004TL7567 A. Takemura, K. Fujiwara, A. Murai, H. Kawai, and T. Suzuki, *Tetrahedron Lett.*, 2004, **45**, 7567.
2004TL8061 M. Takemoto, Y. Iwakiri, Y. Suzuki, and K. Tanaka, *Tetrahedron Lett.*, 2004, **45**, 8061.
2004TL9335 T. Ikemoto, T. Ito, A. Nishiguchi, and K. Tomimatsu, *Tetrahedron Lett.*, 2004, **45**, 9335.
2004TL9607 S. Kotha and K. Singh, *Tetrahedron Lett.*, 2004, **45**, 9607.
2005BMC2389 L. L. Parker, F. M. Anderson, C. C. O'Hare, S. M. Lacy, J. P. Bingham, D. J. Robins, and J. A. Hartley, *Bioorg. Med. Chem.*, 2005, **13**, 2389.
2005BMCL4359 S. Olson, S. D. Aster, K. Brown, L. Carbin, D. W. Graham, A. Hermanowski-Vosatka, C. B. LeGrand, S. S. Mundt, M. A. Robbins, J. M. Schaeffer, L. H. Slossberg, M. J. Szymonifka, R. Thieringer, S. D. Wright, and J. M. Balkovec, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4359.
2005BML2011 Y. Usuki, K. Mitomo, N. Adachi, X. Ping, K. Fujita, O. Sakanaka, K. Iinuma, H. Iio, and M. Taniguchi, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2011.
2005CRV4314 T. Nakata, *Chem. Rev.*, 2005, **105**, 4314.
2005CRV4379 M. Inoue, *Chem. Rev.*, 2005, **105**, 4379.
2005JA1146 F. Dubnikova, R. Kosloff, J. Almog, Y. Zeiri, R. Boese, H. Itzhaky, A. Alt, and E. Keinan, *J. Am. Chem. Soc.*, 2005, **127**, 1146.
2005JA11240 Y. Furuya, K. Ishihara, and H. Yamamoto, *J. Amer. Chem. Soc.*, 2005, **127**, 11240.
2005JA12182 K. Tomooka, N. Komine, D. Fujiki, T. Nakai, and S.-I. Yanagitsuru, *J. Am. Chem. Soc.*, 2005, **127**, 12182.
2005JMC7192 J. Gao, F. R. Woolley, and R. A. Zingaro, *J. Med. Chem.*, 2005, **48**, 7192.
2005JOC115 A. C. Benniston, P. Gunning, and R. D. Peacock, *J. Org. Chem.*, 2005, **70**, 115.
2005JOC1552 M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. H. King, P. N. Horton, and M. B. Hursthouse, *J. Org. Chem.*, 2005, **70**, 1552.
2005JOC2206 A. Padwa, S. M. Lynch, J. M. Mejía-Oneto, and H. Zhang, *J. Org. Chem.*, 2005, **70**, 2206.
2005JOC3838 R. Kaul, S. Surprenant, and W. D. Lubell, *J. Org. Chem.*, 2005, **70**, 3838.
2005JOC5519 S. S. Kinderman, M. M. T. Wekking, J. H. Van Maarseveen, H. E. Schoemaker, H. Hiemstra, and F. P. J. T. Rutjes, *J. Org. Chem.*, 2005, **70**, 5519.
B-2005MI67 M. Schroder and V. Lippolis; in 'Macrocyclic Chemistry: Current Trends and Future Perspectives', K. Gloe, Ed.; Springer, Dordrecht, 2005, p. 67, (ISBN-10 1-4020-3364-8).
2005OBC97 S. A. Dietrich, L. Banfi, A. Basso, G. Damonte, G. Guanti, and R. Riva, *Org. Biomol. Chem.*, 2005, **3**, 97.
2005OL975 J. P. Collman and R. A. Decreau, *Org. Lett.*, 2005, **7**, 975.
2005OL4033 M. T. Crimmins, P. J. McDougall, and K. A. Emmitte, *Org. Lett.*, 2005, **7**, 4033.
2005OL4301 G. H. Posner, M. A. Hatcher, and W. A. Maio, *Org. Lett.*, 2005, **7**, 4301.
2005OL4781 T. Yang, C. Lin, H. Fu, Y. Jiang, and Y. Zhao, *Org. Lett.*, 2005, **7**, 4781.
2005PCA11870 M. Elango and V. Subramanian, *J. Phys. Chem. A*, 2005, **109**, 11870.
2005PHC(17)418 G. R. Newkome; in 'Progress in Heterocyclic Chemistry', G. W. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2005, vol. 17, p. 418.
2005SC1115 H. Eshghi and A. Hassankhani, *Synth. Commun.*, 2005, **35**, 1115.

- 2005SL631 T. Yamanaka, M. Ohkubo, M. Kato, Y. Kawamura, A. Nishi, and T. Hosokawa, *Synlett*, 2005, 631.
- 2005T2659 J. B. Bremner and D. F. Perkins, *Tetrahedron*, 2005, **61**, 2659.
- 2005T7392 A. Takemura, K. Fujiwara, K. Shimawaki, A. Murai, H. Kawai, and T. Suzuki, *Tetrahedron*, 2005, **61**, 7392.
- 2005T7456 E. Manzo, M. L. Ciavatta, M. Gavagnin, R. Puliti, E. Mollo, Y.-W. Guo, C. A. Mattia, L. Mazzarella, and G. Cimino, *Tetrahedron*, 2005, **61**, 7456.
- 2005T7499 A. R. Battle and L. Spiccia, *Tetrahedron*, 2005, **61**, 7499.
- 2005T12371 N. C. Meyer, C. Bolm, G. Raabea, Ulrich, and Kölle,, *Tetrahedron*, 2005, **61**, 12371.
- 2006BMC3766 G. Ding, F. Liu, T. Yang, Y. Jiang, H. Fu, and Y. Zhao, *Biorg. Med. Chem.*, 2006, **11**, 3766.
- 2006CEJ7133 A. Nonat, C. Gateau, P. H. Fries, and M. Mazzanti, *Chem. Europ. J.*, 2006, **12**, 7133.
- 2006CRV911 A. Parenty, X. Moreau, and J.-M. Campagne, *Chem. Rev.*, 2006, **106**, 911.
- 2006JA1371 M. T. Crimmins, B. H. Brown, and H. R. Plake, *J. Am. Chem. Soc.*, 2006, **128**, 1371.
- 2006JA3926 J. J. Fleming and J. Du Bois, *J. Am. Chem. Soc.*, 2006, **128**, 3926.
- 2006JCR(S)218 H. Eshghi, A. Hassankhani, and E. Mosaddegh, *J. Chem. Res. Synop.*, 2006, **4**, 218.
- 2006JMC2681 Y. Nakagawa, K. Irie, R. C. Yanagita, H. Ohigashi, K. Tsuda, K. Kashiwagi, and N. Saito, *J. Med. Chem.*, 2006, **49**, 2681.
- 2006JME760 B. Hoefgen, M. Decker, P. Mohr, A. M. Schramm, S. A. F. Rostom, H. El-Subbagh, P. M. Schweikert, D. R. Rudolf, M. U. Kassack, and J. Lehmann, *J. Med. Chem.*, 2006, **49**, 760.
- 2006JNP567 X. Luo, F. Li, J. Hong, C.-O. Lee, C. J. Sim, K. S. Im, and J. H. Jung, *J. Nat. Prod.*, 2006, **69**, 567.
- 2006JOC3804 M. Amat, C. Escolano, O. Lozano, A. Gómez-Esqué, R. Giera, E. Molins, and J. Bosch, *J. Org. Chem.*, 2006, **71**, 3804.
- 2006JOC4170 X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. Shen, and M. R. Tracey, *J. Org. Chem.*, 2006, **71**, 4170.
- 2006JOC5498 W. Migda and B. Rys, *J. Org. Chem.*, 2006, **71**, 5498.
- 2006MI1823 M. Nakanishi and C. Bolm, *Adv. Synth. Catal.*, 2006, **348**, 1823.
- 2006OL963 K. Tomooka, M. Suzuki, M. Shimada, S.-I. Yanagitsuru, and K. Uehara, *Org. Lett.*, 2006, **8**, 963.
- 2006OL2851 S. Surprenant and W. D. Lubell, *Org. Lett.*, 2006, **8**, 2851.
- 2006OL5279 I. Shiina, Y. Takasuna, R. Suzuki, H. Oshiumi, Y. Komiyama, S. Hitomi, and H. Fukui, *Org. Lett.*, 2006, **8**, 5279.
- 2006OL5897 S. V. Pansare and V. A. Adsool, *Org. Lett.*, 2006, **8**, 5897.
- 2006SL383 J. P. Michael, C. B. de Koning, and D. P. Pienaar, *Syn. Lett.*, 2006, 383.
- 2006T11670 C. Guarise, L. J. Prins, and P. Scrimin, *Tetrahedron*, 2006, **62**, 11670.
- 2006TL3541 T. Nabeshima, Y. Tanaka, T. Saiki, S. Akine, C. Ikeda, and S. Sato, *Tetrahedron*, 2006, **47**, 3541.
- 2006TL3673 J. H. Koek and E. W. J. M. Kohlen, *Tetrahedron Lett.*, 2006, **47**, 3673.
- 2007JOC376 A. Scarso, G. Zaupa, F. B. Houillon, L. J. Prins, and P. Scrimin, *J. Org. Chem.*, 2007, **72**, 376.

Biographical Sketch



Dmytro O. Tymoshenko received his M.S. (chemical engineering) from the Ukrainian University of Chemical Engineering (UUCE) of Dnepropetrovsk, Ukraine. Later on, as a scientist at the Department of Macromolecular Compounds of the UUCE, he received his Ph.D. in 1986, with a thesis focused on the synthesis and properties of water-soluble polymer carriers for drug immobilization and transport. His tenure at UUCE included positions of Assistant Professor and Associate Professor, while his research was focused on various aspects of heterocyclic synthesis and synthesis on polymer supports. His postdoctoral experience was gained with Volodymyr Syromyatnikov at the National Taras Shevchenko University of Kiev, Ukraine, and Alan Katritzky at the University of Florida. In 2000, he joined Albany Molecular Research, Inc., in Albany, NY, as senior research scientist, leading the parallel synthetic chemistry research program and working in the area of medicinal chemistry. His research interests include synthesis and reactivity of heterocycles and polymer-supported reagents and their application in organic synthesis.

14.11

Ten-membered Rings or Larger with One or More Nitrogen Atoms

P. Hermann and J. Kotek

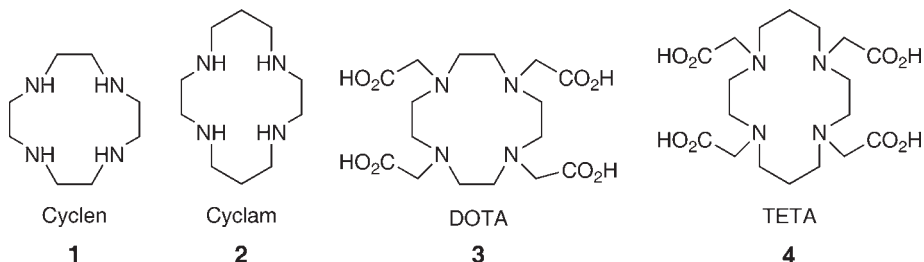
Universita Karlova, Prague, Czech Republic

© 2008 Elsevier Ltd. All rights reserved.

14.11.1	Introduction	614
14.11.2	Theoretical Methods	614
14.11.3	Experimental Structural Methods	615
14.11.3.1	Structures of Mono- and Diazamacrocycles	615
14.11.3.2	Structures of Triazamacrocycles	616
14.11.3.3	Structures of Polyazamacrocycles with Four and More Nitrogen Atoms	616
14.11.4	Thermodynamic Aspects	617
14.11.5	Ring Syntheses	618
14.11.5.1	Synthesis of Mono- and Diazamacrocycles	618
14.11.5.2	Synthesis of Triazamacrocycles	619
14.11.5.3	Synthesis of Tetraazamacrocycles	621
14.11.5.4	Synthesis of Polyazamacrocycles with Five and More Nitrogen Atoms	629
14.11.5.5	Synthesis of Polycycles by Ring-Closure Reactions	632
14.11.6	Reactivity of Tetraazamacrocycles	632
14.11.6.1	Protection Strategies	633
14.11.6.2	N-Functionalized Derivatives	639
14.11.6.2.1	Monosubstituted derivatives	639
14.11.6.2.2	Di- and trisubstituted derivatives	639
14.11.6.2.3	Tetrasubstituted derivatives	643
14.11.6.2.4	Phosphorus acid pendant arm derivatives	646
14.11.6.3	Synthesis of Polycycles from Macrocyclic Precursors	647
14.11.6.4	C-Functionalized Derivatives	650
14.11.7	Syntheses of Particular Classes of Compounds and Critical Comparison of Various Routes Available	652
14.11.8	Important Compounds and Applications	653
14.11.8.1	Metal Complexation	653
14.11.8.2	Anion Complexation	654
14.11.8.3	Contrast Agents for MRI	654
14.11.8.4	Radiopharmaceuticals	654
14.11.8.5	Luminescence Probes	655
14.11.8.6	Potential Drugs	655
14.11.9	Further Developments	656
	References	657

14.11.1 Introduction

Since publication of CHEC-II(1996), the field covered by this chapter has expanded enormously. The development is driven mainly by an extensive use of the cycles in metal and/or anion complexation, in modeling of enzyme reactions, in catalysis, and, mostly, in medicine as contrast agents (CAs) for magnetic resonance imaging (MRI), radiopharmaceuticals, or drugs. The chemistry is mainly focused on derivatives of two of the most important macrocyclic rings: 1,4,7,10-tetraazacyclododecane (cyclen) **1** and 1,4,8,11-tetraazacyclotetradecane (cyclam) **2**. From related compounds, tetrakis(acetic acid) derivatives DOTA **3** (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and TETA **4** (TETA = 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid) and their analogs/derivatives are of the main interest.



Because of the extensive utilization, syntheses of the most common rings have been greatly improved and some of them have become commercially available for a reasonable price. The organic chemistry of macrocycles has been covered by several reviews <1996SL933, 1997CCR35, 2000IEC3499, 2000SL561, 2003CCR27, 2003JHC1, 2005CHE1447>.

This chapter does not cover cyclic amides and peptides, since their number would enormously expand this text. They are reviewed only if they serve as reaction intermediates during synthesis of cyclic amines. In addition, metal ions complexation will be presented in required minimum, for example, if it serves for template formation during ring synthesis or as a main topic in some application. In this chapter, most of the sections deal with the literature data for all cycle types, except Section 14.11.6, which focuses mainly on chemistry of cyclen and cyclam and their analogs and derivatives. In Section 14.11.8, we give only a brief overview of the utilizations and provide a reader with reviews where more detailed information may be found.

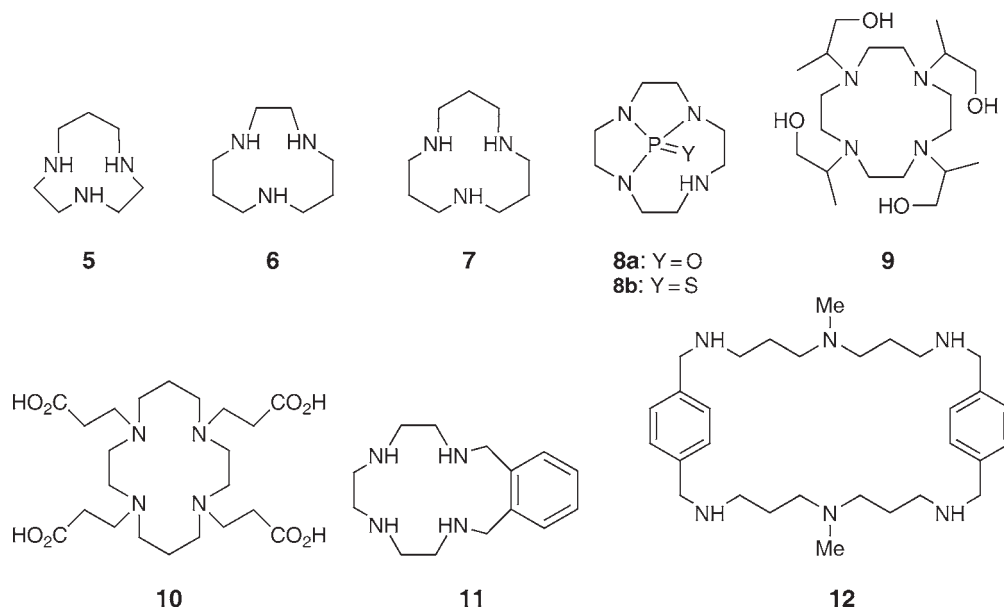
14.11.2 Theoretical Methods

Most of the theoretical works dealing with this class of macrocycles is devoted to the calculation of the structure and properties of their complexes.

Solvation of cyclen **1** was studied using Monte Carlo (MC) simulations <1996JPC17655, 1997JCF3045>. Potentials for cyclen were calculated by an *ab initio* method. It was found that the water hydration sphere is composed from three layers: two water molecules are strongly bound in close vicinity, six molecules form the inner hydration sphere, and 54 molecules should be present in the outer hydration sphere. The solvent is somewhat arranged up to 8–9 Å from the cyclen molecule. If simulation was done in water–ammonia solution, the results were similar except that the outer sphere accommodates three ammonia molecules. *Ab initio* calculations of conformations of cyclen **1**, 1,4,7-triazacyclododecane **5**, 1,4,8-triazacycloundecane **6**, and 1,5,9-triazacyclododecane **7** in different protonation states showed that the conformations are stabilized by intramolecular hydrogen bonds and, therefore, some nitrogen atoms are oriented ‘inward’ to the cycle cavity <1996JP21161>. Ethylene bridges are in a *gauche* conformation and propylene bridges exhibit some conformational freedom. The results are in full agreement with solid-state and solution results discussed in Sections 14.11.3 and 14.11.4. Molecular mechanics (MM) simulations were used for the determination of stable conformations of all protonated forms of cyclam **2** <1996JP21925>. It was found that less protonated forms are stabilized by intramolecular hydrogen bonds that leads to a very stable arrangement with inward orientation of all nitrogen atoms, especially in diprotonated form $H_2\text{cyclam}^{2+}$. Binding of the next proton must open this conformation and an unusual (reverse) order of values of the measured dissociation constants pK_1 (1.91) and pK_2 (1.61) was explained by large conformation change from such inward conformation, what leads to an easier binding of the fourth proton <1996JP21925>. Transannular interactions were studied on phosphoryl <1999JCR(S)526, 1999JRM2240> and thiophosphoryl <1999HCA790> cyclen derivatives **8a** and **8b** by MM calculations. The interaction of phosphorus atom with the cycle was

increased after deprotonation of the last amine proton to negatively charged amide. The conformations of tetrakis(hydroxoprop-2-yl)cyclen derivative **9** were studied by MO calculations. The results were correlated with dynamic nuclear magnetic resonance (NMR) spectroscopy <1997JA6126>.

Conformations of variously protonated tetrakis(propionate)-TETA analog **10** were studied by a linear combination of atomic orbitals (LCAO) local density functional (LDF) approach <1995NJC839>, and the results were correlated with X-ray crystallography. MM modeling was used to find the lowest-energy conformations in the free benzotetraaza ligand **11** <2003DT1852>. Anion recognition by large 30-membered hexaazamacrocyclic **12** was investigated by MM and/or molecular dynamics (MD) <2003DT4261, 2006NJC247>.

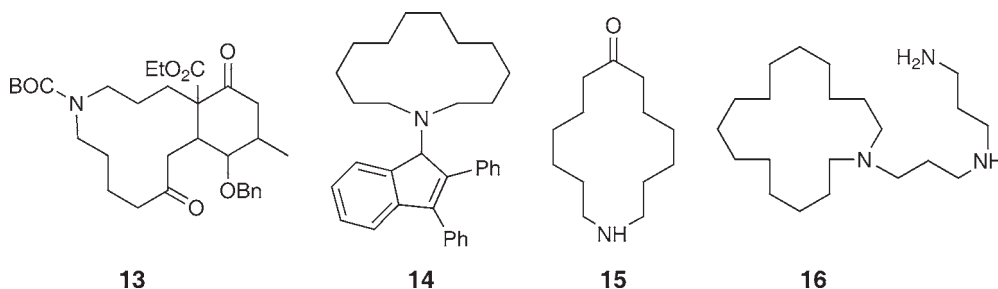


14.11.3 Experimental Structural Methods

Since 1995, more than 250 single-crystal X-ray structures of organic compounds (excluding their metal complexes) relevant for this chapter were deposited in the Cambridge Structural Database (CSD). Therefore, only brief overview of the reported structures is given here.

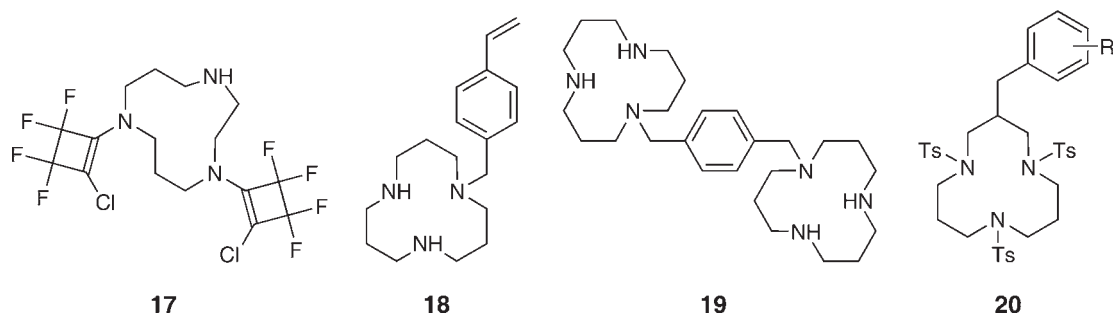
14.11.3.1 Structures of Mono- and Diazamacrocycles

The crystal analyses of *N*-BOC-azacyclododecane fused with substituted cyclohexane ring **13** <2005AGE6038>, *N*-indenyl azacyclotridecane **14** <1998JOM83>, protonated azacyclotetradecan-8-one **15** (in malate or tartate salts) <1999JA2919>, and trifluoroacetate of azacyclohexadecane-based mutuporamine **16** <2002JOC245> were reported.



14.11.3.2 Structures of Triazamacrocycles

1,2-Dichlorotetrafluorocyclobutene was reacted with macrocyclic amines introducing 2-chloro-3,3,4,4-tetrafluorocyclobutenyl substituent on nitrogen atoms. Double-substituted 1,4,8-triazacycloundecane **17** and fully substituted 1,5,9-triazacyclododecane were analyzed by X-ray diffraction. The study revealed planar arrangement around substituted nitrogen atoms due to the extreme electron-withdrawing effect <1998IC5342>. Single crystals of diprotonated *N*-benzyl-1,5,9-triazacyclododecane <1997TL1911> (protons are bound on both secondary amino groups) and monoprotonated (on one of secondary amines) *N*-(*p*-vinyl)benzyl-1,5,9-triazacyclododecane **18** <1999JP11621> in nitrate salts were analyzed. The structure of bis(macrocyclic) **19** consisting of two 1,5,9-triazacyclododecane units bridged by a *p*-xylylene group was reported as the diperchlorate salt (each macrocyclic unit is protonated on one of the secondary amino groups) <1997TL1911>. Once-protonated macrocycles adopt a close inward structure, in which proton is bound in the central cavity by intramolecular hydrogen bonds to the other nitrogen atoms, with short N–N distances around 3.0 Å. Contrariwise, diprotonation of the skeleton opens the cyclic backbone (shortest intramolecular N–N distance ~ 3.6 Å) and leads to intermolecular hydrogen bonding. A series of *N,N',N''*-tritosylated 1,5,9-triazacyclododecanes **20** substituted in C3 position by different benzyl groups was deposited in CSD by a personal communication <2000MI>.



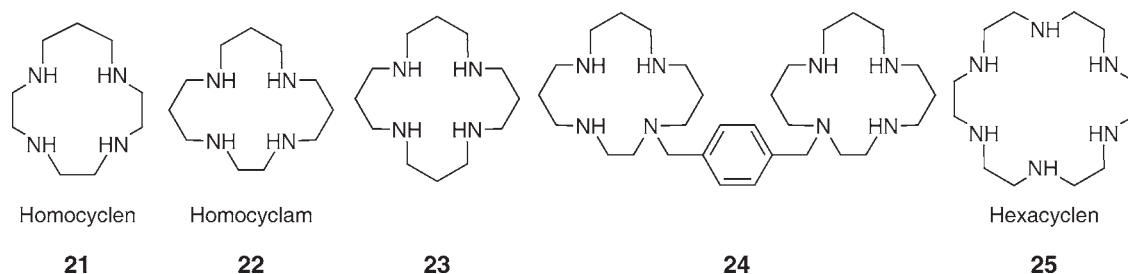
14.11.3.3 Structures of Polyazamacrocycles with Four and More Nitrogen Atoms

A majority of the crystal structures relevant for this chapter belong to derivatives of cyclen **1** (ca. 50 structures) and cyclam **2** (ca. 130 structures). Among them, several structures of homocyclen **21** derivatives (homocyclen = 1,4,7,10-tetraazacyclotridecane) and larger homocyclam **22** (homocyclam = 1,4,8,12-tetraazacyclopentadecane) and 1,5,9,13-tetraazacyclohexadecane **23** derivatives have appeared.

The structural characteristics of cyclen and cyclam and their carboxylic and amidic derivatives in variously protonated states as well as their metal complexes were excellently reviewed by Guilard and co-workers <1998CCR1313>. As those derivatives are frequently used in the complexation of transition metal or lanthanide ions, the space arrangement, exact protonation sites, and presence of intramolecular hydrogen bonds are of interest from the point of view of kinetics of complex formation/dissociation. Since the number of related structures is very high, but no new remarkable information appeared since Guilard's review, derivatives of these macrocycles are not discussed in detail.

The structure of monoperchlorate of 12,12-dimethyl-homocyclen was reported <1997AXC586>. The structure of the bis(macrocyclic) **24** where *p*-xylylene group bridges nitrogen atoms N1 of two homocyclam units was reported <1997NCS129>. From 16-membered tetraaza-rings, *N,N',N'',N'''*-tetramethyl-1,5,9,13-tetraazacyclohexadecane was structurally characterized <2004MI>.

Simple 1,4,7,10,13,16-hexaazacyclooctadecane **25** (hexacyclen), used in anion complexation studies (see Section 14.11.8.2), was crystallized in differently protonated (four- or sixfold) forms as sulfate, hydrogen sulfate, chloride–hydrogen sulfate, dithionate <2004NJC1301>, chloride, bromide, iodide–triiodide <2004NJC1160>, several dihydrogen phosphates <2004IC6936>, dihydrogen diphosphate <1999JA6807>, differently protonated trifluoromethanesulfonates <1995AXC1407>, hydrogen oxalate–oxalate, trifluoroacetate, picolinate, and bis(*p*-nitrophenyl)-phosphate <2005MI713>. In addition, structures of *N*-substituted derivatives, namely 1,10-dimethyl derivative in the form of dihydrogen diphosphate salt <1999JA6807> and 1,10-dimethyl-4,7,13,16-tetrakis(2,3-dihydroxybenzoyl) derivative <1998JCD359>, were solved.



From larger macrocyclic rings, only the structures of 1,4,7,10,13,16,19,22-octaazacyclotetracosane in fully protonated nitrate form <1999NJC1007> and its octa(*N*-acetate) derivative in the form of Bu^t ester <1997CB267> were reported.

14.11.4 Thermodynamic Aspects

Most of the thermodynamic studies have been performed in aqueous solutions as the cycles and their derivatives are first of all ligands for complexation of water-soluble metal ions. Numerous compounds have been studied and, therefore, only a general overview of trends is given. More information can be found in commercial databases such as NIST Standard Reference Database 46 (Critically Selected Stability Constants of Metal Complexes) or The IUPAC Stability Constants Database (SC-Database) or in reviews <2005PAC1445> (critically evaluated data for DOTA **3** and TETA **4**), <1999CCR97> (protonation constants of polyamines) and <2000CCR309> (protonation constants of polyamino-polycarboxylic acids). Overall basicity of the ligands is mostly the main determinant for values of stability constants of metal complexes.

Triazacycloalkanes and their derivatives were not studied extensively. 1,5,9-triazacyclododecane **7** is a rather basic amine ($pK_3 \sim 12.5$), whereas, the other dissociation constants are $\log K_2 = 7.54$ and $\log K_1 = 2.38$.

Tetraazacycloalkanes (cyclen **1** and cyclam **2**) have two high dissociation constants ($\log K_{3,4} > 10$) and corresponding two protons are bound to the opposite nitrogen atoms (to minimize electrostatic repulsion). Next protonations are possible only in very acidic medium ($pK_{1,2} < 1-2$). This protonation scheme is preserved in almost all derivatives of these two cycles. Basicity of *N*-substituted cycles depends on nature of the substituents. Simple alkylation leads to lowering (0.5–1 orders of magnitude) of the last two dissociation constants as tertiary amines are generally less basic than the secondary ones. Derivatization with anionic pendant arms mostly increases values of the last dissociation constants, for example, the methylphosphonate derivatives are highly basic with last pK_A values > 13 . Acetate pendants are protonated in acidic region (pH 3–5) depending on other substituents. Phosphonate pendants are first protonated in neutral solutions (pH 5.5–8) and these groups as well as phosphinates are fully protonated only in strongly acidic solution (pH < 2). Comparing these common anionic pendant arms, the following overall basicity sequence of amino groups can be derived <2001CCR287>: phosphinates $<$ acetates $<$ phosphonates. The order is given by electronic properties of the pendants (double-charged phosphonates spread electronic density to the close nitrogen atoms enhancing their basicity; phosphinates have more electron-withdrawing character than acetates). With neutral pendant arms (amides, hydroxyalkyls, methylpyridines, etc.), effects of substitution (tertiary amine) and electron-withdrawing character of the groups commonly lead to a lowering of basicity of nitrogen atoms ($pK_A \sim 9-10$).

The partially protonated cyclen and cyclam and their derivatives are present in aqueous solution in some stable conformations stabilized by intramolecular hydrogen bonds. It leads, for example, to broad signals in NMR at room temperature and intermediate pH. Such hydrogen bond-stabilized structures are sometimes rather stable as it was proved, for example, in the case of 1,8-bis(methylphosphonic acid) cyclam derivatives where solution structure is probably the same as found in the solid state <2000CCC1289>. These closed structures are opened after full protonation.

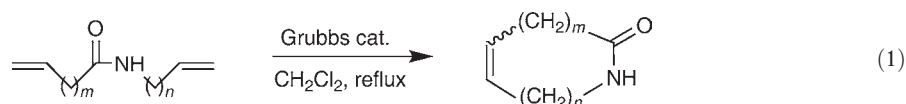
Larger cycles (five and more nitrogen atoms) have the values of dissociation constants spread through almost the entire pH region and are sometimes grouped into clusters if equivalent distant sites are protonated. At intermediate pH, there are several protons bound and such species are able to bind anions (Section 14.11.8.2) by electrostatic attraction and/or through hydrogen bonds. Similar considerations are valid for polycycles; in addition, protonation of polycycles can be almost independent on each other (depending on their structure).

14.11.5 Ring Syntheses

In this chapter, reactions leading to macrocyclic ring formation will be reviewed. Generally, they can be divided into several types: (1) ring closure reactions, where ring is formed by cyclization of linear substrate(s); (2) ring expansion reactions, where a small fragment is incorporated into a larger cyclic framework; (3) opening of internal bond(s) in fused bicyclic systems; and (4) cyclization on a template. From the latter type, only works where ring synthesis was followed by the template removal (mostly dissociation of metal ion, but also cleavage of carbon fragment) will be discussed.

14.11.5.1 Synthesis of Mono- and Diazamacrocycles

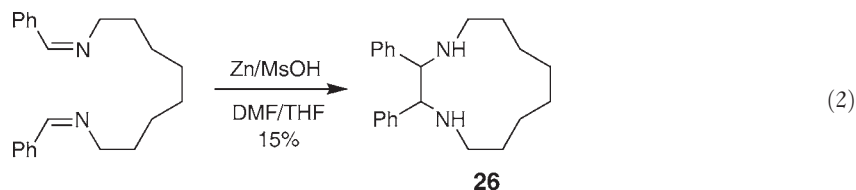
In general, ring-closing metathesis (RCM) of double-unsaturated linear compounds leads to cyclic monoolefines. This approach can be applied to linear amines or amides affording unsaturated amino or lactam rings of variable size [<1999MI75>](#). Such reaction is generally efficiently catalyzed by Grubbs catalyst ($[\text{Cl}_2(\text{PCy}_3)_2\text{Ru}(=\text{CHPh})]$) and was used for formation of lactam rings containing up to 18 atoms ([Equation 1](#) [<2002JOC245>](#)).



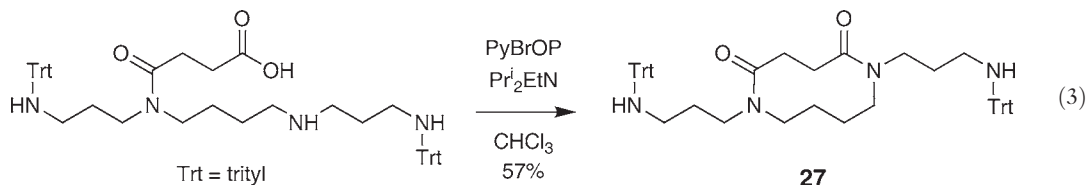
RCM of linear amides was successfully applied to the synthesis of several natural products like halicloresin [<2001NJC1347>](#). This compound was also obtained employing RCM on bis(olefinic) amine [<2001TL3287>](#). Mutuporamines (e.g., **16**), alkaloids isolated from marine sponge *Xestospongia exigua*, are 13–15-membered monoaza-cycles with *N*-polyamino substituents. They were revealed as anti-metastatic and anti-angiogenic agents. Several of their analogs were prepared by the RCM method. The largest ring reported, 18-membered unsaturated lactam, was accompanied by a 36-membered by-product of [1+1] metathesis reaction [<2002JOC245>](#).

Another general method for the introduction of a nitrogen atom into a macrocyclic skeleton is via the Beckmann reaction. Rearrangement of cyclotridecanone oxime led to cyclic lactam, which was reduced to amine by lithium aluminium hydride (LAH). Further substitution yielded 14-membered mutuporamine [<1999TL5401>](#). Dieckmann condensation was used for the preparation of 14-membered aza ketone **15** [<1999JA2919>](#), but no experimental details were given.

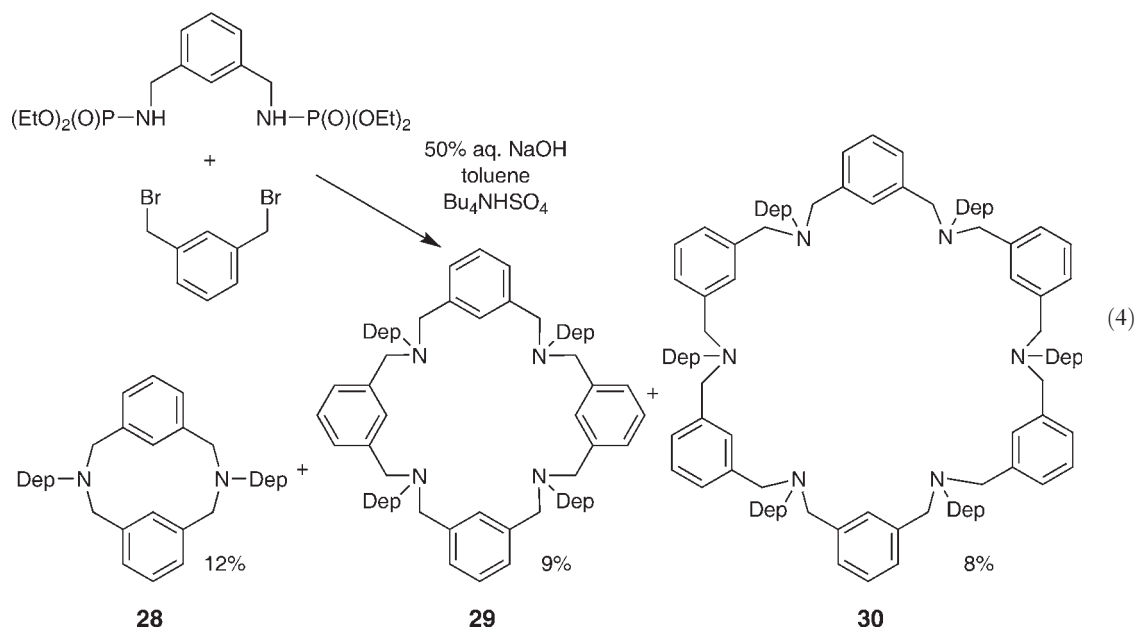
2,3-Diphenyl-1,4-diazacyclododecan **26** was prepared by the zinc reduction of bis(imine) formed from linear amine and benzaldehyde ([Equation 2](#) [<1995JOC3980>](#)).



Peptide coupling reagent bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBrOP) was used in synthesis of 10-membered succinyl bis(amide) **27** in 57% yield ([Equation 3](#) [<2002TL2593>](#)). Similarly, 1,6-diazacyclodecane substituted on only one nitrogen atom was prepared by reaction of *N*-trityl-protected linear triamine with succinyl anhydride. The amides were further reduced to amines using LAH [<2002TL2593>](#).



The series of arene-containing polyazamacrocycles was prepared by reaction between diethoxyphosphoryl (Dep)-protected 1,3-bis(aminomethyl)benzene and 1,3-bis(bromomethyl)benzene, giving cyclic products **28–30** ([Equation 4](#) [<2005S2845>](#)). Analogous tetraaza and hexaaza macrocycles were formed by reaction of 1,4-bis(bromomethyl)benzene with the protected amine in 11% and 14% yields, respectively [<2005S2845>](#).



14.11.5.2 Synthesis of Triazamacrocycles

Ten-membered *N,N',N''*-tris(tosyl)-1,4,7-triazacyclodecane **31** was obtained by Richman–Atkins reactions of fully tosylated *N,N'*-bis(ethanol-2-yl)-1,3-diaminopropane with tosylamide in nearly quantitative yield (Scheme 1) <2001EJO4233>. Interestingly, reaction with benzylamine afforded the analogous macrocyclic product **32** in much lower yield (25%) <2001EJO4233>. Similar 10-membered triazamacrocycle **33** was obtained by the cyclization with propyleneglycol bis(triflate) in 33% yield (Scheme 1) <1999TL7687>.

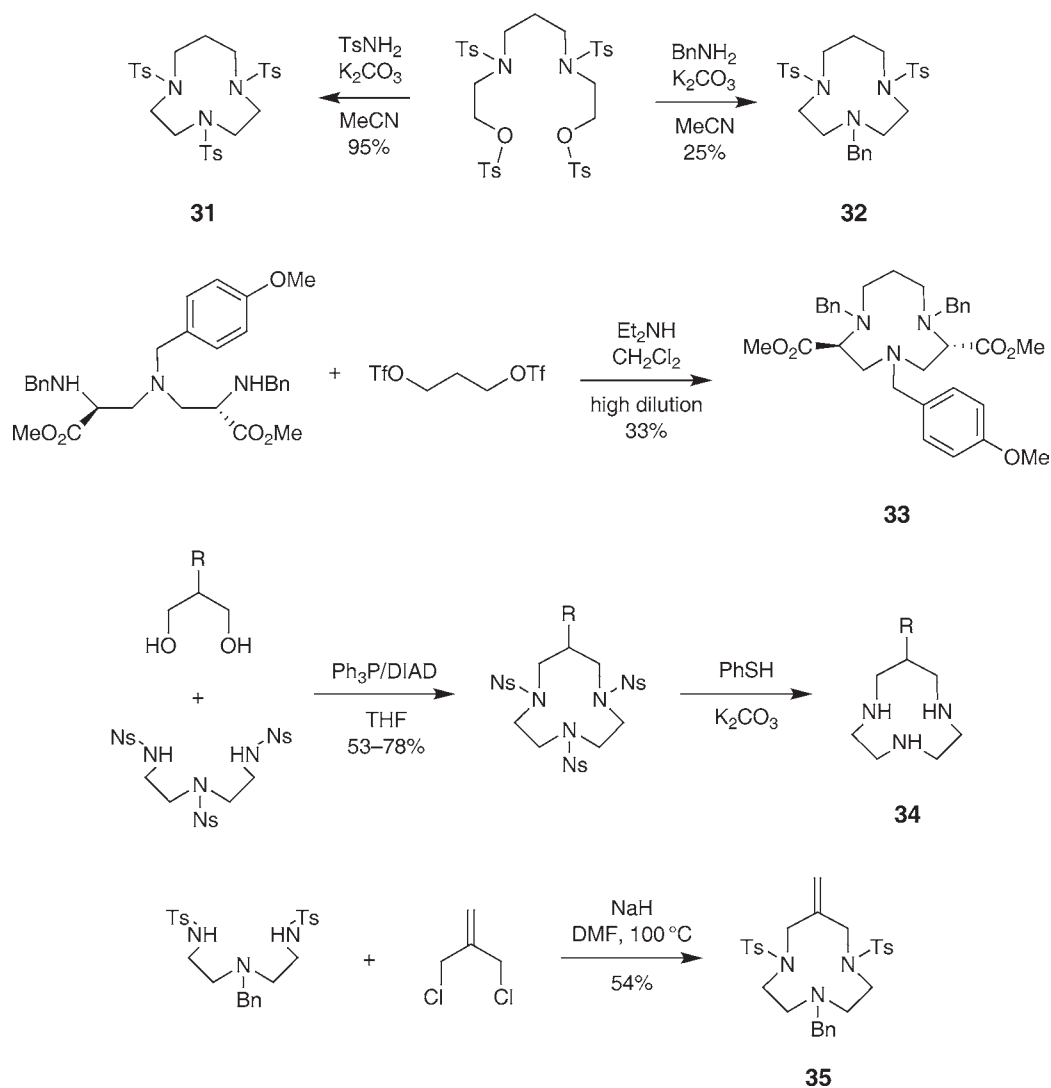
Interestingly, analogous cyclization using ethyleneglycol ditosylate proceeds as a [2+2] reaction affording an 18-membered hexaaza ring, as the main product (see Section 14.11.5.4). C9-Substituted 1,4,7-triazacyclodecanes **34** were prepared by Mitsunobu reaction between tris(nosyl)diethylenetriamine and appropriately C2-substituted 1,3-propanediol using Ph_3P /diisopropyl azodicarboxylate-mediated coupling with cyclization yields 53–78% (Scheme 1) <2005TL4387>. Improved Richman–Atkins cyclization of tris(SES)-dipropylenetriamine (SES = 2-(trimethylsilyl)-ethanesulfonyl) with propyleneglycol ditosylate led to cyclic product in 73% yield <2001JOC2722>. The deprotection is facile (CsF) and affords 1,5,9-triazacyclodecane **7** in 81% yield. The approach was expanded to a series of triazamacrocycles up to 19 ring members with cyclization yields varying in range 21–54% <2003T10165>. Various substituted 1,5,9-triazacyclodecanes were also prepared by the sulfonylamide method. Cyclization of tosylated triamine with 3-chloro-2-chloromethyl-1-propene affords methylene-substituted macrocycle **35** (Scheme 1) in 54% <2006JMC1291>.

A malonate cyclization method <1996JP21109, 2002TL9385> allows facile preparation of mono-*N*-substituted derivatives **36** (Scheme 2).

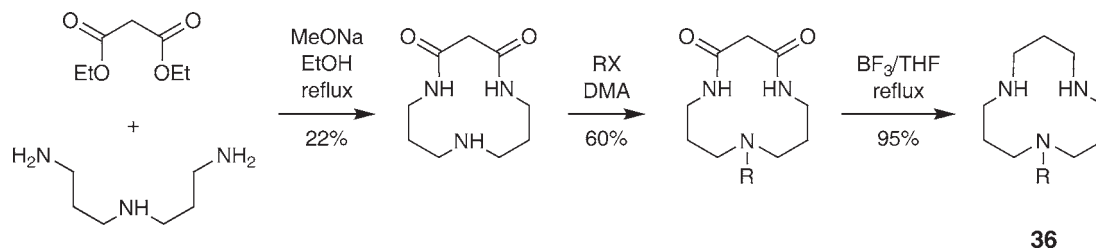
The approach can be used also for the synthesis of C3-substituted cycle by reaction of triamine with C-substituted malonate <1996JP21109>. Alternatively, C3-substituted derivatives of 1,5,9-triazacyclodecane **37** can be obtained by the method illustrated (Scheme 3) (see Chapters 12.03 and 12.19) <1998BCC132, 2004BCC174>.

Direct alkylation of Dep-protected dipropylenetriamine by bis(chloromethyl)arenes led to aryl-containing macrocycles in high yields. The protecting phosphate moiety can be easily cleaved under acidic conditions giving macrocycles **38** and **39** (Scheme 4) <2000HCA793>.

Similar reaction of tris(SES) triamines (diethylenetriamine and dipropylenetriamine) with a series of bis(bromomethyl)arenes (naphthalene, anthracene) afforded arene-containing macrocycles in high yields <2001JOC2722>. Alternatively, *o*-nitrobenzenesulfonyl (nosyl, Ns) <2001BML1521> or nosyl/trifluoroacetyl <2001OL3499> derivatives of ethylene-propylenetriamine and dipropylenetriamine were cyclized with methyl 3,5-bis(bromomethyl)benzoate



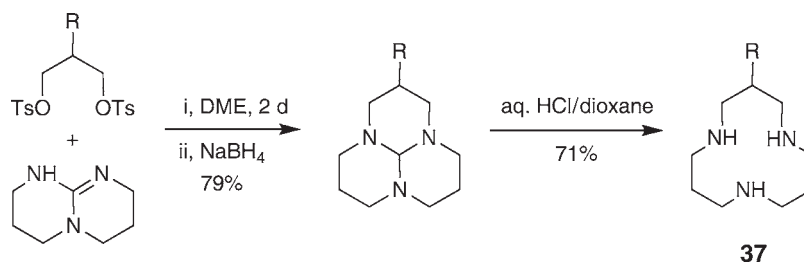
Scheme 1



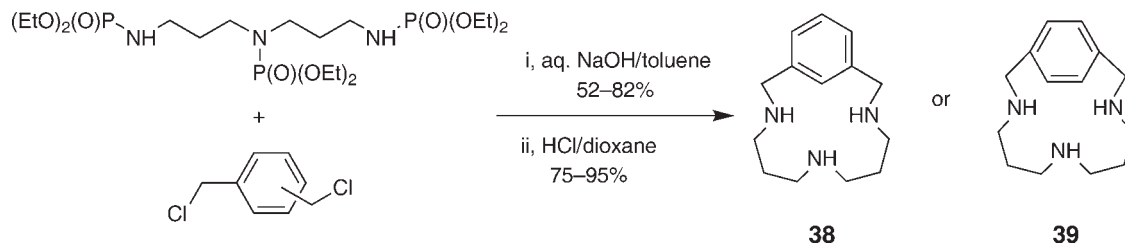
Scheme 2

in moderate yields. Compounds analogous to **38** were obtained by the Richman–Atkins cyclization of bis(bromomethyl)-arenes with tosylated dipropylenetriamine [<2005CEJ5146>](#).

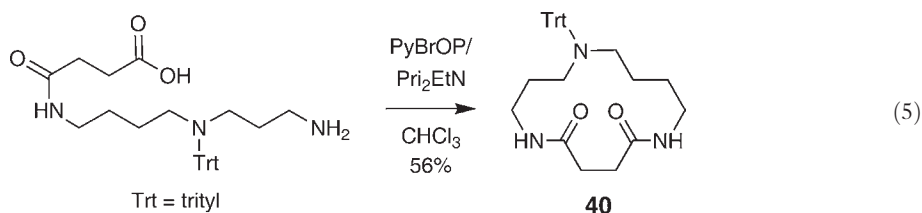
PyBrOP-mediated cyclization of *N'*-trityl-protected linear triamine with succinyl anhydride was used to form the 14-membered triaza ring **40** in 56% yield (Equation 5) [<2002TL2593>](#), which was further reduced to amine using LAH. Similar methodology was applied in synthesis of a 15-membered ring.



Scheme 3



Scheme 4



Large symmetrical triazamacrocycles with 21, 24, and 27 atoms (1,8,15-triazacycloheptacosane, 1,9,17-triazacyclotetracosane, and 1,10,19-triazacycloheptacosane) were prepared by Richman–Atkins methodology with cyclization yields of 26–46% [\[1996JHC2013\]](#).

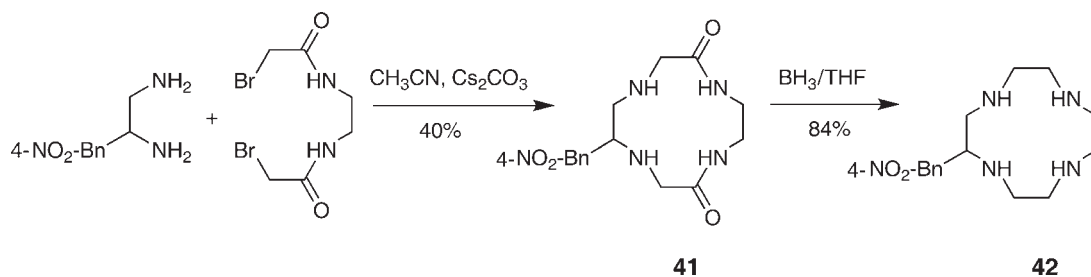
14.11.5.3 Synthesis of Tetraazamacrocycles

Among tetraazamacrocycles, two of them – cyclen **1** and cyclam **2** – have prominent positions, as many of important diagnostic and therapeutic reagents are derivatives of these two macrocycles. The classical formation of cyclen **1**, homocyclen **21**, and cyclam **2** is Richman–Atkins synthesis employing tosylamides [\[1974JA2268\]](#). This general synthesis is ‘atom noneffective’ (in the final step, large tosylate groups must be removed to get the target azacycle) and gives variable yields. However, due to its generality, this approach is still the method of choice for more complicated systems. The large series of tri- to octaaza macrocycles with 10–34 atoms in the cycle was prepared by this method, with orthogonally tosyl (Ts)/Bn-protected amino groups [\[2000BCJ693\]](#). The Ts group can be replaced by other sulfonate groups as, for example, methanesulfonyl (mesyl, Ms) or trifluoromethanesulfonyl (triflyl, Tf) groups leading to precursors with a higher reactivity, or by Ns or 2-SES, which are easily cleaved. Now, the classical method is less commonly used for synthesis of the underivatized cycles [\[1995CJC685, 1999SC4279, 2004JMO163, 1997JCD895\]](#). An optimized procedure for synthesis of several cycles appeared in a practical handbook [\[B-1996MI\]](#).

Reaction of pentatosylate of $\text{NH}(\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{OH})_2$ with TsNH_2 led to cyclen tetratosylate (acetonitrile, K_2CO_3 , 95%); surprisingly, the same reaction with BnNH_2 completely failed [\[2001EJO4233\]](#). Cyclam **2** was synthesized by the uncommon [2+2] condensation of $\text{TsNHCH}_2\text{CH}_2\text{CH}_2\text{NHTs}$ and $\text{TsOCH}_2\text{CH}_2\text{OTs}$ followed by deprotection [\[2004JMO163\]](#). Orthogonally protected Ts_2Tf_2 cyclam was obtained by reaction of appropriately substituted 3,2,3-tet (3,2,3-tet = 1,5,8,12-tetraazadodecane) and 1,2-dibromoethane [\[2000T4759\]](#). The sulfonamide cyclization was also used for the synthesis of C-substituted optically active cyclen **1** (bis(Prⁱ) derivative) [\[2002NJC1054\]](#) and cyclam **2** (mono(Me) [\[2002SC2441\]](#), bis(Me) [\[2002OL949\]](#), or cyclohexyl and bis(cyclohexyl) [\[1999TA2515\]](#) derivatives) as

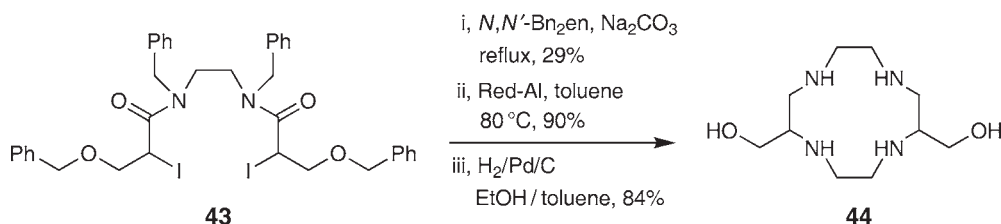
well as a number of analogs of *p*-xylylene-bis(cyclam) (AMD-3100, anti-HIV drug, see [Section 14.11.5.5](#)) <1996JOC1519, 1996TL5301, 1997USP6512478>. *N*-Phenyl cyclen <2000AGE1052> and 1,11-Me₂cyclam <1996ICA321> were also prepared by this approach. Methods for the high yield and fast tosyl group(s) removal from such macrocycles have been published: heating at 180 °C (conc. H₂SO₄, 8–10 min <1995SC3181>) or microwave irradiation (conc. H₂SO₄ for 30–400 s <2003PJC85>, 25% H₂SO₄ for 30 min <1999MC66>). This classical cyclization afforded also labeled fully C-deuterated D₁₆-cyclen, which was used for synthesis of D₁₆-labeled DOTA <1999JP2493>.

Another alkylation approach, so-called ‘crab-like synthesis’, employs α-halogen acetamides <1993SL611, 2000IEC3499>. It can be illustrated on the synthesis of **42** (Scheme 5) <1996NJC585>. Ethylenediamine-*N,N'*-bis(bromoacetamide) reacts with 1-(4-nitrobenzyl)ethylenediamine in presence of Cs₂CO₃ under medium dilution to give a reasonable 40% yield of dioxocyclen **41** and, after reduction with BH₃·THF, the derivative **42** is obtained (THF = tetrahydrofuran).



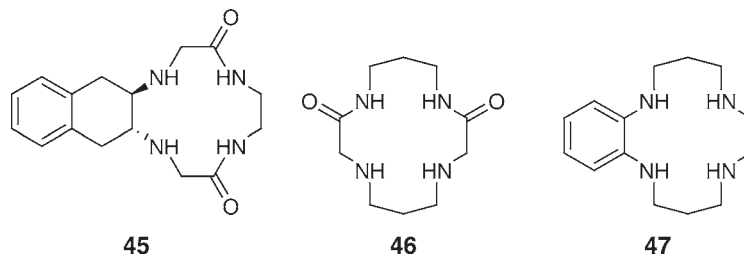
Scheme 5

The bis(hydroxomethyl)cyclen **44** was prepared by this strategy starting from **43** and *N,N'*-dibenzyl-ethylenediamine (Scheme 6) <2001ICA218>.



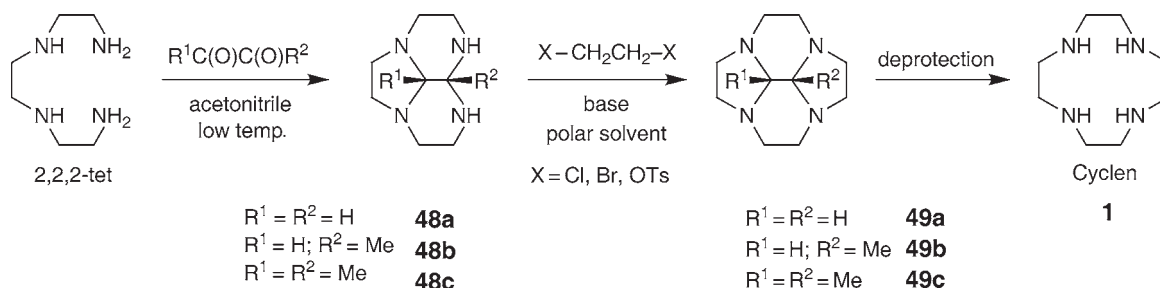
Scheme 6

Reaction of ethylenediamine-*N,N'*-bis(chloroacetamide) and *trans*-1,2,3,4-tetrahydro-naphthalene-2,3-diamine produced cyclic amide **45**, which was reduced to the free amine <1999CCR451>. The diamide **46** as well as the analogous cyclen and homocyclen diamides were obtained by the reaction of bis(tosyl) or bis(benzyl) diamines (ethylenediamine or 1,3-propylenediamine) with bis(chloroacetamide) of the diamines and after removal of protecting groups from the cyclic products (cyclization yields 21–53%) <1999CJC614>.

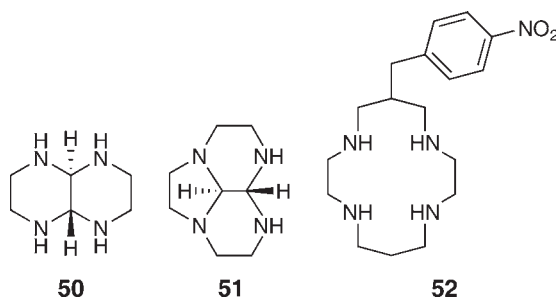


Arylation of 3,2,3-tet with 1,2-dibromobenzene (Pd(0), 2,2-bis(diphenyl-phosphanyl)-1,1-binaphthyl (BINAP), NaOBu^t, dioxane, reflux 70 h) led to benzocyclam **47** in a low yield (12%) <2003TL1433>. Low yields of other tetraazacycles were obtained similarly with other amines and arylhalogenides.

The most important improvement in the synthesis of cyclen **1**, homocyclen **21**, and cyclam **2** was brought by employment of so-called ‘carbon template’ method. It is based on rigidifying of linear tetraamine in a position suitable for cyclization by formation of bis(aminal). The approach is illustrated by synthesis of cyclen **1** starting from 2,2,2-tet (2,2,2-tet = 1,4,7,10-tetraazadecane, triethylenetetraamine) and vicinal dicarbonyl compounds (glyoxal, pyruvic aldehyde, or butan-2,3-dione) (**Scheme 7**) (see Chapters 10.19 and 12.18). R^1, R^2 -*cis*-isomers of tetraamine bis(aminals) (e.g., **48**) with maximum number of six-membered cycles are especially suitable for cyclization to compounds **49** with bis(electrophiles) <1998TL6861>. Therefore, isomerization of the aminals derived from open-chain amines was carefully investigated <1999TL2517, 2000EJO33, 2003EJO1050, 2005JOC7042>. The R^1, R^2 -*trans*-aminals may be also cyclized but, especially in case of cyclam, the aminal bridge is impossible to remove <2000CCC243, 2005JOC7042>. Reacting 2,3,2-tet (2,3,2-tet = 1,4,8,11-tetraazaundecane) and phenylglyoxal produced an aminal giving cyclam **2** after cyclization with 1,3-dibromopropane and carbon template removal <2003T4573>. Another key reaction is deprotection. The most problematic is glyoxal bridge removal. The most common strategy is the reaction with hydroxylamine <1998ACS1402> or hydrazine <1999TL2517> in alcohols under reflux, or reaction with linear polyamines. The combination of oxidation (e.g., with Br_2 or KMnO_4) with hydrolysis in strong aqueous base <2000SC15> was also used. The macrocyclic aminals derived from glyoxal homologs can be decomposed with strong aqueous acids or bases. Cyclen **1** was also easily prepared from the glyoxal-ethylenediamine condensation product **50** (1,4,5,8-tetraazadecalin) (see Chapters 10.19 and 12.18) and $\text{ClCH}_2\text{CH}_2\text{Cl}$ followed by oxidative deprotection <2000SC15>. Similarly, the reaction of the *trans*-isomer **51** with diethyl oxalate (see Chapters 10.19 and 12.18), amide reduction ($\text{BH}_3\cdot\text{SMe}_2$), and the aminal bridge removal led to cyclen **1** <1999TL2517>. An isomeric mixture of dioxocyclam aminals was obtained by reacting an equilibrium mixture of **50** and its *cis*-isomer with methyl acrylate (2 equiv) <2002JP2552>. These diamides were reduced ($\text{BH}_3\cdot\text{SMe}_2$) to mixture of *cis*- and *trans*-cyclam glyoxal aminals. The aminal strategy was also used to synthesize numerous other derivatives, for example, **52** (intermediate in syntheses of radiopharmaceuticals; see Section 14.11.8.4) <2004TL3059>, and other C- and N-monosubstituted derivatives <2002CC312, 2005JOC7042, 2004CC588>.

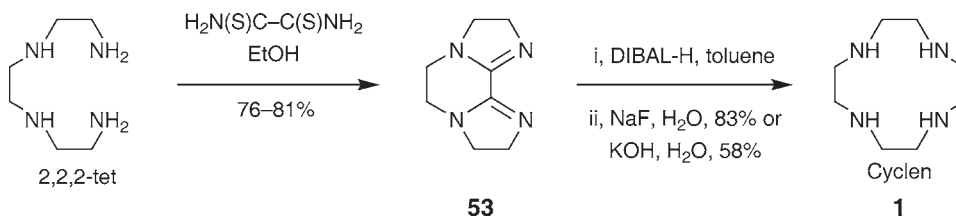


Scheme 7

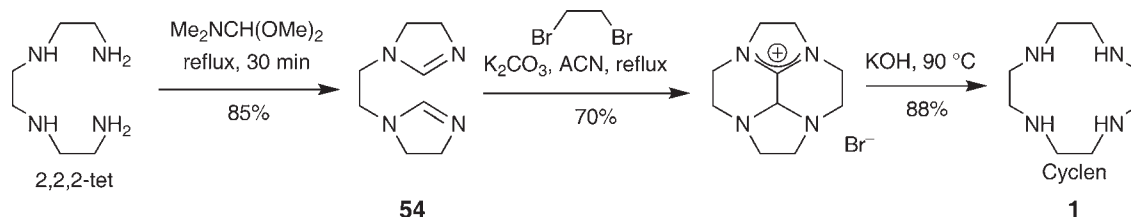


Compound **53** is a key intermediate in another effective method for cyclen **1** production <1996JOC5186, 2001OS(78)73>. The method employs dithiooxamide for rigidifying of linear amine 2,2,2-tet and reduction of **53** (**Scheme 8**) (see Chapter 11.16); 2,2,9,9-Me₄-cyclen was prepared by analogous way from linear 2,2,9,9-Me₄-2,2,2-tet (12% overall yield) <2002ICA45>.

Cyclen **1** was also synthesized (**Scheme 9**) (see Chapter 4.02) through the bis(imidazoline) derivative **54**, which reacted with 1,2-dibromoethane, and the carbon bridge was removed with strong aqueous base <2002JOC4081>.

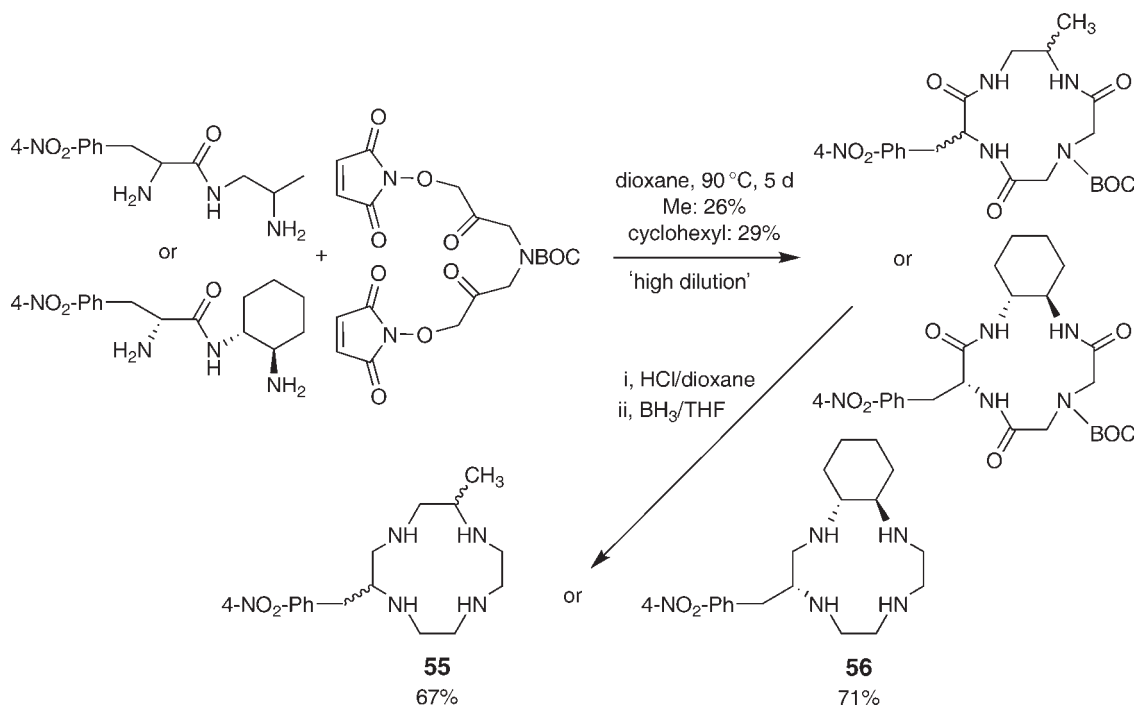


Scheme 8



Scheme 9

Another general method for the synthesis of these macrocycles is the reaction of amines with (active) esters of carboxylic acids leading to oxoderivatives of the cycles. The amides can be reduced to amines or directly used for further transformations or complexation of metal ions. Two cyclens **55** and **56**, as intermediates for the synthesis of bifunctional DOTA derivatives, were obtained by condensation shown in Scheme 10 between appropriate diamine-amide and active ester of *N*-BOC-iminodiacetic acid (BOC = *t*-butoxycarbonyl), followed by deprotection and reduction [<2003NMB581>](#).



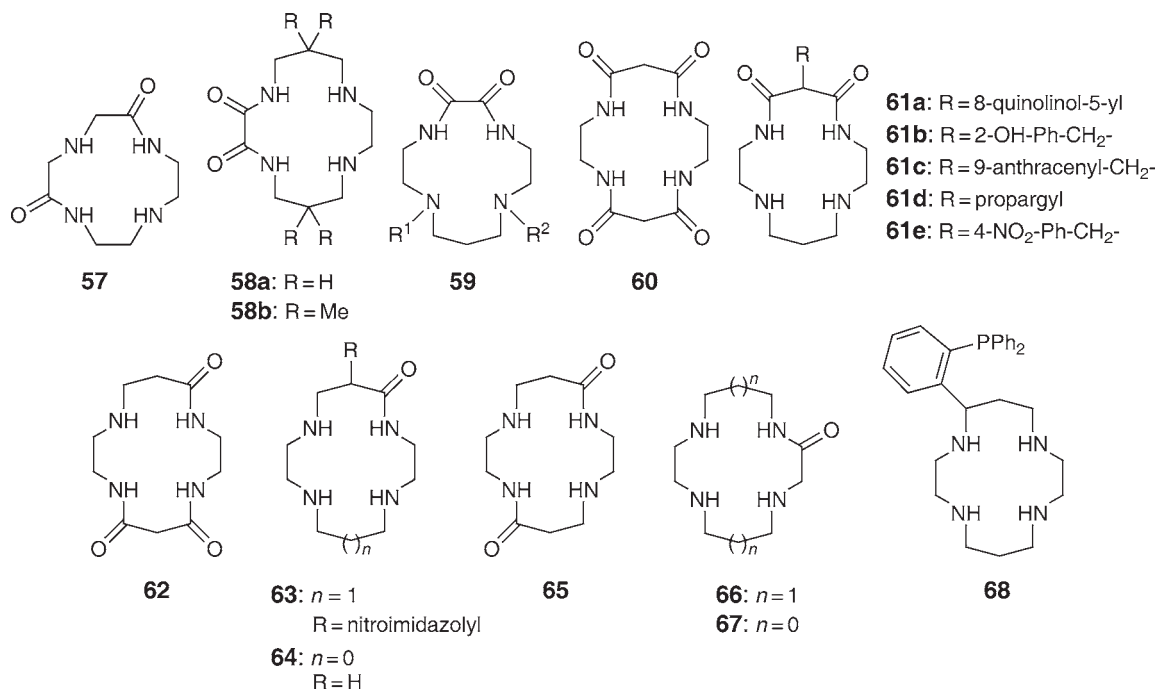
Scheme 10

Reaction of diethyl iminodiacetate with diethylenetriamine in refluxing MeOH (7 days) under high-dilution conditions led to 2,6-dioxacyclen **57** in a low yield (10%) [<1999SC4279>](#). Optically active C-substituted derivatives

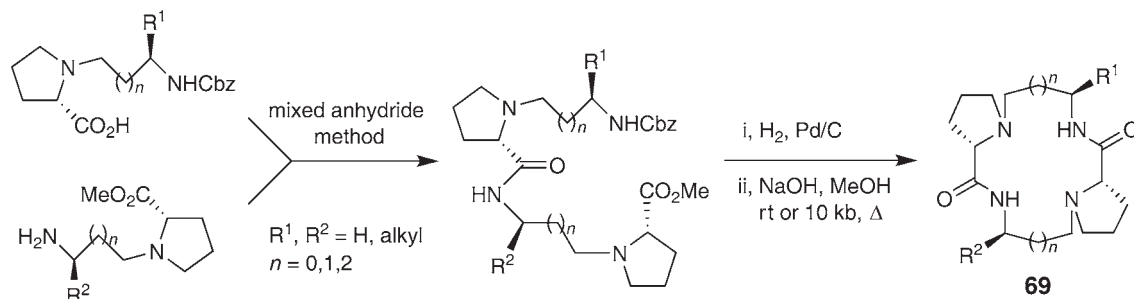
were prepared analogously (yields 10–16%) <2002TL3935, 2003SC1911>. 2,3-Dioxocyclam **58a** was prepared by reaction of 3,2,3-tet and dimethyl oxalate in refluxing EtOH under high-dilution conditions in a low yield (17%) <1999JCD1925, 2004IC8023>. An expected by-product was derived from a [2+2] cyclization (tetraoxo-derivative of octaazamacrocyclic) <2004IC8023>. Similarly, cycle **58b** was obtained from Me₄-3,2,3-tet and diethyl oxalate (yield 14%); the amide was reduced to 6,6,13,13-Me₄-cyclam with BH₃ in refluxing THF <1998CR557>.

2,3-Dioxohomocyclen derivatives **59** are products of the reaction of 4,8-disubstituted-1,4,8,11-tetraazaundecane with dimethyl oxalate with a moderate yield of cyclization (e.g., 35% for Et₂ derivative) <2005OBC4268>. Tetraoxocyclam **60** was prepared by a [2+2] reaction of malonic acid and ethylenediamine in CH₂Cl₂ in presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) at 0 °C <2004JIB1712>. Similarly, DCC/DMAP-mediated [2+2] condensation of malonic (or butanedioic) acid with ethylenediamine (or propylenediamine) afforded series of tetraamidic macrocycles with 14, 16, and 18 ring members. The amidic groups were reduced to amines using LAH <2004JIB1712>.

A general strategy is derived from a reaction of (substituted) malonate diester (dimethyl or diethyl) with 2,3,2-tet or 2,2,2-tet leading to the diamides of cyclam or homocyclen. It is mostly run under high-dilution conditions and reaction time varying between days and weeks in refluxing alcohols; yields are rather low (mostly <25%). It gave cyclam derivatives with different substituents in position C13, as quinoline **61a** <2001CJC221>, phenol **61b** <1996IC5851>, anthracene **61c** <1996CEJ75>, or propargyl **61d** <2006CEJ5535>. The diamide **61e** was also synthesized by this strategy (refluxing MeOH, 21 d, yield 78%) and it was reduced by BH₃·THF (yield 97%) to an important amine **52**, which was used as an intermediate in the syntheses of radiopharmaceuticals (see Section 14.11.8.4) <1995BCC296>; the same reaction sequence, but with lower overall yield of **52**, was also used by other authors <1997S1010>. 11,13-Dioxohomocyclen was also prepared in this way (yield 15–17%) <1996IC4649, 1999IJA609>. An elegant large-scale condensation of dimethyl malonate with NH₂CH₂CH₂NHCH₂CH₂C(O)NHCH₂CH₂NH₂ in refluxing MeOH led to trioxocyclam **62** (yield 35% on 67 g scale), which was used for production of antiviral *p*-xylylene-bis(cyclam) derivative (AMD-3100, see Section 14.11.6.3) <2003JOC6435>. Analogous condensation of methyl acrylates with 2,3,2-tet led to the 5-oxocyclam derivative **63** (its Tc-complex was used for a targeting of hypoxic tissue <2001BMCL71>) or with 2,2,2-tet to give 11-oxohomocyclen **64** <2001ICA180>. A [2+2] condensation of ethylenediamine with methyl acrylate can be used for the economical production of cyclam as a final product despite an extremely low yield (1.5%) of such cyclization <2000JCD1873, 2001CEJ2848>. Both reagents are very cheap and target 5,12-dioxocyclam **65** precipitates during development of the reaction mixture in almost pure form. Cyclization between bromoacetate and 3,2,3-tet or 2,2,2-tet produced 2-oxocyclam **66** (yield 7%) or 2-oxocyclen **67** (yield 8%), respectively <2002ICA119>. Triphenylphosphine-modified cyclam **68** (and its phosphinoyl) were obtained by the condensation of 2,3,2-tet and *o*-(Ph₂P)-cinnamic acid ethyl ester, followed by borane reduction <1996ICA151>.



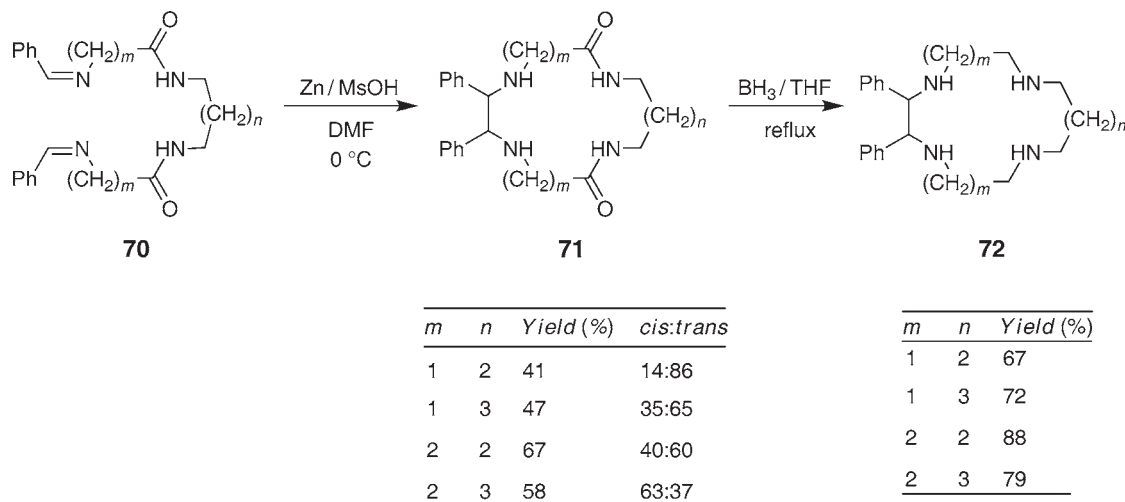
To synthesize optically active pyrrolidine derivatives **69**, properly protected amino acids were condensed by mixed anhydride method, followed by removal of Cbz-protection (Cbz = benzyloxycarbonyl) by hydrogenation; the cyclization was accomplished in MeOH in presence of NaOH at room temperature or under a high pressure (10 kb) and higher temperature (50 °C) (**Scheme 11**) (see Chapter 4.02) <2000TL5967, 2001TA111, 2005T9031>. Yields were from low to good depending mainly on type and number of substituents on the cyclam ring carbon atoms. The diamides were reduced to monoamides or amines with $\text{BH}_3\cdot\text{SMe}_2$ in THF under reflux.



Scheme 11

Cyclotetramerization of *N*-benzylaziridines produced *N,N',N'',N'''*-tetrabenzylcyclen or its symmetric C-tetrasubstituted derivatives and the corresponding cyclen and its derivatives were obtained after removal of the *N*-benzyl groups <2002IC6846>. The reaction was investigated in more detail and was shown to proceed by a photoelectron transfer (PET) mechanism in presence of Brønsted acid and radical initiator <1999CEJ2993, 2000EJO1037, 2001ICA218>.

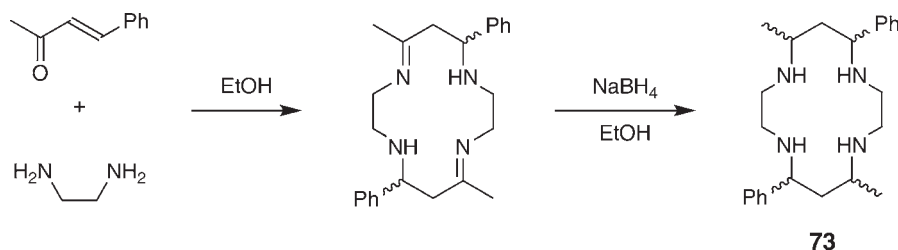
A series of 12- to 15-membered C-substituted cycles were prepared according to **Scheme 12**. Amide-benzylimines **70** were reductively coupled to the cycles **71** in a moderate yields and the cyclic amides were reduced with borane to give the free amines **72** <1995JOC3980>. Similarly, some other C-substituted derivatives were obtained <1995JOC3980>.



Scheme 12

Another method useful for preparation of C-substituted cyclams **73** is a [2+2] condensation between ethylenediamine and 2-unsaturated ketones (**Scheme 13**) <2003ICA1>.

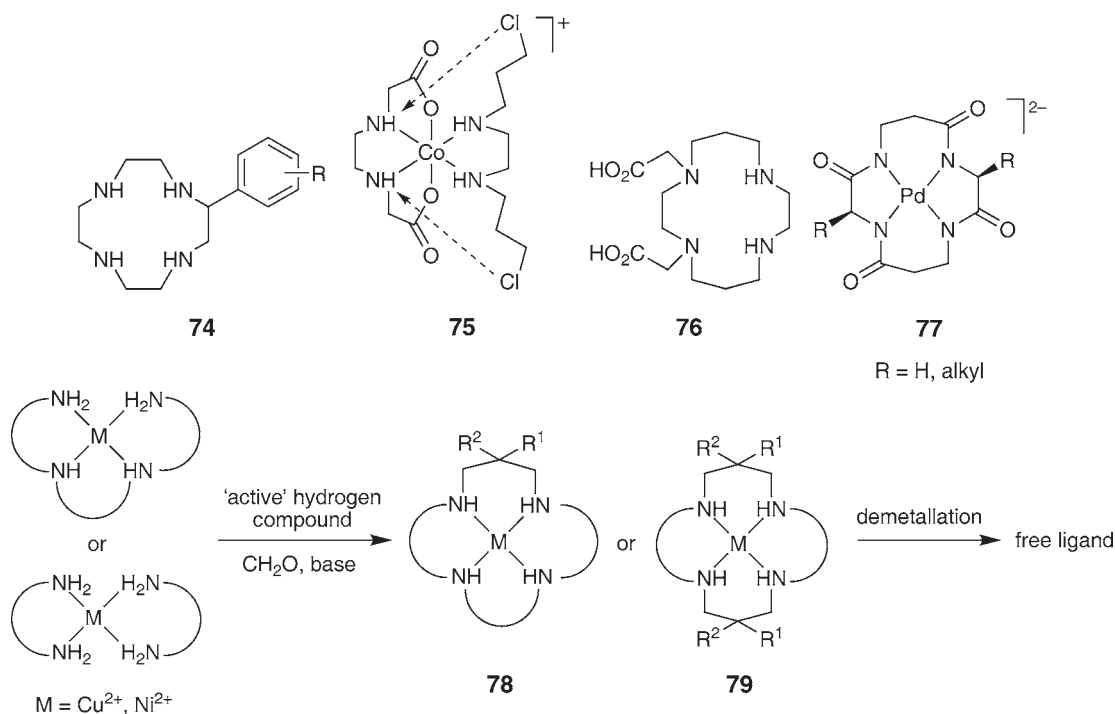
The metal template method is commonly used for the syntheses of metal complexes of ligands derived from the title macrocycles. Mostly, the central ion could not be removed to get a free cyclic ligand; thus, there are limited examples of ligand syntheses by this method. C-Aryl cyclen derivatives **74** were prepared using the small Fe^{3+} ion as a template <1998NJC1359>. Condensation of Fe(III) complex of 2,2,2-tet with arylglyoxals formed imine complexes,



Scheme 13

which were reduced (NaBH_4) to complexes of cyclens and the free amines were obtained after iron removal with mineral acid. Glyoxal itself was fully unreactive [\[1998NJ1359\]](#). Base-induced ring closure in trivalent cobalt complex **75** led to Co(III) complex of 1,4-bis(carboxymethyl)cyclam [\[1996CC1303\]](#). Cobalt was removed from the complex by a reaction with excess of KCN in the presence of CoCl_2 in refluxing aqueous solution (20 h). The free ligand **76** was isolated after acidification as hydrochloride [\[2006DT152\]](#). Palladium(II) tetrapeptide complexes **77** were synthesized by intramolecular cyclization of Pd(II)-bis(dipeptide methyl ester) complexes [\[1998AGE1086\]](#) and corresponding cyclam derivatives were obtained after metal ion removal with HCl gas in MeOH followed with amide bonds reduction (LiAlH_4) [\[2003ZNB447\]](#).

Numerous 13-membered and larger macrocycles were synthesized by template reaction employing Cu^{2+} or Ni^{2+} tetraamino complexes, as shown in a general scheme (Scheme 14). The complexes of (poly)amine(s) (ethylenediamine, propylene-1,3-diamine, 2,2,2-tet, 2,3,2-tet, or 3,2,3-tet) were condensed under basic conditions with formaldehyde (less frequently with other aldehyde or ketone) and a compound with 'active' acidic hydrogen atoms (nitroethane and other nitroalkanes, malonate diesters, etc.) to give complexes of macrocycles with the general formula **78** or **79**. The cyclization can be considered as a Mannich reaction [\[1996SL933\]](#). Divalent copper is used more frequently and it can be removed from the complexes by reaction with elemental zinc in strongly acidic solution as a copper metal; during this reaction, the nitro group ($\text{R}^1 = \text{NO}_2$, when nitroalkanes were used in the cyclization step) is often reduced to an amino group. However, only complexes are mostly prepared, but such cases are not considered here.

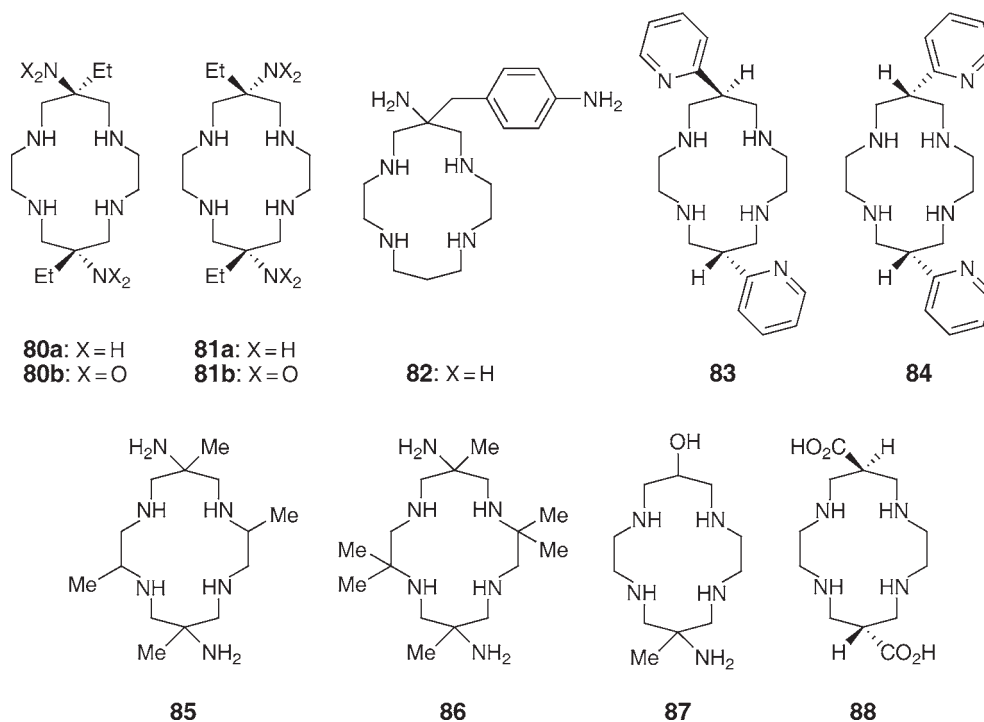


Scheme 14

For **79**, two main isomers with different mutual positions of substituents on the central propylene carbons are possible. They are traditionally labeled as '*trans*' (or '*anti*') (particular substituents are located on opposite sides of the macrocyclic ring) or '*cis*' (or '*syn*') (substituents are on the same side of the macrocycle ring).

This strategy was used for synthesis of isomers **80a** and **81a** <1996IC2045>. Reaction of 1-nitropropane, formaldehyde, and Cu(II)-ethylenediamine complex led to mixture of [Cu(**80b**)]²⁺ and [Cu(**81b**)]²⁺ complexes having nitro groups. During demetallation with zinc dust, reduction of nitro group to amino group occurred and the free ligands **80a** and **81a** were isolated.

Similarly, utilization of 1-nitro-2-(4-nitrophenyl)ethane, Cu(II) salt, and 2,3,2-tet gave cyclam derivative **82** <1999ICA40>. Ligands **83** and **84** were obtained using ethyl 2-pyridylacetate as the compound with active hydrogen atom <2001IC2335>. Methylated cyclam derivatives **85** and **86** were obtained analogously through Cu(II) complexes of Me-substituted ethylenediamine <1997AJC529>. Reaction of the Cu(II) complex of HO-substituted 2,3,2-tet with nitroethane and CH₂O led to macrocycle **87** after zinc dust demetallation <2004IC1689>; similarly, the reaction of diethyl malonate, formaldehyde, and [Cu(en)₂]²⁺ produced the *trans*-isomer **88** <1997POL599>.

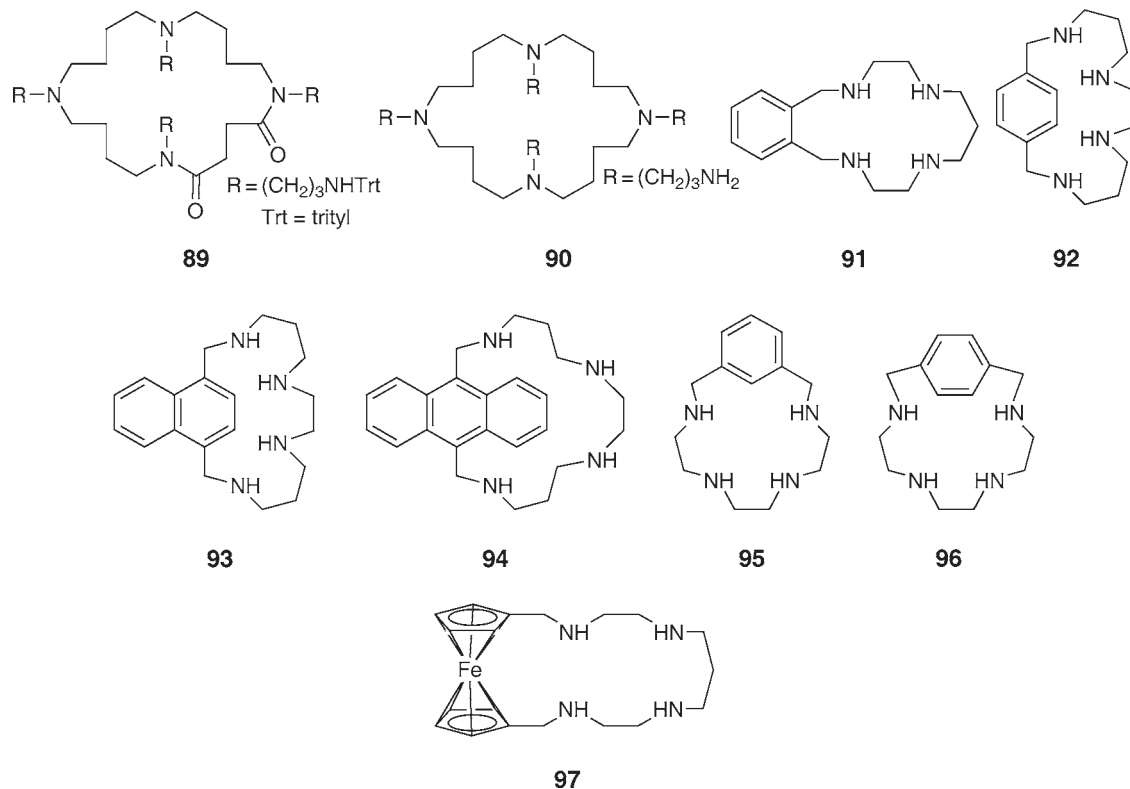


Methods used for the synthesis of larger tetraazacycles are, in principle, the same as those applied for synthesis of cyclen, homocyclen, and cyclam. Homocyclam **22** was synthesized by tosylamide method from differently substituted (by benzyl and tosyl groups) linear precursors leading to 1-benzyl or 12-benzyl protected cycles, after tosyl group removal <1995T1197>. Tosylamide method also afforded 1,5,9,13-tetraazacyclohexadecane **23** in a simple form <1995CJC685> or, similarly as above, in the '*trans*' 1,9-dibenzyl protected form <1998SC285>. Furthermore, a large library of cyclic polyamines (N₃₋₈, 12–34-membered cycles) was prepared by the tosylamide method; in some cases, benzylated precursors were used leading to benzyl-protected cycles <2000BCJ693>.

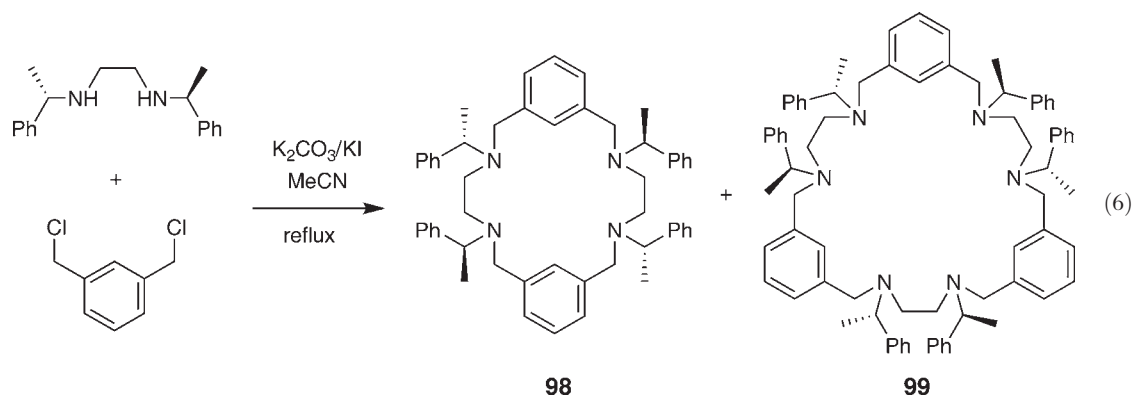
1,6,11,16-Tetraazacycloicosane substituted on each nitrogen atom with the $-(CH_2)_3NH_2$ group was obtained by methodology shown in (Equations 3 and 5). Reaction of trityl-protected precursor with succinic anhydride afforded bis(amide) **89**. It was reduced (LAH) and deprotected to give **90** <2002TL2593>.

The simplest benzocyclophane **11** was produced by reaction of tosylated 2,2,2-tet with 1,2-bis(bromomethyl)benzene (95%) followed by deprotection with Na amalgam (12%) <2003DT1852> or through glyoxal amination method (as well as its homolog **91**, 50%) in yield 29% over ring closure and deprotection steps <2000CCC99>. Also, other cyclophanes were synthesized by the sulfonamide method employing the tosyl group (e.g., **92** which was subsequently N-permethylated) <2004OBC816>. A series of arylene-containing triaza and tetraaza macrocycles (e.g., **93** and **94**) was prepared by reaction of pernosylated (removable by PhSH) amines with bis(bromomethyl)arenes (benzene, naphthalene, phenanthrene), with cyclization yields ranging from 70% to 98% <1998TL3799, 2002T2839>.

Direct alkylation of diethoxyphosphoryl-protected 2,2,2-tet by appropriate xylylene chlorides afforded *meta*- and *para*-benzotetraazacyclophanes **95** and **96** in high yield, analogously as mentioned above for smaller triazarings **38** and **39** <2000HCA793>. Ferrocene-1,1'-dicarbaldehyde reacted with amines of different size to give intermediate Schiff bases, which were borohydride-reduced to afford ferrocene cyclophanes, for example, **97** <1996ICA143, 2005EJI383>.



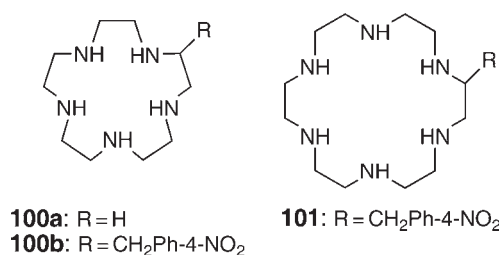
Arene-containing 18-membered tetraazamacrocyclic **98** (Equation 6) was prepared by [2+2] cyclization of substituted ethylenediamine and 1,3-bis(chloromethyl)benzene in 14% yield as well as **99** formed by a [3+3] reaction (4%) <2006TL2371>.



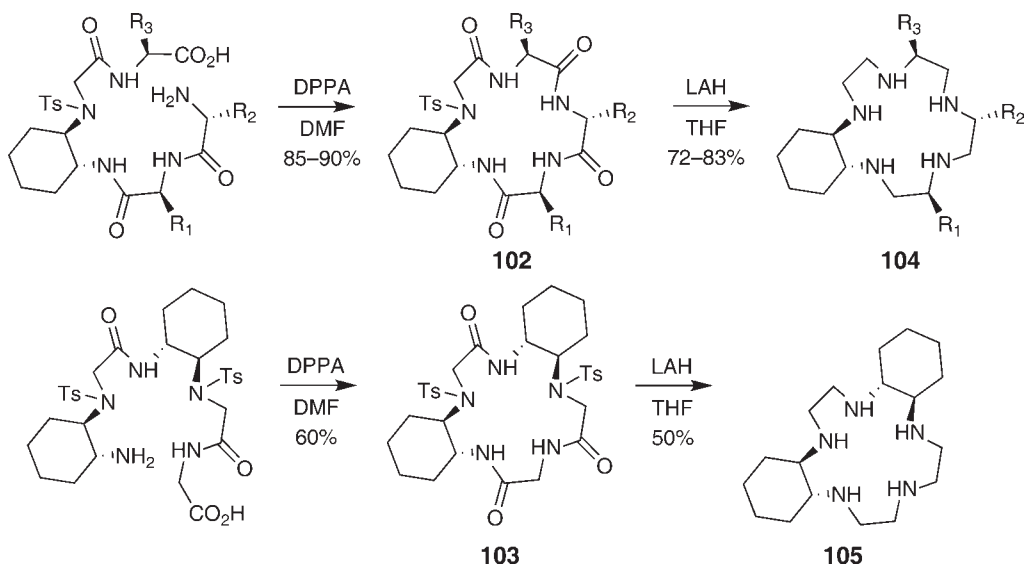
14.11.5.4 Synthesis of Polyazamacrocycles with Five and More Nitrogen Atoms

Principally, the same ring closure reactions as for tetraazacycles (Section 14.11.5.3) can be applied for preparation of larger polyazamacrocycles; however, mostly tosylamide and peptide-like syntheses are employed. In addition, metal template or cyclization reactions between carbonyl compounds and amines (and reduction of intermediate Schiff base) are often utilized.

The simplest 1,4,7,10,13-pentaazacyclopentadecane **100a** was obtained using tosylamide method in a reasonably high overall yield <1999SC2817, 2000MI585>. Precursor for bifunctional azacycle **100b** was prepared by the condensation of dipeptide amide Phe(NO₂)-Gly-ethylenediamine with protected active ester of iminodiacetic acid (28%), followed by deprotection and borane reduction <2001NMB409>. Richman–Atkins tosylamide, crab-like, and peptide condensation methods were applied for cyclization leading to a small library of C-substituted skeleton **100a** (methyls, cycloalkyls) after appropriate deprotection/reduction <1996IC5213>. Reaction of 2,2,2-tet or 3,2,3-tet with diethyl iminodiacetate in MeOH led to 2,6-dioxo derivative of **100a** (55%) or its 17-membered analog (48%) <1997JCD3637>. 1,4,7,10,13,16-Hexaazacyclooctadecane ('hexacyclen') **25**, its 20-membered analog, and 21-membered heptaazacycle were obtained using tosylamide procedure (some *N*-benzyl substituted) and they were further modified to get *N*-CH₂CH₂NH₂ ligands <2003OBC854>. Two routes to precursor of bifunctional hexacyclen **101** were published: reaction of dimethyl *p*-nitrobenzyl-substituted iminodiacetate with tetraethylenepentamine gave dioxo-hexacyclen in 50% yield <2000TL7207>, and reaction of BOC-N[CH₂C(O)NHCH₂CO₂Su]₂ with ethylenediamine derivative of *p*-NO₂-Phe led to cyclization product in yield 19% <2000BCC510>. The oxocycles were deprotected/reduced to the target **101**. Sequential condensation of iminodiacetic acid active esters and *N,N'*-Bn₂ethylenediamine afforded tetralactam (1,7,10,16-Bn₄-2,6,11,15-tetraoxohexacyclen), which was subsequently modified in position N4 and N13 with Me, CH₂CO₂Me, CH₂C(O)NMe₂, or CH₂(py-2) groups <1996T9793, 1999HCA543>.

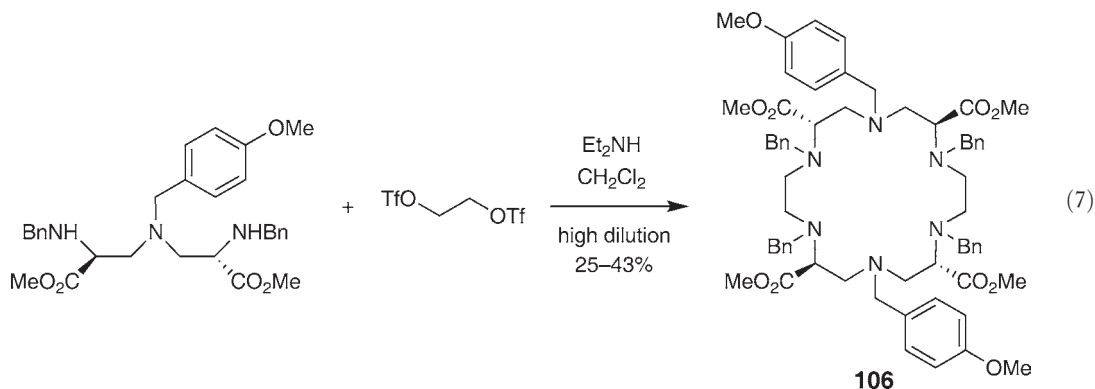


DPPA-mediated cyclization was used for formation of 15-membered pseudopeptides **102** and **103** containing one <1997TL779> or two <1997TL3143> *trans*-cyclohexane-1,2-diamine fragments. The amidic groups were successfully reduced by LAH affording cyclic pentaamines **104** and **105** (Scheme 15).



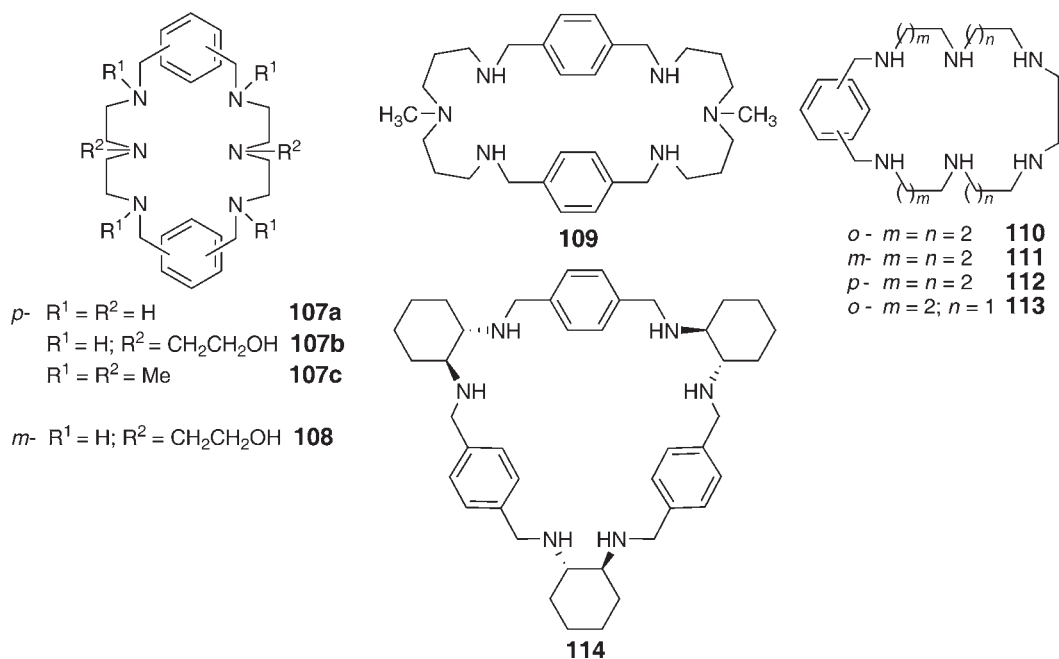
Scheme 15

The 18-membered hexaazamacrocycle **106** was obtained by a Richman–Atkins cyclization (Equation 7) <1999TL7687>. The [2+2] reaction of $\text{TfOCH}_2\text{CH}_2\text{OTf}$ with R,R -(*p*-MeO-Bn)- $\text{N}[\text{CH}_2\text{CH}(\text{CO}_2\text{Me})\text{NHBn}]_2$ under high dilution led to an optically pure hexaprotected carboxylated hexacyclen derivative. Surprisingly, analogous reaction with $\text{TfO}(\text{CH}_2)_3\text{OTf}$ led only to [1+1] product <1999TL7687>.



The Richman–Atkins tosylamide method also served as a method of choice for the synthesis of 22-membered cyclohexane-containing hexaazamacrocycles <1999TA367>. The Schiff base obtained by condensation of an appropriate phthalic dialdehyde and $(\text{NH}_2\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{CH}_2\text{OH}$ was reduced with NaBH_4 to get hydroxoethyl-substituted hexaazacycles **107b** and **108** in moderate yields <2002IC1807, 2002JCD4042>. Alkylation approach was chosen for the synthesis of hexamethylamine **107c** <1995IC552> starting from fully N-methylated precursors. Amine **107a** and its N-permethylated derivative **107c** were also obtained by Schiff base condensation, its borohydride reduction and reductive methylation by formaldehyde/formic acid mixture <2001JCD240>. The [2+2] reaction of nosylated C2,C7-(Pr^i)₂-diethylenetriamine and *p*-bis(bromomethyl)benzene gave the optically active tetra- Pr^i derivative of cycle **107** <2002OL949>.

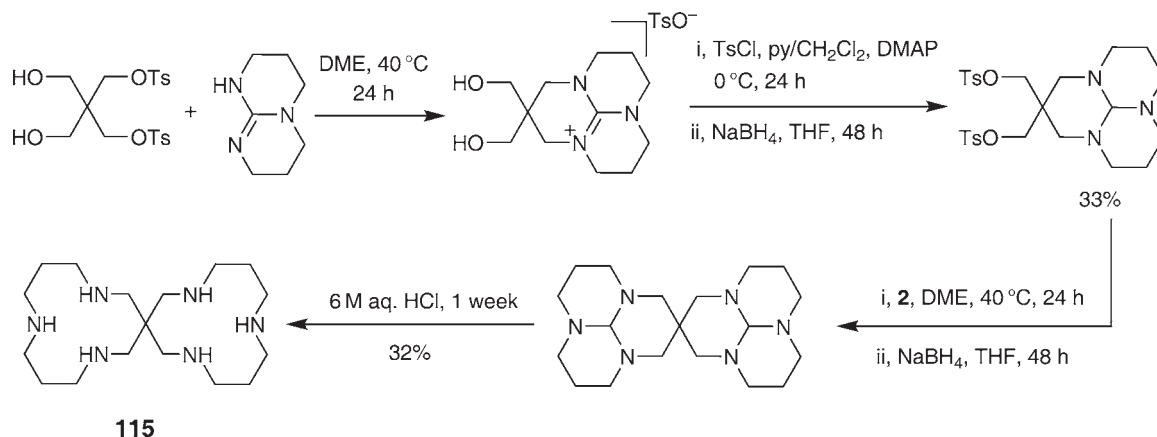
The product from a reaction of terephthalaldehyde and $\text{MeN}(\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2)_2$ was reduced to dimethylated 30-membered macrocycle **109** <2003DT4261>. Macrocycles **110** and **112** <2000JCS(P)1323>, and **111** <1996ICA287> and **113** <2004DT94> were also synthesized by the tosylamide approach in moderate yields. Condensation of terephthalaldehyde with *meso*- or *R,R*-1,2-diaminocyclohexane in presence of NaBH_4 afforded achiral or optically pure macrocycle **114** in a high yield <2003OBC2795>. Tosylamide strategy was used to produce the large tosylated 1,4,7,10,13,16,19,22-octaazacyclotetracosane in 71% yield and it was deprotected to the amine in 74% yield <1997CB267>. Products of [2+2] condensation of 3,2,3-tet or 3,3,3-tet (3,3,3-tet = 1,5,9,13-tetraazatridecane) or their C-methylated derivatives and diethyl oxalate at a concentration of 0.75 M for the reactants were isolated in 50–70% and the tetraoxomacrocycles were reduced with borane to corresponding 28- or 30-membered octaazacycles <1999TL79>.



14.11.5.5 Synthesis of Polycycles by Ring-Closure Reactions

Another family of macrocycles consists from ‘polycycles’ – compounds where two or more macrocycles are linked together through a spacer. Most of such compounds are synthesized directly from appropriate macrocycles or their derivatives (Section 14.11.6.3); however, there are some examples where the polycycles were obtained from acyclic precursors.

The spiro derivative of 1,5,9-triazacyclododecane **115** was prepared starting from ditosylated pentaerythritol (Scheme 16) (see Chapters 12.04 and 12.19) <2001TL2735>.



Scheme 16

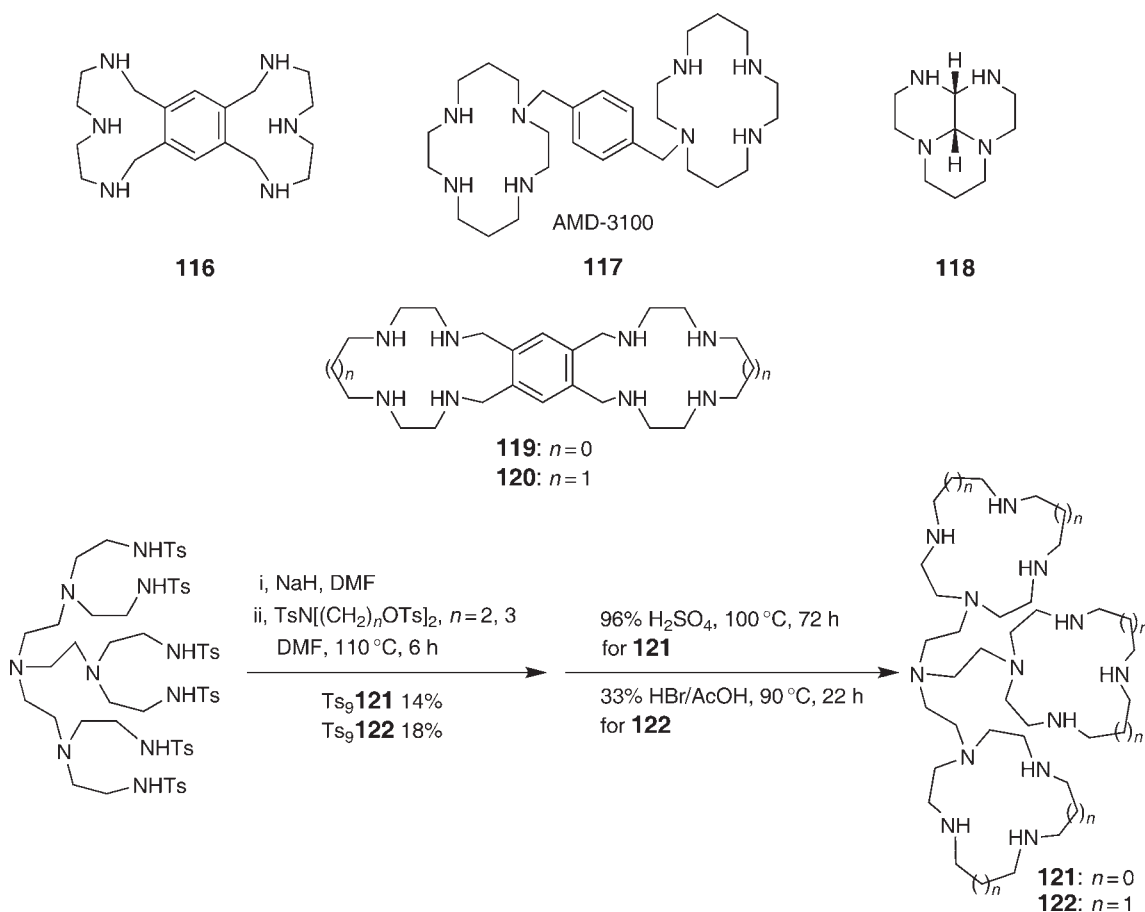
Compound **19** with two 1,5,9-triazacyclododecane units linked by *p*-xylylene bridge was obtained in very low yield from the cyclization of the bridged dipropyleneetriamine tetratosylamide with $\text{MsO}(\text{CH}_2)_3\text{OMs}$ <1997TL1911>.

Durene derivative **116** as its hexatosylamide was isolated as a single product from the reaction of diethylenetriamine tritosylamide and 1,2,4,5-tetrakis(bromomethyl)benzene in 63% yield <1999CCC1827>. Important bis(cyclam) derivative **117** (also called AMD-3100) was synthesized starting from 1,5,8,12-tetraazadodecane-1,5,12-tritosylamide <1996TL5301>. It reacted with 1,4-bis(bromomethyl)benzene and the formed tosylamide was cyclized with bis(tosyl) ethyleneglycol to give the bicyclic hexatosylamide, which was isolated in an overall 25% yield. Glyoxal aminated of 2,2,2-tet **48a** and 2,3,2-tet **118** (see Chapter 12.19) were reacted with 1,2,4,5-tetrakis(bromomethyl)benzene to give bis(tetraazamacrocycles) **119** (9%) and **120** (22%) after deprotection in aqueous acid <2000CCC99>. Some other bis(macrocycles) were obtained by ring-closure reactions during syntheses of libraries of bis(cyclam) analogs <1995JME366, 1999JME3971>.

Tritopic cyclen- and isocyclam- (isocyclam = 1,4,7,11-tetraazacyclotetradecane) based ligands **121** and **122** were prepared according to Scheme 17. Tosylated tren derivative (tren = tris(2-aminoethyl)amine) was cyclized under Richman–Atkins conditions to give the fully tosylated amines in relatively high yield considering the [1+3] reaction <2002JOC9107>.

14.11.6 Reactivity of Tetraazamacrocycles

The most pronounced reactivity of title macrocycles is derivatization of nitrogen atoms. The most common reaction used for modification of nitrogen atoms is a nucleophilic substitution. It employs electrophiles such as halogen or sulfonate (Ts, Ms, Tf, Ns) derivatives (alkyls, aryls, acyls) and the reaction is carried out in presence of a base. As the macrocyclic amines themselves are rather strong bases (Section 14.11.4), for full substitution, carbonates, hydroxides, or large excess of organic non-nucleophilic amines should be used. However, if partial substitution is required, the basicity of the macrocyclic amines themselves is convenient as a partial protonation protects the nitrogen atom(s) against substitution; some examples of the approach are shown in Section 14.11.6.1 describing protecting strategies. Other common reactions for ring nitrogen modification involve ring opening of small heterocycles (oxiranes, aziridines) (Chapters 1.01 and 1.03), nucleophilic additions (acrylic derivatives), reductive amination of aldehydes or ketones, Mannich reaction (phenols, phosphorus compounds), or metal-catalyzed couplings (aryls). For synthesis of



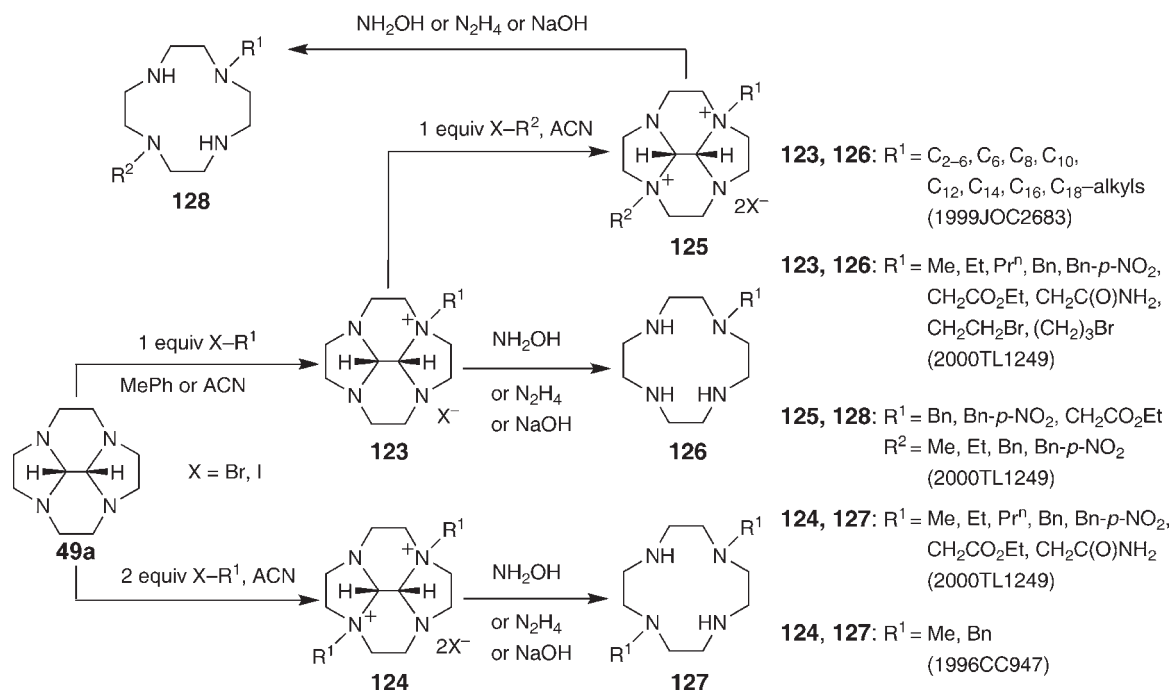
Scheme 17

partially substituted derivatives, direct reactions of the cycles with other reagents under controlled conditions (stoichiometry, temperature, presence/absence of base etc.) or reactions with appropriately protected cycle are used. In Section 14.11.6.2, we review N-functionalized derivatives of tetraazamacrocycles, where the substituents are bound to the rings only through the nitrogen atoms. Compounds with any modification of ring carbon atoms are covered in Section 14.11.6.4 together with their nitrogen atom derivatives. Section 14.11.6.3 deals with strategies of preparation of polycycles from mono(macrocyclic) precursors.

14.11.6.1 Protection Strategies

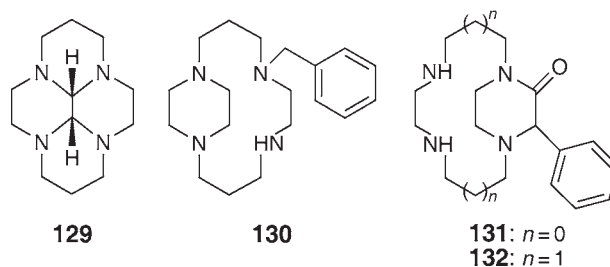
Reaction of cyclen **1** with glyoxal produced *cis*-aminal **49a** (see Volumes **10** and **11**) <1996CC947>. The same aminal can be prepared by ring-closure reactions (Section 14.11.5.3). The aminal can be considered as tri- or ‘*trans*’-diprotected forms of the cycle. It reacts with 1 or 2 equiv of suitable nucleophile to give the mono- or ‘*trans*’ (1,7-) disubstituted cycle after deprotection (Scheme 18) <1999JOC2683, 2000TL1249>. If monosubstitution is desired, the reaction is performed with 1 equiv of a nucleophile in solvents (toluene, acetonitrile) supporting precipitation of the monoquarternary salt **123**; temperature and reaction time depend on the reactivity of the nucleophile. If the reaction is run in more polar solvents (acetonitrile) with 2 equiv or excess of the nucleophile, disubstituted products **124** and **125** precipitated (Scheme 18). The carbon bridge is removed by reaction with NH₂OH/anhydrous EtOH, NH₂NH₂·H₂O, or with concentrated aqueous NaOH (depending on substituents R¹ and R²) to give amines **126–128**.

Analogous *cis*-glyoxal aminal **129** derived from cyclam **2** was prepared similarly <1996CC947>, and it was used for the same kind of protection leading to the analogous mono- and ‘*trans*’ (1,8-) disubstituted cyclam derivatives.



Scheme 18

Mono-, 1,8-di-, and mixed 1,8-disubstituted cyclams ($\text{R}^1, \text{R}^2 = \text{Me}$ and/or CH_2Ph) were obtained after the quaternization <1996CC947, 2000CCC243> and deprotection with hydroxylamine (monosubstitution) or aqueous NaOH (disubstitution). Borohydride reduction of the benzyl ammonium salt of aiminal **129** led to the reinforced mono-benzylated cyclam derivative **130** <1995PJC1039>. Phenylglyoxal also gave analogous *cis*-aminals when reacted with cyclen **1** (EtOH, 1 week, 60%) or cyclam **2** (EtOH, 4 h, 95%) and the aminals were transformed back to the starting amines (6 M aq., HCl, 70 °C, 2 h) <2003T4573>. Both the aminals are partially hydrolyzed under reflux in DMF/ H_2O to give lactams **131** or **132** (60% or 100%, respectively) (see Chapter 8.03) <2003T4573>.

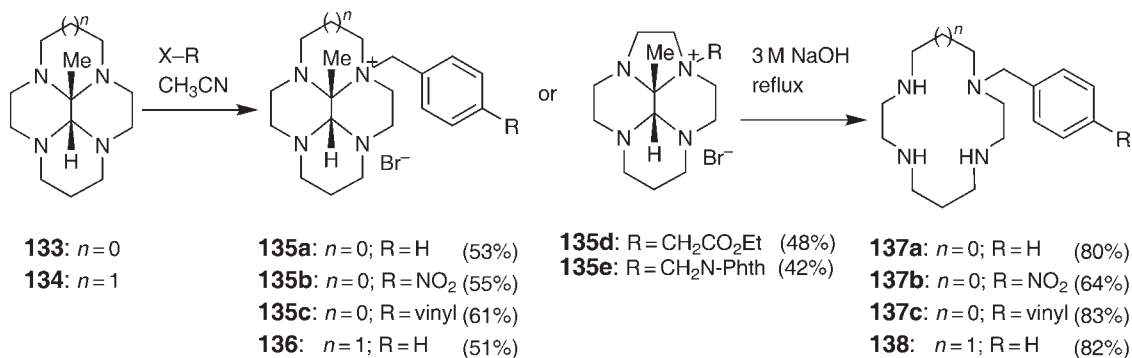


Pyruvic aminals **133** and **134** are alkylated by alkylhalogenides selectively on a nitrogen atom close to the methyl group to give alkylhomocyclens **137** or benzylcyclam **138** after carbon bridge removal from the quarternary salts **135** and **136** (Scheme 19) <2002CC312, 2005JOC7042>. If the *trans*-isomer of aiminal **134** was used in the reaction, it was alkylated but the carbon bridge could not be removed <2005JOC7042>.

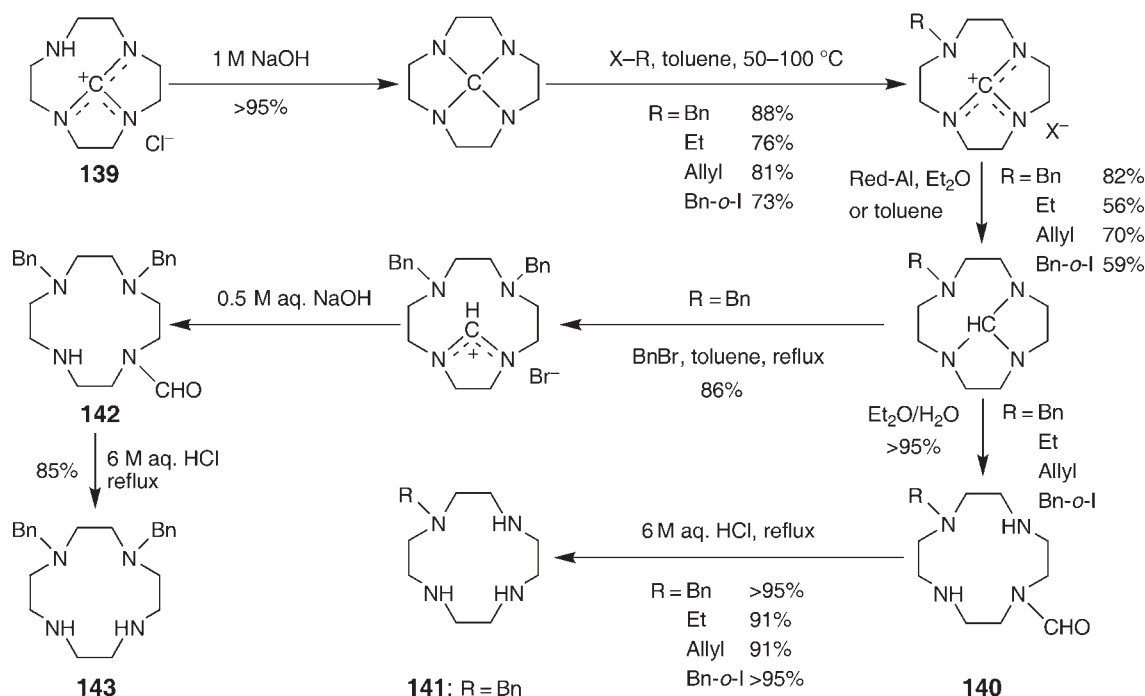
Guanidinium salt **139** was synthesized from the reaction of dry cyclen **1** hydrochloride with tetraethyl orthocarbonate (EtOH, reflux, 19 h, 96%) and transformed into various cyclen derivatives (Scheme 20) <1998ACS1247>.

The derivatives involve several orthogonally protected cyclens (e.g., '*trans*' formyl-Bn-cyclen **140** and formyl-Bn₂cyclen **142**) as well as Bn-cyclen **141** and '*cis*' (1,4-) Bn₂cyclen **143**. The compound **140** was also obtained by reaction of Bn-cyclen **141** with $\text{Me}_2\text{NCH(OEt)}_2$ (benzene, reflux, 2–4 h) followed by hydrolysis of the formed orthoamide <1995JP12995>.

Reaction of cyclam **2** with aqueous formaldehyde (room temperature, 1–2 h, >90%) <1993JA6580> or with CH_2Cl_2 (CH_2Cl_2 /30% aq. NaOH, reflux, 36 h, 88%) <1998EJO1971> led to the synthesis of formaldehyde aiminal **144**.

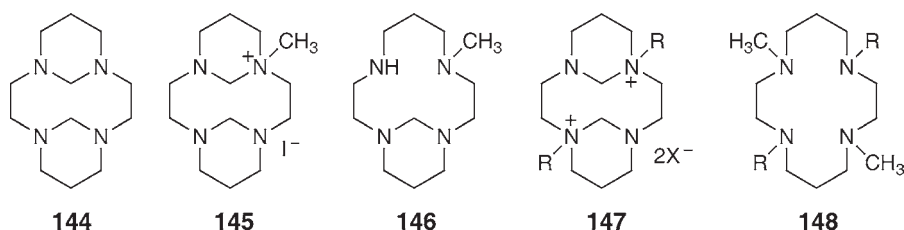


Scheme 19



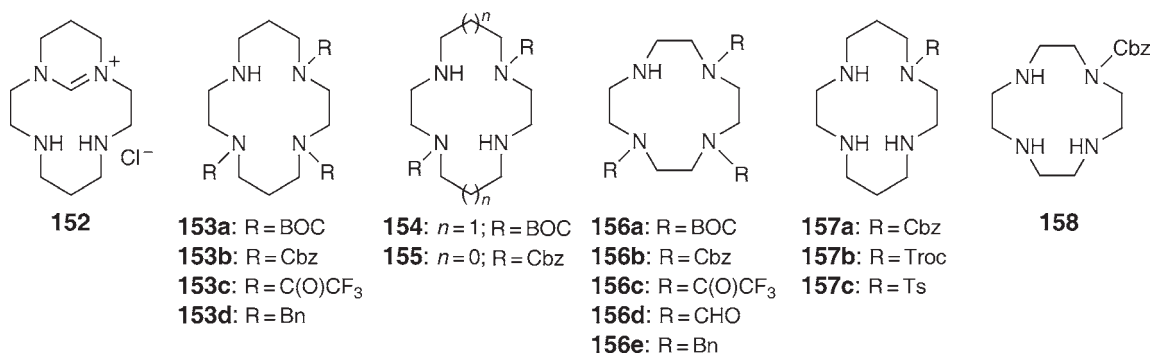
Scheme 20

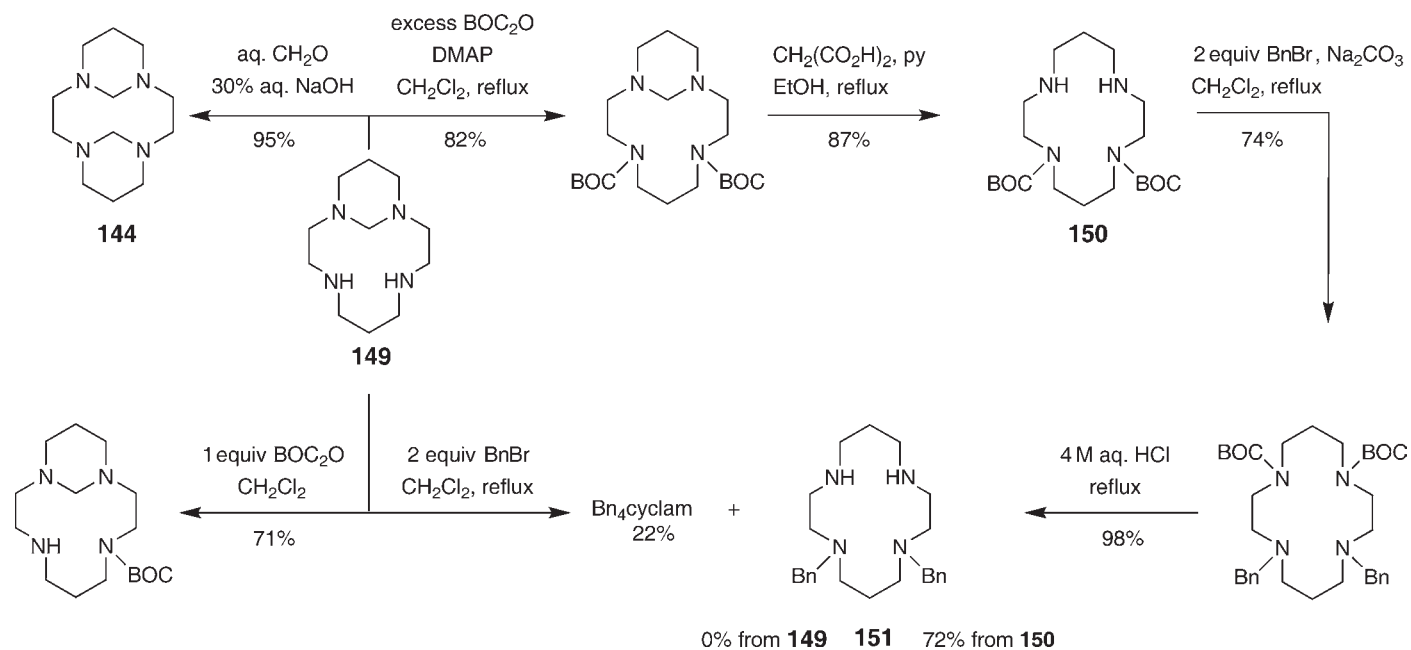
Similar to the above glyoxal strategy, mono- or symmetrical/unsymmetrical ‘*trans*’ (1,8-)cyclams can be prepared; however, reactivity of aminal **144** toward nucleophiles is higher than that of **129**. Monomethylcyclam was prepared by reaction of **144** with MeI (1 equiv) in Et₂O and the insoluble monoquaternary salt **145** (isolated in 88%) was hydrolyzed [\[1999TL2315, 2000CR211\]](#). Salt **145** reacted with excess of the second nucleophile to give analogous nonsymmetrical diquaternary salts (reflux in MeCN, 4 h; R = 2-picoyl (40%), CH₂C(O)NMe₂ (86%)) or with 3 M aqueous NaOH producing monoaminal **146** [\[1999TL2315\]](#). The symmetrical ‘*trans*’ disubstituted salts **147** were obtained by alkylation of **144** with excess nucleophiles in MeCN [\[1998EJO1971, 1999TL2315\]](#). The CH₂-bridges from disubstituted salts were removed by reaction with alkaline hydroxide [\[1998EJO1971, 1999TL2315\]](#). Reduction of salts **147** (excess NaBH₄, EtOH/H₂O, reflux) gave the fully substituted cyclams **148** [\[1998EJO1971\]](#). Reduction of aminal **144** provided **146** (Pd/C, H₂, EtOH) or separable mixture of 1,4- and 1,8-dimethylcyclams (Raney-Ni, liq. NH₃, EtOH→130 atm, 60 °C, 336 h) [\[1998HCA1765\]](#).



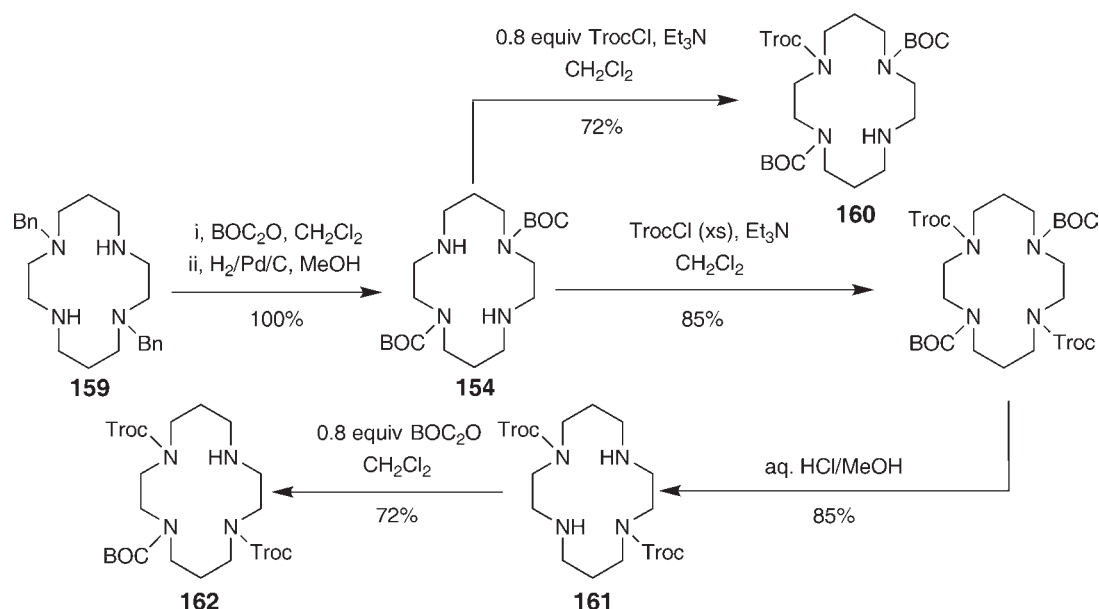
Refluxing cyclam **2** in CH_2Cl_2 in the presence of $\text{R}_3\text{Sn-NEt}_2$ ($\text{R} = \text{Et}, n\text{-Bu}$) produced monoaminal **149** in 77% yield [\[1997SL1190\]](#). It was transformed into a number of other cyclam derivatives ([Scheme 21](#)); in this way, two 1,11-diprotected cyclam derivatives **150** and **151** were obtained. Reaction of cyclam with $\text{Me}_2\text{NCH(OMe)}_2$ in refluxing CHCl_3 for 18 h gave compound **152** (75%) [\[1998CC827\]](#). It was transformed into BOC derivative **150** (72%) and further reaction produced 1,11-BOC₂-4,8-Bn₂cyclam (95%) and finally 1,11-Bn₂cyclam **151** (92%) [\[2001AJC291\]](#).

Carbamates and amides form another class of protecting groups. 1,11-Diprotected cyclam **150** (39%) was obtained in the reaction of cyclam **2** with BOC_2O (1.8 equiv) in CH_2Cl_2 at room temperature in mixture with BOC₃cyclam **153a** (19%) and 1,8-BOC₂cyclam **154** (25%), separable by column chromatography [\[1995TL4995\]](#). Important BOC₃cyclam **153a** was later synthesized in higher yields: 67% [\[1996BSF65\]](#), 71% [\[2002CEJ4965\]](#), or 51% [\[2006EJI2357\]](#). BOC₃cyclen **156a** was analogously prepared in CH_2Cl_2 (2.4 equiv BOC_2O , rt, 70%) [\[1996BSF65\]](#) or in $\text{CHCl}_3/\text{NEt}_3$ (3 equiv BOC_2O , rt, 72% or 90%) [\[1997JA3068, 2004JA9248\]](#). Carbamates **153a** and **156a** can be also obtained from chlorotriptyl resin after reaction of the resin with the starting amines and carbamoylation with BOC_2O in good yields (**153a** (77%) and **156a** (80%)) [\[2004SL453\]](#). Reaction of cyclen with CbzCl yielded Cbz₃-cyclen **156b** [\[1996LA935\]](#). Alternatively, Cbz_2O (2.8 equiv, $\text{CHCl}_3/\text{NEt}_3$, 7 h, 73%) was used for cyclen triprotection as **156b** [\[2002IC6816\]](#). Similarly, cyclam and Cbz_2O afforded Cbz₃cyclam **153b** (36%) [\[2006EJI2357\]](#). Cyclam **153c** and cyclen **156c** tris-protected by trifluoroacetate group are easily afforded almost quantitatively reacting the amines in MeOH with excess of $\text{CF}_3\text{CO}_2\text{Et}$ in presence of excess of NEt_3 [\[2003TL2481, 2002USP6489472\]](#). These triprotected cycles can be easily transformed to the monoprotected ones. Triformylcyclen **156d** was produced by reaction of cyclen with excess of chloral hydrate (EtOH, 60 °C, 3 h) to get the product in 92% yield (methyl or ethyl formates or formic acid gave much lower yields) [\[2000TL6527\]](#). Reaction of **156a** [\[2004JA9248, 2001JA1123\]](#), **156d** [\[2003CC766, 2004JME6625\]](#), or **153c** [\[2002USP6489472\]](#) with CbzCl and tris-deprotection led to Cbz-cyclam **157a** or Cbz-cyclen **158**, respectively. Similarly, 2,2,2-trichloroethoxycarbonyl chloride (TrocCl) reacted with carbamate **153a** to give the fully substituted cyclam, which was deprotected to Troc-cyclam **157b** (85%) and further transformed to 1,4,8-tribenzylcyclam **153d** (35%) [\[2001AJC291\]](#). Monotosyl-cyclam **157c** is the product of the reaction between trifluoroacetamide **153c** and TsCl [\[2002USP6489472\]](#) or ethyl tosylate [\[2003CC2894\]](#), followed by deprotection. An elegant approach employing differences in pK_A of ring nitrogen atoms was used for the synthesis of cyclen 1,8-carbamates. Cyclen has two high pK_A 's (around 10, see [Section 14.11.4](#)) and two low pK_A 's (around 1). Conducting the reaction of cyclen and carbamoyl chlorides in water at controlled pH 2–3 during the chloride addition led exclusively to the 'trans' protected cyclens [1,8-(CO_2R)₂; yields: $\text{R} = \text{Me}$ (93%), Et (98%), vinyl (90%), benzyl **155** (88%)] [\[1995CC185, 1997S759\]](#). Benzyl carbamate **155** was also obtained almost quantitatively by another reaction (cyclen + CbzCl , EtOH/ $\text{CH}_2(\text{OMe})_2$, 24 h, 98%) [\[1996BML2063\]](#). Orthogonally BOC- and Troc- protected cyclams **160** and **162** were devised by Chartres *et al.* [\[2006T4173\]](#) starting from readily available 1,8-Bn₂cyclam **159** (obtained through formaldehyde aminal protection, see above). Intermediates **154** and **161** were reacted with 0.8 equiv of the protecting reagents, giving reasonable yields of final products ([Scheme 22](#)).





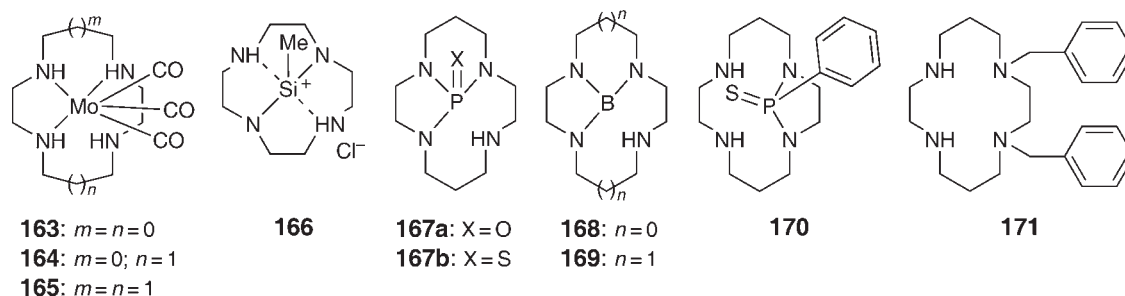
Scheme 21



Scheme 22

Triprotection of the 12–16-membered tetraazacycles was also achieved through organometallic approaches. Chromium(0) or molybdenum(0) tricarbonyl triamino complexes (e.g., **163–165**) <1995JOM215> are substituted with acylhalogenides or aldehydes and N-monosubstituted products are obtained after oxidative deprotection in strong acid and acylamide/enamine reduction to amines <1995TL79>.

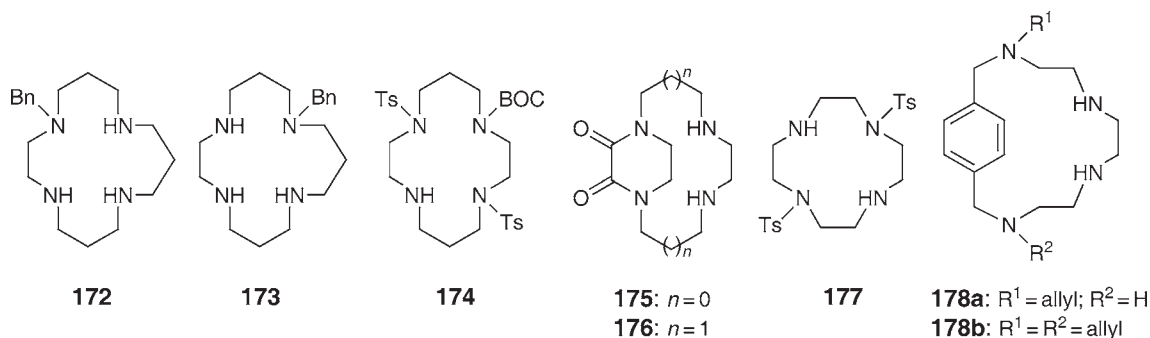
The same reagent can produce ‘*trans*’-disubstituted amines if excess of nucleophile (symmetrical substitution) or sequential addition of two different nucleophiles (nonsymmetrical substitution) is used <1996ICA105>. Silicon hypervalent amide **166** prepared from MeSiCl₃ and cyclen similarly gave ‘*trans*’ symmetrically or nonsymmetrically substituted cyclens <1995CCC1233>. As with the above reagents, phosphoric acid triamides **8** and **167** served as triprotection or ‘*trans*’ diprotection of the ring nitrogen atoms. The phosphoryl derivatives are prepared by transamination of P(NMe₂)₃ followed by aq. NaOH oxidative hydrolysis <1991AG(E)560> or by reaction of the amines with POCl₃ <1998SC2903>. The thiophosphoryl group is introduced by sulfur oxidation of above P(III) transamination product <1996T2995>. In a similar approach, reaction of B(NMe₂)₃ and cyclen (toluene, reflux, 4 h) led to boron triamide **168**, which was directly alkylated with 1 equiv alkyl halide and the product was hydrolyzed with 4 M NaOH (Bn-cyclen **141** 98%, allylcyclen 60%) <2001T2385>. Cyclam also affords similar boron-protected compound **169**. Cyclam was successfully protected in the ‘*cis*’ 1,4-position by PhP(S)Cl₂ giving thiophosphondiamide **170** (1:1 molar ratio, 2 equiv NEt₃, CHCl₃, rt, 3 days, 40–50%) (see Chapters 6.12, 6.14, 9.16, 9.18, 9.19, 12.12 and 12.13) <2006CCC337> which was alkylated with benzyl bromide followed by acid hydrolysis to give 1,4-dibenzylcyclam **171** (65%). Reaction with cyclen led to a very low yield of the analogous thiophosphondiamide <2006CCC337>.



In principle, any compound prepared by a ring-closure reaction in Section 14.11.5.3 and substituted with a removable substituent on ring nitrogen atoms can serve as a protected cycle. This is particularly true of a full range of the cyclic amides and sulfonamides (mostly tosylamides). Examples of the approach are **172** and **173** prepared by the tosylate method from tosylated and benzylated precursors <1995T1197>. Protected 16-membered ‘*trans*’ 1,9-dibenzyl-1,5,9,13-tetraazacyclohexadecane was also obtained in this way <1998SC285>.

Another orthogonally protected cyclam is **174** <1998IC1575>. Very useful are oxalylcyclen **175** and oxalylcyclam **176** prepared by reaction of the amines with diethyl oxalate (96% and 82%, respectively) <1999JCS(P1)3499>. It was used to prepare different 1,4-substituted cycles, for example, 'cis' 1,4-Bn₂cyclen **143** (75%) and 1,4-Bn₂cyclam **171** (71%). Monobenzylicyclen **141** (81%) and -cyclam **138** (88%) were also easily obtained by direct alkylation of excess of amine (0.4–0.5 equiv BrCH₂Ph, K₂CO₃, MeCN, 55–60 °C); using other solvents gave lower yields <2002TL3217>. The same group of authors prepared, by a similar approach, 1,4-Bn₂cyclen **143** (78%), 1,4-allyl₂cyclen (73%), 1,4,7-Bn₃cyclen **156e** (86 %), or 1,4,7-allyl₃cyclen (76%) (CHCl₃/NEt₃, 2.0 or 3.5 equiv of nucleophile, rt) <2004T5595>. Reaction of 2 equiv TsCl with cyclen in pyridine led to a high yield of 1,7-Ts₂cyclen (80–90%) **177** <1994TL3707, 1995ACS547, 1998IC3989>.

Cyclen **1**, cyclam **2**, or homocyclam **22** selectively react with $\text{PhCH}=\text{N}-\text{N}(\text{Me})\text{P}(\text{S})\text{Cl}_2$ only in position 1,4 with formation of phosphordiamides similar to **170** (with diazaphospholane ring). Otherwise, the hardly obtainable, selectively monoalkylated or symmetrically dialkylated, derivatives (e.g., **178a** or **178b**) of series of benzenecyclophanes (*p*-xylylene or *p*-Me₄xylylene; tri- or tetraazacycles, ethylene or propylene chains (e.g., **39**, **92**, or **96**)) were synthesized through metal ion (Zn^{2+} or Pd^{2+}) protection of the nonbenzylic amines ($\text{R}-\text{X}$, MeCN or CHCl_3 , K_2CO_3 , rt, moderate yields; $\text{R} = \text{CH}_2\text{Ph}$, allyl, $\text{CH}_2\text{CO}_2\text{Et}$, $\text{CH}_2\text{Ph}-p\text{-NO}_2$, $\text{CH}_2\text{Ph}-p\text{-OMe}$; $\text{X} = \text{Br}$, Cl) [<1998JOC1810>](#).



14.11.6.2 N-Functionalized Derivatives

14.11.6.2.1 Monosubstituted derivatives

Macrocycles modified on one nitrogen atom are often starting materials for nonsymmetrically substituted derivatives or for further substitution on the pendant arm. Some examples have been already shown in [Section 14.11.6.1](#) (if the substituent has a character of protecting group) or can be also found below (if they are prepared in the first step in synthetic sequence where remaining nitrogen atoms were further substituted). Most of polymacrocycles can be considered as monosubstituted simple cycles ([Sections 14.11.5.5 and 14.11.6.3](#)). The commonly utilized methods are a reaction with excess of the cyclic amine or a reaction with a triprotected cycle. A wide range of derivatives was prepared; therefore, only some representative examples starting from representatively protected cycles were chosen. They are listed in [Table 1](#) (cyclens) in accordance with [Scheme 23](#) and [Table 2](#) (cyclams) following [Scheme 24](#).

Cyclen **1** and cyclam **2** were used for modification of β -cyclodextrin in one position 6 [<1997JP13157, 2000BMC647>](#). A series of monosubstituted cyclen and cyclam derivatives having different pendant arms (Bn, $\text{CH}_2\text{CO}_2\text{Et}$, allyl, hydroxoalkyls, Ac β -glucopyranoside, 15-crown-5, 18-crown-6) was easily synthesized under controlled conditions (MeCN, 55–60 °C, 0.4–0.5 equiv of alkylation agent, 5 equiv K_2CO_3) in reasonable yields (66–91%) [<2002TL3217>](#). Addition of 1 equiv of TsOH (as a strong acid) led to a high selectivity for monosubstituted products during Michael addition of cyclam to a series of acrylic acid derivatives (CHCl_3 , rt, 16 h, 40–80%) [<1999JP1811>](#). The derivatives involve amides (alkyls, benzo-18-crown-6, sugar derivative), acrylonitrile, and acrylic esters (alkyls). Chlorotriptyl-resin was used for the synthesis of BOC-cyclam- $\text{CH}_2\text{CO}_2\text{H}$ starting with cyclam [<1997TL3219>](#).

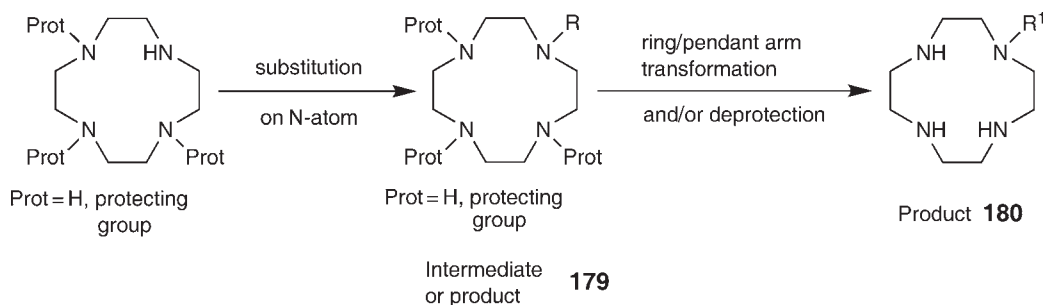
Derivatives of pentaazacycle **100a** having $\text{CH}_2\text{Ph}-p\text{-CO}_2\text{H}$ [<1996IC3821>](#) or $(\text{CH}_2)_3\text{N}^+\text{Et}_3$ [<2000MI585>](#) pendant groups were prepared by direct reaction of electrophiles with the cycle.

14.11.6.2.2 Di- and trisubstituted derivatives

If nonprotected cycles are used in the reaction, a number of substituents, and a place of reaction, are often controlled by conditions (mainly by stoichiometry and solvent used). Direct reaction with amines is simple to run but may lead to inseparable reaction mixture. Selective protection adds several extra synthetic steps. Overall yields of both ways can be, therefore, comparable as well as time consumption. Isomers can be prepared with two or more substituents, (depending on the symmetry of the macrocycle). For cyclen and cyclam, they are commonly called '*trans*'

Table 1 Monosubstituted cyclen derivatives according to **Scheme 23**

Cycle	<i>R</i> in intermediate/product 179	<i>R</i> ¹ in product 180	Reference
1	CH ₂ Ph, CPh ₃ , CH ₂ CO ₂ Bu ^t , CH ₂ CH(OMe) ₂ , CH ₂ CH(O ₂ C ₂ H ₄), CH ₂ CH ₂ CH(O ₂ C ₂ H ₄)	further 'trans' protected with —CHO	1995JP12995
1	CH ₂ CH ₂ SH	CH ₂ CH ₂ S-S-protein	2002ICA123
8b	C(O)C ₂ H ₅ , C(O)Ph,	CH ₂ CH ₂ CH ₃ , CH ₂ Ph	1996T2995
49a	Me, Bn, <i>n</i> -Bu, (CH ₂) ₃ NPhth		2001NJC1168
Ph-49	CH(Ph)CO ₂ H		2003T4573
57	2,6-dioxo-10-(<i>n</i> -C ₁₆ H ₃₃)-cyclen	<i>n</i> -C ₁₆ H ₃₃	1996JA10963
156a	C ₃ -, C ₈ -, C ₁₂ - and C ₁₆ - <i>n</i> -alkyl	C ₃ -, C ₈ -, C ₁₂ - and C ₁₆ - <i>n</i> alkyl	1998JA10019
156a	CH ₂ -(1-naphthyl)	CH ₂ -(1-naphthyl)	1999JA5426
156a	(CH ₂) ₄ OH	(CH ₂) ₄ O ₂ C-C(Me)=CH ₂	2006AGE2745
156a	C(O)CH ₂ Br	C(O)CH ₂ -flavine derivative	2004JOC8183,
			2004CEJ6224
156a	CH ₂ CO ₂ H	Coupling to peptides or nucleobases	2002OL4155,
			2005JA9593
156a	C(O)CH ₂ NH ₂	C(O)CH ₂ NHC(O)-(benzo-19-crown-6)	2005OBC3877
156a	CH ₂ Ph-4-I	CH ₂ Ph-4-[L-CH(NHCbz)(CO ₂ Me)]	2006T1360
156a	Ph-2,4-(NO ₂) ₂	Ph-2,4-(NO ₂) ₂	1998ICA424
156a	CH ₂ -calix[4]arene	CH ₂ -calix[4]arene	2004OL241
156a	calix[4]arene	calix[4]arene	2006T5748
156b	CH ₂ C(O)NH(CH ₂) ₃ NHBOC	CH ₂ C(O)(CH ₂) ₃ NH-R; R = H, or Arg	1996LA935
156b	C(O)N- <i>n</i> -Bu	C(O)N- <i>n</i> -Bu	2001EJO1943
156d	Bn, Et, <i>n</i> -C _{4,10,16} -alkyl, allyl, propargyl, CH ₂ Fc, CH ₂ (anthracene-9-yl)	Bn, Et, <i>n</i> -C _{4,10,16} -alkyl, allyl, propargyl, CH ₂ Fc, CH ₂ (anthracene-9-yl)	2000TL6527
163	C(O)Ph, C(O)Et	CH ₂ Ph, (CH ₂) ₂ CH ₃	1995TL79
163	CH ₂ CH ₂ Ph, CH ₂ CHPh ₂ , CH ₂ CH(Me)Ph, (CH ₂) ₈ CH ₃		1995TL79
168	Et, <i>n</i> -Bu, Pr ⁱ , Bn, C(O)Ph, allyl, but-2-yn		2001T2385

**Scheme 23**

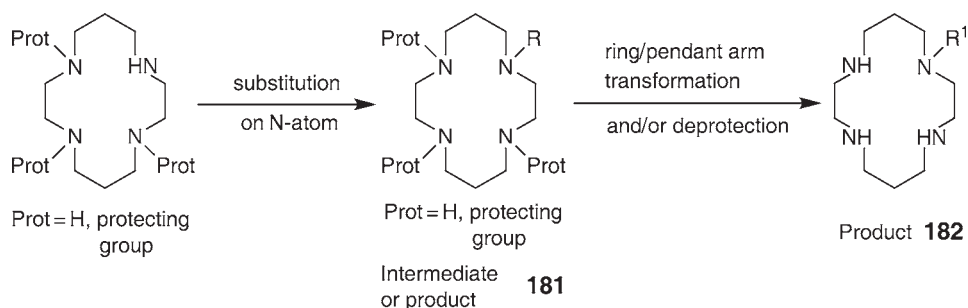
(substituents are bound on the opposite nitrogen atoms) or '*cis*' (substituents are placed on the adjacent nitrogen atoms). If the alkylation reactions are run with free amines in a less polar solvent, HX acid evolved is partially neutralized by the basic macrocycle and one proton is able to form a hydrogen bond between two ethylenediamine nitrogen atoms to block them against substitution leading to formation of '*cis*' derivatives. This is well illustrated in the synthesis of '*cis*' (1,4-)substituted cyclens (CHCl₃, 10 equiv NEt₃, 2 equiv alkylation reagent, rt) <2003JOC2956, 2004T5595>. In contrast, in polar solvents (water, alcohols), opposite nitrogen atoms are protonated to minimize charge repulsion that may lead to formation of '*trans*' isomers <1995CC185, 1997S759>.

Some representative disubstituted cyclen **1** derivatives are listed in **Table 3** and cyclam **2** derivatives are listed in **Table 4**. Disubstituted derivatives where the substituents serve as protecting groups as well as some another disubstituted macrocycles were also shown in **Section 14.11.6.1**.

In addition to triprotected cycles (**Section 14.11.6.1**), some trisubstituted cycles are very important. In particular, DO3A **183** (DO3A = 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid) or its esters are intermediates for a number of unsymmetrically substituted cyclen derivatives (see below). The most important ester is tris(Bu^t) ester **184**.

Table 2 Monosubstituted cyclam derivatives according to **Scheme 24**

Cycle	<i>R</i> in intermediate/product 181	<i>R</i> ¹ in product 182	Reference
2	CH ₂ -(anthracen-9-yl)		1996CEJ75
2	Ph- <i>p</i> -CN		1998JA1474
2	(CH ₂) ₃ Si(OEt) ₃		2002JMC2255
2	CH ₂ CH ₂ CO ₂ H		2004DT2115
2	CH ₂ -(2,2'-bipyridin-5-yl)		1995ICA159
2	CH ₂ Ph- <i>p</i> -(2,2':6',2''terpyridin-4'-yl)		2000EJI741
2	CH ₂ CH ₂ CN	CH ₂ CH ₂ CH ₂ NH ₂	2003ICA205
129	Bn		2000CCC243
Ph- 129	CH(Ph)CO ₂ H		2003T4573
150	1,11-BOC ₂ -4-(CH ₂) ₄ CO ₂ Et	Used for synthesis polycycles	1998TL853, 1999JME229
153a	CH ₂ CH ₂ NH-dansyl	CH ₂ CH ₂ NH-dansyl	2002CEJ4965
153a	CH ₂ Ph- <i>p</i> -CH ₂ Br	CH ₂ Ph- <i>p</i> -CH ₂ NHCH ₂ CH ₂ -N(CH ₂ CH ₂ NH ₂) ₂	1999CEJ683
153a	CH ₂ CO ₂ H	CH ₂ C(O)NH-CH ₂ CH ₂ N(CH ₂ CH ₂ NH ₂) ₂	2003DT3939
153a,b	<i>L</i> -C(O)CH(Me)NHBOC	<i>L</i> -C(O)CH(Me)NH ₂	2006EJI2357
153c	CH ₂ Ph- <i>o</i> -NO ₂		2005OL3417
165	C(O)Ph, C(O)Et, C(O)CHMe ₂ , C(O)(CH ₂) ₁₀ CH ₃ , 2-furyl	CH ₂ Ph, (CH ₂) ₂ CH ₃ , CH ₂ CHMe ₂ , (CH ₂) ₁₁ CH ₃ , CH ₂ -(2-furyl)	1995TL79
167a	P=O triamide; CH ₂ CH ₂ CO ₂ Et	CH ₂ CH ₂ CH ₂ OH	1999EJO3257

**Scheme 24****Table 3** Disubstituted cyclen **1** derivatives

Position	<i>R</i> ¹ or <i>R</i> ²	Reference
1,4	(CH ₂) ₃ OH	1999ICA103
1,4	CH ₂ CO ₂ Bu ^t	2003JOC2956
1,4 ^a	CH ₂ CO ₂ Bu ^t , CH ₂ Ph, allyl, CH(Me)CO ₂ Et, CH ₂ C(O)NH-R ³ , R ³ = CHPh ₂ , (<i>S</i>)-CH(Me)Ph, (CH ₂) ₅ Me	2004T5595
1,4 ^a	CH ₂ CO ₂ H, CH ₂ Ph, CH ₂ (2-pyridyl), <i>n</i> -Pr, CH ₂ CH ₂ CO ₂ H	1999JP13499
1,4 ^b	CH ₂ (2-pyridyl), CH ₂ CH ₂ CO ₂ H	1999JP13499
1,7 ^c	Me, CH ₂ Ph	1995CC1233
1,7 ^a	Me, CH ₂ Ph, propargyl, <i>n</i> -Pr	1996CC2157
1,7 ^a	CH ₂ CH ₂ OH, CH ₂ CO ₂ Bu ^t , CH ₂ CO ₂ H, CH ₂ CH ₂ NH ₂	1995CC185
1,7	CH ₂ CO ₂ Me	1996BML2063
1,7	CH ₂ CO ₂ Bu ^t	1997S759
1,7	CH ₂ CO ₂ H	1997JCD317
1,7 ^a	CH ₂ (1-naphthyl), CH ₂ (4-quinolyl)	1999JA5426
1,7 ^{a,d}	CH ₂ CO ₂ Bu ^t , CH ₂ CO ₂ H	1999SC4279
1,7	CH ₂ (anthracen-9-yl)	2005IEC847

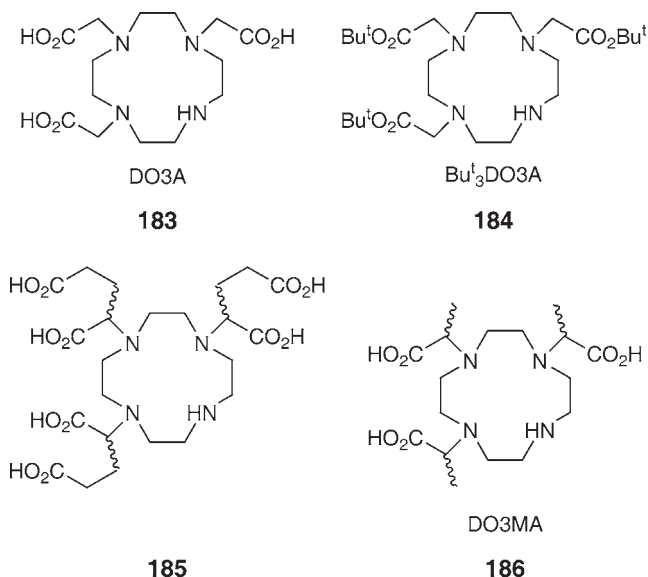
^aOnly symmetrical products.^bOnly unsymmetrical products.^cSymmetrical and unsymmetrical products.^d3,11-dioxocyclen derivatives.

Table 4 Disubstituted cyclam **2** derivatives

Position	R^1 or R^2	Reference
1,4 ^a	$\text{CH}_2\text{CO}_2\text{H}$, CH_2Ph , $\text{CH}_2(2\text{-pyridyl})$, $n\text{-Pr}$, $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	1999JP13499
1,4 ^b	$\text{CH}_2(2\text{-pyridyl})$, $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	1999JP13499
1,4 or 1,8 or 1,11	$\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$	2003EJO3985
1,8 ^a	Me, $\text{CH}_2(2\text{-pyridinyl})$	1998EJO1971
1,8 ^c	Me, $\text{CH}_2(2\text{-pyridinyl})$, $\text{CH}_2\text{C}(\text{O})\text{NMe}_2$	1999TL2315
1,8	$\text{CH}_2\text{C}(\text{O})\text{NMe}_2$	2000CR211
1,8 ^c	Me, CH_2Ph	2000CCC243
1,8	Allyl	2003IC7156
1,8	$\text{CH}_2[(6\text{-HOCH}_2)\text{pyridin-2-yl}]$	2003JHC383
1,8 ^d	$\text{C}(\text{O})\text{CH}_2\text{Cl}$, $\text{C}(\text{O})\text{Ph-}p\text{-CH}_2\text{Cl}$	2001AJC291, 2006T4173
1,8 or 1,11	$(\text{CH}_2)_4\text{CO}_2\text{Et}$ as bis(BOC) protected	1998TL853, 1999JME229
1,8 or 1,11	$\text{CH}_2(2\text{-pyridinyl})^a$	2000JCD1873
1,11	$\text{CH}_2\text{CH}_2\text{OH}$	1998CC827

^aOnly symmetrical products.^bOnly unsymmetrical products.^cSymmetrical/unsymmetrical products.^dBis(BOC)-protected.

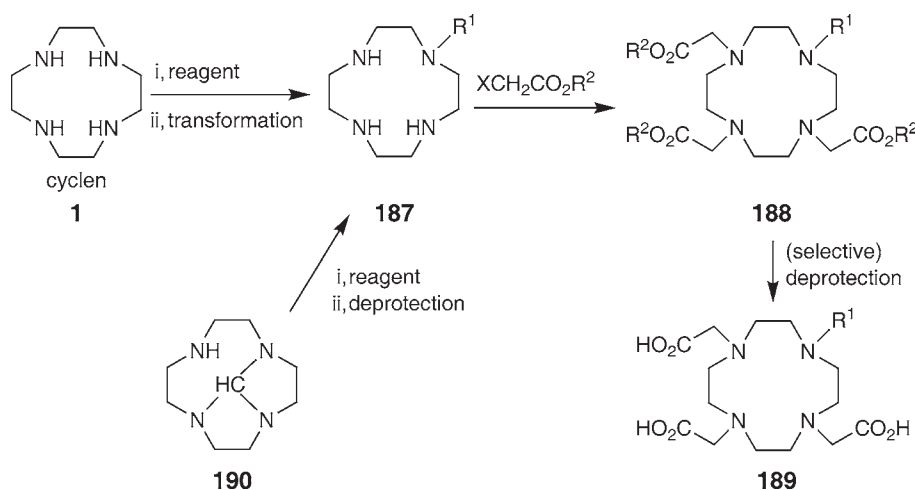
Several very similar syntheses have appeared. All are based on addition of approximately 3 equiv of $\text{BrCH}_2\text{CO}_2\text{Bu}^t$ to solution of cyclen in an organic solvent in presence of weaker base: 3 equiv X–R, 3 equiv NaOAc, dimethylacetamide, rt, 19 days, 56% <1996WO28433>; 3.1 equiv X–R (dropwise addition at 0 °C), 3.1 equiv NaHCO_3 , MeCN, rt, 48 h, 42% <2002JP2348>; 3 equiv X–R (dropwise addition at for 4 h), 3 equiv K_2CO_3 , CHCl_3 , rt, 72 h, 73% <2002JCD48>; 3.5 equiv X–R (dropwise addition), 10 equiv NEt_3 , CHCl_3 , rt, 20 h, 77% <2004T5595>. The ester is isolated as monohydrobromide salt. HBr evolved by a reaction that blocks the last nitrogen atom from substitution due to protonation. Triethyl ester of DO3A was also prepared but the yield (72%) seems to be incorrect taking in account the reaction conditions <2001NJC336>. DO3A was also directly synthesized from cyclen and chloroacetic acid (3 equiv, pH 5 then pH 10, –4 °C, 3 h; slow heating to 50 °C, 4 h; 50 °C for 8 h; 70%) <2005EJI3918>. Full methyl ester of glutaryl-DO3A derivative was obtain (as mixture of diastereoisomers) under similar conditions to those for DO3A ester and was hydrolyzed to the acid **185** <2000JA9674>. Similarly, triethyl ester of DO3MA **186** (DO3MA = 1,4,7,10-tetraazacyclododecane-1,4,7-tris[(methyl)acetic] acid), allylcyclen, and Bn_3cyclen **156e** were afforded <2004T5595>. Other trisubstituted cyclen derivatives involved a number of derivatives of 1,4,7,10-tetraazacyclododecane-1,4-diacetic acid (1,4-DO2A) with one more substituent <2003JOC2956>. Parker and co-workers prepared cyclen-1,8- $(\text{CH}_2\text{C}(\text{O})\text{NHR})_2$ -4-(azathioxanthone derivatives) ($\text{R} = \text{CH}(\text{Me})\text{CO}_2\text{Et}$, $\text{CH}(\text{Bn})\text{CO}_2\text{Et}$) <2005EJO4249, 2006JA2294>. 1,4-DO2A appended with one $-\text{CH}_2\text{C}(\text{O})\text{NH}(\text{CH}_2)_3\text{NH}_2$ pendant arm was also synthesized <1996BMCL2063>.



Triamide of TE3A (TE3A = 1,4,8,11-tetraazacyclotetradecane-1,4,8-triacetic acid) was obtained in almost quantitative yield from the reaction of cyclam and $\text{ICH}_2\text{C}(\text{O})\text{NH}_2$ in acetone in presence of *N,N*-diisopropylethylamine (DIPEA) and it was hydrolyzed to the acid <1999TL381>. Synthesis of TE3A triethyl ester was described <2001NJC336>. Another trisubstituted cyclam derivative is octyl₃cyclam <2002ANA229>.

14.11.6.2.3 Tetrasubstituted derivatives

There are two general strategies for the synthesis of a very important group of compounds – DO3A derivatives substituted on the last nitrogen atom. The first approach (Scheme 25) involves the synthesis of N-monosubstituted cyclen derivatives **187** (see also above) followed by alkylation of the remaining nitrogen atoms with salts or esters of halogenoacetic acids (mostly with *t*-butyl bromoacetate) to **188** and (selective) deprotection/transformation to zwitterionic **189** or to other forms of the ligands. Some examples are listed in Table 5. The second approach (Scheme 26) employs DO3A **183**, mostly in the form of tris-*t*-butyl ester **184**, and the last nitrogen atom is modified to obtain the target ligand **188**. It is fully or partially deprotected or transformed to **189** if zwitterionic or other forms are necessary. The approach is covered in Table 6.



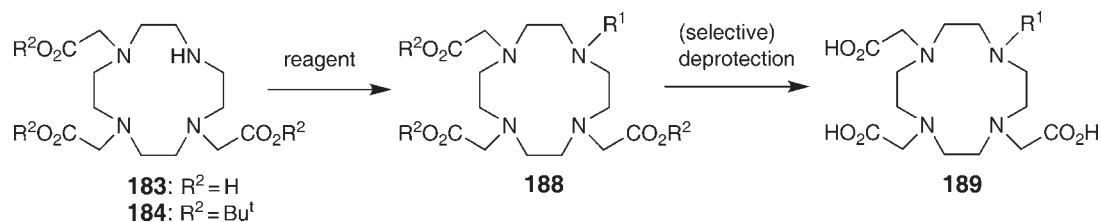
Scheme 25

The alkylations are generally run in water at pH 8–10 at higher temperature (halogenoacetic acids) or in acetonitrile with K_2CO_3 as a base at room temperature ($\text{XCH}_2\text{CO}_2\text{R}$, X = halogen, OTs, OMs, OTf, Scheme 25). Other conditions for the esters involve heating to reflux and/or other solvents (DMF, EtOH, MeOH) as well as other bases (NaHCO_3 , Na_2CO_3 , Cs_2CO_3 , tertiary amines) are used less frequently. Sodium cation can form complexes with the intermediate esters, which are hardly separable from noncomplexed compounds; however, in some cases, sodium complexes can be used for convenient purification of the esters <2004OBC570>. Some methods lead to orthogonally protected DOTA **3** esters, which are subsequently selectively deprotected and used for further derivatization (e.g., amide or peptide bond formation; see also below). Other reactions also used for nitrogen modification are the same as already given above: oxirane ring opening for alcohol pendant arms, aziridine opening for amines, or addition to double bond (acrylic derivatives).

DOTA monoamides **192** are probably the most diverse class of these ligands. The compounds can be synthesized according to Schemes 25 (see Chapter 11.12) and 26 ($\text{R}^1 = (\text{substituted})\text{acetamide}$). In addition, they are prepared directly from H_4dota or their tris(esters) **191** by amide bond formation employing methods for peptide synthesis (Scheme 27). Solid-phase peptide synthesis (SPPS) has been increasingly used for preparation of the oligopeptide derivatives. In some cases, the other reactive group in the pendant amide side chain is used for further reaction to conjugate ligand to other molecules.

Table 5 Selected derivatives of DO3A synthesized according to **Scheme 25** to give **189**

<i>Cyclen form</i>	<i>Reagent</i>	<i>R</i> ¹	<i>X</i>	<i>R</i> ²	<i>References</i>
1	BrCH ₂ CO ₂ Bn	CH ₂ CO ₂ Bn	Br	Bu ^t	1999CEJ1974 ^a
1	BrCH ₂ CO ₂ Bn	CH ₂ CO ₂ Bn	Br	Me	2006BCC1105 ^b
1	BrCH ₂ CO ₂ <i>t</i> -Bu	CH ₂ CO ₂ <i>t</i> -Bu	Br	Bn	2001BCC1081 ^c
1	BrCH ₂ CO ₂ Et	CH ₂ CO ₂ Et	Br	Bu ^t	2004CEJ5804 ^d
1	BrCH(Ph- <i>p</i> -NO ₂)CO ₂ H	CH(Ph- <i>p</i> -NO ₂)CO ₂ H	Br	Na ⁺	1996IC2726
1	BrCH[(CH ₂) _{<i>n</i>} CH ₃]CO ₂ <i>t</i> -Bu (<i>n</i> = 9, 11, 13)	CH[(CH ₂) _{<i>n</i>} CH ₃]CO ₂ <i>t</i> -Bu (<i>n</i> = 9, 11, 13)	Br	Bu ^t	2002JIS757 ^e
1	BrCH ₂ Ph- <i>p</i> -CO ₂ H	CH ₂ Ph- <i>p</i> -CO ₂ H	Br	Na ⁺	2005CEJ5531
1	2-(BrCH ₂)-4-NO ₂ -phenol	2-CH ₂ -phenol-4-NO ₂	Br	K ⁺	2004JA9248
1	4,4-Me ₂ -2,6,8-trioxabicyclo[5.1.0]octane	CH(CH ₂ OH)CH(OH)CH ₂ OH	Cl	Na ⁺	1996SC1595
1	Ac ₂ -tartaric acid anhydride	CH ₂ [CH(OH)] ₂ CH ₂ OH	Cl	Na ⁺	1996SC1595
1	Bromosuccinic acid bis(CHPh ₂) ester	CH(R ³)CH ₂ (R ³) (R ³ = CO ₂ CHPh ₂)	Br	Bu ^t	1999JIS341
1	6-TsO-β-CD	6-β-CD	Cl	Na ⁺	1997JP13157, 2001AJC535
1	ClCH ₂ C(O)-(NO ₄ -crown-15)	CH ₂ CH ₂ -(NO ₄ -crown-15)	Br	Bu ^t	2004TL6055 ^e
1	BrCH ₂ CH ₂ NHBOC	CH ₂ CH ₂ NHBOC	Br	Me	2006NMB773 ^f
49a	C _{2-6,8,10,12,14,16,18} <i>n</i> -alkyl iodide	C _{2-6,8,10,12,14,16,18} <i>n</i> -alkyl	Cl	Na ⁺	1999JOC2683
163	BrCH ₂ CH ₂ OMe	CH ₂ CH ₂ OMe	Cl	Na ⁺	1996AGE655, 2000ICA226
190	4,4-Me ₂ -2,6,8-trioxabicyclo[5.1.0]octane	Acetonide protected CH(CH ₂ OH)CH(OH)CH ₂ OH	Cl	K ⁺	1996ICA191, 1997IC6086
190	Oxirane	CH ₂ CH(OH)R ³ (R ³ = C _{2,6,10,14} <i>n</i> -alkyl)	Br	Bu ^t	2000JP21047 ^e

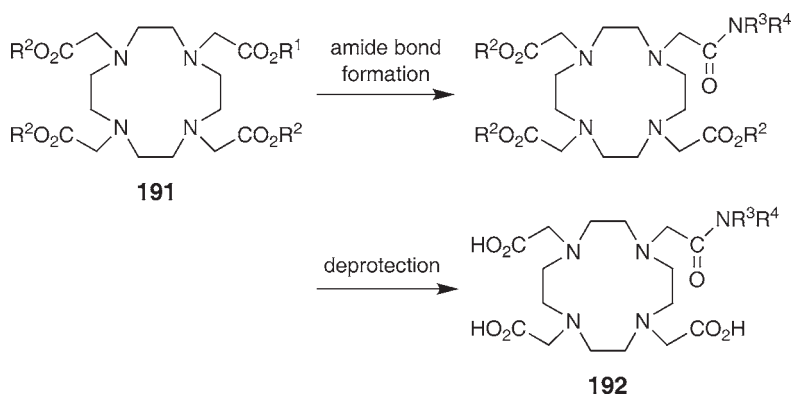
^aTris(Bu^t) ester for peptide synthesis.^bIsolated as triMe ester and used for coupling with oligonucleotides.^cTris(Bn) ester of H₄dota.^dIsolated as tris(Bu^t)mono(Et) ester.^eFully deprotected to zwitterionic form.^fFully deprotected to free NH₂.**Scheme 26**

In principle, the same synthetic strategies as given for derivatives of DO3A in **Schemes 25 and 26** can be applied for tris(amides) of DO3A according to formula **193**.

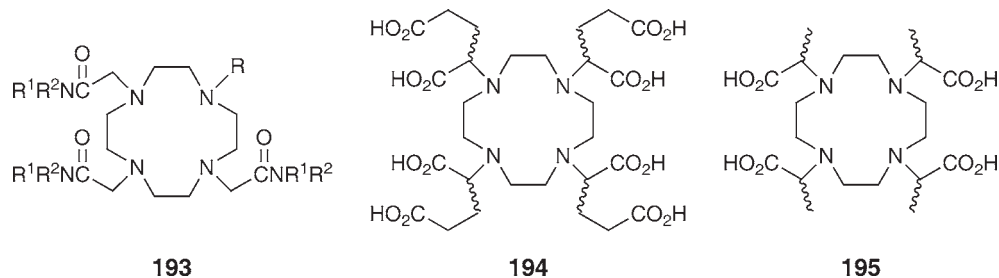
In the last relevant group of compounds are derivatives substituted on all nitrogen atoms by the same, mainly alkyl, groups. Alkylation reagents are often very active (e.g., allyl, benzyl, α-carboxyl, etc.). From synthetic point of view, modification of all four nitrogen atoms is done mostly by alkylation in presence of large excess of a strong base. As no special aspects occur in such syntheses, these derivatives are omitted from this chapter, with a few exceptions. There is a small class of tetrasubstituted cyclens where another substituent is placed on the carbon of the pendant arms. Examples are DOTA-like compounds **194** <2000JA9781> and **195** <2003OBC1707>. All possible diastereoisomers of the ligand

Table 6 Selected derivatives of DO3A synthesized according to [Scheme 26](#) to give [189](#)

R^2	Reagent	R^1	References
Et	$\text{BrCH}_2\text{Ph-}p\text{-NO}_2$	$\text{CH}_2\text{Ph-}p\text{-NO}_2$ ($\text{CH}_2\text{Ph-}p\text{-NH}_2$ after reduction)	1996TL7515, 2003JA10526
Bu ^t	Diethyl squarate	Ethyl squarate amide	1999BCC192 ^a
Bu ^t	2-(ClCH ₂)py-4-R ³ ($R^3 = \text{H}$, <i>N</i> -morpholine)	2-CH ₂ py-4-R ³ ($R^3 = \text{H}$, <i>N</i> -morpholine)	1999NJC669
Bu ^t	Aziridine- <i>N</i> -SO ₂ -Ph- <i>p</i> -R ³ ($R^3 = \text{CF}_3$, Me, OMe)	CH ₂ CH ₂ NH-SO ₂ -Ph- <i>p</i> -R ³ ($R^3 = \text{CF}_3$, Me, OMe)	2000CC707, 2001JA7601
H	Oxirane-R ³ ($R^3 = \text{Et}$, <i>n</i> -C ₆ H ₁₃)	CH ₂ CH(OH)-R ³ ($R^3 = \text{Et}$, <i>n</i> -C ₆ H ₁₃)	2000JP21047
Bu ^t	10-[I-(CH ₂) ₅]-9(10 <i>H</i>)-acridone derivatives	[10-(CH ₂) ₅]-9(10 <i>H</i>)-acridone derivatives	2000JP22359, 2002JP2348
Bu ^t	$\text{BrCH}_2\text{Ph-}p\text{-Br}$ or $\text{ClCH}_2\text{Ph-}p\text{-C(O)NHR}^3$ ($R^3 = \text{Ph-}p\text{-CH}_2\text{PO}_3\text{Et}_2$)	$\text{CH}_2\text{Ph-}p\text{-Br}$ or $\text{CH}_2\text{Ph-}p\text{-C(O)NHR}^3$ ($R^3 = \text{Ph-}p\text{-CH}_2\text{PO}_3\text{Et}_2$)	2000JIS488
Et	$\text{BrCH}_2\text{CH}_2\text{NPh}$	$\text{CH}_2\text{CH}_2\text{NPh}$ ($\text{CH}_2\text{CH}_2\text{NH}_2$ after Ph removal)	2001NJC336
Bu ^t	$\text{BrCH}_2\text{CH}_2\text{NHBoc}$	$\text{CH}_2\text{CH}_2\text{NH}_2$; conjugated to biotin or fluorescamine	2006BCC773, 2005JA12847
H	$\text{BrCH}_2\text{CH}_2\text{CO}_2\text{H}$	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	2001IC4310
Bu ^t	$\text{BrCH}_2\text{CH}_2\text{CO}_2t\text{-Bu}$	$\text{CH}_2\text{CH}_2\text{CO}_2t\text{-Bu}$	2005DT2713 ^a
Bu ^t	$\text{BrCH}_2\text{C(O)Ph-}p\text{-R}^3$ ($R^3 = \text{H}$, OMe, NMe ₂)	$\text{CH}_2\text{C(O)Ph-}p\text{-R}^3$ ($R^3 = \text{H}$, OMe, NMe ₂)	2002JCD48
Bu ^t	2-(ClCH ₂)phenanthroline	2-CH ₂ phenanthroline	2002IC2777
Bu ^t	2,6-(ClCH ₂) ₂ -5-Me-phenol	2,6-[(Bu ^t ₃ do3a)CH ₂] ₂ -5-Me-phenol	2003CC1550 ^b
Bu ^t	1,4-(BrCH ₂) ₂ benzene	(Bu ^t ₃ do3a) ₂ - <i>p</i> -xylylene	2003DT3780 ^c
Bu ^t	$\text{Br(CH}_2)_n\text{NHCO(pyridin-2-yl)}$; $n = 2, 3$	$(\text{CH}_2)_n\text{NHCO(pyridin-2-yl)}$; $n = 2, 3$	2004DT1441
Bu ^t	ClCH ₂ -pyridine <i>N</i> -oxide	CH ₂ -pyridine <i>N</i> -oxide	2004CC2602
Bu ^t	ClCH ₂ tetraazatriphenylene derivative	CH ₂ tetraazatriphenylene derivative	2005OBC1013
Bu ^t	ClCH ₂ -Ph- <i>p</i> -CO ₂ Et	CH ₂ -Ph- <i>p</i> -CO ₂ Et	2005CC259 ^a
DOTA ^d	F, Cl or NO ₂ substituted phenols	$\text{CH}_2\text{CO}_2\text{R}^3$ ($R^3 = \text{F}$, Cl or NO ₂ substituted benzenes)	2005BCC237 ^c
Bu ^t	$\text{BrCH}_2\text{C(O)Ph-}p\text{-O(CH}_2)_3\text{OBz}$	$\text{CH}_2\text{C(O)Ph-}p\text{-O(CH}_2)_3\text{OH}$	2006JMAC741
Bu ^t	$\text{ClCH}_2\text{C(O)NH-Ph-}p\text{-(N}_2\text{O}_{3,4}\text{-crown-Ph)}$	$\text{CH}_2\text{C(O)NH-Ph-}p\text{-(N}_2\text{O}_{3,4}\text{-crown-Ph)}$	2005DT3204

^aFully deesterified.^bBis(H₃do3a) bridged by 2,6-(CH₂)₂-5-Me-phenol.^cBis(H₃do3a) bridged by *p*-xylylene.^dDOTA used as starting material.^eDOTA active esters as the products.**Scheme 27**

194 were separated <2000JA9781>. If the side-chain carboxylates of **194** are coupled with hydrophilic dendrimer-like substituents, this strategy leads to very efficient MRI contrast agents <2001MMR121, 2005CC474, 2006CC1064>.



14.11.6.2.4 Phosphorus acid pendant arm derivatives

Synthesis of phosphorus acid derivatives is mostly different from those used for ‘normal’ organic substituents and, therefore, will be treated separately. Phosphorus acid derivatives are mostly prepared by the Mannich reaction between the amine, formaldehyde, and phosphorus components. The phosphorus component is H_3PO_3 , $\text{HP}(\text{O})(\text{OR})_2$, or $\text{P}(\text{OR})_3$ for phosphonic acids and H_3PO_2 , $\text{R}'\text{-PO}_2\text{H}_2$, $\text{R}'\text{-P}(\text{O})(\text{OR})(\text{H})$, or $\text{R}'\text{-P}(\text{OR})_2$ for phosphinic acids. Generally, the Mannich reaction mostly gives only moderate yields and products are hard to purify; the main impurities are N-methylated and/or phosphorus acid condensation products. With phosphorus acids, the reaction is usually run in strongly acidic solutions (azeotropic HCl) to reduce extent of N-methylation. Typically, the reaction needs elevated temperature to proceed. Phosphorus esters are used in organic solvents such as THF, CHCl_3 , and toluene, or without solvents; for phosphonates, triethyl phosphite is the reagent of choice. If an alkylation approach is chosen, the most reactive triflates should be used <2004MI194>. Generally, phosphorus acid esters are more difficult to hydrolyze than corresponding carboxylate esters; alkaline hydrolysis of phosphonate diesters leads to phosphonate monoesters.

Macrocyclic ligands with four phosphonate (starting from H_3PO_3 <2001NMB709> or from $\text{P}(\text{OEt})_3$ <2003JIC217>), phosphonate monoester (e.g., trifluoroethyl <1997IC4128> and butyl <2001EJI813>), or phosphinate pendant arms (e.g., hydrogen <1995JCD1133>, phenyl <2000EJI195>, and benzyl <1997JCD3623>) were synthesized. Similar to Scheme 25, tris(phosphorus acid) derivatives were obtained, with phosphonate <2001IC6572, 2003JIC217>, butyl phosphonate monoester <2001MI239>, methylphosphinate <1995JCD2259, 1998JP22129, 2001JA12866, 1998JCD881> or phenylphosphinate <2000JCD141> moieties.

Syntheses of other, differently substituted, ligands containing phosphorus acids in pendant(s) arm(s) were published. ‘trans’-Cyclen derivatives containing two acetate pendants and two $-\text{CH}_2\text{P}(\text{O})(\text{OEt})(\text{OH})$ or $-\text{CH}_2\text{P}(\text{O})(\text{Et})(\text{OH})$ groups were produced by the Mannich reaction <1997IC1495> as well as ‘trans’ $\text{Me}_2\text{R}_2\text{cyclen}$, where R is $-\text{CH}_2\text{P}(\text{O})(\text{OEt})(\text{OH})$ <2003OBC879> or $-\text{CH}_2\text{P}(\text{O})(\text{OH})_2$ <2005EJI2027>. DO3A was used as a macrocyclic reagent for the synthesis of derivatives having three acetate and one phosphorus acid pendant arms. The Mannich reaction with $\text{HP}(\text{O})(\text{OEt})_2$ produced phosphonic acid derivative <2005CEJ2373>, and reactions with 4- $\text{NO}_2\text{PhCH}_2\text{PO}_2\text{H}_2$ <2005OBC112> or PhPO_2H_2 <2006CCC264> afforded phosphinic acid ligands with *p*-nitrobenzyl or phenyl side chains. The nitro derivative was reduced to amino derivative to get a bifunctional ligand <2005OBC112>. Ditopic derivative $[\text{DO3A-CH}_2\text{P}(\text{O})(\text{OH})\text{CH}_2\text{Ph-4-NH}]_2\text{C}=\text{S}$ was prepared from the above aminobenzyl derivative through its isocyanate $\text{DO3A-CH}_2\text{P}(\text{O})(\text{OH})\text{CH}_2\text{Ph-4-N}=\text{C}=\text{S}$ <2006DT2323>. A series of ‘trans’ (1,7-)bis(methylphosphonic acids) having one position substituted with 7-fluoro-isoquinoline-3- CH_2- group and the last one with another methylphosphonic acid or with acetic groups were prepared <2001TL3823, 2002OL1075, 2004BCC1488, 2005TL4707>. The acetate pendant arm was used for conjugation of the ligand to biologically active molecules.

Disubstituted cyclen phosphonic acid and its ester, cyclen-1,7- $(\text{CH}_2\text{PO}_3\text{H}_2)_2$ and $-\text{[CH}_2\text{P}(\text{O})(\text{OEt})(\text{OH})]_2$, were obtained from ‘trans’-cyclen carbamates <1995CC185, 1998IC69>. Conditions for removal of protecting groups from esters of 1,7-Cbz₂cyclen-4,10- $(\text{CH}_2\text{PO}_3\text{H}_2)_2$ have been reported in <2003SC457>. Synthesis of acetylsalicylamide of cyclen modified in 4,10-position with $-\text{CH}_2\text{P}(\text{O})(\text{OEt})_2$ groups was published <2004MI21>. ‘trans’-Derivatives $\text{R}^1\text{R}^2\text{-cyclam-}(\text{CH}_2\text{PO}_3\text{H}_2)_2$, where R^1 and R^2 are H, Me, or CH_2Ph <2000CCC1289>, were obtained from dibenzylcyclam **159**, or its methyl or benzyl-methyl analogs, respectively. Similarly, ‘cis’ 1,4-bis(methylphosphonic acid)cyclam was prepared from dibenzylcyclam **171** or using phenylthiophosphonyl **170** protection <2006CCC337>. In the last case, cyclam-*N,N',N''*-tris(methylphosphonic acid) was obtained as a by-product. The Mannich reaction of Tfa₃cyclam **153c** with formaldehyde and $\text{P}(\text{OEt})_3$ and hydrolysis produced cyclam having one

methylphosphonic acid pendant arm <2005DT2908>. Hexacyclen **25** was fully methylphosphonated by Mannich reaction of the amine, CH₂O, and H₃PO₃ <1999JP21973>.

14.11.6.3 Synthesis of Polycycles from Macrocyclic Precursors

Bis(cyclens) **196** are a rather diverse family of compounds. Some examples of them are listed in Table 7.

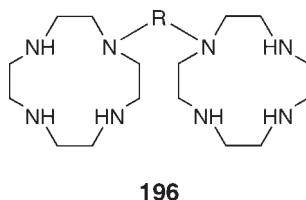
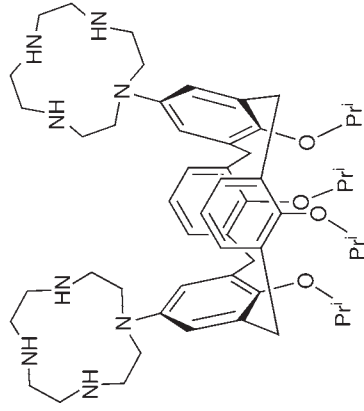


Table 7 Synthesis of bis(cyclens) **196**

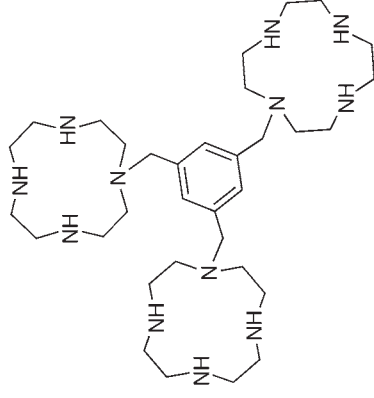
Precursor	Reagent	Product 196	References
1	<i>p</i> -(BrCH ₂) ₂ Ph	<i>p</i> -Xylylene-(cyclen) ₂	1996CEJ617
1	<i>m</i> -(BrCH ₂) ₂ Ph	<i>m</i> -Xylylene-(cyclen) ₂	1996H(42)775
8a	<i>p</i> -(BrCH ₂) ₂ Ph	<i>p</i> -Xylylene-(cyclen) ₂	1998SC2903
49a	<i>m</i> -(BrCH ₂) ₂ Ph or <i>p</i> -(BrCH ₂) ₂ Ph	<i>m</i> -, <i>p</i> -Xylylene-(cyclen) ₂	2001NJC1168
49a , 129	Br(CH ₂) _{<i>n</i>} Br; <i>n</i> = 3, 4, 5	Cyclen-(CH ₂) _{<i>n</i>} -cyclen; <i>n</i> = 3, 4, 5	2001NJC1168
49a	2,5-(BrCH ₂)pyridine	2,5-(Cyclen-CH ₂)pyridine	2005EJI2658
49a	2,5-(BrCH ₂) ₂ thiophene	2,5-(CyclenCH ₂) ₂ -thiophene	2001NJC1168
156a	1,2-[ClC(O)] ₂ Ph, <i>m</i> - or <i>p</i> -(BrCH ₂) ₂ Ph	<i>o</i> -, <i>m</i> -, <i>p</i> -Xylylene-(cyclen) ₂	1996BSF65
156a	2,6-(BrCH ₂) ₂ -pyridine, 2,6-(BrCH ₂) ₂ -phenols, 2,9-(BrCH ₂) ₂ -phenanthroline, Br(CH ₂) ₃ Br, chlorohydrine	Cyclens bridged by 2,6-(CH ₂) ₂ -pyridine, 2,6-(CH ₂) ₂ -phenols, 2,9-(CH ₂) ₂ -phenanthroline, (CH ₂) ₃ , or CH ₂ CH(OH)CH ₂	2005JIB1661
156a, b	1,3-(OCN) ₂ Ph-4-Me	1,3-[Cyclen-C(O)NH] ₂ Ph-4-Me	2001EJO1943
156b	OCN(CH ₂) ₆ CNO	Cyclen-C(O)NH(CH ₂) ₆ NHC(O)-cyclen	2001EJO1943
156d	<i>m</i> -, <i>p</i> -(BrCH ₂) ₂ Ph	<i>m</i> -, <i>p</i> -Xylylene-(cyclen) ₂	2000TL6527
168	<i>p</i> -(BrCH ₂) ₂ Ph	<i>p</i> -Xylylene-(cyclen) ₂	2001T2385
168	1,2-[ClC(O)] ₂ Ph	1,2-[Cyclen-C(O)] ₂ Ph	2001T2385
Ts31	4,5-bis(BrCH ₂) ₂ Ph-1,2-Br ₂	4,5-(Cyclen-CH ₂) ₂ Ph-1,2-Br ₂	1995JCM16, 1995JRM301 ^a

^aUsed for synthesis of Cu-phthalocyanine-(cyclen)₈.

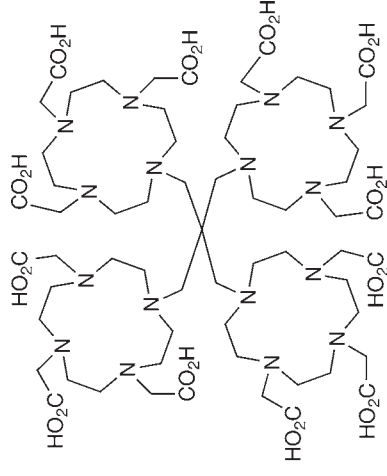
There are some other polycyclic derivatives of cyclen. A series of calix[4]arenes substituted with one or two cyclen ring(s) was prepared starting from BOC₃cyclen **156a** and appropriately substituted calix[4]arenes (5- or 5,17-position) in *cone* or *1,3-alternate* conformations: directly bound to the arene (e.g., **197**) (25–65% yield in the amine–arene coupling step) <2006T5748> or bound through methylene spacer (22–40% in the alkylation step) <2004OL241>. A protected tris(cyclen) was synthesized using BOC₃cyclen **156a** and 1,3,5-tris(bromomethyl)benzene in 85% yield and it was hydrolyzed to amine **198** (88%) <1997JA3068>. The same compound can be obtained from triformylcyclen **156d** <2000TL6527>. Kimura and co-workers also prepared linear tris(cyclen): cyclen-(*p*-xylylene)-cyclen-(*p*-xylylene)-cyclen <2001JA7911>. Reaction of tetrabromide C(CH₂Br)₄ with triethyl ester of DO3A **183** followed by ester hydrolysis led to tetratopic DO3A derivative **199** in a relatively high yield (28% over two steps) <2005IC9434>. Alkylation of *p*- or *m*-xylylene-linked cyclen units with ethyl bromoacetate led to the corresponding bis(DO3A) derivatives **200** <2006CEJ6841>. Quarternization of glyoxal aminal **49a** with Br(CH₂)_{*n*}NPh₂ (*n* = 2, 3, 4) produced the monosalts, which were further reacted with 1,4-(BrCH₂)₂benzene, and, after deprotection, bis(cyclens) **201** appended with aminoalkyl arms were obtained <2001NJC1168, 2005EJO2044>. Oligopeptides having 2–4 cyclen units were immobilized on polystyrene and their copper(II) complexes were used as artificial proteases <2003JA14580>.



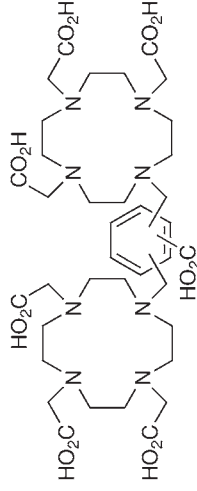
197



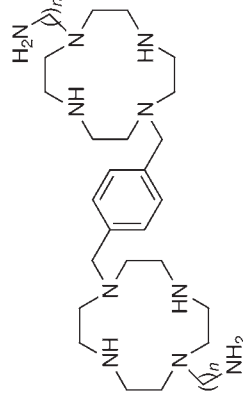
198



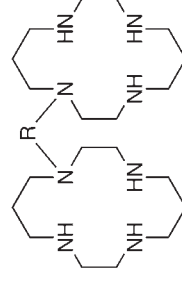
199



1,3-200a
1,4-200b
1-CO₂H, 3,5-200c



201a: $n=2$
201b: $n=3$
201c: $n=4$



202

117: R = *p*-xylylene

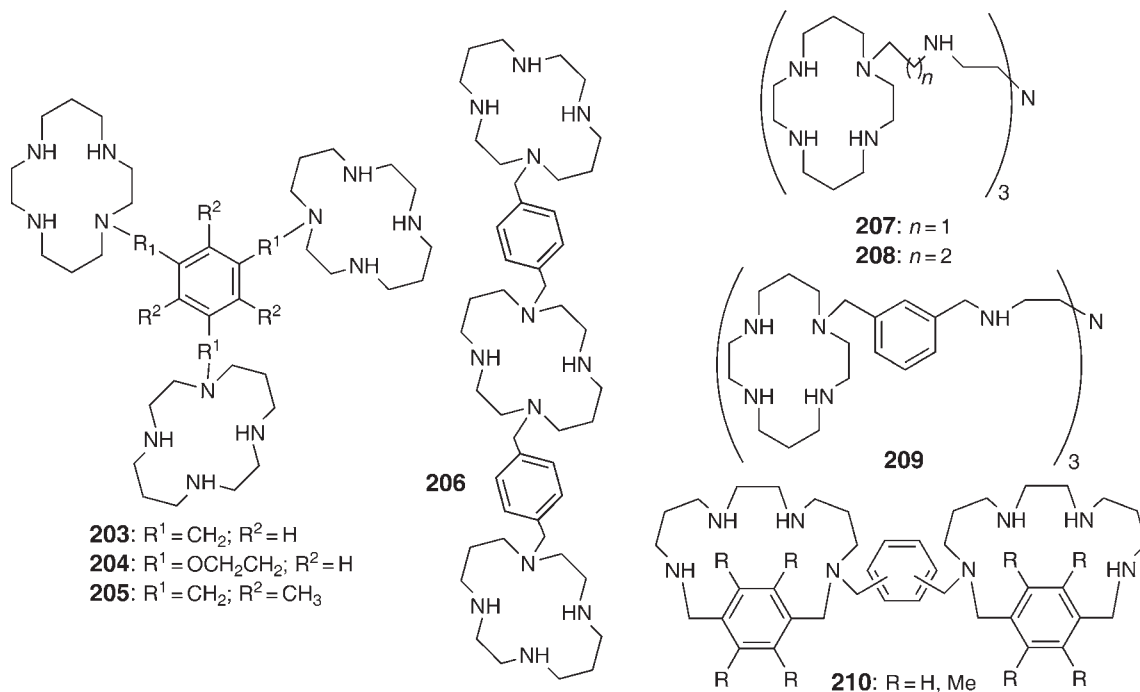
Among bis(cyclams), the most important derivative has *p*-xylylene bridge between two cyclam units (**117**, AMD-3100). This compound inhibits replication of HIV-1 and HIV-2 and numerous of its analogs **202** have been synthesized. Orthogonal tosyl-diethoxyphosphoryl protection of nitrogen atoms in a number of tetraaza rings was employed to get libraries of azacycles of different sizes connected by a number of linkers (mostly aromatic or heterocyclic) <1995JMC366, 1996JME109>. Other ways of synthesis of **117** and bis(cyclams) **202** are listed in Table 8.

Table 8 Synthesis of bis(cyclams) **202**

Precursor	Reagent	Product 202	Reference
2	$(\text{CH}_2)_n(\text{NHC}(\text{O})\text{CH}=\text{CH}_2)_2$; $n = 1, 2, 6$	$(\text{CH}_2)_n(\text{NHC}(\text{O})\text{CH}_2\text{CH}_2\text{-cyclam})_2$; $n = 1, 2, 6$	1999TL287
2	1,8-Cl ₂ -anthracene	Anthracene-1,8-(cyclam) ₂	2002TL1193
62	<i>p</i> -(BrCH ₂) ₂ Ph	<i>p</i> -Xylylene-(cyclam) ₂	2003JOC6435
129, 49a	Br(CH ₂) _{<i>n</i>} Br; $n = 3, 4, 5$	Cyclen-(CH ₂) _{<i>n</i>} -cyclen; $n = 3, 4, 5$	2001NJC1168
129	<i>m</i> -(BrCH ₂) ₂ Ph or <i>p</i> -(BrCH ₂) ₂ Ph	<i>m</i> -, <i>p</i> -Xylylene-(cyclam) ₂	2001NJC1168
129	2,5-(BrCH ₂) ₂ thiophene	2,5-(Cyclam-CH ₂) ₂ -thiophene	2001NJC1168
129	2,5-(BrCH ₂)pyridine	2,5-(Cyclen-CH ₂)pyridine	2005EJ12658
153a	1,2-[ClC(O)] ₂ Ph, <i>m</i> - or <i>p</i> -(BrCH ₂) ₂ Ph	<i>o</i> -, <i>m</i> -, <i>p</i> -Xylylene-(cyclam) ₂	1996BSF65
153a	1,8-(ClC(O)) ₂ anthracene	Anthracene-1,8-(CH ₂ -cyclam) ₂	1996BSF65
153c	<i>p</i> -(BrCH ₂) ₂ Ph	<i>p</i> -Xylylene-(cyclam) ₂	2003TL2481
167a	<i>o</i> -, <i>m</i> -, <i>p</i> -(BrCH ₂) ₂ Ph	<i>o</i> -, <i>m</i> -, <i>p</i> -Xylylene-(cyclam) ₂	1996TL7711
169	<i>trans</i> -ClCH=CHCl	<i>trans</i> -(Cyclam)CH=CH(cyclam)	1996TL7711
174	<i>m</i> -, <i>p</i> -(BrCH ₂) ₂ Ph	<i>m</i> -, <i>p</i> -Xylylene-(1,8-Ts ₂ cyclam) ₂	1998IC1575

A small library of aryl- and alkyl-linked cyclams, which were further substituted in different positions with $-(\text{CH}_2)_4\text{CO}_2\text{H}$ pendant arms, was synthesized to get AZT-bis(cyclams) conjugates (AZT = azidothymidine) <1998TL853, 1999JME229>.

Several tritopic cyclam derivatives were obtained. Starting from di- and tri-BOC-protected cyclams **154** or **153a** and combining alkylation, reduction, and deprotection steps, triangular **203** and **204** or linear **206** were synthesized <2001AJC291>. Tris(trifluoroacetamide) **153c** was used as a protected precursor in preparation of polycycle **205** <2005OL2603>. Other examples are tren-based ligands **207**, **208** <2004DT2115> and **209** <2005DT2138>. Two cyclophane units were linked through xylylene spacers to give ditopic macrocycles **210** with protection of ethylenediamine nitrogen atoms by zinc(II) coordination <1998CC1823>.

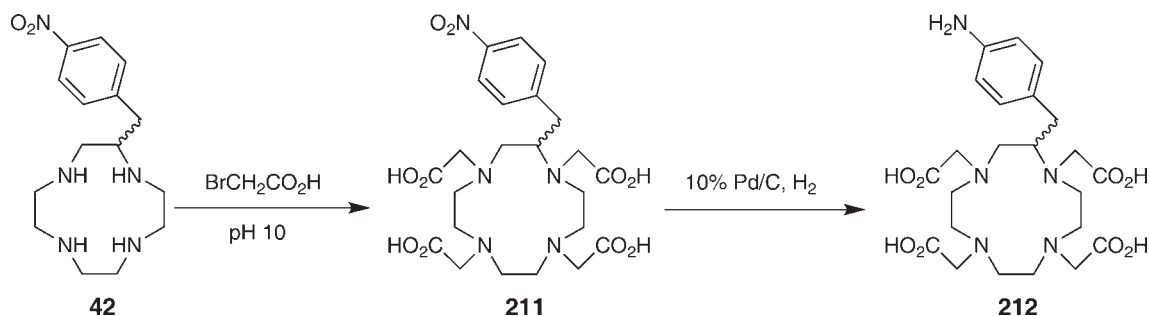


Syntheses of polycycles consisting from tetraazacycles of different sizes and/or larger than 14-membered ones were published <1996BSF65, 1996TL7711, 2001NJC1168>. Four cyclam units were connected together with *m*-xylylene linkers in a [4+4] cyclization reaction of amina **129** with 1,3-bis(bromomethyl)benzene (yield 20%) to form, after removal of the glyoxal bridges, a tetratopic extra large ‘macrocycle’ <2004NJC173>.

14.11.6.4 C-Functionalized Derivatives

In this section, reactivity of cycles with at least one substituent on the ring carbon atoms will be covered. As in Sections 14.11.6.1–14.11.6.3, the reactivity in this class of compounds is again connected with substitutions on nitrogen atoms (to the best of our knowledge, there is no report on direct reactivity of ring carbon atoms). Therefore, ring C-substituted macrocycles are available only through ring-closure reactions as described in Section 14.11.5. An interest in modification of carbon atoms of the large cycles comes from the search for bifunctional ligands and/or ligands showing higher stereochemical rigidity after complexation with metal ions.

Bifunctional DOTA analog **212** occupies a prominent position among these C-substituted macrocycles. It is by far the most commonly used bifunctional ligand (except DOTA-monoamides) in the form of its --N=C=S or $\text{--C(O)CH}_2\text{Br}$ derivatives. This ligand was obtained in an improved overall yield (Scheme 28) taking into account the synthesis of amine **42** <1996NJC585>; Scheme 28 illustrates how such aminobenzyl bifunctional ligands having pendant arms are prepared from the nitrobenzyl derivatives (e.g., **211**) which themselves are obtained from nitrobenzyl macrocycles (**42** in Scheme 28).



Scheme 28

Ligand **211** was also prepared by alkylation with *t*-butyl bromoacetate and hydrolysis <2004IC2845>. Attempts to synthesize pure diastereoisomers of ligand **213** (e.g., *S*-SSSS) with four 1-propionate arms using optically pure $\text{TFOCH}^+(\text{Me})\text{CO}_2\text{Me}$ gave only low yields of the optically pure target products as pendant in position 1 (the closest position to the substituted carbons) was racemized <2005DT3829>.

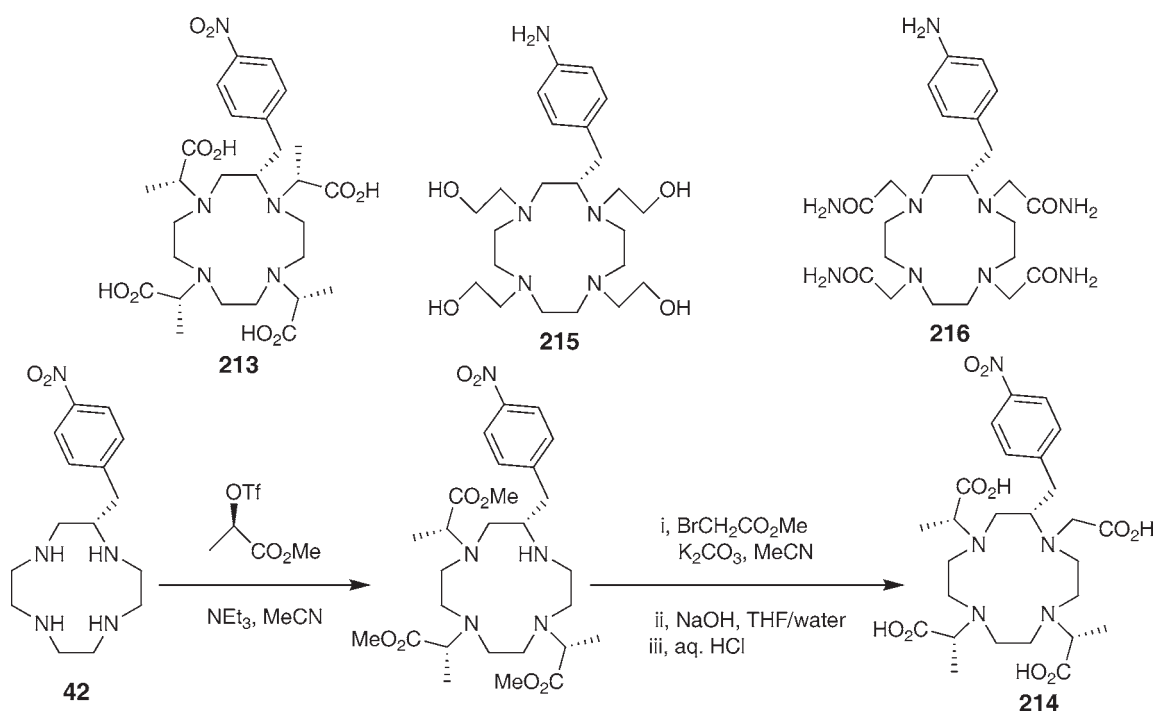
The reason for such behavior can be a steric crowding induced by the bulky nitrobenzyl group. To get pure, but still similar, diastereoisomers, tripropionate ligands were synthesized first and they were reacted with bromoacetate to give tripropionate–monoacetate derivative **214** (Scheme 29) <2005DT3829>. A strategy analogous to Scheme 28 but employing ethylene oxide led to tetraethylhydroxylated derivative **215**, which was used (as --N=C=S derivative) for labeling of oligonucleotides <2000JIS85>. An analog of DOTA-tetraamide **216** was prepared as a ligand suitable for complexation of lead isotopes <2000NMB93>. A series of aryl-substituted DOTA analogs **217** (aryl = Ph, 4- NO_2 -Ph, 3- NO_2 -Ph, 3-CN-Ph, or 4- Bn_2N -Ph) was also obtained but was shown to be unsuitable for complexation of lanthanide(III) ions <1998NJC1359>. Hydrophilic DOTA analogs with two or four **218** hydroxomethyl substituents were synthesized in order to get complexes with an altered pharmacokinetic properties <2001ICA218>.

(2*S*,5*S*,8*S*,11*S*)-2,5,8,11-Me₄cyclen was substituted with four acetic, four (*R*)-2-propionic **219**, or three acetic pendant arms to get very rigid ligands <2002IC6846>.

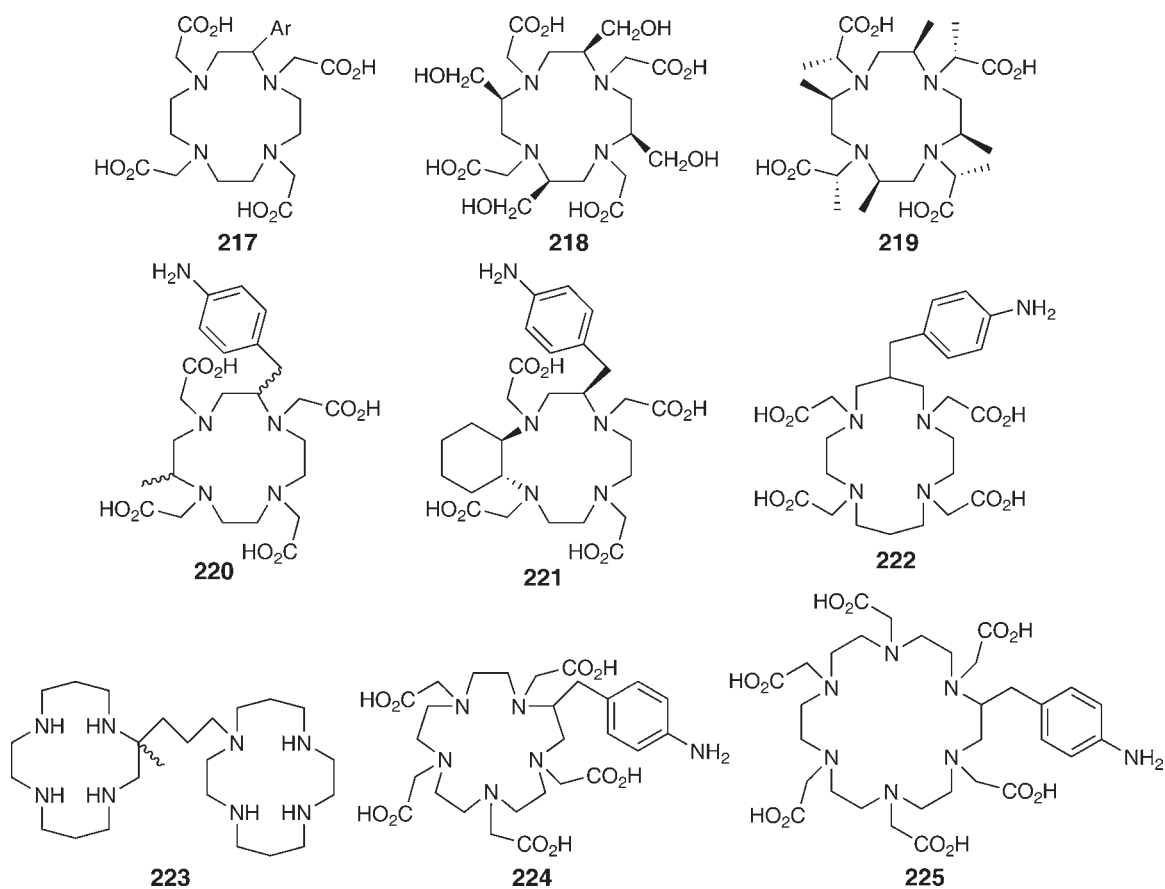
Brechbiel *et al.* prepared **220** and **221** containing methyl or cyclohexyl substituents as bifunctional rigid ligands for radiopharmaceuticals <2003NMB581>.

In the cyclam series, the most common bifunctional ligand is TETA analog **222** <1995BCC296, 1997S1010>. Compound **223** was prepared as an analog of antiviral agent **117** <1996JOC1519>.

Larger azarings are ligands more suitable for larger metal ions. Therefore, bifunctional ligands **224** <2001NMB409> and **225** <2000BCC510, 2000TL7207> were prepared as the potential ligands for complexation of actinium isotopes.



Scheme 29



14.11.7 Syntheses of Particular Classes of Compounds and Critical Comparison of Various Routes Available

Mono- and diazamacrocycles can be conveniently prepared by a catalyzed ($[\text{Cl}_2(\text{PCy}_3)_2\text{Ru}(=\text{CHPh})]$) RCM from bis(olefinic) precursors. The reaction is very general and affords monounsaturated macrocycles in reasonable yields. Furthermore, lactam formations by closure of amino-carboxyl derivatives or by Beckmann rearrangement are also methods of the choice; however, in the first case, the yields are in general low since polymers are usually produced, as the main product.

Method of choice for synthesis of 1,5,9-triazacyclododecane **7** and some of its C-substituted derivatives is a ring closure on a guanidine derivative (Scheme 7). The method mostly gives reasonable yields and cyclic aminal can serve as a protective group.

A big improvement has been made in synthesis of cyclen. For a long time, the amine has been available mostly through classical so-called 'tosylamide' synthesis <1974JA2268>. The method is 'atom noneffective', as most of molecular mass disappears by removal of the sulfonate group. Furthermore, harsh deprotection conditions can interfere with numerous functional groups. The method is time consuming when the protection-deprotection strategy is used.

A breakthrough in cyclen synthesis is the so-called 'carbon template' method. It uses several kinds of carbon bridges to arrange nitrogen atoms into a position suitable for cyclization. The method can be scaled up to industrial levels. For laboratory conditions, syntheses employing dithiooxamide <2001OS73> or butan-2,3-dione <1998TL6861> are suitable as well as the procedure with glyoxal and ethylenediamine <2000SC15>. In addition, cyclen has become commercially available at a reasonable price. If C-substituted cyclen derivatives are desired, the 'crab-like' synthesis with appropriately substituted linear precursors can be a reasonable choice. More complicated derivatives can be prepared by a peptide synthesis under 'high-dilution' conditions or by SPPS; however, the yields are rather low and additional reduction of amide bonds is necessary.

Cyclam is also available by the 'carbon template' method; however, a relatively expensive amine 2,3,2-tet should be used <1998TL6861, 2005JOC7042>. Therefore, a Ni(II) template method is still the most common route; the problematic isolation of a large amount of perchlorate salt of the cyclam-Ni(II) complex can be avoided without significant reduction of yield and purity <1995CJC685>. [2+2] reaction of ethylenediamine with methyl acrylate <2000JCD1873, 2001CEJ2848> can be, despite a very low yield, an interesting route as well as the more convenient sequence employing step-wise reaction of ethylenediamine with methyl acrylate and dimethyl malonate <2003JOC6435>. For C-substituted (on the propylene chain) cycles, reaction of malonyl diesters with 2,3,2-tet is the first choice (but affording rather low yields).

For larger cycles, tosylamide or high-dilution amide condensations were mostly used. In addition, cyclization of amines and aldehydes to get Schiff bases (mostly for [2+2] or [3+3] cyclizations) is convenient. Metal template synthesis is useful only in special cases. Polycycles are conveniently prepared from appropriately protected cycles.

Most of development has been done toward the synthesis of nonsymmetrically substituted cycles. For these purposes, (orthogonally) protected cycles are necessary. Benzyl monoprotected cyclen **141** and cyclam are readily prepared through aminal protection <2000TL1249, 2000CCC243, 2005JOC7042> or by direct reaction with an excess of the cycles <2002TL3217>. Other monoprotected derivatives were prepared from triprotected ones (Section 14.11.6.1). Aminal protection is also suitable for 'trans' dibenzyl-cyclen **127** and cyclam **159** <1998EJO1971, 2000TL1249, 2000CCC243>, which are easily transformed to, for example, 'trans' bis(carbamates). 1,7-Cbz₂cyclen **155** was conveniently obtained by Kovacs's method <1997S759>. Less possibilities are available for 'cis' substitutions. Except multistep transformations from differently protected cycles, 1,4-positions are protected only as oxalylamides **175** and **176** (which are hard to decompose later) <1999JP13499> or, for cyclam, as thiophosphoramidate **170** <2006CCC337> and, for cyclen, as 1,4-dibenzyl derivative **143** <2004T5595>. Among triprotected cycles, the most popular is tris(BOC)-cycles **153a** or **156a** as the reagents, which are compatible with peptide synthesis and similar strategies leading to a monosubstituted cycles (mainly cyclen). However, trifluoroacetamides **153c** and **156c** are prepared almost quantitatively and can be used in next step without purification <2003TL2481>.

To modify one nitrogen atom of the cycles, the first method is a simple reaction of an electrophile (e.g., halogen derivatives or oxiranes) with excess of the cycle. This strategy often gave good results, is simple to run, and the products can be separated due to differences in solubility and/or chromatographic behavior. However, this approach is not general and is suitable only for cheap substrates and, in other cases, the expensive macrocycle should be recycled. An alternative way is the utilization of triprotected cycles, the first choice is by tris(BOC) protection. Synthesis of disubstituted derivative has to rely on protected cycles; the only exception is 1,4-derivatives of cyclen <2003JOC2956, 2004T5595>. The simplest method to get trisubstituted cyclens is the reaction with 3 equiv of electrophile (yields are moderate). In the case of the most important Bu^t₃DO3A **184**, the target product can be easily

isolated in 50–70% yields in pure form as monohydrobromide salt <2002JP2348, 2004T5595>. For syntheses of DOTA derivatives, tris(*t*-butyl) ester of DOTA (having three ester groups and one free carboxylate group) is very important as an intermediate compatible with SPPS <1999CEJ1974>. In other cases, tribenzyl ester of DOTA can be used <2001BCC1081>.

General reaction conditions for modification of the cycles are given at beginning of Sections 14.11.6.2.1 and 14.11.6.2.3.

14.11.8 Important Compounds and Applications

A rich complexation chemistry of these compounds is given by a possibility of substitution(s) of the ring nitrogen atoms with pendant arm(s) bearing a range of coordinating groups (acetates, acetamides, phosphonates/phosphinates, alcohols/phenols, nitrogen heterocycles, etc.). Such substitution changes the solution structure and basicity of the ligands and, consequently, their selectivity for a particular metal ion. Complexes of these ligands exhibit different thermodynamic stabilities and kinetic properties (i.e., rate of complex formation and decomplexation). A number of other properties of the metal complexes may be tuned by N- and C-substitution on the rings. The field of anion recognition has been also highly exploited over last 10 years.

Medicine has shifted the interest to utilization of ‘bifunctional ligands’, which are able to conjugate biologically active compounds (e.g., (oligo)peptides, antibodies or their fragments, sugars, etc.). The conjugates selectively target receptor or tissue of interest delivering imaging and/or therapeutic metal ion (bound by the chelate) to a desired site in the body. The approach is the basis of the emerging field called molecular imaging (MI) and targeted therapy (TT). Metabolites or biologically important molecules may be also imaged by the molecular recognition approach.

14.11.8.1 Metal Complexation

Cyclen **1** with a 12-membered ring is not large enough to allow any metal ion to enter into a plane formed by four nitrogen atoms (at almost any time, all nitrogen atoms are coordinated). Therefore, in all complexes, the metal ion is located above the approximate plane. Cyclen forms relatively stable complexes with most metal ions. On the other hand, cyclam **2** is large enough to be an ideal ligand for octahedral metal ions. In the complexes, more isomeric arrangements are possible (for more details, see 1998CCR1313). With both tetraaza ligands, ML complexes are formed almost exclusively. Substitution of nitrogen atoms greatly alters the properties of the ligands and their complexes (see below).

Larger cycles having more nitrogen atoms can also form stable complexes. Because of the presence of more nitrogen atoms, they easily form dinuclear complexes. The two ions can be bridged by an external ligand(s) and it can be used for tuning of anion-sensing abilities and/or for molecular recognition as models for metal ion cooperativity, for example, in enzymes.

Coordinating pendant arms (acetates, propionates, methylphosphonates/phosphinates, carboxylic amides, alkyl/aryl alcohols, heterocycles as pyridine, imidazole, or 2,2'-bipyridine (Chapters 4.02, 7.02, and 7.03), alkyl/aryl amines) greatly alter the properties of the parent cycles (cyclen, cyclam). First, denticity (a number of available donor atoms of a ligand) of the macrocycle derivatives is increased. It commonly leads to different thermodynamic stability as overall basicity is also changed after the substitution. Stability is generally higher than for parent cycles for ligands with acetate and organophosphorus acid pendant arms. In some cases, kinetic inertness is often increased as well. Selectivity of metal complexation can be changed, for example, presence of neutral pendants as acetamides or hydroxoethyls can increase selectivity for Pb(II) or Cd(II) ions comparing with divalent metal ions of the first transition row.

A prototype ligand having pendant arms is DOTA **3**. It is an ideal ligand for metal ions requiring high coordination number as lanthanide(III) or Pb(II) ions. It has led to a range of applications (some details are given in sections further on). Complex formation is often rather slow as entering metal ions have to disrupt a stable structure of the ligand molecule (with intramolecular hydrogen bonds). In the mechanism, all pendant arms are quickly bound first and metal ion is transferred into the macrocyclic cavity in a rate-determining step <2004CEJ5218>. In octahedral complexes, two pendant arms are not coordinated <1998CCR1313>. Therefore, for octahedral metal ions, macrocycles having only two pendant arms can be more suitable. Similar consideration can be applied to TETA **4** and its derivatives.

Stability constants of complexes can be found in the commercial databases mentioned earlier, Gd(III) constants were reviewed <2000CCR309>, and constants for DOTA and TETA were critically evaluated <2005PAC1445>.

Chemistry of cyclam derivatives and their complexes was also comprehensively reviewed <2004CSR246>. Some additional information can be found below or in other papers <1998AIC75, 2001AIC293, 2001CCR287, B-2003MI1>.

14.11.8.2 Anion Complexation

Besides metal ions, polyazamacrocycles as well as their complexes can be ligands for a range of anions. Azacycles themselves are partially protonated in a wide range of pH and can serve as hydrogen bond donors (protonated amines) and/or acceptors (free amine groups) for a range of anions. In addition, metal ion in complexes where a ligand is not able to saturate all its coordination sites can serve as additional or new anion binding site. Similarly, as given above, combination of a number of donor atoms, ring size, and arrangement as well as choice of metal ion can lead to, in principle, endless possibilities for receptor design <B-1997MI, 2002JCD121, 2002MI129>. Dinuclear complexes can bind anions also as a bridging ligand between the metal centers.

Zinc complexes of cyclen and its derivatives are the examples of such successful design. In the complexes, zinc(II) ion is located above plane the formed by cyclen nitrogen atoms and the fifth (axial) position is available for coordination of another ligand, mostly anion. It was shown that these zinc(II) complexes are very selective for binding of dioximide anions as barbiturate or thymidine. It led to applications in DNA/RNA <2004CRV769> or flavonoids recognitions <2002JA12999>. The same family of complexes was shown to model esterase or phosphatase action due to coordination of carboxylate or phosphate ester to zinc(II) as Lewis-acidic center. Some other macrocyclic complexes can work as artificial metallonucleases <2004MI192>.

Other examples are lanthanide(III) complexes with heptadentate ligands (derivatives of DO3A) where two coordination sites are available for next ligand binding. The complexes were used for molecular recognition of some anions by means of NMR or luminescence spectroscopies <2002JA12697>.

14.11.8.3 Contrast Agents for MRI

MRI is a routine diagnostic tool in modern clinical medicine. MRI is noninvasive, has excellent spatial resolution, and is very suitable for soft tissues. The contrast can be further increased by application of a CA. The substances (mostly Gd(III) complexes) catalyze water proton relaxation. Investigations related with MRI have been probably the main driving force for developments covered in this chapter. In this field, a lot of review articles have appeared. Developments during the 1990s are reported by Caravan *et al.* <1999CRV2293> and in two books <B-2001MI, 2002TCC(221)>. In addition, very recently, a tutorial review nicely explaining meaning of parameters governing efficiency of gadolinium(III)-based CA and principles of designing of a new CA has been published <2006CSR512>. More recent achievements in the field can be found in reviews <2005AIC173, 2006CSR557, 2006CCR1562, 2005MI302>, and <2005MI2271>.

Some modern CAs are organ-specific as they are predominantly localized for a longer time in a specific organ (e.g., in blood stream for angiography). The next generation of CA should be able to response (non)physiological status of tissues as pH, temperature, enzymatic activity, metabolite presence, etc. Properties of such so-called 'smart CA' has been reviewed <2004MI519, 2002AJC551>. The new CA should also image a presence of receptors on cell surface to better delineate differences between health and diseased tissues traveling so into a field of MI. Possibilities and limitations for such utilization can be also found in the papers <2002MI394> and <2005MI143>. Due to an excellent spatial resolution, MRI can be used for tracking of cells in the body or image cell itself and its compartments (if micro-MRI is used) if they are labeled with MRI CA <2005MIM143, 2004MI509>.

Recently, development of a new kind of MRI CA has started. It is based on irradiation (decoupling) of protons that are in chemical exchange with protons of bulk water – chemical exchange saturation transfer (CEST) <2006MI109>. A better contrast of this kind can be achieved with complexes of paramagnetic lanthanide(III) ions (other than Gd(III)) with macrocyclic ligands (e.g., DOTA-tetraamides). The complexes are called PARACEST CAs <2006CSR500, 2006CCR1562>.

14.11.8.4 Radiopharmaceuticals

Nuclear medicine is another field employing macrocyclic ligands for binding of harmful metal radioisotopes. As in the previous case, the dangerous radioisotope may not be released from the drug in the body. Therefore, it must be bound in a stable complex. The main advantage of macrocyclic ligands as DOTA in comparison with acyclic ligands is much higher kinetic inertness of complexes of macrocyclic ligands as this property is decisive for a fate of radioisotopes in

the body. However, a disadvantage of macrocyclic ligands is their rather slow complexation. Metal radioisotope is bound by a bifunctional ligand, which is further conjugated to a (bio)molecule assuring targeting of a particular organ or tissue. More information can be found in a recent book <B-2003MI2>.

Biologically active oligopeptides are the first family of targeting molecule suitable for radiolabeling. Clinically successful drugs are synthetic analogs of somatostatin (e.g., octreotide derivatives) labeled with DOTA-like ligands <B-2003MI2, 2000CME971>. The other labeled oligopeptides involve, for example, bombesin analogs <2005NMB733>. The conjugates are quickly localized in tumors and are eliminated by the kidney; the disadvantage can be back resorption of the oligopeptide conjugates in the kidney leading to kidney radiotoxicity.

Labeled monoclonal antibodies (MABs) are another group of radiopharmaceuticals <B-2003MI2, 2002MI693, 2006JIB882>. Intact MABs have good targeting properties but, due to a high molecular mass, they also have a long blood lifetime and, thus, a relatively high radiotoxicity to nontarget organs. Therefore, their labeled fragments and/or engineered MABs have been developed with an aim that the modified MABs would exhibit better pharmacokinetics but keep a good targeting ability. Several complexes can be bound to one protein molecule. In this case, rate of complexation of metal radioisotopes can be critical as the big proteins cannot be heated to a higher temperature.

14.11.8.5 Luminescence Probes

Another imaging modality used in biology and medicine is optical imaging, which is, generally, very sensitive, much more than, say, MRI. Nowadays, it employs mostly fluorescent organic dyes. However, utilization of lanthanide(III)-based 'dyes' can be a reasonable alternative. Excited lanthanide(III) ions have a rather long lifetime (micro- to milliseconds), which is much longer than the lifetime of excited organic dyes. Their emission is also much more delayed than fluorescence of molecules present in biomaterials (cells, tissues). Therefore, if the beginning of measurement is delayed after excitation, autofluorescence of the biological background has disappeared and only lanthanide(III) luminescence is detected. Another advantage of lanthanide(III) ions is the large redshift between excitation and luminescent light wavelengths. The main disadvantage is, in general, low absorption coefficient of the ions themselves. To reach reasonable quantum yields of the luminescence, they had to be sensitized by energy transfer from close chromophore of suitable properties (absorption of desired wavelength, mutual position of excited levels of chromophore and the ion). Luminescence of lanthanide(III) ions is also quenched by the presence of close O-H oscillators, mostly coordinated water molecules. Thus, polydentate ligands leaving two or one sites or no space for water coordination, having a chromophore group, and, again, exhibiting a high stability are desired. The requirements are nicely fulfilled by appropriately designed macrocyclic ligands. Properties of suitable ligands, chromophores and lanthanide(III) ions, etc., have been detailed <2002CRV1977, 2005CSR1048>. The mechanism of lanthanide(III) sensitization and employment of the particular pathways for detection of changes in pH, cation, or anion concentration has been explained <2000CCR109>. As in previous cases, a suitably designed molecule can be localized in a desired site of cell (or body) and serve as a probe for the biological events in this site <2006DT2757>. As red and near-infrared (near-IR) light penetrates tissues easily, the lanthanide(III)-based probes can be used for imaging in the wavelength range <2005MI1>.

14.11.8.6 Potential Drugs

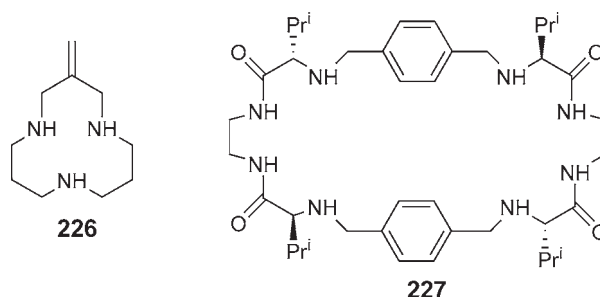
For a long time, medical applications of the azamacrocycles other than these shown above were rather limited. The cycles were sometimes used as detoxification agents in the case of metal overload. At beginning of the 1990s, it was adventitiously discovered that some impurity in cyclam inhibits HIV replication. It was later identified as a compound having two cyclam units. It led to syntheses of a number of analogs, and compound **117** (also called AMD-3100) was found to be the most active. Over the years, it was shown that these bis(cyclic) compounds represent a completely new class of anti-HIV agents. They inhibit entrance of the HIV virus into the cell. Later, it was confirmed that metal complexes of the bis(cycles) are more active than ligands themselves <2003B710>. It can be expected as cyclam is a strong chelator of a number of physiologically available metal ions, mainly for copper(II) and zinc(II). Investigations showed that biological activity could depend, at molecular basis, on conformation of cyclam units in the metal complexes <2002JA9105>. The whole story of the drug is described <2003MI581>. Nevertheless, advanced clinical testing showed some side effects and more analogs and conjugates have been prepared. Yet, this family of macrocycles has potential for use in cancer treatment (recently, another review has been published <2006CME711>).

14.11.9 Further Developments

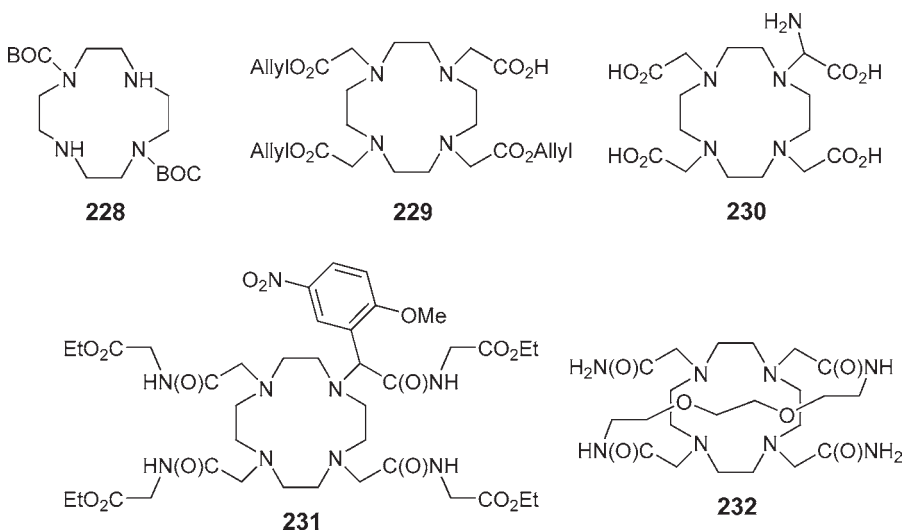
A number of papers dealing with the topic covered in this chapter appeared during 2006/2007. Some selected works will be mentioned below.

Theoretical calculation on conformations of the DOTA **3** derivatives and their complexes appeared giving a better view on interactions of the complexes with specific antibodies <2006IC9225> or their water exchange dynamics <2007PCP1318>.

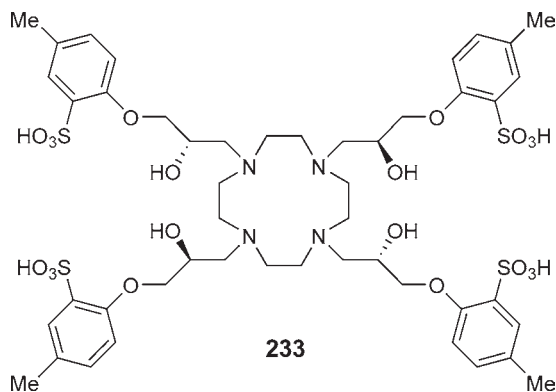
Sulfonamide method utilizing dibromo-alkyne and poly(azasulfonyl)-alkyne derivatives was used for preparation of 14–19-membered diaza- and triazapolyne cycles <2006SL3041>. Number of N-substituted derivatives (including the orthogonally protected ones) of 3-methylidene-1,5,9-triazacyclododecane **226** was prepared and tested as HIV inhibitors <2006JMC1291>. Microwave heating was used to shorten cyclization reaction time for synthesis of tetratosyl derivative of cyclen **1** (3–4 min, 52%) <2006SC653>. 1,4,7,10,13-Pentaaza-14,16-dioxo-hexadecane was prepared by efficient high-dilution synthesis (yield 44%) between BOC-protected open-chain pentaamine and active ester of malonic acid <2007S679>. Tosylamide method was used for synthesis of cycle analogous to **114** where *p*-xylylene groups were replaced with trimethylene chains <2006EJO9887>. Unusual ‘anion template’ method (employing terephthalate anion as a template) was used for synthesis of cyclic pseudopeptides **227** <2006AGE6155>.



An improved method for synthesis of ‘*trans*’ protected 1,7-Cbz₂cyclen **155** and 1,7-BOC₂cyclen **228** as well as trisubstituted cyclens **156a,b** was published employing succinimide carbamates; in the same paper, DOTA tetraester (1,7-Bu₂-4,10-Bn₂) and diester (1,7-Bu₂) were reported <2006TL6937>. DOTA tris(allyl) ester **229** was prepared through mono N-acetic acid derivative of cyclen **187** (R¹ = CH₂CO₂Bu^t) as an alternative to tris(benzyl) or tris(*t*-butyl) **188** (R¹ = CH₂CO₂H) esters of DOTA for SPPS <2006TL5985>. A new bifunctional DOTA derivative **230** having a one-atom spacer was prepared and used for synthesis of peptide conjugates <2006JA14032, 2006TL7327, 2007BCC903>. Another bifunctional ligand, DOTA monohydrazide, was obtained from Bu₃Et ester of DOTA and used for synthesis of DOTA-doxorubicin conjugate <2006IC8489>. A bifunctional ligand for conjugation through thiol groups is DOTA monoamide containing MeSO₂-S-CH₂CH₂NH- side chain <2007XXX24>. Bifunctional DOTA tetraamide ligand **231** is suitable for PARACEST applications <2007XXX55>. Syntheses of interesting ligands for a sensitive visualization of copper and zinc in a biological environment were described. Luminescence of Eu(III) complex of N-propargyl DOTA monoamide (see structure **192**; R³ = H, R⁴ = CH₂C≡CH please insert triple bond) detects Cu(I) thorough catalysis of a ‘click’ reaction of the complex with the dansyl azide derivative <2006JA11370>, the same ligand was used for attachment of its Gd(III) complex to viral particles by the ‘click’ chemistry <2007CC1269>. Copper(II)-responsive MR sensor is based on Gd(III) complex on DO3A **183** derivative having the N-phenyl-iminodiacetate pendant arm on the remaining nitrogen atom <2006JA15942>. Presence of Zn(II) modulates luminescence properties of Eu(III) complex of DO3A **183** derivative with {6-[bis(2-pyridylmethyl)aminomethyl]pyridine-2-yl} methyl pendant arm <2006DT3108> or cyclen **1** monosubstituted with the sulfonamide-quinoline derivative <2006CEJ9066>. DOTA tetraamides having one pendant arm modified with a 1,10-phenantroline <2006IC10040> or 2,2′:6′,2′′-terpyridine <2006OL2727> unit able to coordinate transition metal ions (Fe(II), Ru(II), Ni(II), Cu(II), etc.) were used for design of luminescent d–f metal conjugates. Lanthanide(III) complexes of DOTA tetraamides derived from linear α,ω-diamines were used as catalysts for hydrolysis of phosphate esters <2006CC3791>. DOTA was conjugated through ethylene-diamine chain to DTPA (DTPA = N,N′,N′′,N′′′-diethylenetriaminepentaacetic acid), similarly to a conjugate of two DOTA units with one DTPA molecule <2003JA10526>, enabling preparation of complexes with two different lanthanide(III) ions in one molecule <2006CC4116>. Complexes of another DOTA tetraamide ligand **232** are sterically constrained due to ethyleneglycol bridge spanning ‘*trans*’ amide moieties <2007IC2584>.



Water-soluble anion receptors based on tetrakis(hydroxyalkyl) derivatives (e.g., *S,S,S,S*-**233**) of cyclen **1** were prepared [<2006IC9834>](#). DOTA **3** derivatives where one pendant arm was replaced with methylphosphonic acid ester [<2007DT493>](#) or methylphosphonic acid having propionate side chain [<2007DT535>](#) were synthesized. Reaction of aminal **129** with *t*-butyl bromoacetate followed by reduction (NaBH_4) and acid hydrolysis led to monoacetic acid ligand analogous to cycle **130** [<2007DT971>](#). Hexaacetic acid and other derivatives of macrocycle **114** were prepared [<2006TL6915>](#).



A series of ligands having two or three 1,5,9-triazaacyclododecane units connected by different spacers was synthesized from **37** ($\text{R} = \text{OH}$); the derivative was prepared by carbon template method [<2006JA10716>](#). Zinc(II) complex of ligand composed from two cyclen units connected by 1,3,5-triazine was prepared as recognition site for uracil and its derivatives [<2007L2517>](#). Two DO3A triamide units were connected through *p*-xylylene spacer [<2006IC9465>](#).

Relevant Websites

<http://www.ccdc.cam.ac.uk> – Cambridge Structural Database

<http://www.nist.gov/srd/nist46.htm> – NIST Standard Reference Database 46 (Critically Selected Stability Constants of Metal Complexes)

<http://www.acadsoft.co.uk> – The IUPAC Stability Constants Database (SC-Database)

References

- 1974JA2268 J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.*, 1974, **96**, 2268.
 1991AGE560 A. Filali, J.-J. Yaouanc, and H. Handel, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 560.
 1993JA6580 R. W. Alder, E. Heilbronner, E. Honneger, A. B. McEwen, R. E. Moss, E. Olefirowicz, P. A. Petillo, R. B. Sessions, G. R. Weisman, J. M. White, *et al.*, *J. Am. Chem. Soc.*, 1993, **115**, 6580.

- 1993SL611 K. E. Krakowiak, J. S. Bradshaw, and R. M. Izatt, *Synlett*, 1993, 611.
- 1994TL3707 A. Dumont, V. Jacques, P. Qixiu, and J. F. Desreux, *Tetrahedron Lett.*, 1994, **35**, 3707.
- 1995ACS547 J. Springborg, P. Kofod, C. E. Olsen, H. Toftlund, and I. Søjtofte, *Acta Chem. Scand.*, 1995, **49**, 547.
- 1995AXC1407 P. Thuery, N. Keller, M. Lance, J.-D. Vigner, and M. Nierlich, *Acta Crystallogr., Sect. C*, 1995, **51**, 1407.
- 1995BCC296 J. K. Moran, D. P. Greiner, and C. F. Meares, *Bioconjugate Chem.*, 1995, **6**, 296.
- 1995CC185 Z. Kovacs and A. D. Sherry, *J. Chem. Soc., Chem. Commun.*, 1995, 185.
- 1995CC1233 A. Roignant, I. Gardinier, H. Bernard, J.-J. Yaouanc, and H. Handel, *J. Chem. Soc., Chem. Commun.*, 1995, 1233.
- 1995CJC685 I. Meunier, A. K. Mishra, B. Hanquet, P. Cocolios, and R. Guillard, *Can. J. Chem.*, 1995, **73**, 685.
- 1995IC552 C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, C. Giorgi, P. Paoletti, A. Stafani, and B. Valtancoli, *Inorg. Chem.*, 1995, **34**, 552.
- 1995ICA159 A. M. Josceanu, P. Moore, S. C. Rawle, P. Sheldon, and S. M. Smith, *Inorg. Chim. Acta*, 1995, **240**, 159.
- 1995JCD1133 K. Bazakas and I. Lukeš, *J. Chem. Soc., Dalton Trans.*, 1995, 1133.
- 1995JCD2259 S. Aime, M. Botta, D. Parker, and J. A. G. Williams, *J. Chem. Soc., Dalton Trans.*, 1995, 2259.
- 1995JCM16 E. Agar, B. Bati, E. Erdem, and M. Özdemir, *J. Chem. Res. (S)*, 1995, 16.
- 1995JME366 G. J. Bridger, R. T. Skerlj, D. Thornton, S. Padmanabhan, S. A. Martellucci, G. W. Henson, M. J. Abrams, N. Yamamoto, K. De Vreese, and R. Pauwels, *J. Med. Chem.*, 1995, **38**, 366.
- 1995JOC3980 N. Kise, H. Oike, E. Okazaki, M. Yoshimoto, and T. Shono, *J. Org. Chem.*, 1995, **60**, 3980.
- 1995JOM215 V. Patinec, J.-J. Yaouanc, J.-C. Clément, H. Handel, H. des Abbayes, and M. M. Kubicki, *J. Organomet. Chem.*, 1995, **494**, 215.
- 1995JP12995 P. L. Anelli, L. Calabi, P. Dapporto, M. Murru, L. Paleari, P. Paoli, F. Uggeri, S. Verona, and M. Virtuani, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2995.
- 1995JRM301 E. Agar, B. Bati, E. Erdem, and M. Özdemir, *J. Chem. Res. (M)*, 1995, 301.
- 1995NJC839 V. Dahaoui-Gindrey, C. Lecomte, H. Chollet, A. K. Mishra, C. Mehadji, and R. Guillard, *New J. Chem.*, 1995, **19**, 839.
- 1995PJC1039 R. A. Koliński, *Pol. J. Chem.*, 1995, **69**, 1039.
- 1995SC3181 I. Lázár, *Synth. Commun.*, 1995, **25**, 3181.
- 1995T1197 C. Granier and R. Guillard, *Tetrahedron*, 1995, **51**, 1197.
- 1995TL79 V. Patinec, J.-J. Yaouanc, J.-C. Clément, H. Handel, and H. des Abbayes, *Tetrahedron Lett.*, 1995, **36**, 79.
- 1995TL4995 B. Boitrel, B. Andrioletti, M. Lachkar, and R. Guillard, *Tetrahedron Lett.*, 1995, **36**, 4995.
- 1996AGE655 K. Roth, G. Bartholomae, H. Bauer, T. Frenzel, S. Kossler, J. Platzek, B. Radüchel, and H. J. Weinmann, *Angew. Chem., Int. Ed. Eng.*, 1996, **35**, 655.
- 1996BML2063 M. Kalesse and A. Loos, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2063.
- 1996BSF65 S. Brandés, C. Gros, F. Denat, P. Pullumbi, and R. Guillard, *Bull. Soc. Chim. Fr.*, 1996, **133**, 65.
- 1996CC947 G. R. Weisman, E. H. Wong, D. C. Hill, M. E. Rogers, and D. R. Reed, *Chem. Commun.*, 1996, 947.
- 1996CC1303 D. C. Ware, D. M. Tonei, L.-J. Baker, P. J. Brothers, and G. R. Clark, *Chem. Commun.*, 1996, 1303.
- 1996CC2157 I. Gardinier, H. Bernard, F. Chuburu, A. Roignant, J.-J. Yaouanc, and H. Handel, *Chem. Commun.*, 1996, 2157.
- 1996CEJ75 L. Fabbri, M. Licchelli, P. Pallavicini, A. Perotti, A. Taglietti, and D. Sacchi, *Chem. Eur. J.*, 1996, **2**, 75.
- 1996CEJ617 T. Koike, M. Takashige, E. Kimura, H. Fujioka, and M. Shiro, *Chem. Eur. J.*, 1996, **2**, 617.
- 1996H(42)775 H. Fujioka, T. Koike, N. Yamada, and E. Kimura, *Heterocycles*, 1996, **42**, 775.
- 1996IC2045 P. V. Bernhardt, K. A. Byriel, C. H. L. Kennard, and P. C. Sharpe, *Inorg. Chem.*, 1996, **35**, 2045.
- 1996IC2726 S. Aime, M. Botta, G. Ermondi, E. Terreno, P. L. Anelli, F. Fedeli, and F. Uggeri, *Inorg. Chem.*, 1996, **35**, 2726.
- 1996IC3821 R. J. Motekaitis, B. E. Rogers, D. E. Reichert, A. E. Martell, and M. J. Welch, *Inorg. Chem.*, 1996, **35**, 3821.
- 1996IC4649 Z. Zhang, J. L. Petersen, and A. M. Stolzberg, *Inorg. Chem.*, 1996, **35**, 4649.
- 1996IC5213 D. P. Riley, S. L. Henke, P. J. Lennon, R. H. Weiss, W. L. Neumann, W. J. Rivers, Jr., A. W. Aston, K. R. Sample, H. Rahman, C.-S. Ling, *et al.*, *Inorg. Chem.*, 1996, **35**, 5213.
- 1996IC5851 S. Zhu, F. Kou, H. Lin, C. Lin, M. Lin, and Y. Chen, *Inorg. Chem.*, 1996, **35**, 5851.
- 1996ICA105 V. Patinec, I. Gardinier, J.-J. Yaouanc, J.-C. Clément, H. Handel, and H. des Abbayes, *Inorg. Chim. Acta*, 1996, **244**, 105.
- 1996ICA143 P. D. Beer, Z. Chen, M. G. B. Drew, A. O. M. Johnson, D. K. Smith, and P. Spencer, *Inorg. Chim. Acta*, 1996, **246**, 143.
- 1996ICA151 E. Kimura, Y. Kodama, M. Shionoya, and T. Koike, *Inorg. Chim. Acta*, 1996, **246**, 151.
- 1996ICA287 J. A. Aguilar, E. Garca-España, J. A. Guerrero, S. V. Luis, J. M. Llinares, J. A. Ramirez, and C. Soriano, *Inorg. Chim. Acta*, 1996, **246**, 287.
- 1996ICA321 J. C. A. Boeyens, L. Cook, P. A. Duckworth, S. B. Rahardjo, M. R. Taylor, and K. P. Wainwright, *Inorg. Chim. Acta*, 1996, **246**, 321.
- 1996ICA191 É. Tóth, R. Király, J. Platzek, B. Radüchel, and E. Brücher, *Inorg. Chim. Acta*, 1996, **249**, 191.
- 1996JA10963 E. Kimura, H. Hashimoto, and T. Koike, *J. Am. Chem. Soc.*, 1996, **118**, 10963.
- 1996JHC2013 K. E. Krakowiak, G. Yi, and J. S. Bradshaw, *J. Heterocycl. Chem.*, 1996, **33**, 2013.
- 1996JME109 G. J. Bridger, R. T. Skerlj, S. Padmanabhan, S. A. Martellucci, G. W. Henson, M. J. Abrams, H. C. Joao, M. Witvrouw, K. De Vreese, R. Pauwels, *et al.*, *J. Med. Chem.*, 1996, **39**, 109.
- 1996JOC1519 G. J. Bridger, R. T. Skerlj, S. Padmanabhan, and D. Thornton, *J. Org. Chem.*, 1996, **61**, 1519.
- 1996JOC5186 G. R. Weisman and D. P. Reed, *J. Org. Chem.*, 1996, **61**, 5186. corrigentia: *ibid.* 1997, **62**, 4548.
- 1996JP21109 G. B. Bates and D. Parker, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1109.
- 1996JP21161 P. J. A. Ribeiro-Claro, A. M. Amado, M. P. M. Marques, and J. J. C. Teixeira-Dias, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1161.
- 1996JP21925 R. D. Hancock, R. J. Motekaitis, J. Mashishi, I. Cukrowski, J. H. Reibenspies, and A. E. Martell, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1925.
- 1996JPC17655 S. Hannongbua, *J. Phys. Chem.*, 1996, **100**, 17655.
- 1996LA935 M. Kalesse and A. Loos, *Liebigs Ann. Chem.*, 1996, 935.
- 1996NJC585 A. K. Mishra, J. F. Gestin, E. Benoist, A. Faivre-Chauvet, and J. F. Chatal, *New J. Chem.*, 1996, **20**, 585.
- 1996SC1595 A. A. Formanovsky and I. V. Mikhura, *Synth. Commun.*, 1996, **26**, 1595.
- 1996SL933 A. V. Bordunov, J. S. Brandshaw, V. N. Pastushok, and R. M. Izatt, *Synlett*, 1996, 933.
- 1996T2995 N. Oget, F. Chuburu, J.-J. Yaouanc, and H. Handel, *Tetrahedron*, 1996, **52**, 2995.
- 1996T9793 B. Cathala, K. Raouf-Benckekroun, C. Galaup, C. Picard, L. Cazaux, and P. Tisné, *Tetrahedron*, 1996, **52**, 9793.
- 1996TL5301 D. Xu, P. G. Mattner, K. Prasad, O. Repic, and T. J. Blacklock, *Tetrahedron Lett.*, 1996, **37**, 5301.

- 1996TL7515 A. K. Mishra, K. Draillard, A. Faivre-Chauvet, J. F. Gustin, C. Curtet, and J.-F. Chatal, *Tetrahedron Lett.*, 1996, **37**, 7515.
- 1996TL7711 I. Gardinier, A. Roignant, N. Oget, H. Bernand, J.-J. Yaouanc, and H. Handel, *Tetrahedron Lett.*, 1996, **37**, 7711.
- B-1996MI In 'Macrocyclic Synthesis. A Practical Approach', D. Parker Ed.; Oxford University Press, Oxford, 1996.
- 1996WO28433 L. Schultze and A. R. Bulls (Nycomed Imaging a/s), *PCT Int. Appl. WO 96/28433* (1996).
- 1997AJC529 M. Rossignoli, P. V. Bernhardt, G. A. Lawrence, and M. Maeder, *Aust. J. Chem.*, 1997, **50**, 529.
- 1997AXC586 O. P. Gladkikh, N. F. Curtis, and M. M. Turnbull, *Acta Crystallogr., Sect. C*, 1997, **53**, 586.
- 1997CB267 H. Schumann, U. A. Böttger, K. Zietzke, H. Hemling, G. Kociok-Köhn, J. Pickardt, F. E. Hahn, A. Zschunke, B. Schiefner, H. Gries, *et al.*, *Chem. Ber.*, 1997, **130**, 267.
- 1997CCR35 K. P. Wainwright, *Coord. Chem. Rev.*, 1997, **166**, 35.
- 1997IC1495 J. Huskens, D. A. Torres, Z. Kovacs, J. P. André, C. F. G. C. Geraldès, and A. D. Sherry, *Inorg. Chem.*, 1997, **36**, 1495.
- 1997IC4128 W. D. Kim, G. E. Kiefer, J. Huskens, and A. D. Sherry, *Inorg. Chem.*, 1997, **36**, 4128.
- 1997IC6086 J. Platzek, P. Blaszkiewicz, H. Gries, P. Luger, G. Michl, A. Müller-Farnow, B. Radüchel, and D. Stülze, *Inorg. Chem.*, 1997, **36**, 6086.
- 1997JA3068 E. Kimura, S. Aoki, T. Koike, and M. Shiro, *J. Am. Chem. Soc.*, 1997, **119**, 3068.
- 1997JA6126 R. S. Dhillon, S. E. Madbak, F. G. Ciccone, M. A. Buntine, S. F. Lincoln, and K. P. Wainwright, *J. Am. Chem. Soc.*, 1997, **119**, 6126.
- 1997JCD317 J. M. Weeks, M. R. Taylor, and K. P. Wainwright, *J. Chem. Soc., Dalton Trans.*, 1997, 317.
- 1997JCD895 P.-A. Pittet, D. Früh, V. Tissières, and J.-C. G. Bünzli, *J. Chem. Soc., Dalton Trans.*, 1997, 895.
- 1997JCD3623 S. Aime, A. S. Batsanov, M. Botta, R. S. Dickins, S. Faulkner, C. E. Foster, A. Harrison, J. A. K. Howard, J. M. Moloney, T. J. Norman, *et al.*, *J. Chem. Soc., Dalton Trans.*, 1997, 6323.
- 1997JCD3637 M. W. A. Steenland, I. Dierck, G. G. Hermann, B. Devreese, W. Lippens, J. Van Beeumen, and A. M. Goeminne, *J. Chem. Soc., Dalton Trans.*, 1997, 3637.
- 1997JCF3045 S. Udonsub and S. Hannongbua, *J. Chem. Soc., Faraday Trans.*, 1997, **93**, 3045.
- 1997JP13157 B. L. May, S. D. Kean, C. J. Easton, and S. F. Lincoln, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3157.
- 1997NCS129 M. Evain, A. K. Mishra, J. F. Gustin, A. Faivre-Chauvet, J. F. Chatal, and V. Petricek, *New Cryst. Struct.*, 1997, **212**, 129.
- 1997POL599 Y. Baran, G. A. Lawrence, and E. N. Wilkes, *Polyhedron*, 1997, **16**, 599.
- 1997S759 Z. Kovacs and A. D. Sherry, *Synthesis*, 1997, 759.
- 1997S1010 P. Moreau, M. Tinkl, M. Tsukazaki, P. S. Bury, E. J. Griffen, V. Snieckus, R. B. Maharajh, C. S. Kwok, V. V. Somayaji, Z. Peng, *et al.*, *Synthesis*, 1997, 1010.
- 1997SL1190 R. Guillard, A. G. Bessmertnykh, and I. P. Beletskaya, *Synlett*, 1997, 1190.
- 1997TL779 W. L. Neumann, G. W. Franklin, K. R. Sample, K. W. Aston, R. H. Weiss, D. P. Riley, and N. Rath, *Tetrahedron Lett.*, 1997, **38**, 779.
- 1997TL1911 P. Hubsch-Weber and M.-T. Youinou, *Tetrahedron Lett.*, 1997, **38**, 1911.
- 1997TL3143 W. L. Neumann, G. W. Franklin, K. R. Sample, K. W. Aston, R. H. Weiss, D. P. Riley, and N. Rath, *Tetrahedron Lett.*, 1997, **38**, 3143.
- 1997TL3219 G. Byk, M. Frederick, and D. Schermann, *Tetrahedron Lett.*, 1997, **38**, 3219.
- 1997USP6512478 D. Xu, P. Kapa, O. Repic, and T. J. Blacklock, *US Pat.* 6512478 (1997).
- B-1997MI In 'Supramolecular Chemistry of Anions', A. Bianchi, K. Bowman-James, and E. Garca-España Eds.; Wiley, Chichester, 1997.
- 1998ACS1247 Z. Li and K. Undheim, *Acta Chem. Scand.*, 1998, **52**, 1247.
- 1998ACS1402 R. W. Sadness, M. Gacek, and K. Undheim, *Acta Chem. Scand.*, 1998, **52**, 1402.
- 1998AGE1086 K. Haas, W. Ponikvar, H. Nöth, and W. Beck, *Angew. Chem., Int. Ed.*, 1998, **37**, 1086.
- 1998AIC75 L. F. Lindoy, *Adv. Inorg. Chem.*, 1998, **45**, 75.
- 1998BCC132 J. Hovinen, *Bioconjugate Chem.*, 1998, **9**, 132.
- 1998CC827 P. J. Davies, M. R. Taylor, and K. P. Wainwright, *Chem. Commun.*, 1998, 827.
- 1998CC1823 M. I. Burguete, E. García-España, S. V. Luis, J. F. Miravet, L. Payá, M. Querol, and C. Soriano, *Chem. Commun.*, 1998, 1823.
- 1998CCR1313 M. Meyer, V. Dahanoui-Gindrey, C. Lecomte, and R. Guillard, *Coord. Chem. Rev.*, 1998, **178-180**, 1313.
- 1998CR557 O. Siri, G. Royal, A. Tabard, R. Guillard, V. Huch, and M. Veith, *C. R. Hebd. Seances Acad. Sci., Ser. IIC*, 1998, **1**, 557.
- 1998EJO1971 G. Royal, V. Dahanoui-Gindrey, S. Dahanoui, A. Tabard, R. Guillard, P. Pullumbi, and C. Lecomte, *Eur. J. Org. Chem.*, 1998, 1971.
- 1998HCA1765 A. Comparone and T. A. Kaden, *Helv. Chim. Acta*, 1998, **81**, 1765.
- 1998IC69 L. Burai, J. Ren, Z. Kovacs, E. Brücher, and A. D. Sherry, *Inorg. Chem.*, 1998, **37**, 69.
- 1998IC1575 M. Lachkar, R. Guillard, A. Atmani, A. De Cian, J. Fischer, and R. Weiss, *Inorg. Chem.*, 1998, **37**, 1575.
- 1998IC3989 L. L. Chappell, D. A. Voss, Jr., W. DeW. Horrocks, Jr., and J. R. Morrow, *Inorg. Chem.*, 1998, **37**, 3989.
- 1998IC5342 O. D. Gupta, Jianguo Chen, R. L. Kirchmeier, and J. M. Shreeve, *Inorg. Chem.*, 1998, **37**, 5342.
- 1998ICA424 T. Koike, T. Gotoh, S. Aoki, E. Kimura, and M. Shiro, *Inorg. Chim. Acta*, 1998, **270**, 424.
- 1998JA1474 G. E. Collins, L.-S. Choi, and J. H. Callahan, *J. Am. Chem. Soc.*, 1998, **120**, 1474.
- 1998JA10019 S. Aoki, Y. Honda, and E. Kimura, *J. Am. Chem. Soc.*, 1998, **120**, 10019.
- 1998JCD359 C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, C. Giorgi, L. Messori, M. Migliorini, P. Paoletti, and B. Valtancoli, *J. Chem. Soc., Dalton Trans.*, 1998, 359.
- 1998JCD881 S. Aime, M. Botta, R. S. Dickins, C. L. Maupin, D. Parker, J. P. Riehl, and J. A. G. Williams, *J. Chem. Soc., Dalton Trans.*, 1998, 881.
- 1998JP22129 D. Parker, P. K. Senanayake, and J. A. G. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1998, 2129.
- 1998JOC1810 M. I. Burguete, B. Escuder, J. C. Fras, E. Garca-España, S. V. Luis, and J. F. Miravet, *J. Org. Chem.*, 1998, **63**, 1810.
- 1998JOM83 S. Lafollee-Bezzene, A. Parlier, H. Rudler, J. Vaissermann, and J.-C. Daran, *J. Organomet. Chem.*, 1998, **567**, 83.
- 1998NJC1359 C. D. Edlin, S. Faulkner, D. Parker, M. P. Wilkinson, M. Woods, J. Lin, E. Lasri, F. Neth, and M. Port, *New J. Chem.*, 1998, 1359.
- 1998SC285 D. Fasseur, S. Lacour, and R. Guillard, *Synth. Commun.*, 1998, **28**, 285.
- 1998SC2903 D. Guillame and G. R. Marshall, *Synth. Commun.*, 1998, **28**, 2903.
- 1998TL853 J. Dessolin, G. Quéléver, M. Camplo, and J.-L. Kraus, *Tetrahedron Lett.*, 1998, **39**, 853.
- 1998TL3799 M. I. Burguete, B. Escuder, S. V. Luis, J. F. Miravet, M. Querol, and E. Garca-España, *Tetrahedron Lett.*, 1998, **39**, 3799.

- 1998TL6861 G. Hervé, H. Bernard, N. Le Bris, J.-J. Yaouanc, H. Handel, and L. Toupet, *Tetrahedron Lett.*, 1998, **39**, 6861.
- 1999BCC192 S. Aime, M. Botta, S. G. Crich, G. Giovenzana, G. Palmisano, and M. Sisti, *Bioconjugate Chem.*, 1999, **10**, 192.
- 1999CCC1827 J. Hodačová, J. Závada, and P. C. Junk, *Collect. Czech. Chem. Commun.*, 1999, **64**, 1827.
- 1999CCR451 V. Comblin, D. Gilsoul, M. Hermann, V. Humblet, V. Jacques, M. Mesbahi, C. Sauvage, and J. F. Desreux, *Coord. Chem. Rev.*, 1999, **185–186**, 451.
- 1999CCR97 A. Bencini, A. Bianchi, E. Garca-España, M. Micheloni, and J. A. Ramirez, *Coord. Chem. Rev.*, 1999, **188**, 97.
- 1999CEJ683 L. Fabbri, F. Gatti, P. Pallavicini, and E. Zambambieri, *Chem. Eur. J.*, 1999, **5**, 682.
- 1999CEJ1974 A. Heppeler, S. Froidevaux, H. R. Mäcke, E. Jermann, M. Béhé, P. Powell, and M. Hennig, *Chem. Eur. J.*, 1999, **5**, 1974.
- 1999CEJ2993 A. Cuppolletti, C. Dagostin, C. Florea, C. Galli, P. Gentili, O. Lanzalunga, A. Petride, and H. Petride, *Chem. Eur. J.*, 1999, **5**, 2993.
- 1999CJC614 R. J. Motekaitis, Y. Sun, A. E. Martell, and M. J. Welch, *Can. J. Chem.*, 1999, **77**, 614.
- 1999CRV2293 P. Caravan, J. J. Ellison, T. J. McMurphy, and R. B. Lauffer, *Chem. Rev.*, 1999, **99**, 2293.
- 1999EJO3257 F. Bellouard, F. Chuburu, J.-J. Yaouanc, H. Handel, and Y. Le Mest, *Eur. J. Org. Chem.*, 1999, 3257.
- 1999HCA543 C. Galaup, C. Picard, B. Cathala, L. Cazaux, P. Tisné, H. Autiero, and D. Aspe, *Helv. Chim. Acta*, 1999, **82**, 543.
- 1999HCA790 I. Déchamps-Olivier, J.-P. Barbier, M. Aplincourt, N. Oget, F. Chuburu, and H. Handel, *Helv. Chim. Acta*, 1999, **82**, 790.
- 1999ICA40 G. A. Amadei, M. H. Dickman, R. A. Wazzeh, P. Dimmock, and J. E. Earley, *Inorg. Chim. Acta*, 1999, **288**, 40.
- 1999ICA103 P. J. Davies and K. P. Wainwright, *Inorg. Chim. Acta*, 1999, **294**, 103.
- 1999IJA609 B. Singh and V. L. Singh, *Indian J. Chem., Sect. A*, 1999, **38**, 609.
- 1999JA2919 E. Cheung, M. R. Netherton, J. R. Scheffer, and J. Trotter, *J. Am. Chem. Soc.*, 1999, **121**, 2919.
- 1999JA5426 E. Kikuta, M. Murata, N. Katsube, T. Koike, and E. Kimura, *J. Am. Chem. Soc.*, 1999, **121**, 5426.
- 1999JA6807 C. Bazzicalupi, A. Bencini, A. Bianchi, M. Cecchi, B. Escuder, V. Fusi, E. Garca-España, C. Giorgi, S. V. Luis, G. Maccagni, *et al.*, *J. Am. Chem. Soc.*, 1999, **121**, 6807.
- 1999JIS341 J. P. André, H. R. Mäcke, É. Tóth, and A. A. Merbach, *J. Biol. Inorg. Chem.*, 1999, **4**, 341.
- 1999JRM2240 N. Oget, F. Chuburu, H. Handel, and L. Toupet, *J. Chem. Res. (M)*, 1999, 2240.
- 1999JCD1925 L. Cronin, A. R. Mount, S. Parsons, and N. Robertson, *J. Chem. Soc., Dalton Trans.*, 1999, 1925.
- 1999JCM526 N. Oget, F. Chuburu, H. Handel, and L. Toupet, *J. Chem. Res. (S)*, 1999, 526.
- 1999JME229 J. Dessolin, P. Galea, P. Vlieghe, J.-C. Chermann, and J.-L. Kraus, *J. Med. Chem.*, 1999, **42**, 229.
- 1999JME3971 G. J. Bridger, R. T. Skerlj, S. Padmanabhan, S. A. Martellucci, G. W. Henson, S. Struyf, M. Witvrouw, D. Schols, and E. De Clercq, *J. Med. Chem.*, 1999, **42**, 3971.
- 1999JOC2683 W. C. Baker, M. J. Choi, D. C. Hill, J. L. Thompson, and P. A. Petillo, *J. Org. Chem.*, 1998, **64**, 2683.
- 1999JP1811 H. Fensterbank, J. Zhu, D. Riou, and C. Larpent, *J. Chem. Soc., Perkin Trans. 1*, 1999, 811.
- 1999JP11621 N. J. Long, D. G. Parker, P. R. Speyer, A. J. P. White, and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1621.
- 1999JP13499 F. Bellouard, F. Chuburu, N. Kervarec, L. Toupet, S. Triki, Y. Le Mest, and H. Handel, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3499.
- 1999JP2493 A. Beeby, I. M. Clarkson, R. S. Dickens, S. Faulkner, D. Parker, L. Royle, A. S. de Sousa, J. A. G. Williams, and M. Woods, *J. Chem. Soc., Perkin Trans. 2*, 1999, 493.
- 1999JP21973 J. L. W. Griffin, P. V. Convey, A. Whiting, and R. Davey, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1973.
- 1999MC66 I. V. Kubrakova, A. A. Formanovsky, and I. V. Mikhura, *Mendeleev Commun.*, 1999, 66.
- 1999MI75 A. J. Phillips and A. D. Abell, *Aldrichimica Acta*, 1999, **32**, 75.
- 1999NJC669 S. Aime, A. S. Batsanov, M. Botta, J. A. K. Howard, M. P. Lowe, and D. Parker, *New J. Chem.*, 1999, **23**, 669.
- 1999NJC1007 J. Wioriewicz-Kuczera, K. Kuczera, C. Bazzicalupi, A. Bencini, B. Valtancoli, A. Bianchi, and K. Bowman-James, *New J. Chem.*, 1999, **23**, 1007.
- 1999SC2817 Z. Kovacs, E. A. Archer, M. K. Russell, and A. D. Sherry, *Synth. Commun.*, 1999, **29**, 2817.
- 1999SC4279 V. Montebault, H. Mouaziz, V. Blondeau, R. Touchard, J.-C. Soutif, and J.-C. Brosse, *Synth. Commun.*, 1999, **29**, 4279.
- 1999TA367 I. Alfonso, F. Rebollo, and V. Gotor, *Tetrahedron Asymmetry*, 1999, **10**, 367.
- 1999TA2515 I. Alfonso, C. Astorga, F. Rebollo, and V. Gotor, *Tetrahedron Asymmetry*, 1999, **10**, 2515.
- 1999TL79 R. Tripier, O. Siri, F. Rabiet, F. Denat, and R. Guillard, *Tetrahedron Lett.*, 1999, **40**, 79.
- 1999TL287 B. Gaudinet-Hamann, J. Zhu, H. Fensterbank, and C. Larpent, *Tetrahedron Lett.*, 1999, **40**, 287.
- 1999TL381 I. Lázár, *Tetrahedron Lett.*, 1999, **40**, 381.
- 1999TL2315 C. Bucher, G. Royal, J.-M. Barbe, and R. Guillard, *Tetrahedron Lett.*, 1999, **40**, 2315.
- 1999TL2517 G. Hervé, H. Bernard, N. Le Bris, M. Le Baccon, J.-J. Yaouanc, and H. Handel, *Tetrahedron Lett.*, 1999, **40**, 2517.
- 1999TL5401 J. E. Baldwin, H. R. Vollmer, and V. Lee, *Tetrahedron Lett.*, 1999, **40**, 5401.
- 1999TL7687 B. M. Kim and S. M. So, *Tetrahedron Lett.*, 1999, **40**, 7687.
- 2000AGE1052 T. Hirano, K. Kikuchi, Y. Urano, T. Higuchi, and T. Nagano, *Angew. Chem., Int. Ed.*, 2000, **39**, 1052.
- 2000BCC510 L. L. Cappell, K. A. Deal, E. Dadachova, and M. W. Brechbiel, *Bioconjugate Chem.*, 2000, **11**, 510.
- 2000BCJ693 M. Iwata, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 693.
- 2000BMC647 D. H. Kim and S. S. Lee, *Bioorg. Med. Chem.*, 2000, **8**, 647.
- 2000CC707 M. P. Lowe and D. Parker, *Chem. Commun.*, 2000, 707.
- 2000CCC99 M. Chadim, M. Buděšný, J. Hodačová, and J. Závada, *Collect. Czech. Chem. Commun.*, 2000, **65**, 99.
- 2000CCC243 J. Kotek, P. Hermann, P. Vojtšek, J. Rohovec, and I. Lukeš, *Collect. Czech. Chem. Commun.*, 2000, **65**, 243.
- 2000CCC1289 J. Kotek, P. Vojtšek, I. Čiřáková, P. Hermann, P. Jurečka, J. Rohovec, and I. Lukeš, *Collect. Czech. Chem. Commun.*, 2000, **65**, 1289.
- 2000CCR309 A. Bianchi, L. Calabi, F. Corana, S. Fontana, P. Losi, A. Maicchi, L. Paleari, and B. Valtancoli, *Coord. Chem. Rev.*, 2000, **204**, 309.
- 2000CCR109 D. Parker, *Coord. Chem. Rev.*, 2000, **205**, 109.
- 2000CME971 A. Heppeler, S. Froidevaux, A. N. Eberle, and H. R. Mäcke, *Curr. Med. Chem.*, 2000, **7**, 971.
- 2000CR211 C. Bucher, E. Duval, J.-M. Barbe, J.-N. Verpeaux, C. Amatore, and R. Guillard, *C. R. Hebd. Seances Acad. Sci., Ser. IIC*, 2000, **3**, 211.
- 2000EJI195 J. Rohovec, M. Kývala, P. Vojtšek, P. Hermann, and I. Lukeš, *Eur. J. Inorg. Chem.*, 2000, 195.
- 2000EJI741 M. E. Padilla-Tosta, J. M. Lloris, R. Martínez-Máñez, A. Benito, J. Soto, T. Pardo, M. A. Miranda, and M. D. Marcos, *Eur. J. Inorg. Chem.*, 2000, 741.
- 2000EJO33 G. Hervé, H. Bernard, L. Toupet, and H. Handel, *Eur. J. Org. Chem.*, 2000, 33.

- 2000EJO1037 M. Căprioiu, C. Florea, C. Galli, A. Petride, and H. Petride, *Eur. J. Org. Chem.*, 2000, 1037.
- 2000HCA793 A. Chellini, R. Pagliarin, G. B. Giovenzana, G. Palmisano, and M. Sisti, *Helv. Chim. Acta*, 2000, **83**, 793.
- 2000ICA226 E. Szilágyi, É. Tóth, Z. Kovacs, J. Platzek, B. Radüchel, and E. Brücher, *Inorg. Chim. Acta*, 2000, **298**, 226.
- 2000IEC3499 K. E. Krakowiak and J. S. Bradshaw, *Ind. Eng. Chem. Res.*, 2000, **39**, 3499.
- 2000IR8 E. R. Marinelli, R. Nubeck, B. Song, T. Wagler, R. R. Ranganathan, K. Sukumaran, P. W. Wedeking, A. Nunn, V. M. Runge, and M. F. Tweedle, *Invest. Radiol.*, 2000, **35**, 8.
- 2000JA9674 J. I. Bruce, R. S. Dickins, L. J. Govenlock, T. Gunnlaugsson, S. Lopinski, M. P. Lowe, D. Parker, R. D. Peacock, J. J. B. Perry, S. Aime, *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 9674.
- 2000JA9781 M. Woods, S. Aime, M. Botta, J. A. K. Howard, J. M. Moloney, M. Navet, D. Parker, M. Port, and O. Rousseaux, *J. Am. Chem. Soc.*, 2000, **122**, 9781.
- 2000JCD141 J. Rohovec, P. Vojtišek, P. Hermann, J. Ludvík, and I. Lukeš, *J. Chem. Soc., Dalton Trans.*, 2000, 141.
- 2000JCD1873 A. E. Goeta, J. A. K. Howard, D. Maffeo, H. Puschmann, J. A. G. Williams, and D. S. Yufit, *J. Chem. Soc., Dalton Trans.*, 2000, 1873.
- 2000JIS85 L. Huang, L. L. Chappell, O. Iranzo, B. F. Baker, and J. R. Morrow, *J. Biol. Inorg. Chem.*, 2000, **5**, 85.
- 2000JIS488 S. Aime, E. Gianolio, E. Terreno, G. B. Giovenzana, R. Pagliarin, M. Sisti, G. Palmisano, M. Botta, M. P. Lowe, and D. Parker, *J. Biol. Inorg. Chem.*, 2000, **5**, 488.
- 2000JP21047 C. Gløgård, R. Hovland, S. L. Fossheim, A. J. Aasen, and J. Klaveness, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1047.
- 2000JP21323 J. A. Aguilar, B. Celda, V. Fusi, E. García-España, S. V. Luis, M. C. Martínez, J. A. Ramírez, C. Soriano, and R. Tejero, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1323.
- 2000JP22359 A. Dadabhoy, S. Faulkner, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2359.
- 2000MI585 C. Nicolas, M. Borel, J.-C. Maurizis, N. Gallais, M. Rapp, M. Ollier, M. Verny, and J.-C. Madelmont, *J. Label. Compnd. Radiopharm.*, 2000, **43**, 585.
- 2000MI M. Nieger, E. Weber, and A. Lohner, *Private Communication to CCDC*, 2000.
- 2000NMB93 L. L. Chappell, E. Dadachova, D. E. Milenic, K. Garmestani, C. Wu, and M. W. Brechbiel, *Nucl. Med. Biol.*, 2000, **27**, 93.
- 2000SC15 M. Ferrari, G. B. Giovenzana, G. Palmisano, and M. Sisti, *Synth. Commun.*, 2000, **30**, 15.
- 2000SL561 F. Denat, S. Brandés, and R. Guillard, *Synlett*, 2000, 561.
- 2000T4759 M. T. Barros and F. Siñeriz, *Tetrahedron*, 2000, **56**, 4759.
- 2000TL1249 J. Rohovec, R. Gyepes, I. Císařová, J. Rudovský, and I. Lukeš, *Tetrahedron Lett.*, 2000, **41**, 1249.
- 2000TL5967 M. Achmatowicz and J. Jurczak, *Tetrahedron Lett.*, 2000, **41**, 5967.
- 2000TL6527 V. Boldarini, G. B. Giovenzana, R. Pagliarin, G. Palmisano, and M. Sisti, *Tetrahedron Lett.*, 2000, **41**, 6527.
- 2000TL7207 A. Ouadi, A. Loussouarn, P. Remaud, L. Morandeau, C. Apostolidis, C. Musikas, A. Favra-Chauvet, and J.-F. Gestin, *Tetrahedron Lett.*, 2000, **41**, 7207.
- 2001AIC293 K. P. Wainwright, *Adv. Inorg. Chem.*, 2001, **52**, 293.
- 2001AJC291 Y. Dong and L. F. Lindoy, *Aust. J. Chem.*, 2001, **54**, 291.
- 2001AJC535 S. D. Kean, C. J. Easton, S. F. Lincoln, and D. Parker, *Aust. J. Chem.*, 2001, **54**, 535.
- 2001BCC1081 P. L. Anelli, L. Lattuada, M. Gabellini, and P. Recanati, *Bioconjugate Chem.*, 2001, **12**, 1081.
- 2001BML71 F. Riché, A. de M. d'Hardemare, S. Sépe, L. Riou, D. Farget, and M. Vidal, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 71.
- 2001BML1521 M. C. F. Monnee, A. J. Brouwer, L. M. Verbeek, A. M. A. van Wageningen, and R. M. J. Liskamp, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1521.
- 2001CCR287 I. Lukeš, J. Kotek, P. Vojtišek, and P. Hermann, *Coord. Chem. Rev.*, 2001, **216–217**, 287.
- 2001CEJ2848 H. Plenio, C. Aberle, Y. Al Shihadeh, J. M. Lloris, R. Martínez-Máñez, T. Pardo, and J. Soto, *Chem. Eur. J.*, 2001, **7**, 2848.
- 2001CJC221 X.-C. Su, Z.-F. Zhou, H.-K. Lin, S.-R. Zhu, H.-W. Sun, G.-H. Zhao, and Y.-T. Chen, *Can. J. Chem.*, 2001, **79**, 221.
- 2001EJ1813 L. Burai, R. Király, I. Lázár, and E. Brücher, *Eur. J. Inorg. Chem.*, 2001, 813.
- 2001EJO1943 B. König, M. Pelka, M. Subat, I. Dix, and P. G. Jones, *Eur. J. Org. Chem.*, 2001, 1943.
- 2001EJO4233 S. Pulacchini and M. Watkinson, *Eur. J. Org. Chem.*, 2001, 4233.
- 2001IC2335 P. Comba, S. M. Luther, O. Maas, H. Pritzkow, and A. Vielfort, *Inorg. Chem.*, 2001, **40**, 2335.
- 2001IC4310 D. A. Keire, Y. H. Jang, L. Li, S. Dasgupta, W. A. Goddard, III, and J. E. Shively, *Inorg. Chem.*, 2001, **40**, 4310.
- 2001IC6572 X. Li, S. Zhang, P. Zhao, Z. Kovacs, and A. D. Sherry, *Inorg. Chem.*, 2001, **40**, 6572.
- 2001ICA21 C. B. Smith, J. E. Lincoln, and K. P. Wainwright, *Inorg. Chim. Acta*, 2001, **317**, 21.
- 2001ICA218 P. L. Anelli, A. Beltrami, M. Franzini, P. Paoli, P. Rossi, F. Uggeri, and M. Virtuani, *Inorg. Chim. Acta*, 2001, **317**, 218.
- 2001ICA180 Y. Sun, D. Chen, A. E. Martell, and M. J. Welch, *Inorg. Chim. Acta*, 2001, **324**, 180.
- 2001JA1123 S. Aoki, K. Kawatani, T. Goto, E. Kimura, and M. Shiro, *J. Am. Chem. Soc.*, 2001, **123**, 1123.
- 2001JA7601 M. P. Lowe, D. Parker, O. Reany, S. Aime, M. Botta, G. Castellano, E. Gianolio, and R. Pagliarin, *J. Am. Chem. Soc.*, 2001, **123**, 7601.
- 2001JA7911 E. Kikuta, S. Aoki, and E. Kimura, *J. Am. Chem. Soc.*, 2001, **123**, 7911.
- 2001JA12866 T. Gunnlaugsson, D. A. Mac Dónaill, and D. Parker, *J. Am. Chem. Soc.*, 2001, **123**, 12866.
- 2001JCD240 T. Clifford, A. M. Dandy, P. Lightfoot, D. T. Richens, and R. W. Hay, *J. Chem. Soc., Dalton Trans.*, 2001, 240.
- 2001JOC2722 R. C. Hoye, J. E. Richman, G. A. Dantas, M. F. Lightbourne, and L. S. Shinneman, *J. Org. Chem.*, 2001, **66**, 2722.
- 2001MI239 A. Skwierawska, *J. Supramol. Chem.*, 2001, **1**, 239.
- 2001MMR121 M. Port, C. Corot, O. Rousseaux, I. Raynal, L. Devoldere, J.-M. Idée, A. Dencausse, S. Le Greneur, C. Simonot, and D. Meyer, *Magn. Reson. Mater. Phys. Biol. Med.*, 2001, **12**, 121.
- 2001NJC336 A. K. Mishra and J.-F. Chatal, *New J. Chem.*, 2001, **25**, 336.
- 2001NJC1168 M. Le Baccon, F. Chuburu, L. Toupet, H. Handel, M. Soibinet, I. Deschamps-Olivier, J.-P. Barbier, and M. Aplincourt, *New J. Chem.*, 2001, **25**, 1168.
- 2001NJC1347 M. G. Banwell, A. M. Bray, A. J. Edwards, and D. J. Wong, *New J. Chem.*, 2001, **25**, 1347.
- 2001NMB409 K. Garmestani, Z. Yao, M. Zhang, K. Wong, C. W. Park, I. Pastan, J. A. Carrasquillo, and M. W. Brechbiel, *Nucl. Med. Biol.*, 2001, **28**, 409.
- 2001NMB709 K. Kothari, G. Samuel, S. Banerjee, P. R. Unni, H. D. Sarma, P. R. Chaudhari, T. P. Unnikrishnan, and M. R. A. Pillai, *Nucl. Med. Biol.*, 2001, **28**, 709.
- 2001OL3499 T. Opatz and R. M. J. Liskamp, *Org. Lett.*, 2001, **3**, 3499.

- 2001OS73 G. R. Weisman and D. P. Reed, *Org. Synth.*, 2001, **78**, 73. (Collect. Vol. **10**, 667).
- 2001T2385 F. Chuburu, M. Le Baccon, and H. Handel, *Tetrahedron*, 2001, **57**, 2385.
- 2001TA111 M. Achmatowicz and J. Jurczak, *Tetrahedron Asymmetry*, 2001, **12**, 111.
- 2001TL2735 Q. Wang, S. Mikkola, and H. Lönnberg, *Tetrahedron Lett.*, 2001, **42**, 2735.
- 2001TL3287 M. R. Heinrich and W. Steglich, *Tetrahedron Lett.*, 2001, **42**, 3287.
- 2001TL3823 J. M. M. Griffin, A. M. Skowierawska, H. C. Manning, J. N. Marx, and D. J. Bornhop, *Tetrahedron Lett.*, 2001, **42**, 3823.
- B-2001MI In 'The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging', A. E. Merbach and É. Tóth Eds.; Wiley, Chichester, 2001.
- 2002AJC551 M. P. Lowe, *Aust. J. Chem.*, 2002, **55**, 551.
- 2002ANA229 J. Lizondo-Sabter, R. Martínez-Máñez, F. Sancenón, M.-J. Seguí, and J. Soto, *Anal. Chim. Acta*, 2002, **459**, 229.
- 2002CC312 F. Boschetti, F. Denat, E. Espinosa, and R. Guillard, *Chem. Commun.*, 2002, 312.
- 2002CEJ4965 L. Fabbri, F. Foti, M. Licchelli, P. M. Maccarani, D. Sacchi, and M. Zema, *Chem. Eur. J.*, 2002, **8**, 4965.
- 2002CRV1977 D. Parker, R. S. Dickens, H. Puschmann, C. Crossland, and J. A. K. Howard, *Chem. Rev.*, 2002, **102**, 1977.
- 2002IC1807 S.-A. Li, J. Xia, D.-X. Yang, Y. Xu, D.-F. Li, M.-F. Wu, and W.-X. Tang, *Inorg. Chem.*, 2002, **41**, 1807.
- 2002IC2777 S. Quici, G. Marzanni, M. Cavazzini, P. L. Anelli, M. Botta, E. Gianolio, G. Accorsi, N. Armaroli, and F. Barigelli, *Inorg. Chem.*, 2002, **41**, 2777.
- 2002IC6816 S. C. Burdette and S. J. Lippard, *Inorg. Chem.*, 2002, **41**, 6816.
- 2002IC6846 R. S. Ranganathan, R. K. Pillai, N. Raju, H. Fan, H. Nguyen, M. F. Tweedle, J. F. Desreux, and V. Jacques, *Inorg. Chem.*, 2002, **41**, 6846.
- 2002ICA123 A. Lewin, J. P. Hill, R. Boetzel, T. Georgiu, R. James, C. Kleanthous, and G. R. Moore, *Inorg. Chim. Acta*, 2002, **331**, 123.
- 2002ICA119 D. Chen, Y. Sun, A. E. Martell, and M. J. Welch, *Inorg. Chim. Acta*, 2002, **335**, 119.
- 2002ICA45 D. W. Widlicka, E. H. Wong, G. R. Weisman, R. D. Sommer, C. D. Incavito, and A. R. Rheingold, *Inorg. Chim. Acta*, 2002, **341**, 45.
- 2002JA9105 X. Liang, J. A. Parkinson, M. Weishäupl, R. O. Gould, S. J. Paisey, H.-S. Park, T. M. Hunter, C. A. Blindauer, S. Parsons, and P. J. Sadler, *J. Am. Chem. Soc.*, 2002, **124**, 9105.
- 2002JA12697 R. S. Dickens, S. Aime, A. S. Batsanov, A. Beeby, M. Botta, J. I. Bruce, J. A. K. Howard, C. S. Love, D. Parker, R. D. Peacock, *et al.*, *J. Am. Chem. Soc.*, 2002, **124**, 12697.
- 2002JA12999 R. Reichenbach-Klinke, M. Kruppa, and B. König, *J. Am. Chem. Soc.*, 2002, **124**, 12999.
- 2002JCD48 A. Beeby, L. M. Bushby, D. Maffeo, and J. A. G. Williams, *J. Chem. Soc., Dalton Trans.*, 2002, 48.
- 2002JCD121 R. Reichenbach-Klinke and B. König, *J. Chem. Soc., Dalton Trans.*, 2002, 121.
- 2002JCD4042 D.-X. Yang, S.-A. Li, D.-F. Li, J. Xia, K.-B. Yu, and W.-X. Tang, *J. Chem. Soc., Dalton Trans.*, 2002, 4042.
- 2002JIS757 G. M. Nicolle, É. Tóth, K.-P. Eisenwiener, H. R. Mäcke, and A. E. Merbach, *J. Biol. Inorg. Chem.*, 2002, **7**, 757.
- 2002JP2348 A. Dadabhoy, S. Faulkner, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 2*, 2002, 348.
- 2002JP2552 M. Antoine, H. Bernard, N. Kervarec, and H. Handel, *J. Chem. Soc., Perkin Trans. 2*, 2002, 552.
- 2002JMAC2255 G. Dubois, R. Tripiet, S. Brandés, F. Denat, and R. Guillard, *J. Mater. Chem.*, 2002, **12**, 2255.
- 2002JOC245 D. E. Williams, K. S. Craig, B. Patrick, L. M. McHardy, R. van Soest, M. Roberge, and R. J. Andersen, *J. Org. Chem.*, 2002, **67**, 245.
- 2002JOC4081 P. S. Athey and G. E. Kiefer, *J. Org. Chem.*, 2002, **67**, 4081.
- 2002JOC9107 C. Bazzicalupi, A. Bencini, E. Berni, A. Bianchi, S. Ciattini, C. Giorgi, S. Maoggi, P. Paoletti, and B. Valtancoli, *J. Org. Chem.*, 2002, **67**, 9107.
- 2002MI394 S. Aime, C. Cabella, S. Colombatto, S. G. Crich, E. Gianolio, and F. Maggioni, *J. Magn. Reson. Imag.*, 2002, **16**, 394.
- 2002MI693 D. M. Goldenberg, *J. Nucl. Med.*, 2002, **43**, 693.
- 2002MI129 S. Aoki and E. Kimura, *Rev. Mol. Biotechnol.*, 2002, **90**, 129.
- 2002NJC1054 J. E. W. Scheuermann, F. Ronketti, M. Motevali, D. V. Griffiths, and M. Watkinson, *New. J. Chem.*, 2002, **26**, 1054.
- 2002OL949 B. M. Kim, S. M. So, and H. J. Choi, *Org. Lett.*, 2002, **4**, 949.
- 2002OL1075 H. C. Manning, T. Goebel, J. N. Marx, and D. J. Bornhop, *Org. Lett.*, 2002, **4**, 1075.
- 2002OL4155 W. Jeon, S. J. Son, C. E. Yoo, I. S. Hong, J. B. Song, and J. Suh, *Org. Lett.*, 2002, **4**, 4155.
- 2002SC2441 M. Rubio, C. Astorga, I. Alfonso, F. Rebollo, and V. Gotor, *Synth. Commun.*, 2002, **32**, 2441.
- 2002T2839 M. I. Burguete, B. Escuder, E. García-España, S. V. Luis, and J. F. Miravet, *Tetrahedron*, 2002, **58**, 2839.
- 2002TCC(221) In 'Topics in Current Chemistry', W. Krause Ed.; Springer, Heidelberg, 2002, vol. 221.
- 2002TL1193 I. P. Beletskaya, A. D. Averin, A. G. Bessmertnykh, F. Denat, and R. Guillard, *Tetrahedron Lett.*, 2002, **43**, 1193.
- 2002TL2593 M. Militopoulou, N. Tsiakopoulos, C. Chochos, G. Magoulas, and D. Papaioannou, *Tetrahedron Lett.*, 2002, **43**, 2593.
- 2002TL3217 C. Li and W.-T. Wong, *Tetrahedron Lett.*, 2002, **43**, 3217.
- 2002TL3935 Q. Yuan, E. Fu, X. Wu, M. Fang, P. Xue, C. Wu, and J. Chen, *Tetrahedron Lett.*, 2002, **43**, 3935.
- 2002TL9385 H.-J. Choi, Y.-K. Bae, S.-C. Kang, Y. S. Park, J. W. Park, W.-I. Kim, and T. W. Bell, *Tetrahedron Lett.*, 2002, **43**, 9385.
- 2002USP6489472 C. M. Giandomenico and W. Yang, *US Pat.* 6489472 B2 (2002).
- 2003B710 L. O. Gerlach, J. S. Jakobsen, K. P. Jensen, M. R. Rosenkilde, R. T. Skerlj, U. Ryde, G. J. Bridger, and T. W. Schwartz, *Biochemistry*, 2003, **42**, 710.
- 2003CC766 J. Yoo, D. E. Reichert, and M. J. Welch, *Chem. Commun.*, 2003, 766.
- 2003CC1550 S. J. A. Pope, A. M. Kenwright, S. L. Heath, and S. Faulkner, *Chem. Commun.*, 2003, 1550.
- 2003CC2894 J. A. Halfen and V. G. Young, Jr., *Chem. Commun.*, 2003, 2894.
- 2003CCR27 T. J. Hubin, *Coord. Chem. Rev.*, 2003, **241**, 27.
- 2003DT1852 P. Antunes, P. M. Campello, R. Delgado, M. G. B. Drew, V. Félix, and I. Santos, *Dalton Trans.*, 2003, 1852.
- 2003DT3780 S. J. A. Pope, A. M. Kenwright, V. A. Boote, and S. Faulkner, *Dalton Trans.*, 2003, 3780.
- 2003DT3939 L. Siegfried, M. Honecker, A. Schlageter, and T. A. Kaden, *Dalton Trans.*, 2003, 3939.
- 2003DT4261 S. Carvalho, C. Cruz, R. Delgado, M. G. B. Drew, and V. Félix, *Dalton Trans.*, 2003, 4261.
- 2003EJO1050 F. Chuburu, R. Tripiet, M. Le Baccon, and H. Handel, *Eur. J. Org. Chem.*, 2003, 1050.
- 2003EJO3985 H. Fensterbank, P. Berthault, and C. Larpent, *Eur. J. Org. Chem.*, 2003, 3985.
- 2003IC7156 H. Raznoshik, I. Zilberman, E. Maimon, A. Ellern, H. Cohen, and D. Meyerstein, *Inorg. Chem.*, 2003, **42**, 7156.

- 2003ICA1 D. F. Cook, N. F. Curtis, C. E. F. Rickard, J. M. Waters, and D. C. Weatherburn, *Inorg. Chim. Acta*, 2003, **355**, 1.
- 2003ICA205 K. Q. Ferreira, F. G. Doro, and E. Tfouni, *Inorg. Chim. Acta*, 2003, **355**, 205.
- 2003JA10526 S. Faulkner and S. J. A. Pope, *J. Am. Chem. Soc.*, 2003, **125**, 10526.
- 2003JA14580 C. E. Yoo, P. S. Chae, J. E. Kim, E. J. Jeong, and J. Suh, *J. Am. Chem. Soc.*, 2003, **125**, 14580.
- 2003JHC1 A. H. M. Elwahi, *J. Heterocycl. Chem.*, 2003, **40**, 1.
- 2003JHC383 G. Xue, J. S. Brandshaw, N. K. Dalley, P. B. Savage, and R. M. Izatt, *J. Heterocycl. Chem.*, 2003, **40**, 383.
- 2003JIC217 X. Sun, M. Wuest, Z. Kovacs, A. D. Sherry, R. Motekaitis, Z. Wang, A. E. Martell, M. J. Welch, and C. J. Anderson, *J. Biol. Inorg. Chem.*, 2003, **8**, 217.
- 2003JOC2956 C. Li and W.-T. Wong, *J. Org. Chem.*, 2003, **68**, 2956.
- 2003JOC6435 M. Achmatowicz and L. S. Hegedus, *J. Org. Chem.*, 2003, **68**, 6435.
- 2003MI581 E. De Clerq, *Nat. Rev.*, 2003, **2**, 581.
- 2003NMB581 L. L. Chappell, D. Ma, D. E. Milenic, K. Garmestani, V. Venditto, M. P. Beitzel, and M. W. Brechbiel, *Nucl. Med. Biol.*, 2003, **30**, 581.
- 2003OBC854 Z. Zhang, S. Mikkola, and H. Lönnberg, *Org. Biomol. Chem.*, 2003, **1**, 854.
- 2003OBC879 C. Bianchini, G. Giambastiani, F. Laschi, P. Mariani, A. Vacca, F. Vizza, and P. Zanello, *Org. Biomol. Chem.*, 2003, **1**, 879.
- 2003OBC1707 R. Hovland, A. J. Aesen, and J. Klaveness, *Org. Biomol. Chem.*, 2003, **1**, 1707.
- 2003OBC2795 J. Gao and A. E. Martell, *Org. Biomol. Chem.*, 2003, **1**, 2795.
- 2003PJC85 J. F. Wei, X. Y. Shi, D. P. He, and B. H. Ma, *Pol. J. Chem.*, 2003, **77**, 485.
- 2003SC457 H. C. Manning, A. M. Skowierawska, J. N. Marx, and D. J. Bornhop, *Synth. Commun.*, 2003, **33**, 457.
- 2003SC1911 Q. Yuan, P. Xue, M. Fang, E. Fu, and C. Wu, *Synth. Commun.*, 2003, **33**, 1911.
- 2003T4573 R. Tripier, F. Chuburu, M. Le Baccon, and H. Handel, *Tetrahedron*, 2003, **59**, 4573.
- 2003T10165 L. L. Parker, N. D. Gowans, S. W. Jones, and D. J. Robins, *Tetrahedron*, 2003, **59**, 10165.
- 2003TL1433 I. P. Beletskaya, A. D. Averin, A. A. Borisenko, F. Denat, and R. Guillard, *Tetrahedron Lett.*, 2003, **44**, 1433.
- 2003TL2481 W. Yang, C. M. Giandomenico, M. Sartori, and D. A. Moore, *Tetrahedron Lett.*, 2003, **44**, 2481.
- 2003ZNB447 M. A. Lang and W. Beck, *Z. Naturforsch. B*, 2003, **58**, 447.
- B-2003MI1 N. F. Curtis, in 'Comprehensive Coordination Chemistry II', J. A. McCleverty and T. J. Mayer, Eds.; Elsevier, Amsterdam, 2004, vol. 1, pp. 447–474.
- B-2003MI2 In 'Handbook of Radiopharmaceuticals. Radiochemistry and Applications', M. J. Welch and C. S. Redvanly Eds.; Wiley, Chichester, 2003.
- 2004BCC174 T. Niittymäki, U. Kaukinen, P. Virta, S. Mikkola, and H. Lönnberg, *Bioconjugate Chem.*, 2004, **15**, 174.
- 2004BCC1488 H. C. Manning, T. Goebel, R. C. Thompson, R. R. Price, H. Lee, and D. J. Bornhop, *Bioconjugate Chem.*, 2004, **15**, 1488.
- 2004CC588 F. Boschetti, F. Denat, E. Espinosa, J.-M. Lagrange, and R. Guillard, *Chem. Commun.*, 2004, 588.
- 2004CC2602 M. Polášek, J. Rudovský, P. Hermann, I. Lukeš, L. V. Elst, and R. N. Muller, *Chem. Commun.*, 2004, 2602.
- 2004CEJ5218 J. Moreau, E. Guillon, J.-C. Pierrard, J. Rimbault, M. Port, and M. Aplincourt, *Chem. Eur. J.*, 2004, **10**, 5218.
- 2004CEJ5804 J. P. André, C. F. G. C. Galdes, J. A. Martins, A. E. Merbach, M. I. M. Prata, A. C. Santos, J. J. P. de Lima, and É. Tóth, *Chem. Eur. J.*, 2004, **10**, 5804.
- 2004CEJ6224 R. Cibulka, R. Vasold, and B. König, *Chem. Eur. J.*, 2004, **10**, 6223.
- 2004CRV769 S. Aoki and E. Kimura, *Chem. Rev.*, 2004, **104**, 769.
- 2004CSR246 X. Liang and P. J. Sadler, *Chem. Soc. Rev.*, 2004, **33**, 246.
- 2004DT94 J. A. Aguilar, M. G. Bassallote, L. Gil, J. C. Hernández, M. A. Máñez, E. García-España, C. Soriano, and B. Verdejo, *Dalton Trans.*, 2004, 94.
- 2004DT1441 A. Congreve, D. Parker, E. Gianolio, and M. Botta, *Dalton Trans.*, 2004, 1441.
- 2004DT2115 L. Siegfried, N. McMahon, T. A. Kaden, C. Palivan, and G. Gescheidt, *Dalton Trans.*, 2004, 2115.
- 2004IC1689 J. M. Harowfield, Y. Kim, G. A. Koutsantonis, Y. H. Lee, and P. Thuéry, *Inorg. Chem.*, 2004, **43**, 1689.
- 2004IC2845 M. Woods, Z. Kovacs, R. Kiraly, E. Brücher, S. Zhang, and A. D. Sherry, *Inorg. Chem.*, 2004, **43**, 2845.
- 2004IC6936 A. C. Warden, M. Warren, M. T. W. Hearn, and L. Spiccia, *Inorg. Chem.*, 2004, **43**, 6936.
- 2004IC8023 L. Cronin, P. A. McGregor, S. Parsons, S. Teat, R. O. Gould, V. A. White, N. J. Long, and N. Robertson, *Inorg. Chem.*, 2004, **43**, 8023.
- 2004JA9248 M. Woods, G. E. Kiefer, S. Bott, A. Castillo-Muzquiz, C. Eshelbrenner, L. Michaudet, K. McMillan, S. D. K. Mudigunda, D. Ogrin, G. Tirsó, *et al.*, *J. Am. Chem. Soc.*, 2004, **126**, 9248.
- 2004JIB1712 R. V. Singh and A. Chaudhary, *J. Inorg. Biochem.*, 2004, **98**, 1712.
- 2004JME6625 J. Yoo, D. E. Reichert, and M. J. Welch, *J. Med. Chem.*, 2004, **47**, 6625.
- 2004JMOC163 T. H. Bennur, D. Srinivas, and S. Sivasanker, *J. Mol. Catal. A*, 2004, **207**, 163.
- 2004JOC8183 O. Wiest, C. B. Harrison, N. J. Saettel, R. Cibulka, M. Sax, and B. König, *J. Org. Chem.*, 2004, **69**, 8183.
- 2004MI192 J. R. Morrow and O. Iranzo, *Curr. Opin. Chem. Biol.*, 2004, **8**, 192.
- 2004MI509 S. Aime, A. Barge, C. Cabella, S. G. Crich, and E. Gianolio, *Curr. Pharm. Biotechnol.*, 2004, **5**, 509.
- 2004MI519 M. P. Lowe, *Curr. Pharm. Biotechnol.*, 2004, **5**, 519.
- 2004MI21 A. M. Skowierawska, E. Paluszkievicz, M. Przyborowska, and T. Ossowski, *J. Inclusion Phenom. Macrocyclic Chem.*, 2004, **49**, 21.
- 2004MI A. Mehta, H. W. Schmalte, and H. Berke, *Private Communication to CCDC*, 2004.
- 2004NJC173 R. Tripier, S. Develay, M. Le Baccon, F. Chuburu, F. Michaud, and H. Handel, *New J. Chem.*, 2004, **28**, 173.
- 2004NJC1160 A. C. Warden, M. Warren, M. T. W. Hearn, and L. Spiccia, *New J. Chem.*, 2004, **28**, 1160.
- 2004NJC1301 A. C. Warden, M. Warren, M. T. W. Hearn, and L. Spiccia, *New J. Chem.*, 2004, **28**, 1301.
- 2004OBC570 M. Botta, S. Quici, G. Pozzi, G. Marzanni, R. Pagliarin, S. Barra, and S. G. Crich, *Org. Biomol. Chem.*, 2004, **2**, 570.
- 2004OBC816 M. T. Albelda, J. C. Frías, E. García-España, and S. V. Luis, *Org. Biomol. Chem.*, 2004, **2**, 816.
- 2004OL241 G. Ozturk and E. U. Akkaya, *Org. Lett.*, 2004, **6**, 241.
- 2004MI194 M. R. Chavez, P. Zhao, Z. Kovacs, and A. D. Sherry, *Lett. Org. Chem.*, 2004, **1**, 194.
- 2004SL453 M. Oliver, M. R. Jorgensen, and A. D. Miller, *Synlett*, 2004, 453.
- 2004T5595 C. Li and W.-T. Wong, *Tetrahedron*, 2004, **60**, 5595.
- 2004TL3059 E. A. Lewis, C. C. Allan, R. W. Boyle, and S. J. Archibald, *Tetrahedron Lett.*, 2004, **45**, 3059.

- 2004TL6055 C. Li and W.-T. Wong, *Tetrahedron Lett.*, 2004, **45**, 6055.
- 2005AGE6038 D. A. Evans and J. R. Scheerer, *Angew. Chem., Int. Ed.*, 2005, **44**, 6038.
- 2005AIC173 S. Aime, M. Botta, and E. Terreno, *Adv. Inorg. Chem.*, 2005, **57**, 173.
- 2005BCC237 W. Mier, J. Hoffend, S. Krämer, J. Schuhmacher, W. E. Hull, M. Eisenhut, and U. Haberkorn, *Bioconjugate Chem.*, 2005, **16**, 237.
- 2005CC259 S. Faulkner and B. P. Burton-Pye, *Chem. Commun.*, 2005, 259.
- 2005CC474 D. A. Fulton, M. O'Halloran, D. Parker, K. Senanayake, M. Botta, and S. Aime, *Chem. Commun.*, 2005, 474.
- 2005CEJ2373 J. Rudovský, P. Cígler, J. Kotek, P. Hermann, P. Vojtěšek, I. Lukeš, J. A. Peters, L. V. Elst, and R. N. Muller, *Chem. Eur. J.*, 2005, **11**, 2373.
- 2005CEJ5146 R. Xifra, X. Ribas, A. Llobet, A. Poater, M. Duran, M. Solà, T. D. P. Stack, J. Benet-Buchholz, B. Donnadieu, J. Mahía, *et al.*, *Chem. Eur. J.*, 2005, **11**, 5146.
- 2005CEJ5531 E. Terreno, M. Botta, P. Boniforte, C. Bracco, L. Milone, B. Mondino, F. Uggeri, and S. Aime, *Chem. Eur. J.*, 2005, **11**, 5531.
- 2005CHE1447 O. V. Kulikov, V. I. Pavlovsky, and S. A. Andronati, *Chem. Heterocycl. Compd.*, 2005, **41**, 1447.
- 2005CSR1048 J.-C. Bünzli and C. Piguet, *Chem. Soc. Rev.*, 2005, **34**, 1048.
- 2005DT2138 M. Soibinet, D. Gusmeroli, L. Siegfried, T. A. Kaden, C. Palivan, and A. Schweiger, *Dalton Trans.*, 2005, 2138.
- 2005DT2713 Z. Jászberényi, A. Sour, É. Tóth, M. Benmelouka, and A. E. Merbach, *Dalton Trans.*, 2005, 2713.
- 2005DT2908 S. Fižerová, J. Kotek, I. Císařová, P. Hermann, K. Binnemans, and I. Lukeš, *Dalton Trans.*, 2005, 2908.
- 2005DT3204 T. Gunnlaugsson and J. P. Leonard, *Dalton Trans.*, 2005, 3204.
- 2005DT3829 M. Woods, M. Botta, S. Avedano, J. Wang, and A. D. Sherry, *Dalton Trans.*, 2005, 3829.
- 2005EJI383 P. Comba, G. Linti, K. Merz, H. Pritzkow, and F. Renz, *Eur. J. Inorg. Chem.*, 2005, 383.
- 2005EJI2027 G. Giambastiani, W. Oberhauser, C. Bianchini, F. Laschi, L. Sorace, P. Brueggeller, R. Gutmann, A. Orlandini, and F. Vizza, *Eur. J. Inorg. Chem.*, 2005, 2027.
- 2005EJI2658 S. El Ghachtouli, C. Cadiou, I. Déchamps-Olivier, F. Chuburu, M. Aplincourt, V. Turcry, M. Le Baccon, and H. Handel, *Eur. J. Inorg. Chem.*, 2005, 2658.
- 2005EJI3918 S. J. Ratnakar and V. Alexander, *Eur. J. Inorg. Chem.*, 2005, 3918.
- 2005EJO2044 C. Anda, A. Bencini, E. Berni, S. Ciatini, F. Chuburu, A. Danesi, C. Giorgi, H. Handel, M. Le Baccon, and P. Paoletti, *Eur. J. Org. Chem.*, 2005, 2044.
- 2005EJO4249 J. Yu and D. Parker, *Eur. J. Org. Chem.*, 2005, 4249.
- 2005IC9434 B. Jebasingh and V. Alexander, *Inorg. Chem.*, 2005, **44**, 9434.
- 2005IEC847 Y. Shiraishi, Y. Kohno, and T. Hirai, *Ind. Eng. Chem. Res.*, 2005, **44**, 847.
- 2005JA9593 S. Ho Yoo, B. J. Lee, H. Kim, and J. Suh, *J. Am. Chem. Soc.*, 2005, **127**, 9593.
- 2005JA12847 J. A. Duimstra, F. J. Femia, and T. J. Meade, *J. Am. Chem. Soc.*, 2005, **127**, 12847.
- 2005JIB1661 Q.-X. Xiang, J. Zhang, P.-Y. Liu, C.-Q. Xia, Z.-Y. Zhou, R.-G. Xue, and X.-Q. Yu, *J. Inorg. Biochem.*, 2005, **99**, 1661.
- 2005JOC7042 F. Boschetti, F. Denat, E. Espinosa, A. Tabard, Y. Dory, and R. Guillard, *J. Org. Chem.*, 2005, **70**, 7042.
- 2005MI2271 H. Kobayashi and M. W. Brechbiel, *Adv. Drug. Deliv. Rev.*, 2005, **57**, 2271.
- 2005MI713 A. C. Warden, M. Warren, M. T. W. Hearn, and L. Spiccia, *Cryst. Growth Des.*, 2005, **5**, 713.
- 2005MI302 V. J. Venditto, C. A. S. Regino, and M. W. Brechbiel, *Mol. Pharm.*, 2005, **2**, 302.
- 2005MIM143 M. Modo, M. Hoehn, and J. W. M. Bulte, *Mol. Imag.*, 2005, **4**, 143.
- 2005NMB733 C. J. Smith, W. A. Volkert, and T. J. Hofmann, *Nucl. Med. Biol.*, 2005, **32**, 733.
- 2005MI1 S. Faulkner, S. J. A. Pope, and B. P. Burton-Pye, *Appl. Spectrosc. Rev.*, 2005, **40**, 1.
- 2005OBC112 J. Rudovský, J. Kotek, P. Hermann, I. Lukeš, V. Mainero, and S. Aime, *Org. Biomol. Chem.*, 2005, **3**, 112.
- 2005OBC1013 R. A. Poole, G. Bobba, M. J. Cann, J.-C. Trias, D. Parker, and R. D. Peacock, *Org. Biomol. Chem.*, 2005, **3**, 1013.
- 2005OBC3877 P. T. Gunning, *Org. Biomol. Chem.*, 2005, **3**, 3877.
- 2005OBC4268 V. A. White, N. J. Long, and N. Robertson, *Org. Biomol. Chem.*, 2005, **3**, 4268.
- 2005OL2603 L. Fabbri, F. Foti, and A. Taglietti, *Org. Lett.*, 2005, **7**, 2603.
- 2005OL3417 M. Boicchi, L. Fabbri, F. Foti, E. Monzani, and A. Poggi, *Org. Lett.*, 2005, **7**, 3417.
- 2005PAC1445 G. Anderegg, F. Arnaud-Neu, R. Delgado, J. Felcman, and K. Popov, *Pure Appl. Chem.*, 2005, **77**, 1445.
- 2005S2845 H. Takemura, G. Wen, and T. Shinmyozu, *Synthesis*, 2005, 2845.
- 2005T9031 M. Achmatowicz, A. Szumna, T. Zieliński, and J. Jurczak, *Tetrahedron*, 2005, **61**, 9031.
- 2005TL4387 J. Hovinen and R. Sillanpää, *Tetrahedron Lett.*, 2005, **46**, 4387.
- 2005TL4707 H. C. Manning, M. Bai, B. A. Anderson, R. Lisiak, L. E. Samuelson, and D. J. Bornhop, *Tetrahedron Lett.*, 2005, **46**, 4707.
- 2006AGE2745 S. Hwang, W. Cha, and M. E. Meyerhoff, *Angew. Chem., Int. Ed.*, 2006, **45**, 2745.
- 2006AGE6155 M. Bru, I. Alfonso, M. I. Burguete, and S. V. Luis, *Angew. Chem. Int. Ed.*, 2006, **45**, 6155.
- 2006BCC773 A. Mishra, J. Pfeuffer, R. Mishra, J. Engelmann, A. K. Mistra, K. Ugurbil, and N. K. Logothetis, *Bioconjugate Chem.*, 2006, **17**, 773.
- 2006BCC1105 L. Jaakkola, A. Ylikovski, and J. Hovinen, *Bioconjugate Chem.*, 2006, **17**, 1105.
- 2006CC1064 D. A. Fulton, E. M. Elemento, S. Aime, L. Chaabane, M. Botta, and D. Parker, *Chem. Commun.*, 2006, 1064.
- 2006CCC264 P. Vojtěšek and J. Rohovec, *Collect. Czech. Chem. Commun.*, 2006, **71**, 264.
- 2006CCC337 T. Vitha, J. Kotek, J. Rudovský, V. Kubiček, I. Císařová, P. Hermann, and I. Lukeš, *Collect. Czech. Chem. Commun.*, 2006, **71**, 337.
- 2006CC3791 A.-M. Fanning, S. E. Plush, and T. Gunnlaugsson, *Chem. Commun.*, 2006, 3791.
- 2006CC4116 M. S. Tremblay and D. Sames, *Chem. Commun.*, 2006, 4116.
- 2006CCR1562 A. Aime, S. G. Crich, E. Gianolio, G. B. Giovenzana, L. Tei, and E. Terreno, *Coord. Chem. Rev.*, 2006, **250**, 1562.
- 2006CEJ5535 A. Aurora, M. Boiocchi, G. Dacarro, F. Foti, C. Mangano, P. Pallavicini, S. Patroni, A. Taglietti, and R. Zanoni, *Chem. Eur. J.*, 2006, **12**, 5535.
- 2006CEJ6841 J. Costa, E. Balogh, V. Turcry, R. Tripier, M. Le Baccon, F. Chuburu, H. Handel, L. Helm, É. Tóth, and A. E. Merbach, *Chem. Eur. J.*, 2006, **12**, 6841.
- 2006CEJ9066 S. Aoki, K. Sakamura, N. Matsuo, Y. Yamada, R. Takasawa, S. Tanuma, M. Shiro, K. Takeda, and E. Kimura, *Chem. Eur. J.*, 2006, **12**, 9066.
- 2006CME711 F. Liang, S. Wan, Z. Li, X. Xiong, L. Yang, X. Zhou, and C. Wu, *Curr. Med. Chem.*, 2006, **13**, 711.

- 2006CSR500 M. Woods, D. E. Woessner, and A. D. Sherry, *Chem. Soc. Rev.*, 2006, **35**, 500.
2006CSR512 P. Caravan, *Chem. Soc. Rev.*, 2006, **35**, 512.
2006CSR557 M. Bottrill, L. Kwok, and N. J. Long, *Chem. Soc. Rev.*, 2006, **35**, 557.
2006DT152 D. M. TONEI, D. C. Ware, P. J. Brothers, P. G. Plieger, and G. R. Clark, *Dalton Trans.*, 2006, 152.
2006DT2323 J. Rudovský, M. Botta, P. Hermann, A. Koridze, and S. Aime, *Dalton Trans.*, 2006, 2323.
2006DT2757 S. Pandya, J. Yu, and D. Parker, *Dalton Trans.*, 2006, 2757.
2006DT3108 S. A. J. Pope and R. H. Laye, *Dalton Trans.*, 2006, 3108.
2006EJ12357 C. Schickaneder, F. W. Heinemann, and R. Alsasser, *Eur. J. Inorg. Chem.*, 2006, 2357.
2006EJO9887 C. Pena, I. Alfonso, and V. Gotor, *Eur. J. Org. Chem.*, 2006, 3887.
2006IC8489 L. Frullano, B. Tejerina, and T. J. Meade, *Inorg. Chem.*, 2006, **45**, 8489.
2006IC9225 E. Y. Lau, F. C. Lightstone, and M. E. Colvin, *Inorg. Chem.*, 2006, **45**, 9225.
2006IC9465 A. J. Harte, P. Jensen, S. E. Plush, P. E. Kruger, and T. Gunnlaugsson, *Inorg. Chem.*, 2006, **45**, 9465.
2006IC9834 A. Damsyik, S. F. Lincoln, and K. P. Wainwright, *Inorg. Chem.*, 2006, **45**, 9834.
2006IC10040 K. Sénéchal-David, S. J. A. Pope, S. Quinn, S. Faulkner, and T. Gunnlaugsson, *Inorg. Chem.*, 2006, **45**, 10040.
2006JA2294 J. Yu, D. Parker, R. Pal, R. A. Poole, and M. J. Cann, *J. Am. Chem. Soc.*, 2006, **128**, 2294.
2006JA10716 Q. Wand and H. Lönnberg, *J. Am. Chem. Soc.*, 2006, **128**, 10716.
2006JA11370 R. F. H. Viguier and A. N. Hulme, *J. Am. Chem. Soc.*, 2006, **128**, 11370.
2006JA14032 B. Yoo and M. D. Pagel, *J. Am. Chem. Soc.*, 2006, **128**, 14032.
2006JA15942 E. L. Que and C. J. Chang, *J. Am. Chem. Soc.*, 2006, **128**, 15942.
2006JIB882 T. M. Corneillie, P. A. Whetstone, and C. F. Meares, *J. Inorg. Biochem.*, 2006, **100**, 882.
2006JMC741 A. Quici, M. Cavazzini, M. C. Raffo, L. Armelao, G. Bottaro, *et al.*, *J. Mater. Chem.*, 2006, **16**, 741.
2006JMC1291 T. W. Bell, S. Anugu, P. Bailey, V. J. Catalano, K. Dey, M. G. B. Drew, N. H. Duffy, Q. Jin, M. F. Samala, A. Sodoma, W. H. Welch, D. Schols, and K. Vermeire, *J. Med. Chem.*, 2006, **49**, 1291.
2006JME1291 T. W. Bell, S. Anugu, P. Bailey, V. J. Catalano, K. Dey, M. G. B. Drew, N. H. Duffy, Q. Jin, M. F. Samala, and A. Sodoma, *J. Med. Chem.*, 2006, **49**, 1291.
2006MI109 J. Zhou and P. C. M. van Zijl, *Progress NMR Spectrosc.*, 2006, **48**, 109.
2006NJC247 S. Carvalho, R. Delgado, N. Fonseca, and V. Félix, *New J. Chem.*, 2006, **30**, 247.
2006OL2727 K. Sénéchal-David, J. P. Leonard, S. E. Plush, and T. Gunnlaugsson, *Org. Lett.*, 2006, **8**, 2727.
2006SC653 B. Jebasingh and V. Alexander, *Synth. Commun.*, 2006, **36**, 653.
2006SL3041 I. Gonzáles, A. Roglans, J. Benet-Buchholz, and P. Roura, *Synlett*, 2006, 3041.
2006T1360 M. Kruppa, G. Imperato, and B. König, *Tetrahedron*, 2006, **62**, 1360.
2006T4173 J. D. Chartres, L. F. Lindoy, and G. V. Meehan, *Tetrahedron*, 2006, **62**, 4173.
2006T5748 V. Šrastný, P. Lhoták, I. Stibor, and B. König, *Tetrahedron*, 2006, **62**, 5748.
2006TL2371 L. Ai, J. Xiao, X. Shen, and C. Zhang, *Tetrahedron Lett.*, 2006, **47**, 2371.
2006TL5985 B. Wängler, C. Beck, U. Wagner-Utermann, E. Schirmacher, C. Bauer, F. Rösch, R. Schirmacher, and M. Eisenhut, *Tetrahedron Lett.*, 2006, **47**, 5985.
2006TL6915 N. Kuhnert, D. Göbel, C. Thiele, B. Renault, and B. Tang, *Tetrahedron Lett.*, 2006, **47**, 6915.
2006TL6937 L. M. De León-Rodríguez, Z. Kovacs, A. C. Esqueda-Oliva, and A. D. Miranda-Olvera, *Tetrahedron Lett.*, 2006, **47**, 6937.
2006TL7327 B. Yoo and M. D. Pagel, *Tetrahedron Lett.*, 2006, **47**, 7327.
2007BCC903 B. Yoo and M. D. Pagel, *Bioconjugate Chem.*, 2007, **18**, 903.
2007CC1269 D. E. Prasuhn, Jr., R. M. Yeh, A. Obenaus, M. Manchester, and M. G. Finn, *Chem. Commun.*, 2007, 1269.
2007DT493 P. Lebeduškova, P. Hermann, L. Helm, É. Tóth, J. Kotek, K. Binnemans, J. Rudovský, I. Lukeš, and A. E. Merbach, *Dalton Trans.*, 2007, 493.
2007DT535 M. Försterová, I. Svobodová, P. Lubal, P. Táborský, J. Kotek, P. Hermann, and I. Lukeš, *Dalton Trans.*, 2007, 535.
2007DT971 J. D. Silversides, C. C. Allan, and S. J. Archibald, *Dalton Trans.*, 2007, 971.
2007IC2584 J. Vipond, M. Woods, P. Zhao, G. Tircsó, J. Ren, S. G. Bott, D. Ogrin, G. E. Kiefer, Z. Kovacs, and A. D. Sherry, *Inorg. Chem.*, 2007, **46**, 2584.
2007S679 C. Da Pieve, A. Medina-Molner, and B. Spingler, *Synthesis*, 2007, 679.
2007XXX24 D. Thonon, V. Jacques, and J. F. Desreux, *Contrast Media Mol. Imag.*, 2007, **2**, 24.
2007XXX55 C. Adair, M. Woods, P. Zhao, A. Pasha, P. M. Winter, G. M. Lanza, P. Athey, A. D. Sherry, and G. E. Kiefer, *Contrast Media Mol. Imag.*, 2007, **2**, 55.
2007PCP1318 R. J. Dimelow, N. A. Burton, and I. H. Hillier, *Phys. Chem. Chem. Phys.*, 2007, **9**, 1318.
2007L2517 D. S. Turygin, M. Subat, O. A. Raitman, S. L. Selector, V. V. Arslanov, B. König, and M. A. Kalina, *Langmuir*, 2007, **23**, 2517.

Biographical Sketch



Petr Hermann finished his M.Sc. degree under the supervision of Prof. Ivan Lukeš at the Department of Inorganic Chemistry of Universita Karlova (Charles Univeristy) in Prague in 1987. He started his graduate studies in Lukeš' lab a year later, working on synthesis of phosphonodipeptides and investigation of their complexing properties. He received his Ph.D. degree in 1993. In 1990, he spent three months in Gdańsk (Poland) synthesizing optically active α -aminophosphonic acids with Prof. J. Rachoń. From 1993 to 1995, he was a postdoctoral fellow at the University of Massachusets (Amherst) in the laboratory of Prof. L. D. Quin, where he worked on synthesis and reactivity of derivatives of thiophosphoric acids. He became a lecturer at his alma mater in 1993 and docent in 2004. He has been a member of the editorial board of the *Collection of Czechoslovak Chemical Communications* since 1997. His current research interests are focused on synthesis and complexing abilities of tetraazamacrocycles having phosphorus acid pendant arms. The complexes are investigated as possible contrast agents for MRI and/or for nuclear medicine applications.



Jan Kotek is a former student of Prof. I. Lukeš and Dr. P. Hermann. He finished his M.Sc. degree thesis dealing with synthesis and complexes of phosphonic acid derivatives of cyclam in 1999. In the same year, he started his Ph.D. studies in the same lab studying complexes of phosphorus acid derivatives of macrocycles. He spent a year with Dr. J. A. Peters in Delft (the Netherlands) working on synthesis of phosphorus acid analogs of DTPA and NMR characterization of their complexes. He received his Ph.D. degree in 2003. Later, he was a postdoctoral fellow in Leuven (Belgium) under the supervision of Prof. K. Binnemans. He studied absorption and luminescent properties of lanthanide(III) complexes with macrocyclic ligands. In 2003, he won the second prize in a student competition 'Prix de Chimie' organized by the French Embassy in Prague and he was granted with a fellowship to spent a month in Prof. Guillard's group in Dijon (France). He has been a lecturer in his department since 2000. Now he is a member of Prof. Lukeš' team involved mostly in synthesis, potentiometric, and X-ray studies of macrocyclic ligand and their complexes.

14.12

Ten-membered Rings or Larger with One or More Oxygen Atoms

S. Pappalardo

Università di Catania, Catania, Italy

M. F. Parisi

Università di Messina, Messina, Italy

© 2008 Elsevier Ltd. All rights reserved.

14.12.1	Introduction	667
14.12.2	Crown Ethers as Molecular Receptors	668
14.12.2.1	Cation and Anion Complexation	669
14.12.2.2	Ion-Pair Recognition	672
14.12.2.3	Chiral Recognition and Separations	678
14.12.3	Crown Ether-Based Sensors	683
14.12.3.1	Ion-Selective Electrodes	683
14.12.3.2	Sensors Based on CPs	688
14.12.3.3	Fluorescence Sensing (PET)	694
14.12.3.4	Molecular Switching	699
14.12.4	Crown Ether Supramolecular Assemblies	702
14.12.4.1	Pseudorotaxanes and Rotaxanes	702
14.12.4.2	Catenanes	722
14.12.4.3	Dendrimers	723
14.12.4.4	Miscellaneous Systems	730
14.12.5	Crown Ether-Related Macrocycles	731
14.12.5.1	Calixtubes	731
14.12.5.2	Oxacalixarenes	735
14.12.6	Conclusions and Outlook	739
14.12.7	Further Developments	739
	References	741

14.12.1 Introduction

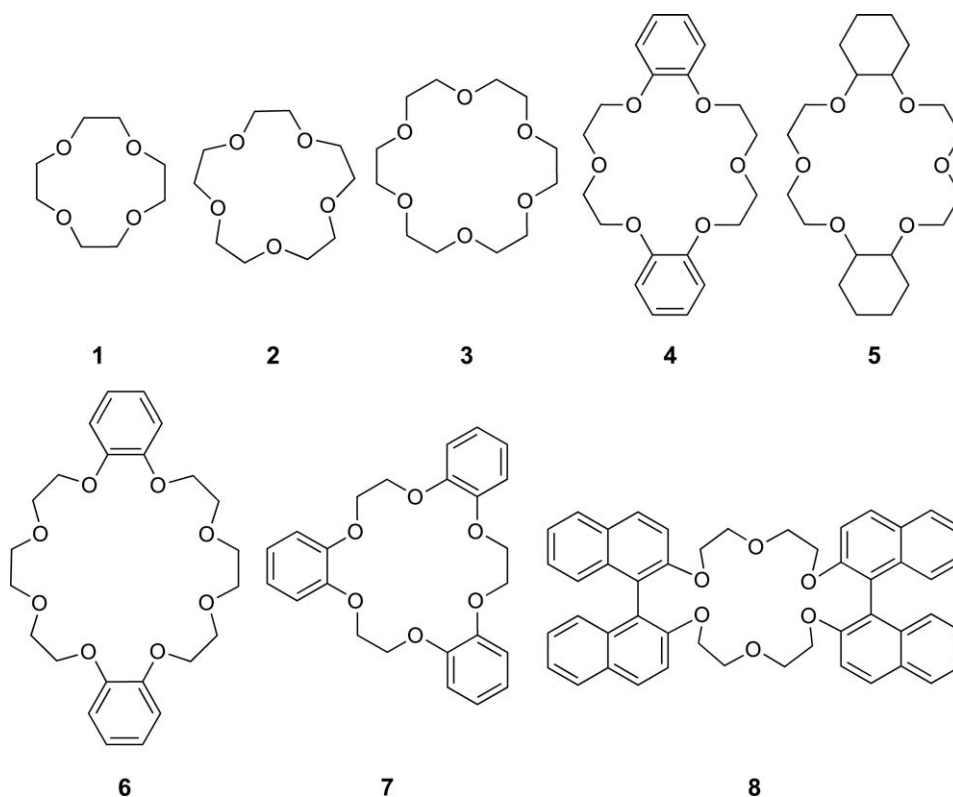
This chapter, by analogy with CHEC-II(1996) <1996CHEC-II(9)809> and CHEC(1984) <1984CHEC(7)731>, deals with cyclic molecules belonging to the family of crown ethers. Among 10-membered rings or larger – bearing only oxygen atoms – these compounds have been, and still are, by far the most intensively studied. Crown ethers were first described in 1967 <1967JA7017> by Pedersen and have played a major role in the growth of host–guest and supramolecular chemistry ever since. In the past decade alone, about 500–600 publications per year have appeared.

The structure, reactivity, and synthesis of crown ether progenitors were extensively covered in CHEC(1984) <1984CHEC(7)731>. In synchrony with the evolution of the field, sections concerning crown-related macrocycles and their applications were introduced in CHEC-II(1996) <1996CHEC-II(9)809>. Crown ethers, over the years, have evolved from final synthetic targets to building blocks for the construction of highly sophisticated architectures and/or essential molecular components deputed to execute specific functional tasks (e.g., sensing, switching, shuttling). In an attempt to provide a coherent and updated account, which reflects recent developments, current state of the art, and new trends in the field, sections have been further reorganized here with respect to the standard chapter arrangement of this series. Because of the enormous structural diversity of crown ether-based derivatives, which range from extremely simple unfunctionalized monocyclic compounds to multicomponent supramolecular assemblies or dendritic/polymeric species, it is inevitable that coverage of their chemistry is going to be less linear and systematic than that in some other chapters of this volume.

There are four main sections in this chapter. Three of them deal with molecular recognition, sensing, and supramolecular self-assembly of crown ethers. The fourth one is about emerging classes of oxygen-containing macrocycles, such as calixtubes and oxacalixarenes. Emphasis has been given to their properties and usefulness, rather than their synthesis as such. The primary sources cited herein should therefore be consulted to this end.

14.12.2 Crown Ethers as Molecular Receptors

The fundamental aspects of crown ethers have been discussed in previous publications, CHEC(1984) <1984CHEC(7)731> and CHEC-II(1996) <1996CHEC-II(9)809>. Undoubtedly, the most striking property of crown ethers is their ability to form complexes with a wide variety of metal ions, including alkali, alkaline earth, transition metal, lanthanoid, as well as inorganic and organic ammonium ions. Compounds **1–8** are among the most common crown ethers, and provide the basic skeleton for the majority of the compounds discussed in this chapter. In its essence, cation complexation by crown ethers is due to a Lewis acid–base interaction <1963JA3533, 1966SCI172>, optimal binding normally being achieved when the crown ether's interior cavity ('hole') is about the same size as a given cation ('hole size relationship') <1967JA7017>. In this case, the stoichiometry of the complex is very often 1:1, with the cation accommodated inside the cavity of the crown ether ring. However, when the size of the cation is larger than that of the cavity, 1:2 or 2:3 metal-to-crown complexes are generally formed <1998CCR1211, 1998AGE172>. The former usually adopts a 'sandwich' structure with the cation located between two crown ether units, while the latter consists of the flatwise arrangement of three crown ether rings, each separated from the next by a cation.



On the other hand, complexes of crown ethers with ammonium (and alkylammonium) ions are characterized by the presence of directionality. In NH_4^+ complexes, three of the four H-bonds coordinate nicely to alternating oxygen atoms in 18-crown-6 or larger crowns (e.g., 21-crown-7), while smaller crown ethers (e.g., 12-crown-4, 15-crown-5) cannot bind more than two of the three NH bonds. Crown ethers also bind neutral molecules containing acidic hydrogens (MeCN, MeNO₂, Me₂CO, Me₂CO₃, urea, thiourea, etc.) by using specific hydrogen-bonding interactions <2002RJD163>.

Over the years, a range of structurally diverse crown ethers has been prepared and fundamental studies has been conducted on them to understand host–guest interactions in solution and the solid state. This has provided the basis for the growth of supramolecular chemistry, and novel applications for crown ethers are now proliferating in several fields of chemistry and biology. In this section, we present a selection of the new trends that have emerged in the literature in the last decade in the field of ion, ion-pair, and chiral molecular recognition.

14.12.2.1 Cation and Anion Complexation

The Lewis acid character of crown ether complex ‘supercations’ and their remarkable propensity to associate with anions have been exploited to create new hybrid materials with interesting potentialities by choosing appropriate combinations of inorganic and organic components.

p-Sulfonatocalix[4]arene shows no tendency to interact with neutral 18-crown-6; however, when its tetrasodium salt is used, two *p*-sulfonatocalix[4]arene units assemble in a head-to-head manner around a [sodium–18-crown-6]⁺ complex to form a dimeric superanionic capsule, shown in Figure 1, that is capable of selectively crystallizing polynuclear aquated metal cations from mixtures within minutes <2006CEJ2772>. Further developments of these findings await for practical applications in analytical and separation sciences.

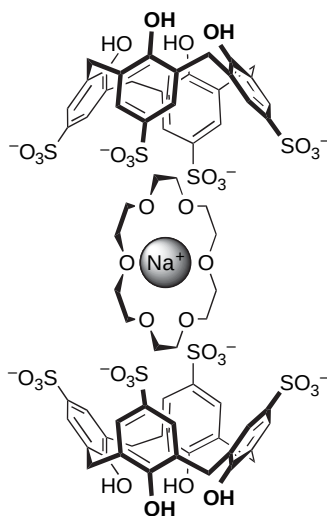


Figure 1 The capsular assembly of the *p*-sulfonatocalix[4]arene units and the [3-Na]⁺ complex.

The first examples of new inorganic polymers with organic spacers (IPOS) system with the general formula [H–G][M–L], where the organic ‘supercation’ [H–G]⁺ is a host (H)–guest (G) complex, such as [(crown ether)–(alkali metal)]⁺, and the inorganic anion [M–L][–] is a metal (M)–ligand (L) coordination polymer, such as [Cd(SCN)₃][–]_∞, were described by Zhang *et al.* <1996JA11813>. These systems were obtained by mixing 18-crown-6, MSCN (M = Na⁺, K⁺), and CdSO₄ in water and characterized by physical measurements and X-ray crystallography. Crystals of these hybrid materials show interesting physical properties, such as nonlinear optical (NLO) effects. A scrutiny of the two structures revealed parallel or antiparallel arrangements of infinite anionic [Cd(SCN)₃][–]_∞ chains, probably caused by the ionic and van der Waals interactions of the one-dimensional (1-D) anionic polymeric chains with the monomeric [H–K]⁺ or dimeric [H–Na]₂²⁺ ‘supercations’. Substantial control over the crystal symmetry is exerted by tuning the stereochemistry of the ‘supercations’, which has an influence on the arrangement of the anionic polymeric chains. These findings may be useful for the development of new strategies in materials fabrication at the molecular engineering level.

Polyoxometalate (POM) chemistry has received considerable attention because of its potential in sorption clathration, catalysis, NLO materials, liquid crystals, charge-transfer salts, electric conductivity, magnetism, and photochemistry, as documented by a series of recent reviews <1998CRV3, 1998CRV51, 1998CRV199, 1998CRV239, 1998CRV273, 1998CRV359>. Hybrid materials derived from POMs and crown ethers have been derived from binary molybdophosphate acid (H₃PMo₁₂O₄₀·*n*H₂O)/18-crown-6 <2000JST(524)133> or ternary molybdophosphate acid/dibenzo-18-crown-6/NaCl mixtures <2001IC5468>. Single crystal X-ray structural data of the former material are consistent with a [C₁₂H₂₄O₆][H₃PMo₁₂O₄₀]·22H₂O formulation. An oxonium ion is located at the center of the crown ether cavity and hydrogen-bonded to it. In the unit cell, the α-Keggin molybdophosphate anions and crown ether units are alternatively arranged in good order along the *c*-axis. On the other hand, the latter complex of composition {[Na(dibenzo-18-crown-6)(MeCN)]₃[PMo₁₂O₄₀]} has an unusual structure in which the Keggin polyoxoanion supports three [Na(dibenzo-18-crown-6)(MeCN)]⁺ supercations through the three terminal oxygen atoms in a single M₃O₁₃ triplet.

Within the precincts of organic–inorganic hybrid materials, it is worth mentioning an interesting copper-aqua-crown ether complex, supported by a Lindqvist-type POM anion [Mo₆O₁₉]^{2–}, obtained by inclusion of the relatively small Cu²⁺ ion into

the considerably larger cavity of crown ether **6** <2005IC7313>. In the crystal, the Cu^{2+} ion resides exactly at the center of the cavity, and is coordinated by two *trans*-ethereal oxygens of the crown unit and four water molecules to give a distorted octahedral geometry around copper, as depicted in **Figure 2**. The Cu^{2+} ion is held in position by a pattern of six hydrogen bonds of coordinated water molecules with the crown ether oxygen atoms. The supercation and supporting POM anion assemble via intermolecular $\text{O}-\text{H} \cdots \text{O}$ hydrogen bonds to give a supramolecular sandwich-type chain-like arrangement.

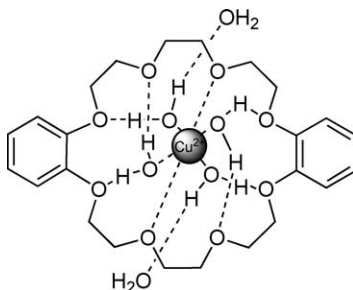


Figure 2 Schematic representation of the H-bonding array in $[\mathbf{6} \cdot \text{Cu}(\text{H}_2\text{O})_4]^{2+}$ supercation.

Hydrated protons $[\text{H}(\text{H}_2\text{O})_n]^+$ are known to play an important role in proton-transfer reactions in chemical and biological systems. The structural characterization of complex $[\text{H}_{13}\text{O}_6][\text{PtCl}_5(\text{H}_4\text{O}_2)] \cdot \mathbf{3}_2$, obtained by treatment of **3** with an aqueous solution of $\text{H}_2[\text{PtCl}_6] \cdot 6\text{H}_2\text{O}$ <1997IC2195>, has offered a good chance to study the clustering behavior of protonated water molecules. The X-ray crystal structure has shown anionic $[\text{PtCl}_5(\text{H}_4\text{O}_2)]^-$ and cationic $[\text{H}_{13}\text{O}_6]^+$ species, which are separated by a crown ether unit. The $[\text{H}_{13}\text{O}_6]^+$ cations, exhibiting the structure $[\text{H}_3\text{O}(\text{H}_4\text{O}_2)_2(\text{H}_2\text{O})]^+$, are also separated by crown ether units so that the crystal is threaded by chains built up of $\mathbf{3}/[\text{H}_{13}\text{O}_6]^+$ units at which the $\mathbf{3}/[\text{PtCl}_5(\text{H}_4\text{O}_2)]^-$ moieties are fixed as lateral branches. Thus, $[\text{H}_{13}\text{O}_6]^+$ cations are embedded in a cage of three crown ether molecules, as sketched in **Figure 3**.

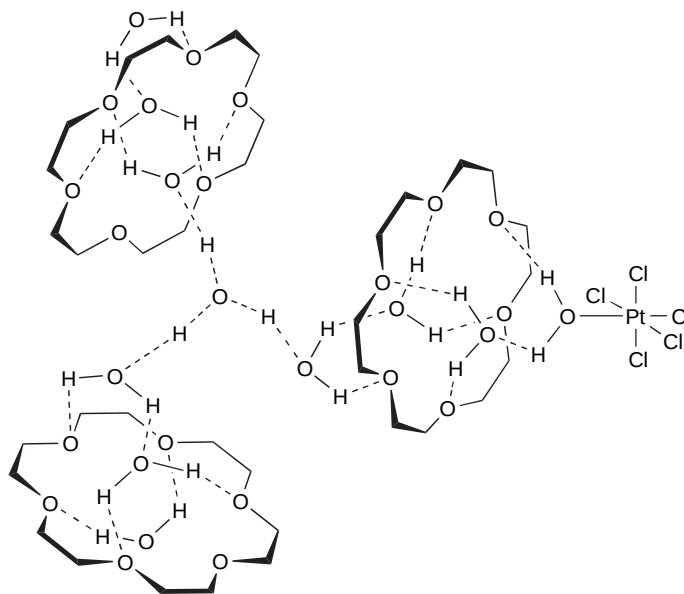


Figure 3 Schematic representation of the embedding of $[\text{H}_{13}\text{O}_6]^+$ cation in the cage generated by three molecules of **3**.

Organometallic compounds are well known for their utility in organic synthesis both as reagents and catalysts. In several cases, the outcome of their preparation strongly depends on the presence of an appropriate crown ether. Crown ether coordination to the metal likely increases the stability and reactivity of organometallic compounds by reducing their extent of aggregation. Notable examples of crown ethers supporting specific anions or cations are

offered by the preparation of organolanthanoid complexes, which are expected to have a rich chemistry <1998CC1843>, the thermally sensitive neutral and cationic trimethylsilylmethyl complexes of the rare earth metals of molecular composition $[\text{Ln}(\text{CH}_2\text{SiMe}_3)_3(12\text{-crown-4})]$ <2003JCD3622>, the formation of the charge-separated barium triphenylmethanide <2001AGE2658>, and the heavier alkali metal complexes of 2-phenylamidopyridine <2004JCD2514>. The geometry of the latter two complexes, as deduced from X-ray studies, is shown in Figure 4.

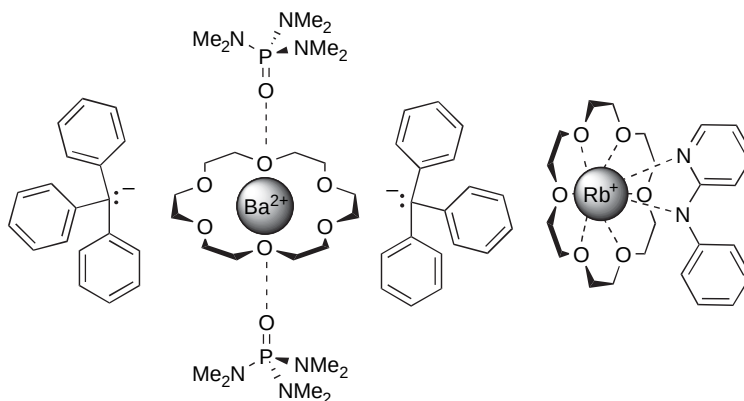


Figure 4 Charge-separated Ba^{2+} (left) and contact ion-pair Rb^{+} (right) complexes with **3**.

Similar arguments are also valid for the successful preparation of hydridophosphinemetalates (shown in Figure 5) from the reaction of transition metal halide complexes with KH and suitable crown ether reagents <1998JA13138>. These materials are quite interesting for their reactivity as strong nucleophiles and reductants.

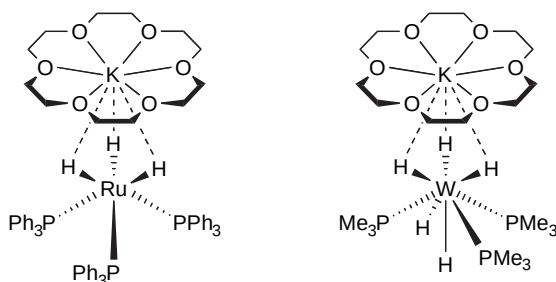


Figure 5 Transition metal hydrides interacting with $[3\cdot\text{K}]^{+}$ supercation.

Crown ether **4** has been shown to be a source of unusual dinuclear silver(I) complexes <2002ICA(332)18>. In the crystal, the silver ions interact with the crown ether ligand at both the hard donor ethereal oxygens and soft benzene ring carbon atoms via intermolecular cation- π -interaction in η^2 -fashion, as depicted in Figure 6. The dimeric structure is further stabilized by the occurrence of intermolecular π - π -interactions between facing benzo groups.

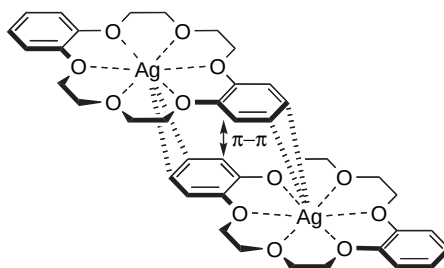
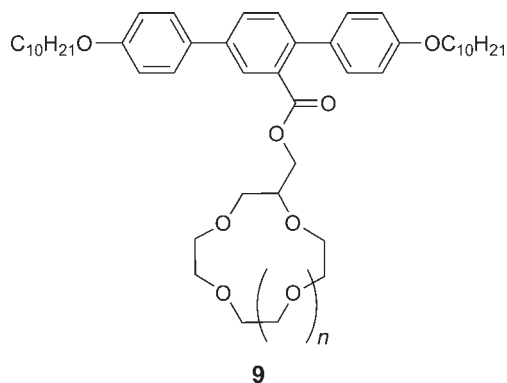
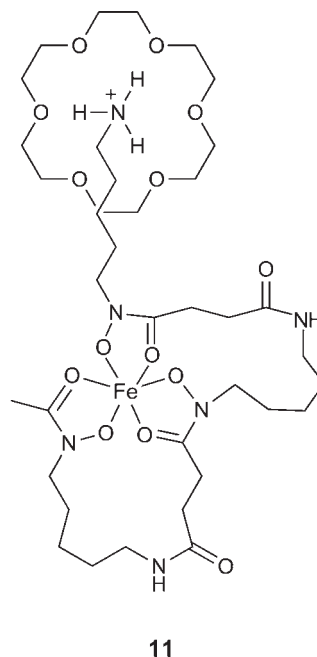
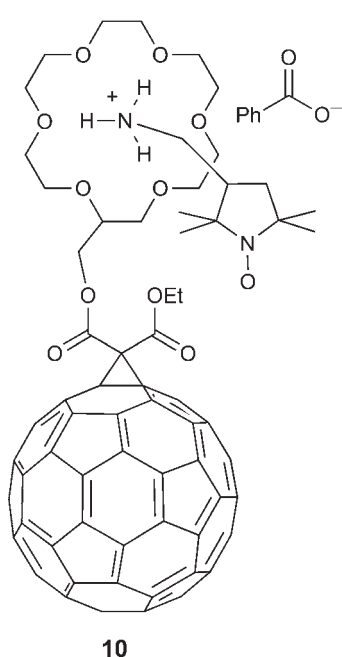


Figure 6 Schematic view of the dinuclear Ag^{+} complex with **4**.

Langmuir films of rod-shaped amphiphilic ionophores **9** with laterally grafted crown ether units of different ring size ($n = 1-3$) have been successfully exploited to investigate alkali metal ion molecular recognition processes at the air-water interface <1998L5245>.



The well-known tendency of 18-crown-6 derivatives to form host-guest complexes with primary alkylammonium ions via hydrogen-bonding interaction with alternating ethereal oxygens has been used for specific applications. These include: (1) the first observation of a radical triplet pair (RTP) that forms upon photoexcitation of the host-guest complex **10** between a [60]fullerene-crown ether conjugate and the benzoate ammonium salt of 3-amino-methyl-[2,2,5,5-tetramethylpyrrolidin-1-oxyl] <2001CC311> and (2) the formation of ionophore-siderophore host-guest supramolecular assemblies **11** involving 18-crown-6 congeners and ferrioxamine B, to mimic some aspects of the molecular recognition of this siderophore at the interface between the cell and the environment through second coordination sphere host-guest complexation <2003JA14760>.



14.12.2.2 Ion-Pair Recognition

Ion-pair recognition, that is, the simultaneous binding of cationic and anionic guest species, is an emerging field of topical interest in supramolecular chemistry because of its implications in various sectors of biology and analytical and environmental chemistry. Several aspects of ion-pair complexation have already been reviewed <1998CC443, 2001AGE486, 2001JPH69, 2003CCR191>. Researchers are increasingly aware of the drawbacks associated with the deleterious role played by ion-pairing in the binding of guest salts by artificial receptors. Ion-pair recognition is currently being tackled either by exploiting the dual (or 'binary' <2002AGE2122>) host strategy, which relies on the

synergistic action of a combination of synthetically accessible cation and anion receptors, or by using the synthetically more demanding heteroditopic receptors, which combine cation and anion recognition sites covalently bound within their structures. According to the first strategy, by using a combination of an appropriate crown ether, as a cation receptor, and either amide <2000CC187>, sulfonamide <2001CC1620>, ureido <2005JA1810>, thioureido <1999ANS1185>, or calix[6]pyrrole <2000CC1207>, as an anion receptor, strong enhancements in the binding, extraction, and/or transport of zwitterion species <1994JA11588> as well as ion-paired salts through liquid membranes have been reported. The complexes likely exhibit pairwise anion/cation separations, as schematically shown in **Figure 7**, for the extraction of CsNO_3 by a combination of tetrabenzo-24-crown-8 as a Cs^+ cation complexing agent with a family of tripodal nitrate anion hosts derived from tris(2-aminoethyl)amine (tren) <2000ANC5258>.

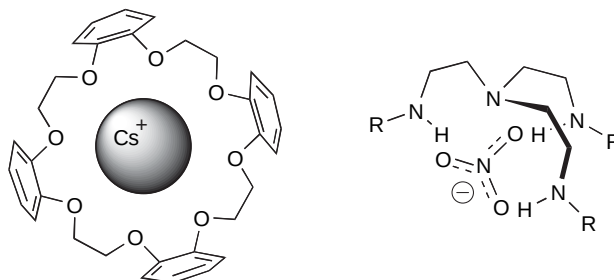
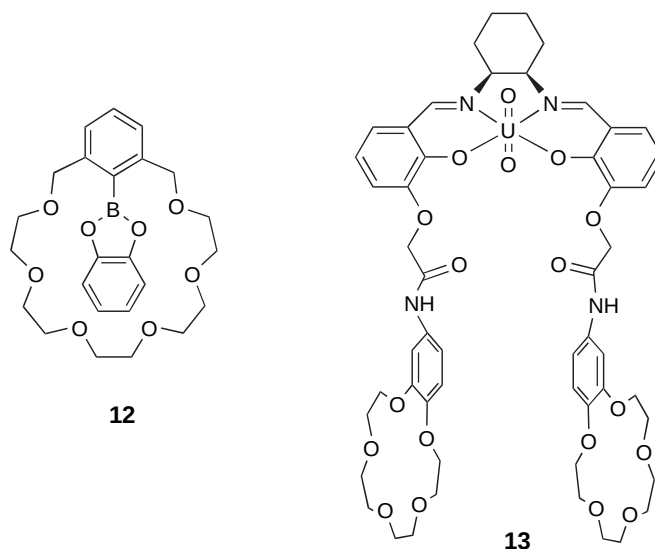


Figure 7 Pairwise cation/anion separation of CsNO_3 by a combination cation and anion receptors.

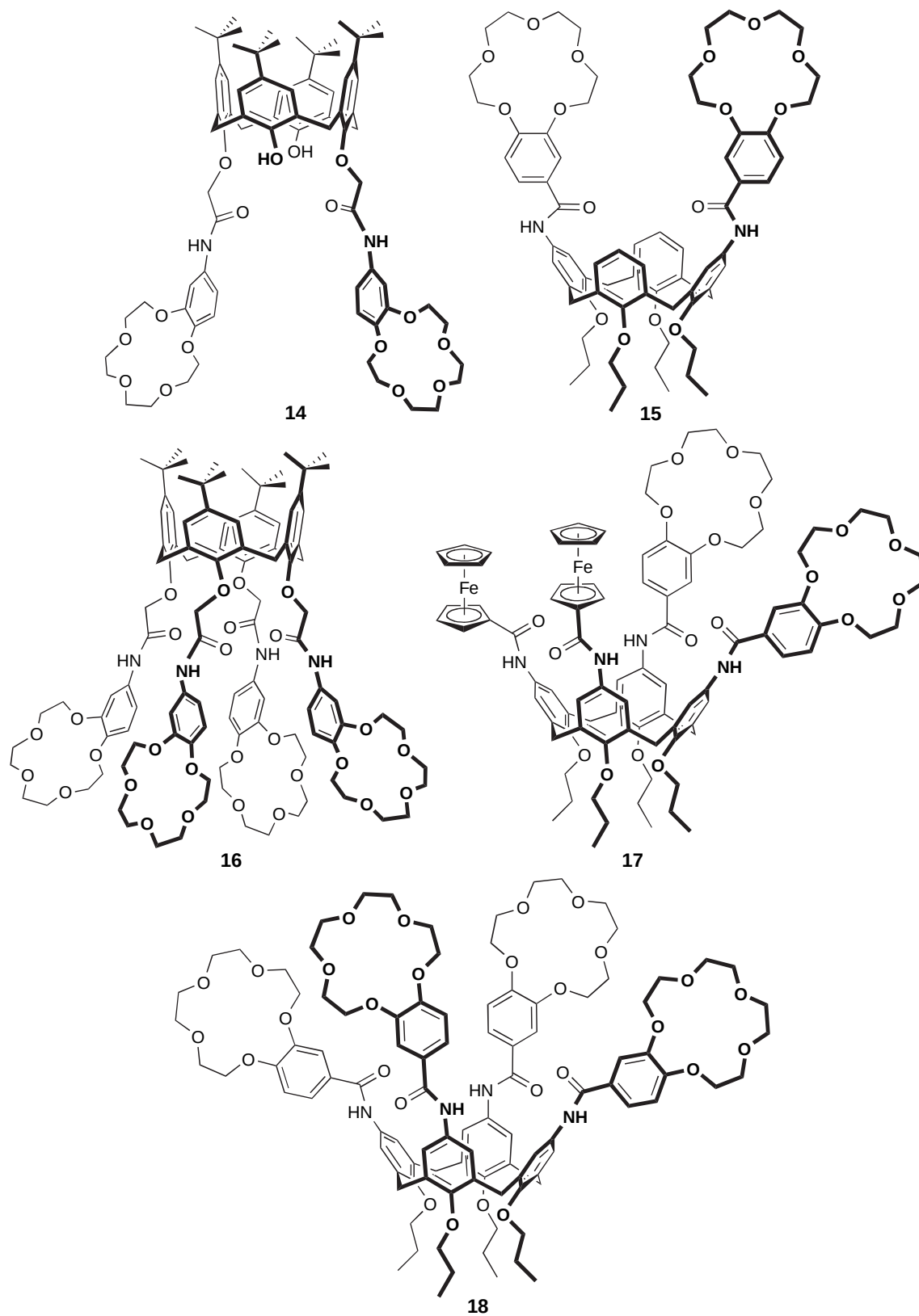
On the other hand, crown ether cation receptors covalently linked to Lewis-acidic groups, hydrogen-bonding or positively charged centers acting as anion-binding sites, have produced a variety of heteroditopic receptors, which very often show cooperative and allosteric binding behaviors. Reetz and co-workers provided an early example of heteroditopic receptor **12**, by covalently linking a crown ether with a Lewis acid boron center <1991AGE1472>. Crown **12** was able to simultaneously bind potassium and fluoride ions. The X-ray crystal structure showed that the K^+ ion is bound within the macrocyclic polyether cavity, while the F^- ion binds to the Lewis-acidic boron center. ^{13}C and ^{11}B nuclear magnetic resonance (NMR) spectroscopy have provided evidence for the existence of the ditopic complex in solution.

Reinhoudt and co-workers have designed **13**, consisting of two benzo-15-crown-5 ether units covalently bound to a salophen unit via amide bonds, for the simultaneous binding of potassium and dihydrogenphosphate ions. K^+ ion is sandwiched between the two crown units, while H_2PO_4^- anion is grasped by the amide and Lewis-acidic uranyl anion-recognition sites <1994AGE467>.



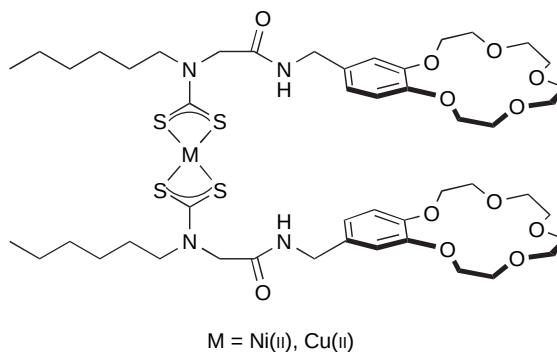
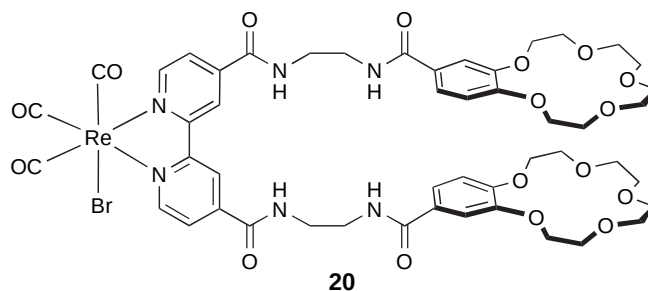
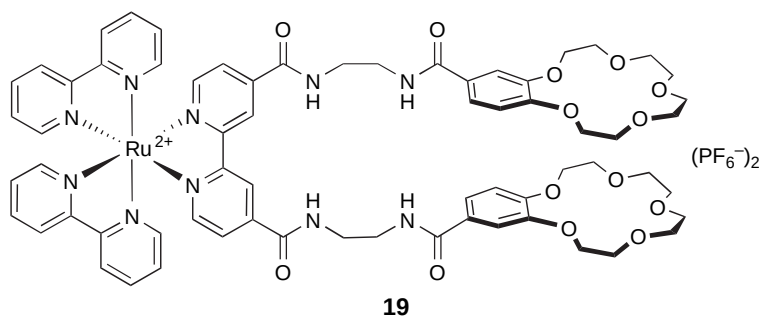
The calix[4]arene platform has been widely used by Beer and co-workers to produce the heteroditopic receptors **14–18** by attaching benzo-15-crown-5 ether moieties at either the upper or lower rim through amide linkers. Compound **17** contains additional ferrocene subunits at the upper rim <1995JCD3117, 2003JCD4451>. Noteworthy, K^+ ion forms 1:1 intramolecular sandwich complexes with the benzo-15-crown-5 moieties of **14**, **15**, and **17** enhancing the strength of

anion (Cl^- , PhCO_2^- , and H_2PO_4^-) binding in polar media via favorable electrostatic effects and preorganization of the amide groups. In addition, bis(ferrocene)-containing calixarene **17** is capable of electrochemical anion recognition, the electrochemical response to benzoate anions amplifying significantly in the presence of potassium ions.

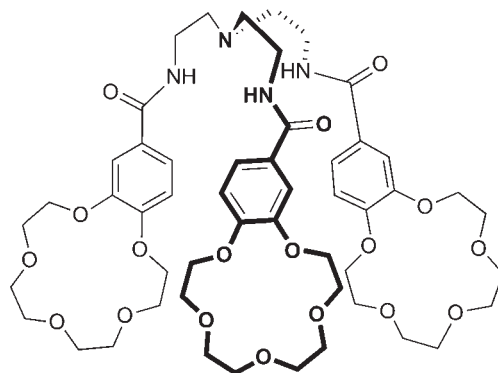


Heteroditopic ruthenium(II) and rhenium(I) bipyridyl bis(benzo-15-crown-5) ion-pair receptors **19** and **20** display, upon K^+ complexation, a remarkable switch in anion selectivity <1998CC825>. In the absence of K^+ , receptors **19** and **20** exhibit a selectivity preference for $H_2PO_4^-$ over Cl^- . However, addition of KPF_6 caused in both cases, the formation of a sandwich K^+ complex, which shows a reversed Cl^- over $H_2PO_4^-$ binding selectivity because of a more favorable electrostatic attraction between K^+ - and Cl^- -bound ions (positive binding cooperativity).

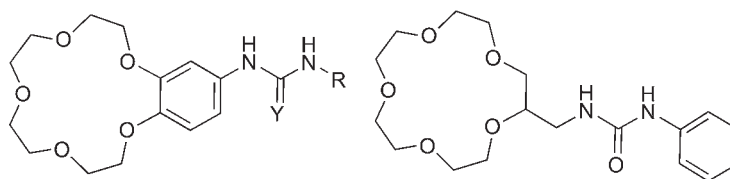
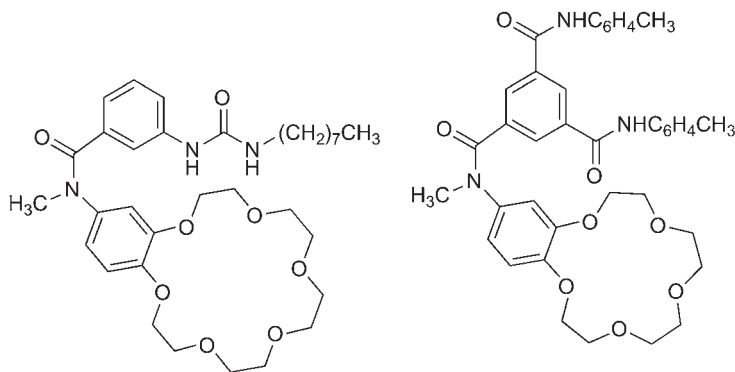
Similarly, nickel(II) and copper(II) transition metal dithiocarbamate ion-pair receptors **21**, containing amide- and crown ether-recognition sites, bind alkali metal cations and various anions. The sandwich K^+ complex of the nickel(II) receptor cooperatively enhanced the binding of acetate anion, while the copper(II) receptor electrochemically can sense anions and cations via perturbation of the copper(II)/copper(I) dithiocarbamate redox couple <2002JSU89>.



The tren-based heteroditopic receptor **22**, featuring a tripodal tetrahedral amide hydrogen-bond anion-recognition site in combination with benzo-15-crown-5 ether cation-binding moieties, has been found to cooperatively bind chloride, iodide, and perchlorate anions via co-bound crown ether-complexed sodium cations. It also can efficiently extract the radioactive sodium pertechnetate from simulated aqueous nuclear waste streams. The anion-binding affinity of **22** is considerably reduced in the absence of a co-bound cation <1999CC1253>.

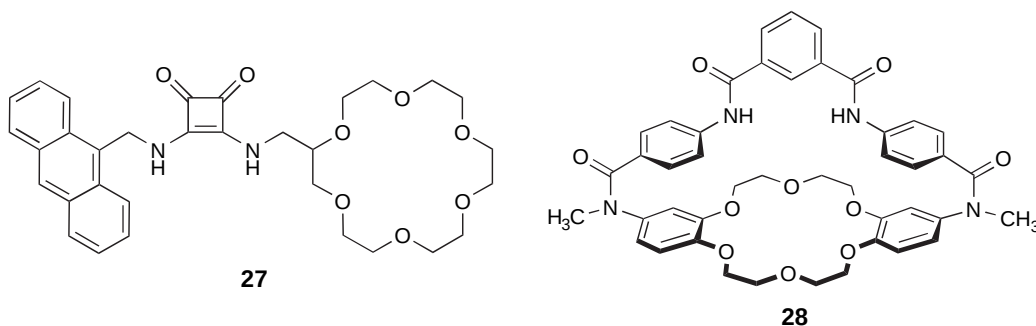
**22**

Solution- (NMR) and solid-state X-ray studies have provided evidence that 4-phenylureabenzo-15-crown-5 **23a** and its Na^+X^- complexes ($\text{X}^- = \text{F}^-, \text{Cl}^-, \text{NO}_3^-, \text{CF}_3\text{SO}_3^-$) self-organized to generate dimeric or tubular polymeric structures thanks to two encoded features: the heteroditopic nature of the receptor (possessing both cation- and anion-binding sites), and the ability of the urea functions to undergo hydrogen-bonding head-to-tail association, as the guide for supramolecular interactions <2003OL3073>. Recent studies on an extended series of alkylurea derivatives of **23** have shown their ability to form aggregates in the solution phase, channel-like arrays in the solid phase, and functional ion channels in planar bilayer membranes <2006JA9541>. U-tube transport experiments have shown that the synergetic ion-pair recognition favors the transport of highly hydrophilic anions. In accordance with these findings, thiourea-functionalized benzo-15-crown-5 **23b** displayed enhanced anion-binding affinity in the presence of Na^+ ions <1999CL1185>. When absorbed at the 1,2-dichloroethane–water interface, **23** exhibited selective binding of the very hydrophilic H_2PO_4^- over hydrophobic anions ($\text{H}_2\text{PO}_4^- > \text{Cl}^-, \text{ClO}_4^-, \text{Br}^-, \text{CH}_3\text{COO}^-$) via the formation of hydrogen bonds <2002NJC1102>. Crown ether receptors with juxtaposed urea or 1,3-phthalimide anion binding sites **24–26** were designed to bind ‘contact ion pairs’, even though their structures have enough flexibility to accommodate ‘solvent-separated ion pairs’ <2000OL3099>.

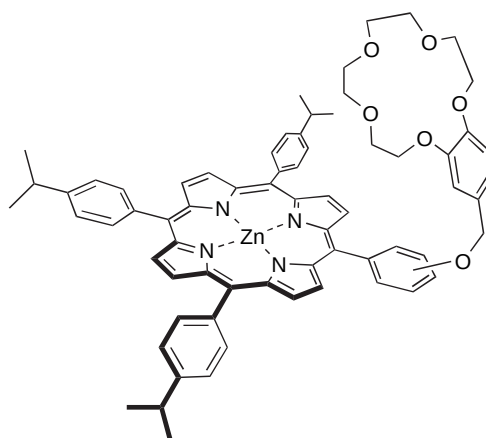
**23a**: Y = O; R = Ph**23b**: Y = S; R = CH_3 **24****25****26**

The effectiveness of squaramide derivatives in the molecular recognition of anions <1999AGE2208> has led to the design of the heteroditopic anthryl squaramide 18-crown-6 conjugate **27**. PB86/SVP-optimized structures suggested that **27** is capable of forming contact ion pair complexes with AcONa and AcOK <2005OL1437>. On the other hand, bicyclic

receptor **28**, comprising a dibenzo-18-crown-6 unit and a bridging 1,3-phenyldicarboxamide moiety, has been shown by an X-ray diffraction study to form a solvent-separated ion pair complex with NaCl [**28**·Na⁺·CHCl₃·Cl⁻] <2000JA6201>.

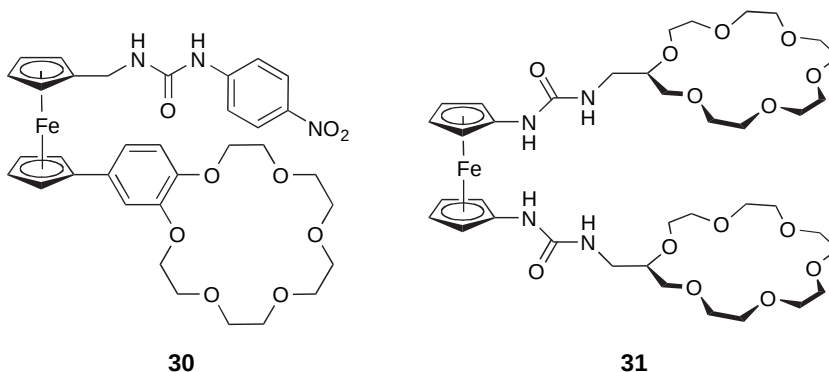


The covalent anchoring of a benzo-15-crown-5 moiety to the *meta* or *para* phenolic oxygen of a zinc tetraphenyl porphyrin via ether formation has produced *m*-**29** and *p*-**29**, respectively. These heteroditopic receptors can bind NaCN in a ditopic fashion with a visible color change, in contrast with other sodium salts (including F⁻, Cl⁻, Br⁻, I⁻, and SCN⁻), which are bound in a monotopic fashion without a color change <2002CC512>.

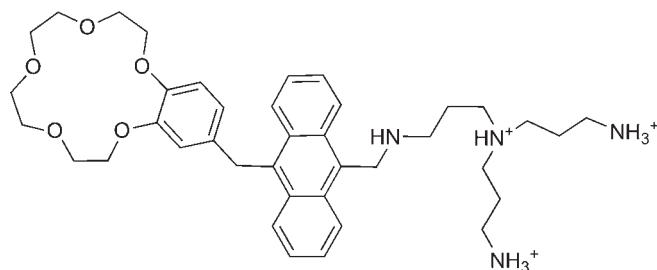


m-**29** = *meta*-substitution
p-**29** = *para*-substitution

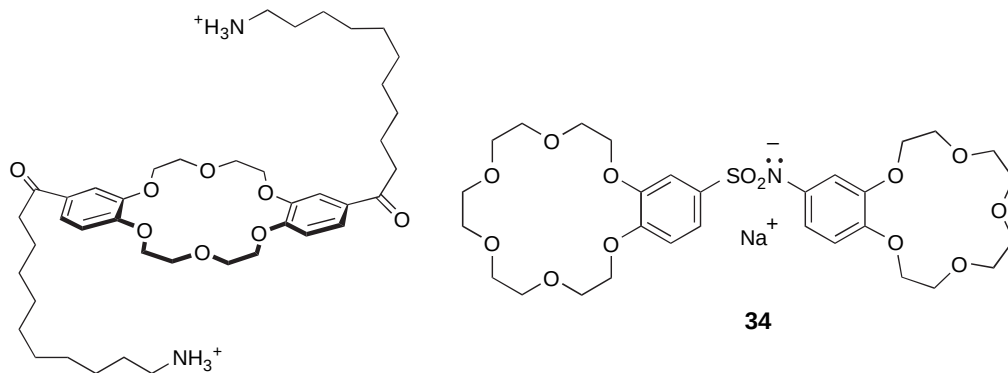
Heteropolytopic receptors **30** and **31** combine the redox activity of the ferrocene spacer with the anion-binding ability of the (*p*-nitrophenyl)urea group(s) and (benzo)-18-crown-6 unit(s) as the alkaline metal cation-binding site(s). Ferrocene **30** can function as a chromogenic molecular switch by using appropriate combinations of anions and cations in solution to control its color <2003CC64>, while **31** showed electrochemical responses to dihydrogenphosphate and fluoride anions. Potentially interfering Cl⁻, Br⁻, HSO₄⁻, and NO₃⁻ anions had no effect on the differential pulse voltammetry experiments, even when they were present in large excess <2005JCD1159>.



Sensor **32** <2003CC2010>, built up according to the receptor₁(cationic)–spacer₁–fluorophore–spacer₂–receptor₂(anionic) format by choosing a benzo-15-crown-5 unit as a sodium receptor, a tris(3-aminopropyl)amine unit in the triply protonated form as a phosphate anion binder, and a 9,10-anthracenodiyl moiety to detect fluorescence changes upon simultaneous binding of the salt, behaved as an AND logic gate <2002CC2461> having sodium and phosphate as ionic inputs and fluorescence enhancements as output.

**32**

Multifunctional (di)benzo-18-crown-6 derivatives **33** <1997LA1853> and **34** <1999T9221> have been designed for multipoint molecular recognition of zwitterionic amino acids by exploiting a combination of noncovalent interactions. Bis-crown **34** was also active in the transport of zwitterionic phenylalanine through bulk liquid membranes as a function of the co-transported alkali cation.

**33****34**

14.12.2.3 Chiral Recognition and Separations

Chiral recognition is a chemical interaction, frequently occurring in living systems, by which a given chiral molecule (receptor/host) recognizes a particular stereoisomer (substrate/guest). Studies aimed at mimicking such phenomena have led to a better understanding of the fundamental mechanisms governing molecular recognition. This process takes place via noncovalent host–guest interactions that typically involve van der Waals, electrostatic, or hydrogen-bonding attractions tempered by steric repulsions. The elucidation of the chiral recognition event has important consequences in a wide range of disciplines, including analytical and separation sciences, biochemistry, pharmaceuticals, and catalysis. Nowadays, a rigorous assessment of the enantiomeric purity of chiral natural or synthetic products is a recommended step for their utilization in medicine, the food industry, and agriculture <2001JCH(906)3>.

Among the wide variety of synthetic chiral hosts capable of chiral discrimination, chiral crown ethers (typically 18-crown-6 ether derivatives) are the molecules of choice for the chiral recognition and separation of chiral primary amines, amino alcohols, amino acids, and even peptides <1997CRV3313>. The primary driving force for host/guest recognition is provided by the tripodal arrangement of the three $^+\text{NH}\cdots\text{O}$ hydrogen bonds between the ethereal oxygens of the 18-crown-6 framework and the ammonium moiety of the enantiomer (see Figure 8). However, for an efficient enantiodiscrimination to occur, a minimum of three simultaneous host/guest interactions should operate <1952JCS3940>, of which at least one must be stereoselective. These requirements are hopefully met by endowing the structure of the crown ether host with chiral barrier(s) and/or function(s) capable of establishing specific noncovalent interactions with one of the two enantiomers.

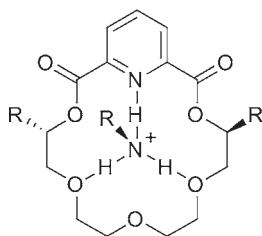
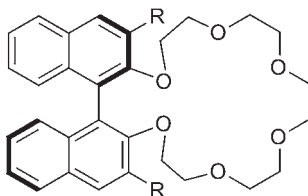


Figure 8 Tripodal alkylammonium recognition by a chiral pyridino-18-crown-6 ether.

Pioneering studies by Cram and co-workers employed crown ether arrays **35a–c** incorporating a 2,2'-dihydroxy-1,1'-binaphthyl unit as the chiral barrier [<1975PAC327>](#). Enhancements in the chiral recognition of amino acids were obtained by placing large substituents, at the 3,3'-positions of the binaphthyl moiety, so as to raise its steric barrier. 3,3'-Diphenyl derivative **35c** is often the benchmark to which other chiral crown ethers are compared [<1981JOC393>](#).

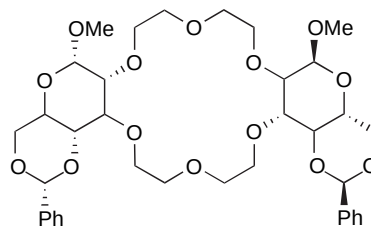
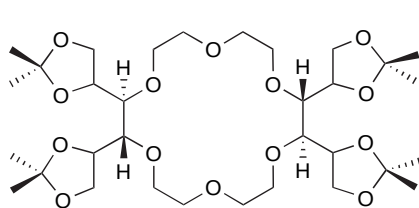


35a: R = H

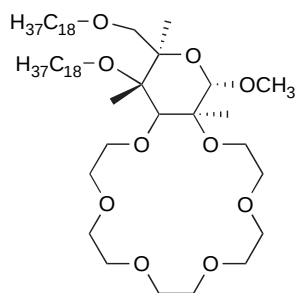
35b: R = Me

35c: R = Ph

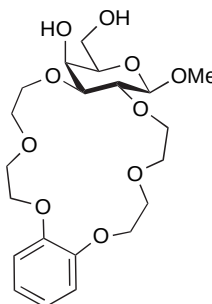
Over the years, a vast assortment of chiral macrocycles, exemplified by compounds of type **36** [<1979CSR85>](#), **37** [<1998JPM69>](#), and **38** [<2001TA1125>](#), has been prepared by incorporating chiral carbohydrate residues into the 18-crown-6 or benzo-18-crown-6 scaffolds. Further chiral 18-crown-6 ethers of type **39** and azophenolic pseudo-18-crown-6 ethers of type **40** have also been synthesized by stepwise procedures starting from enantiomerically pure *cis*-1-phenylcyclohexane-1,2-diol, *trans*-1-phenylcyclohexane-1,2-diol, and *trans*-1,2-diphenylcyclohexane-1,2-diol building blocks [<1996CCR199>](#). Other important classes of C_2 -symmetric chiral 18-crown-6 ether receptors include (*R*)-(+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid **41**, obtained by Lehn from readily available L-tartaric acid [<1975AGE764, 1980HCA2096, 1988JPM351>](#), (–)-2,3-*O*-isopropylidene-D-threitol-derived crown ethers **42** and **43**, containing side lipophilic chains [<2005TA2673>](#), and **44**, bearing two polynuclear aromatic sidearms [<2005TL4331>](#).



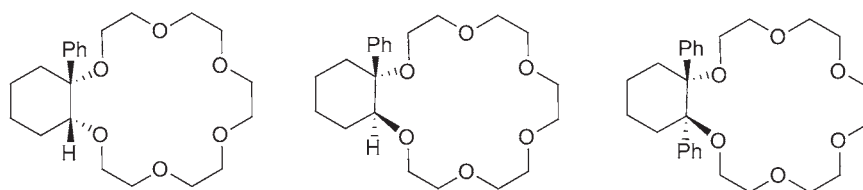
36



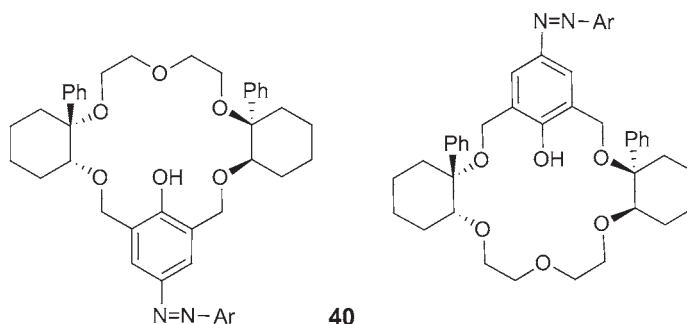
37



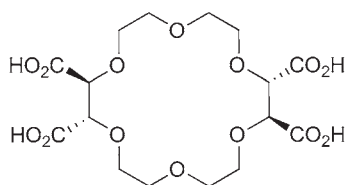
38



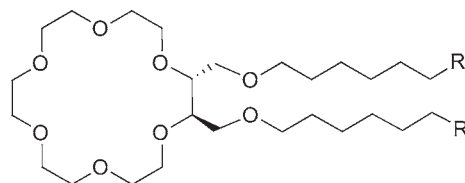
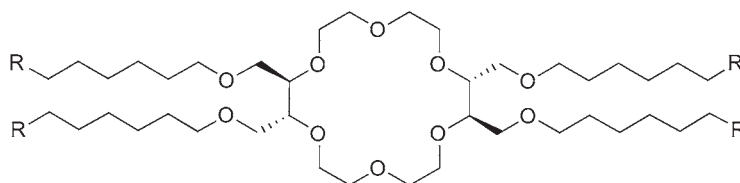
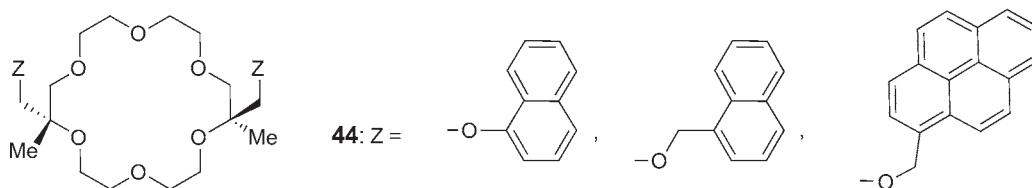
39



40



41

42: R = OCH₂Ph, OH43: R = OCH₂Ph, OH

44: Z =

As previously stated, the determination of optical purity is a critical issue in several fields. Although a variety of techniques of assaying exact enantiomeric composition have been developed, so far high-performance liquid chromatography (HPLC) separation of enantiomers on crown ether-based chiral stationary phases (CSPs) is probably the most efficient, accurate, and convenient means for the direct resolution of underivatized chiral amino compounds <2003JSS242>. Early CSPs, obtained by dynamically coating chiral crown ethers (e.g., **35c**) on octadecyl silica gel, showed serious drawbacks associated with the leaching of the selector when using mobile phases with an elevated CH₃OH content <1992JCH(625)101>. Conversely, robust CSPs resulted from the covalent bonding of the selector to a solid support, such as aminopropylsilanized silica gel. The most popular CSPs are those derived from crown ether **41** <1998JCH(805)85, 2003JCH(984)163, 2005MIJ213> and chiral pseudo-18-crown-6 ethers <2005JCH(1078)35, 2005CH142>. Some of these are shown in **Figure 9**.

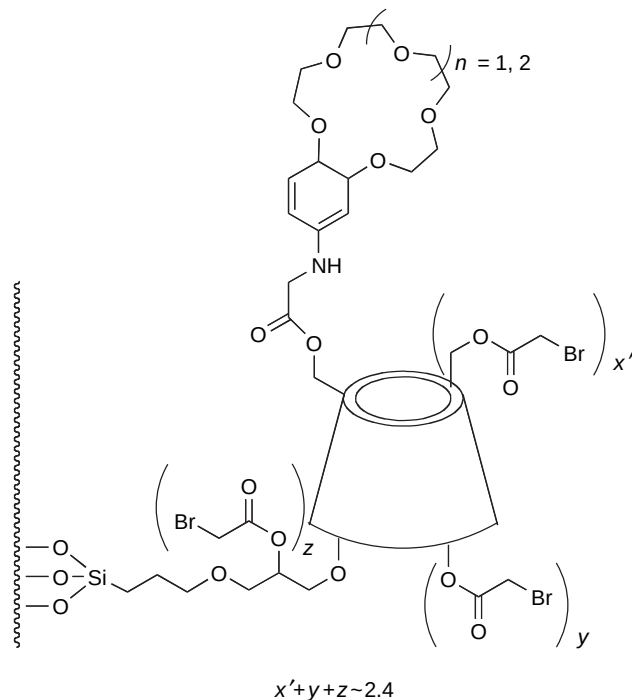
These CSPs are able efficiently to separate most of the tested analytes, which encompass amino acids, amino acid methyl esters, amino alcohols, and lipophilic amines.

Capillary electrophoresis (CE) provides a valid alternative to HPLC methods for chiral separations. The direct resolution of racemates requires only an enantiomerically pure additive (chiral selector) to be dissolved in the running buffer. The experimental conditions affecting the separations and an overview of practical applications have been compiled <1999ELP2605>.

Tetraacid **41** is among the most effective chiral selectors used in CE for the separation of the enantiomers of primary amines. So far, more than 100 structurally diverse amines (amino acids <1992ANC2815, 2004ELP2755, 2005CHR505>, small peptides <1996ANC2361>, pharmaceutical drugs <1997JCH(757)225>, and hormones <1997JCH(757)328> have been successfully separated.

Synergistic effects in terms of efficiency of CE enantioseparation have been observed when a second (not necessarily chiral) selector is added in the same buffer system. It has been demonstrated that a combination of 18-crown-6 and β -cyclodextrin can achieve or enhance enantioselective separations of nonpolar amines, which are rarely observed with cyclodextrins alone <1997JCH(781)129, 1997JCH(695)157>. The formation of a ternary sandwich complex (dual complex) is postulated to be responsible for such a beneficial effect.

The above-mentioned results have contributed to the development of hybrid CSPs **45** based on crown ether-cyclodextrin conjugates, which have found important applications in capillary electrochromatography (CEC) to separate chiral amino compounds <2002HCA3283>. CEC is a promising liquid chromatography technique, which combines the high efficiency of CE with the high selectivity of HPLC methods <2000EL3220>.



45

NMR spectroscopy is another suitable analytical tool for the rapid determination of the enantiomeric composition of chiral compounds, and for the assignment of their absolute configurations <2003CH256, 2004CRV17>. Chiral crown ethers are widely employed as chiral discriminating agents or chiral solvating agents (CSAs) toward protonated primary amines <1988TS207, 1997CRV3313, 1997MRC273, 2000JOC1243>. The interaction of the CSAs with the various analytes produces mixtures of diastereomeric complexes that normally display different NMR chemical shifts.

Comparative studies of the NMR discriminating ability of a number of structurally diverse chiral crown ethers for protonated amines, amino alcohols, and underivatized amino acids have shown that commercially available (*R*)-(+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid **41** provides the best enantiodiscrimination in the ^1H NMR spectrum of most substrates <1997MRC273, 2000JOC1243, 2000TL3769, 2001TA1125>. The addition of lanthanide(III) nitrate salts to crown–substrate mixtures often enhanced the enantiomeric discrimination in the ^1H NMR spectra whenever chiral crown ethers are endowed with carboxylic acid (as in **41**) or β -diol unit(s) (as in **38**) capable of forming a chelate bond with the metal ion <2001TA1125, 2004ANB1536>.

Studies aimed at clarifying the mechanism of enantioselection associated with **41**, making use of a combination of molecular dynamics calculations and NMR techniques <2001J(P2)1685>, as well as X-ray diffraction data <2004OBC3470>, have led to a better comprehension of the subtle interactions that characterize and differentiate the diastereomeric complexes of tetra-acid **41** with the D,L-amino acid pairs.

Recent studies have demonstrated the unusual ability of **41** compared to other 18-crown-6 ethers (devoid of carboxylic acid groups) to associate with and enantiomerically discriminate neutral secondary amines in CD_3OD . By assuming a proton transfer from the side carboxylic acid functionality of the crown ether to the nitrogen, the resulting secondary ammonium ion is believed to form two $\text{NH}^+\cdots\text{O}$ hydrogen bonds with the ethereal crown ether oxygens and an ion pair with the carboxylate anion <2006OL2823>.

14.12.3 Crown Ether-Based Sensors

A chemical sensor is a composite device capable of transforming a chemical response into a signal analytically useful to quantify the presence of an analyte. In order to sense biologically and environmentally important ions, sophisticated crown ether-derived host molecules (sensing agents or chemosensors) with specific functions have been developed with the aim of amplifying signal transduction associated with the molecular recognition event. An artificial host molecule can be viewed as a potential chemosensor if analyte binding occurs in a reversible manner. This allows analyte concentration to be measured at equilibrium by analyzing signal transduction originating from either the chemosensor-bound species or the analyte-free chemosensor.

Owing to their relative ease of synthesis and structural modification, crown ethers are attractive targets as ionophores and selective sensing agents for a broad range of inorganic ions; for a recent review, see <2004CRV2723>. In the following subsections, we will survey a selection of crown ether-based host molecules typically used as chemosensors for the detection of ions by making use of analytical methods, such as ion-selective electrodes (ISEs), conjugated polymers (CPs), and fluorescent sensors.

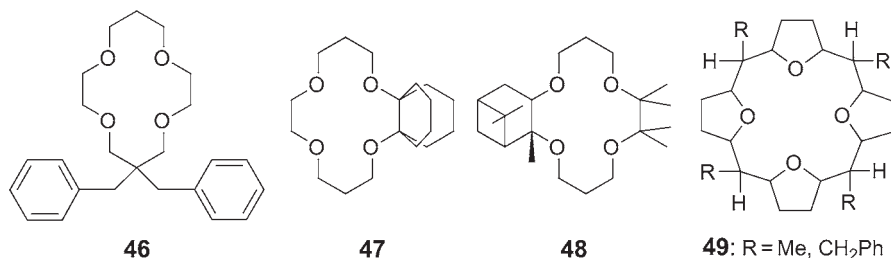
14.12.3.1 Ion-Selective Electrodes

ISEs are one of the most convenient and reliable analytical tools for estimating metal ion concentrations. They have been studied for more than three decades, and are now routinely employed for direct potentiometric measurements of various ionic species in environmental, industrial, and clinical samples <1997JCE171, 1997JCE177>. The method relies on the electrochemical signal transduction triggered by a molecular recognition process that takes place at the interface of an organic membrane and an aqueous solution, and leads to a guest-selective increase in the membrane potential. Efficient charge separation between the complexed cationic hosts (lipophilic) and their counteranions (hydrophilic) is achieved by exploiting either natural (e.g., valinomycin) or synthetic (e.g., crown ether) ionophores, as long as they are capable of selectively forming inclusion-type complexes with the target analytes. Special emphasis has been placed on the composition of the membrane phase and on the development of new ionophores, with the aim of enhancing the potentiometric response characteristics (e.g., selectivity, sensitivity, linear range, and lifetime) of the ISEs.

ISE crown ether-sensing agents (for leading reviews, see <1998CRV1593, 1998JPM165>) have been developed according to the following guiding principles: (1) molecules structured in compliance with the ‘hole size relationship’ ensure the formation of tightly encapsulated 1:1 host–guest complexes; (2) bis-crowns having a flexible spacer and size of the crown rings slightly smaller than the target metal cation selectively form sandwich-type intramolecular 1:1 complexes; (3) bulky substituents, positioned at the periphery of a crown ether ring fitting the target metal ion, avoid the formation of intermolecular 2:1 sandwich-type complexes with the larger cations <1986J(P2)1945>.

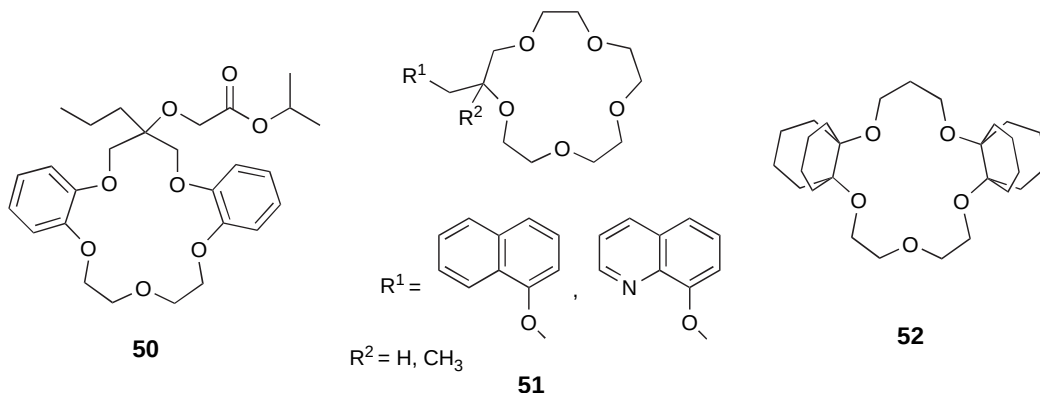
The major interest for Li^+ analysis arises from the prophylactic and therapeutic action of Li^+ in various affective disorders. Since the therapeutic action of Li^+ is limited by adverse side effects above 2.0–2.5 mM Li^+ , monitoring of this analyte is indispensable. Reagents and methods (including ISE) for achieving high lithium over sodium selectivity and their use in blood lithium measurement have been reviewed <1996JPB899>. Enhanced lithium

selectivity was obtained with lipophilic 14-crown-4 derivatives bearing large substituents or an additional binding site in the sidearm <1986J(P2)1945, 1998ANC4286>, and even a bulky decaline <1993AC3404> or pinane <1993AC2704> ‘block’ subunit into the ethano-bridge section of the base crown ring, best represented by 46–48. The latter was used in combination with a lipophilic anion dye to develop a flow-through optical sensor probe, which exhibits a remarkable Li^+/Na^+ selectivity ($\sim 10\,000$) with a detection limit $1 \times 10^{-5} \text{ M}$ without interference from sodium. Tetrahydrofuran-based 16-crown-4 derivatives 49 having different substituents at four bridged carbon positions have also been employed as neutral carriers in the fabrication of lithium ISEs <1993BKC123, 1995BKC197, 1997AN1445>. The crown 49 with only methyl groups at the four bridged positions ($\text{R} = \text{CH}_3$) exhibited the best selectivity for Li^+ over other cations. Although the Li^+/Na^+ selectivity was not very high ($\log K^{\text{pot}} = -2.8$), the serum components do not interfere significantly with the lithium measurements.

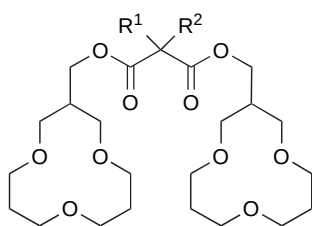


A major interest for Na^+ analysis with ISEs comes from clinical chemistry <1988AN373>. ISEs based on lariat dibenzo-16-crown-5 ether 50 display an inverted Na^+/Li^+ selectivity (~ 5000) <1995ANC2405>. On the other hand, tuning of the structure of lariat crown ethers 51 has been reported to lead to significant shifts in Na^+/K^+ selectivity. Subtle change of a single atom in the sidearm structure, to induce coordinating ability to the sidearm, suffices to alter the Na^+/K^+ selectivity by roughly 5 orders of magnitude <2002ELA186>.

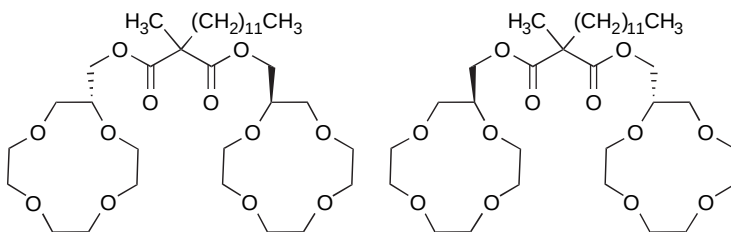
In the quest for highly lipophilic sodium-selective ionophores derived from 16-crown-5, whose cavity fits the size of Na^+ ion, various derivatives differing for the type, number, and position of the bulky blocking walls present in the crown ether ring have been evaluated. The 16-crown-5 derivatives having two bulky ‘block’ subunits showed high Na^+ selectivity relative to K^+ , the bis-decalino derivative 52 exhibiting the highest Na^+/K^+ selectivity (~ 1000) <1996ANC208>.



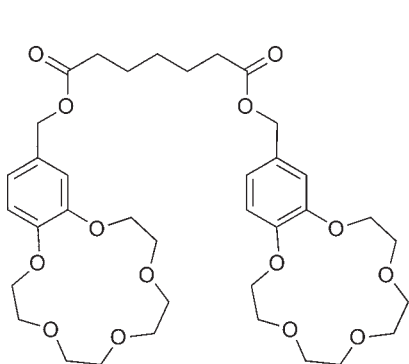
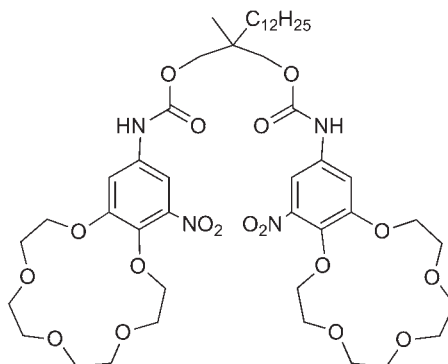
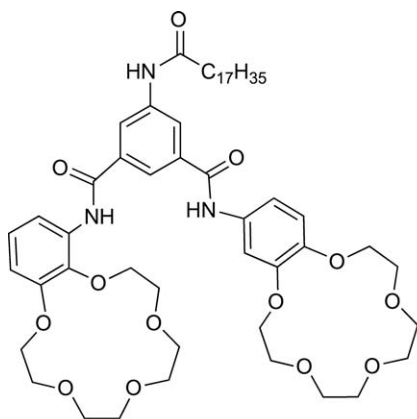
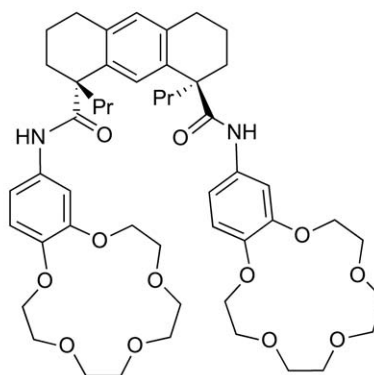
Bis(crown ether)s connected by a flexible spacer are a source of intramolecular sandwich-type complexes with alkali metal ions <B-1992MI(45)198, 1994CRV939>. A conformational analysis (based on a combination of semi-empirical and *ab initio* methods) performed on 12-crown-3 and 12-crown-4 has predicted that, in the case of the sandwich-type complexation, the nucleophilic cavity of 12-crown-3 rather than that of 12-crown-4 would be more prone to complexation with the Na^+ ion. Accordingly, ISEs based on bis(12-crown-3) derivatives with dialkylmalonate spacers 53 displayed the highest selectivity for Na^+ ions among the alkali and alkaline earths investigated, which was superior to the Na^+ selectivity reached with the bis(12-crown-4) analogue <2003ANA291>. It is interesting to emphasize that ISEs based on enantiomerically pure (*R,R*)-(+)- or (*S,S*)-(–)-bis(12-crown-4) derivatives 54 showed an Na^+/K^+ selectivity <1997CL49>, which is about twice that of the corresponding optically inactive compound <1982JEC99>.

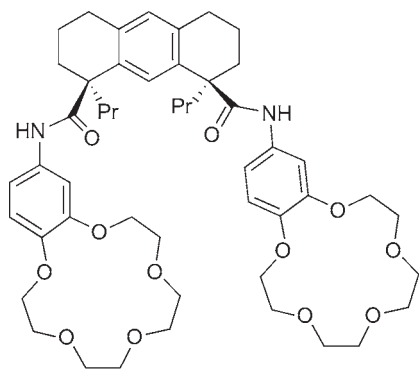
**53**

R^1	R^2
Dodecyl	Methyl
Benzyl	Methyl
β -Naphthyl	Methyl
Benzyl	Benzyl

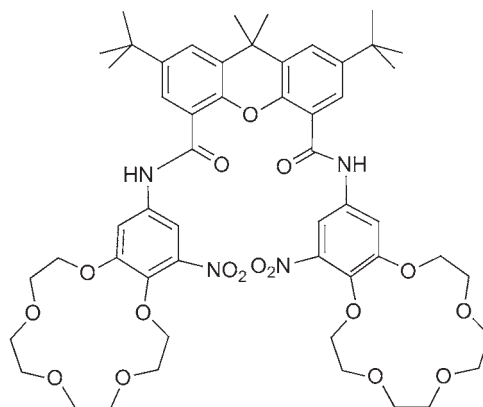
**54**

Potassium ISEs are currently used in medical practice for the determination of K^+ concentration in biological fluids, especially in blood. For this purpose, bis(crown ether) ionophores consisting of two benzo-15-crown-5 moieties connected by a flexible (heptanedioate [<1979JEC91>](#), dialkylmalonate [<1990MKA157>](#)) or conformationally constrained (isophthaloyl [<1998ANS169>](#), octahydroanthracene-1,8-dicarbonyl [<1998ANS1009, 1999BKC556>](#), and xanthene-4,5-dicarbonyl [<1997ANS325, 1998JPM119>](#)) bridge, **55** and **56**, respectively, have been designed for the selective K^+ binding over Na^+ , due to the formation of sandwich-type K^+ complexes. The observed selectivities of ISEs prepared with bis(15-crown-5 ether)s are much higher than those observed with large ring monocrowns [<1998CRV1593>](#), sometimes being comparable with those obtained with ISEs based on the naturally occurring antibiotic valinomycin [<1997JCE159, B-1990M11>](#).

**55a****55b****56a****56b**



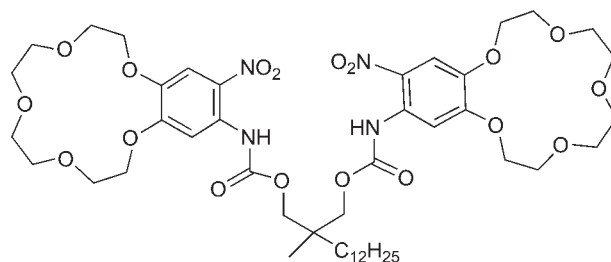
56c



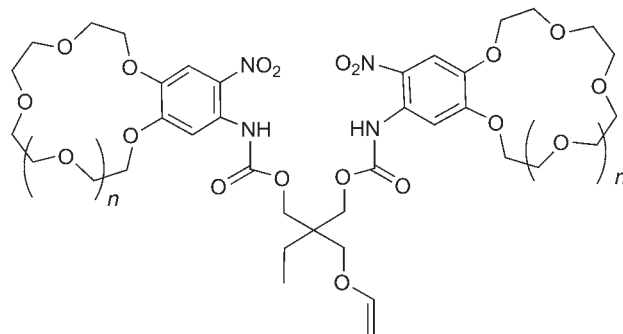
56d

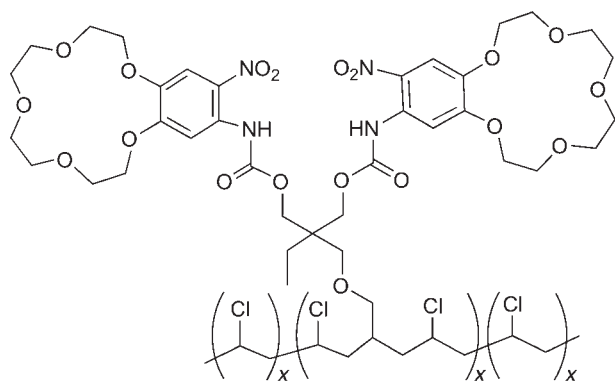
Structural modifications in the spacer of bis(nitrobenzo-15-crown-5) ionophores endowed with urethane functionalities have been shown to have an effect on ISE selectivities [<1985FZA157, 1989ALE1185, 1990MKA157>](#). Compound **57**, having a 2,2-dodecylmethylpropano bridge connecting the two urethane units, shows the best selectivity over Na^+ ($\log K^{\text{pot}}_{\text{K}^+/\text{Na}^+} = -3.2$). The improved selectivity has been attributed to the high lipophilicity of the ionophore, and to the nitrourethane moieties, that provide a beneficial preorganizing factor by the formation of intramolecular hydrogen bonds between the nitro and NH groups [<1989ALE1185>](#).

ISE's analytical parameters (lifetime, response stability, selectivity, etc.) strongly depend on the possible leaching of the different membrane components (plasticizer, ionophore, lipophilic additive) [<1980ANC692>](#). In order to overcome ISE drawbacks arising from the loss of ionophore and plasticizer, copolymers containing grafted monocrown or bis-crown ether potassium ionophores have been designed and synthesized, by using appropriate 'co-monomers' such as 4-acryloylamido-benzocrown ethers **59** [<2000ELA178>](#) or bis(benzocrown ether)s with terminal alkenyl groups **58** [<2003JPM45, 2003JPM53>](#). The ISEs based on copolymer-immobilized potassium ionophores (e.g., PVC-58 copolymer) were found to show slightly improved $\log K^{\text{pot}}_{\text{K}^+/\text{Na}^+}$ and a longer lifetime [<2005AN63>](#).

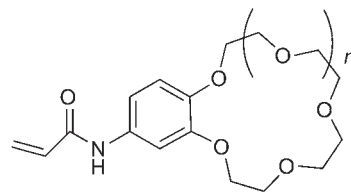


57

58: $n = 1, 2$

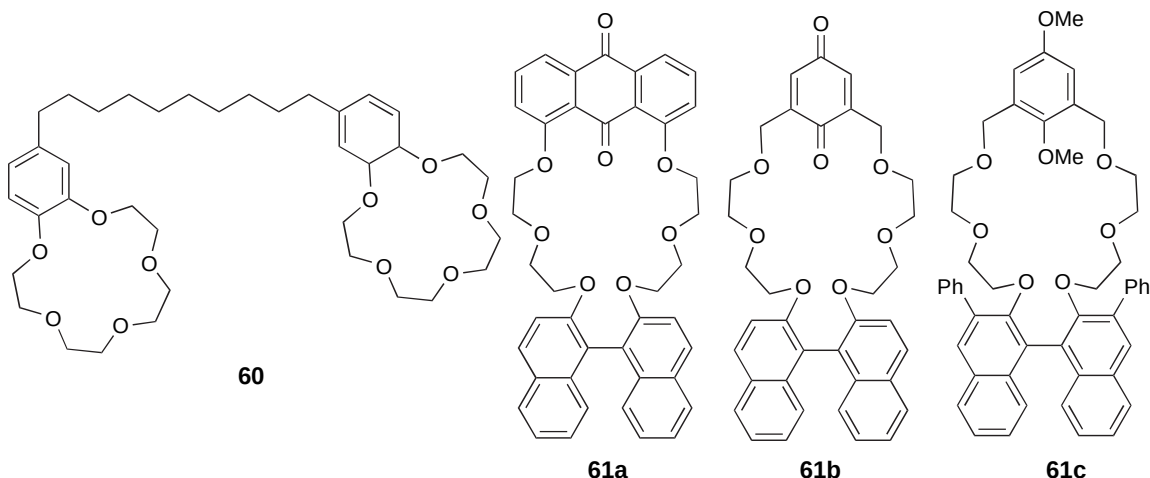


PVC-58
X = random



59: $n = 1, 2$

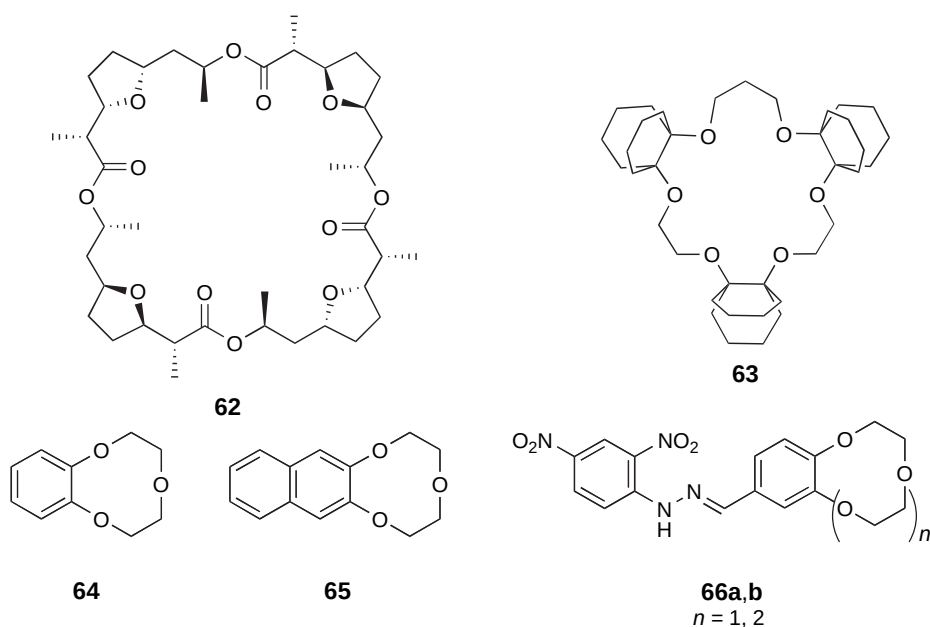
ISEs based on decylidene bis(4'-benzo-15-crown-5) **60** showed a moderate Rb^+ selectivity over K^+ and Cs^+ <1997MIJ348>, while those derived from binaphthyl crown ethers **61a–c**, incorporating anthraquinone, benzoquinone, and 1,4-dimethoxybenzene, respectively, showed a better Rb^+ selectivity over NH_4^+ , alkali, and alkali earth metal ions <2004ELA1785>.



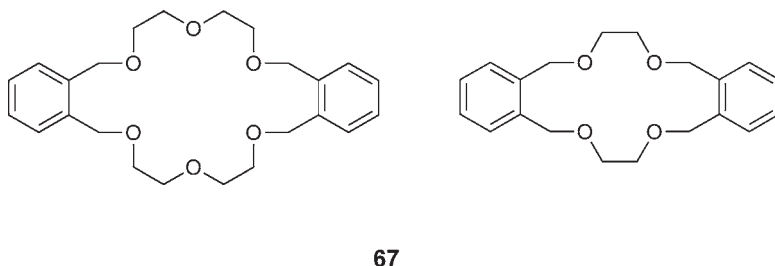
Although the interest for NH_4^+ analysis in environmental control and clinical chemistry is large, the number of crown ether-based ammonium ionophores used for ISEs is very small. Until recently, the only available practically used ammonium ionophore was the macrotetrolide antibiotic nonactin **62** <1998CRV1593>. At the beginning of this century, the 19-membered crown-6 **63**, incorporating three decalino subunits within the macrocyclic ring, was successfully designed and synthesized, which displayed a NH_4^+ selectivity superior to that of nonactin <2000ANC2200>. The NH_4^+/K^+ and $\text{NH}_4^+/\text{Na}^+$ selectivities of the resulting ISE were 10 and 3000, respectively. NH_4^+ ISEs were also prepared by using tetrahydrofuran-based 16-crown-4 derivatives **49** ($\text{R} = \text{H}, \text{Me}$) as the sensing agents. The ISE based on **49** ($\text{R} = \text{H}$) showed enhanced selectivity coefficients for the NH_4^+ ion with respect to an interfering K^+ ion ($\log K^{\text{pot}}_{\text{NH}_4^+/\text{K}^+} = -1.84$). For comparison, the ISE based on nonactine gave ($\log K^{\text{pot}}_{\text{NH}_4^+/\text{K}^+} = -0.92$ <2004BKC59>).

The selectivities of Cs^+ ISEs based on dibenzo-18-crown-6 derivatives <1986FZA241> or 2,3-benzoquinone 15-crown-5 ethers <1996ANI27> are of limited interest, because they are not dissimilar to those found with ionophore-free ion-exchanger ISEs <1977ANA399>. Nowadays, the best Cs^+ selectivities are obtained by using calixarene-derived crown ethers <B-2001MI365>.

Among alkali and alkaline earth metal cations, Be^{2+} ion has received little attention, despite its wide industrial uses. The high toxicity and debated carcinogenicity of this element have increased the need for beryllium-selective sensors. Be^{2+} ISEs with good selectivity and sensitivity have been prepared by using benzo-9-crown-3 **64** <1998ALE5259>, naphtho-9-crown-3 **65** <2003ANSI353>, and 2,4-dinitrophenylhydrazone benzo-crown ether derivatives **66a** and **66b** <2003ALE317, 2004SSA315>. The polyvinyl chloride (PVC) membrane sensor based on benzo-12-crown-4 derivative **66b** shows nanolevel detection ($7.0 \times 10^{-7} \text{ M}$) and excellent discriminating ability toward Be^{2+} against alkali, alkaline earth, transition, and heavy metal ions.



Low-symmetry crown ethers, possessing $(3m + n)$ -crown- m scaffolds, show a less pronounced binding ability than symmetrical crown ethers, but display much higher selectivities for specific cations [<B-1990MI429>](#). For instance, polymer membrane thallium(I)-selective electrodes based on dibenzo-crown ether derivatives **67** have been developed [<1996CCR171>](#), because of the environmental and biological implications associated with the poisoning of Tl^+ ions.

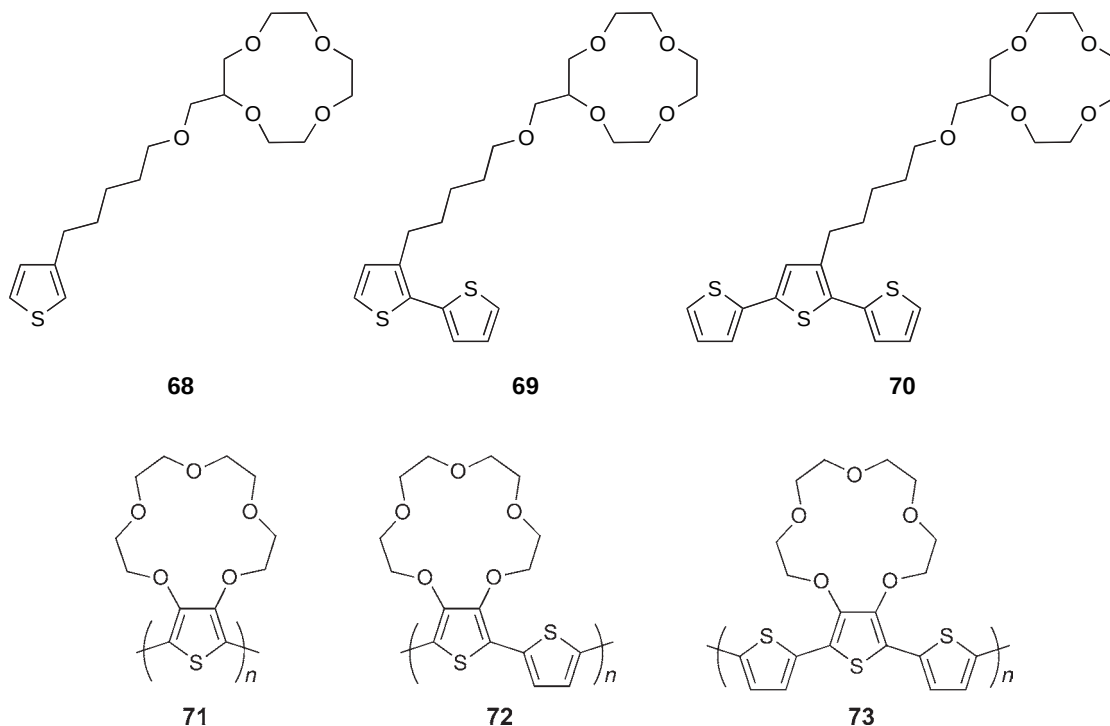


14.12.3.2 Sensors Based on CPs

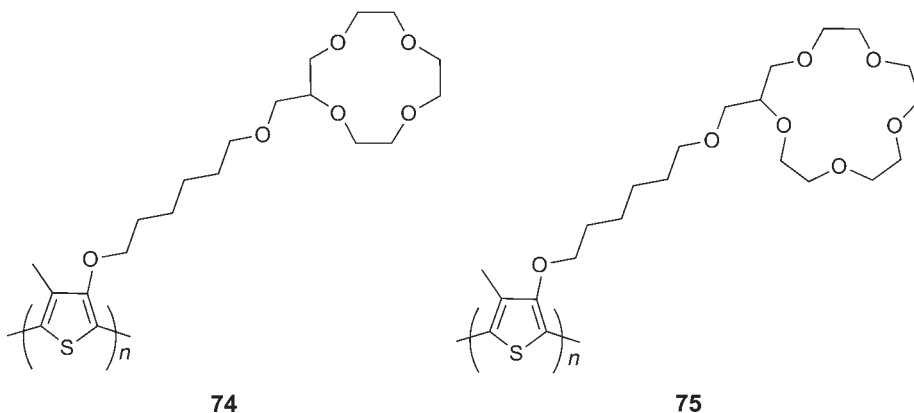
CPs have received considerable attention because of their unique optical, electrochemical, and electric properties, which make them versatile materials for a wide range of applications [<B-1991MI1, B-1997MI1>](#). CP functionalization by introducing suitable groups (recognition sites) along the conjugated backbone produced smart materials that are capable of detecting, transducing, or amplifying chemical information into an optical or electrical signal. The host-guest interactions that occur at the recognition sites influence the electronic properties and the redox chemistry of the conjugated backbone. This principle has been exploited for the construction of sensors, in which the selective and reversible binding of a given analyte allows the modulation or switching of the transport behavior of the conjugated chains. Excellent reviews have appeared concerning the chemical or electrochemical synthesis and applications of crown ether-containing CPs [<1997CSR247, 1998PAC1253, 1998CCR1211, 2000CRV2537>](#). The electrochemical approach to CPs seems to be more advantageous than chemical synthesis, because the polymer is obtained in one step, as a film deposited onto the electrode surface, from the oxidation of the relevant monomer in solution [<1992CRV711>](#).

Ionoresponsive poly(thiophene) CPs, possessing pendant crown ether moieties tethered with long alkyl chains or 15-crown-5 ether subunits directly grafted to the polymer backbone, have been prepared by electropolymerization of mono-, bi-, and terthiophene monomers **68–70** [<1993AM848>](#) and **71–73** [<1995APL124>](#), respectively. Although in the former CPs the crown ether and polymer backbone are electronically decoupled by long insulating alkyl chains, alkali metal ion sensing causes an increase in the oxidation potential of the polymer. The CP derived from **69** has been revealed to be the most sensitive to Li^+ and least sensitive to K^+ ions [<1993AM848>](#). Conversely, CPs based on **71–73**

are more sensitive to Na^+ ions, the oxidation potential of the polymers shifting to much higher potentials. This is caused by electron donation from the ethereal oxygen(s) of the crown ether moiety to the thiophene ring(s), which subtracts electron density to the CP backbone, thereby enhancing the oxidation potential of the polymer.



The ionochromism of regioregular poly(3-alkoxy-4-methylthiophene)s with pendant 12-crown-4 **74** and 15-crown-5 **75** moieties has been investigated by ultraviolet–visible (UV–Vis) spectroscopy [<1999JMC2133>](#). Alkali metal ion addition (Li^+ , Na^+ , K^+) to the CPs produced changes in their absorption maxima, the largest responses being observed with **74**/ Na^+ and **75**/ K^+ couples, and the smallest ones upon Li^+ addition in both cases. This behavior has been attributed to the ability of 12-crown-4 and 15-crown-5 subunits to form stable intra- and intermolecular 2:1 sandwich complexes with Na^+ and K^+ ions, respectively. Side-chain ordering is therefore necessary to compensate for the ion binding. This results in a planarization of the CP backbone, leading to increased conjugation lengths, which account for the intensification of absorptions at higher wavelengths [<1999JMC2133>](#).



CPs **76** and **77**, having bithiophene units incorporated into the crown ether ring, were designed to induce a twisting of the polymer backbone upon metal ion binding [<1993JA12214, 1994AM595>](#). The planar-to-twisted conformational change of the polymer backbone, taking place via rotation about the bithiophene axis (see [Figure 10](#)), lowers

the effective conjugation length because of a reduced π -orbital overlap, thereby reducing CP conductivity. The ionochromic response of polymers **76** and **77** upon exposure to alkali metal salt solutions was commensurate to the extent of twisting, which was determined by the binding affinity of the crown ether unit for a given analyte. As expected from the binding studies on appropriate models, CP **76** with 17-crown-5 recognition sites showed the largest response to Na^+ , and CP **77** with the larger 20-crown-6 subunits was most responsive to K^+ .

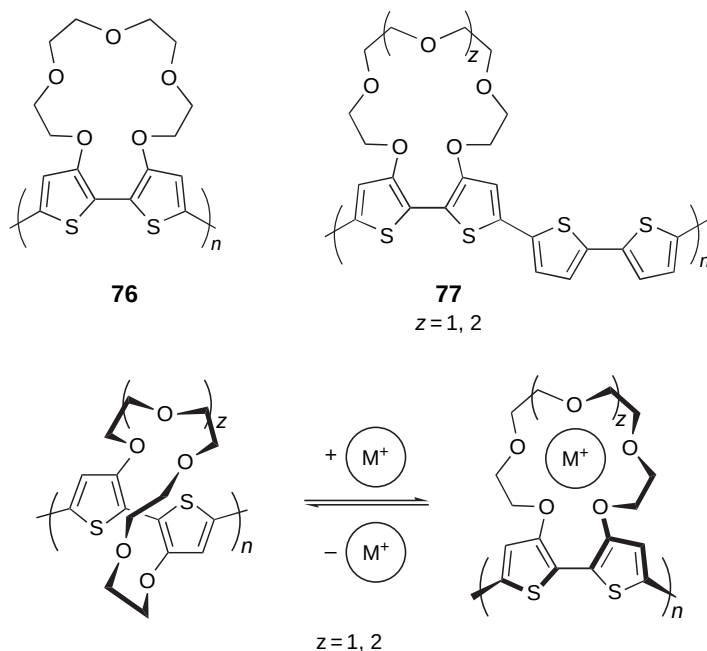
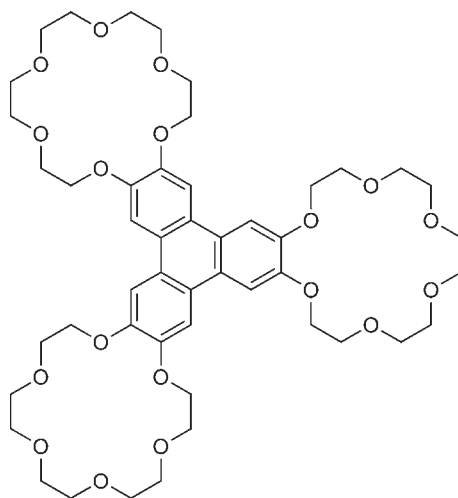
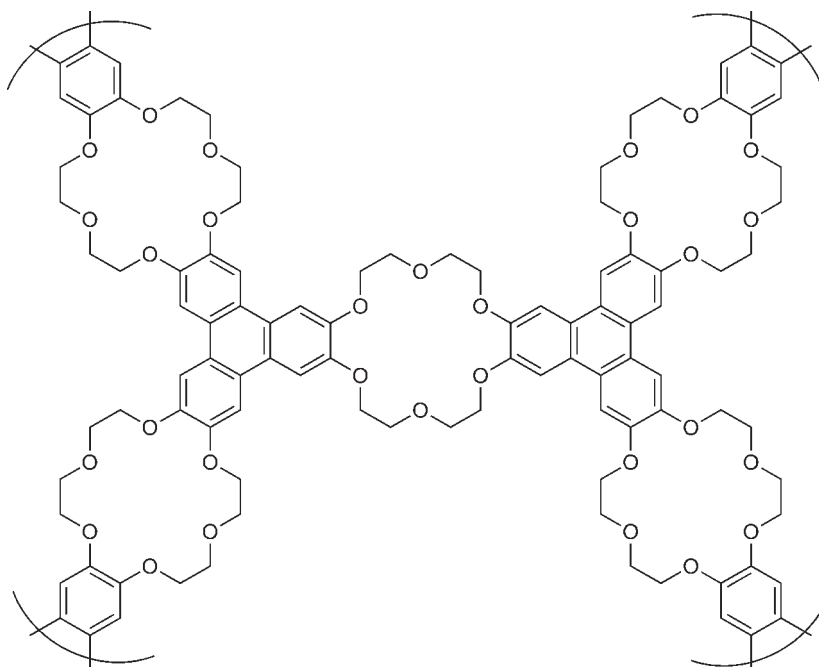


Figure 10 Ion complexation induces a twisting of the polymer backbone, reducing the effective conjugation length of the polythiophene, and consequently its conductivity.

Crown ether-functionalized polyphenylenes are a class of electroactive polymers obtained by electropolymerization (anodic coupling) of (di)benzo- or (bi)naphthalene-crown ethers <1998CCR1211, 1998PAC1253>. Tricyclic triphenylene derivatives, such as **78**, can be electrogenerated from benzo-15-crown-5 <1989NJC131> and benzo-18-crown-6 <1992JEC399>. Similarly, the anodic oxidation of dibenzo-crown ethers has produced poly(dibenzo-crown ethers), best represented by **79**, where triphenylene moieties are presumably two-dimensionally linked via polyether bridges.

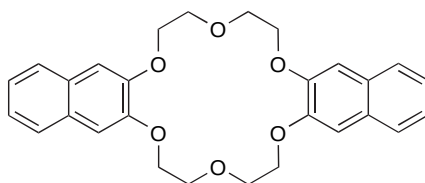


78

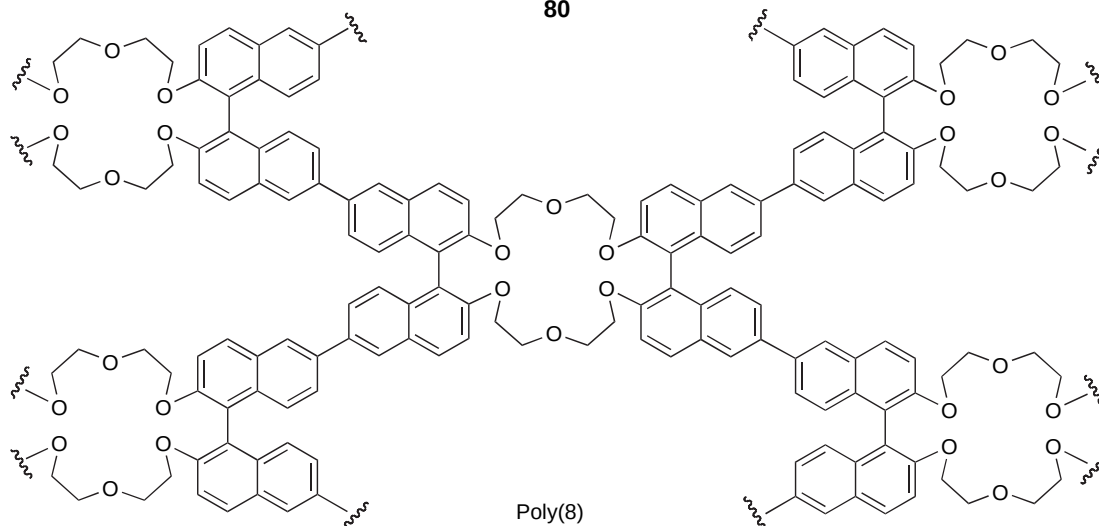


79

These unconjugated polymers possess remarkable structural, electrochemical, and complexing properties [<1985NJC419, 1988JEC117, 1992BSF37, 1993SM\(58\)51, 1994SM\(65\)55>](#), where the triphenylene subunits are the only electroactive centers. However, an extension of the electropolymerization studies to dinaphtho-18-crown-6 **80** [<1995SM\(75\)103>](#) and (*S,S*)- or (*R,R*)-bis-binaphtho-22-crown-6 **8** [<1998SM\(93\)115>](#) has yielded the corresponding CPs. Simonet and co-workers have provided evidence for the occurrence of regioselective oxidative C–C coupling at the 6- and 6'-positions of the binaphthalene moieties. Furthermore, on the basis of UV–Vis and IR spectroscopic data, the structure shown has been proposed for CP poly(**8**). CP poly(**8**) showed binding properties similar to those of the monomeric precursor **8**.

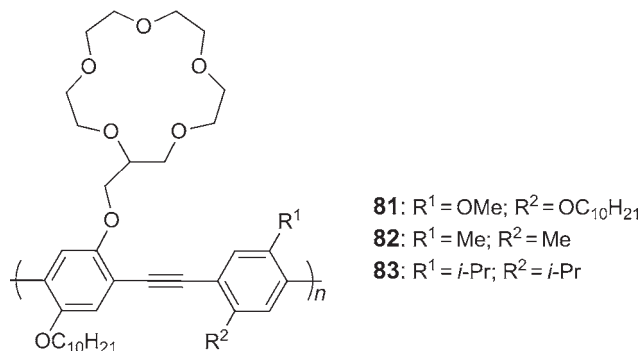


80

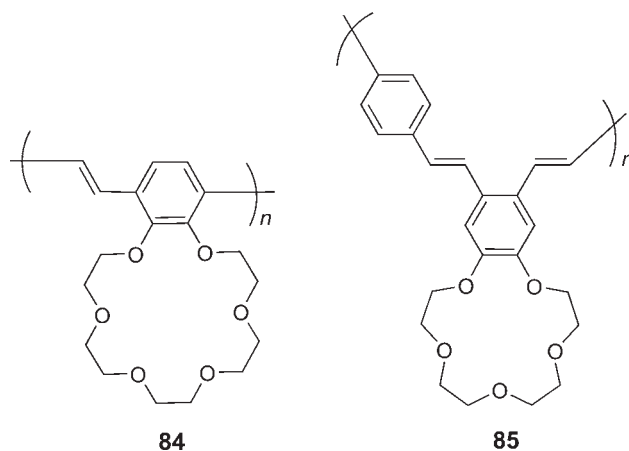


Poly(8)

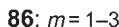
Regioregular poly(*p*-phenylene ethynylene)s **81–83**, carrying pendant 15-crown-5 moieties, have been designed as highly sensitive and selective fluorescent ion chemosensors, which exploit a new transduction mechanism based on a specific K^+ -induced aggregation of CPs <2000AGE3868>. Interpolymer π -stacking aggregation occurs via formation of K^+ ion bridges between two 15-crown-5 units on different polymer chains. The process can be detected by both UV–Vis (red shifted absorption) and fluorescence (quenching) spectroscopy. By contrast, the formation of 1:1 Li^+ or Na^+ complexes with **81–83** does not produce appreciable effects on their spectroscopic properties. The effectiveness of aggregation and sensitivity of these sensors are influenced by the bulkiness of the side groups attached to the second repeating unit of the polymer, so that the large isopropyl groups in **83** prevented π -stacking aggregation with any ion.



Similarly, the incorporation of crown ether units into poly(*p*-phenylene vinylene) CPs, as in **84**, greatly improved the photoluminescence and electroluminescence of these materials, as a result of interchain interactions in the polymer, allowing their use in light-emitting diodes <2002PCB10618>. Poly(*p*-phenylene vinylene) oligomer **85**, containing benzo-15-crown-5 units in the backbone, showed a marked enhancement of the polymer backbone fluorescence emission in the presence of metal ions, such as Eu^{3+} , Na^+ , and Ca^{2+} <2003JFL427>.



Poly(methylsilylene-*p*-phenylene)s carrying Si-linked benzocrown ether and ethoxy pendant groups **86** (parameters x and y are associated with the benzo crown vs. ethoxy ratio present in the polymer) showed ionochromic behavior, and responded selectively to alkali and alkaline earth metal ions in the emission spectra, depending on the crown ether ring size. These polymers also display solvatochromic properties by changing the solvent polarity in the absence of metal ions <2006OM2225>.



<2003JMC800>.



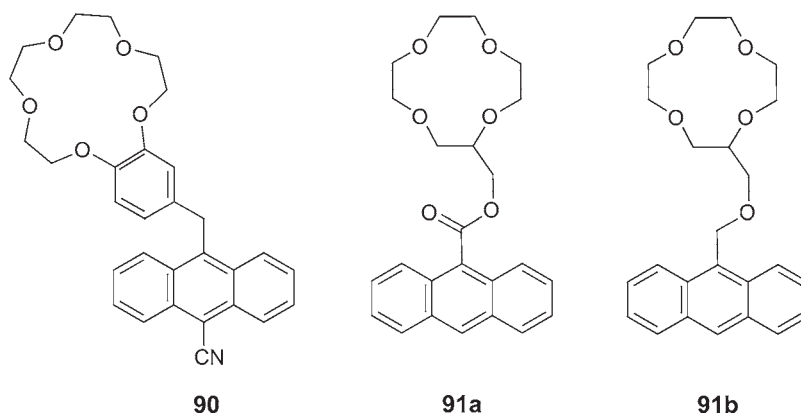
species.



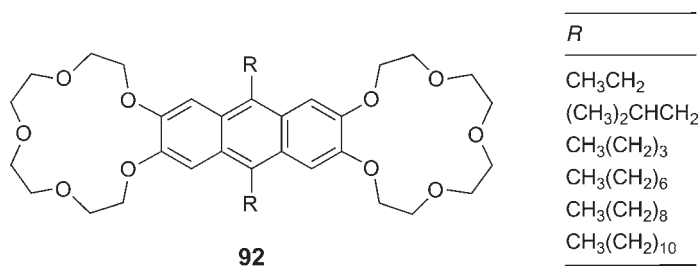
14.12.3.3 Fluorescence Sensing (PET)

An optical chemosensor consists of a molecule incorporating an artificial binding site, a chromophore or fluorophore, and a mechanism for communication between the two. Important features of optical sensor design include analyte affinity, choice of chromophore or fluorophore, binding selectivity, and optical signaling mechanism. Upon analyte binding, the signaling moiety (fluorophore) converts the chemical information (recognition event) into an optical signal expressed as a change in its photophysical characteristics. In the most commonly encountered structures, the signaling mechanism involves photoinduced electron transfer (PET), perturbation of the internal charge transfer (ICT), intra- or intermolecular energy transfer, and excimer or exciplex formation or disappearance. Most of these issues have been addressed in recent books and reviews <1985ACR65, 1994ACR302, 1996CCR199, B-2001MI1, B-2001MI93, 2001PAC503, 2001RCR1017, B-2001MI2, 2004CSR589, 2004CRV1687>.

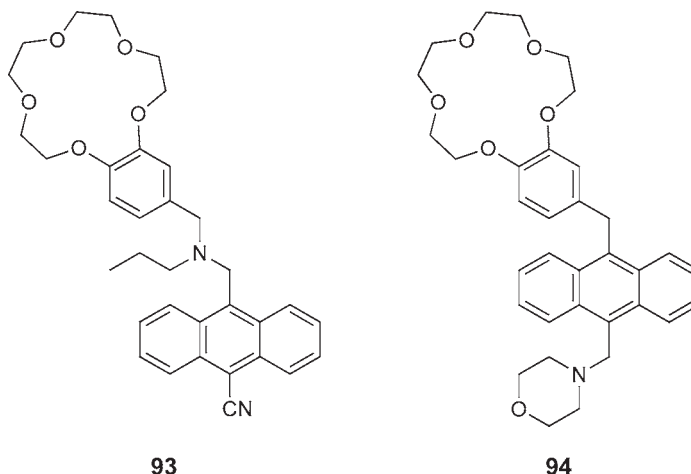
The anthracene unit has been widely used as the fluorophore of optical chemosensors. In a PET sensor, binding of a substrate is usually signaled by a 'switching off/on' of the fluorescence in the absence/presence of the metal ions, based on an electron transfer from the donor to the acceptor in a metal-free state and its coordination to the metal ions in a metal-bound state <1997CRV1515>. Compound **90**, set up according to the fluorophore-spacer-receptor format, provided an early testimony to the general success of the PET sensor design principle, and responded perceptively to Na^+ ions <1989CC1183>. Similarly, **91**, possessing 12-crown-4 moieties attached to the anthracene fluorophore via ester **91a** or ether **91b** linkages, exhibit quenching or enhancement of the fluorescence intensity, respectively, upon exposure to alkaline earth metal ions <1997J(P1)1357>. Molecule **91b** recognized Ca^{2+} more strongly than Ba^{2+} ions.



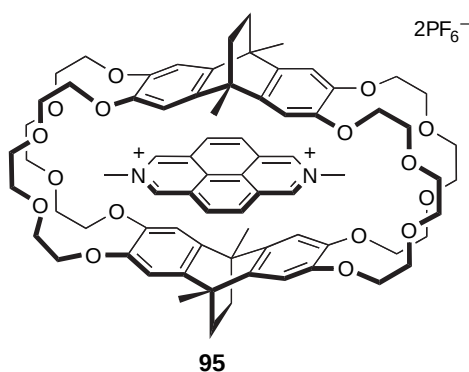
9,10-Dialkyl-substituted anthracene-bridged bis-crown ethers **92** formed 1:1 and 1:2 (crown to metal) complexes with alkali metal ions <1999J(P2)1193>. The stability constants of the latter were suggestive of a negative cooperation effect between the two crown ether units ($K_{\text{M}_2\text{L}}/K_{\text{ML}} < 0.25$). The derivative with $\text{R} = \text{Et}$ showed a decrease in the ligand fluorescence upon K^+ addition, which excluded the formation of sandwich complexes (absence of the excimer band).



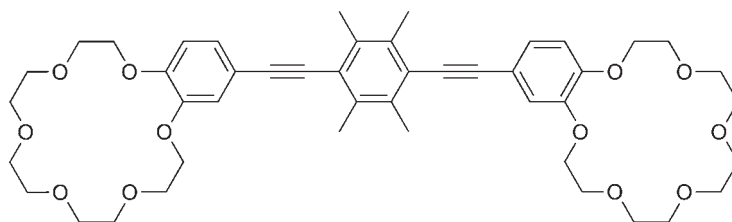
Multimodular systems, such as **93** that combines a benzocrown ether binding site for Na^+ and an amino receptor for H^+ , have been exploited for the development of ‘off–on’ signaling operations <1996AN1759>. ‘Fluorophore–spacer₁–receptor₁–spacer₂–receptor₂’ format **93** represents a two-input AND logic operation at the molecular level if one considers H^+ and Na^+ as two ionic inputs, fluorescence as the output, and exciting light as the power supply. Excellent fluorescence enhancements have been achieved by minimizing the distance of both receptors from the anthracene fluorophore. For instance, **94** displayed AND gate action with a strong fluorescence signal and ‘off–on’ digital action <1997JA7891>.



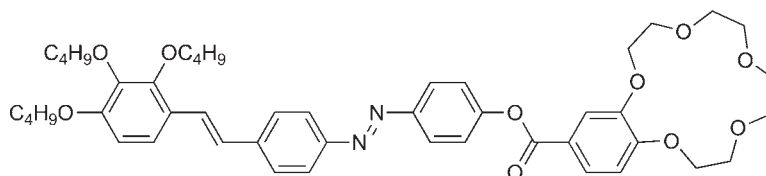
Supramolecular host–guest complexes have been used as efficient optical probes for detecting target analytes at low concentrations <1999OL1697, 2002PCA2020>. Inclusion of dimethyldiazapyrenium ion (DMDAP) inside the cavity of a crown ether-based molecular cage via multiple C–H···O interactions, to produce the strong supramolecular complex **95**, quenched the fluorescence signal of the guest at concentrations as low as 1×10^{-5} M. An equimolar solution of the molecular cage and DMDAP (1×10^{-5} M) is highly selective for Ca^{2+} ions (relative to biologically important interfering ions, such as Li^+ , Na^+ , K^+ , and Mg^{2+}), restoring the fluorescence signal of the ejected guest. Hence, supramolecular complex **95** behaved as a fluorescent probe for Ca^{2+} ions <2006CEJ4594>.



Chemosensor **96**, consisting of two 18-crown-6 moieties bound to the outer phenyl rings of a 1,4-di(phenylethynyl)durene chromophore, was able to discriminate between the early and late lanthanide ions through quenching of the chromophore fluorescence. The largest changes in the chromophore fluorescence were observed upon Ce^{3+} , Pr^{3+} , and Nd^{3+} coordination to the crown ether <2000T7045>. On the other hand, benzo-15-crown-5-derived sensor **97**, possessing a diazostilbene chromophore subunit, was not fluorescent, but emitted strong luminescence in the presence of the aforesaid ions, providing distinctive emission wavelengths for each lanthanide ion <2003JLU13>.

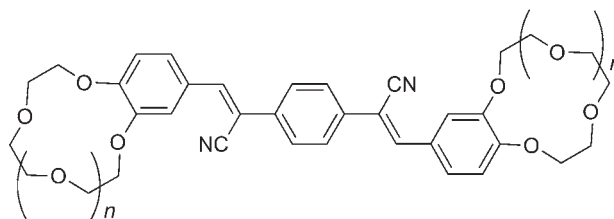


96

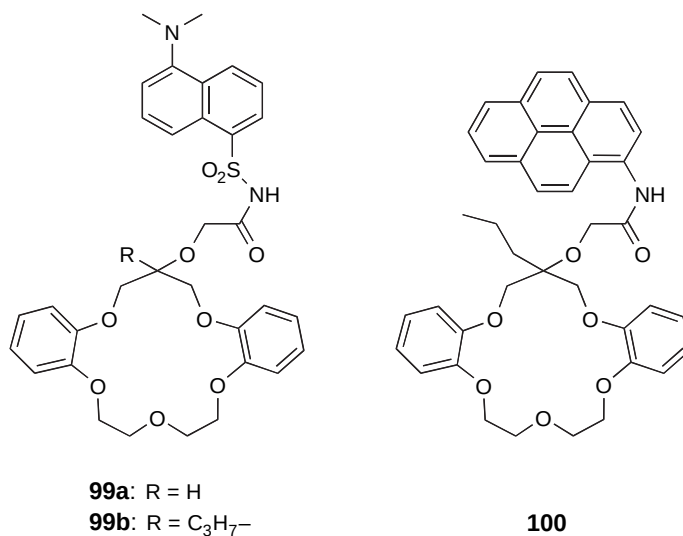


97

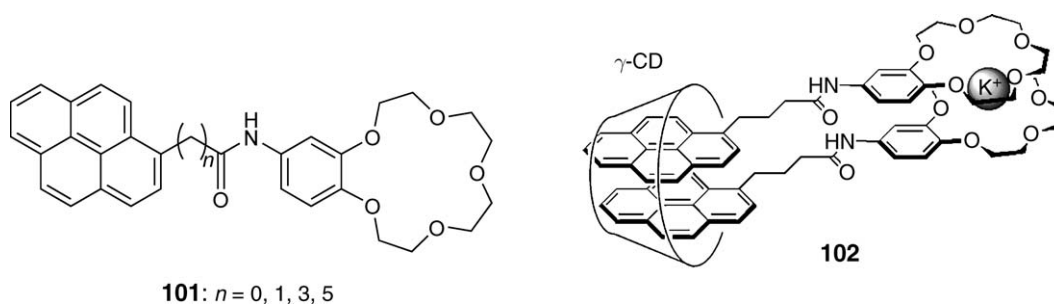
The *Z-Z* isomers of distyrylbenzene derivatives with crown ether rings of varying size attached to each benzene (12-crown-4 **98a**, 15-crown-5 **98b**, and 18-crown-6 **98c**) can form intermolecular sandwich complexes with Na^+ , K^+ , and Cs^+ ions, respectively [\[2002JPCB833\]](#). The formation of the self-assembled sandwich structure was associated with a dramatic increase in the fluorescence intensity of the chromophore for sensor molecules **98b** and **98c** with K^+ [\[1999JA5599\]](#) and Cs^+ [\[2000CC695\]](#), respectively. The observed self-assembling fluorescence enhancement (SAFE) was a response to the ‘rigidification’ of the chromophore upon substrate binding [\[2001JA1260\]](#).

**98a:** $n = 1$ **98b:** $n = 2$ **98c:** $n = 3$

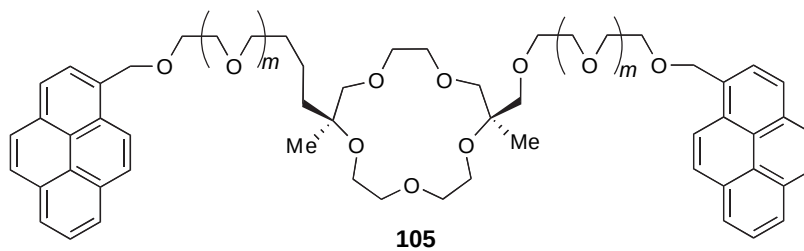
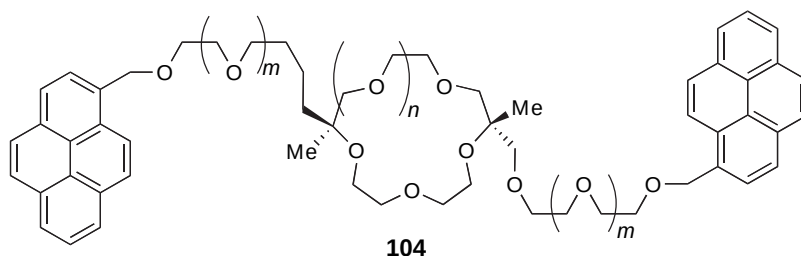
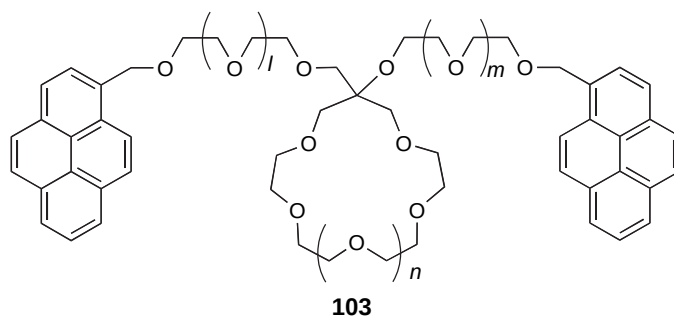
Crown ether-based chromoionophores have been utilized in the photometric determination of alkali metal and alkali earth metal ions in aqueous solution [\[1998JPM251\]](#). Extraction of alkali metal ions from water into 1,2-dichloroethane by proton-ionizable dibenzo-16-crown-5 fluoroionophores **99** (BF), having a dansylamide moiety, was signaled by a fluorescence intensity increase in their emission spectra [\[2000ANA57\]](#). K_{ex} data and selectivity coefficients have shown that chemosensor **99a** had a high affinity for both Na^+ and K^+ ions, while **99b** was much more selective for Na^+ , because of a more favorable spatial orientation of the carboxyl group of the sidearm. Replacement of the dansyl by a pyrenyl fluorophore, as in **100**, has led to a new design concept for metal ion sensing in aqueous solvents [\[2000J\(P2\)1003\]](#). The highly selective Na^+ binding by **100** promoted the dissociation of the acidic *N*-arylcaboxamido proton under alkaline conditions, which resulted in a ratiometric emission response due to ICT from the donor carboxyamido anion to the electronically conjugate pyrene acceptor. The emission intensity ratio increased by enhancing Na^+ concentration, while no fluorescence response was induced by the presence of Li^+ , K^+ , or Cs^+ ions.



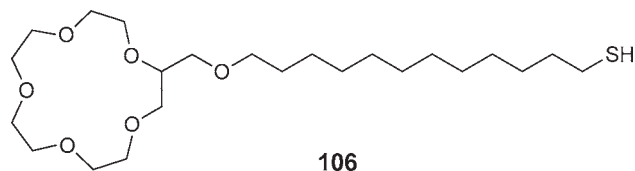
Simple alkali metal ion PET sensors behave as ratiometric fluorescent sensors when a π - π -interaction is possible between the donor and acceptor moieties, leading to the formation of an intramolecular donor-acceptor exciplex. Ratiometric signaling of alkali metal ions can be achieved by controlling the intramolecular exciplex formation as a function of metal ion addition <1999J(P2)141>. Sensors **101**, composed of pyrenyl (acceptor) and an amidobenzo-crown ether (donor) groups connected by a $-(CH_2)_n-$ spacer, behave either as simple PET sensors or as a ratiometric sensor toward alkali metal ions based on the length of the spacer <2005JMC2755>. Optimal spatial arrangement of donor and acceptor groups for exciplex formation has been attained with a trimethylene spacer. Besides, a combination of **101** ($n = 3$ or 5) and γ -cyclodextrin has been exploited for alkali metal ion sensing in water, via selective formation of supramolecular 2:1 sandwich complexes **102** with K⁺ <2000ANC5841>. Crown **101** ($n = 1$) showed no response for alkali metal ions in the presence of γ -cyclodextrin. Complexes **102** exhibited characteristic pyrene dimer emission. With a trimethylene spacer, the apparent association constant for K⁺ of $(3.8 \pm 1.3) \times 10^9 \text{ M}^{-2}$ was only slightly affected by the presence of Na⁺ ions.



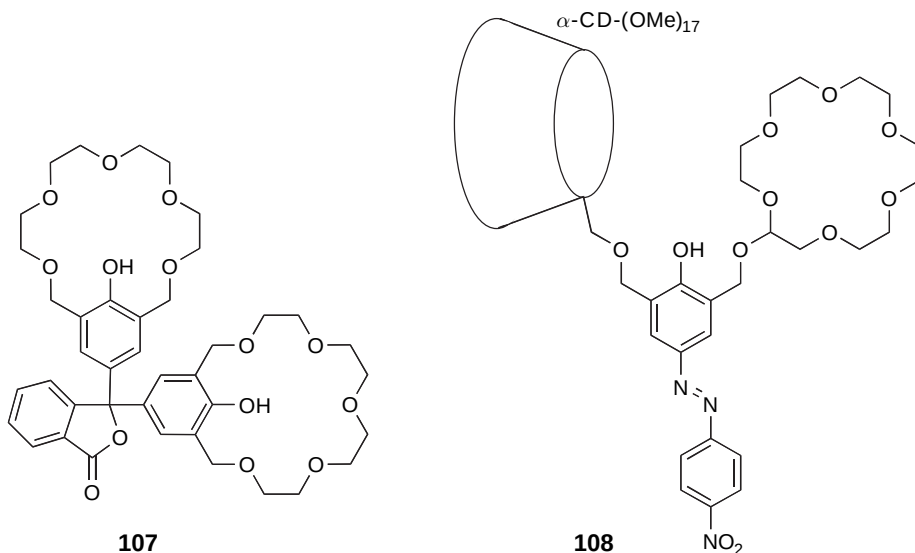
Lariat crown ethers with two terminal pyrenyl sidearms connected to the same carbon **103** ($l = 0, 1$; $m = 0-2$; $n = 0-2$) or to two different carbon atoms **104** ($m = 0-2$; $n = 1, 2$) and **105** ($m = 0, 1$) showed intramolecular excimer emission in the free state (π - π -stacking of the pyrene rings), whose intensity decreases with the increase of monomer emission intensity upon metal ion complexation <2002OL2641, 2004JOC4403>. This response has been ascribed to the cooperative participation of one of the two sidearms in the complexation of the crown ring with the metal ion, which renders inoperative the π - π -stacking of aromatic rings. Most of these fluorophores show alkaline earth over alkali metal ion selectivities.



Nanosized metal particles have recently emerged as an important type of colorimetric reporter, mainly because the transition of the nanoparticles from dispersion to aggregation exhibited a distinct change in color, a phenomenon termed ‘surface plasmon adsorption’ (SPA) [<1996NAT607, 1997SCI1078, 2000JA4640, 2001NL165>](#). Gold nanoparticles, modified with 15-crown-5 ether mercapto derivative **106**, have been reported to exhibit excellent selectivity toward K^+ in aqueous matrix containing physiologically important interfering ions, and excess amount of Na^+ ions [<2002ANC330>](#). The K^+ -recognition event, taking place via the usual 2:1 (crown to metal) sandwich complexation, is signaled by the change in color of the solution from red to blue, in response to SPA of dispersed and aggregated nanoparticles.

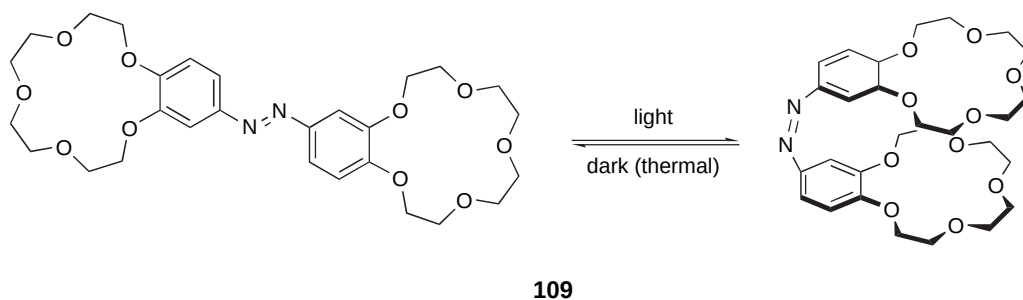


Although a myriad of chromogenic sensor molecules undergoing color changes upon substrate binding are known, less common are host molecules capable of visual determination of certain attributes (e.g., chirality [<1996NAT522>](#)) of targeted guests. Here reported are two intriguing examples associated with length or functional group discrimination. Sensor **107**, comprising two pseudo-crown ether loops incorporated into the phenol residues of a phenolphthalein platform, allowed the visual determination of the chain length of linear diamines. The most dramatic color changes were seen with 1,8-diaminooctane and 1,9-diaminononane, while diamines shorter than 1,5-diaminopentane gave no coloration that can be detected by the naked eye [<1999JA3807>](#). Sensor **107** also develops a brilliant purple color in the presence of dipeptides with a specific amino acid sequence [<2002OL2313>](#). On the other hand, azophenol dye **108**, carrying an 18-crown-6 subunit and a permethylated α -cyclodextrin, was capable of discriminating among 1°, 2°, and 3° amines in chloroform solution by developing unique color changes [<2006OL3009>](#). The high selectivity of **108** toward amines has been ascribed to the formation of efficient H-bond interactions between the ethereal oxygens of the crown loop and the hydrogen atoms of the alkylammonium ion (generated from the acid–base interaction of the phenolic hydroxyl group with the amine), and to the hydrophobic interaction between the α -cyclodextrin and the lipophilic tail of the amine.



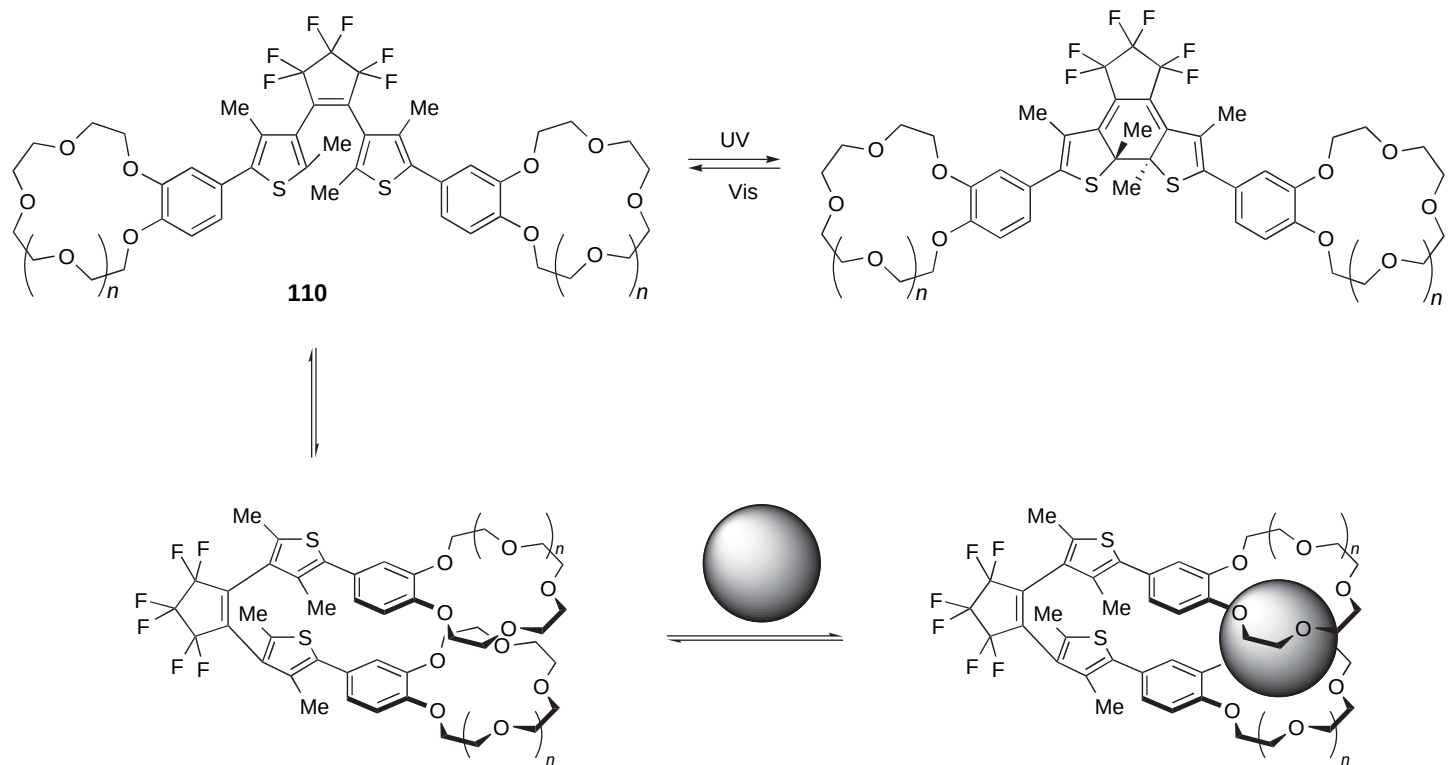
14.12.3.4 Molecular Switching

Molecular switching involves changes in charge state, conformation, or structure that enable or prevent cation complexation in a host structure that previously could not or could, respectively, bind a guest [<B-2002MI331>](#). Among the earliest examples of molecular switching were those involving azobenzenes. In the early 1980s, Shinkai and co-workers first reported that the azobenzene moiety, present in bis(crown ether) **109**, underwent photochemical/thermal isomerization between its *trans*- (*E*)- and *cis*- (*Z*)-forms ([Scheme 1](#)), and showed a good potential as a photoresponsive switch [<1980JA5860>](#). The *trans*-isomer displayed a high affinity for Na⁺ ions, while the *cis*-isomer permitted the crown ether moieties to act cooperatively in the binding of K⁺ and larger cations [<1982JA1960>](#). Therefore, metal ion affinity of the ligand can be modulated by the geometry of the molecule, that is, controlled by light. As a practical application of these findings, the catalytic activity of the bis-barium complex of the azobis(benzo-18-crown-6) analogue of **109** in the basic ethanolysis of esters and anilides can be reversibly activated–deactivated by light-induced changes in molecular geometry [<2003JA2224>](#).



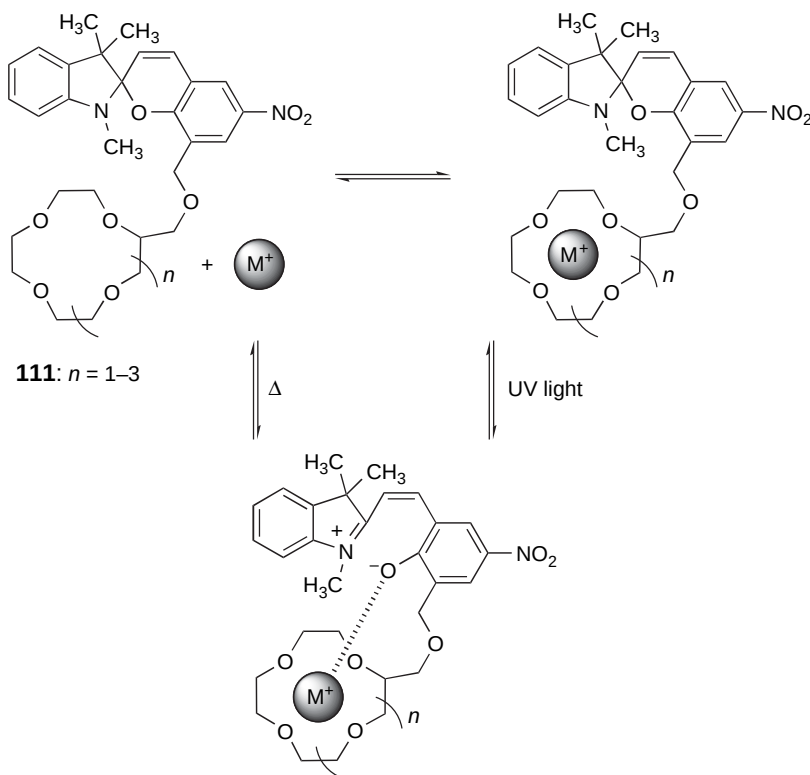
Scheme 1

Rotation around the carbon–carbon bond linking the thiophene and cyclopentene groups of photoresponsive dithienylethene bis(benzocrown ether) tweezers **110** allowed the existence of two interconverting conformers, consistent with a parallel or antiparallel disposition of the crown ether moieties. The latter conformer was photochemically reactive, and underwent a cyclization upon irradiation with UV light to give a colored planar closed-ring form. It then reverted fully to the initial open form by exposure to visible light ([Scheme 2](#)). The two crown ether moieties of the open form captured large alkali metal ions, which were released by the photogenerated closed-ring form [<1998JOC6643, 1998TL7717>](#).



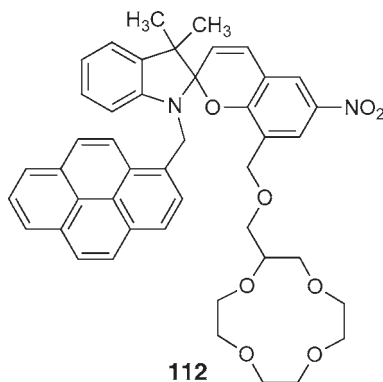
Scheme 2

The photochromism of spirobenzopyrans is a well-documented phenomenon that arises from the photoinduced reversible isomerization between spirobenzopyran and merocyanine forms <B-1999MI1>. In spirobenzopyrans carrying a crown ether moiety (e.g., **111**), this interconversion process is affected by metal ion complexation. A strong interaction of the crown ether unit with a metal ion caused the thermal isomerization of the spirobenzopyran residue to the corresponding merocyanine form with simultaneous suppression of the UV-induced isomerization process (negative photochromism) (Scheme 3). Conversely, a weak metal ion interaction induced a positive photochromism <2001JOC1533, 2002EJO655>.



Scheme 3

Chemically modified crowned spirobenzopyran **112**, containing a pyrenyl fluorophore attached at the nitrogen atom, can function as a fluorescence emission switch <2004T6029>. This sensor displayed a quenching of the PET fluorescence emission of the fluorophore in the absence of metal ions (the merocyanine form was not produced). When, however, the spiro form of **112** was converted into the merocyanine form by metal ion complexation of the crown ether portion of the molecule, a fluorescence resonance energy transfer (FRET) from the pyrene to the merocyanine moiety took place, producing fluorescence emission.



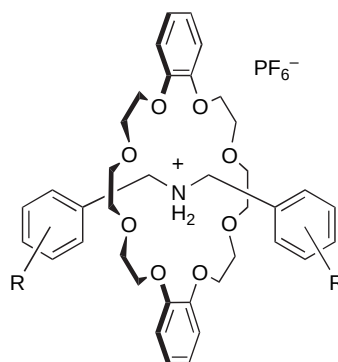
14.12.4 Crown Ether Supramolecular Assemblies

This topic was partially covered in CHEC-II(1996) <1996CHEC-II(9)809> under the subentry ‘Catenanes and Rotaxanes’. In this section, emphasis is given to the design and construction (and to some extent, the properties) of supramolecular architectures derived from or incorporating crown ethers rather than to the synthesis of the crown ether component present in them. The crown ether rings described herein are either covalently linked (dendrimers), mechanically interlocked (rotaxanes, catenanes), or just bound by noncovalent interactions (pseudorotaxanes) to the rest of the supermolecule to which they belong.

14.12.4.1 Pseudorotaxanes and Rotaxanes

The term rotaxane derives from Latin (*rota* = wheel and *axis* = axle) and is descriptive of a family of molecules whose structure is best described as being formed by a macrocyclic component (the wheel) in which a rod-like component (the axle) – with two bulky end groups or ‘stoppers’ – reminiscent of a dumbbell has been threaded through. When the two stoppers of the axle are not large enough to prevent the threading/dethreading process or are altogether absent, the two-component complex is referred to as a [2]pseudorotaxane. The dumbbell and the encircling macrocycle of a [2]rotaxane are not covalently linked to each other, yet, because of mechanical interlocking, dissociation into the individual components is prevented. General overviews on interlocked molecules <1999CRV1643, B-1999MI2, 2000CCR5, 2004TCC141, 2005TCC203> as well as more specific ones dealing with rotaxanes and polyrotaxanes <1998APL3, 1999CCR139, 2004APS1, 2005PPO982, 2006CRV782, 2006POJ1> containing different types of wheels have recently been published. For the nomenclature of interlocked molecules, the reader is referred to a recent article <2000JPR437>.

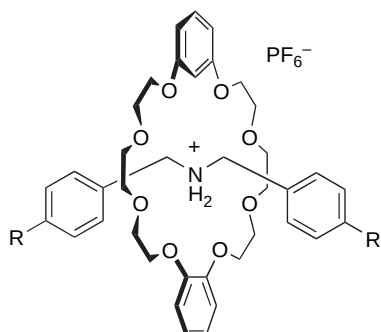
Rotaxane formation requires either threading of the axle through a macrocycle (i.e., pseudorotaxane assembly) followed by stopper addition, or, vice versa, wrapping of an acyclic species around a dumbbell. In the absence of any specific interactions between the two starting components, rotaxane yields are generally low unless template-directed methods <B-1999MI3> are employed. The discovery by Stoddart and co-workers <1995AGE1865> that secondary dialkylammonium ions are able to thread through suitably sized macrocyclic polyethers to form stable 1:1 inclusion complexes paved the way for the assembly of a wide series of pseudorotaxanes and rotaxanes. The dibenzylammonium ion was shown (^1H NMR) to self-assemble with dibenzo-24-crown-8 (DB24C8) to form [2]pseudorotaxane **113** ($\text{R} = \text{H}$) both in solution and the gas phase. This supramolecular structure is stabilized and held together in the solid state primarily by a combination of hydrogen bonds [$^+\text{NH} \cdots \text{O}$ and $\text{CH} \cdots \text{O}$] and additionally by π - π -stacking interactions between one of the phenyl rings of the cation and one of the catechol units of the crown ether macrocycle <1996CEJ709, 1996CC1483>.



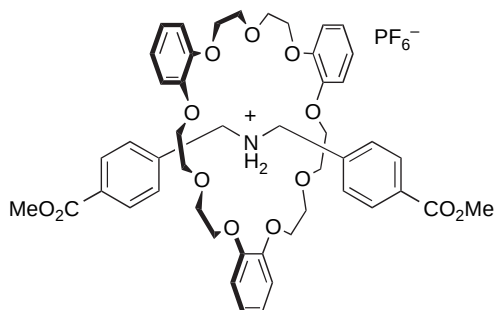
113: $\text{R} = \text{H}, \text{OMe}, \text{Me}, \text{Cl}, \text{Br}, \text{CO}_2\text{H}, \text{or NO}_2$

Structures **114–118** are just a few of the many examples of [2]pseudorotaxanes that have been prepared over the past 10 years, either by varying the size of the polyether wheel or the structure of the cationic axle. Dibenzylammonium ions are still able to thread through and rest within the cavity of crown ethers wider than DB24C8, such as benzo-*meta*-phenylene[25]crown-8 and tribenzo[27]crown-9, to afford [2]pseudorotaxane **114** <1999TL3661, 2000CEJ2274> and **115** <2000OL61>, respectively. In both instances, threading was confirmed by ^1H NMR spectroscopy, X-ray analysis, and MS, but, according to NMR measurements, binding of R_2NH_2^+ salts to both macrocycles was found to be less efficient than that observed with DB24C8. Similar complexation studies carried out on (*R,S*)-benzo-2,2'-binaphtho-26-crown-8 pseudorotaxane **116** revealed that the replacement of one of the catechol units of DB24C8 with the

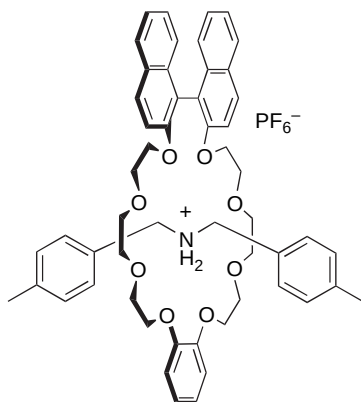
less-preorganized binaphthol residue lowers the stability of the resulting pseudorotaxane <1999CC1251>. When four aromatic units are present on the macrocycle, no binding of dialkylammonium salts has been detected in solution and formation of pseudorotaxane **117** only occurred in the solid state, where the crystal superstructure was additionally stabilized by arrays of [C–H···F] hydrogen bonds between the wheel/axle components and the hexafluorophosphate anions <1999OL1917>. Derivative **118**, bearing a fullerene unit both on the wheel and the axle components, underwent, upon pH variation, a reversible threading/dethreading process, which can be monitored by looking at the partial quenching of luminescence of the catechol rings associated with the threading event <1999J(P2)1577>.



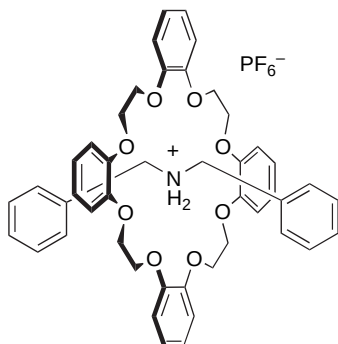
114: R = H, CO₂Me



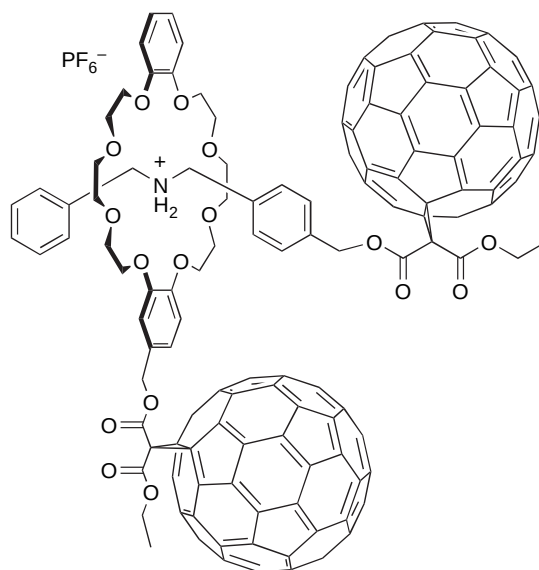
115



116

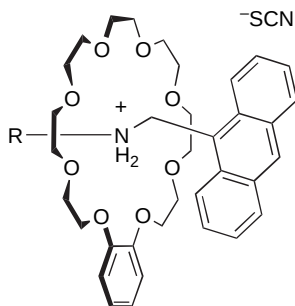


117



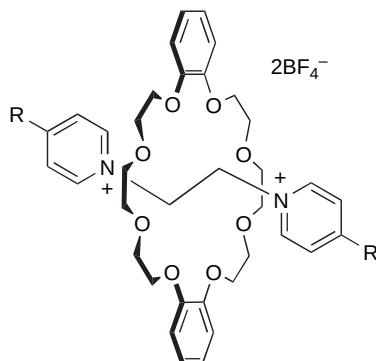
118

Crown ether-based pseudorotaxane binding constants depend not only on the size of the macrocycle, but also on the structure of the secondary dialkylammonium cationic component used, whose steric and electronic effects play key roles. Derivatives, such as **119**, where a bulky group is already attached to one end of the axle (also known as ‘semiorotaxanes’) have systematically been investigated by Busch and co-workers [<2002PNA4830>](#). Threading of secondary dialkylammonium thiocyanates, bearing the anthracen-9-yl methyl group at one end, through benzo-24-crown-8 is not sensibly affected by the length of the second aliphatic chain (the R group of **119** containing up to 18 carbon atoms), but is disfavored when a branching side chain is moved closer and closer to the nitrogen atom. Furthermore, a weakening in the binding is observed when a phenyl ring is close to the amino group, whereas a more remote position (e.g., γ -position) of the aromatic unit provides an opposite effect.

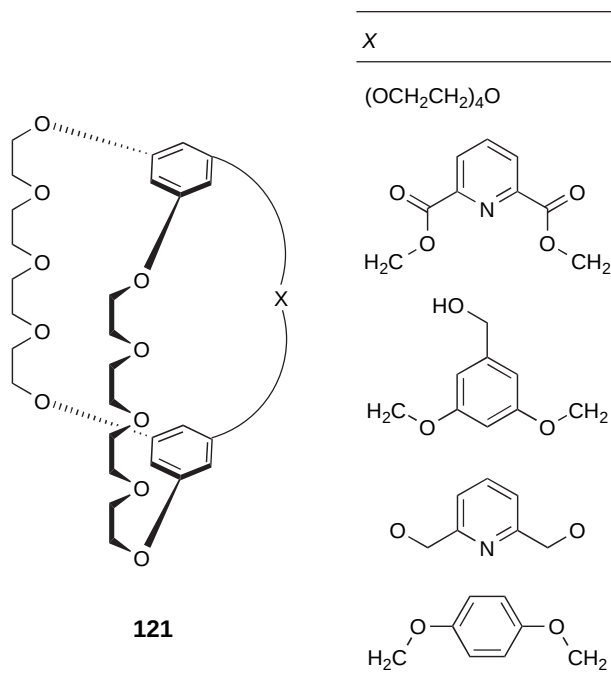
**119**

Binding constants between DB24C8 and substituted dibenzylammonium salts vary considerably according to the substitution pattern present on the aromatic rings. For instance, electron-donating substituents inhibit the threading (e.g., **113** with R = *p*-OMe) by reducing the hydrogen-bond-donating ability of the dibenzylammonium cation [<1998J\(P2\)2117>](#). Steric effects arising from minute changes in the bulkiness of 4-substituted dibenzylammonium and bicycloalkylmethylammonium axles have also been shown to produce detrimental effects on pseudorotaxane formation [<1998JA2297>](#). As expected for a hydrogen-bond-driven self-assembly process, binding constants for a given ring/axle pair were found to be strongly influenced by the solvent used, with K_a values ranging from zero to $2 \times 10^4 \text{ M}^{-1}$ in DMSO- d_6 and CDCl_3 , respectively [<1995AGE1865>](#). Pseudorotaxane self-assembly benefits from low-dielectric-constant media; however, depending on the type of salt used as an axle, ion-pairing effects between the dialkylammonium cation and its counteranion may vary considerably and, because of this, a model that takes ion-pair interactions into consideration has been proposed [<2003JA7001>](#).

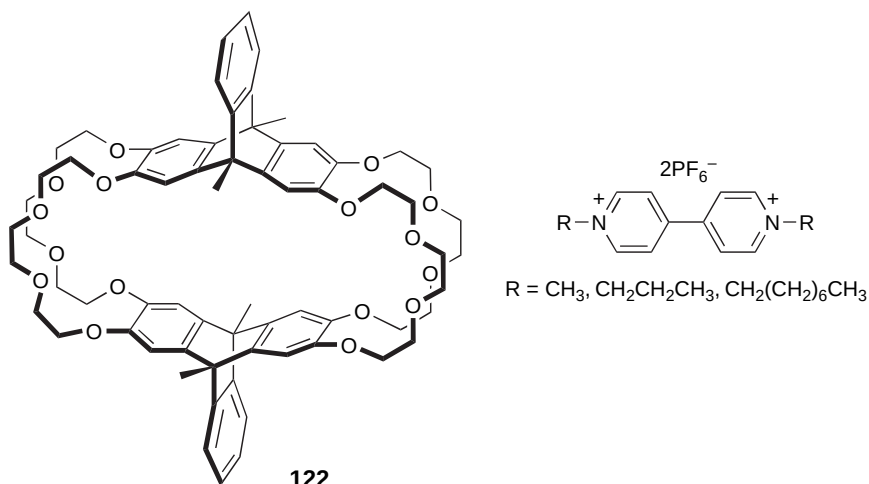
An alternative axle for 24-crown-8 macrocycles was introduced by Loeb and co-workers [<1998AGE2838, 2006OBC667>](#), who reported the formation of [2]pseudorotaxanes **120** from DB24C8 and a series of 1,2-bis(pyridinium)ethane dications, both in solution and the solid state. In particular, the X-ray crystal structure of **120** (R = CO_2Et) showed that the threading of the dication through the macrocycle cavity was stabilized by eight ion-dipole $^+\text{N} \cdots \text{O}$ interactions, eight $\text{CH} \cdots \text{O}$ hydrogen bonds (between alternate oxygen atoms of the crown ether and both bridging methylene and α -pyridinium hydrogens), and π -stacking interactions (between the electron-rich catechol and the electron-poor pyridinium rings of the crown ether and the salt, respectively).

**120**: R = H, Me, Ph, CO_2Et

Several bis(*m*-phenylene)-32-crown-10-based cryptands with a variety of different moieties on the third bridge, best represented by **121**, have been studied with respect to their ability to form with paraquat and bisparaquat derivatives [2]- and [3]pseudorotaxane-like' structures. These inclusion complexes are observed both in the solid state (X-ray analysis) and in solution, where very high association constants have been measured by means of ^1H NMR spectroscopy <1999OL1001, 2003JA9272, 2005JOC3231, 2006CC1929>.

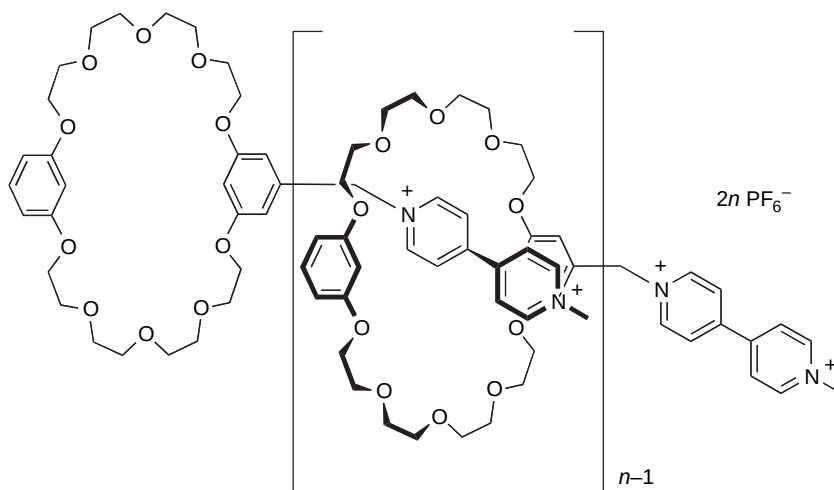
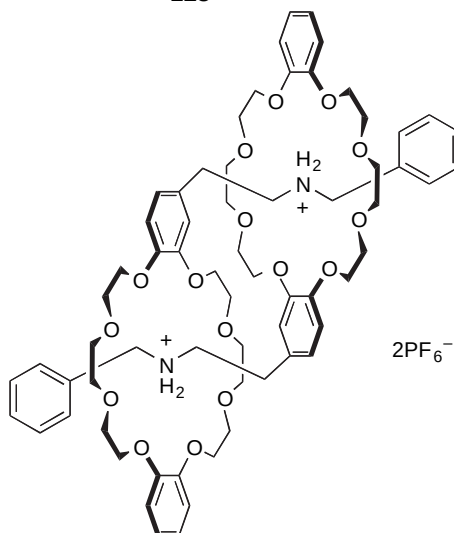


The triptycene-based cylindrical macro-tricyclic host **122**, containing two dibenzo-24-crown-8 polyether rings, formed in solution very stable 1:1 charge-transfer complexes with the *N,N'*-dialkyl-4,4'-bipyridinium derivatives shown. The solid-state structures of these pseudorotaxane architectures showed the guests being included, by way of multiple hydrogen bonding and π - π -stacking interactions, in the center of the macro-tricyclic host with the N-substituents either pointing to ($\text{R}=\text{CH}_3$) or threading through ($\text{R}=(\text{CH}_2)_7\text{CH}_3$) the two opposite DB24C8 portals <2006OL211>.

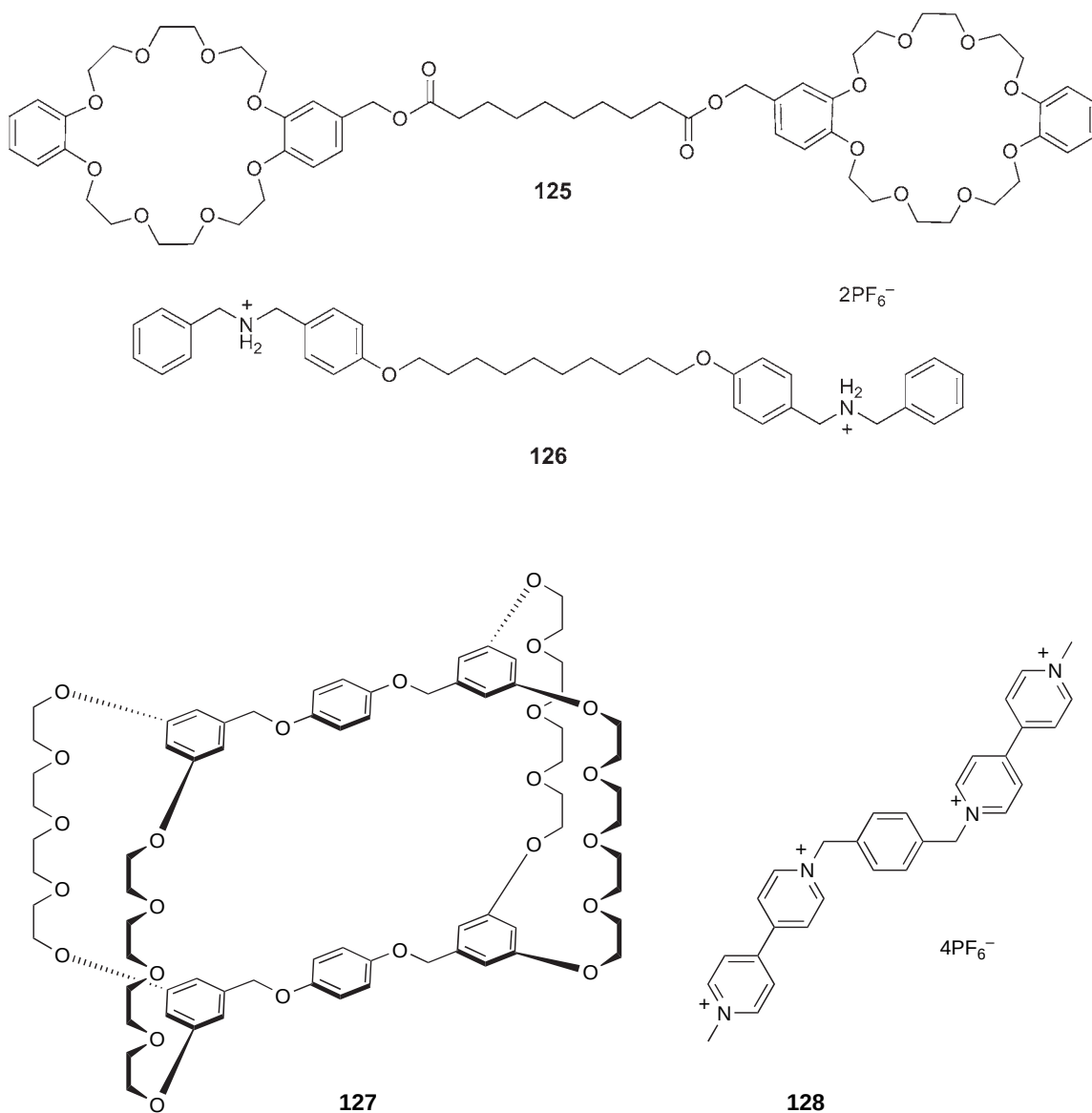


Monofunctionalized bis(*m*-phenylene)-32-crown-10 macrocycles, endowed with an appropriate sidearm on one of the aromatic rings, behave as heteroditopic monomers (AB-type), and, as a result of iterative intermolecular

bipyridinium/32-crown-10 recognition processes, spontaneously self-assemble to produce in solution pseudorotaxane arrays **123** <1998AGE2361>. According to ^1H NMR measurements (end-group titration), these oligomeric/polymeric species comprise up to 50 self-complementary units linearly arranged and held together by noncovalent interactions, that is, supramolecular polymers <2001CRV4071>. Cyclic dimeric pseudorotaxanes, known as ‘daisy chains’ (e.g., **124**), on the other hand, were found to preferentially self-assemble from very similar heteroditopic monomers comprising crown ether loops of different sizes grafted with a secondary dialkylammonium <1998AGE1294, 2001JOC6857> or dipyridinium <1998AGE1913> tail.

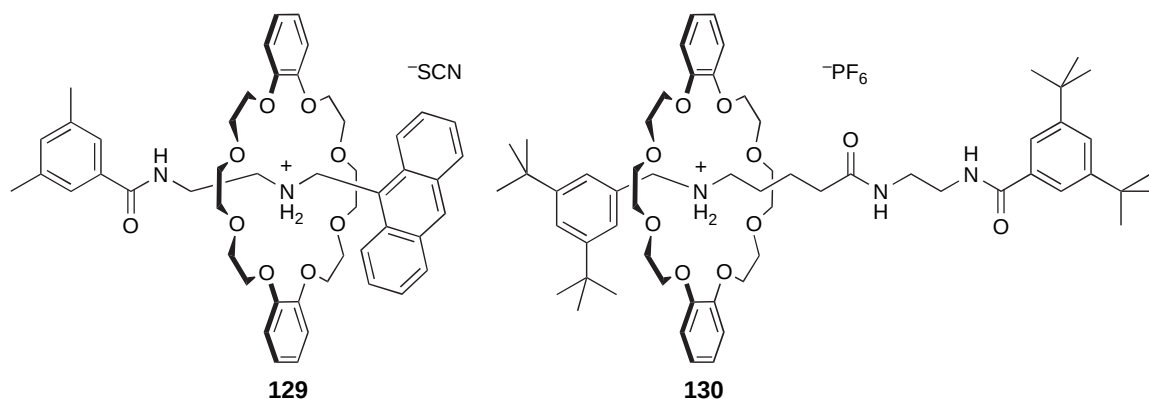
**123****124**

Noncovalent self-assembly of complementary pairs of homoditopic building blocks (AA/BB-type), such as bis(crown ether) **125** and diammonium salt **126**, has afforded well-defined supramolecular oligomeric/polymeric assemblies <2003JA3522>. In dilute solutions, entropy favored the formation of the cyclic dimer, whereas high equimolar concentration (≥ 0.5 M) of the two components led almost exclusively to linear species aggregation, as revealed by ^1H NMR analysis and viscosity measurements. Closely related linear poly[3]pseudorotaxane supramolecular arrays have also been prepared from cylindrical bis(crown ether) **127** and bisparaquat derivative **128** <2005CC1696>.

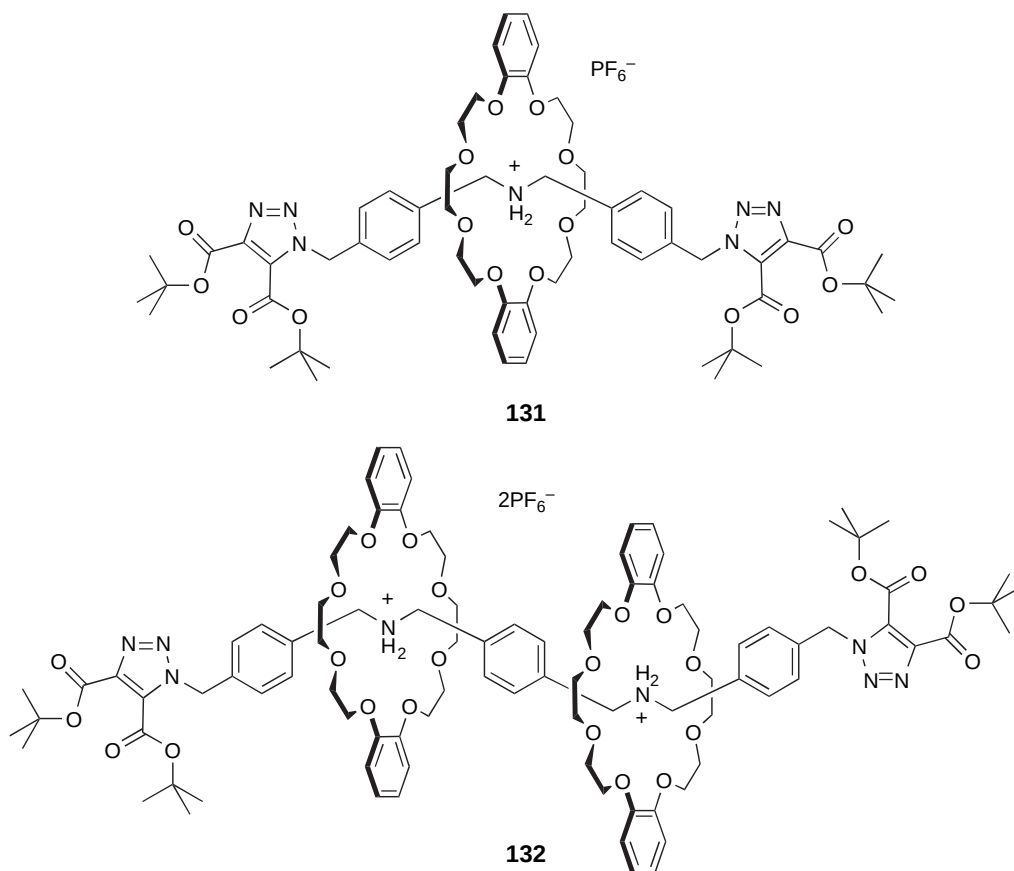


Pseudorotaxane studies have been of key relevance in providing the background knowledge for the design and development of rotaxanes. As mentioned above, the wheel and dumbbell components are held together by a mechanical bond, yet, despite the fact that these units are not covalently linked to one another, a rotaxane is by most definitions a well-defined chemical entity. According to the ‘threading-followed-by-stoppering’ strategy, formation of [2]rotaxanes requires addition of sufficiently bulky stoppers to the axle of a [2]pseudorotaxane precursor to prevent dethreading. Crucial to the success of the stoppering step is the fine-tuning of the reaction type and conditions to avoid disruption of the weak forces (e.g., hydrogen bonding, ion–dipole, and π – π -stacking interactions), keeping the pseudorotaxane components together.

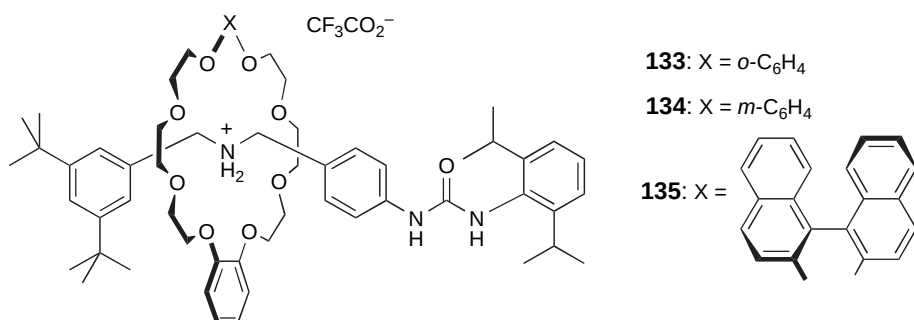
Compound **129** – the first [2]rotaxane of the dialkylammonium ion/crown ether family ever to be reported – was obtained by Busch and co-workers via acylation of a pseudorotaxane precursor bearing an anthracenyl-substituted ethylenediammonium axle, in a biphasic $\text{CHCl}_3/\text{H}_2\text{O}$ system [\[1995CC1289\]](#). Amide-bond formation has also been used for the attachment of the second stopper to [2]rotaxane **130** [\[2001OL2485\]](#). In this case, however, the final interlocking step was carried out between a preformed dicyclocarbodiimide-activated [2]rotaxane precursor and an N-substituted ethylenediamino stopper.



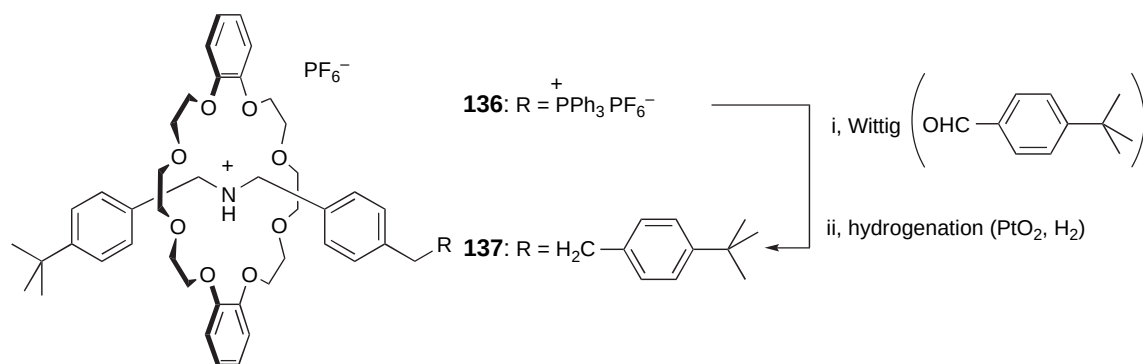
Stoddart and co-workers have developed a variety of elegant stopping strategies for dibenzylammonium-derived pseudorotaxanes. The 1,2,3-triazole stoppers present in [2]rotaxane **131** and [3]rotaxane **132** were generated by 1,3-dipolar cycloaddition reactions between bis(azidomethyl)-substituted cation and dication axles in the presence of di-*tert*-butyl acetylenedicarboxylate <1996CEJ729, 1996TL6217>.



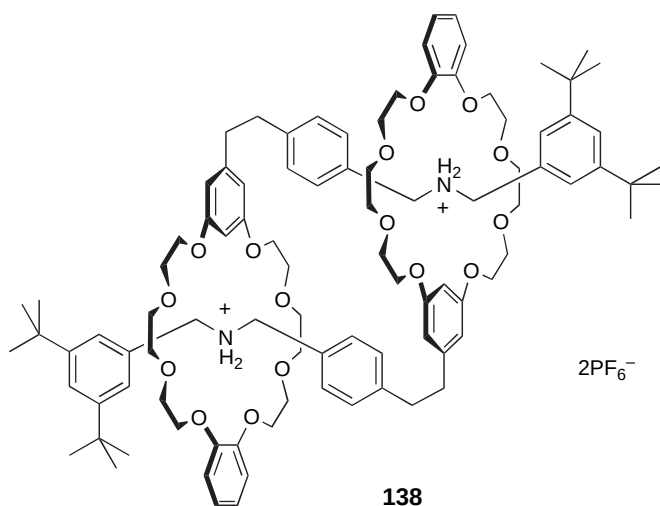
Compounds **133–135**, incorporating wheels of different sizes (i.e., **133**: dibenzo-24-crown-8 <1999TL3669>, **134**: benzo-*m*-phenylene-25-crown-8 <2000CEJ2274>, and **135**: (*R,S*)-benzo-2,2'-binaphtho-26-crown-8 <1999CC1251>), around the same asymmetric ureido-containing dumbbell, have all been readily obtained from the corresponding pseudorotaxane precursors by reacting the *p*-anilino end group of the threaded axle with 2,6-diisopropylphenyl isocyanate.



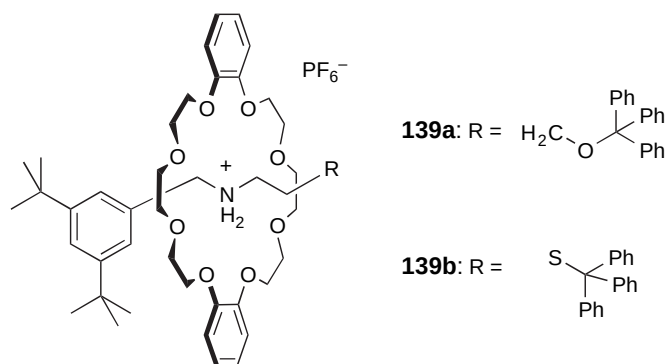
S_N1 reactions were used for the introduction of triphenylphosphonium stopper(s) onto axles bearing *p*-bromo-methyl end group(s) <1999OL129>. A Wittig reaction followed by hydrogenation (**Scheme 4**) was then employed for the postassembly conversion of the ‘exchangeable’ triphenylphosphonium stopper of [2]rotaxane **136** into the ‘permanent’ one present in **137** <2000JA164>, as well as the preparation of the cyclic dimeric ‘daisy chain’ **138** <2002CC2948>.



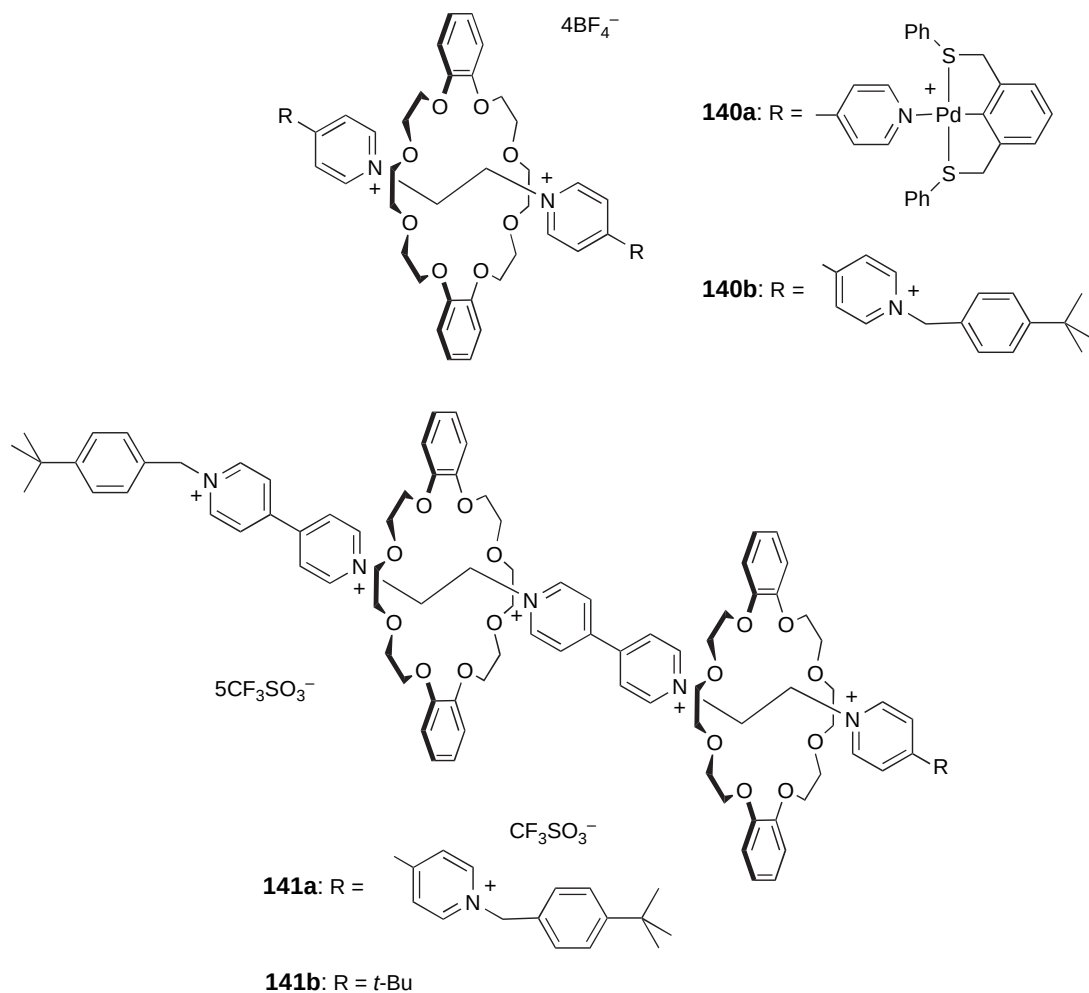
Scheme 4



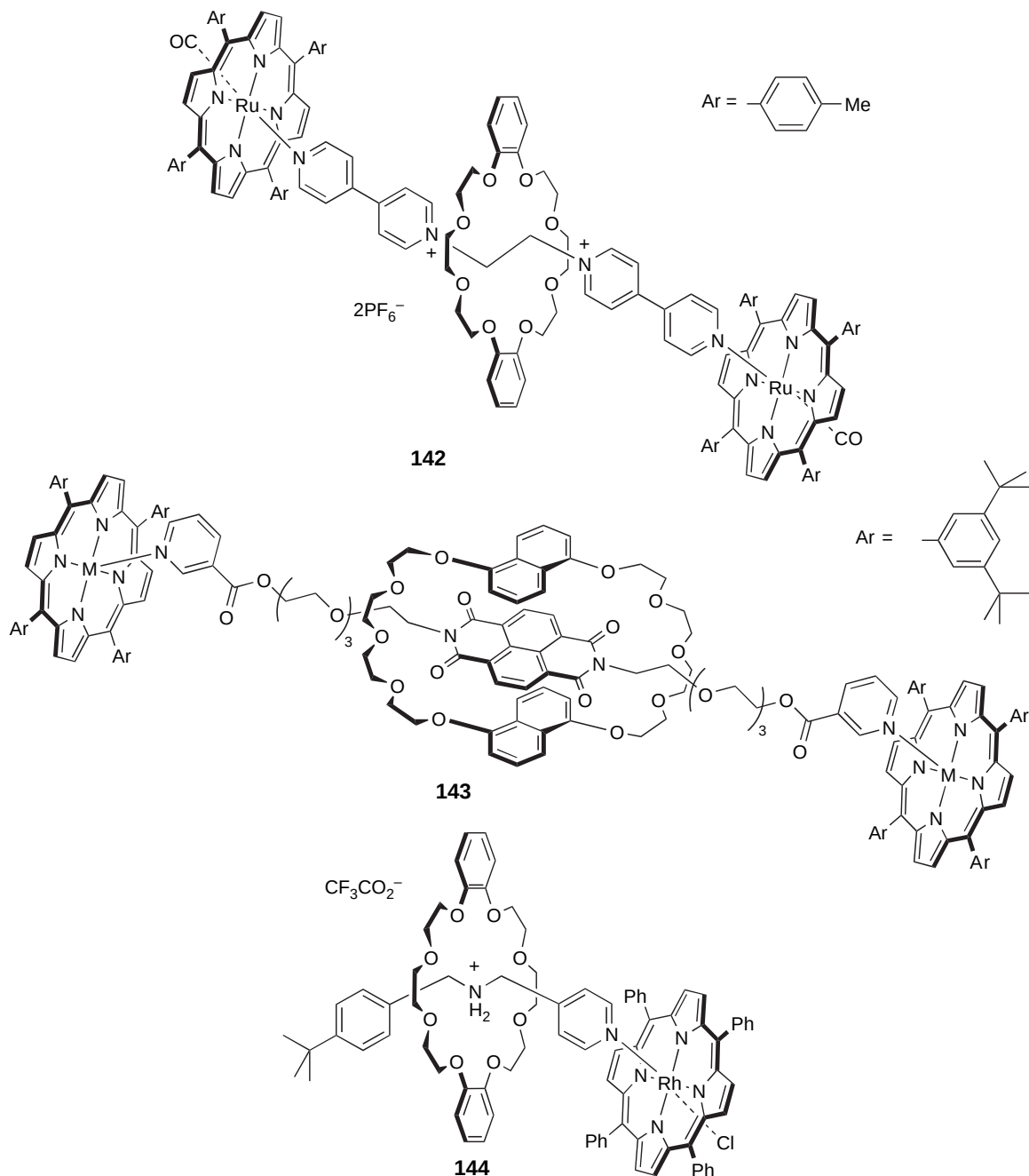
Tritylative end-capping of preformed pseudorotaxanes consisting of a DB24C8 wheel and secondary ammonium axles bearing either a terminal thiol or hydroxy functionality have yielded the corresponding rotaxanes **139** <2002T6609>.



Pseudorotaxane precursors consisting of bis(pyridinium)ethane axles and 24-membered crown ethers have also been converted to [2]rotaxanes and [*n*]rotaxanes. For example, the terminal pyridine nitrogen atoms of pseudorotaxane **120** (R = 4-pyridyl) underwent coordination of organopalladium fragments or N-alkylation with *tert*-butylbenzyl groups to afford [2]rotaxanes **140a** and **140b** <1998CC2757>. Symmetrical and unsymmetrical [3]rotaxanes **141a** and **141b** have also been prepared, from extended axles containing two binding sites, by taking advantage of the same template motif <2000CC845>.



Selected examples of rotaxanes bearing very bulky stoppers include a [2]rotaxane with fullerenes <2003AGE3158>, [2]-, [3]-, and [4]rotaxanes end-capped with dendritic moieties <1996JA12012>, as well as derivatives **142** <2000CC847>, **143** <2001NJC166>, and **144** <2003EJO3744>, which rely on axially coordinated metalloporphyrins as stoppers.

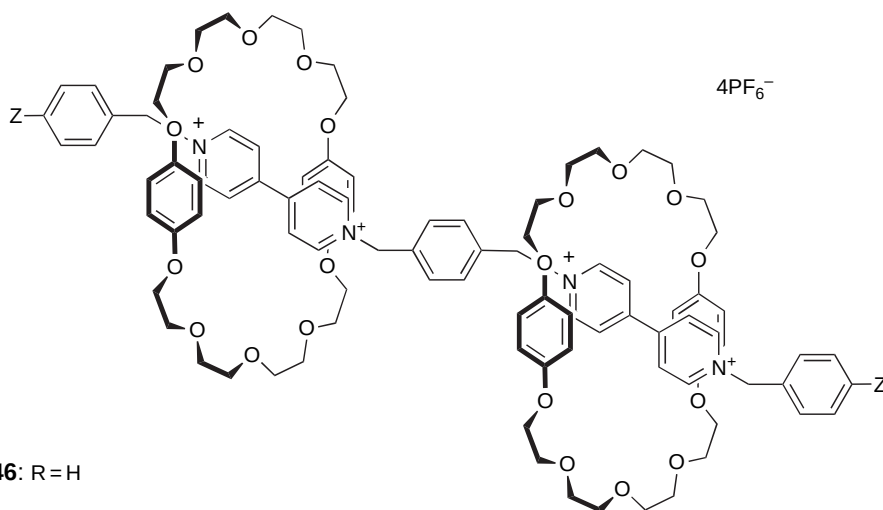


Rotaxanes can also be prepared by the so-called 'slipping' method. This is a thermodynamically driven self-assembly strategy, developed by the Stoddart group in the early 1990s, which relies upon the size complementarity between preformed macrocyclic and dumbbell-shaped components <1998JA9318>. The macrocycle has to possess a cavity that is just large enough to slip over the bulky stoppers attached to the ends of the dumbbell under the influence of an appropriate amount of thermal energy <1997JA302>. Once the ring is trapped by the dumbbell component and the heat is discontinued, the energy barrier required for 'deslipping' is far too high and dethreading is therefore severely disfavored.

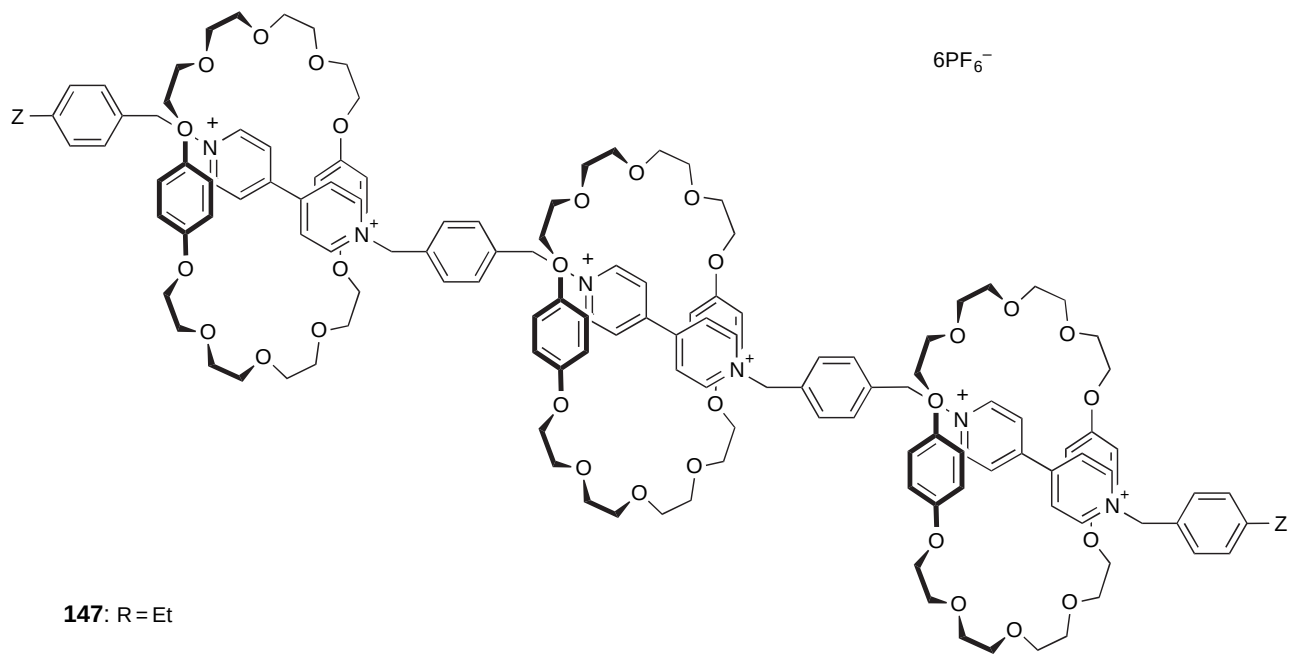
The synthesis of rotaxanes (and catenanes) carried out under kinetically controlled conditions has as a drawback the employment of an irreversible bond-forming final step, which may yield competitive or unwanted non-interlocked by-products. Methods allowing interlocking to occur in a thermodynamically controlled manner have therefore been developed, so that by-products can be recycled to afford the energetically, most favored, interlocked species, via reversible breakage/formation of covalent bonds ('dynamic covalent chemistry') <2002AGE898>.

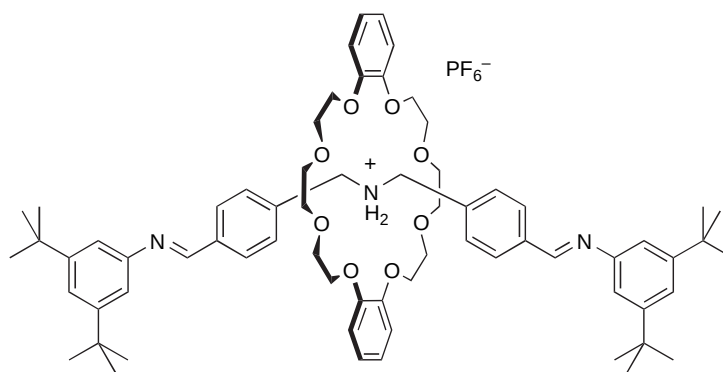
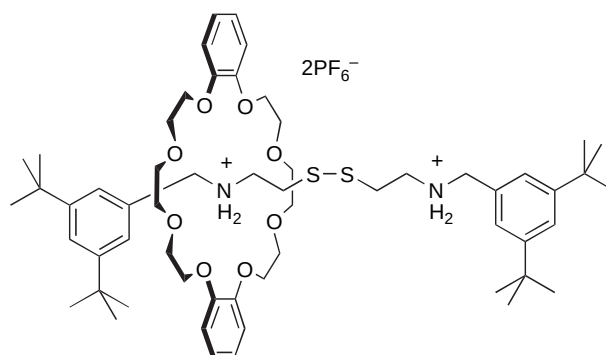
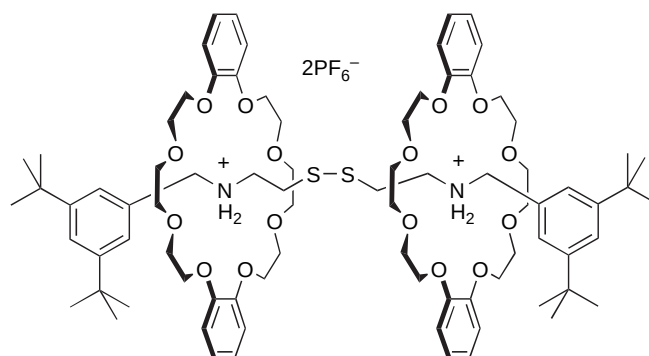
Chemical structures of two macrocyclic receptors. The left structure is a 18-crown-6 derivative with two phenyl groups substituted with a Z group, and a central pyridine ring substituted with a Z group. It is shown with 2PF₆⁻ counterions. The right structure is a 18-crown-6 derivative with two phenyl groups substituted with a Z group, and a central pyridine ring substituted with a Z group. It is shown with R = H, Me, Et.

145: R = H, Me, Et

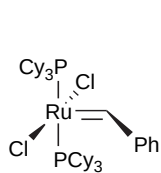
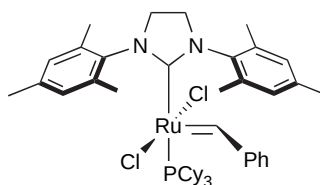


146: R = H

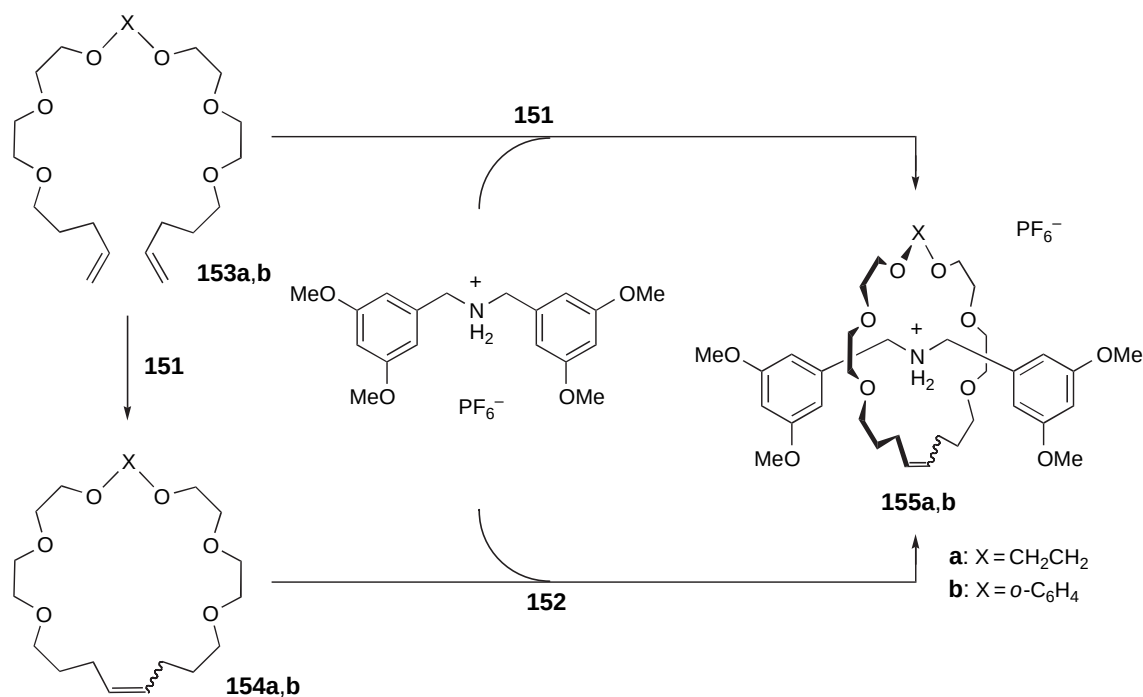


**148****149****150**

Ring-closing metathesis (RCM) and ring-opening–ring-closing metathesis (RORCM) reactions of olefinic derivatives [<2001ACR18>](#), mediated by Grubbs' first- or second-generation catalysts [151](#) [<1996JA100>](#) and [152](#) [<1999OL953>](#), respectively, have provided access to rotaxanes [155](#) [<2003AGE3281>](#). [Scheme 5](#) shows that either the open-chain vinyl polyether derivatives [153](#) or the unsaturated rings [154](#) are able to afford upon RCM or RORCM reaction, in the presence of the appropriate catalyst and a preformed secondary ammonium dumbbell, the same rotaxanes [155](#) as mixtures of (*E*)- and (*Z*)-isomers, which could then be hydrogenated to yield a stable rotaxane.

**151****152**

Cy = cyclohexyl



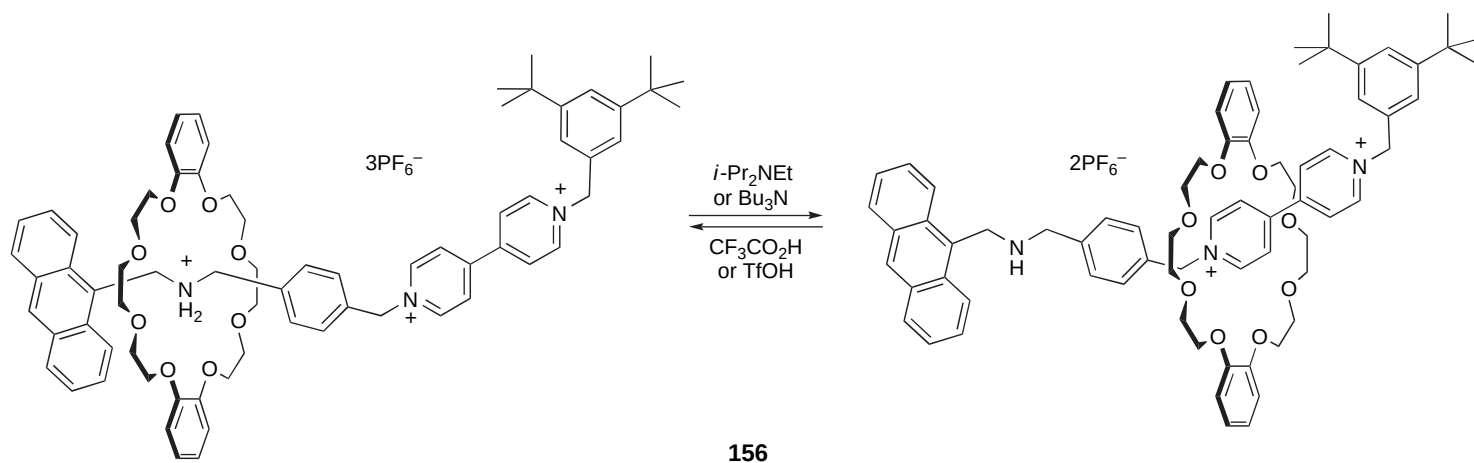
Scheme 5

[2]Rotaxanes in which the dumbbell component possesses two distinct recognition sites for the encircling macrocycle ('stations') are currently attracting considerable attention because of their potential applications in the development of molecular shuttles, machines, switches, logic gates, and memory devices; for recent reviews, see [<2004AJC301>](#) and [<B-2003MI1>](#). In such systems, commonly referred to as 'switchable rotaxanes', the ring component preferentially rests on the site with which stronger noncovalent interactions take place. It is then possible, by means of an external stimulus (e.g., chemical, electrochemical, or photochemical), to alter the binding properties of the sites and, as a result, make the ring component move from the original recognition site to the other one. In the best possible scenario, the properties of the two recognition sites can be switched reversibly back by another stimulus, so that a molecular shuttle is ultimately generated.

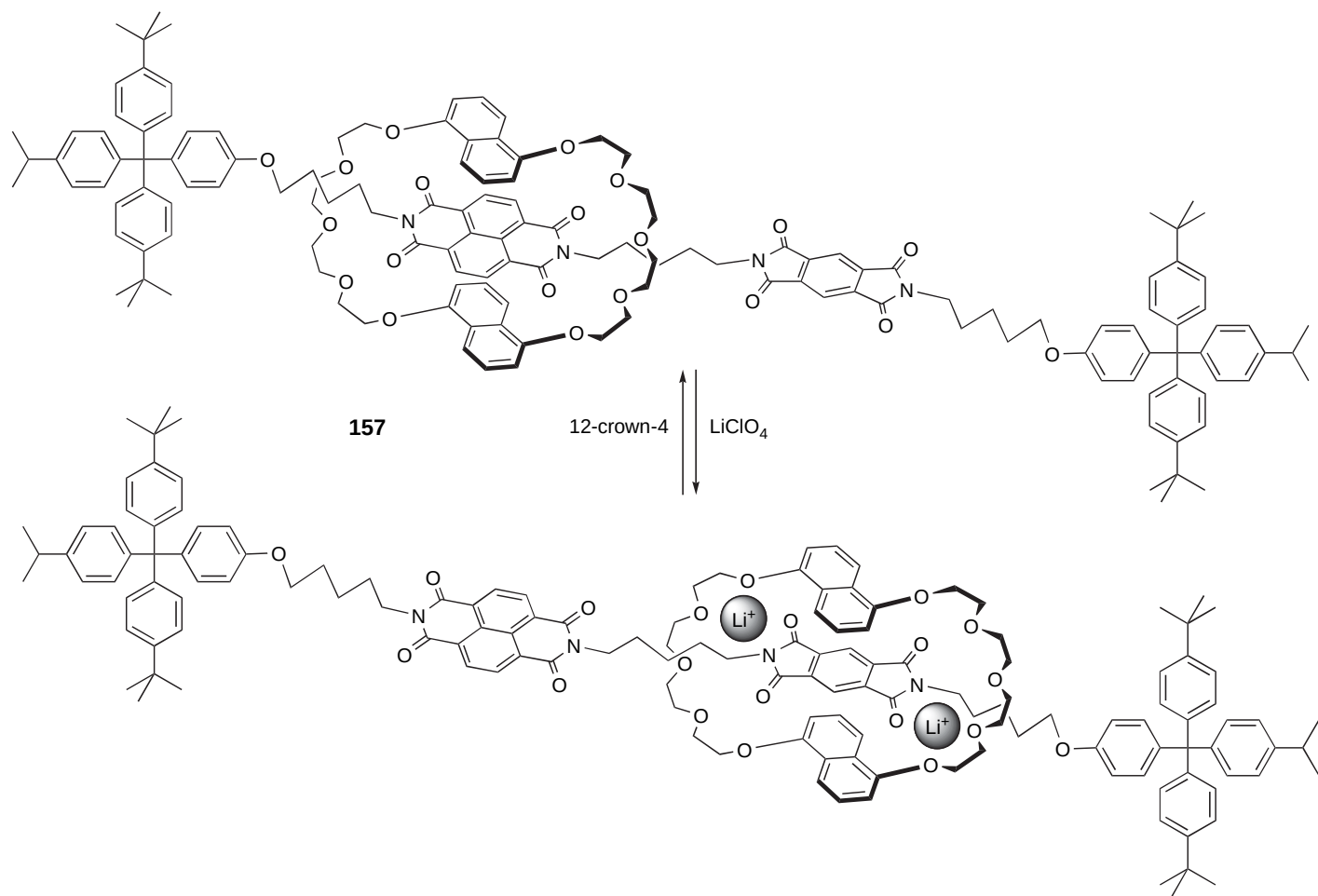
[2]Rotaxane **156**, possessing a secondary dialkylammonium (NH₂⁺) and a 4,4'-bipyridinium (Bpym²⁺) moiety (i.e., the two stations for the DB24C8 wheel) together with a fluorescent and redox-active anthracene stopper unit, has been shown to act as a controllable molecular shuttle [<1998JA11932>](#). Acid-base switching experiments ([Scheme 6](#)), monitored by ¹H NMR spectroscopy as well as electrochemical and photophysical techniques, demonstrated that, upon addition of an appropriate base to a solution of **156**, the crown ether switched from the NH₂⁺ to the Bpym²⁺ station. Treatment with acid restored the NH₂⁺ center and reversed the process.

Derivative **157** is an example of a neutral bistable [2]rotaxane, based on π -electron donor/acceptor interactions, which is able to undergo electrochemical as well as chemical (Li⁺ ions) switching [<2004CEJ6375>](#). The crown ether component of this rotaxane preferentially encircled the 1,4,5,8-naphthalenetetracarboxylate diimide (NpI) unit because of the more pronounced electron-withdrawing character of this moiety with respect to the pyromellitic diimide (PmI) one. However, since the pole-dipole interactions involving Li⁺ ions and the polyether oxygen atoms are stronger in the case of a PmI encircled unit, addition of Li⁺ ions to [2]rotaxane **157** induced the macrocycle to move from the NpI- to the PmI-recognition site. By subsequently adding the cation receptor 12-crown-4 to the mixture, the lithium ions were sequestered and the initial ground state was restored ([Scheme 7](#)).

The synthesis of a triphenylene-derived tris(crown ether) [<2000OL1221>](#) has allowed the assembly of a number of either interwoven **158a** or interlocked **158b** supermolecules, according to the size of the stoppers present on the complementary trifurcated tricationic component employed [<2003CEJ5348, 2004CEJ1926>](#). The formation of these complex molecules termed 'superbundles' relies on the well-known ability of secondary ammonium ions to thread through DB24C8 derivatives and particularly on the cooperative – and as a result enhanced – effect that the triple threading provides (multivalency). Fluorescence titration experiments, as well as electrochemical and ¹H

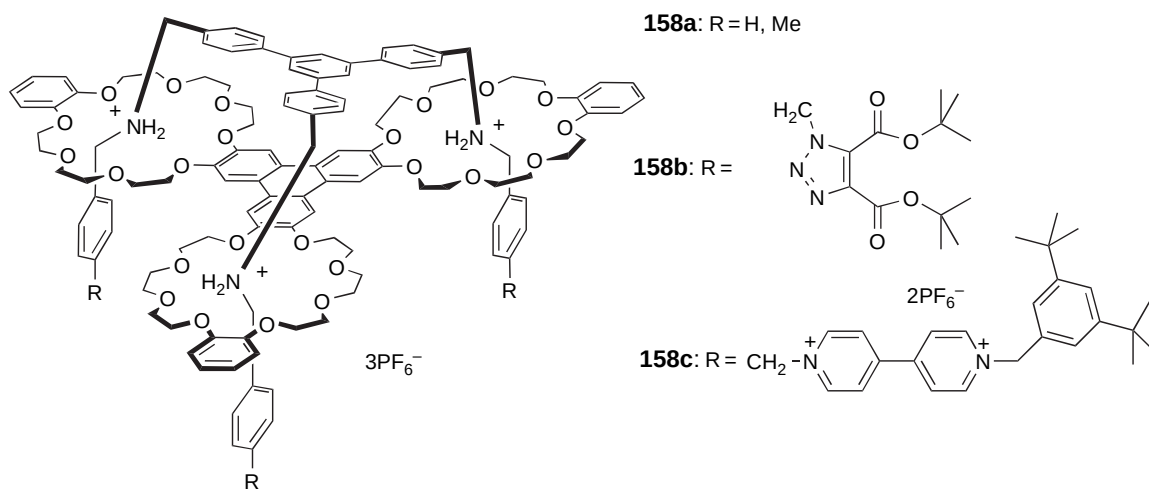


Scheme 6



Scheme 7

NMR data on the dethreading/rethreading and deprotonation/reprotonation mechanisms of these species, have ultimately led to the design and construction of the acid/base-driven 'molecular elevator' **158c** <2004SCI1845, 2006JA1489>.



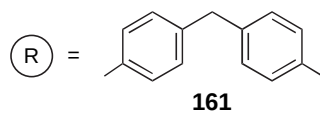
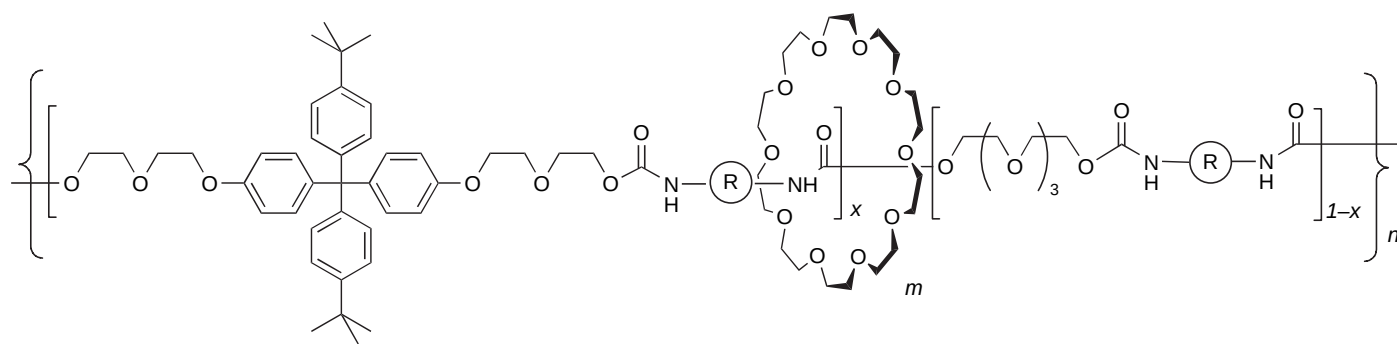
The convergence of polymer and supramolecular sciences has offered in recent years great opportunities for new materials with unique properties and novel practical applications. Polypseudorotaxanes and polyrotaxanes, that is, polymeric species incorporating pseudorotaxane and rotaxane units, respectively, are among the end products of these overlapping areas of chemistry. The considerable interest in the assembly of these architectures is related to the production of materials with novel properties (e.g., solubility, viscosity, glass transition, and mechanical behavior), which might result from flexible and movable connections between cyclic and linear components. Depending on the location of their constituent units, polypseudorotaxanes/polyrotaxanes can be divided into main-chain or side-chain systems <1993AM11>. In the former, the (pseudo)rotaxane components are part of the backbone; in the latter they are present as pendant groups.

Polyrotaxanes were first prepared in 1976, by Zilkha and co-workers from crown ethers and oligoethylene glycols <1976JA5206>. In more recent years, major contributions to the field of crown ether-based polypseudorotaxanes have come from the group of Gibson <1994PPO843, 2005PPO982>. Several main-chain polypseudorotaxanes containing polyester <1991PLC204, 1995JA852, 1997MM3711>, polyurethane <1994JA537>, polystyrene <1999PLM1823>, polyacrylate, and poly(methyl methacrylate) <2001PSA1978> backbones have been prepared by carrying out *in situ* polymerization of suitable monomers in the presence of unfunctionalized crown ethers. Step-growth polymerization is the method most commonly employed, although hydrogen-bond-driven polypseudorotaxane formation has also been reported from preformed polyurethane backbones in combination with 30-crown-10 or 42-crown-14 rings <1998MM1814>. Poly(ester rotaxane)s **159** <1996MM7029> and **160** <1997MM4807> were obtained by introducing bulky blocking groups into the diols and/or the diacid dichlorides undergoing polycondensation. This trapping method prevents threaded crown ether molecules from slipping off the backbone during polymerization and provides species with a high average number of macrocycles per repeat unit (*m/n* value). Formation of these polyrotaxanes was proven by hydrolytic recovery of the constituent crown ether, 2-D nuclear Overhauser enhancement spectroscopy (NOESY) spectra, and gel permeation chromatography (GPC) analysis.

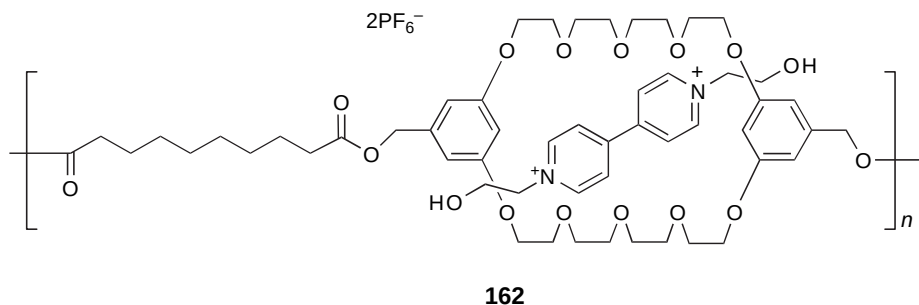
Step-growth polymerization of diols with blocking groups and bisisocyanates, using a crown ether as the solvent, has afforded poly(urethane rotaxane)s **161** <1997AGE2331, 1998MM308>. These polyrotaxanes behave as solvent-responsive polymeric molecular switches. In chloroform, their crown ether rings are preferentially resting close to the urethane sites, as a result of intercomponent [N–H···O] hydrogen bondings, whereas in DMSO they are in the proximity of the blocking groups.

Main-chain poly(styrene rotaxane)s <1997MM337, 1999PLM1823> were obtained by free radical polymerization of styrene in the presence of crown ethers using initiators incorporating bulky blocking groups to prevent dethreading of the macrocyclic components.

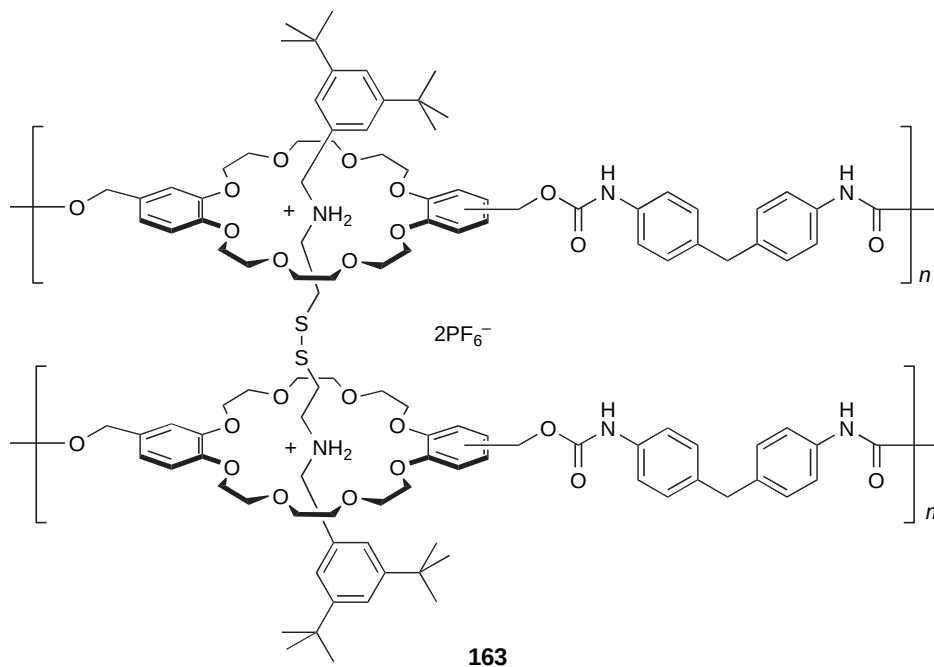




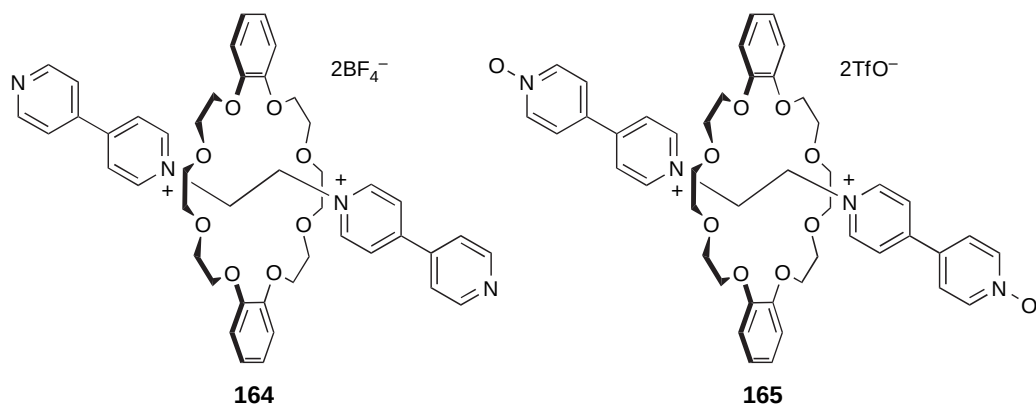
The reaction of poly(methacryloyl chloride) with crown ethers bearing a hydroxymethyl functionality has afforded, depending on the solvent and concentrations, branched and/or mechanical cross-linked polyrotaxanes, with cross-linking occurring as a result of a hydrogen-bond-driven threading process between the hydroxymethyl group of one crown ether moiety of one polymeric backbone through the cavities of the macrocycles appended to another [\[1997JA5862\]](#). By a similar strategy, control of the polymerization conditions (solvent or bulk) between dihydroxy- and dicarboxyl-functionalized crown ethers and appropriate linking units has provided access to poly(urethane rotaxane)s [\[1997JA8585\]](#) and poly(ester rotaxane)s [\[1997T15197\]](#) with different polymeric topology (linear, branched, or cross-linked) as revealed by 2-D NOESY NMR spectra. Main-chain polyester polypseudorotaxane **162**, embedding crown ether units into the backbone, was obtained from bis(5-hydroxymethyl-1,3-phenylene)-32-crown-10 and sebacoyl chloride followed by bipyridinium salt addition [\[1998AGE310, 1998MM5278\]](#). The polycondensation process relied in this case on DMSO as a cosolvent, to suppress hydrogen-bond formation (between the polyether oxygen atoms and the hydroxyl hydrogen atoms) and consequent self-threading of the macrocyclic components.



Polyrotaxane networks **163** have been developed as prototype 'recyclable' cross-linked polymers [\[2004AGE966\]](#). These systems, which comprise a poly(crown ether)polyurethane and a bisammonium disulfide salt, are cross-linked via mechanical bonds ([3]rotaxane-like substructures) and are capable of undergoing reversible assembly and disassembly as they rely on thiol–disulfide reactions. Macroscopically, cross-linking determines gelation while de-cross-linking enables recovery of the starting materials.



Metal-organic rotaxane frameworks (MORFs) are a new type of solid-state polyrotaxane architecture recently developed by Loeb [\[2005CC1511\]](#). [2]Pseudorotaxane **164** or its bis(*N*-oxide) analogue **165** were shown to undergo metal–ligand self-assembly reactions in the presence of transition (Co, Cd, Ni) or lanthanide (Sm, Eu, Gd, Tb) metal ions, respectively, to provide in turn linear 1-D and square-grid 2-D or interpenetrated cube-like 3-D coordination networks.

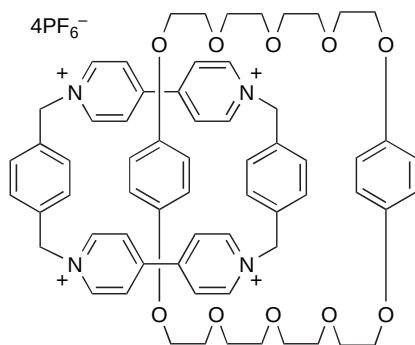


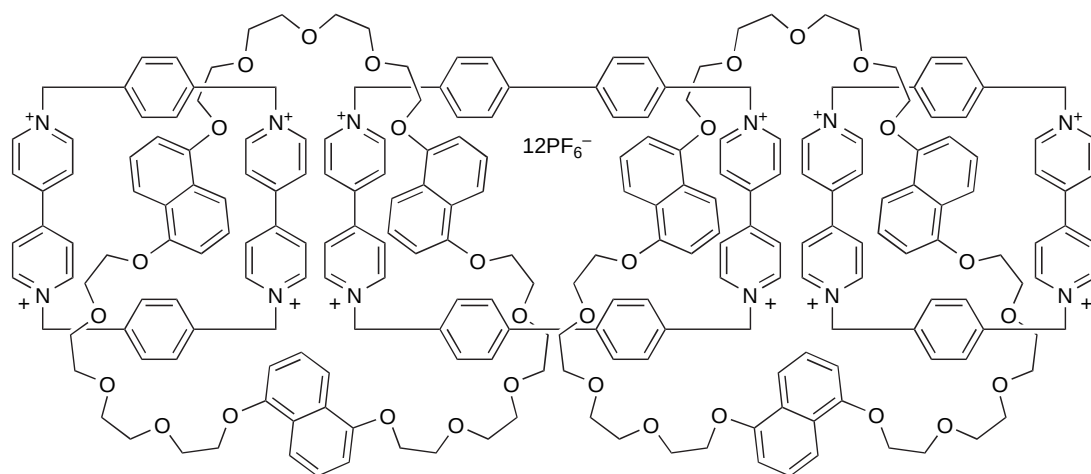
14.12.4.2 Catenanes

Catenanes, as the name of Latin origin suggests (*catena* = chain), are chain-like molecules composed of at least two cyclic compounds (i.e., a [2]catenane) that are not covalently linked to one another but nevertheless cannot be separated unless covalent bond breakage occurs. Catenanes thus belong, together with rotaxanes (Section 14.12.4.1), to the wider family of interlocked molecules.

Earlier examples of low-yielding catenane syntheses were based on statistical <1960JA4433> or direct step-by-step <B-1971MI1> methods. Modern and far more efficient synthetic procedures became available after 1983, when the group of Sauvage exploited for the first time the template effect of transition metal ions (Cu(I)) for the assembly of phenanthroline-based [2]catenanes <1983TL5095>. Several template-directed synthetic strategies involving either charged or neutral species, as templates, were then developed, templation being secured by a variety of noncovalent interactions (e.g., metal–ligand coordination, hydrogen bonding, π – π -stacking, and hydrophobic contacts). For comprehensive and updated accounts on this class of supermolecules, possessing crown ethers as well as other macrocyclic rings, the following review articles are recommended <1999ACR53, B-1999MI2, 1999CRV1643, 2000CCR5, 2002SL1743, 2004TCC141, 2005TCC203>.

The synthesis of catenanes incorporating crown ether rings was pioneered in the late 1980s by the Stoddart group. [2]Catenane **166** <1989AGE1396>, the progenitor of this family, was obtained in remarkably good yields (70%) from *p*-xylylene dibromide and an appropriate bis(pyridinium) salt in the presence of bis-*p*-phenylene-34-crown-10 as a result of a favorable combination of π – π -stacking and charge-transfer interactions, as well as hydrogen bondings. Subsequent to this synthetic landmark, various modifications of this template motif were used for the assembly of several [2]catenanes <1995CRV2725> including chiral ones <1999EJO995>. Linear and branched oligocatenanes ranging from [3]- to [7]catenane <1997AGE2070, 1998JA4295, 2000EJO1121>, including [5]catenane **167**, known as olympiadane <1994AGE1286>, were also synthesized and characterized by X-ray analyses. The number of interlocked macrocycles within each catenane could also be determined by MS, using a variety of ionization techniques. [*n*]Catenanes were found to display a quite complex electrochemical behavior, resulting from the presence of many, mutually interacting, electroactive units.





167

On the other hand, a number of polymeric species such as poly[2]catenane **168** and poly(bis[2]catenane) **169** were generated by polymerization or copolymerization of appropriate [2]catenane or bis[2]catenane monomers <1998EJO2109>.

Catenane assembly, mediated by neutral π -donor/ π -acceptor components, has been investigated by Sanders and co-workers <2002SL1743>. [2]Catenanes **173** and **174** were prepared (Scheme 8) by oxidative dimerization of the two bis-ethynyl diimides **171** and **172** (derived from pyromellitic and 1,4,5,8-naphthalenetetracarboxylic dianhydrides) in the presence of bis-1,5-(dinaphtho)-38-crown-10 **170** <1997CC897, 1998CEJ608>. Additional examples of [2]catenanes incorporating a diimide-based cyclophane as the electron-poor ring are provided by derivatives **175** <2004OL655> and **176** <1998JA1096, 1999J(P1)1057>. The former contains, as a second ring, a less common asymmetric crown ether-bearing ester linkages. The latter comprises a hybrid crown macrocycle that becomes part of the catenane either as a preformed ring or as a result of a tandem hetero-catenation process – which involves concomitant closure of the two different rings – between **171** and the appropriate bis-acetylenic precursor.

[2]Catenane **177**, devoid of triple bonds, has been prepared by macrocyclization of a 1,4,5,8-naphthalenetetracarboxylate diimide precursor bearing ethylene glycol chains and pyromellitic diimide, under standard Mitsunobu alkylation conditions, in the presence of crown ether **170** <2000OL449>.

Derivative **178** containing a dibenzo-34-crown-10 ring interlocked with macrocycles incorporating two 4,4'-dipyridyl moieties tethered by different aryl spacers acts as bistable [2]catenane <2006OL2119>. Variable-temperature (VT) NMR studies were used to determine the activation energy required for the conformational interconversions and to demonstrate that, by appropriate incorporation of bulky groups on one or both of the aryl linkers, it was possible to block one or both of the two circumrotation pathways.

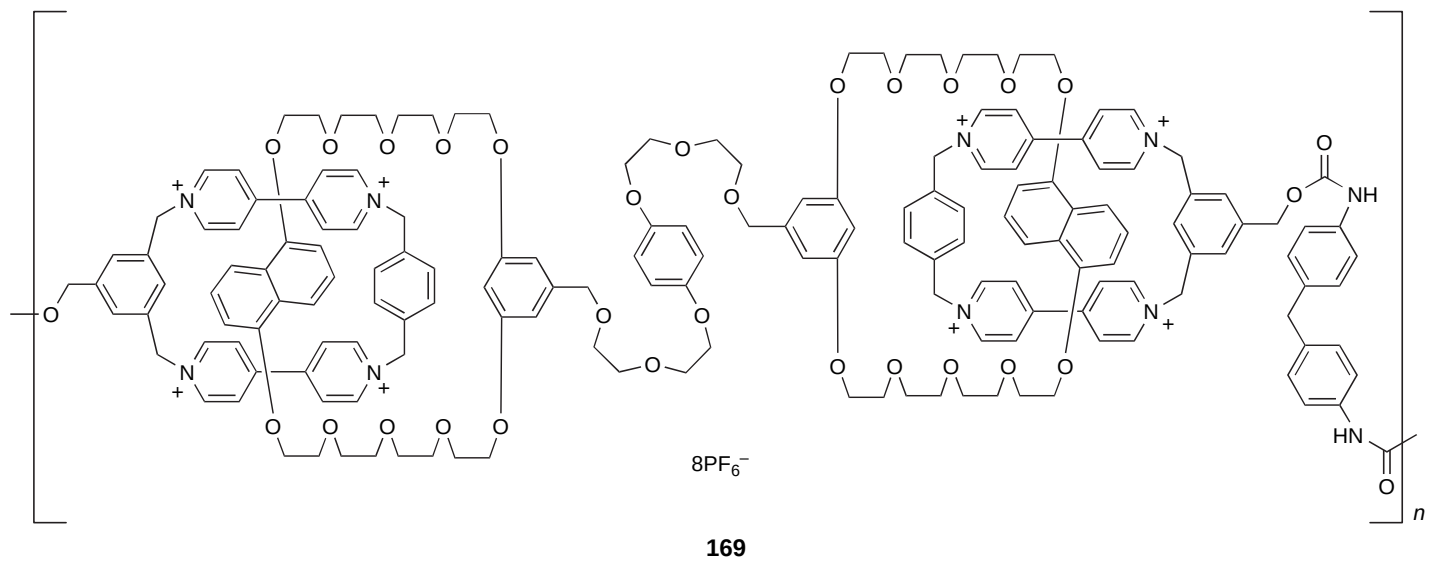
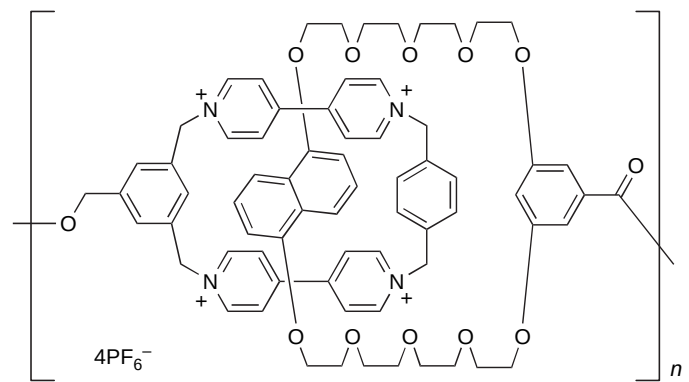
RCM and RORCM reactions in the presence of Grubbs' catalysts **151** <1996JA100> and **152** <1999OL953> have also been employed for catenane synthesis under reversible thermodynamic conditions. The isomeric (*E/Z*)-mixture of [2]catenanes **179** was obtained <1998NJC1019> by RCM of an appropriate diimide bearing ethenyl-terminated alkyl chain in the presence of crown ether **170** and catalyst **151**. Similarly, initial pseudorotaxane formation followed by metathesis reaction of the double bonds present on the secondary alkylammonium ion axle has afforded [3]catenane **180** as well as [2]catenane **181** <2003TL5773>.

Interlocking of [2]catenane **182** (*E/Z*)-mixture) was accomplished by templated RCM of an appropriate acyclic ethenyl precursor as well as RORCM of the two separate constituent rings <2005OL2129>. Post assembly hydrogenation was then used to convert the (*E/Z*)-isomeric mixture of **182** into a single saturated species.

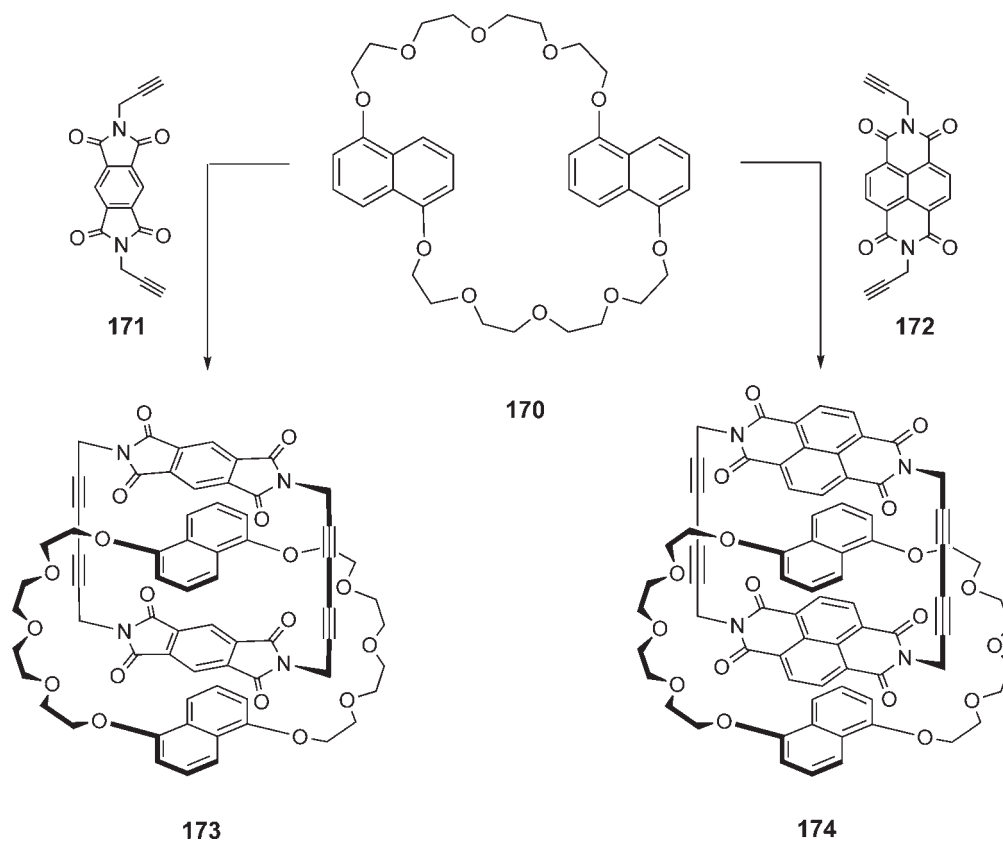
A triptycene-based tris(crown ether) has very recently been used to form a tris[2]pseudorotaxane precursor and this has in turn been converted into [4]pseudocatenane **183** by means of threefold olefin metathesis, in the presence of Grubbs' catalyst **152**, followed by hydrogenation <2005JA13158>.

14.12.4.3 Dendrimers

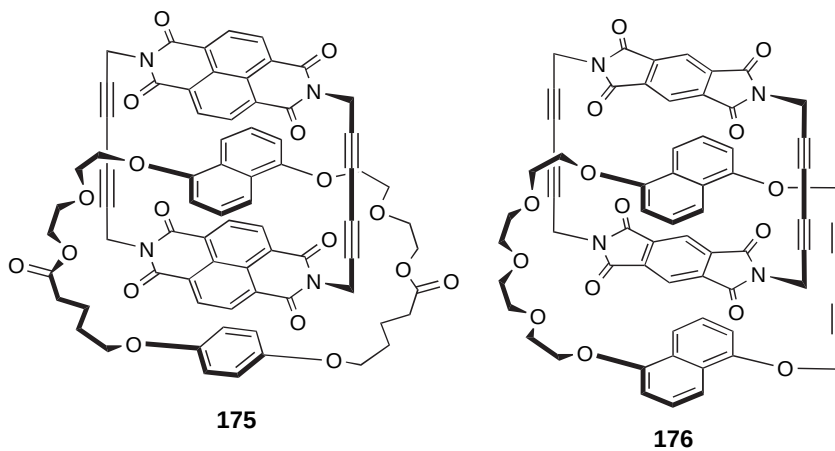
Dendrimers are highly ordered, regularly branched macromolecules consisting of a core (or focal moiety), an outer layer of terminal groups (or end -groups), and a number of intermediate branches connecting the two. Dendritic

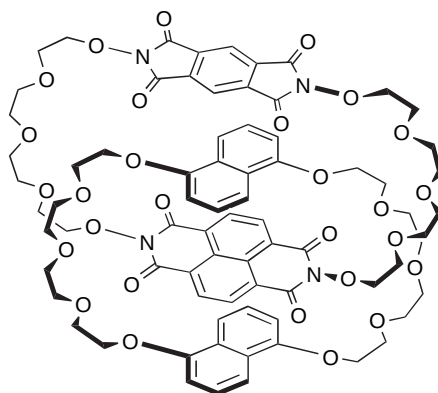


molecules present a globular and very regular architecture made of concentric layers of branching points, known as 'generations'. For a full discussion of the chemistry of this class of compounds, a number of recent reviews are available <1999CRV1689, 2001CRV3819, B-2001MI3, B-2002MI1>.

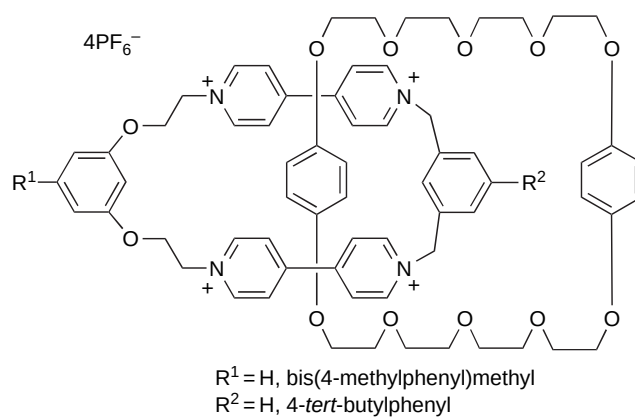


Scheme 8

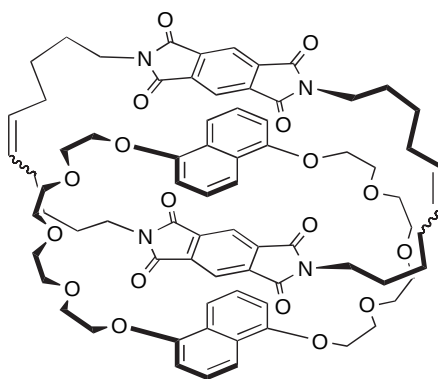




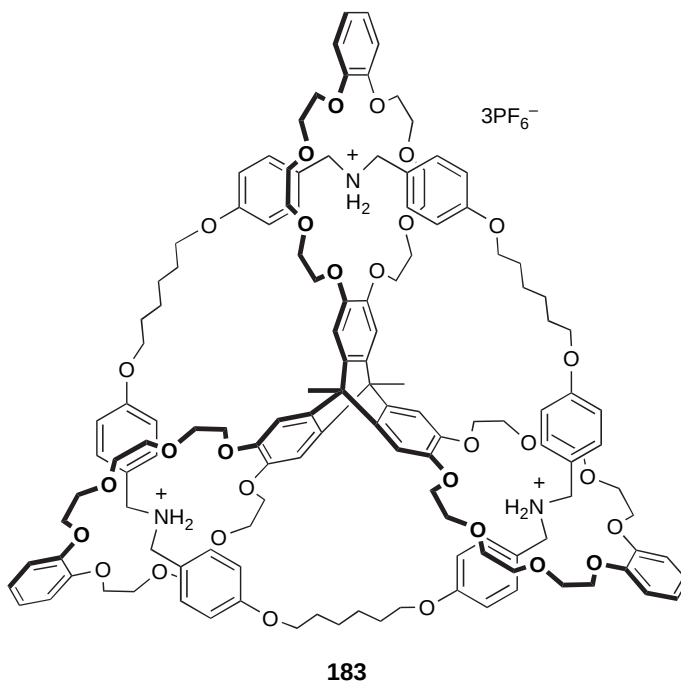
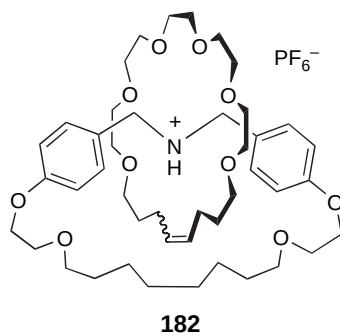
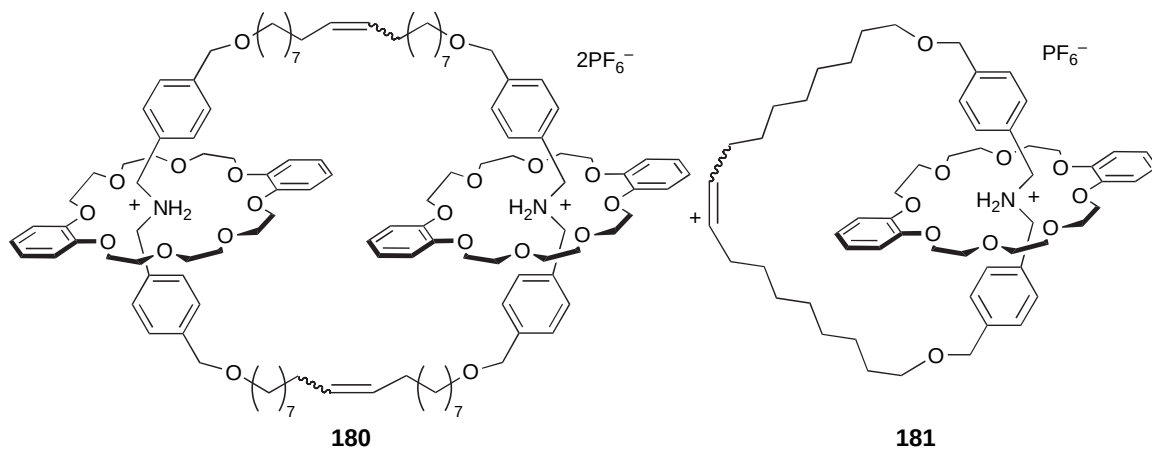
177



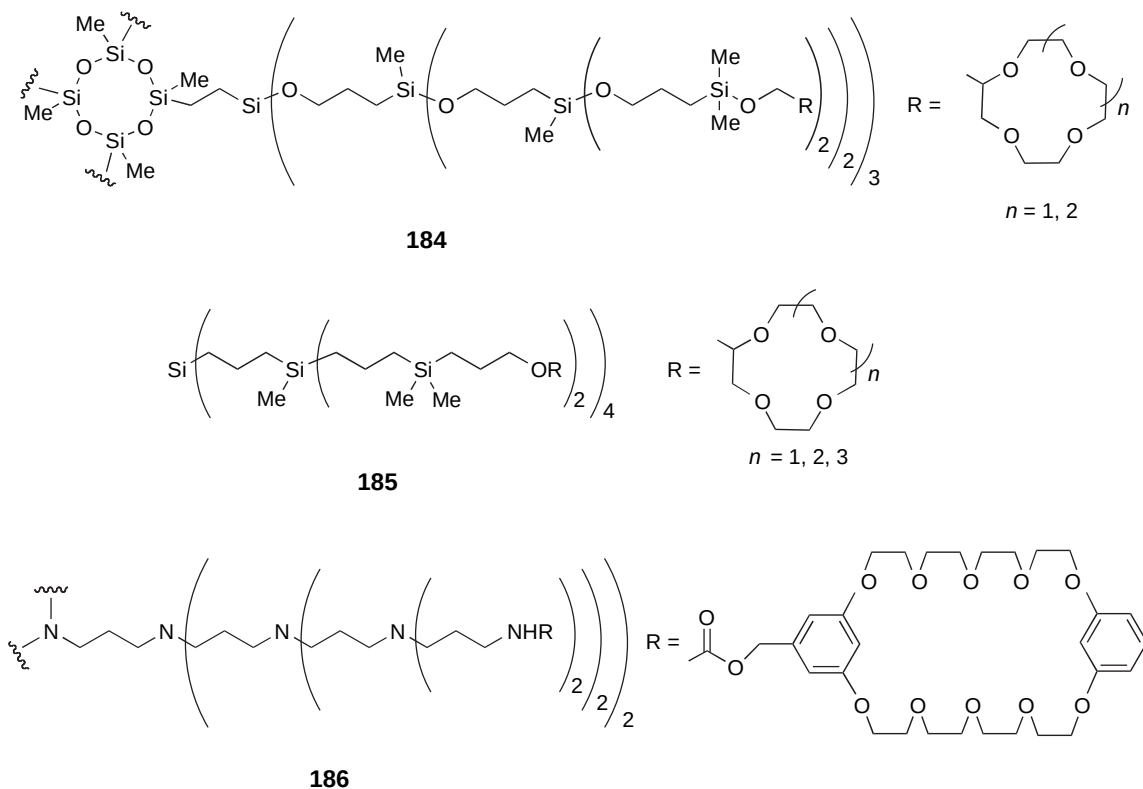
178



179



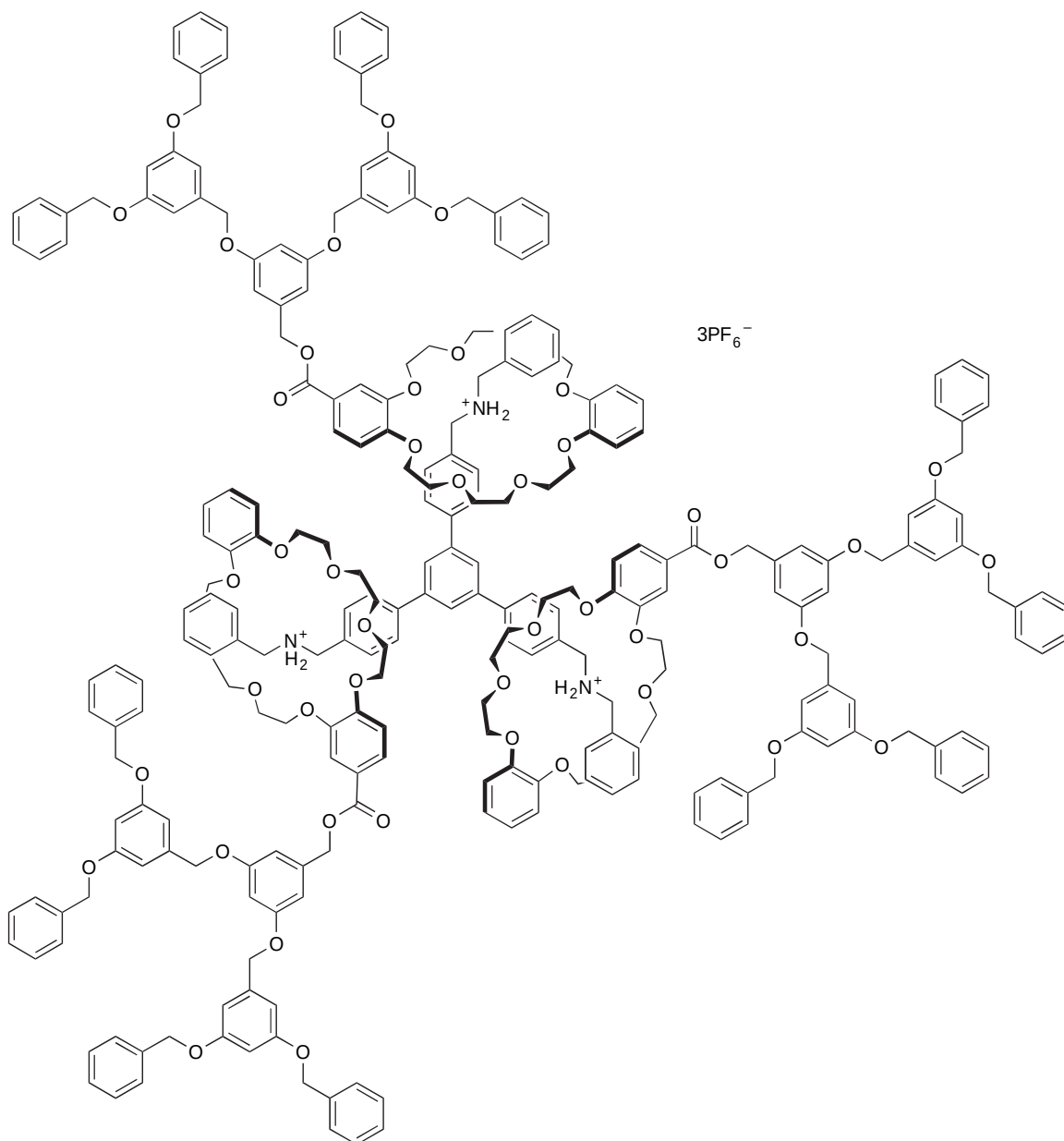
Different types (and generations) of dendrimers have been derivatized at their terminal groups with crown ether rings of various sizes (12-crown-4, 15-crown-5, 18-crown-6, and bis(*m*-phenylene)-32-crown-10) to provide the corresponding carbosiloxane **184** <2002BKC637>, carbosilane **185** <2004S1243, 2005JOM(690)696>, and poly(propyleneimine) **186** <2003JOC2385> dendrimers. Dendrimers **185** were characterized by IR, ^1H and ^{13}C NMR, as well as $^{29}\text{Si}\{^1\text{H}\}$ NMR spectroscopy, and tested as potential alkali metal ionophores by electrospray ionization time-of-flight (ESI-TOF) MS. Compounds **186**, on the other hand, were investigated (NMR) in detail with respect to their ability to generate, as such and after protonation at the nitrogen atoms, multiple pseudorotaxanes in the presence of paraquat derivatives.

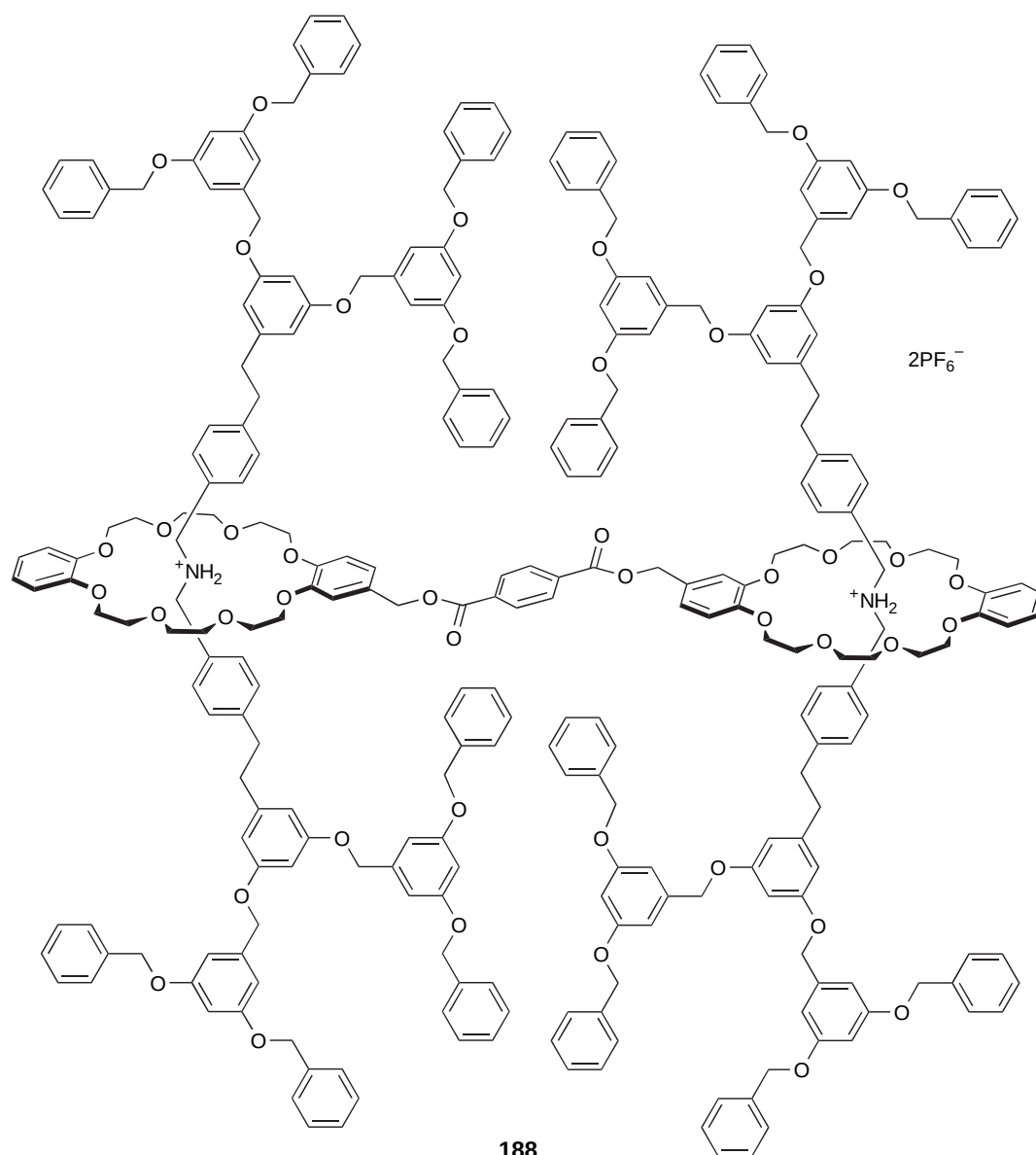


Dendrimer synthesis does not necessarily require covalent bond formation; it may also rely on templating effects and noncovalent interactions between the different building blocks (dendrons). Over the past 10 years, following the report of Zimmerman and co-workers on hydrogen-bond-driven self-assembly of carboxylic acid-containing dendrons into hexameric rosettes <1996SCI1095>, research in the field of supramolecular dendrimers has indeed blossomed and has become very active in connection with catalysis, drug delivery, light-energy harvesting, and sensing. For more comprehensive coverage of this topic refer to the following reviews <B-2000MI359, 2001TCC95, 2005PPO220, 2006CC34>.

Dendritic pseudorotaxanes, such as **187**, were first reported by Gibson and co-workers <1998AGE3275, 2002JA4653>. Formation of these species from DB24C8-modified Fréchet-type dendrons (first, second, and third generations) and a tritopic secondary ammonium salt was detected by both NMR spectroscopy and matrix-assisted laser desorption ionization (MALDI)-TOF mass spectrometry. Extensive NMR studies, in different solvents, showed the self-assembly of the trivalent template with the successive generations of dendrons being highly cooperative.

Mechanically branched dendritic rotaxane **188** was prepared by Stoddart and co-workers by the threading-followed-by-stoppering method [<2002OL679>](#). The dendritic branching acts as stoppers, converting the initial noncovalently held pseudorotaxane structure into a permanently interlocked rotaxane. Stoddart's group has also assembled supramolecular dendrimer **189** [<2002OL3565>](#), by taking advantage of the thermally induced 'slipping' technique. Two Fréchet-type dendrons were first appended to a DB24C8 macrocycle and the resultant bis-dendron was then exposed to a structurally related dendron derivatized with a secondary dialkylammonium ion at the focal point. Slipping/deslipping studies were carried out in refluxing CH_2Cl_2 and DMSO, respectively, and followed by ^1H NMR.





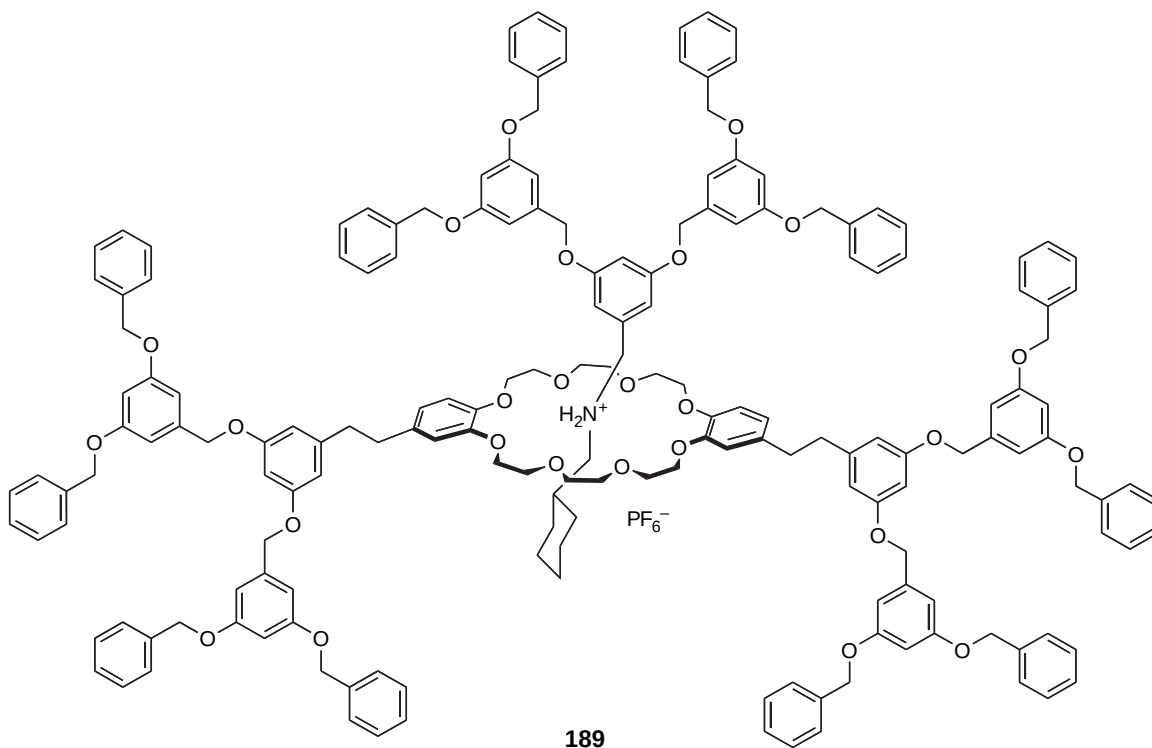
Smith and co-workers prepared the dendritic assembly **190** from two L-lysine dendrons, bearing a benzo-18-crown-6 unit at the focal point, and 1,4-bis(aminomethyl)benzene dihydrochloride. They then studied by NMR analysis the disassembly process induced by addition of potassium ions <2002AGE3254, 2003T3999>.

14.12.4.4 Miscellaneous Systems

Fenniri and co-workers have recently described <2002PNA6487, 2002JA11064> a sophisticated example of hierarchical self-assembly <2003JMC2661> leading to chiral helical rosette nanotubes. In water, building blocks **191** first self-assembled into hexameric rosettes, via multiple hydrogen-bonding interactions, and then underwent a second level of organization to produce stacks with a nanotubular structure.

The bicyclic heteroaromatic bases **191** possess arrays of complementary donor–donor–acceptor and acceptor–acceptor–donor hydrogen bond sites and an additional benzocrown ether moiety. Structure and dimension of the nanotubes were determined by NMR, dynamic light scattering, small-angle X-ray scattering, and transmission electron microscopy. Addition of sodium or potassium ions did not interfere with the stability of the multichannel

nanotubular architecture formed. On the other hand, in the case of the racemic (left- and right-handed) helical nanotubes derived from **191** ($n = 2$), addition of a variety of zwitterionic amino acids promoted the formation of only the homochiral form. Circular dichroism (CD) spectroscopy revealed that the supramolecular process obeys the ‘all-or-none’ principle, that is, the vast majority of amino acid ‘promotor’ molecules have to electrostatically interact with the crown ether appendages for complete chiral induction to occur.



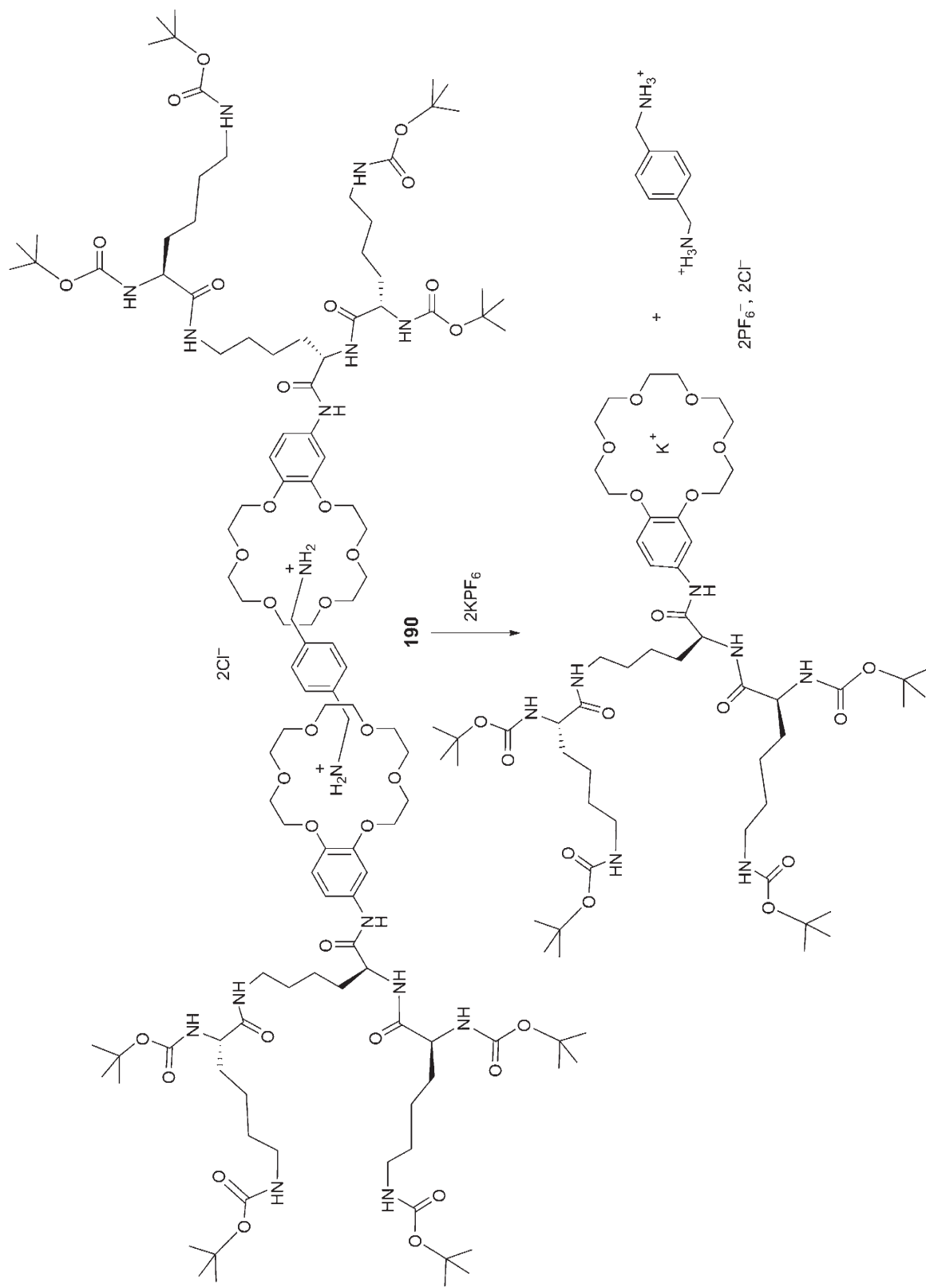
Nolte and co-workers have synthesized phthalocyanine **192**, which possesses four crown ether rings and eight chiral alkyl side chains. In chloroform, **192** self-assembled into columnar arrays, as a result of intermolecular π - π -interactions, resulting in the formation of a gel. Left-handedly twisted bundles were observed, consisting of fibers having the diameter of one columnar stack of **192**. With the help of CD spectroscopy, it was demonstrated that the molecules within one fiber are organized into a right-handed helix. It was shown that through a stepwise hierarchical assembly process these right-handed helices yielded a supercoiled structure with an opposite helicity. Addition of alkali metal ions, which bind to the crown ether rings of **192**, converted the helical structures into straight fibers, confirming the assembly mechanism <1999SCI785>.

14.12.5 Crown Ether-Related Macrocycles

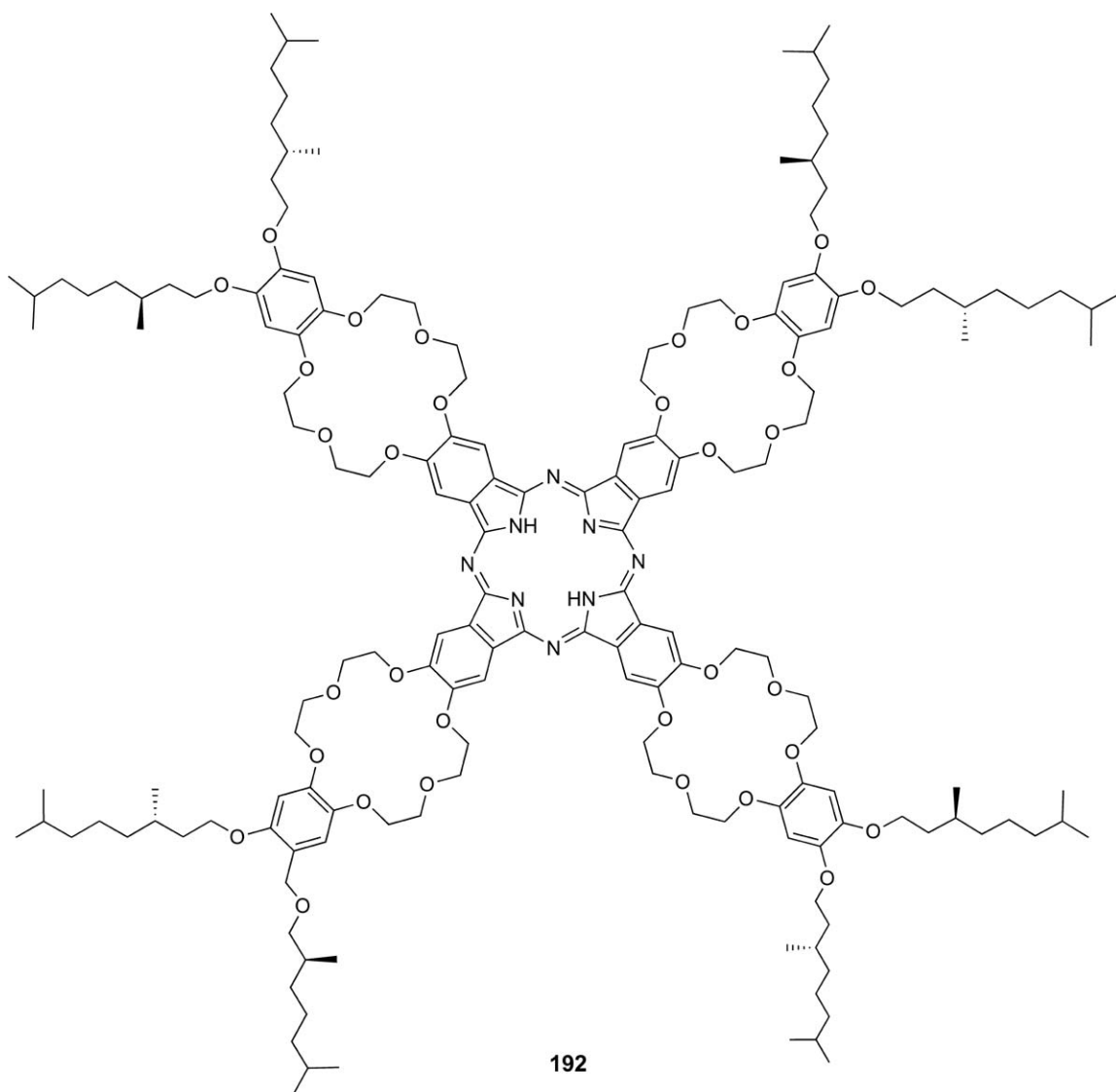
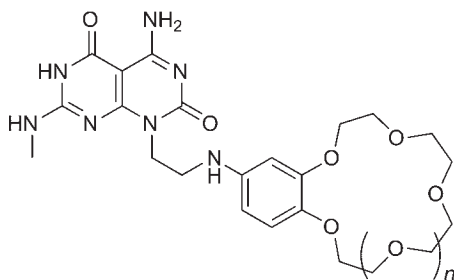
14.12.5.1 Calixtubes

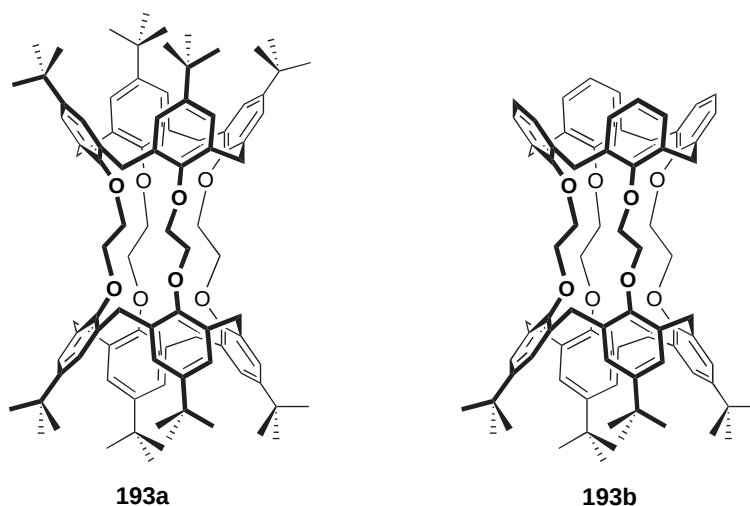
The 3-D concave architecture of calixarenes, their ready availability, tunable size, and versatility of derivatization, both at the upper and lower rim, have rendered this class of compounds one of the prime molecular platforms for the design of ion-selective ionophores and for the study of molecular encapsulation <1995AGE713, 1997CRV1713, B-1998MI1, B-2001MI4>.

Calixtubes are cryptand-like ionophores that can be viewed as 3-D hybrids of calixarenes and crown ethers. They are comprised of two calix[4]arene moieties joined at their lower rims via four ethylene units to provide a rigid arrangement of eight oxygen donor atoms, which proved highly selective for potassium complexation over all group IA metal cations <1997AGE1840, 2002JA1341>. The calix[4]arene units in these compounds serve as size discriminatory filters for cations entering in a manner similar to that for tyrosine-based filters in cellular potassium ion



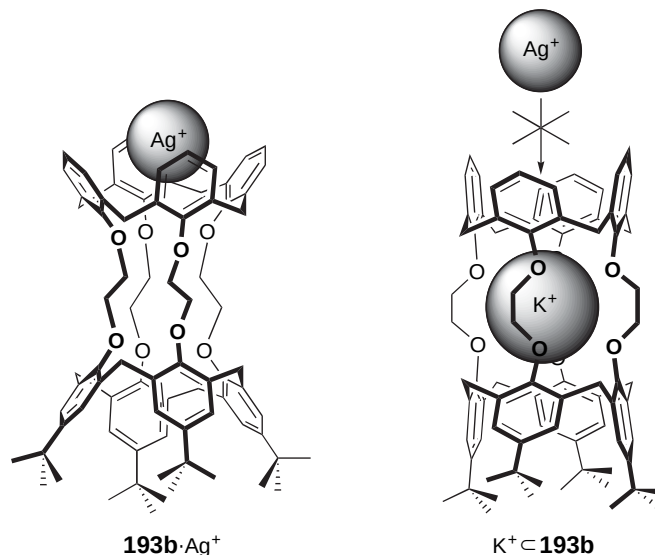
channels <1996SCI163>. By using a combination of ^1H NMR studies and molecular modeling simulations on a range of symmetric and asymmetric calix[4]tubes featuring various upper rim substituents on the calix[4]arene units, best exemplified by **193a** and **193b**, respectively, Beer and co-workers have shown that the potassium ion is complexed via the axial route, and that the rate of complexation can be associated with the original torsion angles of the oxygen donor array and its ease of reorganization to accommodate the potassium cation.



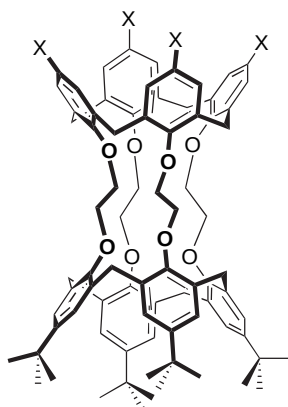


Molecular dynamics simulations on symmetrical calix[4]tubes with a series of different metal ions <2002PCP3849>, while confirming the high potassium selectivity, have shown that once the ion enters the tube at the upper rim of one calix[4]arene, an intermediate complex with C_{2v} symmetry was formed by cation- π -interaction with the aromatic rings. Subsequently, the ion moves to the center of the tube, where it is eventually locked via binding to the eight oxygen donor atoms with concomitant all-*gauche*-rearrangement of the four O-CH₂-CH₂-O linkages (approximate C_{4v} symmetry of the cage complex). Ions smaller than K⁺ more easily get to the center of the tube, while larger ions remain in the intermediate C_{2v} -symmetric position close to the aromatic rings, as elegantly shown by ²⁰⁵Tl NMR and X-ray diffraction studies on the dithallium complex with the *p*-*t*-octyl derivative of **193a** <2003IC729>.

Likewise, Lhoták and co-workers have demonstrated that asymmetric calix[4]tube **193b** behaves as a ditopic soft/hard receptor in Ag⁺/K⁺ complexation <2002TL2857>. The free receptor adopted a pinched cone conformation (C_{2v} symmetry), and was suitably preorganized for Ag⁺ complexation. X-Ray diffraction studies have shown that the silver cation was sandwiched between the two distal coplanar phenyl rings of the de-*tert*-butylated calix[4]arene fragment via a double η^1 -binding mode. However, the soft binding site of **193b** was switched off in the presence of K⁺, because its inclusion inside the oxygen-8 cage induced a C_{4v} -symmetric conformational reorganization of the receptor favoring the release of Ag⁺ ion.

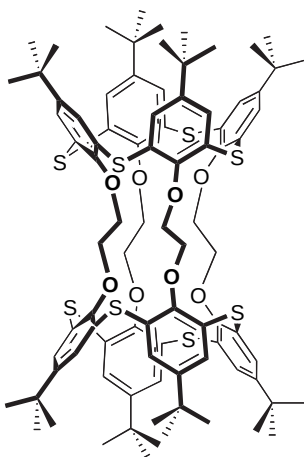


Direct bromination or iodination of asymmetric calix[4]tubes having free *p*-positions at one calix[4]arene fragment, for example **193b**, has provided an easy entry to halo-functionalized calix[4]tubes, for example **193c** <2003OBC1232>. Although ionophores **193c** retain the usual K⁺ selectivity, they showed a reduced uptake in comparison to their alkylated counterparts, because of the destabilization of the π -metal cation arene-bound intermediate due to the electron-withdrawing character of halogen substituents.



193c: X = Br, I

The recent discovery of viable synthetic routes to the sulfur-bridged thiacalixarene analogues <1997TL3971> has led to an extension of the calix[4]tube family of ionophores to encompass the thiacalix[4]tube **194**, which provided entrance filters and a molecular cavity of slightly larger size relative to the parent calix[4]tubes **193** <2001NJC1355>. X-Ray crystal data and dynamic NMR studies on **194** have shown a flattened cone conformation for the two thiacalixarene moieties, which rapidly exchanged between the two extreme C_{2v} conformations at room temperature. The fluxionality of **194**, in combination with molecular modeling results and the absence of an apparent templation effect in the formation of the tube, could account for the observed lack of selectivity for K^+ ion.



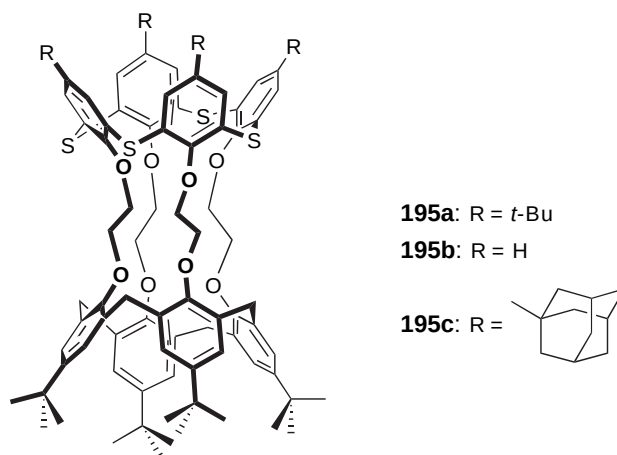
194

The replacement of one thiacalix[4]arene fragment of **194** with a *p*-*tert*-butylcalix[4]arene subunit has afforded heterocalix[4]tubes **195**, which possess a slightly smaller molecular cavity and a higher rigidity relative to **194** <2006OBC1555>. Metal ion uptake by **195** was greatly influenced by the nature of upper rim substituents on the thiacalix[4]arene fragment. The adamantane-containing heterocalix[4]tube **195c** displayed unique ionophore properties, since it was capable of quantitatively binding potassium (swiftly) and rubidium (slowly) cations.

14.12.5.2 Oxacalixarenes

Heterocalixarenes are macrocycles comprised of aromatic rings bridged by atoms other than carbon that in the past few years have received special attention as new potential scaffolds for the design of supramolecular structures <2000EJI2303>. Oxygen-bridged calixarenes, henceforth referred to as oxacalixarenes, can be viewed as rigid crown ethers built up with fully aromatic rings only. The *meta*-bridged 16-membered oxacalix[4]arene **196a** was first synthesized in modest yield in 1966 by direct nucleophilic aromatic substitution (S_NAr) of resorcinol with 1,5-dichloro-2,4-dinitrobenzene <1966TL2837>.

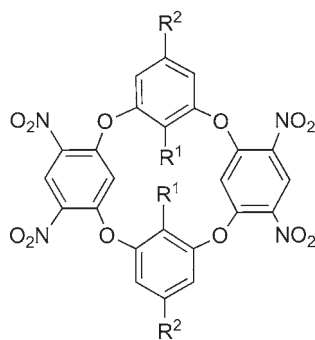
Subsequently, papers in the mid-1970s extended this procedure to the preparation of isomeric 14- and 18-membered macrocycles with an alternating *m*-,*o*-,*m*-,*o*- and *m*-,*p*-,*m*-,*p*-bridging sequence, by using pyrocatechol and hydroquinone, as the nucleophilic components, respectively <1974T727, 1974JHC899>. Since then, only sporadic studies were conducted on related compounds <1996JOC2553, 1998CC265>, probably due to the limited solubility of earlier materials, which hampered their purification and characterization <1976T2567>. Quite recently, however, Katz and co-workers have achieved an important breakthrough in oxacalix[4]arene chemistry in which they found that various tetranitrooxacalix[4]-arenes **196** can be generated in excellent yield by a room temperature S_NAr reaction of resorcinols (nucleophilic components) with 1,5-difluoro-2,4-dinitrobenzene (electrophilic component) in DMSO under basic conditions <2005OL91>. The reaction did not need high-dilution conditions, and tolerated a wide range of substituents on the nucleophilic component, chosen to also impart better solubility characteristics to the macrocycles. This procedure allowed the intriguing one-step preparation of oxacalix[4]arenes **196d–f** endowed with reactive functional groups (formyl, ester, and hydroxyl) at two distal exocyclic positions, which are amenable to further chemical alteration. Besides, nucleophilic 1,2,3-tri(hydroxy)benzenes displayed a great deal of regioselectivity in this S_NAr reaction, providing a very effective route to oxacalix[4]-arenes with endocyclic distal hydroxyl groups.



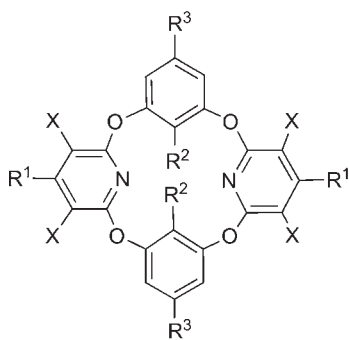
The excellent yields of the cyclic tetramer over potentially accessible larger structures have been demonstrated to result from thermodynamic product control under equilibrating conditions <2006OL2755, 2006TL4041>. The facile and selective formation of a specific molecule in a thermodynamically controlled reaction, where the covalent bond has the ability to be formed and reversibly broken, is the subject matter of dynamic covalent chemistry <2002AGE898>.

Oxacalix[4]arenes **196a–j** generally adopt the 1,3-alternate conformation in both the solid state and solution, regardless of functional group substitution on the aromatic rings. In the solid state, the electrophilic component aromatic rings approach coplanarity, while the nucleophilic component rings are eclipsing and nearly parallel. This particular conformation was apparently enforced by maintenance of conjugation between the bridging oxygen atoms and the nitro-bearing aromatic rings. It should be emphasized, however, that dipropyl derivative **196j** can be obtained as *syn*- (1,3-alternate) and *anti*- (partial cone) atropisomers under kinetically controlled conditions <2006TL4041>, suggesting that the bulkiness of the propyl group is sufficient to inhibit the interconversion process of oxacalix[4]-arenes via the endocyclic substituent through-the-annulus mechanism <B-1998MI1>.

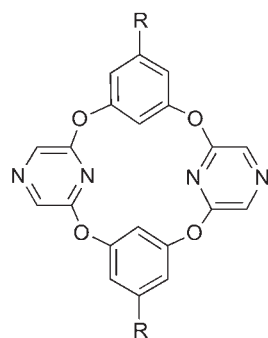
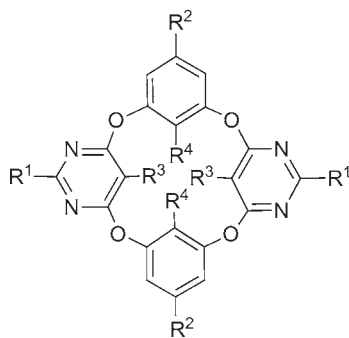
The use of di-halo-*N*-heterocycles (2,6-dihalopyridines, 2,6-dichloropyrazine, 4,6-dihalopyrimidines, and *sym*-trichlorotriazine), as the electrophilic component in the S_NAr reactions with resorcinols, has expanded calixarene structural diversity to oxacalix[2]arene[2]pyridines **197** <2002JFC(116)19, 2003OBC2137, 2006OL2755>, oxacalix[2]arene[2]pyrazines **198** <2006OL2755>, oxacalix[2]arene[2]pyrimidines **199** <2006OL2755, 2006OL4161>, and oxacalix[2]arene[2]triazine **200** <2004JA15412>. Apart from triazine-containing macrocycle **200** and fluorinated **197i** and **197j** – obtained by a two-step sequence involving the preparation of an appropriate linear trimer intermediate, followed by a ring-closure reaction with resorcinol or bis-silylated resorcinols, respectively – the remaining oxacalixarenes **197–199** have been synthesized in high yield by the standard S_NAr reaction.

**196**

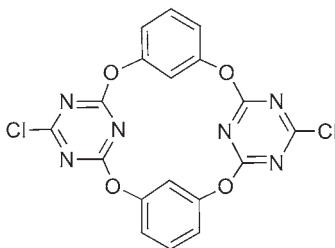
	R^1	R^2
a	H	H
b	H	Me
c	H	<i>n</i> -Pentyl
d	H	CHO
e	H	CO ₂ Me
f	H	OH
g	OH	H
h	OH	<i>t</i> -Bu
i	OH	CO ₂ Et
j	<i>n</i> -Pr	H

**197**

	X	R^1	R^2	R^3
a	Cl	H	H	<i>n</i> -Pentyl
b	Cl	H	H	CO ₂ Me
c	CN	H	H	CO ₂ Me
d	CN	H	H	<i>n</i> -Pentyl
e	CN	H	OH	CO ₂ Et
f	CN	H	OH	<i>t</i> -Bu
g	CN	Et	H	Me
h	CN	Et	OH	CO ₂ Et
i	F	CF(CF ₃) ₂	H	H
j	F	CF(CF ₃) ₂	H	Me

**198:** R = Me, *n*-pentyl, CO₂Me**199**

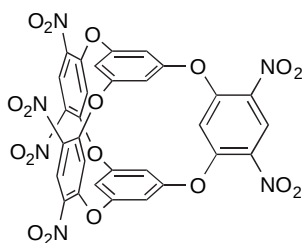
	R^1	R^2	R^3	R^4
a	H	Me	H	H
b	H	H	H	Me
c	H	<i>n</i> -Pentyl	H	H
d	Ph	H	H	H
e	Ph	Me	H	H
f	Ph	H	H	OH
g	SMe	Me	H	H

**200**

Tuning of the experimental conditions can give access to the larger oxacalixarenes in reasonable yields. When the reaction of 2,6-dichloropyrazine and 5-methylresorcinol (orcinol) was typically conducted under kinetic control conditions (DMSO/Cs₂CO₃, 50 °C, 18 h), the cyclic hexamer (18%), octamer (11%), and decamer (6%) were isolated along with the tetramer **198** (R = Me) (36%) <2006OL2755>. Similarly, the condensation of equimolar amounts of 4,6-dichloro-2-phenylpyrimidine and orcinol (DMF/K₂CO₃, 70 °C, 48 h) afforded, after chromatography, the corresponding cyclic octamer (10%), decamer (8%), hexamer (8%), dodecamer (8%), and tetramer **199e** (30%) <2006OL4161>.

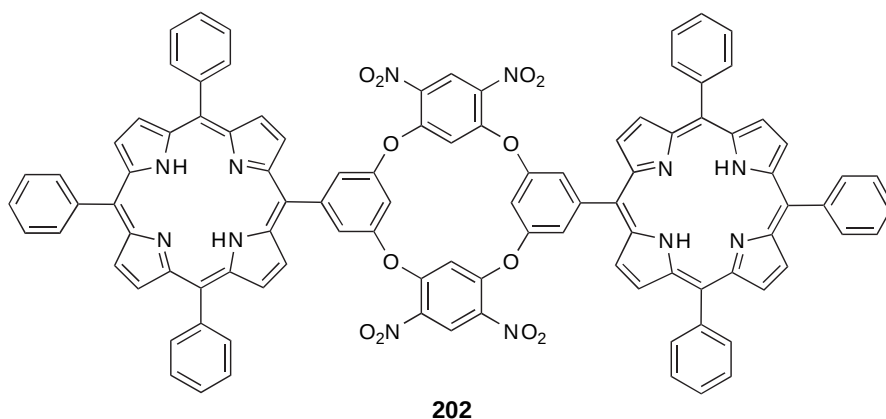
A comparison of the solid-state structural features of oxacalix[4]arenes with embedded N-heterocycles **197–200** has revealed important similarities and differences relative to **196**. Whereas all of them maintain the 1,3-alternate conformation imposed by the conjugation of the oxygens with the electron-poor heterocyclic rings, minor to substantial differences are found in the shape of the calixarene cavity, depending on the identity of the incorporated N-heterocycles. In fluorinated pyridino-derivative **197j**, the phenyl rings are parallel to each other (the dihedral angle between their planes is 1.0°) and almost perfectly overlapped. The symmetrical orientation of the two pyridine rings instilled *C*_{2v} symmetry <2002JFC(116)19, 2003OBC2137>. The inclination of the phenyl rings in oxacalix[2]arene[2]triazine **200** is only slightly different to that of **197j**. As a result of a weak π – π -stacking interaction, the benzene units make angles of 89.3° and 77.4° with the best plane containing the four bridged oxygens, while the pair of triazine rings tends to be nearly coplanar <2004JA15412>. On the other hand, important differences are found in pyrazino and pyrimidino derivatives **198** (R = Me) and **199e**, respectively, compared to **196**. In the former, the interplanar angles are 99.6° between the N-heterocyclic rings and 41.3° between the benzene rings, while in the latter both the nucleophilic- as well as the electrophilic-component aromatic rings are positioned almost perpendicular to each other (interplanar angles of 86.1° and 86.7°), resulting in a highly symmetrical cavity. These findings clearly indicated that fine-tuning of the oxacalix[4]arene cavity can be achieved by a proper choice of the N-heterocyclic component.

When the reaction of 1,5-difluoro-2,4-dinitrobenzene with 1,3,5-tri(hydroxy)benzene (phloroglucinol) was conducted in a 3:2 molar ratio, it produced under optimized S_NAr conditions (DMSO/NEt₃, 80 °C, 12 h) bicyclooxacalix[4]arene **201** in a 58% isolated yield <2005OL3505>. In the solid state, bicyclic molecule **201** adopts a near-*D*_{3h}-symmetric, all-1,3-alternate conformation. The phloroglucinol units are eclipsed (centroid distance 4.83 Å), and the electrophilic component rings point directly into the formed cavity. An extension of the electrophilic component to a variety of 2,6-dichloropyridines has offered an efficient one-pot entry to bicyclooxacalixarene analogues of **201**, incorporating nitro, cyano, and chloro groups onto the external surface and nitrogen atoms on the internal surface.

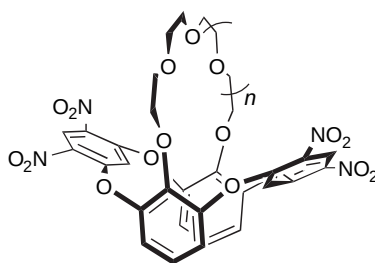


201

The remarkable efficiency of the S_NAr reaction to oxacalix[4]arenes, and their tendency to adopt discrete 1,3-alternate conformations, have recently been exploited to design and synthesize oxacalix[4]arene-locked cofacial bisporphyrin **202**, which was obtained in 91% yield by reacting equimolar amounts of 1,5-difluoro-2,4-dinitrobenzene and the appropriate resorcinol-containing porphyrin under standard conditions (DMSO, finely ground K₂CO₃, rt, 20 min) <2006JOC1233>. By using granular K₂CO₃ or by changing the experimental conditions (solvent, reaction time), sizeable amounts of the cyclic hexamer and octamer were also obtained. In the crystal, **202** adopts a 1,3-alternate conformation with the two rings carrying nitro groups forming a dihedral angle of 60.6° and the two rings carrying porphyrins more nearly parallel, forming a dihedral angle of 8.7°. The two porphyrin ring systems are thus also nearly parallel (dihedral angle 2.8°), with a plane-to-plane distance of 3.81 Å.



Finally, oxacalix[4]arene **196g** has been exploited to generate the first oxacalix[4]arene crown ethers **203** by reaction with the appropriate oligoethyleneglycol ditosylates [<2006SMC111>](#).



14.12.6 Conclusions and Outlook

This chapter has hopefully made clear that crown ether chemistry, almost 40 years from its birth, is still attracting a great deal of interest from the scientific community worldwide. Unfortunately, space limitations, coupled with the vast number of reports published over the past decade, have made it impossible to provide a completely comprehensive survey on this class of macrocycle and, inevitably, some of their aspects and applications have been neglected or left out altogether. We hope our readers will forgive us if they have not found in this brief overview all the information they were looking for. By the same token, we trust that colleagues will excuse us for not having cited some important examples of their creative endeavors. Throughout, lists of review and monograph articles have been provided to assist the reader in the search for more comprehensive information on different topics.

Crown ether research, as it stands today, does not seem to be suffering from any age crisis. On the contrary, it appears that many new developments are underway. Judging from the most recent accounts that have appeared in the literature, there is plenty of room in the years to come for further investigations in the field of polymer- and dendrimer-based new tunable materials, as well as in the construction of nanosize molecular devices. Furthermore, the never-ending quest for chirally discriminating host molecules and increasingly sensitive and selective sensors for analytes of both biomedical and environmental interest calls for additional studies on crown ethers.

14.12.7 Further Developments

In keeping with the trend observed in the past few years, over the months in which the whole of CHECH III was put together and edited, studies in the field of crown ethers have progressed with the turbulent pace typical of cutting-edge research. Predictably, new ideas have emerged and consolidated topics of interest have been further developed.

As far as cation complexation by crown ethers is concerned, N-(dithiocarbamato)-2-aminomethyl-15(18)-crown-5(6) ethers, obtained by reaction of the appropriate amino precursor with CS₂ and alkali metal hydroxide <2006BCC473>, form highly stable cationic ^{99m}Tc-nitrido complexes, which have been evaluated as radiopharmaceuticals for heart imaging <2006NMB419, 2007JCD1183>.

In relation to the optical sensing of crown ethers, a sophisticated three-input molecular AND logic gate, based on three chemical inputs, has been developed from sensor **32** for the detection of congregations of chemical species <2006JA4950>. The AND gate operates in water and responds to Na⁺, H⁺, and Zn²⁺ inputs with an enhanced fluorescence signal when pre-set concentration thresholds are exceeded. Future applications in medicine for rapid disease screening are expected. Boron dipyrin (BDP) bearing crown ethers of varying cavity sizes (15-crown-5, 18-crown-6, and 21-crown-7) at the *meso*-position were recently employed as chemosensors for cation detection in solution <2007TL1977>. In the absence of metal cations, the emission of the BDP moiety was found to be quenched to some extent by an ICT process from the donor oxygen atoms to the acceptor BDP unit. Coordination of metal ions to the oxygen donor atoms in the crown ether cavity inhibited ICT to the BDP acceptor, leading to cation-induced fluorescence enhancement as a function of crown ether cavity and metal ion size. A fluorescent chemosensor based on benzo-15-crown-5 having a naphthaleneacetamido functionality showed 'Off-On' fluorescent response upon the addition of Mg²⁺ ions <2007TL1859>. Chemosensor **107**, in addition to its capacity of visual determination of certain attributes (chirality, length, peptide sequence) of targeted guests, has also been found to exhibit opposite behaviors toward sodium and potassium ions caused by bidirectional complexation <2006OL5797>.

A number of novel supramolecular assemblies derived from DB24C8 have been described. These include a [2]pseudorotaxane bearing the bis(benzimidazolium) cation <2007OL497> as the axel component, 2,6-pyridinocryptands for paraquat derivative recognition <2007JOC3381>, [2]rotaxanes <2006JOC5093, 2007TL3409> – obtained by way of new end-capping protocols (that is, sequential double-acylation and conjugate addition of thiol to N-substituted maleimides under basic conditions) on *sec*-ammonium axels – as well as a [3]rotaxane <2007TL2797>. Among other mechanically interlocked systems desymmetrized [2]catenanes, possessing bipyridinium/pyromellitic units <2007OL2577>, and [3]catenanes, generated by metal-directed self-assembly of either *N*-monoalkyl-4,4'-bipyridinium or *N*-monoalkyl-2,7-diazapyrenium derivatives with different crown ethers <2007OL675>, have been reported.

Crown ether moieties grafted onto triptycene scaffolds have been actively studied with respect to their ability to act as molecular tweezers <2007OL895> for paraquat derivatives, to form bis[2]pseudorotaxanes <2006OL1069> or dendritic [3]pseudorotaxanes <2006OL1859> with appropriate secondary ammonium salts, and to generate interlocked chiral [4]pseudocatenanes <2006CEJ5603>, by means of dynamic covalent chemistry (threefold metathesis reactions) followed by deprotonation and further functionalization. Triptycene-based cylindrical macrotricyclic polyethers have also been investigated in the context of switchable complexation processes of charged <2007JOC3108> and neutral <2007JOC7287> guests under cation control. Further investigations on bis(*m*-phenylene)-32-crown-based cryptands **121** have shown these host molecules to be able to form, in solution and in the solid state, 1:1 inclusion complexes with the herbicide diquat <2007TL2829> and *N,N'*-dimethyl-2,7-diazapyrenium bis(hexafluorophosphate) <2007TL7537> as well as [3]pseudorotaxanes with bispyridinium salts <2007T2875>.

A 'molecular plug-socket connector' <2007JA4633> and a 'supramolecular nanovalve' <2006OL3363> are, among others, two of the most recent examples of molecular-level devices to have been described. The former molecule consists of a secondary dialkylammonium center, a biphenyl spacer, and a 1,4-benzo-1,5-naphtho[36]crown-10 ring that, in the presence of DB24C8 and the 1,1'-dioctyl-4,4'-bipyridinium dication, is able to form a three-component assembly via two supramolecular connections reversibly controlled by acid/base and redox external inputs. The latter was built by grafting naphthalene-containing dialkylammonium threads onto the surface of mesoporous silica MCM-41, followed by loading of the resulting hybrid material with coumarin 460, and by finally capping the pores with DB24C8 rings. Controlled release of the fluorescent coumarin 460 molecules from the pores was then analyzed by fluorescent spectroscopy as a function of the size of the base used to disrupt the [2]pseudorotaxane that keeps the nanovalve shut.

18-Crown-6 ethers functionalized with up to third generation dendritic branches based on L-lysine <2006NJC1243> have been studied as a prototype 'carrier system', in connection with the controlled binding and release of molecules of pharmaceutical interest such as dopamine both in solution and in the gel-phase. [2]Rotaxanes, containing a diarginine-derivatized DB24C8 unit as the wheel and either a cleft <2006JA12229> or a cyclophane pocket <2007JA7284> as one blocking group ('cleft-[2]rotaxane' and 'cyclophane-[2]rotaxane', respectively), have been shown to behave as effective cellular transport agents. The potential of these two molecules for therapeutic purposes is demonstrated by their ability to bind and deliver, via a mechanism which is believed to involve the sliding motion of the wheel along the axel, peptides of different polarities across the membrane of African green monkey kidney cells, COS-7, and human ovarian carcinoma cell line, ES-2.

In the context of new oxacalixarene systems, functionalized oxacalix[2]arene[2]triazines, obtained by S_NAr reaction of bis-chlorinated **200** with various N-heterocyclic group-containing amines, selectively form 1:1 complexes with Cu^{2+} ion probably via a chelating interaction effect <2007JOC3757>. The base-catalyzed reaction of the usual electrophilic components (1,5-difluoro-2,4-dinitrobenzene, 2,3,5,6-tetrachloropyridine, or sym-trichloro-triazine) with 2,7-dihydroxytritycene as the nucleophilic component has led to diastereomeric mixtures of expanded oxacalix[4]arenes, which assemble into organic tubular structures in the solid state <2007JOC3880>. Other expanded macrocycles comprise oxacalix[4]arenes and [14]oxacyclophanes bearing 1,8-naphthyridine units, obtained by condensation of 2,7-dichloro-naphthyridine with dihydroxynaphthalenes. These systems show increased size of the recognition cavity, and function as molecular tweezers capable of binding acidic aromatic guests in solution <2007CC1026>.

The concept of dynamic covalent chemistry in the synthesis of oxacalixarenes is further reinforced by the product distribution(s) observed under different experimental conditions (nature and amount of base, solvent, temperature) in the one-step or [3+1] fragment S_NAr condensation of 2-substituted resorcinols and 1,5-difluoro-2,4-dinitrobenzene <2007TL3029>, or *meso*-(3,5-dihydroxyphenyl)triphenylporphyrin and fluorodinitrobenzene-containing trimers <2007T4011>. The introduction of sterically bulky groups onto the aromatic rings of electrophilic and nucleophilic components of the [3+1] fragment coupling reaction can lead to the formation of both thermodynamically favored 1,3-alternate and kinetically controlled flattened partial cone tetraoxacalix[2]arene[2]triazines. The flattened partial cone conformer, which was stable due to the steric effect, converted into the 1,3-alternate conformer via ether bond cleavage upon treatment with an inorganic base <2007OL2847>. New perspectives in anion binding by oxacalixarenes have emerged from a theoretical study, based on density functional theory calculations, which has predicted that a bicyclooxacalixarene analogue of **201**, possessing parallel *sym*-triazine subunits in place of benzene rings, may behave as a neutral anion binder, selectively entrapping F^- in the gas phase (−80.5 kcal/mol) as well as in CH_2Cl_2 (−14.7 kcal/mol) via strong $C-H\cdots F^-$ hydrogen bonds and $\pi\cdots F^-$ interaction <2007OL4219>.

References

- 1952JCS3940 C. Dalglish, *J. Chem. Soc.*, 1952, 3940.
 1960JA4433 E. Wasserman, *J. Am. Chem. Soc.*, 1960, **82**, 4433.
 1963JA3533 R. G. Pearson, *J. Am. Chem. Soc.*, 1963, **85**, 3533.
 1966SCI172 R. G. Pearson, *Science*, 1966, **151**, 172.
 1966TL2837 N. Sommer and H. A. Staab, *Tetrahedron Lett.*, 1966, **25**, 2837.
 1967JA7017 C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 7017.
 B-1971MI1 G. Schill; 'Catenanes, Rotaxanes and Knots', Academic Press, New York, 1971.
 1974JHC899 E. E. Gilbert, *J. Heterocycl. Chem.*, 1974, **11**, 899.
 1974T727 F. P. A. Lehmann, *Tetrahedron*, 1974, **30**, 727.
 1975AGE764 J.-M. Girondeau, J.-M. Lehn, and J.-P. Sauvage, *Angew. Chem., Int. Ed.*, 1975, **14**, 764.
 1975PAC327 D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newcomb, P. Moreau, F. De Jong, G. W. Gokel, and D. H. Hoffman, *Pure Appl. Chem.*, 1975, **43**, 327.
 1976JA5206 G. Agam, D. Graiver, and A. Zilkha, *J. Am. Chem. Soc.*, 1976, **98**, 5206.
 1976T2567 F. Bottino, S. Foti, and S. Pappalardo, *Tetrahedron*, 1976, **32**, 2567.
 1977ANA399 C. J. Coetzee and A. J. Basson, *Anal. Chim. Acta*, 1977, **92**, 399.
 1979CSR85 J. F. Stoddart, *Chem. Soc. Rev.*, 1979, **8**, 85.
 1979JEC91 K. Kimura, T. Maeda, H. Tamura, and T. Shono, *J. Electroanal. Chem.*, 1979, **95**, 91.
 1980ANC692 U. Oesch and W. Simon, *Anal. Chem.*, 1980, **52**, 692.
 1980HCA2096 J.-P. Behr, J.-M. Girondeau, R. C. Heyward, J.-M. Lehn, and J.-P. Sauvage, *Helv. Chim. Acta*, 1980, **63**, 2096.
 1980JA5860 S. Shinkai, T. Nakaji, Y. Nishida, T. Ogawa, and O. Manabe, *J. Am. Chem. Soc.*, 1980, **102**, 5860.
 1981JOC393 D. S. Lingenfelter, R. C. Helgeson, and D. J. Cram, *J. Org. Chem.*, 1981, **46**, 393.
 1982JA1960 S. Shinkai, T. Ogawa, Y. Kusano, O. Manabe, K. Kikukawa, T. Goto, and T. Matsuda, *J. Am. Chem. Soc.*, 1982, **104**, 1960.
 1982JEC99 T. Shono, M. Okahara, I. Ikeda, K. Kimura, and H. Tamura, *J. Electroanal. Chem.*, 1982, **132**, 99.
 1983TL5095 C. O. Dietrich-Buchecker, J.-P. Sauvage, and J.-P. Kintzinger, *Tetrahedron Lett.*, 1983, **24**, 5095.
 1984CHEC(5)731 A. D. Hamilton; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 5, p. 731.
 1985ACR65 H.-G. Löhr and F. Vögtle, *Acc. Chem. Res.*, 1985, **18**, 65.
 1985FZA157 E. Lindner, K. Tóth, M. Horváth, E. Pungor, B. Ágai, I. Bitter, L. Töke, and Z. Hell, *Fresenius Z. Anal. Chem.*, 1985, **322**, 157.
 1986FZA241 B. Rieckemann and F. Umland, *Fresenius Z. Anal. Chem.*, 1986, **323**, 241.
 1985NJC419 V. Le Berre, L. Angely, N. Simonet-Gueguen, and J. Simonet, *New J. Chem.*, 1985, **9**, 419.
 1986J(P2)1945 K. Kimura, H. Yano, S. Kitazawa, and T. Shono, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1945.
 1988AN373 H. G. J. Worth, *Analyst*, 1988, **113**, 373.
 1988JEC117 V. Le Berre, L. Angely, N. Simonet-Gueguen, and J. Simonet, *J. Electroanal. Chem.*, 1988, **240**, 117.
 1988JPM351 J.-M. Lehn, *J. Inclusion Phenom.*, 1988, **6**, 351.
 1988TS207 J. F. Stoddart, *Top. Stereochem.*, 1988, **17**, 207.

- 1989AGE1396 P. R. Ashton, T. T. Goodnow, A. E. Kaifer, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vicent, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1396.
- 1989ALE1185 K. Tóth, E. Lindner, M. Horváth, J. Jeney, I. Bitter, B. Ágai, T. Meisel, and L. Töke, *Anal. Lett.*, 1989, **22**, 1185.
- 1989CC1183 A. P. de Silva and K. R. A. S. Sandanayake, *J. Chem. Soc., Chem. Commun.*, 1989, 1183.
- 1989NJC131 V. Le Berre, L. Angely, N. Simonet-Gueguen, and J. Simonet, *New J. Chem.*, 1989, **13**, 131.
- B-1990MI1 Y. Umezawa; 'Handbook of ISEs: Selectivity Coefficients', CRC Press, Boca Raton, FL, 1990.
- B-1990MI429 K. Kimura and T. Shono; in 'Cation Binding by Macrocycles', Y. Inoue and G. W. Gokel, Eds.; Marcel Dekker, New York, 1990, ch. 6, p. 429.
- 1990MKA157 E. Lindner, K. Tóth, J. Jeney, M. Horváth, E. Pungor, I. Bitter, B. Ágai, and L. Töke, *Mikrochim. Acta*, 1990, **1**, 157.
- 1991AGE1472 M. T. Reetz, C. M. Niemeyer, and K. Harms, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1472.
- B-1991MI1 In 'Conjugate Polymers', J. L. Brédas and R. Silbey, Eds.; Kluwer, Dordrecht, 1991.
- 1991PLC204 C. Wu, M. C. Bheda, C. Lim, Y. X. Shen, J. Y. Sze, and H. W. Gibson, *Polym. Commun.*, 1991, **32**, 204.
- 1992ANC2815 R. Kuhn, F. Ermi, T. Bereuter, and J. Häusler, *Anal. Chem.*, 1992, **64**, 2815.
- 1992BSF37 V. Questaigne, J. Simonet, and A. Rousseau, *Bull. Soc. Chim. Fr.*, 1992, **129**, 37.
- 1992CRV711 J. Roncali, *Chem. Rev.*, 1992, **92**, 711.
- 1992JCH(625)101 T. Shinbo, T. Yamaguchi, H. Yanagishita, D. Kitamoto, K. Sakaki, and M. Sugiura, *J. Chromatogr.*, 1992, **625**, 101.
- 1992JEC399 J. Simonet and J. M. Chapuzet, *J. Electroanal. Chem.*, 1992, **322**, 399.
- B-1992MI(45)198 K. Kimura and T. Shono; in 'Studies in Organic Chemistry', M. Hiraoka, Ed.; Elsevier Science, Amsterdam, 1992, vol. 45, ch. 4, p. 198.
- 1993ANC2704 K. Watanabe, E. Nakagawa, H. Yamada, H. Hisamoto, and K. Suzuki, *Anal. Chem.*, 1993, **65**, 2704.
- 1993ANC3404 K. Suzuki, H. Yamada, K. Sato, K. Watanabe, H. Hisamoto, Y. Tobe, and K. Kobiro, *Anal. Chem.*, 1993, **65**, 3404.
- 1993AM11 H. W. Gibson and H. Marand, *Adv. Mater.*, 1993, **5**, 11.
- 1993AM848 P. Bäuerle and S. Scheib, *Adv. Mater.*, 1993, **5**, 848.
- 1993BKC123 J. S. Kim, S. O. Jung, S. S. Lee, and S.-J. Kim, *Bull. Korean Chem. Soc.*, 1993, **14**, 123.
- 1993CC1269 P. R. Ashton, M. Bělohradský, D. Philp, and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1993, 1269.
- 1993CC1274 P. R. Ashton, M. Bělohradský, D. Philp, N. Spencer, and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1993, 1274.
- 1993JA12214 M. J. Marsella and T. M. Swager, *J. Am. Chem. Soc.*, 1993, **115**, 12214.
- 1993SM(58)51 J. Rault-Berthelot and L. Angely, *Synth. Met.*, 1993, **58**, 51.
- 1994ACR302 A. W. Czarnik, *Acc. Chem. Res.*, 1994, **27**, 302.
- 1994AGE467 D. M. Rudkevich, Z. Brzozka, M. Palys, H. C. Visser, W. Verboom, and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 467.
- 1994AGE1286 D. B. Amabilino, P. R. Ashton, A. S. Reder, N. Spencer, and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1286.
- 1994AM595 T. M. Swager and M. J. Marsella, *Adv. Mater.*, 1994, **6**, 595.
- 1994CRV939 H. An, J. S. Bradshaw, R. M. Izatt, and Z. Yan, *Chem. Rev.*, 1994, **94**, 939.
- 1994JA537 Y. X. Shen, D. Xie, and H. W. Gibson, *J. Am. Chem. Soc.*, 1994, **116**, 537.
- 1994JA11588 M. T. Reetz, J. Huff, J. Rudolph, K. Toellner, A. Deege, and R. Goddard, *J. Am. Chem. Soc.*, 1994, **116**, 11588.
- 1994PP0843 H. W. Gibson and P. T. Engen, *Prog. Polym. Sci.*, 1994, **19**, 843.
- 1994SM(65)55 J. Rault-Berthelot and L. Angely, *Synth. Met.*, 1994, **65**, 55.
- 1995AGE713 V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713.
- 1995AGE1865 P. R. Ashton, P. J. Campbell, E. J. T. Chrystal, P. T. Glink, S. Menzer, D. Philp, N. Spencer, J. F. Stoddart, P. A. Tasker, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1865.
- 1995ANC2405 A. Ohki, J. P. Lu, J. L. Hallman, X. Huang, and R. A. Bartsch, *Anal. Chem.*, 1995, **67**, 2405.
- 1995APL124 P. Bäuerle and S. Scheib, *Acta Polym.*, 1995, **46**, 124.
- 1995BKC197 S. O. Jung, S. S. Park, B. G. Kim, and S.-J. Kim, *Bull. Korean Chem. Soc.*, 1995, **16**, 197.
- 1995CC747 D. B. Amabilino, P. R. Ashton, M. Bělohradský, F. M. Raymo, and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1995, 747.
- 1995CC1289 A. G. Kolchinski, D. H. Busch, and N. W. Alcock, *J. Chem. Soc., Chem. Commun.*, 1995, 1289.
- 1995CRV2725 D. B. Amabilino and J. F. Stoddart, *Chem. Rev.*, 1995, **95**, 2725.
- 1995JA852 H. W. Gibson, S. Liu, P. Lecavalier, C. Wu, and Y. X. Shen, *J. Am. Chem. Soc.*, 1995, **117**, 852.
- 1995JA7017 Q. Zhou and T. M. Swager, *J. Am. Chem. Soc.*, 1995, **117**, 7017.
- 1995JA12593 Q. Zhou and T. M. Swager, *J. Am. Chem. Soc.*, 1995, **117**, 12593.
- 1995JCD3117 P. D. Beer, M. G. B. Drew, R. J. Knubley, and M. I. Ogden, *J. Chem. Soc., Dalton Trans.*, 1995, 3117.
- 1995SM(75)103 J. Simonet, H. Patillon, C. Belloncle, N. Simonet-Gueguen, and P. Cauliez, *Synth. Met.*, 1995, **75**, 103.
- 1996AN127 M. G. Fallon, D. Mulcahy, W. S. Murphy, and J. D. Glennon, *Analyst*, 1996, **121**, 127.
- 1996AN1759 A. P. de Silva, T. Gunnlaugsson, and T. E. Rice, *Analyst*, 1996, **121**, 1759.
- 1996ANC208 K. Suzuki, K. Sato, H. Hisamoto, D. Siswanta, K. Hayashi, N. Kasahara, K. Watanabe, N. Yamamoto, and H. Sasakura, *Anal. Chem.*, 1996, **68**, 208.
- 1996ANC2361 D. Riester, K.-H. Wiesmüller, D. Stoll, and R. Kuhn, *Anal. Chem.*, 1996, **68**, 2361.
- 1996CC1483 P. T. Glink, C. Schiavo, J. F. Stoddart, and D. J. Williams, *Chem. Commun.*, 1996, 1483.
- 1996CCR171 M. Ouchi and T. Hakushi, *Coord. Chem. Rev.*, 1996, **148**, 171.
- 1996CCR199 K. Naemura, Y. Tobe, and T. Kaneda, *Coord. Chem. Rev.*, 1996, **148**, 199.
- 1996CEJ709 P. R. Ashton, E. J. T. Chrystal, P. T. Glink, S. Menzer, C. Schiavo, N. Spencer, J. F. Stoddart, P. A. Tasker, A. J. P. White, and D. J. Williams, *Chem. Eur. J.*, 1996, **2**, 709.
- 1996CEJ729 P. R. Ashton, P. T. Glink, J. F. Stoddart, P. A. Tasker, A. J. P. White, and D. J. Williams, *Chem. Eur. J.*, 1996, **2**, 729.
- 1996CHEC-II(9)809 B. Dietrich; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 809.
- 1996JA100 P. Schwab, R. H. Grubbs, and J. W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100.
- 1996JA4931 P. R. Ashton, R. Ballardini, V. Balzani, M. Bělohradský, M. T. Gandolfi, D. Philp, L. Prodi, F. M. Raymo, M. V. Reddington, N. Spencer, J. F. Stoddart, M. Venturi, and D. J. Williams, *J. Am. Chem. Soc.*, 1996, **118**, 4931.
- 1996JA11813 H. Zhang, X. Wang, and B. K. Teo, *J. Am. Chem. Soc.*, 1996, **118**, 11813.

- 1996JA12012 D. B. Amabilino, P. R. Ashton, V. Balzani, C. L. Brown, A. Credi, J. M. J. Fréchet, J. W. Leon, F. M. Raymo, N. Spencer, J. F. Stoddart, and M. Venturi, *J. Am. Chem. Soc.*, 1996, **118**, 12012.
- 1996JOC2553 E. F. Boros, C. W. Andrews, and A. O. Davis, *J. Org. Chem.*, 1996, **61**, 2553.
- 1996JPB899 G. D. Christian, *J. Pharm. Biomed. Anal.*, 1996, **14**, 899.
- 1996MM7029 C. Gong and H. W. Gibson, *Macromolecules*, 1996, **29**, 7029.
- 1996NAT522 Y. Kubo, S. Maeda, S. Tokita, and M. Kubo, *Nature*, 1966, **382**, 522.
- 1996NAT607 C. A. Mirkin, R. L. Letsinger, R. C. Mucic, and J. J. Storhoff, *Nature*, 1996, **382**, 607.
- 1996SCI163 D. Dougherty, *Science*, 1996, **271**, 163.
- 1996SCI1095 S. C. Zimmerman, F. Zeng, D. E. C. Reichert, and S. V. Kolotuchin, *Science*, 1996, **271**, 1095.
- 1996TL6217 P. R. Ashton, P. T. Glink, J. F. Stoddart, S. Menzer, P. A. Tasker, A. J. P. White, and D. J. Williams, *Tetrahedron Lett.*, 1996, **37**, 6217.
- 1997AGE1840 P. Schmitt, P. D. Beer, M. G. B. Drew, and P. D. Sheen, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1840.
- 1997AGE2070 D. B. Amabilino, P. R. Ashton, S. E. Boyd, J. Y. Lee, S. Menzer, J. F. Stoddart, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2070.
- 1997AGE2331 C. Gong and H. W. Gibson, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2331.
- 1997AN1445 Y. R. Kang, K. M. Lee, H. Nam, G. S. Cha, S. O. Jung, and J. S. Kim, *Analyst*, 1997, **122**, 1445.
- 1997ANS325 T. D. Chung, S.-K. Chang, J. Park, and H. Kim, *Anal. Sci.*, 1997, **13** (Suppl.), 325.
- 1997CC897 D. G. Hamilton, J. K. M. Sanders, J. E. Davies, W. Clegg, and S. J. Teat, *Chem. Commun.*, 1997, 897.
- 1997CL49 Y. Shibutani, S. Mino, S. S. Long, T. Moriuchi-Kawatami, K. Yakabe, and T. Shono, *Chem. Lett.*, 1997, 49.
- 1997CRV1515 A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, and T. E. Rice, *Chem. Rev.*, 1997, **97**, 1515.
- 1997CRV1713 A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713.
- 1997CRV3313 X. X. Zhang, J. S. Bradshaw, and R. M. Izatt, *Chem. Rev.*, 1997, **97**, 3313.
- 1997CSR247 S. J. Higgins, *Chem. Soc. Rev.*, 1997, **26**, 247.
- 1997IC2195 D. Steinborn, O. Gravenhorst, H. Hartung, and U. Baumeister, *Inorg. Chem.*, 1997, **36**, 2195.
- 1997JA302 M. Asakawa, P. R. Ashton, R. Ballardini, V. Balzani, M. Bělohradský, M. T. Gandolfi, O. Kocian, L. Prodi, F. M. Raymo, J. F. Stoddart, and M. Venturi, *J. Am. Chem. Soc.*, 1997, **119**, 302.
- 1997JA5862 C. Gong and H. W. Gibson, *J. Am. Chem. Soc.*, 1997, **119**, 5862.
- 1997JA7891 A. P. de Silva, H. Q. N. Gunaratne, and C. P. McCoy, *J. Am. Chem. Soc.*, 1997, **119**, 7891.
- 1997JA8585 C. Gong and H. W. Gibson, *J. Am. Chem. Soc.*, 1997, **119**, 8585.
- 1997JCE159 M. S. Frant, *J. Chem. Educ.*, 1997, **74**, 159.
- 1997JCE171 T. S. Light, *J. Chem. Educ.*, 1997, **74**, 171.
- 1997JCE177 C. C. Young, *J. Chem. Educ.*, 1997, **74**, 177.
- 1997JCH(757)225 H. Nishi, K. Nakamura, H. Nakai, and T. Sato, *J. Chromatogr. A*, 1997, **757**, 225.
- 1997JCH(757)328 Y. Mori, K. Ueno, and T. Umeda, *J. Chromatogr. A*, 1997, **757**, 328.
- 1997JCH(781)129 W. X. Huang, S. D. Fazio, and R. V. Vivilecchia, *J. Chromatogr. A*, 1997, **781**, 129.
- 1997JCH(695)157 W. X. Huang, H. Xu, S. D. Fazio, and R. V. Vivilecchia, *J. Chromatogr. B*, 1997, **695**, 157.
- 1997JP(1)1357 S. Iwata, H. Matsuoka, and K. Tanaka, *J. Chem. Soc., Perkin Trans. I*, 1997, 1357.
- 1997LA1853 M. Barboiu, C. T. Supuran, A. Scozzafava, F. Briganti, C. Luca, G. Popescu, L. Cot, and N. Hovnanian, *Liebigs Ann./Rec.*, 1997, 1853.
- B-1997MI1 T. Skotheim, J. R. Reynolds, and R. L. Elsenbaumer, Eds.; 'Handbook of Conducting Polymers', Marcel Dekker, New York, 1997.
- 1997MIJ348 Y. Yunhui, B. Yunmei, L. Mei, F. Jin, and X. Zhiwen, *Microchem. J.*, 1997, **55**, 348.
- 1997MM337 S.-H. Lee, P. T. Engen, and H. W. Gibson, *Macromolecules*, 1997, **30**, 337.
- 1997MM3711 H. W. Gibson, S. Liu, C. Gong, Q. Ji, and E. Joseph, *Macromolecules*, 1997, **30**, 3711.
- 1997MM4807 C. Gong, Q. Ji, T. E. Glass, and H. W. Gibson, *Macromolecules*, 1997, **30**, 4807.
- 1997MRC273 S. E. Weinstein, M. S. Vining, and T. J. Wenzel, *Magn. Reson. Chem.*, 1997, **35**, 273.
- 1997SCI1078 R. Elghanian, J. J. Storhoff, R. C. Mucic, R. L. Letsinger, and C. A. Mirkin, *Science*, 1997, **277**, 1078.
- 1997T15197 H. W. Gibson, S. S. Nagvekar, J. Powell, C. Gong, and W. S. Bryant, *Tetrahedron*, 1997, **53**, 15197.
- 1997TL3971 H. Kumagai, M. Hasegawa, S. Miyanari, Y. Sugawa, Y. Sato, T. Hori, S. Ueda, H. Kamiyama, and S. Miyano, *Tetrahedron Lett.*, 1997, **38**, 3971.
- 1998AGE172 R. W. Saalfrank, N. Low, S. Kareth, V. Seitz, F. Hampel, D. Stalke, and M. Teichert, *Angew. Chem., Int. Ed.*, 1998, **37**, 172.
- 1998AGE310 C. Gong and H. W. Gibson, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 310.
- 1998AGE1294 P. R. Ashton, I. Baxter, S. J. Cantrill, M. C. T. Fyfe, P. T. Glink, J. F. Stoddart, A. J. P. White, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1294.
- 1998AGE1913 P. R. Ashton, I. W. Parsons, F. M. Raymo, J. F. Stoddart, A. J. P. White, D. J. Williams, and R. Wolf, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1913.
- 1998AGE2361 N. Yamaguchi, D. S. Nagvekar, and H. W. Gibson, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 2361.
- 1998AGE2838 S. J. Loeb and J. A. Wisner, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 2838.
- 1998AGE3275 N. Yamaguchi, L. M. Hamilton, and H. W. Gibson, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 3275.
- 1998ALE5259 M. R. Ganjali, A. Moghimi, and M. Shamsipur, *Anal. Lett.*, 1998, **70**, 5259.
- 1998ANC4286 S. Sawada, H. Torii, T. Osakai, and T. Kimoto, *Anal. Chem.*, 1998, **70**, 4286.
- 1998ANS169 Z. Xia, I. H. A. Badr, S. L. Plummer, L. Cullen, and L. G. Bachas, *Anal. Sci.*, 1998, **14**, 169.
- 1998ANS1009 K.-C. Oh, E. C. Kang, Y. L. Cho, K.-S. Jeong, E.-A. Yoo, and K.-J. Paeng, *Anal. Sci.*, 1998, **14**, 1009.
- 1998APL3 A. Harada, *Acta Polym.*, 1998, **49**, 3.
- 1998CC265 A. S. Abd-El-Aziz, C. R. de Denus, M. J. Zaworotko, and C. V. Sharma, *Chem. Commun.*, 1998, 265.
- 1998CC443 M. M. G. Antonisse and D. N. Reinhoudt, *Chem. Commun.*, 1998, 443.
- 1998CC825 P. D. Beer and S. W. Dent, *Chem. Commun.*, 1998, 825.
- 1998CC1843 Y. K. Gun'ko, P. B. Hitchcock, and M. F. Lappert, *Chem. Commun.*, 1998, 1843.

- 1998CC2757 S. J. Loeb and J. A. Wisner, *Chem. Commun.*, 1998, 2757.
1998CCR1211 B. Fabre and J. Simonet, *Coord. Chem. Rev.*, 1998, **178–180**, 1211.
1998CEJ608 D. G. Hamilton, J. E. Davies, L. Prodi, and J. K. M. Sanders, *Chem. Eur. J.*, 1998, **4**, 608.
1998CRV3 L. C. Baker and D. C. Glick, *Chem. Rev.*, 1998, **98**, 3.
1998CRV51 Y. P. Jeannin, *Chem. Rev.*, 1998, **98**, 51.
1998CRV199 N. Mizuno and M. Misono, *Chem. Rev.*, 1998, **98**, 199.
1998CRV239 A. Müller, F. Peters, M. T. Pope, and D. Gatteschi, *Chem. Rev.*, 1998, **98**, 239.
1998CRV273 E. Coronado and J. Gómez-García, *Chem. Rev.*, 1998, **98**, 273.
1998CRV359 D. E. Katsoulis, *Chem. Rev.*, 1998, **98**, 359.
1998CRV1593 P. Bühlmann, E. Pretsch, and E. Bakker, *Chem. Rev.*, 1998, **98**, 1593.
1998EJO2109 C. Hamers, F. M. Raymo, and J. F. Stoddart, *Eur. J. Org. Chem.*, 1998, 2109.
1998JA1096 D. G. Hamilton, N. Feeder, L. Prodi, S. J. Teat, W. Clegg, and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1998, **120**, 1096.
1998JA2297 P. R. Ashton, I. Baxter, M. C. T. Fyfe, F. M. Raymo, N. Spencer, J. F. Stoddart, A. J. P. White, and D. J. Williams, *J. Am. Chem. Soc.*, 1998, **120**, 2297.
1998JA4295 D. B. Amabilino, P. R. Ashton, V. Balzani, S. E. Boyd, A. Credi, J. Y. Lee, S. Menzer, J. F. Stoddart, M. Venturi, and D. J. Williams, *J. Am. Chem. Soc.*, 1998, **120**, 4295.
1998JA9318 F. M. Raymo, K. N. Houk, and J. F. Stoddart, *J. Am. Chem. Soc.*, 1998, **120**, 9318.
1998JA11932 P. R. Ashton, R. Ballardini, V. Balzani, I. Baxter, A. Credi, M. C. T. Fyfe, M. T. Gandolfi, M. Gómez-López, M.-V. Martínez-Díaz, A. Piersanti, N. Spencer, J. F. Stoddart, M. Venturi, J. P. White, and D. J. Williams, *J. Am. Chem. Soc.*, 1998, **120**, 11932.
1998JA13138 D. G. Gusev, A. J. Lough, and R. H. Morris, *J. Am. Chem. Soc.*, 1998, **120**, 13138.
1998JOC6643 M. Takeshita and M. Irie, *J. Org. Chem.*, 1998, **63**, 6643.
1998JCH(805)85 Y. Machida, H. Nishi, K. Nakamura, H. Nakai, and T. Sato, *J. Chromatogr. A*, 1998, **805**, 85.
1998JP(2)2117 P. R. Ashton, M. C. T. Fyfe, S. K. Hickingbottom, J. F. Stoddart, A. J. P. White, and D. J. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1998, 2117.
1998JPM69 M. Kozbial, M. Pietraszkiewicz, and O. Pietraszkiewicz, *J. Inclusion Phenom.*, 1998, **30**, 69.
1998JPM119 Y. H. Cho, S. G. Rha, S.-K. Chang, T. D. Chung, K. Cho, and H. Kim, *J. Inclusion Phenom.*, 1998, **31**, 119.
1998JPM165 K. Odashima, *J. Inclusion Phenom.*, 1998, **32**, 165.
1998JPM251 T. Hayashita, N. Teramae, T. Kuboyama, S. Nakamura, H. Yamamoto, and H. Nakamura, *J. Inclusion Phenom.*, 1998, **32**, 251.
1998L5245 R. Plehnert, J. A. Schröter, and C. Tschierske, *Langmuir*, 1998, **14**, 5245.
B-1998MI1 C. D. Gutsche; in 'Monographs in Supramolecular Chemistry, Vol. 6: Calixarenes Revisited', J. F. Stoddart, Ed.; The Royal Society of Chemistry, Cambridge, 1998.
1998MM308 C. Gong, T. E. Glass, and H. W. Gibson, *Macromolecules*, 1998, **31**, 308.
1998MM1814 C. Gong, Q. Ji, C. Subramaniam, and H. W. Gibson, *Macromolecules*, 1998, **31**, 1814.
1998MM5278 C. Gong, P. B. Balanda, and H. W. Gibson, *Macromolecules*, 1998, **31**, 5278.
1998NJC1019 D. G. Hamilton, N. Feeder, S. J. Teat, and J. K. M. Sanders, *New J. Chem.*, 1998, 1019.
1998PAC1253 J. Simonet, *Pure Appl. Chem.*, 1998, **70**, 1253.
1998SM(93)115 C. Belloncle, B. Fabre, P. Cauliez, and J. Simonet, *Synth. Met.*, 1998, **93**, 115.
1998TL7717 M. Takeshita, C. Fong Soong, and M. Irie, *Tetrahedron Lett.*, 1998, **39**, 7717.
1999ACR53 M. Fujita, *Acc. Chem. Res.*, 1999, **32**, 53.
1999AGE2208 S. Tomàs, R. Prohens, G. Deslongchamps, P. Ballester, and A. Costa, *Angew. Chem., Int. Ed.*, 1999, **38**, 2208.
1999ANSI1185 M. M. Murad, T. Hayashita, K. Shigemori, S. Nishizawa, and N. Teramae, *Anal. Sci.*, 1999, **15**, 1185.
1999BKC556 K.-C. Oh, E. C. Kang, C. Eun, K.-S. Jeong, and K.-J. Paeng, *Bull. Korean Chem. Soc.*, 1999, **20**, 556.
1999CC1251 S. J. Cantrill, M. C. T. Fyfe, A. M. Heiss, J. F. Stoddart, A. J. P. White, and D. J. Williams, *Chem. Commun.*, 1999, 1251.
1999CC1253 P. D. Beer, P. K. Hopkins, and J. D. McKinney, *Chem. Commun.*, 1999, 1253.
1999CCR139 M. C. T. Fyfe and J. F. Stoddart, *Coord. Chem. Rev.*, 1999, **183**, 139.
1999CL1185 S. Nishizawa, K. Shigemori, and N. Teramae, *Chem. Lett.*, 1999, 1185.
1999CRV1643 F. M. Raymo and J. F. Stoddart, *Chem. Rev.*, 1999, **99**, 1643.
1999CRV1689 G. R. Newkome, E. He, and C. N. Moorefield, *Chem. Rev.*, 1999, **99**, 1689.
1999EJO995 P. R. Ashton, A. M. Heiss, D. Pasini, F. M. Raymo, A. N. Shipway, J. F. Stoddart, and Neil Spencer, *Eur. J. Org. Chem.*, 1999, 995.
1999ELP2605 R. Kuhn, *Electrophoresis*, 1999, **20**, 2605.
1999JA3807 K. Fuji, K. Tsubaki, K. Tanaka, N. Hayashi, T. Otsubo, and T. Kinoshita, *J. Am. Chem. Soc.*, 1999, **121**, 3807.
1999JA5599 W.-S. Xia, R. H. Schmehl, and C.-J. Li, *J. Am. Chem. Soc.*, 1999, **121**, 5599.
1999JMC2133 A. Boldea, I. Lévesque, and M. Leclerc, *J. Mater. Chem.*, 1999, **9**, 2133.
1999JP(1)1057 D. G. Hamilton, L. Prodi, N. Feeder, and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1057.
1999JP(2)141 S. Nishizawa, M. Watanabe, T. Uchida, and N. Teramae, *J. Chem. Soc., Perkin Trans. 2*, 1999, 141.
1999JP(2)1577 F. Diederich, L. Echegoyen, M. Gómez-López, R. Kessinger, and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1577.
1999JP(2)1193 R. Ostaszewski, A. Božek, M. Palys, and Z. Stojek, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1193.
B-1999MI1 J. C. Crano and R. J. Gugliemetti; 'Organic Photochromic, and Thermochromic Compounds', Plenum, New York, 1999.
B-1999MI2 In 'Molecular Catenanes, Rotaxanes, and Knots', J.-P. Sauvage and C. Dietrich-Buchecker, Eds.; Wiley-VCH, Weinheim, 1999.
B-1999MI3 In 'Templated Organic Synthesis', F. Diederich and P. J. Stang, Eds.; Wiley VCH, Weinheim, 1999.
1999OLI29 S. J. Rowan, S. J. Cantrill, and J. F. Stoddart, *Org. Lett.*, 1999, **1**, 129.
1999OL953 M. Scholl, S. Ding, C. W. Lee, and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953.
1999OL1001 W. S. Bryant, J. W. Jones, P. E. Mason, I. Guzei, A. L. Rheingold, F. R. Fronczek, D. S. Nagvekar, and H. W. Gibson, *Org. Lett.*, 1999, **1**, 1001.
1999OL1363 S. J. Cantrill, S. J. Rowan, and J. F. Stoddart, *Org. Lett.*, 1999, **1**, 1363.

- 1999OL1697 S. P. Gromov, E. N. Ushakov, A. I. Vedernikov, N. A. Lobova, M. V. Alfimov, Y. A. Strelenko, J. K. Whitesell, and M. A. Fox, *Org. Lett.*, 1999, **1**, 1697.
- 1999OL1917 P. R. Ashton, S. J. Cantrill, J. A. Preece, J. F. Stoddart, Z.-H. Wang, A. J. P. White, and D. J. Williams, *Org. Lett.*, 1999, **1**, 1917.
- 1999PLM1823 H. W. Gibson, P. T. Engen, and S.-H. Lee, *Polymer*, 1999, **40**, 1823.
- 1999SCI785 H. Engelkamp, S. Middelbeek, and R. J. M. Nolte, *Science*, 1999, **284**, 785.
- 1999T9221 M. D. Barboiu, N. D. Hovnanian, C. Luca, and L. Cot, *Tetrahedron*, 1999, **55**, 9221.
- 1999TL3661 P. R. Ashton, R. A. Bartsch, S. J. Cantrill, R. E. Hanes, Jr., S. K. Hickingbottom, J. N. Lowe, J. A. Preece, J. F. Stoddart, V. S. Talanov, and Z.-H. Wang, *Tetrahedron Lett.*, 1999, **40**, 3661.
- 1999TL3669 S. J. Cantrill, D. A. Fulton, M. C. T. Fyfe, J. F. Stoddart, A. J. P. White, and D. J. Williams, *Tetrahedron Lett.*, 1999, **40**, 3669.
- 2000AGE3868 J. Kim, D. T. McQuade, S. K. McHugh, and T. M. Swager, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 3868.
- 2000ANA57 A.-J. Tong, Y.-S. Song, L.-D. Li, T. Hayashita, N. Teramae, C. Park, and R. A. Bartsch, *Anal. Chim. Acta*, 2000, **420**, 57.
- 2000ANC2200 K. Suzuki, D. Siswanta, T. Otsuka, T. Amano, T. Ikeda, H. Hisamoto, R. Yoshihara, and S. Ohba, *Anal. Chem.*, 2000, **72**, 2200.
- 2000ANC5258 K. Kavallieratos, A. Danby, G. J. Van Berkel, M. A. Kelly, R. A. Sachleben, B. A. Moyer, and K. Bowman-James, *Anal. Chem.*, 2000, **72**, 5258.
- 2000ANC5841 A. Yamauchi, T. Hayashita, A. Kato, S. Nishizawa, M. Watanabe, and N. Teramae, *Anal. Chem.*, 2000, **72**, 5841.
- 2000CC187 K. Kavallieratos, R. A. Sachleben, G. J. Van Berkel, and B. Moyer, *Chem. Commun.*, 2000, 187.
- 2000CC695 W.-S. Xia, R. H. Schmehl, and C.-J. Li, *Chem. Commun.*, 2000, 695.
- 2000CC845 S. J. Loeb and J. A. Wisner, *Chem. Commun.*, 2000, 845.
- 2000CC847 K. Chichak, M. C. Walsh, and N. R. Branda, *Chem. Commun.*, 2000, 847.
- 2000CC1207 G. Cafeo, F. H. Kohnke, G. L. La Torre, A. J. White, and D. J. Williams, *Chem. Commun.*, 2000, 1207.
- 2000CCR5 T. J. Hubin and D. H. Busch, *Coord. Chem. Rev.*, 2000, **200–202**, 5.
- 2000CEJ2274 S. J. Cantrill, D. A. Fulton, A. M. Heiss, A. R. Pease, J. F. Stoddart, A. J. P. White, and D. J. Williams, *Chem. Eur. J.*, 2000, **6**, 2274.
- 2000CL18 Y. Furusho, T. Hasegawa, A. Tsuboi, N. Kihara, and T. Takata, *Chem. Lett.*, 2000, 18.
- 2000CRV2537 D. T. McQuade, A. E. Pullen, and T. M. Swager, *Chem. Rev.*, 2000, **100**, 2537.
- 2000EJ12303 B. König and M. H. Fonseca, *Eur. J. Inorg. Chem.*, 2000, 2303.
- 2000EJO1121 P. R. Ashton, V. Baldoni, V. Balzani, C. G. Claessens, A. Credi, H. D. A. Hoffmann, F. M. Raymo, J. F. Stoddart, M. Venturi, A. J. P. White, and D. J. Williams, *Eur. J. Org. Chem.*, 2000, 1121.
- 2000ELA178 L. Y. Heng and E. A. H. Hall, *Electroanalysis*, 2000, **12**, 178.
- 2000EL3220 T. de Boer, R. A. De Zeeuw, G. J. De Jong, and K. Ensing, *Electrophoresis*, 2000, **21**, 3220.
- 2000JA164 S. J. Rowan and J. F. Stoddart, *J. Am. Chem. Soc.*, 2000, **122**, 164.
- 2000JA4640 J. J. Storhoff, A. A. Lazarides, R. C. Mucic, C. A. Mirkin, R. L. Letsinger, and G. C. Schatz, *J. Am. Chem. Soc.*, 2000, **122**, 4640.
- 2000JA6201 M. J. Deetz, M. Shang, and B. D. Smith, *J. Am. Chem. Soc.*, 2000, **122**, 6201.
- 2000JC1243 T. J. Wenzel and J. E. Thurston, *J. Org. Chem.*, 2000, **65**, 1243.
- 2000JP(2)1003 T. Hayashita, S. Taniguchi, Y. Tanamura, T. Uchida, S. Nishizawa, N. Teramae, Y. S. Jin, J. C. Lee, and R. A. Bartsch, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1003.
- 2000JPR437 O. Safarowsky, B. Windisch, A. Mohry, and F. Vögtle, *J. Prakt. Chem.*, 2000, **342**, 437.
- 2000JT(524)133 W. You, E. Wang, Q. He, L. Xu, Y. Xing, and H. Jia, *J. Mol. Struct.*, 2000, **524**, 133.
- B-2000MI359 D. A. Tomalia and I. Majoros; in 'Supramolecular Polymers', A. Ciferri, Ed.; Marcel Dekker, New York, 2000, p. 359.
- 2000OL61 S. J. Cantrill, M. C. T. Fyfe, A. M. Heiss, J. F. Stoddart, A. J. P. White, and D. J. Williams, *Org. Lett.*, 2000, **2**, 61.
- 2000OL449 J. G. Hansen, N. Feeder, D. G. Hamilton, M. J. Gunter, J. Becher, and J. K. M. Sanders, *Org. Lett.*, 2000, **2**, 449.
- 2000OL1221 M. C. T. Fyfe, J. N. Lowe, J. F. Stoddart, and D. J. Williams, *Org. Lett.*, 2000, **2**, 1221.
- 2000OL3099 R. Shukla, T. Kida, and B. D. Smith, *Org. Lett.*, 2000, **2**, 3099.
- 2000T7045 W.-S. Xia, R. H. Schmehl, and C.-J. Li, *Tetrahedron*, 2000, **56**, 7045.
- 2000TL3769 T. J. Wenzel and J. E. Thurston, *Tetrahedron Lett.*, 2000, **41**, 3769.
- 2001ACR18 T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18.
- 2001AGE486 P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**, 486.
- 2001AGE2658 J. S. Alexander and K. Ruhlandt-Senge, *Angew. Chem., Int. Ed.*, 2001, **40**, 2658.
- 2001CC311 E. Sartori, L. Garlaschelli, A. Toffoletti, C. Corvaja, M. Maggini, and G. Scorrano, *Chem. Commun.*, 2001, 311.
- 2001CC1620 K. Kavallieratos and B. A. Moyer, *Chem. Commun.*, 2001, 1620.
- 2001CRV3819 S. M. Grayson and J. M. J. Fréchet, *Chem. Rev.*, 2001, **101**, 3819.
- 2001CRV4071 L. Brunsveld, B. J. B. Folmer, E. W. Meijer, and R. P. Sijbesma, *Chem. Rev.*, 2001, **101**, 4071.
- 2001IC5468 W. You, E. Wang, Y. Xu, Y. Li, L. Xu, and C. Hu, *Inorg. Chem.*, 2001, **40**, 5468.
- 2001JA1260 S. A. McFarland and N. S. Finney, *J. Am. Chem. Soc.*, 2001, **123**, 1260.
- 2001JCH(906)3 N. M. Maier, P. Franco, and W. Lindner, *J. Chromatogr. A*, 2001, **906**, 3.
- 2001JOC1533 M. Tanaka, M. Nakamura, M. A. A. Salhin, T. Ikeda, K. Kamada, H. Ando, Y. Shibutani, and K. Kimura, *J. Org. Chem.*, 2001, **66**, 1533.
- 2001JOC6857 S. J. Cantrill, G. J. Youn, J. F. Stoddart, and D. J. Williams, *J. Org. Chem.*, 2001, **66**, 6857.
- 2001JP(2)1685 E. Bang, J.-W. Jung, W. Lee, D. W. Lee, and W. Lee, *J. Chem. Soc., Perkin Trans. 2*, 2001, 1685.
- 2001JPM69 G. J. Kirkovits, J. A. Shriver, P. A. Gale, and J. L. Sessler, *J. Inclusion Phenom.*, 2001, **41**, 69.
- B-2001MI1 C. M. Rudzinski and D. G. Nocera; in 'Optical Sensors and Switches', V. Ramamurthy and K. S. Schanze, Eds.; Marcel Dekker, New York, 2001, ch. 1, p. 1.
- B-2001MI2 In 'Molecular Switches', B. Feringa, Ed.; Wiley-VCH, Weinheim, Germany, 2001.
- B-2001MI3 In 'Dendrimers, and Other Dendritic Polymers', J. M. J. Fréchet and D. A. Tomalia, Eds.; Wiley, New York, 2001.
- B-2001MI4 In 'Calixarenes 2001', Z. Asfari, V. Böhmer, J. Harrowfield, and J. Vicens, Eds.; Kluwer Academic Publishers, Dordrecht, 2001.
- B-2001MI93 A. P. de Silva, D. B. Fox, T. S. Moody, and S. M. Weir; in 'Optical Sensors and Switches', V. Ramamurthy and K. S. Schanze, Eds.; Marcel Dekker, New York, 2001, ch. 2, p. 93.
- B-2001MI365 A. Casnati, R. Ungaro, Z. Asfari, and J. Vicens; in 'Calixarenes 2001', Z. Asfari, V. Böhmer, J. Harrowfield, and J. Vicens, Eds.; Kluwer Academic Publishers, Dordrecht, 2001, ch. 20, p. 365.
- 2001NJC166 M. J. Gunter, N. Bampas, K. D. Johnstone, and J. K. M. Sanders, *New J. Chem.*, 2001, **25**, 166.

- 2001NJC1355 S. E. Matthews, V. Felix, M. G. B. Drew, and P. D. Beer, *New J. Chem.*, 2001, **25**, 1355.
2001NL165 Y. Kim, R. C. Johnson, and J. T. Hupp, *Nano Lett.*, 2001, **1**, 165.
2001OL2485 D. W. Zehnder, II, and D. B. Smithrud, *Org. Lett.*, 2001, **3**, 2485.
2001PAC503 A. P. de Silva, D. B. Fox, T. S. Moody, and S. M. Weir, *Pure Appl. Chem.*, 2001, **73**, 503.
2001PSA1978 H. W. Gibson, W. S. Bryant, and S.-H. Lee, *J. Polym. Sci., Polym. Chem., Part A*, 2001, **39**, 1978.
2001RCR1017 V. A. Bren, *Russ. Chem. Rev.*, 2001, **70**, 1017.
2001TA1125 T. J. Wenzel, J. E. Thurston, D. C. Sek, and J.-P. Joly, *Tetrahedron Asymmetry*, 2001, **12**, 1125.
2001TCC95 S. C. Zimmerman and L. J. Lawless, *Top. Curr. Chem.*, 2001, **217**, 95.
2002AGE898 S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 898.
2002AGE2122 G. Cafeo, G. Gattuso, F. H. Kohnke, A. Notti, S. Occhipinti, S. Pappalardo, and M. F. Parisi, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 2122.
2002AGE3254 G. M. Dykes, D. K. Smith, and G. J. Seeley, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 3254.
2002ANC330 S.-Y. Lin, S.-W. Liu, C.-M. Lin, and C.-H. Chen, *Anal. Chem.*, 2002, **74**, 330.
2002BKC637 C. Kim and H. Kim, *Bull. Korean Chem. Soc.*, 2002, **23**, 637.
2002CCS12 Y.-H. Kim and J.-I. Hong, *Chem. Commun.*, 2002, 512.
2002CC2461 G. J. Brown, A. P. de Silva, and S. Pagliari, *Chem. Commun.*, 2002, 2461.
2002CC2948 S.-H. Chiu, S. J. Rowan, S. J. Cantrill, J. F. Stoddart, A. J. P. White, and D. J. Williams, *Chem. Commun.*, 2002, 2948.
2002EJO655 A. M. A. Salhin, M. Tanaka, K. Kamada, H. Ando, T. Ikeda, Y. Shibutani, S. Yajima, M. Nakamura, and K. Kimura, *Eur. J. Org. Chem.*, 2002, 655.
2002ELA186 J. C. Ball, J. R. Allen, J.-Y. Ryu, S. Vickery, L. Cullen, P. Bukowski, T. CynKowski, and S. Daunert, *Electroanalysis*, 2002, **14**, 186.
2002HCA3283 Y. Gong and H. K. Lee, *Helv. Chim. Acta*, 2002, **85**, 3283.
2002ICA(332)18 M. Wen, M. Munakata, Y. Suenaga, T. Kuroda-Sowa, and M. Maekawa, *Inorg. Chim. Acta*, 2002, **332**, 18.
2002JA1341 S. E. Matthews, P. Schmitt, V. Felix, M. G. B. Drew, and P. D. Beer, *J. Am. Chem. Soc.*, 2002, **124**, 1341.
2002JA4653 H. W. Gibson, N. Yamaguchi, L. Hamilton, and J. W. Jones, *J. Am. Chem. Soc.*, 2002, **124**, 4653.
2002JA11064 H. Fenniri, B.-L. Deng, and A. E. Ribbe, *J. Am. Chem. Soc.*, 2002, **124**, 11064.
2002JFC(116)19 R. D. Chambers, P. R. Hoskin, A. Khalil, P. Richmond, G. Sandford, D. S. Yufit, and J. A. K. Howard, *J. Fluorine Chem.*, 2002, **116**, 19.
2002JPCB833 W.-S. Xia, R. H. Schmehl, C.-J. Li, J. T. Mague, C.-P. Luo, and D. M. Guldi, *J. Phys. Chem. B*, 2002, **106**, 833.
2002JSU89 N. G. Berry, T. W. Shimell, and P. D. Beer, *J. Supramol. Chem.*, 2002, **2**, 89.
B-2002MI1 G. R. Newkome, C. N. Moorefield, and F. Vöglle, 'Dendrimers, and Dendrons: Concepts, Syntheses, Applications', VCH, Weinheim, 2002.
B-2002MI331 T. W. Bell and N. M. Hext; in 'Optical Biosensors: Present, and Future', F. S. Ligler and C. Rowe Taitt, Eds.; Elsevier Science, Amsterdam, 2002, ch. 11, p. 331.
2002NJC1102 K. Shigemori, S. Nishizawa, T. Yokobori, T. Shioya, and N. Teramae, *New J. Chem.*, 2002, **26**, 1102.
2002OL679 A. M. Elizarov, S.-H. Chiu, P. T. Glink, and J. F. Stoddart, *Org. Lett.*, 2002, **4**, 679.
2002OL2313 K. Tsubaki, T. Kusumoto, N. Hayashi, M. Nuruzzaman, and K. Fuji, *Org. Lett.*, 2002, **4**, 2313.
2002OL2641 Y. Nakahara, Y. Matsumi, W. Zhang, T. Kida, Y. Nakatsuji, and I. Ikeda, *Org. Lett.*, 2002, **4**, 2641.
2002OL3565 A. M. Elizarov, T. Chang, S.-H. Chiu, and J. F. Stoddart, *Org. Lett.*, 2002, **4**, 3565.
2002PCA2020 E. N. Ushakov, S. P. Gromov, A. I. Vedernikov, E. V. Malysheva, A. A. Botsmanova, M. V. Alfimov, B. Eliasson, U. G. Edlung, J. K. Whitesell, and M. A. Fox, *J. Phys. Chem. A*, 2002, **106**, 2020.
2002PCB10618 S. Wang, Y. Liu, H. Liu, G. Yu, Y. Xu, X. Zhan, F. Xi, and D. Zhu, *J. Phys. Chem. B*, 2002, **106**, 10618.
2002PCP3849 V. Felix, S. E. Matthews, P. D. Beer, and M. G. B. Drew, *Phys. Chem. Chem. Phys.*, 2002, **4**, 3849.
2002PNA4830 T. Clifford, A. Abushamleh, and D. H. Busch, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 4830.
2002PNA6487 H. Fenniri, B.-L. Deng, A. E. Ribbe, K. Hallenga, J. Jacob, and P. Thiagarajan, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 6487.
2002RJD163 V. P. Barannikov, S. S. Guseinov, and A. I. V'yugin, *Russ. J. Coord. Chem.*, 2002, **28**, 163.
2002SL1743 L. Raehm, D. G. Hamilton, and J. K. M. Sanders, *Synlett*, 2002, 1743.
2002T6609 Y. Furusho, G. A. Rajkumar, T. Oku, and T. Takata, *Tetrahedron*, 2002, **58**, 6609.
2002TL2857 J. Budka, P. Lhoták, I. Stibor, V. Michlová, J. Sykora, and I. Cisarová, *Tetrahedron Lett.*, 2002, **43**, 2857.
2003AGE3158 Y. Nakamura, S. Minami, K. Iizuka, and J. Nishimura, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 3158.
2003AGE3281 A. F. M. Kilbinger, S. J. Cantrill, A. W. Waltman, M. W. Day, and R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 3281.
2003ALE317 M. R. Ganjali, A. Datar, M. Faal-Rastegar, and A. Moghimi, *Anal. Lett.*, 2003, **36**, 317.
2003ANA291 T. Moriuchi-Kawakami, R. Aoki, K. Morita, H. Tsujioka, K. Fujimori, Y. Shibutani, and T. Shono, *Anal. Chim. Acta*, 2003, **480**, 291.
2003ANSI353 M. R. Ganjali, A. Datar, M. Faal-Rastegar, and A. Moghimi, *Anal. Sci.*, 2003, **19**, 353.
2003CC64 H. Miyaji, S. R. Collinson, I. Prokes, and J. H. R. Tucker, *Chem. Commun.*, 2003, 64.
2003CC2010 A. P. de Silva, G. D. McClean, and S. Pagliari, *Chem. Commun.*, 2003, 2010.
2003CCR191 P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 191.
2003CEJ2895 Y. Furusho, T. Oku, T. Hasegawa, A. Tsuboi, N. Kihara, and T. Takata, *Chem. Eur. J.*, 2003, **9**, 2895.
2003CEJ5348 V. Balzani, M. Clemente-León, A. Credi, J. N. Lowe, J. D. Badjić, J. F. Stoddart, and D. J. Williams, *Chem. Eur. J.*, 2003, **9**, 5348.
2003CH256 T. J. Wenzel and J. D. Wilcox, *Chirality*, 2003, **15**, 256.
2003EJO3744 T. Ikeda, M. Asakawa, M. Goto, Y. Nagawa, and T. Shimizu, *Eur. J. Org. Chem.*, 2003, 3744.
2003IC729 S. E. Matthews, N. H. Rees, V. Felix, M. G. B. Drew, and P. D. Beer, *Inorg. Chem.*, 2003, **42**, 729.
2003JA2224 R. Cacciapaglia, S. Di Stefano, and L. Mandolini, *J. Am. Chem. Soc.*, 2003, **125**, 2224.
2003JA3522 H. W. Gibson, N. Yamaguchi, and J. W. Jones, *J. Am. Chem. Soc.*, 2000, **125**, 3522.
2003JA7001 J. W. Jones and H. W. Gibson, *J. Am. Chem. Soc.*, 2003, **125**, 7001.
2003JA9272 F. Huang, F. R. Fronczek, and H. W. Gibson, *J. Am. Chem. Soc.*, 2003, **125**, 9272.
2003JA14760 S. Dhungana, P. S. White, and A. L. Crumbliss, *J. Am. Chem. Soc.*, 2003, **125**, 14760.

- 2003JCD3622 S. Arndt, P. M. Zeimentz, T. P. Spaniol, J. Okuda, M. Honda, and K. Tatsumi, *J. Chem. Soc., Dalton Trans.*, 2003, 3622.
- 2003JCD4451 A. J. Evans and P. D. Beer, *J. Chem. Soc., Dalton Trans.*, 2003, 4451.
- 2003JCH(984)163 M. H. Hyun, Y. J. Cho, J. A. Kim, and J. S. Jin, *J. Chromatogr. A*, 2003, **984**, 163.
- 2003JFL427 G. Ramachandran, G. Simon, Y. Cheng, T. A. Smith, and L. Dai, *J. Fluoresc.*, 2003, **13**, 427.
- 2003JLU13 V. Bekiar, P. Judeinstein, and P. Lianos, *J. Lumin.*, 2003, **104**, 13.
- 2003JMC800 Q. Sun, H. Wang, C. Yang, and Y. Li, *J. Mater. Chem.*, 2003, **13**, 800.
- 2003JMC2661 J. A. A. W. Elemans, A. E. Rowan, and R. J. M. Nolte, *J. Mater. Chem.*, 2003, **13**, 2661.
- 2003JOC2385 J. W. Jones, W. S. Bryant, A. W. Bosman, R. A. J. Janssen, E. W. Meijer, and H. W. Gibson, *J. Org. Chem.*, 2003, **68**, 2385.
- 2003JPM45 R. Berezki, B. Ágai, I. Bitter, L. Töke, and K. Tóth, *J. Inclusion Phenom.*, 2003, **45**, 45.
- 2003JPM53 R. Berezki, B. Ágai, and I. Bitter, *J. Inclusion Phenom.*, 2003, **47**, 53.
- 2003JSS242 M. H. Hyun, *J. Sep. Sci.*, 2003, **26**, 242.
- B-2003MI1 V. Balzani, A. Credi, and M. Venturi, 'Molecular Devices, and Machines: A Journey into the Nano World', Wiley-VCH: Weinheim, 2003.
- 2003OBC1232 S. E. Matthews, V. Felix, M. G. B. Drew, and P. D. Beer, *Org. Biomol. Chem.*, 2003, **1**, 1232.
- 2003OBC2137 R. D. Chambers, P. R. Hoskin, A. R. Kenwright, A. Khalil, P. Richmond, G. Sandford, D. S. Yufit, and J. A. K. Howard, *Org. Biomol. Chem.*, 2003, **1**, 2137.
- 2003OL3073 M. Barboiu, G. Vaughan, and A. van der Lee, *Org. Lett.*, 2003, **5**, 3073.
- 2003T3999 G. M. Dykes and D. K. Smith, *Tetrahedron*, 2003, **59**, 3999.
- 2003TL5773 H. Iwamoto, K. Itoh, H. Nagamiya, and Y. Fukazawa, *Tetrahedron Lett.*, 2003, **44**, 5773.
- 2004AGE966 T. Oku, Y. Furusho, and T. Takata, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 966.
- 2004AJC301 A. H. Flood, R. J. A. Ramirez, W.-Q. Deng, R. P. Muller, W. A. Goddard, III, and J. F. Stoddard, *Aust. J. Chem.*, 2004, **57**, 301.
- 2004ANB1536 T. J. Wenzel, B. E. Freeman, D. C. Sek, J. J. Zopf, T. Nakamura, J. Yongzhu, K. Hirose, and Y. Tobe, *Anal. Bioanal. Chem.*, 2004, **378**, 1536.
- 2004APS1 T. Tanaka, N. Kihara, and Y. Furusho, *Adv. Polym. Sci.*, 2004, **171**, 1.
- 2004BKC59 H. Y. Jin, T. H. Kim, J. Kim, S. S. Lee, and J. S. Kim, *Bull. Korean Chem. Soc.*, 2004, **25**, 59.
- 2004CEJ1926 J. D. Badjić, V. Balzani, A. Credi, J. N. Lowe, S. Silvi, and J. F. Stoddard, *Chem. Eur. J.*, 2004, **10**, 1926.
- 2004CEJ6375 T. Iijima, S. A. Vignon, H.-R. Tseng, T. Jarroson, J. K. M. Sanders, F. Marchioni, M. Venturi, E. Apostoli, V. Balzani, and J. F. Stoddard, *Chem. Eur. J.*, 2004, **10**, 6375.
- 2004CRV17 J. M. Seco, E. Quinoa, and R. Riguera, *Chem. Rev.*, 2004, **104**, 17.
- 2004CRV2723 G. W. Gokel, W. M. Leevy, and M. E. Weber, *Chem. Rev.*, 2004, **104**, 2723.
- 2004CRV1687 L. Pu, *Chem. Rev.*, 2004, **104**, 1687.
- 2004CSR589 T. W. Bell and N. M. Hext, *Chem. Soc. Rev.*, 2004, **33**, 589.
- 2004ELA1785 M. H. Ho, M.-H. Piao, Y. J. Cho, and Y.-B. Shim, *Electroanalysis*, 2004, **16**, 1785.
- 2004ELP2755 H.-J. Park, Y. Choi, W. Lee, and K.-R. Kim, *Electrophoresis*, 2004, **25**, 2755.
- 2004JA15412 M.-X. Wang and H.-B. Yang, *J. Am. Chem. Soc.*, 2004, **126**, 15412.
- 2004JCD2514 S. T. Liddle, W. Clegg, and C. A. Morrison, *J. Chem. Soc., Dalton Trans.*, 2004, 2514.
- 2004JOC4403 Y. Nakahara, T. Kida, Y. Nakatsuji, and M. Akashi, *J. Org. Chem.*, 2004, **69**, 4403.
- 2004OBC3470 H. Nagata, H. Nishi, M. Kamiguchi, and T. Ishida, *Org. Biomol. Chem.*, 2004, **2**, 3470.
- 2004OL655 G. D. Fallon, M. A.-P. Lee, S. J. Langford, and P. J. Nichols, *Org. Lett.*, 2004, **6**, 655.
- 2004S1243 R. Buschbeck, H. Lang, S. Agarwal, V. K. Saini, and V. K. Gupta, *Synthesis*, 1243.
- 2004SCI1845 J. D. Badjić, V. Balzani, A. Credi, S. Silvi, and J. F. Stoddard, *Science*, 2004, **303**, 1845.
- 2004SSA315 M. R. Ganjali, M. Ghorbani, P. Norouzi, A. Daftari, M. Faal-Rastegar, and A. Moghimi, *Sens. Actuators B*, 2004, **100**, 315.
- 2004T6029 S. A. Ahmed, M. Tanaka, H. Ando, K. Tawa, and K. Kimura, *Tetrahedron*, 2004, **60**, 6029.
- 2004TCC141 C. A. Schalley, T. Weilandt, J. Brüggemann, and F. Vögtle, *Top. Curr. Chem.*, 2004, **248**, 141.
- 2005AN63 R. Berezki, R. E. Gyurcsányi, B. Ágai, and K. Tóth, *Analyst*, 2005, **130**, 63.
- 2005CC1511 S. J. Loeb, *Chem. Commun.*, 2005, 1511.
- 2005CC1696 F. Huang and H. W. Gibson, *Chem. Commun.*, 2005, 1696.
- 2005CH142 K. Hirose, J. Yongzhu, T. Nakamura, R. Nishioka, T. Ueshige, and Y. Tobe, *Chirality*, 2005, **17**, 142.
- 2005CHR505 Y. Kuwahara, H. Nagata, H. Nishi, Y. Tanaka, and K. Kakehi, *Chromatographia*, 2005, **62**, 505.
- 2005IC7313 V. Shivaiah and S. K. Das, *Inorg. Chem.*, 2005, **44**, 7313.
- 2005JA1810 B. P. Hay, T. K. Firman, and B. Moyer, *J. Am. Chem. Soc.*, 2005, **127**, 1810.
- 2005JA13158 X.-Z. Zhu and C.-F. Chen, *J. Am. Chem. Soc.*, 2005, **127**, 13158.
- 2005JCD1159 F. Orón, A. Tàrraga, M. D. Velasco, and P. Molina, *J. Chem. Soc., Dalton Trans.*, 2005, 1159.
- 2005JCH(1078)35 K. Hirose, J. Yongzhu, T. Nakamura, R. Nishioka, T. Ueshige, and Y. Tobe, *J. Chromatogr. A*, 2005, **1078**, 35.
- 2005JMC2755 N. B. Sankaran, S. Nishizawa, M. Watanabe, T. Uchida, and N. Teramae, *J. Mater. Chem.*, 2005, **15**, 2755.
- 2005JOC3231 F. Huang, K. A. Switek, L. N. Zakharov, F. R. Fronczek, C. Slebodnick, M. Lam, J. A. Golen, W. S. Bryant, P. E. Mason, A. L. Rheingold, M. Ashraf-Khorassani, and H. W. Gibson, *J. Org. Chem.*, 2005, **70**, 3231.
- 2005JOM(690)696 R. Buschbeck and H. Lang, *J. Organomet. Chem.*, 2005, **690**, 696.
- 2005MIJ213 W. Lee, J. Y. Jin, and C.-S. Baek, *Microchem. J.*, 2005, **80**, 213.
- 2005OL91 J. L. Katz, M. B. Feldman, and R. R. Conry, *Org. Lett.*, 2005, **7**, 91.
- 2005OL1437 A. Frontera, M. Orell, C. Garau, D. Quiñero, E. Molins, I. Mata, and J. Morey, *Org. Lett.*, 2005, **7**, 1437.
- 2005OL2129 E. N. Guidry, S. J. Cantrill, J. F. Stoddard, and R. H. Grubbs, *Org. Lett.*, 2005, **7**, 2129.
- 2005OL3505 J. L. Katz, K. J. Selby, and R. R. Conry, *Org. Lett.*, 2005, **7**, 3505.
- 2005PPO220 D. K. Smith, A. R. Hirst, C. S. Love, J. G. Hardy, S. V. Brignell, and B. Huang, *Prog. Polym. Sci.*, 2005, **30**, 220.
- 2005PPO982 F. Huang and H. W. Gibson, *Prog. Polym. Sci.*, 2005, **30**, 982.
- 2005TA2673 M. Colera, A. M. Costero, P. Gavina, and S. Gil, *Tetrahedron Asymmetry*, 2005, **16**, 2673.
- 2005TCC203 F. Aricó, J. D. Badjić, S. J. Cantrill, A. H. Flood, K. C.-F. Leung, Y. Liu, and J. F. Stoddard, *Top. Curr. Chem.*, 2005, **249**, 203.
- 2005TL4331 Y. Nakatsuji, Y. Nakahara, A. Muramatsu, T. Kida, and M. Akashi, *Tetrahedron Lett.*, 2005, **46**, 4331.
- 2006BCC473 Y.-S. Kim, Z. J. He, W. Y. Hsieh, and S. Liu, *Bioconjugate Chem.*, 2006, **17**, 473.

- 2006CC34 D. K. Smith, *Chem. Commun.*, 2006, 34.
2006CC1929 F. Huang, C. Slebodnick, K. A. Switek, and H. W. Gibson, *Chem. Commun.*, 2006, 1929.
2006CEJ2772 S. J. Dalgarno, J. Fisher, and C. L. Raston, *Chem. Eur. J.*, 2006, **12**, 2772.
2006CEJ4594 C.-F. Lin, Y.-H. Liu, C.-C. Lai, S.-M. Peng, and S.-H. Chiu, *Chem. Eur. J.*, 2006, **12**, 4594.
2006CEJ5603 X.-Z. Zhu and C.-F. Chen, *Chem. Eur. J.*, 2006, **12**, 5603.
2006CRV782 G. Wenz, B.-H. Han, and A. Müller, *Chem. Rev.*, 2006, **106**, 782.
2006JA1489 J. D. Badjić, C. M. Ronconi, J. F. Stoddart, V. Balzani, S. Silvi, and A. Credi, *J. Am. Chem. Soc.*, 2006, **128**, 1489.
2006JA9541 A. Cazacu, C. Tong, A. van der Lee, T. M. Fyles, and M. Barboiu, *J. Am. Chem. Soc.*, 2006, **128**, 9541.
2006JA4950 S. C. Magri, G. J. Brown, G. D. McClean, and A. P. de Silva, *J. Am. Chem. Soc.*, 2006, **128**, 4950.
2006JA12229 X. Bao, I. Isaacsohn, A. F. Drew, and D. B. Smithrud, *J. Am. Chem. Soc.*, 2006, **128**, 12229.
2006JOC1233 E. Hao, F. R. Fronczek, and M. H. Vicente, *J. Org. Chem.*, 2006, **71**, 1233.
2006JOC5093 Y. Tachibana, H. Kawasaki, N. Kihara, and T. Takata, *J. Org. Chem.*, 2006, **71**, 5093.
2006NMB419 S. Liu, Z. J. He, W. Y. Hsieh, and Y.-S. Kim, *Nucl. Med. Biol.*, 2006, **33**, 419.
2006OBC667 S. J. Loeb, J. Tiburcio, S. J. Vella, and J. A. Wisner, *Org. Biomol. Chem.*, 2006, **4**, 667.
2006OBC1555 E. Khomich, M. Kashapov, I. Vatsouro, E. Shokova, and V. Kovalev, *Org. Biomol. Chem.*, 2006, **4**, 1555.
2006OL211 Q.-S. Zong and C.-F. Chen, *Org. Lett.*, 2006, **8**, 211.
2006OL1069 T. Han and C.-F. Chen, *Org. Lett.*, 2006, **8**, 1069.
2006OL1859 Q.-S. Zong, C. Zhang, and C.-F. Chen, *Org. Lett.*, 2006, **8**, 1859.
2006OL2119 R. L. Halterman, D. E. Martyn, X. Pan, D. B. Ha, M. Frow, and K. Haessig, *Org. Lett.*, 2006, **8**, 2119.
2006OL2755 J. L. Katz, B. J. Geller, and R. R. Conry, *Org. Lett.*, 2006, **8**, 2755.
2006OL2823 A. E. Lovely and T. J. Wenzel, *Org. Lett.*, 2006, **8**, 2823.
2006OL3009 J. H. Jung, S. J. Lee, J. S. Kim, W. S. Lee, Y. Sakata, and T. Kaneda, *Org. Lett.*, 2006, **8**, 3009.
2006OL3363 T. D. Nguyen, K. C.-F. Leung, M. Liong, C. D. Pentecost, J. F. Stoddart, and J. I. Zink, *Org. Lett.*, 2006, **8**, 3363.
2006OL4161 W. Maes, W. Van Rossom, K. Van Hecke, L. Van Meervelt, and W. Dehaen, *Org. Lett.*, 2006, **8**, 4161.
2006OL5797 K. Tsubaki, D. Tanima, Y. Kuroda, K. Fujii, and T. Kawabata, *Org. Lett.*, 2006, **8**, 5797.
2006OM2225 J. Ohshita, T. Uemura, T. Inoue, K. Hino, and A. Kunai, *Organometallics*, 2006, **25**, 2225.
2006POJ1 T. Takata, *Polymet J.*, 2006, **38**, 1.
2006SMC111 V. Csokai, B. Kulik, and I. Bitter, *Supramol. Chem.*, 2006, **18**, 111.
2006TL4041 H. Konishi, K. Tanaka, Y. Teshima, T. Mita, O. Morikawa, and K. Kobayashi, *Tetrahedron Lett.*, 2006, **47**, 4041.
2007CC1026 J. L. Katz, B. J. Geller, and P. D. Foster, *Chem. Commun.*, 2007, 1026.
2007JA4633 G. Rogez, B. F. Ribera, A. Credi, R. Ballardini, M. T. Gandolfi, V. Balzani, Y. Liu, B. H. Northrop, and J. F. Stoddart, *J. Am. Chem. Soc.*, 2007, **129**, 4633.
2007JA7284 X. Wang, X. Bao, M. McFarland-Mancini, I. Isaacsohn, A. F. Drew, and D. B. Smithrud, *J. Am. Chem. Soc.*, 2007, **129**, 7284.
2007JCD1183 S. Liu, *J. Chem. Soc., Dalton Trans.*, 2007, 1183.
2007JOC3108 T. Han, Q.-S. Zong, and C.-F. Chen, *J. Org. Chem.*, 2007, **72**, 3108.
2007JOC3381 H. W. Gibson, H. Wang, C. Slebodnick, J. Merola, W. S. Kassel, and A. L. Rheingold, *J. Org. Chem.*, 2007, **72**, 3381.
2007JOC3757 H.-B. Yang, D.-X. Wang, Q.-Q. Wang, and M.-X. Wang, *J. Org. Chem.*, 2007, **72**, 3757.
2007JOC3880 C. Zhang and C.-F. Chen, *J. Org. Chem.*, 2007, **72**, 3880.
2007JOC7287 T. Han and C.-F. Chen, *J. Org. Chem.*, 2007, **72**, 7287.
2007NJC1243 S. V. Brignell and D. K. Smith, *New J. Chem.*, 2007, **31**, 1243.
2007OL497 L. Li and G. J. Clarkson, *Org. Lett.*, 2007, **9**, 497.
2007OL675 M. Chas, V. Blanco, C. Peinador, and J. M. Quintela, *Org. Lett.*, 2007, **9**, 675.
2007OL895 X.-X. Peng, H.-Y. Lu, T. Han, and C.-F. Chen, *Org. Lett.*, 2007, **9**, 895.
2007OL2577 Y. Liu, L. M. Klivansky, S. I. Khan, and X. Zhang, *Org. Lett.*, 2007, **9**, 2577.
2007OL2847 Q.-Q. Wang, D.-X. Wang, Q.-Y. Zheng, and M.-X. Wang, *Org. Lett.*, 2007, **9**, 2847.
2007OL4219 C.-S. Zuo, J.-M. Quan, and Y.-D. Wu, *Org. Lett.*, 2007, **9**, 4219.
2007T2829 F. Huang, C. Slebodnick, K. A. Switek, and H. W. Gibson, *Tetrahedron*, 2007, **63**, 2829.
2007T2875 F. Huang, C. Slebodnick, E. J. Mahan, and H. W. Gibson, *Tetrahedron*, 2007, **63**, 2875.
2007T4011 L. Jiao, E. Hao, F. R. Fronczek, K. M. Smith, and M. G. H. Vicente, *Tetrahedron*, 2007, **63**, 4011.
2007TL1859 H. Hama, T. Morozumi, and H. Nakamura, *Tetrahedron Lett.*, 2007, **48**, 1859.
2007TL1977 J. D. Blakemore, R. Chitta, and F. D'Souza, *Tetrahedron Lett.*, 2007, **48**, 1977.
2007TL2797 S. Takashi and T. Takata, *Tetrahedron Lett.*, 2007, **48**, 2797.
2007TL3029 H. Konishi, T. Mita, O. Morikawa, and K. Kobayashi, *Tetrahedron Lett.*, 2007, **48**, 3029.

Biographical Sketch



Sebastiano Pappalardo is a professor of organic chemistry at the University of Catania. With the exception of sabbaticals in 1982 and 1985 as a visiting research scientist at Louisiana State University, working with the group of George R. Newkome, his academic career has mainly evolved at the University of Catania, where he graduated in chemistry in 1970. A central theme of his current research is the design of new synthetic receptors for the molecular recognition of organic salts, and the evaluation of their potential in host–guest and supramolecular chemistry.



Melchiorre F. Parisi graduated in Chemistry at the University of Messina and obtained a Ph.D. in Organic Chemistry from the University of Oxford, under the supervision of Professor Jack E. Baldwin, in 1986. Between 1987 and 1988, he worked as a postdoctoral research fellow with Professor Robert H. Abeles at Brandeis University (CNR-NATO, Advanced Fellowship Program). He currently holds the position of Associate Professor of Organic Chemistry at the University of Messina. His most recent research interests lie in the field of host–guest and supramolecular chemistry.

14.13

Ten-membered Rings or Larger with One or More Sulfur Atoms

H. Eckert

Technical University of Munich, Garching, Germany

M. Koller

Bundeswehr Institute of Pharmacology and Toxicology, Munich, Germany

© 2008 Elsevier Ltd. All rights reserved.

14.13.1	Introduction	752
14.13.2	Theoretical Methods	752
14.13.3	Experimental Structural Methods	753
14.13.3.1	X-Ray Crystallography	753
14.13.3.2	NMR Spectroscopy	754
14.13.3.3	ESR Spectroscopy	755
14.13.3.4	IR Spectroscopy	755
14.13.3.5	UV/Vis Spectroscopy	755
14.13.3.6	Mass Spectrometry	756
14.13.3.7	Cyclovoltammetry	756
14.13.4	Thermodynamic Aspects	756
14.13.5	Reactivity of Fully Conjugated Rings	758
14.13.6	Reactivity of Nonconjugated Rings	758
14.13.6.1	Reactivity of Ring Carbon Atoms	758
14.13.6.2	Reactivity of Ring Sulfur Atoms	759
14.13.7	Reactivity of Substituents Attached to Ring Carbon Atoms	759
14.13.8	Reactivity of Substituents Attached to Ring Sulfur Atoms	759
14.13.9	Ring Syntheses from Acyclic Compounds	775
14.13.9.1	Dithiols and Their Sodium Salts as Starting Material in Thiocrown Formation	788
14.13.9.2	Thioacetamide as Starting Material in Crown Thioether Formation	788
14.13.9.3	Formation of Cyclic Di- and Symmetrical Tetrasulfides by Oxidation of Dithiols	788
14.13.9.3.1	Bromine as oxidizing agent	788
14.13.9.3.2	Cesium fluoride–Celite as catalyst for oxidation by atmospheric oxygen	789
14.13.9.4	Template Synthesis: Preparation of Thialactones	789
14.13.9.5	Preparation of a Cyclic Heptasulfane Using Titanocene Pentasulfide as Sulfur-Donating Compound	790
14.13.10	Ring Syntheses by Transformation of Another Ring	790
14.13.10.1	Ring Extension	790
14.13.10.1.1	Thiirane as starting ring system	790
14.13.10.1.2	Thietane as starting ring system	791
14.13.10.1.3	Insertion of α -phosphorylcarbene moiety into a disulfide bond	792
14.13.10.2	Ring Contraction	793
14.13.11	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	793
14.13.11.1	Thiacrowns	793
14.13.11.2	Thiacrown-Derivatized TTFs	793

14.13.12 Important Compounds and Applications	795
14.13.12.1 Metal-Selective Electrodes	795
14.13.12.2 Thiacrown-Assisted Metal Transfer	795
14.13.12.3 Polymer-Bound Thiacrowns for Extraction of Heavy Metals from Wastewaters	795
14.13.12.4 Thiacrowns and Their Metal Complexes Applied in Catalysis	796
14.13.12.5 Application of Thiacrowns and Their Metal Complexes in Cancer Therapy	796
14.13.13 Further Developments	796
References	797

14.13.1 Introduction

This chapter should be seen as continuation of Chapter 9.30 of CHEC-II(1996). Especially, its table 2 collecting the syntheses of the sulfur macrocycles has only been slightly modified and filled with the current data. In principle, nomenclature, stereochemical aspects, and specific reactions of the sulfur macrocycles are more or less the same as previously discussed in the former edition. Thus, only new and/or unusual sulfur ring systems (see Figure 1), synthetic routes, and further findings are described herein, meaning that for the basics CHEC-II(1996) should also be considered. On the other hand, plenty of papers have been published over the past decade dealing with chemistry, structure, and applications of homo- and/or heteroleptic metal complexes containing sulfur macrocycles, as ligands. Regarding the pure number of papers, this seems to be of special interest and we decided to present a summarizing table of the complexes found in the literature together with the appropriate references.

14.13.2 Theoretical Methods

Molecular mechanics (MMX) are used to calculate the lowest energy conformers (the global minimum) of diverse sulfur macrocycles <1998JOC181, 1995IC5410, 1997JCD1889, 2001ICA(317)91, 1999JOM(587)207, 2000PCA652, 2004JMM55, 2001PCA11266>. The lowest-energy structures of 10S3, for example, do not exhibit completely endodentate orientation of the sulfur atoms meaning that endodentate complexation of transition metals with 10S3 requires higher energies than for complex formation with 9S3 where all three sulfur atoms are endodentate in the lowest-energy conformers <1999JOM(587)207>. In 2,5,8-trithia[9]-*m*-cyclophane (= 2,5,8-trithia[9]-*m*-benzenophane) (Figure 3), all three sulfur atoms appear to be exclusively exodentate in the solid state as supported by ¹H nuclear magnetic resonance (NMR) results, but a molecular dynamics calculation in the gas phase provides data for the completely endodentate orientation, which is very close in energy to the exodentate conformer <1995IC5410>.

A detailed discussion of the different programs for calculation in molecular modeling is presented by Gloe and co-workers <1999JPR202>, while Jagannadh *et al.* compared the results for relative conformational energies of 9S3 released by different calculating programs <2004JMM55>. Further data obtained for the conformers of 12S4 and 15S5 are listed by Hill and Feller <2000PCA652> and for 12S4 and 14S4 by Bultinck *et al.* <2001PCA11266>, respectively. In the latter work, the 36 lowest energy structures of 14S4 are theoretically examined. In some other cases, the calculated values are compared with the experimental data provided by X-ray crystallography, for example, where relatively good correlations are found <1999JPR202, 1998JOC181>.

Further theoretical studies consider the interactions between sulfur macrocycles and metals centered within the rings. Force-field calculations show that the ligand field strength of the macrocycles (compared for one metal) is depending on ring size and follows the order: 9S3 > 10S3 > 11S3-1,4,7 and 11S3-1,4,8 > 12S3 <2001ICA(317)91>. Hambley has examined bonding in Pt- and Pd-complexes using the van der Waals radii of Pt(II) and Pd(II), as parameters in molecular mechanics and additionally considering nonbonding parameters for Pt. Hereby, the results obtained for the Pt...S distances correlate much better with the experimental data than in other model calculations and show that the attraction between Pt and S is very weak <1998IC3767>.

Blower *et al.* have used extended Hückel theory (EHT) to find an explanation for the spontaneous C–S bond cleavage in 9S3 complexes of Re and Tc with loss of ethene, while the analogous complexes of higher transition metals become more and more stable <1999JCD3759>.

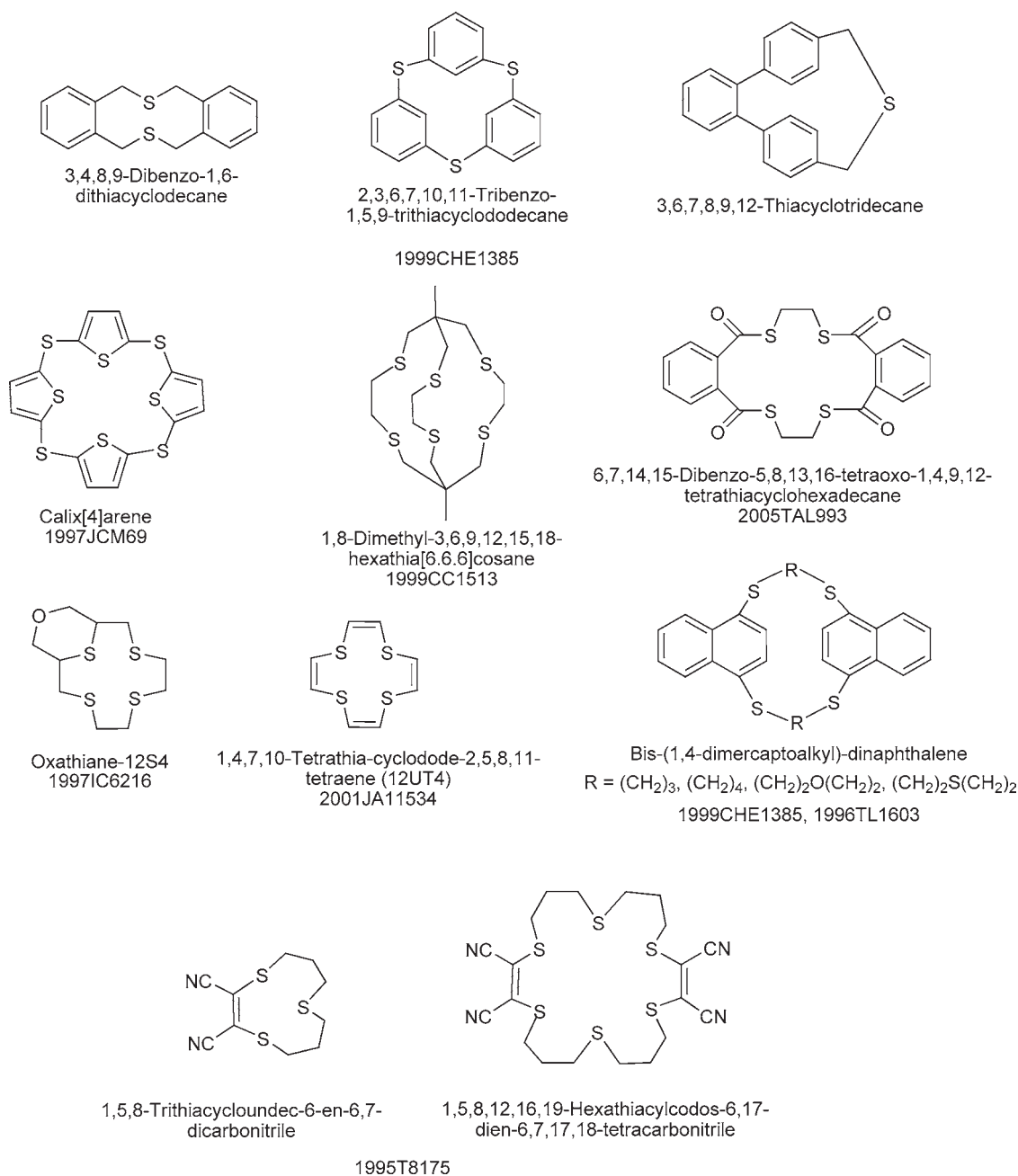


Figure 1 Structure and nomenclature of new sulfur macrocycles.

14.13.3 Experimental Structural Methods

14.13.3.1 X-Ray Crystallography

X-Ray crystallography is one of the most important tools for structural analysis in complex chemistry. Therefore, X-ray data for thiacycrown metal complexes are provided by nearly all references listed in [Table 1](#) and will not be further discussed here.

In the preceding edition CHEC-II(1996), typical bond lengths and angles in ‘pure’ sulfur rings are listed in Table 1, for basic structural information. During the past decade, only X-ray structures of special ring systems have been published: substituted rings including isomeric forms of Me₃-12S3 <1996OM2489> and especially the *R,R,R*-isomer of Me₃-12S3 <2000JOM(596)115>, Me₆-12S3, Me₈-16S4, and Me₁₀-20S5 <1997OM2612>, Cl₂-14S4 and 12S4-(CH₂SCH₃)₂ <1997JOC8459>, nitrile-substituted thiacyclobutanes (Figure 1) <1995T8175>, tetrabenzocyclo-18S6 <1999T10057>, Me-12S3-acid <1998HAC123>, diadamantyl-16S6 <2003AXCo314>, and 19S6-TTF (TTF = tetrathiafulvalene; Figure 4) <1999CC1417>, further carbonyl-containing systems such as 16S4-tetrone and 24S6-hexone <1996JA9442>, unsaturated systems <2001JA11534>, and finally a disulfide <1997OM1430>.

Interestingly, the methyl substitution in Me₃-12S3 leads to a loss of the exact square-like ring form compared to unsubstituted 12S3 where every edge is formed by four atoms; however, in Me₃-12S3, only two edges are formed by four atoms and the other two edges by three and five atoms, respectively. The methyl groups point to the outside of the ring, while the methylene groups are directed to the inside. These effects are responsible for the conformation of this ring system <2000JOM(596)115>. Comparing diadamantyl-16S6, where a spiro ring system is formed by connecting the thioacetal units with adamantanes, and ‘pure’ 16S6, again a structural change caused by the adamantanes can be observed. While 16S6 shows two crystallographically independent half molecules located around crystallographic inversion centers yielding a *C_i* symmetry, the substitution at the thioacetal units causes a square-like ring with *C₁* symmetry, where the four S-atoms belonging to the thioacetal units are endodentate, while the two other S-atoms are exodentate <2003AXCo314>.

In the case of geminal disubstitution, for example, in Me-12S3-acid, no structural changes are observed. X-Ray crystallography of Me-12S3-acid exhibits the same basic ring form as in unsubstituted 12S3 or 12S3-OH. Its geminal substituents are positioned in one ‘corner’ of the square-like ring structure to minimize transannular steric repulsion <1998HAC123>.

In the unsaturated system 18UT6 (as well as in 21UT7, 24UT8, and 27UT9), all sulfur atoms are oriented toward the inside of the ring while in the corresponding saturated 18S6 only four S-atoms show endodentate orientation. The C–S bond lengths as well as the intramolecular distances across the cavity are shorter than in the corresponding saturated rings meaning that the cavities are smaller in unsaturated thiacyclobutanes <2001JA11534>.

14.13.3.2 NMR Spectroscopy

The ¹H and ¹³C NMR studies are more or less obligatory in structural analysis after the synthesis of new ring systems; the data are provided by the references listed in Table 2. Especially in those cases where a larger ring is formed beside the smaller system and where a separation of the compounds is impossible, ¹H and ¹³C NMR can be used to determine the ratio of the products <1995OM4594, 2001ICC671>.

Regarding the small unsaturated rings 1,4-dithiin, 9UT3, 12UT4, and 15UT5, a shift to the lower field is observed in ¹H and ¹³C NMR when ring size is increasing. In contrast, an upfield shift occurs for the larger macrocycles 18UT6, 21UT7, 24UT8, and 27UT9 with increasing ring size. This fact is explained by the authors as due to increasing electron density at the olefin moiety, which is increasing with ring size for the larger systems and increasing with decreasing ring size for the smaller rings <2001JA11534>.

Examining metal complexes, special nuclei NMR is additionally used: ¹⁹⁵Pt <2006JCX83, 2003JCD3981, 2005EJI479, 2001JOM(637)683, 2001POL3333, 1996JCD2979, 2002POL879>, ¹¹³Cd <2006JCD3534, 2002ICA(338)182>, ¹⁹⁹Hg <2003JCX623, 2005IC5696>, ⁵⁹Co <1998ICA(274)192>, ⁵⁵Mn <1999JCD2343>, and ¹¹B in the complex anion BPh₄[−] <1996JCD4003>. In case of ¹⁹⁹Hg, the signal is significantly shifted downfield when the ring size of the ligand is increasing (9S3: −275 ppm; 10S3: −598 ppm), whereas it is shifted upfield when the number of S-atoms is growing within the ring (12S3: −795 ppm; 12S4: −718 ppm) <2005IC5696>. A similar effect can be observed for ⁵⁵Mn <1999JCD2343>, ⁵⁹Co <1998ICA(274)192>, ¹¹³Cd <2006JCD3534>, and ¹⁹⁵Pt <2001POL3333>. An interesting aspect of analyzing the shift of ¹⁹⁵Pt signals is the orientation of the lone electron pairs at the sulfur atoms of tetrathiacrown complexes. While all electron pairs belonging to the four sulfur atoms in 12S4 and 14S4 point to the same side, the lone pairs in 16S4 are directed oppositely (e.g., two up, two down), which results in a shift of 400 ppm <2001POL3333, 1996JCD2979>. Furthermore, the oxidation from Pt(II) to Pt(IV) is also indicated by a signal shift, which is measured in ¹⁹⁵Pt NMR at 1200–1600 ppm for the dichloride complexes and 650–900 ppm for the dibromide complexes, respectively <1996JCD2979>.

The ¹³C NMR of 9S3 shows a shift for the α-C-atom after complexation with platinum compared to the spectrum of the free ring, which is interpreted as being caused by increasing ring strain during complexation <2006JCD3534>.

In heteroleptic complexes, the ^{13}C NMR spectrum of the ring atoms shows two peaks when a chiral co-ligand is bound together with a thiacrown. When the other ligand is achiral, only one peak is observed <2003JCD3981>.

Further NMR studies are performed to examine kinetic effects as the exchange of ligands <1995IC5410>, solvolysis <1995TMC583>, complex formation, and decomposition within 140 min ($\text{HgCl}_2 + 18\text{UT6}$) <2003JOC3480>, dynamic behavior of complexes at different temperatures <1995OM3704, 1995IC6319>, and titration of thiacrowns with silver ions <1999CC1417>.

14.13.3.3 ESR Spectroscopy

Electron spin resonance (ESR) spectroscopy is applied in structural analysis when compounds with unpaired electrons (radicals) have to be examined. Since there are hints of ring-opening reactions of thiacrowns caused by γ -rays of radioactive metals chelated by thiacrowns, an ESR study has been performed to see the extent of this effect. During radiolytic ring opening of 18S6 by H-atom abstraction and C–S bond dissociation, radicals are formed that have been monitored and confirmed by ESR <1998JRNC39>.

Regarding thiacrown–metal complexes, ESR can help distinguishing high- and low-spin complexes. In the case of $[\text{Co}(20\text{S6})](\text{ClO}_4)_2$, the ESR pattern refers to a low-spin complex while replacing two sulfur atoms by oxygen atoms (20S4O2) makes a high-spin complex <1995JC1023>.

By applying ESR spectroscopy, Kirmse and co-workers proved the existence of unusual oxidation states, as Au(II) and Ag(II) were stabilized by different thiacrowns <2002ZFA34, 2004ZFA2669>.

14.13.3.4 IR Spectroscopy

Infrared (IR) spectroscopy is routinely used in characterization of synthetic products and the key data are listed in those papers dealing with sulfur ring syntheses (Table 2). No special applications of IR spectroscopy have been found in the present literature.

14.13.3.5 UV/Vis Spectroscopy

Ultraviolet/visible (UV/Vis) spectroscopy is often applied to follow the progress of reactions such as the complex formation with Ni <1999IC5906> or iodine <2000JPM277>, the four-electron oxidation of $[\text{Au}_2(28\text{S8})]^{2+}$ to $[\text{Au}_2(28\text{S8})]^{6+}$ <1998JCD2931>, or a ligand reaction in a heteroleptic 9S3 complex of Ru(II) <2004EJI612>. Further UV/Vis studies have been undertaken to characterize the redox behavior of the Ru(II)/Ru(III) couple in 9S3 complexes where cyclovoltammetry (CV) failed to explain the possible oxidation process. Theoretically, two forms of oxidation could occur with NaOCl at pH 2.5: formation of a μ -oxo species or the oxidation of the 9S3 ligand to the corresponding sulfoxide. As no Ru–O–Ru band can be observed in the UV/Vis spectrum, the latter possibility – the oxidation of the sulfur macrocycle – becomes evident <2004EJI612>.

The UV/Vis spectra of Cu(II) with tetrathiaethers show two charge-transfer bands near 400 nm and around 600 nm. Interestingly, the shift of the 400 nm peak to higher wavelengths is obviously corresponding to the ring size of the ligand (12S4–16S4), while no such trend can be seen for the 600 nm band <1997IC6216>. Regarding free sulfur rings, the wavelength is also shifted to higher levels when the ring size is increasing in unsaturated macrocycles <2001JA11534> or when the number of S-atoms is growing within the ring system <1992PS151>.

Grant *et al.* found a correlation between complex geometry and visible absorption in Pd- and Pt-complexes; thus the complexes with 9S3 and 10S3 are intensely colored (blue-green and orange for Pd and Pt, respectively) and show absorptions at about 610 nm (Pd) or 430 nm (Pt); the corresponding compounds with 18S6 and 20S6 are yellow or colorless and do not show any absorption bands. This effect seems to be due to the interactions of the metal center with the axial S-atoms; only for the complexes of 9S3 and 10S3, the axial S–M distances lie within 3.11 Å, which seems to be the longest distance where excitement by visible light is still possible. Consequently, the missing of the absorption lines in 18S6 and 20S6 complexes shows that the axial S–M interactions are extremely weak or do not exist <1996ICA(246)31>.

14.13.3.6 Mass Spectrometry

Besides NMR spectroscopy, mass spectrometry (MS) has become a useful tool in characterizing synthetic products. Especially in sulfur ring synthesis, where in most cases a mixture of monomers, dimers, and oligomers is formed, MS can help to distinguish between these products by providing the exact molecular masses <2003PS1295, 2004JOC8550, 1995CJC1023>, while NMR may not be able to resolve those mixtures.

Owing to the stormy development of mass spectrometers connected to electrospray ion (ESI) sources during the last 15 years, it is now possible to directly examine 9S3 complexes of Ru and Tc concerning the breaking of C–S bonds, which causes a loss of ethene. This effect has been measured by applying different cone voltages to the compounds passing the ESI source during their introduction to the MS instrument and comparing the resulting mass spectra. The Ru complex is significantly more stable than the corresponding Tc complex. Extending this test method to Re and Os, an obvious trend is seen. While the ethene loss of the Re^+ and Tc^+ complexes is nearly complete at 10 V, Re^{2+} , Tc^{2+} , Os^{2+} , and Ru^{2+} complexes remain intact. When a cone voltage of 30 V is applied, 20% of Re^{2+} –, 50% of Tc^{2+} –, 70% of Os^{2+} –, and 90% of Ru^{2+} –9S3 complex remain unreacted <1999JCD3759>. An earlier work shows that the corresponding Fe-complex is the most stable in this context <2002ICC832>.

Brodbeck and co-workers have applied the ESI-MS technique to determine the chelating selectivity of thiacycrows with a selection of heavy metals, for example, Cu, Zn, Cd, Hg, and Pb, where there is a high selectivity for Hg <2002ANC4423>.

14.13.3.7 Cyclovoltammetry

CV is the method of choice for the determination of redox potentials of sulfur rings or their metal complexes. Only few works have been performed on free sulfur rings, as the authors of CHEC-II(1996) have already noted, while considerable knowledge about the redox behavior of the complexes has been collected which may be dependent on ring size <1996ICA(244)73> or complex geometry <1996ICA(246)31> or is not influenced by the ligands <2005JOM(690)629>.

The copper(II)/(I) redox system is extremely well examined in which Rorabacher and co-workers have published numerous papers over the past decade. They extensively investigated its electron-transfer kinetics influenced by different substitution of 14S4 rings <1997IC4484, 1997IC4475, 1995IC1954, 1997IC3253, 1999IC4322, 1995IC6053, 2000IC2897, 2003JCD1577, 1995IC357, 2001JA5720>. Finally, the redox potentials belonging to this system are summarized in a recent review article <2004CRV651>.

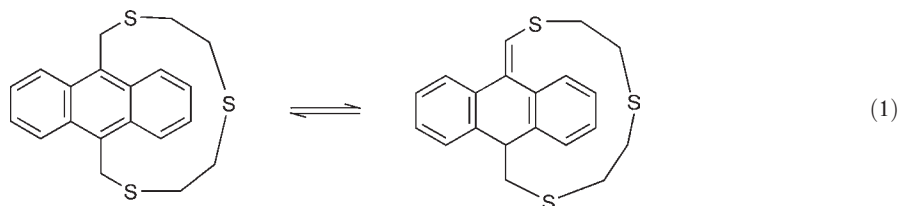
Kamigata and co-workers have examined the redox behavior of unsaturated thiacycrows (15UT5–27UT9) and found irreversible oxidation peaks at +0.79, +0.77, +0.75, +0.60, and +0.55 V, respectively. This trend indicates that the larger rings are more easily oxidized than the smaller cycles. The corresponding CV of 18S6 shows an irreversible peak at +1.05 V meaning that the saturated system is notably more stable than the unsaturated macrocycle <2002JOC6632, 2001JA11534>. Interestingly, when HgCl_2 is chelated by 18S6, the CV shows a reversible wave for the redox couple of $\text{Hg(II)}/(\text{I})$ at -0.43 V and an irreversible reduction wave from Hg(I) to Hg(0) at -0.72 V. In contrast, the CV of the corresponding 18UT6 complex does not show any peaks. Neither oxidation of the macrocycle nor reduction of HgCl_2 occurs, obviously due to the different electronic environment provided by the unsaturated macrocycle <2003JOC3480>.

When a quasi-planar TTF is bridged by a thiacycrown (e.g., 19S6–TTF, Figure 4) the voltammogram presents two one-electron processes whose potentials are similar to the values of the parent TTF structure (0.59 and 0.89 V) meaning that the redox behavior is mainly controlled by the TTF moiety. Still, comparing the titration of three TTF-thiacycrows (a = 19S6–TTF, b = 23S7–TTF, c = 21S7–TTF) with Ag^+ , only one compound (c) shows a positive shift of the first oxidation potential during CV indicating a higher complexation capacity for Ag^+ . Furthermore, repeating this experiment with other metal cations such as Na^+ , K^+ , Cs^+ , Mg^{2+} , Ba^{2+} , Ni^{2+} , Zn^{2+} , Cd^{2+} , and Cr^{3+} , the above-mentioned shift is not observed illustrating the selectivity for Ag^+ of compound c <1999CC1417, 2000CSR153>.

14.13.4 Thermodynamic Aspects

The influence of ring size and structure over the melting points of thiamacrocycles has been reflected by the authors of CHEC-II(1996) and is not discussed herein. The melting points of the newly synthesized ring systems are listed in Table 2 as far as they are available from the original references.

An interesting thermodynamic aspect is the tautomerism of a trithianonyl-bridged anthracene (see Equation 1) <1999CHE1385>. The tautomerism of substituted anthracene as, say, 9-methylantracene is well known and has been energetically analyzed. The energy difference between the 9-methylantracene and the second tautomeric form 9-methylenedihydroanthracene (MDA) has been determined to be 40 kcal mol⁻¹. As there is further knowledge about other substituted anthracenes, where the MDA tautomer is more stable than the anthracene itself, Rosenfeld and co-workers have examined the trithianonyl-bridged anthracene <1998JOC181>. In this case, the lowest-energy conformer of the anthracene tautomer has been calculated with 65.73 kcal mol⁻¹ and the second with 66.96 kcal mol⁻¹. For the MDA tautomer, the five lowest-energy conformers have been found with 65.37, 65.90, 65.91, 66.12, and 68.07 kcal mol⁻¹, respectively. Although both tautomers presented in Equation (1) are very close in their energies, the NMR data support only the anthracene structure.



Regarding the thermodynamics of the sulfur macrocycles' complex chemistry, two main aspects shall be discussed here: (1) the influence of the metallic center over the complex stability and (2) the macrocyclic effect. Shamsipur and co-workers have examined the influence of seven different cations which are chelated 1:1 with 18S6-tetraone. Comparing the resulting complex stabilities, they found the following order: Zn²⁺ < Co²⁺ < Ni²⁺ < Cu²⁺ < Cd²⁺ < Pb²⁺ < Hg²⁺. From this order, it is clear that the ionic radius is contributing greatly to complex stability. The better the match of ionic radius with cavity size formed by 18S6-tetraone, the more stable is the complex. But comparing Pb²⁺ and Hg²⁺, which have the same ionic radius, it is obvious that the ionic radius is not the only factor influencing the complex stability. As a main group element Pb²⁺ has a somewhat harder acidic character than Hg²⁺, thus being responsible for its weaker interactions with the sulfur ring <1998JCF1959>.

Considering the influence of the sulfur macrocycles over complex stability, the so-called 'macrocyclic effect' is worth mentioning. This term is well known and is used to describe the fact that complexes with macrocyclic ligands are thermodynamically more stable than those formed by their open-chain analogues <2003AXCo314>. As it has been suggested that the enhanced stability might be mainly due to a slower solvolysis, Durrant *et al.* have investigated the solvolysis of three molybdenum thioether complexes [Mo(CO)₃(L)] with dimethyl sulfoxide (DMSO) at 35 °C, where L = 9S3, ttob (TT[9]OB, see Figure 3), and ttn = 2,5,8-trithianonane. In fact, they found an enormous difference between the half-life times of the macrocyclic complexes and the open-chain complex: 62 and 13 days for 9S3 and ttob, respectively, but only less than 12 s for the ttn complex <1995TMC583>.

In the case of thiaethers, the macrocyclic effect is smaller than that of cyclic amines, for example. In contrast to the N-atoms, which exhibit an endodentate orientation, the S-atoms tend to orient themselves in an exodentate manner. Thus, for complex formation, the S-atoms have to change their orientation to make interaction with the metallic center possible. And this means an unfavorable entropic effect, which reduces the macrocyclic effect <2006IC923>. In conclusion, substituents on the ring system, which are able to direct the S-atoms into an endodentate orientation – a fact that can be considered as preorganization <1997JCD1889> – should provide complexes with higher stability constants because the negative entropy contribution is missing. In fact, this was already confirmed in 1990 by Desper and Gellman for *gem*-dimethylated 14S4 rings in Ni(II) complexes <1990JA6732>.

Rorabacher and co-workers, who have performed numerous studies of substituted 14S4 rings, have determined the stability constants of Cu(II) and Cu(I) complexes formed with cyclopentyl- and cyclohexylsubstituted 14S4 ligands and found mixed results. The stability increases 10-fold for each *cis*-cyclopentyl substitution and 30-fold for each *cis*-cyclohexyl moiety. In both cases, the stability decreases threefold for *anti-cis,cis* compared to *syn-cis,cis*. Regarding the *trans*-substitution, stability decreases 10-fold for the cyclopentyl moieties and increases 30-fold for the cyclohexyl units, meaning that a doubly *trans*-cyclopentyl-substituted 14S4-Cu(II) complex is 10⁵-fold less stable than its homologue, because the rigid cyclopentyl moiety seems to push the S-atoms into an unfavorable position within the ring system. Concerning the Cu(I) complexes, these effects are less pronounced with one exception; the *meso-trans,trans*-cyclopentyl-substituted ligand provides a 200-fold less stable complex than the nonsubstituted 14S4 <2006IC923>.

14.13.5 Reactivity of Fully Conjugated Rings

There are few conjugated sulfur ring systems beyond those discussed in CHEC-II(1996). In their review article <1999CHE1385>, Litvinova and Anisimov present a family of macrocycles consisting of three to eight benzene rings bridged by three to eight sulfur atoms, which are shown in Figure 2 together with a tetrabenzotetra-18S6 containing two olefinic moieties synthesized by Nakayama *et al.* <1999T10057>. Unfortunately, no additional information except their synthetic path is given. The more interesting conjugated systems were synthesized in 2001 <2001JA11534>: the unsaturated thiacyclics, which are abbreviated by the authors as 9UT3, 12UT4, etc., in analogy to the saturated compounds 9S3, 12S4 (see Figures 1 and 2). Again, little is presented about their reactivity except that they are more easily oxidized (see also Section 14.13.3.7) and the 'UTs' form a smaller cavity than the corresponding saturated rings and thus show a slightly different selectivity in metal chelating chemistry.

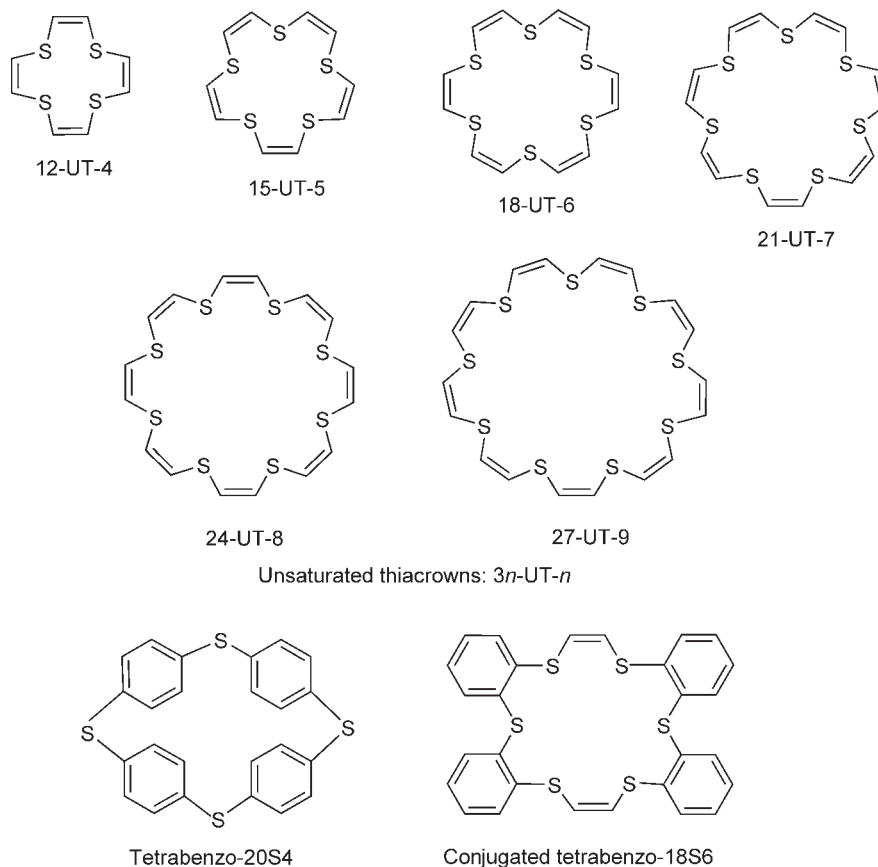
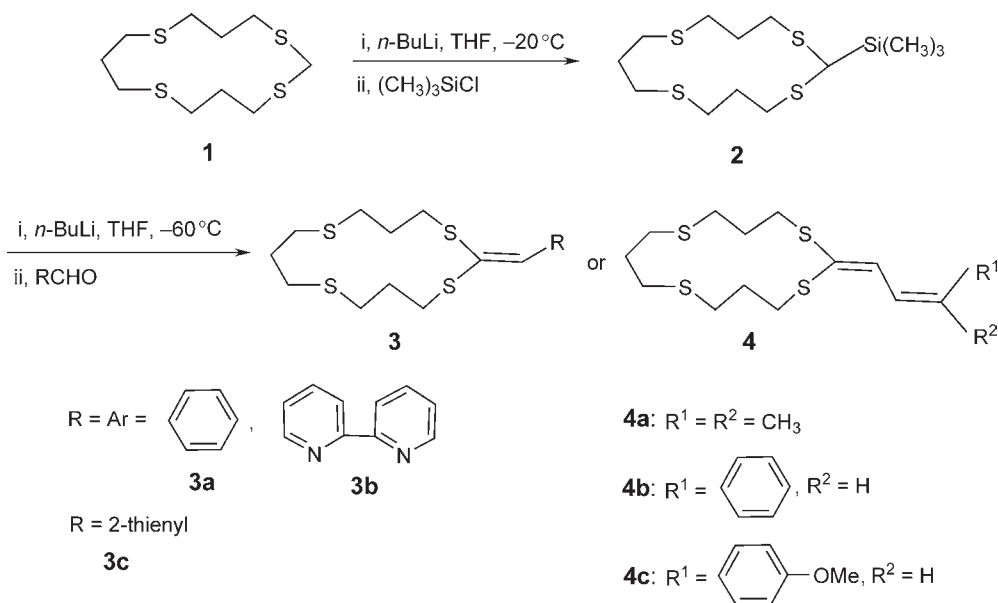


Figure 2 Conjugated sulfur macrocycles.

14.13.6 Reactivity of Nonconjugated Rings

14.13.6.1 Reactivity of Ring Carbon Atoms

Thiacyclics can be functionalized by using the respectively functionalized educt, for example, by a hydroxy group <2006POL599, 1998CC1637, 1996IC3420, 1998HAC123>, a keto carbonyl or an ether moiety <1999CHE1385>, or by using a phthalate for the preparation of a thialactone <2005TAL993>. In contrast, the direct functionalization of the ring seems to be limited to the transformation of dithioacetals. As the authors of CHEC-II(1996) have already outlined, the methylene unit within a dithioacetal is easily deprotonated by butyllithium. This initiating step has been applied by Kellogg and co-workers to introduce olefinic substituents **3a-c** and **4a-c** via silylation of **2** <1998TL6357>. As presented in Scheme 1, a number of different compounds have been synthesized this way.



Scheme 1

14.13.6.2 Reactivity of Ring Sulfur Atoms

The thiacrowns' reactivity – regarded as a whole – is mainly guided by the soft nucleophilic character of the sulfur atoms. Their property as soft electron-donating compounds makes them especially suitable for the complexation of transition metals, while their 'hard' oxygen analogues prefer the 'hard' metals of the first and second main group. Therefore, syntheses, X-ray crystallographic structures, as well as physical and chemical properties of diverse homoleptic and heteroleptic complexes with thiacrown ligands have been published and are summarized in [Table 1](#). Since 9S3 has special chelating properties [<1999JPR202>](#), the 9S3 complexes are also included in [Table 1](#). The structures of unusual sulfur ring ligands found in [Table 1](#) are presented in [Figure 3](#).

14.13.7 Reactivity of Substituents Attached to Ring Carbon Atoms

One of the most encountered substituents to thiacrowns is the hydroxy function because it can be esterified with anthracene-9-carbonyl chloride to produce a fluorescent chemosensor for copper(II) [<1997ICA\(257\)69>](#) and it is very suitable for an exchange against other functional groups. Comba *et al.* reacted 14S4-OH with CCl_4 to create 14S4-Cl, which then can be heated to 153°C to give a 13S4- CH_2Cl ring (see also [Section 14.13.10.2](#)) [<1997JOC8459>](#). Baumann *et al.* used the hydroxy group to connect 14S4 or 17S5 rings to a polymeric backbone of polystyrene to enhance the extraction of Hg^{2+} from aqueous solutions, for example, wastewater [<1998CC1637, 2000RFP111>](#). Starting from a hydroxy moiety, it is exchanged with chloride which is then reacted to a secondary amine. Finally, the resulting methyl amine is reacted with a vinylbenzyl unit that is then connected to polystyrene [<1998CC1637>](#).

A somewhat simpler way to an Hg^{2+} and Ag^+ extracting polymer was suggested by Tsuda and co-workers; starting from hydroxy-14S4 (or hydroxy-20S6), they added 4-chloromethylstyrene to generate an ether, which is then polymerized [<1996RFP47>](#). The resulting polymer can be directly used to extract heavy metals.

Another interesting thiacrown functionalization is the introduction of a maleonitrile moiety by direct reaction of disodium dithiomaleonitrile with a ditosylate [<1995T8175>](#). This dinitrile can then be used together with dibutyl-substituted benzodinitrile to prepare a monothiacrown norphthalocyanine [<2000T7371>](#).

14.13.8 Reactivity of Substituents Attached to Ring Sulfur Atoms

Since there are no examples found for the substitution at the sulfur atoms in the present literature, except the articles about the metal complexes collected in [Table 1](#), further discussion is omitted.

Table 1 Metal complexes of sulfur macrocycles in order of the metal's position within the periodic system of the elements (PSE) and further according to ring size; notification of the complexes is taken from the original references

<i>Metal</i>	<i>Complex</i>	<i>Remarks</i>	<i>References</i>
<i>Main group elements</i>			
Al	[AlMe ₃ (12S4)]		1998JCD3961
	[AlMe ₃ (14S4)]		1998JCD3961
Tl	[Tl(9S3)](PF ₆)		1998JCD3961
	[Tl(18S6)](PF ₆)		1998JCD3961
	[Tl(24S8)](PF ₆)		1998JCD3961
Sn	[SnCl ₃ (9S3)] ₂ (SnCl ₆)		2004ICA(357)2115
	[(SnCl ₃) ₃ (9S3)] ₂		1998JCD3961
	[SnCl ₄) ₂ (18S6)]·CH ₃ CN		1998JCD3961
Pb	[Pb(9S3)(H ₂ O)](ClO ₄) ₂		2003JCX445
	[Pb(9S3) ₂ (OCIO ₃) ₂], [Pb(9S3) ₂ (ClO ₄) ₂]		1998JCD3961, 2003JCX445
	[Pb(10S3)(H ₂ O)](ClO ₄) ₂		2003JCX445
	[Pb ₂ (24S8)](ClO ₄) ₄		1998JCD3961
	[Pb ₂ (28S8)](ClO ₄) ₄		1998JCD3961
Sb	[SbCl ₃ (9S3)]		1998JCD3961
	[SbCl ₃ (9S3)] _∞		2000IC1035
	[SbCl ₃ (18S6)]		1998JCD3961
Bi	[BiCl ₃ (12S4)]		1998JCD3961
	[BiCl ₃ (15S5)]·0.5CH ₃ CN		1998JCD3961
	[(BiCl ₃) ₂ (24S8)]		1998JCD3961
<i>Transition metals</i>			
Sc		No complexes found	
Y		No complexes found	
La	[La-fullerene(UT15S5)]	Host–guest complex (1:1)	2006CC3585
	[La-fullerene(UT18S6)]	Host–guest complex (1:1)	2006CC3585
	[La-fullerene(UT21S7)]	Host–guest complex (1:1)	2006CC3585
	[La-fullerene(UT24S8)]	Host–guest complex (1:1)	2006CC3585
Ti	[Ti(NBu ^t)(9S3)Cl ₂], <i>fac</i> -[Ti(NBu)Cl ₂ (9S3)]		1998CC1007, 2004ICA(357)2115
	<i>fac</i> -[TiOCl ₂ (9S3)]		2004ICA(357)2115
	[TiCl ₃ (9S3)](SbCl ₆)		2004ICA(357)2115
	[TiX ₃ (9S3)]X	X = Cl, Br, I	2004ICA(357)2115
	[TiX ₃ (10S3)]X	X = Cl, Br, I	2004ICA(357)2115
		Six-coordinate cationic complexes	
Zr	[ZrCl ₄ (9S3)]	Seven-coordinate neutral complex; sensitive to hydrolysis	2002JCD3153, 2004ICA(357)2115
	[ZrCl ₄ (10S3)]		2004ICA(357)2115
Hf	[HfCl ₄ (9S3)]	Seven-coordinate neutral complex; sensitive to hydrolysis	2004ICA(357)2115

V	[V(9S3)Cl ₃], [VCl ₃ (9S3)]	X = Cl, Br, I	1995ICA(234)35, 1997JCD1639
	[VX ₃ (9S3)]		1998JCD2191
	[VO(9S3)Cl ₂], [VOCl ₂ (9S3)], [VCl ₂ O(9S3)]		1995IC396, 1995ICA(234)35, 1998JCD2191
	[VI ₂ (THF)(9S3)]		1998JCD2191
	[V(10S3)Cl ₃]		1995ICA(234)35
	[VX ₃ (10S3)]		1998JCD2191
	[{VCl ₂ [μ-η ¹ :η ³ -16S4]}] _n]Cl _n		1998JCD2191
	[(VX ₃) ₂ (μ-18S6)]		1998JCD2191
	[NbCl ₅) ₂ (14S4)]		2001AXC36
Nb		No tantal complexes found	
Ta			
Cr	[Cr(9S3) ₂] ²⁺	Reaction of CrCl ₃ with 12S3, 14S4, 15S5, 16S4, and 24S6 produced highly sensitive complexes which were only stable enough for a short-term spectroscopic identification	1999JCD3759
	[Cr(9S3) ₂] ³⁺		1995IC396
	[Cr(9S3)Cl ₃]		1995ICA(234)35
	[CrX ₃ (9S3)]		1995IC396, 1997JCD1639
	[Cr(CO) ₃ (9S3)]		1995TMC583
	[Cr(9S3)(triflate) ₃]		1995ICA(234)35
	[Cr(10S3)Cl ₃]		1995ICA(234)35
	[CrX ₃ (10S3)]		1997JCD1639
	[Cr(11S3)Cl ₃]		1995ICA(234)35
Mo	[CrCl ₂ (14S4)](PF ₆)	X = Cl, Br, I, and A ⁻ = PF ₆ ; X = I and A ⁻ = BF ₄	1995IC396
	<i>cis</i> -[CrX ₂ (14S4)](A ⁻)		1997JCD1639
	<i>cis</i> -[CrCl ₂ (14S4)] ⁺		1996JCD2979
	[CrX ₂ (16S4)](A)		1997JCD1639
	[Cr(18S6)Cl ₃]		1995ICA(234)35
	[(CrX ₃) ₂ (μ-18S6)]		1997JCD1639
	[Cr(bzo ₂ -18S6)(CO) ₃]		1995ICA(234)35
	[Cr(20S6)Cl ₃]		1995ICA(234)35
	[Mo(9S3) ₂] ²⁺		1999JCD3759
	[MoCl ₃ (9S3)]		1995TMC583, 1997JCD1639
	[Mo(CO) ₃ (9S3)]	ttob = 2,5,8-trithia-[9]- <i>o</i> -benzenophane (Figure 3) ttob = 2,5,8-trithia-[9]- <i>o</i> -benzenophane (Figure 3)	1995TMC583, 2002ICC832
	[Mo(CO) ₃ (ttob)]		1995TMC583
	[MoCl ₃ (ttob)]		1995TMC583
	[MoBr ₂ (CO) ₂ (ttob)]		1995TMC583
	[MoI(CO) ₃ (9S3)](A)		1996JCD4003
	[MoI(CO) ₂ (PPh ₃)(9S3)][MoI ₃ (CO) ₄]		1996JCD4003
	[Mo(10S3)(CO) ₃]		1999JOM(587)207, 2003IC96
	[Mo(CO) ₃ (TT[9]OB)]		1990IC4084, 1991IC4644
	[Mo ₂ I ₄ (CO) ₆ -(μ[12S4-S,S',S'',S'''])]		1997JCD509
	[Mo ₂ I ₄ (CO) ₆ -(μ[14S4-S,S',S'',S'''])]		1997JCD509

(Continued)

Table 1 (Continued)

<i>Metal</i>	<i>Complex</i>	<i>Remarks</i>	<i>References</i>
	[Mo(CO) ₃ (16S4- η^3)]		1995TMC583
	[Mo ₂ I ₄ (CO) ₆ -(μ [16S4-S,S',S'',S'''])]		1997JCD509
	[Mo ₃ Cl ₉ (16S4) ₂] _n		1997JCD509
	[Mo ₂ Cl ₅ (16S4) ₂]Cl·0.33C ₆ H ₁₄		1997JCD509
	[Mo ₂ Cl ₅ (16S4) ₂](BPh ₄)·Et ₂ O		1997JCD509
	<i>trans</i> -[Mo(N ₂) ₂ (Me ₈ -16S4)]		1989AGE1040, 1995ICA(231)95, 1995TMC583
	<i>trans</i> -[Mo(CO) ₂ (Me ₈ -16S4)]		1995TMC583
	[Mo(CO) ₂ (Me ₈ -16S4)] ⁺		1995TMC583
	<i>trans</i> -[MoX ₂ (Me ₈ -16S4)] ⁿ⁺	X = Br, I; n = 0, 1	1995ICA(231)95
	<i>trans</i> -[MoS ₂ (Me ₈ -16S4)], <i>trans</i> -[Mo(S) ₂ (<i>syn</i> -Me ₈ -16S4)]		1995ICA(231)95, 2006IC679
	[MoI(N ₂ CH ₂ Ph)(Me ₈ -16S4)]		1989AGE1040
	[MoI(N ₂)(Me ₈ -16S4)]		1989AGE1040
	<i>trans</i> -[Mo(OSO ₂ CF ₃)(CO)(Me ₈ -16S4)]		1995TMC583
	<i>trans</i> -[MoS(SMe)(Me ₈ -16S4)](I)		2006IC679
	[MoX(CO) ₂ (Me ₈ -16S4)][MoX ₃ (CO) ₄]	X = Br, I	1997JCD509
	[Mo(18S6)Cl ₃] ³⁺		1995ICA(234)35
	[Mo(18S6)(CO) ₃]		1995ICA(234)35
W	[W(CO) ₃ (9S3)]		1995TMC583
	[WI(CO) ₃ (9S3)](BPh ₄)		1996JCD4003
	[WI(CO) ₂ (PPh ₃)(9S3)][WI ₃ (CO) ₄]		1996JCD4003
	[WI(CO) ₂ [P(OPh) ₃](9S3)][WI(CO) ₄]		1996JCD4003
	[W(CO) ₅ (12S3)]		1996CB313
	[W(CO) ₅] ₂ (12S3)		1996CB313
	[WI(CO) ₂ (12S4)][WI ₃ (CO) ₄]		1997JCD509
	[W ₂ I ₄ (CO) ₆ -(μ -14S4-S,S',S'',S''')]		1997JCD509
	[WI(CO) ₂ (16S4)][WI ₃ (CO) ₄]		1997JCD509
	[WI(CO) ₂ (Me ₈ -16S4)][WI ₃ (CO) ₄]		1997JCD509, 1996JCD4003
	[WI(CO) ₃ (Me ₈ -16S4)][WI ₃ (CO) ₄]		1997JCD509
Mn	[Mn(9S3) ₂] ²⁺		1999JCD3759
	<i>fac</i> -[Mn(CO) ₃ (9S3)]Br		1999JCD2343
	<i>fac</i> -[Mn(CO) ₃ (10S3)]Br		1999JCD2343
	<i>fac</i> -[Mn(CO) ₃ (10S3)](MnBr ₄)		1999JCD2343
Tc	[Tc(9S3) ₂] ²⁺		1997AGE1205, 2002ICC832
	[Tc(9S3) ₂] ²⁺ (A ⁻) ₂	A ⁻ = BF ₄ , PF ₆	1999JCD3759
	[Tc(9S3)(SCH ₂ CH ₂ SCH ₂ CH ₂ S)] ⁺		1997AGE1205, 1999JCD3759
	[TcNCl(14S4)][TcNCl ₄]		1993POL2995
	[TcNCl(14S4)](BPh ₄)		1993POL2995
	[TcNCl(16S4)][TcNCl ₄]		1993POL2995

Re	[TcN(Cl){(OH) ₂ -16S4}]Cl [TcNCl(18S6)][TcNCl ₄] [Re(9S3) ₂] ²⁺ [Re(9S3) ₂] ²⁺ (A ⁻) ₂ [Re(9S3) ₂](PF ₆) ₂ ·2CH ₃ NO ₂	Ring system: dihydroxy-16S4	1993POL2995, 1995JCD3215 1993POL2995 1997AGE1205, 2002ICC832 1999JCD3759 1995CC161
	[Re(9S3)O ₃] ⁺ , [ReO ₃ (9S3)] ⁺ [[Re(9S3) ₂](BF ₄)] ⁺ [Re(CO) ₃ (9S3)] ⁺ [Re(9S3)(SCH ₂ CH ₂ SCH ₂ CH ₂ S)] ⁺ [Re ₂ Cl ₆ (9S3)] [[Re ₂ (CO) ₉] ₂ (12S3)] [Re ₂ (CO) ₉ (<i>cis,cis,cis</i> -Me ₃ -12S3)]	A ⁻ = BF ₄ , PF ₆ First homoleptic rhenium(II) complex; used in ¹⁸⁶ Re radiotherapy	1995ICA(234)35, 1995CC161 1995CC161 1995CC161, 1996BCC165 1997AGE1205, 1999JCD3759, 2002ICC832 1995ICA(234)35 1996CB313 1996OM2489
Fe	[Re ₃ (CO) ₁₀ (μ-S(CH ₂) ₃ -12S3)(μ-H) ₃] [Re ₃ (CO) ₁₀ (μ-S(CH ₂) ₃ -16S4)(μ-H) ₃] [Re ₃ (CO) ₁₀ (μ-S(CH ₂) ₃ -24S6)(μ-H) ₃] [ReBr(CO) ₃ (15S5)] [Fe(9S3) ₂] ²⁺ , [Fe(9S3) ₂](BF ₄) ₂	Synthesized for characterization of the <i>cis,cis,cis</i> -form of Me ₃ -12S3	1995CRV2587, 2000ACR171 1995CRV2587 1995CRV2587 2001AXC36 1995ICA(231)95, 2001ICA(317)91, 2002ICC832
	[Fe(9S3) ₂](A) ₂ [Fe(9S3) ₂] ³⁺ [Fe(9S3) ₂](ClO ₄) ₂ [Fe(9S3)(9S3O)] ²⁺ [Fe(9S3)Cl ₃] [Fe(η ⁵ -Cp)(9S3)] ⁺ [Fe(9S3) ₂][FeCl ₄]·2H ₂ O [Fe(10S3) ₂] ²⁺ , <i>cis</i> - and <i>trans</i> -[Fe(10S3) ₂] ²⁺ [Fe(10S3) ₂](ClO ₄) ₂ [Fe(keto-10S3) ₂] ²⁺ [Fe(η ⁵ -Cp)(10S3)] ⁺ [CpFe(10S3)](PF ₆) [Fe(11S3) ₂](ClO ₄) ₂ [Fe(18S6)] ²⁺ [Fe(dibenzo-18S6)] ²⁺ [Fe(20S6)] ²⁺ [Fe(20S6)](ClO ₄) ₂	A ⁻ = PF ₆ , ClO ₄ , 1/2 Sb ₂ Cl ₈ ²⁻ , 1/2 FeCl ₄ ²⁻ Cp = cyclopentadienyl 11S3 = 1,4,7- and 1,4,8-isomer	1995ICA(231)95, 2001ICA(317)91, 2002ICC832 1995ICA(231)95 1995CJC1023 2001ICA(317)91 1995ICA(234)35, 1996POL559 1999JOM(587)207, 2005JOM(690)629 1996POL559 1999JOM(587)207, 2001ICA(317)91 1995CJC1023 2001ICA(317)91 2005JOM(690)629 1999JOM(587)207, 2003IC96 2001ICA(317)91 2001ICA(317)91 2001ICA(317)91 1995CJC1023

(Continued)

Table 1 (Continued)

<i>Metal</i>	<i>Complex</i>	<i>Remarks</i>	<i>References</i>
Ru	[Ru(9S3)] ²⁺		1996ICA(244)73, 2002JOM(664)161, 2003IC96, 2004AGE3938, 2006IC2619
	[Ru(9S3) ₂] ²⁺ , [Ru(9S3) ₂] ²⁺ (A [−]) ₂	A [−] = BF ₄ , PF ₆	1999JCD3759, 2002ICC832
	[RuCl(9S3)] ⁺		1998CC1429, 2002IC2250
	[Ru(<i>n</i> ⁶ -Ar)(9S3)] ²⁺		2005JOM(690)629, 2006ACR301
	[Ru(C ₆ Me ₆)(9S3)] ²⁺ , [Ru(C ₆ Me ₆)(9S3)](PF ₆) ₂		1995CJC1102, 1996JA4984, 2002JOM(664)161, 2003IC96
	[RuCp [*] (9S3)] ⁺ , [RuCp [*] (9S3)](PF ₆)	Cp [*] = Me ₅ -cyclopentadienyl	2002JOM(664)161, 2006ACR301
	[RuCp(9S3)](PF ₆)	Cp = cyclopentadienyl; heteroleptic sandwich complex	1999JOM(587)207, 2002JOM(664)161, 2003IC96
	[{Ru(9S3)} ₂ (μ-L ₂)](CF ₃ SO ₃) ₂	L = S ₂ CNMe ₂ [−] , 2-sulfanylbzothiazole (btt [−]) or 2-sulfanylpyridine (pyt [−])	1996JCD1237
	[Ru(9S3)(MeCN) ₃](CF ₃ SO ₃) ₂		1996IC4548, 1996JCD1237, 1999NJC1015
	[Ru{HB(pz) ₃ }(9S3)](CF ₃ SO ₃) ₂	pz = pyrazol-1-yl	1996JCD1237
	[1-Ph-3,3,3-(9S3)-κ ³ -S,S',S''-3,1,2- <i>closo</i> -RuC ₂ B ₉ H ₁₀]		1996IC4548
	[1,2-Ph ₂ -3,3,3-(9S3)-κ ³ -S,S',S''-3,1,2- <i>pseudocloso</i> -RuC ₂ B ₉ H ₉]		1996IC4548
	[RuCl(PPh ₃)(9S3)] ₂ ²⁺		1995IC796
	[Ru(9S3)(phen)(OH ₂)](ClO ₄) ₂	phen = 1,10-phenantroline	2004EJI612
	[Ru(9S3)(phen)Cl] ⁺	phen = 1,10-phenantroline	2004EJI612
	[Ru(9S3)(phen)(py)] ²⁺	phen = 1,10-phenantroline; py = pyridine	2004EJI612
	[Ru(9S3)(py) ₃] ²⁺	py = pyridine	2004EJI612
	[(RuCl(9S3)) ₂ bpta](PF ₆) ₂	bpta = 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine	1998CC1429, 2006IC821
	[RuCl ₂ (DMSO)(9S3)]		1999NJC1015, 2001ICA(323)157, 2001JCD1628, 2002IC2250, 2004AGE3938, 2005EJI3423, 2006ICA(359)759
	[RuCl ₂ (PPh ₃)(9S3)]		2006ICA(359)759
	[RuCl(DMSO) ₂ (9S3)](CF ₃ SO ₃) ₂		2005EJI3423
	[Ru(DMSO) ₃ (9S3)](CF ₃ SO ₃) ₂		2005EJI3423
	[RuCl ₂ (pta)(9S3)]	pta = 1,3,5-triaza-7-phosphaadamantane	2005EJI3423, 2006IC1289
	[RuCl(pta) ₂ (9S3)](CF ₃ SO ₃) ₂	pta = 1,3,5-triaza-7-phosphaadamantane	2005EJI3423, 2006IC1289
	[RuCl(en)(9S3)](CF ₃ SO ₃) ₂	en = ethylenediamine	2005EJI3423
	[RuCl(enac)(9S3)](CF ₃ SO ₃) ₂	enac = 1,2-bis(isopropyleneimino)ethane	2005EJI3423
	[Ru(H ₂ O)(enac)(9S3)] ²⁺	enac = 1,2-bis(isopropyleneimino)ethane	2005EJI3423
	[RuCl(bipy)(9S3)](CF ₃ SO ₃) ₂	bipy = 2,2'-bipyridine	2005EJI3423
	[Ru(H ₂ O)(bipy)(9S3)] ²⁺	bipy = 2,2'-bipyridine	2005EJI3423
	[Ru(DMSO-S)(bipy)(9S3)](CF ₃ SO ₃) ₂	bipy = 2,2'-bipyridine	2005EJI3423

[Ru(H ₂ O)(phen)(9S3)](ClO ₄) ₂	phen = 1,10-phenantroline	2005EJI3423
[RuCl(H ₂ O)(pta)(9S3)] ⁺	pta = 1,3,5-triaza-7-phosphaadamantane	2005EJI3423
[Ru(H ₂ O) ₂ (pta)(9S3)] ²⁺	pta = 1,3,5-triaza-7-phosphaadamantane	2005EJI3423
[[Ru(9S3)Cl] ₂ (bpym)]Cl ₂ ·4H ₂ O	bpym = 2,2'-bipyrimidine	2002IC2250
[[Ru(9S3)Cl] ₂ (bpym)](PF ₆) ₂ ·1.5H ₂ O	bpym = 2,2'-bipyrimidine	2002IC2250
[[Ru(9S3)Cl] ₂ (bptz)](PF ₆) ₂ ·4H ₂ O	bptz = 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine	2002IC2250
[[Ru(9S3)Cl] ₂ (dpp)](PF ₆) ₂ ·H ₂ O	dpp = 2,3-bis(2-pyridyl)pyrazine	2002IC2250
[Ru(9S3)(PhCN) ₃](PF ₆) ₂		2001ICA(323)157
[Ru(9S3)(PhCN) ₂ Cl](PF ₆)		2001ICA(323)157
[Ru(9S3)Cl(pyz) ₂](PF ₆) ₂	pyz = pyrazine	2001ICA(323)157
[Ru(9S3)(pyd) ₃](PF ₆) ₂	pyd = pyridazine	2001ICA(323)157
[Ru(9S3)(dcb) ₃](PF ₆) ₂	dcb = 1,2-dicyanobenzene	2001ICA(323)157
[Ru(9S3)(py) ₃](PF ₆) ₂	py = pyridine	2001ICA(323)157
[Ru(9S3)(py) ₂ Cl] ⁺	py = pyridine	2001ICA(323)157
[[Ru(μ-S ₂ -CNMe ₂)(9S3)] ₂ (CF ₃ SO ₃) ₂]		1996JCD1237
[Ru ₃ (CO) ₇ (μCO) ₂ (1,1,1-η ³ -9S3)]		1995OM3704
[Ru ₆ (CO) ₁₄ (η ³ -9S3)(μ ₆ -C)]		1995OM1739
[TiCl ₂ Ru(PPh ₃)(9S3)] ₂ ²⁺		1995IC796
[Ru(CH=CHR)(CO)(PPh ₃)(9S3)]Cl	R = not specified	1995CJC1102
[Ru(Me ₂ SO)Cl ₂ (9S3)]		1998CC1429
[Ru(10S3) ₂] ²⁺		1999JOM(587)207, 2003IC96
[Ru(10S3) ₂](A) ₂	A ⁻ = ClO ₄ , BF ₄ , BPh ₄	1996ICA(244)73
[RuCp(10S3)](PF ₆)	Heteroleptic sandwich complex	1999JOM(587)207, 2003IC96
[Ru(η ⁶ -Ar)(10S3)] ²⁺		2005JOM(690)629
[Ru(C ₆ Me ₆)(10S3)] ²⁺ , [Ru(C ₆ Me ₆)(10S3)](PF ₆) ₂		2002JOM(664)161, 2003IC96
[Ru(11S3) ₂](PF ₆) ₂	11S3 = 1,4,7-isomer	2001ICA(317)91
[Ru(η ⁶ -Ar)(11S3)] ²⁺		2005JOM(690)629
[Ru(C ₆ Me ₆)(11S3)] ²⁺ , [Ru(C ₆ Me ₆)(11S3)](PF ₆) ₂		2002JOM(664)161, 2003IC96
[RuCl ₂ (DMSO)(T [†] T[9]OC)]	T [†] T[9]OC = 2,5,8-trithia[9]-o-cyclophane (Figure 3)	1995CJC1102
[RuCl ₂ (PPh ₃)(T [†] T[9]OC)]		1995CJC1102
[RuHCl(PPh ₃) ₂ (T [†] T[9]OC)]		1995CJC1102
[Ru(12S3) ₂] ²⁺		1996ICA(244)73
[Ru(C ₆ Me ₆)(12S3)] ²⁺ , [Ru(C ₆ Me ₆)(12S3)](PF ₆) ₂		2002JOM(664)161, 2003IC96
[Ru ₃ (CO) ₇ (μCO) ₂ (1,1,1-η ³ -12S3)]		1995OM3704
[Ru ₄ (CO) ₁₁ (12S3)(μ-H) ₄]		1995OM4594
[Ru ₅ (CO) ₁₁ (μ-η ³ -12S3)(μ ₅ -C)]		1995CRV2587
[Ru ₅ (CO) ₁₃ (μ-η ¹ -12S3)(μ ₅ -C)]		1995CRV2587
[Ru ₆ (CO) ₁₃ (μ ₃ -η ³ -12S3)(μ ₆ -C)]		1995CRV2587, 1995OM1739
[Ru ₆ (CO) ₁₅ (μ ₄ -η ² -CO)(μ-η ³ -12S3)]		1995CRV2587
[Ru(12S4)(bipy)] ²⁺	bipy = 2,2'-bipyridine	1999NJC1015, 2006IC821

(Continued)

Table 1 (Continued)

<i>Metal</i>	<i>Complex</i>	<i>Remarks</i>	<i>References</i>
	[Ru(12S4)(phen)] ²⁺	phen = 1,10-phenanthroline	1999NJC1015
	[Ru(12S4)(5-phen)] ²⁺	5-phen = 5-phenyl-1,10-phenanthroline	1999NJC1015
	[Ru(12S4)(dip)] ²⁺	dip = 4,7-diphenyl-1,10-phenanthroline	1999NJC1015
	[Ru(12S4)(5,6-dione)] ²⁺	5,6-dione = 1,10-phenanthroline-5,6-dione	1999NJC1015
	[Ru(12S4)(dipa)] ²⁺	dipa = dipyridylamine	1999NJC1015
	[Ru(12S4)(dbp)] ²⁺	dbp = 4,4'-diphenyl-2,2'-dipyridyl	1999NJC1015
	[Ru(12S4)(pda)] ²⁺	pda = <i>o</i> -phenyldiamine	1999NJC1015
	[Ru(12S4)(MeCN) ₂] ²⁺		1999NJC1015
	[Ru(12S4)(MeCN)Cl] ⁺		1999NJC1015
	[Ru(12S4)(ind)Cl] ⁺	ind = indazole	1999NJC1015
	[Ru(12S4)Cl(DMSO)] ⁺ , [Ru(12S4)(DMSO)Cl]Cl		2001JCD1628, 2006IC821, 2006ICA(359)759
	[Ru(12S4)Cl(PPh ₃)] ⁺		2006ICA(359)759
	[(Ru(12S4)) ₂ bpta](PF ₆) ₄	bpta = 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine	2006IC821
	[Ru(14S4)Cl] ⁺		2001JCD1628
	<i>cis</i> -[RuCl ₂ (14S4)]		1995IC396, 1996JCD2979
	[Ru(14S4)Cl(L)](A)	L = MeCN, Si(OEt) ₃ (CH ₂) ₃ CN; A ⁻ = Cl, PF ₆	2001JCD1628
	[Ru(14S4)Cl(DMSO)] ⁺ , [Ru(14S4)(DMSO)Cl]Cl		2001JCD1628, 2006IC821, 2006ICA(359)759
	[Ru(14S4)Cl(PPh ₃)] ⁺		2006ICA(359)759
	[(Ru(14S4)) ₂ bpta](PF ₆) ₄	bpta = 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine	2006IC821
	<i>trans</i> -[RuH(Cl)(<i>syn</i> -Me ₄ -14S4)]		1995ICA(231)95
	<i>trans</i> -[Ru ₂ H(μ -H)Cl(<i>syn</i> -Me ₄ -14S4) ₂]Cl		1995ICA(231)95
	<i>cis</i> -[RuCl ₂ (Me ₆ -15S4)]		1995ICA(231)95
	<i>trans</i> -[RuH(Cl)(<i>syn</i> -Me ₆ -15S4)]		1995ICA(231)95
	<i>trans</i> -[RuH(η^1 -BH ₄)(Me ₆ -15S4)]		1995ICA(231)95
	[Ru(16S4)Cl(L)] ⁺	L = DMSO, PPh ₃	2006ICA(359)759
	<i>cis</i> -[RuCl ₂ (Me ₈ -16S4)]		1995ICA(231)95
	<i>trans</i> -[RuH(Cl)(<i>syn</i> -Me ₈ -16S4)]		1995ICA(231)95
	<i>trans</i> -[RuH(η^1 -BH ₄)(Me ₈ -16S4)]		1995ICA(231)95
	<i>trans</i> -[Ru(OR) ₂ (<i>anti</i> -Me ₈ -16S4)] ⁺	R = Me, Et	1995ICA(231)95
	[Ru ₆ (CO) ₁₅ (μ - η^2 -16S4)(μ_6 -C)]		1995CRV2587, 1995OM1739
	[Ru(dibenzo-18S6)](PF ₆) ₂		2003IC96
Os	[Os(9S3) ₂] ²⁺		2002ICC832
	[Os(9S3) ₂] ²⁺ (A ⁻) ₂	A ⁻ = BF ₄ , PF ₆	1999JCD3759
	[Os ₃ (CO) ₁₀ (μ -3,3-Me ₂ -12S3)]		1995CRV2587, 2000ACR171
	[Os ₄ (CO) ₁₁ (12S3)(μ -H) ₄]		1995OM4594
	[Os ₄ (CO) ₁₃ (μ - η^1 -12S3)(μ_5 -C)]		1995CRV2587

Co	[Co(9S3) ₂] ²⁺		1995CJC1023
	[Co(9S3)(H ₂ O) ₃] ³⁺		1998ICA(274)192
	[Cp*Co(9S3)] ²⁺	Cp* = Me ₅ -cyclopentadienyl	1995IC796
	[Co(9S3)]Cl ₃		1998ICA(274)192
	[Co(10S3) ₂] ²⁺		1995CJC1023, 1999JOM(587)207
	[Co(9S3)(10S3)](ClO ₄) ₃		1998ICA(274)192
	[Co(10S3) ₂](PF ₆) ₃		1998ICA(274)192
	[Co(10S3-OH) ₂](ClO ₄) ₂		1995CJC1023
	[Co(11S3)](BF ₄) ₂	11S3 = 1,4,7- and 1,4,8-isomer	2001ICA(317)91
	[Co(11S3)](PF ₆) ₃	11S3 = 1,4,7-isomer	2001ICA(317)91
	[Co(18S6)] ²⁺		1995CJC1023
	[Co(18S6)](BF ₄) ₂		1998ICA(274)192
	[Co(18S6)](ClO ₄) ₃		1998ICA(274)192
	[Co(20S6)](ClO ₄) ₂		1995CJC1023
	[Co(20S6)](BF ₄) ₂		1998ICA(274)192
	[Co(20S6)](BF ₄) ₃ ·2H ₂ O		1998ICA(274)192
	[Co(24S6)] ³⁺	No crystals available	1998ICA(274)192
Rh	[Rh(9S3)] ³⁺		1996JCD1237, 2005JOM(690)629
	[Rh(9S3) ₂](CF ₃ SO ₃) ₃		1995IC796
	[RhX ₃ (9S3)]	X = Cl, I	1996JCD1237
	[Rh(9S3) ₂](PF ₆) ₃		1995IC796
	[Rh(COD)(9S3)](PF ₆)	COD = 1,4-cyclooctadiene	1997OM4517
	[Rh(dppf)(9S3)](PF ₆)	dppf = 1,1'-bis(diphenylphosphino)ferrocene	1997OM4517
	[Rh(PPh ₃) ₂ (9S3)](PF ₆)		1997OM4517
	[Rh(CO)(PPh ₃)(9S3)](A)	A ⁻ = PF ₆ , ClO ₄	1996JCD1237, 1997OM4517
	[Rh(CS)(PPh ₃)(9S3)](ClO ₄)		1997OM4517
	[Rh(η ² -SCS)(PPh ₃)(9S3)](PF ₆)		1997OM4517
	[RhI ₂ (PPh ₃)(9S3)](A)	A ⁻ = PF ₆ , ClO ₄	1996JCD1237, 1997OM4517
	[Rh(C ₂ H ₄)(L)(9S3)] ⁺	L = C ₂ H ₄ , PPh ₃	1996JCD1237
	[Cp*Rh(9S3)] ²⁺	Cp* = Me ₅ -cyclopentadienyl	1995IC796
	[Rh{S(CH ₂) ₂ S(CH ₂) ₂ SCH=CH ₂ }(9S3)] ²⁺		1996JCD1237
	[Rh(η ⁵ -C ₅ Me ₅)(9S3)](ClO ₄) ₂		1996JCD1237
	[Rh(η ⁵ -Cp*)(9S3)]Cl ₂ ·5H ₂ O	Cp* = Me ₅ -cyclopentadienyl; mixed sandwich complex	2005JOM(690)629
	[Rh(CO)(PPh ₃)(9S3)]ClO ₄ ·ClO ₄		1995IC796
	[Rh(9S3)(PPh ₃) ₂](ClO ₄) ₂ ·2ClO ₄		1995IC796
	[Rh(9S3)(SPh) ₃]·CH ₃ CN		1995IC796
	[Rh(9S3)(κ ³ -HB(pz) ₃)] ²⁺	pz = pyrazol-1-yl	2005JOM(690)629
	[Rh{HB(pz) ₃ }(9S3)](CF ₃ SO ₃) ₂	pz = pyrazol-1-yl	1996JCD1237
	[(9S3)Rh(μ-SPh) ₃ Rh(C ₅ Me ₅)] ²⁺		1996JCD1237
	[(9S3)Rh(μ-SPh) ₃ RhCp*](ClO ₄) ₂ ·CH ₃ CN·CH ₂ Cl ₂	Cp* = Me ₅ -cyclopentadienyl	1995IC796
	[RhCl(MeCN) ₂ (9S3)](CF ₃ SO ₃) ₂		1996JCD1237

(Continued)

Table 1 (Continued)

<i>Metal</i>	<i>Complex</i>	<i>Remarks</i>	<i>References</i>
Ir	[RhCl(pymt)(9S3)](CF ₃ SO ₃)	pymt = pyrimidine-2-thiolate	1996JCD1237
	[Rh(pymt) ₂ (9S3)](CF ₃ SO ₃)	pymt = pyrimidine-2-thiolate	1996JCD1237
	[RhCl(S ₂ CNEt ₂)(9S3)](CF ₃ SO ₃)		1996JCD1237
	[(9S3)Rh(μ -SPh) ₃ IrCp*](ClO ₄) ₂ ·0.5CH ₃ CN·0.5CH ₂ Cl ₂	Cp* = Me ₅ -cyclopentadienyl	1995IC796
	[Rh(η^5 -Cp*)(10S3)](PF ₆) ₂ ·2CH ₃ NO ₂	Cp* = Me ₅ -cyclopentadienyl; mixed sandwich complex	2005JOM(690)629
	[Rh(12S4)(phi)] ³⁺	phi = 9,10-phenanthrenequinone diimine	1999NJC1015
	<i>cis</i> -[RhCl ₂ (14S4)] ⁺		1995IC396, 1996JCD2979
	<i>trans</i> -[RhCl ₂ (16S4)] ⁺		1996JCD2979
	[Ir(9S3) ₂] ³⁺		2005JOM(690)629
	[Cp*Ir(9S3)] ²⁺	Cp* = Me ₅ -cyclopentadienyl	1995IC796
	[Ir(η^5 -Cp*)(9S3)](PF ₆) ₂	Cp* = Me ₅ -cyclopentadienyl	2005JOM(690)629
	[Ir(9S3)(CO)(PPh ₃)] ⁺		1995IC796
	[Ir(η^5 -Cp*)(10S3)](PF ₆) ₂	Cp* = Me ₅ -cyclopentadienyl	2005JOM(690)629
	<i>cis</i> -[IrCl ₂ (14S4)] ⁺		1995IC396, 1996JCD2979
Ni	[Ni(9S3) ₂] ²⁺		1995CJC1023, 2001ICA(317)91,
	[Ni(10S3) ₂] ²⁺		2001JOM(637)683
	[Ni(9S3)(dppf)] ²⁺	dppf = 1,1'-bis(diphenylphosphino)ferrocene	2001JOM(637)683
	[Ni ₂ Cl ₃ (9S3)] ²⁺		1995IC796
	[Ni(10S3) ₂] ²⁺		1995CJC1023, 1999JOM(587)207,
			2001ICA(317)91
	[Ni(10S3-OH) ₂](ClO ₄) ₂		1995CJC1023
	[Ni(keto-10S3) ₂] ²⁺		1995CJC1023
	[Ni(11S3) ₂](BF ₄) ₂	11S3 = 1,4,7- and 1,4,8-isomer	2001ICA(317)91
	[Ni(12S3) ₂] ²⁺		2001ICA(317)91
	[Ni(12S4)Cl ₂]		1999NJC1015
	[Ni(14S4)](BF ₄) ₂		1995JCD3215, 2000IC1444
	[Ni(<i>cis</i> -cyhx-14S4)](ClO ₄) ₂	cyhx = cyclohexyl	2000IC1444
	[Ni(<i>trans</i> -cyhx-14S4)](ClO ₄) ₂	cyhx = cyclohexyl	2000IC1444
	[Ni(<i>syn-cis,cis</i> -dicyhx-14S4)](ClO ₄) ₂	cyhx = cyclohexyl	2000IC1444
	[Ni(<i>anti-cis,cis</i> -dicyhx-14S4)](ClO ₄) ₂	cyhx = cyclohexyl	2000IC1444
	[Ni(<i>meso-trans,trans</i> -dicyhx-14S4)](ClO ₄) ₂	cyhx = cyclohexyl	2000IC1444
	[Ni(<i>dl-trans,trans</i> -dicyhx-14S4)](ClO ₄) ₂	cyhx = cyclohexyl	2000IC1444
	[Ni(<i>cis,trans</i> -dicyhx-14S4)](ClO ₄) ₂	cyhx = cyclohexyl	2000IC1444
	[Ni(18S6)] ²⁺		1995CJC1023
	[Ni(20S6)](ClO ₄) ₂		1995CJC1023
	[Ni(24S6)] ²⁺		1995CJC1023

Pd	[Pd(9S3)] ²⁺ [Pd(9S3) ₂] ²⁺ <i>cis</i> -[Pd(9S3)Cl ₂], [PdCl ₂ (9S3)] [Pd(9S3)X ₂] [Pd(9S3)(L)] [Pd(9S3)(bpy)](PF ₆) ₂ [Pd(9S3)(phen)(PF ₆) ₂ ·CH ₃ NO ₂] <i>cis</i> -[Pd(9S3)Cl(L)](PF ₆) <i>cis</i> -[Pd(9S3)(L)](PF ₆) ₂	X = Cl, Br L = 2 PPh ₃ , bpy (2,2'-bipyridine), phen(1,10-phenanthroline) bpy = 2,2'-bipyridine phen = 1,10-phenanthroline L = PPh ₃ , P(C ₆ H ₁₁) ₃ L = 2 PPh ₃ , CH ₂ (PPh ₂) ₂ (dppm), C ₂ H ₄ (PPh ₂) ₂ (dppe), CH ₃ C(PPh ₂) ₃ , [Ph ₂ P(O),CH ₂] ₂ CCH ₃ , bipy, phen (1,10-phenanthroline) dppf = 1,1'-bis(diphenylphosphino)ferrocene	1996ICA(246)31 1991IC4644, 1995JCD4045, 1998IC3767 1996JCD1885, 1998IC3767 1995JCD4045 1995JCD4045 1995IC6319, 2006JCX83 2006JCX83 1996JCD1885 1996JCD1885
	[Pd(9S3)(dppf)](PF ₆) ₂ ·CH ₃ NO ₂ [Pd(10S3) ₂] ²⁺ [PdCl ₂ (10S3)] [Pd(11S3)](PF ₆) ₂ [PdCl ₂ (TT[9]OB)]·DMSO [PdCl ₂ (TT[9]MB)] [Pd(12S4)] ²⁺ [Pd(2,3-benzo-13S4)](PF ₆) ₂ [Pd(14S4)] ²⁺ [Pd(14S4-(OH) ₂)]Cl ₂ ·2H ₂ O [Pd(2,3-benzo-14S4-(OH) ₂)](PF ₆) ₂ [Pd(L)](PF ₆)Cl [Pd(16S4)] ²⁺ [Pd(L)(L')](BF ₄)	11S3 = 1,4,7-isomer TT[9]OB = 2,5,8-trithia[9]- <i>o</i> -benzenophane (Figure 3) TT[9]MB = 2,5,8-trithia[9]- <i>m</i> -benzenophane (Figure 3) L = 2,3,9,10-dibenzo-14S4-(OH) ₂ L = 2,14-dithia[15]- <i>m</i> -cyclophane (Figure 3); L' = CH ₃ CN, pyridine, or <i>o</i> -aminopyridine	2001JOM(637)683 1996ICA(246)31, 1998IC5299, 1998IC3767, 2005EJI479 1998IC3767 2001ICA(317)91 1991IC4644 1991IC4644 1995JCD4045, 1996JCD2979 1997JCD1889 1995JCD4045, 1996JCD2979 1997JCD1889 1997JCD1889 1997JCD1889 1995IC651, 1995JCD4045, 1996JCD2979 1994IC4351
Pt	[Pd(18S6)] ²⁺ [Pd(20S6)] ²⁺ [Pd(20S6)](PF ₆) ₂ [[Pd(η ³ -C ₃ H ₅)] ₂ (20S6)](ClO ₄) ₂		1995JCD4045, 1996ICA(246)31, 2005EJI479 1998IC5299 1996ICA(246)31 1995CJC1023 1996ICA(246)31 1998IC3767, 2001POL3333, 2005EJI479 2005EJI479 1996JCD2979 1998IC3767, 2001IC564, 2002POL879, 2003JCD3981, 2004POL1361, 2006CC3540
	[Pt(9S3)] ²⁺ [Pt(9S3) ₂] ²⁺ , [Pt(9S3) ₂](PF ₆) ₂ [Pt(9S3) ₂](A) ₂ ·2CH ₃ NO ₂ [Pt(9S3) ₂] ⁴⁺ [Pt(9S3)Cl ₂], [PtCl ₂ (9S3)]	A ⁻ = PF ₆ , BF ₄ , CF ₃ SO ₃ , BPh ₄	

(Continued)

Table 1 (Continued)

<i>Metal</i>	<i>Complex</i>	<i>Remarks</i>	<i>References</i>
	[Pt(9S3)X ₂]	X = Cl, Br, I	2001POL3333
	[Pt(9S3)(phpy)](PF ₆)	phpy = 2-phenylpyridine	2005IC8182
	[Pt(9S3)(tmphen)](PF ₆) ₂	tmphen = 3,4,7,8-tetramethyl-1,10-phenanthroline	2006JCX83
	[Pt(9S3)(bpy)](PF ₆) ₂ , [Pt(9S3)(bipy)](PF ₆) ₂	bpy, bipy = 2,2'-bipyridine	2004POL1361, 2006JCX83
	[Pt(9S3)(Me ₂ bipy)](PF ₆) ₂ ·2.5CH ₃ NO ₂	Me ₂ bipy = 4,4'-dimethyl-2,2'-bipyridine	2004POL1361
	[Pt(9S3)(Alk ₂ bipy)](PF ₆) ₂	Alk ₂ bipy = 4,4'-dialkyl-2,2'-bipyridine; alkyl = <i>tert</i> -butyl, nonyl	2004POL1361
	[Pt(9S3)(5,5'-dmbpy)](PF ₆) ₂	5,5'-dmbpy = 5,5'-dimethyl-2,2'-bipyridine	2006JCX83
	[Pt(9S3)(phen)](PF ₆) ₂	phen = 1,10-phenanthroline	1995IC6319, 2004POL1361, 2006JCX83
	[Pt(9S3)(Me ₄ phen)](PF ₆) ₂	Me ₄ phen = 3,4,7,8-tetramethyl-1,10-phenanthroline	2004POL1361
	[Pt(9S3)(4,4'-dmbpy)](PF ₆) ₂ ·2.5CH ₃ NO ₂	4,4'-dmbpy = 4,4'-dimethyl-2,2'-bipyridine	2006JCX83
	[Pt(9S3)(dbbpy)](PF ₆) ₂ ·CH ₃ NO ₂	dbbpy = 4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine	2006JCX83
	[Pt(9S3)(dtfmbpy)](PF ₆) ₂ ·CH ₃ NO ₂	dtfmbpy = 5,5'-ditrifluoromethyl-2,2'-bipyridine	2006JCX83
	[Pt(9S3)(dppm)] ²⁺ , [Pt(9S3)(dppm)](PF ₆) ₂	dppm = bis-(diphenylphosphino)methane	2001IC564, 2001JOM(637)683
	[Pt(9S3)(dppf)](PF ₆) ₂ ·CH ₃ NO ₂	dppf = 1,1'-bis(diphenylphosphino)ferrocene	2001JOM(637)683
	[Pt(9S3)(<i>R</i> -BINAP)](PF ₆) ₂ ·CH ₃ NO ₂	<i>R</i> -BINAP = 1,1'-binaphthalene-bis(α -diphenylphosphine)	2003JCD3981
	[Pt(9S3)(<i>R,R</i> -chiraphos)](PF ₆) ₂	chiraphos = 2,3-bis(diphenylphosphino)butane	2003JCD3981
	[Pt(9S3)(PPh ₃) ₂] ²⁺ , [Pt(9S3)(PPh ₃) ₂](PF ₆) ₂ ·2CH ₃ NO ₂		2001IC564, 2001JOM(637)683
	[Pt(9S3)(PPh ₃)Cl](PF ₆)		2002POL879
	[Pt(phpy)(9S3)] ₂ Ag(MeCN) ₂ (PF ₆) ₃	phpy = 2-phenylpyridine	2005IC8182
	[Pt ₄ (9S3) ₄ (4,4'-bipy) ₄](CF ₃ SO ₃) ₈	4,4'-bipy = 4,4'-bipyridine	2006CC3540
	[Pt(10S3)Cl ₂], [PtCl ₂ (10S3)]		1998IC3767, 2001POL3333, 2002POL879
	[Pt(10S3) ₂] ²⁺ , [Pt(10S3) ₂](PF ₆) ₂ ,		1996ICA(246)31, 1998IC5299, 1998IC3767,
	[Pt(10S3) ₂](PF ₆) ₂ ·2CH ₃ NO ₂		2001POL3333, 2005EJI479, 2005EJI479
	[Pt(10S3)(PPh ₃)Cl](PF ₆)		2002POL879
	[Pt(11S3)Cl ₂]	11S3 = 1,4,7-isomer	2001ICA(317)91
	[Pt(12S4)] ²⁺ , [Pt(12S4)](A) ₂	A ⁻ = Cl, PF ₆	1996ICA(246)31, 1996JCD2979, 2001JCD456,
			2001POL3333
	[PtX ₂ (12S4)](PF ₆) ₂	X = Cl, Br	1996JCD2979
	[Pt(14S4)] ²⁺ , [Pt(14S4)](PF ₆) ₂		1996ICA(246)31, 1996JCD2979,
			2001POL3333
	[PtX ₂ (14S4)](PF ₆) ₂	X = Cl, Br	1996JCD2979
	[Pt(15S5)](PF ₆) ₂		2001POL3333
	[Pt(16S4)] ²⁺		1995IC651, 1998IC5299

Cu	[Pt(16S4)](PF ₆) ₂ , [Pt(16S4)](PF ₆) ₂ ·2CH ₃ CN		1996JCD2979, 2001POL3333
	[PtX ₂ (16S4)](PF ₆) ₂	X = Cl, Br	1996JCD2979
	[Pt(18S3) ₂] ⁴⁺		1996JCD2979
	[Pt(18S6)] ²⁺		1996ICA(246)31, 2005EJI479
	[Pt(18S6)](A) ₂	A [−] = BF ₄ , BPh ₄ , PF ₆ , ClO ₄	2001POL3333, 2005EJI479
	[Pt(20S6)] ²⁺		1998IC5299
	[Pt(20S6)] ₂ (PF ₆) ₂ ·CH ₃ NO ₂		1996ICA(246)31
	[Cu(9S3)](A) ₂	A [−] = BF ₄ , ClO ₄	2004ZFA2725
	[Cu(η ³ -9S3)(η ¹ -9S3)](PF ₆)		1996OM5425
	[(9S3)Cu(CN)(Cu(9S3))](BF ₄)		2004ZFA2725
	[(9S3)Cu(CN)(Cu(9S3))](TCNQ) ₂	TCNQ = 7,7',8,8'-tetracyanoquinodimethanid	2004ZFA2725
	[Cu(NCS)(TT[9]OB)]	TT[9]OB = 2,5,8-trithia[9]- <i>o</i> -benzenophane (Figure 3)	1991IC4644
	[Cu(PPh ₂ Me)(TT[9]OB)]	TT[9]OB = 2,5,8-trithia[9]- <i>o</i> -benzenophane (Figure 3)	1991IC4644
	<i>anti</i> -[Cu ₂ (L)(PPh ₂ Me) ₂](ClO ₄) ₂	L = 2,5,8,17,20,23-hexathia[9](1,2)[9](6,5)-cyclophane (Figure 3)	1991CC1119
	<i>anti</i> -[Cu ₂ (L)(PPh ₂ CH ₂ CH ₂ PPh ₂)(PF ₆) ₂	L = 2,5,8,17,20,23-hexathia[9](1,2)[9](6,5)-cyclophane (Figure 3)	1991CC1119
	[CuCl ₂ (12S3)]		2001AXC36
	[Cu(η ³ -12S3)(η ¹ -12S3)] ₂ [Ru ₆ (CO) ₁₆ (μ ₆ -C)]		1996OM5425
	[CuX(12S4)]	X = Cl, Br, I	2001JCD456
	[Cu(12S4)(H ₂ O)] ²⁺ , [Cu(12S4)(H ₂ O)](ClO ₄) ₂		2001JCD456, 2002ZFA34
	[Cu ₄ X ₄ (12S4) ₂] _∞	X = Br, I	2001JCD456
Ag	[CuCl{12S4-(<i>o</i> -dimethoxy-benzene) ₄ }]	For structural formula of this complex please see Figure 3	2001JCD456
	[{Cu(μ-η ¹ -η ³ -14S4)} _n]		1998JCD2191
	[{Cu(14S4)(ClO ₄) _∞ }, [Cu(14S4)(ClO ₄) _∞]		1998JCD2931, 2001JCD456
	[Cu(14S4)](ClO ₄) ₂		1995JCD3215
	[{Cu(14S4)](ClO ₄) _∞		1995JCD3215
	[Cu(16S4)](ClO ₄) ₂		1995JCD3215
	[Cu ₂ I ₂ (16S4) ₂] _∞		2001JCD456
	[Cu{(OH) ₂ (16S4)}](ClO ₄) ₂	Ring system: dihydroxy-16S4	1995JCD3215
	[Cu(18S6)]picrate ₂		2001AXC36
	[CuCl ₂ (18S6)] _∞	Polymeric exodentate complex	2001AXC36
	[Cu ₂ (24S8)](BF ₄) ₂		1991CC1119, 1998JCD3961
	[Cu ₂ (28S8)] ²⁺ , [Cu ₂ (28S8)](A) ₂	A [−] = ClO ₄ , PF ₆	1991CC1119, 1998JCD2931, 1998JCD3961
	[Ag(9S3) ₂] ⁺		1995JCD3215, 1998JCD2931
	[Ag ₃ (9S3) ₃] ³⁺ , {Ag(9S3)} ₃ ³⁺		1995JCD3215, 1997CB425, 2000IC1035
	[Ag(L) _n](A) _n	L = 2,5,8,10,12-pentathiobicyclo[7.3.0]dodeca-1(9)-ene-11-thione (see Figure 3); A [−] = NO ₃ , ClO ₄ , BF ₄ , PF ₆	1997CB425
	[Ag(hfpd)(9S3)] _∞	hfpd = 1,1,1,5,5,5-hexafluoropentanedione	2000IC1035

(Continued)

Table 1 (Continued)

<i>Metal</i>	<i>Complex</i>	<i>Remarks</i>	<i>References</i>
	$\{[\text{Ag}(\text{T}^{\text{T}}[9]\text{OB})](\text{CF}_3\text{SO}_3)\}_4$	$\text{T}^{\text{T}}[9]\text{OB} = 2,5,8\text{-trithia}[9]\text{-}o\text{-benzenophane}$ (Figure 3)	1996ICA(246)207
	$\{[\text{Ag}(\text{T}^{\text{T}}[9]\text{OB})](\text{BF}_4)\}_4 \cdot 2\text{CH}_3\text{CN}$	$\text{T}^{\text{T}}[9]\text{OB} = 2,5,8\text{-trithia}[9]\text{-}o\text{-benzenophane}$ (Figure 3)	1996ICA(246)207
	$\{[\text{Ag}(12\text{S}3)(\text{CF}_3\text{SO}_3)(\text{MeCN})]_{\infty}\}$		1995JCD3215, 1998JCD2931
	$\{[\text{Ag}(\text{Me}_2\text{-T}^{\text{T}}[9]\text{OB})](\text{BF}_4)\}_4 \cdot 2\text{CH}_3\text{CN}$	$\text{Me}_2\text{-T}^{\text{T}}[9]\text{OB} = 2,5,8\text{-trithia}[9]\text{-}o\text{-dimethylbenzenophane}$	1996ICA(246)207
	$\{[\text{Ag}(\text{L})](\text{CF}_3\text{SO}_3)\} \cdot \text{CH}_3\text{CN}$	$\text{L} = 2,5,8\text{-trithia}[9]\text{-}m\text{-cyclophane} = \text{T}^{\text{T}}[9]\text{MB}$ (Figure 3)	1995IC5410
	$[\text{Ag}(12\text{S}4)](\text{CF}_3\text{SO}_3)$, $[\text{Ag}(12\text{S}4)](\text{PF}_6)$		2004ZNB1077, 2004ZFA2669
	$[\text{Ag}(12\text{S}4)]^{2+}$		2004ZFA2669
	$[\text{Ag}(\text{bicyclo-14S}4)](\text{CF}_3\text{SO}_3)$	bicyclo-14S4 = 3,6,9,14-tetrathiabicyclo-[9.2.1]tetradeca-11,13-diene (Figure 3)	2002SAC222, 2004ZNB1077
	$[\text{Ag}_2(\text{hfpd})_2(14\text{S}4)]_{\infty}$	hfpd = 1,1,1,5,5,5-hexafluoropentanedione	2000IC1035
	$[\text{Ag}(15\text{S}5)]^+$		1998JCD2931
	$[\text{Ag}_2(15\text{S}5)_2]^{2+}$		1995JCD3215
	$[\text{Ag}(15\text{UT}5)](\text{CF}_3\text{COO})$		2002JOC6632
	$[\text{Ag}(16\text{S}4)]^+$, $[\text{Ag}(16\text{S}4)](\text{PF}_6)$		2004ZFA2669
	$[\text{Ag}(16\text{S}4)]^{2+}$		2004ZFA2669
	$[\text{Ag}(16\text{S}4)(\text{BF}_4)]_{\infty}$		1997CC1943
	$\{[\text{Ag}\{(\text{OH})_2(16\text{S}4)(\text{NO}_3)\}_{\infty}]\}$	Ring system: dihydroxy-16S4	1995JCD3215, 1998JCD2931, 2000IC1035
	$\{[\text{Ag}(\text{OH})_2(16\text{S}4)(\text{COOMe})]_{\infty}\}$	Ring system: dihydroxy-16S4	1998JCD2931, 1995JCD3215
	$[\text{Ag}(2,6\text{-diketo-16S}5)](\text{CF}_3\text{SO}_3) \cdot \text{EtOH}$		1995ICA(230)133
	$[\text{Ag}(16\text{S}6)](\text{ClO}_4)$		1995JCD3215
	$[\text{Ag}(18\text{S}6)]^+$, $[\text{Ag}(18\text{S}6)](\text{PF}_6)$		1995AGE2374, 1997AGE2786, 1998JCD2931, 1999CC1513, 2004ZFA2669
	$[\text{Ag}(18\text{S}6)](\text{A})$	$\text{A}^- = \text{CF}_3\text{SO}_3, \text{BF}_4, \text{PF}_6$	1995AGE2374, 2004ZNB1077
	$\{[\text{Ag}(18\text{S}6)(\text{Br})]_{\infty}\}$		1995JCD3215, 1998JCD2931
	$[\text{Ag}(18\text{S}6)]^{2+}$		2004ZFA2669
	$[\text{Ag}(18\text{S}6)]\text{I}_3$		1995AGE2374
	$\{[\text{Ag}(18\text{S}6)]\text{I}_7\}_n$		1995AGE2374
	$[\text{Ag}_n(18\text{S}6)](\text{CF}_3\text{COO})_n$	$n = 2, 4$	2002JOC6632
	$[\text{Ag}_2(\text{pic})(18\text{S}6)]\text{pic}$	pic = picrate	2004ZNB1077
	$[\text{Ag}(18\text{UT}6)](\text{CF}_3\text{COO})$		2002JOC6632
	$[\text{Ag}(19\text{S}6)\text{-OH}]^+$, $[\text{Ag}(19\text{S}6)\text{-OH}](\text{CF}_3\text{SO}_3)$		1996BCC165, 1996IC3420
	$[\text{Ag}(20\text{S}6)\text{-OH}](\text{BF}_4)$		1996IC3420
	$[\text{Ag}_2(21\text{UT}7)](\text{CF}_3\text{COO})_2$		2002JOC6632
	$\{[\text{Ag}(24\text{S}8)(\text{CF}_3\text{SO}_3)_2(\text{MeCN})_2]_{\infty}\}$		1998JCD2931

	$[\text{Ag}_2(24\text{S8})(\text{CF}_3\text{SO}_3)_2(\text{MeCN})]_\infty$ $\{[\text{Ag}(\text{L})](\text{TsO})\}_\infty$	$\text{L} = 1\text{-hydroxymethyl-10-methyl-3,8,12,17,20,25-hexathiabicyclo[8.8.8]hexacosane}$ (Figure 3)	1997CC1943 1999CC1513
Au	$[\text{Ag}(27\text{S9})]^+$, $[\text{Ag}(27\text{S9})(\text{PF}_6)]$ $[\text{Ag}(27\text{S9})]^{2+}$ $[\text{Ag}_2(28\text{S8})](\text{NO}_3)_2$ $[\text{Au}(9\text{S3})_2]^{2+}$, $[\text{Au}(9\text{S3})_2](\text{BF}_4)_2$ $[\text{Au}(12\text{S4})]^{2+}$ $[\text{Au}(18\text{S6})](\text{BF}_4)_2$ $[\text{Au}_2(24\text{S8})](\text{PF}_6)_2$ $[\text{Au}(27\text{S9})](\text{BF}_4)_2$ $[\text{Au}_2(28\text{S8})](\text{PF}_6)_2$ $[\text{Au}_2(28\text{S8})]^{6+}$		2004ZFA2669 2004ZFA2669 1998JCD2931, 1998JCD3961 2002ZFA34, 2004ZFA2669 2002ZFA34, 2004ZFA2669 2004ZFA2669 1998JCD2931 2004ZFA2669 1998JCD2931, 1998JCD3961 1998JCD2931
	Zn $[\text{Zn}(10\text{S3})](\text{ClO}_4)_2 \cdot 2\text{CH}_3\text{NO}_2$ $[\text{Zn}(10\text{S3})_2](\text{BF}_4)_2$		2002ICA(338)182 2002ICA(338)182
	Cd $[\text{Cd}(9\text{S3})_2](\text{A})_2$ $[\text{Cd}(9\text{S3})_2](\text{ClO}_4)_2 \cdot 2\text{CH}_3\text{NO}_2$ $[\text{Cd}(9\text{S3})_2](\text{BF}_4)_2 \cdot 2\text{CH}_3\text{NO}_2$ $[\text{CdI}_2(9\text{S3})_2]$ $[\text{Cd}(10\text{S3})_2](\text{ClO}_4)_2$ $[\text{Cd}(10\text{S3})](\text{ClO}_4)_2 \cdot 2\text{CH}_3\text{NO}_2$ $[\text{Cd}(12\text{S3})_2](\text{ClO}_4)_2$ $[\text{Cd}(12\text{S4})_2](\text{ClO}_4)_2 \cdot 2\text{CH}_3\text{NO}_2$ $[\text{Cd}(14\text{S4})](\text{ClO}_4)_2 \cdot \text{H}_2\text{O}$ $[\text{Cd}(15\text{S5})](\text{ClO}_4)_2$ $[\text{Cd}(15\text{S5})_2](\text{ClO}_4)_2 \cdot \text{H}_2\text{O}$ $[\text{Cd}(16\text{S4})](\text{ClO}_4)_2$ $[\text{Cd}(16\text{S4})_2](\text{ClO}_4)_2$ $[\text{Cd}(18\text{S6})\text{I}_2]$ $[\text{Cd}(18\text{S6})\text{Cl}_2]$ $[(\text{CdI}_2)(24\text{S8})]$	$\text{A}^- = \text{ClO}_4, \text{PF}_6$	2006JCS(D)3534 2002ICA(338)182, 2003JCX445 1998JCD3961 1998JCD3961 2006JCD3534 2002ICA(338)182 2006JCD3534 2006JCD3534 2006JCD3534 2006JCD3534 1998JCD3961 2006JCD3534 1998JCD3961 2004ZNB1077 2003JOC3480 1998JCD3961
	Hg $[\text{Hg}(9\text{S3})](\text{PF}_6)_2$ $[\text{Hg}(9\text{S3})_2](\text{A})_2$ $[\text{Hg}(9\text{S3})_2](\text{PF}_6)_2$ $[\text{MeHg}(9\text{S3})](\text{BF}_4)$ $\{[\text{Hg}(9\text{S3})_2](\text{HgI}_3)_2\}_\infty$ $[\text{Hg}(10\text{S3})_2](\text{PF}_6)_2$ $[\text{Hg}(10\text{S3})](\text{ClO}_4)_2 \cdot 2\text{CH}_3\text{NO}_2$ $[\text{Hg}(10\text{S3})_2](\text{A})_2$ $[\text{Hg}(11\text{S3})](\text{ClO}_4)_2$ $[\text{Hg}(11\text{S3})\text{Cl}_2]$	$\text{A}^- = \text{ClO}_4, \text{PF}_6$ $\text{A}^- = \text{ClO}_4, \text{PF}_6$ 11S3 = 1,4,8-isomer 11S3 = 1,4,8-isomer	1998JCD3961 2002ICA(338)182, 2003JCX623, 2005IC5696 1998JCD2931 2006PCA9451 2000IC1035 2003JCX623 2002ICA(338)182 2005IC5696 2001ICA(317)91 2001ICA(317)91

(Continued)

Table 1 (Continued)

<i>Metal</i>	<i>Complex</i>	<i>Remarks</i>	<i>References</i>
	[Hg(12S3) ₂](ClO ₄) ₂		2005IC5696
	[Hg(12S4)](PF ₆) ₂		2005IC5696
	[HgI(12S4)][Hg ₂ I ₆]·CH ₂ Cl ₂		2004ZNB1077
	[HgCl ₂ (14S4)]		1998JCD3961
	[(HgCl ₂) ₂ (14S4)]		1998JCD2931, 2001AXC36
	[Hg(14S4)](ClO ₄) ₂		2005IC5696
	[Hg(14S4)(OH ₂)](ClO ₄) ₂		1998JCD3961
	[Hg(14S4)(OH ₂)(ClO ₄) ₂]		1998JCD2931
	[HgI ₂ (14S4)]		2004ZNB1077
	{[(HgI ₂) ₂ (14S4)]} _∞		1998JCD2931
	{[Hg(14S4)I ₂]} _∞		1995JCD3215
	[Hg(15S5)(PF ₆) ₂]		1998JCD2931
	[Hg(15S5)](A) ₂	A [−] = ClO ₄ , PF ₆	1998JCD3961, 2005IC5696
	[Hg ₅ (15S5) ₃ Cl ₁₀]		2003JOC3480
	[Hg(16S4)(ClO ₄) ₂]		1998JCD2931
	[Hg(16S4)](ClO ₄) ₂		1998JCD3961, 2005IC5696
	[(HgCl ₂) ₂ (16S4)]		1998JCD2931
	{[(HgCl ₂) ₂ (16S4)]} _∞		1998JCD2931
	[Hg(18S6)](A) ₂	A [−] = ClO ₄ , PF ₆	2005IC5696
	[Hg(18S6)Cl ₂]		2003JOC3480
	[Hg(18UT6)Cl ₂]		2003JOC3480
	[Hg ₂ (21S7)Cl ₄]		2003JOC3480
	[Hg(21UT7)Cl ₂]		2003JOC3480
	[(HgBr ₂) ₂ (24S8)]		1998JCD2931, 1998JCD3961
	[(HgBr ₂) ₂ (28S8)]		1998JCD2931

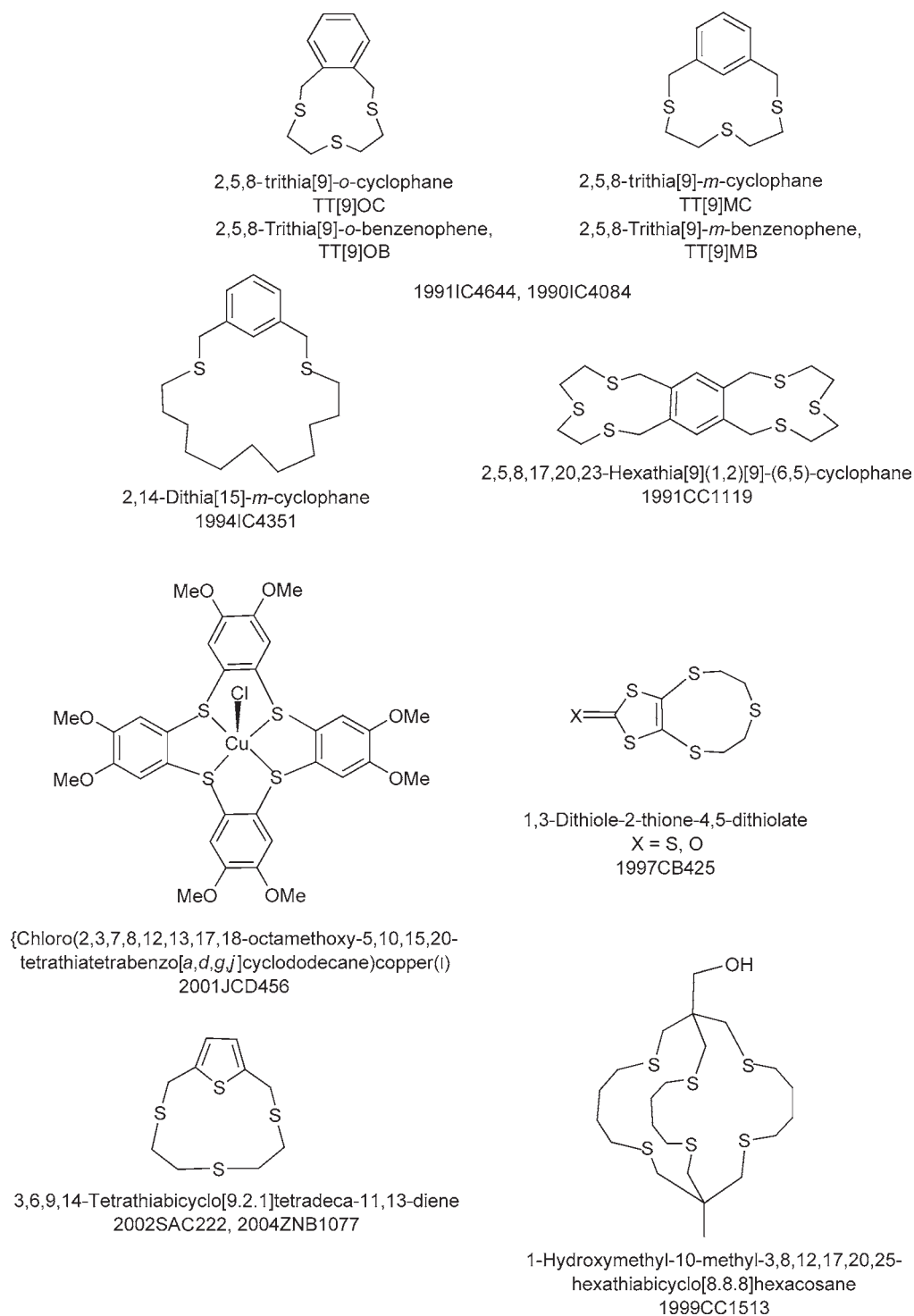


Figure 3 Structures of particular ligands from Table 1.

14.13.9 Ring Syntheses from Acyclic Compounds

In analogy to CHEC-II(1996), all ring syntheses and their according references are summarized in Table 2.

Table 2 Synthetic methods for sulfur-containing macrocycles in order of ring size, number of sulfur atoms, and substitution grade (the method code is specified at the end)

Macrocycle	Educts	Conditions	Method	Yield (%)	m.p. (°C)	References
<i>Thiacrown ethers</i>						
10S2	Dihalogenid 1: (CH ₂) ₄ Dihalogenid 2: (CH ₂) ₄	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst K ₂ CO ₃ , DMF, 120 °C	B	8	90–92	2003PS1295
10S3	TsO-(CH ₂) ₂ -S-(CH ₂) ₂ -S-(CH ₂) ₃ -OTs + HS-(CH ₂) ₂ -SH	K ₂ CO ₃ , DMF, 120 °C	A2	14	n.sp.	2005TL8057
2-Octyl-10S3	1-octyl-3-thiapentane-1,5-dithiol + 1,3-dibromopropane	Cs ₂ CO ₃ , dry DMF, 60 °C, 2 × 9 h	A	44	Oil	1995T4065
3-OH-10S3	2-mercaptoethyl sulfide + 1,3-dichloro-2-propanol	Na _{met.} , ethanol _{abs.} , reflux, 7 h	A3	41	87–89	1995CJC1023
10S3-9,9-di-MeOH	bis(2-mercaptoethyl) sulfide + 2,2-bis(bromomethyl-1,3-propanediol	Cs ₂ CO ₃ , anhydrous DMF, 60 °C, 42 h	A	10.4	157–158	1998HAC123
9-Me-10S3-9-COOH	bis(2-mercaptoethyl) sulfide + 3,3'-dichloropivalic acid	Cs ₂ CO ₃ , anhydrous DMF, rt, 66 h	A	33.5	225–227	1998HAC123
11S3 (1,5,9)	TsO-(CH ₂) ₃ -S-(CH ₂) ₂ -S-(CH ₂) ₃ -OTs + HS-(CH ₂) ₂ -SH	K ₂ CO ₃ , DMF, 150 °C	A2	47	n.sp.	2005TL8057
11S3 (1,5,9)	TsO-(CH ₂) ₃ -S-(CH ₂) ₂ -S-(CH ₂) ₃ -OTs + HS-CH ₂ -(CHCH ₂ OH)-SH	K ₂ CO ₃ , DMF, 90 °C	A2	40	n.sp.	2005TL8057
11S3 (1,4,7)	TsO-(CH ₂) ₂ -S-(CH ₂) ₄ -S-(CH ₂) ₂ -OTs + HS-(CH ₂) ₂ -SH	K ₂ CO ₃ , DMF, 150 °C	A2	28	n.sp.	2005TL8057
9,10-(OH) ₂ -11S3 (1,4,7)	Bis(2-mercaptoethyl) sulfide + 1,4-dibromo-2,3-butanediol	Cs ₂ CO ₃ , anhydrous DMF, 60 °C, 42 h	A	14.1	178–180	1998HAC123
11S3-2-en-2,3-dinitril (1,4,8)	Disodium dithiomaleonitrile + 4-thianonane-1,9-ditosylate	DMF, 90 °C, 20 h	A1/A2	47	152–155	1995T8175
2,5,8-Trithia[9]- <i>o</i> -benzenenophane (TT[9]OB)	3-Thiapentane-1,5-dithiol + α,α'-dibromo- <i>o</i> -xylene	K _{met.} , anhydr. EtOH, 84 h	A	21	98.5–100	1990IC4084
2,5,8-Trithia[9]- <i>o</i> -benzenenophane (TT[9]OB)	3-Thiapentane-1,5-dithiol + α,α'-dibromo- <i>o</i> -xylene	Cs ₂ CO ₃ , DMF, 55 °C, 24 h	A	n.sp.	n.sp.	1996ICA(246)207
Me ₂ -TT[9]OB	3-Thiapentane-1,5-dithiol + 1,2-dibromomethyl-4,5-dimethylbenzene	Cs ₂ CO ₃ , DMF, 55 °C, 24 h	A	n.sp.	n. sp.	1996ICA(246)207
2,5,8-Trithia[9]- <i>m</i> -benzenenophane (TT[9]MB)	3-Thiapentane-1,5-dithiol + α,α'-dibromo- <i>m</i> -xylene	K _{met.} , anhydr. EtOH, 4 h	A	46	144–145	1990IC4084
2,5,8-Trithia[9](9,10)anthracenophane ('11S3')	2-Mercaptoethylsulfide + 9,10-bis(chloromethyl)anthracene	KOH, EtOH (95%), reflux, 3 h	A	54	>210	1998JOC181

11S4 (thioacetal) (1,3,6,9)	3,6-Dithiaoctane-1,8-dithiol + methylene bromide	Cs ₂ CO ₃ , DMF, 55 °C	A	67	n.sp.	1998TL6357
3,9-Dithiabicyclo[9.3.1]-pentadeca-1(15), 11,13-triene ('benzo-12-S2')	Penta-1,5-dithiol + α,α' -dichloro- <i>m</i> -xylene	KOH, butan-1-ol, 18 h	A	30	n.sp.	1991JCD1969
12S3	TsO-(CH ₂) ₃ -S-(CH ₂) ₃ -S-(CH ₂) ₃ -OTs + HS-(CH ₂) ₂ -SH	K ₂ CO ₃ , DMF, 150 °C	A2	47	n.sp.	2005TL8057
12S3	Thietane + [W(CO) ₅ -thietane] as catalyst	14.5 mg catalyst, 94 °C (b.p. of thietane), 48 h	C	n.sp.	n.sp.	1996CB313
12S3	Thietane + [Os ₄ (CO) ₁₁ (thietane)(μ -H) ₄] as catalyst	14 mg catalyst, 94 °C (b.p. of thietane), 24 h	C	Ratio 12S3:24S6 = 6:1	n.sp.	1995OM4594
12S3	Thietane + [Re ₂ (CO) ₉ (thietane)] as catalyst	15 mg catalyst, 94 °C (b.p. of thietane), 24 h	C	Ratio 12S3:24S6 = 5.7:1	n.sp.	1995OM1748, 2000ACR171
12S3	Thietane + [Re ₃ (CO) ₁₀ -(μ -S-(CH ₂) ₃ -12S3)(μ -H) ₃] as catalyst	17 mg catalyst, 94 °C (b.p. of thietane), 48 h	C	Ratio 12S3:24S6 = 0.56:1	n.sp.	1995CRV2587
12S3-di-MeOH	Bis(3-mercaptopropyl) sulfide + 2,2-bis(bromomethyl)-1,3-propanediol	Cs ₂ CO ₃ , anhydrous DMF, 60 °C, 42 h	A	9.2	170–172	1998HAC123
3,6,9-Trithiabicyclo[9.3.1]-pentadeca-1(15),11,13-triene ('benzo-12S3')	Bis(2-mercaptoethyl) sulfide + α,α' -dichloro- <i>m</i> -xylene	KOH, butan-1-ol, 18 h	A	30	n.sp.	1991JCD1969
Me-12S3-COOH	Bis(3-mercaptopropyl) sulfide + 3,3'-dichloropivalic acid	Cs ₂ CO ₃ , anhydrous DMF, rt, 66 h	A	10.8	181–183	1998HAC123
3,7,11-Me ₃ -12S3 in two isomeric forms: <i>cis,trans,trans</i> and <i>cis,cis,cis</i> (60:13)	3-Methyl-thietane + [Re ₂ (CO) ₉ -3-Me-thietane] or [W(CO) ₅ -3-Me-thietane] as catalyst	108–109 °C (b.p. of 3-Me-thietane), 10 mg catalyst, 24 h in the dark	C	n.sp.	n.sp.	1996OM2489, 2000ACR171, 2000JOM(596)115
Me ₆ -12S3	3,3-Dimethylthietane + [Re ₂ (CO) ₉ (3,3-Me ₂ -thietane)] as catalyst	16 mg catalyst, 100 °C, 72 h	C	10	n.sp.	1997OM2612, 2000ACR171, 2000JOM(596)115
12S4	Thiirane + [W(CO) ₅ (NCCH ₃)] as catalyst	10 mg catalyst, DMAD (1 ml), CH ₂ Cl ₂ , 25 °C, 6 h	C	n.sp.	n.sp.	1997OM1430, 2000JOM(596)115, 2000ACR171, 2002JOM(652)51
12S4	Thiirane + [Mn(NCMe)(PPhMe ₂)(CO) ₄](BPh ₄) as catalyst	19.7 mg catalyst, rt, 48 h	C	36	n.sp.	2001ICC671
12S4 (di-thioacetal) (1,3,7,9)	4,6-Dithianonane-1,9-dithiol + methylene bromide	Cs ₂ CO ₃ , DMF, 55 °C	A	68	n.sp.	1998TL6357
12UT-4	<i>cis</i> -1,2-Dichloroethylene + Na ₂ S	acetonitrile, rt, 45 h	A1	Trace	n.sp.	2001JA11534
2-Octyl-12S4	4-Octyl-3,6-dithiaoctane-1,8-dithiol + 1,1-dibromoethane	Cs ₂ CO ₃ , dry DMF, 60 °C, 2 × 9 h	A	40	72–74	1995T4065

(Continued)

Table 2 (Continued)

<i>Macrocycle</i>	<i>Educts</i>	<i>Conditions</i>	<i>Method</i>	<i>Yield (%)</i>	<i>m.p. (°C)</i>	<i>References</i>
Oxathiane-12S4 (Figure 1)	<i>cis</i> -2,5-Bis(chloromethyl)-1,4-oxathiane + 3-thiapentane-1,5-dithiol	K ₂ CO ₃ , DMF, 80–110 °C	A	12	102–105	1997IC6216
2,6-Diketo-12S4	Thiodiglycolyl dichloride + 2-mercaptoethyl sulfide	Dry benzene, 50–60 °C, 3 d	A	11	119–121	1995ICA(230)133
2,8-(CH ₂ SCH ₃) ₂ -12S4	14S4-Cl ₂ + sodium methylthiolate	DMF, 65 °C, 28 h	D	19	n.sp.	1997JOC8459
13S3 (1,5,9)	TSO-(CH ₂) ₃ -S-(CH ₂) ₄ -S-(CH ₂) ₃ -OTs + HS-(CH ₂) ₂ -SH	K ₂ CO ₃ , DMF, 150 °C	A2	24	n.sp.	2005TL8057
(OH) ₂ -13S3	Bis(3-mercaptopropyl) sulfide + 1,4-dibromo-2,3-butanediol	Cs ₂ CO ₃ , anhydrous DMF, 60 °C, 42 h	A	11.4	149–152	1998HAC123
13S4	X-(CH ₂) ₂ -S-(CH ₂) ₂ -S-(CH ₂) ₃ -X + HS-(CH ₂) ₂ -SH (X = Cl, OTs)	K ₂ CO ₃ , DMF, 120 °C	A or A2	14	n.sp.	2005TL8057
13S4 (Thioacetal) (1,3,7,10)	4,7-Dithiadecane-1,10-dithiol + methylene bromide	Cs ₂ CO ₃ , DMF, 55 °C	A	54	n.sp.	1998TL6357
HO-13S4	1,3-Dichloro-2-propanol + 3,6-dithiaoctane-1,8-dithiol	K ₂ CO ₃ , DMF, 80–110 °C	A	28.6	127–128	1997IC6216
HO-13S4	1,3-Dichloro-2-propanol + 3,6-dithiaoctane-1,8-dithiol	Cs ₂ CO ₃ , DMF, 75 °C, 48 h	A	14.5	n.sp.	2006POL599
13S4-CH ₂ Cl	14S4-Cl	DMF, reflux, 26 h	D	94	n.sp.	1997JOC8459
13S4-CH ₂ SCH ₃	13S4-CH ₂ Cl + methylthiolate	DMF, 65 °C, 38 h	S	86	Colorless oil	1997JOC8459
2,3-Benzo-13S4	3,7-dithianonane-1,9-dithiol + (η^5 -cp)(η^6 -1,2-dichlorobenzene)iron(II) bis(hexafluorophosphate)	Dry THF, K ₂ CO ₃ , 60 °C, 24 h, column chromatography	A	30	n.sp.	1997JCD1889
14S2-(1,7)	Dihalogenid 1: (CH ₂) ₆ Dihalogenid 2: (CH ₂) ₆	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	12	78–79	2003PS1295
14S2-(1,9)	Dihalogenid 1: (CH ₂) ₈ Dihalogenid 2: (CH ₂) ₄	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	10	65–67	2003PS1295
(2,5,8)-14S3-1,9-dione	2,2-Dibutyl-2-stanna-1,3,6-trithiacyclooctane + pimeloyl dichloride	Dry CHCl ₃ , reflux, 16 h, 2,2'-bipyridine, column chromatography for separation from the dimeric product	T	62	118–119	2004JOC8550
14S4 (1,4,7,12)	X-(CH ₂) ₂ -S-(CH ₂) ₄ -S-(CH ₂) ₂ -X + HS-(CH ₂) ₂ -SH (X = Cl, OTs)	K ₂ CO ₃ , DMF, 150 °C	A or A2	5	n.sp.	2005TL8057

14S4 (1,4,7,11)	X-(CH ₂) ₃ -S-(CH ₂) ₂ -S-(CH ₂) ₃ -X + HS-(CH ₂) ₂ -SH (X = Cl, OTs)	K ₂ CO ₃ , DMF, 150 °C	A or A2	2	n.sp.	2005TL8057
14S4	Dihalogenid 1: 2(CH ₂) ₃ Dihalogenid 2: 2(CH ₂) ₂	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	10	118–119	2003PS1295
14S4 (thioacetal) (1,3,7,11)	4,8-Dithiaundecane-1,11-dithiol + methylene bromide	Cs ₂ CO ₃ , DMF, 55 °C	A	75	n.sp.	1998TL6357
<i>cis</i> -Cyclopentyl-14S4	1,2-Ethanedithiol + <i>cis</i> -1,2-bis((3-chloropropyl)thio)cyclopentane	Cs ₂ CO ₃ , DMF, 65–70 °C, 12.5 h	A	17.4	71–72	2000IC2897
<i>trans</i> -Cyclopentyl-14S4	1,2-Ethanedithiol + <i>trans</i> -1,2-bis((3-chloropropyl)thio)cyclopentane	Cs ₂ CO ₃ , DMF, 65–70 °C, 12.5 h	A	25	75–76	2000IC2897
6-Octyl-14S4	3,7-Dithianonane-1,9-dithiol + 1-chloro-2-chloromethyl-decane	Cs ₂ CO ₃ , dry DMF, 60 °C, 2 × 9 h	A	19	41	1995T4065
OH-14S4	3,7-dithia-1,9-nonanedithiol + 1,3-dichloro-2-propanol	Na _{met} , ethanol, 4 d, then reflux for 12 h	A3	66	111–113	1996RFP47
14S4- <i>p</i> -vinyl-benzylether	OH-14S4 + <i>p</i> -chloromethylstyrene	NaH, DMF, 0 °C during addition of <i>p</i> -chloromethylstyrene, then room temperature, 4 h	S	61	Viscous liquid product	1996RFP47
3-Cl-14S4	3-OH-14S4 + CCl ₄	PPh ₃ , 32 h, 76.5 °C	S	93	n.sp.	1997JOC8459
NHMe-14S4	First step: 28S4-OH + SOCl ₂ Second step: product of first step (2-chloromethyl-14S4) + CH ₃ NH ₂	First step: CH ₂ Cl ₂ , 6 h, MeOH, solvent removed Second step: CH ₃ CN, Na ₂ CO ₃ , 0 °C, 12 h	Dissoc.	100	Yellow oil	2000RFP111
N(Me)(4-vinylbenzyl)-14S4	NHMe-14S4 + 4-vinylbenzyl chloride	CH ₃ CN, Na ₂ CO ₃ , reflux, 12 h	S	66	Colorless oil	2000RFP111
2-MeOH-14S4	Br-(CH ₂) ₃ -S-(CH ₂) ₂ -S-(CH ₂) ₃ -Br + HS-CH ₂ -(CHCH ₂ OH)-SH	Cs ₂ CO ₃ , 45 °C	A	57	n.sp.	2005TL8057
3,10-Cl ₂ -14S4	3,10-OH-14S4 + CCl ₄	PPh ₃ , 76.5 °C, 42 h	S	89	n.sp.	1997JOC8459
14S4-2-en-2,3-dinitrile	Disodium dithiomaleonitrile + 4,7-dithiadodecane-1,12-ditosylate	DMF, 90 °C, 20 h	A1/A2	45	125–127	1995T8175
2,3-Benzo-14S4	1,2-Bis((3-chloropropyl)thio)benzene + 1,2-ethanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C	A	10.9	116–117	1995IC357
2,3- <i>cis</i> -Cyclohexano-14S4	<i>cis</i> -1,2-Bis((3-chloropropyl)thio)cyclohexane + 1,2-ethanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C	A	28.5	92–93	1995IC357
2,3,9,10-Dibenzo-14S4	1,2-Bis((3-chloropropyl)thio)benzene + 1,2-ethanedithiol	K ₂ CO ₃ , DMF, 85–95 °C	A	35.9	153–154	1995IC357
2,3-Benzo-9,10- <i>cis</i> -cyclohexano-14S4	1,2-Bis((3-chloropropyl)thio)benzene + <i>cis</i> -1,2-cyclohexanedithiol	K ₂ CO ₃ , DMF, 85–95 °C	A	14.7	103–104	1995IC357
2,3-Benzo-9,10- <i>trans</i> -cyclohexano-14S4	1,2-Bis((3-chloropropyl)thio)benzene + <i>trans</i> -1,2-cyclohexanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C	A	18.6	76–78	1995IC357

(Continued)

Table 2 (Continued)

<i>Macrocyclic</i>	<i>Educts</i>	<i>Conditions</i>	<i>Method</i>	<i>Yield (%)</i>	<i>m.p. (°C)</i>	<i>References</i>
<i>syn</i> -2,3,9,10- <i>cis,cis</i> -Dicyclohexano-14S4	<i>cis</i> -1,2-Bis((3-chloropropyl)thio)cyclohexane + 1,2-cyclohexanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C, separation of the diastereomeric mixture by silica gel/CH ₂ Cl ₂	A	7.9	113–114	1995IC357
<i>anti</i> -2,3,9,10- <i>cis,cis</i> -Dicyclohexano-14S4	<i>cis</i> -1,2-Bis((3-chloropropyl)thio)cyclohexane + 1,2-cyclohexanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C, separation of the diastereomeric mixture by silica gel/CH ₂ Cl ₂	A	15.5	182–184	1995IC357
<i>meso</i> -2,3,9,10- <i>trans,trans</i> -Dicyclohexano-14S4	<i>trans</i> -1,2-Bis((3-chloropropyl)thio)cyclohexane + <i>trans</i> -1,2-cyclohexanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C, separation of the diastereomeric mixture by fractionated recrystallization	A	11.8	162–164	1995IC357
<i>d,l</i> -2,3,9,10- <i>trans,trans</i> -Dicyclohexano-14S4	<i>trans</i> -1,2-bis((3-chloropropyl)thio)cyclohexane + <i>trans</i> -1,2-cyclohexanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C, separation of the diastereomeric mixture by fractionated recrystallization	A	9.4	111–114	1995IC357
2,3- <i>cis</i> -9,10- <i>trans</i> -Dicyclohexano-14S4	<i>trans</i> -1,2-bis((3-chloropropyl)thio)cyclohexane + <i>cis</i> -1,2-cyclohexanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C	A	21.2	103–105	1995IC357
<i>syn</i> -2,3,9,10- <i>cis,cis</i> -Dicyclopentano-14S4	<i>cis</i> -1,2-Bis((3-chloropropyl)thio)cyclopentane + <i>cis</i> -1,2-cyclopentanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C, separation of the diastereomeric mixture by silica gel/CH ₂ Cl ₂	A	11	139–141	2006IC923
<i>anti</i> -2,3,9,10- <i>cis,cis</i> -Dicyclopentano-14S4	<i>cis</i> -1,2-Bis((3-chloropropyl)thio)cyclopentane + <i>cis</i> -1,2-cyclopentanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C, separation of the diastereomeric mixture by silica gel/CH ₂ Cl ₂	A	16	150–151	2006IC923
<i>meso</i> -2,3,9,10- <i>trans,trans</i> -Dicyclopentano-14S4	<i>trans</i> -1,2-Bis((3-chloropropyl)thio)cyclopentane + <i>trans</i> -1,2-cyclopentanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C, separation of the diastereomeric mixture by fractionated recrystallization	A	13	119–120	2006IC923
<i>d,l</i> -2,3,9,10- <i>trans,trans</i> -Dicyclopentano-14S4	<i>trans</i> -1,2-Bis((3-chloropropyl)thio)cyclopentane + <i>trans</i> -1,2-cyclopentanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C, separation of the diastereomeric mixture by fractionated recrystallization	A	12	83–84	2006IC923
2,3- <i>cis</i> -9,10- <i>trans</i> -Dicyclopentano-14S4	<i>trans</i> -1,2-Bis((3-chloropropyl)thio)cyclopentane + <i>cis</i> -1,2-cyclopentanedithiol	Cs ₂ CO ₃ , DMF, 85–95 °C	A	19	82–83	2006IC923
2,3-Benzo-6,13-(OH) ₂ -14S4	1,10-Dichloro-4,7-dithiadecane-2,9-diol + benzene-1,2-dithiol	dry DMF, Cs ₂ CO ₃ , 100 °C, 18 h	A	30 (total for <i>cis</i> - and <i>trans</i> -isomers)	148	1997JCD1889

2,3,9,10-Dibenzo-6,13(OH) ₂ -14S4 15S4	5,6-Benzo-1,10-dichloro-4,7-dithiadecane-2,9-diol + benzene-1,2-dithiol X-(CH ₂) ₃ -S-(CH ₂) ₃ -S-(CH ₂) ₃ -X + HS-(CH ₂) ₂ -SH (X = Cl, OTs)	Dry DMF, Cs ₂ CO ₃ , 100 °C, 24 h K ₂ CO ₃ , DMF, 150 °C	A A or A2	20 7	210 n.sp.	1997JCD1889 2005TL8057
HO-15S4 15S5	1,3-Dichloro-1-propanol + 4,7-dithiadecane-1,10-dithiol Thiirane + [W(CO) ₅ (NCCH ₃)] as catalyst	K ₂ CO ₃ , DMF, 80–110 °C 10 mg catalyst, DMAD (1 ml), CH ₂ Cl ₂ , 25 °C, 6 h	A C	23.4 n.sp.	85–86 n.sp.	1997IC6216 1997OM1430, 2000ACR171, 2002JOM(652)51
15S5 2,6-Diketo-15S5	Thiirane + [Mn(NCMe)(CO) ₅](BPh ₄) as catalyst Thiodiglycolyl dichloride + 1,4,7,10-tetrathiadecane	19.9 mg catalyst, rt, 48 h Dry benzene, 50–60 °C, 3 d	C A	24 51	n.sp. 92–94	2001ICC671 1995ICA(230)133
15UT-5 16S4 (1,4,8,13)	<i>cis</i> -1,2-Dichloroethylene + Na ₂ S X-(CH ₂) ₃ -S-(CH ₂) ₄ -S-(CH ₂) ₃ -X + HS-(CH ₂) ₂ -SH (X = Cl, OTs)	Acetonitrile, rt, 45 h K ₂ CO ₃ , DMF, 120 °C	A1 A or A2	8 24	n.sp. n.sp.	2001JA11534 2005TL8057
16S4	Dihalogenid 1: 2(CH ₂) ₃ Dihalogenid 2: 2(CH ₂) ₃	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	10	51–53	2003PS1295
HO-16S4 3-Octyl-16S4	1,3-Dichloro-2-propanol + 4,8-dithiaundecane-1,11-dithiol 4,8-Dithiaundecane-1,11-dithiol + 1-chloro-2-chloromethyl-decane	K ₂ CO ₃ , DMF, 80–110 °C Cs ₂ CO ₃ , dry DMF, 60 °C, 2 × 9 h	A A	32 5	74–76 Oil	1997IC6216 1995T4065
Me ₈ -16S4 16S4-2,6,10,13-tetrone	3,3-dimethylthietane + [Re ₂ (CO) ₉ (3,3-Me ₂ -thietane)] as catalyst β-propiothirolactone + [Re ₂ (CO) ₉ (NCMe)] as catalyst	16 mg catalyst, 100 °C, 72 h 25 °C	C C	3 22	n.sp. n.sp.	1997OM2612 1996JA9442
3,4,11,12-Dibenzo-2,5,10,13-tetralactone-16S4 2,6-Diketo-16S5	phthalic acid + ethanedithiole Thiodiglycolyl dichloride + 1,4,8,11-tetrathiaundecane	DCC/DMAP, CHCl ₃ , 0 °C, 8 h Dry benzene, 50–60 °C, 3 d	O A	80 15.5	280 79–80	2005TAL993 1995ICA(230)133
2,10-Diphenyl-16S6 (1,3,6,9,11,14 = diacetal) Thiacalix[4]arene ('16S8') 17S2	3-Thiapentane-1,5-dithiol + benzaldehyde Thiophene + SCl ₂ Dihalogenid 1: (CH ₂) ₁₀ Dihalogenid 2: (CH ₂) ₅	Benzene, TsOH, 80 °C, 8 h BuLi–TMEDA Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	A2 O B	62 1 21	n.sp. n.sp. 69–71	1995CTC289 1997JCM69 2003PS1295
(2,5,8,11)-17S4-1,12-dione	2,2-Dibutyl-2-stanna-1,3,6,9-tetrathiacycloundecane + pimeloyl dichloride	Dry CHCl ₃ , reflux, 16 h, 2,2'-bipyridine, column chromatography for separation from the dimeric product	T	45	Colorless oil	2004JOC8550

(Continued)

Table 2 (Continued)

Macrocyclic	Educts	Conditions	Method	Yield (%)	m.p. (°C)	References
17S5-OH	2,3-Dimercapto-1-propanol + 4,7,10-trithiadecane-1,13-di-OTs	Cs ₂ CO ₃ , DMF, 90 °C, 24 h	A	29	37–39	1998CC1637, 2000RFP111
17S5-NHMe	Educt: 17S5-OH	2 step process as for 14S4-NHMe	S	62	Yellow oil	1998CC1637, 2000RFP111
17S5-N(Me)(4-vinylbenzyl)	17S5-NHMe + 4-vinylbenzyl chloride	CH ₃ CN, reflux, 12 h	S	76	Yellow oil	2000RFP111
18S2	Dihalogenid 1: (CH ₂) ₈ Dihalogenid 2: (CH ₂) ₈	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	25	51–52	2003PS1295
18S4	Dihalogenid 1: 2(CH ₂) ₄ Dihalogenid 2: 2(CH ₂) ₃	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	24	59–60	2003PS1295
Dinaphthalene-18S4 (tricyclic) (Figure 1)	1-Bromo-4-iodo-naphthalene + propyl-1,3-dithiolate	Light	A	13	Dec.	1996TL1603
18S6	Thiirane + [Mn(NCMe(CO) ₅](BPh ₄) as catalyst	19.9 mg catalyst, rt, 48 h	C	9.9	n.sp.	2001ICC671
18UT-6	<i>cis</i> -1,2-Dichloroethylene + Na ₂ S + 15-crown-5 as phase-transfer catalyst	0.1 equiv catalyst, acetonitrile, 40 °C, 45 h	A 1	19	n.sp.	2001JA11534
Dioctyl-18S6 (as by-product of 2-octyl-9S3)	1-Octyl-3-thiapentane-1,5-dithiol + 1,2-dichloroethane	Cs ₂ CO ₃ , dry DMF, 60 °C, 2 × 9 h	A	24	Oil	1995T4065
2,6,11,15-Tetraketo-18S6	Thiodiglycolyl dichloride + 1,2-ethanedithiol	Dry benzene, 50–60 °C, 3 d	A	10.8	172–173	1995ICA(230)133
2,3,5,6,11,12,14,15- Tetrabenzo-18S6	Bis(<i>o</i> -mercaptophenyl) sulfide + 1,2-dibromoethane	Cs ₂ CO ₃ , DMF, room temperature, 25 h	A	19	198–198.5	1999T10057
2,3,7,8,10,11,15,16- tetrabenzo- 18S6-2,5,8,11,14,17-hexaene	Bis(<i>o</i> -mercaptophenyl) sulfide + <i>cis</i> -1,2-dichloroethylene	EtONa, EtOH, reflux, 6 h	A	20	248–250	1999T10057
2,3,11,12-(1',3'- Dithiole-2'-one) ₂ -18S6 ^b	Dicesium 1,3-dithiole-2-one-4,5-dithiolate + 3-thia-1,5-dibromopentane	DMF, 45 min	A	75	229–231	1996LA551
2,3,11,12-(1',3'- Dithiole-2'-thione) ₂ -18S6 ^b	Dicesium 1,3-dithiole-2-thione-4,5-dithiolate + 3-thia-1,5-dibromopentane	DMF, 45 min	A	79	247–249	1996LA551
Tetrathiafulvalene-18S6 ^c	2,3,11,12-(1',3'-dithiole-2'-thione) ₂ -18S6 ^b	P(OEt) ₃ , 140 °C, 2 h	O	48	282–283 (dec.)	1996LA551
19S6-OH	1,9-Mercapto-3,7-dithia-5-nonanol + 3,6-dithia-1,8-dichlorooctane	Cs ₂ CO ₃ , DMF, 60 °C, 80 h, then room temperature, 24 h	A	32	n.sp.	1996IC3420
(<i>E,Z</i>)-3,8-2,7-Bis (methylsulfanyl) tetrathiafulvalene-19S6 ^d (Figure 4)	(<i>E,Z</i>)-3,6(7)-Bis(3-bromopropylsulfanyl)- 2,7(6)-bis(methylsulfanyl)- tetrathiafulvalene <1996BCC165> + propane-1,3-dithiol	Cs ₂ CO ₃ , DMF	A	60	n.sp.	1999CC1417

20S4	Dihalogenid 1: 2(CH ₂) ₄ Dihalogenid 2: 2(CH ₂) ₄	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst Light	B	14	31–32	2003PS1295
Dinaphthaline-20S4 (tricyclic) (Figure 1)	1-Bromo-4-iodo-naphthaline + butyl-1,4-dithiolate		A	16	175–179	1996TL1603
(2,5,8,11,14)-20S5-1, 15-dione	2,2-Dibutyl-2-stanna-1,3,6,9,12-pentathiaicyclotetradecane + pimeloyl dichloride	Dry CHCl ₃ , reflux, 16 h, 2,2'-bipyridine, column chromatography for separation from the dimeric product	T	28	Colorless oil	2004JOC8550
Me ₁₀ -20S5	3,3-Dimethylthietane + [Re ₂ (CO) ₉ (3,3-Me ₂ -thietane)] as catalyst	16 mg catalyst, 100 °C, 72 h	C	3	n.sp.	1997OM2612
20S6	2-Mercaptoethyl sulfide + 1,3-dibromo-2-propane	Na _{met.} , ethanol _{abs.} , reflux, 7 h	A3	40	122–124	1995CJC1023
20S6 (thioacetal) (1,3,6,10,14,18)	3,7,11,15-Tetrathiaheptadecane-1,17-dithiol + methylene bromide	Cs ₂ CO ₃ , DMF, 55 °C	A	75	n.sp.	1998TL6357
20S6-OH	1,9-Mercapto-3,7-dithia-5-nonanol + 3,7-dithia-1,9-dichlorononane	Cs ₂ CO ₃ , DMF, 60 °C, 80 h, then rt, 24 h	A3	35	n.sp.	1996IC3420
20S6-OH	3,6,10,13-Tetrathia-1,15-pentadecanedithiol + 1,3-dichloro-2-propanol	Na _{met.} , ethanol, 4 d, then reflux for 12 h	A3	n.sp.	n.sp.	1996RFP47
20S6- <i>p</i> -vinyl-benzylether	OH-20S6 + <i>p</i> -chloromethyl-styrene	NaH, DMF, 0 °C during addition of <i>p</i> -chloromethylstyrene, then rt, 4 h	S	36	n.sp.	1996RFP47
20S6-(OH) ₂	2 1,3-dichloropropane-2-ol + 2 3-thia-1,5-pentanedithiol	Cs ₂ CO ₃ , DMF, 75 °C, 48 h	A	22 (2 isomers)	n.sp.	2006POL599
2,6,12,16-Tetraketo-20S6	Thiodiglycolyl dichloride + 1,3-propanedithiol	Dry benzene, 50–60 °C, 3 d	A	33.8	131–132	1995ICA(230)133 1997LA2177, 2000CSR153
Tris(dimethyl-sulfidotetrathiafulvalene)-21S6 (1,4,8,11,15,18)						
21UT-7	<i>cis</i> -1,2-Dichloroethylene + Na ₂ S + 15-crown-5 as phase-transfer catalyst	0.4 equiv catalyst, acetonitrile, 40 °C, 45 h	A1	16	n.sp.	2001JA11534
(<i>E,Z</i>)-3,8-2,7-Bis(methylsulfanyl)tetrathiafulvalene–21S7 ^d (Figure 4)	(<i>E,Z</i>)-3,6(7)-Bis(3-bromopropylsulfanyl)-2,7(6)-bis(methylsulfanyl)tetrathiafulvalene <1998EJO1861> + 4-thiapentane-1,5-dithiol	Cs ₂ CO ₃ , DMF	A	52	n.sp.	1999CC1417
22S2	Dihalogenid 1: (CH ₂) ₁₀ Dihalogenid 2: (CH ₂) ₁₀	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	19	48–50	2003PS1295

(Continued)

Table 2 (Continued)

Macrocycle	Educts	Conditions	Method	Yield (%)	m.p. (°C)	References
Dinaphthaline-22S6 (tricyclic) (Figure 1)	1-Bromo-4-iodo-naphthaline + 2-sulfidopentyl-1,5-dithiolate	Light	A	20	164–168	1996TL1603
22S6-2,13-dien-2,3,13,14-tetranitrile (by-product of 11S3-2-en-2,3-dinitrile)	Disodium dithiomaleonitrile + 4-thianonane-1,9-ditosylate	DMF, 90 °C, 20 h	A1/A2	12	129–132	1995T8175
1-Hydroxymethyl-9-methyl-3,7,11,15,18,22-hexathiabicyclo[7.7.7]-tricosane (23S6)	CH ₃ C(CH ₂ -S-(CH ₂) ₃ -SH) ₃ + HO-CH ₂ C(CH ₂ OTs) ₃	Cs ₂ CO ₃	A	<30	n.sp.	1999CC1513
(<i>E,Z</i>)-3,8-2,7-Bis(methylsulfanyl)-tetrathiafulvalene-23S7 ^d 24S6 ^a	(<i>E,Z</i>)-3,6(7)-Bis(3-bromopropylsulfanyl)-2,7(6)-bis(methylsulfanyl)tetrathiafulvalene <1998EJO1861> + 4-thiaheptane-1,7-dithiol Thietane + [W(CO) ₅ -thietane] as catalyst	Cs ₂ CO ₃ , DMF	A	49	n.sp.	2002ICA(338)182
24S6 ^a	Thietane + Ru ₄ (CO) ₁₁ (thietane)(μ-H) ₄ as catalyst	14.5 mg catalyst, 94 °C (b.p. of thietane), 48 h	C	n.sp.	n.sp.	1996CB313
24S6 ^a	Thietane + Re ₂ (CO) ₉ (thietane) as catalyst	14 mg catalyst, 94 °C (b.p. of thietane), 24 h	C	Ratio 12S3:24S6 = 0.7:1	n.sp.	1995OM4594
24S6 ^a	Thietane + Re ₃ (CO) ₁₀ (μ-S-(CH ₂) ₃ -12S3)(μ-H) ₃ as catalyst	15 mg catalyst, 94 °C (b.p. of thietane), 72 h	C	Ratio 12S3:24S6 = 1.3:1	n.sp.	1995OM1748
3,3,7,7,11,11,15,15,19,19,23,23-Me ₁₂ -24S6	3,3-Me ₂ -thietane + Re ₃ (CO) ₁₀ (μ-S-(CH ₂) ₃ -12S3)(μ-H) ₃ as catalyst	17 mg catalyst, 94 °C (b.p. of thietane), 48 h	C	Ratio 12S3:24S6 = 0.56:1	n.sp.	1995CRV2587
24S6-2,6,10,14,18,22-hexone	β-Propiothiolacton + [Re ₂ (CO) ₉ (NCMe)] as catalyst	17 mg catalyst, 94 °C (b.p. of thietane), 48 h	C	n.sp.	n.sp.	1995CRV2587
24UT-8	<i>cis</i> -1,2-Dichloroethylene + Na ₂ S + 15-crown-5 as phase-transfer catalyst	25 °C	C	2	n.sp.	1996JA9442
2,3,14,15-(1',3'-dithiole-2'-thione) ₂ -24S8 ^b	Dicesium 1,3-dithiole-2-thione-4,5-dithiolate + 3,6-dithia-1,8-dibromooctane	0.4 equiv catalyst, acetonitrile, 40 °C, 45 h	A1	10	n.sp.	2001JA11534
Tetrathiafulvalene-24S8 ^c	2,3,14,15-(1'3'-Dithiole-2'-thione) ₂ -24S8 ^b	DMF, 45 min	A	81	187–189	1996LA551
1-Hydroxymethyl-10-methyl-3,8,12,17,20,25-hexathiabicyclo[8.8.8]-hexacosane (26S6) (Figure 3)	CH ₃ C(CH ₂ -S-(CH ₂) ₄ -SH) ₃ + HO-CH ₂ C(CH ₂ OTs) ₃	P(OEt) ₃ , 140 °C, 2 h	O	29	277–279 (dec.)	1996LA551
		Cs ₂ CO ₃	A2	<30	n.sp.	1999CC1513

26S8-(OH) ₂	2,1,3-Dichloropropane-2-ol + 2,3,6-dithiaoctane-1,8-dithiole	Cs ₂ CO ₃ , DMF, 75 °C, 48 h	A	2.5	n.sp.	2006POL599
27UT-9	<i>cis</i> -1,2-Dichloroethylene + Na ₂ S	Acetonitrile, rt, 45 h	A1	6	n.sp.	2001JA11534
2,3,5,6,11,12,14,15, 20,21,23,24-Hexabenzotriphenyl- 27S9	Bis(<i>o</i> -mercaptophenyl) sulfide + 1,2-dibromoethane	Cs ₂ CO ₃ , DMF, rt, 25 h	A	5	148.5– 149	1999T10057
28S4-(1,7,14,21)	Dihalogenid 1: 2(CH ₂) ₆ Dihalogenid 2: 2(CH ₂) ₆	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	22	71–73	2003PS1295
28S4-(1,9,14,23)	Dihalogenid 1: 2(CH ₂) ₈ Dihalogenid 2: 2(CH ₂) ₄	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	9	47–48	2003PS1295
(2,5,8,16,19,22)-28S6- 1,9,15,23-tetraone	2,2-Dibutyl-2-stanna-1,3,6-trithiacyclooctane + pimeloyl dichloride	Dry CHCl ₃ , reflux, 16 h, 2,2'-bipyridine, column chromatography for separation from the monomeric product	T	20	98–100	2004JOC8550
30S6	Dihalogenid 1: 3 (CH ₂) ₄ Dihalogenid 2: 3 (CH ₂) ₄	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. CsOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	5	71–73	2003PS1295
2,3,17,18-(1',3'- Dithiole-2'-thione) ₂ -30S10 ^b	Dicesium 1,3-dithiole-2-thione-4,5-dithiolate + 3,6,9-trithia-1,11-dibromoundecane	DMF, 45 min	A	76	198–200	1996LA551
Tetrathiafulvalene-30S10 ^c	2,3,17,18-(1',3'-Dithiole-2'-thione) ₂ -30S10 ^b	P(OEt) ₃ , 140 °C, 2 h	O	50	279–281 (dec.)	1996LA551
34S4	Dihalogenid 1: 2 (CH ₂) ₁₀ Dihalogenid 2: 2 (CH ₂) ₅	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	4	57–59	2003PS1295
(2,5,8,11,19,22,25,28)- 34S8-1,12,18,29-tetraone	2,2-Dibutyl-2-stanna-1,3,6,9-tetrathiacycloundecane + pimeloyl dichloride	Dry CHCl ₃ , reflux, 16 h, 2,2'-bipyridine, column chromatography for separation from the monomeric product	T	9	Colorless wax	2004JOC8550

(Continued)

Table 2 (Continued)

<i>Macrocycle</i>	<i>Educts</i>	<i>Conditions</i>	<i>Method</i>	<i>Yield (%)</i>	<i>m.p. (°C)</i>	<i>References</i>
36S4	Dihalogenid 1: 2(CH ₂) ₈ Dihalogenid 2: 2(CH ₂) ₈	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst DMF, 45 min	B	9	53–56	2003PS1295
2,3,20,21-(1',3'- Dithiole-2'-thione) ₂ -36S12 ^b	Dicesium 1,3-Dithiole-2-thione-4,5-dithiolate + 3,6,9,12- tetrathia-1,14-dibromotetradecane		A	58	188–191	1996LA551
Tetrathiafulvalene-36S12 ^c (2,5,8,11,14,22,25,28,31,34)- 40S10-1,15,21,35-tetraone	2,3,20,21-(1',3'-dithiole-2'-thione) ₂ -36S12 ^b 2,2-Dibutyl-2-stanna-1,3,6,9,12- pentathiacyclotetradecane + pimeloyl dichloride	P(OEt) ₃ , 140 °C, 2 h Dry CHCl ₃ , reflux, 16 h, 2,2'-bipyridine, column chromatography for separation from the monomeric product	O T	0.5 7	n.sp. Colorless wax	1996LA551 2004JOC8550
44S4	Dihalogenid 1: 2(CH ₂) ₁₀ Dihalogenid 2: 2(CH ₂) ₁₀	Step 1: CHCl ₃ , reflux 2–3 h Step 2: benzene/aq. NaOH, 60–65 °C, 6 h; TBAB as phase-transfer catalyst	B	18	70–72	2003PS1295
<i>Disulfides</i>						
10S2	1,8-Octanedithiol	Br ₂ , hydrated silica gel, CH ₂ Cl ₂	Oxid.	86	n.sp.	2002TL6271
10S4	2 Propane-1-3-dithiol	CsF–celite, O ₂ , CH ₃ CN	Oxid.	84	53–54	2003TL6789
12S6	Thiirane + [W(CO) ₅ -(NCMe)] as catalyst	CH ₂ Cl ₂ , 10 mg catalyst, 25 °C, 6 h	C	16	n.sp.	1996JA10674, 1997OM1430, 2000ACR171, 2002JOM(652)51
12S6	HS-CH ₂ -CH ₂ -SH	Re(Me ₂ SO) as catalyst	Oxid.	13	n.sp.	1997JA9309
16S8	Thiirane + [W(CO) ₅ -(NCMe)] as catalyst	CH ₂ Cl ₂ , 10 mg catalyst, 25 °C, 6 h	C	6	n.sp.	1996JA10674, 1997OM1430, 2000ACR171, 2002JOM(652)51
16S8	HS-CH ₂ -CH ₂ -SH	Re(Me ₂ SO) as catalyst	Oxid.	9	n.sp.	1997JA9309
20S10	Thiirane + [W(CO) ₅ -(NCMe)] as catalyst	CH ₂ Cl ₂ , 10 mg catalyst, 25 °C, 6 h	C	5	n.sp.	1996JA10674, 1997OM1430, 2000ACR171, 2002JOM(652)51
20S10	HS-CH ₂ -CH ₂ -SH	Re(Me ₂ SO) as catalyst	Oxid.	13	n.sp.	1997JA9309

Polysulfanes

1,2,3,4,5,6,7-Heptathiononane (9S7)	$\text{C}_2\text{H}_4(\text{SCl})_2 + \text{Cp}_2\text{TiS}_5$ <1992PS151>	CH_2Cl_2 , 20 °C, 40 min	O	31	63	1991CB2357
9-Methyl-1,2,3,4,5,6,7-benzoheptathionine	$\text{H}_3\text{C}-\text{C}_6\text{H}_3(\text{SCl})_2 + \text{Cp}_2\text{TiS}_5$ <1992PS151>	CCl_4 , 20 °C, 40 min	O	60	84.5	1991CB2357

^aRecently, it was outlined by Adams that 24S6 is not a pure product but a mixture of smaller ring systems <2000ACR171>.

^bFor clearness, the sulfur atoms within the two 1,3-dithiole-2-thione moieties are not encountered in the thiacyclopentadiene ring system.

^cFor clearness, the sulfur atoms within the TTF moiety are not encountered in the thiacyclopentadiene ring system.

^dIn this case, two sulfur atoms of the bridged TTF unit are integrated in the thiacyclopentadiene ring system.

DMAD, dimethyl acetylenedicarboxylate; TBAB, tetrabutylammonium bromide; n.sp.: not specified.

Method code:

A: α,ω -dithiols + α,ω -dihalogenides, M_2CO_3 (Section 14.13.9.1).

A1: α,ω -dihalogenides + Na_2S .

A2: α,ω -dithiols + α,ω -ditosylates.

A3: α,ω -dithiols + α,ω -dihalogenides, Na_{met} .

B: thioacetamide as educt (Section 14.13.9.2).

C: catalytic ring extension (Section 14.13.10.1).

D: ring contraction (Section 14.13.10.2).

Dissoc.: dissociation.

O: other.

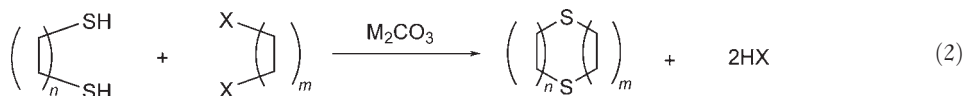
Oxid: oxidation.

S: substitution.

T: Template synthesis (Section 14.13.9.4).

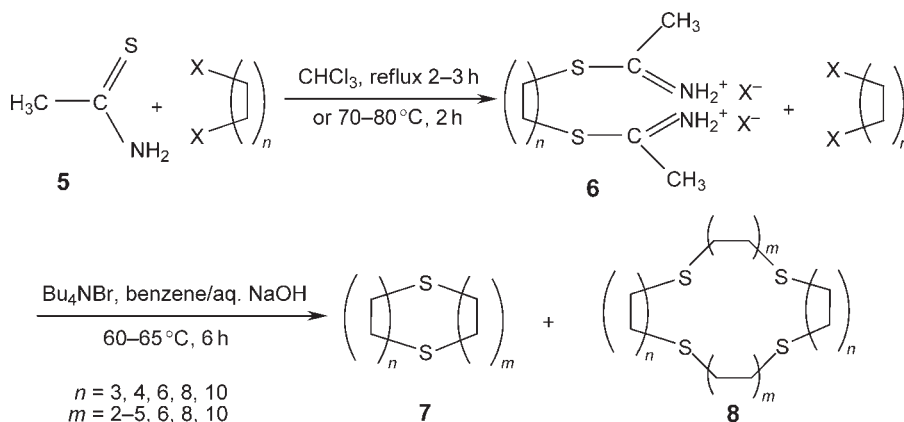
14.13.9.1 Dithiols and Their Sodium Salts as Starting Material in Thiacycrown Formation

As outlined in CHEC-II(1996) (Chapter 9.30, Table 2), the main route to sulfur macrocycles (especially thiacycrowns) is by reacting α,ω -dithiols with α,ω -dihalides under alkaline conditions generally Cs_2CO_3 or in some cases K_2CO_3 (Equation 2). This all-purpose method is still in use <1995T4065, 1996IC3420, 1997JCD1889, 1998HAC123, 1999T10057, 2005TL8057> and only minor modifications have been incorporated, such as using tosylates instead of halides <2000RFP111, 1998CC1637, 1995T8175, 2005TL8057>, metallic sodium in place of carbonate <1996RFP47, 1995CJC1023>, or adding 15-crown-5, as phase-transfer catalyst leaving out the base completely <2001JA11534>. Again, the range of yields is as wide as shown in table 2 of the former edition (1–90%).



14.13.9.2 Thioacetamide as Starting Material in Crown Thioether Formation

A new cyclization process was published in 2003 <2003PS1295>, where dithiols are substituted by dithioiminium salts, which can be created by reacting thioacetamide **5** with α,ω -dihalides. In a second step, the dithioiminium salts **6** are treated with (different) α,ω -dihalides adding sodium hydroxide, as base, and tetrabutylammonium bromide, as phase-transfer catalyst (Scheme 2). Thus, two kinds of macrocycles are found in the final reaction mixture: XS2 (1:1 ratio) **7** and (2X)S4 (2:2 ratio) **8**.



Scheme 2

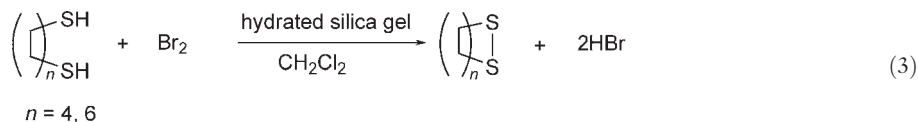
The main advantage of this convenient two-step process is avoiding the unpleasant odor of the dithiols, whereas the yields of the resulting macrocycles are lower than in the above-mentioned general procedure. With only one exception (37%), yields do not exceed 25%. As for the side products, linear polymeric sulfides occur. Only by varying the alkali metal of the hydroxide, the result of the reaction can be influenced. Using cesium instead of sodium hydroxide, the 1:1 ratio product is nearly completely suppressed (2% compared to 8%) and the yield of the 2:2 ratio product is elevated from 14% to 17%. Furthermore, the 3:3 ratio product (3X)S6 is generated, as a third macrocycle, with a yield of 5%.

14.13.9.3 Formation of Cyclic Di- and Symmetrical Tetrasulfides by Oxidation of Dithiols

14.13.9.3.1 Bromine as oxidizing agent

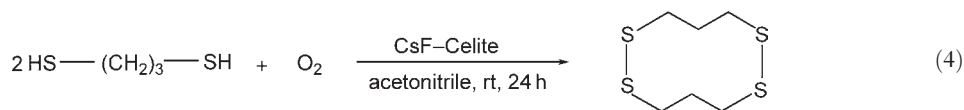
It is commonly known that disulfides are formed by oxidation of thiols, thus numerous oxidizing agents can be applied: Ce(IV) , MnO_4^- , H_2O_2 , halogens, *et al.* Halogens are readily available and cheap but the resulting hydrogen halides cause undesirable side reactions, which are difficult to avoid. Therefore, a new simple approach to make disulfides by oxidation of thiols is by using neat bromine <2002TL6271>. The reaction is carried out on hydrated silica gel, which neutralizes the resulting HBr and simplifies product extraction. In two cases, the method has been tested for cyclization of 1,6-hexanedithiol

and 1,8-octanedithiol (Equation 3). The yields of the cyclic disulfides are found to be 91% and 86%, respectively, which is significantly higher than that of other oxidative ring formations previously published <1989CSR409, 1994JCS1354>.



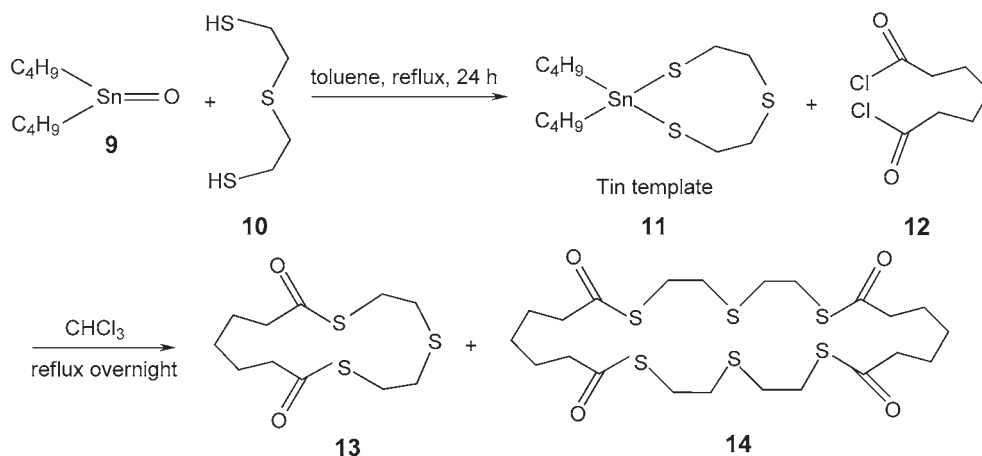
14.13.9.3.2 Cesium fluoride–Celite as catalyst for oxidation by atmospheric oxygen

Another oxidation process for dithiols simply applies atmospheric oxygen at 25 °C using CsF adsorbed onto Celite, as a catalytic solid base <2003TL6789>. In this case, two dithiols are condensed to symmetric tetrasulfides (Equation 4). Concerning the mechanism, the authors suggest a twofold action: (1) activation of the thiol group by the fluoride ion whose ionic character is enhanced by the cesium cation, and (2) activation of the alkyl group by a Lewis acid-type effect. Further benefit by CsF–Celite is gained in the workup procedure which is reduced to filtration only. Two cyclic tetrasulfides besides a number of linear disulfides have been synthesized this way with good yields: 8S4 with 79% and 10S4 (presented by Equation 4) with 84%.



14.13.9.4 Template Synthesis: Preparation of Thialactones

When α,ω -dithiols are reacted with dibutyltin oxide, stannathianes are formed and used as templates for the preparation of thialactones <2004JOC8550> (Scheme 3). The example template shown in Scheme 3 is easily obtained, when dibutyltin oxide **9** is suspended in toluene and heated to reflux. Then 3-thiapentane-1,5-dithiol **10** dissolved in toluene is added dropwise and the resulting mixture is refluxed for 24 h. After cooling to 25 °C the product is concentrated by vacuum and the residue is purified by chromatography to give 2,2-dibutyl-2-stannatrithia-cyclooctane **11** in 83% yield. When **11** is treated with pimeloyl dichloride **12**, two thialactones are obtained: **13** (1:1 ratio product, 63%), and **14** (2:2 ratio product, 20%).



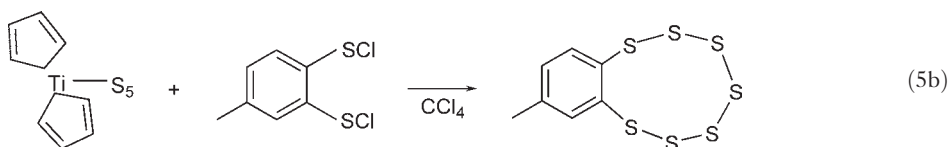
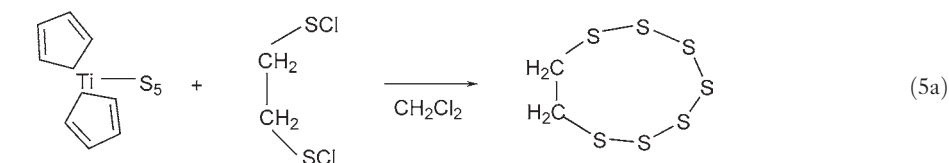
Scheme 3

Further attempts have been made to synthesize tin templates containing larger rings, for example, 2,2-dibutyl-2-stanna-1,3,6,9-tetrathiacycloundecane **11a** from 3,6-dithiaoctane-1,8-dithiol **10a** and 2,2-dibutyl-2-stanna-1,3,6,9,12-pentathiacyclotetradecane **11b** from 3,6,9-trithiaundecane-1,11-dithiol **10b**. Both **11a** and **11b** cannot be prepared applying the same conditions as for **11**. In case of the higher homologue tin templates, catalytic amounts of *p*-toluenesulfonic acid have to be added for a successful conversion. Since these templates decompose on silica gel,

separation of the products is only possible by fractionated crystallization. The 2,2-dibutyl-2-stanna-1,3,6,9,12-pentathiacyclotetradecane **11b** could not be purified and has been directly treated with **12** to give both thialactones with a yield of 28% for the 1:1 ratio product and 7% for the 2:2 ratio product, respectively.

14.13.9.5 Preparation of a Cyclic Heptasulfane Using Titanocene Pentasulfide as Sulfur-Donating Compound

According to Equations (5a) and (5b), sulfur-rich rings can be formed by reacting Cp_2TiS_5 with ethyl-1,2-bis(sulfenyl chloride) or the 3,4-sulfenyl chloride of toluene at 25 °C in dichloromethane (DCM) and CCl_4 , respectively. In both cases, the side products are homologous linear sulfides (S_n , $n = 2\text{--}11$ for the ethyl series and $n = 5\text{--}7$ and $9\text{--}11$ for the aromatic variants). Nevertheless, the cyclic products can be isolated by column chromatography with a yield of 31% for the C-2 product and 61% for the aromatic heptasulfane <1991CB2357>.

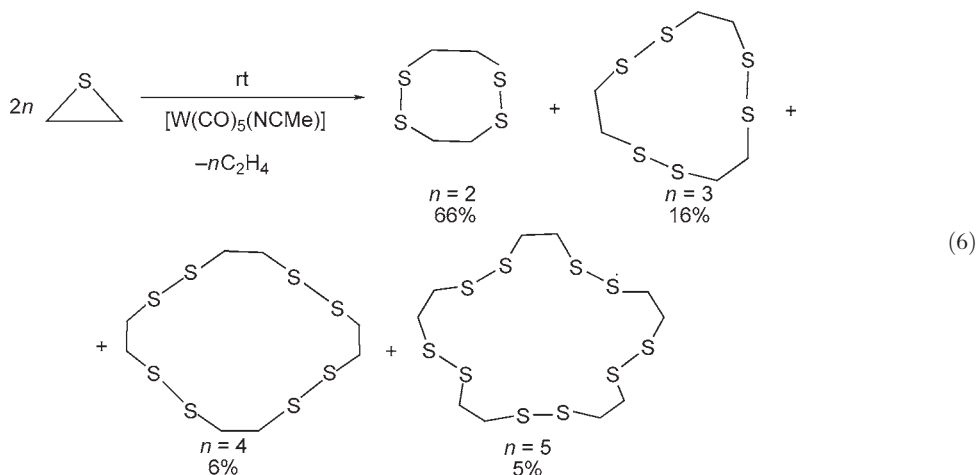


14.13.10 Ring Syntheses by Transformation of Another Ring

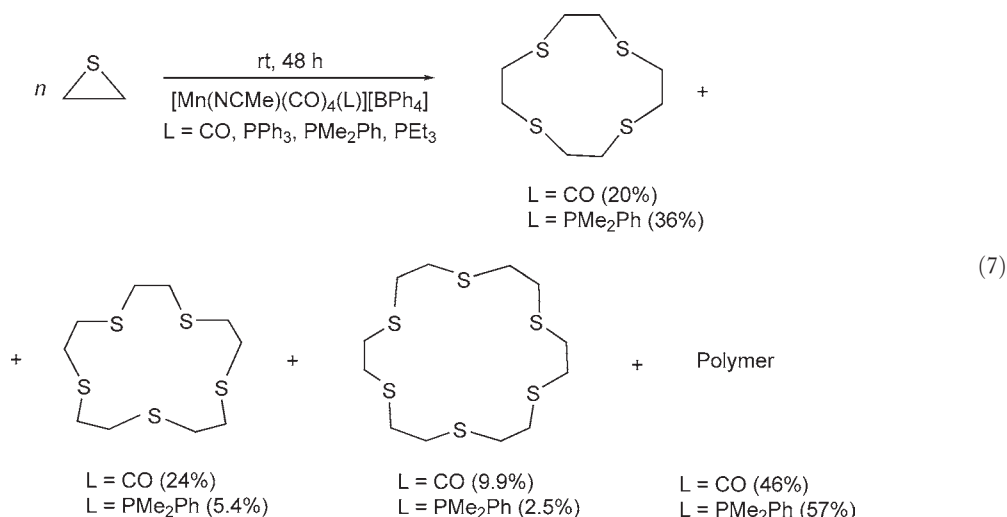
14.13.10.1 Ring Extension

14.13.10.1.1 Thiirane as starting ring system

Two different sulfur-containing ring systems can be derived from the strained three-membered thiirane depending on the catalyst used. With $[\text{W}(\text{CO})_5(\text{NCMe})]$ <1996JA10674, 2000ACR171, 1997OM1430>, cyclic disulfides are formed (Equation 6), which can be separated by thin-layer chromatography (TLC) on silica gel.

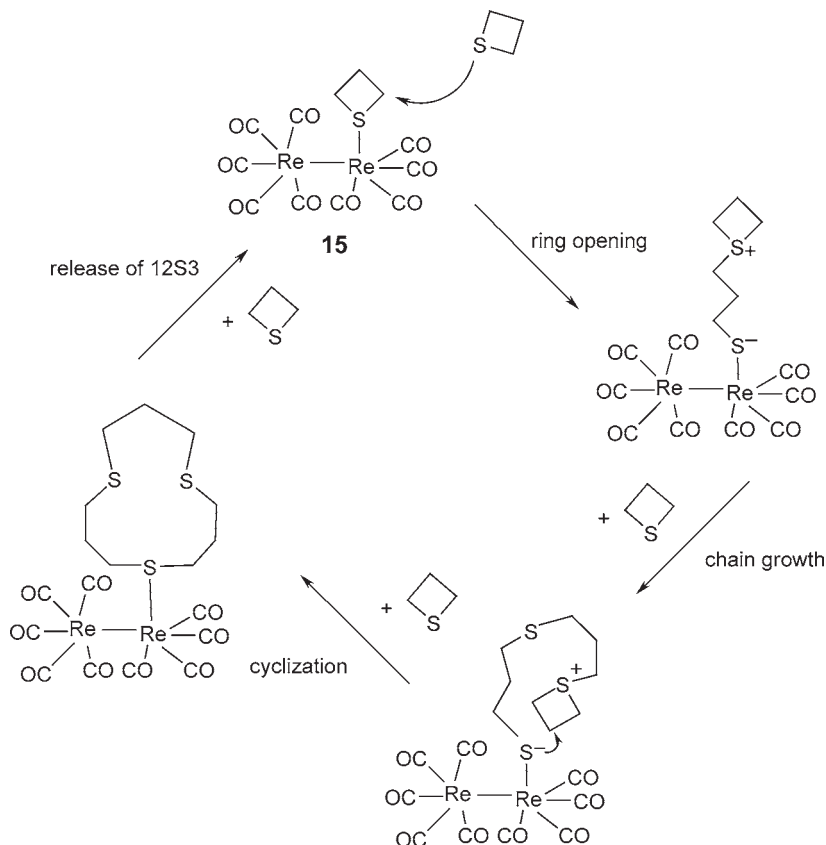


If $[\text{W}(\text{CO})_5(\text{NCMe})]$ is used in combination with dimethyl acetylenedicarboxylate (DMAD) <2002JOM(652)51> or when some kind of cationic manganese carbonyl complex <2001ICC671> is employed, instead of the tungsten catalyst, symmetrical crown thioethers are obtained (Equation 7). Substitution of one carbonyl moiety by a phosphinic ligand significantly enhances the catalytic activity of the manganese complex resulting in higher yields for 12S4 but unfortunately also for the polymer.



14.13.10.1.2 Thietane as starting ring system

When the four-membered thietane is used, only as the educt, thiacycrown (e.g., 12S3, 16S4, and 24S6) are formed by action of a metal catalyst [<1995OM4594>](#). The initial step of this catalytic ring-opening cyclooligomerization (ROC) [<1996CB313>](#) is the binding of a metal carbonyl complex to a thietane via its sulfur atom forming **15**. When a second thietane is connected, the first ring is opened and chain growth is started. The following thietane leads to further chain growth or to cyclization. Finally, 12S3, 16S4, or 24S6 is released from the metal complex, while **15** is reconstituted by additional thietane [<1995CRV2587>](#). This proposed mechanism is presented by [Scheme 4](#).



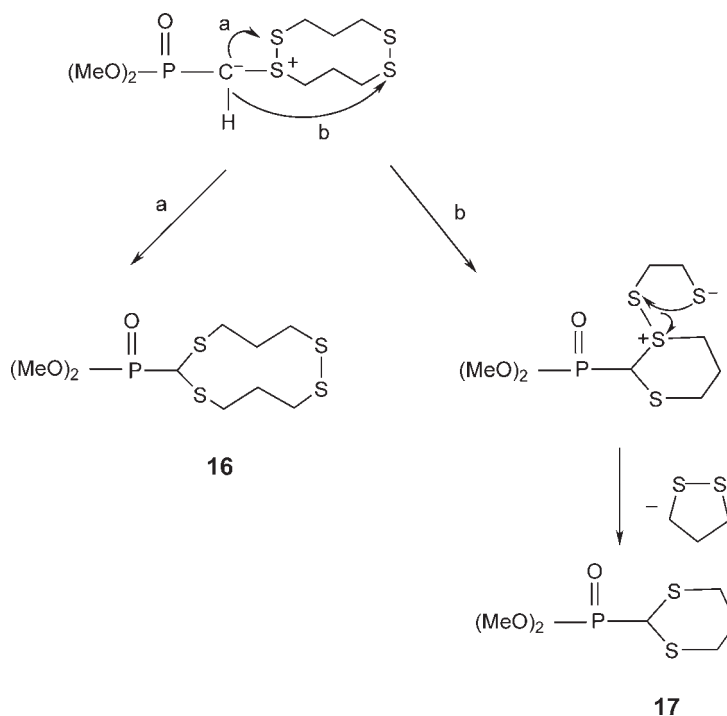
Scheme 4

Adams *et al.* have tested different catalysts, different amounts of catalyst, and different reaction times to see which would deliver the best results <1995OM1748, 1995OM4594, 1996OM2489, 1996CB313>. The highest 12S3:24S6 ratio (8:1) has been found for 14.8 mg of $[\text{Os}_4(\text{CO})_{11}(12\text{S3})(\mu\text{-H})_4]$, and a reaction time of 24 h under the irradiation of a tungsten lamp <1995OM4594>. But in this case, the overall yield is not really high: only 332 mg of the product is formed. Using 12.2 mg of $[\text{Os}_4(\text{CO})_{11}(\text{thietane})(\mu\text{-H})_4]$, as catalyst, 458 mg of the product is realized with a 12S3:24S6 ratio of 4:1. From the point of view of 24S6 synthesis, the best result is given by 10 mg of $\text{Cr}(\text{CO})_6$ and a reaction time of 24 h, where a 12S3:24S6 ratio of 0.4:1 is obtained. But again, the overall yield with 97 mg is still rather poor <1996CB313>.

Besides the examination of the pure ROC mechanism by trying different catalytic conditions, Adams *et al.* have focused on the cyclooligomerization of substituted thietanes: 3-methyl-thietane <1996OM2489>, 3,3-dimethyl-thietane <1997OM2612>, and β -propiothirolactone <1996JA9442>. In the case of 3-methylthietane, two isomers are formed: *cis,cis,cis*-3,7,11-Me₃-12S3 and *cis,trans,trans*-3,7,11-Me₃-12S3. This isomerization is induced by the different orientation of the methyl group within the ring <1996OM2489>. An interesting variant is found when the chiral 2-methylthietane is employed in cyclooligomerization as its pure (*R*)-enantiomer: Only *R,R,R*-2,6,10-Me₃-12S3 and *R,R,R,R*-2,6,10,14-Me₄-16S4 are obtained via the catalytic reaction with $[\text{Re}_2(\text{CO})_9(2\text{-Me-thietane})]$ <2000JOM(596)115>. Unfortunately, this catalyst is not the most active as shown earlier <1996OM2489>, and, furthermore, 2-methyl-thietane is less reactive than 3-methyl-thietane, which seems due to steric effects caused by the direct neighborhood of sulfur atom and methyl group <2000JOM(596)115>.

14.13.10.1.3 Insertion of α -phosphorylcarbene moiety into a disulfide bond

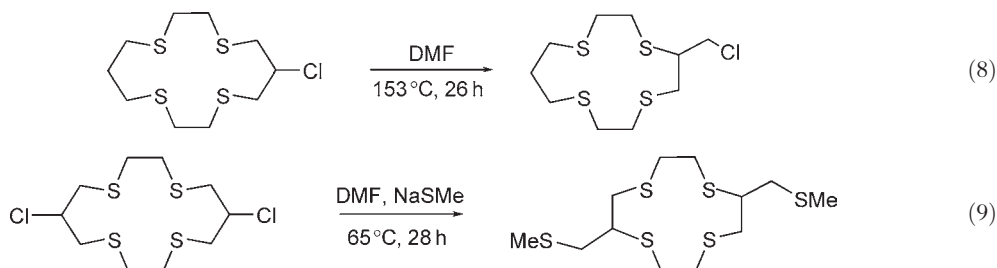
A special ring-extension reaction is presented by Mikołajczyk *et al.*, who treated disulfides with diazomethanephosphonates under catalysis with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ <1996S1232>. The resulting products are thioacetals by an insertion into the S–S bond of the disulfide. When 1,2,6,7-tetrathiacyclodecane is employed as the disulfide, two products are generated: the phosphonic ester of the corresponding tetrathiacycloundecane **16** (the extended ring system) and the phosphonic ester of 1,3-dithiacyclohexane **17**, which is the rearrangement product of the 10-membered ring that occurred during insertion. The proposed mechanism of this process is shown in Scheme 5.



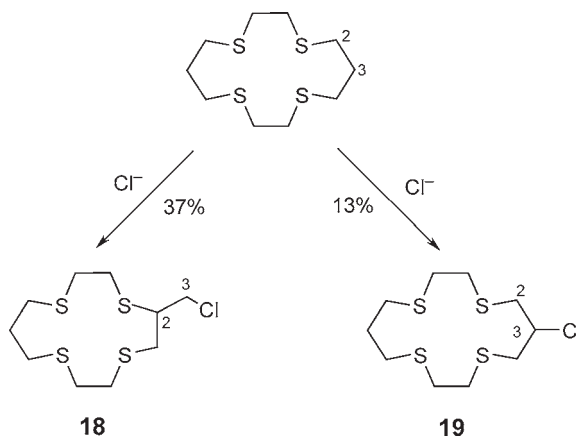
Scheme 5

14.13.10.2 Ring Contraction

To our knowledge, the only ring-contraction reaction is presented by Comba *et al.* <1997JOC8459>. Starting from Cl-14S4, ClCH₂-13S4 is prepared when it is heated to reflux in dimethylformamide (DMF; Equation 8). When Cl₂-14S4 is employed and NaSMe is added to the reaction mixture, a double contraction affording (MeSCH₂)₂-12S4 is realized (Equation 9).



Further studies in this field have shown that chlorination of pure 14S4 leads to two products depending on which C-atom within the ring is attacked by the chloride ion. If the attack takes place at C-3, a 'normal' chlorination occurs and Cl-14S4 is formed. If C-2 is attacked, the contracted ring system ClCH₂-13S4 is realized (Scheme 6). According to the findings of Comba *et al.*, the latter is preferred as can be seen from the yields within the reaction mixture: ClCH₂-13S4 **18** (37%) and Cl-14S4 **19** (13%).



Scheme 6

14.13.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

14.13.11.1 Thiacro crowns

The main class of sulfur macrocycles discussed in this chapter is the symmetrical variety, better known as thiacro crowns. As mentioned above, the best synthetic route to thiacro crowns is generally used and has only been slightly varied in selected cases (see Section 14.13.9.1). Nevertheless, other routes have been investigated, but neither the synthesis via thioacetamide (see Section 14.13.9.2) nor the catalytic ring-opening oligomerization (see Section 14.13.10.1.2) gives good yields. Especially, the latter reaction seems to be more of an artifact than of synthetic benefit. At least, thioacetamide helps to avoid the unpleasant odor of the dithiols, which might be an inducement enough to leave the 'classic' synthetic route.

14.13.11.2 Thiacro crown-Derivatized TTFs

The authors of CHEC-II(1996) have already presented a special procedure where a symmetrically double-bridged TTF is formed (see Scheme 1 of CHEC-II(1996)). In the past decade, not only the same reaction type has been

extended to the preparation of larger rings <1996LA551> but also a number of further derivatives consisting of tetrathiafulvalene and thiacyclopentadiene units in various combinations have been synthesized <1997LA2177, 2000CSR153, 1999CC1417>. A selection of those structural formulas is presented in Figure 4.

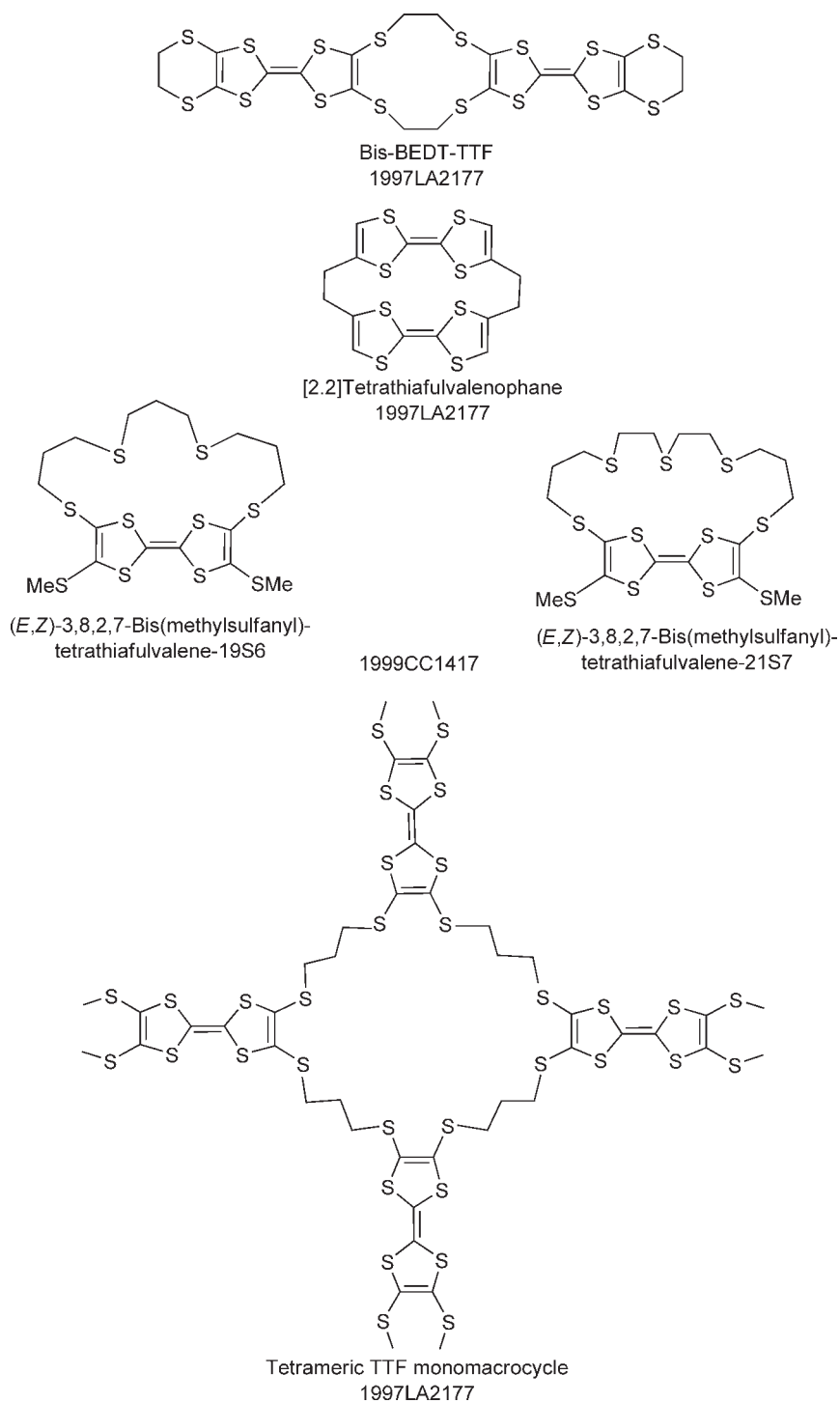
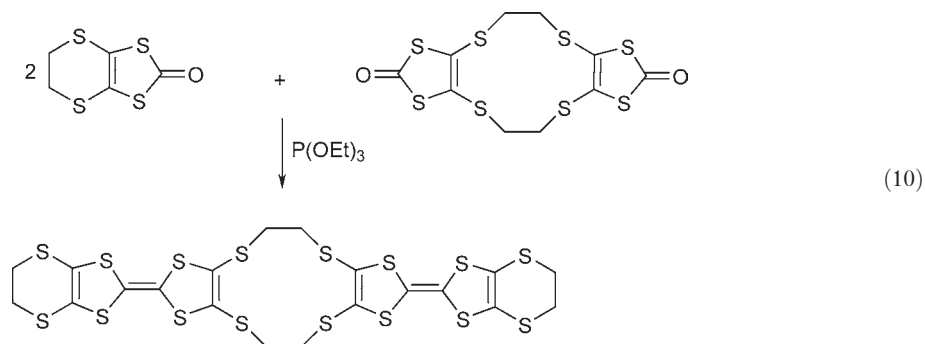


Figure 4 Sulfur macrocyclic derivatives of tetrathiafulvalene (TTF).

Concerning the synthesis of the TTF derivatives, no special arrangements are necessary; the singly bridged TTFs, for example, are synthesized via the ‘classic’ route starting from an appropriately substituted TTF <1999CC1417>, and the TTFs with a thiacycrown center are prepared by an intermolecular phosphite coupling in analogy to the intramolecular reaction mentioned in CHEC-II(1996) <1997LA2177> (Equation 10). Larger ring systems are formed using TTF chains ending in nitrile functions, aqueous cesium hydroxide, and 1,3-diiodopropane, which is only a variant of the general procedure <1997LA2177>. The yields of these processes are rather high and range from 38% to 78%.



14.13.12 Important Compounds and Applications

14.13.12.1 Metal-Selective Electrodes

As shown through Table 1, the sulfur macrocycles are essential in chelating metal cations. Thus, this property is used in designing special membrane electrodes, where the sulfur rings are embedded as ionophores. The desired selectivity is created by ring size and ring substitution: 12S4 for Cd(II) <2001TAL1065>, 3,6,9,14-tetrathiabicyclo[9.2.1]tetradeca-11,13-diene (see Figure 3) for Cu(II) <2002SAC222>, B₂O₄16S4 (see Figure 1) is selective for Tl(I) <2005TAL993>, 18S6 for Ag(I) <2000SPT147, 1999ANA111, 2003JSL227, 2004AJC161>, and 18S6-tetraone for Hg(II) <1997ANC3693> and 20S6 for Pd(II) <1997JRN105>. Concerning the selectivity for Ag(I), Wróblewski and Brzózka show that CH₂=14S4 exhibits the highest selectivity toward Ag(I) compared to 14S4 and keto-14S4, but that, all in all, two linear thioethers are even superior to the vinyl macrocycle <1995SAC183>.

14.13.12.2 Thiacycrown-Assisted Metal Transfer

Normally, it is difficult to transfer metal ions across a water/organic solvent interface, which would be a convenient method for extraction of heavy metals. To perform this extraction despite this fact, Katano and Senda successfully tested the transfer of Pb²⁺ across a water/nitrobenzene interface by 18S6 <1996ANS683>.

With respect to this approach, Girault and co-workers have investigated the use of some thiacycrowns as additives in the organic phase to enhance the extraction of Pb²⁺, Cd²⁺, Zn²⁺, and Cu²⁺ and have controlled the success by CV <1998JEC29>. Again, it has been proven that ring size and number of donor atoms are essential for effective chelating a metal ion. Thus, only Pb²⁺ can be transferred easily from water to 1,2-dichloroethane by assistance of 14S4, while with other ions and thiacycrowns (16S4, 10S3, 9S3, trithiane) no further ideal system could be found.

14.13.12.3 Polymer-Bound Thiacycrowns for Extraction of Heavy Metals from Wastewaters

When thiacycrowns, such as 14S4, 17S5, or 20S6, are bound to a polymeric backbone (see Section 14.13.7), they can be used as extractants for heavy metals. Baumann *et al.* have shown that their polymer-bound thiacycrowns can extract Hg(II) highly selectively and completely (95–99%) from acidic aqueous solutions even in the presence of other cations. Furthermore, the authors also describe a regeneration procedure, that is, the mercury is quantitatively stripped from the thiacycrown by dithizone and the regenerated polymer is separated by filtration making it available for reuse <2000RFP111>.

Another polymer that is suitable for the extraction of Hg(II) and Ag(I) but does not have the extraction capacity as that of Baumann's polymer: 48–68% and 39–68% for Hg(II) and Ag(I), respectively. Yamashita *et al.* reported a regeneration procedure of the extracting polymer in which the polymer after treatment with 3 mol l^{-1} ammonium hydroxide was reused <1996RFP47>.

A somewhat similar approach to the extraction of Ag(I) has been performed by Shamsipur and Mashhadizadeh, who modified an octadecyl-bonded silica membrane disk with 18S6. This modified solid phase can be similarly used as commercially available solid-phase extraction cartridges. An aqueous solution containing silver ions is passed through the bed and then, after adsorption, the Ag(I) is desorbed by a thiosulfate-containing eluent. The capacity of one disk modified by 10 mg of 18S6 is found to be $210 \mu\text{g}$ of Ag(I) <2000FJA246>.

14.13.12.4 Thiocrowns and Their Metal Complexes Applied in Catalysis

Some investigators have tested thiocrowns and their metal complexes in catalytic processes and have indeed found activity in some special cases: $[\text{Rh}(\text{PPh}_3)_2(9\text{S}3)](\text{PF}_6)$ at a concentration of 5 mol% helps to remove mercury from bis(alkynyl)mercurials leaving dialkynes <1997OM4517>, Ru(II)thiocrowns have been applied in hydrogen transfer catalysis <2006ICA(359)759>, and 14S4 have been tested in lipase-catalyzed reactions, which are used to synthesize insect pheromones <1997JOC9165>.

14.13.12.5 Application of Thiocrowns and Their Metal Complexes in Cancer Therapy

Two possible antitumor actions are prospectively discussed: first, the direct cytostatic effect of three different Ru(9S3) complexes <2005EJI3423>, and, second, the complexation of a radioactive cation, which then can be guided into the tumor by the thiocrown ligand <1996BCC165>. In the case of the ruthenium complexes, which were tested against one immortal cell line (mouse adenocarcinoma cells) and against normal human mammary cells, indeed one suitable candidate has been found, viz. $[\text{RuCl}(\text{PTA})_2(9\text{S}3)][\text{OTf}]$. Applying this compound for 24 h, proliferation of the cancer cells was stopped completely at a concentration of 1 mmol l^{-1} . On the other hand, the normal human cells did not exhibit any changes in their cell growth during the same application time and under the same concentration of the above-mentioned Ru-complex.

Concerning the destruction of tumors by radiation, ^{111}Ag seems to be a promising radionuclide exhibiting a suitable half-life time and a low γ -abundance of 7% that helps to minimize the side reaction with the bone marrow. Thus, Schubiger *et al.* have tailored a thiocrown with an especially high affinity to Ag(I): 19S6-OH: <1996BCC165, 1996IC3420>. Unfortunately, the authors did not report on further tests, for example, the stability of 19S6-OH when bound to ^{111}Ag could be a problem as Nesterov and co-workers have outlined <1998JRN339>. All in all, these approaches to cancer therapy seem to be of real interest but to our knowledge they are not yet of practical relevance.

14.13.13 Further Developments

Alberto *et al.* report on further syntheses of S_6 thioether cages in analogy to 1,8-dimethyl-3,6,9,12,15,18-hexathia[6.6.6]-cosane (see Figure 1). The synthetic route to these cages is more or less the same as reported earlier <1999CC1513>, but the cage dimensions have been varied and different substituents have been introduced (e.g., nitro instead of methyl). Again, the complexes formed by the cages with Ag(I) have been investigated <2007NJC409>.

Torroba and García-Valverde describe a number of large rings formed by thiophene units only but without sulfur bridges as seen in calix[4]arene (Figure 1). The largest molecule consists of 54 chain members forming a cavity size of 2 nm in diameter <2006AGE8092>.

The calixarenes themselves are also still under investigation: Tran and Georgiou have synthesized a naphthalene variant, (1,4-linked)-homothiacalixarene <2007NJC921>, while Wu *et al.* report on a calixarene based on *p*-benzene sodium sulfonate which is reacted with Cu(II) <2007CGD1>.

Nion *et al.* give a different view on interactions between thiocrowns and metals: instead of the 'normal' reaction of a thiocrown with a metal cation they react the thiocrowns with gold surfaces and receive self-assembled monolayers. Interestingly, this is only seen with 12S4 and 18S6 but not with 14S4 <2007JA2450>. 14S4 is applied as reaction partner for a $\text{Pd}_2\text{Br}_6\text{N}_2\text{Se}_2$ complex where the rectangular Se_2N_2 is framed by two PdBr_3 units. When 14S4 is mixed with this complex and stirred for 1 h the highly reactive Se_2N_2 is released and dimerized to Se_4N_4 when stirred for a further hour <2007CC3054>.

References

- 1989AGE1040 T. Yoshida, T. Adachi, T. Ueda, M. Kaminaka, N. Sasaki, T. Higuchi, T. Aoshima, I. Mega, Y. Mizobe, and M. Hidai, *Angew. Chem., Int. Ed.*, 1989, **28**, 1040.
- 1989CSR409 D. D. Beer, *Chem. Soc. Rev.*, 1989, **18**, 409.
- 1990IC4084 B. de Groot and S. J. Loeb, *Inorg. Chem.*, 1990, **29**, 4084.
- 1990JA6732 J. M. Desper and S. H. Gellman, *J. Am. Chem. Soc.*, 1990, **112**, 6732.
- 1991CB2357 R. Steudel, S. Förster, and J. Albertsen, *Chem. Ber.*, 1991, **124**, 2357.
- 1991CC1119 S. J. Loeb and G. K. H. Shimizu, *J. Chem. Soc., Chem. Commun.*, 1991, 1119.
- 1991IC4644 B. de Groot, G. S. Hanan, and S. J. Loeb, *Inorg. Chem.*, 1991, **30**, 4644.
- 1991JCD1969 J. Casabó, L. Mestres, L. Escriche, F. Teixidor, and C. Pérez-Jiménez, *J. Chem. Soc., Dalton Trans.*, 1991, 1969.
- 1992PS151 U. Westphal and R. Steudel, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1992, **65**, 151.
- 1993POL2995 H.-J. Pietzch, H. Spies, P. Leibnitz, and G. Reck, *Polyhedron*, 1993, **12**, 2995.
- 1994IC4351 J. E. Kickham and S. J. Loeb, *Inorg. Chem.*, 1994, **33**, 4351.
- 1994JCS1354 A. R. Ramesha and S. Chandrasekaran, *J. Chem. Soc. Perkin 1*, 1994, **767**, 1354.
- 1995AGE2374 A. J. Blake, R. O. Gould, S. Parsons, C. Radek, and M. Schröder, *Angew. Chem., Int. Ed.*, 1995, **34**, 2374.
- 1995CC161 S. O. C. Matondo, P. Mountford, D. J. Watkin, W. B. Jones, and S. R. Cooper, *J. Chem. Soc., Chem. Commun.*, 1995, 161.
- 1995CJC1023 C. R. Lucas, S. Liu, and J. N. Bridson, *Can. J. Chem.*, 1995, **73**, 1023.
- 1995CJC1102 B. de Groot, H. A. Jenkins, S. J. Loeb, and S. L. Murphy, *Can. J. Chem.*, 1995, **73**, 1102.
- 1995CRV2587 R. D. Adams and S. B. Falloon, *Chem. Rev.*, 1995, **95**, 2587.
- 1995CTC289 J. Dowden, J. D. Kilburn, and P. Wright, *Contemp. Org. Synth.*, 1995, **2**, 289.
- 1995IC357 L. Aronne, B. C. Dunn, J. R. Vyvyan, C. W. Souvignier, M. J. Mayer, T. A. Howard, C. A. Salhi, S. N. Goldie, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 1995, **34**, 357.
- 1995IC396 N. R. Champness, S. R. Jacob, and G. Reid, *Inorg. Chem.*, 1995, **34**, 396.
- 1995IC651 N. R. Champness, P. F. Kelly, W. Levason, G. Reid, A. M. Z. Slawin, and D. J. Williams, *Inorg. Chem.*, 1995, **34**, 651.
- 1995IC796 H.-J. Kim, J.-H. Lee, I.-H. Suh, and Y. Do, *Inorg. Chem.*, 1995, **34**, 796.
- 1995IC1954 B. C. Dunn, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 1995, **34**, 1954.
- 1995IC5410 J. Casabó, T. Flor, M. N. S. Hill, H. A. Jenkins, J. C. Lockhart, S. J. Loeb, I. Romero, and F. Teixidor, *Inorg. Chem.*, 1995, **34**, 5410.
- 1995IC6053 C. A. Salhi, Q. Yu, M. J. Heeg, N. M. Villeneuve, K. L. Juntunen, R. R. Schroeder, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 1995, **34**, 6053.
- 1995IC6319 H. Nikol, H.-B. Bürgi, K. I. Hardcastle, and H. B. Gray, *Inorg. Chem.*, 1995, **34**, 6319.
- 1995ICA(230)133 C. R. Lucas and S. Liu, *Inorg. Chim. Acta*, 1995, **230**, 133.
- 1995ICA(231)95 T. Yoshida, T. Adachi, T. Ueda, H. Akao, T. Tanaka, and F. Goto, *Inorg. Chim. Acta*, 1995, **231**, 95.
- 1995ICA(234)35 G. J. Grant, K. E. Rogers, W. N. Setzer, and D. B. VanDerveer, *Inorg. Chim. Acta*, 1995, **234**, 35.
- 1995JCD3215 M. Munakata, L. P. Wu, M. Yamamoto, T. Kuroda-Sowa, and M. Maekawa, *J. Chem. Soc., Dalton Trans.*, 1995, 3215.
- 1995JCD4045 A. J. Blake, R. O. Gould, C. Radek, and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 1995, 4045.
- 1995OM1739 R. D. Adams, S. B. Falloon, K. T. McBride, and J. H. Yamamoto, *Organometallics*, 1995, **14**, 1739.
- 1995OM1748 R. D. Adams and S. B. Falloon, *Organometallics*, 1995, **14**, 1748.
- 1995OM3704 R. D. Adams and J. H. Yamamoto, *Organometallics*, 1995, **14**, 3704.
- 1995OM4594 R. D. Adams and S. B. Falloon, *Organometallics*, 1995, **14**, 4594.
- 1995SAC183 W. Wróblewski and Z. Brzózka, *Sens. Actuat. B*, 1995, **24-25**, 183.
- 1995T4065 V. Guyon, A. Guy, J. Foos, M. Lemaire, and M. Draye, *Tetrahedron*, 1995, **51**, 4065.
- 1995T8175 S. J. Lange, J. W. Sibert, C. L. Stern, A. G. M. Barrett, and B. M. Hoffman, *Tetrahedron*, 1995, **51**, 8175.
- 1995TMC583 M. C. Durrant, B. Goerdt, C. Hauser, T. Krawinkel, and R. L. Richards, *Transition Met. Chem.*, 1995, **20**, 583.
- 1996ANS683 H. Katano and M. Senda, *Anal. Sci.*, 1996, **12**, 683.
- 1996BCC165 P. A. Schubiger, R. Alberto, and A. Smith, *Bioconjugate Chem.*, 1996, **7**, 165.
- 1996CB313 R. D. Adams, S. B. Falloon, J. L. Perrin, J. A. Queisser, and J. H. Yamamoto, *Chem. Ber.*, 1996, **129**, 313.
- 1996CHEC-II(1996) S. R. Cooper, W. B. Jones, and S. C. Rawle, *Chapter 9.30.9.1.2 Cyclic disulfides*, 1996, 851.
- 1996IC3420 R. Alberto, W. Nef, A. Smith, T. A. Kaden, M. Neuburger, M. Zehnder, A. Frey, U. Abram, and P. A. Schubiger, *Inorg. Chem.*, 1996, **35**, 3420.
- 1996IC4548 A. J. Welch and A. S. Weller, *Inorg. Chem.*, 1996, **35**, 4548.
- 1996ICA(244)73 G. J. Grant, B. M. McCosar, W. N. Setzer, J. D. Zubkowski, E. J. Valente, and L. F. Mehne, *Inorg. Chim. Acta*, 1996, **244**, 73.
- 1996ICA(246)31 G. J. Grant, N. J. Spangler, W. N. Setzer, D. G. VanDerveer, and L. F. Mehne, *Inorg. Chim. Acta*, 1996, **246**, 31.
- 1996ICA(246)207 H. A. Jenkins, S. J. Loeb, and A. Malats i Riera, *Inorg. Chim. Acta*, 1996, **246**, 207.
- 1996JA4984 M. A. Bennett, L. Y. Goh, and A. C. Willis, *J. Am. Chem. Soc.*, 1996, **118**, 4984.
- 1996JA9442 R. D. Adams, M. Huang, W. Huang, and J. A. Queisser, *J. Am. Chem. Soc.*, 1996, **118**, 9442.
- 1996JA10674 R. C. Adams, J. A. Queisser, and J. H. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 10674.
- 1996JCD1237 K. Brandt and W. S. Sheldrick, *J. Chem. Soc., Dalton Trans.*, 1996, 1237.
- 1996JCD1885 A. J. Blake, Y. V. Roberts, and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 1996, 1885.
- 1996JCD2979 A. J. Blake, M. J. Bywater, R. D. Crofts, A. M. Gibson, G. Reid, and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 1996, 2979.
- 1996JCD4003 P. K. Baker, S. J. Coles, M. C. Durrant, S. D. Harris, D. L. Hughes, M. B. Hursthouse, and R. L. Richards, *J. Chem. Soc., Dalton Trans.*, 1996, 4003.
- 1996LA551 M. Wagner, S. Zeltner, and R.-M. Olk, *Liebigs Ann. Chem.*, 1996, 551.
- 1996OM2489 R. D. Adams, J. A. Queisser, and J. H. Yamamoto, *Organometallics*, 1996, **15**, 2489.
- 1996OM5425 R. D. Adams, R. Layland, and K. McBride, *Organometallics*, 1996, **15**, 5425.
- 1996POL559 V. A. Grillo, L. R. Gahan, G. R. Hanson, and T. W. Hambley, *Polyhedron*, 1996, **15**, 559.
- 1996RFP47 K. Yamashita, K. Kurita, K. Ohara, K. Tamura, M. Nango, and K. Tsuda, *React. Funct. Polym.*, 1996, **31**, 47.
- 1996S1232 M. Mikołajczyk, M. Mikina, P. P. Graczyk, and P. Balczewski, *Synthesis*, 1996, 1232.
- 1996TL1603 R. Beugelmans, M. Chhani, and M. Souflaoui, *Tetrahedron Lett.*, 1996, **37**, 1603.

- 1997AGE1205 G. E. D. Mullen, M. J. Went, S. Wocadlo, A. K. Powell, and P. J. Blower, *Angew. Chem., Int. Ed.*, 1997, **36**, 1205.
- 1997AGE2786 T. Gyr, H. R. Mäcke, and M. Hennig, *Angew. Chem., Int. Ed.*, 1997, **36**, 2786.
- 1997ANC3693 A. R. Fakhari, M. R. Ganjali, and M. Shamsipur, *Anal. Chem.*, 1997, **69**, 3693.
- 1997CB425 M. Wagner, U. Drutkowski, P. Jörcchel, R. Kempe, E. Hoyer, and R.-M. Olk, *Chem. Ber.*, 1997, **130**, 425.
- 1997CC1943 A. J. Blake, W.-S. Li, V. Lippolis, and M. Schröder, *Chem. Commun.*, 1997, 1943.
- 1997IC3253 B. C. Dunn, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 1997, **36**, 3253.
- 1997IC4475 N. M. Villeneuve, R. R. Schroeder, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 1997, **36**, 4475.
- 1997IC4484 B. C. Dunn, P. Wijetunge, J. R. Vyvyan, T. A. Howard, A. J. Grall, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 1997, **36**, 4484.
- 1997IC6216 K. Krylova, K. D. Jackson, J. A. Vroman, A. J. Grall, M. R. Snow, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 1997, **36**, 6216.
- 1997ICA(257)69 G. De Santis, L. Fabbri, M. Licchelli, C. Mangano, D. Sacchi, and N. Sardone, *Inorg. Chim. Acta*, 1997, **257**, 69.
- 1997JA9309 J. B. Arterburn, M. C. Perry, S. L. Nelson, B. R. Dible, and M. S. Holguin, *J. Am. Chem. Soc.*, 1997, **119**, 9309.
- 1997JCM69 B. König, M. Rödel, I. Dix, and P. G. Jones, *J. Chem. Res. (S)*, 1997, 69.
- 1997JCD509 P. K. Baker, M. C. Durrant, S. D. Harris, D. L. Hughes, and R. L. Richards, *J. Chem. Soc., Dalton Trans.*, 1997, 509.
- 1997JCD1639 S. J. A. Pope, N. R. Champness, and G. Reid, *J. Chem. Soc., Dalton Trans.*, 1997, 1639.
- 1997JCD1889 P. Comba, A. Fath, A. Kühner, and B. Nuber, *J. Chem. Soc., Dalton Trans.*, 1997, 1889.
- 1997JOC8459 P. Comba, A. Fath, B. Nuber, and A. Peters, *J. Org. Chem.*, 1997, **62**, 8459.
- 1997JOC9165 T. Itoh, K. Mitsukura, W. Kanphai, Y. Takagi, H. Kihara, and H. Tsukube, *J. Org. Chem.*, 1997, **62**, 9165.
- 1997JRN105 M. Draye, A. Favre-Réguillon, G. Le Buzit, J. Foos, M. Lemaire, and A. Guy, *J. Radioanal. Nucl. Chem.*, 1997, **220**, 105.
- 1997LA2177 M. B. Nielsen and J. Becher, *Liebigs Ann./Recl.*, 1997, 2177.
- 1997OM1430 R. D. Adams and J. H. Yamamoto, *Organometallics*, 1997, **16**, 1430.
- 1997OM2612 R. D. Adams, J. L. Perrin, J. A. Queisser, and J. B. Wolfe, *Organometallics*, 1997, **16**, 2612.
- 1997OM4517 A. F. Hill and J. D. E. T. Wilton-Ely, *Organometallics*, 1997, **16**, 4517.
- 1998CC1007 P. J. Wilson, A. J. Blake, P. Mountford, and M. Schröder, *Chem. Commun.*, 1998, 1007.
- 1998CC1429 S. Roche, L. J. Yellowlees, and J. A. Thomas, *Chem. Commun.*, 1998, 1429.
- 1998CC1637 T. F. Baumann, J. G. Reynolds, and G. A. Fox, *Chem. Commun.*, 1998, 1637.
- 1998EJO1861 F. Le Derf, M. Sallé, N. Mercier, J. Becher, P. Richomme, A. Gorgues, J. Orduna, and J. Garín, *Eur. J. Org. Chem.*, 1998, 1861.
- 1998HAC123 M. B. Setzer, S.-Y. Liou, G. E. Easterling, R. C. Simmons, L. M. Gullion, E. J. Meehan, G. J. Grant, and G. M. Gray, *Heteroatom Chem.*, 1998, **9**, 123.
- 1998IC3767 T. W. Hambley, *Inorg. Chem.*, 1998, **37**, 3767.
- 1998IC5299 G. J. Grant, D. F. Galas, M. W. Jones, K. D. Loveday, W. T. Pennington, G. L. Schimek, C. T. Eagle, and D. G. VanDerveer, *Inorg. Chem.*, 1998, **37**, 5299.
- 1998ICA(274)192 G. J. Grant, S. S. Shoup, C. E. Hadden, and D. G. VanDerveer, *Inorg. Chim. Acta*, 1998, **274**, 192.
- 1998JCD2191 S. C. Davies, M. C. Durrant, D. L. Hughes, C. Le Floch, S. J. A. Pope, G. Reid, R. L. Richards, and J. R. Sanders, *J. Chem. Soc., Dalton Trans.*, 1998, 2191.
- 1998JCD2931 A. J. Blake, W.-S. Li, V. Lippolis, A. Taylor, and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 1998, 2931.
- 1998JCD3961 A. J. Blake, D. Fenske, W.-S. Li, V. Lippolis, and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 1998, 3961.
- 1998JCF1959 M. R. Ganjali, A. Rouhollahi, A. R. Mardani, and M. Shamsipur, *J. Chem. Soc., Faraday Trans.*, 1998, **94**, 1959.
- 1998JEC29 G. Lager, L. Tomaszewski, M. D. Osborne, B. J. Seddon, and H. H. Girault, *J. Electroanal. Chem.*, 1998, **451**, 29.
- 1998JOC181 B. Blackwell, S. M. Ngola, H. Peterson, S. Rosenfeld, C. W. Tingle, J. P. Jasinski, Y. Li, and J. E. Whittum, *J. Org. Chem.*, 1998, **63**, 181.
- 1998JRCN39 S. Küçükyavuz, S. V. Nesterov, and A. M. Önal, *J. Radioanal. Nucl. Chem.*, 1998, **230**, 39.
- 1998TL6357 J. Buter, R. H. Meijer, and R. M. Kellogg, *Tetrahedron Lett.*, 1998, **39**, 6357.
- 1999ANA111 M. H. Mashhadizadeh and M. Shamsipur, *Anal. Chim. Acta*, 1999, **381**, 111.
- 1999CC1417 F. Le Derf, M. Mazari, N. Mercier, E. Levillain, P. Richomme, J. Becher, J. Garín, J. Orduna, A. Gorgues, and M. Sallé, *Chem. Commun.*, 1999, 1417.
- 1999CC1513 R. Alberto, D. Angst, U. Abram, K. Ortner, T. A. Kaden, and A. P. Schubiger, *Chem. Commun.*, 1999, 1513.
- 1999CHE1385 V. V. Litvinova and A. V. Anisimov, *Chem. Heterocycl. Compd.*, 1999, **35**, 1385.
- 1999IC4322 K. Krylova, C. P. Kulatilake, M. J. Heeg, C. A. Salhi, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 1999, **38**, 4322.
- 1999IC5906 C. P. Kulatilake, S. N. Goldie, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 1999, **38**, 5906.
- 1999JCD2343 J. Connolly, A. R. J. Genge, W. Levason, S. D. Orchard, S. J. A. Pope, and G. Reid, *J. Chem. Soc., Dalton Trans.*, 1999, 2343.
- 1999JCD3759 G. E. D. Mullen, T. F. Fässler, M. J. Went, K. Howland, B. Stein, and P. J. Blower, *J. Chem. Soc., Dalton Trans.*, 1999, 3759.
- 1999JOM(587)207 G. J. Grant, T. Salupo-Bryant, L. A. Holt, D. Y. Morrissey, M. J. Gray, J. D. Zubkowski, E. J. Valente, and L. F. Mehne, *J. Organomet. Chem.*, 1999, **587**, 207.
- 1999JPR202 T. Rambusch, K. Hollmann-Gloe, and K. Gloe, *J. Prakt. Chem.*, 1999, **341**, 202.
- 1999JJC1015 T. M. Santos, B. J. Goodfellow, J. Madureira, J. P. de Jesus, V. Félix, and M. G. B. Drew, *New J. Chem.*, 1999, **23**, 1015.
- 1999T10057 J. Nakayama, A. Kaneko, Y. Sugihara, and A. Ishii, *Tetrahedron*, 1999, **55**, 10057.
- 2000ACR171 R. D. Adams, *Acc. Chem. Res.*, 2000, **33**, 171.
- 2000CSR153 M. B. Nielsen, C. Lomholt, and J. Becher, *Chem. Soc. Rev.*, 2000, **29**, 153.
- 2000FJA246 M. Shamsipur and M. H. Mashhadizadeh, *Fresenius J. Anal. Chem.*, 2000, **367**, 246.
- 2000IC1035 A. J. Blake, N. R. Champness, K. M. Howdle, and P. B. Webb, *Inorg. Chem.*, 2000, **39**, 1035.
- 2000IC1444 C. P. Kulatilake, S. N. Goldie, M. J. Heeg, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 2000, **39**, 1444.
- 2000IC2897 P. Wijetunge, C. P. Kulatilake, L. T. Dressel, M. J. Heeg, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 2000, **39**, 2897.
- 2000JOM(596)115 R. D. Adams, J. L. Perrin, J. A. Queisser, and R. D. Rogers, *J. Organomet. Chem.*, 2000, **596**, 115.
- 2000JPM277 M. Shamsipur and M. H. Mashhadizadeh, *J. Incl. Phenom. Macrocycl. Chem.*, 2000, **38**, 277.
- 2000PCA652 S. E. Hill and D. Feller, *J. Phys. Chem. A*, 2000, **104**, 652.
- 2000RFP111 T. F. Baumann, J. G. Reynolds, and G. A. Fox, *React. Funct. Polym.*, 2000, **44**, 111.

- 2000SPT147 M. Shamsipur and M. H. Mashhadizadeh, *Sep. Purif. Technol.*, 2000, **20**, 147.
- 2000T7371 S. J. Lange, J. W. Sibert, A. G. M. Barrett, and B. M. Hoffman, *Tetrahedron*, 2000, **56**, 7371.
- 2001AXC36 A. J. Blake, V. Lippolis, S. Parsons, and M. Schröder, *Acta Crystallogr., Sect. C*, 2001, **57**, 36.
- 2001IC564 G. J. Grant, I. M. Poullas, D. F. Galas, D. G. VanDerveer, J. D. Zubkowski, and E. J. Valente, *Inorg. Chem.*, 2001, **40**, 564.
- 2001ICA(317)91 G. J. Grant, S. S. Shoup, C. L. Baucom, and W. N. Setzer, *Inorg. Chim. Acta*, 2001, **317**, 91.
- 2001ICA(323)157 S. Roche, S. E. Spey, H. Adams, and J. A. Thomas, *Inorg. Chim. Acta*, 2001, **323**, 157.
- 2001ICC671 R. D. Adams, K. Brosius, and O.-S. Kwon, *Inorg. Chem. Commun.*, 2001, **4**, 671.
- 2001JA5720 Q. Yu, C. A. Salhi, E. A. Ambundo, M. J. Heeg, L. A. Ochrymowycz, and D. B. Rorabacher, *J. Am. Chem. Soc.*, 2001, **123**, 5720.
- 2001JA11534 T. Tsuchiya, T. Shimizu, and N. Kamigata, *J. Am. Chem. Soc.*, 2001, **123**, 11534.
- 2001JCD456 N. R. Brooks, A. J. Blake, N. R. Champness, P. A. Cooke, P. Hubberstey, D. M. Proserpio, C. Wilson, and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 2001, 456.
- 2001JCD1628 M. Pillinger, I. S. Gonçalves, A. D. Lopes, J. Madureira, P. Ferreira, A. A. Valente, T. M. Santos, J. Rocha, J. F. S. Menezes, and L. D. Carlos, *J. Chem. Soc., Dalton Trans.*, 2001, 1628.
- 2001JOM(637)683 G. J. Grant, S. M. Carter, A. LeBron Russell, I. M. Poullas, and D. G. VanDerveer, *J. Organomet. Chem.*, 2001, **637–639**, 683.
- 2001PCA11266 P. Bultinck, A. Huyghebaert, C. Van Alsenoy, and A. Goemine, *J. Phys. Chem. A*, 2001, **105**, 11266.
- 2001POL3333 G. J. Grant, C. G. Brandow, D. F. Galas, J. P. Davis, W. T. Pennington, E. J. Valente, and J. D. Zubkowski, *Polyhedron*, 2001, **20**, 3333.
- 2001TAL1065 M. Shamsipur and M. H. Mashhadizadeh, *Talanta*, 2001, **53**, 1065.
- 2002ANC4423 S. M. Williams, J. S. Brodbelt, A. P. Marchand, D. Cal, and K. Mlinarić-Majerski, *Anal. Chem.*, 2002, **74**, 4423.
- 2002IC2250 C. S. Araújo, M. G. B. Drew, V. Félix, L. Jack, J. Madureira, M. Newell, S. Roche, T. M. Santos, J. A. Thomas, and L. Yellowlees, *Inorg. Chem.*, 2002, **41**, 2250.
- 2002ICA(338)182 M. L. Helm, C. M. Combs, D. G. VanDerveer, and G. J. Grant, *Inorg. Chim. Acta*, 2002, **338**, 182.
- 2002ICC832 F. E. Sowrey, P. J. Blower, J. C. Jeffery, E. J. MacLean, and M. J. Went, *Inorg. Chem. Commun.*, 2002, **5**, 832.
- 2002JCD3153 R. Hart, W. Levason, B. Patel, and G. Reid, *J. Chem. Soc., Dalton Trans.*, 2002, 3153.
- 2002JOC6632 T. Tsuchiya, T. Shimizu, K. Hirabayashi, and N. Kamigata, *J. Org. Chem.*, 2002, **67**, 6632.
- 2002JOM(652)51 R. D. Adams, K. M. Brosius, and O.-S. Kwon, *J. Organomet. Chem.*, 2002, **652**, 51.
- 2002JOM(664)161 L. Y. Goh, M. E. Teo, S. B. Khoo, W. K. Leong, and J. J. Vittal, *J. Organomet. Chem.*, 2002, **664**, 161.
- 2002POL879 G. J. Grant, D. F. Galas, and D. G. VanDerveer, *Polyhedron*, 2002, **21**, 879.
- 2002ASH4423 M. H. Mashhadizadeh, A. Mostafavi, R. Razavi, and M. Shamsipur, *Sens. Actuat. B*, 2002, **86**, 222.
- 2002TL6271 M. H. Ali and M. McDermott, *Tetrahedron Lett.*, 2002, **43**, 6271.
- 2002ZFA34 M. Kampf, R.-M. Olk, and R. Kirmse, *Z. Anorg. Allg. Chem.*, 2002, **628**, 34.
- 2003AXCo314 A. Višnjevac, B. Kojić-Prodić, M. Vinković, and K. Mlinarić-Majerski, *Acta Crystallogr., Sect. C*, 2003, **59**, o314.
- 2003IC96 R. Y. C. Shin, M. A. Bennett, L. Y. Goh, W. Chen, D. C. R. Hockless, W. L. Keong, K. Mashima, and A. C. Willis, *Inorg. Chem.*, 2003, **42**, 96.
- 2003JCD1577 S. Galijasevic, K. Krylova, M. J. Koenigbauer, G. S. Jaeger, J. D. Bushendorf, M. J. Heeg, L. A. Ochrymowycz, M. J. Taschner, and D. B. Rorabacher, *J. Chem. Soc., Dalton Trans.*, 2003, 1577.
- 2003JCD3981 G. J. Grant, J. A. Pool, and D. G. VanDerveer, *J. Chem. Soc., Dalton Trans.*, 2003, 3981.
- 2003JCX445 M. L. Helm, K. D. Loveday, C. M. Combs, E. L. Bentzen, D. G. VanDerveer, R. D. Rogers, and G. J. Grant, *J. Chem. Crystallogr.*, 2003, **33**, 445.
- 2003JOC3480 T. Tsuchiya, T. Shimizu, K. Hirabayashi, and N. Kamigata, *J. Org. Chem.*, 2003, **68**, 3480.
- 2003JCX623 M. L. Helm, D. G. VanDerveer, and G. J. Grant, *J. Chem. Crystallogr.*, 2003, **33**, 623.
- 2003JSL227 M. Shamsipur, Z. Talebpour, and N. Alizadeh, *J. Solut. Chem.*, 2003, **32**, 227.
- 2003PS1295 T. Takido, M. Toriyama, K. Ogura, H. Kamijo, S. Motohashi, and M. Seno, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 1295.
- 2003TL6789 S. T. A. Shah, K. M. Khan, M. Fecker, and W. Voelter, *Tetrahedron Lett.*, 2003, **44**, 6789.
- 2004AGE3938 N. Shan, S. J. Vickers, H. Adams, M. D. Ward, and J. A. Thomas, *Angew. Chem., Int. Ed.*, 2004, **43**, 3938.
- 2004AJC161 M. Fainerman-Melnikova, L. F. Lindoy, S.-L. Liou, J. C. McMurtrie, N. P. Green, A. Nezhdali, G. Rounaghi, and W. N. Setzer, *Aust. J. Chem.*, 2004, **57**, 161.
- 2004CRV651 D. B. Rorabacher, *Chem. Rev.*, 2004, **104**, 651.
- 2004EJI612 X. Sala, A. Poater, I. Romero, M. Rodríguez, A. Llobet, X. Solans, T. Parella, and T. M. Santos, *Eur. J. Inorg. Chem.*, 2004, 612.
- 2004ICA(357)2115 W. Levason, B. Patel, and G. Reid, *Inorg. Chim. Acta*, 2004, **357**, 2115.
- 2004JMM55 B. Jagannadh, S. S. Reddy, and R. P. Thangavelu, *J. Mol. Model.*, 2004, **10**, 55.
- 2004JOC8550 I. Vujasinović, J. Veljković, and K. Mlinarić-Majerski, *J. Org. Chem.*, 2004, **69**, 8550.
- 2004POL1361 G. J. Grant, K. N. Patel, M. L. Helm, L. F. Mehne, D. W. Klinger, and D. G. VanDerveer, *Polyhedron*, 2004, **23**, 1361.
- 2004ZFA2669 M. Kampf, J. Griebel, and R. Kirmse, *Z. Anorg. Allg. Chem.*, 2004, **630**, 2669.
- 2004ZFA2725 T. Naito, K. Nishibe, and T. Inabe, *Z. Anorg. Allg. Chem.*, 2004, **630**, 2725.
- 2004ZNB1077 J. Pickardt, L. von Chrzanowski, R. Studel, and M. Borowski, *Zeitschr. Naturforsch. B*, 2004, **59**, 1077.
- 2005EJI479 G. J. Grant, W. Chen, A. M. Goforth, C. L. Baucom, K. Patel, P. Repovic, D. G. VanDerveer, and W. T. Pennington, *Eur. J. Inorg. Chem.*, 2005, 479.
- 2005EJI3423 B. Serli, E. Zangrando, T. Gianferrara, C. Scolaro, P. J. Dyson, A. Bergamo, and E. Alessio, *Eur. J. Inorg. Chem.*, 2005, 3423.
- 2005IC5696 M. L. Helm, G. P. Helton, D. G. VanDerveer, and G. J. Grant, *Inorg. Chem.*, 2005, **44**, 5696.
- 2005IC8182 D. E. Janzen, L. F. Mehne, D. G. VanDerveer, and G. J. Grant, *Inorg. Chem.*, 2005, **44**, 8182.
- 2005JOM(690)629 G. J. Grant, J. P. Lee, M. L. Helm, D. G. VanDerveer, W. T. Pennington, J. L. Harris, L. F. Mehne, and D. W. Klinger, *J. Organomet. Chem.*, 2005, **690**, 629.
- 2005TAL993 A. K. Singh and P. Saxena, *Talanta*, 2005, **66**, 993.
- 2005TL8057 W. Qu, D. B. Rorabacher, and M. J. Taschner, *Tetrahedron Lett.*, 2005, **46**, 8057.
- 2006ACR301 R. Y. C. Shin and L. Y. Goh, *Acc. Chem. Res.*, 2006, **39**, 301.
- 2006AGE8092 T. Torroba and M. García-Valverde, *Angew. Chem. Int. Ed.*, 2006, **45**, 8092.
- 2006CC3540 D. E. Janzen, K. N. Patel, D. G. VanDerveer, and G. J. Grant, *Chem. Commun.*, 2006, 3540.

- 2006CC3585 T. Tsuchiya, H. Kurihara, K. Sato, T. Wakahara, T. Akasaka, T. Shimizu, N. Kamigata, N. Mizorogi, and S. Nagase, *Chem. Commun.*, 2006, 3585.
- 2006IC679 S. J. Smith, C. M. Whaley, T. B. Rauchfuss, and S. R. Wilson, *Inorg. Chem.*, 2006, **45**, 679.
- 2006IC821 M. Newell, J. D. Ingram, T. L. Easun, S. J. Vickers, H. Adams, M. D. Ward, and J. A. Thomas, *Inorg. Chem.*, 2006, **45**, 821.
- 2006IC923 S. H. Kakos, L. T. Dressel, J. D. Bushendorf, C. P. Kotarba, P. Wijetunge, C. P. Kulatilleke, M. P. McGillivray, G. Chaka, M. J. Heeg, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.*, 2006, **45**, 923.
- 2006IC1289 A. Romerosa, T. Campos-Malpartida, C. Lidrissi, M. Saoud, M. Serrano-Ruiz, M. Peruzzini, J. A. Garrido-Cárdenas, and F. García-Maroto, *Inorg. Chem.*, 2006, **45**, 1289.
- 2006IC2619 F. A. Cotton, C. Y. Liu, C. A. Murillo, and X. Wang, *Inorg. Chem.*, 2006, **45**, 2619.
- 2006ICA(359)759 N. Shan, H. Adams, and J. A. Thomas, *Inorg. Chim. Acta*, 2006, **359**, 759.
- 2006JCD3534 M. L. Helm, L. L. Hill, J. P. Lee, D. G. VanDerveer, and G. J. Grant, *J. Chem. Soc., Dalton Trans.*, 2006, 3534.
- 2006JCX83 D. E. Janzen, K. Patel, D. G. VanDerveer, and G. J. Grant, *J. Chem. Crystallogr.*, 2006, **36**, 83.
- 2006PCA9451 B. Ni, J. R. Kramer, R. A. Bell, and N. H. Werstiuk, *J. Phys. Chem. A*, 2006, **110**, 9451.
- 2006POL599 M. W. Glenny, L. G. A. van de Water, J. M. Vere, A. J. Blake, C. Wilson, W. L. Driessen, J. Reedijk, and M. Schröder, *Polyhedron*, 2006, **25**, 599.
- 2007CC3054 S. M. Aucott, D. Drennan, S. L. M. James, P. F. Kelly, and A. M. Z. Slawin, *Chem. Commun.*, 2007, 3054.
- 2007CGD1 M. Wu, D. Yuan, Y. Huang, W. Wei, Q. Gao, F. Jiang, and M. Hong, *Crystal Growth and Design*, 2007, **1**.
- 2007JA2450 A. Nion, P. Jiang, A. Popoff, and D. Fichou, *J. Am. Chem. Soc.*, 2007, **129**, 2450.
- 2007NJC409 R. Alberto, D. Angst, K. Ortner, U. Abram, P. A. Schubiger, and T. A. Kaden, *New J. Chem.*, 2007, **31**, 409.
- 2007NJC921 H.-A. Tran and P. E. Georghiou, *New J. Chem.*, 2007, **31**, 921.

Biographical Sketch



Heiner Eckert was born in Munich, Germany, where he gained his diploma in chemistry at the Technical University of Munich (TUM) in 1973, going on to receive his Ph.D. with *summa cum laude* under Prof. Ivar Ugi three years later. In 1977, he founded Dr. Eckert GmbH, a company specializing in developing fine chemicals and processes for chemical production, which he sold in 2002. In 2005, Eckert gained his Habilitation and the *venia legendi* in chemistry at the TUM. At present, he is working as *privatdozent* at the TUM, with his research interest in development of new methods and reactions in chemical syntheses. Eckert has published numerous scientific papers and patents (natural product syntheses, metal phthalocyanine catalysts) as well as the book *Phosgenations – A Handbook*, and indeed the Eckert hydrogenation catalysts are named for him. His invention of the solid reagent triphosgene as a safe and effective substitute for the dangerous gas phosgene is nowadays commonly used in every laboratory worldwide. His current research is focused on developing additional functionalizing of selected components of multicomponent reactions.



Marianne Koller was born in Bavaria, Germany, in 1958. She did her diploma in chemistry at the Technical University of Munich in 1984 and received her Ph.D. with *magna cum laude* under Prof. Ivar Ugi in 1989. During the following years, she specialized on instrumental analytics. Since 1995, she has been responsible for the development of GC–MS and LC–MS methods for the detection of chemical warfare agents in biomedical samples (verification) at the German Forces. Sulfur mustard, whose homologues can be used as educts in the synthesis of sulfur macrocycles, is one of her objects of interest.

14.14

Ten-membered Rings or Larger with One or More Nitrogen and Oxygen and/or Sulfur Atoms

G. W. Gokel and E. K. Elliott

Washington University School of Medicine, St. Louis, MO, USA

© 2008 Elsevier Ltd. All rights reserved.

14.14.1	Introduction	803
14.14.1.1	Discovery of Crown Ethers	804
14.14.1.2	Nomenclature and Structural Variety	805
14.14.2	Synthetic Methods	805
14.14.3	Host–Guest Complexation	807
14.14.4	Theoretical Methods	808
14.14.5	Experimental Structural Methods: X-Ray Crystal Structures	809
14.14.5.1	Crown Ethers as Tools to Explore Cation–Pi Interactions	809
14.14.5.2	The Imidazole Heterocycle as a Donor for Alkali Metals	813
14.14.5.3	Heteromacrocycles Used to Study Double and Triple Bond Cation–Pi Interactions	813
14.14.6	Thermodynamic Aspects	813
14.14.7	Modification and Reactivity of Ring Side Chains	814
14.14.7.1	Fluorescent Crowns	814
14.14.7.2	Fluorescent Cryptands	815
14.14.7.3	Crown Ether Lipoic Acid Derivatives	816
14.14.7.4	Incorporation of Main Group Elements into Macrocyclic Side Chains	817
14.14.8	Ring Closure from Acyclic Components	817
14.14.8.1	Cyclodextrin-Mediated Ring Closure	817
14.14.8.2	Polymeric Resins from Epichlorohydrin	817
14.14.8.3	Polymeric Crowns	817
14.14.9	Improved Synthetic Methods and Complex Receptors	819
14.14.9.1	Methodology	819
14.14.9.2	Receptor ‘Fusion’	820
14.14.10	Complexation of Metal Ions	820
14.14.11	Ammonium Ion Binding	820
14.14.12	Heteromacrocyclic-Based Ion Channel Models	822
14.14.13	Conclusion	822
	References	824

14.14.1 Introduction

This chapter focuses on heterocycles that are 10 atoms or larger in size. Rings of this dimension are usually referred to as ‘macrocycles’ or ‘heteromacrocycles’. Such compounds have been known for many years in several forms. The most abundant family of large ring heteromacrocycles is that of crown ethers and their relatives. The discovery of crown ethers was motivated by a desire to bind metal cations. This is also possible with many smaller ring heterocyclic compounds. 2,2′-Bipyridine, for example, is an excellent bidentate Lewis basic donor. Crown ether compounds are typically multidentate. 2,2′-Bipyridine is illustrated in **Figure 1** along with an all-nitrogen

heteromacrocycle designated '14-ane-4' (sometimes referred to as a 'cyclam'), a heteromacrocycle arising from the condensation of four molecules of furan with four molecules of acetone, and pyrido-18-crown-6.

Bipyridine is bidentate: it has two Lewis basic sites that can coordinate a cation or other Lewis acid. 14-Ane-4 is tetradentate, by virtue of the four Lewis basic electron pairs on the nitrogen atoms. The acetone–furan cyclic tetramer is also tetradentate but the Lewis basic donors in this case are oxygen atoms. The pyridocrown shown on the right-hand side of **Figure 1** is hexadentate by virtue of one nitrogen and five oxygen atoms. All four of these structures are heterocycles. Bipyridine is actually two pyridine heterocycles that are linked. The furan–acetone tetramer and crown are both true heteromacrocycles but both contain heterocyclic units within them. These are sometimes called 'subcyclic' units.

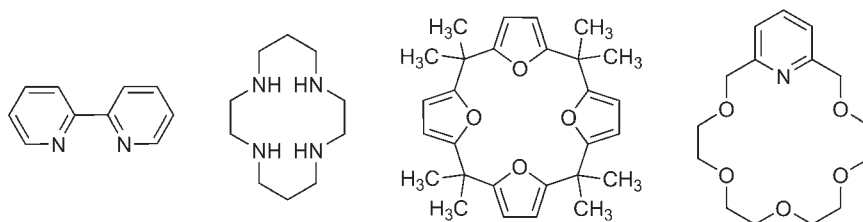


Figure 1

An important class of large ring heteromacrocycles is that of cyclic peptides. Many of these are known and there is considerable variety, owing to the differences in amino acid side chains. A cyclic hexapeptide is illustrated in **Figure 2**. The common amino acids have the structure $\text{H}_2\text{N}-\text{CHR}-\text{COOH}$, in which the saturated carbon is chiral. When two or more amino acids are linked, they form an amide or 'peptide bond', which has the structure $\sim\text{HN}-\text{CHR}-\text{CO}-\text{NH}-\text{CHR}-\text{CO}\sim$. The amide link is shown in bold type.

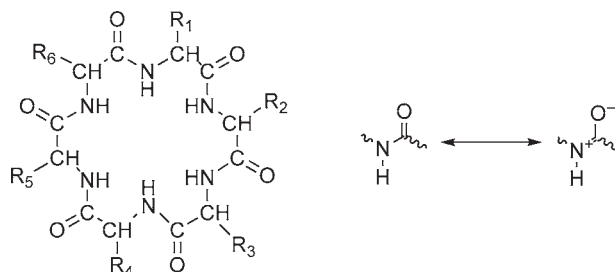


Figure 2

In principle, either the carbonyl oxygen or the amide nitrogen could serve as the donor group. In fact, amide resonance, illustrated on the right-hand side of **Figure 2**, makes oxygen the more Lewis basic element. The variety of structures represented by the single figure on the left-hand side is remarkable. Even assuming that all six R-groups are identical, there are still six chiral carbons present. Thus, 2^6 or 64 stereoisomers are possible on that basis alone. Although the common amino acids are limited to 20, hundreds of different side chains occur naturally and even more have been made by synthetic chemists.

Despite their superficial similarity to many crowns, the cyclic peptides really comprise a separate family of heteromacrocycles. They are mentioned here to recognize their similarities and differences but they are not discussed further in this chapter.

14.14.1.1 Discovery of Crown Ethers

This chapter is an update and, as such, will not cover the Nobel Prize winning discovery of crown ethers. It is worth briefly noting, however, that the class of compounds now known generally as crown ethers were discovered by Pedersen in the 1960s <1967JA7017>. At the time, his goal was to prepare bidentate, bis(phenol) compounds that

could bind such divalent cations as calcium. He treated monoprotected catechol with 2,2'-dichlorodiethyl ether. The former contained some unprotected catechol, which gave rise to a macrocyclic side product containing two catechols rather than a bridged bis(catechol) that still possessed two phenolic hydroxyl groups.

Pedersen was intrigued by the fact that the side product could complex cations even though infrared evidence for any hydroxyl group was lacking. He correctly deduced the cyclic structure and set about a systematic exploration of variations in ring sizes, heteroatoms, fused groups, and the cations bound. He has summarized these efforts <1988SCI536>. The importance of this discovery was that these compounds could bind alkali metal cations, which have only s-orbitals available for interactions. The rich inorganic and organometallic chemistries of transition metals are possible because those metals have available d- and/or f-orbitals.

14.14.1.2 Nomenclature and Structural Variety

Pedersen examined space-filling molecular models of the heteromacrocycles and observed that they bound cations in a manner similar to the crowning of a regal head. He was inspired to call these compounds crown ethers in part for that reason and in part because their systematic names are impossibly cumbersome <1967JA7017>. Lehn and co-workers faced a similar dilemma when they reported compounds that were essentially crown ethers having a third ethyleneoxy strand <1969TL2885>. They dubbed their cation-encapsulating structures 'cryptands' and the complexes cryptates <1970JA2916>. Addition of a fourth strand led to spherands (see below).

Crown ethers are typically named by identifying both the ring size and the heteroatoms. Thus, the common macrocycle 1,4,7,10,13,16-hexaoxacyclooctadecane is named more economically, if less systematically, as 18-crown-6. Unless otherwise specified, it is assumed that ethylene units separate the heteroatoms. This assumption applies as well to the cryptands, which are named by the number of heteroatoms present in each of the three chains.

Cation complexes of cryptands were called cryptates and those of spherands, spherates. The name 'coronand' was suggested for crown ethers and their complexes would therefore be 'coronates' <1980ICAL45>. The latter nomenclature has proved to be acceptable to the community but it has not been universally adopted. A reasonable and systematic approach, based on principles of polymer nomenclature, has appeared but has not found wide acceptance <1984JCI266>.

There is now an almost bewildering array of large ring receptor molecules that are either of unique composition or fusions of other receptors. **Figure 3** shows nine examples. 18-Crown-6 is probably the most widely used and studied of the simple macrocycles as is [2.2.2]cryptand among the heterobicyclics. Spherands are molecules that were designed to include a cation within a 'spherical' array of Lewis basic donor groups. The spherand shown in the top row of **Figure 3** presents a cation with a tetrahedral array of nitrogen donors or an octahedron of oxygen atoms. The spherand shown in the bottom row has six methoxy groups arranged octahedrally and the scaffold for the donors is the more rigid of the two.

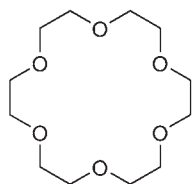
The three structures shown at the right of the second line represent important families of receptor molecules that have been extensively studied in their own right. The aromatic spherand grew out of crown ether chemistry while calixarene chemistry developed on a separate evolutionary pathway. Still, their similarity is apparent. The structures of calixarenes and resorcarenes (also resorcinarenes) are included here because they have often been fused to macrocycles to form complex receptor systems. A few examples of fused receptor systems are discussed below.

14.14.2 Synthetic Methods

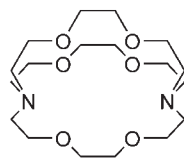
In principle, simple crown ethers can be prepared by cyclooligomerization of ethylene oxide. This reaction has been reported. Although 12- to 18-membered ring crowns were obtained, the major product was invariably dioxane. This may be a useful method to obtain these simple crowns inexpensively but it is neither generally extensible <1976CC295> nor particularly adaptable to the research laboratory.

A more general approach to the macrocycle is to use short-chained oligoethylene oxide derivatives. For example, the diols $\text{H}(\text{OCH}_2\text{CH}_2)_n\text{OH}$ ($n = 1-3$) are useful crown ether precursors and they can be obtained commercially. Note that they should be carefully distilled prior to use as shorter and longer oligomers can readily contaminate them. These oligoethylene glycols can be converted into the corresponding dichlorides, dimesylates, ditosylates, etc.

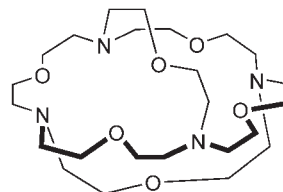
When diols and dihalides are allowed to react under basic conditions, products resulting from multiple displacements are possible. Thus, 18-crown-6 can be formed as shown above as well as 36-crown-12. The latter is less likely than the former owing to its large size. Typically, linear oligomerization would predominate during the synthesis. Addition of template ions has often proved to be useful in altering the balance of product between cyclic and linear materials.



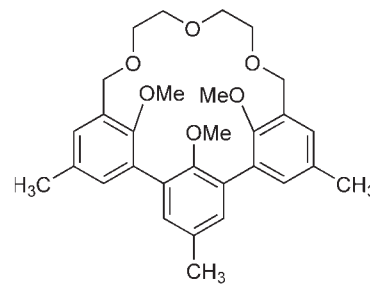
18-crown-6



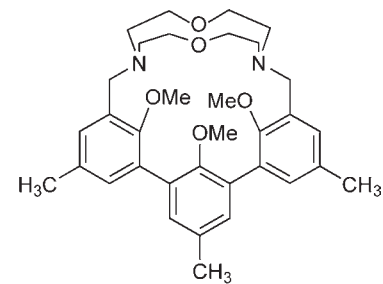
[2.2.2]cryptand



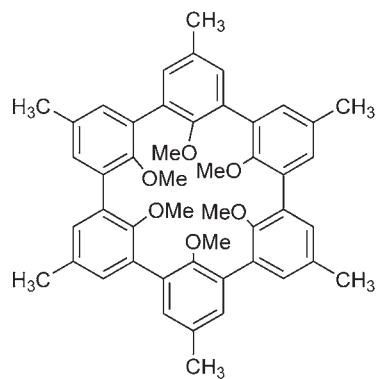
a spherand



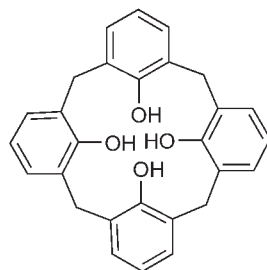
a hemispherand



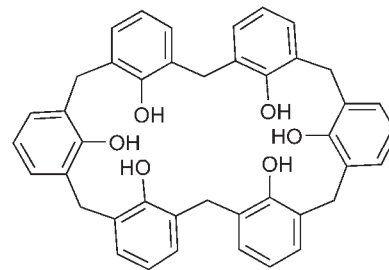
a cryptaspherand



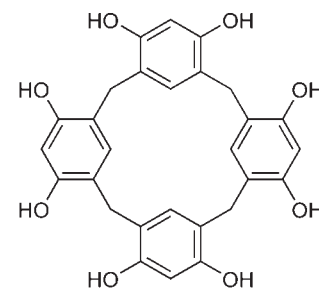
a spherand



calix[4]arene



calix[6]arene



[4]resorcarene

Figure 3

Reactions such as the one that gave Pedersen the first crown can produce additional products. Thus, catechol (1,2-dihydroxybenzene) reacts with $\text{O}(\text{CH}_2\text{CH}_2)_2\text{Cl}$ in the presence of base to give dibenzo-18-crown-6. Tribenzo-27-crown-9 and benzo-9-crown-3 have also been identified as resulting from this process. For this reason, such crown preparations are sometimes referred to as ‘shotgun’ reactions. Attempts have been made to direct the cyclization to the correct receptor size by including a K^+ template ion to direct formation of 18-membered ring.

The preparation of crown ethers differs principally owing to the presence or absence of nitrogen. The preparation of all-oxygen heteromacrocycles has largely involved the Williamson ether synthesis. The preparation of aza-, diaza-, or triazacrowns has usually required the formation of cyclic amides, followed by reduction. The latter method applies to cryptands as well and has been used for that purpose since 1969. The methods are well known and shown in the lower panel of Figure 4.

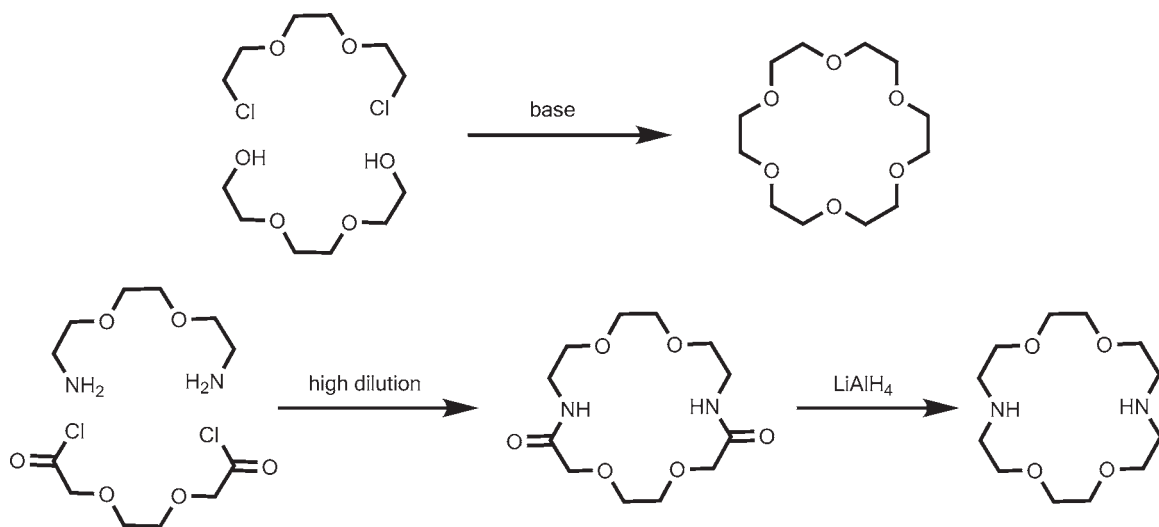
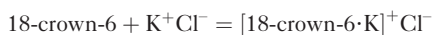


Figure 4

The preparation of cryptands involves cyclization followed by reduction to afford the diazacrown. A large family of diazacrowns is available by this reaction but the resulting compound may be further treated with a diacyl chloride. This process is simply a repetition of the two-step sequence shown in Figure 4 for diazacrown and results ultimately in the cryptand known as [2.2.2].

14.14.3 Host–Guest Complexation

Early in the development of the field, compounds were often prepared to define the limits of both the synthetic methods and the stable products that could be formed. To date, many thousands of heteromacrocycles have been prepared. The dominant application of the vast family of host or receptor molecules has been to bind or complex a guest structure. The guests can be metal cations, organic cations, neutral substrates, anions, or complementary molecules. The complexation process can be understood from the simple example of 18-crown-6 complexing K^+Cl^- in solution. Ignoring structural and solvation/desolvation issues, the process can be described simply as



Simple as this equation is, there are many variables involved. The position of the equilibrium will be defined by the constant, K_{eq} . This will, in turn, be determined by the rates of complexation and decomplexation ($k_{\text{f}}/k_{\text{r}}$ or $k_{\text{complex}}/k_{\text{release}}$). These rates will be solvent dependent because solvation of the starting materials and products must both be altered during the complexation process. Further, the rates of binding and release will vary with the steric

accessibility to the binding cavity. Thus, 18-crown-6 binds cations rapidly in water but it also releases them rapidly so overall binding strength is low. In solvents of low polarity, solvent competition is reduced and although the rates presumably remain high, the overall reaction (K_{eq}) more strongly favors complex formation. More sterically hindered [2.2.2]cryptand binds cations somewhat more slowly in water than does 18-crown-6, but the ion release rate is far slower than for 18-crown-6. Thus, the ratio k_1/k_{-1} (k_f/k_r) for [2.2.2]cryptand typically leads to strong binding (large K_{eq}) for alkali metal cations of appropriate size.

As the receptors have become more complex, forces such as H-bonding and dipole–dipole interactions have augmented the ion–dipole complexation mechanism typical of crown ethers. This has increased the importance of conformational analysis for the receptors and an understanding of structure. Ultimately, however, the binding of a guest by a host molecule is defined by the equilibrium constant for that system in a particular solvent and at a specified temperature.

The measurement of complexation has been accomplished by a variety of techniques. For alkali metal cations with simple crowns, calorimetric and ion selective electrodes have been, by far, the most common. Nuclear magnetic resonance (NMR) methods have also been used commonly and increasingly as the receptors and their substrates become more complex.

14.14.4 Theoretical Methods

Figure 5 shows two possible structures for the binding of the hydronium ion to 18-crown-6. In structure **A**, the three H atoms bind linearly to alternating O atoms. Structure **B** shows bifurcated H bonds to the six O atoms. Solid-state infrared (IR) spectroscopy and computational studies support the arrangement in **A** for both 18-crown-6 <2002JA4473> and dibenzo-18-crown-6 <2006SAA532>, while solution IR studies have caused controversy.

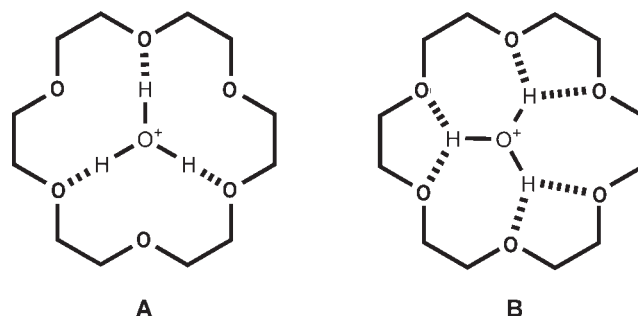


Figure 5

A discrepancy between solution-state IR results and theoretical data for the $\text{H}_3\text{O}^+\cdot 18\text{-crown-6}$ complex has been noted <2004JPCA907>. The calculations and solid-state IR data reported in this work agree with previously published work suggesting three linear $\text{O}\cdots\text{H}$ bonds (structure **A**). It was concluded from an analysis of the IR spectrum that a structure of the type shown in **B** reflects the solution situation. Wipff and co-workers refuted <2004JPCA11463> the previous IR analysis, concluding that structure **A** was correct. This agrees with solid-state IR data for the crystalline complex and with computational results at various *ab initio* and DFT levels.

An *ab initio* study of 18-crown-6 with alkaline earth metals Mg^{2+} , Ca^{2+} , Sr^{2+} , Ba^{2+} , and Ra^{2+} has been reported <1996JA6052>. The binding geometries of each cation–crown complex were investigated using both restricted Hartree–Fock (RHF) and second-order Moller–Plesset perturbation (MP2) levels of theory. Solvation effects were found to determine cation selectivity. In the gas phase, 18-crown-6 binds Mg^{2+} preferentially, while Ba^{2+} is the favored cation in solution. Using the same level of theory as the dication study, they extended these studies to 12-crown-4/alkali metal cation complexes <1998PCA3813>. The theoretical structures and binding enthalpies were compared with previously published collision-induced dissociation (CID) measurements <1996JPC1605, 1996JPC16116, 1997PCA6125, 1997PCA831, 1997PCA7007>. The theoretical binding enthalpies for Li^+ , Na^+ , and K^+ matched the CID results within experimental error, although agreement between theory and experiment was less satisfactory for Rb^+ and Cs^+ .

Computational methods have been applied to study the conformations of free and metal-complexed oxathiacyclic crown ethers **1–4** shown in **Figure 6**. The results were compared to variable temperature NMR and T_1 spin-lattice relaxation time measurements <2001JP2988>. Theoretical studies included simulated ^1H NMR spectra using PERCH and molecular modeling with PM3 semi-empirical quantum-chemical calculations. The NMR and the computational data both show that Ag^+ coordinates equally well to S and O atoms, Bi^{3+} and Sb^{3+} prefer O atoms, and that Pt^{2+} and Pd^{2+} prefer *exo*-cyclic coordination only to the S atoms in this maleonitrile macrocycle.

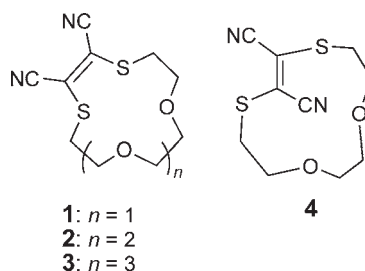


Figure 6

Spherands, crownphanes, and crown ether analogs have also been studied by computational methods. Free energy perturbation (FEP) and molecular dynamics (MD) simulations <1995JPC10081, 1999JPC10015> of anisole- and phenanthroline-derived spherands in solution show qualitative agreement between theoretical and experimental results for **6–8** (see **Figure 7**). Binding and selectivity data for **5** was less satisfactory. The latter discrepancy was thought to arise from the computational methodology. In other cases, computationally intensive *ab initio* calculations were conducted on model systems (e.g., **9**) rather than crownophane **10** <2001JA4255>. A number of other computational studies have been reported as well: **11**<1999MRC401>, and 10-crown-3 <1997MRC283> and 13-crown-4 (1998MRC687) derivatives.

14.14.5 Experimental Structural Methods: X-Ray Crystal Structures

Analysis of solid-state structures has played an important role in understanding crown and cryptand conformation. A variety of interactions between these heteromacroyclic receptors and metal cations, ammonium ions, and other species have been revealed. The earliest work in this area revealed that crowns and cryptands crystallize in conformations in which one or more methylene group(s) rotate inward to fill the molecular void, if this is permitted by the overall size of the macrocyclic ring. In fact, molecules such as 12-crown-4 are remarkably congested and have little or no internal cavity (i.e., hole). This is apparent in **Figure 8**, which shows space-filling molecular models of 12-crown-4 (left) and 15-crown-5 (right).

The general complexation phenomenon as it is now well known to occur with crown ethers such as 18-crown-6 is shown schematically in **Figure 9**. When a macrocycle is in solution, it may be well solvated. In such a case, it may be unnecessary for either of the two methylenes to rotate inward. Of course, the schematic represents the structure in the solid state. In any event, when complexation occurs, the methylene groups rotate outward so that the macrocyclic ring can accommodate the cation. The Lewis basic oxygen atoms interact in the ion-dipole sense with the Lewis acidic cation. In the case of 18-crown-6, the macrocyclic ring adopts a D_{3d} conformation. The anion that was part of the original M^+X^- salt is a Lewis base as well. It will typically be in contact with the ring-bound cation. Alternately, a water molecule may be in contact with the cation and, in turn, hydrogen-bonded to the anion. Of course, other solvent molecules may occupy vacant valence positions on the cation. It is often observed in the solid state that an infinite chain of $(\text{M}^+ \cdots \text{X}^-)_n$ is formed in which the macrocycle is present on alternate atoms (the cations).

14.14.5.1 Crown Ethers as Tools to Explore Cation- π Interactions

In the 1960s, there was considerable skepticism about the existence or importance of C-H hydrogen bonds <1962NAT68>. Eventually, these interactions were recognized, quantified, and largely accepted by the community <1996ACR441>. In the 1990s, similar skepticism existed concerning the existence or importance of alkali metal cation- π interactions. This issue was of particular relevance to the biological community because the concentration

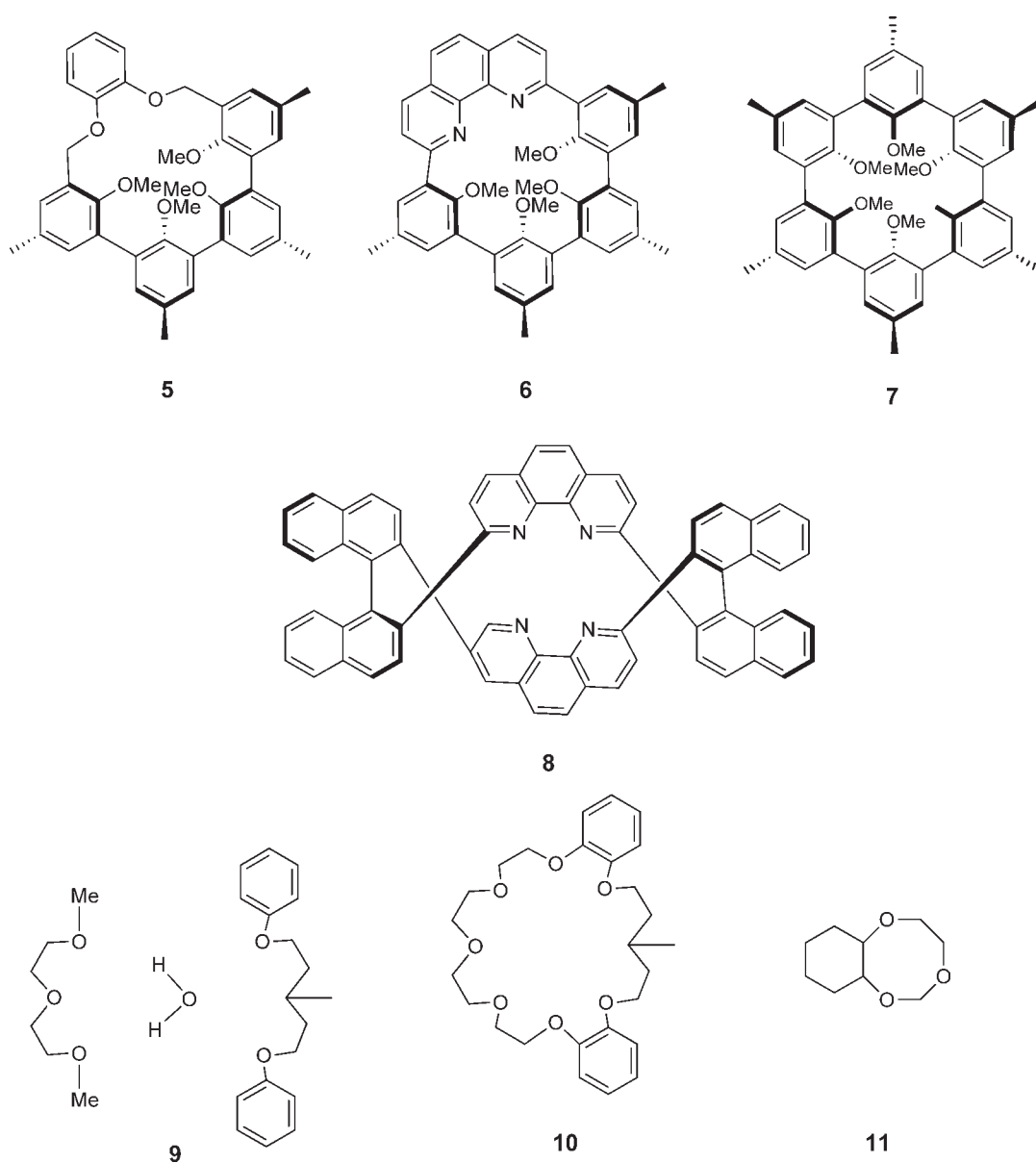


Figure 7

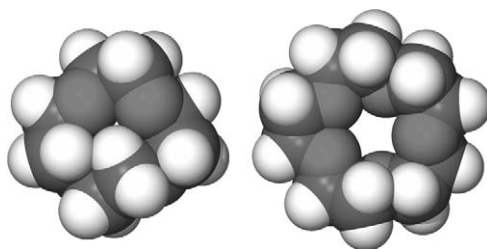


Figure 8

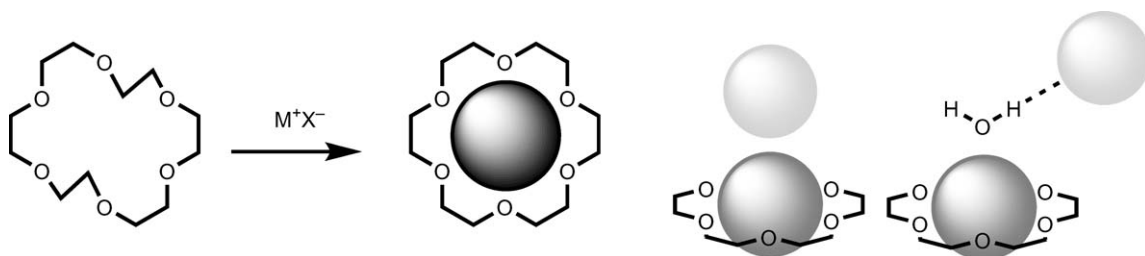


Figure 9

of Na^+ is typically ~ 100 mM in the periplasm and the concentration of K^+ is commonly ~ 100 mM within cells. Thus, proteins in which phenylalanine, tyrosine, or tryptophan was present would encounter these cations and cation– π interactions could influence conformation and reactivity.

4,13-Diaza-18-crown-6 with ethylene side chains terminated by benzene, phenol, or indole proved to be ideal vehicles to study such interactions <2002ACR878, 2003CC2947>. The diazacrown was already well known to complex alkali metal cations, although both Na^+ and K^+ were bound relatively weakly by the parent macrocycle. When the two macroring nitrogens were substituted by $\text{CH}_3\text{OCH}_2\text{CH}_2\sim$ chains, the side-chain oxygen atoms served as apical sigma donors and the binding constant was considerably increased <1995SMC45>. Similarly, substitution of the macroring nitrogens by $\sim\text{CH}_2\text{CH}_2\text{Ar}$ gave evidence of axial π donor interactions when complexing either Na^+ or K^+ .

Four solid-state structures are illustrated in Figure 10. At the left is the structure of *N,N'*-bis(2-indolyethyl)-4,13-diaza-18-crown-6 <1999JA5613>. The macroring is shaped approximately like a parallelogram and the two indolyethyl side chains are in the 'gauche' conformation and extended from the macrocycle. The indole residues show no evidence of interaction with each other or with the macrocycle. This conformation is also observed for the corresponding macrocycle having 4-hydroxyphenyl termini (not shown <1999JA8405>).

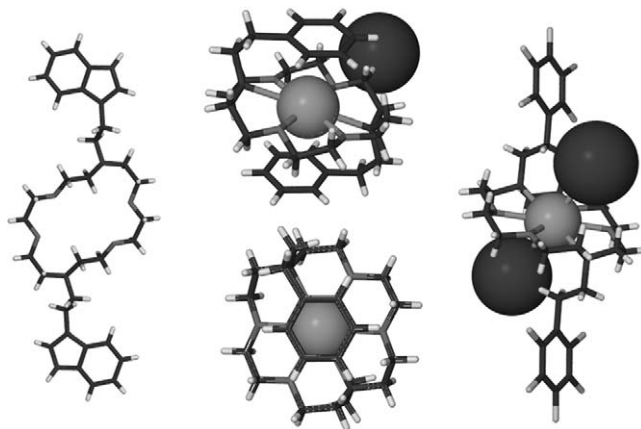


Figure 10

The two center structures show the complex that forms between *N,N'*-bis(2-phenylethyl)-4,13-diaza-18-crown-6 and KI <2000PNAS6271>. The K^+ ion is bound in the center of the macroring, as expected for any 18-crown-6 macrocycle. The twin sidearms of the bibrachial lariat ether turn inward in this complex and the arenes serve as apical donors. The top center structure shows the symmetrically bound cation and illustrates that the iodide anion is excluded from the cation's solvation sphere. The bottom center structure shows the superimposition of the two benzene rings upon each other and upon the K^+ ion. Note in the bottom center structure that the iodide anion is not illustrated. The ideal sandwich of arene–cation–arene confirms the cation– π interaction between benzene and K^+ .

Similar structures were obtained for the macrocycles having either 3-indolyl or 4-hydroxyphenyl termini when complexing either Na^+ or K^+ . A variety of anions such as iodide, tetrafluoroborate, hexafluorophosphate, and

thiocyanate gave similar results. Indeed, so similar were the solid-state structures, that a control was required to eliminate the possibility of apical complexation resulting only from crystal packing forces. Thus, the analog of *N,N'*-bis(2-phenylethyl)-4,13-diaza-18-crown-6 was prepared in which each phenyl group was replaced by pentafluorophenyl <2000PNAS6271>. Fluorine is the most electronegative element so the presence of five of them in $\text{C}_6\text{F}_5\text{CH}_2\text{CH}_2\sim$ converts the arene from a pi-donor (Lewis base) to a pi-acceptor (Lewis acid). The right-hand structure in **Figure 10** shows that although all elements of the complexes are similarly sized, when the phenyl groups are fluorinated, the sidearms are turned away from the cation, which is in contact with the iodide anion. Indeed, the salt, K^+I^- , forms an infinite $(\text{K}^+\cdots\text{I}^-)_n$ chain within the crystal, as described above. The conclusion was that the cation–pi effect may be augmented in the solid state by crystal packing, but it is a significant force that is not observed when sterics remain similar but electrostatics are reversed.

An interesting and significant question concerning indole arose during these studies. Calculations of electron distribution in indole invariably showed that the benzo subunit was more electron rich than the pyrrolo subcyclic unit <1996JA2307, 2000JA870, 2000JPC(A)8067>. In the lariat ether model systems, the pyrrolo subunit was always closest to the cation. It was thought that this might result from steric interference to complexation caused by the presence of the medial macrocyclic belt. Alternate models were therefore prepared to test this possibility. Specifically, smaller macrocycles ($18 \rightarrow 15$) were used so that complexed cations would be ‘perched’ on the macrocyclic ring, rather than nested within it. It was thought that this would encourage intimate cation–pi contact and cause the interaction with indole to occur at the benzene subunit (see compound **12** in **Figure 11**). A solid-state structure of the **12**·NaBPh₄ complex showed a ‘perched’ Na^+ and an axial cation–pi interaction that was shortened owing to absence of apparent steric hindrance. Even so, the cation–pi interaction was between Na^+ and the benzene ring <2002CC1810>.

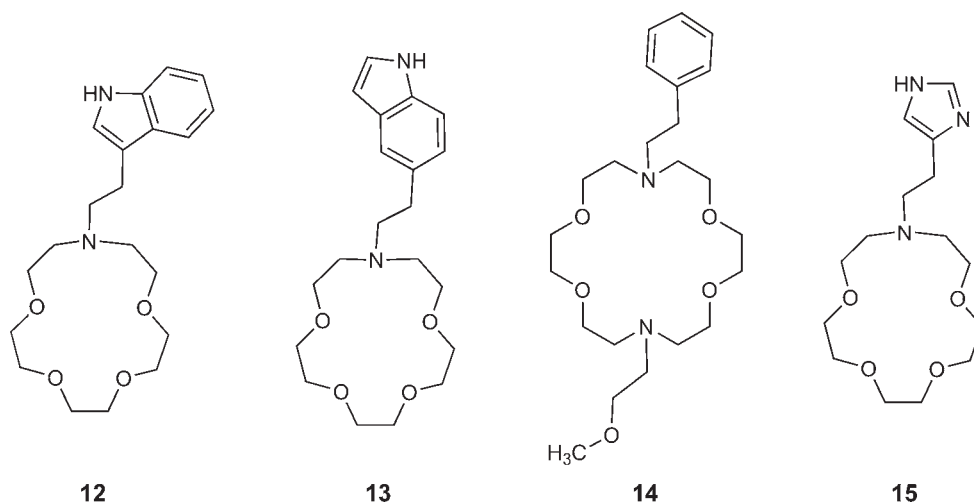


Figure 11

In tryptophan, the indole residue is attached to the amino acid’s side chain at indole’s position 3. When the point of attachment was moved to indole position 5, however, macrocycle **13** complexed NaBPh₄ in the pi-fashion but benzene rather than pyrrole was clearly the donor group <2002JA10940>. One may conclude that **12** is a less reasonable model than is **13**. In fact, both unequivocally confirm the cation–pi interaction. Further, the fact that cation–pi interactions are prominent in both cases means that in the natural environment, the rarest of the 20 common amino acids is a truly versatile pi donor.

Another control experiment was run to further confirm the significance of the cation–pi interaction in these bibracchial lariat ether model complexes. In this case, a diaza-18-crown-6 derivative was prepared in which a 2-phenylethyl pi-donor sidearm was attached to one nitrogen and a 2-methoxyethyl sigma donor was attached to the other <2002CC1808>. The structure is illustrated as **14**, above. The solid-state structure of the **14**·KI complex showed the typical apical solvation of the ring bound cation. In this case, however, one apex was solvated in the pi-fashion (benzene) and the other by the oxygen sigma donor.

14.14.5.2 The Imidazole Heterocycle as a Donor for Alkali Metals

There are four aromatic residues among the 20 common amino acids: benzene, phenol, indole, and imidazole. Of these, the first three are clearly electron rich. The heterocycle imidazole is electron poor and possesses nitrogen sigma donor groups along its periphery. Imidazole is well known as a donor for transition metals, but its ability to interact with sodium or potassium is of greater relevance to biology. The bibracchial lariat ether model system was therefore applied as before to determine the type of complex that occurred between alkali metals and imidazole. The model system is shown above as **15**. When complexed to NaBPh₄, the imidazole in the sidearm served as a sigma donor to the ring-bound cation <2002CC1810>.

14.14.5.3 Heteromacrocycles Used to Study Double and Triple Bond Cation- π Interactions

The work described above was undertaken for the fundamental chemical information that it revealed <2001JA3092>. The donors were limited, however, to those of greatest biological relevance. From the organic chemist's perspective, isolated double and triple bonds comprise interesting potential pi-donors. Thus, diaza-18-crown-6 receptors were prepared in which the nitrogen atoms were attached either to 3-butenyl <2001CC1858> or to 3-butynyl side chains <2001JA9486>. The results of these studies are shown schematically in **Figure 12**.

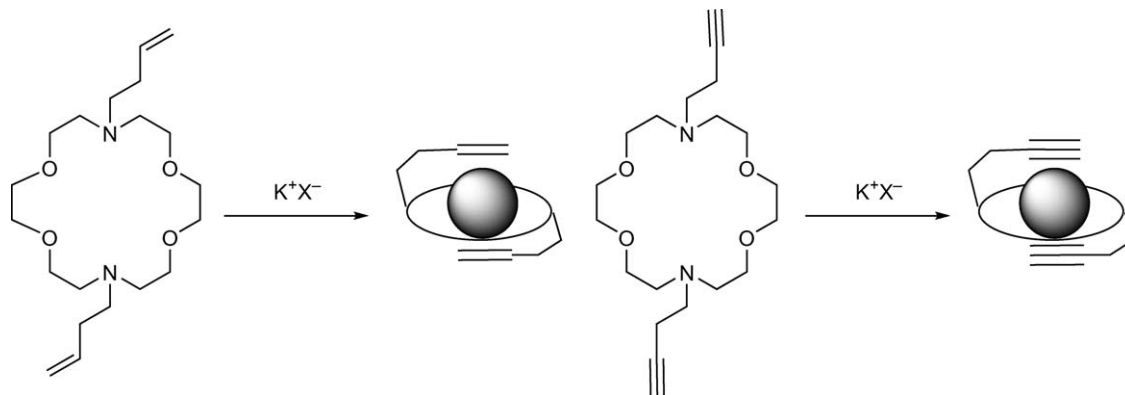


Figure 12

Solid-state structures of both double and triple bond complexes of K⁺ were obtained. In both cases, the alkali metal ion was bound in the center of the macroring and the sidearm unsaturation provided apical pi-donor interactions. When Na⁺ was complexed by the butynyl-side-chained receptor, a *syn* complex was formed. In this case, Na⁺ was cradled by the macroring and the two triple bonds coordinated from the same side of the ring <2001JA9486>. Such contrasting *syn* and *anti* complexation had previously been observed when the side chains were small sigma donors: ~CH₂CH₂OH. As observed above, complexation of Na⁺ by the hydroxyethyl lariat ethers was *syn* but complexation of K⁺ was *anti* <1987JA3716>.

14.14.6 Thermodynamic Aspects

Extensive thermodynamic studies of receptor-substrate or host-guest interactions have been reported in several reviews <1995CRV2529>. As receptors have become more elaborate, questions of host conformation complicate the binding process. Insight has been gained in several systems by use of NMR in concert with molecular modeling. The conformations of cyclotrimeratrylenes, spherands, and calixarenes have been studied by using this combination of methods <2001JOC2900>. An even greater range of spectroscopic techniques was applied in the study of a bis(crown) dye that interacts both with cations at the macroring and with itself <2004NJC295>.

A detailed study of a small-ring macrocycle that incorporates oxygen, sulfur, and a maleonitrile subunit within it has been discussed in Section 14.14.2 <2001JP2988>. Structures for the conformations are drawn above in Figure 6.

14.14.7 Modification and Reactivity of Ring Side Chains

During nearly four decades of study, it has become clear that extremely large heteromacrocylic rings can be prepared and that nearly any combination of O, N, and/or S can be included within the cycle. Numerous subcyclic units including hydrocarbons (cyclohexane, naphthalene, etc.) and heterocycles (furan, pyridine, imidazole, quinoline, etc.) have also been incorporated. Heteromacrocycles have also been fused with other receptors such as calixarenes to make calixcrowns. In recent years, the fusion of receptors and variations in the attached sidearms has been a dominant theme.

14.14.7.1 Fluorescent Crowns

Blending of crown compounds with fluorescent residues to create sensors has been frequently investigated. The principle dates back to the early 1980s when changes in the UV-visible spectrum occurred when a cation was bound in the macroring <1984TCC39>. The principle is the same for side chains containing fluorescent residues but sensitivity is usually greater. Unfortunately, the greater sensitivity is often accompanied by complications such as photoelectron energy transfer (PET) quenching. The latter phenomenon has been studied by DeSilva and co-workers and reviewed recently <1997CRV1515, 1999PNAS8336>.

Many of the examples of fluorescent sensors employ relatively simple macrocycles to which the fluorescent residue is attached as a sidearm. In early work in this area, a number of fluorescent lariat ethers were reported that had been designed to function as fluorescent indicators for intracellular sodium cation <1989JBC19449>. Naphthalene and the substituted naphthalene derivative in which the dansyl groups were attached to macrocycles to sense cations such as zinc and copper <2004IC6114>. The dansyl group is highly fluorescent and has also been incorporated in both one- and two-armed lariat ether receptors, shown in Figure 13 <2002JPH249, 1999SMC163, 1999JA9043>.

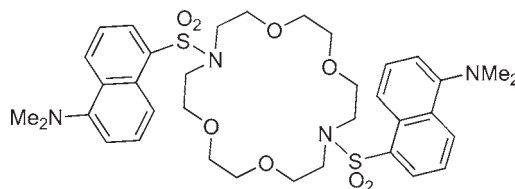


Figure 13

The fluorescent hydrocarbon anthracene has also been appended to heteromacrocycles in various sensor applications. In one receptor, aza-18-crown-6 was used as the cation complexing agent and anthracene was coupled to the macroring nitrogen atom <1998TL4807>. A closely related derivative was reported in which aza-18-crown-6 was again the cation binding site but the fluorescent sensor was present as an *N*-(9-anthracenylmethyl) side chain. This receptor was developed to detect the marine natural product saxitoxin <2002JA13448>. In earlier work, two anthracene molecules were used as bridge units between two diaza-18-crown-6 molecules to form a ditopic cryptand <1984B4059>.

The hydrocarbon side chains have been further extended to pyrene, which is highly fluorescent and also forms dimers known as excimers. The excimers are thought to be face-to-face dimers that have an extended molecular orbital, affording a new, red-shifted fluorescence emission. Pyrene has been incorporated into a variety of sidearm-containing macrocycles in which the ring is intended to bind cations <2002OL2641, 2004JOC4403, 2005OBC1787>. In an interesting application involving two supramolecular systems, β -cyclodextrin was added to the receptor system to enhance excimer formation by the sensor <2000ANC5841>. The cyclodextrin residue has also been covalently linked to a benzocrown in recently described receptors <2004OBC1542, 2004OBC2359>. Additional examples of fluorescent crowns are shown in Figure 14 <2002TL7243, 2004IC5195, 2002JA6246, 1998MI251, 2005OBC1787>.

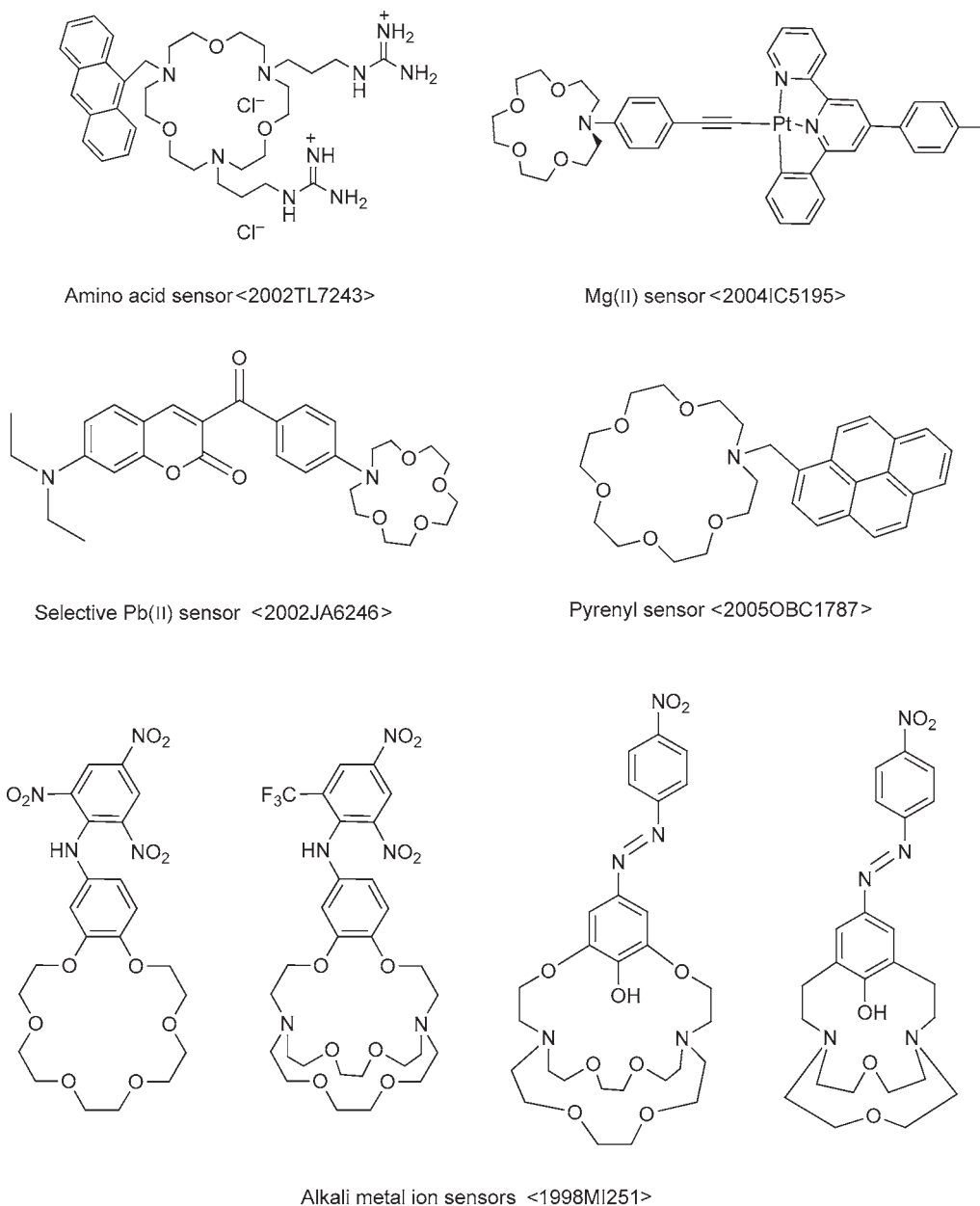


Figure 14

Fluorescent macrocycles have also been used to complex intracellular ions and image vital tissues. 8-Hydroxyquinoline derivatives of diaza-18-crown-6 have been used complex intracellular Mg^{2+} in mouse mammary cells. Fluorescent images of the vital cells were obtained by two-photon microscopy <2006JA344>.

14.14.7.2 Fluorescent Cryptands

Dinitroazobenzene was used as the fluorescent residue in a chiral receptor molecule that incorporated both a crown ether and calixarene, the structure of which is shown in **Figure 15**. Formally, this comprises a ditopic cryptand but such a simple nomenclature is clearly inadequate <2004CH1174>.

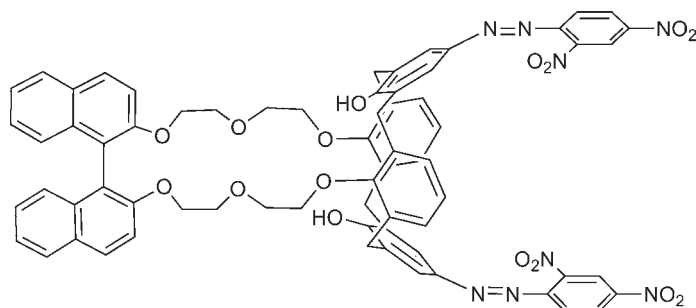


Figure 15

An important goal for analytical applications is to sense cations in aqueous solution where cation binding strength by simple macrocycles is often weak. Further, it is important to be able either to recover or reuse difficult-to-prepare or expensive sensor molecules. The high sensitivity of fluorescence is an obvious advantage. If the sensor can be polymer bound, however, it should be recoverable and therefore economical to use in analytical applications. A fluorescent, polymer-bound K^+ -selective cryptand was developed by He *et al.* <2003JA1468, 2003ANC549>. In an extension of the work described above, Nakahara and co-workers used pyrene as a reporter in a cryptand designed to detect and complex cations <2005OBC1787>. Finally, a cryptand was formed from a fluorescent, bibracchial lariat ether by an unexpected $4\pi + 4\pi$ cycloaddition reaction of the anthracene-containing sidearms <2002CEJ3331>.

The number of fluorescent receptor molecules is considerable and only a few of the structures are shown. In general, their intended function is similar although not all are equally successful <2001JHC1113, 2003ANC549, 2004JA9291, 2004OL1071, 2004BML5313, 2005BML1851>. We note particularly the work of Valeur and co-workers who have developed several fluorescent sensor molecules and have summarized the field in a monograph <B-2002MI1>.

14.14.7.3 Crown Ether Lipoic Acid Derivatives

An interesting system involving multiple heterocycles was reported by Strasdeit *et al.* <2002M1097>. They prepared an imidazolyl amide derivative of lipoic acid and used it to acylate either aza-15-crown-5 or aza-18-crown-6. The side chain of the resulting crown ethers was terminated by a 1,2-dithiane. Reduction of the crown amide afforded the *N*-alkylated macrocycle after air oxidation to restore the dithiane from the reduced 1,3-dithiol. Reduction of the dithiane without converting the amide to the amine could be effected by using NaBH_4 instead of LiAlH_4 (Figure 16).

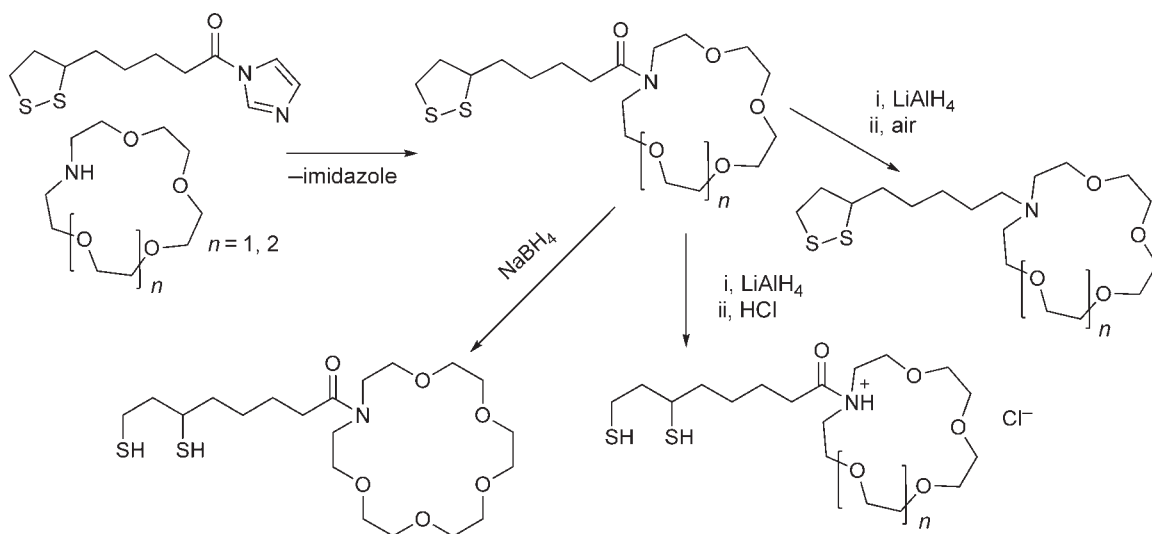


Figure 16

14.14.7.4 Incorporation of Main Group Elements into Macrocyclic Side Chains

An unusual system involves the incorporation of a main group element, that is, germanium, within the macrocyclic side chain. This is shown in **Figure 17**. The compounds were prepared in order to assess alkali metal cation transport. This was done but the results proved equivocal <2001JOM108>.

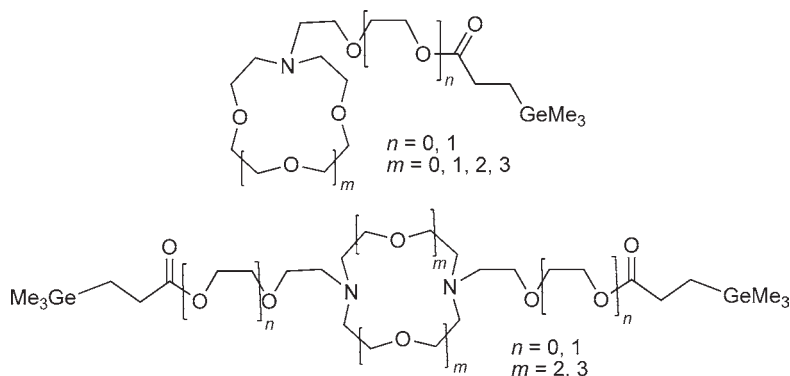


Figure 17

14.14.8 Ring Closure from Acyclic Components

Literally thousands of heteromacrocycles are now known. Many additional compounds have been prepared during the past decade but, for the most part, the synthetic approaches are traditional. Recent work has often focused on developing sidearm receptor molecules (see Section 14.14.7.1), mixed receptor systems such as calix-crowns (Section 14.14.7.2), and oligomers or polymers containing crown residues.

14.14.8.1 Cyclodextrin-Mediated Ring Closure

An interesting conversion of a bis(styrene) crown precursor was reported recently <2001MI35>. The [2+2]-photodimerization of **16** was found to occur in solution to afford a cyclobutane-containing crown ether. The reaction product was formed only in 10% yield when irradiated at >280 nm in aqueous base solution. However, when γ -cyclodextrin was present, the hydrophobic styryl residues were apparently confined within its interior cavity and the yield rose to 39%. A similar reaction was performed to afford the diaza-18-crown-6 derived cryptand. In the latter case, cyclization failed in the absence of the cyclodextrin (**Figure 18**).

14.14.8.2 Polymeric Resins from Epichlorohydrin

Epichlorohydrin has proved to be a versatile sidearm precursor for a variety of lariat ether compounds <1992CSR39>. It has recently been used for the formation of macrorings by reaction of the oxirane fragment (see **Figure 19**). Thus, epichlorohydrin was treated with BF₃·Et₂O to give an oligomeric dichloride. This, in turn, was treated with triethanolamine to form 13-crown-4 derivatives that include a single nitrogen. The macrocycles were included in a network that was used to complex metal ions such as Ag⁺ and Au³⁺. When 1-chloro-2,3-epithiopropene replaced epichlorohydrin in the initial step, macrocycles containing O, S, and N were formed. The oxygen- and sulfur-containing resins were assayed for selective binding in the presence of other metals such as Pb²⁺, Cu²⁺, and Zn²⁺ <1997MI931>.

14.14.8.3 Polymeric Crowns

Several examples have recently been reported of vinyl-substituted crowns that were polymerized under anionic conditions to pendant crown polymer systems <2002MM2432, 2002PLM3469, 2005PB237>. Typical examples of



Figure 18



Figure 19

the pendant residues are illustrated in **Figure 20** as **17** and **18**. This work has been expanded to azacrowns, to which naphthalenes have been attached. The result is polymeric azacrowns of higher overall hydrophobicity <2005PB237>. The right-hand portion of **Figure 20** shows the overall transformation and the naphthalene substitution pattern.

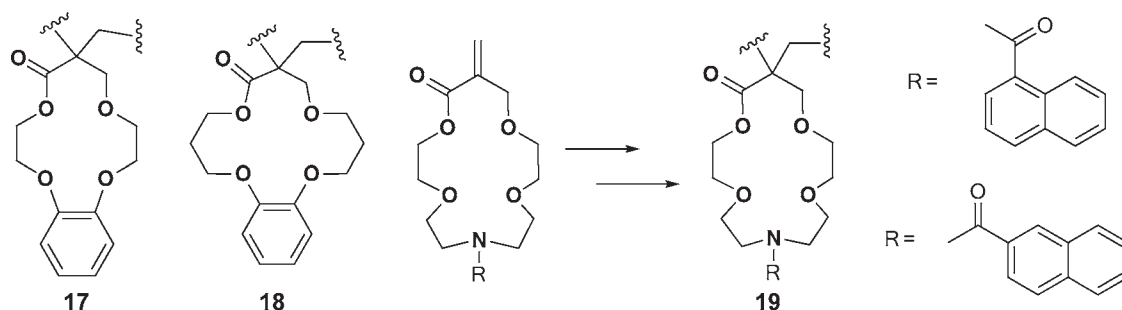


Figure 20

14.14.9 Improved Synthetic Methods and Complex Receptors

As noted above, a major focus of effort in this area has been to develop improved synthetic methods for macrocycles or to 'blend' either properties or receptors <1999T9425, 1996T6713>. Examples of both types are illustrated in the following sections.

14.14.9.1 Methodology

Although the preparation of macrocycles often involves improved methods, several efforts have been made particularly to improve synthetic approaches. In an unusual approach, 4,13-diaza-18-crown-6 was converted to its bis(methyl) aminal. The $\text{CH}_3\text{OCH}_2\text{N}$ side-chain residues are labile and permitted a Mannich-type reaction with various bis(phenols) under acid catalysis <1995JOC4912>. Two of the resulting structures are shown as **20** and **21** in **Figure 21**. Not all phenols proved to be successful substrates for this reaction but compound **20** was formed in 25% yield.

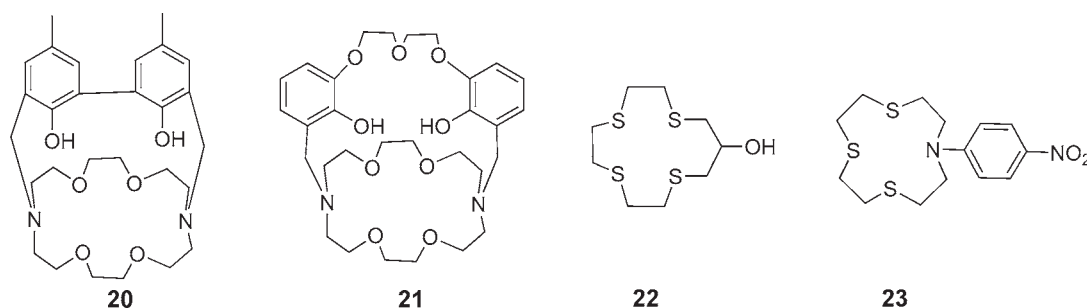


Figure 21

Efforts have also been made to improve the methodology used to prepare various mixed donor macrocycles especially applicable to binding transition metal cations <2006POL599>. Various approaches were tried including amide formation followed by reduction (see **Figure 4**). Activated leaving groups such as tosylate were employed and

cesium was used as the counter-cation in the nucleophilic ring closure reactions. Even so, some macrocycles such as **22** were obtained as mixtures with the larger ring homolog and in relatively poor yield. The synthesis of structure **23** represents an alternative to palladium coupling as a means to introduce an aromatic sidearm.

Tanaka and co-workers have also prepared a variety of mixed donor macrocycles, albeit by more traditional methods <2001JOC7008>. They surveyed the complexation ability of the macrocycles obtained with a range of alkali and transition metal cations.

14.14.9.2 Receptor 'Fusion'

It was noted in Section 14.14.1.2 that many novel receptor systems are mixtures or fusions of previously known guest molecules. A 'cryptaspherand', for example, is shown in **Figure 3**. An interesting amalgam of receptor systems was based on relatively simple azacrowns that were converted into tetracrowns by virtue of phthalocyanine formation. In the sequence shown in **Figure 22**, the dibromocrown is converted to the tridecyloxyphenyl amide. This is then treated with CuCN to convert the bromides to nitriles. Cyclization with a zinc or nickel salt and base affords the complexed phthalocyanine <1999MI339, 2004POL1931>. A motivation for these studies was the expectation that the resulting compounds would exhibit mesogenic properties. Indeed, thermotropic liquid crystalline behavior was demonstrated for both the nickel and zinc complexes.

14.14.10 Complexation of Metal Ions

A major focus of macrocycle chemistry from its inception has been the development of receptors for ions and molecules. The interactions of heteromacrocycles with alkali and alkaline earth metals, coinage and transition metals, organic cations, polar molecules, and other species have all been studied. A survey of metal ion binding was noted in the previous section <2001JOC7008>. Recent examples include complexation of transition metal salts <2001CC2678>, Pt(II) coordination by thiocrowns <2005IC8602>, and a study using polarography to quantitate macrocycle-cation interaction <2000MI1277>. An interesting variation was the co-complexation of urea or thiourea and silver cations <2005IC8690>.

In addition to homogeneous complexation, ions may be extracted from various solvents or membranes by use of heteromacrocycles. Extraction may be quantified by monitoring a counterion. For example, a metal cation paired with picrate anion will be colored and can be assayed by visible spectrophotometry <1997MI931, 1998T13421, 2000ICA77, 2004ANC2773>.

Extensive work has also been reported by which isotope separations are effected using heteromacrocycles. This work was pioneered by Stevenson <1986NAT522, 1992ANC607>. Additional examples and extensions of this work have been reported during the past decade. These efforts include the purification of Li⁺ isotopes <2002JN67, 2002ZNB107> and the separation of Mg²⁺ isotopes <2002JN129, 2002ZNB1072>.

14.14.11 Ammonium Ion Binding

The binding of ammonium ion, NH₄⁺, by 18-crown-6 was demonstrated early in the history of macrocycle chemistry. The O–H–N in crowns or N–H–N interaction in azacrowns has been characterized by a variety of techniques, including NMR, calorimetry, and X-ray crystal structure analysis. Recent studies in this area have shown that both quaternary and secondary ammonium salts can form complexes with crowns. In the latter case, a rotaxane molecule was prepared by treatment of a dibenzylammonium salt with dibenzo-24-crown-8 and other macrocycles, including pyrido-24-crown-8. The solid-state structure of the *pseudo*-rotaxane structure obtained with pyrido-24-crown-8 is shown in the left panel of **Figure 23**.

In a case involving a less traditional interaction, a quaternary pyridinium salt inserted into a dibenzo-24-crown-8 macrocycle to form a rotaxane structure <2004CEJ5406>. The resulting structure was characterized by X-ray crystallography and is shown in **Figure 23**, right panel. In addition to ion–dipole interactions, the crystal structure reveals several C–H···O hydrogen bonds involving both aliphatic and aromatic C–H groups <2001JCD3135>.

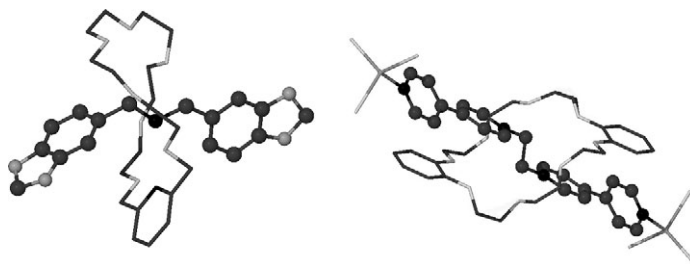


Figure 23

14.14.12 Heteromacrocycle-Based Ion Channel Models

Crown ethers were incorporated into channel model systems more than 15 years ago. The earliest of these included a central crown ether with polyfunctional chains extended in each direction from it <1988TL3803>. No ion transport data were reported in this paper. Later work using NMR analysis confirmed ion flux but the rates were relatively slow <1992AGE1637>. Another effort used a similar strategy in which tartaric acid subunits within the central macrocycle comprised the central unit and scaffold for the membrane spanning chains <1989JA767>. Ion transport was assayed by competition with proton transport <1993JA12315>. These two channel mimics are illustrated in Figure 24.

Extensive studies <1995JA7665> have been conducted with a tris(macrocycle) channel model (top structure, Figure 25) that was disclosed about the same time <1990JA1287>. These compounds, also known as 'hydraphiles', have been shown to insert in the bilayer, to conduct cations, and to exhibit classical open–close behavior both in planar bilayers <1997JA7887> and in living cells <2004JA15747>. The highest activity in the family was observed when the two sidearms were connected through a fourth macrocycle as shown in the lower structure of Figure 25 <2000CC2373>.

A fluorescent derivative was prepared and it was demonstrated by fluorescence microscopy that the hydraphiles insert in the phospholipid bilayers of the bacterium *Escherichia coli* <2002JA9022>. The channels are symmetrical and therefore nonrectifying. As such, they permit ions to pass readily in both directions through the organism's outer (plasma) membrane. This makes the hydraphiles toxic to bacteria because the channels permit internal and external ion asymmetry to be disrupted <2005OBC1647, 2005OBC3544, 2005CCC89>.

It was also found that biological activity depended on the overall length of the hydraphile synthetic channel <2002JA1848, 2005CCC89>. If the channel was too short to span the bilayer, it exhibited little toxicity. When it was of appropriate length, it was potent. Channels that were longer than the bilayer proved to be toxic, but less so than those of optimal length. This length dependence was also exploited as a means for dynamic assessment of bilayer thickness <2005JA636>. In this case, optimal activity of the channel reflected a match with the bilayer thickness, even when additives such as cholesterol were present. An additional example of a macrocycle-based synthetic ion channel that shows biological activity was reported by Voyer and co-workers <2004BMC1279>.

14.14.13 Conclusion

The evolution of crown ether chemistry saw intense effort to design and synthesize novel molecules and to characterize their complexation behavior. As the field matured, macrocycles became more complex and sophisticated in design, complexity, and selectivity. During the past decade, they have served as scaffolds for the development of a wide variety of selective complexing agents, sensors, visualization agents, and models for biological phenomena. In short, heteromacrocycles have entered the organic chemist's toolbox as an important building block that is likely to be utilized in even more complex and imaginative structures and applications than currently envisioned.

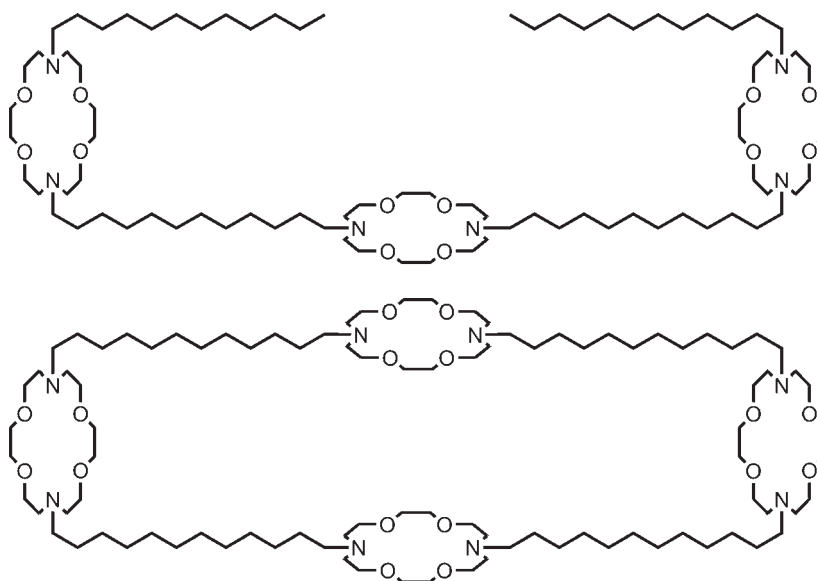


Figure 25

References

- 1962NAT68 D. J. Sutor, *Nature*, 1962, **195**, 68.
 1967JA7017 C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 7017.
 1969TL2885 B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Lett.*, 1969, 2885.
 1970JA2916 J. M. Lehn, J. P. Sauvage, and B. Dietrich, *J. Am. Chem. Soc.*, 1970, **92**, 2916.
 1976CCC295 J. Dale and K. Daasvatn, *J. Chem. Soc., Chem. Commun.*, 1976, 295.
 1980ICAL45 E. Weber and F. Vögtle, *Inorg. Chim. Acta*, 1980, **45**, L45.
 1984B4059 U. Herrmann, B. Tümmler, G. Maas, P. K. T. Mew, and F. Vögtle, *Biochemistry*, 1984, **23**, 4059.
 1984JCI266 R. B. Fox, *J. Chem. Inf. Comput. Sci.*, 1984, **24**, 266.
 1984TCC39 M. Takagi and K. Ueno, *Top. Curr. Chem.*, 1984, **121**, 39.
 1986NAT522 G. R. Stevenson, M. P. Espe, R. C. Reiter, and D. J. Lovett, *Nature*, 1986, **323**, 522.
 1987JA3716 K. A. Arnold, L. Echegoyen, F. R. Fronczek, R. D. Gandour, V. J. Gatto, B. D. White, and G. W. Gokel, *J. Am. Chem. Soc.*, 1987, **109**, 3716.
 1988SCI536 C. J. Pedersen, *Science*, 1988, **241**, 536.
 1988TL3803 L. Jullien and J.-M. Lehn, *Tetrahedron Lett.*, 1988, 3803.
 1989JA767 V. E. Carmichael, P. J. Dutton, T. M. Fyles, T. D. James, J. A. Swan, and M. Zojaji, *J. Am. Chem. Soc.*, 1989, **111**, 767.
 1989JBC19449 A. Minta and R. Y. Tsien, *J. Biol. Chem.*, 1989, **264**, 19949.
 1990JA1287 A. Nakano, Q. Xie, J. V. Mallen, L. Echegoyen, and G. W. Gokel, *J. Am. Chem. Soc.*, 1990, **112**, 1287.
 1992AGE1637 M. J. Pregel, L. Jullien, and J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1637.
 1992ANC607 G. R. Stevenson, T. D. Halvorsen, K. A. Reidy, and J. T. Ciszewski, *Anal. Chem.*, 1992, **64**, 607.
 1992CSR39 G. W. Gokel, *Chem. Soc. Rev.*, 1992, **21**, 39.
 1993JA123115 T. M. Fyles, T. D. James, and K. C. Kaye, *J. Am. Chem. Soc.*, 1993, **115**, 12315.
 1995CRV2529 R. M. Izatt, K. Pawlak, and J. S. Bradshaw, *Chem. Rev.*, 1995, **95**, 2529.
 1995JA7665 O. Murillo, S. Watanabe, A. Nakano, and G. W. Gokel, *J. Am. Chem. Soc.*, 1995, **117**, 7665.
 1995JOC4912 A. V. Bordunov, N. G. Lukyaneko, V. N. Pastushok, K. E. Krakowiak, J. S. Bradshaw, N. K. Dalley, and X. Kou, *J. Org. Chem.*, 1995, **60**, 4912.
 1995JPC10081 Y. Sun, J. W. Caldwell, and P. A. Kollman, *J. Phys. Chem.*, 1995, **99**, 10081.
 1995SMC45 K. A. Arnold, J. C. Hernandez, C. Li, J. V. Mallen, A. Nakano, O. F. Schall, J. E. Trafton, M. Tsesarskaja, B. D. White, and G. W. Gokel, *Supramol. Chem.*, 1995, **5**, 45.
 1996ACR441 G. R. Desiraju, *Acc. Chem. Res.*, 1996, **29**, 441.
 1996JA2307 S. Mecozzi, A. P. West, Jr., and D. A. Dougherty, *J. Am. Chem. Soc.*, 1996, **118**, 2307.
 1996JA6052 E. D. Glendening and D. Feller, *J. Am. Chem. Soc.*, 1996, **118**, 6052.
 1996JPC1605 M. B. More, E. D. Glendening, D. Ray, D. Feller, and P. B. Armentrout, *J. Phys. Chem.*, 1996, **100**, 1605.
 1996JPC16116 D. Ray, D. Feller, M. B. More, E. D. Glendening, and P. B. Armentrout, *J. Phys. Chem.*, 1996, **100**, 16116.
 1996T6713 B. Agai, V. Nemeth, Z. Bocskei, K. Simon, I. Bitter, and L. Toke, *Tetrahedron*, 1996, **52**, 6713.
 1997CRV1515 A. P. de Silva, H. Q. Gunaratne, T. Gunnlaugsson, A. J. Huxley, C. P. McCoy, J. T. Rademacher, and T. E. Rice, *Chem. Rev.*, 1997, **97**, 1515.
 1997JA7887 C. L. Murray, E. S. Meadows, O. Murillo, and G. W. Gokel, *J. Am. Chem. Soc.*, 1997, **119**, 7887.
 1997MI931 F. Gao, and Y. Xu, *J. Appl. Poly. Sci.*, 1997, 931.

- 1997PCA831 M. B. More, D. Ray, and P. B. Armentrout, *J. Phys. Chem. A*, 1997, **101**, 831.
1997PCA6125 S. E. Hill, E. D. Glendening, and D. Feller, *J. Phys. Chem. A*, 1997, **101**, 6125.
1997PCA7007 M. B. More, D. Ray, and P. B. Armentrout, *J. Phys. Chem. A*, 1997, **101**, 7007.
1997MRC283 G. W. Buchanan, M. Gerzain, and K. Bourque, *Mag. Res. Chem.*, 1997, **35**, 283.
1998MI251 T. Hayashita, N. Teramae, T. Kuboyama, S. Nakamura, H. Yamamoto, and H. Nakamura, *J. Incl. Phen. Mac. Chem.*, 1998, **32**, 251.
1998PCA3813 S. E. Hill, D. Feller, and E. D. Glendening, *J. Phys. Chem. A*, 1998, **102**, 3813.
1998MRC687 G. W. Buchanan, M. Gerzain, and R. C. Laister, *Mag. Reson. Chem.*, 1998, **36**, 687.
1998T13421 A. M. Marchand, A. S. McKim, and K. A. Kumar, *Tetrahedron*, 1998, **54**, 13421.
1998TL4807 B. Witulski, Y. Zimmermann, V. Darcos, J.-P. Desvergne, D. M. Bassani, and H. Bouas-Laurent, *Tetrahedron Lett.*, 1998, **39**, 4807.
1999JA5613 S. L. De Wall, E. S. Meadows, L. J. Barbour, and G. W. Gokel, *J. Am. Chem. Soc.*, 1999, **121**, 5613.
1999JA8405 S. L. De Wall, L. J. Barbour, and G. W. Gokel, *J. Am. Chem. Soc.*, 1999, **121**, 8405.
1999JA9043 E. Abel, G. E. M. Maguire, O. Murillo, I. Suzuki, and G. W. Gokel, *J. Am. Chem. Soc.*, 1999, **121**, 9043.
1999JPC10015 J. Vacek, and P. A. Kollman, *J. Phys. Chem. A*, 1999, **103**, 10015.
1999MI339 M. Kandaz, and O. Bekaroglu, *J. Porphyrins Phthalocyanines*, 1999, **3**, 339.
1999MRC401 G. W. Buchanan, A. B. Driega, R. C. Laister, and K. Bourque, *Mag. Reson. Chem.*, 1999, **37**, 401.
1999PNAS8336 A. P. de Silva, J. Eilers, and G. Zlokarnik, *Proc. Natl. Acad. Sci. USA*, 1999, **96**, 8336.
1999SMC163 E. S. Meadows, S. L. De Wall, P. W. Salama, E. Abel, and G. W. Gokel, *Supramol. Chem.*, 1999, **10**, 163.
1999T9425 S. Elshani, C. M. Wai, N. R. Natale, and R. A. Bartsch, *Tetrahedron*, 1999, **55**, 9425.
2000MI1277 M. Hojo, I. Hisatsune, H. Tsurui, and S. Minami, *Anal. Sci.*, 2000, **16**, 1277.
2000ANC5841 A. Yamauchi, T. Hayashita, A. Kato, S. Nishizawa, M. Watanabe, and N. Teramae, *Anal. Chem.*, 2000, **72**, 5841.
2000CC2373 H. Shabany, and G. W. Gokel, *Chem. Commun.*, 2000, 2373.
2000ICA77 L. G. A. van der Water, F. ten Hoote, W. L. Driessen, J. Reedijk, and D. C. Sherrington, *Inorg. Chim. Acta*, 2000, **303**, 77.
2000JA870 J. P. Gallivan and D. A. Dougherty, *J. Am. Chem. Soc.*, 2000, **122**, 870.
2000PCA8067 R. C. Dunbar, *J. Phys. Chem. A*, 2000, **104**, 8067.
2000PNAS6271 S. L. De Wall, E. S. Meadows, L. J. Barbour, and G. W. Gokel, *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 6271.
2001CC1858 J. Hu, L. J. Barbour, and G. W. Gokel, *Chem. Commun.*, 2001, 1858.
2001CC2678 J. B. Love, J. M. Vere, M. W. Glenny, A. J. Blake, and M. Schroder, *Chem. Commun.*, 2001, 2678.
2001JA3092 E. S. Meadows, S. L. De Wall, L. J. Barbour, and G. W. Gokel, *J. Am. Chem. Soc.*, 2001, **123**, 3092.
2001JA4255 S. Tsuzuki, H. Houjou, Y. Nagawa, M. Goto, and K. Hiratani, *J. Am. Chem. Soc.*, 2001, **123**, 4255.
2001JA9486 J. Hu, L. J. Barbour, and G. W. Gokel, *J. Am. Chem. Soc.*, 2001, **123**, 9486.
2001JCD3135 G. J. E. Davidson, S. J. Loeb, N. A. Parekh, and J. A. Wisner, *J. Chem. Soc., Dalton Trans.* 2001, 3135.
2001JP2988 E. Kleinpeter, M. Grotjahn, K. D. Klika, H.-J. Drexler, and H.-J. Holdt, *J. Chem. Soc., Perkin 2*, 2001, 988.
2001JHC1113 A.-M. Patellis, J.-P. Galy, J. Kister, R. Chicheportiche, and J. Elguero, *J. Heterocyclic Chem.*, 2001, **38**, 1113.
2001MI35 S. Inokuma, K. Kimura, T. Funaki, and J. Nishimura, *J. Incl. Phen. Mac. Chem.*, 2001, **39**, 35.
2001JOC2900 K. Agbaria, S. E. Biali, V. Bohmer, J. Brenn, S. Cohen, M. Frings, F. Grynspan, J. M. Harrowfield, A. N. Sobolev, and I. Thondorf, *J. Org. Chem.*, 2001, **66**, 2900.
2001JOC7008 M. Tanaka, M. Nakamura, T. Ikeda, K. Ikeda, H. Ando, Y. Shibutani, S. Yajima, and K. Kimura, *J. Org. Chem.*, 2001, **66**, 7008.
2001JOM108 R. Suzuki, T. Matsumoto, K. Tanaka, Y. Takeuchi, and T. Taketomi, *J. Organomet. Chem.*, 2001, **636**, 108.
2002ACR878 G. W. Gokel, L. J. Barbour, R. Ferdani, and J. Hu, *Acc. Chem. Res.*, 2002, **35**, 878.
2002CC1808 J. Hu, L. J. Barbour, and G. W. Gokel, *Chem. Commun.*, 2002, 1808.
2002CC1810 J. Hu, L. J. Barbour, R. Ferdani, and G. W. Gokel, *Chem. Commun.*, 2002, 1810.
2002CEJ3331 G. McSkimming, J. H. R. Tucker, H. Bouas-Laurent, J.-P. Desvergne, S. J. Coles, M. B. Hursthouse, and M. E. Light, *Chem. Eur. J.*, 2002, **8**, 3331.
2002JA1848 P. H. Schlesinger, R. Ferdani, J. Liu, J. Pajewska, R. Pajewski, M. Saito, H. Shabany, and G. W. Gokel, *J. Am. Chem. Soc.*, 2002, **124**, 1848.
2002JA4473 M. Buhl and G. Wipff, *J. Am. Chem. Soc.*, 2002, **124**, 4473.
2002JA6246 C.-T. Chen and W.-P. Huang, *J. Am. Chem. Soc.*, 2002, **124**, 6246.
2002JA9022 W. M. Leevy, G. M. Donato, R. Ferdani, W. E. Goldman, P. H. Schlesinger, and G. W. Gokel, *J. Am. Chem. Soc.*, 2002, **124**, 9022.
2002JA10940 J. Hu, L. J. Barbour, and G. W. Gokel, *J. Am. Chem. Soc.*, 2002, **124**, 10940.
2002JA13448 R. E. Gawley, S. Pinet, C. M. Cardona, P. K. Datta, T. Ren, W. C. Guida, J. Nydick, and R. M. Leblanc, *J. Am. Chem. Soc.*, 2002, **124**, 13448.
2002JPH249 H. Sulowska, W. Wicz, J. Młodzianowski, M. Przyborowska, and T. Ossowski, *J. Photochem. Photobiol.*, A, 2002, **150**, 249.
2002JRN67 D. W. Kim, *J. Radioanal. Nuc. Chem.*, 2002, **253**, 67.
2002JRN129 D. W. Kim, *J. Radioanal. Nuc. Chem.*, 2002, **252**, 129.
2002M1097 M. Wilhelm, E. Berssen, R. Koch, and H. Strasdeit, *Monatsh. Chem.*, 2002, **133**, 1097.
2002MM2432 S. Habaue, M. Morita, and Y. Okamoto, *Macromolecules*, 2002, **35**, 2432.
2002OL2641 Y. Nakahara, Y. Matsumi, W. Zhang, T. Kida, Y. Nakatsuiji, and I. Ikeda, *Org. Lett.*, 2002, **4**, 2641.
2002PLM3469 S. Habaue, M. Morita, and Y. Okamoto, *Polymer*, 2002, **43**, 3469.
2002TL7243 S. Sasaki, A. Hashizume, D. Citterio, E. Fujii, and K. Suzuki, *Tetrahedron Lett.*, 2002, **43**, 7243.
2002ZNB107 D. W. Kim, C. S. Kim, N.-S. Lee, H. Ryu, J. S. Kim, and Y. H. Jang, *Z. Naturforsch. Sect. B*, 2002, **57**, 107.
2002ZNB1072 D. W. Kim, H. I. Ryu, and B. K. Jeon, *Z. Naturforsch. Sect. B*, 2002, **57**, 1072.
2003ANC549 H. He, M. A. Mortellaro, M. J. Leiner, S. T. Young, R. J. Fraatz, and J. K. Tusa, *Anal. Chem.*, 2003, **75**, 549.
2003CC2947 G. W. Gokel, *Chem. Commun.*, 2003, 2847.
2003JA1468 H. He, M. A. Mortellaro, M. J. Leiner, R. J. Fraatz, and J. K. Tusa, *J. Am. Chem. Soc.*, 2003, **125**, 1468.
2004ANC2773 H. Luo, S. Dai, and P. V. Bonnesen, *Anal. Chem.*, 2004, **76**, 2773.
2004BMC1279 E. Biron, F. Otis, J. C. Meillon, M. Robitaille, J. Lamothe, P. Van Hove, M. E. Cormier, and N. Voyer, *Bioorg. Med. Chem.*, 2004, **12**, 1279.
2004BML5313 V. M. Martin, A. Rothe, Z. Diwu, and K. R. Gee, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5313.

- 2004CEJ5406 A. R. Williams, B. H. Northrop, K. N. Houk, J. F. Stoddart, and D. J. Williams, *Chem. Eur. J.*, 2004, **10**, 5406.
- 2004CH1174 M. Kubiyini, K. Pal, P. Barayani, A. Grofcsik, I. Bitter, and A. Grun, *Chirality*, 2004, **16**, 174.
- 2004IC5195 Q.-Z. Yang, L.-Z. Wu, H. Zhang, B. Chen, Z.-X. Wu, L.-P. Zhang, and C.-H. Tung, *Inorg. Chem.*, 2004, **43**, 5195.
- 2004IC6114 M. P. Clares, J. Aguilar, R. Aucejo, C. Lodeiro, M. T. Albelda, F. Pina, J. C. Lima, A. J. Parola, J. Pina, J. S. d. Melo, *et al. Inorg. Chem.*, 2004, **43**, 6114.
- 2004JA9291 S. J. K. Pond, O. Tsutsumi, M. Rumi, O. Kwon, E. Zojer, J.-L. Bredas, S. R. Marder, and J. W. Perry, *J. Am. Chem. Soc.*, 2004, **126**, 9291.
- 2004JA15747 W. M. Leevy, J. E. Huettner, R. Pajewski, P. H. Schlesinger, and G. W. Gokel, *J. Am. Chem. Soc.*, 2004, **126**, 15747.
- 2004JOC4403 Y. Nakahara, T. Kida, Y. Nakatsuji, and M. Akashi, *J. Org. Chem.*, 2004, **69**, 4403.
- 2004PCA907 E. S. Stoyanov and C. A. Reed, *J. Phys. Chem. A*, 2004, **108**, 907.
- 2004PCA11463 M. Buhl, R. Ludwig, R. Schurhammer, and G. Wipff, *J. Phys. Chem. A*, 2004, **108**, 11463.
- 2004NJC295 N. Marcotte, F. Rodrigues, D. Lavabre, and S. Fery-Forgues, *New. J. Chem.*, 2004, **28**, 295.
- 2004OBC1542 Y. Liu, Y.-W. Yang, L. Li, and Y. Chen, *Org. Biomol. Chem.*, 2004, **2**, 1542.
- 2004OBC2359 Y. Liu, Z.-Y. Duan, Y. Chen, J.-R. Han, and L. Cui, *Org. Biomol. Chem.*, 2004, **2**, 2359.
- 2004OL1071 L.-L. Zhou, H. Sun, H.-P. Li, H. Wang, X.-H. Zhang, S.-K. Wu, and S.-T. Lee, *Org. Lett.*, 2004, **2**, 1071.
- 2004POL1931 F. Yilmaz, D. Atilla, and V. Ahsen, *Polyhedron*, 2004, **23**, 1931.
- 2005BML1851 V. V. Martin, A. Rothe, and K. R. Gee, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1851.
- 2005CC89 W. M. Leevy, M. E. Weber, P. H. Schlesinger, and G. W. Gokel, *Chem. Commun.*, 2005, 89.
- 2005IC8602 J. W. Sibert, P. B. Forshee, and V. Lynch, *Inorg. Chem.*, 2005, **44**, 8602.
- 2005IC8690 V. Amendola, D. Esteban-Gomez, L. Fabbri, M. Licchelli, E. Monzani, and F. Sancecnon, *Inorg. Chem.*, 2005, **44**, 8690.
- 2005JA636 M. E. Weber, P. H. Schlesinger, and G. W. Gokel, *J. Am. Chem. Soc.*, 2005, **126**, 636.
- 2005OBC1647 W. M. Leevy, M. E. Weber, M. R. Gokel, G. B. Hughes-Strange, D. D. Daranciang, R. Ferdani, and G. W. Gokel, *Org. Biomol. Chem.*, 2005, **3**, 1647.
- 2005OBC1787 Y. Nakahara, T. Kida, Y. Nakatsuji, and M. Akashi, *Org. Biomol. Chem.*, 2005, **3**, 1787.
- 2005OBC3544 W. M. Leevy, S. T. Gammon, T. Levchenko, D. D. Daranciang, O. Murillo, V. Torchilin, D. Piwnica-Worms, J. E. Huettner, and G. W. Gokel, *Org. Biomol. Chem.*, 2005, **3**, 3544.
- 2005PB237 S. Habaue, Y. Akagi, M. Sato, and A. Niimi, *Polym. Bull.*, 2005, **54**, 237.
- 2006EJO1050 J. Roxburgh Craig and G. Sammes Peter, *Eur. J. Org. Chem.*, 2006, 1050.
- 2006IC5407 Esteban-Gomez David, Platas-Iglesias Carlos, Enriquez-Perez Teresa, Avecilla Fernando, de Blas Andres, and Rodriguez-Blas Teresa, *Inorg. Chem.*, 2006, 5407.
- 2006ICA649 Kruszynski Rafal, Siwy Mariola, Porwolik-Czomperlik Iwona, and Trzesowska Agata, *Inorg. Chim. Acta*, 2006, 649.
- 2006JA344 G. Farruggia, S. Iotti, L. Prodi, M. Montalti, N. Zaccaroni, P. B. Savage, V. Trapani, P. Sale, and F. I. Wolf, *J. Am. Chem. Soc.*, 2006, **128**, 344.
- 2006JPH268 S. Benco John, R. Lambert Christopher, and McGimpsey W. Grant, *Photochemistry and Photobiology*, 2006, 268.
- 2006OBC4543 Dalla Cort Antonella, Mandolini Luigi, Pasquini Chiara, and Schiaffino Luca, *Org. Biomol. Chem.*, 2006, 4543.
- 2006POL599 M. W. Glenny, L. G. A. van de Water, J. M. Vere, A. J. Blake, C. Wilson, W. L. Driessen, J. Reedijk, and M. Schroder, *Polyhedron*, 2006, **25**, 599.
- 2006S756 B. Forshee Philip and W. Sibert John, *Synthesis*, 2006, 756.
- 2006SAA532 M. Dulak, R. Bergougnant, K. M. Fromm, H. R. Hagemann, A. Y. Robin, and T. A. Wesolowski, *Spectrochim. Acta, Part A*, 2006, **64**, 532.
- 2006TA2358 Kovacs Ilona, Huszthy Peter, Bertha Ferenc, and Sziebert Denes, *Tetrahedron Asymmetry*, 2006, 2358.
- 2006TL3541 Nabeshima Tatsuya, Tanaka Yasushi, Saiki Toshiyuki, Akine Shigehisa, Ikeda Chusaku, and Sato Soichi, *Tetrahedron Lett.*, 2006, 3541.
- 2006TL4817 Couty Francois, Evano Gwilherm, Menguy Laurence, Steimetz Vincent, and Toumi Mathieu, *Tetrahedron Lett.*, 2006, 817.
- B-2002MI1 B. Valeur, 'Molecular Fluorescence', Wiley-VCH, Weinheim, 2001.
- 2007CPL403 Maruyama Yutaka, Matsugami Masaru, and Hirata Fumio, *Chem. Phys. Lett.*, 2007, 403.
- 2007ICA814 Adams Harry and D. Ward Michael, *Inorg. Chim. Acta*, 2007, 814.
- 2007JST151 Lu Li-Hwa, Su Chia-Ching, and Hsieh Tian-Jye, *J. Mol. Struct.*, 2007, 151.
- 2007OBC1007 O. A. Fedorova, E. N. Andryukhina, Yu. V. Fedorov, M. A. Panfilov, M. V. Alfimov, G. Jonusauskas, A. Grelard, and E. Dufourc, *Org. Biomol. Chem.*, 2007, 1007.

Biographical Sketch



George Gokel earned his B.S. at Tulane University in New Orleans and his Ph.D. (chemistry) at the University of Southern California in Los Angeles. After postdoctoral work with Donald Cram at UCLA and a brief period in DuPont's Central Research Department, Dr. Gokel began an academic career. He has held faculty positions in the chemistry departments at the Pennsylvania State University, the University of Maryland, and the University of Miami. He was professor in the Departments of Chemistry and Molecular Biology & Pharmacology at the Washington University School of Medicine until 2006. He is currently Distinguished Professor of Science at the University of Missouri in St. Louis, MO, USA. His major interest is in developing synthetic organic model systems that can be used to mimic and to understand biological phenomena. Two areas of current effort involve the development of synthetic ion channels and receptors for cation complexation, particularly involving cation- π interactions.



Elizabeth Elliott was born in Saint Louis, MO, USA. In 2002, she received her B.S. degree in chemistry from American University in Washington, DC. Currently, she is pursuing her Ph.D. in chemistry at Washington University in Saint Louis. Under the guidance of Professor George W. Gokel, Elizabeth is working on the characterization of cation- π interactions in solution and in lipid bilayers.

14.15

Ten-membered Rings or Larger with One or More Oxygen and Sulfur Atoms

Y. Habata

Toho University, Chiba, Japan

© 2008 Elsevier Ltd. All rights reserved.

14.15.1	Introduction	829
14.15.2	Crown-Related Macrocycles	829
14.15.2.1	Aliphatic Oxa-thiacrown Ethers	830
14.15.2.2	Oxa-thiacrown Ethers Containing Aliphatic Rings in a Cyclic Structure	832
14.15.2.3	Oxa-thiacrown Ethers Containing Double Bonds in the Cyclic Structure	834
14.15.2.4	Oxa-thiacrown Ethers Containing Conjugating Rings in a Cyclic Structure	836
14.15.2.5	Oxa-thiacrown Ethers Containing Tetrathiafulvalene Units	842
14.15.2.6	Cyclophane-Type Oxa-thiacrown Ethers	843
14.15.2.7	Oxa-thiacrown Ethers Containing Additional Binding Sites	845
14.15.2.8	Oxa-thiacrown Ethers Containing Porphyrin Units	847
14.15.3	Crown-Related Macrocycles with Calixarene Units	849
14.15.3.1	Oxa-thiacrown Ethers Containing One Crown Unit and One Calixarene Unit	849
14.15.3.2	Oxa-thiacrown Ethers Containing Two Crown Units and One Calixarene Unit	850
14.15.3.3	Oxa-thiacrown Ethers Containing Two Calixarene Units	851
14.15.4	Crown-Related Macrocycles to Build Catenanes and Rotaxanes	852
14.15.5	Macrocycles, Not Classified with Crown Ethers	856
14.15.5.1	Macrocycles Containing Sugar Units	856
14.15.5.2	Cyclic Peptides by Dynamic Combinatorial Chemistry	856
14.15.5.3	Macrocyclic Diacyl or Dialkyl Glycerols	856
14.15.6	Further Developments	858
	References	859

14.15.1 Introduction

Since the pioneering works by Pedersen <1971JOC254> and Bradshaw *et al.* <1973JHC1, 1974JHC45, 1976JOC134>, many kinds of crown ethers containing O and S atoms in the cyclic structures have been reported.

Recently, crown-related macrocycles have been applied to new supramolecular systems such as porphyrins, calixarenes, catenanes, and rotaxanes, and so on. To cover the widespread area in limited pages, this chapter mainly focuses on the syntheses and functions of crown-related macrocycles having 10-membered rings or larger with one or more O and S atoms. Therefore, the standard arrangement in 12 sections could not be applied in this chapter related to that of CHEC-II(1996) (Chapters 9.29 and 9.31).

14.15.2 Crown-Related Macrocycles

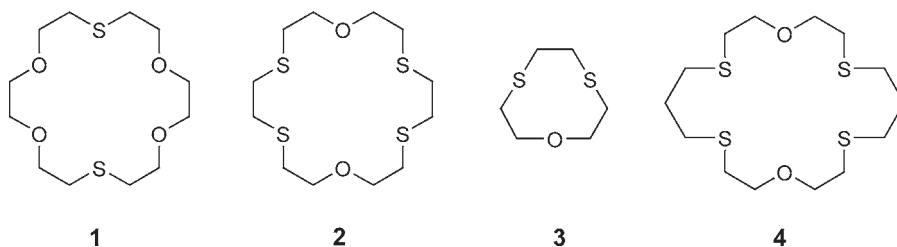
Recently many oxa-thiacrown ethers have been reported in last decade. In this section, oxa-thiacrown ethers are classified into eight groups according to their structures.

14.15.2.1 Aliphatic Oxa-thiacrown Ethers

General synthetic methods of crown ethers containing O and S atoms in the aliphatic cyclic structures, named oxa-thiacrown ethers, have already reported by the Pedersen and Bradshaw groups. Recent studies on the aliphatic oxa-thiacrown ethers have shifted to the structural study of metal complexes and complexation properties.

Rottgers and Sheldrick have recently reported that 1,10-dithia-18-crown-6 **1** formed lamellar coordination polymer with CuI and ion-ligating iodocuprate(I) based on two-dimensional coordination networks with CuI and alkali metal cations <2000MI271>. Both anionic frameworks contain characteristic iodocuprate(I) chains that are bridged in a μ -S1,S10 manner by **1**. However, the structure-directing influence of the alkali metal cation manifests itself in both the connectivity pattern and the stoichiometry of the resulting CuI-based network.

X-Ray structures of the salt-free tetrathia-18-crown-6 **2** and metal complexes of **2** with $\text{Pt}(\text{PF}_6)_2$ and $\text{Ni}(\text{BF}_4)_2$ were reported by Grant *et al.* <1998IC5299, 2000ICA250>. In the salt-free **2**, two C–O bond lengths average 1.411(6) Å, and the four C–S bond lengths average 1.501(6) Å. The C–C–O–C bonds all adopt an *anti*-conformation within an average 3° deviation. Half of the O–C–C–S bonds are *gauche* and the other half are *anti*, a compromise between the conformational preferences of the individual C–O and C–S bonds. Three-quarters of the C–C–S–C bonds are *gauche* (within an 8° deviation), and all of the S–C–C–S bonds are *anti*.

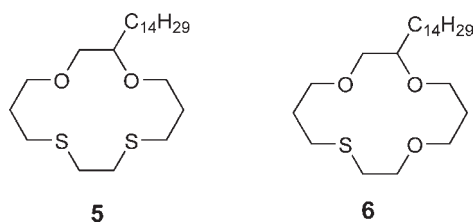


When **2** forms a complex with $\text{Pt}(\text{PF}_6)_2$, the Pt^{2+} lies at an inversion center surrounded by a distorted square planar array of four atoms. The two oxygen atoms lie *trans* to each other and oriented away from the Pt center, precluding any Pt–O interactions. In the complex, the S–O–S unit adopts a meridional rather than facial coordination mode. The Pt–O distances in **2**– $\text{Pt}(\text{PF}_6)_2$ complex is 3.730(5) Å and the Pt–S bond lengths average 2.317(2) Å. In this structure, the platinum(II) ion lies 0.018 Å above the mean plane of the four sulfur atoms.

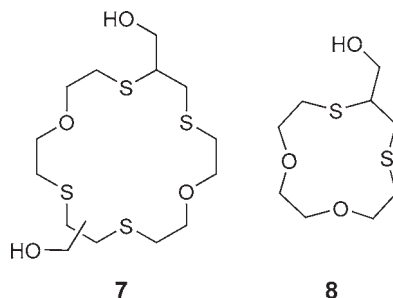
When **2** interacts with $\text{Ni}(\text{BF}_4)_2$, **2** is coordinated in a distorted octahedral fashion to the Ni^{2+} with *trans* oxygen atoms, and a diethylene S–O–S linkage that is meridional. All six donor atoms are bound to the nickel center. The crystal is racemic with four pairs of enantiomers per unit cell. In the structure, the two Ni–O bonds average 2.068(7) Å in length, while the four Ni–S bonds average 2.370(3) Å.

Nine-membered oxa-thiacrown ether **3** forms 2:1 (host/guest) complexes with $\text{Pt}(\text{PF}_6)_2$, $\text{Pd}(\text{PF}_6)_2$, $\text{Cu}(\text{BF}_4)_2$, and $\text{Ni}(\text{BF}_4)_2$ <1998IC5299, 2000ICA250>. In the **3**– $\text{Pt}(\text{PF}_6)_2$ complex, the Pt^{2+} lies at an inversion center surrounded by a distorted square planar array of four sulfur atoms similar to the **2**– $\text{Pt}(\text{PF}_6)_2$ complex. The distance between the Pt and O atoms in the **3**– $\text{Pt}(\text{PF}_6)_2$ is 3.44(5) Å, greater than the sum of the van der Waals radii for the two atoms (3.3 Å). The Pd^{2+} complex of **3** shows a similar structure to the analogous Pt^{2+} complex <2000ICA250>. The four sulfur atoms form a square plane around the Pd^{2+} center, and both oxygen atoms are again directed away from the palladium. The Pd–S bond lengths average 2.313(2) Å. The Pd–O distance in the complex is 3.379(5) Å, exceeding the sum of the van der Waals radii and far too great to allow any Pd–O interactions. The Cu^{2+} complex with **3** shows an interesting Jahn–Teller distortion from an octahedral geometry resulting in coordinate bonds, which are all remarkably similar in length (Cu–S bond lengths 2.3293(6)–2.355(2) Å).

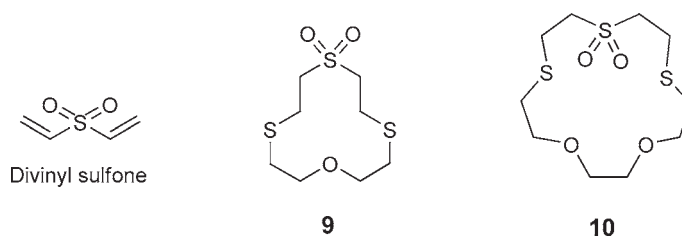
The X-ray structure of Co^{2+} complex with dioxatetrathia-20-crown-6 **4** having two trimethylene units in the ring structure was reported by Lucas *et al.* In the Co^{2+} complex with **4**, the Co–S lengths are 2.444(2) Å, the Co–O lengths are 2.098(6) Å, and the coordination sphere bond angles range from 80.43(5)° to 99.57(5)°. The detailed structure of the complex is compared with the structures of Co^{2+} complexes with trithia-10-crown-3 and 15-crown-5. Oxathia-14-crown-4 having one or two S atoms in the ring system with long alkyl chain, **5** and **6**, were prepared to develop Ag^+ ion-selective optodes <1995ANC1315> and electrodes <1996ANC4166>.



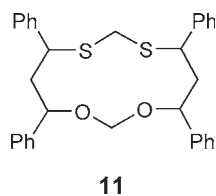
Oxa-thiacrown ethers, **7** and **8**, having hydroxymethyl groups on the crown rings, were prepared [<1996MC9>](#) and immobilized on a silica matrix coated with ω -(triethoxysilyl)undecanoic acid.



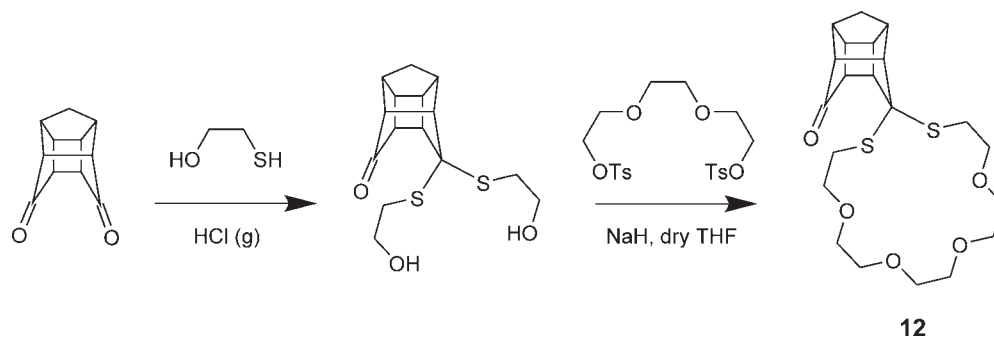
Teyssot *et al.* reported that the Michael addition of bis(nitrogen or sulfur) nucleophiles to divinyl sulfone provided the corresponding macrocyclic adducts in good yields [<2003EJO54>](#). For example, **9** and **10** have been prepared in 82% and 80% yields, by the reaction of divinyl sulfone with bis(2-mercaptoethyl)ether and 4,7-dioxa-1,10-dithiadecane, respectively. The X-ray structure of **10** was also reported.



Oxa-thiacrown ethers **11** and **12** possessing a thioacetal unit have been prepared by Llorca *et al.* [<1997AXC816>](#), and Romanski and Marchand [<2004PJC223>](#), respectively. The X-ray structure of **11** showed that the S and O atoms were located at side positions of the quadrilateral.

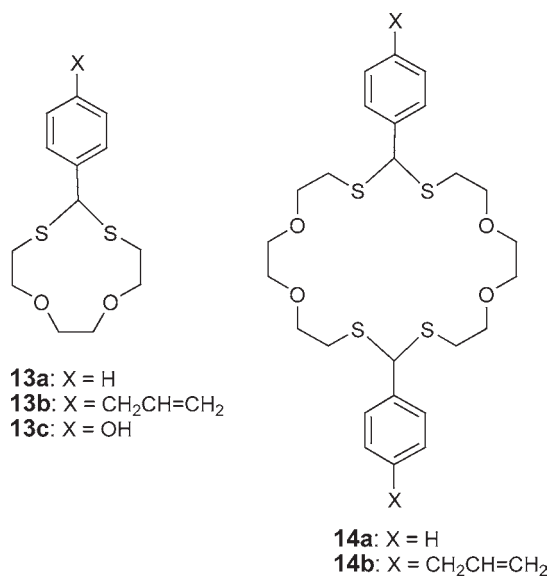


Compound **12** was prepared in two steps from pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}] undecane-8,11-dione as shown in [Scheme 1](#).



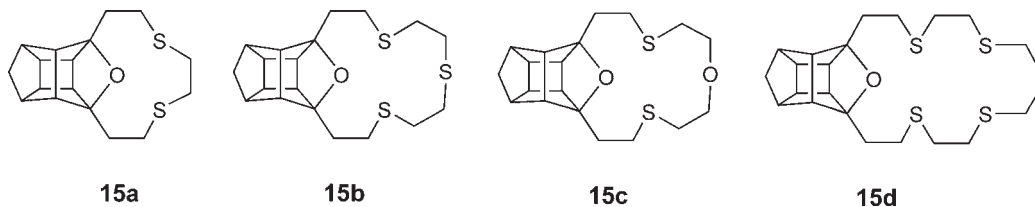
Scheme 1

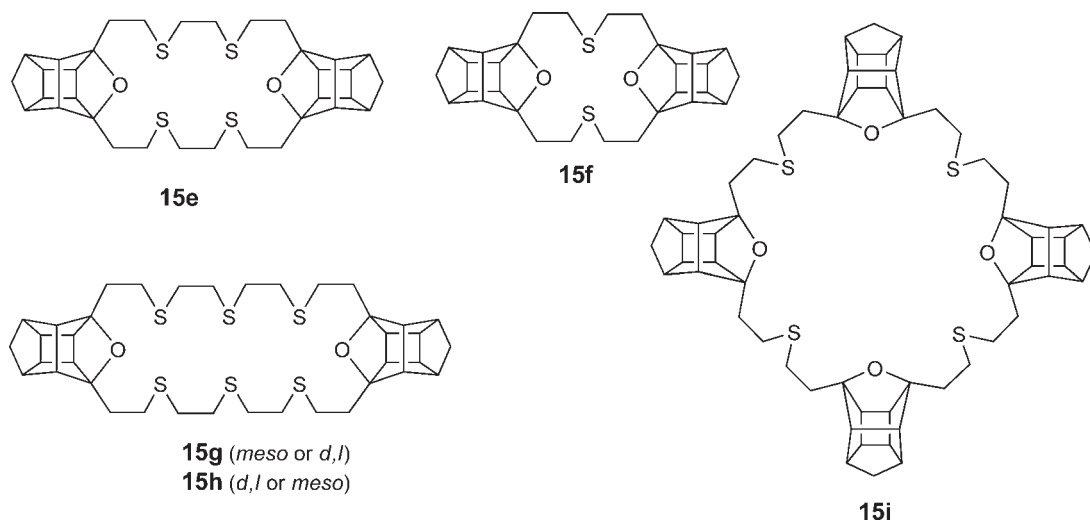
Compounds **13a–c** and **14a,b** were observed during preparation of polymercaptals [<1996MI191>](#). Detailed ^1H and ^{13}C nuclear magnetic resonance (NMR) spectral data of these compounds were reported.



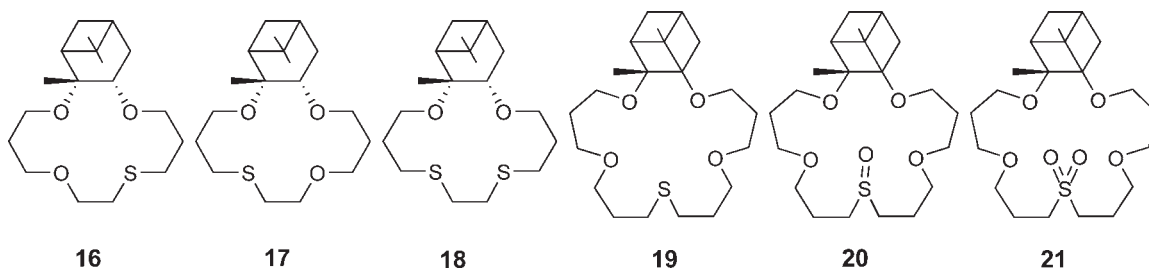
14.15.2.2 Oxa-thiacrown Ethers Containing Aliphatic Rings in a Cyclic Structure

Marchand *et al.* have reported the synthesis and X-ray structures of the cage-annulated oxa-thiacrown ethers **15** [<2002JCX447>](#). Using these oxa-thiacrown ethers except for **15g** and **15h**, Williams *et al.* measured the electrospray ionization (ESI) mass spectrometry (MS) of the complexes with Hg^{2+} , Pb^{2+} , Cd^{2+} , and Zn^{2+} cations [<2002ANC4423>](#). All of the macrocycles in series bound the mercury ion very selectively and efficiently in the presence of many other metal ions.

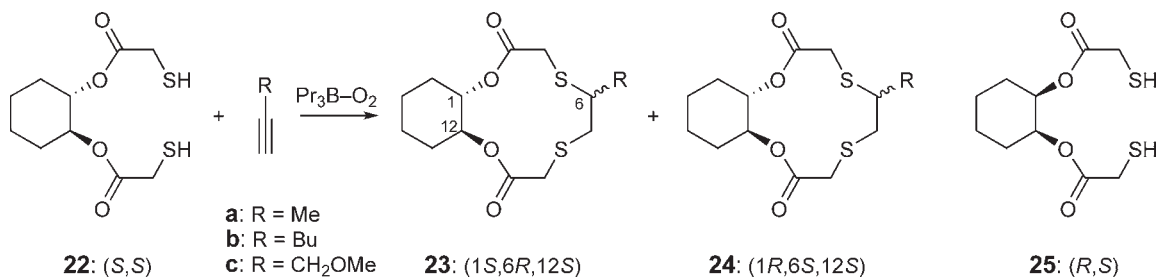




Suzuki and co-workers have prepared 14-membered and 19-membered oxa-thiacrown ethers containing a pinane subunit **16–21** <1995ANC1315, 1996ANC4166>. These compounds were used as ion-selective optodes and electrodes. The best Ag^+ selective electrode was prepared with **17** in which the ion selectivity of the electrode for Ag^+ was over 10^4 times that for other metal cations.

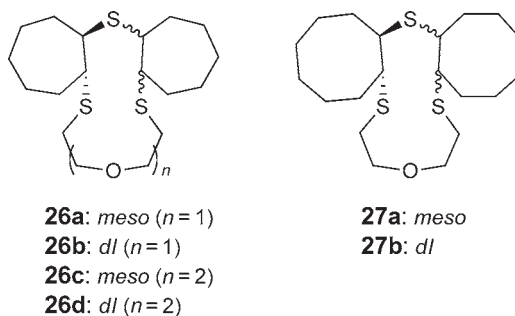


Troyansky *et al.* reported that homolytic cycloaddition of dithiols derived from *trans*- and *cis*-1,2-cyclohexanediols to alkynes, induced by $\text{Pr}_3\text{B}-\text{O}_2$, offered an extremely simple approach to *trans*- and *cis*-cyclohexano-fused 12-membered crown thioethers <1995TL11431>. The reaction of **22** (*S,S*) proceeded with a pronounced remote 1,6-asymmetric induction to give predominantly **23** (1*S*, 6*R*, 12*S*), while **25** (*S*, *R*) reacted nonstereoselectively (Scheme 2).

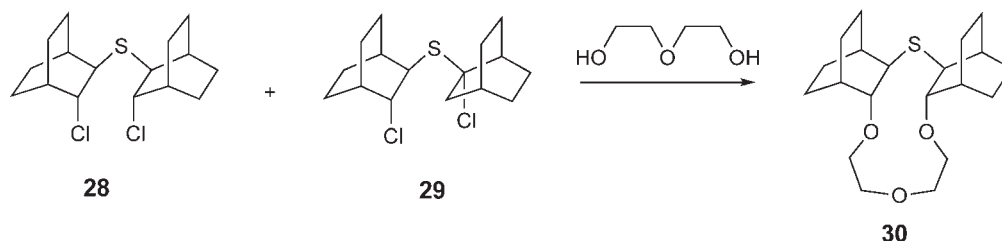


Scheme 2

Using bis(2-chlorodicycloheptyl)sulfide and bis(2-chlorodicyclooctyl)sulfide, oxa-thiacrown ethers **26a** and **27b** were prepared <2002CHE456>. The dichlorodicycloalkyl sulfides with dithiols gave a mixture of the corresponding diastereoisomers of oxa-thiacrown ethers in ratios of $\sim 1:1$, which agrees well with results obtained previously for cyclohexane derivatives.



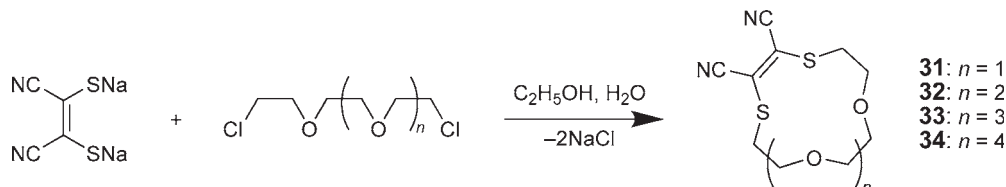
The oxa-thiacrown ether having bicyclo[2.2.2]octane units was prepared from a mixture of dichloro sulfides **28** and **29** <2002CHE261>. The reaction of the mixture with diethylene glycol by a high-dilution method led to the formation of only one stereoisomer of **30** in 40% yield (Scheme 3).



Scheme 3

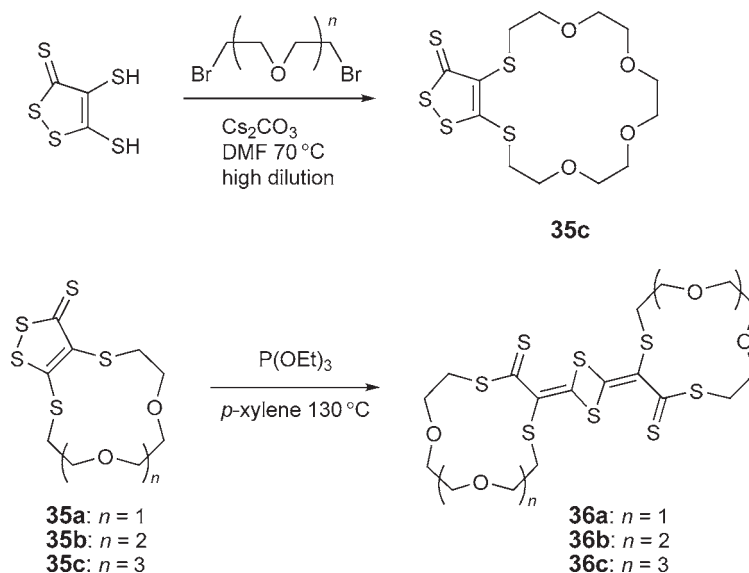
14.15.2.3 Oxa-thiacrown Ethers Containing Double Bonds in the Cyclic Structure

Preparation, X-ray structure, and complexing properties of the oxa-thiacrown ethers with 1,2-dicyano-1,2-dithioethene units **31–33** were reported for the first time by Holdt in 1993 <1993PAC477>. A synthon for the synthesis of unsaturated oxa-thiacrown ethers is (*Z*)-disodium-1,2-dicyanoethene-1,2-dithiolate. Compounds **31–34** were synthesized by high-dilution reactions of the dithiolate with oligoethylene glycol dichlorides in aqueous ethanol. Using the crown ethers, two groups have reported the structures of metal complexes. Sibert *et al.* reported an improved synthesis of **32** and **33** as well as the X-ray structures of their AgBF_4 complexes <1995IC2300>. The structure of the Ag^+ complex with **32** contains two unique, co-crystallized, 1:1 Ag complexes, a polymeric form and a discrete monomeric form. The structure of the Ag^+ complex with **33** is polymeric and consists of an endocyclic Ag^+ ion coordinated by three of the four macrocyclic O donor atoms and only one S atom. On the other hand, Holdt and co-workers reported that **32** forms 2:1 (host/guest) and 1:2 (host/guest) complexes with AgPF_4 and AgClO_4 , respectively <1996CB807, 1999ICA305>. They also reported AgPF_6 complexes with **31**, **33**, and **34** <1996CB807> and CsSbCl_6 complex with **34** (Scheme 4) <1998ZFA1376>.



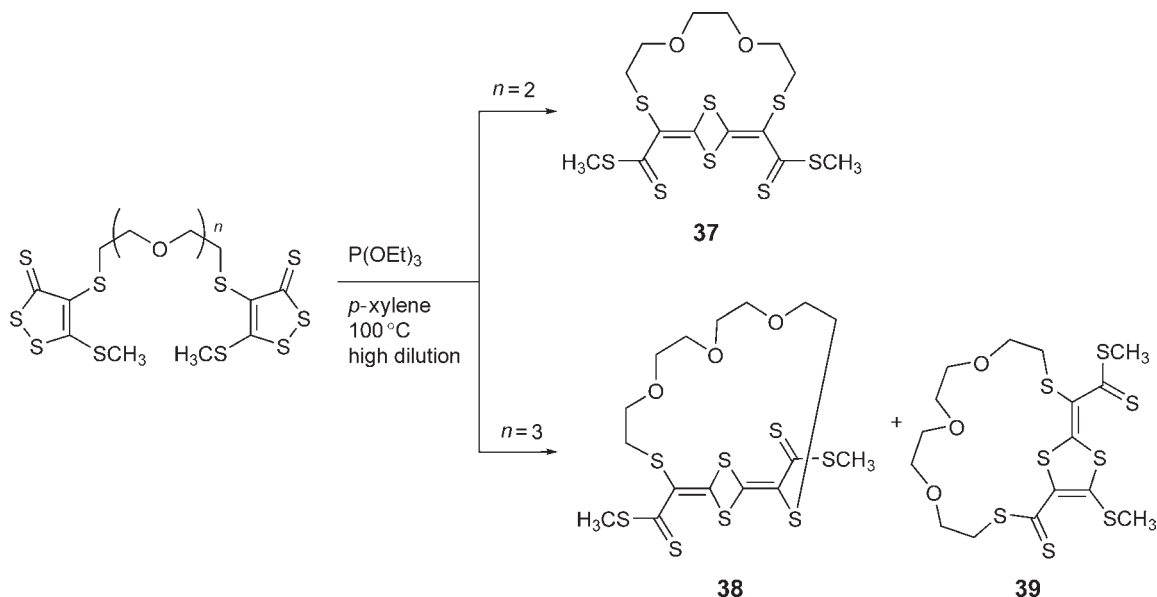
Scheme 4

Oxa-thiacrown ethers having a 1,2-dithiole-3-thione unit <1998JPR450> have also been prepared by Holdt and co-workers. 4,5-Dimercapto-1,2-dithiole-3-thione was reacted with 1,14-dibromo-3,6,9,12-tetraoxatetradecane in the presence of Cs_2CO_3 under high-dilution conditions to give **35** in 11% yield. The oxa-thiacrown ethers **35a–c** <1994SUL177> were converted to bis(dithiacrown ether) **36a–c** with $\text{P}(\text{OEt})_3$ in *p*-xylene (Scheme 5). The configurations of the thiodesaurine units in **36a–c** are (*E*)-configuration. They applied the dimerization of 1,2-dithiole-3-thione to an intramolecular macrocyclization <1998CC1653>.



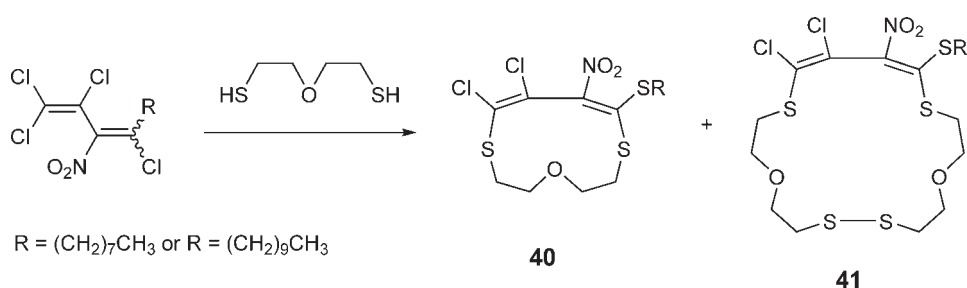
Scheme 5

When a starting material having triethyleneglycol unit ($n=2$) was used, (*Z*)-**37** was obtained, whereas a starting material having longer ethyleneoxy unit ($n=3$) not only gave (*E*)-**38**, but also (*E*)-**39** possessing a 1,3-dithiafulven unit in 11–18% and 10–23% yields, respectively (Scheme 6). The X-ray crystal structures for **37** and **38** were also reported.



Scheme 6

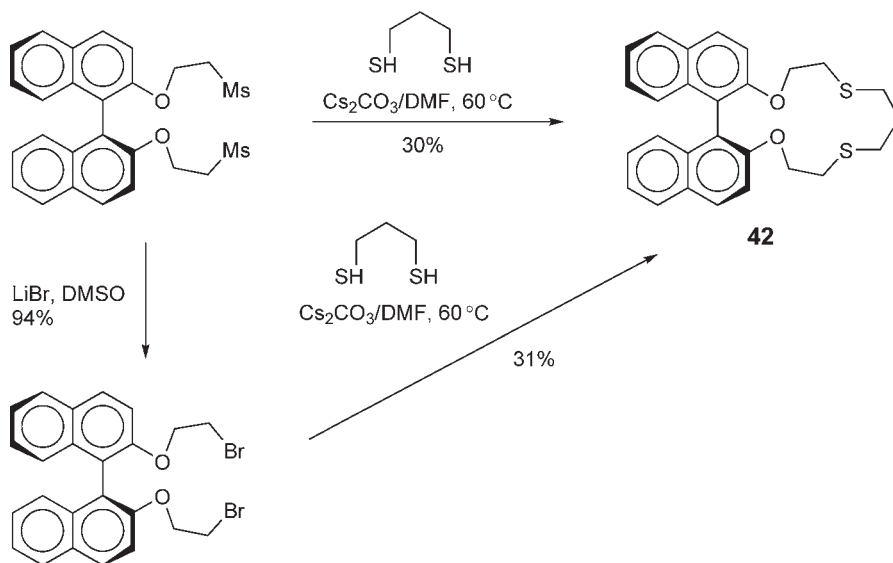
Oxathiacrown ethers containing a diene unit **40** and **41** were prepared by the reaction of 1,3,5,5-tetrachloro-2-nitrobutadiene derivatives with bis(2-mercaptoethyl) ether (Scheme 7) <2002PS2529>. The authors reported that **40** formed by the cyclization of an intermediate $(\text{Cl}_2\text{C}=\text{CCl}-\text{C}(\text{NO}_2)=\text{C}(\text{SR})-\text{S}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{S}^-\text{Na}^+)$. Compound **41** was prepared by the cyclization of the intermediate $(\text{Na}^+\text{S}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{S}-\text{ClC}=\text{CCl}-\text{C}(\text{NO}_2)=\text{C}(\text{SR})-\text{S}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{S}^-\text{Na}^+)$ or $\text{Cl}_2\text{C}=\text{CCl}-\text{C}(\text{NO}_2)_2=\text{C}(\text{SR})-\text{S}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{S}-\text{S}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{S}^-\text{Na}^+)$, which were obtained by the reaction of 1,3,5,5-tetrachloro-2-nitrobutadiene derivatives with bis(2-mercaptoethyl) ether. In this report, the *E/Z* stereochemistry of these compounds was not reported.



Scheme 7

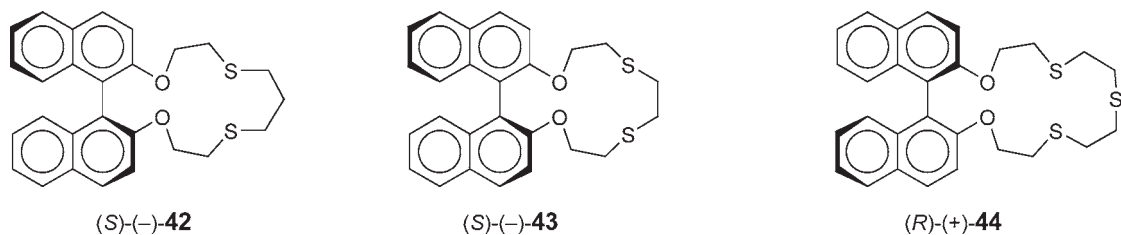
14.15.2.4 Oxa-thiacrown Ethers Containing Conjugating Rings in a Cyclic Structure

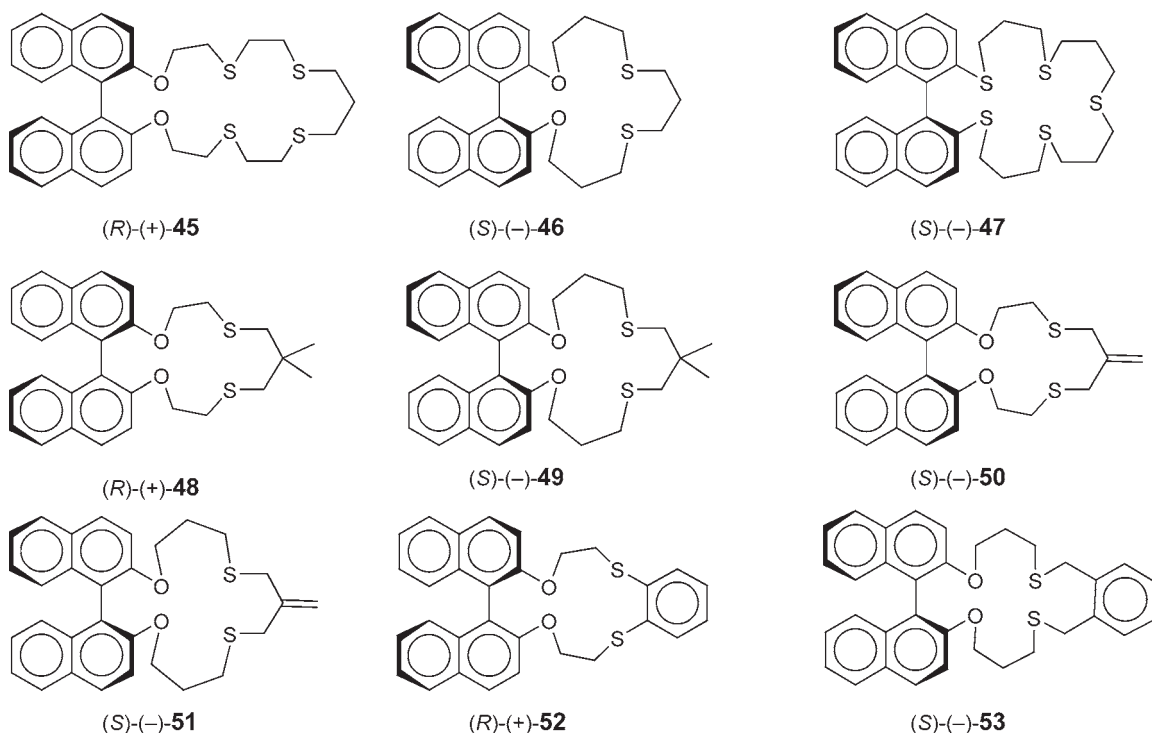
Chiral oxa-thiacrown ethers containing a 1,1'-binaphthyl unit have been prepared by Stock and Kellogg <1996JOC3093>. To prepare **42**, they used either the bis-mesylate or dibromide (Scheme 8); however, changing the leaving group did not help improve the yields of cyclization products.



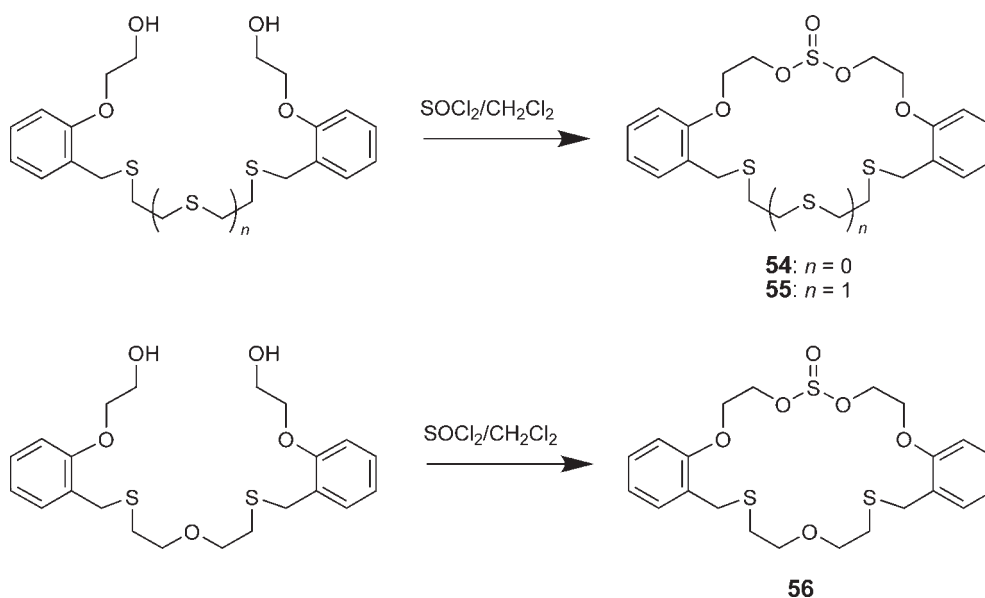
Scheme 8

Compounds **43–45** were synthesized in an analogous manner by cyclization of the bis-mesylate. The propylene-bridged oxa-thiacrown ethers **46** and **47** were prepared from dibromide having trimethylene units.



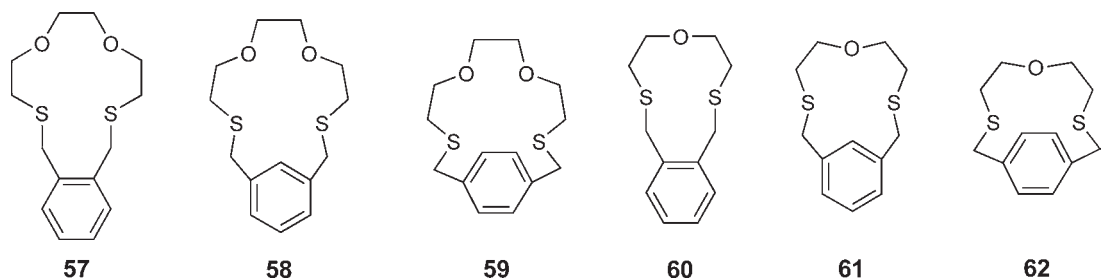


Oxa-thiacrown ethers containing sulfoxide groups were prepared by Ashram <2005MI199>. Compounds **54–56** were prepared by the reaction of corresponding diols with freshly distilled thionyl chloride in anhydrous dichloromethane at room temperature for 0.5 h. The yields of **54**, **55**, and **56** were 45%, 38%, and 30%, respectively. Conductometric titration studies in pure acetonitrile were employed to investigate their binding affinities toward Ag^+ , Cu^{2+} , Pb^{2+} , Cd^{2+} , Zn^{2+} , Co^{2+} , Ni^{2+} , Co^{2+} , Cr^{3+} , and Hg^{2+} ; there was a selectivity for Ag^+ and Cu^{2+} over the other metals investigated. Compound **54** has the highest selectivity toward Ag^+ . The X-ray structure of **56** was also reported (Scheme 9).

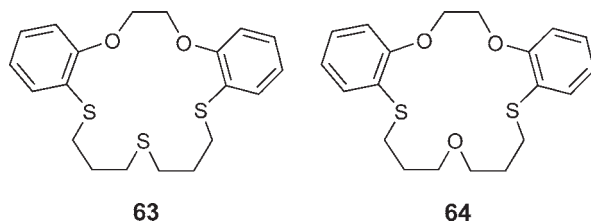


Scheme 9

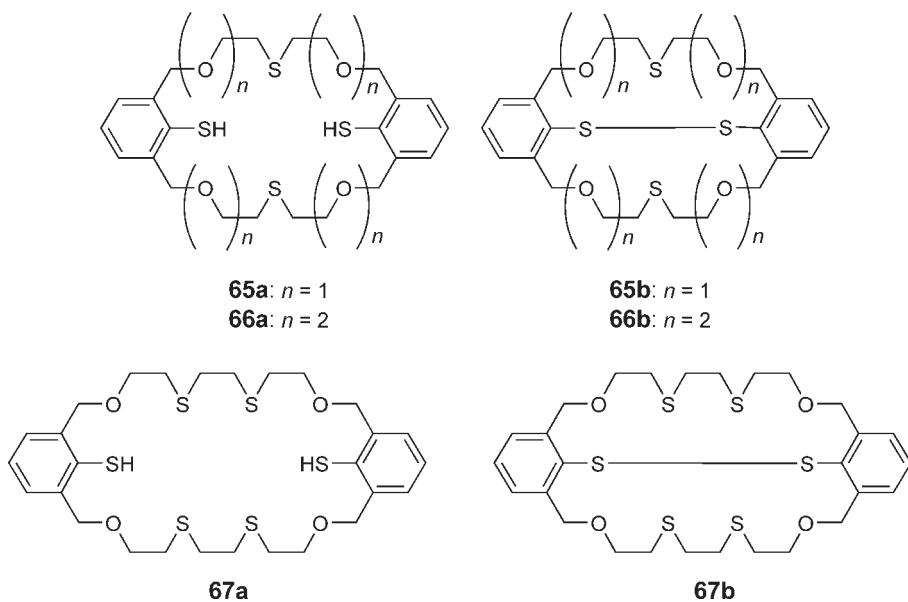
An isomeric series of oxa-thiacrown ethers incorporating the xylyl moiety at the *ortho* **57**, *meta* **58**, and *para* **59** positions have been prepared by Lee *et al.* Extraction and transport behavior of these isomeric oxa-thiacrown ethers toward silver picrate have been examined <2001MI241>. These ligands were also tested as Ag^+ ion-selective electrodes <2001AN1773>. An isomeric series of smaller oxa-thiacrown ethers **60–62** has been employed to examine the influence of the ring rigidity on Ag^+ coordination modes. Compounds **60** and **62** afforded a sandwich complex ($\text{Ag}^+:\text{60} = 1:2$) and infinite one-dimensional complexes, respectively; otherwise, **61** gave the one-dimensional, 2:3 club sandwich, and unique 2:4 bridged dinuclear complexes, in which their topologies vary with the solvent used <2006IC952>.



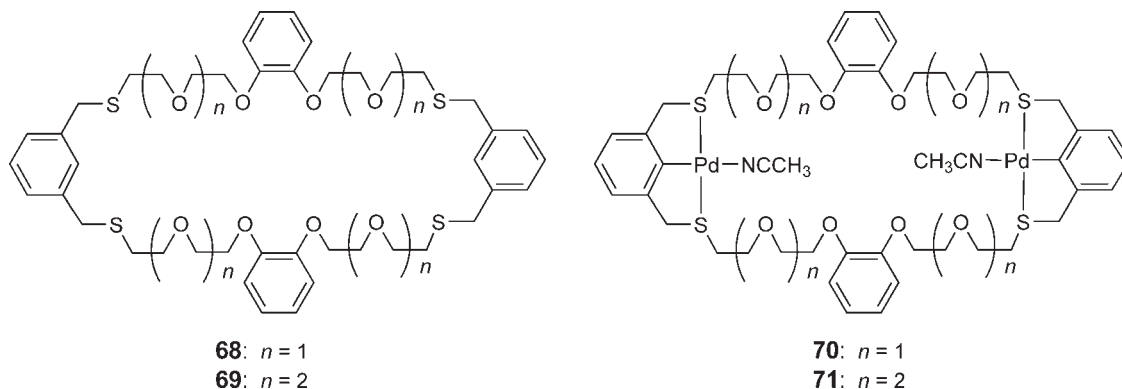
Lee and co-workers have also reported dibenzo oxa-thiacrown ethers <2005JCD2352>. Compounds **63** formed a sandwich structure with AgClO_4 , $[\text{Ag}(\text{63})_2](\text{ClO}_4)_4$, while **64** formed a dimeric structure, $\{[\text{Ag}(\text{64})(\text{CH}_3\text{CN})](\text{ClO}_4)_2\}_2$, and one-dimensional polymeric structure, $\{[\text{Ag}_4(\text{64})_2(\text{CH}_3\text{OH})_2](\text{ClO}_4)_4\}_n$, in CH_3CN and CH_3OH , respectively.



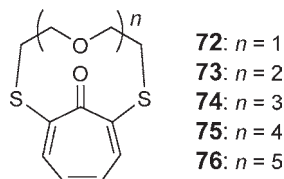
Nabeshima and co-workers have prepared a series of oxa-thiacrown ethers containing thiols **65a–67a** and a disulfide group **65b–67b** inside the ring <2001HAC276>. The metal-transport ability of these ligands was examined by single-ion transport experiments. All the hosts except **65b** exhibited effective and selective Ag^+ transport. In **66** and **67**, the disulfides, **66b** and **67b**, transported Ag^+ ions more effectively than the dithiol derivatives **66a** and **67a**.



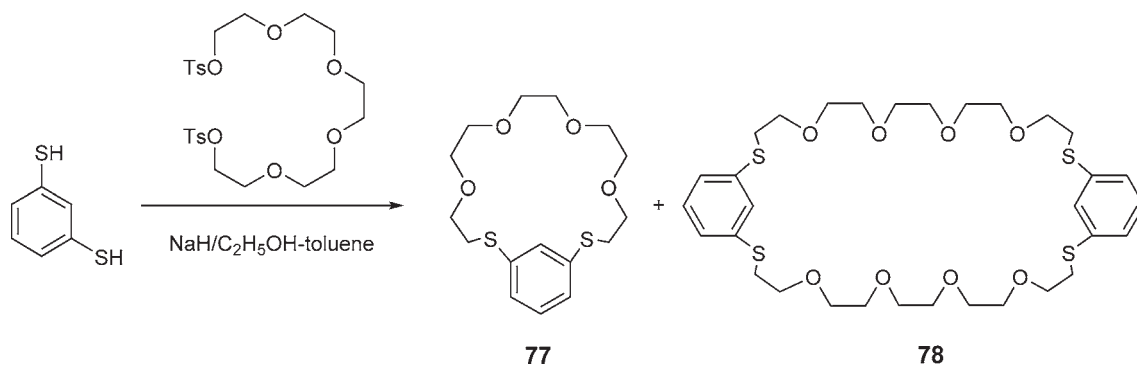
Metalloreceptors **70** and **71** were prepared from corresponding 42- and 54-membered oxa-thiacrown ethers **68** and **69**, respectively <2004EJI3779>, by treatment with $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ in MeCN in 51% and 63% yields, respectively. Metalloreceptor **71** formed a 1:1 complex with 4,4'-bipyridine. The stoichiometry between **71** and 4,4'-bipyridine was confirmed by the ^1H NMR and ultraviolet-visible (UV-Vis) titration experiments and ESI-MS.



X-Ray structures of the HgCl_2 complexes with oxa-thiacrown ethers having a tropone ring, **72–76** have been reported <1998H(47)149, 2000H(53)535> in which **72**, **73**, and **74** formed 1:2, 1:2, and 1:2.5 (host/ HgCl_2) complexes, respectively.



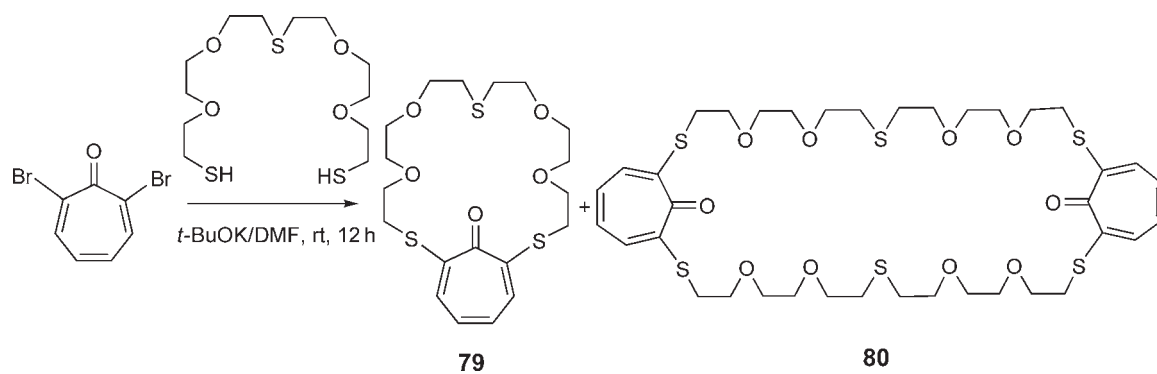
Oxa-thia 19- and 38-membered crown ethers **77** and **78** were prepared by the reaction of 1,3-benzenedithiol with pentaethylene glycol ditosylate in the presence of NaH in 58% and 7% yields, respectively (Scheme 10) <1997H(46)509>.



Scheme 10

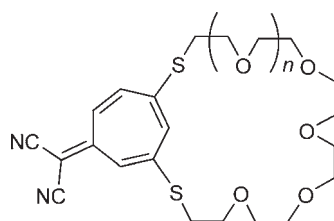
Using crown ethers **75** and **77**, UV-Vis measurements, association constants, and transport experiments toward Li^+ , Na^+ , K^+ , NH_4^+ , Mg^{2+} , Ca^{2+} , Ba^{2+} , Zn^{2+} , Cd^{2+} , and Hg^{2+} were conducted <1997H(46)509>. Their results suggested that troponoid thiacycrown ether **75** is a more effective carrier of Hg^{2+} than the benzenoid-thiacrown ether **77** with the similar cavity size, and an increasing order of the association constants of **75** is $\text{Na}^+ < \text{K}^+ < \text{NH}_4^+ < \text{Li}^+ < \text{Mg}^{2+} < \text{Zn}^{2+} < \text{Cd}^{2+} < \text{Hg}^{2+} < \text{Ba}^{2+} < \text{Ca}^{2+}$ in MeCN.

Base-mediated condensation reaction of 2,7-dibromotropone with dithiol afforded the 22-membered **79** and 44-membered products **80** in 62% and 24%, respectively (Scheme 11) <2004H(62)149>. Compound **79** was used as a carrier through a chloroform liquid membrane; however, the guest selectivity of **79** was lower than that of the corresponding pentaoxadithiacrown ether **76**.



Scheme 11

Oxa-thiacrown ethers containing 8,8-dicyanoheptafulvene units [<1995CL629, 1995H\(49\)385, 2000AXC644>](#) were prepared by Takeshita and co-workers. Compounds **81**, **82**, **83a**, and **83b** have been prepared and their HgCl_2 complexes have been investigated.

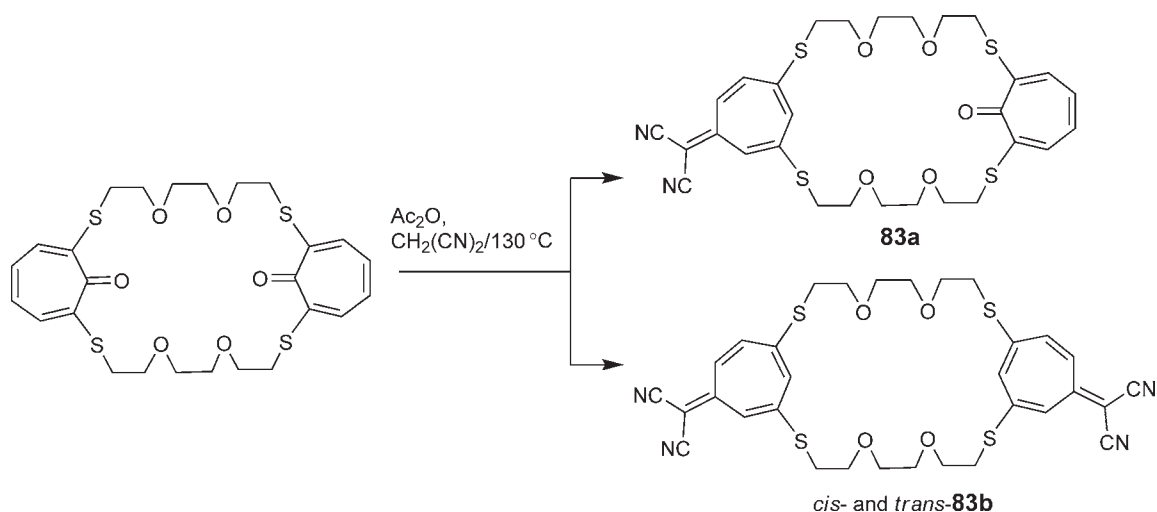


81: $n = 0$

82: $n = 1$

In the X-ray structure of **82**– HgCl_2 complex, Hg^{2+} ion was surrounded by only the five donor oxygens in a pentagonal bipyramidal coordination and the two sulfurs in the crown ring were not coordinated; on the other hand, Hg^{2+} ion was bound by four oxygen and one sulfur atoms in **81**– HgCl_2 complex.

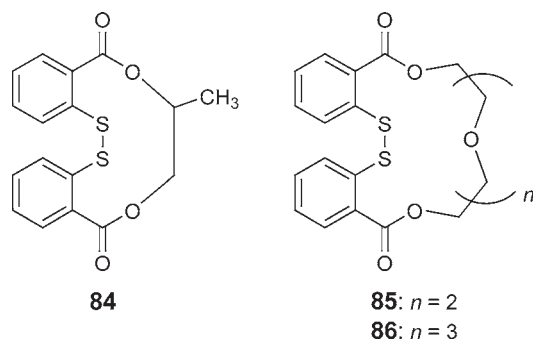
Compounds **83a** and **83b** were prepared by heating an Ac_2O solution of tetraoxadithiatropone-crown ether via a remote substitution reaction in 42% and 11% yields, respectively ([Scheme 12](#)).



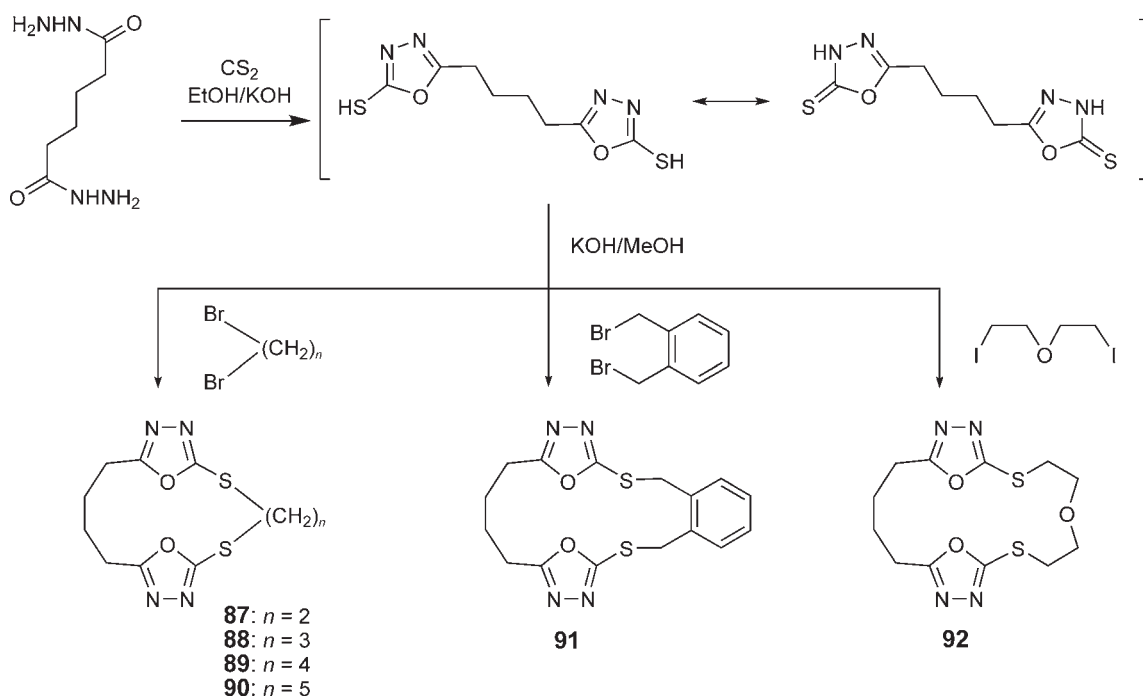
Scheme 12

Compound **83a** having a 8,8-dicyanoheptafulvene and a tropone unit formed a 1:2 (host/guest) complex with HgCl_2 <1995H(41)1901>. The X-ray structural analysis revealed that the two aromatic rings were almost planar and the eight heteroatoms of the ethereal ring, each set of the consecutive two oxygen atoms and one sulfur atoms on the tropone ring coordinated to one Hg^{2+} ion, but the two sulfur atoms on the heptafulvene part were coordination free. The interatomic distance of the two Hg^{2+} was 4.248 Å.

The macrocyclic thiaether-esters **84**, **85**, and **86** were prepared by the reaction of 2,2'-dithiobenzoic acid dichloride with corresponding diols in 31%, 80%, and 85% yields, respectively <2005PS1953>. The complexation abilities of these thiaether-esters toward Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Sr^{2+} , Ba^{2+} , Co^{2+} , and Ni^{2+} were measured by the solvent extraction experiments. The results showed that **84** exhibits stronger selectivity toward Li^+ , **85** toward Ba^{2+} , and **86** toward K^+ .



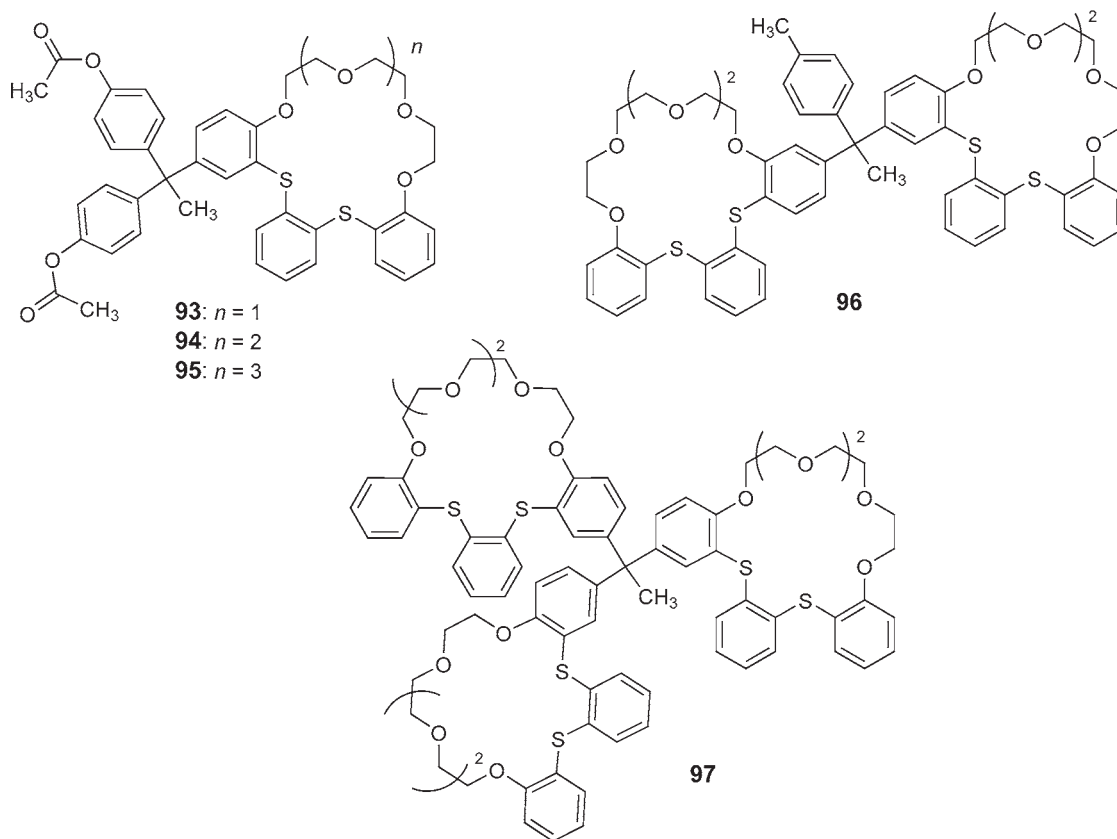
Oxa-thiacrown ethers containing oxadiazole units **87–92** were prepared from 1,4-bis(5-mercapto-1,3,4-oxadiazol-2-yl)butane and various 1,ω-dihaloalkanes in the presence of KOH (Scheme 13) <2003HAC273>. When organic bases, such as triethylamine or pyridine, were employed, the cyclic products were not obtained; therefore, K^+ ions would help in the cyclization.



Scheme 13

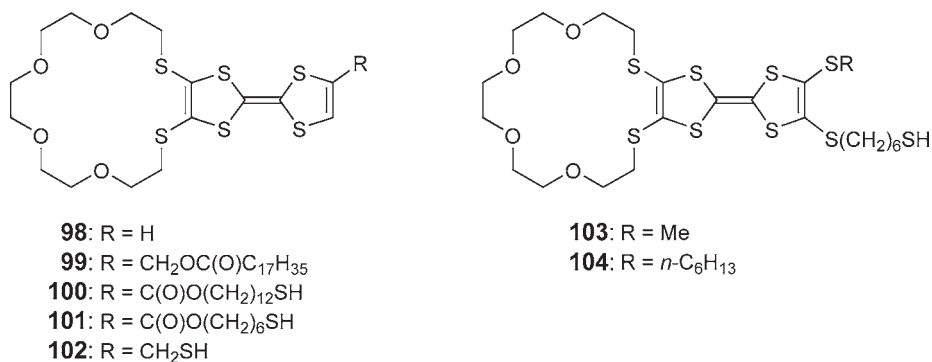
Mono-, bis-, and tris-dithiapentaoxacrown ethers were prepared in order to study the complexation of bis- and tris-crown ethers in which the cyclic structures are bonded to the same carbon atoms <1999SMC263>. The extraction of

Ag^+ by the 21-membered mono- **94**, bis- **96**, and tris-crown ethers **97** increased linearly with the number of the crown rings in the molecule, meaning that the complexation of Ag^+ by one cavity does not interfere with the complexation of the remaining cavities in the molecule. Extractability of Ag^+ by the 18-membered **93** is essentially the same as that by **94** having a 21-membered ring, whereas a 24-membered **95** showed a low extractability of Ag^+ , presumably due to the large cavity size to comfortably accommodate the Ag^+ ion. The authors also reported the ^1H NMR studies for Ag^+ , single transport of Ba^{2+} , Ag^+ , and Pb^{2+} , and competitive transport of Ba^{2+} , Ag^+ , and Pb^{2+} , and Cu^{2+} ions.



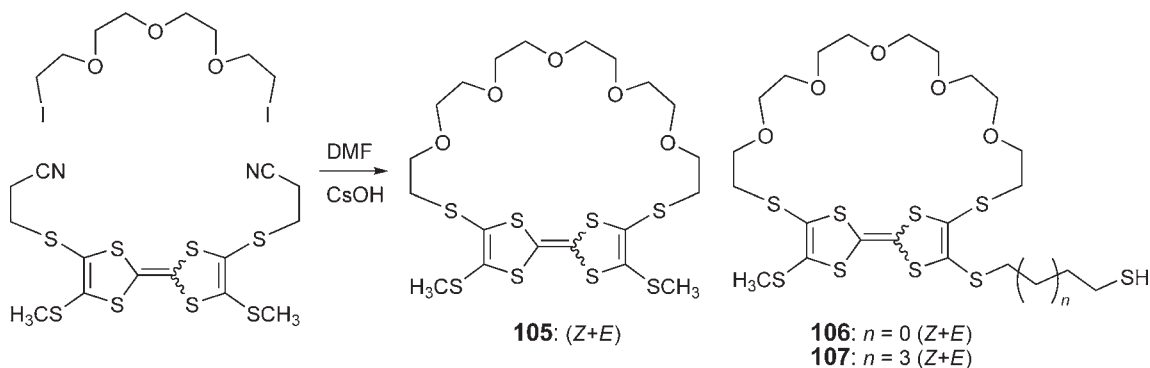
14.15.2.5 Oxa-thiacrown Ethers Containing Tetrathiafulvalene Units

Two types of oxa-thiacrown ethers containing tetrathiafulvalene (TTF) units have been reported by the Bryce and Salle groups. One is represented by the dithiatetraoxa-18-crown-6-ether derivatives substituted at the 2,3-positions of the TTF unit **98–104**, and the other is derived from the tetrathiapentaoxa-24-membered crown ether derivatives annelated in the 2,7- (or 2,6-) positions of the TTF unit **105–107**.



Bryce and co-workers reported that the crown-annulated TTF derivatives **98** and **99** were used for UV-Vis spectroscopic and electrochemical studies of metal complexation <1996J(P2)1587>. Solution electrochemical studies showed that metal complexation to the crown unit leads to a small anodic shift in the first oxidation potential of the TTF system. Langmuir-Blodgett films of amphiphilic **99** have been assembled on solid substrates by Y-type deposition. Compounds **100–104** were used to prepare self-assembled monolayers on gold and platinum surfaces <1998AM395, 2000JOC8269>. The self-assembled monolayers of **104** were the most stable in this series of TTF-crowns. Electrochemical data for the self-assembled monolayers of **100–104** in MeCN showed two reversible one-electron waves, typical of the TTF system. The self-assembled monolayers of **102–104** exhibited an electrochemical response in aqueous electrolytes, which was observed between 50 and 100 cycles.

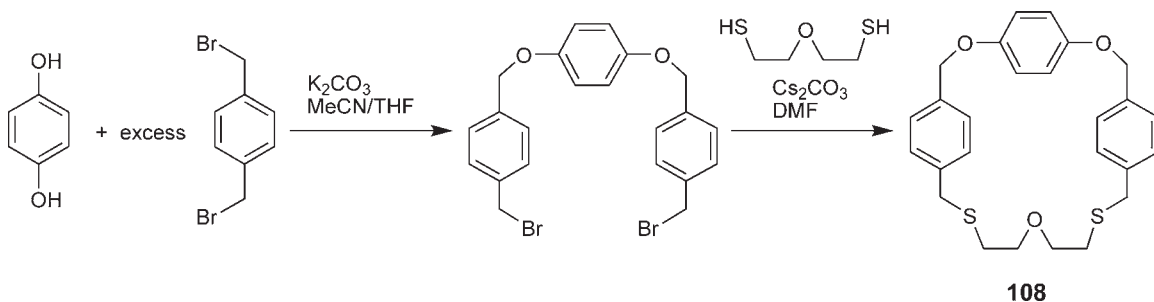
Salle and co-workers have prepared tetrathiapentaoxa-24-membered crown ether derivatives annulated in the 2,7- (or 2,6-) positions of the TTF unit. Compound **105** was prepared under high-dilution conditions in dimethylformamide (DMF) in the presence of CsOH, and was obtained as *Z/E* isomeric mixture in relative amounts of 90:10 (Scheme 14) <1999IC6096>. Complexation studies for **105** were carried out by liquid secondary ionization mass spectrometry (LSI-MS), ^1H NMR, and voltammetry titrations on addition of Ba^{2+} . These data suggested that **105** forms 1:1 complex with Ba^{2+} . The log *K* values for the interaction between **105** and Ba^{2+} were 3.5 (LSI MS), 4.17 (NMR), and 4.28 (voltammetry). In the X-ray structure, the bending angle of the TTF skeleton changed from 5.1° in the free ligand to 29.6° in the (*Z*-**105**)- Ba^{2+} complex. Compounds **106** and **107** were also prepared <2002NJC1320>, and formed highly stable self-assembled monolayers on gold bead electrodes over a large potential window at high scan rates, and upon repeated cycling. Recognition of Ba^{2+} was detected by the cyclic voltammetry for the self-assembled monolayer of **106**.



Scheme 14

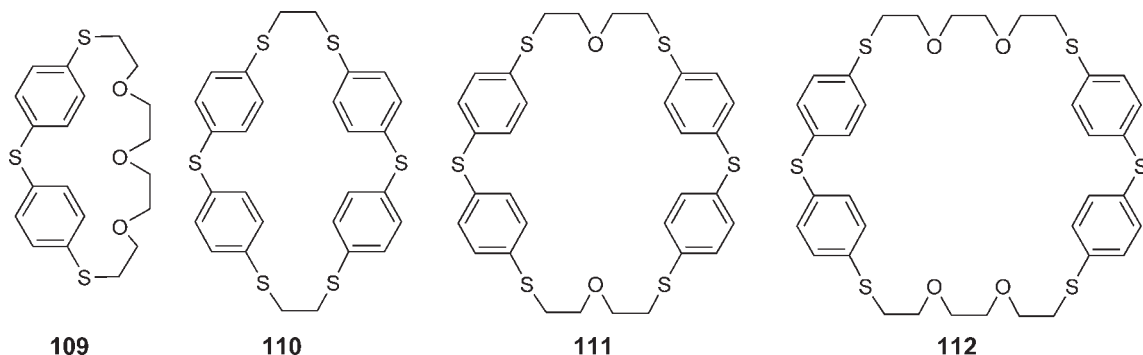
14.15.2.6 Cyclophane-Type Oxa-thiacrown Ethers

Introduction of cyclophane unit, as an integral part of the crown ether, instilled unique properties. Stoddart and co-workers prepared the oxa-thiacrown ether incorporating a rigid 'horseshoe-shaped' aromatic moiety **108** in two steps from hydroquinone and an excess of 1,4-bis(bromomethyl)benzene <1997JCD1496>. Yields of the first intermediate and **108** were 40% and 61%, respectively. The CuI complex with **108** was a 2:1 ($\text{Cu}^+/\text{108}$) complex, as a one-dimensional infinite array of cubane-like units consisting of four Cu, four iodine, and four sulfur atoms from four different macrocycles (Scheme 15).

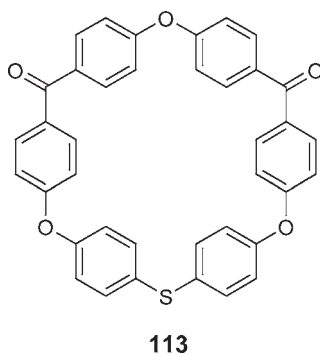


Scheme 15

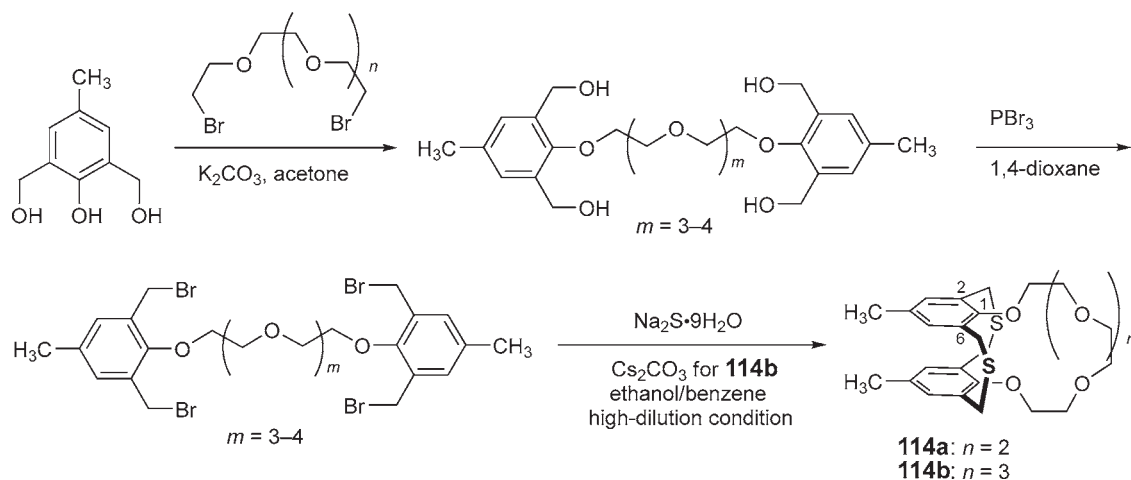
Dehaen and co-workers have prepared a series of oxa-thiacrown ethers containing *p*-phenylene units **109–112** using 4,4'-thiobisbenzenethiol as a starting material <1996BSB151, 1999MI1109>. These ligands were applied to Pb^{2+} -selective solvent polymeric membrane electrodes.



Zolotukhin *et al.* have prepared the macrocyclic poly(arylene thioether ketone) **113** to study ring-opening polymerization <2004MM2041>. Compound **113** was prepared by the reaction of 4,4'-bis(4''-fluorobenzoyl)diphenyl ether with 4,4'-thiodiphenol in *N,N*-dimethylacetamide under a high dilution condition in a poor 9% yield. Structure of **113** was confirmed by X-ray analysis.

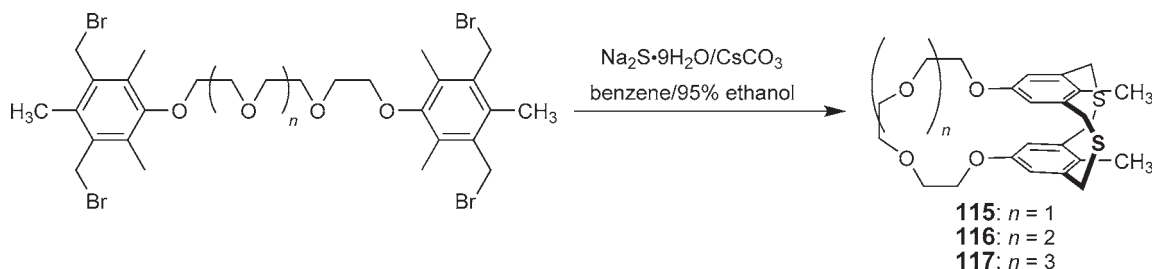


A series of dithia[n.3.3](1,2,6)crownophanes consisting of a dithia[3.3]metacyclophane moiety were prepared by Xu and Lai <2002OL3211, 2002TL9199>. These compounds were prepared in three steps, as shown in Scheme 16. Yields of the cyclization steps for **114a** and **114b** were 60% and 51%, respectively. The X-ray structures showed that **114a**– NaClO_4 and **114b**– KClO_4 were 1:1 coordination polymers, and **114b**– NaClO_4 was a dimeric 2:2 complex. The log *K* values of the interaction between alkali metal ions with **104** are: Li^+ (3.57), Na^+ (4.26), K^+ (5.77), Rb^+ (5.21), and Cs^+ (4.55).



Scheme 16

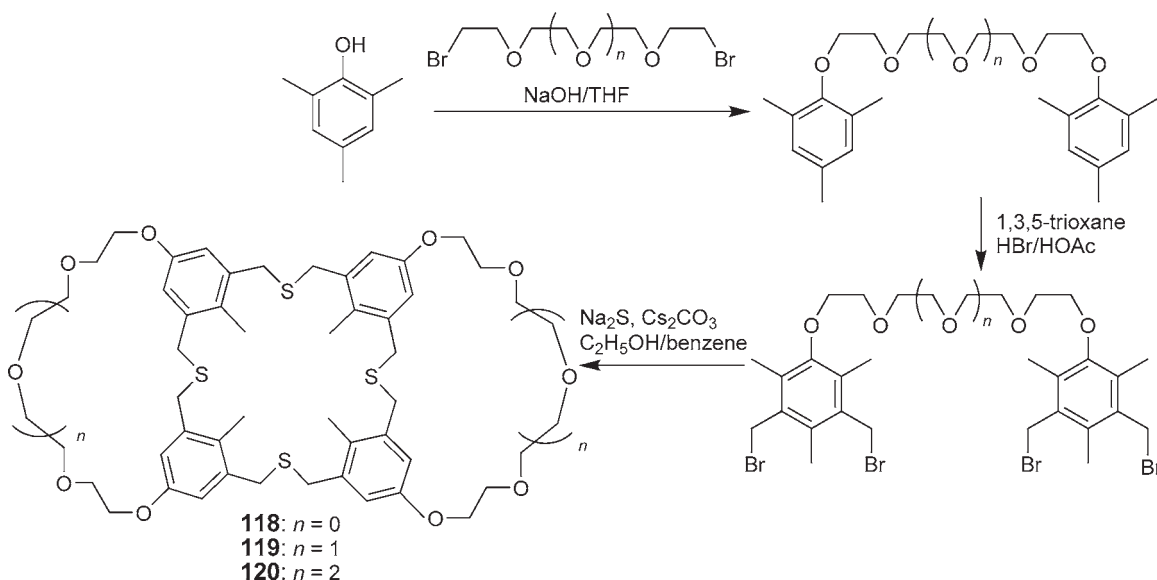
Lai and co-workers have also prepared a series of dithia[n.3.3](1,3,5)crownophanes <2003OL2781, 2005TL2431>. In order to prepare **115–117**, they attempted a synthetic route via a dithia[3.3]metacyclophane derivative <2005TL2431>; however, the procedure was unsuccessful because of the significant steric hindrance of the *ortho*-methyl and opposite aryl groups. An alternative synthesis of **115–117** is showed in Scheme 17. In this method, **115**, **116**, and **117** were obtained in 15%, 20%, and 31% yields, respectively.



Scheme 17

The log K values of the interaction between alkali metal ions with **116**, which resembles 15-crown-5 in the crown unit, are: Na^+ (3.68), K^+ (4.62), Rb^+ (3.61), and Cs^+ (2.27). Whereas the log K values for **117**, which resemble 18-crown-6 in the crown unit, are: Na^+ (3.85), K^+ (5.00), Rb^+ (5.15), and Cs^+ (5.29). Their complexation behavior exhibited an unusual ion selectivity preference due to the presence of a 'breathing' process of the dithia[3.3]metacyclophane moiety, which indirectly controls the ion selectivity through the adjustment of the cavity size of the crown unit.

Crown-tetrathia[3.3.3.3]metacyclophanes **118–120**, which have two crown moieties and one metacyclophane unit, have been prepared via intermolecular coupling reactions <2005T9248> as shown in Scheme 18. The X-ray crystal analysis of **119** showed that the compound adopted a perpendicular conformation in which two aromatic rings were inclined to be perpendicular to the opposite aromatic rings. The variable-temperature ^1H NMR spectra for **119** and **118** suggested that the energy barrier for interconversion of **119** was estimated to be $12.1 \text{ kcal mol}^{-1}$, whereas **118** showed two non-interconvertible conformers at room temperature, which tended to interconvert at elevated temperature; however, many conformers coexisted at low temperature.

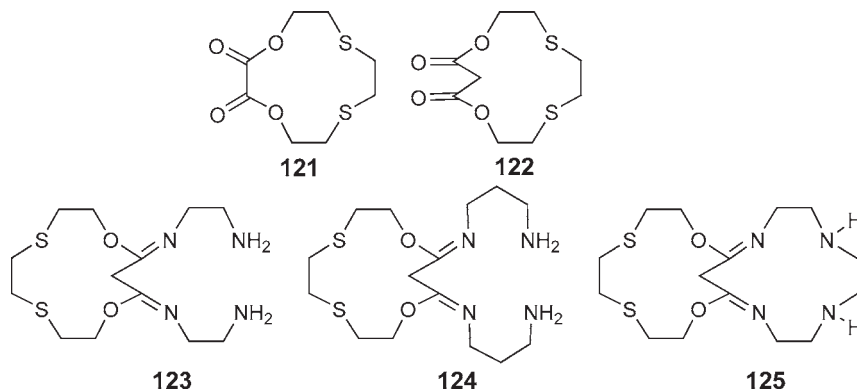


Scheme 18

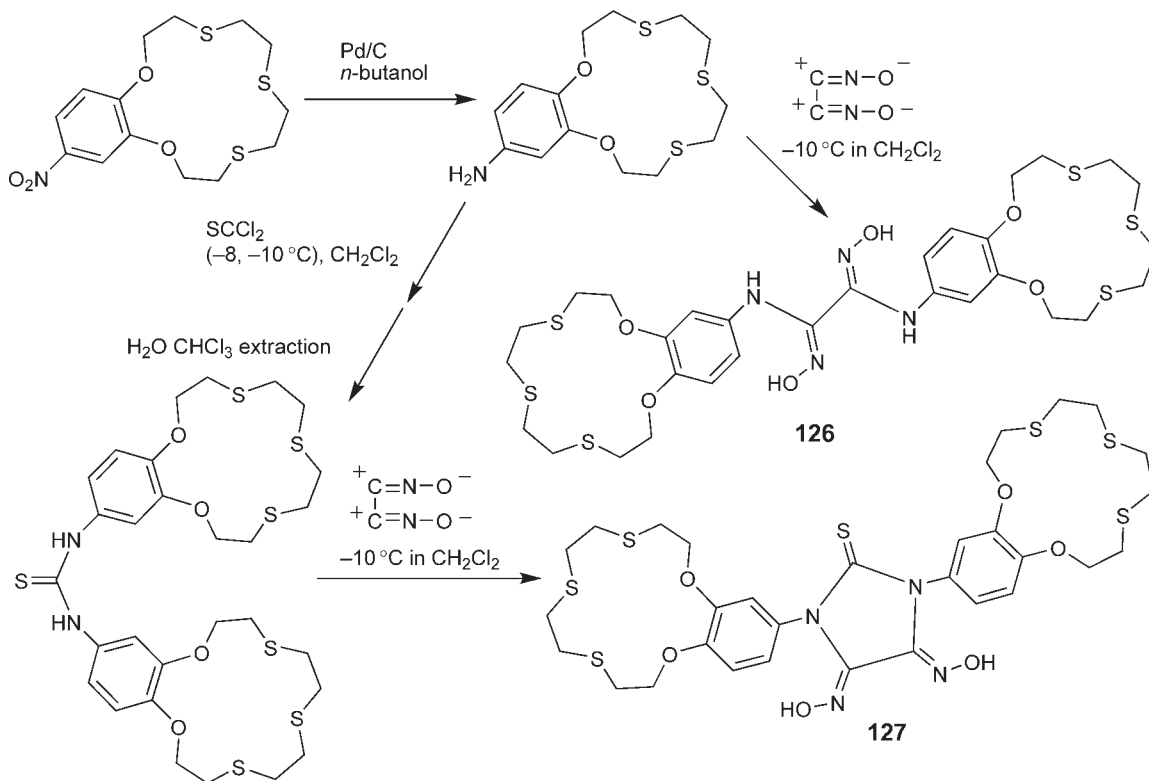
14.15.2.7 Oxa-thiacrown Ethers Containing Additional Binding Sites

In this section, several crown ethers containing additional binding sites, except calixarene and porphyrin units, are summarized.

Oxa-thiacrown ethers having additional binding sites, based on dioxadithia-12-crown-4, have been prepared by Karaboccek *et al.* Compounds **121** and **122** were prepared by the reaction of 1,8-dihydroxy-3,6-dithiaoctane with corresponding acid chlorides in 60% and 70% yields, respectively. These compounds formed 1:2:1 (host:Cu(ClO₄)₂:bpy or phen) and 1:1:1:2 (host:Cu(ClO₄)₂:Ni(ClO₄)₂:bpy or phen) complexes using the crown ring and diketone moieties <2003TML529>. Using **122** as the starting material, **123**, **124**, and **125** were also prepared in 50%, 55%, and 70%, respectively <2003JHC639>. From the semi-empirical AM1 calculations for these compounds, it was shown that **123–125** possess intramolecular hydrogen bonding in amine moieties.



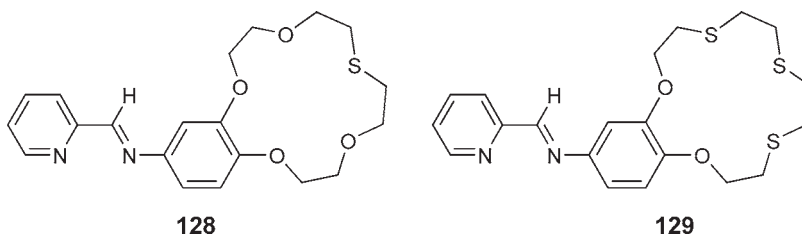
Gok and co-workers reported bis-oxathiacrown ethers containing diaminoglyoxime **126** and (*E,E*)-dioxime moieties **127** <1996POL3933, 2004JCR265>. Compound **126** was prepared in two steps from 4-nitrobenzo-dioxa-trithia-15-crown-5. After reduction of the nitrobenzocrown ether, the aminobenzocrown ether was reacted with cyanogen di-*N*-oxide to give diaminoglyoxime crown ether **126** in 76%. The aminobenzocrown ether was reacted with thiocarbonyl dichloride to afford thiourea crown ether, and then the thiourea derivative was converted to **127** by cyanogen di-*N*-oxide in 39% yield (Scheme 19).



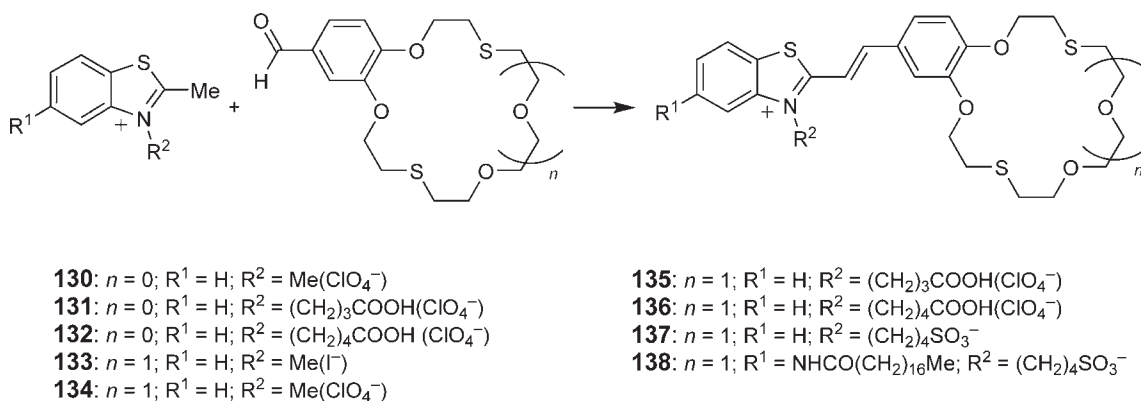
Scheme 19

When these compounds form complexes with Ni^{2+} or Co^{2+} , the diaminoglyoxime or dioxime moieties interacted with the metal ions to give 2:1 (host: M^{2+}) complexes.

Oxa-thiacrown ethers having diimine units **128** and **129** were prepared by the reaction of corresponding 4-aminobenzocrown ethers with 2-pyridinecarbaldehyde to give 85% and 92% yields, respectively. These oxa-thiacrown ethers were used to investigate their ability to act as spectrochemical and luminescence ion probes for soft metal ions <1995JCD3615>.



Fedorova *et al.* reported the synthesis and complexing properties of styryl dye containing benzodithia crown ethers and *N*-(4-sulfobutyl)benzothiazolium fragments **130–138** <1996J(P2)1441, 1997RCB2099, 1997SAA1853, 1999JA4992, 2002NJC543>. The general synthetic method is illustrated in **Scheme 20**. 4-Formylbenzocrown ethers were reacted with 3-substituted-2-methylbenzothiazolium salts to give the styryl dye crowns, which have significant selectivity toward heavy metal ions such as Hg^{2+} and Ag^{2+} and the selectivity changed with structural changes from the *trans*- and *cis*-forms. For example, **137** was shown to be 11 times more selective for Hg^{2+} upon *trans* $\rightarrow$ *cis* photoisomerization.

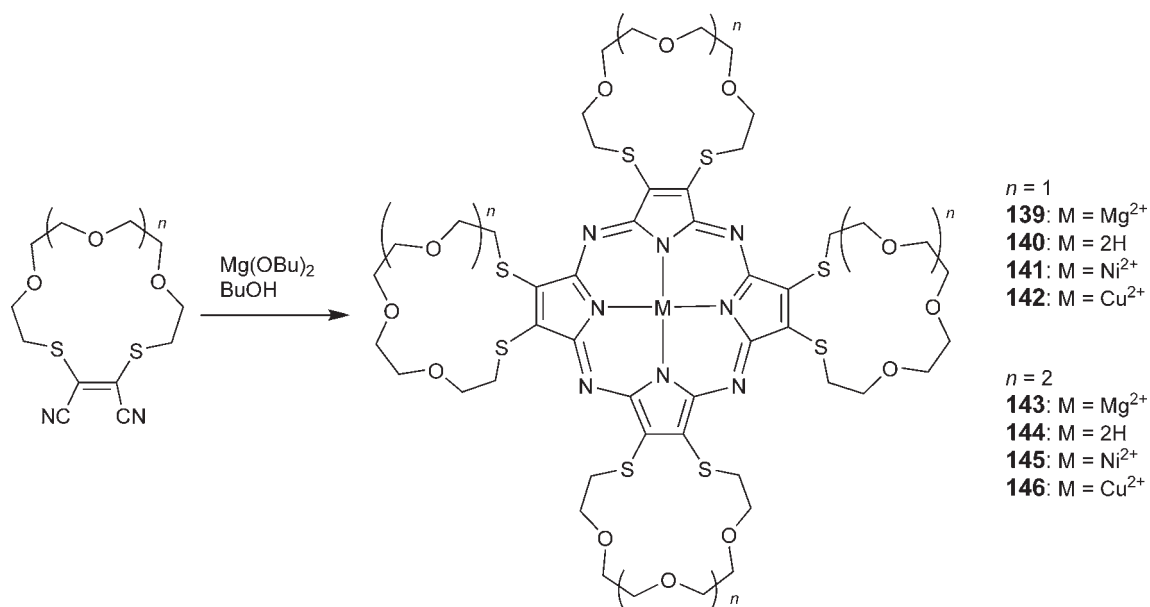


Scheme 20

14.15.2.8 Oxa-thiacrown Ethers Containing Porphyrin Units

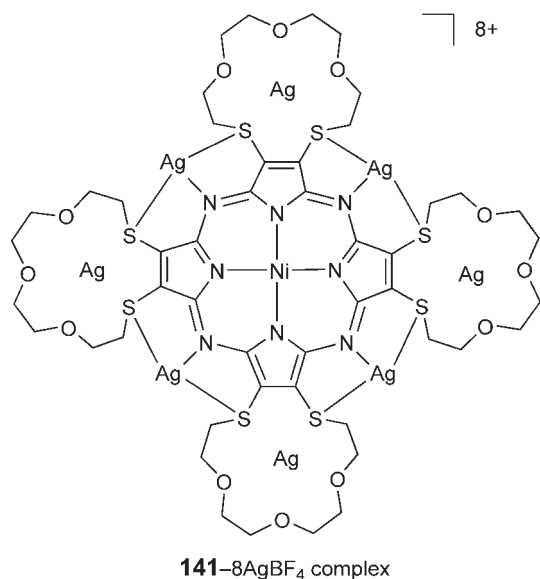
Oxa-thiacrown ethers containing phthalocyanine and porphyrin units were summarized in 826 pages in CHEC-II(1996) (9, 9.29.2.3.3); however, oxa-thiacrown ethers containing porphyrin units have not been reported in the previous review.

Hoffman *et al.* have reported the synthesis of tetrakis-, tris-, and monothiacrown ethers containing a tetra-azaporphyrin unit **139–152**. The first porphyradine crown ethers were prepared by the Mg^{2+} template cyclization of the appropriate crowned derivative of dithiomaleonitrile **32** and **33** to afford **139** and **143**, respectively, in ca. 35% yields. Treatment of **139** and **143** with trifluoroacetic acid provided the metal-free porphyrazines **140** and **144**, respectively. Subsequent reaction with $\text{Ni}(\text{OAc})_2$ or $\text{Cu}(\text{OAc})_2$ quantitatively produced **141**, **142**, **145**, and **146** (**Scheme 21**).



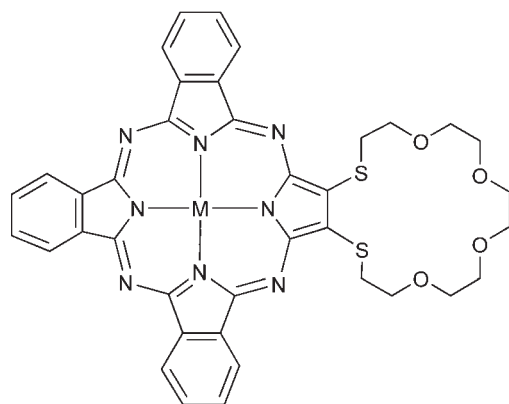
Scheme 21

Complex **141** formed a octanuclear Ag^+ complex [<1995AGE2020>](#), where the X-ray structure showed that the four Ag^+ ions are coordinated in an endocyclic fashion by the crown moieties and four Ag^+ ions occupy the *meso*-pockets.



They have also prepared mono- **147–149** and tris-crown ethers **150–152** containing the tetraazaporphyrin unit. Singly crowned porphyrazine **147** was prepared by the reaction of >15 equiv of 1,2-dicyanobenzene and 1 equiv of **33** under classic Linstead macrocyclization conditions. On the other hand, tris-crowned porphyrazine **150** was prepared by the reaction of 3 equiv of **32** and 1 equiv of 1,2-dicyano-1,2-bis(11-hydroxyundecylthio)ethylene. Rapid complexation of Ag^+ was observed for **147–149**, with weaker complexation of Hg^{2+} and Na^+ observed only by MS. There was

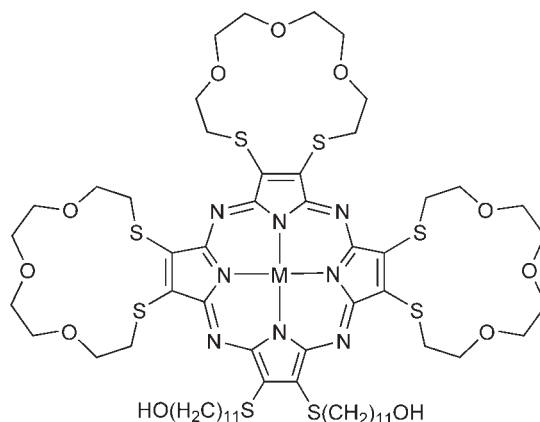
no evidence for complexation of Pb^{2+} <2000T7371>. Compounds **151** and **152** showed ion specific UV-Vis spectral changes in the presence of Ag^+ and Hg^{2+} . Binding of Ag^+ to **151** was described by a 1:1 binding isotherm, whereas binding of Hg^{2+} to **151** appeared more complex. For **152**, binding of Ag^+ and Hg^{2+} also can be fit to a 1:1 isotherm <2003IC814>.



147: M = Mg

148: M = 2H

149: M = Ni



150: M = Mg

151: M = H_2

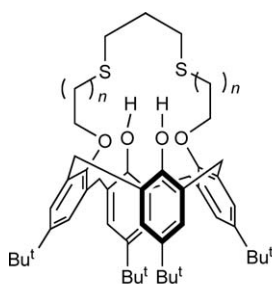
152: M = $\text{Co}^{3+}(\text{Py})_2$

14.15.3 Crown-Related Macrocycles with Calixarene Units

Calixarenes are a cyclic arene, which form complexes with ions and neutral guests; they have been reviewed by Shinkai <1997CRV1713> and Gutsche <B-1998MI1>. In this chapter, oxa-thiacrown ethers containing calixarene and thiacalixarene units are reviewed.

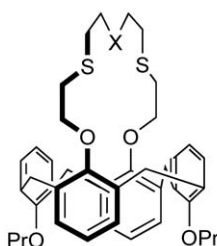
14.15.3.1 Oxa-thiacrown Ethers Containing One Crown Unit and One Calixarene Unit

The first oxa-thiacrown ethers containing calix[4]arene unit **153** and **154** were reported by Huang and co-workers <2001MI125>. These dioxadithia-crown ethers showed an extraction selectivity for Ag^+ ions. Sim *et al.* prepared the trioxadithia- and dioxatrithiacrown ethers, possessing a calix[4]arene unit (**155** and **156**) <2002BKC879>. These oxa-thiacrown ethers also showed selectivity toward Ag^+ ions. Asfari and co-workers reported the preparation of dioxatetrathiacrown ethers **157** and **158** <2005SMC221> and the complexation properties of these oxa-thiacrown ethers toward Cd^{2+} , Hg^{2+} , and Pb^{2+} .



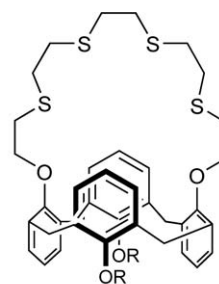
153: $n = 1$

154: $n = 2$



155: X = O

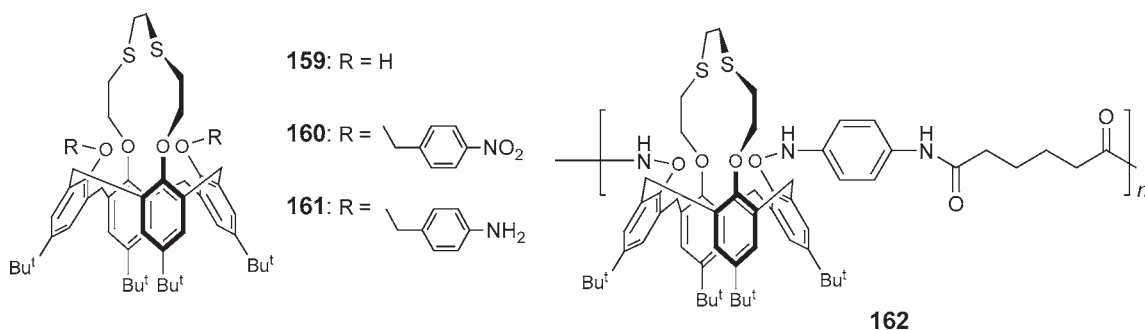
156: X = S



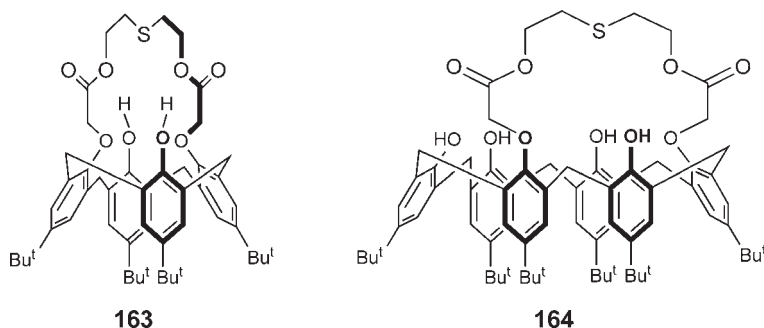
157: R = H

158: R = $\text{O}(\text{CH}_2)_4\text{OAc}$

Oligomeric oxa-thiacrown ether having calix[4]arene **162** have been prepared in three steps from **159** by Yilmaz and co-workers <2003PSA186>. In liquid-liquid extraction experiments, **159**, **160**, and **161** showed a good extraction ability toward Cu^{2+} , Hg^{2+} , and Pb^{2+} ions, whereas the oligomeric **162** lost the selectivity, because of the structural and collective/cooperative behavior of the crown moieties where the amide bridges may also play an important role at the water-dichloromethane interface.

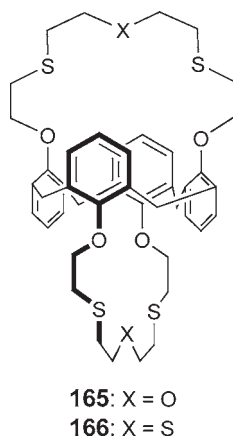


Oxa-thiacrown ether-esters having calix[4]arene **163** and calix[6]arene **164** were prepared by Yang *et al.* <2005MI42>. In both compounds, only the 1,3-bridged calix[4]- and calix[6]arenes were isolated.

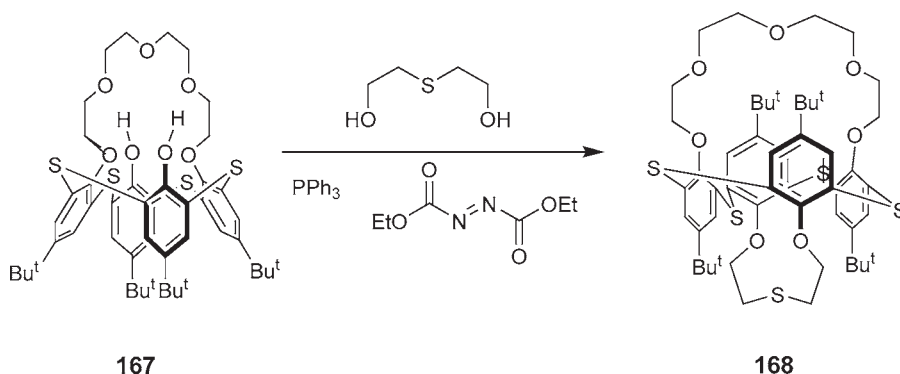


14.15.3.2 Oxa-thiacrown Ethers Containing Two Crown Units and One Calixarene Unit

Two dioxo-trithia- and two trioxa-dithiacrown ethers connected to one calix[4]arene unit have been prepared by Sim *et al.* <2002BKC879>. Macrocycles **165** and **166** have an Ag^+ selectivity in metal picrate extraction, but the percentage extractability was lower than those of corresponding monocrown derivatives **155** and **156** due not only to electrostatic repulsion between the two metal ions, but also to an induced conformation change that does not favor binding of the second metal. The extractability is consistent with the result of silver ion-induced chemical shift change upon the complexation.



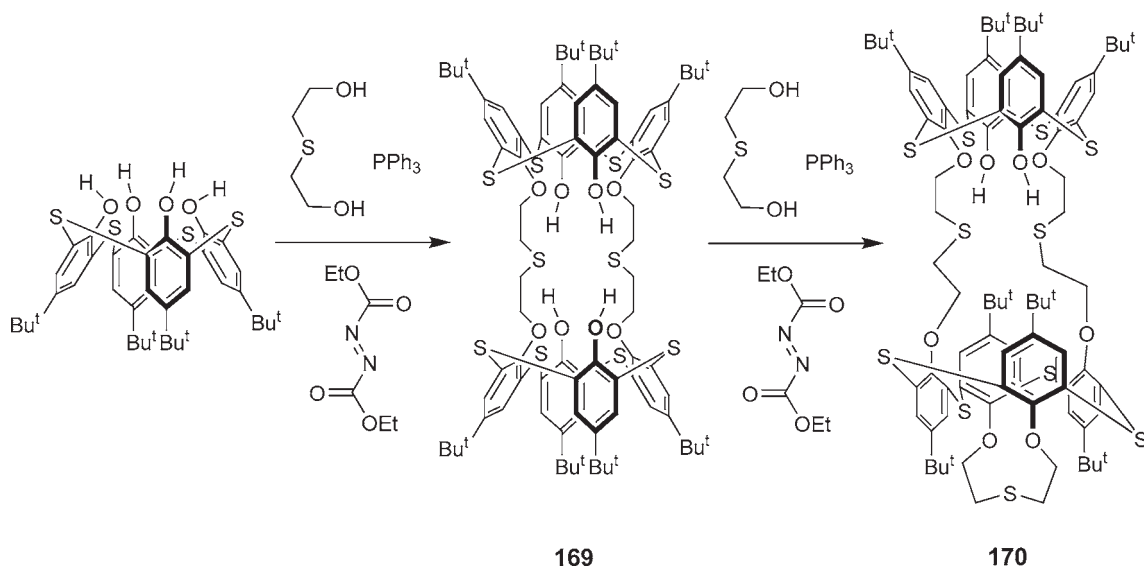
Bitter and co-workers reported that a crown containing two types of bridging units connected to one thiacalix[4]arene **168** <2004TL12059> from crown ether having thiacalix[4]arene **167** by the Mitsunobu reaction (Scheme 22).



Scheme 22

14.15.3.3 Oxa-thiacrown Ethers Containing Two Calixarene Units

Bitter and co-workers have also prepared a 'thiacalixtube', such as **170**, by the Mitsunobu reaction <2004TL12059>. Interestingly, a dimer **169** was prepared from thiacalix[4]arene with thiodiethylene glycol under Mitsunobu condition in 90% yield (Scheme 23).

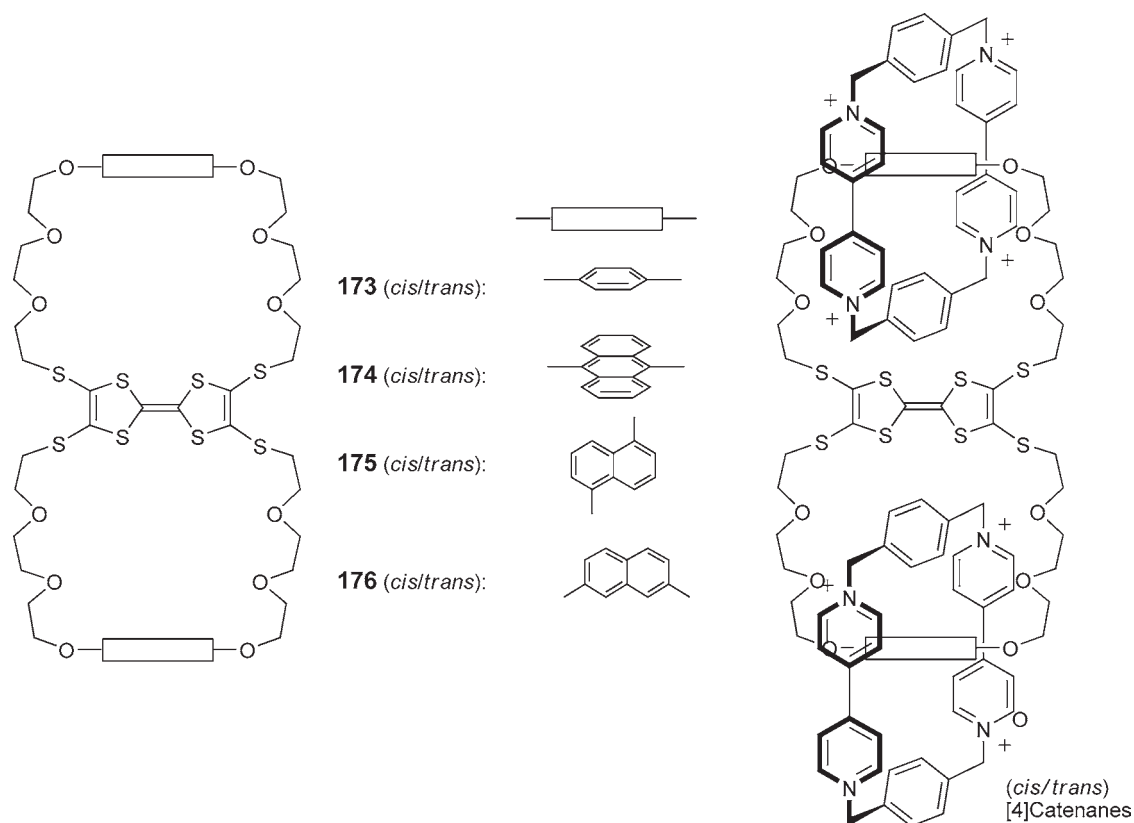


Scheme 23

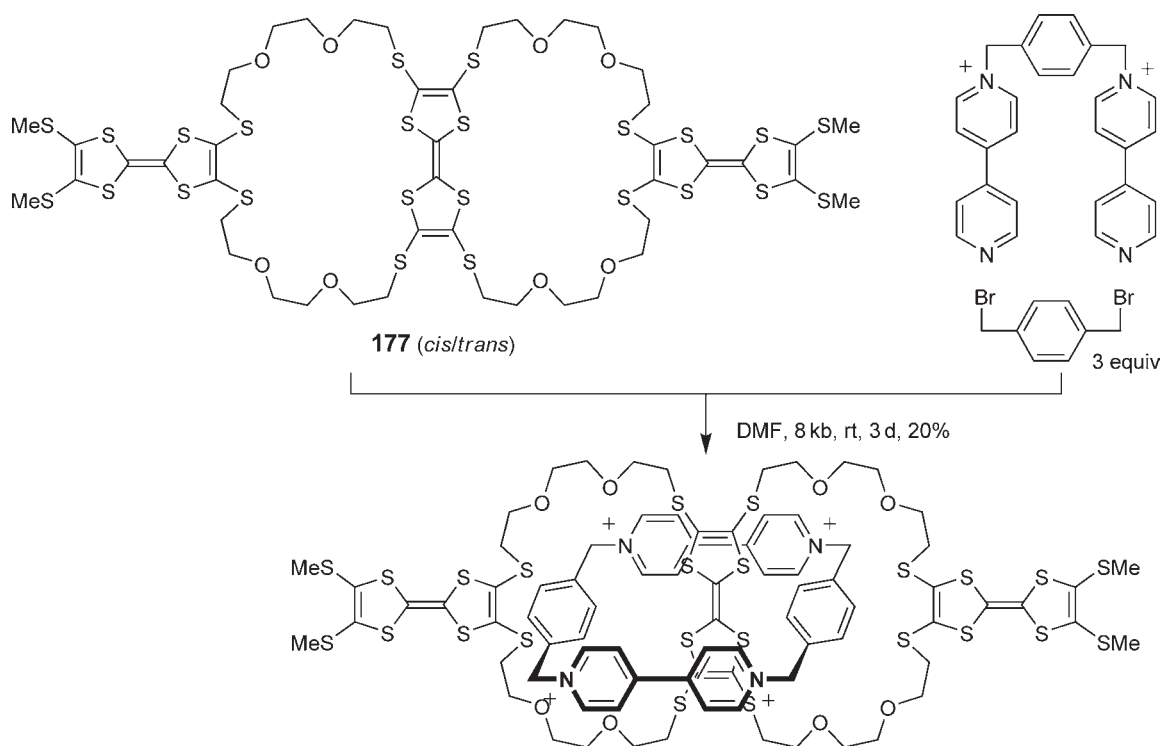
Becher and co-workers have reported [2]catenanes, [3]pseudocatenanes, and [4]pseudocatenanes using tetrathiafulvalene-based thiacyclopentadiene derivatives. Macrocycles **171** and **172** formed the corresponding [2]catenanes in 12% and 14% yields, respectively (**Scheme 24**).



Compounds **173–176** possessing two crown moieties formed [3]pseudocatenanes and [4]catenanes depending on the aromatic moieties in the crown rings. When *cis/trans*-**175** was employed, [4]catenane was obtained.

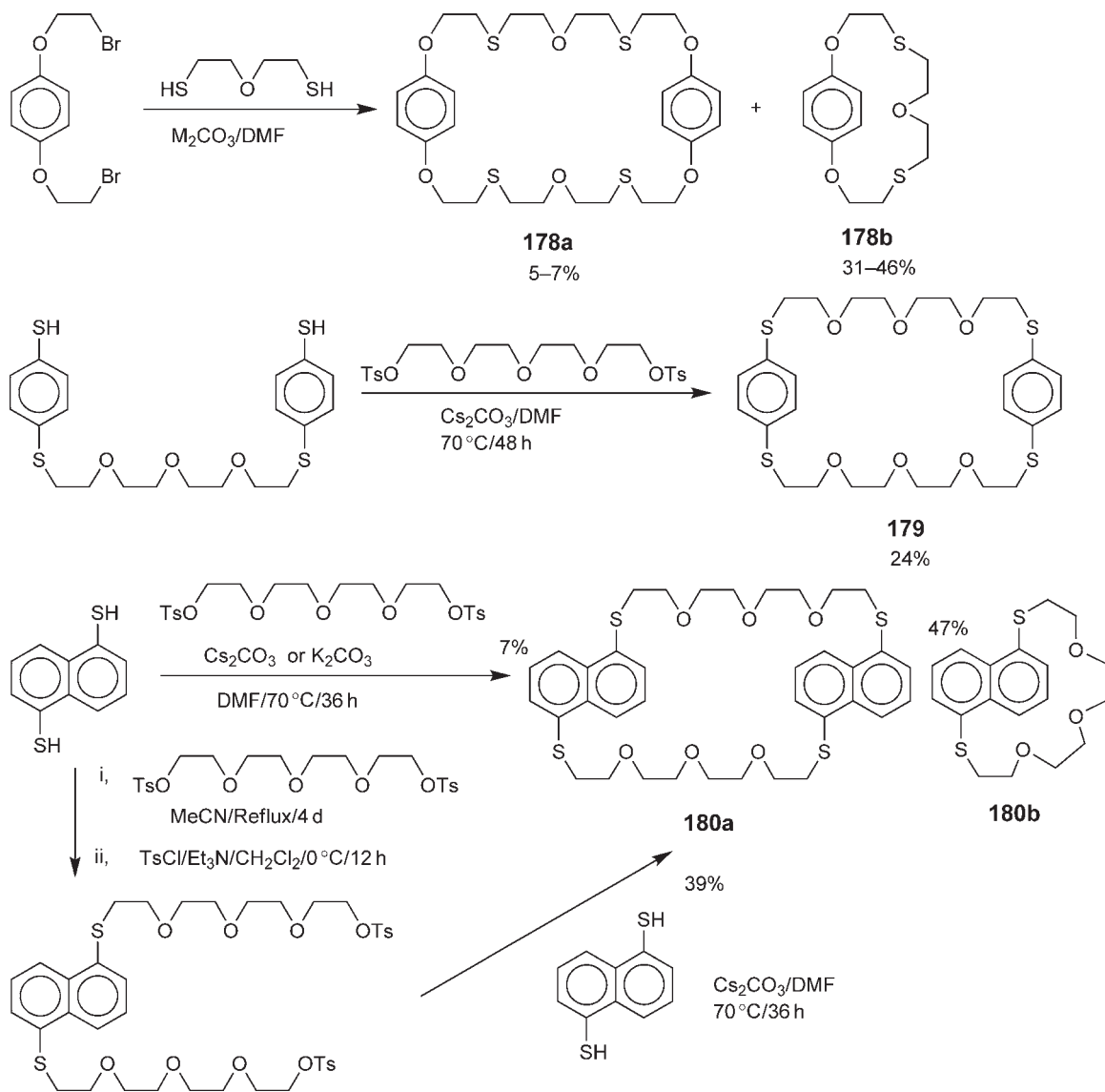


They have also reported that **177** formed a *cis*-[3]pseudocatenane incorporating three tetrathiafulvanene units under ultrahigh pressure (8×10^5 kPa) (**Scheme 25**) <1996CC639>.



Scheme 25

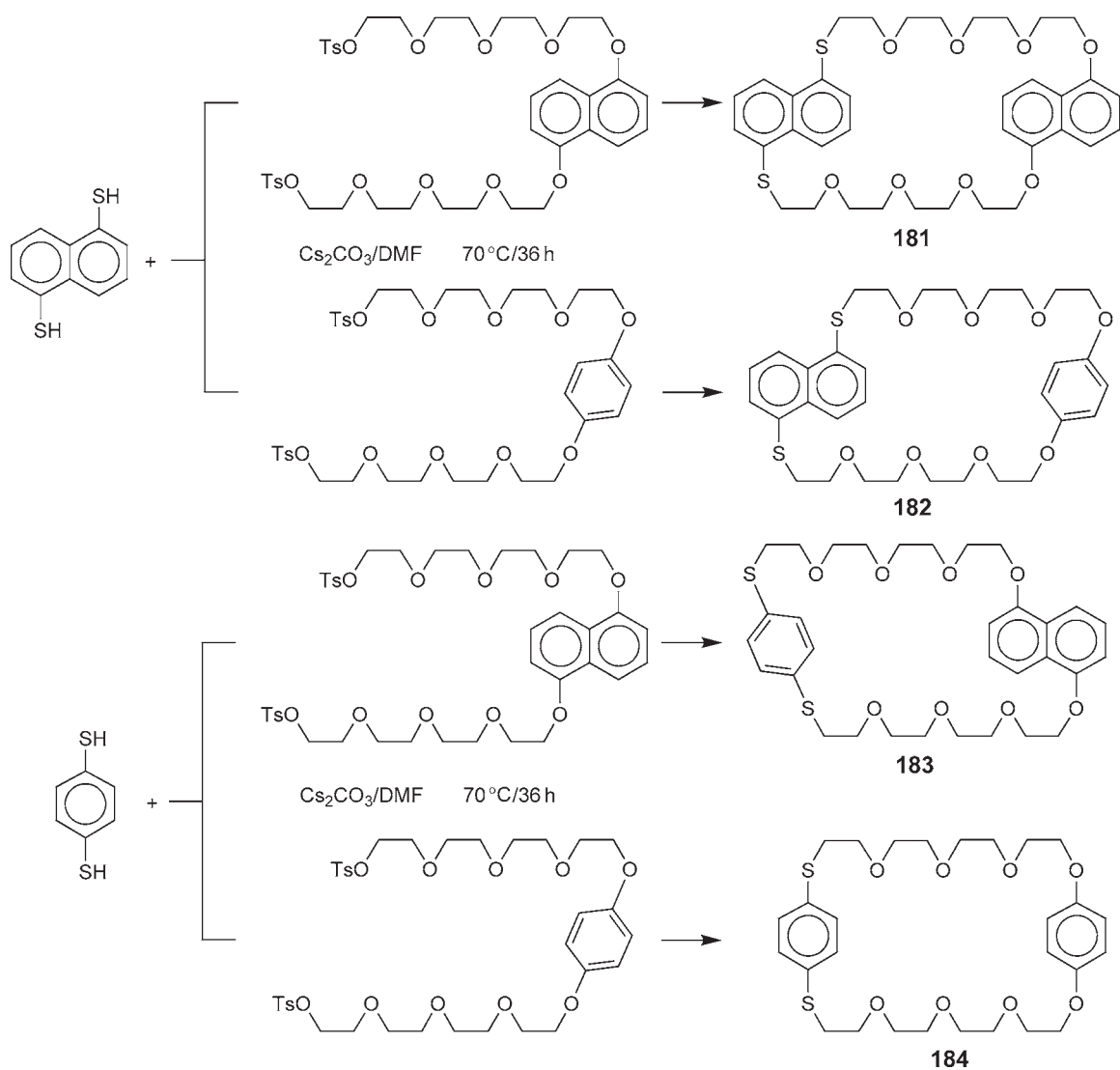
Stoddart and co-workers reported [2]catenanes and [2]pseudorotaxanes incorporating aromatic oxa-thiacrown ethers **178–184** <1997CEJ772>. Synthetic procedures of cyclization and yields of the symmetrical oxa-thiacrown ethers **178a–180b** are summarized in **Scheme 26**.



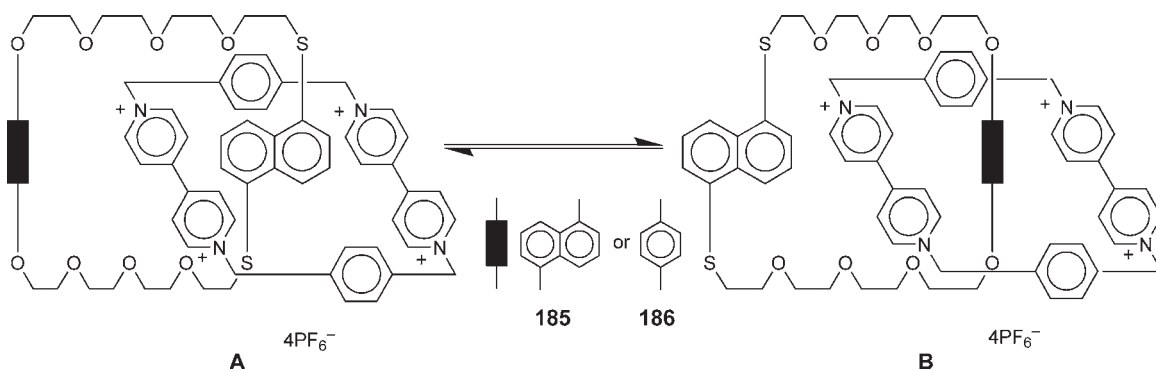
Scheme 26

They also prepared the unsymmetrical oxa-thiacrown ethers **181–184** (**Scheme 27**).

The [2]catenanes **185** and **186** incorporated different π -electron-rich macrocyclic components. As a result, their ¹H NMR spectra showed the existence of two translational isomers in solution as shown in **Scheme 28**. The ratios between the two translational isomers **A** and **B** of [2]catenanes **185** (by **181**-[cyclobis(paraquat-*p*-xylylene)][PF₆]₄) and **186** (by **182**-[cyclobis(paraquat-*p*-xylylene)][PF₆]₄) are 60:40 and 70:30 at –30 °C, respectively. Increasing the temperature up to +30 °C resulted in an increase of the population of the translational isomers **B** in **185** and **186** to 55:45 and 30:70, respectively. A temperature dependence of the equilibrium between the translational isomers associated with **185** and **186** was observed. These [2]catenanes can be regarded as temperature-responsive molecular switches.



Scheme 27

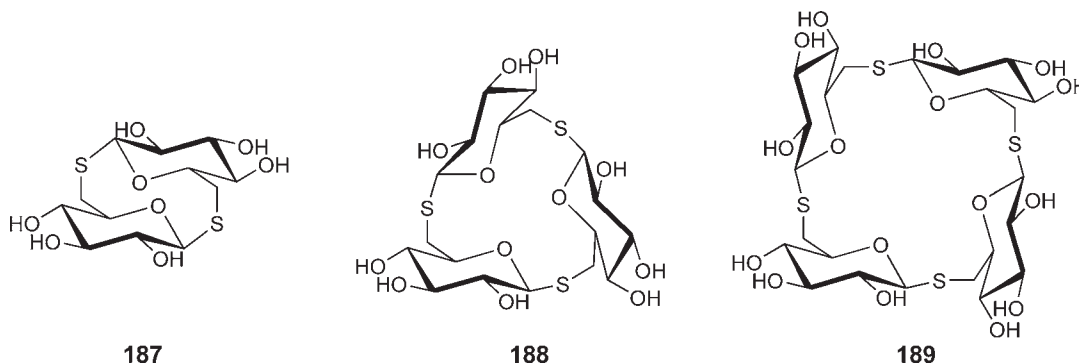
Scheme 28 Translational isomers associated with the [2]catenanes **185** and **186**.

14.15.5 Macrocycles, Not Classified with Crown Ethers

In this section, some macrocycles that are not classified with crown ethers are summarized.

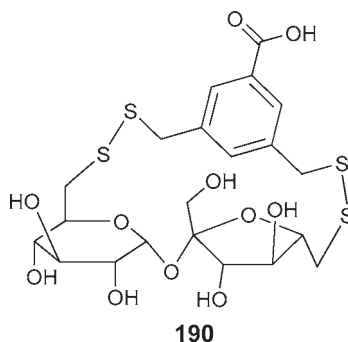
14.15.5.1 Macrocycles Containing Sugar Units

Fan and Hindsgaul have reported cyclic di-, tri-, and tetrasaccharides **187–189** <2002OL4503>, in which the crucial macrocyclization was achieved through a base-promoted intramolecular S_N2 glycosylation in remarkably high yields (92–95%) and with a well-controlled stereochemistry.



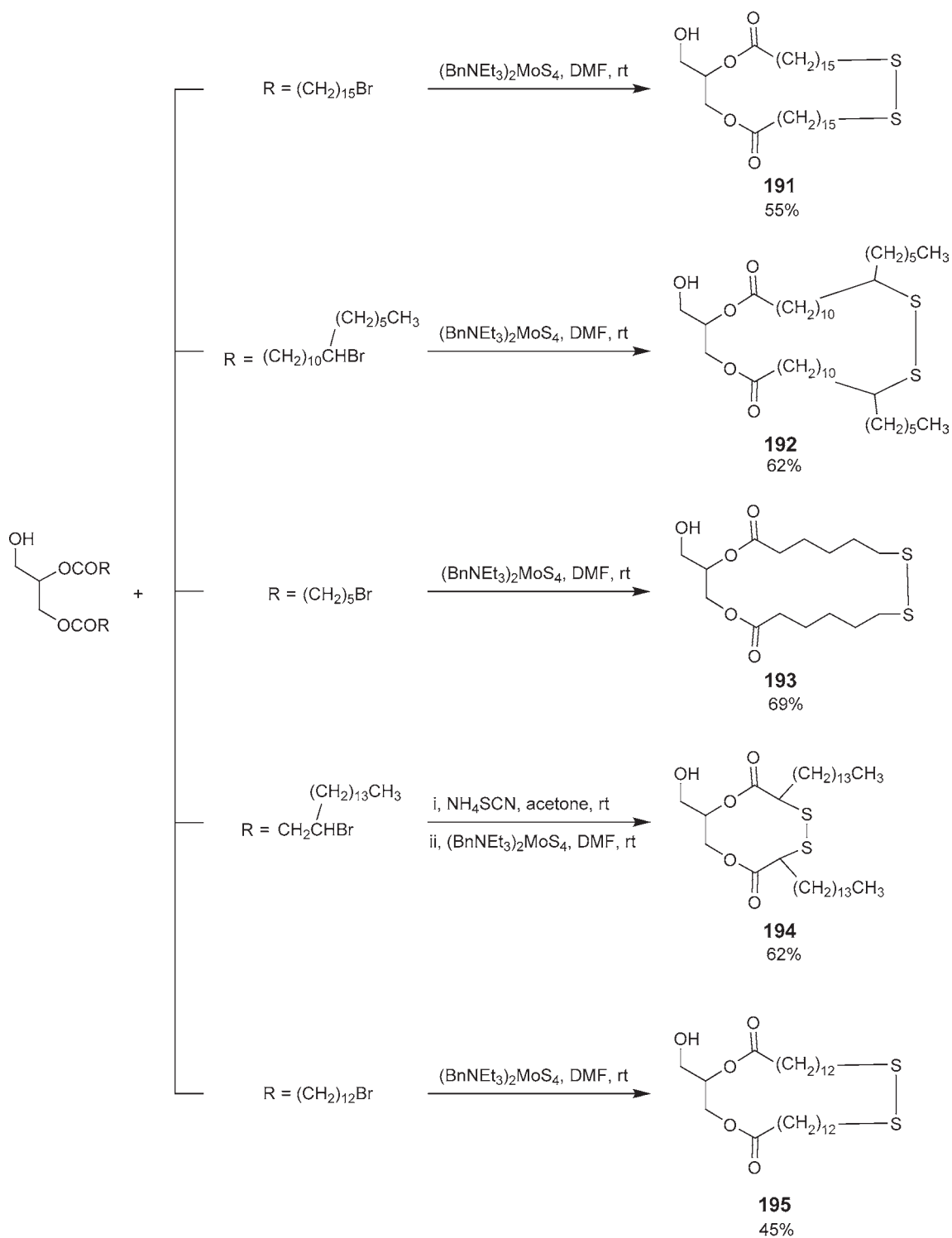
14.15.5.2 Cyclic Peptides by Dynamic Combinatorial Chemistry

Sanders and co-workers have applied dynamic combinatorial chemistry to the synthesis of macrocyclic disulfides in water <2000JA12063>. They prepared over 100 macrocycles which were in some cases separated in mass by only 0.17 amu from four different dithiol building blocks.



14.15.5.3 Macrocyclic Diacyl or Dialkyl Glycerols

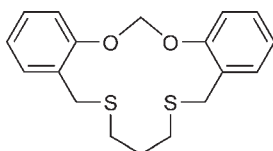
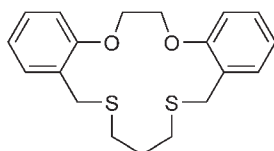
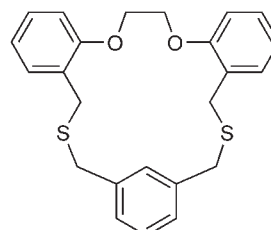
Macrocyclic diacyl and dialkyl glycerols containing a disulfide tether **191–195** have been prepared by Bhattacharya *et al.* (Scheme 29) <1998JOC9232>. Benzyltriethylammonium tetrathiomolybdate has been used to convert individual bis(ω -bromoacyl)glycerols to their respective macrocyclic disulfides.



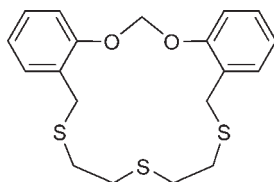
Scheme 29

14.15.6 Further Developments

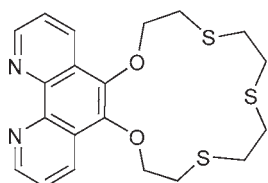
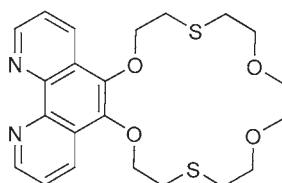
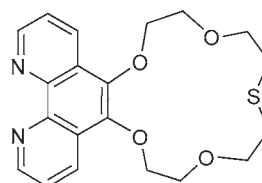
In the last section, very recent results on the ten-membered rings or larger with one or more oxygen and sulfur atoms are summarized. Some research groups reported new oxa-thiacrown ethers which show unique structures with heavy metal ions. Lee *et al.* prepared 14-membered oxa-thiacrown ethers with different inter-donor distances (**196** and **197**). The structures of AgClO_4 complexes with them are quite different; the oxa-thiacrown ether having methylene and trimethylene units in the cyclic moiety **196** forms a poly(bicyclic dimer), while **197** having two ethylenoxy units forms a discrete cyclic tetramer <2006EJI3525>. Lee *et al.* have reported that **198** form a binuclear cyclic dimer with silver picrate <2006JST201>.

**196****197****198**

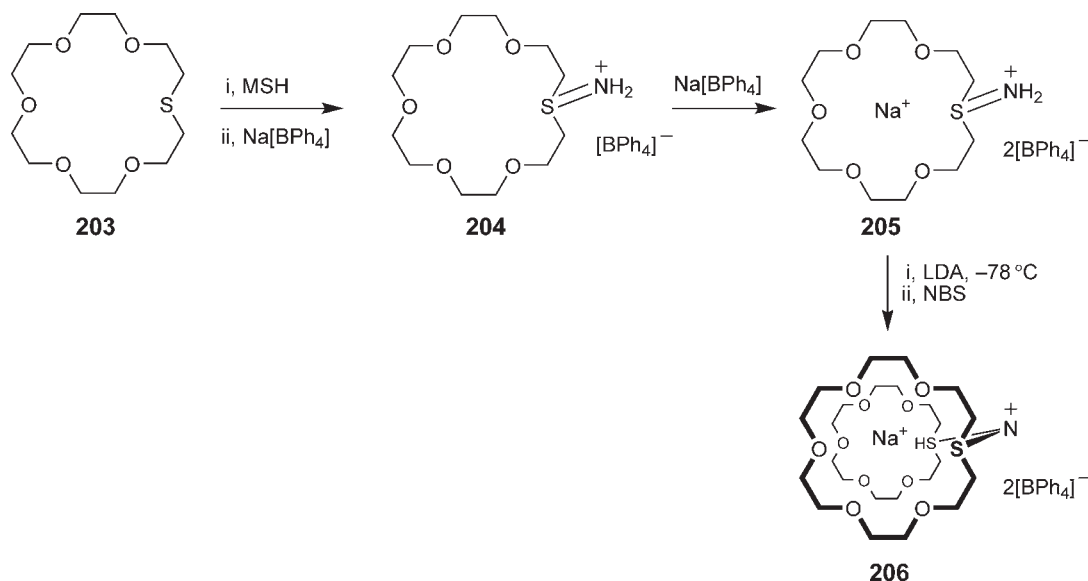
Ring expanded analogue of **196** (**199**) was also prepared by Lee *et al.* <2006IC3487>. The reaction of **199** with K_2PdCl_4 afforded an exo-coordinated complex [*cis*- $\text{Cl}_2\text{Pd199}$]. The complex [*cis*- $\text{Cl}_2\text{Pd199}$] can be manipulated to provide a hetero-binuclear complex $\{[\text{Pd199Ag}(\text{NO}_3)_{2.5}](\text{NO}_3)_5\}_n$ with an excess of AgNO_3 .

**199**

A series of ruthenium (II) diimine complexes containing oxa-thiacrown derived from 1,10-phenanthroline have been synthesized and characterized <2007IC720>. The crystal structures of $[\text{Ru}(\text{bpy})_2\text{200}](\text{PF}_6)_2$, $[\text{Ru}(\text{bpy})_2\text{201}](\text{ClO}_4)_2$, $[\text{Ru}(\text{bpy})_2\text{202}](\text{ClO}_4)_2$ have been determined. The luminescence properties of $[\text{Ru}(\text{bpy})_2\text{200}](\text{ClO}_4)_2$ were found to be sensitive and selective toward the presence of Hg^{2+} ions in an acetonitrile solution.

**200****201****202**

Elsegood *et al.* reported that the reaction of monothia-18-crown-6 **203** with *o*-mesitylsulfonylhydroxylamine (MSH) results in the formation of $\{[18\text{ancO}_5\text{SNH}_2]\}^+$ as the $[\text{mesSO}_3]$ salt, which in turn may be converted to the $[\text{BPh}_4]^-$ salt **204** by addition of $\text{Na}[\text{BPh}_4]$ <2007JCD1665>. If the latter conversion is performed in the presence of excess $\text{Na}[\text{BPh}_4]$ then **205** is obtained. Linked oxa-thiacrown ether **206** was obtained by the reaction of **205** with LDA at low temperature. The crystal structures of **205** and **206** were also determined.



Scheme 30

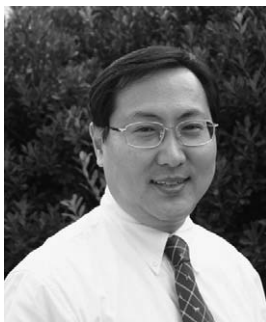
References

- 1971JOC254 C. J. Pedersen, *J. Org. Chem.*, 1971, **36**, 254.
 1973JHC1 J. S. Bradshaw, J. Y. Hui, B. L. Haymore, J. J. Christensen, and R. M. Izatt, *J. Heterocycl. Chem.*, 1973, **10**, 1.
 1974JHC45 J. S. Bradshaw, J. Y. Hui, Y. Chan, B. L. Haymore, R. M. Izatt, and J. J. Christensen, *J. Heterocycl. Chem.*, 1974, **11**, 45.
 1976JOC134 J. S. Bradshaw, R. A. Reeder, M. D. Thompson, E. D. Flanders, R. L. Carruth, R. M. Izatt, and J. J. Christensen, *J. Org. Chem.*, 1976, **41**, 134.
 1993PAC477 H.-J. Holdt, *Pure Appl. Chem.*, 1993, **65**, 477.
 1994SUL177 A. Spannenberg, D. Abeln, J. Kopf, A. Knöchel, and H.-J. Holdt, *Sulfur Lett.*, 1994, **17**, 177.
 1995AGE2020 J. W. Sibert, S. J. Lange, C. L. Stern, A. G. M. Barrett, and B. M. Hoffman, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2020.
 1995ANC1315 H. Hisamoto, E. Nakagawa, K. Nagatsuka, Y. Abe, S. Sato, D. Siswanta, and K. Suzuki, *Anal. Chem.*, 1995, **67**, 1315.
 1995CL629 K. Kubo, A. Mori, N. Kato, and H. Takeshita, *Chem. Lett.*, 1995, 629.
 1995H(41)1901 N. Kato, K. Kubo, A. Mori, and H. Takeshita, *Heterocycles*, 1995, **41**, 1901.
 1995H(49)385 K. Kubo, A. Mori, and H. Takeshita, *Heterocycles*, 1998, **49**, 385.
 1995IC2300 J. W. Sibert, S. J. Lange, D. J. Williams, A. G. M. Barrett, and B. M. Hoffman, *Inorg. Chem.*, 1995, **34**, 2300.
 1995JCD3615 V. W.-W. Yam, Y.-L. Pui, W.-P. Li, K. K.-W. Lo, and K.-K. Cheung, *J. Chem. Soc., Dalton Trans.*, 1998, 3615.
 1995TL11431 E. I. Troyansky, R. F. Ismagilov, V. V. Samoshin, Y. A. Strelenko, D. V. Demchuk, G. I. Nikishin, S. V. Lindeman, V. N. Khurstal'ov, and Y. T. Struchkov, *Tetrahedron*, 1995, **42**, 11432.
 1996ANC4166 D. Siswanta, K. Nagatsuka, H. Yamada, K. Kumakura, H. Hisamoto, Y. Shichi, K. Toshima, and K. Suzuki, *Anal. Chem.*, 1995, **68**, 4166.
 1996BSB151 G. L. Abbe, J. Nouwen, R. Goossens, and W. Dehaen, *Bull. Chem. Soc. Chim. Belg.*, 1996, **105**, 489.
 1996CB807 H.-J. Drexler, H. Reinke, and H.-J. Holdt, *Chem. Ber.*, 1996, **129**, 807.
 1996CC639 Z.-T. Li and J. Becher, *J. Chem. Soc., Chem. Commun.*, 1996, 639.
 1996CEJ624 Z.-T. Li, P. C. Stein, J. Becher, D. Jensen, P. Mork, and N. Svenstrup, *Chem. Eur. J.*, 1996, **2**, 624.
 1996JOC3093 H. T. Stock and R. M. Kellogg, *J. Org. Chem.*, 1996, **61**, 3093.
 1996J(P2)1441 M. V. Alfimov, Y. V. Fedorov, O. A. Fedorova, S. S. Gromov, R. E. Hester, I. K. Lednev, J. N. Moore, V. P. Oleshko, and A. I. Vedernikov, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1441.
 1996J(P2)1587 R. Dieing, V. Morisson, A. J. Moore, L. M. Goldenberg, M. R. Bryce, J.-M. Raoul, M. C. Petty, J. Garin, M. Saviron, I. K. Lednev, *et al.*, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1587.
 1996MC9 E. I. Troyansky, M. S. Pogossyan, N. M. Samoshina, G. I. Nikishin, V. V. Samoshin, L. K. Shpigun, N. E. Kopytova, and P. M. Kamilova, *Mendeleev Commun.*, 1996, 9.
 1996MI191 S. Sensfuss, *Die Angew. Makromol. Chim.*, 1996, **234**, 191.
 1996POL3933 Y. Gok, *Polyhedron*, 1996, **15**, 22.
 1997AXC816 J. Llorca, E. Molins, A. Flores-Vela, S. Cruz-Sanchez, and E. Juaristi, *Acta Crystallogr., Sect. C*, 1997, **53**, 558.
 1997CEJ772 M. Asakawa, P. R. Ashton, W. Dehaen, G. L'abbe, S. Menzer, J. Nouwen, F. M. Raymo, J. F. Stoddart, M. S. Tolley, S. Toppert, *et al.*, *Chem. Eur. J.*, 1997, **3**, 772.
 1997CRV1713 A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713.
 1997H(46)509 A. Mori, K. Kubo, and H. Takeshita, *Heterocycles*, 1997, **46**, 509.
 1997JCD1496 P. R. Ashton, A. L. Burns, C. G. Claessens, G. K. H. Shimizu, K. Small, J. F. Stoddart, A. J. P. White, and D. J. Williams, *J. Chem. Soc., Dalton Trans.*, 1997, 1493.
 1997RCB2099 M. V. Alfimov, A. I. Vedernikov, S. P. Gromov, Y. V. Fedorov, and O. A. Fedorova, *Russ. Chem. Bull.*, 1997, **46**, 2099.

- 1997SAA1853 M. V. Alfimov, Y. V. Fedorov, O. A. Fedorova, S. P. Gromov, R. E. Hester, I. K. Lednev, J. N. Moore, V. P. Oleshko, and A. I. Vedernikov, *Spectrochim. Acta, Part A*, 1997, **53**, 1853.
- 1998AM395 A. J. Moore, L. M. Goldenberg, M. R. Bryce, M. C. Petty, A. P. Monkman, C. Marenco, J. Yarwood, M. J. Joyce, and S. N. Port, *Adv. Mater. (Weinheim, Ger.)*, 1998, **10**, 395.
- 1998CC1653 S. Rudershausen, H.-J. Holdt, H. Reinke, H.-J. Drexler, M. Michalik, and Joachim Teller, *Chem. Commun.*, 1998, 1653.
- 1998H(47)149 A. Mori, K. Kubo, N. Kato, H. Takeshita, M. Shiono, and N. Achiwa, *Heterocycles*, 1998, **47**, 149.
- 1998IC5299 G. J. Grant, D. F. Galas, M. W. Jones, K. D. Loveday, W. T. Pennington, G. L. Schimek, C. T. Eagle, and D. G. VanDerveer, *Inorg. Chem.*, 1998, **37**, 5299.
- 1998JOC9232 S. Bhattacharya, S. Ghosh, and K. R. K. Easwaran, *J. Org. Chem.*, 1998, **63**, 9232.
- 1998JPR450 S. Rudershausen, H.-J. Drexler, and H.-J. Holdt, *J. Prakt. Chem.*, 1998, **340**, 450.
- B-1998MI1 C. D. Gutsche; 'Calixarenes', Royal Society of Chemistry, Letchworth, UK, 1998.
- 1998ZFA1376 H.-J. Drexler, H. Reinke, and H.-J. Holdt, *Z. Anorg. Allg. Chem.*, 1998, **624**, 1376.
- 1999IC6096 F. L. Derf, M. Mazari, N. Mercier, E. Levillain, P. Richomme, J. Becher, J. Garin, J. Orduna, A. Gorgues, and M. Salle, *Inorg. Chem.*, 1999, **38**, 6096.
- 1999ICA305 H.-J. Drexler, M. Grotjahn, E. Kleinpeter, and H.-J. Holdt, *Inorg. Chem. Acta*, 1999, **285**, 305.
- 1999JA4992 M. V. Alfimov, S. P. Gromov, Y. V. Fedorov, O. A. Fedorova, A. I. Vedernikov, A. V. Churakov, L. G. Kuz'mina, J. A. Howard, S. Bossmann, A. Braun, *et al.*, *J. Am. Chem. Soc.*, 1999, **121**, 4992.
- 1999MI1109 H. Radecka, J. Radecki, and W. Dehaen, *Anal. Sci.*, 1999, **15**, 1109.
- 1999SMC263 K. S. Kim, E. K. Lee, and K. Kim, *Supramol. Chem.*, 1999, **10**, 263.
- 2000AXC644 K. Kubo, N. Kato, A. Mori, and H. Takeshita, *Acta Crystallogr., Sect. C*, 2000, **56**, 644.
- 2000H(53)535 K. Kubo, N. Kato, A. Mori, and H. Takeshita, *Heterocycles*, 2000, **53**, 535.
- 2000ICA250 G. J. Grant, M. W. Jones, K. D. Loveday, D. G. VanDerveer, W. T. Pennington, C. T. Eagle, and L. F. Mehne, *Inorg. Chim. Acta*, 2000, **300–302**, 250.
- 2000JA12063 S. Otto, R. L. E. Furlan, and J. K. M. Sanders, *J. Am. Chem. Soc.*, 2000, **122**, 12063.
- 2000JOC8269 A. J. Moore, L. M. Goldenberg, M. R. Bryce, M. C. Petty, A. P. Monkman, J. Moloney, J. A. K. Howard, M. J. Joyce, and S. N. Port, *J. Org. Chem.*, 2000, **65**, 8269.
- 2000MI271 T. Rottgers and W. S. Sheldrick, *J. Solid State Chem.*, 2000, **152**, 271.
- 2000T7371 S. J. Lange, J. W. Sibert, A. G. M. Barrett, and B. M. Hoffman, *Tetrahedron*, 2000, **56**, 7371.
- 2001AN1773 I. Yoon, Y. H. Lee, S. S. Lee, S. C. Lee, and S. B. Park, *Analyst*, 2001, **126**, 1773.
- 2001HAC276 T. Nabeshima, T. Aoki, T. Haruyama, T. Shinnai, H. Ohshiro, T. Saiki, and Y. Yano, *Heteroatom Chem.*, 2001, **12**, 276.
- 2001MI125 J. Xie, Q.-Y. Zheng, Y.-S. Zheng, C.-F. Chen, and Z.-T. Huang, *J. Incl. Phenom. Macrocycl. Chem.*, 2001, **40**, 125.
- 2001MI241 B. L. Lee, Y. H. Lee, I. Yoon, J. H. Jung, K.-M. Park, and S. S. Lee, *Microchem. J.*, 2001, **68**, 241.
- 2002ANC4423 S. M. Williams, J. S. Brodbelt, A. P. Marchand, D. Cal, and K. Mlinaric-Majerski, *Anal. Chem.*, 2002, **74**, 4423.
- 2002BKC879 W. Sim, J. Y. Lee, J. Kwon, M. J. Kim, and J. S. Kim, *Bull. Korean Chem. Soc.*, 2002, **23**, 879.
- 2002CHE261 A. A. Abramov, A. V. Anisimov, and A. A. Bobyleva, *Chem. Heterocycl. Compd.*, 2002, **38**, 261.
- 2002CHE456 D. V. Nasyrov, A. A. Bobyleva, A. A. Abramov, S. N. Anfilogova, M. A. Vasil'kov, and A. V. Anisimov, *Chem. Heterocycl. Compd.*, 2002, **38**, 456.
- 2002JCX447 A. P. Marchand, D. Cal, K. Mlinaric-Majerski, K. Ejsmont, and W. H. Watson, *J. Chem. Crystallogr.*, 2002, **32**, 447.
- 2002NJC543 O. A. Fedorova, Y. V. Fedorov, A. I. Vedernikov, O. V. Yescheulova, S. P. Gromov, M. V. Alfimov, L. G. Kuz'mina, A. V. Churakov, J. A. K. Howard, S. Y. Zzitsev, *et al.*, *New J. Chem.*, 2002, **26**, 543.
- 2002NJC1320 G. Trippé, M. Ocafrain, M. Besbes, V. Monroche, J. Lyskawa, F. L. Derf, M. Salle, J. Becher, B. Colonna, and L. Echegoyen, *New J. Chem.*, 2002, **26**, 1320.
- 2002OL3211 J. Xu and Y.-H. Lai, *Org. Lett.*, 2002, **4**, 3211.
- 2002OL4503 L. Fan and O. Hindsgaul, *Org. Lett.*, 2002, **4**, 4503.
- 2002PS2529 C. Ibis and G. Aydinli, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 2529.
- 2002TL9199 J. Xu and Y.-H. Lai, *Tetrahedron Lett.*, 2002, **43**, 9199.
- 2003EJO54 M. Teyssot, M. Fayolle, C. Philouze, and C. Dupuy, *Eur. J. Org. Chem.*, 2003, **54**.
- 2003HAC273 M. S. Chande, A. A. Godbole, and C. Sajithkumar, *Heteroatom Chem.*, 2003, **14**, 273.
- 2003IC814 S. L. J. Michel, A. G. M. Barrett, and B. M. Hoffman, *Inorg. Chem.*, 2003, **42**, 814.
- 2003JHC639 S. Karabocek, K. Serbest, I. Degirmencioglu, N. Karabocek, and M. Er, *J. Heterocycl. Chem.*, 2003, **40**, 639.
- 2003OL2781 J. Xu, Y.-H. Lai, and W. Wang, *Org. Lett.*, 2003, **5**, 2781.
- 2003PSA186 M. Tabakci, S. Memon, M. Yilmaz, and D. M. Roundhill, *J. Polym. Sci., Part A: Polymer Chemistry*, 2004, **42**, 186.
- 2003TML529 S. Karabocek, I. Degirmencioglu, and N. Karabocek, *Transition Met. Chem.*, 2003, **28**, 529.
- 2004EJI3779 T. Nabeshima, D. Nishida, S. Akine, and T. Saiki, *Eur. J. Inorg. Chem.*, 2004, 3779.
- 2004H(62)149 K. Kubo, A. Mori, and T. Nishimura, *Heterocycles*, 2004, **62**, 149.
- 2004JCR265 H. Kantekin, U. Ocak, Y. Gok, and H. Alp, *J. Coord. Chem.*, 2004, **57**, 265.
- 2004MM2041 M. G. Zolotukhin, S. Fomine, H. M. Colquhoun, Z. Zhu, M. G. G. Drew, R. H. Olley, R. A. Fairman, and D. J. Williams, *Macromolecules*, 2004, **37**, 2041.
- 2004PJC223 J. Romanski and A. P. Marchand, *Pol. J. Chem.*, 2004, **78**, 223.
- 2004TL12059 V. Csokai, B. Balazs, G. Toth, G. Horvath, and I. Bitter, *Tetrahedron*, 2004, **60**, 12059.
- 2005JCD2352 I. Yoon, J. Seo, J.-E. Lee, M. R. Song, S. Y. Lee, K. S. Choi, O.-S. Jung, K.-M. Park, and S. S. Lee, *Dalton Trans.*, 2005, 2352.
- 2005MI199 M. Ashram, *J. Incl. Phenom. Macrocycl. Chem.*, 2005, **51**, 199.
- 2005MI42 F. Yang, H. Guo, and J. Lin, *Chem. J. Internet*, 2005, **7**, 42.
- 2005PS1953 S. M. Seyed, M. Shadkam, and A. Ziafati, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 1953.
- 2005SMC221 M. Duta, Z. Asfari, N. Kruchinina, P. Thuery, A. Hagege, and M. Leroy, *Supramol. Chem.*, 2005, **17**, 221.
- 2005T9248 J.-W. Xu, W.-L. Wang, and Y.-H. Lai, *Tetrahedron*, 2005, **61**, 9248.
- 2005TL2431 J.-W. Xu, T.-T. Lin, and Y.-H. Lai, *Tetrahedron*, 2005, **61**, 2431.
- 2006EJI3525 S. Y. Lee, J. Seo, I. Yoon, C. Kim, K. S. Choi, J. S. Kim, and S. S. Lee, *Eur. J. Inorg. Chem.*, 2006, 3525.
- 2006IC952 J. Seo, M. R. Song, J.-E. Lee, S. Y. Lee, I. Yoon, K.-M. Park, J. Kim, J. H. Jung, S. B. Park, and S. S. Lee, *Inorg. Chem.*, 2006, **45**, 952.

- 2006IC3487 I. Yoon, J. Seo, J. Lee, K. Park, J. S. Kim, M. S. Lah, and S. S. Lee, *Inorg. Chem.*, 2006, **45**, 3487.
2006JST201 J. Seo, M. R. Song, K. F. Sultana, H. J. Kim, J. Kim, and S. S. Lee, *J. Mol. Struct.*, 2007, **827**, 201.
2007IC720 M. Li, W. Chu, N. Zhu, and W. Yam, *Inorg. Chem.*, **46**, 720.
2007JCD1665 M. R. J. Elsegood, P. F. Kelly, G. Reid, and P. M. Staniland, *J. Chem. Soc., Dalton Trans.*, 2007, 1665.

Biographical Sketch



Yoichi Habata was born in Nayoro, Japan. After graduating from Toho University, Funabashi, Japan, in 1982, he entered the Ph.D. program in chemistry at Toho University. His Ph.D. degree work was under the direction of Professor Sadatoshi Akabori. After receiving Ph.D. degree in 1987, he served Lion Co. Ltd., Tokyo, Japan, as a researcher. He continued working in crown ether chemistry during his industrial years. He joined Toho University Chemistry Department in 1989 as a research associate. He spent the 1995–96 academic year as a postdoctoral fellow in the laboratory of Professor Jerald S. Bradshaw at the Brigham Young University, Provo UT, working on the synthesis of chiral crown ethers and podands. After he returned to the Toho University, he was promoted to associate professor in 1998 and professor in 2005.

His research interests are synthesis and complexation properties of chiral and achiral macrocyclic ligands and construction of supramolecular structures by combination of flexible ligands and metal ions.

14.16

Rings containing Selenium or Tellurium

G. L. Sommen

Lonza AG, Walliser Werke, Visp, Switzerland

© 2008 Elsevier Ltd. All rights reserved.

14.16.1	Introduction	864
14.16.1.1	General Introduction	864
14.16.1.2	Nomenclature	864
14.16.2	Theoretical Methods	865
14.16.2.1	<i>Ab Initio</i> Calculation	865
14.16.2.2	Density Functional Theory	865
14.16.2.3	Molecular Dynamics Simulation	866
14.16.3	Experimental Structural Methods	866
14.16.3.1	X-Ray Structure Determinations	866
14.16.3.2	NMR Spectra	870
14.16.3.2.1	Proton spectra	870
14.16.3.2.2	Carbon spectra	870
14.16.3.2.3	⁷⁷ Se and ¹²⁵ Te spectra	870
14.16.3.3	Mass Spectra	872
14.16.3.4	Ultraviolet Spectra	872
14.16.3.5	Titration Calorimetry	872
14.16.3.6	Photoelectron Spectroscopy	873
14.16.3.7	Oxidation Potentials and Cyclic Voltammetry	873
14.16.3.8	Raman Spectrometry	873
14.16.4	Thermodynamic Aspects	874
14.16.4.1	Conformational Aspects	874
14.16.4.2	Chromatography	875
14.16.5	Reactions	875
14.16.5.1	Elimination of the Heteroatom to Form a Nonaromatic Species	875
14.16.5.2	Elimination of the Heteroatom in Heterocyclophanes	876
14.16.5.3	Oxidation of the Heteroatom	876
14.16.5.4	Complexation with Heavy Metals	877
14.16.5.5	Other Reactions	880
14.16.6	Synthesis	880
14.16.6.1	Synthesis of Rings in which Formation of a C–X Bond is the Ring-Closure Step	880
14.16.6.2	Synthesis of Rings in which Formation of a C–X Bond is not the Ring-Closure Step	894
14.16.6.3	Transformation of a Chalcogen-Containing Ring	895
14.16.7	Further Developments	897
	References	898

14.16.1 Introduction

14.16.1.1 General Introduction

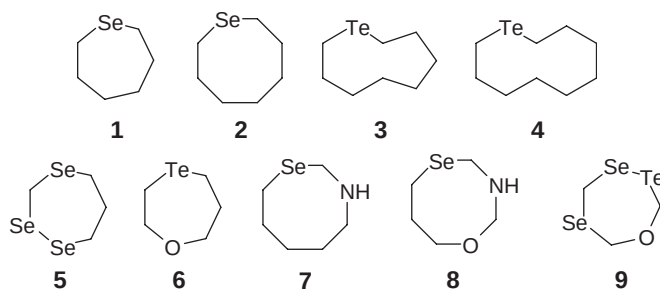
This chapter is intended to update the previous work concentrating on major new preparations, reactions, and concepts. A short paragraph has been provided at the beginning of each main section, explaining the major advances, since the publication of the earlier chapters and also any major deficiencies in CHEC-II(1996) that will now be addressed. This chapter, dealing with seven- or more membered rings containing selenium or tellurium, has previously been covered in CHEC(1984) (volume 5, chapters 18–22) and in 21 pages in CHEC-II(1996) (volume 9 and chapter 33). However, CHEC(1984) did not provide a specific chapter for selenium and tellurium ring systems, but rather it was diluted into five chapters dealing with the size of the ring and not the heteroatom. Reginald Mitchell and Helen Mitchell covered a much more precise chapter (CHEC-II(1996), chapter 9.33, pp. 925–945), which will be the foundation for the following work. This chapter reviews large or medium-sized fused and nonfused heterocycles containing one or more selenium or tellurium combined or not with other heteroatoms for the period 1996 to November 2006.

14.16.1.2 Nomenclature

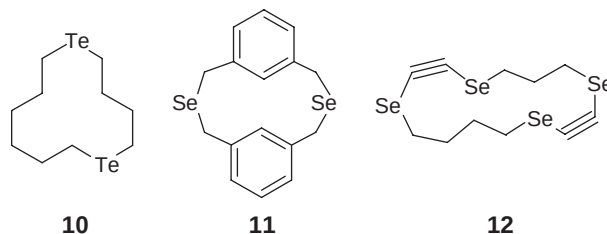
Some of the nomenclature was already mentioned in CHEC-II(1996) by describing five examples of different sizes. Still, due to its high complexity and confusion, this section is included, so as to complete the discussion. The level of complication is increasing with the size of the ring. Examples, which will be used, will be explained with the increasing ring size.

The saturated seven-membered rings are named selenepane **1** or tellurepane for a tellurium-containing ring. Fully unsaturated rings are called selenepin or tellurepin. Analogously, eight-membered heterocycles are named selenocanes **2** and selenocins (tellurocanses and tellurocins), nine-membered ones are selenonanes (selenonins) and telluronanes (telluronins), and ten-membered ones are tellurecanses (tellurecins). Finally, larger ring systems, 11- and 12-membered, are respectively called selenacycloundecane and selenacyclododecane (for heterocycles with one atom of selenium).

Although the combination with two or more atoms of selenium does not change the name of the heterocycle, but it is completed by di-, tri-, tetra-, penta-, etc. (for one, two, three, or more selenium atoms), preceded by the position number of each atom. For example, **5** would be called [1,3,4]triselenepane. When other heteroatoms are present in the ring, the name of the heterocycle is preceded by the corresponding abbreviation, so that **6** will be called [1,4]oxatellurepane. The name of the heterocycle is the one carrying the heaviest heteroatom, so that example **9** will be [1,4,6,3]oxadiselenatellurepane. It has to be noted that there are some variations/exceptions when an atom of nitrogen is present. The ‘az’ abbreviation is not written as usual, that is, before the chemical name, but within it. Example **7** will then be named [1,3]selenazocane and example **8** [1,5,3]oxaselenazocane.



For larger rings, heteracycloalkane or heteraannulene are used; for example, **10** will be called 1,6-ditelluracyclododecane, while **11** will be 2,11-diselena[3.3]metacyclophane. The last ring mentioned here is exemplified by **12**, which is a 15-member heterocycle containing four atoms of selenium; it is called 1,4,8,11-tetraselena-cyclopentadeca-2,9-diyne.



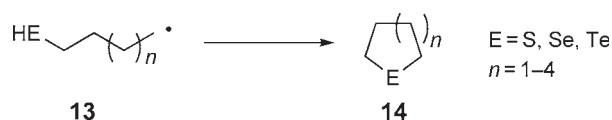
Most of the work on such compounds has been directed toward their synthesis, with some emphasis on their conformations and reactions. Unlike the smaller ring systems, aromatic ring examples are relatively unknown.

14.16.2 Theoretical Methods

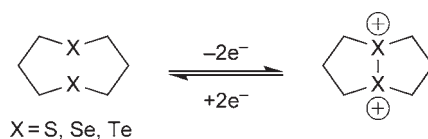
This topic was for the most part not examined in CHEC(1984) and CHEC-II(1996). A much more detailed section is herein reviewed.

14.16.2.1 *Ab Initio* Calculation

Ab initio calculations using a pseudopotential (DZP) basis set and with the inclusion of electron correlation (MP2) predicted that intramolecular homolytic substitution at the chalcogen atom in the 4-chalcogenyl-1-alkyl **13** proceeded preferentially with the degenerate translocation of the chalcogen-containing moiety and with ring closure for the lower homologues ($n = 1$ and 2). All reactions involving homolytic substitution at the tellurium atom are predicted to proceed with the involvement of [9-Te-3] hypervalent intermediates, while the analogous reactions involving sulfur and selenium are calculated to proceed without the involvement of intermediates at all levels of theory, except during the 1,6-translocation of selanyl, in which a shallow local minimum was located on the potential energy surface at the MP2/DZP level of theory. Energy barriers for ring-closure reactions of between 48.4 ($n = 1$, E = Te) and 162.6 kJ mol⁻¹ ($n = 2$, E = S) were calculated and expected to decrease significantly with the inclusion of better leaving groups. Energy barriers for translocation reactions of between 62.8 (1,7-tellanyl transfer) and 139.3 kJ mol⁻¹ (1,5-sulfanyl transfer) are predicted at the MP2/DZP level of theory; these high-energy barriers are presumably a consequence of unfavorable factors associated with ring size and long carbon–chalcogen separations in transition states and intermediates **14** ($n = 2-4$), which lead to significant deviations from the ideal arrangement of attacking and leaving radicals preferred in homolytic substitution reactions at chalcogen <1999JOC1131>.

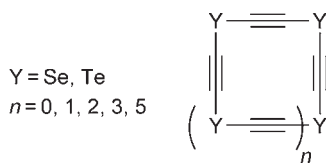


The molecular and electronic structures of the dications of three homonuclear and three heteronuclear dichalcogenacyclooctanes were investigated by *ab initio* molecular orbital calculations. Four energy-minimum structures were located for each dication. Three of those (chair-chair, boat-boat, and boat-chair) have the *cis*-configuration with respect to the chalcogen lone pairs, and the remaining one has the *trans*-configuration. The *cis*-isomers were found to be much more stable than the *trans*-isomer. Among the three *cis*-structures, the stability is in the order of boat-chair > boat-boat > chair-chair for all dications. This order can be explained by considering the nonbonding H···H interactions (see Chapter 10.01) <2000HAC31, 1993PS261>.



14.16.2.2 Density Functional Theory

Density functional theory (DFT) studies on [M]chalcogena[M]pericyclynones ($n = 0-3, 5$) demonstrate their relative stability and hence their possible existence as stable species. By minimizing repulsive interactions between the chalcogens' lone pairs, the molecules adopt structures that resemble, in shape, cycloalkanes or elemental chalcogens. [3]Chalcogena[3]pericyclynones may be interconverted with their valence tautomers, benzene derivatives with three fused three-membered rings <2004OL589>.



The structures and spectroscopic properties of $\text{Se}_n\text{S}_{8-n}$ ring molecules have been studied by the use of *ab initio* molecular orbital techniques and density functional techniques involving Stuttgart relativistic large core effective core potential approximation with double zeta basis sets for valence orbitals augmented by two polarization functions for both sulfur and selenium. Full geometry optimizations have been carried out for all 30 isomers at the Hartree–Fock level of theory. The optimized geometries, calculated fundamental vibrations, and Raman intensities of the $\text{Se}_n\text{S}_{8-n}$ molecules agree closely with experimental information when available. The nuclear magnetic shielding tensor calculations have been conducted by the gauge-independent atomic orbital method at the DFT level using Becke’s three-parameter hybrid functional with Perdew/Wang 91 correlation. The isotopic shielding tensors correlate well with the observed chemical shift data. The calculated chemical shifts provide a definite assignment of the observed ^{77}Se NMR spectroscopic data and can be used in the prediction of the chemical shifts of the unknown $\text{Se}_n\text{S}_{8-n}$ rings <2002CJC1435>. Potential energy landscapes of Se_8 , Te_8 , and $\text{Se}_n\text{S}_{8-n}$ clusters were determined using disconnectivity graphs. Inherent structures include both ring and chain configurations with rings especially dominant in Se_8 <2006MI023202>.

14.16.2.3 Molecular Dynamics Simulation

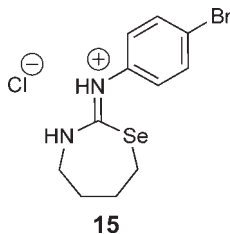
The first principles molecular dynamics simulation has been applied, based on the linearized-augmented-plane-wave (LAPW) method, to Se_8 and Se_8^+ clusters. The equilibrium structures have been obtained for Se_8 and Se_8^+ clusters; for the ionized cluster Se_8^+ , a remarkable change from that for the neutral cluster has been found, which reflects the strong electron–lattice coupling in the cluster <1997MI1660, 1997MI75, 1997MI472>.

14.16.3 Experimental Structural Methods

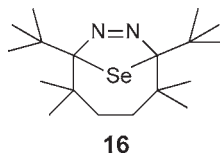
14.16.3.1 X-Ray Structure Determinations

In CHEC-II(1996), this topic was discussed following the ring size for some of the major compounds, described in the literature.

1. *Seven-membered ring systems.* X-Ray analysis was performed on selenazepane **15**, synthesized for the first time in 2005. The Se–C bond is short (1.902 Å) as a result of some conjugation of the lone pair with the π -system. The plane of the aromatic ring is twisted by 52.1° out of the plane defined by Se–C–N–N. Both NH groups form a hydrogen bond with the same chloride ion and thereby link the cations and anions into ion pairs <2005TL6723>.

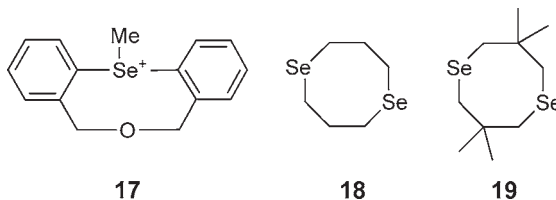


The structure of **16** was confirmed by X-ray crystallography <2000JOC1799>.

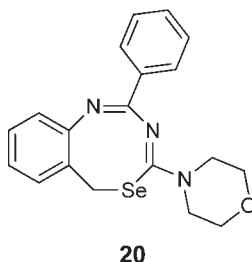


2. *Eight-membered ring systems.* The crystal structure of the selenonium salt **17** has been determined by X-ray diffraction analysis. The bond lengths are 1.942 Å for Se–C(1), 1.946 Å for Se–C(2), and 1.945 Å for Se–C(3). It is interesting to

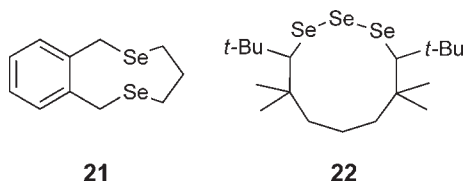
note that the transannular $O \cdots Se$ contact is 2.609 Å, which is significantly shorter than the sum of the Van der Waals radii (3.40 Å) of the two elements. The bond angle of $C(1)-Se-C(2)$ is 102.1°. The $C(3)-Se-O$ angle is 172.5°; this linear alignment of $C \cdots Se \cdots O$ showed the hypervalent nature of the selenium atoms. Thus, the configuration about the selenium atom is a slightly distorted trigonal bipyramidal structure <1995TL6275>. The crystal structure of [1,5]diselenocane **18** has been elucidated by X-ray crystallography <1997JCD3493, 1993PS261>. A new diselena eight-membered ring **19** has been characterized by X-ray diffraction. Selected interatomic distances are $Se(1)-C(1)$ 1.961 Å, $Se(1)-C(3)$ 1.974 Å, $C(1)-C(2)$ 1.520 Å, and $C(2)-C(3')$ 1.520 Å <1997CC525>.



The crystal structure of **20** established the eight-membered 6*H*-[5,1,3]benzoselenadiazocine ring. The crystal actually proved to be a co-crystal of composition 0.94($C_{19}H_{19}N_3OSe$), 0.06($C_{19}H_{18}ClN_3OSe$), MeOH. This conclusion was based on the observation that, although the initially developed structural model corresponded with the expected **20**, one peak of residual electron density of $1.9 e^{-3}$ remained ca. 1.6 Å from C-9 of the phenyl ring. Given the chemical evidence, which indicated that the crystals contained a small amount of a corresponding compound that is Cl-substituted at C-9, the peak was assigned as a partial-occupancy Cl-atom. The site occupation factor of this Cl-atom was refined to a value of 0.060(2). Therefore, the crystal appeared to be a mixture of two compounds: ca. 94% is the expected **20**, while ca. 6% is the corresponding compound, which is Cl-substituted at C-9. The asymmetric unit in the structure also contained one molecule of MeOH. The OH group of the MeOH molecule formed an intermolecular H-bond with N-5 of the eight-membered ring of the Se compound <2004HCA1452>.

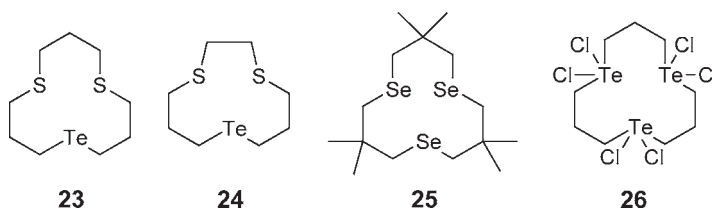


3. *Nine- and 10-membered ring systems.* The crystal structure of 5,8,9,11-tetrahydro-7*H*-6,10-diselena-benzocyclonene **21** has been determined <1997JCD3493>. Some relevant bond distances and angles of the 10-membered triselenecane **22** are: $Se(1)-Se(2)$ 2.320 Å, $Se(2)-Se(3)$ 2.305 Å, $Se(1)-Se(2)-Se(3)$ 109.6° <2002HAC351>.

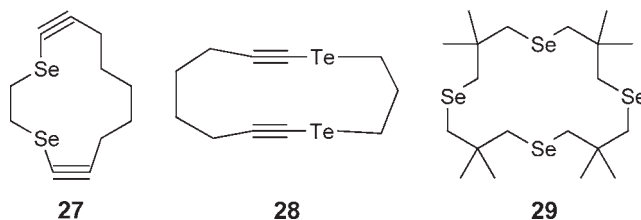


4. *The 11- and 12-membered ring systems.* The crystal structures of [12]aneS₂Te **23** and [11]aneS₂Te **24** have been determined. The structures showed discrete molecular species, with no significant intermolecular contacts. The dithiatellura analogue, [12]aneS₂Te **23**, adopted a very similar distribution of torsion angles in the solid state, with one *gauche* and one *anti* C-Te-C-C torsion and three of the four C-S-C-C torsions being *gauche*, and with a S-atom occupying a corner of the approximate square. The $C(1)-Te(1)-C(9)$ angle of 94.2° was considerably smaller than the C-S-C angles (100.4° and 101.3°), consistent with less s orbital character in the Te-C bonding (owing to the larger energy gap between the s and p orbitals of Te when compared to S). This trend in bond angles was also observed in the structure of [11]aneS₂Te, although the torsion angles showed greater deviations from strictly *gauche* or *anti*, presumably due to restrictions imposed by the smaller ring size. This species also adopted an

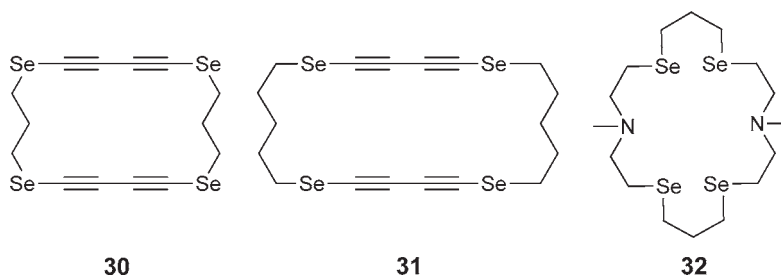
approximately square arrangement, in this case with the Te-atom on a corner and the S-atoms on edges <2003JCD2434>. Selected interatomic distances of the new triselenium 12-membered ring **25** are: Se(1)–C(1) 1.965 Å, Se(1)–C(9) 1.953 Å, Se(2)–C(3) 1.952 Å, Se(2)–C(4) 1.957 Å, Se(3)–C(6) 1.97 Å, and Se(3)–C(7) 1.97 Å <1997CC525>. Crystals of **26** were obtained by slow evaporation of a solution in dimethylformamide (DMF) containing dissolved **26**. The Te–Cl distance range from 2.44 to 2.58 Å, which is characteristic of hypervalent bonding and is significantly longer than the sum of the tellurium and chlorine covalent radii (2.36 Å), and longer than the Te–Cl single covalent bonds of 2.31 and 2.33 Å (TeCl₄) <1996OM5112>.



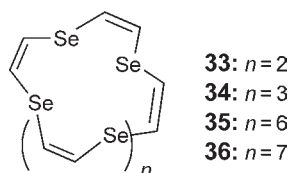
5. *The 13-, 14-, 15-, and 16-membered ring systems.* Gleiter and co-workers were able to isolate single crystals of the diselenium 13-membered ring **27** and the ditellura 14-membered ring **28**, which allowed them to carry out X-ray diffraction studies <2003OBC2788>. Selected interatomic distances of the new tetraselenium 16-membered ring **29** are: Se(1)–C(1) 1.961 Å, Se(1)–C(6) 1.967 Å, Se(2)–C(3) 1.961 Å, Se(2)–C(4) 1.956 Å, C(1)–C(2) 1.540 Å, C(2)–C(3) 1.570 Å, C(4)–C(5) 1.550 Å, and C(5)–C(6) 1.510 Å <1997CC525>.



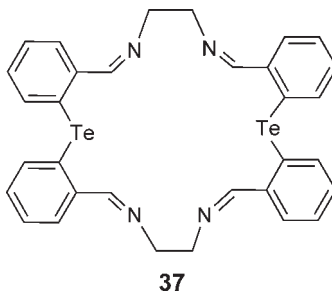
6. *The 17-membered and larger ring systems.* Twenty- and 22-membered cyclic bis(1,3-butadiynes) **30** and **31** with selenium centers placed in the α -position to the 1,3-butadiyne units were synthesized and determined by X-ray analysis <2004JOC2945>. X-Ray crystallographic structure was obtained for **32**, which showed a cavity size estimated to be $7.8 \times 7.4 \text{ Å}^2$. The diagonal Se–Se distances are 10.1 and 937 Å, respectively <2005MI191>.



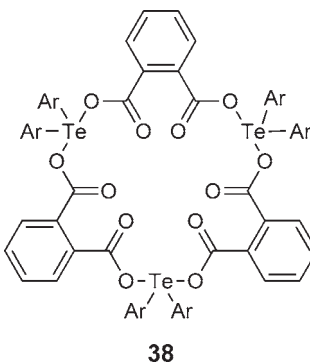
The crystal structures of unsaturated selenacrown ethers **33–36** were determined by X-ray crystallographic analysis. The bond lengths and angles were almost normal for all of the compounds. Their crystal structures indicated that all of the olefin moieties have *cis*-geometry and all of the selenium atoms lie almost on their respective planes. The most interesting point in these structures is the shape and size of the cavity. The cavities of large unsaturated selenacrown ethers are elliptically slender, whereas the structures of the corresponding unsaturated thiacycrown ethers became rounder with increasing ring size. The longest widths of the cavities surrounded by selenium atoms of **33–36** are 3.41, 5.98, and 8.36 Å, respectively, whereas the shorter ones are 1.16, 1.05, and 1.40 Å <2003OL1443, 2005JOC5036>.



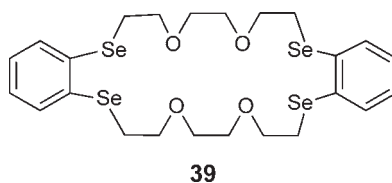
The crystal structure has been obtained for **37** and was found to be triclinic with the space group P1 with $a=7.956(3)$, $b=9.885(2)$, $c=10.068(2)$ Å, and $Z=1$. Two opposite aromatic rings in the macrocycle are coplanar. The Te(1)–C(1) distance is 2.117 Å, which is in excellent agreement with the sum of the Pauling single-bond covalent radii for tellurium (1.37 Å) and the sp^2 -hybridized carbon (0.74 Å). However, the Te(1)–C(9) bond is slightly longer (0.05 Å) than the sum of the relevant covalent radii <1996JCD1203, 2000CCR49>.



The molecular structure of the hypervalent macrocycle **38** was determined by X-ray crystallographic analysis, which showed three Te atoms and three phthalates, and possessed Te–O₂C bond lengths of 2.133–2.166 Å, CO₂–Te–O₂C bond angles of 161.8–168.3°, and C–Te–C bond angles of 96.2–100.3°. The macrocycle consists of two ditelluroxanes and two phthalates, and the unit cell containing four independent molecules. The respective average bond lengths and angles are in the range of 2.23–2.29 Å for Te–O₂C, 1.99–2.03 Å for Te–O, 166.1–168.7° for O–Te–O₂C, 96–101° for C–Te–C, and 114–126° for Te–O–Te. These data clearly indicated that **38** has trigonal bipyramidal geometry for the Te-atoms and hypervalent Te–O apical bonds. All the atoms of the respective macrocyclic rings are roughly coplanar. The halves of the carbonyl O-atoms and the tolyl groups are directed inward and outward, respectively, to the respective macrocyclic rings. By contrast, the other halves of the carbonyl O-atoms and the tolyl groups are vertically directed to the respective macrocyclic planes so as to be placed as the opposite site <2001CC1428>.



The structural parameters and conformation in the solid state of one representation of the macrocycle **39** have been determined by X-ray diffraction and it was found that this selenoether possesses a crystallographic center of symmetry and the metric parameters were found to be the typical values <1997JCD1043>.

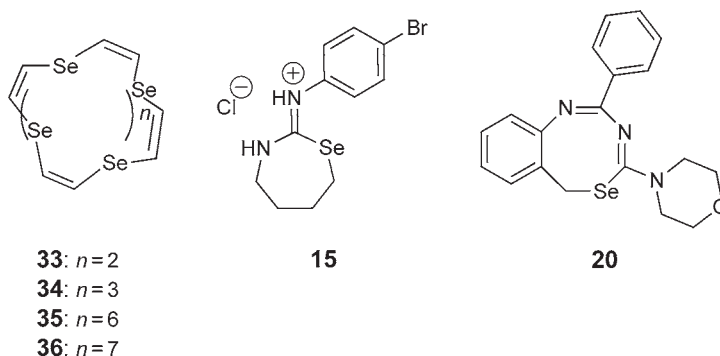


14.16.3.2 NMR Spectra

CHEC-II(1996) possessed little novel nuclear magnetic resonance (NMR) information, since nearly all papers cited proton and carbon spectra to characterize the compounds. Nevertheless, in the last decade, considerable attention has been focused on the Se and Te NMR. Proton and carbon shifts were already reviewed in CHEC-II(1996); only some examples to complete the understanding of the influence of selenium or tellurium will be herein considered.

14.16.3.2.1 Proton spectra

The ^1H NMR spectra of **33–36** showed a singlet, indicating that **33–36** exhibit flexibility to some extent, in solution. The ^1H NMR signals were shifted upfield with increasing ring size for **33–36** in CDCl_3 (^1H NMR (ppm): **33**, 7.16; **34**, 7.12; **35**, 7.09; **36**, 7.08). These results suggested that the electron density of the olefin moieties is increased and that of selenium is decreased with increasing ring size of the unsaturated selenacrown ethers. The chemical shifts on the ^1H NMR spectra were also found at lower fields than those of the corresponding sulfur analogues <2003OL1443, 2005JOC5036>. In selenazepane **15**, $-\text{CH}_2-\text{Se}$ appears at 1.69–1.79 in a multiplet <2005TL6723>. Benzoselenadiazocines **20** have a benzylic CH_2 group close to the selenium atom, where the two hydrogens are different and appear at 4.50 and 3.35 <2004HCA1452>.



14.16.3.2.2 Carbon spectra

The ^{13}C NMR spectra of selenacrown ethers were recorded, compared, and shown to be almost the same as those of the sulfur analogues ^{13}C NMR (ppm): **33**, 127.0; **34**, 125.7; **35**, 124.8; **36**, 124.3 <2003OL1443, 2005JOC5036>. In the saturated seven-membered selenazepane **15**, typically $\text{N}-\text{C}(\text{N})-\text{Se}$ appears at: δ 167.3–168.2, $-\text{CH}_2-\text{Se}$ at δ 24.9–26.8 <2005TL6723>. In the eight-membered ring **20**, $-\text{CH}_2-\text{Se}$ shifts are δ 24.3–27.2, $\text{N}-\text{C}(\text{N})-\text{Se}$ appear at δ 159.3–161.1 <2004HCA1452>. Diselena 13-membered ring **27** has a $-\text{CH}_2-\text{Se}$ group at δ 18.1 and the ditellura 14-membered ring **28** has a $-\text{CH}_2-\text{Te}$ shift at δ 9.3, $-\text{C}\equiv\text{C}-\text{Se}(\text{Te})$ appears at 100.7 and 57.9 for **27** and 31.4 and 113.4 for **28** <2003OBC2788>.

14.16.3.2.3 ^{77}Se and ^{125}Te spectra

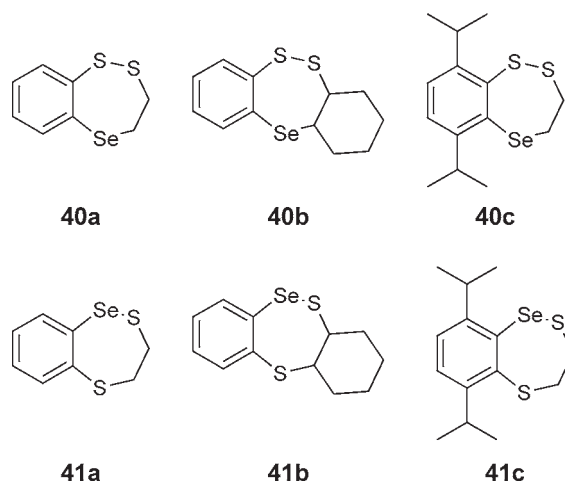
There is considerable interest in ^{77}Se NMR parameters <1995MI1, B-1996MI1> as a result of the numerous applications of selenium compounds in synthesis and their biochemical relevance. Chemical shifts $\delta^{77}\text{Se}$ are diagnostic for different classes of selenium compounds, and their trends can be predicted by calculations, which include electron correlation effects. Similar to $\delta^{77}\text{Se}$, a large data set exists for electron-mediated (indirect) spin–spin coupling constants $^nJ(^{77}\text{Se}, \text{X})$. These data appear to be less well understood when compared with chemical shifts $\delta^{77}\text{Se}$. A major problem related to coupling constants is the fact that the different contributions arising from various coupling mechanisms, such as the Fermi contact term (FC), spin–orbital term (SO), and the spin–dipole term (SD), are not accessible by experiments.

Furthermore, frequently the sign of J is unknown. Recent progress in the calculation of isotropic spin–spin coupling constants $^nJ(\text{A}, \text{X})$ by using DFT methods is promising, since both the approximate magnitude and the sign of coupling constants are reproduced in many cases. Wrackmeyer has published an in-depth study on indirect nuclear ^{77}Se – ^{77}Se spin–spin constants by DFT calculations <2005STC67>. Some coupling constants were calculated at the B3LYP/6-311+G(d,p) level of theory and the values were compared with available experimental data. There

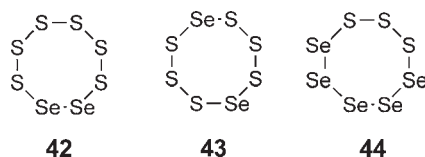
are rather large deviations between experimental and calculated $\delta^{77}\text{Se}$ data, although the trends are correctly predicted. The differences may result from errors related to dynamical correlation effects in the DFT treatment. However, the agreement between experimental and calculated values $J(^{77}\text{Se}, ^{77}\text{Se})$ is reasonably good. The calculations of coupling constants $J(^{77}\text{Se}, ^{77}\text{Se})$ at the B3LYP/6-311+G(d,p) level of theory can be used to gain insight into the various contributions to J . Clearly, FC is not the dominating coupling mechanism, and both SD and paramagnetic spin-orbital (PSO) interactions can become quite large.

The rather small magnitude frequently observed for $^1J(^{77}\text{Se}, ^{77}\text{Se})$ turns out to be the result of the cancelling contributions arising from the various coupling mechanisms, and, therefore, the sign of $^1J(^{77}\text{Se}, ^{77}\text{Se})$ may be either positive or negative. The results are stimulating to studying the other selenium-element coupling constants by calculation, in particular $J(^{77}\text{Se}, ^{13}\text{C})$, for which a large experimental data set is available <1995MI1>, and which appear to be of considerable theoretical interest.

The chemical shifts for $^{77}\text{Se}\{^1\text{H}\}\text{NMR}$ were observed at 363.6 ppm for **40a**, 419.3 ppm for **40b**, and 272.2 ppm for **40c** to show selenide bonding, Ph-Se-CH- ; whereas, those of selenenyl sulfide bonding, Ph-Se-S-CH- , appeared at 497.3 ppm for **41a**, 490.0 ppm for **41b**, and 408.1 ppm for **41c**, respectively <1997TL5821>.

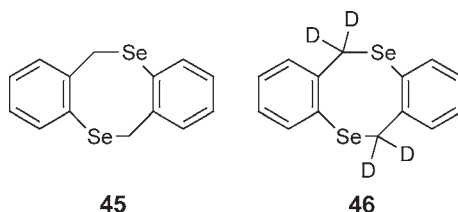


The assignment of the ^{77}Se NMR chemical shifts for individual eight-membered selenium sulfide heterocycles **42–44** is based on the coupling information from the spectra of ^{77}Se -enriched samples. The ^{77}Se resonances can be divided into three groups depending on the chemical nature of its nearest neighbors to the active selenium nucleus. The resonances of the selenium atoms with two sulfur neighbors appear above 690 ppm, the selenium atoms with one sulfur and one selenium neighbor show a chemical shift in the region 690–620 ppm, and the chemical shifts of the selenium atoms with two selenium neighbors lie below 620 ppm. The presence of sulfur and selenium atoms in other positions relative to the active nucleus also influences the shielding and thus the chemical shift (see Chapters **13.15** and **13.17**) <1998ACS1188>.



The ^{77}Se NMR spectra of selenacrown ethers **33–36** were recorded and compared. Signals were shifted downfield with increasing ring size ^{77}Se NMR (ppm): **33**, 336.5; **34**, 350.1; **35**, 353.7; and **36**, 354.9 <2003OL1443, 2005JOC5036>.

The replacement of hydrogen atoms with deuterium caused large deuterium-induced isotope shifts in the ^{77}Se NMR. For both conformers **45** and **46**, the resonance of the deuterated compound shifted upfield with respect to the parent compound. The isotope shift ($\Delta\delta$, an upfield shift) was 4.22 ppm for **45** and 4.03 ppm for **46**. These values were definitely larger than that observed for **46** ($\Delta\delta = 3.78$ ppm). These differences, $\Delta\Delta\delta = +0.44$ ppm for **45** and $+0.25$ ppm for **46**, can be considered as the isotope shifts due to the $\text{C-H} \cdots \text{Se}$ nonbonded interaction <1996BCJ1825>.

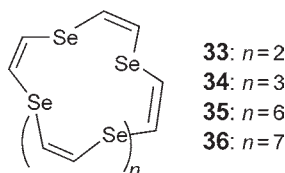


14.16.3.3 Mass Spectra

Size distribution of positive and negative tellurium clusters in the size range from 2 to 56 atoms was investigated by secondary-ion mass spectrometry (SIMS). Cluster ions were produced by the 12 keV Xe^+ ion bombardment of a sample tellurium sheet and were mass-analyzed using sector-type double-focusing mass spectrometers. It was found that a discontinuous variation of cluster-ion intensity appeared at specific numbers of n . These numbers were 5, 8, 12, 15, 19, and 23 for positive clusters and 6, 10, 13, and 16 for negative clusters. The dissociation pattern was also investigated by an acceleration voltage scanning method. It was found that Te_2 , Te_5 , and Te_6 fragmentation events often occurred. Observation of specific fragmentation patterns suggested the existence of nonsequential fragment channels [<1996MI577>](#).

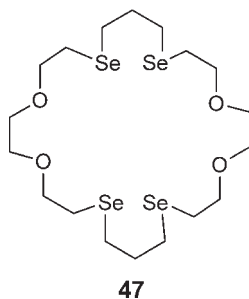
14.16.3.4 Ultraviolet Spectra

The ultraviolet (UV) spectra of unsaturated selenacrown ethers have been studied in detail by Kamigata and co-workers, and a comparison has been made between the calculated and observed transitions. The UV spectrum of **33** showed an absorption maximum at 260 nm in dichloromethane. Compounds **34–36** also showed absorption maximums in the similar region. The extinction coefficients increased with increasing ring size. The absorption maximums were also found to shift to longer wavelengths with decreasing solvent polarity indicating that the absorptions are assigned to $n \rightarrow \pi^*$ transitions [<2003OL1443, 2005JOC5036>](#).



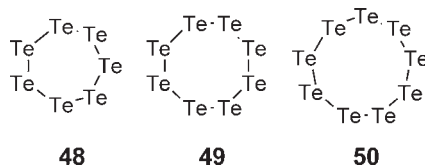
14.16.3.5 Titration Calorimetry

The thermodynamic parameters and relative cation selectivity of some alkali and heavy metal cations with 1,5,14,18-tetraselena-8,11,21,24-tetracyclohexacosane **47** (selena-26-crown-8) were investigated for the first time by titration calorimetry in water–MeCN (1:24 v/v) at 25 °C to show the contrasting complexation behavior between Ag^+ and alkali Tl^+ and a very high Ag^+ selectivity, originating from the exclusive contribution of the enthalpy term probably owing to the partially covalent interaction between Ag^+ and Se-donor [<1999JCM284>](#).



14.16.3.6 Photoelectron Spectroscopy

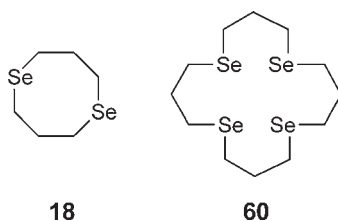
Isolated tellurium clusters **48–50** (Te_n : $n = 7–9$) were produced in a supersonic molecular beam and their vacuum–UV–photoelectron spectra were recorded at a photon energy of $h\nu = 8.3 \text{ eV}$ by a photoionization–photoelectron–photoion triple coincidence method. The trimer and tetramer were obtained as stable species in the tellurium cluster beam, unlike sulfur and selenium. The spectra of the odd-membered tellurium clusters have a tendency to be split and broadened, in contrast to those of the seven-membered clusters. For the clusters with $n > 5$, the spectra of tellurium clusters are similar to those of selenium counterparts, which may suggest a resemblance to the geometric structures between small tellurium and selenium clusters (see Chapters **14.09** and **14.10**) <2002MI337>. A similar study has been conducted by Curtiss and co-workers on selenium clusters <1998CPL(287)282>.



14.16.3.7 Oxidation Potentials and Cyclic Voltammetry

Electrochemistry of unsaturated selenacrown ethers has been described and compared in detail by Kamigata and co-workers. The unsaturated selenacrown ethers **33–36** showed irreversible cyclic voltammograms. The potential was scanned at 100 mV s^{-1} versus Fc/Fc^+ toward the cathodic direction and back again. Single oxidation peaks were observed at $+0.752$ **33**, $+0.743$ **34**, $+0.736$ **35**, and $+0.729$ **36**, indicating that the large unsaturated selenacrown ethers are more easily oxidized than the smaller ones, perhaps due to the delocalization effect of the resulting cation <2003OL1443, 2005JOC5036>.

Selenium coronands 8Se_2 **18** and 16Se_4 **60** were electrochemically oxidized at carbon electrodes. Cyclic voltammograms of 8Se_2 in MeCN–TEAP were found to be quasi-reversible (TEAP = tetraethylammonium perchlorate). Following the oxidation of 8Se_2 to form a radical cation, either a second electron is removed to form a diradical cation with subsequent formation of a transannular bond or, alternatively, the radical cation undergoes transannular stabilization prior to losing a second electron. Under the fast scan rate regime, two oxidation peaks were observed due to the one-electron transfer steps. A cyclic voltammetric study showed that the redox chemistry of 16Se_4 in MeCN–TEAP was slightly different from that of 8Se_2 . Each oxidation peak corresponded to a one-electron transfer. The radical cation formed rapidly underwent transannular stabilization and a new selenium–selenium bond is formed <1996CJC533, 2000CJC598>.



14.16.3.8 Raman Spectrometry

Raman spectra of sulfur, selenium, and tellurium clusters confined in the large zeolite A cavities with diameters of $\sim 1.4 \text{ nm}$ have been studied by Poborchii. It was shown that sulfur is stabilized in the form of S_8 rings. Selenium was stabilized in the form of Se_{12} and Se_8 rings. Se_{12} rings showed dominant bands in the Raman spectra but they were less stable than Se_8 rings under laser illumination with a wavelength of 514.5 nm . Tellurium was stabilized in the form of Te_8 rings. Low-frequency strong and broad bands at ~ 40 and 29 cm^{-1} observed in the spectra of zeolite A with sulfur and with selenium, respectively, were attributed to fibrations of the ring molecules with the zeolite cavities <1998MI347, 1997MI1660, 1998MI513>.

The S_xSe_y clusters have been crystallized by vacuum distillation. The Raman scattering was measured from samples deposited along the region of the temperature gradient. The results showed a systematic shift of the spectral peaks along the gradient indicating that the S_xSe_{8-x} with the larger values of x crystallized at lower temperatures. The crystal is in a rhombic structure which was not reported in the literature. These compounds are not stable in solution and are difficult to separate into single phases in solid form <1996MI12>.

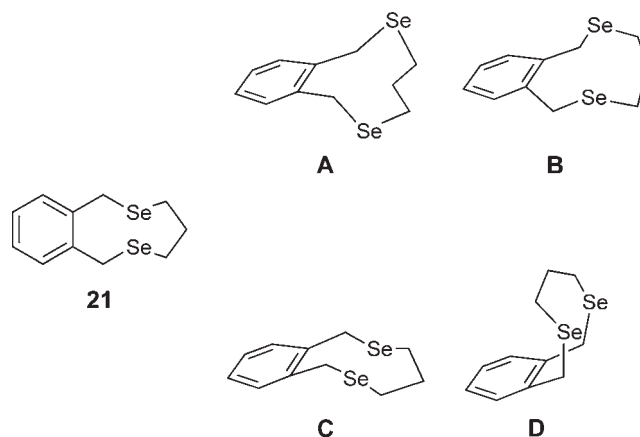
Electron–phonon coupling in Se-species confined in the nanoporous matrix has been investigated by using Raman spectra performed with different laser lines from deep blue to near infrared. The spectra strongly depended on the energy of the excitation laser lines. The one-phonon symmetric A1 modes for Se single helix and Se_8 rings are enhanced in the vicinity of their absorption bands. Detailed analysis showed that the Raman band in the high-frequency range of $450\text{--}550\text{ cm}^{-1}$ is composed of three individual second-order Raman bands for the confined Se-species. These two-phonon Raman shifts occurred at twice the frequency shift of the first-order Raman lines and their intensities were also enhanced when the excitation laser energy matches an electronic transition in Se-nanospecies <2005MI071902>.

14.16.4 Thermodynamic Aspects

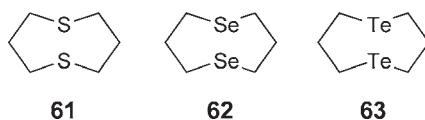
14.16.4.1 Conformational Aspects

The structures of the seven ring systems could be investigated in the solid state. These investigations revealed that the molecular structures are determined by the rigid $SeC\equiv CSe$ units, which try to adopt torsion angles of the $CH_2\text{--}Se$ σ -bonds between 60° and 90° . In the solid state, the systems **5**(3.3) and **5**(5.5) showed columnar structures that can be traced back to close contacts between Se-atoms of neighboring rings <2002JOC4290>.

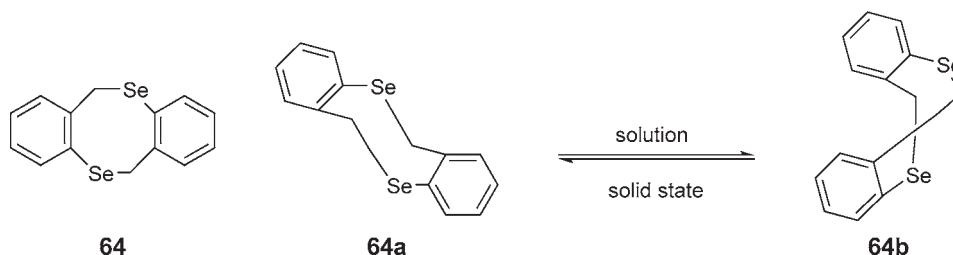
The conformational behavior of 5,8,9,11-tetrahydro-7H-6,10-diselena-benzocyclononene **21** in solution has been explored by multinuclear NMR, and the ground-state conformation in solution was deduced to be the same as that of the sulfur analogue. It is evident that the ground-state conformation is **A** and it is predisposed toward bridging coordination. There are reasonably low energy alternatives, which could chelate to a single metal (**C** and **D**). Conformer **C** has an energy ca. $5\text{ kJ}\cdot\text{mol}^{-1}$ above the ground state and appears well suited for chelation to give a monomeric complex. Possible monomeric and polymeric complex structures were both successfully modeled by coupling conformers **A** and **C** <1999JCD1077>.



Energy-minimum structures of 1,5-dithiacyclooctane **61**, 1,5-diselenacyclooctane **62**, and 1,5-ditelluracyclooctane **63** were calculated by the *ab initio* molecular orbital method. Nine energy-minimum structures were obtained for each compound. A twist-boat-chair structure is the most stable for **61** and **62**, whereas a boat-boat structure is the most stable for **62** <1999HAC159>.



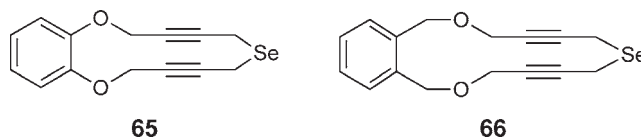
There are two conformers for **64** in which only the chair conformer **64a** exists in the solid state, whereas the boat is preferred in solution. The ratio of **64a** and **64b** on CDCl_3 at -22°C is 83:17 according to ^1H NMR integration. This ratio remains unchanged within experimental error upon deuteration of four benzylic protons of **64**: the ratio of **64a-*d*₄** and **64b-*d*₄** is 85:15 under the same conditions. This implies that replacement of the hydrogen atoms with deuterium at the benzylic carbons does not cause significant conformational changes in either conformer <1996BCJ1825>.



Raithby and co-workers have published in 1997 an excellent in-depth article dealing with conformational analysis of 14- and 16-membered unsaturated oxa, thia, and seleno macrocyclic ligands. Crystallographic results retrieved from the Cambridge Structural Database (CSD) have been used to perform systematic conformational analyses of the free and metal-coordinated ligands 1,4,8,11-tetraselenacyclotetradecane, 1,5,9,13-tetraselenacyclohexadecane, and their derivatives. Conformational classifications, established using symmetry-modified Jarvis–Patrick cluster analysis, have been displayed in torsional space by principal components analysis (PCA) plots. Relative molecular mechanics energies of free macrocycles in the observed conformations were compared with the cluster populations and the effect of metal coordination investigated <1997STC385>.

14.16.4.2 Chromatography

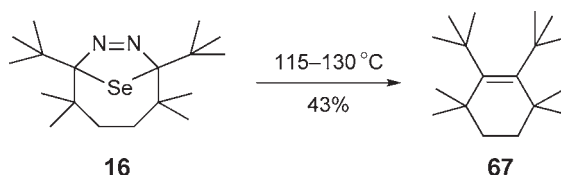
Saturated macrocycles **25**, **29**, **32**, and **60** were always purified by flash chromatography using hexane/ethyl acetate (1/1), as eluent <2000IC2558>. Dichloromethane <2000JOC1799> or pentane <2002HCA351> were used to purify the smaller ring, like **16**, and benzene for selenacrown ethers **47** <2000CCL66>. Three percent of triethylamine v/v was used in a mixture of hexane/toluene (3/1) to purify cyclic tetraselenydiynes **30** and **31** <2002JOC4290, 2002OL339>. Pure hexane was used in the purification of the 13- and 15-membered selenium–alkyne-containing ring **65** and **66** <2002EJO3198>.



14.16.5 Reactions

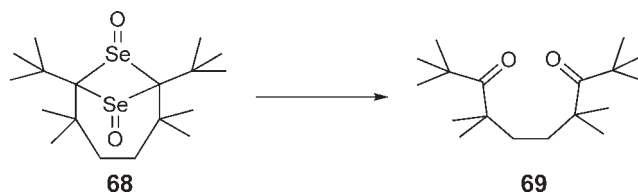
14.16.5.1 Elimination of the Heteroatom to Form a Nonaromatic Species

The selenadiazoline **16** is thermally stable up to 105°C , its melting point in the dark. Thermolysis of **16** without a solvent at $115\text{--}130^\circ\text{C}$ or in refluxing 1,3-dimethyl-2-imidazolidinone (DMI) gave the desired cyclohexene **67** in 43% and 7% yield, respectively, as colorless crystals (Scheme 1) <2002HAC351>.



Scheme 1

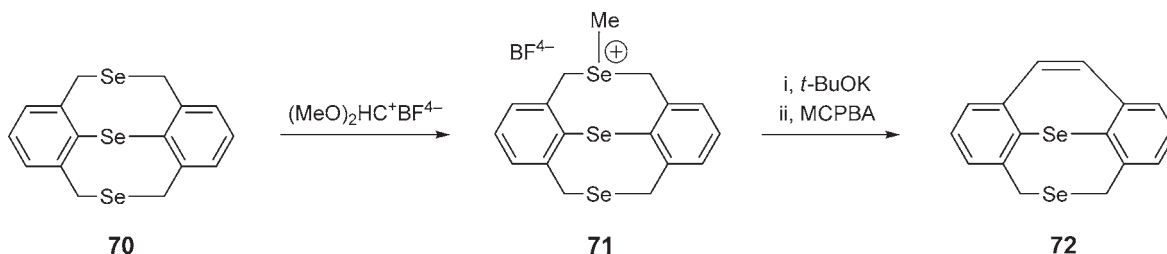
Thermolysis or photolysis of **68** resulted in the formation of mainly the 1,6-diketone **69** and elemental selenium; only a trace of **68** was detected by ^1H NMR spectroscopy in the photolysis (Scheme 2) <2000JOC1799>.



Scheme 2

14.16.5.2 Elimination of the Heteroatom in Heterocyclophanes

Benzylic selenonium salt **71** of 1,11-methanoselenenomethano-5*H*,7*H*-dibenzo[*b,g*][1,5]diselenocine **70** was treated with *tert*-BuOK to give the corresponding Stevens-type rearrangement product, which was converted into a new heterocycle, 1,11-etheno-5*H*,7*H*-dibenzo[*b,g*][1,5]diselenocine (Scheme 3), **72** upon treatment with *m*-chloroperbenzoic acid (MCPBA) <1995H(41)1127>.



Scheme 3

14.16.5.3 Oxidation of the Heteroatom

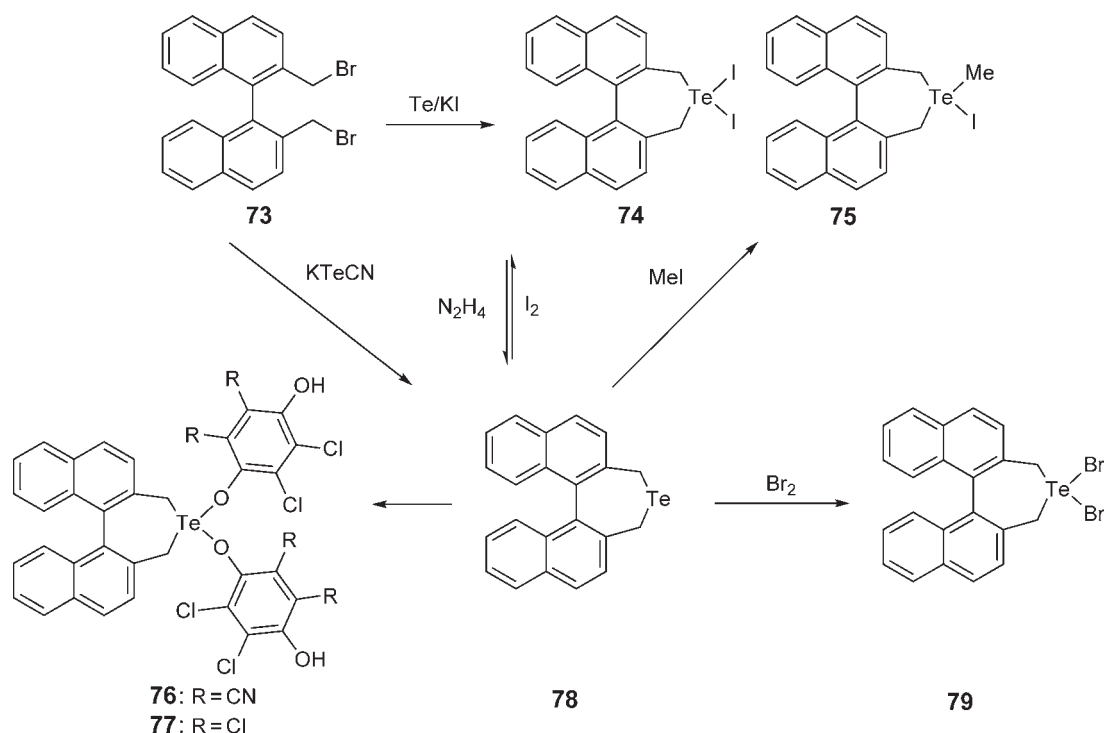
Treatment of the binaphthyl **73** with KTeCN gave **78**, which is quite stable at room temperature and soluble in common organic solvents. Treatment of **78** with iodomethane gave the corresponding tellurepinium iodide **75**. Compound **78** was also prepared by reducing its diiodo **74** with hydrazine which in turn can be prepared directly from the treatment of **73** with tellurium powder and potassium iodide using 2-methoxyethanol, as solvent. Treatment of **78** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and 2,3,5,6-tetrachloro-1,4-benzoquinone (TCQ) did not afford the expected 1:1 charge-transfer complexes, but rather the oxygenated products **76** and **77** were obtained. **78** was also reacted with bromine to afford the 1,1-dibromo derivative **79** (Scheme 4) <2004JOM(689)2377, 1996RTC427>. A similar oxidation behavior was studied by Furukawa and co-workers on a tellurium-and-sulfur eight-membered ring system <1996OM1913>.

The first synthesis of (*R*)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]selenepin oxide **81** has been described by Procter and Rayner via the oxidation of the novel C_2 -symmetrical selenide **80** with MCPBA <2000SC2975>. In comparison, conversion of the 1,3-diselenetane **82** to the diselenoxide **68** was performed in a high yield by oxidation with dimethyldioxirane <2000JOC1799>.

Chloroselenepine **84** was obtained from ketone **83** by reduction of a Grignard reagent, followed by chlorination with *N*-chlorosuccinimide in good yields <2001HAC317>.

Thiophenol (6 equiv) reacted with hexachlorotritellurane **26** in the presence of triethylamine in dimethyl sulfoxide (DMSO) under an Ar atmosphere at 50 °C for 10 min to give the disulfide as the oxidation product and neutral tritellurane **85** as the reduction product. Thus, the tritellurane can act as an oxidant <1996OM5112>.

The two-electron oxidation of 1,5-diselenacyclooctane **86** or 1,5-ditelluracyclooctane **87** with 2 equiv of NOBF_4 gave the diselenide dication salt, 1,5-diselenoniabicyclo[3.3.0]octane bis(tetrafluoroborate) **88** or the ditelluride dication salt **89**, respectively (Scheme 5: see Chapter 10.01) <1992PS131>.



Scheme 4

14.16.5.4 Complexation with Heavy Metals

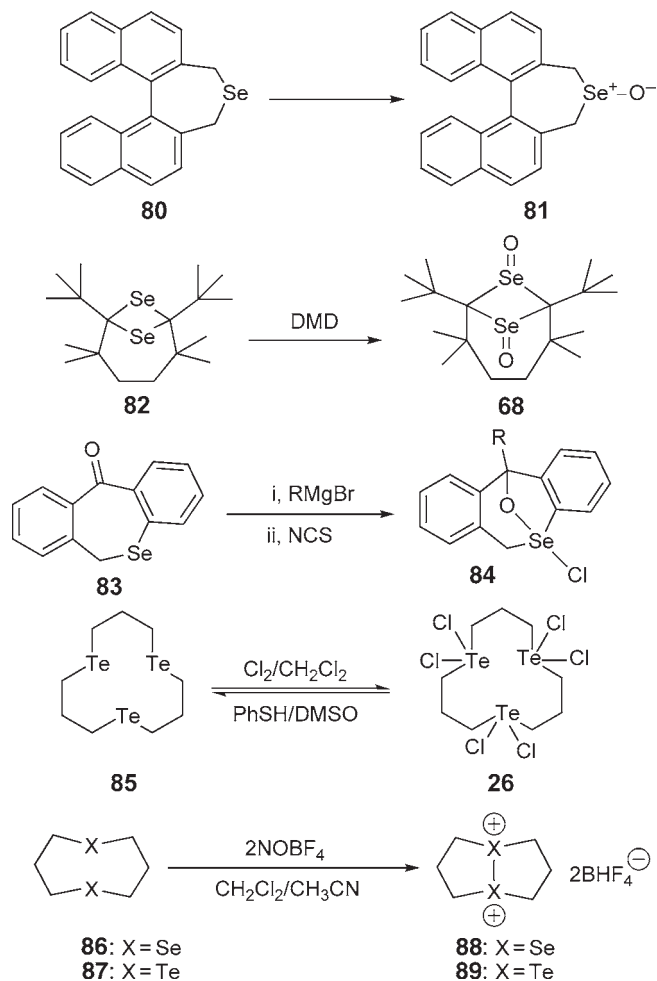
In CHEC-II(1996), only very few metal complexes involving large ring heterocycles were reported. In the last decade, new information and studies have been conducted on selenium- and tellurium-containing large rings, especially crown ethers capitalizing on their very special features and characteristics.

Numerous complexes of $[18]\text{aneO}_4\text{Te}_2$ (L) in which the ligand behaves only as a Te_2 donor have been synthesized, including *cis*- $[\text{MX}_2\text{L}]$ ($\text{M} = \text{Pd}$ or Pt ; $\text{X} = \text{Cl}$ or Br), $[\text{RhCl}_2\text{L}_2]\text{Y}$ ($\text{Y} = \text{Cl}$ or PF_6), $[\text{CuL}_2]\text{BF}_4$, $[\text{AgL}_2]\text{BF}_4$, and $[\text{Cu}_2\text{L}][\text{BF}_4]_2$. The complexes have been characterized by microanalysis, multinuclear NMR spectroscopy (^1H , $^{125}\text{Te}\{^1\text{H}\}$, ^{195}Pt , ^{63}Cu), electrospray ionization (ESI) mass spectrometry, UV/visible and infrared (IR) spectroscopy, as appropriate. Two complexes of $[9]\text{aneO}_2\text{Te}$, *cis*- $[\text{MCl}_2\{[9]\text{aneO}_2\text{Te}\}_2]$ ($\text{M} = \text{Pd}$ or Pt) were also reported, together with the selenoether complex $[\text{PtCl}_2\{[18]\text{aneO}_4\text{Se}_2\}]$. The X-ray structures of $[\text{MCl}_2\{[18]\text{aneO}_4\text{Te}_2\}]$ ($\text{M} = \text{Pt}$ or Pd) and $[\text{PtCl}_2\{[18]\text{aneO}_4\text{Se}_2\}]$ all reveal *cis*-square planar coordination with no interaction between the metal (Pt or Pd) and the ether oxygens. Dropwise addition of a dilute MeCN solution of $[\text{PtX}_2(\text{MeCN})_2]$ ($\text{X} = \text{Cl}$ or Br) or $[\text{PdX}_2(\text{MeCN})_2]$ to a refluxing solution of $[18]\text{aneO}_4\text{Te}_2$ in $\text{CH}_2\text{Cl}_2/\text{MeCN}$ formed yellow solutions, which gave complexes possessing an $[\text{MX}_2\{[18]\text{aneO}_4\text{Te}_2\}]$ stoichiometry <2003JCD2852>.

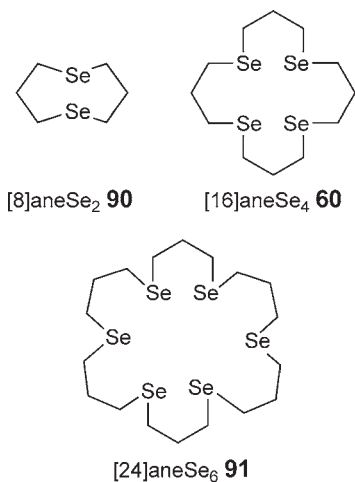
Treatment of SbX_3 ($\text{X} = \text{Cl}$, Br , or, in some cases, I) with 1 molar equiv of L ($\text{L} = \text{MeS}(\text{CH}_2)_2\text{SMe}$, $\text{MeS}(\text{CH}_2)_3\text{SMe}$, $\text{MeSe}(\text{CH}_2)_2\text{SeMe}$, $\text{MeC}(\text{CH}_2\text{SMe})_3$, $\text{MeC}(\text{CH}_2\text{SeMe})_3$, $[12]\text{aneS}_4$ (1,4,7,10-tetrathiacyclododecane), $[14]\text{aneS}_4$ (1,4,8,11-tetrathiacyclotetradecane), $[16]\text{aneS}_4$ (1,5,9,13-tetrathiacyclohexadecane), $[8]\text{aneSe}_2$ (1,5-diselenacyclooctane), or $[16]\text{aneSe}_4$ **60** (1,5,9,13-tetraselenacyclohexadecane)) in anhydrous CH_2Cl_2 , MeCN, or tetrahydrofuran (THF) solution generated colorless to red-orange powdered solids involving a 1:1 Sb:L ratio in most cases, and occasionally a 2:1 Sb:L ratio <2001JCD1621>.

Treatment of BiX_3 ($\text{X} = \text{Cl}$ or Br) with $[8]\text{aneSe}_2$ **90** (1,5-diselenacyclooctane), $[16]\text{aneSe}_4$ **60** (1,5,9,13-tetraselenacyclohexadecane), and $[24]\text{aneSe}_6$ **91** (1,5,9,13,17,21-hexaselenacyclotetracosane) gave in moderate to high yield as intensely colored powdered solids, possessing a $[\text{BiX}_3(\text{L})]$ formula (where L is **90**, **60**, or **91**). The crystal structures of $[\text{BiCl}_3\{[8]\text{aneSe}_2\}]$ and $[\text{BiBr}_3\{[16]\text{aneSe}_4\}]$ each revealed infinite one-dimensional ladder structures derived from almost planar Bi_2X_6 dimer units linked by μ -bridging cyclic selenoethers. Each Bi is coordinated to a Se_2X_4 donor set, with the Se-donor atoms occupying mutually *trans*-coordination sites. The selenoether ligands

adopted exocyclic arrangements and, in $[\text{BiBr}_3 \cdot ([16]\text{aneSe}_4)]$, it is two *trans* Se-atoms which coordinated with Bi(III), leaving the other two Se-atoms noncoordinating. The structures of these species are contrasted with related complexes involving acyclic selenoether ligands and with the few structurally characterized bismuth(III) halide complexes with macrocyclic thioether ligands <2000JCD2163>.

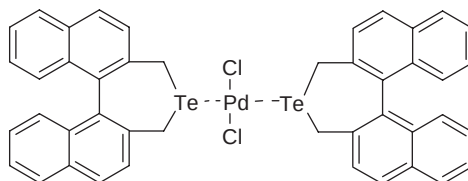


Scheme 5



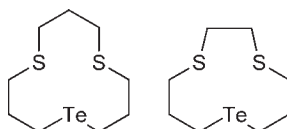
The [16]aneSe₄ **60**, when treated with SnX₄ (X = Cl or Br), afforded [SnX₄([16]aneSe₄)], while reaction of [8]aneSe₂ **90** gave [SnCl₄([8]aneSe₂)]. These species represent the first examples of Sn(IV) halide adducts with neutral group 16 ligands, which adopt polymeric structures. The complexes are all chain polymers, although there is unexpected structural dependence upon the macrocycle ring size, giving each a distinct structural form <2003NJC1784>. Similar selenoether ligands have been investigated for the complexation with arsenic <2002IC2070>, nickel <1998JCD2185>, copper <2000CJC598>, iridium <1996JCD3713>, ruthenium <1993CC1716, 1997JCD3719>, chromium <1997POL4253>, palladium <1995IC651, 1995POL2753, 1996IC3667>, and platinum <1995IC651, 1995POL2753>.

Reaction of **78** with [PdCl₂(CNPh)₂], which was performed in dry toluene in 1:2 molar ratio, gave an orange mononuclear palladium(II) complex **92** <2004JOM(689)2377>.

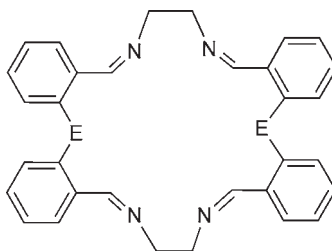
**92**

Cyclic di- and tetraselenoetheral ligands were synthesized in order to prepare transition metal carbonyl complexes and hence study their spectroscopic and structural properties. Crystal structures with Mn(CO)₄ were obtained in refluxing toluene and analyzed, although these species decompose rapidly in coordinating solvents <1999JCD1077>. A similar study has been conducted on the same nine-membered ring system but different cations, such as silver, copper, or gold, were used for complexation <1997JCD3493>. The homologous [MCl₃(1,5-diselenacyclooctane)] (M = As, Sb, Bi) ladder structures formed from planar M₂Cl₆ units linked by selenoetheral ligands with *trans* Se-atoms reveal unexpected structural patterns <2004JCD980>.

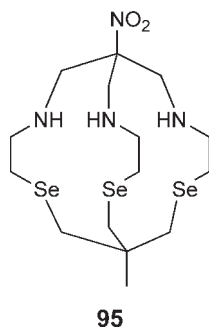
The ligating properties of the new dithiatellura macrocycles **23** and **24** have been investigated with a variety of transition metal species giving *fac*-[Mn(CO)₃(L)]CF₃SO₃, *cis*-[MCl₂(L)] (M = Pd or Pt), [Rh(Cp*)(L)]-(PF₆)₂, [Cu(L)]BF₄, and [Ag(L)]CF₃SO₃. Where possible, the mode of coordination has been established by spectroscopic methods; ring-size effects were established and the data were compared with other complexes incorporating related cyclic and acyclic ligands <2003JCD2434>.

**23****24**

Interaction of the 22-membered selenaza macrocycle **93** with Pt(II) led to the formation of the novel cationic Pt(IV) metallamacrocyclic complex via an oxidative addition of a C–Se bond to Pt(II), whereas the corresponding reactions of **94** with Pd(II) afforded cationic complexes with differing ligating properties <2004CC322, 2000CC143>. Complexation of **93** and **94** with nickel(II) <2004JOM(689)1452> and mercury(II) has also been described <1996JCD1203, 2000CCR49>.

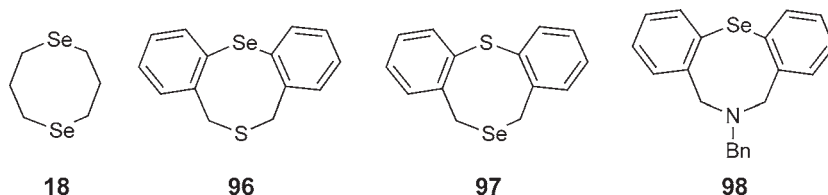
**93**: E = Se**94**: E = Te

One of a new series of complexes of mixed selenium–nitrogen donor atom cage ligands has been presented by Jackson and co-workers <1996CC143>. The cobalt complex of the nitro-capped cage with an N₃Se₃ **95** donor set was prepared using nitromethane, formaldehyde, and an opened starting selenium-containing ligand already complexed by trichlorocobalt.



14.16.5.5 Other Reactions

Kataoka *et al.* described the utility of some chalcogenides, as catalyst, in the Baylis-Hillman reaction. A wide range of studies were actually published or on-going on this type of reaction. Reaction time was the most important parameter till the asymmetry appeared. Thus, chalcogenide catalysts were examined in the presence of a Lewis acid, which gave good results with eight-membered selenium-containing heterocycles, such as [1,5]diselenocane **18** and its benzo-fused sulfur or nitrogen derivatives **96–98** (see Chapter 14.07) <1998T11813, 1998CC197>.



Takaguchi *et al.* have reported that vicinal dibromoalkanes **99** are debrominated to alkenes **101** by treatment with 1,5-dichalcogenacyclooctane **18** under neutral conditions induced by transannular interaction. This is the first example of dehalogenation by using an organoselenium compound <1998J(P1)3147>. The reactivity of the tellurathia dication salt **102** was examined. Treatment of 2 equiv of benzenethiol with dication **102** in MeCN under argon at room temperature afforded the diphenyl disulfide **104**, as the oxidation product, and the tellurathiacin **103**, as the reduction product (see Chapter 10.01) <1996OM1913>. RCpCoL_2 complexes ($\text{L}_2 = (\text{CO})_2$ or cyclooctadiene (COD); $\text{R} = \text{H}$, CO_2Me , trimethylsilyl (TMS)) **105** were reacted with various alkynes **106** substituted with chalcogen atoms adjacent to the triple bonds. These reactions yielded hetero-substituted CpCo-capped cyclobutadienes **107** and superphanes that were dependent on the ring size of the corresponding cyclic diene used as starting material (Scheme 6). Reactions in cyclooctane afforded not only the CpCo-capped cyclobutandieno superphanes, but also mixed cyclobutadieno and cyclopentadiene superphanes <2004JOM(689)3132>.

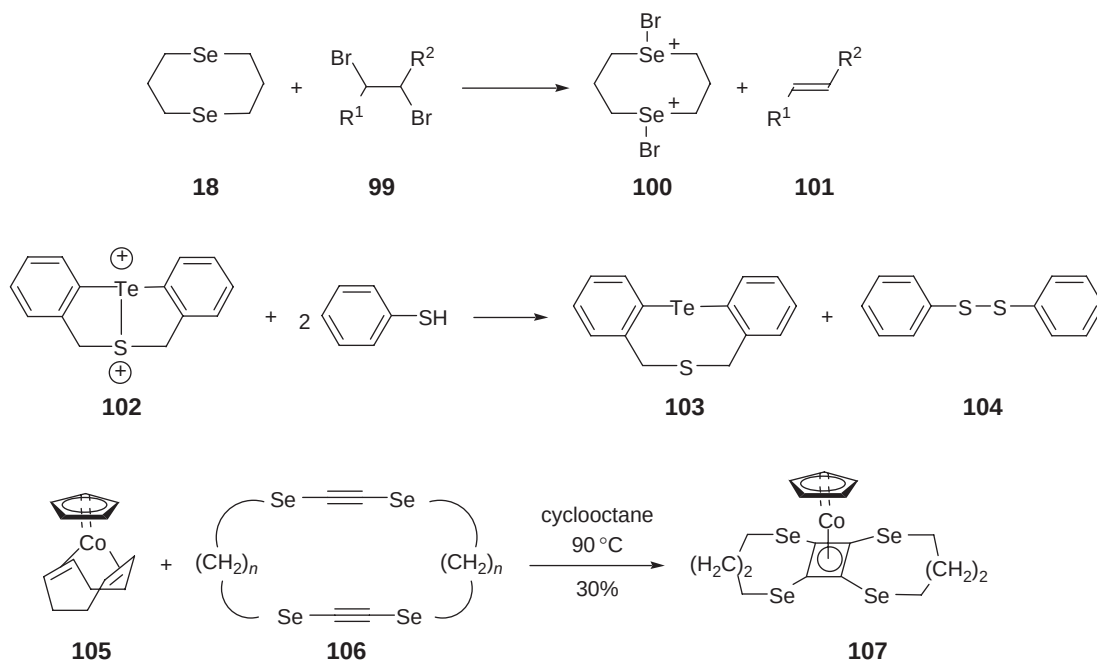
14.16.6 Synthesis

Selenium and tellurium can be introduced into organic compounds as the element, as a reduced ($-\text{Se}^{2-}$) species, or as an oxidized (SeO_2) species. Use of the reduced form is by far the most common and will be discussed first. Unlike in CHEC-II(1996), sodium selenide or telluride can be synthesized, used, and handled quite easily. Air and moisture should be, of course, avoided but these conditions are not the hardest to take care of.

In forming the ring, the C–Se–C bond can be premade and thus not be involved in the ring-closure step. More commonly, the C–Se–C bonds are formed during the ring-closure step. The latter is considered first.

14.16.6.1 Synthesis of Rings in which Formation of a C–X Bond is the Ring-Closure Step

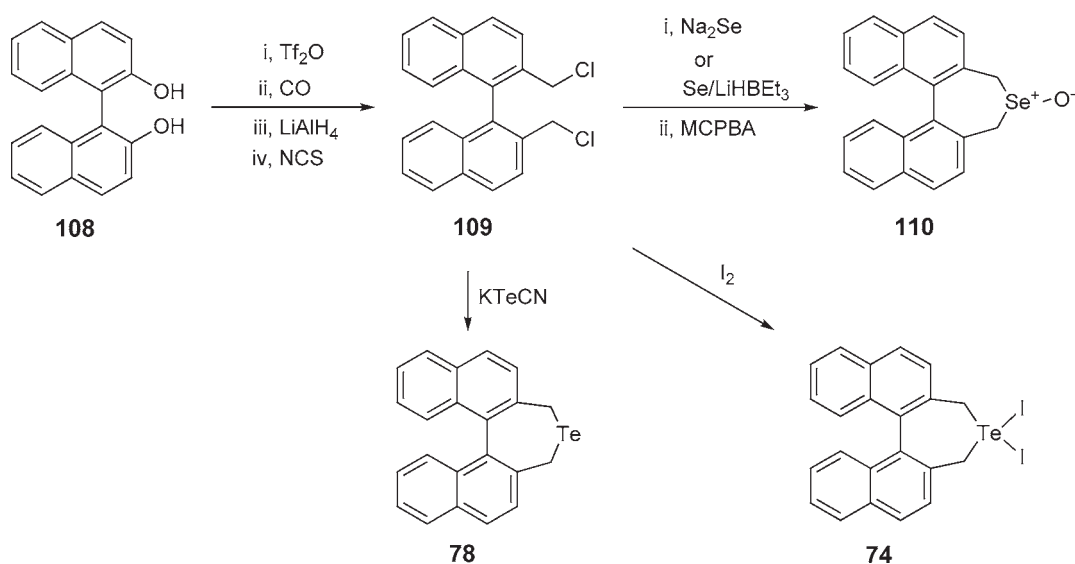
In recent years, binaphthyl-containing compounds have been used extensively as the chiral auxiliaries and enantio-merically pure ligands in asymmetric syntheses. A limited number of heterocyclic derivatives are now beginning to appear and are being investigated as new reagents in a variety of asymmetric processes.



Scheme 6

The first synthesis of (*R*)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]selenepin oxide **110** has been achieved from (*R*)-(+)-1,1'-bi-2-naphthol, which in turn was obtained by resolution of *rac*-1,1'-bi-2-naphthol. Palladium-catalyzed alkoxy carbonylation of the alcohol **108** gave a dimethyl ester which was then reduced by LiAlH₄, and the resultant diol converted to key intermediate chloride **109**. Cyclization with sodium selenide gave a novel enantiomerically pure selenide, which upon oxidation yielded the desired selenoxide **110** <2000SC2975>.

Synthesis of the racemic cyclic telluride (2,7-dihydro-1*H*-dinaphtho[*c,e*]tellurepin **78**), possessing a *C*₂ axis, was based on the reaction of 2,2'-bis(chloromethyl)-1,10-binaphthalene **109** with potassium tellurocyanate in dry DMSO. Reaction of **109** with iodine gave the diiodo derivative (**Scheme 7**) <2004JOM(689)2377, 1996RTC427>.



Scheme 7

Dibenzo[*b,f*]tellurepane **112** has been obtained by reacting the dilithiated **111** with TeI₂ in CHCl₃ in a moderate 32% yield (**Scheme 8**) <1992CHC115>.



Chemical reaction scheme showing the synthesis of various seleno- and telluro-derivatives from compound **113**.

Starting material **113** (a substituted cyclohexane derivative) reacts with reagents **i, HBr** and **ii, NaSSO₂Me** to form intermediate **116**.

Intermediate **116** can be converted to **115** using **NaHSe** or **WSe₄²⁻**.

Intermediate **116** can be converted to **117** using **Na₂Se**.

Intermediate **116** can be converted to **118** using **NaHTe**.

Intermediate **116** can be converted to **119** using **NaHTe**.

Intermediate **116** can be converted to **120** using **Na₂Se**.

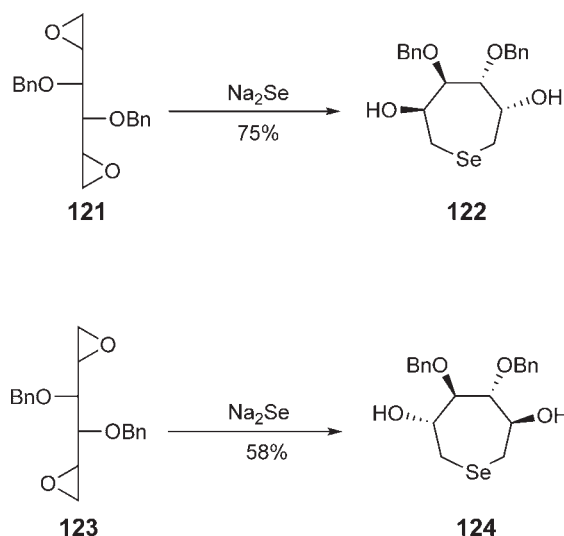
Intermediate **116** can be converted to **114** using **Na₂Se₂**.

Scheme 9

Based on this unfortunate result, **119** was envisioned a synthesis of the elusive 1,6-epitelluro **119**. Thus, the above sequence was repeated but with sodium ditelluride as the reagent; the only product formed was that from a simple base-induced elimination, the alkene **118** [<2005AJC188>](#). A very similar study has been published by an Indian

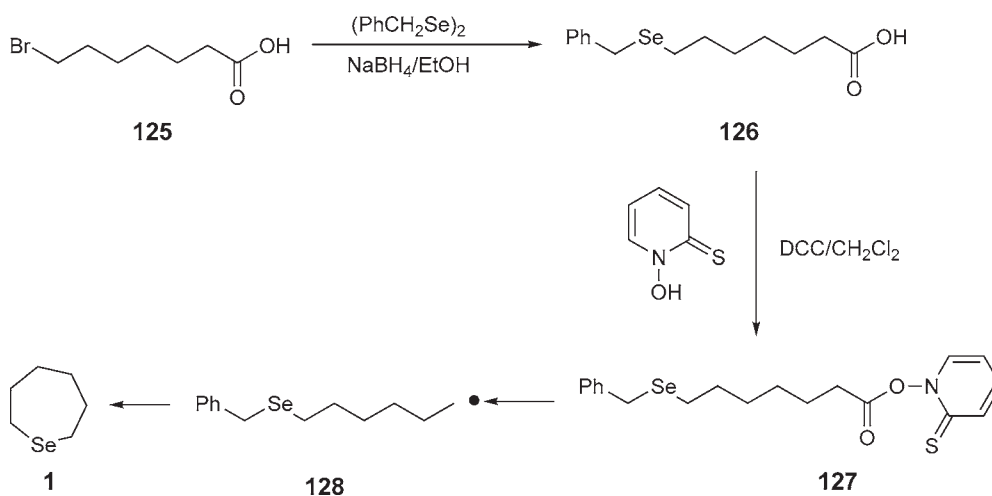
team on the use of tetraselenotungstate; the reaction of WSe_4^{2-} with **116** led to the formation of **115** in 94% yield (see Chapter 13.03) <2005PAC145>.

The selenide anion can be used in the heterocyclization of polyhydroxylated selenopane **122** and **124** starting from 1,2:5,6-dianhydro-3,4-*O*-methylidene-L-iditol **121** or from D-mannitol **123** in variable yield (Scheme 10). A general, known method is to combine an acylation for purification and deacetylation by methanolysis but Le Merrer *et al.* simplified this procedure to obtain directly the crystalline selenopane after flash chromatography. Deprotection of these seleno compounds gave an inextractable mixture <1997T16731>.



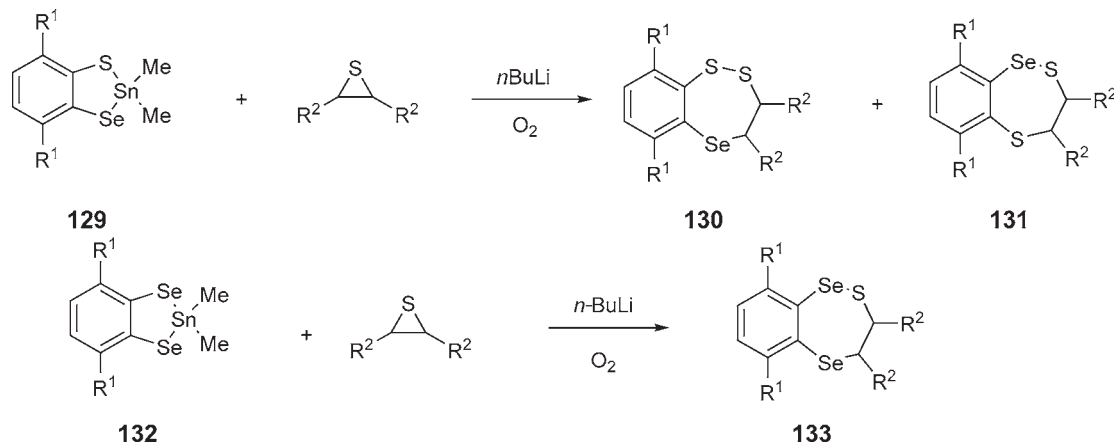
Scheme 10

In an attempt to prepare selenopane **1**, 7-(benzylseleno)heptanoic acid **126** was converted to the corresponding yellow thiohydroxamic ester **127** in the usual way (Scheme 11). In an NMR experiment, the thiohydroxamic ester **127** was irradiated and converted into selenopane in ca. 50% yield. When the preparation of selenopane **1** was repeated on a preparative scale, extensive formation of a white precipitate was observed. Attempted isolation of 1,1-dibromoselenopane yielded no product. Selenopane is known to polymerize readily <1993TL2557>.



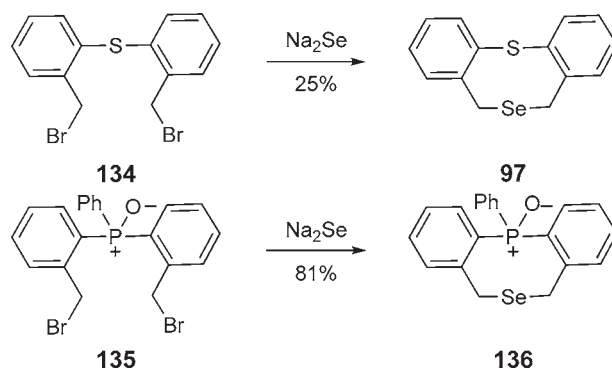
Scheme 11

Sato *et al.* described three types of 1,2,5-benzotrichalcogenepins (**130**, **131**, and **133**) containing sulfur and selenium prepared by the reaction of the corresponding 2,2-dimethyl-1,3,2-benzodichalcogenastannoles **129** with thiiranes using *n*-butyllithium in an oxygen atmosphere (Scheme 12; see Chapter 13.15) <1997TL5821>.



Scheme 12

The chalcogenide **97**, 10*H*,12*H*-dibenzo[*c,f*][1,5]selenathiocin, has been synthesized by the reaction between bis(2-bromomethylphenyl)sulfide **134** and sodium selenide in a mixture of THF and ethanol at 0°C for 17 h in rather poor yield (25%) <1998T11813>. A new phosphorus–selenium eight-membered heterocycle **136** has been synthesized from the bis-bromide **135** by treatment with sodium selenide in ethanol at room temperature in 81% yield (Scheme 13) <1995H(41)2647>.

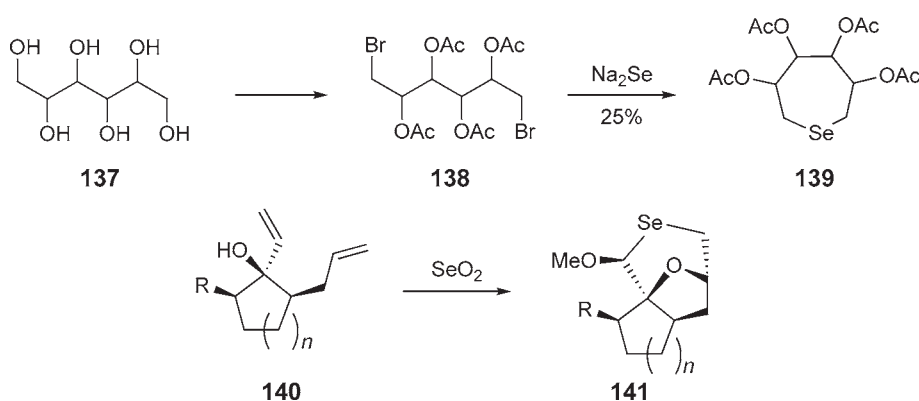


Scheme 13

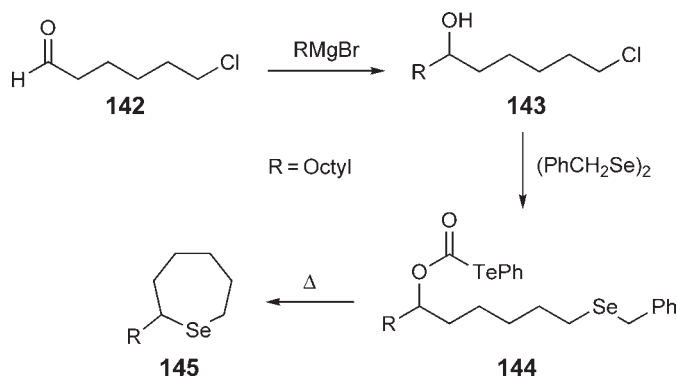
Benazza *et al.* have reported a general, short, and efficient synthesis affording polyhydroxylated tetrahydroselenophene, tetrahydroselenopyrane, and selenepane **139** rings from peracetylated α,ω -dibromo- α,ω -dideoxyalditols **138** with *erythro*-, D,L-*threo*-, *xyl*o-, *ribo*-, D-*arabino*-, D-*manno*-, and D-*gluco*-configurations. The latter are obtained directly by bromination of the corresponding alditols **137** <2004T2889>.

The formation of the selenium-containing product **141** during the reaction of selenium dioxide with hydroxydiolefins **140** has been confirmed through the synthesis and reactivity studies with selected model compounds (Scheme 14). The isolation of 8-oxa-3-selenabicyclo[3,2,1]octanes and dimeric selenium compounds has been observed with cyclohexanyl and cyclopentanyl derivatives <1993JOC7942, 1995TL8097>.

Telluroformates **144** were prepared by the treatment of alcohols **143** with a solution of phosgene in toluene, followed by sodium phenyltelluroate, and were isolated as yellow/orange viscous oil in 74% yield. It seems reasonable to say that the saturated selenium-containing rings **145** were formed through intramolecular ‘nucleophilic’ substitution of the benzylseleno moiety in telluroformates **144** with decarboxylative loss of phenyl telluride (Scheme 15) <1998JOC3032>.



Scheme 14



Scheme 15

A new selenium-containing pyrimidine derivative **147** has been prepared by an alkylation of 6-methyl-2-selenoxypyrimidin-4-one **146** with 1,4-dibromobutane in the presence of sodium hydride in good yield (Scheme 16) <1996MI96>.

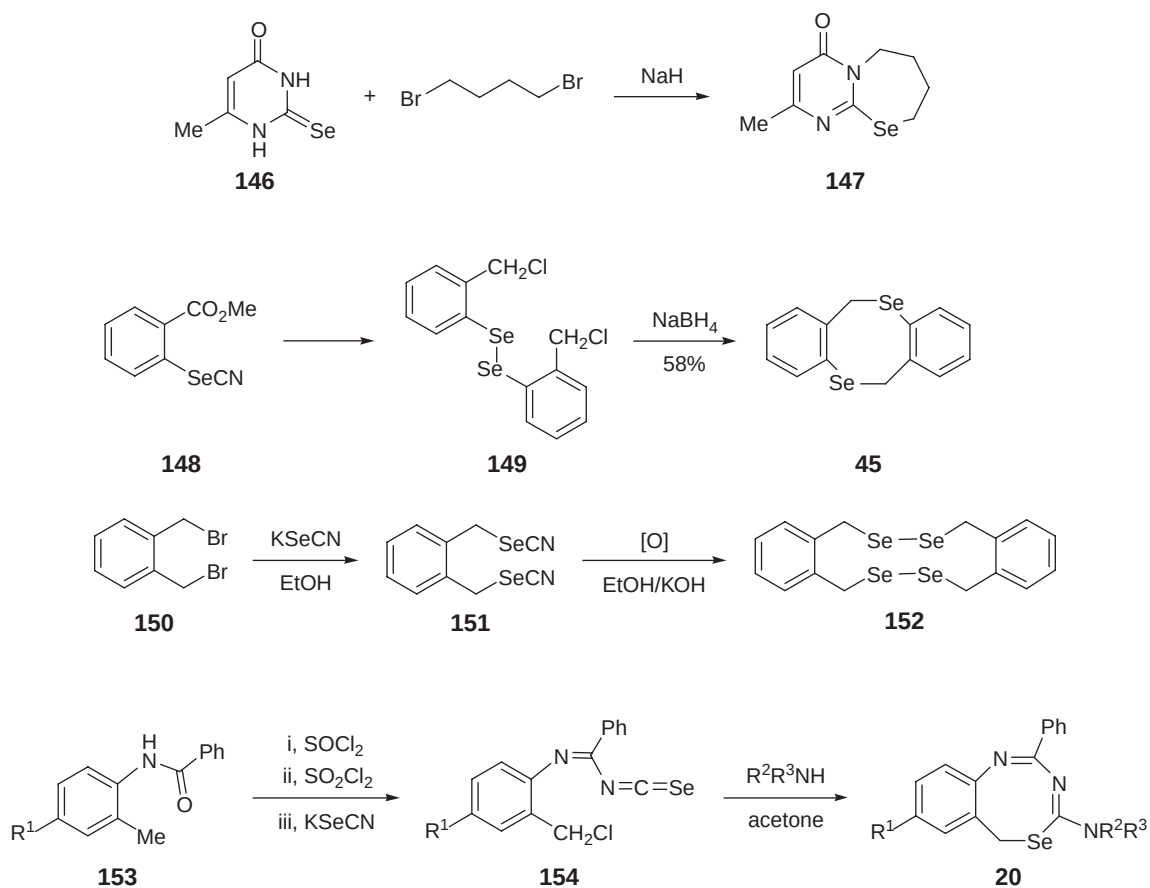
Compound **45** was easily synthesized from bis[(2-chloromethyl)phenyl] diselenide **149** by a reduction with sodium borohydride. The 4-deuterated derivative has been prepared in a similar way by using LiAlD_4 followed by treatment with thionyl chloride <1992PS125, 1996BCJ1825>.

A new selenium-containing macrocycle, 5,8,13,16-tetrahydro-6,7,14,15-tetraselena-dibenzo[*a,g*]cyclododecene **152** was prepared by oxidation of 1,2-bis(selenocyanatomethyl)benzene **151** in a moderate yield <1994H(38)491>.

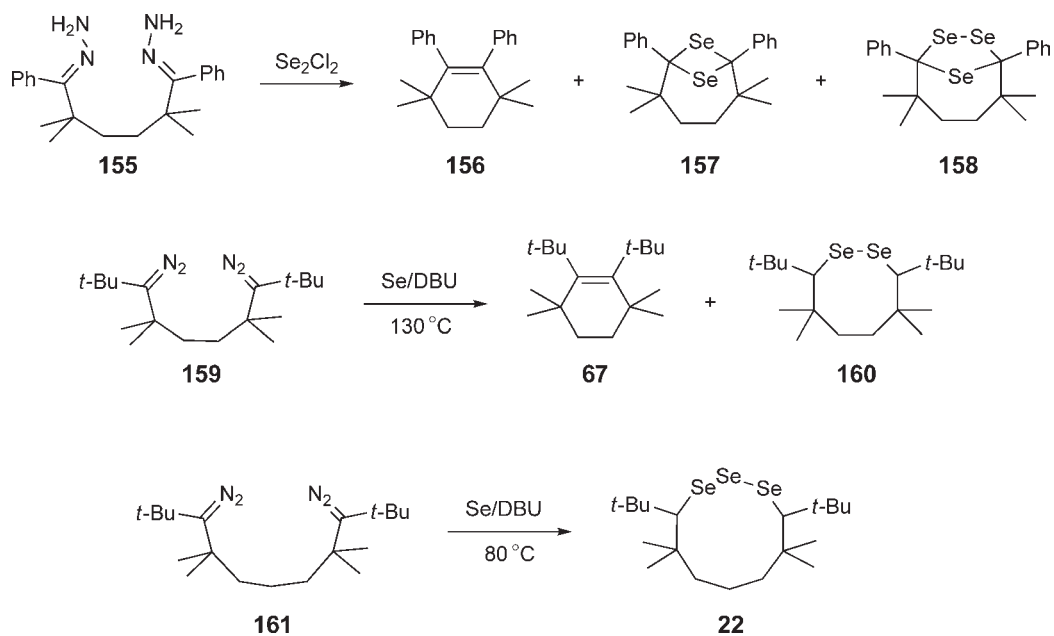
According to a known procedure <1996CCC1681>, *N*-(2-chloromethyl)phenylbenzimidoyl chloride was prepared from *N*-(2-methylphenyl)benzamide **153** by consecutive treatment in refluxing SOCl_2 and with SO_2Cl_2 in boiling benzene in the presence of AIBN. Freshly prepared KSeCN is added to the mixture to afford the isoselenocyanate **154** in good yields. The latter reacted with primary and secondary amines in acetone to give after an intramolecular cyclization the eight-membered ring called [5,1,3]benzoselenazocine **20** <2004HCA1452>.

The dihydrazino diphenyl derivative **155** reacted with Se_2Cl_2 in the presence of (*n*-Bu) $_3\text{N}$ to produce the cyclohexene **156** along with the bicyclic selenium compounds **157** and **158** <2000JOC1799>. Similarly, the same authors proposed a variation of the starting material **159**, which was prepared from dihydrazone **155** by oxidation with Nickel peroxide. Compound **159** was heated with an excess amount of elemental selenium in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 130 °C to yield **67** in 64% yield along with 1,2-diselenocane **160** in 13% yield. The reaction, in which a catalytic amount of selenium (10 mol%) was used, yielded **67** in a lower yield (28%). Next, 1,7-bis(diazo)heptane **161**, prepared by oxidation of the corresponding dihydrazone, was heated with elemental selenium in DBU at 80 °C to give the 1,2,3-triselenecane **22** in 15% yield, as the only identifiable product (Scheme 17). When the reaction of **161** with elemental selenium was conducted without DBU at higher temperatures, diselenone **22** appeared in 7% yield <2002HAC351>.

When dichloride **163** is treated with hydroxylamine, the reaction produced the cyclic 10-membered diselenide **164** in 47% yield. The same dichloride **163** can also be reacted with 1,2-ethanethiol to give the cyclic eight-membered heterocycle **162** in 45% yield <2002T7531>. The reaction of 2-phenyl-5,6-dihydro-4*H*-[1,3]oxazine

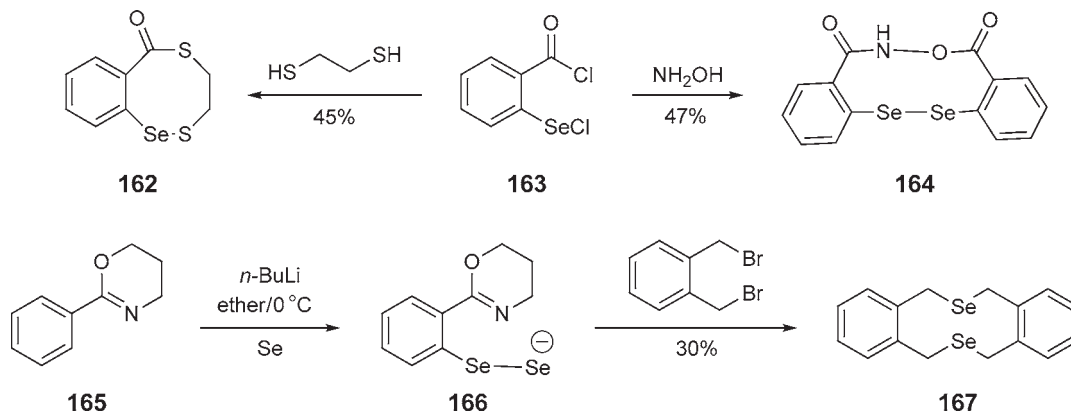


Scheme 16



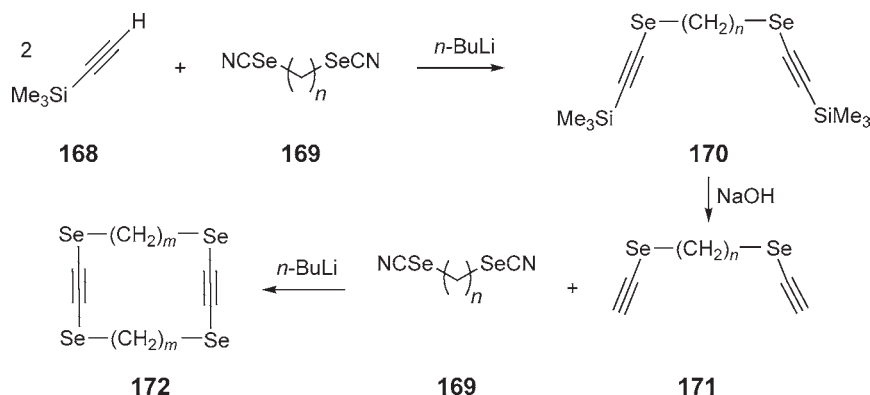
Scheme 17

165 with *n*-butyllithium, followed by elemental selenium, gave lithium aryldiselenolate **166**. This anion reacted with α,α' -dibromo-*ortho*-xylene to give the 10-membered diselenocine **167** in 30% yield (Scheme 18) <2004OM4199>.



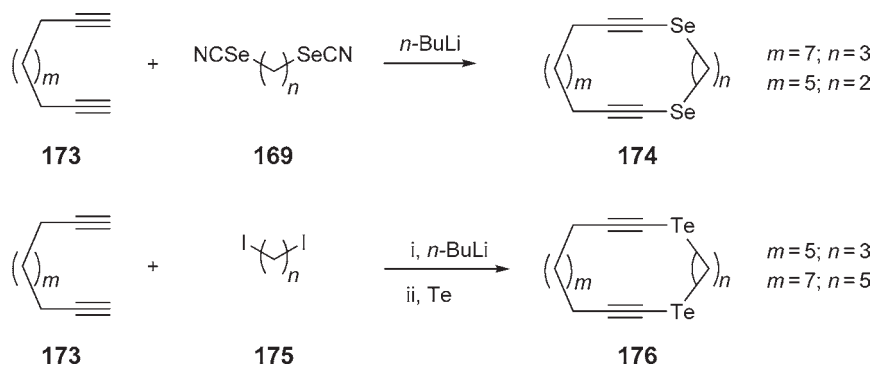
Scheme 18

The synthesis of cyclic tetraselenadiynes could be achieved by a stepwise approach. Key steps were the reaction of the lithium salt of trimethylsilylacetylene **168** with α,ω -diselenocyanatoalkanes **169**. By treating the bis-lithium salt of the resulting α,ω -diselenaalkadiynes **170** again with **169**, the cyclic tetraselenadiynes **172** resulted with methylene chains between the Se–C≡C–Se units (Scheme 19) <2002JOC4290>.



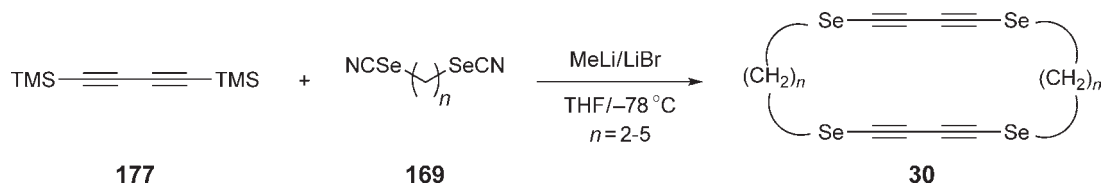
Scheme 19

To prepare the desired cyclic diselenadiynes **174**, Gleiter and co-workers made use of a protocol that was used to prepare the corresponding cyclic tetraselenadiynes **172**. The preparation commenced by the bislithiation of the α,ω -alkadiynes **173**, which were prepared in THF from the hydrocarbons with 2 equiv of *n*-butyllithium. To this solution, α,ω -diselenocyanate **169** was added. This one-pot procedure afforded the cyclic diynes **174** in 20–50% yield as white- to yellow-colored solids. To obtain the corresponding ditellura rings, the bis-lithium salts of α,ω -alkadiynes **173** were treated with freshly ground tellurium metal and α,ω -diiodoalkanes **175**. This one-pot reaction produced the cyclic diynes **176** in 40% yield as pale yellow solids <2003OBC2788>. Close contacts between the chalcogen atoms in cyclic diynes are used to create columnar structures in the solid state. Rigid and fairly planar cycles with chalcogen centers are the preconditions for forming those columnar structures (Scheme 20) <2002OL339>.



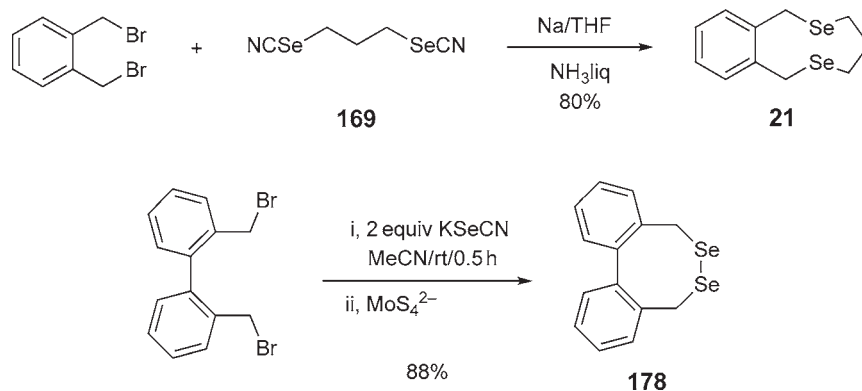
Scheme 20

Cyclic bis(1,3-butadiynes) with selenium centers placed in the α -position to the 1,3-butadiyne units **177** were synthesized by a Glaser coupling of the corresponding open-chain α,ω -diselenocyanatoalkanes **169**. A four-component cyclization was applied by Gleiter and co-workers by reacting α,ω -diselenocyanatoalkanes **169** with dilithium-1,3-butadiynide. This concept afforded the cyclic dimer **30**. Tubular structures in the solid state with short distances between the chalcogen centers of neighboring stacks were encountered for **30**. The elastic properties of these macrocycles are due to the flexible methylene chains and the easily variable torsional angles between the rigid 1,3-butadiyne rods (Scheme 21) <2004JOC2945>.



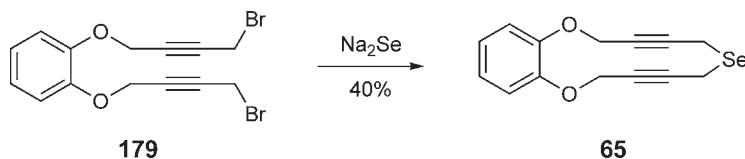
Scheme 21

A very similar approach has been studied by Levason and co-workers on the synthesis of the nine-membered ring **21**. The $\text{NCSe}(\text{CH}_2)_3\text{SeCN}$ was added to a solution of Na in THF–liquid NH_3 , generating $\text{NaSe}(\text{CH}_2)_3\text{SeNa}$ *in situ*. Dropwise addition of α,α' -dibromo-*o*-xylene gave **21**, which was isolated in greater than 80% yield <1997JCD3493>. Various functionalized selenocyanates, generated *in situ* from the corresponding alkyl halides, underwent a facile reductive coupling on treatment with benzytriethylammonium tetrathiomolybdate under very mild conditions to give the corresponding diselenides **178** in very good yields (Scheme 22) <1997CC1021, 2003EJI277>.



Scheme 22

The 13-membered cyclic selenide **65** and 15-membered **66** were obtained by treatment of a $\text{CH}_2\text{Cl}_2/\text{MeOH}$ solution of the corresponding dipropargyl dibromide **179** with an aqueous solution of sodium hydroselenide under high-dilution conditions (Scheme 23) <2002EJO3198>.



Scheme 23

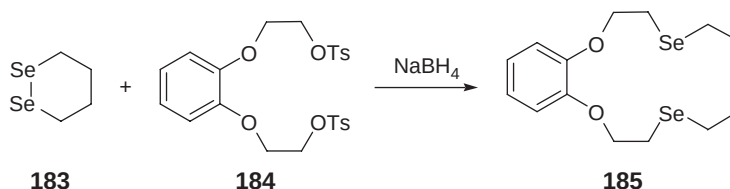
Heterocyclic selenium sulfides can be prepared from the molten mixtures of selenium and sulfur and by a variety of synthetic routes. Most reactions, however, produce complicated molecular mixtures and their characterization of which has turned to be rather difficult. Laitinen and co-workers have described the synthesis of eight-membered ring containing sulfur and selenium. The reaction of $[\text{Ti}(\text{Me}_5\text{C}_5)_2\text{S}_3]$ and Se_2Cl_2 initially produced a mixture of 1,2- Se_2S_6 **180**, 1,5- Se_2S_6 **181**, and 1,2,3,4,5- Se_5S_2 **182** that can be inferred to be formed as a consequence of a rapid decomposition of 1,2- Se_2S_3 (Scheme 24; see Chapter 14.09) <1998ACS1188>. Similarly, the 10-membered selenium-sulfur heterocycle has been studied by the same authors <1997PS253>.



Scheme 24

The chemistry of crown ethers has developed rapidly over the last 10 years, a great number of new crown compounds have been synthesized, and their applications have been broadened. As a novel kind of crown ether, selenacrown ether, has been initiated in recent years. Since selenium is a softer base than the oxygen atom, selenacrown ether forms stable complexes with soft metal cations. Because of its complicated characteristic, selenacrown ethers become a part of crown ether that cannot be neglected.

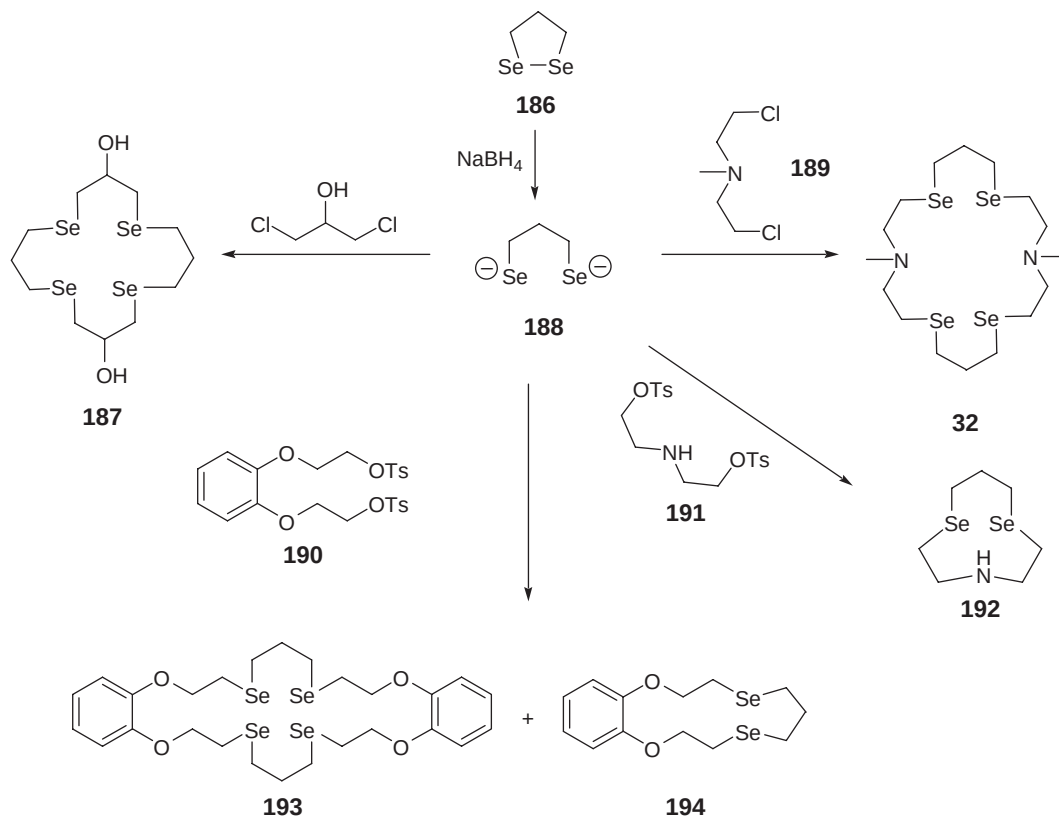
The reduction of [1,2]diselenane **183** with sodium borohydride opened the heterocycle to a 1,4-diselenol-butane salt. The latter reacted with the *o*-bis(tosyloxyethoxy)benzene derivative **184**, affording 6,7,9,10,11,12,14,15-octahydro-5,16-dioxo-8,13-diselena-benzocyclotetradecene **185** in 37% yield (Scheme 25) <2000CCL66>.



Scheme 25

The new selenacrown ether *N,N'*-dimethyl-1,11-diaza-4,8,14,18-tetraselenacycloicosane **32** has been synthesized and characterized <2005MI191>. Xu *et al.* have reported the first selenacrown and selenazacrown ethers bearing a hydroxy group. In this series, the key step is the preparation of the diselenide intermediate **188** by a reduction with potassium borohydride. It can then be condensed with dihalides or diol ditosylates **191** to give the aza 10-membered

ring **192** and the dihydroxyl 16-membered ring **187** <1996CCL515>. A very similar approach has been described by Pinto and co-workers <1996CJC533>. Diselena- **193** and tetraselena-crown ethers **194** were synthesized by condensation of diol ditosylates **190** with sodium propane-1,3-bisselenolate **188** (Scheme 26) <1994CCL49>.



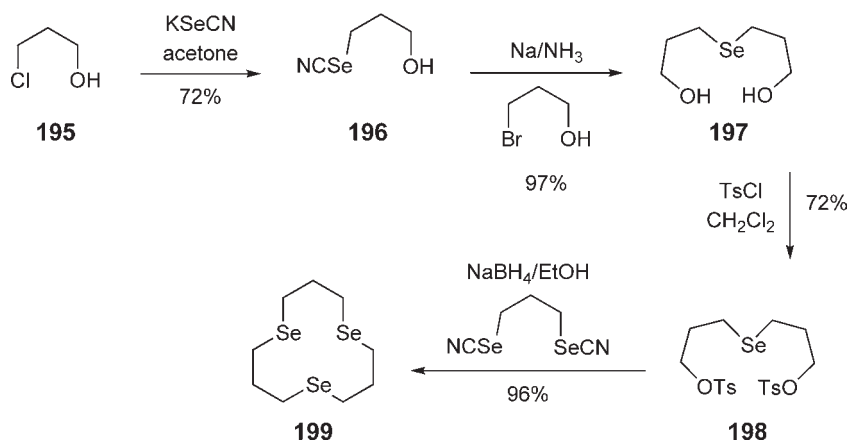
Scheme 26

Two calix[4](diselena)crown ethers were synthesized by reaction of the disodium salt of 1,3-propanediselenanol **188** with the preorganized 1,3-dibromoethoxycalix[4]arenes. These potentially ionophoric calixcrown selenoethers form interesting infinite aggregate sheets via self-inclusion and intermolecular Se $\cdots$ Se interactions in the solid state <2002TL131>.

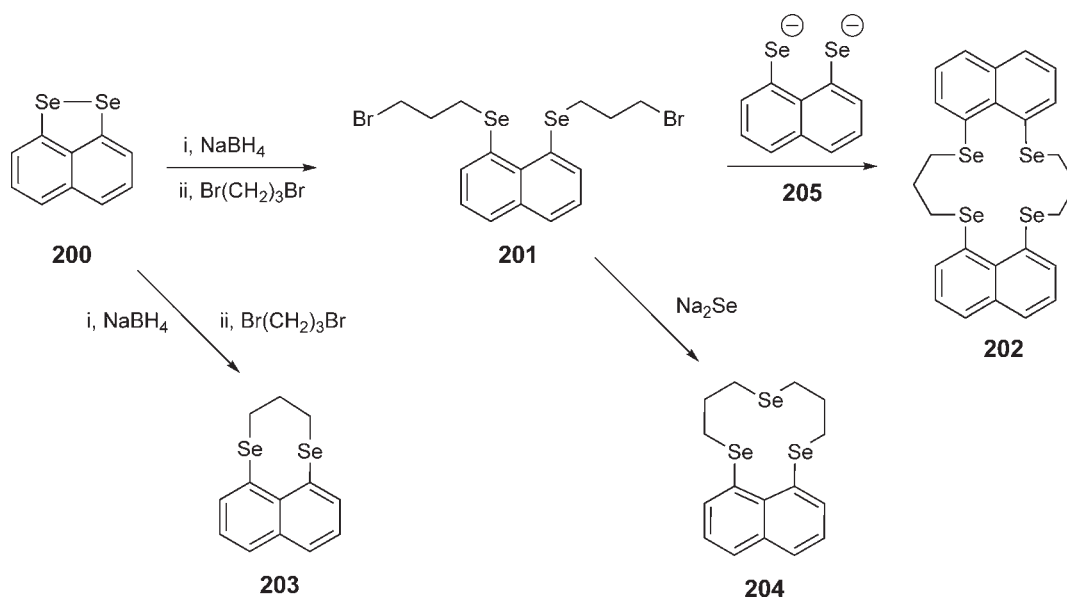
The key diol containing one selenium atom, 4-seleneheptan-1,7-diol **197**, was obtained in 97% yield from the reaction of 3-bromo-1-propanol and the selenolate anion derived from 3-selenocyanato-1-propanol **196** by sodium metal reduction in liquid ammonia. The ditosylate **198**, obtained from **197**, was then heated with the bis-selenolate anion derived from 1,3-bis-selenocyanatopropane to give the target selenium coronand, 1,5,9-triselenacyclododecane [12Se3] **199**, in 96% yield (Scheme 27) <1995CJC113, 1996CJC533>.

New macrocyclic polyselenides containing naphthalene rings **203** and **204** were synthesized by Furukawa and co-workers in 1996. The cyclic bis-selenide **203** was prepared by the reaction of naphtho[1,8][*c,d*]-1,2-diselenole **200** with 1,3-dibromopropane (1 equiv) using a high-dilution method. However, when the diselenide **200** was treated with a large amount of 1,3-dibromopropane, the dibromide **201** was obtained instead of **203**. Dibromide **201** reacted with Na₂Se to give the cyclic tris-selenide **204**, while the reaction of dibromide **201** with the disodium diselenolate **205** afforded the cyclic tetraselenide **202** (Scheme 28) <1996J(P1)1783>.

The unsaturated selenacrown ethers, 15-membered **33**, 18-membered **34**, 21-membered **35**, and 24-membered **36**, were obtained together with 1,4-diselenin **211** by reacting sodium selenide with *cis*-dichloroethene in the presence of a phase-transfer catalyst <2003OL1443, 2005JOC5036>. The new macrocycle, [18]aneO₄Te₂ **207**, has been obtained in good yield (ca. 50–55%) by reaction of Na₂Te with (CH₂OCH₂CH₂Cl)₂ **206** in liquid ammonia. The reaction is convenient in that there is no need to use high-dilution conditions. Recrystallization from CH₂Cl₂–Et₂O under



Scheme 27

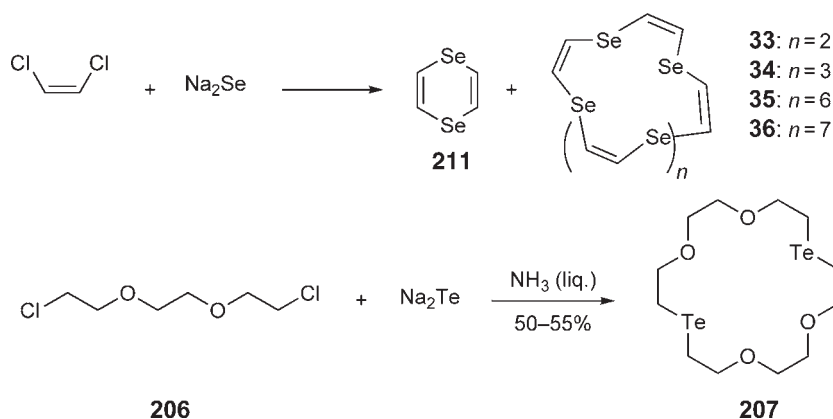


Scheme 28

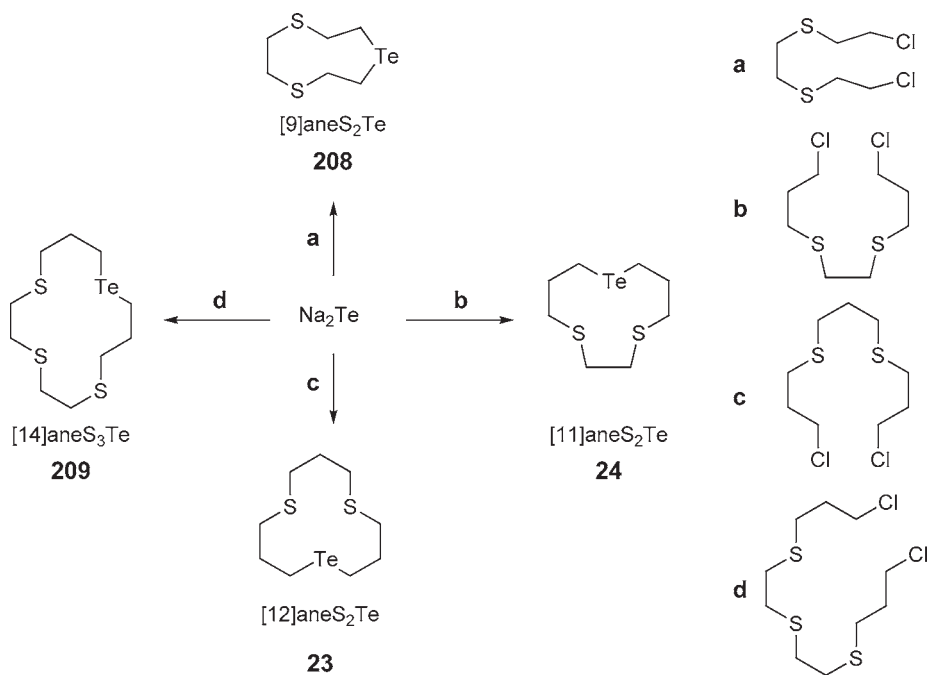
nitrogen gave the [18]aneO₄Te₂ **207**, as a yellow, slightly air sensitive solid, which was fully characterized by ¹H, ¹³C{¹H}, and ¹²⁵Te{¹H} NMR spectroscopy (Scheme 29) <2003JCD2852>.

In recent years, thioetheral macrocycles have attracted considerable interest in the chemical community. A variety of ring sizes have been prepared and their metal ion chemistry studied, yielding a diverse range of structures and unexpected electronic and redox responses.

The preparations of the first examples of mixed thioether/telluroether macrocycles, [9]aneS₂Te (1,4-dithia-7-telluracyclononane **208**), [11]aneS₂Te (1,4-dithia-8-telluracycloundecane **24**), [12]aneS₂Te (1,5-dithia-9-telluracyclododecane **23**), and [14]aneS₃Te (1,4,7-trithia-11-telluracyclotetradecane **209**), via a 'disguised dilution' method were described, together with the crystal structure of [Ag([11]aneS₂Te)]BF₄ which serves to authenticate the macrocyclic ligand (Scheme 30) <2001CC427>. In a typical preparation, a freshly prepared sample of Na₂Te in liquid NH₃ was taken to -78 °C and a THF solution of the appropriate α,ω-dichlorothioalkane species was added dropwise over ca. 30 min. Evaporation of the NH₃, followed by subsequent hydrolysis and extraction with CH₂Cl₂, yielded a red oil. The macrocyclic ligands are obtained as light yellow, poorly soluble solids in moderate yields (20–30%) <2003JCD2434>.



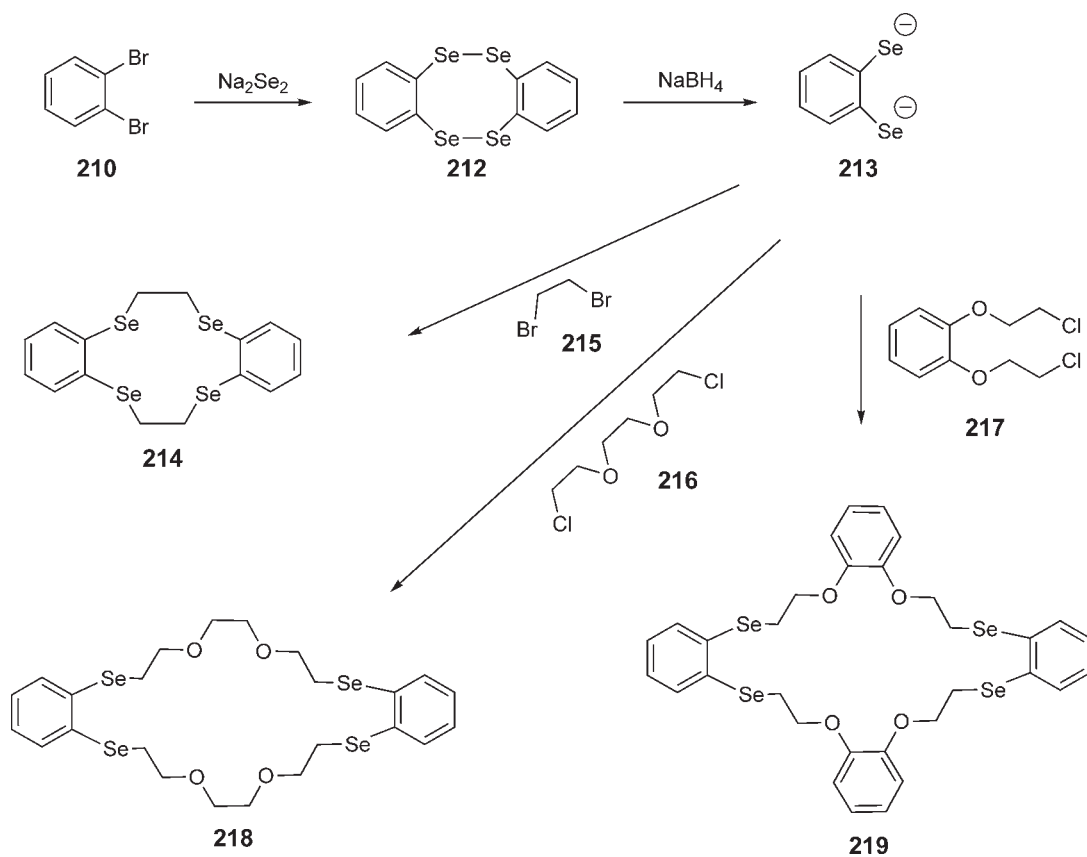
Scheme 29



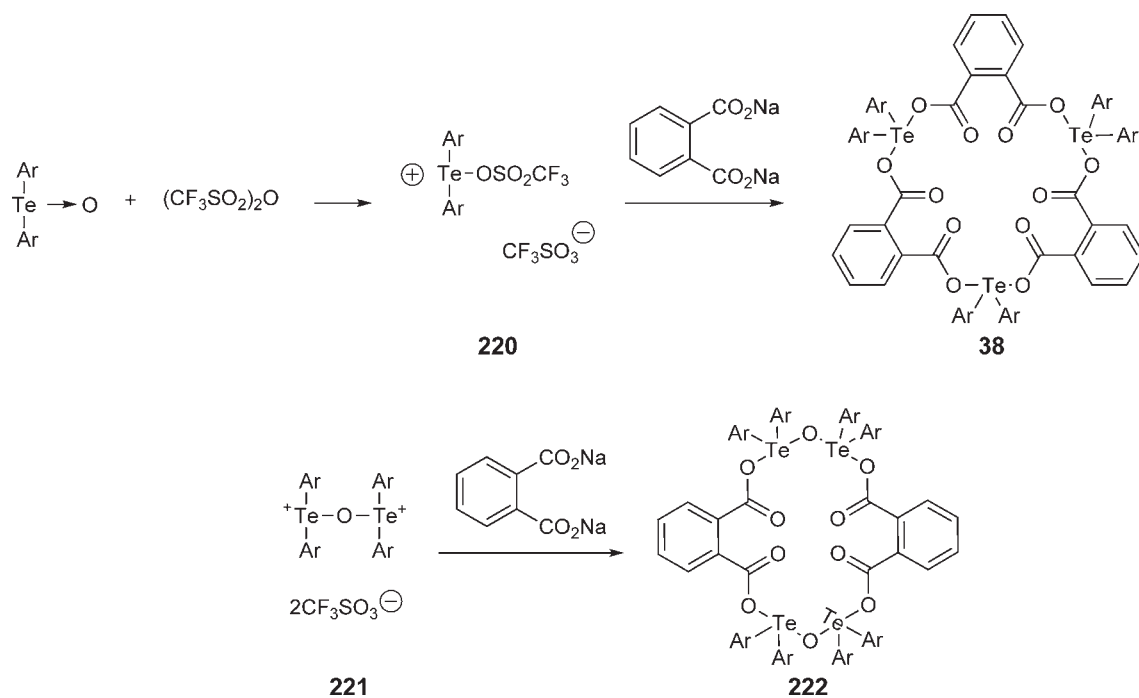
Scheme 30

An improved method for the preparation of selenacrown ethers has been described by Xu and co-workers. The synthesis of poly-(*o*-diselenobenzene) was detailed as the key intermediate for the syntheses of *o*-benzene diselenium type of selenacrown ethers. Under alkaline conditions, 5,6,11,12-tetraselena-dibenzo[*a,e*]cyclooctene **212** was reduced with potassium borohydride to give *o*-benzenediselenolate anion **213**, which condensed with dihalides **215–217** and different 12- and 24-membered selenacrown ethers **218** and **219** were isolated in good yields (Scheme 31) <1995MI1559, 1997JCD1043, 1999JCD1039>.

Two types of macrocyclic multitelluranes with hypervalent Te–O apical linkages in the main chain were prepared by the reaction of a telluronium salt **220** or a cationic ditelluroxane **221** with phthalate via [3+2] and [2+2] assembly, respectively <2001CC1428>. The generation of the telluronium salt **220** *in situ* by the reaction of bis(4-methylphenyl) telluroxide with 1 equiv of triflic anhydride in MeCN at 240 °C, followed by the addition of 1 equiv of sodium phthalate at room temperature, gave the hypervalent macrocycle **38** in 76% yield after recrystallization. Treatment of the cationic ditelluroxane **221** with the same phthalate in MeCN at room temperature produced the hypervalent macrocycle **222** in 14% yield after recrystallization (Scheme 32).



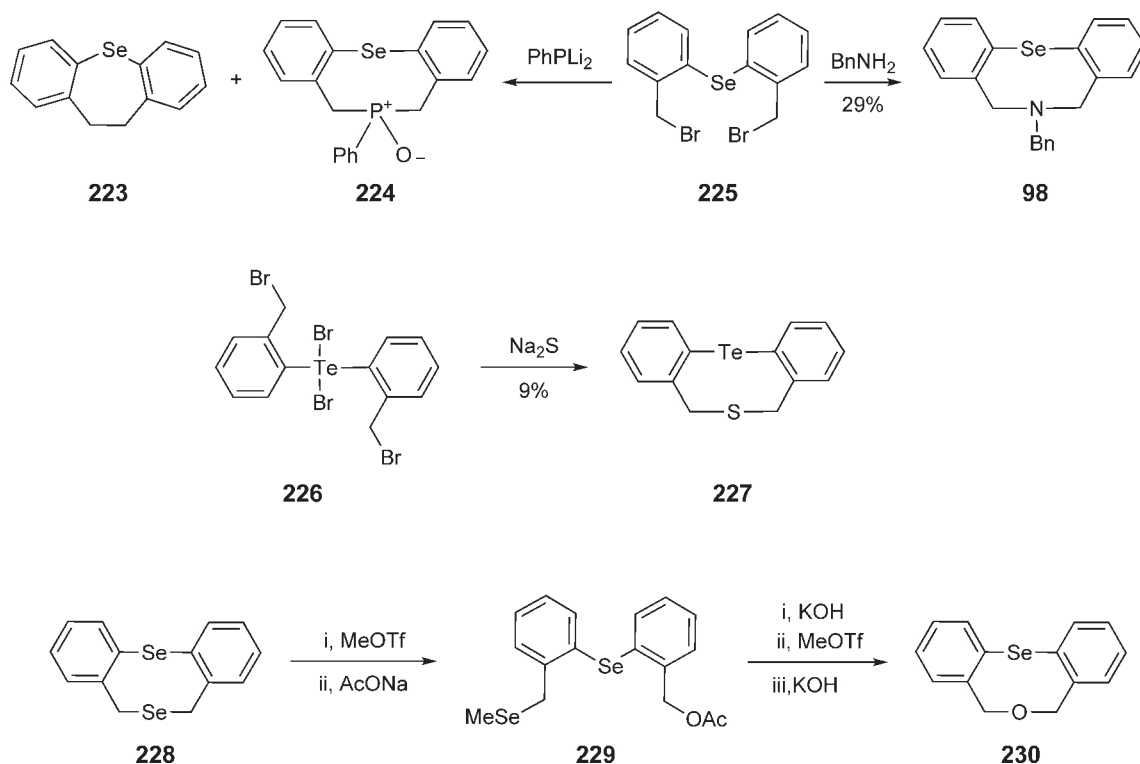
Scheme 31



Scheme 32

14.16.6.2 Synthesis of Rings in which Formation of a C–X Bond is not the Ring-Closure Step

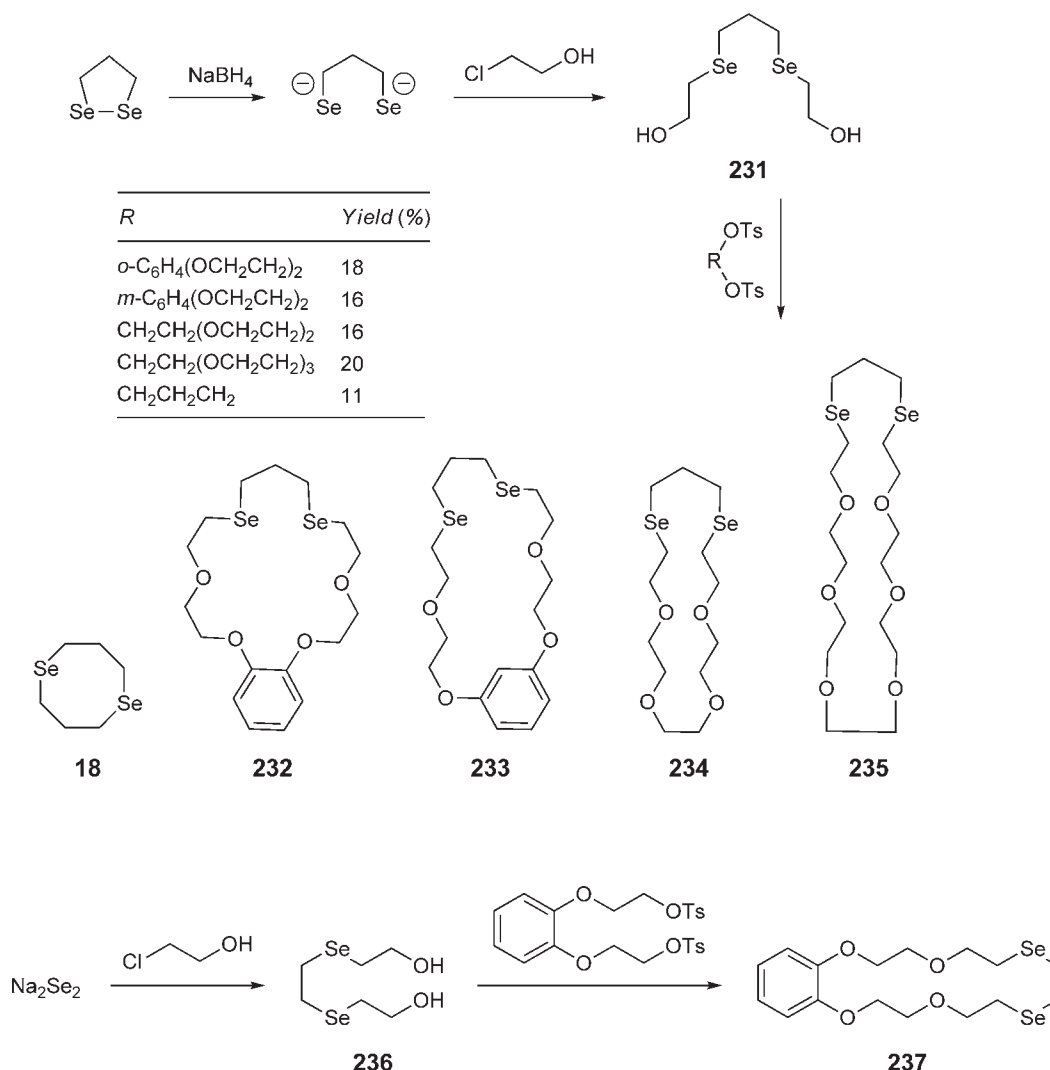
The chalcogenide **98** named 6-benzyl-6,7-dihydro-5*H*-dibenzo[*b,g*][1,5]selenazocine has been synthesized by the reaction between bis(2-bromomethylphenyl)selenide **225** and benzyl amine and triethylamine in chloroform at reflux for 10 h in 29% yield <1998T11813>. Two new phosphorus–selenium seven- and eight-membered heterocycles **224** and **223** have been also synthesized from the selenide **225** by treatment with PhPLi₂ in THF at room temperature in 75% and 2% yield, respectively <1995H(41)2647>. A new heterocycle containing tellurium and sulfur, 5*H*,7*H*-dibenzo[*b,g*][1,5]tellurathiocin **227**, has been synthesized. Treatment of the tetrabromide **226** with 2.2 equiv of sodium sulfide in a mixture of dichloromethane and ethanol at room temperature afforded 9% of the eight-membered ring <1996OM1913>. A new heterocycle, 5*H*,7*H*-6-oxa-12-selena-dibenzo[*a,d*]cyclooctene **230**, has been prepared from the benzylic selenonium salt 5*H*,7*H*-6,12-diselena-dibenzo[*a,d*]cyclooctene **228** (Scheme 33) <1995TL6275>.



Scheme 33

Xu and co-workers described the synthesis of the key intermediate containing two selenium atoms: 3,7-diselena-1,9-nonadiol **231**, by which five new diselenacrown ethers were easily prepared. The treatment of the starting diol with various ditosylate derivatives afforded eight-membered **18**, 19-membered **232** and **234**, 20-membered **233**, and 25-membered ring **235**. Another starting diol **236** was prepared in order to get a new 18-membered selenium-containing crown ether **237** (Scheme 34) <1996MI436>.

The reduction of the di(selenocyanato)propane **169** with sodium borohydride gave the corresponding diselenolate, which reacted with 3-chloropropan-1-thiol to give the dithiol **238** in 60% yield. A soft base like cesium carbonate in DMF was able to deprotonate the dithiol and treatment with 1,3-dibromopropane afforded the sulfur and selenium 16-membered ring heterocycles **239** in 22% yield <2000IC2558>. Bis(*o*-formylphenyl)telluride **241** was synthesized



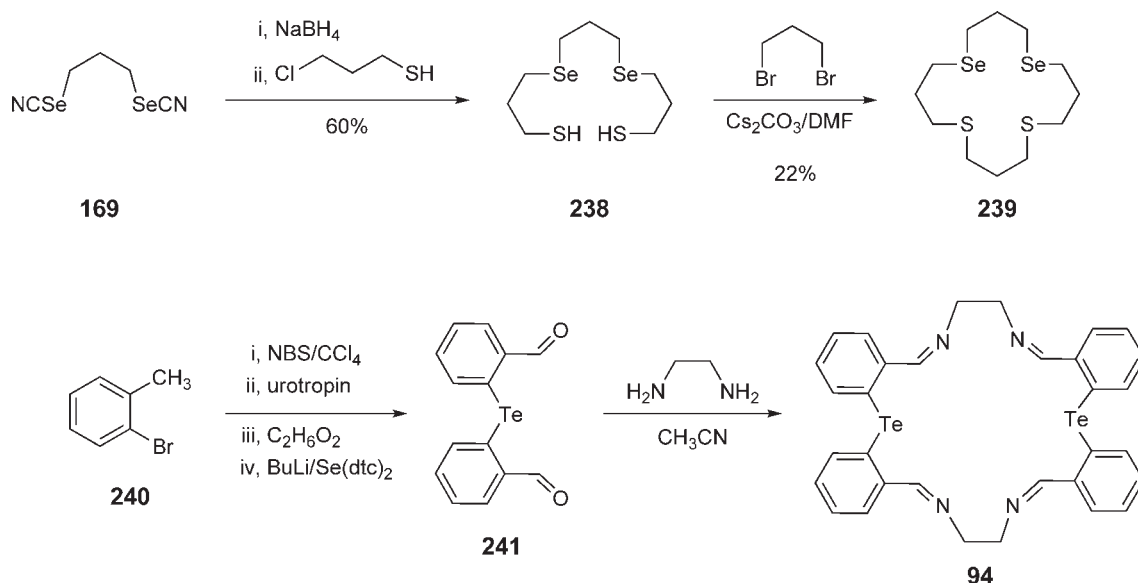
Scheme 34

using the ortholithiation methodology. The reaction of *o*-lithiobenzaldehyde acetal with Te(dtc)₂ (dte = diethyl-dithiocarbamate) afforded bis(*o*-formylphenyl)telluride acetal in good yield. The key starting material **240** was isolated as pale yellow solid upon refluxing acetal in concentrated HCl. Then, the reaction of **241** with 1,2-diaminoethane in MeCN afforded the 22-membered azaditellurium ring **94** (Scheme 35) <2001JOM(623)87, 2004CC322, 2000CC143, 2000CCR49, 2004JOM(689)1452>.

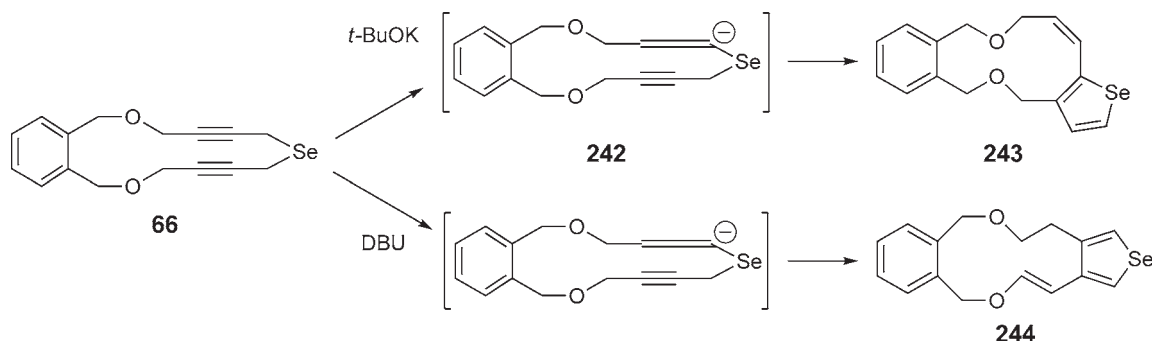
14.16.6.3 Transformation of a Chalcogen-Containing Ring

A few examples of ring transformation were mentioned in CHEC-II(1996) (pp. 943–944). Many of these were again reviewed in articles published by Russian teams <1997RCR923, 2002CHE1437>. Although, there has been limited chemistry over this topic from the period 1996 to 2006, a brief overview will be given here.

Braverman *et al.* have surprisingly found that a cycloaromatization took place on the use of a strong base, *t*-BuOK in dry THF. Selenide **66** reacted almost spontaneously with formation of 2-vinylselenophene **243**. Selenide **66** reacted with DBU in DMSO in a similar manner with the formation of a selenophene derivative **244**, but the reaction was much slower in that it was complete only after 2 days (Scheme 36) <2002EJO3198>.



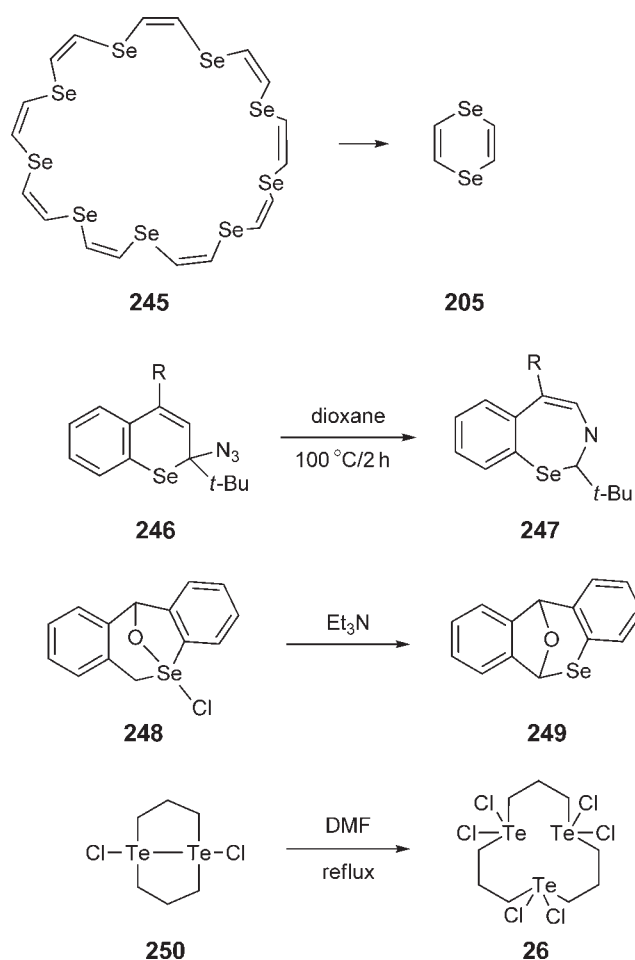
Scheme 35



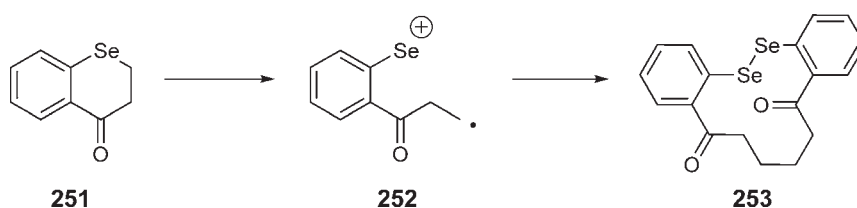
Scheme 36

The thermal reactions of the unsaturated selenacrown ether **245** afforded 1,4-diselenin **205** along with polymeric materials, whereas **245** was thermally stable even at 100 °C (see Chapter 7.11) <2003OL1443, 2005JOC5036>. The thermolysis of the 2-azidoselenochromene **246** at 100 °C in refluxing dioxane resulted in a ring-expansion with denitrogenation to give the desired stable 2-*tert*-butyl-1,3-benzoselenazepine **247** in 69% yield. Thermal decomposition of the azide probably involved the assisted elimination of nitrogen to form an azirine intermediate <2004CPB485>. The reaction of the chloro selenopine **248** with dry triethylamine in dichloromethane afforded a rearrangement of the Se–O bond in order to get the 6,11-epoxy-11-phenyl-6,11-dihydrodibenzo[*b,e*]selenopine **249** in only 18% yield <2001HAC317>. Furukawa and co-workers reported the first synthesis of 1,1,5,5,9,9-hexachlorotritelluracyclododecane **26**, a monocyclic multitellurium moiety, which is composed of three hypervalent tellurium(IV) atoms. Compound **26** is prepared by pyrolysis of ditellurane **250** in DMF at 160 °C in 44% yield by a ring expansion, in which the eight-membered ring expanded to a 12-membered ring, evidently as a result of a deep-seated fragmentation and subsequent recombination (Scheme 37) <1996OM5112>.

Electrochemically generated cation radical **252** derived from the cyclic alkylphenyl selenide **251** can react via two parallel paths: deprotonization with the formation of compounds containing double bonds in the selenium-bearing rings and homolytic cleavage of the C(sp³)–selenium bond, followed by dimerization and formation of a diselenide **253** with an extended ring (Scheme 38) <1987ZOB609>.



Scheme 37



Scheme 38

14.16.7 Further Developments

A small amount of new materials/studies have appeared since the beginning of the editorial process. Only a few examples will be mentioned here as key papers for the next review. Block *et al.* <2006JACS14949> published the synthesis and characterization of more than 40 new 4- to 12-membered ring heterocycles containing various combinations of Group 14 and 16 elements Si, Sn, S, Se, and Te.

Very unusual and rare novel cyclic tetraselenides of mannose have been described by Chandrasekaran *et al.* starting from mannose <2007TL2091>. The reactivity of the reagent tetramethylammonium tetraselenotungstate $(\text{Et}_4\text{N})_2\text{WSe}_4$ has been compared with the well-known transfer reagents Li_2Se_2 and Na_2Se_2 .

A huge work has also been edited in 2006 in *Science of Synthesis* <B-2006MI1000> which contains a lot of information on selenium and tellurium-containing heterocycles especially on seven or more membered ring systems.

References

- 1987ZOB609 V. V. Zhuikov, V. Z. Latypova, M. Yu. Postnikova, and Yu. M. Kargin, *Zh. Obshch. Khim.*, 1987, **57**, 609.
- 1992CHC115 A. A. Ladatko, A. V. Zakharov, I. D. Sadekov, and V. I. Minkin, *Chem. Heterocycl. Compds.*, 1992, **28**, 115.
- 1992PS125 M. Iwaoka and S. Tomoda, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1992, **67**, 125.
- 1992PS131 H. Fujihara and N. Furukawa, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1992, **67**, 131.
- 1993CC1716 P. F. Kelly, W. Levason, G. Reid, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1993, 1716.
- 1993JOC7942 A. S. Feliciano, M. Medarde, J. L. López, M. A. Salinero, and M. L. Rodríguez, *J. Org. Chem.*, 1993, **58**, 7942.
- 1993PS261 N. Furukawa, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1993, **74**, 261.
- 1993TL2557 L. J. Benjamin, C. H. Schiesser, and K. Sutej, *Tetrahedron Lett.*, 1993, **49**, 2557.
- 1994CCL49 W. P. Li, X. F. Liu, X. R. Lu, and H. S. Xu, *Chin. Chem. Lett.*, 1994, **5**, 49.
- 1994H(38)491 S. Ogawa, S. Ohara, Y. Kawai, and R. Sato, *Heterocycles*, 1994, **38**, 491.
- 1995CJC113 I. Cordova-Reyes, E. VandenHoven, A. Mohammed, and B. M. Pinto, *Can. J. Chem.*, 1995, **73**, 113.
- 1995H(41)1127 H. Fujihara, T. Nakahodo, H. Mima, and N. Furukawa, *Heterocycles*, 1995, **41**, 1127.
- 1995H(41)2647 H. Fujihara, T. Nishioka, H. Mima, and N. Furukawa, *Heterocycles*, 1995, **41**, 2647.
- 1995IC651 N. R. Champness, P. F. Kelly, W. Levason, G. Reid, A. M. Z. Slawin, and D. J. Williams, *Inorg. Chem.*, 1995, **34**, 651.
- 1995MI1 W. P. Li, X. F. Liu, X. R. Lu, and H. S. Xu, *Chin. Chem. Lett.*, 1995, **27**, 1.
- 1995MI1559 W.-P. Li, J. Wu, X.-F. Liu, and H.-S. Xu, *Chin. J. Chin. Univ.*, 1995, **16**, 1559.
- 1995POL2753 N. R. Champness, W. Levason, J. J. Quirk, G. Reid, and C. S. Frampton, *Polyhedron*, 1995, **14**, 2753.
- 1995TL6275 H. Fujihara, T. Nakahodo, and N. Furukawa, *Tetrahedron Lett.*, 1995, **36**, 6275.
- 1995TL8097 M. Medarde, J. L. López, M. A. Morillo, F. Tomé, M. Adeva, and A. S. Feliciano, *Tetrahedron Lett.*, 1995, **36**, 8097.
- 1996BCJ1825 M. Iwaoka, H. Komatsu, and S. Tomoda, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1825.
- 1996CC143 R. Bhula, A. P. Arnold, G. J. Gainsford, and W. G. Jackson, *Chem. Comm.*, 1996, 143.
- 1996CCC1681 M. Bodajla, S. Stankovsky, K. Spirková, and S. Jantová, *Collect. Czech. Chem. Commun.*, 1996, **61**, 1681.
- 1996CCL515 H.-S. Xu, J. Wu, G. Y. Xiang, and X.-F. Liu, *Chin. Chem. Lett.*, 1996, **7**, 515.
- 1996CJC533 I. Cordova-Reyes, H. Hu, J.-H. Gu, E. VandenHoven, A. Mohammed, S. Holdcroft, and B. M. Pinto, *Can. J. Chem.*, 1996, **74**, 533.
- 1996IC3667 R. J. Batchelor, F. W. B. Einstein, I. D. Gay, J.-H. Gu, B. M. Pinto, and X.-M. Zhou, *Inorg. Chem.*, 1996, **35**, 3667.
- 1996JCD1203 S. C. Menon, H. B. Singh, R. P. Patel, and S. K. Kulshreshtha, *J. Chem. Soc., Dalton Trans.*, 1996, 1203.
- 1996JCD3713 W. Levason, J. J. Quirk, and G. Reid, *J. Chem. Soc., Dalton Trans.*, 1996, 3713.
- 1996JP11783 H. Fujihara, M. Yabe, and N. Furukawa, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1783.
- B-1996MI1 T. Klapötke and M. Broschag, 'Compilation of Reported ⁷⁷Se NMR Chemical Shifts', Wiley, Chichester, 1996.
- 1996MI12 A. Kasuya, K. Watanabe, H. Takahashi, K. Toji, K. Motomiya, and Y. Nishina, *Mater. Sci. Eng.*, 1996, **A217–A218**, 12.
- 1996MI96 K. I. Nurbaev, K. A. Zakhidov, E. O. Oripov, R. A. Smiev, and K. M. Shakhidoyatov, *Uzb. Khim. Zh.*, 1996, **1–2**, 96.
- 1996MI436 W.-P. Li, J. Wu, J.-G. Zhang, X.-F. Liu, and H.-S. Xu, *Yonji Huaxue*, 1996, **16**, 436.
- 1996MI577 H. Ito, T. Sakurai, T. Matsuo, T. Ichihara, and I. Katakuse, *Surface Rev. Lett.*, 1996, **3**, 577.
- 1996OM1913 Y. Takaguchi, H. Fujihara, and N. Furukawa, *Organometallics*, 1996, **15**, 1913.
- 1996OM5112 Y. Takaguchi, E. Horn, and N. Furukawa, *Organometallics*, 1996, **15**, 5112.
- 1996RTC427 A. Y. Al-Rubaie, A. Y. Al-Marzook, and S. A. N. Al-Jadaan, *Recl. Trav. Chim. Pays-Bas*, 1996, **115**, 427.
- 1997CC525 R. D. Adams and K. T. McBride, *Chem. Commun.*, 1997, 525.
- 1997CC1021 K. R. Prabhu and S. Chandrasekaran, *Chem. Commun.*, 1997, 1021.
- 1997JCD1043 A. Mazouz, P. Meunier, M. M. Kubicki, B. Hanquet, R. Amardeli, C. Borner, and A. Zahidi, *J. Chem. Soc., Dalton Trans.*, 1997, 1043.
- 1997JCD3493 D. G. Booth, W. Levason, J. J. Quirk, G. Reid, and S. M. Smith, *J. Chem. Soc., Dalton Trans.*, 1997, 3493.
- 1997JCD3719 W. Levason, J. J. Quirk, G. Reid, and S. M. Smith, *J. Chem. Soc., Dalton Trans.*, 1997, 3719.
- 1997MI75 K. Uehara, M. Ishitobi, T. Oda, and Y. Hiwatari, *Mol. Simul.*, 1997, **19**, 75.
- 1997MI472 K. Uehara, M. Ishitobi, T. Oda, and Y. Hiwatari, *Z. Phys.*, 1997, **D40**, 472.
- 1997MI1660 A. Goldbach and M.-L. Saboungi, *Ber. Buns. Phys. Chem.*, 1997, **101**, 1660.
- 1997POL4253 W. Levason, G. Reid, and S. N. Smith, *Polyhedron*, 1997, **16**, 4253.
- 1997PS253 R. S. Laitinen, J. Taavitsainen, H. Tiainen, and P. Pekonen, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1997, **124–125**, 253.
- 1997RCR923 V. P. Litvinov and V. D. Dyachanko, *Russ. Chem. Rev.*, 1997, **66**, 923.
- 1997T16731 F. H. Allen, P. R. Raithby, and G. P. Shields, *Struct. Chem.*, 1997, **8**, 385.
- 1997TL5821 Y. Le Merrer, M. Fuzier, I. Dosbaa, M.-J. Foglietti, and J.-C. Depazay, *Tetrahedron*, 1997, **53**, 16731.
- 1997TL5821 R. Sato, S. Sanada, M. Okanuma, T. Kimura, and S. Ogawa, *Tetrahedron Lett.*, 1997, **38**, 5821.
- 1998ACS1188 P. Pekonen, J. Taavitsainen, and R. S. Laitinen, *Acta Chem. Scand.*, 1998, **52**, 1188.
- 1998CC197 T. Kataoka, T. Iwama, and S.-I. Tsujiyama, *Chem. Commun.*, 1998, 197.
- 1998CPL(287)282 S. Kohara, A. Goldbach, N. Koura, M.-L. Saboungi, and L. A. Curtiss, *Chem. Phys. Lett.*, 1998, **287**, 282.
- 1998JCD2185 M. K. Davies, W. Levason, and G. Reid, *J. Chem. Soc., Dalton Trans.*, 1998, 2185.
- 1998JOC3032 M. L. Lucas and C. H. Schiesser, *J. Org. Chem.*, 1998, **63**, 3032.
- 1998JP13147 Y. Takaguchi, A. Hosokawa, S. Yamada, J. Motoyoshiya, and H. Aoyama, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3147.
- 1998MI347 A. A. Demkov and O. F. Sankey, *Microporous Mesoporous Mater.*, 1998, **21**, 347.
- 1998MI513 V. V. Poborchii, *Solid State Commun.*, 1998, **107**, 513.
- 1998T11813 T. Kataoka, T. Iwana, S.-I. Tsujizama, T. Iwamura, and S.-I. Watanabe, *Tetrahedron*, 1998, **54**, 11813.
- 1999HAC159 N. Nakayama, O. Takahashi, O. Kikuchi, and N. Furukawa, *Heteroatom Chem.*, 1999, **10**, 159.
- 1999JCM284 Y. Liu, S.-P. Dong, Y. Inoue, and T. Wada, *J. Chem. Res. (S)*, 1999, 284.
- 1999JCD1039 C. Borner, R. Amardeli, P. Meunier, and J. C. Daran, *J. Chem. Soc., Dalton Trans.*, 1999, 1039.
- 1999JCD1077 M. K. Davies, M. C. Durrant, W. Levason, G. Reid, and R. L. Richards, *J. Chem. Soc., Dalton Trans.*, 1999, 1077.
- 1999JOC1131 C. H. Schiesser and L. M. Wild, *J. Org. Chem.*, 1999, **64**, 1131.
- 2000CJC598 R. J. Batchelor, F. W. B. Einstein, I. D. Gay, J.-H. Gu, B. M. Pinto, and X.-M. Zhou, *Can. J. Chem.*, 2000, **78**, 598.

- 2000CC143 S. C. Menon, A. Panda, H. B. Singh, and R. J. Butcher, *Chem. Commun.*, 2000, 143.
2000CCL66 Y. Liu and H.-Y. Zhang, *Chi. J. Chem.*, 2000, **18**, 66.
2000CCR49 A. K. Singh and S. Sharma, *Coord. Chem. Rev.*, 2000, **209**, 49.
2000HAC31 N. Nakayama, O. Takahashi, O. Kikuchi, and N. Furukawa, *Heteroatom Chem.*, 2000, **11**, 31.
2000IC2558 R. J. Batchelor, F. W. B. Einstein, I. D. Gay, J.-H. Gu, S. Mehta, B. M. Pinto, and X.-M. Zhou, *Inorg. Chem.*, 2000, **39**, 2558.
2000JCD2163 A. J. Barton, A. R. J. Genge, W. Levason, and G. Reid, *J. Chem. Soc., Dalton Trans.*, 2000, 2163.
2000JOC1799 A. Ishii, C. Tsuchiya, T. Shimada, K. Furusawa, T. Omata, and J. Nakazama, *J. Org. Chem.*, 2000, **65**, 1799.
2000SC2975 D. J. Procter and C. M. Rayner, *Synth. Comm.*, 2000, **30**, 2975.
2001CC427 W. Levason, S. D. Orchard, and G. Reid, *Chem. Commun.*, 2001, 427.
2001CC1428 K. Kobayashi, H. Izawa, K. Yamaguchi, E. Horn, and N. Furukawa, *J. Chem. Soc., Chem. Commun.*, 2001, 1428.
2001HAC317 T. Kataoka, T. Iwamura, H. Tsutsui, Y. Kato, Y. Banno, Y. Aoyama, and H. Shimizu, *Heteroatom Chem.*, 2001, **12**, 317.
2001JCD1621 A. J. Barton, N. J. Hill, W. Levason, and G. Reid, *J. Chem. Soc., Dalton Trans.*, 2001, 1621.
2001JOM(623)87 A. Panda, S. C. Menon, H. B. Singh, and R. J. Butcher, *J. Organomet. Chem.*, 2001, **623**, 87.
2002CJC1435 J. Komulainen, R. S. Laitinen, and R. J. Suontamo, *Can. J. Chem.*, 2002, **80**, 1435.
2002CHC1437 P. Arsenyan, K. Oberte, O. Pudova, and E. Lukevics, *Chem. Heterocycl. Compd.*, 2002, **38**, 1437.
2002EJO3198 S. Braverman, M. Cherkinsky, M. L. Birs, and Z. Zafrani, *Eur. J. Org. Chem.*, 2002, 3198.
2002HAC351 A. Ishii, K. Furusawa, T. Omata, and J. Nakayama, *Heteroatom Chem.*, 2002, **13**, 351.
2002IC2070 N. J. Hill, W. Levason, and G. Reid, *Inorg. Chem.*, 2002, **41**, 2070.
2002JOC4290 D. B. Wery, R. Gleiter, and F. Rominger, *J. Org. Chem.*, 2002, **67**, 4290.
2002MI337 K. Nagaya, A. Oohata, I. Yamamoto, and M. Yao, *J. Non-Cryst. Solids*, 2002, **312–314**, 337.
2002OL1443 D. B. Werz, T. H. Staeb, C. Benisch, B. J. Rausch, F. Rominger, and R. Gleiter, *Org. Lett.*, 2002, **4**, 339.
2002T7531 M. Osajda and J. Młochowski, *Tetrahedron*, 2002, **58**, 7531.
2002TL131 X. Zeng, X. Han, L. Chen, Q. Li, F. Xu, X. He, and Z.-Z. Zhang, *Tetrahedron Lett.*, 2002, **43**, 131.
2003BCJ381 Y. Miyake, A. Yamauchi, Y. Nishibayashi, and S. Uemura, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 381.
2003EJI277 J. S. L. Yeo, J. J. Vittal, and T. S. Andy Hor, *Eur. J. Inorg. Chem.*, 2003, 277.
2003JCD2434 M. J. Hesford, W. Levason, M. L. Matthews, S. D. Orchard, and G. Reid, *J. Chem. Soc., Dalton Trans.*, 2003, 2434.
2003JCD2852 M. J. Hesford, W. Levason, M. L. Matthews, and G. Reid, *J. Chem. Soc., Dalton Trans.*, 2003, 2852.
2003NJC1784 W. Levason, M. L. Matthews, R. Patel, G. Reid, and M. Webster, *New. J. Chem.*, 2003, **27**, 1784.
2003OL1443 T. Shimizu, M. Kawaguchi, T. Tsuchiya, K. Hirabayashi, and N. Kamigata, *Org. Lett.*, 2003, **5**, 1443.
2003OBC2788 J. H. Schulte, D. B. Werz, F. Rominger, and R. Gleiter, *Org. Biomol. Chem.*, 2003, **1**, 2788.
2004CPB485 H. Sashida and H. Minamida, *Chem. Pharm. Bull.*, 2004, **52**, 485.
2004CC322 S. Panda, H. B. Singh, and R. J. Butcher, *Chem. Commun.*, 2004, 322.
2004HCA1452 P. K. Atanassov, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2004, **87**, 1452.
2004JCD980 N. J. Hill, W. Levason, R. Patel, G. Reid, and M. Webster, *J. Chem. Soc. Dalton Trans.*, 2000, 980.
2004JOM(689)1452 S. C. Menon, A. Panda, H. B. Singh, R. P. Patel, S. K. Kulshreshtha, W. L. Darby, and R. J. Butcher, *J. Organomet. Chem.*, 2004, **689**, 1452.
2004JOM(689)2377 A. Y. Al-Rubaie, T. A. Fahad, S. A. N. Al-Jadaan, and N. A. Aboud, *J. Organomet. Chem.*, 2004, **689**, 2377.
2004JOM(689)3132 D. B. Werz, J. H. Schulte, R. Gleiter, and F. Rominger, *J. Organomet. Chem.*, 2004, **689**, 3132.
2004JOC2945 D. B. Werz, R. Gleiter, and F. Rominger, *J. Org. Chem.*, 2004, **69**, 2945.
2004OM4199 S. Kumar, K. Kandasamy, H. B. Singh, G. Wolmershäuser, and R. J. Butcher, *Organometallics*, 2004, **23**, 4199.
2004OL589 D. B. Werz and R. Gleiter, *Org. Lett.*, 2004, **6**, 589.
2004T2889 M. Benazza, S. Halila, C. Viot, A. Danquigny, C. Pierru, and G. Demailly, *Tetrahedron*, 2004, **60**, 2889.
2005AJC188 E. D. Goddard-Borger and R. V. Stick, *Aust. J. Chem.*, 2005, **58**, 188.
2005JOC5036 T. Shimizu, M. Kawaguchi, T. Tsuchiya, K. Hirabayashi, and N. Kamigata, *J. Org. Chem.*, 2005, **70**, 5036.
2005MI191 Y. Liu, J.-R. Han, Y.-L. Zhao, H.-Y. Zhang, and Z.-Y. Juan, *J. Incl. Phenom. Macrocyclic Chem.*, 2005, **51**, 191.
2005MI071902 I. L. Li, S. C. Ruan, Z. M. Li, J. P. Zhai, and Z. K. Tang, *Appl. Phys. Lett.*, 2005, **87**, 071902.
2005PAC145 P. R. Sridhar, V. Saravanan, and S. Chandrasekaran, *Pure Appl. Chem.*, 2005, **77**, 145.
2005STC67 B. Wrackmeyer, *Struct. Chem.*, 2005, **16**, 67.
2005TL6723 G. L. Sommen, A. Linden, and H. Heimgartner, *Tetrahedron Lett.*, 2005, **46**, 6723.
2006JACS14949 E. Block, E. V. Dikarev, R. S. Glass, J. Jin, B. Li, X. Li, and S.-Z. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 14949.
B-2006MI1000 V. A. Potapov and B. A. Trofimov; 'Science of Synthesis: Product Subclass 3: 1-(organosufanyl)-, 1-(organoselanyl)-, and 1-(organotellanyl)alk-1-ynes', Georg Thieme Verlag, 2006, 24, 957.
2006MI023202 J. C. Mauro, R. J. Loucks, J. Balakrishnan, and A. K. Varshneya, *Phys. Rev. (A)*, 2006, **73**, 023202.
2007TL2091 K. Sivapriya, P. Suguna, and S. Chandrasekaran, *Tetrahedron Lett.*, 2007, **48**, 2091.

Biographical Sketch



Geoffroy Sommen, born in Thionville (France) in 1976, studied chemistry at the University of Metz where he received his Ph.D. in organic chemistry in 2003 under the direction of Professor Gilbert Kirsch. His scientific interest was focused on the chemistry of thiophenes and selenophenes and their fused systems. In the same year, he joined the group of Professor Alan R. Katritzky where he serves as adjunct scientific assistant in the field of heterocyclic chemistry. Then, he got a grant from the Dr. Helmut Legerlotz Foundation to work with Professor Heinz Heimgartner in the University of Zürich on the synthesis of selenium-containing heterocycles. After this postdoctoral stay, he moved to the contract manufacturer Lonza AG (Switzerland) to work in the process development in the new business department of organic fine chemicals. He recently moved to Lonza Braine (Belgium) to work as Chemical Research Project Leader in peptide and oligonucleotide chemistry.

14.17

Rings containing Phosphorus

A. M. Shestopalov

Zelinsky Institute of Organic Chemistry, Moscow, Russia

A. A. Shestopalov

Duke University, Durham, NC, USA

© 2008 Elsevier Ltd. All rights reserved.

14.17.1	Introduction	901
14.17.2	Experimental Structural Methods	901
14.17.3	Parent Ring with One Phosphorus Atom	913
14.17.3.1	Seven-Membered Rings	913
14.17.3.2	Eight-Membered Rings	920
14.17.3.3	Rings Larger than Eight-Membered	923
14.17.4	Rings with Two or More Heteroatoms	924
14.17.4.1	Rings Containing Two Phosphorus Atoms	924
14.17.4.2	Rings Containing One Phosphorus and One Heteroatom Other than Phosphorus	927
14.17.4.2.1	Rings containing phosphorus and oxygen	927
14.17.4.2.2	Rings containing phosphorus and nitrogen	929
14.17.4.2.3	Rings containing phosphorus and heteroatom other than O or N	932
14.17.4.3	Rings Containing Phosphorus and Two or More Heteroatoms	932
14.17.5	Bicyclic Systems with Bridgehead Phosphorus	940
14.17.6	Further Developments	941
	References	941

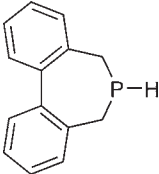
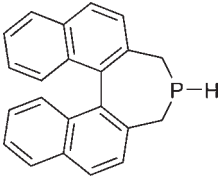
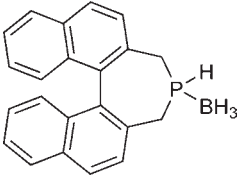
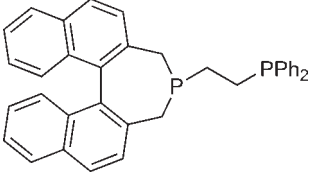
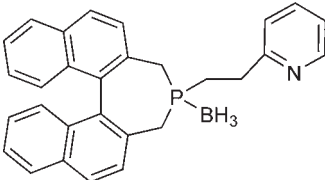
14.17.1 Introduction

This chapter describes phosphorus heterocycles with greater than six-membered rings, which appeared in the literature after 1995. For the phosphorus macrocycles published before 1996, see reviews by Pabel and Wild in CHEC-II(1996) <1996CHEC-II(9)947> and by Caminade and Majoral <1994CRV1183>.

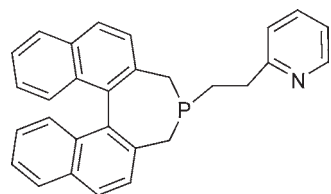
14.17.2 Experimental Structural Methods

The position of the ^{31}P nuclear magnetic resonance (NMR) peaks of the phosphorus-containing heterocycles depends on a type of hybridization of the phosphorus atom, on the nature of the substituents bonded to phosphorus, and, to a lesser degree, on the size of the heterocycle (Table 1). Complex formation of the phosphorus atom with electron-withdrawing atoms causes a significant deshielding effect on the ^{31}P peak's position. Phosphopines with P–N bond usually show the ^{31}P NMR signals in the δ 60–80 ppm region; whereas, complexes of phosphorus with ruthenium(II) or compounds bearing P–Cl fragment experience ^{31}P NMR signal shift into the low-field area of 95–120 ppm. Bicyclic systems with sp^2 phosphorus have the ^{31}P NMR shifts between 260 and 270 ppm. In contrast, phosphorus atoms of **25** and **26** are shielded by sulfur and selenium, which results in the shift of the ^{31}P NMR signals into the high-field region of –65.0 and –41.1 ppm. Alkyl substituents at the α -position to the phosphorus atom only slightly affect the ^{31}P NMR signals. For example, **28–34** show small shift of the ^{31}P NMR signals into the low field with increase of the substituent size from 63.43 to 72.91 ppm. The size of the heterocycle also affects only slightly the ^{31}P NMR signal in phosphorus compounds, for example, **15**, **16**, and **40–42**.

Table 1 Positions of the ^{31}P NMR signals in the phosphorus macrocycles

Compound		^{31}P NMR signal, δ , ppm (CDCl_3)	References
	1	-31.80	1998TL4291
	2	-30.50	1998IC6408
	3	21.17	1998IC6408
	4	9.76 11.66 Mixture of diastereomers	1998IC6408
	5	48.69	1998IC6408

(Continued)



6

6.31

1998IC6408

7

R = -NEt₂

76.8 (CD₂Cl₂)

2003JOM(675)91

8

R = -NMe₂

73.2

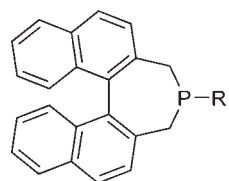
2003JOM(675)91

9

R = -N-*i*-Pr₂

46.0

2003JOM(675)91



10

R =

68.0

2003JOM(675)91

11

R =

74.4 (CD₂Cl₂)

2003JOM(675)91

12

R =

61.5

2003JOM(675)91

13

R =

97.5 (acetone-*d*₆)
(*J*_{P,Rh} = 169.2 Hz)

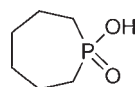
2003JOM(675)91

14

R = Cl

115.1

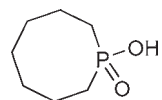
2003JOM(675)91



15

62.00

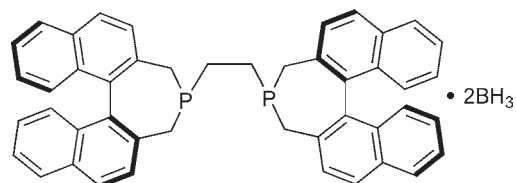
1995JOC6076



16

61.8

1995JOC6076



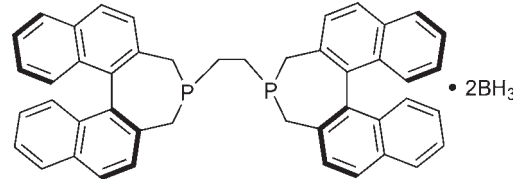
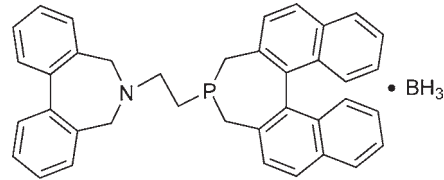
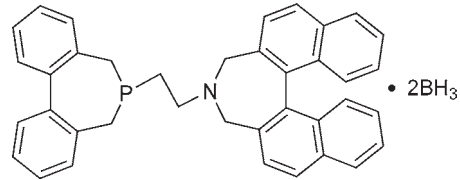
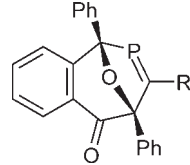
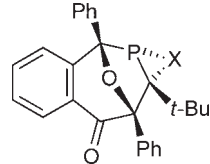
17

50.3

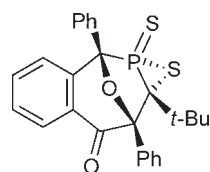
2003JOC3258

(Continued)

Table 1 (Continued)

Compound	^{31}P NMR signal, δ , ppm (CDCl_3)	References
	18	50.7
	19	47.2
	20	44.14
	21	R = Bu ^t 261.4 (C_6D_6)
	22	R = Pen ^t 267.1 (C_6D_6)
	23	R = 1-Me ^c Hex 268.5 (C_6D_6)
	24	R = 1-Ad 267.5 (C_6D_6)
	25	X = S -65.0
	26	X = Se -41.1

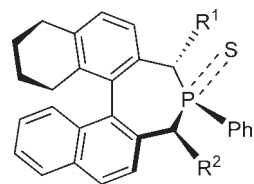
(Continued)



27

21.5

2000T6259



28

$R^1 = R^2 = H$

63.43

2005TA3416

29

$R^1 = Me;$
 $R^2 = H$

67.09

2005TA3416

30

$R^1 = H;$
 $R^2 = Me$

64.69

2005TA3416

31

$R^1 = R^2 = Me$

69.11

2005TA3416

32

$R^1 = R^2 = Et$

70.29

2005TA3416

33

$R^1 = R^2 = i\text{-}Pr$

65.57

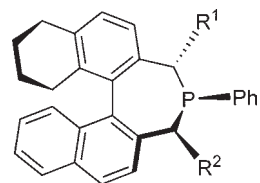
2005TA3416

34

$R^1 = R^2 = n\text{-}Bu$

72.91

2005TA3416



35

$R^1 = H;$
 $R^2 = Me$

18.57

2005TA3416

36

$R^1 = R^2 = Me$

33.09

2005TA3416

37

$R^1 = H; R^2 = Et$

15.09

2005TA3416

38

$R^1, R^2 = Et$

31.51

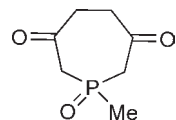
2005TA3416

39

$R^1, R^2 = n\text{-}Bu$

36.21

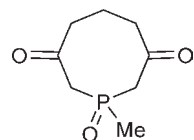
2005TA3416



40

29.8 (DMSO- d_6)

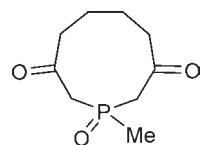
1977JA8370



41

29.0 (DMSO- d_6)

2000T6259



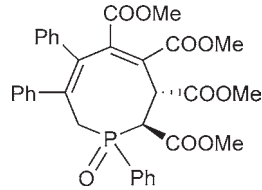
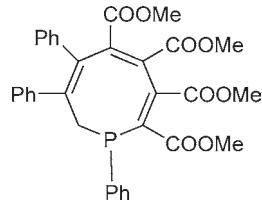
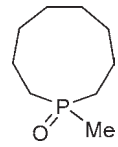
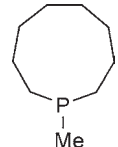
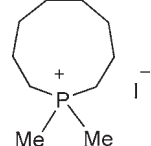
42

32.0 (DMSO- d_6)

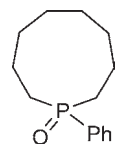
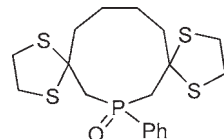
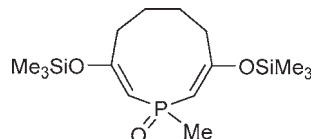
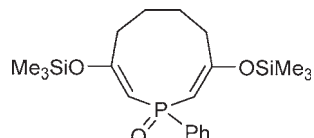
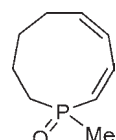
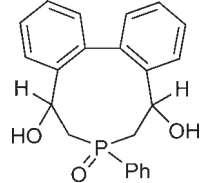
2000T6259

(Continued)

Table 1 (Continued)

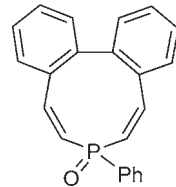
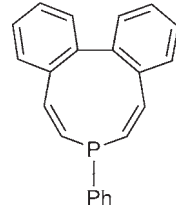
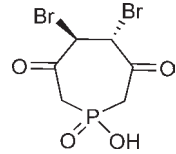
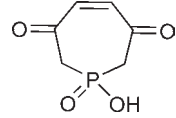
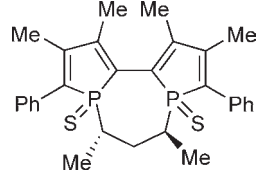
Compound		^{31}P NMR signal, δ , ppm (CDCl_3)	References
	43	26.3	1998HAC9
	44	47.4	1998HAC9
	45	48.9	1977JA8370, 1980JA4838, 1982JOC905
	46	−33.8	1977JA8370, 1980JA4838, 1982JOC905
	47	31.9	1977JA8370, 1980JA4838, 1982JOC905

(Continued)

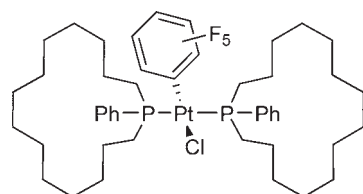
	48	51.1	1977JA8370, 1980JA4838, 1982JOC905
	49	63.8	1977JA8370, 1980JA4838, 1982JOC905
	50	20.3	1977JA8370, 1980JA4838, 1982JOC905
	51	16.1	1977JA8370, 1980JA4838, 1982JOC905
	52	36.2	1977JA8370, 1980JA4838, 1982JOC905
	53	29.9	1977JA8370, 1980JA4838, 1982JOC905

(Continued)

Table 1 (Continued)

Compound		^{31}P NMR signal, δ , ppm (CDCl_3)	References
	54	17.2	1977JA8370, 1980JA4838, 1982JOC905
	55	−24.7	1977JA8370, 1980JA4838, 1982JOC905
	56	1.18	1977JA8370, 1980JA4838, 1982JOC905
	57	30.0	1977JA8370, 1980JA4838, 1982JOC905
	58	67.3 63.3	2003CC1154

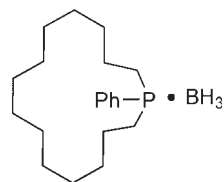
(Continued)



59

7.2 ($^1J_{\text{Pt}} = 2520 \text{ Hz}$)

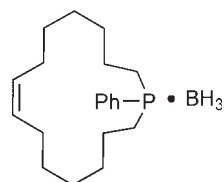
2004JCD1012



60

15.4

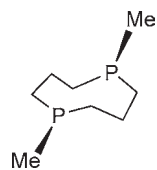
2004JCD1012



61

15.2

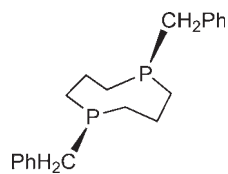
2004JCD1012



62

-39.63

1998J(P1)1643



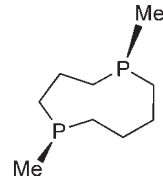
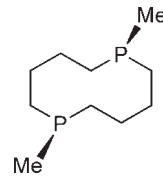
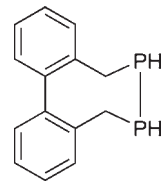
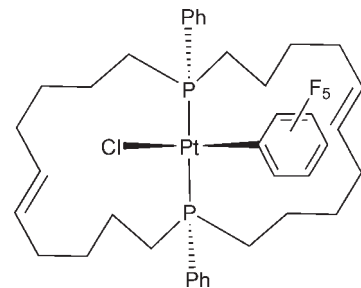
63

-40.24
-21.58

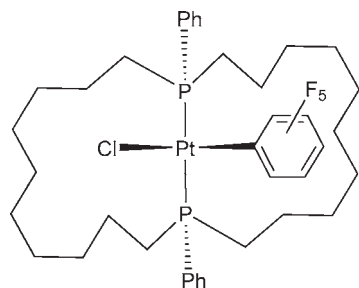
1998J(P1)1643

(Continued)

Table 1 (Continued)

Compound	³¹ P NMR signal, δ, ppm (CDCl ₃)	References	
	64	−39.77	1998J(P1)1643
	65	−37.32	1998J(P1)1643
	66	−129.11 (<i>J</i> _{P,H} = 191 Hz)	1998IC6408
	67	18.7	2004JCD1012

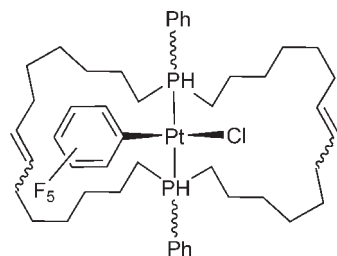
(Continued)



68

16.2

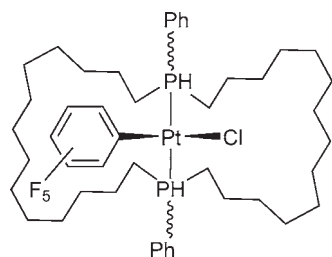
2004JCD1012



69

15.2; 14.8; 13.5 ($^1J_{\text{PtP}} = 2579$ Hz); 10.9; 9.3; 8.7

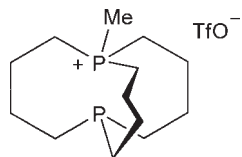
2004JCD1012



70

11.8 ($^1J_{\text{PtP}} = 2560$ Hz)
(*syn*-isomer);
15.8 ($^2J_{\text{PP1}} = 426.8$ Hz, $^1J_{\text{PPt}} = 2610$ Hz);
11.2 ($^2J_{\text{P1P}} = 426.8$ Hz, $^1J_{\text{P1Pt}} = 2556$ Hz)
(*anti*-isomer)

2004JCD1012



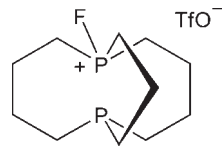
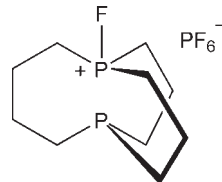
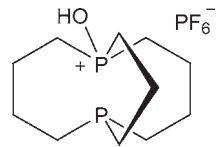
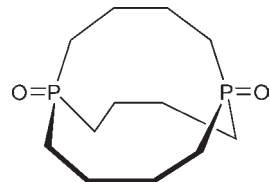
71

-25.87
-13.06

2001J(P2)288

(Continued)

Table 1 (Continued)

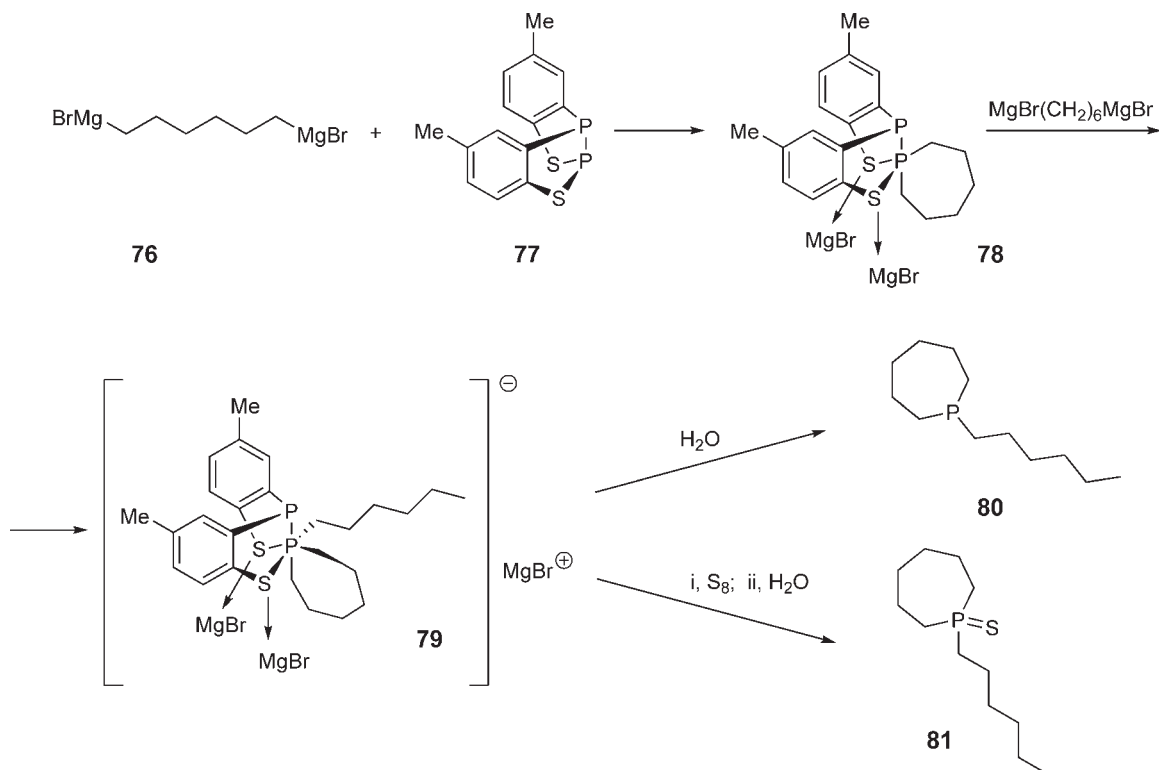
Compound	72	³¹ P NMR signal, δ, ppm (CDCl ₃)	References
		−49.18 (CD ₂ Cl ₂)	2001J(P2)288
	73	−46.54 (CD ₂ Cl ₂)	2001J(P2)288
	74	−21.41	2001J(P2)288
	75	70.72	2001J(P2)288

14.17.3 Parent Ring with One Phosphorus Atom

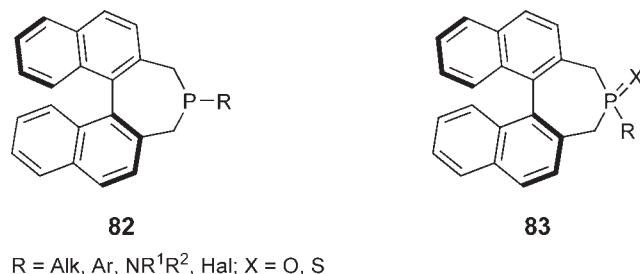
14.17.3.1 Seven-Membered Rings

Methods to synthesize seven-membered rings containing phosphorus were previously described in CHEC-II(1996) <1996CHEC-II(9)947>. Herein, we report new synthetic approaches to these compounds that appeared in the literature after 1995.

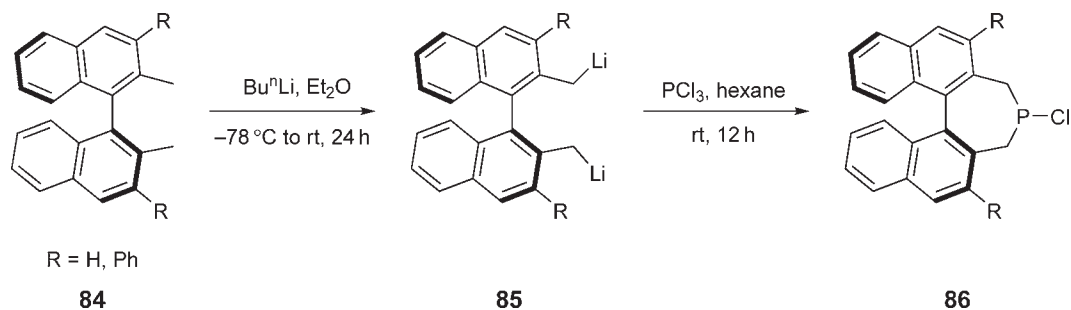
Seven-membered cyclic phosphine **80** and its sulfide **81** were synthesized via a one-pot reaction of 2 equiv of bis-Grignard **76** and a phosphorus-donating reagent **77** <2000SL1685>. Whereas, **80** and **81** were obtained with low yield (20%), which was rationalized by the instability of intermediate **79**, in which hexacoordinated hypervalent phosphorus spiro-conjugated with the seven-membered ring brings destabilization to the whole structure. Molecule **77** was previously shown as a highly reactive phosphorus donating agent, since the phosphorus atoms are bound to two sulfur atoms <1995TL447>.



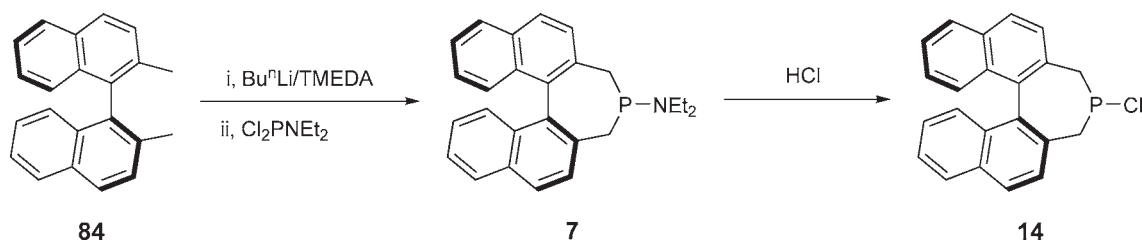
Binaphthophosphine derivatives **82** and **83** are often utilized as chiral auxiliaries in asymmetric hydrogenation reactions <2005TA3416, 2003AGE3509, 2003JOM(675)91, 2002TL4977, 2002TL4849>. They are readily available from the corresponding binaphthyls via several different pathways.



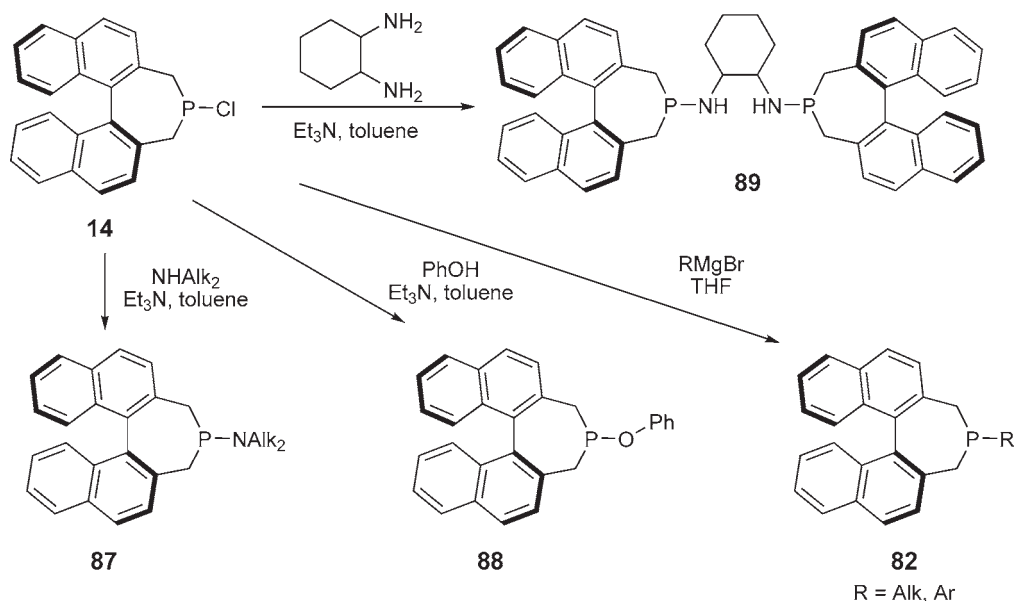
Chlorophosphepines **86** were synthesized in low yield (20–25%) from binaphthyls **84** in two steps, via initial metallation with BuLi and a subsequent reaction of **85** with phosphorus trichloride <2002TL4849>.



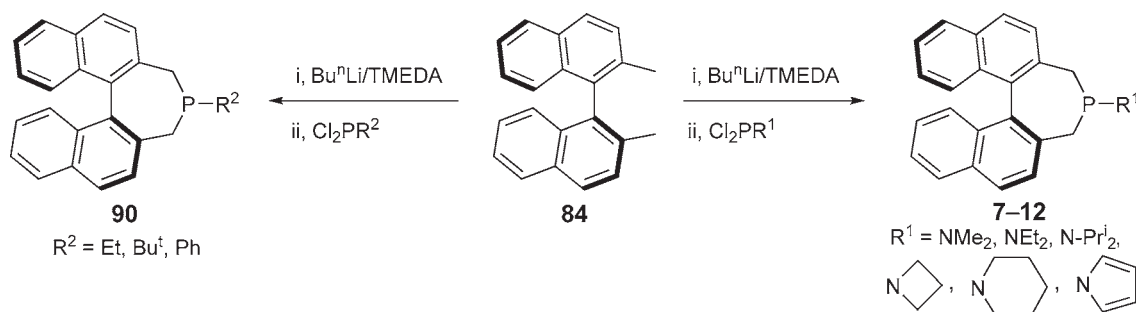
Alternatively, **14** was obtained from **85** (R = H) in 70% yield by its conversion into aminophosphinite **8**, which was then reacted with hydrochloric acid to produce **14** <2003JOM(675)91, 2002TL4977>.



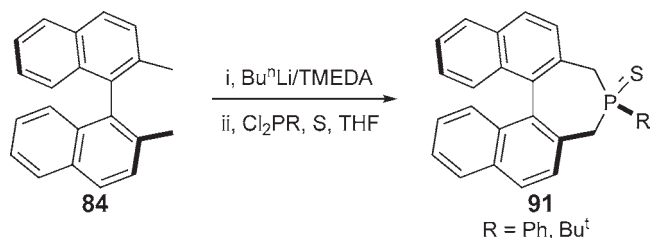
Compound **14** was reacted under mild conditions with different nucleophiles to give various N-, O-, and C-substituted phosphepines **82** and **87–89** in moderate to high yields (60–80%) <2004TA2621, 2003JOM(675)91, 2002TL4977, 2002TL4849>.



Different amino-, alkyl-, and aryl-substituted phosphepines **7–12** and **90** were also obtained in two steps directly from binaphthyl **84** and dichloro-*N,N*-dialkylphosphinamines, dichloro(alkyl)phosphines, or dichloro(aryl)phosphines in 60–80% yields. This method requires initial metallation of 2,2'-dimethylbinaphthyl **84** with *n*-BuLi and isolation of dilithio salt in the crystalline form <2004TA2621, 2003JOM(675)91, 2002TL4977>.

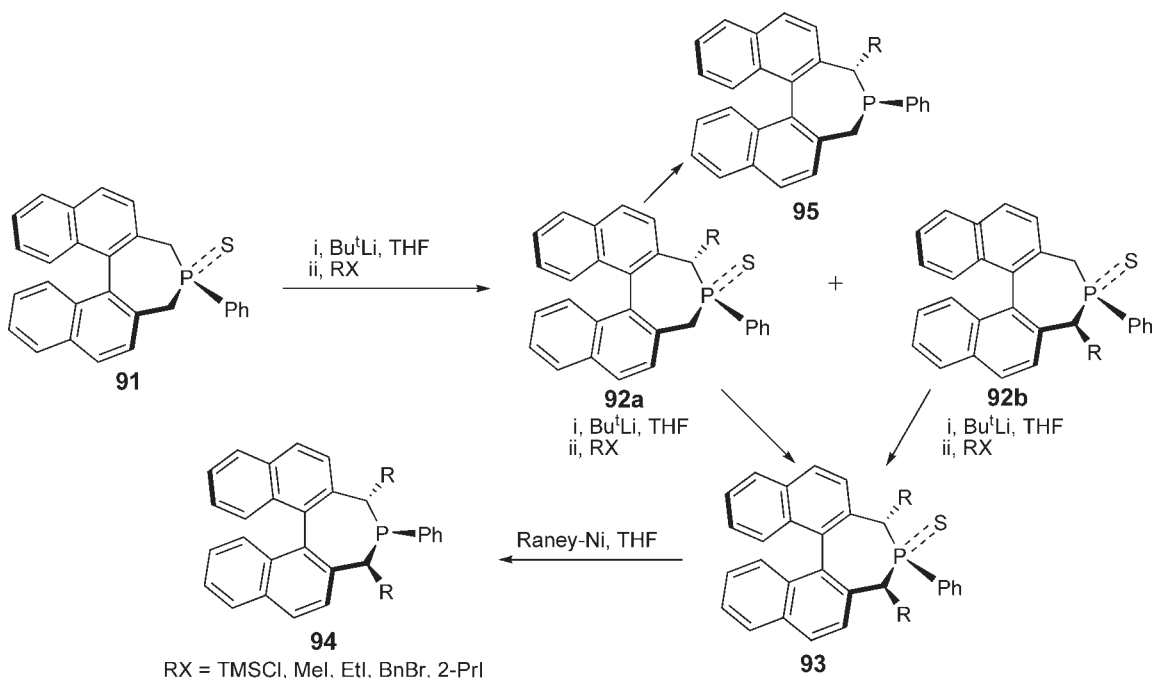


A similar approach was used for the synthesis of sulfides **91** by the one-pot reaction from 2,2'-dimethylbinaphthyl **84**. After lithiation of **84** with Bu^nLi , the generated dilithio salt was cyclized with Cl_2PPh or $\text{Cl}_2\text{P-Bu}^t$ and treated with sulfur to give **91** in 72% and 61% yields <2005TA3416, 2003AGE3509>.

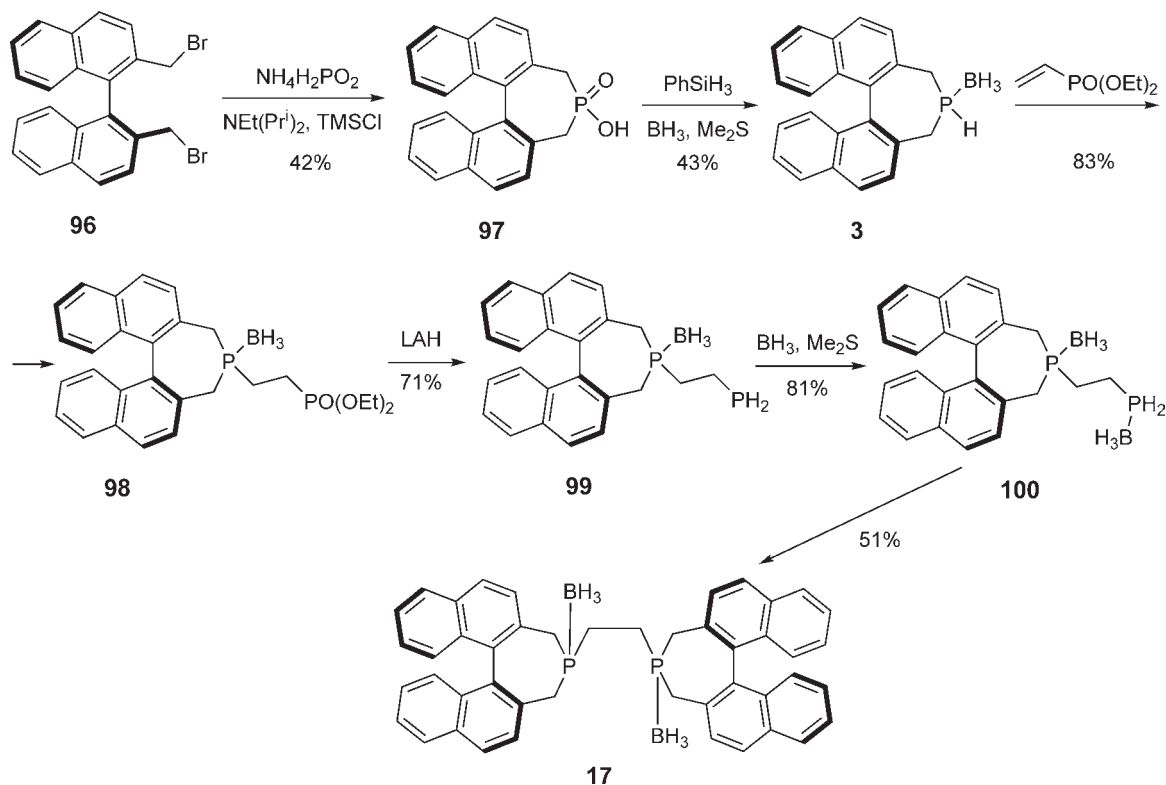


The phenyl-substituted sulfide **91** ($\text{R} = \text{Ph}$) was used for the synthesis of various α -disubstituted phosphepines **93** via sequential deprotonation steps with Bu^tLi and subsequent treatment with trimethylsilyl chloride (TMS-Cl), alkyl iodide, or benzyl bromide <2005TA3416>.

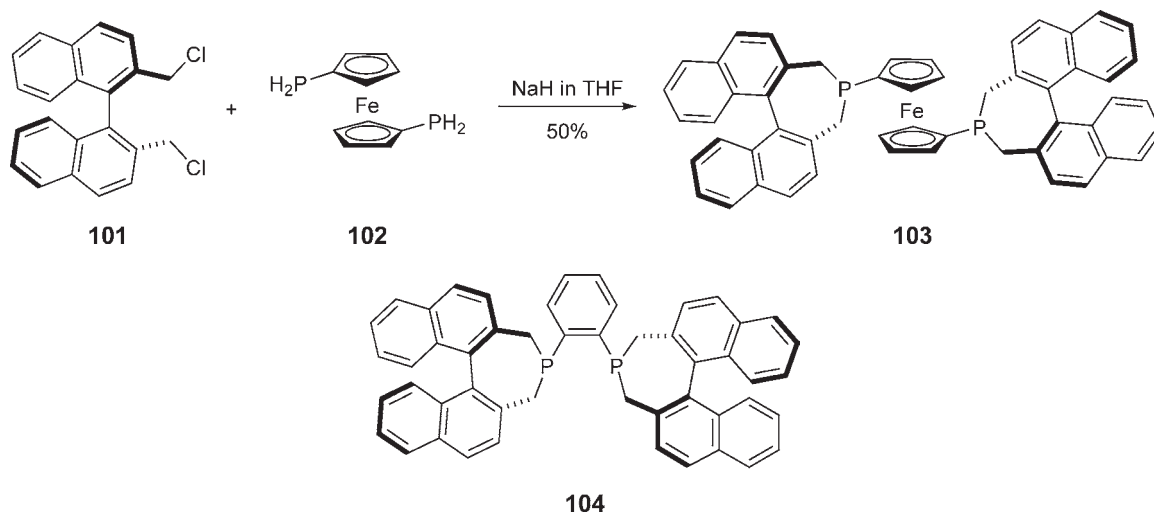
Compounds **93** were obtained in 35–96% yields from α -monosubstituted phosphepines **92a** and **92b**. A separation of the monosubstitution products was performed by column chromatography on silica gel with preferential elution of **92a**. Mono- and disubstituted phosphepines were shown to undergo reduction with Raney-Ni at room temperature to give phosphines **94** <2005TA3416>.



Binaphthophosphepines can also be synthesized from 2,2'-bis(halomethyl)-1,1'-binaphthyls **96**, **101**, and different phosphorus-containing compounds. Thus, the BH_3 adduct **17** was obtained in good yield from 2,2'-bis(bromomethyl)-1,1'-binaphthyl **96** and ammonium hypophosphite in six steps in a good yield <2003JOC3258, 2001OL2525>.

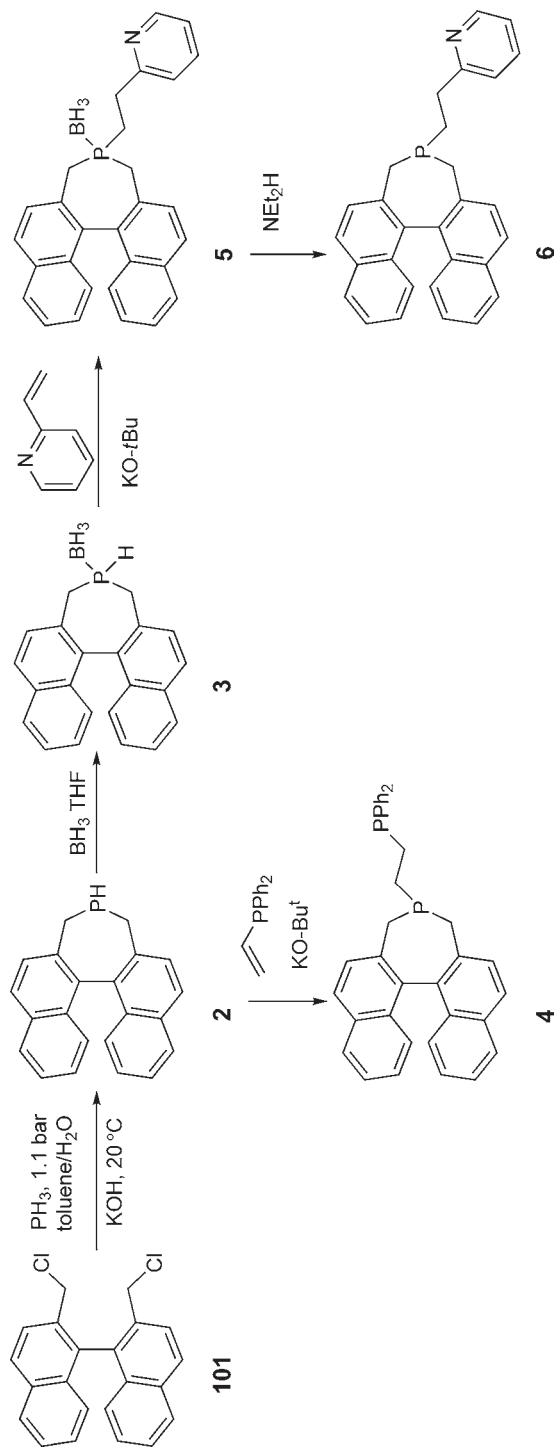


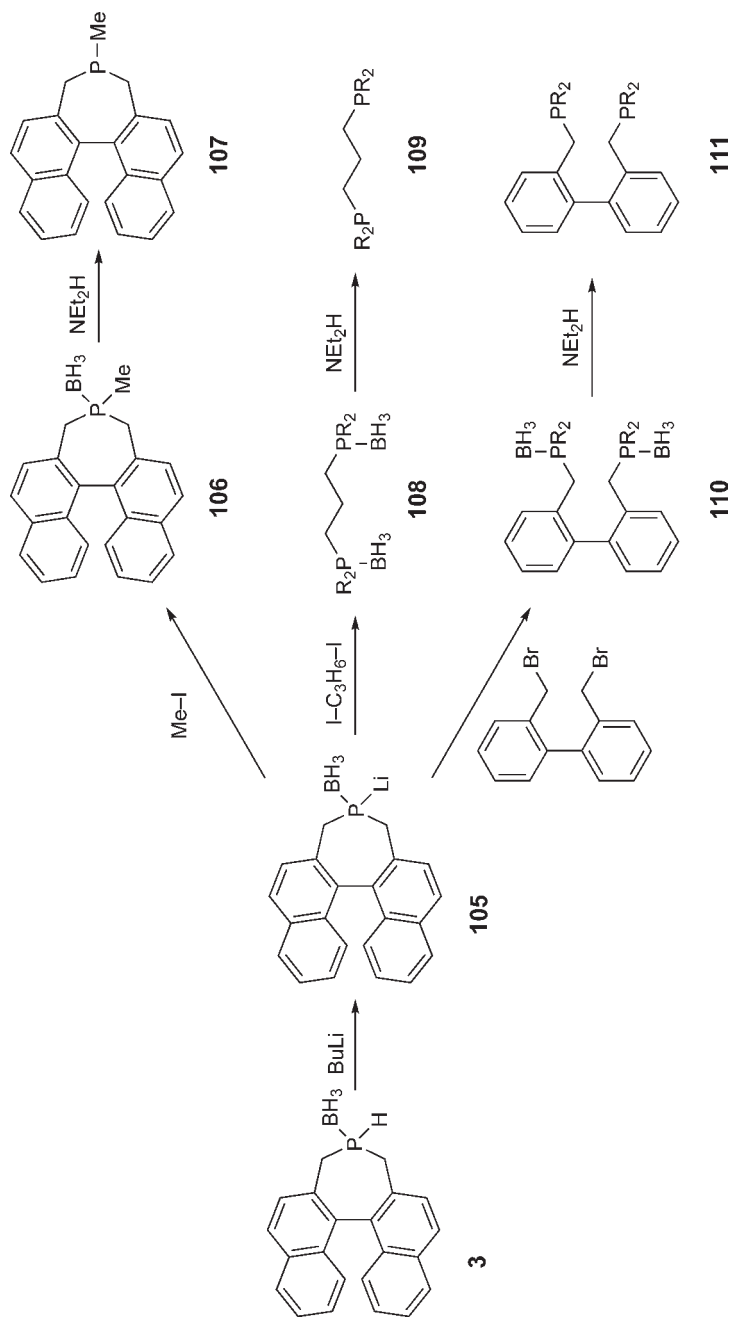
Similarly, (*R,R*)-f-binaphthane **103** and (*R,R*)-binaphthane **104** were obtained in one step directly from 2,2'-bis(chloromethyl)-1,1'-binaphthyl **101** and corresponding phosphines. These molecules were shown to be highly efficient chiral auxiliaries in the enantioselective hydrogenation of acyclic imines <2001AGE3425, 1999OL1679>.



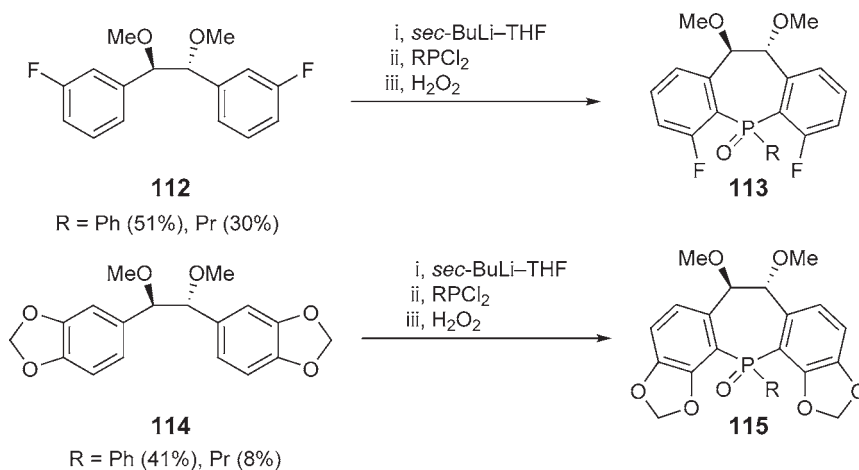
Unsubstituted secondary phosphine **2** was obtained by the reaction of the dichloride **101** with phosphine PH_3 in a toluene/dimethyl sulfoxide (DMSO)/water mixture (75% yield). The reactivity of the PH function of **2** and its BH_3 adduct **3** was examined in deprotonation and alkylation reactions. Compounds **2** and **3** were shown to readily react with diphenyl(vinyl)phosphine and 2-vinylpyridine to give **4** and **5**, respectively. Compound **5** was converted into free trisubstituted phosphine **6** upon treatment with diethylamine <1998IC6408>.

Attempts to deprotonate **2** with BuLi gave a mixture of unidentified side products; however, deprotonation of **3** with BuLi and subsequent alkylation of the lithium salt **105** with different primary alkyl halides gave various alkyl-substituted BH_3 adducts **106**, **108**, and **110**, which were converted into the corresponding free phosphines **107**, **109**, and **111** upon treatment with diethylamine <1998IC6408>.

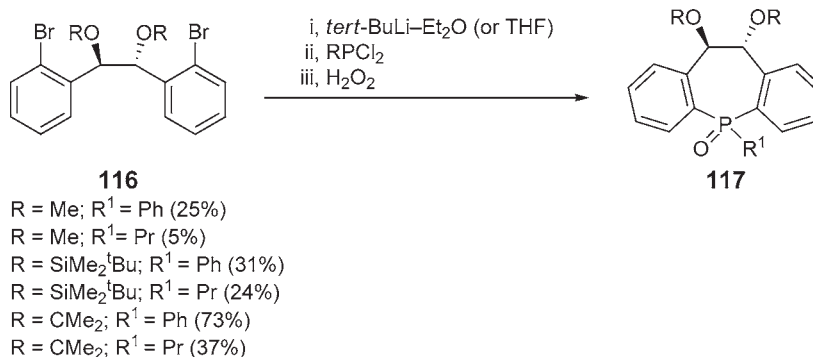




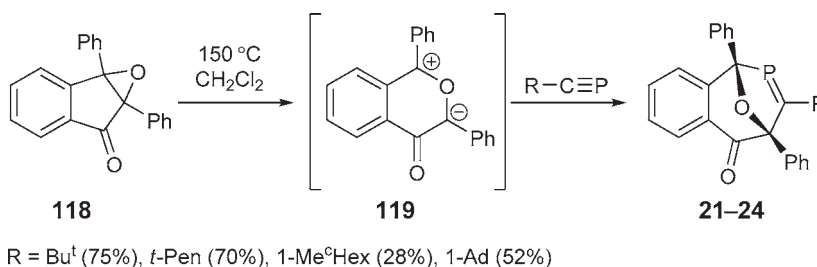
Phosphpepin oxides can be prepared from derivatives of 1,2-diphenylethane-1,2-diol by a double *ortho*-lithiation reaction or by bromine/lithium exchange, and by the subsequent reaction of the dilithiated salts with dichlorophosphines and oxidation with H_2O_2 <2001J(P1)279, 1996TL5609, 1996TA989>. Thus, homochiral dibenzophosphpepin oxides **113** and **115** were prepared by *ortho*-lithiation of **112** and **114** with *sec*-BuLi, respectively; in both cases, yields of the final phosphpepin oxides were higher for the phenyl-substituted versus the related propyl-substituted compound <1996TA989, 2001J(P1)279>.



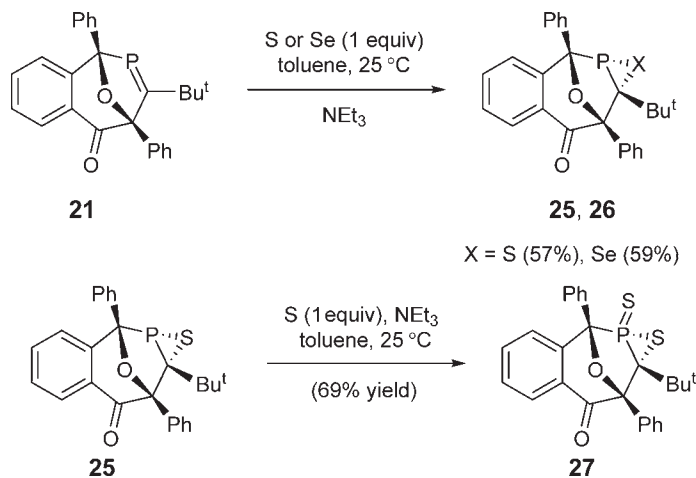
Similarly, phosphpepin oxides **117** were synthesized from 1,2-bis(2-bromophenyl)-1,2-dialkoxy(silyloxy)ethanes **116** using bromine/lithium exchange. Conversion of the dibromides **116** into dilithiated salts was achieved upon treatment with *tert*-BuLi <1996TL5609, 2001J(P1)279>. Physical and chemical properties of the phosphpepin 5-oxides were also investigated <1996TA989, 1996TL5609, 1997JOM(529)279, 1998J(P1)249, 2001J(P1)279>.



Various bicyclic phosphalkenes **21–24** were synthesized from oxirane **118**. Acceptor-substituted oxiranes underwent a ring opening under thermal stress to give the unstable carbonyl ylides. It was shown that upon heating 2,3-diphenylindenone oxide **118** underwent conversion into ylide **119**, which can react with various phosphalkynes in [3+2] cycloaddition reaction to give **21–24** <2000T6259>.



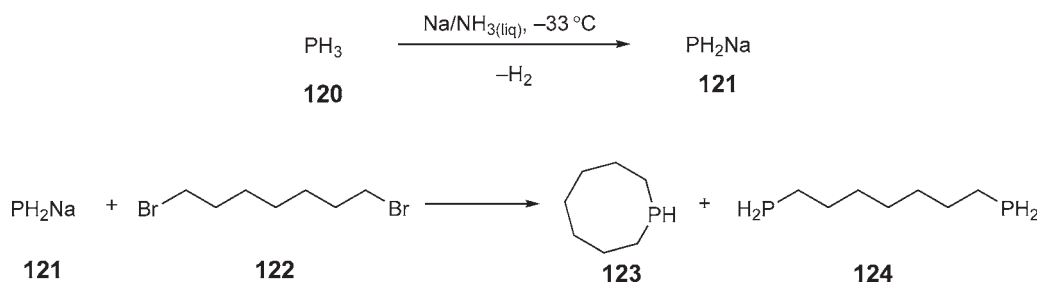
These phosphalkenes **21–24** were reacted with equimolar amount of sulfur or gray selenium to give the related polycycles **25** and **26**. In turn, thiaphosphirane **25** was shown to react with another equivalent of sulfur to generate thioxothiaphosphirane **27**.



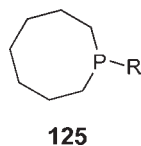
14.17.3.2 Eight-Membered Rings

Eight-membered ring molecules containing phosphorus can be obtained following similar cyclization methods after that of the smaller rings. Although some of these methods allow the preparation of the desired target compounds in just one or two steps, directly from the commercially available reagents, they generally suffer from low regioselectivity and poor yields <1963USP3086053, 1995JOC6076>.

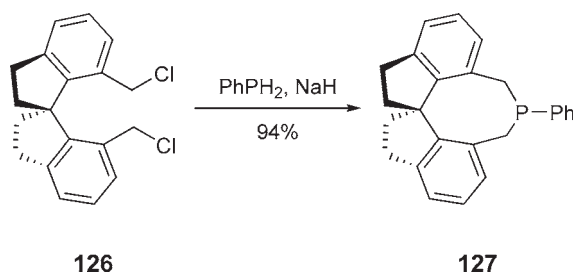
Phosphocane **123** was obtained from the phosphine **120** and 1,7-dibromoheptane **122** along with 1,7-diphosphinoheptane **124**; subsequent separation of the desired **123** from the mixture was achieved by fractional distillation.



Primary organophosphines were shown to react under the same conditions to give phosphocanes **125** (R = Alk, Ar) in mixtures with the corresponding diphosphinoalkanes <1963USP3086053>.

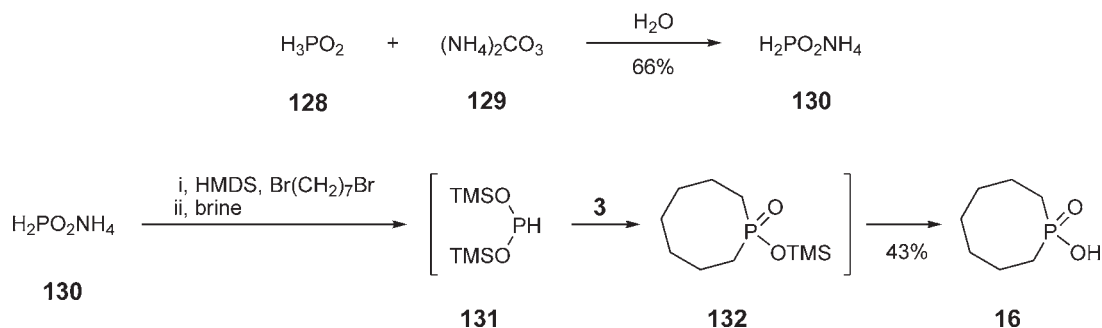


A similar method was used to obtain the *s*-SPINOL derivative **127** from the dielectrophilic precursor **126** <2005OL2333>. In contrast to the previously mentioned method, this reaction proceeds with a high yield (94%) and high regioselectivity, which can probably be explained by the favorably constrained conformation of **126** and by the bulkiness of the phenylphosphine.

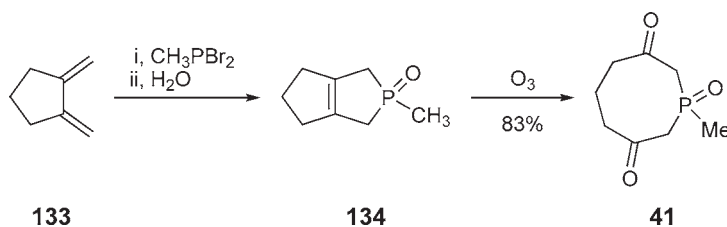


Compound **127** was exploited as an efficient ligand for Pd-catalyzed enantioselective allylation of aldehydes with allylic alcohols <2005OL2333>.

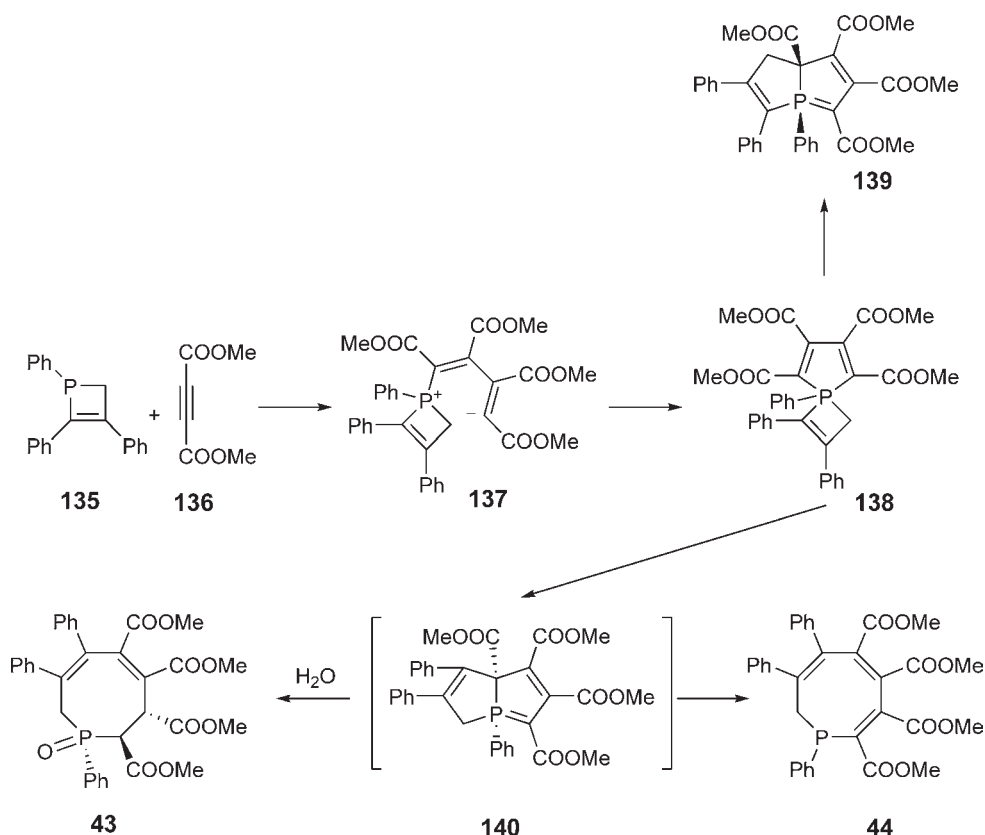
An analogous approach was employed to obtain an eight-membered-ring phosphocanic acid **16** by a double-Arbuzov reaction of the bis(trimethylsiloxy)phosphine (BTSP) with the dielectrophilic 1,7-dibromoheptane. Although this reaction yielded final product only in 43%, it proceeded with high regioselectivity and a very simple isolation and purification of the final acid **16** by the extraction with organic solvent from a water solution was reported <1995JOC6076>.



A different approach to eight-membered ring phosphorus compounds can be realized by the ring opening of the cycles. Thus, bicyclic phospholene **134** was used as a precursor to the diketo derivative **41** <1977JA8370>. The McCormack cycloaddition of 1,2-dimethylenecycloalkane **133** to a phosphorus halide afforded bicyclic phospholene **134** in a good yield, which in the next step was subjected to the ring-opening ozonolysis at -78°C in MeOH to give exclusively **41** in 83% yield.



Another example of a ring-opening reaction that led to the eight-membered-ring phosphocanes was suggested as a result of the interaction between 1 equiv of 1,3,4-triphenyl-1,2-dihydrophosphite **135** and 2 equiv of dimethyl acetylenedicarboxylate (DMAD) **136** <1998HAC9>. This reaction gave three major products each of which contained one molecule of dihydrophosphite **135** and two molecules of DMAD.



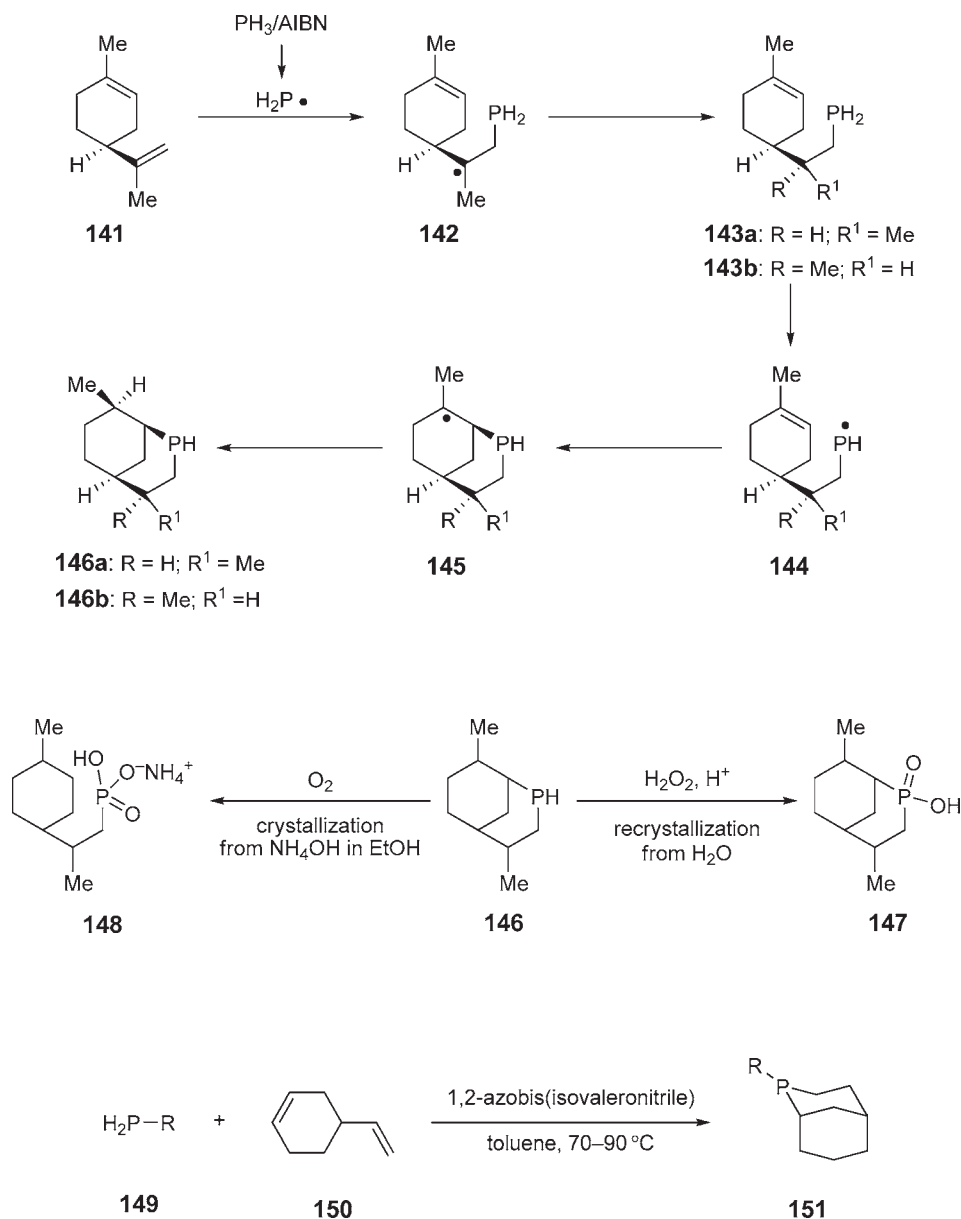
A proposed mechanism for the formation of the products **139**, **43**, and **44** involves sequential Michael additions of the dihydrophosphite **135** to DMAD **136** to form a zwitterionic intermediate **137**, which cyclized with the resulting anion to give a spirocyclic phosphole **138**, and lastly a 1,2-shift of the methylene group to yield the phospholophosphole ylide **139**. An alternative rearrangement of the spirocyclic intermediate **138** resulted in a 1,2-shift of the other dihydrophosphite ring carbon, and in generation of an isomeric phospholophosphole ylide **140**, which would yield the tetrahydrophosphocin oxide **43**, if reacted with water. A spontaneous ring opening of the isomeric intermediate **140**, without hydrolysis, would give the dihydrophosphocin **44**. Difference in the reactivity between the intermediate **140** and ylide **139** can be explained by the increased stability of **139** due to the conjugation of the double bond in **139** to the phosphonium ion. Molecular structures of the dihydrophosphocin oxide **43** and phospholophosphole ylide **139** were studied by X-ray analysis <1998HAC9>.

Bicyclic eight-membered ring phosphorus compounds are usually obtained by the free radical reactions of the corresponding alkenes with phosphines. In most cases, these reactions require the presence of such free radical initiators as azobis(isobutyronitrile) (AIBN) or azobis(isovaleronitrile) (VAZO).

Reaction of the (*S*)-(-)-limonene **141** with phosphine in the presence of the AIBN produced a diastereomeric mixture of 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonanes **146a** and **146b** in a ratio 1:0.8, with an overall yield of the two isomers as 85% <2001TL2609>.

Phosphabicyclo[3.3.1]nonanes **146a** and **146b** were converted into the phosphinic acid, 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonan-2-ol 2-oxide **147**, upon treatment with hydrogen peroxide under acidic catalysis. The structure of phosphinic acid **147** was accomplished by an X-ray analysis. Additionally, it was shown that if phosphines **146a** and **146b** were exposed to air, they underwent a rapid oxidation to yield the ammonium salt of 2-(4-methylcyclohexyl)propylphosphonic acid **148**, whose structure was also confirmed by the X-ray analysis <2001TL2609>.

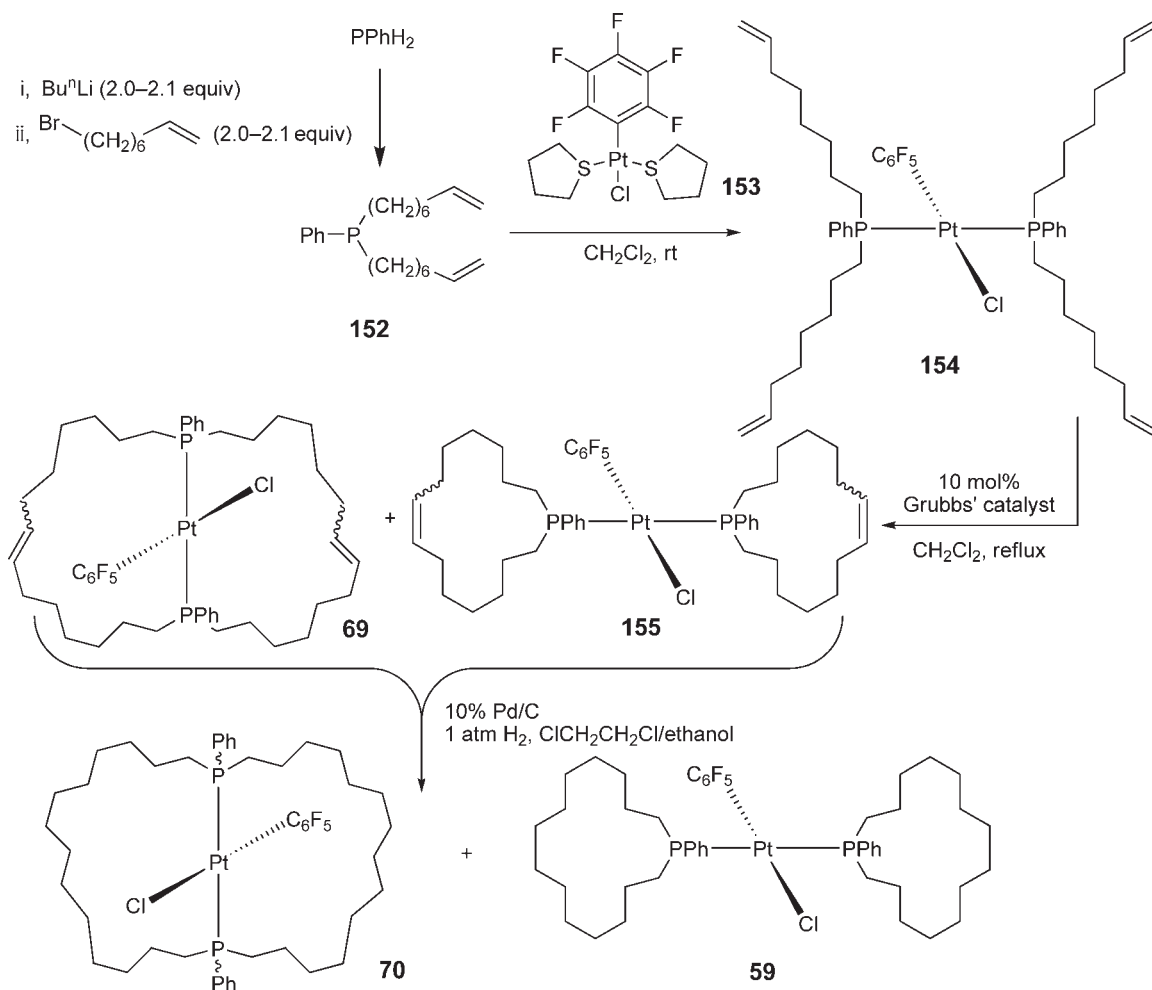
In a similar manner, phosphorus-substituted [3.3.1]phosphabicyclononanes **151** (R = dodecyl, cyclohexyl, phenyl) were obtained by the reactions of the 4-vinylcyclohexene **150** with the corresponding phosphines **149** in the presence of the azobis(isovaleronitrile) <2003WO2003068786A1>.



14.17.3.3 Rings Larger than Eight-Membered

Heterocycles larger than eight-membered containing one phosphorus were previously reviewed in CHEC-II(1996) <1996CHEC-II(9)947>.

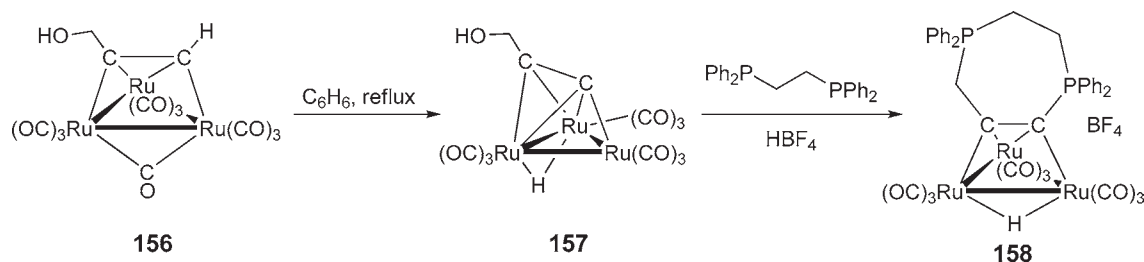
Interesting examples of the synthesis of a 15-membered cyclic phosphine via alkyl metatheses were published by Gladysz and co-workers <2004JCD1012>. Alkyl-containing phosphine **152** was obtained from the corresponding alkylbromide and phenylphosphine, and then with the platinum tetrahydrothiophene complex **153** gave the adduct **154**. Grubbs' catalyst was used to promote a ring-closing metathesis of adduct **154** to give a mixture of 15-membered cyclic phosphine **155**, 30-membered cyclic diphosphine **69**, and other cyclized compounds. Both unsaturated macrocycles **69** and **155** were hydrogenated with a Pd/C catalyst to give the saturated cyclic phosphines **70** and **59** in high yield, respectively.



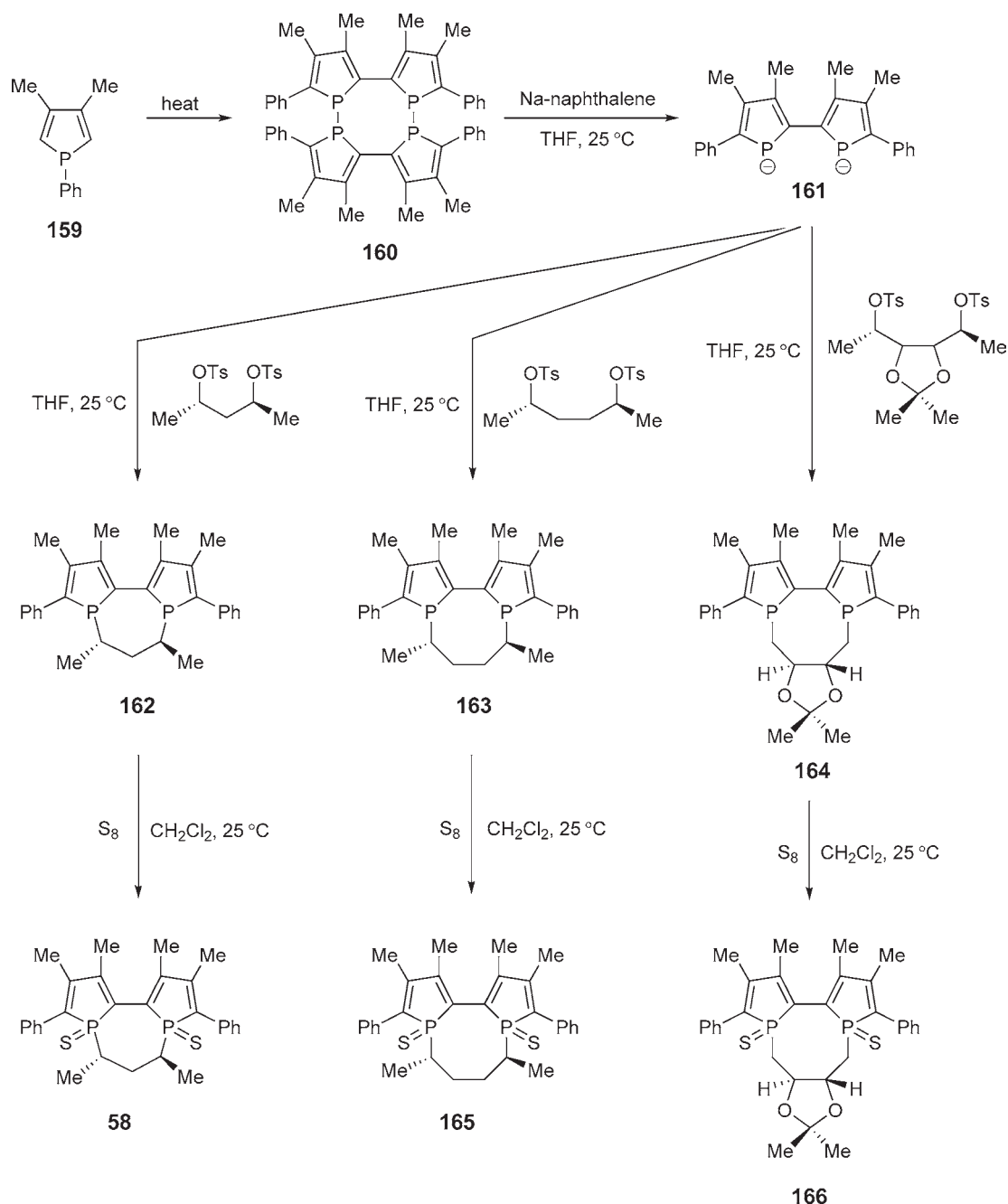
14.17.4 Rings with Two or More Heteroatoms

14.17.4.1 Rings Containing Two Phosphorus Atoms

The derivative of 1,4-diphosphhepane **158** was obtained from the hydroxymethyl-alkynyl ruthenium complex **157**, which underwent dehydration upon treatment with HBF_4 in CH_2Cl_2 . Subsequently, the generated alkene endured a double nucleophilic attack by bidentate (diphenylphosphino) ethane to give cationic cluster **158** in 94% yield <2006ICA(359)938>. The structure of **158** was confirmed by the X-ray data.



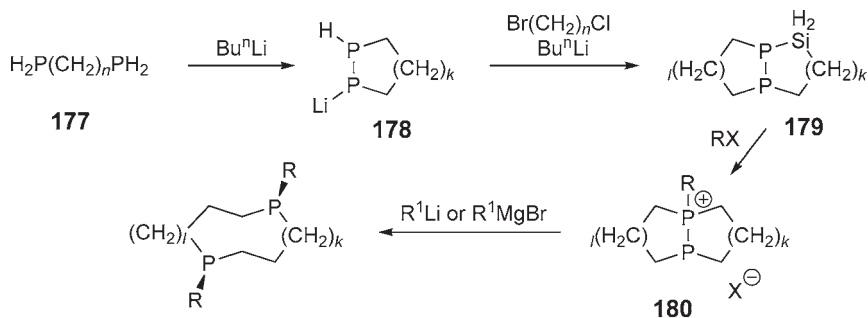
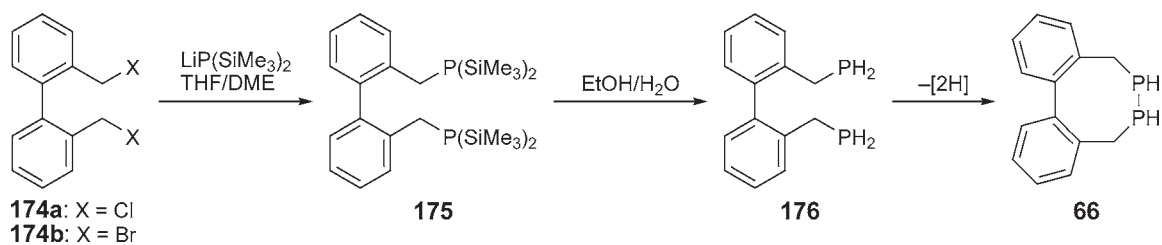
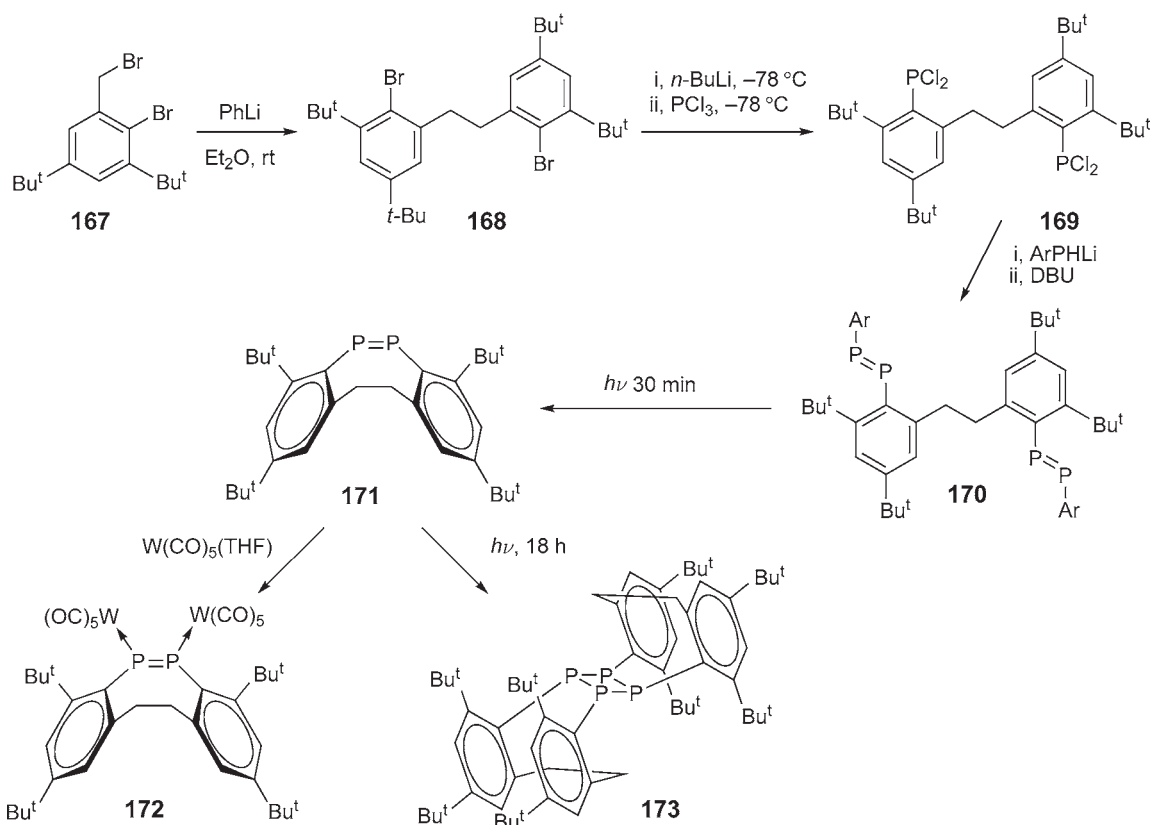
Diastereomeric mixtures (three isomers) of 2,2'-biphospholes **162–164** were synthesized by asymmetric alkylation of 2,2'-biphospholyl anion **161** with enantiomerically pure diol ditosylates. The generated 2,2'-biphospholes were converted into the more stable disulfide derivatives **58**, **165**, and **166** <2005OM5549, 2003CC1154>. Dianion **161** was generated in two steps from 1-phenyl-2,3-dimethylphosphole **159** by pyrolysis and subsequent treatment of the formed phosphole tetramer **160** with sodium naphthalene. Structures of the diastereomers of disulfides **58** and **165** were established by the X-ray crystallographic data.



Internal diphosphene **171** was obtained (10% yield) from a mixture with other diphosphenes upon irradiation of the benzene-*d*₆ solution of **170** with a 500 W Xe-lamp at 25 °C for 30 minutes. When THF solution of an excess amount of W(CO)₅(THF) was added to a photolysis mixture of **170** after 30 min irradiation, red crystals of **172** were isolated in 7% yield. Upon 18 h irradiation of **170**, cyclotetraphosphane **173** was obtained in 61% yield <1996TL7815>.

Tetrahydro-1,2-diphosphocine **66** was isolated as a by-product in the synthesis of 1,1'-biphenyl-bridged diprimary phosphine **176** <1998IC6408>.

Monoquaternization of *cis*-diphosphabicycloalkanes **179**, followed by the treatment of the monoquaternary salts **180** with alkylolithium or Grignard reagents to stereoselectively cleave P–P bond, produced *cis*-disubstituted diphosphacycloalkanes **68**, **181**, **182**, **63–65**, and **183**. Di-quaternization of **179**, and subsequent hydrolysis and reduction with LiAlH₄, gave the *trans*-isomers of **62** and **64** <1998J(P1)1643>.

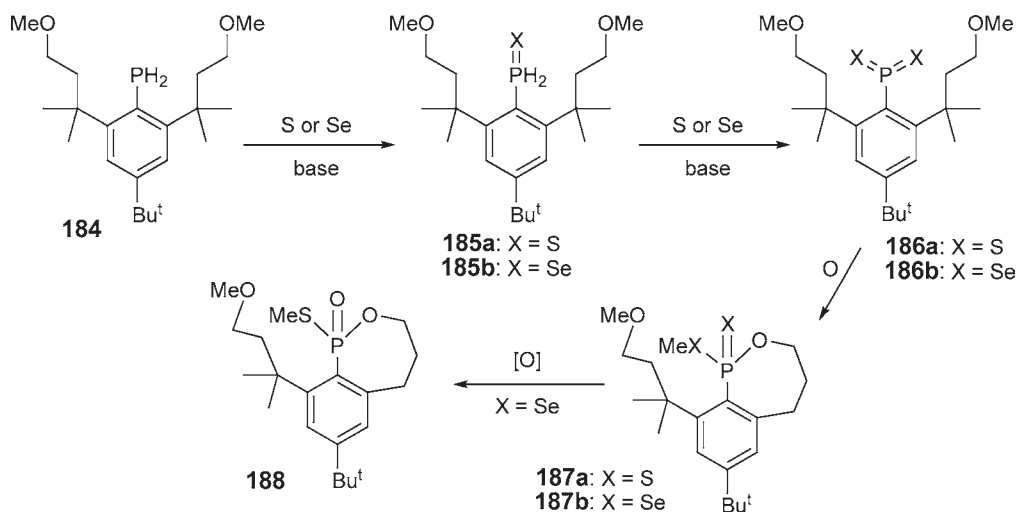


- 62** $k = l = 1$; $\text{R} = \text{R}^1 = \text{Me}$
181 $k = l = 1$; $\text{R} = \text{Me}$; $\text{R}^1 = \text{Bz}$
182 $k = l = 1$; $\text{R} = \text{Bz}$; $\text{R}^1 = \text{Ph}$
63 $k = l = 1$; $\text{R} = \text{R}^1 = \text{Bz}$
64 $k = 2$; $l = 1$; $\text{R} = \text{R}^1 = \text{Me}$
65 $k = l = 2$; $\text{R} = \text{R}^1 = \text{Me}$
183 $k = l = 2$; $\text{R} = \text{R}^1 = \text{Bz}$

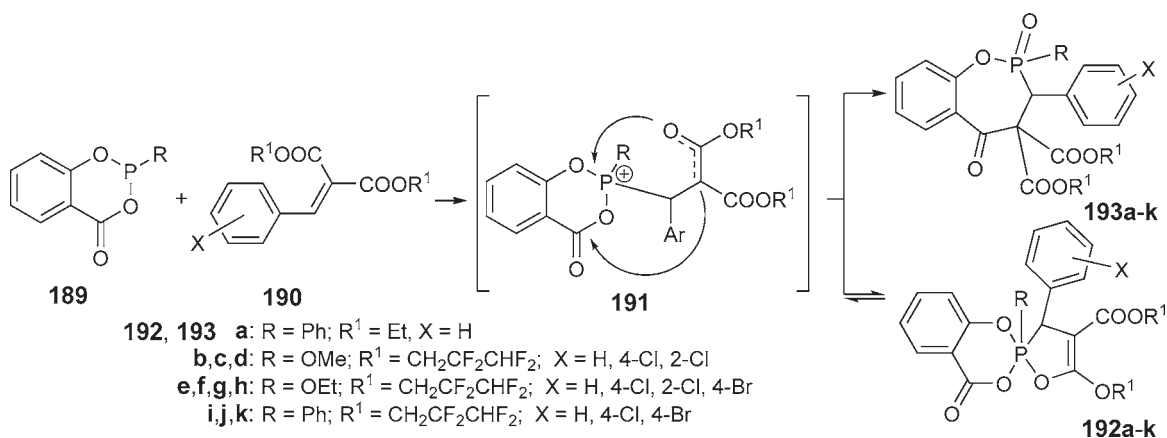
14.17.4.2 Rings Containing One Phosphorus and One Heteroatom Other than Phosphorus

14.17.4.2.1 Rings containing phosphorus and oxygen

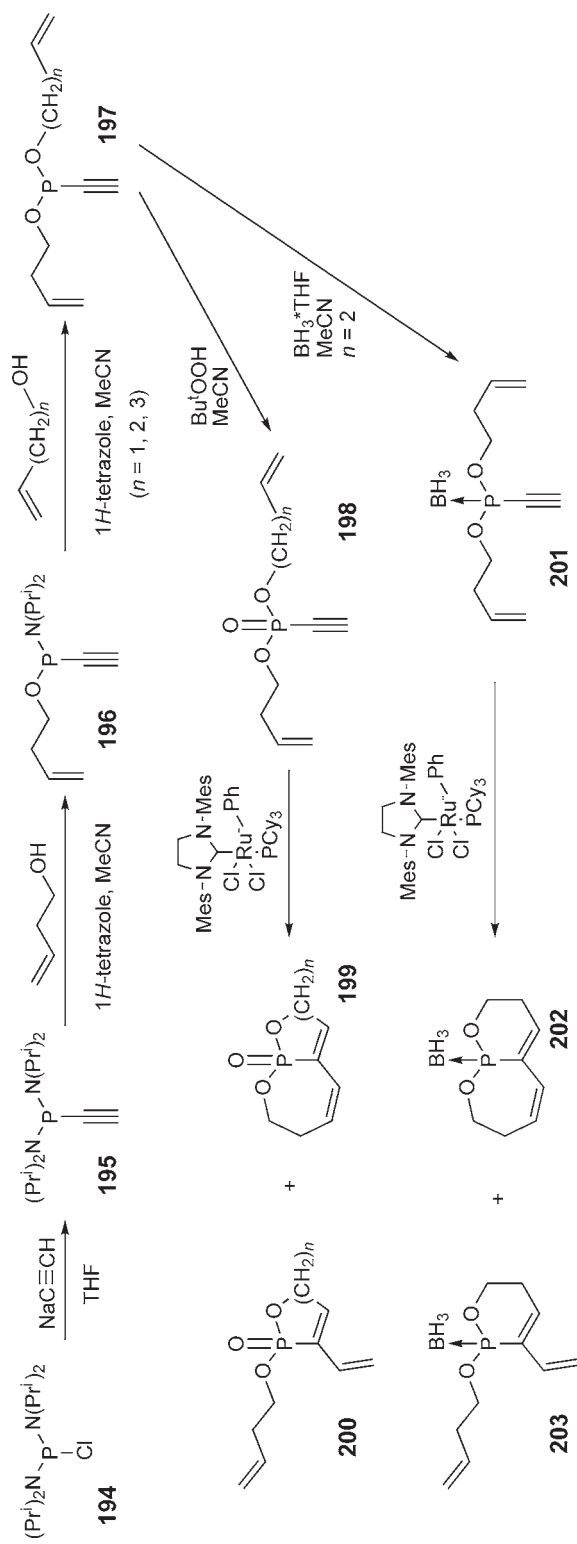
Phosphine **184** was treated at 25 °C with elemental S₈ or Se in the presence of a catalytic amount of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) to produce dichalcocoxophosphoranes **186a** and **186b**; however, **186a** changed to **187a** in the reaction mixture, probably via an intramolecular rearrangement. Similarly, **186b** changed to **188** during the isolation process, possibly as a result of the rearrangement, followed by oxidation <2000T43>.



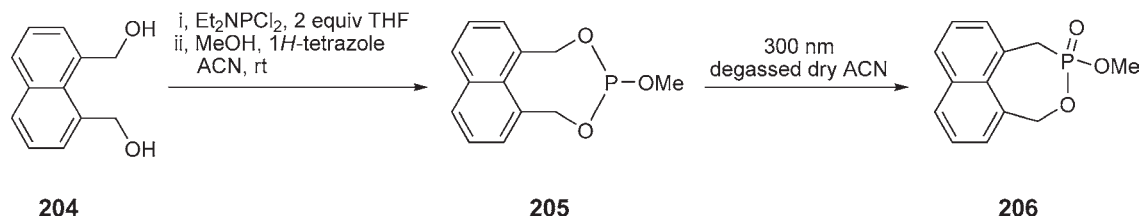
The reaction of dioxaphosphorin-4-ones **189** with arylidenemalononic acid esters **190** produced oxaphosphepin-2,5-diones **193a–k** with high regio- and stereoselectivity under mild conditions (90–95% yield). It was also shown that this reaction gave phosphorane derivatives **192a–k** as by-products (5–10% yield); however, due to reversibility of the second pathway, **192a–k** were easily converted into **193a–k**, respectively, under mild heating <2001RJC525, 2004ARK95>.



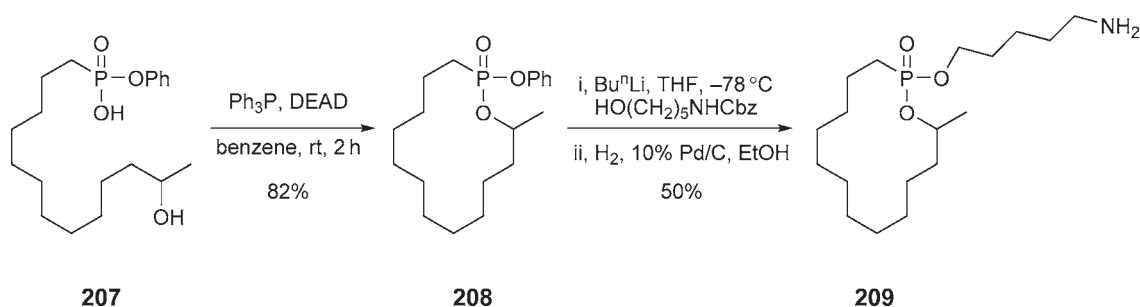
Mono- and bicyclic phosphorus heterocycles **199**, **200**, **202**, and **203** were synthesized starting from the bifunctional phosphorylating agent bis(diisopropylamino)ethynyl phosphine **195** via ring-closing enyne metathesis using 4,5-dihydroimidazol-2-ylidene ruthenium benzylidene complex, as a catalyst. Bicyclic phosphorus oxides **199** were obtained in 66–83% yield, whereas phosphorus borane derivative **202** was isolated in 74% yield <2001TL8231>.



Direct irradiation of the eight-membered dioxaphosphocine **205** in argon-saturated MeCN at 300 nm produced the ring-constructed oxaphosphepinoxide **206** in 45% isolated yield via a photo-Arbusov rearrangement. Dioxaphosphocine **205** was prepared from naphthylmethyl diol **204** by the reaction with Cl_2PNEt_2 and subsequent 1*H*-tetrazole-catalyzed coupling of the produced intermediate with 1 equiv of MeOH <2002JOM(646)239>.

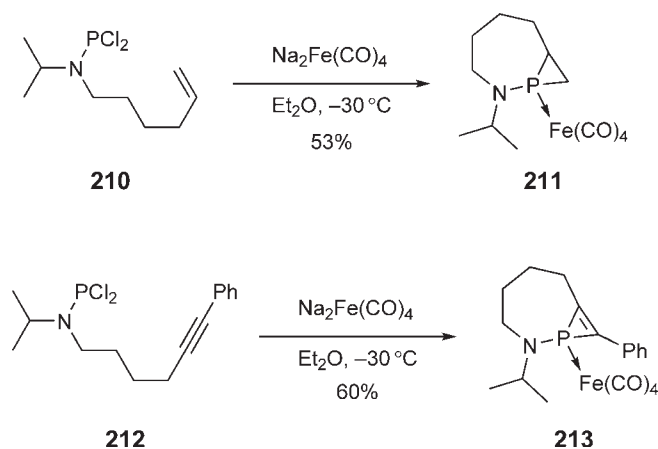


The 14-membered ring phosphonate **208** was synthesized via cyclization of the acyclic precursor **207** using the Mitsunobu reaction. Macrocycle **208** was obtained in 82% yield as a mixture of two diastereomers (5:1). The phenyl moiety in **208** was substituted with *N*-Cbz-protected aminopentanol, followed by hydrogenolysis in EtOH with hydrogen and 10% Pd/C to afford amine **209** in 50% yield <2001OL643, 2002CJC1643>.

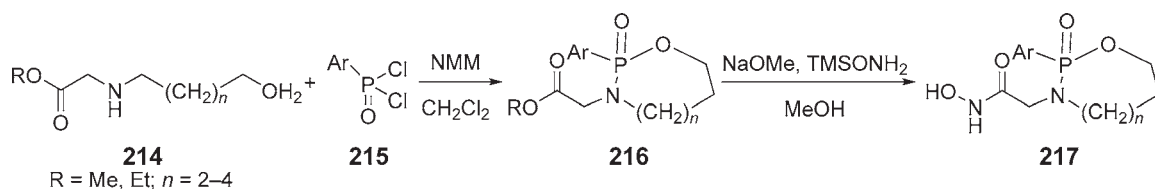


14.17.4.2.2 Rings containing phosphorus and nitrogen

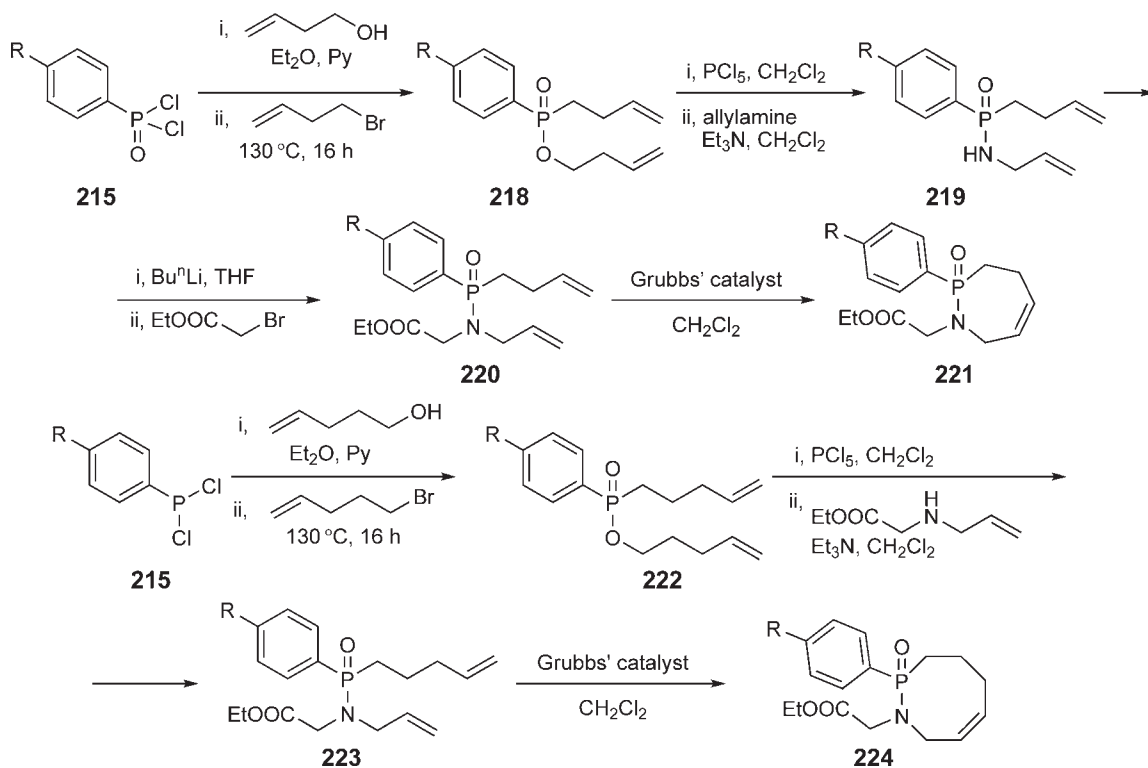
Highly strained bicyclic 2-aza-1-phosphiranes **211** and **213** were prepared as Fe/P-clusters by the reaction of $\text{Na}_2\text{Fe}(\text{CO})_4 \cdot 1,5$ -dioxane (Collman's reagent) with corresponding dichloro(dialkylamino)phosphanes **210** and **212** in Et_2O at -30°C . X-Ray studies demonstrated that saturated bicyclic complex **211** was remarkably stable <2005CEJ3631, 2005JOC8110>.



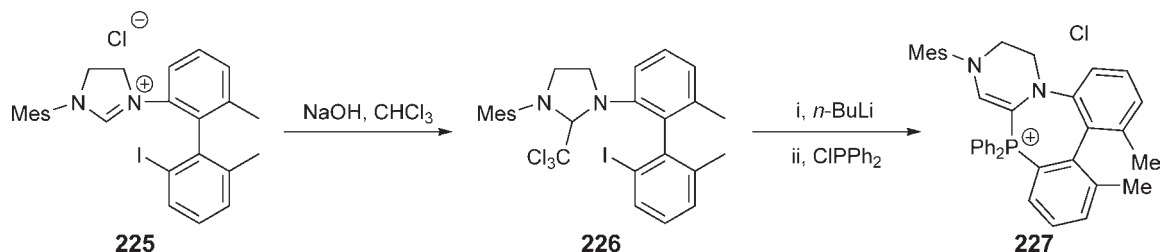
The cyclophosphonamide hydroxamic acids **217** were prepared by cyclization of the *N*-hydroxyalkyl amino acid esters **214** with phosphonyl dichlorides **215**, and by subsequent conversion of the ester group to a hydroxamic acid upon treatment with hydroxylamine and NaOMe in MeOH <2003BMC5461>.



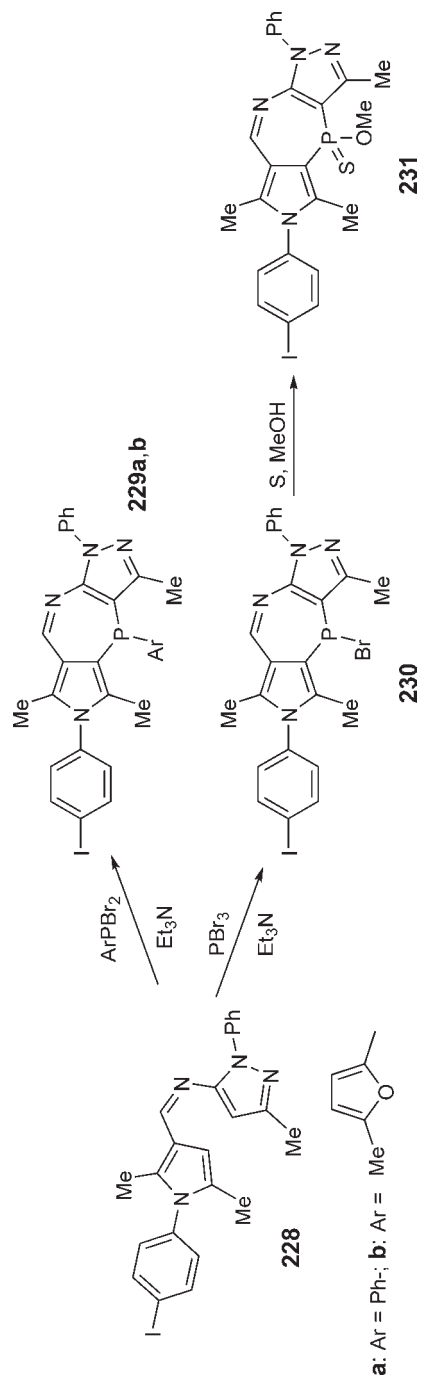
Dichloroarylphosphines **215** were treated with unsaturated alcohols and the corresponding bromides to effect Arbuzov-type rearrangement to alkyl alkenyl(aryl)phosphinates **218** and **222**. In turn, these phosphinates were cleaved with phosphorus pentachloride, and amidated with allyl amine or *N*-allylglycine ethyl ester to give phosphinamides **219** or **223**, respectively; the former was alkylated with ethyl bromoacetate, and the resulting phosphinamides **220** and **223** were cyclized in the presence of Grubbs' catalyst via ring-closing metathesis to the cyclic phosphinamides **221** and **224**, respectively <2003BMC5461>. Compounds **217** and **224** were tested as potent inhibitors of matrix metalloproteinases.



Seven-membered ring phosphonium salt **227** was obtained from biphenyl iodide **225** via the rearrangement of *N*-heterocyclic carbene. The latent carbene of **225** was protected as its chloroform adduct **226**, which was lithiated and then reaction with chlorodiphenylphosphine triggered the ring expansion by a single carbon and provided phosphonium salt **227**, the structure of which was established through spectroscopic and X-ray crystallographic analyses <2006OM4238>.

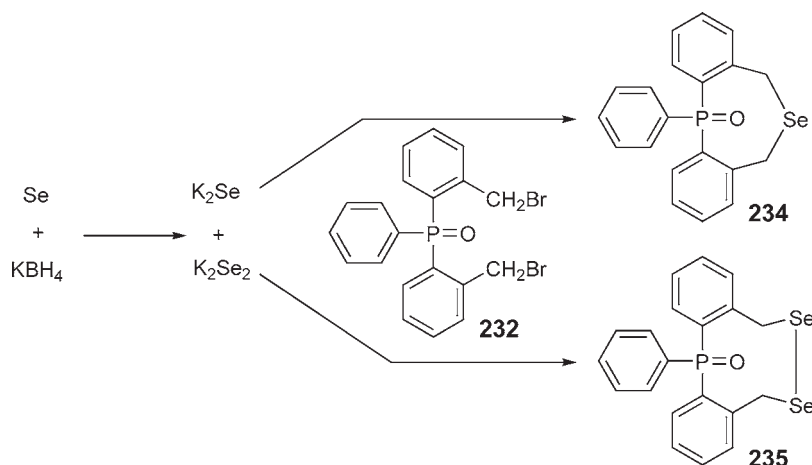


The tricyclic **229a**, **229b**, and **230** were prepared by the reaction of the Schiff base **228** with dibromoarylphosphines or with PBr_3 in the presence of Et_3N . Azaphosphepinethione **231** was obtained from **230** upon treatment with elemental sulfur in MeOH <1998CHE1098>.

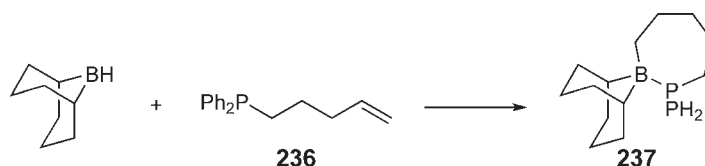


14.17.4.2.3 Rings containing phosphorus and heteroatom other than O or N

Facile synthesis of macrocycles **234** and **235** containing a phosphine oxide group and selenium atoms was recently developed [<2001J\(P1\)1140>](#). Pulverized Se(0) was reduced with KBH_4 in absolute alcohol to produce a mixture of potassium selenide and potassium diselenide, which reacted with **232** to give a mixture of diselenaphosphoninone **234** and selenaphosphocinone **235**.

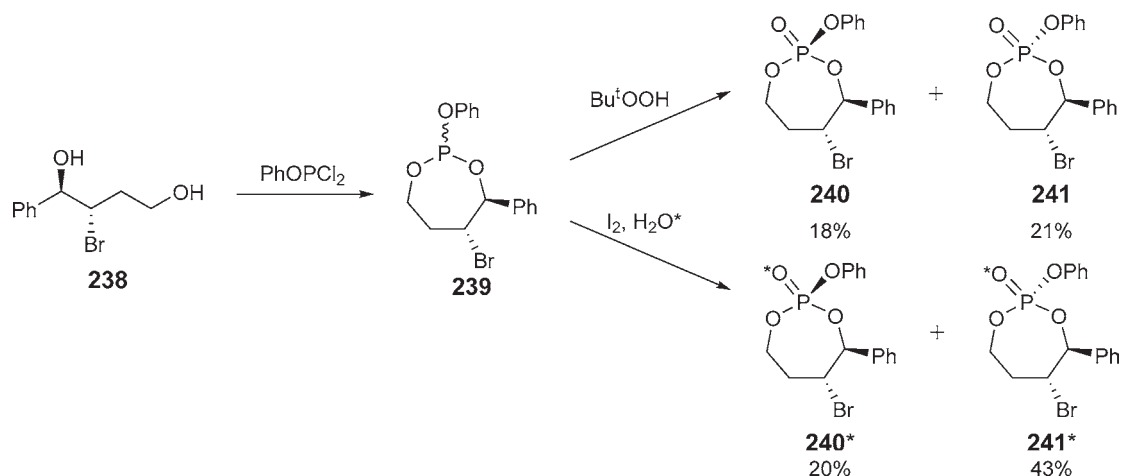


The phosphine-borane **237** with the P-B bond was integrated into a seven-membered ring prepared from $\text{Ph}_2\text{P}(\text{CH}_2)_3\text{CH}:\text{CH}_2$ by hydroboration using 9-borabicyclononane. The structure of **237** was confirmed by the X-ray diffraction [<1997CB951>](#).

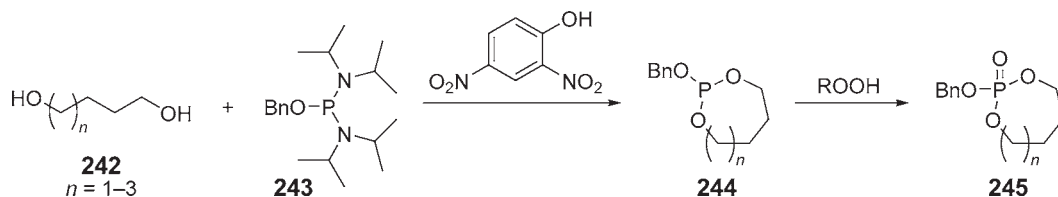


14.17.4.3 Rings Containing Phosphorus and Two or More Heteroatoms

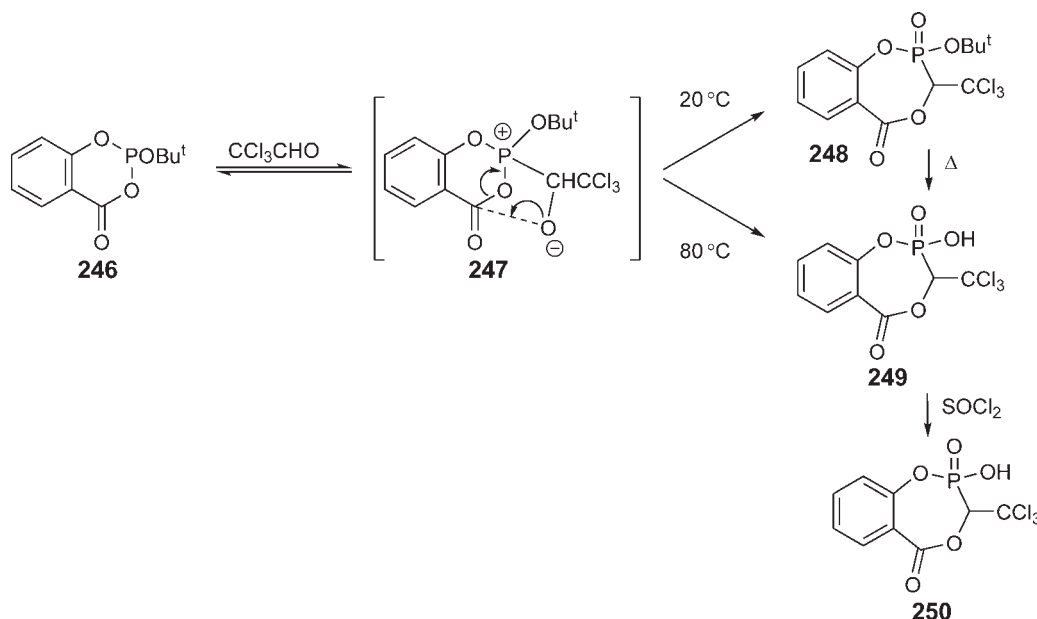
1,3,2-Dioxophosphhepanes are most commonly synthesized from the corresponding 1,4-diols and substituted dichlorophosphites. Thus, *erythro*-1-phenyl-2-bromo-1,4-butanediol **238** was converted to the diastereomeric 2-phenoxy-1,3,2-dioxophosphhepane **239** by the reaction with phenyl dichlorophosphite. Oxidation of **239** *in situ* with *tert*-butyl hydroperoxide afforded the two cyclic phosphates **240** and **241**. The structure of the minor isomer **240** was investigated by the X-ray crystallography. Treatment of **239** with iodine and 10% ^{17}O -labeled water enabled the regioselective preparation of the mono- ^{17}O -labeled substrates **240*** and **241***. The compounds were used to study the contraction of 4-phenyl-2-phenoxy-2-oxo-1,3,2-dioxophosphorinan-5-yl radicals [<2002JOC3360>](#).



2,4-Dinitrophenol was used with benzyloxy-bis(diisopropylamino)phosphine **243** to synthesize the cyclic phosphate derivatives **244** of a series of alkane diols ($\text{HO}-(\text{CH}_2)_n-\text{OH}$; $n = 4-6$) in good isolated yields [<2004TL1001>](#).



The reaction of 2-*tert*-butoxy-5,6-benzo-1,3,2-dioxaphosphinin-4-one **246** with 2,2,2-trichloroacetaldehyde proceeded through the expansion of the six-membered heterocycle to form 2-hydroxy-3-trichloromethyl-6,7-benzo-1,4,2-dioxaphosphepin-5-one-2-oxide **249**, as a single diastereomer. The product was chlorinated with thionyl chloride to obtain substituted 2-chloro-1,4,2-dioxaphosphepin-5-one-2-oxide **250** [<2002RJC1186, 2003RJC1367, 2004RJC1861>](#).

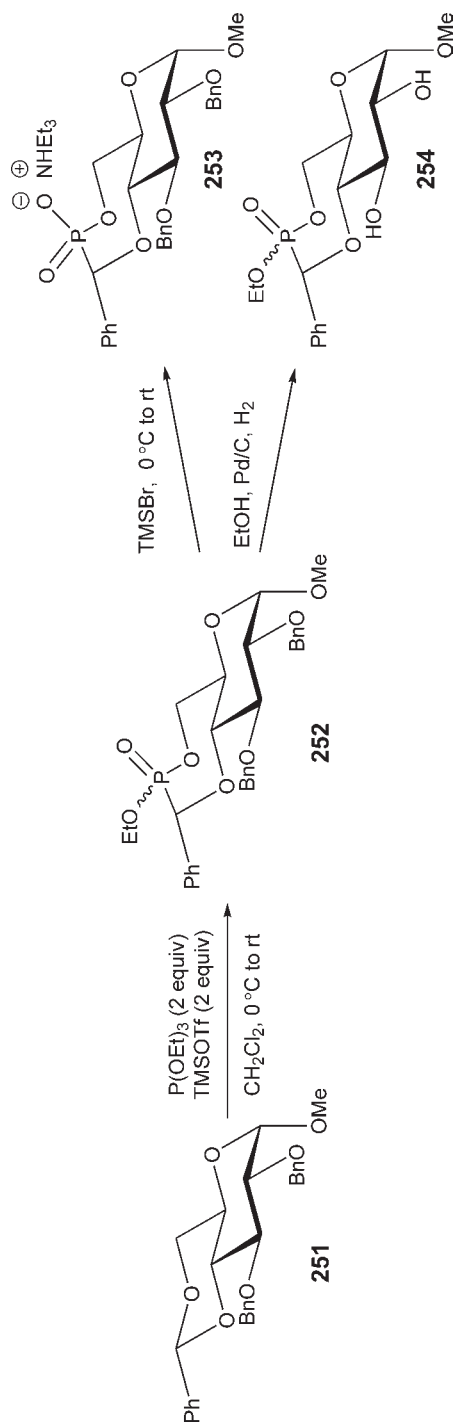


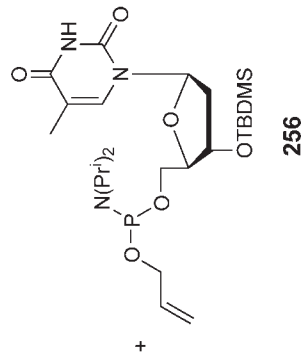
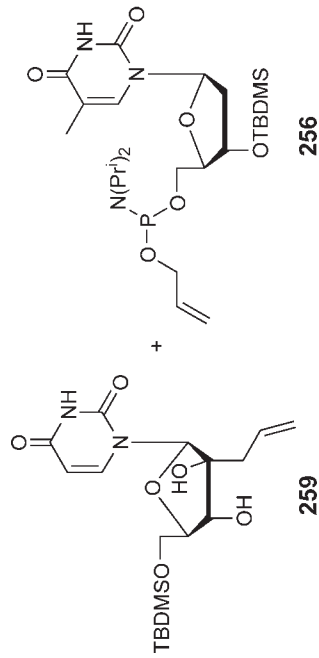
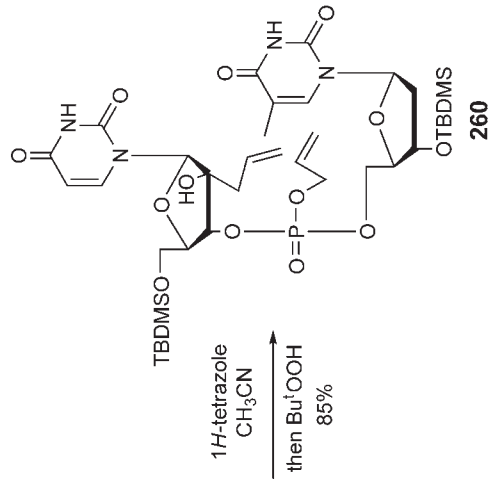
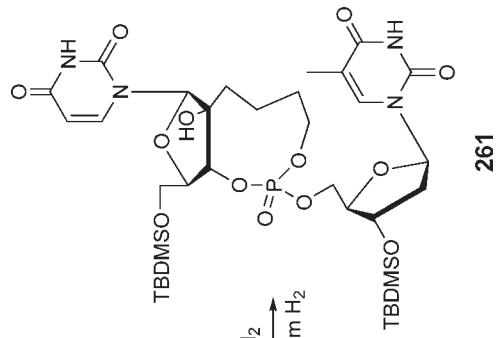
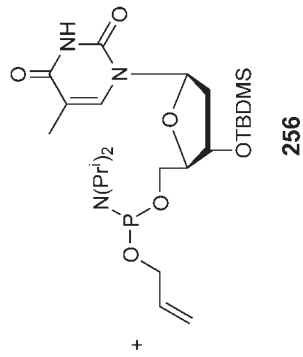
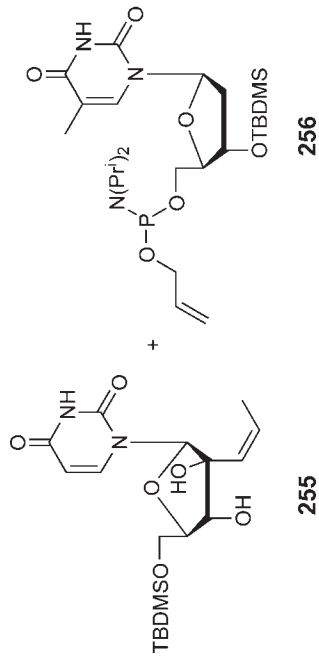
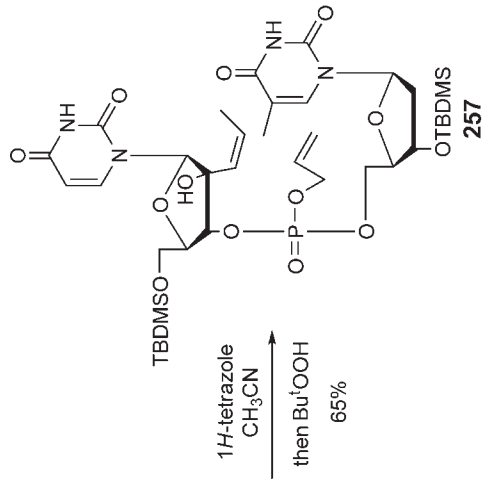
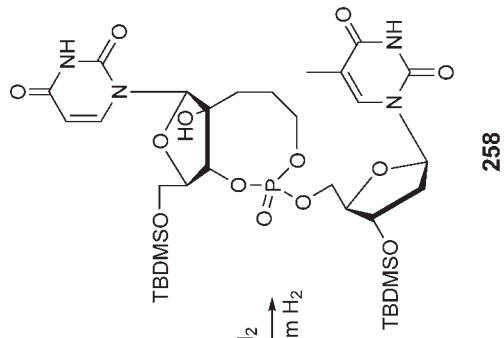
The seven-membered phostone **252** was synthesized by the reaction of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene- α (β)-D-glucopyranoside **251** with triethyl phosphate and trimethylsilyl trifluoromethanesulfonate. Protecting the acetal group of **251** interacted with triethyl phosphite and opened to give **252**, which can be further selectively hydrolyzed or deprotected to give **253** or **254** [<2003TL8797>](#).

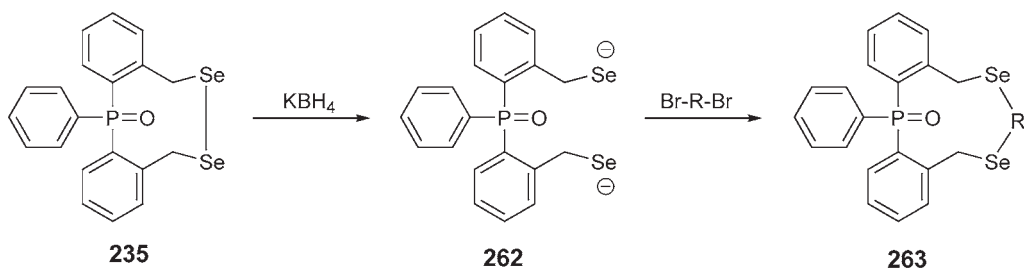
Dinucleotides containing an extra eight- and nine-membered phosphorus heterocyclic ring were synthesized by the ring-closing alkene metathesis reactions from nucleotide substrates with introduced double bond. Monomers **255** and **259** were both coupled to the phosphoramidite **256** and the resulting dimers **257** and **260** were subjected to a tandem ring-closing metathesis/hydrogenation procedure leading to the saturated products **258** and **261** in a low and good yield, respectively [<2005NN1015, 2005NN349>](#).

A facile synthetic method for a series of macrocycles containing a phosphine oxide group and two selenium atoms was published [<2001J\(P1\)1140>](#). Macrocycles **263** were obtained by a one-pot reaction from **235**, which was generated *in situ* by the previously described procedure from a mixture of potassium selenide and potassium diselenide and dibromides **232**. Without isolation, diselenide **235** was treated with potassium borohydride and sodium hydroxide to form a diselenide anion **262**, which was allowed to react with various dibromides to give macrocycles **263** with moderate yields.

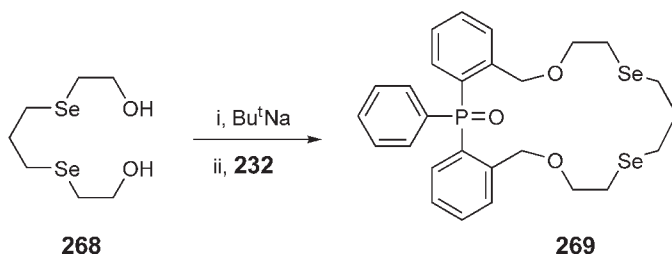
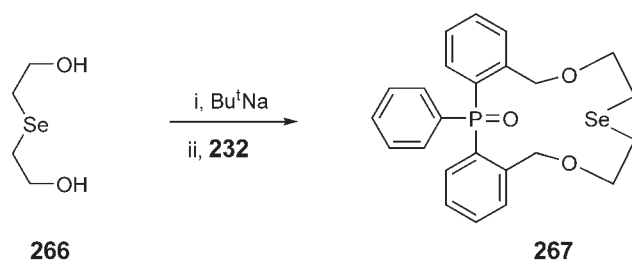
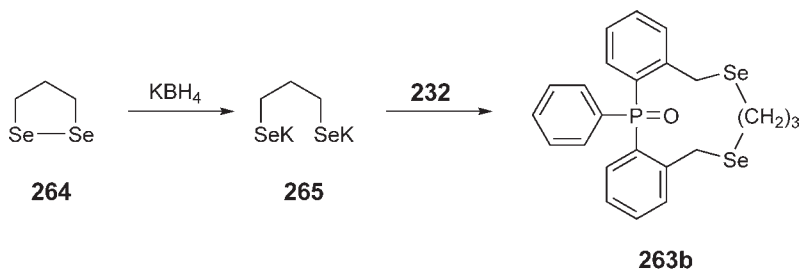
Alternatively, macrocycle **263b** ($\text{R} = (\text{CH}_2)_3$) was synthesized by the reduction of 1,2-diselenacyclopentane **264** with potassium borohydride, followed by the condensation of the resulting potassium diselenide **265** with dibromide **232** in 27% yield. Two related macrocycles **267** and **269**, containing two ethereal oxygen atoms, were also synthesized by the similar condensation from corresponding diols **266** and **268** in 26% and 22% yields, respectively [<2001J\(P1\)1140>](#).



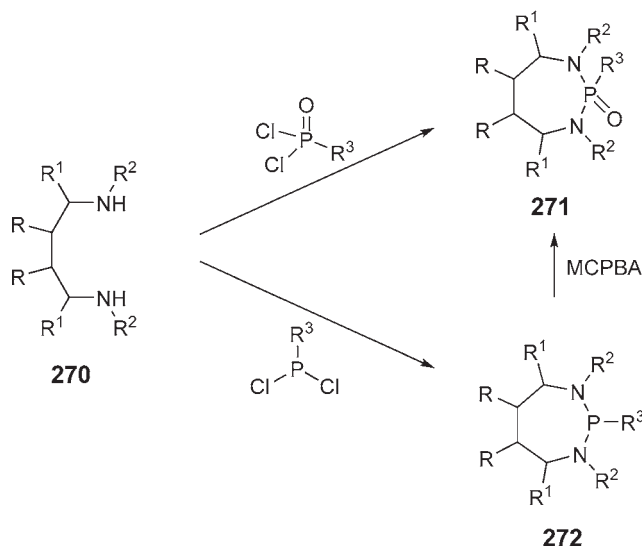




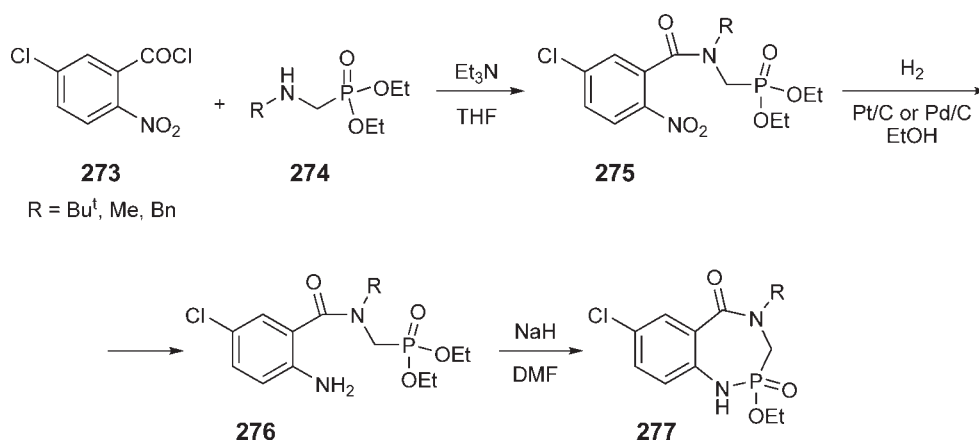
<i>R</i>	Yield (%)	<i>R</i>	Yield (%)
-CH ₂ -	24%		26%
-(CH ₂) ₃ -	22%		16%
-(CH ₂) ₄ -	25%		35%
-(CH ₂) ₅ -	12%		
-(CH ₂) ₆ -	19%		
-(CH ₂) ₂ -O-(CH ₂) ₂ -	30%		
-[(CH ₂) ₂ -O] ₂ -(CH ₂) ₂ -	21%		
-(CH ₂ -CHOH-CH ₂ -	15%		



Typically, 1,3,2-diazaphosphepanes **272** and 1,3,2-diazaphosphepin-2-oxides **271** were obtained by the reaction of the corresponding lithiated primary or secondary diamines **270** and substituted dichlorophosphines or phosphonic dichlorides <1996JA7404, 1999JOC1958, 2000JOC7913, 2003JCD387, 2003S1809, 2004EJO3557, 2005ASC61>.

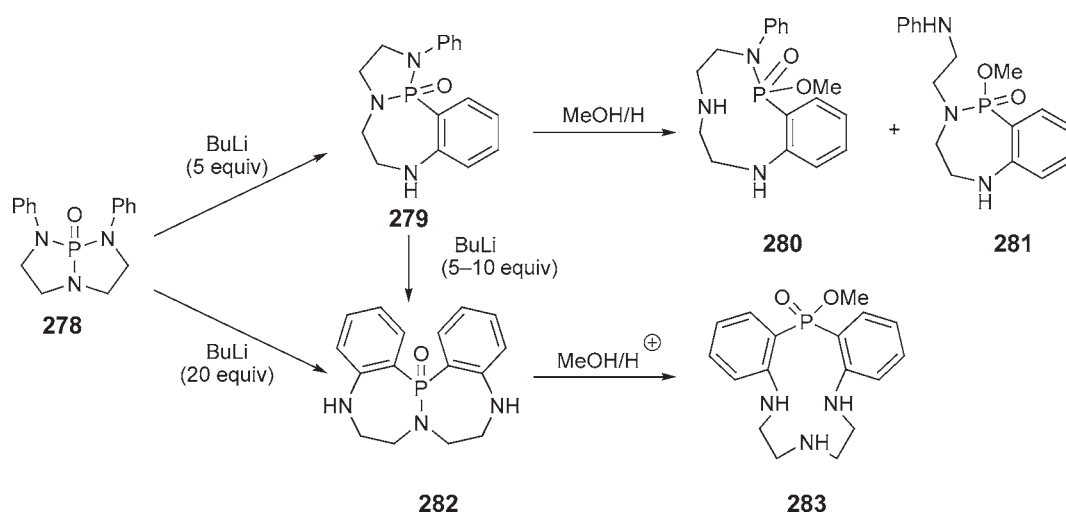


Synthesis of 1,4,2-benzodiazaphosphepin-5-one 2-oxides **277** was conducted in good overall yield from 5-chloro-2-nitrobenzoyl chloride **273** and substituted (amino)methylphosphonates **274**. The key step in this method is the base-induced cyclization of (2-aminobenzamido)methylphosphonates **276** to the 1,4,2-benzodiazaphosphepin-5-one 2-oxides **277** <1999JOC8156>.

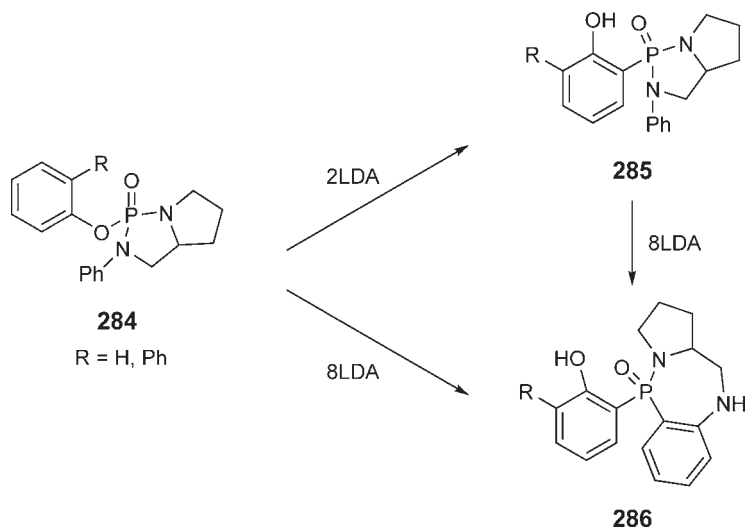


Phosphabicyclo[3.3.0]octane **278** underwent lithiation-induced rearrangement with single or double N → C migration of the phosphorus atom, leading to the bicyclic phosphonic diamide **279** or the bicyclic, symmetrical phosphinic amide **282** depending on the excess of BuLi. The product of single migration **279** was also converted into **282** upon further treatment with BuLi. The molecular structures of **279** and **282** were investigated by X-ray analysis, which revealed the presence of an unusually long phosphoryl bond in the symmetrical phosphinic amide **282** <1999CC853, 2000S565>.

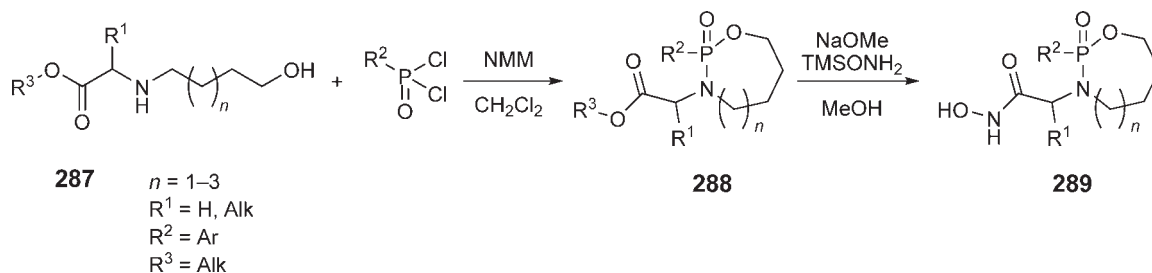
Nucleophilic cleavage of the P–N bond(s) in **279** by MeOH provided new seven- and 10-membered cyclic phosphonic amidoesters **280** and **281** <1999JCM656>. Likewise, it was found that **282** underwent methanolysis along the longest P–N bond to give the 12-membered cyclic phosphinic ester **283** <2000JST(522)249>.



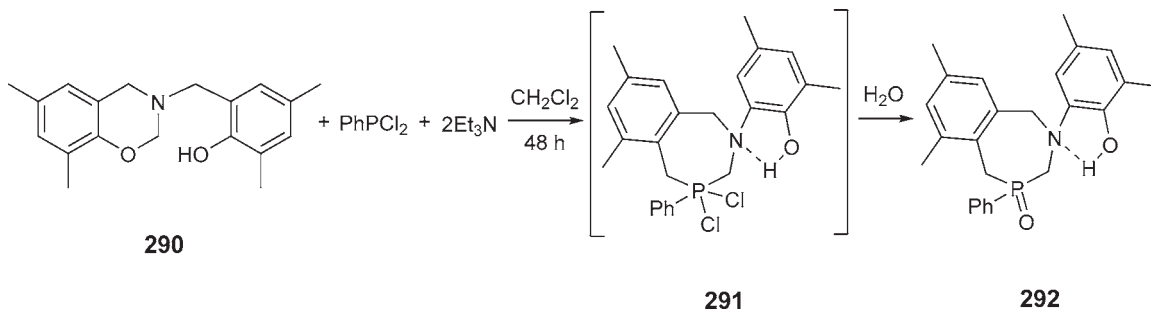
The reaction of pure diastereomer **284** in the presence of 2 equiv of lithium diisopropylamide (LDA) led to the stereospecific formation of the hydroxyphenyldiazaphospholidine oxide **285** in 94% yield. When the reaction was performed with 8 equiv of LDA, it produced 1,5,2-diazaphosphpepin-2-oxides **286** in 89% yield. The reaction proceeds via two diastereoselective 1,3-migration rearrangements, and a stereospecific ring expansion <1999AGE1479>.



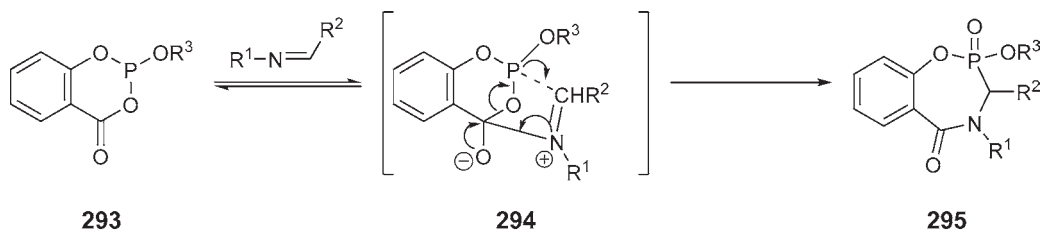
Seven-, eight-, and nine-membered heterocycles containing nitrogen, oxygen, and phosphorus atoms **288** were prepared by the reaction of phosphonic dichlorides with corresponding amino alcohols **287**. Obtained esters **288** were converted into hydroxamic acids **289** upon treatment with NaOMe and *O*-(trimethylsilyl)hydroxylamine <2003BMC5461>.



Compound **290** was reacted with dichloro(phenyl)phosphine in the presence of Et_3N ; this led to a ring-opening reaction with the breakage of the $\text{O}-\text{CH}_2$ bond, insertion of the phosphorus atom, and formation of the intermediate **291**, which gave upon hydrolysis the cyclic phosphoryl-containing product **292** <1998IC4945>.



Similar to the synthesis of 1,4,2-dioxaphosphepin-5-one-2-oxide **249**, 1,4,2-oxazaphosphepine-5-one-2-oxides **295** were prepared from 1,3,2-dioxaphosphorin-4-ones **293** and corresponding imines by the ring-expansion reaction <2004RJC32, 2004RJC969>.

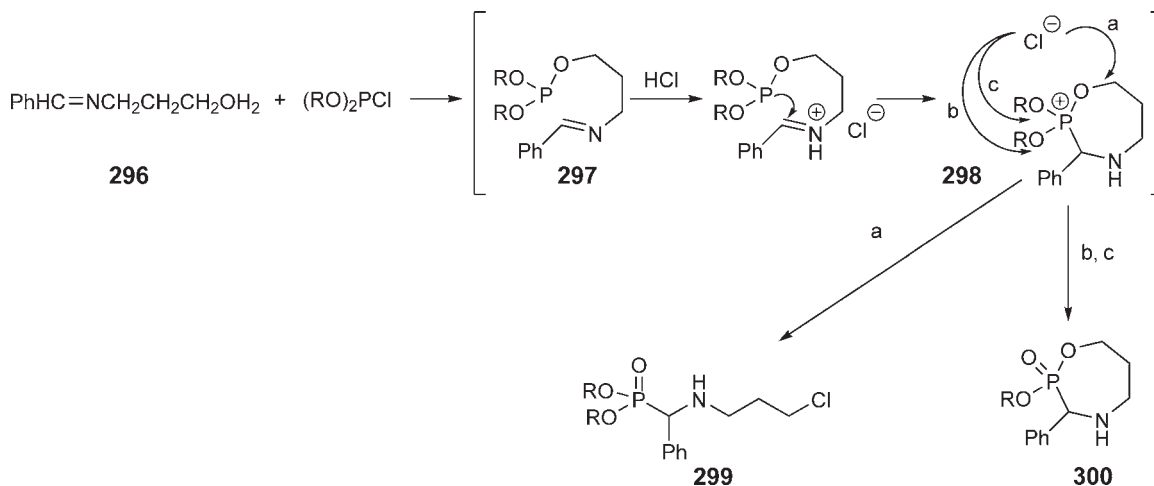


$\text{R}^1 = \text{Me}, \text{PhCH}_2$

$\text{R}^2 = \text{Ph}, \text{C}_6\text{H}_4\text{OMe-4}, \text{C}_6\text{H}_4\text{NMe}_2\text{-4}$

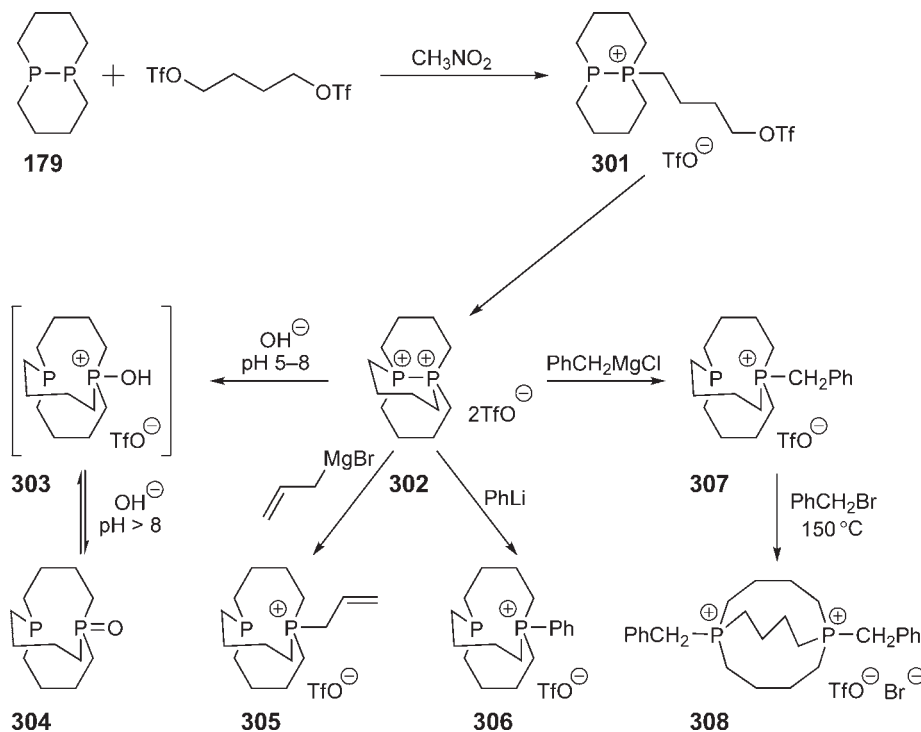
$\text{R}^3 = \text{CH}_2\text{CF}_3, \text{CH}_2\text{CF}_2\text{CF}_2\text{H}, \text{CH}(\text{CF}_3)_2, \text{C}_6\text{F}_5$

The reactions of γ -aldiminoalcohol **296** with diethyl and diisopropyl phosphorochloridites in CHCl_3 at 0°C afforded diastereomeric mixtures of substituted benzylphosphonates **299** and **300**, respectively, which are believed to be formed from a common intermediate, **298** <2005RCB1496>.

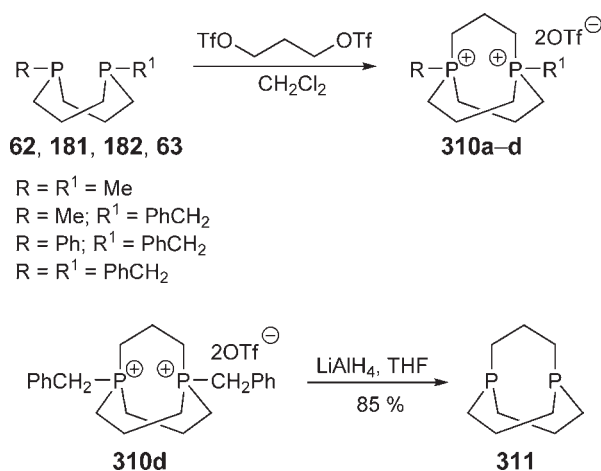


14.17.5 Bicyclic Systems with Bridgehead Phosphorus

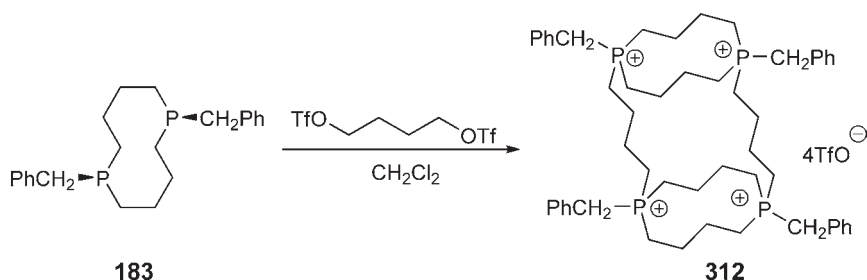
1,6-Diphosphoniatricyclo[4.4.4.0]tetradecane bis-triflate **302** was obtained by the reaction of 1,5-bis(trifluoromethanesulfonyloxy)pentane with 1,6-diphosphabicyclo[4.4.0]decane **179** in 35% yield in a polar solvent, for example, MeCN. Tricyclic [4.4.4.0]tetradecane **302** was reacted with different nucleophiles to give corresponding bridge-headed biphosphines **304–308**.



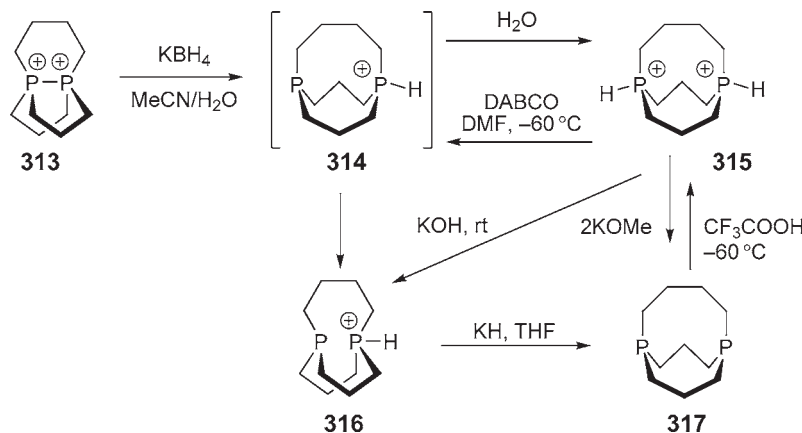
1,5-Diphosphabicyclo[3.3.3]undecane **311** was synthesized from 1,5-dibenzyl-1,5-diphosphacyclooctane **63** in two steps with good overall yield. A series of bicyclic dications **310a–d** were prepared from **62**, **181**, **182**, and **63** under mild conditions with high yields [\[1998J\(P1\)1657\]](#).



Although the preparation of **310a–d** was successful, a similar ring-closure procedure gave a different outcome with the 10-membered ring diphosphine. When *cis*-1,6-dibenzyl-1,6-diphosphacyclodecane **183** was reacted with $(\text{CH}_2\text{CH}_2\text{OTf})_2$ under analogous conditions, macrocycle **312** was obtained [\[1998J\(P1\)1657\]](#).



Similarly to the synthesis of **304–308**, bicyclic diphosphine **317** with two bridgehead phosphorus atoms was synthesized from tricyclic diprophonium salt **313** by the reduction with KBH_4 [<2000AGE2879>](#).



For the structural and conformational studies of the bridgehead phosphorus compounds, see other publications by Alder *et al.* [<2001J\(P2\)288](#), [2001J\(P2\)282](#), [1998J\(P1\)1643>](#).

14.17.6 Further Developments

Additional synthetic methods and properties of phosphorus heterocycles with greater than a six-membered ring, which appeared in the literature in 2007, are described in the following references: [<2007OM713](#), [2007JA2764](#), [2007OM810](#), [2007OPRD568](#), [2007ARK50](#), [2007JAP2005223809](#), [2007WO2006IB52374>](#), and [<2007EJO108>](#).

References

1963USP3086053	R. I. Wagner, <i>US Pat.</i> US 3086053, 1963, 19630416, 4pp.
1977JA8370	L. D. Quin and E. D. Middlemass, <i>J. Am. Chem. Soc.</i> , 1977, 99 , 8370.
1980JA4838	E. D. Middlemass and L. D. Quin, <i>J. Am. Chem. Soc.</i> , 1980, 102 , 4838.
1982JOC905	L. D. Quin, E. D. Middlemass, and N. S. Rao, <i>J. Org. Chem.</i> , 1982, 47 , 905.
1994CRV1183	A.-M. Caminade and J. P. Majoral, <i>Chem. Rev.</i> , 1994, 94 , 1183.
1995JOC6076	J.-L. Montchamp, F. Tian, and J. W. Frost, <i>J. Org. Chem.</i> , 1995, 60 , 6076.
1995TL447	G. Baccolini, G. Orsolan, and E. Mezzina, <i>Tetrahedron Lett.</i> , 1995, 36 , 447.
1996CHEC-II(9)947	M. Pabel and S. B. Wild; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 947.
1996JA7404	S. E. Denmark, S. B. D. Winter, X. Su, and K.-T. Wong, <i>J. Am. Chem. Soc.</i> , 1996, 118 , 7404.
1996TA989	S. Warren and P. Wyatt, <i>Tetrahedron Asymmetry</i> , 1996, 7 , 989.
1996TL5609	S. Warren and P. Wyatt, <i>Tetrahedron Lett.</i> , 1996, 37 , 5609.
1996TL7815	M. Yoshifuji, N. Shinohara, and K. Toyota, <i>Tetrahedron Lett.</i> , 1996, 37 , 7815.
1997CB951	M. Sigl, A. Schier, and H. Schmidbaur, <i>Chem. Ber.</i> , 1997, 130 , 951.
1997JOM(529)279	C. Gueguen, P. O'Brien, S. Warren, and P. Wyatt, <i>J. Organomet. Chem.</i> , 1997, 529 , 279.
1998CHE1098	A. A. Tolmachev, A. O. Pushechnikov, D. G. Krotko, S. P. Ivonin, and A. N. Kostyuk, <i>Chem. Heterocycl. Compd. (Engl. Transl.)</i> , 1998, 34 , 1098.
1998HAC9	E. M. Hanawalt, K. M. Doxsee, G. S. Shen, T. J. R. Weakley, C. B. Knobler, and H. Hope, <i>Heteroatom Chem.</i> , 1998, 9 , 9.
1998IC4945	N. V. Timosheva, A. Chandrasekaran, R. O. Day, and R. R. Holmes, <i>Inorg. Chem.</i> , 1998, 37 , 4945.

- 1998IC6408 F. Bitterer, O. Herd, M. Kuhnel, O. Stelzer, N. Weferling, W. S. Sheldrick, J. Hagel, and N. Rosch, *Inorg. Chem.*, 1998, **37**, 6408.
- 1998J(P1)1643 R. W. Alder, C. Ganter, M. Gil, R. Gleiter, C. J. Harris, S. E. Harris, H. Lange, A. G. Orpen, and P. N. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1643.
- 1998J(P1)1657 R. W. Alder, D. D. Ellis, R. Gleiter, C. J. Harris, H. Lange, A. G. Orpen, D. Read, and P. N. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1657.
- 1998J(P1)249 S. Warren and P. Wyatt, *J. Chem. Soc., Perkin. Trans. 1*, 1998, 249.
- 1998TL4291 E. Soulier, J.-C. Clement, J.-J. Yaouanc, and H. Abbayes, *Tetrahedron Lett.*, 1998, **39**, 4291.
- 1999AGE1479 O. Legrand, J. M. Brunel, and G. Buono, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 1479.
- 1999CC853 S. A. Bourne, Z. He, T. A. Modro, and P. H. Van Rooyen, *J. Chem. Soc., Chem. Commun.*, 1999, 853.
- 1999JCM656 Z. He and T. A. Modro, *J. Chem. Res. (S)*, 1999, 656.
- 1999JOC1958 S. E. Denmark, X. Su, Yu. Nishigaichi, D. M. Coe, K.-T. Wong, S. B. D. Winter, and J. Y. Choi, *J. Org. Chem.*, 1999, **64**, 1958.
- 1999JOC8156 G. M. Karp, *J. Org. Chem.*, 1999, **64**, 8156.
- 1999OL1679 D. Xiao, Z. Zhang, and X. Zhang, *Org. Lett.*, 1999, **1**, 1679.
- 2000AGE2879 R. W. Alder and D. Read, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 2879.
- 2000JOC7913 K. T. Sprott and P. R. Hanson, *J. Org. Chem.*, 2000, **65**, 7913.
- 2000JST(522)249 S. A. Bourne, Z. He, and T. A. Modro, *J. Mol. Struct.*, 2000, **522**, 249.
- 2000S565 Z. He and T. A. Modro, *Synthesis*, 2000, 565.
- 2000SL1685 G. Baccolini, C. Boga, and U. Negri, *Synlett*, 2000, 1685.
- 2000T43 M. Yoshifuji, M. Nakazawa, T. Sato, and K. Toyota, *Tetrahedron*, **56**, 43.
- 2000T6259 S. G. Ruf, J. Dietz, and M. Regitz, *Tetrahedron*, 2000, **56**, 6259.
- 2001AGE3425 D. Xiao and X. Zhang, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3425.
- 2001J(P1)279 P. Wyatt, S. Warren, M. McPartlin, and T. Woodroffe, *J. Chem. Soc., Perkin. Trans. 1*, 2001, 279.
- 2001J(P1)1140 J. L. Li, J. B. Meng, Y. M. Wang, J. T. Wang, and T. Matsuura, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1140.
- 2001J(P2)282 R. W. Alder, C. P. Butts, A. G. Orpen, D. Read, and J. M. Oliva, *J. Chem. Soc., Perkin Trans. 2*, 2001, 282.
- 2001J(P2)288 R. W. Alder, C. P. Butts, A. G. Orpen, and D. Read, *J. Chem. Soc., Perkin Trans. 2*, 2001, 288.
- 2001OL2525 R. Stranne, J.-L. Vasse, and C. Moberg, *Org. Lett.*, 2001, **3**, 2525.
- 2001OL643 M. D. Pungente and L. Weiler, *Org. Lett.*, 2001, **3**, 643.
- 2001RJC525 L. M. Burnaeva, V. F. Mironov, S. V. Romanov, G. A. Ivkova, I. L. Shulaeva, and I. V. Konovalova, *Russ. J. Gen. Chem. (Engl. Transl.)*, **71**, 525.
- 2001TL2609 A. Robertson, C. Bradaric, C. S. Frampton, J. McNulty, and A. Capretta, *Tetrahedron Lett.*, 2001, **42**, 2609.
- 2001TL8231 M. S. M. Timmer, H. Ovaa, D. V. Filippov, G. A. Marel, and J. H. Boom, *Tetrahedron Lett.*, 2001, **42**, 8231.
- 2002CJC1643 M. D. Pungente, L. Weiler, and H. J. Ziltener, *Can. J. Chem.*, 2002, **80**, 1643.
- 2002JOC3360 D. Crich, F. Sartillo-Piscil, L. Quintero-Cortes, and D. J. Wink, *J. Org. Chem.*, 2002, **67**, 3360.
- 2002JOM(646)239 M. S. Landis, N. J. Turro, W. Bhanthumnavin, and W. G. Bentrude, *J. Organomet. Chem.*, 2003, **646**, 239.
- 2002RJC1186 I. V. Konovalova, L. M. Burnaeva, V. F. Mironov, A. T. Gubaidullin, A. B. Dobrynin, I. A. Litvinov, S. V. Romanov, T. A. Zyablikova, and O. V. Yashagina, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2002, **72**, 1186.
- 2002TL4849 Y. Chi and X. Zhang, *Tetrahedron Lett.*, 2002, **43**, 4849.
- 2002TL4977 K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, and M. Beller, *Tetrahedron Lett.*, 2002, **43**, 4977.
- 2003RJC1367 V. F. Mironov, G. A. Ivkova, L. M. Burnaeva, I. V. Konovalova, and R. Z. Musin, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2003, **73**, 1367.
- 2003AGE3509 W. Tang, W. Wang, Y. Chi, and X. Zhang, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 3509.
- 2003BMC5461 M. D. Sorensen, L. K. A. Blahr, M. K. Christensen, T. Hoyer, S. Latini, P.-J. V. Hjarnaa, and F. Bjorkling, *Bioorg. Med. Chem.*, 2003, 5461.
- 2003CC1154 C. Ortega, M. Gouygou, and J.-C. Daran, *J. Chem. Soc., Chem. Commun.*, 2003, 1154.
- 2003JCD387 M. P. Magee, H.-Q. Li, O. Morgan, and W. H. Hersh, *J. Chem. Soc., Dalton Trans.*, 2003, 387.
- 2003JOC3258 J.-L. Vasse, R. Stranne, R. Zalubovskis, C. Gayet, and C. Moberg, *J. Org. Chem.*, 2003, **68**, 3258.
- 2003JOM(675)91 K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, and M. Beller, *J. Organomet. Chem.*, 2003, **675**, 91.
- 2003S1809 M. T. Reetz, H. Oka, and R. Goddard, *Synthesis*, 2003, 1809.
- 2003TL8797 J. Moravcova, H. Heissigerova, P. Kocalka, A. Imberty, D. Sykora, and M. Fris, *Tetrahedron Lett.*, 2003, **44**, 8797.
- 2003WO2003068786A1 W. Janse Van Rensburg, H. Van Rensburg, and A. J. Robertson, *PCT Int. Appl. WO 2003068786 A1*, 2003, 20030821, 19pp.
- 2004ARK95 V. F. Mironov, E. R. Zagidullina, G. A. Ivkova, A. B. Dobrynin, A. T. Gubaidullin, S. K. Latypov, R. Z. Musin, I. A. Litvinov, A. A. Balandina, and I. V. Konovalova, *ARKIVOC*, 2004, xii, 95.
- 2004EJO3557 C. Monti, C. Gennari, R. M. Steele, and U. Piarulli, *Eur. J. Org. Chem.*, 2004, 3557.
- 2004JCD1012 T. Shima, E. B. Bauer, F. Hampel, and A. Gladysz, *J. Chem. Soc., Dalton Trans.*, 2004, 1012.
- 2004RJC32 V. F. Mironov, A. T. Gubaidullin, L. M. Burnaeva, I. A. Litvinov, G. A. Ivkova, S. V. Romanov, T. A. Zyablikova, A. I. Konovalov, and I. V. Konovalova, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2004, **74**, 32.
- 2004RJC969 G. A. Ivkova, V. F. Mironov, E. R. Zagidullina, and I. V. Konovalova, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2004, **74**, 969.
- 2004RJC1861 A. T. Gubaidullin, L. M. Burnaeva, V. F. Mironov, I. A. Litvinov, Yu. Yu. Kotorova, G. A. Ivkova, E. I. Goryunov, I. V. Konovalova, and T. A. Mastryukova, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2004, **74**, 1861.
- 2004TA2621 K. Junge, B. Hagemann, S. Enthaler, A. Spannenberg, M. Michalik, G. Oehme, A. Monsees, T. Riermeier, and M. Beller, *Tetrahedron Asymmetry*, 2004, **15**, 2621.
- 2004TL1001 E. J. Amigues and M. E. Migaud, *Tetrahedron Lett.*, 2004, **45**, 1001.
- 2005ASC61 R. Hilgraf and A. Pfaltz, *Adv. Synth. Catal.*, 2005, **347**, 61.
- 2005CEJ3631 M. L. G. Borst, N. Riet, R. H. Lemmens, F. J. J. Kanter, M. Schakel, A. W. Ehlers, A. M. Mills, M. Lutz, A. L. Spek, and K. Lammertsma, *Chem. Eur. J.*, 2005, **11**, 3631.
- 2005JOC8110 M. L. G. Borst, A. W. Ehlers, and K. Lammertsma, *J. Org. Chem.*, 2005, **70**, 8110.
- 2005NN349 P. Nielsen and P. Borsting, *Nucleos. Nucleot. Nucleic Acids*, 2005, **24**, 349.

- 2005NN1015 S. I. Steffansen, M. S. Christensen, P. Borsting, and P. Nielsen, *Nucleos. Nucleot. Nucleic Acids*, 2005, **24**, 1015.
- 2005OL2333 S.-F. Zhu, Y. Yang, L. X. Wang, B. Liu, and Q.-L. Zhou, *Org. Lett.*, 2005, **7**, 2333.
- 2005OM5549 E. Robe, C. Ortega, M. Mikina, M. Mikolajczyk, J.-C. Daran, and M. Gouygou, *Organometallics*, 2005, **24**, 5549.
- 2005RCB1496 E. V. Bayandina, E. Yu. Davydova, M. N. Dimukhametov, A. B. Dobrynin, I. A. Litvinov, R. Z. Musin, and V. A. Al'fonsov, *Russ. Chem. Bull.*, 2005, **54**, 1496.
- 2005TA3416 P. Kasák, K. Mereiter, and M. Widhalm, *Tetrahedron Asymmetry*, 2005, **16**, 3416.
- 2006ICA(359)938 M. I. Bruce, K. A. Kramarczuk, B. W. Skelton, A. H. White, and N. N. Zaitseva, *Inorg. Chim. Acta*, **359**, 938.
- 2006OM4238 A. W. Waltman, T. Ritter, and R. H. Grubbs, *Organometallics*, 2006, **25**, 4238.
- 2007ARK50 K. Junge, B. Hagemann, S. Enthaler, G. Erre, and M. Beller, *ARKIVOC (Arkive For Organic Chemistry)*, 2007, **V**, 50.
- 2007EJO108 R. Zalubovskis, E. Fjellander, Z. Szabo, and C. Moberg, *Eur. J. Org. Chem.*, 2007, 108.
- 2007JA2764 B. K. Corkey and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 2764.
- 2007JAP2005223809 D. Mayama and H. Keido, *Jpn. Pat.*, JP 2005223809, 2007, 2007039357, 11pp.
- 2007OM713 R. A. Baber, M. F. Haddow, A. J. Middleton, A. G. Orpen, P. G. Pringle, A. Haynes, G. L. Williams, and R. Papp, *Organometallics*, 2007, **26**, 713.
- 2007OM810 J. Durand, S. Gladiali, G. Erre, E. Zangrando, and B. Milani, *Organometallics*, 2007, **26**, 810.
- 2007OPRD568 S. Enthaler, G. Erre, K. Junge, J. Holz, A. Boerner, E. Alberico, I. Nieddu, S. Gladiali, and M. Beller, *Org. Process Res. Dev.*, 2007, **11**, 568.
- 2007WO2006IB52374 R. Winde, R. W. Karch, A. Rivas-Nass, O. Briel, R. P. Toozee, G. S. Forman, and W. H. Meyer, *PCT Int. Appl.*, WO 2006IB52374, 2007, 2007010453.

Biographical Sketch



Anatoliy M. Shestopalov was born in Khmel'nyts'kyy, Ukraine, in 1954. He studied chemistry and biology at the Shevchenko National Pedagogical University (Lugansk, Ukraine), where he received his M.S. degree in chemistry and biology in 1979. In 1985, he graduated with a Ph.D. degree ("Development of the methods of synthesis, and investigation of chemical properties and biological activities of 3-cyanopyridine-2(1*H*)-thiones and products of their transformation") from the Institute of Chemical Aids of Plant Protection in Moscow, Russia. After a postdoctoral stay at the Zelinsky Institute of Organic Chemistry in Moscow, he received his Doctor of Science degree in chemistry ("Quaternized azines in the synthesis of carbo- and heterocyclic compounds") in 1991 at the Zelinsky Institute of Organic Chemistry. He is now a full professor, research supervisor, and head of scientific group at the Zelinsky Institute of Organic Chemistry. His research interests include regio- and stereoselective synthesis of carbo- and heterocyclic compounds, multicomponent reactions, chemistry of N-, O-, S-, Se-containing heterocycles, and chemistry of physiologically active compounds. He is an author of more than 250 scientific publications.



Alexander A. Shestopalov was born in Lugansk, Ukraine, in 1980. He studied chemistry at the Moscow State University, where he was awarded with M.S. degree in chemistry in 2002. Later in 2002, he joined Prof. Katritzky's laboratory at the University of Florida as a research scholar in chemistry. In 2004, he graduated from the Zelinsky Institute of Organic Chemistry in Russia with a Ph.D. degree ("Synthesis of substituted carbo- and heterocycles by multicomponent reactions of carbonyl compounds and derivatives of cyanoacetic acid"). He is now pursuing another doctoral degree at the Duke University. His research interests include heterocyclic chemistry, synthetic methodology, multicomponent synthesis, peptide chemistry, surface chemistry, and soft lithography.

14.18

Rings containing Arsenic, Antimony, or Bismuth

V. D. Romanenko

Institute of Bioorganic Chemistry and Petrochemistry, Kiev, Ukraine

J.-M. Sotiropoulos

Université de Pau et Pays de l'Adour, Pau, France

© 2008 Elsevier Ltd. All rights reserved.

14.18.1	Introduction	945
14.18.2	Theoretical Methods	954
14.18.3	Experimental Structural Methods	955
14.18.3.1	X-Ray Studies	955
14.18.3.2	NMR Studies	958
14.18.3.3	Mass Spectroscopy	959
14.18.4	Thermodynamic Aspects	959
14.18.5	Reactivity of Fully Conjugated Rings	962
14.18.6	Reactivity of Nonconjugated Rings	962
14.18.7	Reactivity of Substituents Attached to Ring Carbon Atom	962
14.18.8	Reactivity of Substituents Attached to Ring Heteroatom	963
14.18.9	Ring Syntheses from Acyclic Compounds	965
14.18.9.1	Rings Containing Arsenic	965
14.18.9.1.1	Benzarsepins and related fused heterocyclic systems	965
14.18.9.1.2	Arsocanes	966
14.18.9.1.3	Macrocyclic esters of arsenic(III) acids and thioacids	967
14.18.9.2	Rings Containing Antimony	968
14.18.9.2.1	Benzostibepins and related fused heterocyclic systems	968
14.18.9.2.2	Stibocanes and stibatranes	969
14.18.9.2.3	Macrocyclic esters of antimony acids	970
14.18.9.3	Rings Containing Bismuth	971
14.18.9.3.1	Benzobismepins and related fused heterocyclic systems	971
14.18.9.3.2	Bismocanes and bismatranes	971
14.18.9.3.3	Macrocyclic esters of bismuth(III) and bismuth(V) acids and thioacids	972
14.18.10	Ring Syntheses by Transformations of Another Ring	973
14.18.11	Important Compounds and Applications	974
14.18.12	Further Developments	976
References		976

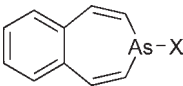
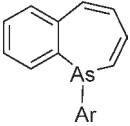
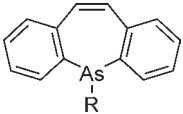
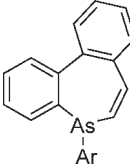
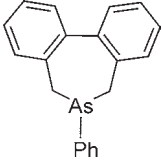
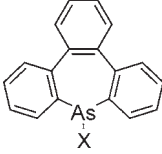
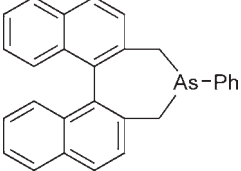
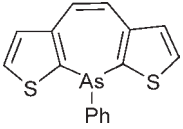
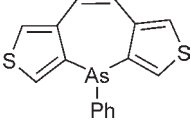
14.18.1 Introduction

As in CHEC-II(1996) <1996CHEC-II(9)971>, this chapter covers chemistry of seven-membered and larger rings containing arsenic, antimony, and bismuth. Some of the important literature, which was published before 1996 but had not appeared in CHEC(1984) and CHEC-II(1996) is also covered in the present chapter. Since 1995, no general review focused on preparation and properties of these heterocyclic compounds has appeared, although several reviews of more limited scope were published. Macrocyclic arsine ligands have been extensively reviewed in *Comprehensive Coordination Chemistry II* <2003CCC-II475>. A detailed survey on benzazepines and their group 15 analogs is provided by Meigh <2004SOS825>. Recent advances in the chemistry of organoantimony and bismuth homocycles were reviewed by Breunig and Rösler <2000CSR403>. Readers are referred to other publications

<2001MI1, 1999MI45, 1998MI403, B-1994MI725> for a more thorough treatment of the structure and bonding aspects of organoarsenic, -antimony, and -bismuth chemistry.

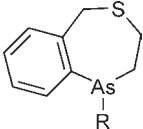
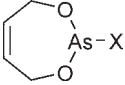
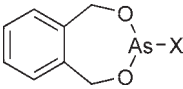
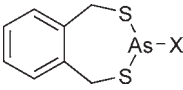
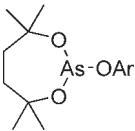
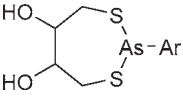
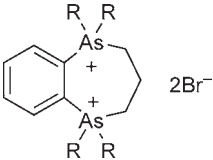
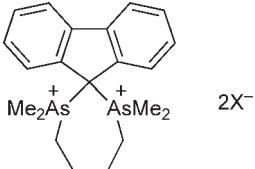
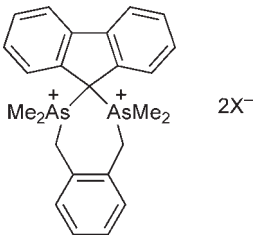
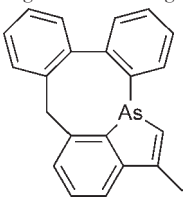
Tables 1–3 provide a quick reference guide to seven-membered and larger rings containing As, Sb, and Bi, which are known.

Table 1 Seven-membered and larger arsenic heterocycles

Ring system	Comments	References
<i>Seven-membered ring</i>		
	Rare system; few examples, particularly of 3-phenyl and 3-chloro derivatives	1996CC2183, 2003CPB1283
	Rare system; As-oxide also described	1996CHEC-II(9)972, 1999CPB1108
	Rare system; few examples	1996CC2183, 2003CPB1283
	Rare system; few examples	1996CHEC-II(9)972
	Only one example	1996CHEC-II(9)972
	Rare system	1996CHEC-II(9)972
	Rare system; C ₂ -symmetric chiral arsine	2002TA2187
	Only one example	1997H(45)1899
	Only one example	1997H(45)1899

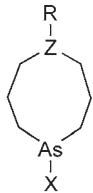
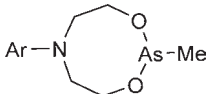
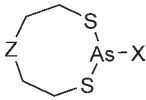
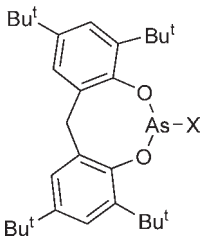
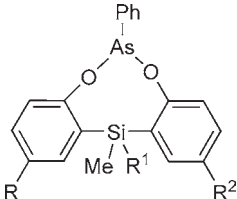
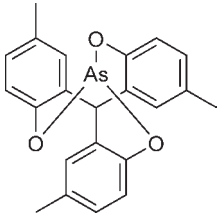
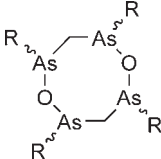
(Continued)

Table 1 (Continued)

<i>Ring system</i>	<i>Comments</i>	<i>References</i>
	Rare system	1996CHEC-II(9)972
	Common system	1996CHEC-II(9)972
	Extremely common system; extensively covered in literature	1996CHEC-II(9)972
	Common system	1996CHEC-II(9)972
	Common system	2003PS1653
	Fairly common system	1993MI261
	Few examples	1996CHEC-II(9)972
	Rare system	1996CHEC-II(9)972
	Rare system	1996CHEC-II(9)972
<i>Eight-membered ring</i>		
	Only one example	1996CHEC-II(9)972

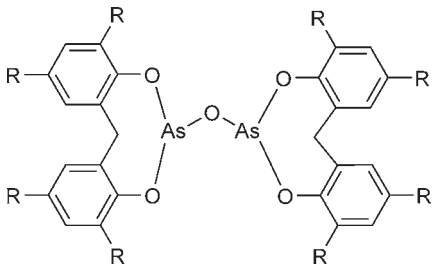
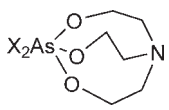
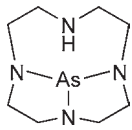
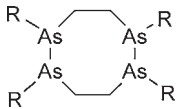
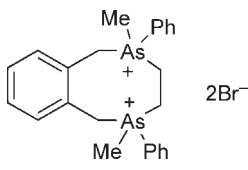
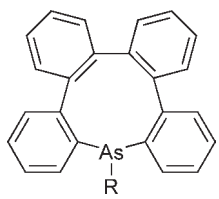
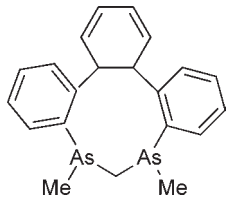
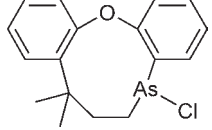
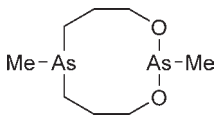
(Continued)

Table 1 (Continued)

<i>Ring system</i>	<i>Comments</i>	<i>References</i>
 Z = NR, O, S, Se X = Cl, Br	Common system	1994POL365
	Common system	1994JPR421
 Z = O, S	Common system	1995MI725, 1996ICA31, 1996JCD4235
	Few examples	1999PS191
	Few examples	1990ZFA51
	Fairly common system	2001IC856
	Common system	1996CHEC-II(9)972

(Continued)

Table 1 (Continued)

<i>Ring system</i>	<i>Comments</i>	<i>References</i>
	Common system	1995J(P1)2945
	Fairly common system	1994ZOB1998
	Fairly common system	1992OM3748
	Few examples	1996CHEC-II(9)972
	Rare system	1996CHEC-II(9)972
<i>Nine-membered and larger rings</i>		
	Rare system	1996CHEC-II(9)972
	Rare system	1996CHEC-II(9)972
	Only one example	1996CHEC-II(9)972
	Rare system	1996CHEC-II(9)972

(Continued)

Table 1 (Continued)

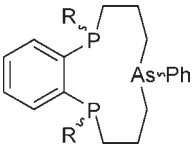
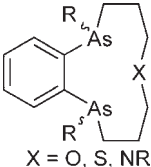
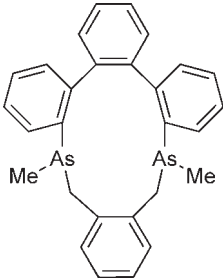
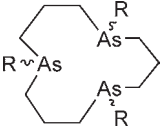
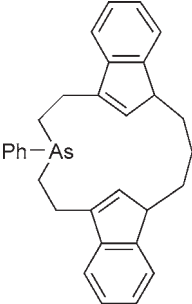
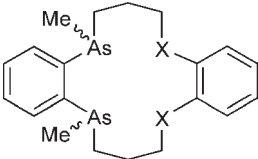
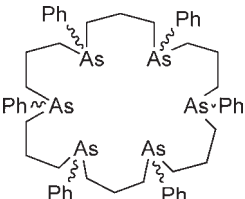
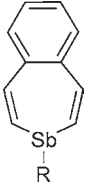
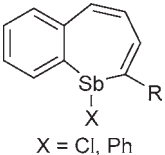
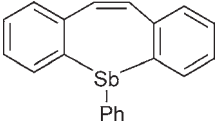
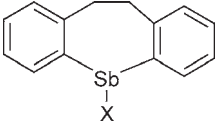
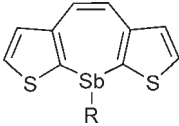
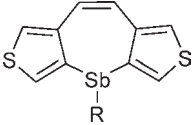
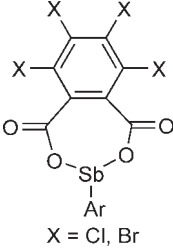
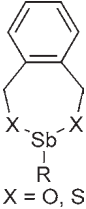
<i>Ring system</i>	<i>Comments</i>	<i>References</i>
	Few examples reported in earlier literature	1996CHEC-II(9)972
 X = O, S, NR	Few examples reported in earlier literature	1996CHEC-II(9)972
	Only one example	1996CHEC-II(9)972
	Fairly common system	1996CHEC-II(9)972
	Only one example	1996CHEC-II(9)972
 X = O, S, AsMe	Few examples reported in earlier literature	1996CHEC-II(9)972
	Few examples reported in earlier literature	1996CHEC-II(9)972

Table 2 Seven-membered and larger antimony heterocycles

Ring system	Comments	References
<i>Seven-membered rings</i>		
	Rare system; few examples	2003CPB1283, 1996CC2183
 X = Cl, Ph	Only few examples	1998CC767, 2000J(P1)1965, 2000H(53)49
	Only one example	2004SOS825, 1996CHEC-II(9)972
	Few examples	1996CHEC-II(9)972
	Only one example	1997H(45)1899
	Only one example	1997H(45)1899
 X = Cl, Br	Common system	1997MI630
 X = O, S	Fairly common system	1996CHEC-II(9)972

(Continued)

Table 2 (Continued)

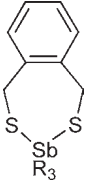
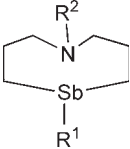
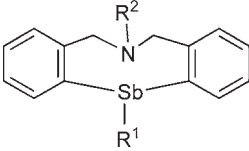
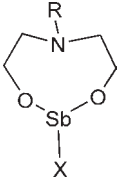
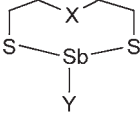
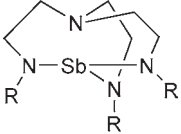
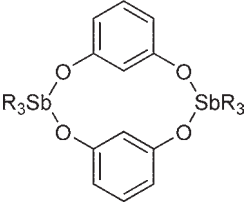
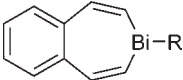
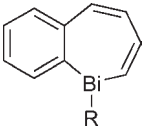
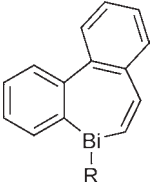
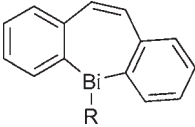
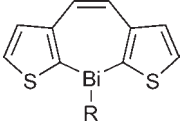
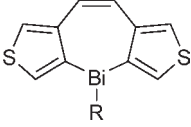
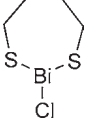
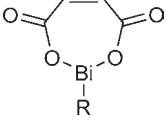
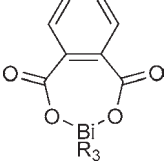
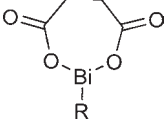
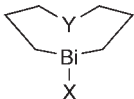
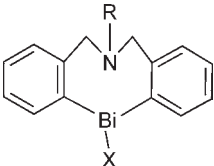
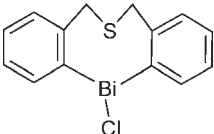
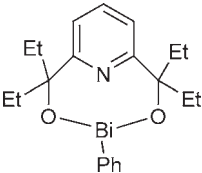
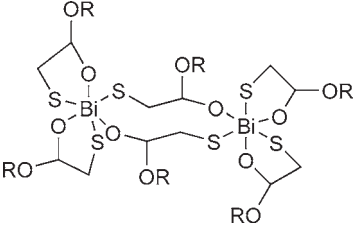
<i>Ring system</i>	<i>Comments</i>	<i>References</i>
	Fairly common system	1996CHEC-II(9)972
<i>Eight-membered and larger rings</i>		
	Common system	1998POL2655
	Common system	2003TL8589, 1996CHEC-II(9)972
	Common system	2001DOK502
	Common system	1998SAA85
X = O, S, NR; Y = Cl, Br		
	Common system	2002IC6147
R = Me, Me ₃ Si		
	Fairly rare system	1995IZV748

Table 3 Seven-membered and larger bismuth heterocycles

<i>Ring system</i>	<i>Comments</i>	<i>References</i>
	Rare system; few examples	1996CC2183, 2003CPB1283
	Few examples	1996CHEC-II(9)972
	Rare system	1996CHEC-II(9)972, 1993CC1817
	Rare system	1993CC1817
	One example	1997H(45)1899
	One example	1997H(45)1899
	Common system	1996JA3225
	Common system; fused derivatives known	1996CHEC-II(9)972
	Common system	1996CHEC-II(9)972
	Common system	1996CHEC-II(9)972

(Continued)

Table 3 (Continued)

Ring system	Comments	References
 X = Cl, Br; Y = NR, O, S, Se	Common system	1994POL365
	Common system	2004JOM3012, 2005AAC2729
	Common system	2005AAC2729
	Only one example	2000JPP2000026335
	Rare system	2003IC3136

14.18.2 Theoretical Methods

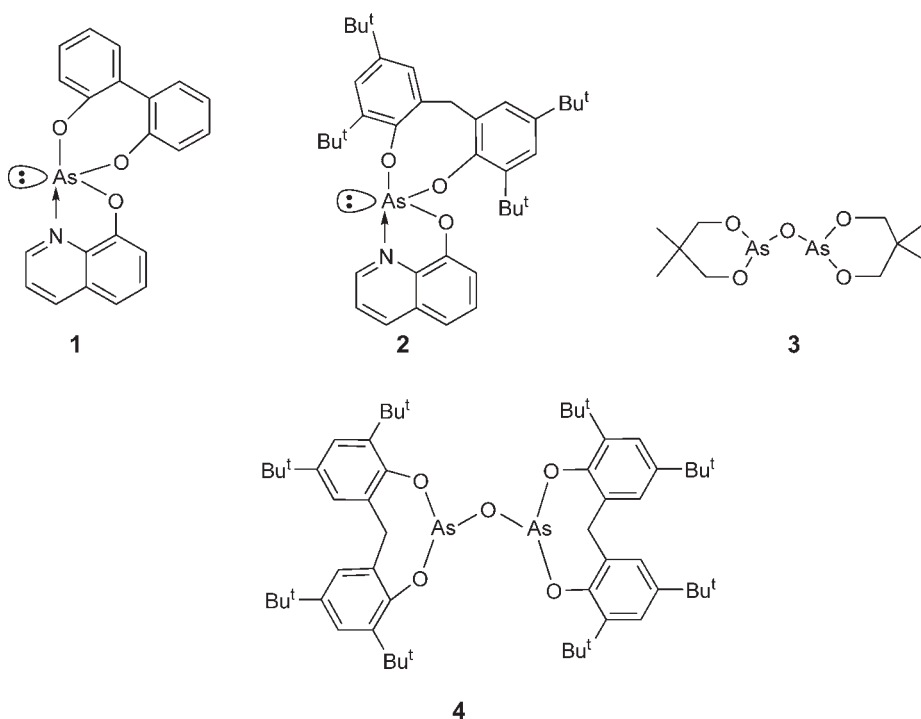
Until now, the large number of electrons in seven- and larger-membered rings containing arsenic, antimony, or bismuth and, perhaps, rather specialized nature of the subject, have precluded broad application of *ab initio* methods to the calculation of the heterocycles. Moreover, only a few semi-empirical molecular orbital (MO) calculations have been performed. Thus, structural, spectroscopic and electrochemical data, and semi-empirical MO calculations on the extended Hückel level for 11 antimony compounds $\text{RSb}(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{NR}^1$ ($\text{R} = \text{Cl, Br, I, NCS, OSiPh}_3$; $\text{R}^1 = \text{Me, Bz, Bu}^i$) have been compared to the analogous data of $\text{RAs}(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{NR}^1$ and $\text{RBi}(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{NR}^1$ which contain As(III) and Bi(III) as central atoms. The following three points were noted: (1) the ligand sequence $\text{Cl} < \text{I} < \text{NCS}$ holds for an increasing approach $\text{N} \cdots \text{Sb}$; (2) the effect of electronegativity and the effect of n - or π - σ^* charge transfer into the LUMO at Sb(III) are counteractive; and (3) the intramolecular donor strength increases in the following order: $\text{NBu}^i < \text{NBz} < \text{NMe}$. Experimental data (X-ray structure analysis, Mössbauer spectroscopy, nuclear magnetic resonance (NMR) spectroscopy and electrochemistry) are in a rough agreement with the assumed bonding scheme of hypervalency: four-electron three-center interaction and its main control by a partial charge transfer from the ligand into the three-center LUMO <1998POL2655>. In addition, an application of the Varshni relationship between bond length and vibrational data upon heterocycles of the types $\text{HlgE}(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{NR}^1$ ($\text{R}^1 = \text{Me, Bz, Bu}^i$), $\text{HlgE}(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{X}$, and $\text{HlgE}(\text{SCH}_2\text{CH}_2)_2\text{X}$ ($\text{E} = \text{As, Sb, Bi}$; $\text{X} = \text{O, S}$; $\text{Hlg} = \text{Cl, Br, I}$) has been studied. The usefulness of the Varshni constants has been demonstrated by estimation of distances and stretching frequencies for As/Sb/Bi-Hlg bonds <1998SAA85>.

Shutov *et al.* carried out density functional theory (DFT) calculations on $E[N(\text{SiMe}_3)\text{CH}_2\text{CH}_2]_3\text{N}$ ($E = \text{P}, \text{Sb}, \text{Bi}$) up to the PBE level of theory <2002IC6147>. The structural data obtained from geometry optimization on antimony and bismuth derivatives reproduced experimental trends, that is, a decrease in the $\text{N}_{\text{dat}}\text{--}E$ distance from Sb to Bi. The values of electron density in $\text{N}_{\text{dat}}\text{--}E$ critical point and the Laplacian of charge density for the azabismatrane indicated that a closed-shell interaction existed between Bi atom and N_{dat} atom.

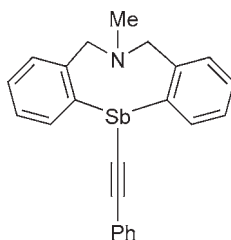
14.18.3 Experimental Structural Methods

14.18.3.1 X-Ray Studies

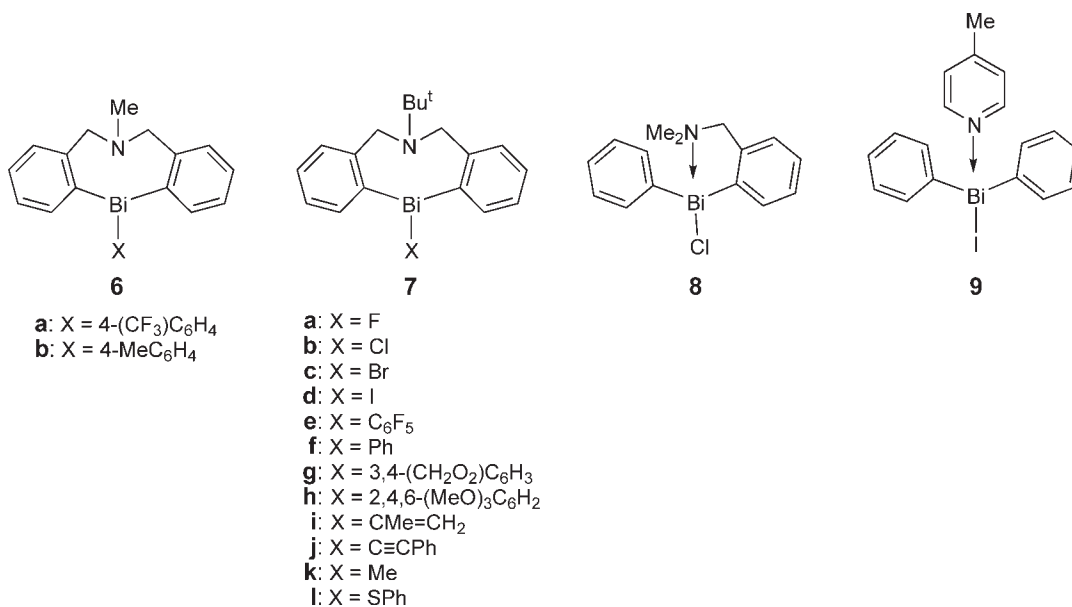
Several X-ray structures of As/Sb/Bi-containing macrocycles have been published. Thus, X-ray structures of the cyclic seven- and eight-membered arsenites **1** and **2** have been described <1999PS191>. Both compounds show intramolecular $\text{N} \rightarrow \text{As}$ coordination with a distorted trigonal bipyramidal geometry around As; the stereochemistry active lone pair on As is located approximately in the equatorial plane and the coordinated N is in the apical position. In the 2,2'-biphenoxy compound **1** having no electron-donating substituents on the aromatic rings the arsenic is the most acidic leading to the strongest $\text{N} \rightarrow \text{As}$ interaction ($d_{\text{N} \rightarrow \text{As}}$: **1**, 2.434 Å; **2**, 2.534 Å). The apical As–O bonds are longer than the equatorial As–O bonds as expected in trigonal bipyramidal geometry for such systems. An X-ray analysis has also been performed for bis(5,5-dimethyl-1,3,2-dioxarsenan-2-yl) ether **3** and bis(2,4,8,10-tetra-*tert*-butyl-12*H*-dibenzo[*d,g*][1,3,2]dioxarsenocin-6-yl) ether **4** <1995J(P1)2945>. The six-membered rings in **3** have a 'chair' conformation and the eight-membered rings in **4** have a 'symmetrical *anti*' conformation. The As–O–C bond angles in **3** (mean: 117.4°) are smaller than those in **4** (mean: 124.5°), which is most likely a result of steric strain in the latter. Also the widening of the As–O–As angle in **4** (139.2°), compared to **3** (125.8°), is probably a result of steric effects.



Single crystal X-ray analysis of the ethynyl-1,5-azastibocine **5a** showed the presence of intramolecular $\text{Sb} \cdots \text{N}$ interaction which should be responsible for the reactivity enhancement of the ethynyl-1,5-azastibocines in Pd-catalyzed cross-coupling reactions with organic halides (see Section 14.18.11). The distance between the antimony and nitrogen atoms (2.538(4) Å) corresponds to 68% of the sum of the van der Waals radii of both elements (3.74 Å). In the crystal central antimony atom exhibited a pseudo-trigonal-bipyramidal structure <2003TL8589>.

**5a**

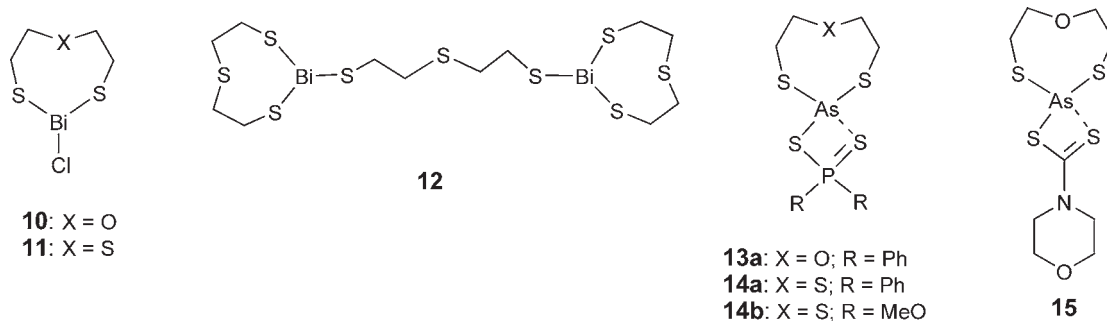
X-Ray data are available also for the 5,6,7,12-tetrahydrodibenz[*c,f*]azabismocines **6** and **7**, with different substituents on the bismuth atom including halogens, alkyl, alkynyl, aryl, or phenylthio groups <1999CL861, 2004JOM3012>. The eight-membered tetrahydroazabismocine ring has proved to be flexible and the hypervalent Bi...N distances vary ranging from 2.568(3) to 2.896(5) Å, depending on the electronic nature of the substituents on the bismuth atom. The structure of chloride **7b** has strong similarity to that of bismuth chloride **8** that have (2-dimethylaminomethyl)phenyl ligand. Structural similarity is also observed between iodides **7d** and **9** (for **7d**, Bi...N 2.569(3) Å, Bi-I 3.0139(3) Å, C(1)–Bi–C(2) 95.6(1)°; for **9**, Bi–N 2.604(7) Å, Bi–I 3.0229(8) Å, C(1)–Bi–C(2) 96.2(3)°]. The hypervalent Bi...N bond distances are in good linear relationship against Hammett's σ_m constants of the substituents on the bismuth atom <2004JOM3012>.



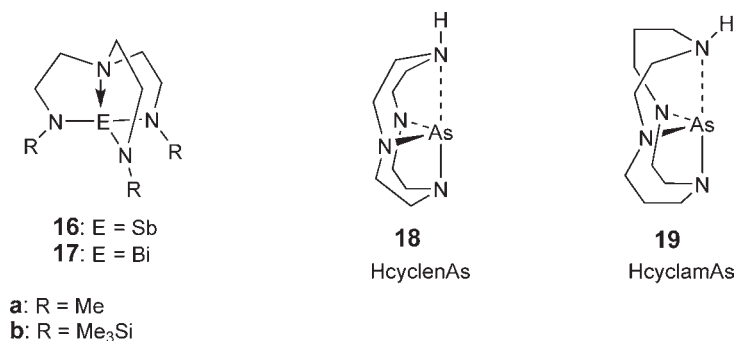
Dithiabismuth(III) heterocycles **10–12** have been crystallized free of solvent and showed molecular structures with significant intermolecular and intramolecular interactions. 2-Chloro-1,3-dithia-6-oxa-2-bismocane **10** and 2-chloro-1,3,6-trithia-2-bismocane **11** can be viewed as eight-membered heterocycles with a 2,6-intramolecular interaction, involving a coordinative donation (from oxygen in **10** or sulfur in **11**) to bismuth. Consistent with this bonding model, the two heterocyclic Bi–S bonds of **11** (2.541 Å) are slightly shorter than the cross-ring Bi–S bond (2.849 Å). The cross-ring S→Bi contacts were also observed in the structure **12**, although they are slightly longer (3.071, 3.197 Å) <1996JA3225>.

The X-ray structures of the arsocanes **13a**, **14a**, and **14b** involving diphenyldithiophosphinate, dimethylphosphorodithioate, and dithiocarbamate substituents have been reported <1996JCD4135, 1995MGC159, 1996ICA31>. All molecules showed an endocyclic, transannular X...As interaction and an exocyclic S...As secondary interaction. For example, the dithiophosphate ligand in **14b** is coordinated as anisobidentate with a secondary exocyclic As...S interaction and a normal exocyclic As–S bond (2.375 Å). The competition between transannular and exocyclic secondary bonding to arsenic led to a transannular As...S interatomic distance (2.911 Å) longer than in the 2-chloro derivative **11** (2.849 Å). The coordination geometry around arsenic can be described in two ways. If the secondary

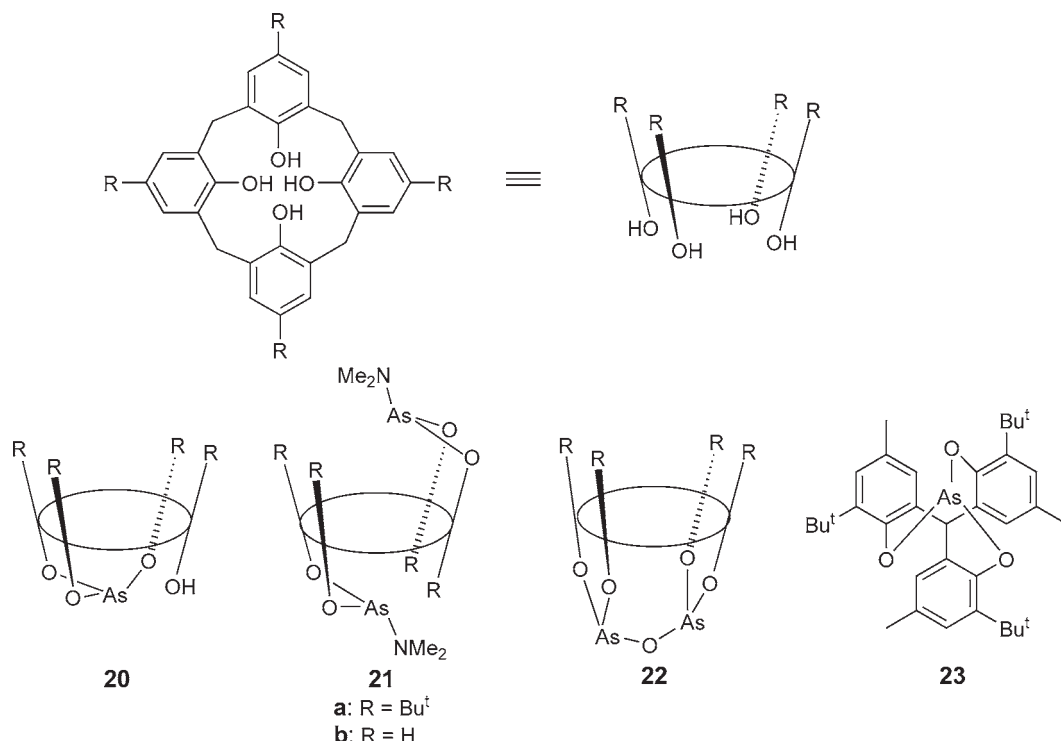
interactions are neglected, the arsenic atom displays the trigonal pyramidal geometry. If secondary bonding is taken into account, the geometry around arsenic can be described as much distorted tetragonal pyramid, and if stereochemical active lone pair is taken into account, it can also be described as distorted ψ -octahedral. The eight-membered rings in **10–15** exhibited various conformations. The oxa derivative **13a** was the example of an arsocane $X(\text{CH}_2\text{CH}_2\text{S})_2\text{AsY}$ with a chair-chair conformation, while the thia derivative **14a**, as with other thiaarsocanes, showed a boat-chair conformation.



A structural study of the first azatranes of the group 15 heavier elements **16** and **17** has been reported, confirming the presence of transannular interaction ($\text{N} \rightarrow \text{E}$) <2002IC6147>. The cross-ring distances $\text{N} \cdots \text{Sb}$ and $\text{N} \cdots \text{Bi}$ in the molecules **16b** and **17b** are 3.200(2) and 3.021(4) Å, respectively. These values are significantly smaller than the sum of the van der Waals radii of E and N (3.74 Å for N–Sb and 3.94 Å for N–Bi). In contrast, the $\text{N} \cdots \text{P}$ distance (3.360 Å) in the structure of $\text{P}[\text{N}(\text{SiMe}_3)\text{CH}_2\text{CH}_2]_3\text{N}$ is slightly longer than the standard sum of phosphorus and nitrogen van der Waals radii (3.35 Å). Thus, the strengthening of intramolecular interaction $\text{N} \rightarrow \text{E}$ in $\text{N}', \text{N}'', \text{N}'''$ -tris(trimethylsilyl)azatranes of group 15 elements increases as $\text{N} \cdots \text{P} < \text{N} \cdots \text{Sb} < \text{N} \cdots \text{Bi}$. This conclusion was also confirmed by theoretical calculations (see Section 14.18.2). Incorporation of arsenic into cyclen, a 12-atom tetraazamacrocycle, and cyclam, a 14-atom tetraazamacrocycle, led to heterocyclic derivatives **18** (HcyclenAs) and **19** (HcyclamAs). Both compounds exist as the transannulated structure. The $\text{N} \cdots \text{As}$ interaction is especially substantial in the cyclen compound **18** where the $\text{N} \cdots \text{As}$ distance is only 0.4 Å longer than the sum of the As and N covalent radii and 1.1 Å shorter than the corresponding van der Waals sum. For cyclam derivative **19**, these values are 0.7 and 0.8 Å, respectively. Thus, these macrocyclic compounds can be envisioned as zwitterionic arsoranide (R_4As^-) species <1992OM3748>.

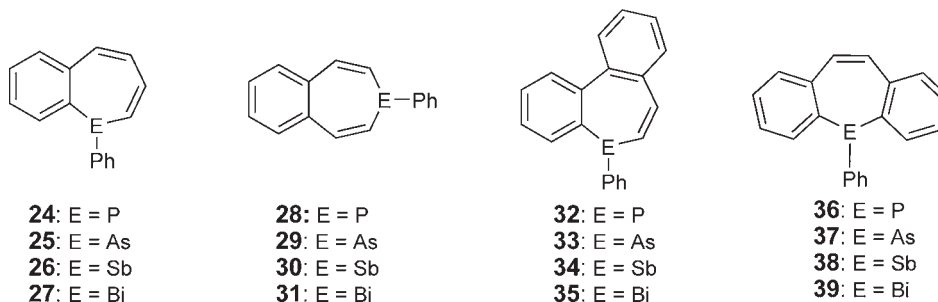


X-Ray studies have confirmed the structures of the monoarsenic **20** and diarsenic **21** and **22** *p*-R-calix[4]arene derivatives obtained from the reactions of *p*-R-calix[4]arenes with tris(dimethylamino)arsine <1995IC3610>. The geometry around each of the arsenic atoms in **20a**, **21b**, **22a**, and **22b** is pyramidal with reasonably small O–As–O and O–As–N angles. The sums of the three bond angles around each arsenic range from 289° to 292° with the exception of **20a** for which the sum is 278°. The phenolic As–O bond lengths range from 1.77 to 1.82 Å in the molecules and are about 0.2 Å longer than the P–O bond lengths in calix[4]arene phosphate. Three of the four calix[4]arene conformations are represented in these structures: **20a** adopts the (flattened) partial cone, **21b** the 1,2-alternate, and **22a** and **22b** the slightly flattened cone. A further interesting example of macrocyclic systems including arsenic atom is sterically crowded, rigid, C_3 -symmetric arsenite **23**. X-Ray structure determination and multinuclear NMR studies of **23** indicated that the tris-phenol ligands have sufficient flexibility to accommodate the arsenic atom. Typical As–O (1.778 Å) and O–As–O (99.6°) bond lengths and angles were measured <2001IC856>.



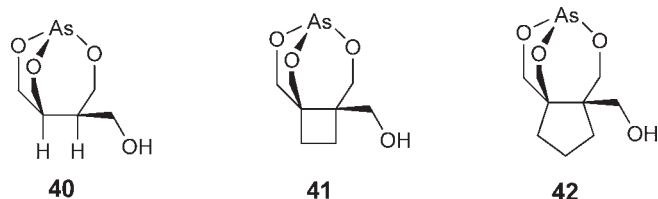
14.18.3.2 NMR Studies

Fully unsaturated seven-membered heterocyclic rings (heteroepins) **24–39** containing the group 15 (P, As, Sb, and Bi) heavier elements were characterized mainly by their ^1H NMR spectra and high-resolution mass spectrometry. The chemical shifts of the heteroepin ring protons are sensitive to a change in the heteroatom <1996CC2183, 1999CPB1108, 2003CPB1283>. Thus the chemical shifts of both H-2 and H-3 protons in 1-benzoheteroepins increase in the order **24** (P) < **25** (As) < **26** (Sb), **27** (Bi), and the H-2 protons resonate at higher field than the H-3 protons. With the exception of **27**, the chemical shifts of both H-4 and H-5 protons decreased in the above order, and the H-5 protons resonated at the lowest field of the four ring protons. For all 3-benzoheteroepins, the chemical shift of the proton at the 1(5)-position was higher than that of the proton at the 2(4)-position. The values of chemical shifts of these protons increased in the order **28** (P) < **29** (As) < **30** (Sb) < **31** (Bi). The ^1H NMR spectra of benzo[*b,d*]heteroepins also showed that the H-7 protons (**32**: δ 7.00; **33**: 7.21; **34**: 7.50; **35**: 8.70) (δ values in ppm) resonated at lower fields than the H-6 protons (**32**: δ 6.71; **33**: 6.85; **34**: 7.01; **35**: 8.14) and the values of chemical shifts of both H-6 and H-7 protons increased in the order **32** (P) < **33** (As) < **34** (Sb) < **35** (Bi), analogous to the H-2 and H-3 protons of the 1-benzoheteroepins. The H-10 and H-11 protons of the dibenzo[*b,f*]arsepin **37** appeared at δ 6.81 <1999CPB1108, 1993CC1817>.



A number of papers have been published which are concerned with the proton NMR characterization of cyclic arsenites <2003PS1653, 2001IC856, 1999PS191, 1999CCL1011, 1995J(P1)2945, 1990ZFA51>. ^1H and ^{13}C NMR spectroscopy have been used to study the structure of mixed glycolate–salicylaldimine derivatives of arsenic(III)

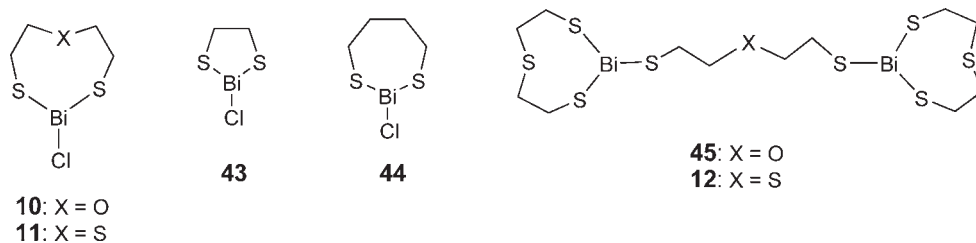
<2001IJA1302, 2002SRI1319>. Cyclic arsenites $X_2As(OCH_2CH_2)_3N$ ($X=Cl, Br; X_2=O$) were characterized by infrared (IR), ^1H and ^{13}C NMR, and mass spectroscopies. These products are regarded as potential arsranes <1994ZOB1998>. Details of the ^1H and ^{13}C NMR spectra of the arsenite esters **40–42** have been published <1990IC4983>. Variable-temperature experiments performed on these compounds showed no evidence of a tri-coordinate–pentacoordinate tautomeric equilibrium; however, deprotonation of **40** and **41** results in ^1H and ^{13}C NMR data consistent with a fluxional anion in which all of the alkoxy arms rapidly exchanged. Because **42** did not exhibit this fluxionality, it was proposed that the higher energy of the envelope form of the cyclopentane ring over the puckered conformation is sufficient to exhibit fluxionality.



Existence of hypervalent bonds in 5,6,7,12-tetrahydridibenz[*c, f*][1,5]azabismocines was confirmed through the single crystal X-ray analysis of **6a** and **6b** (*vide supra*) as well as NMR spectroscopy of **6c–g** (**c**: $X=F$; **d**: $X=Cl$; **e**: $X=I$; **f**: $X=Me$; **g**: $X=Ph$) in solution. ^1H and ^{13}C NMR chemical shifts of the methyl group on nitrogen in **6c–g** were largely affected by the substituents on the bismuth atom and showed linear relationship against Hammett's σ_m constants of the substituents <2004JOM3012>. Evidence was also provided for 1,5-chelation $Sb \cdots N$ in rings $RE[(CH_2)_3]_2NR^1$ ($E=As, Sb, Bi$) via ^{13}C NMR chemical shifts and ^{121}Sb Mössbauer data <1998POL2655>. For $CIE(CH_2CH_2CH_2)_2NMe$ ($E=N, P, As, Sb, Bi$), the values of ^{13}C NMR chemical shifts of the $\alpha-CH_2$ groups (e.g., $As, \delta 34.6$; $Sb, \delta 25.9$; $Bi, \delta 46.6$ ppm) clearly displayed a sequence $N > Bi > P \approx As > Sb$ for the Pauling electronegativities of the group 15 elements <1994POL365>.

14.18.3.3 Mass Spectroscopy

The electron ionization (EI) mass spectra of chloro-1,3-dithia-6-oxa-2-bismocane **10**, 2-chloro-1,3,6-trithia-2-bismocane **11**, 2-chloro-1,3-dithia-2-bismolane **43**, and 2-chloro-1,3-dithia-2-bismepane **44** are summarized in Table 4 <1996JA3225>. Compound **11** showed a weak molecular ion M^{+} and major fragment ions at m/z 336 and 301, which are assumed to have the same structure as M^{+} and $[M-Cl]^+$ ions from **43**. This suggested a thermodynamic preference for the five-membered cycle and implied elimination of SC_2H_4 from M^{+} and $[M-Cl]^+$ ions of **11** followed by ring closure. Similarly, **10** showed a fragment ion (m/z 285) which is the oxa analog of the $[M-Cl]^+$ ion from **43**. Notable in the atmospheric pressure chemical ionization (APCI) spectra of **10**, **11**, and **43** in dimethyl sulfoxide (DMSO) and **12** and **45** in MeCN with 1% HCl are peaks which correspond to $[M-Cl]^+$ ions for **10**, **11**, and **43**, and heterolytic Bi–S cleavage of the tether for **12** and **45**. In addition, APCI technique revealed solvent coordination chemistry of the bismuthenium cations <1996JA3225>. The mass spectra of oxa- and thiaarsocane diorganodithiophosphinates $X(CH_2CH_2S)_2AsS_2PR_2$ ($X=O, S; R=Me, Et, Ph$) are consistent with the mass spectra of other halogeno- and arylmetallocanes <1996JCD4135>.



14.18.4 Thermodynamic Aspects

All obtained 1-benzoheteroepins **24–27** are thermally labile in solution toward heteroatom extrusion and gradually decomposed to naphthalene. The 1-benzoheteroepins **46–49** having the bulky trimethylsilyl group at the 2-position

Table 4 Electron ionization mass spectral data of compounds **10**, **11**, **43**, and **44**

Compound	<i>m/z</i>	% abundance	Ion
10	380	9	M^{+}
	345	8	$[M-Cl]^+$
	285	5	$[BiSC_2H_4O]^+$
	244	9	$[BiCl]^+$
	241	10	$[BiS]^+$
	209	19	Bi^+
	136	100	$[S_2OC_4H_8]^+$
11	396	<1	M^{+}
	361	<1	$[M-Cl]^+$
	336	73	$[ClBiS_2C_2H_4]^+$
	301	30	$[BiC_2H_4]^+$
	241	58	$[BiS]^+$
	209	95	Bi^+
	152	100	$[S_3C_4H_8]^+$
43	336	25	M^{+}
	301	30	$[M-Cl]^+$
	273	10	$[BiS_2]^+$
	244	18	$[BiCl]^+$
	241	58	$[BiS]^+$
	209	77	Bi^+
	92	100	$[S_2C_2H_4]^+$
44	314	35	$[BiCl_3]^+$
	279	100	$[BiCl_2]^+$
	244	19	$[BiCl]^+$
	209	45	Bi^+
	122	3	$[S_2C_4H_8]^+$

are much more stable. The half-lives of **24–27** estimated from ^1H NMR spectral analysis indicate that their thermal stabilities decrease in the order **26** (Sb) > **24** (P) > **25** (As) > **27** (Bi) <1999CPB1108>. 3-Benzoheteroepins **28–31** are far less stable than the corresponding 1-benzoheteroepins except for the phosphepin **28** which is much more stable than others. The bismepin **51** having trimethylsilyl groups in both α -positions is far more stable ($t_{1/2}$ = 34 min at 50 °C) than the corresponding C-unsubstituted bismepin **31** ($t_{1/2}$ = <1 min at 50 °C). The half-lives of **24–31** and **50 and 51** are listed in Table 5. The presumed mechanism of the thermal decomposition of benzoheteroepins involves valence isomerization of the seven-membered ring to the corresponding norcaradiene isomer, followed by irreversible loss of the heteroatom moiety (Scheme 1). The difference in thermal stability between 1-benzoheteroepins and 3-benzoheteroepins was explained by comparison of the ease toward the transformation of **24–27** and **28–31** into the corresponding norcaradiene intermediates. The valence isomerization of 1-benzoheteroepins into *o*-xylylene intermediates should be easier than that of 3-benzoheteroepins into bicycle-octatetraene intermediates <2003CPB1283>.

The dithieno[2,3-*b*;3',2'-*f*]-heteroepins **52–55** are more stable than 1-benzoheteroepins **24–27**, but somewhat less stable than dibenzo[*b,f*]heteroepins **36–39**, and **53** that decomposed completely to the dithienobenzene at 110 °C for 5 h. However, the dithieno[3,4-*b*;3',4'-*f*]heteroepins **56–59** are very stable and remained unchanged even when heated at 180 °C for 24 h, probably because any norcaradiene intermediates cannot be formed from these compounds <1997H(45)1899>.

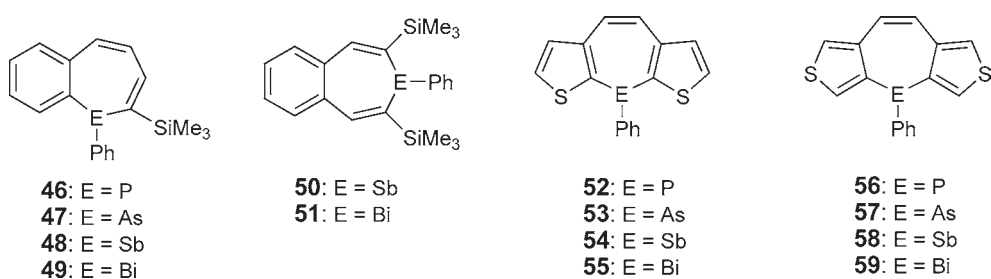
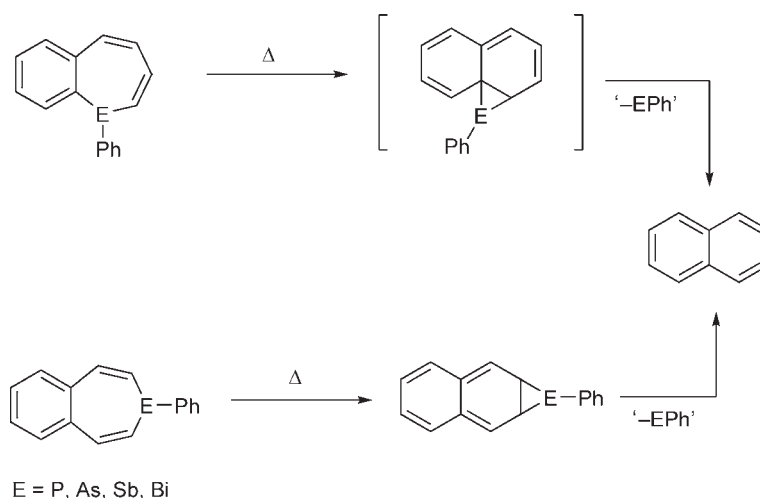


Table 5 Half-lives of benzoheteroeepines **24–31**, **50**, and **51** at 50 °C in toluene

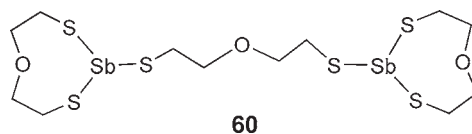
Compound	$t_{1/2}$	References
24 (P)	28 h	1999CPB1108, 1993CC1817
25 (As)	180 min	1999CPB1108, 1993CC1817
26 (Sb)	48 h	1999CPB1108, 1993CC1817
27 (Bi)	18 min	1999CPB1108, 1993CC1817
28 (P)	82 h	2003CPB1283, 1996CC2183
29 (As)	4 min	2003CPB1283, 1996CC2183
30 (Sb)	45 min	2003CPB1283, 1996CC2183
31 (Bi)	<1 min	2003CPB1283, 1996CC2183
50 (Sb)	190 h	2003CPB1283, 1996CC2183
51 (Bi)	34 min	2003CPB1283, 1996CC2183

**Scheme 1**

Some conformational aspects of the seven-membered and larger rings containing arsenic, antimony, or bismuth have already been discussed in CHEC-II <1996CHEC-II(9)971>. Further work has established that the 1-benzostibepine ring **26** exists in boat conformation with the heteroatom at the bow <1999CPB1108>.

The conformational properties of arsocane rings $\text{XC}_4\text{S}_2\text{E}$ (E = As, Sb) support the view that in arsocanes there is a relationship between the strength of the transannular interaction and the conformation of the eight-membered ring. When the transannular interaction is strong the boat-boat conformation tends to be most favorable, thereafter the boat-chair and then the chair-chair conformation <1996JCD4135>. The preferred geometry of several eight-membered arsocane rings is shown in Figure 1.

A particular feature of the molecular structure of **60** in the solid state is the presence of different conformations of the two eight-membered heterocyclic rings, that is, chair-chair for Sb(1) and boat-chair for Sb(2). In both heterocyclic rings, strong transannular $\text{Sb} \cdots \text{O}$ interactions are present <1995ICA31>.



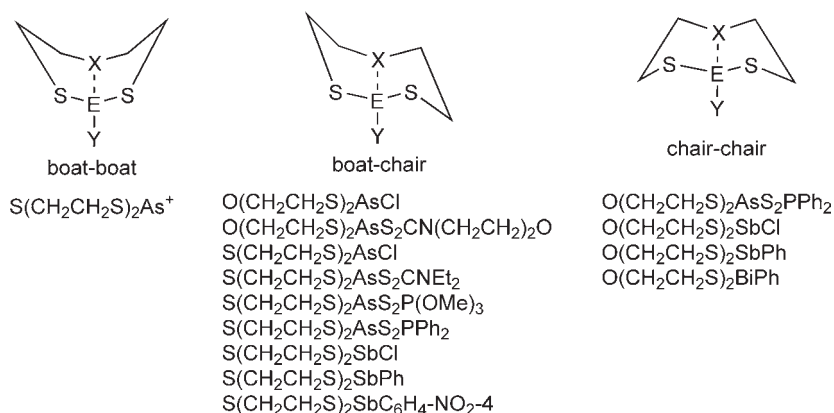


Figure 1 Extreme conformations in metallocanes with the known examples from X-ray diffraction study <1995ICA31, 1996JCD4135>.

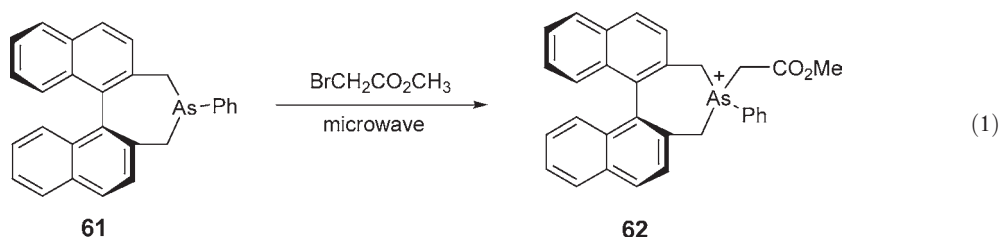
14.18.5 Reactivity of Fully Conjugated Rings

There have been no papers dealing with the synthesis and reactivity of the fully conjugated seven-membered and larger rings containing arsenic, antimony, or bismuth. The fully unsaturated seven-membered heterocycles containing heavier group 15 (As, Sb, Bi) elements (heteroepins) are thermally labile toward heteroatom extrusion and gradually decomposed to naphthalene via the norcaradiene intermediates (*vide supra*). There is, however, lack of information concerning other reactions of these heterocycles and their benzo-fused analogs.

14.18.6 Reactivity of Nonconjugated Rings

The survey of reactivity of nonconjugated seven-membered and larger rings containing As, Sb, and Bi given in CHEC-II(1996) is still noteworthy; no significant new aspects have since been reported. The survey in CHEC-II(1996) covers such reactions as (1) reduction of partially unsaturated rings containing arsenic and antimony; (2) reduction of cyclic esters of arsenic(v) acids into the respective arsenic(III) derivatives; (3) quaternization of cyclic arsenic(III) derivatives; and (4) oxidative halogenation of 5-chloro-10,11-dihydro-5*H*-dibenzo[*b,f*]stibepin into the 5,5,5-trichloro compound <1996CHEC-II(9)971>.

In early work, certain seven-membered and larger cyclic arsines were characterized by preparation and isolation of their arsonium salts by quaternization with alkyl halides. Reaction of more elaborate seven-membered cyclic arsines with activated alkyl bromide is shown in Equation (1). The C_2 -symmetric chiral tertiary arsine **61** reacts with methyl bromoacetate in a pressure tube under microwave irradiation to give the arsonium salt **62** in 71%. The latter was employed in the enantioselective olefination of 4-substituted cyclohexanes via the corresponding stabilized ylide <2002TA2187>.

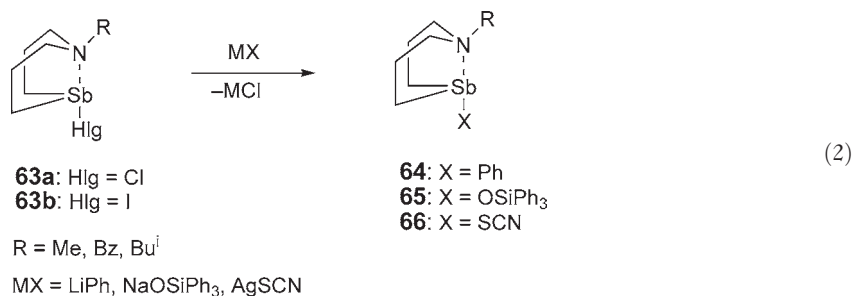


14.18.7 Reactivity of Substituents Attached to Ring Carbon Atom

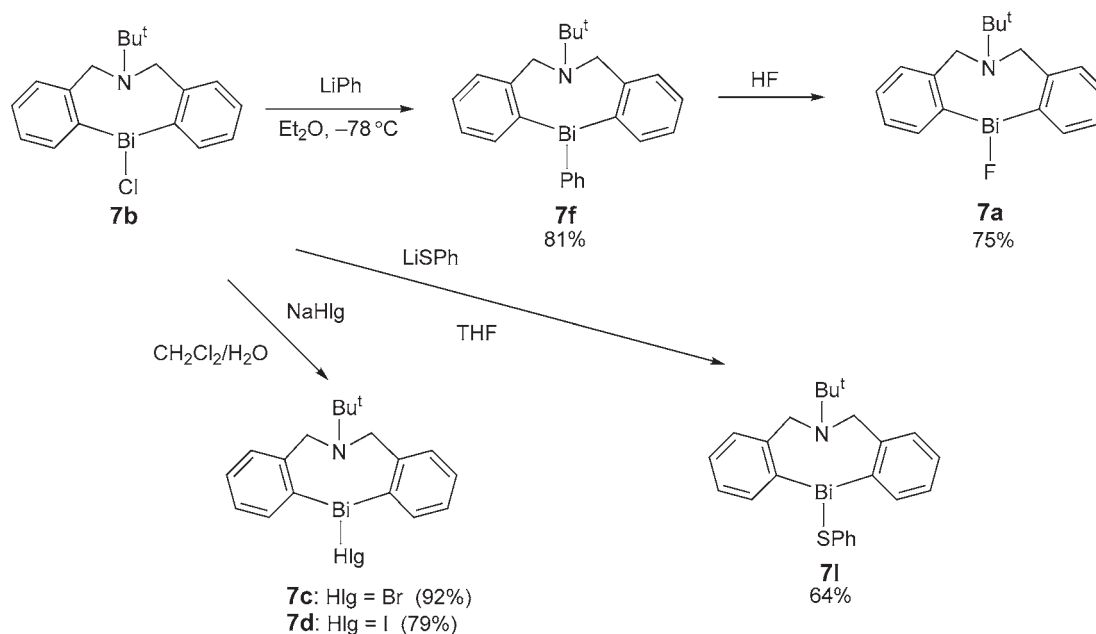
This was reviewed in CHEC-II(1996) <1996CHEC-II(9)971>. There have been no further studies except deprotonation of the cyclic arsenite esters **40–42** reported in Section 14.18.3.2.

14.18.8 Reactivity of Substituents Attached to Ring Heteroatom

The chemistry of the E–Hlg (E = As, Sb, Bi) bonds has been featured prominently in the reported chemistry of seven-membered and larger rings containing arsenic, antimony, and bismuth. In work directed toward the synthesis of heterocyclic systems involving transannular Sb···N interaction, **64** and **65** have been obtained from chloro-substituted stibocanes **63a** by reaction with LiPh in hexane or NaOSiPh₃ in toluene. To obtain the NCS-substituted **66**, the iodo-substituted stibocanes **63b** were reacted with AgSCN in dichloromethane (Equation 2) <1998POL2655>.

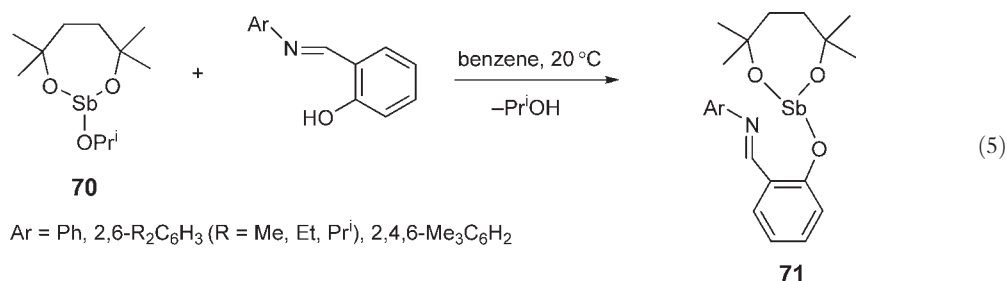
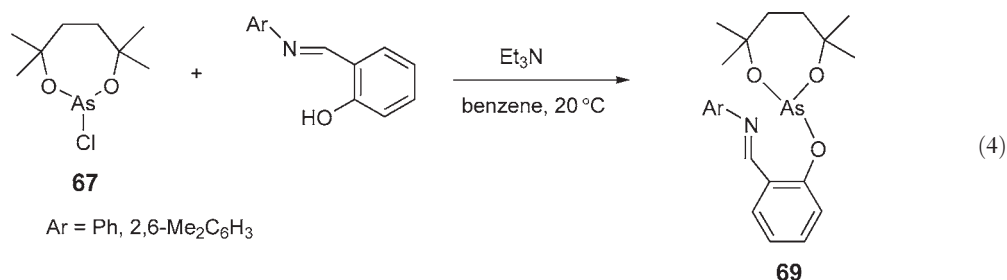
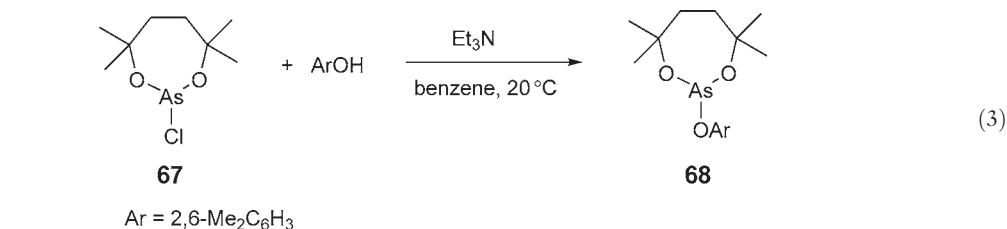


Synthesis of 12-halo-6-*tert*-butyl-5,6,7,12-tetrahydrodibenz[*c, f*][1,5]azabismocines **7a**, **7c**, and **7d** was examined by halogen exchange processes using an excess of NaHlg. Nucleophilic substitution of chloride by fluoride anion was difficult and conversion of **7b** to fluoride **7a** was about 40% even when 100 equiv of NaF was used. Treatment of **7b** with 2 equiv of NH₄F in THF afforded **7a** quantitatively, although again isolation of **7a** was not successful because **7b** easily regenerated during isolation procedure. Pure **7a** was obtained by the reaction of phenyl **7f** with an excess of a dilute aqueous HF solution. In contrast to a chloride/fluoride exchange, conversion of **7b** to bromide **7c** and iodide **7d** in reactions with NaBr and NaI was almost quantitative and pure **7c** and **7d** were obtained in more than 90% yields. Nucleophilic substitution of chloride by organic groups was accomplished by the reaction of **7b** with organolithium or Grignard reagents. Similarly, PhS group was easily introduced by the reaction of **7b** with PhSLi to give **7l** (Scheme 2) <2004JOM3012>.

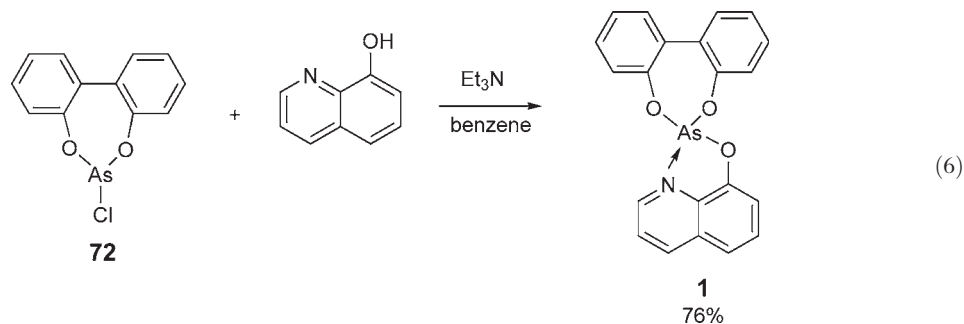


Scheme 2

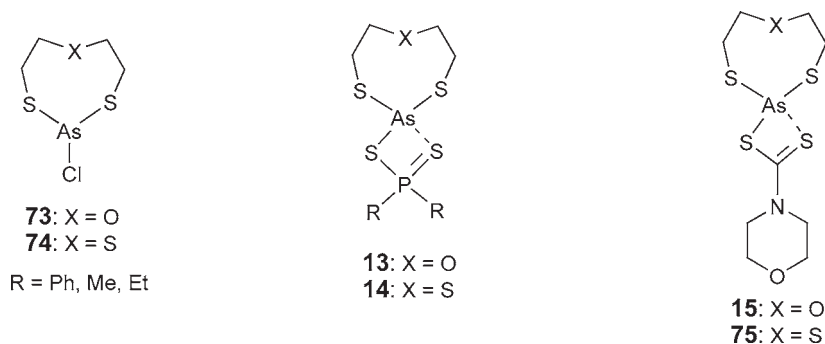
The reaction in a 1:1 molar ratio of the cyclic chloroarsenite **67** and 2,6-dimethylphenol in the presence of 1 equiv of Et₃N in benzene afforded mixed aryloxy–glycolate derivative **68** (Equation 3) <2003PS1653>. Mixed glycolate–salicylaldimine derivative of arsenic(III) has also been successfully prepared by the reaction of **67** with *N*-arylsalicylaldimines using Et₃N as a proton acceptor (Equation 4) <2002SRI1319>. Similar treatment of **70** with *N*-arylsalicylaldimines provided the corresponding cyclic glycolate–salicylaldimine derivative of antimony(III) **71** (Equation 5) <2001IJA1302>.



The cyclic chloroarsenite **72** was reacted with 8-hydroxyquinoline in the presence of triethylamine to give **1** which exhibits intramolecular N → As coordination (Equation 6), which, upon hydrolysis, gave As₂O₃, diol, and 8-hydroxyquinoline <1999PS191>.



The displacement of the halide substituent in chloroarsocanes **73** and **74** with potentially bidentate ligands, such as dithiocarbamates and phosphorodithioates, afforded the corresponding oxa- and thiaarsocane derivatives. Thus, arsocane diorganodithiophosphinates **13** and **14** were prepared from the corresponding chloroarsocane derivatives **73** and **74** and sodium or ammonium dithiophosphinates <1996JCD4135>. 1-Oxa-4,6-dithia-5-arsocane and 1,3,6-trithia-2-arsocane morpholinodithiocarbamates **15** and **75** were obtained by reacting **73** or **74** with sodium dithiocarbamate <1995MGC159>. Oxa- and thiaantibocanes with phosphorodithioate ligands, X(CH₂CH₂S)SbS₂P(OR)₂, can be also prepared via direct Cl/(RO)₂PS₂ exchange <1996ICA31, 1995ICA31>.



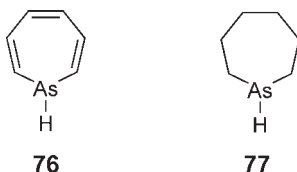
14.18.9 Ring Syntheses from Acyclic Compounds

14.18.9.1 Rings Containing Arsenic

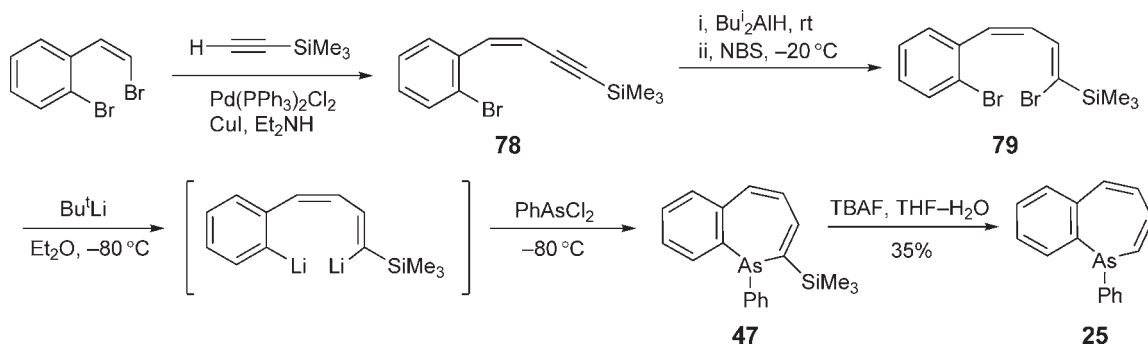
During the decade 1996–2005, in this category of heterocycles, the major interest has been the synthesis and reactions of benzarsepins, arsocanes, and cyclic esters of arsenic(III) acids. In contrast, little work has been done in the area of arsine heteromacrocycles with two or more arsenic atoms. Readers are referred to the corresponding sections of CHEC-II(1996) <1996CHEC-II(9)971> for information concerning earlier works on macrocyclic poly(tertiary arsines) and related compounds.

14.18.9.1.1 Benzarsepins and related fused heterocyclic systems

Both 1*H*-arsepin **76** and arsepan **77** are still unknown, although their fused derivatives have continued to attract interest.



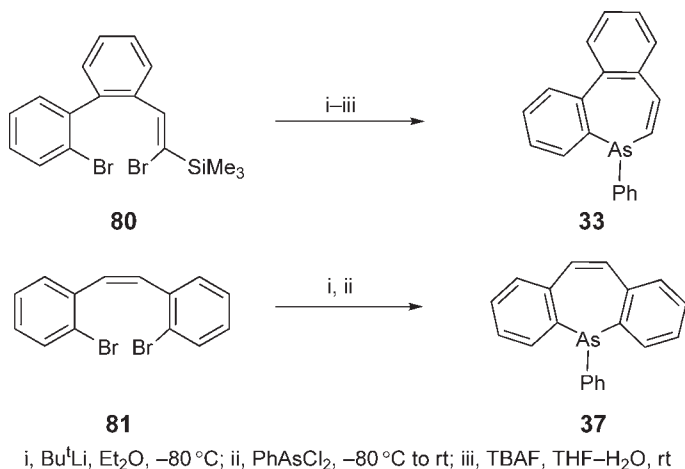
A novel and versatile route to 1-benzarsepins via 1,6-dilithium intermediates has been offered, and this has been extended to the synthesis of other fused systems involving arsepin ring. Synthesis of the 1-phenyl-1*H*-1-benzarsepin **25** was achieved, as follows. But-1-en-3-yne **78** was made available from bis(triphenylphosphine)palladium dichloride–copper(I) iodide-catalyzed reaction of (*Z*)-*o*,*β*-dibromostyrene with trimethylsilylacetylene. Subsequent hydroalumination of **78**, followed by bromination yielded (*Z,Z*)-1-bromobuta-1,3-diene **79**, as the major product along with other stereoisomers. Treatment of **79** with *t*-butyllithium and then with dichlorophenylarsine resulted in ring closure forming the 1-phenyl-2-trimethylsilyl-1*H*-1-benzarsepin **47**. The trimethylsilyl group in **47** was readily removed by treatment with tetrabutylammonium fluoride to give the desired 1-benzarsepin **25** (Scheme 3) <1999CPB1108>. The latter was much less stable than **47** containing the bulky trimethylsilyl group in the 2-position; the half-life ($t_{1/2}$) of **25**, estimated



Scheme 3

from ^1H NMR data, was 67 min at 60°C in toluene. Benzarsepin **25** can be also prepared by flash vacuum pyrolysis (FVP) of dihydrocyclobut[*b*]arsindole <1994CPB2441>.

In a similar vein, the cyclization of 1,6-dilithium intermediates, generated from the dibromovinylbiphenyl **80** and *cis*-*o,o'*-dibromostilbene **81**, has been used for the synthesis of dibenz[*b,d*]arsepin **33** and dibenz[*b,f*]arsepin **37** (Scheme 4), which are far more thermally stable than the arsepin **25** and remained unchanged even when heated at 60°C for 20 h in toluene <1999CPB1108, 1993CC1817>.



Scheme 4

The dithieno[2,3-*b*:3'2'-*f*]-**53** and dithieno[3,4-*b*:3',4'-*f*]arsepin **57** were prepared from 2-bromo-3-iodothiophene and 3-bromo-4-iodothiophene, respectively (Scheme 5). Dithienoarsepins were characterized mainly on the basis of their ^1H NMR spectra, in which only three kinds of vinyl proton signals were observed. The dithienoarsepin **53** is far more stable than **25**, but somewhat less stable than **37**. The arsepin **57** is very stable and remained unchanged even when heated at 180°C for 24 h <1997H(45)1899>.

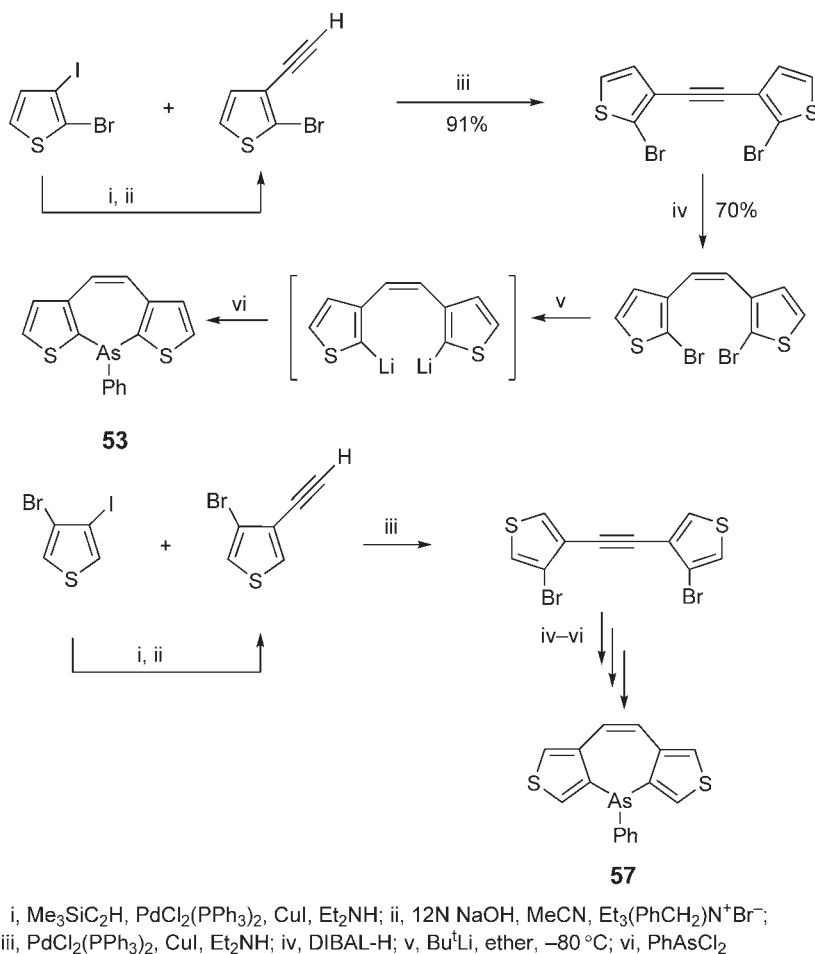
CHEC-II(1996) <1996CHEC-II(9)971> has brought an example of preparation of 3-chloro-3*H*-3-benzarsepin by the reaction of 3-benzostannepin with AsCl_3 . Since then a new approach to the synthesis of 3-phenyl-3-benzarsepin **29** has been designed via (*Z,Z*)-*o*-bis(β -lithiovinyl)benzene **83**, which was derived in two steps from *o*-phthalaldehyde (Scheme 6). The (*Z*)-stereostructure of the vinyl function in **82** was confirmed by its ^1H NMR data, in which two vinyl proton signals appeared at δ 6.55 (β -H) and 7.11 (α -H) indicating that the two vinyl groups are in the *cis*-orientation. The reaction of **82** with *tert*-butyllithium and then dichlorophenylarsine produced the corresponding 3-benzarsepin **29** in 20% yield <2003CPB1283, 1996CC2183>.

Novel C_2 -symmetric chiral arsepin **61** possessing the 1,1'-binaphthyl-2,2'-bis(methylene) backbone was prepared using (*S*)-(-)-1,1'-bi-2-naphthol **84** as the chiral substrate. The dilithio derivative **86**, generated from (*S*)-2,2'-dimethyl-1,1'-binaphthyl **85** and *tert*-butyllithium, reacted with PhAsBr_2 to give arsepin **61** (Scheme 7) <2002TA2187>.

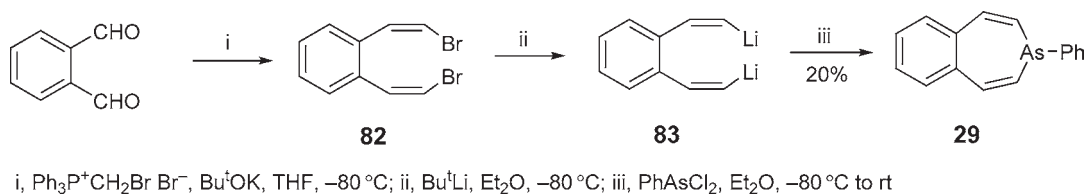
14.18.9.1.2 Arsocanes

Paths to the ligands $(\text{HalCH}_2\text{CH}_2\text{CH}_2)_2\text{Z}$ (Hal = Cl, Br; Z = NR, O, S, Se), to the corresponding Grignard reagents $(\text{HalMgCH}_2\text{CH}_2\text{CH}_2)_2\text{Z}$, and to the eight-membered group 15 heterocycles $\text{HalE}(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{Z}$ (E = As, Sb, Bi; Z = NR), have been described by Bräü *et al.* <1994POL365>. The condensation of dichlorophenylarsine or bis(dimethylamino)methylarsine with diethylene glycol $\text{O}(\text{CH}_2\text{CH}_2\text{OH})_2$ gave the arsocanes $\text{RAs}(\text{OCH}_2\text{CH}_2)_2\text{O}$, which were discussed in CHEC-II(1996) <1996CHEC-II(9)971>. Since then, several new syntheses of arsocanes have been reported starting with bis(dimethylamino)arsines and diols <1999CCL1011, 2000MI930>.

The chloroarsocanes $\text{ClAs}(\text{SCH}_2\text{CH}_2)_2\text{O/S}$ **73** and **74** are available from AsCl_3 and the corresponding glycol ethers <1998MI403>. More recently, reactions of the chloroarsocanes **73** and **74** with the sodium, potassium, or ammonium salts of dithiocarbamates <1995MGC159>, dithiophosphinates <1996JCD4135>, and phosphorodithioates



Scheme 5

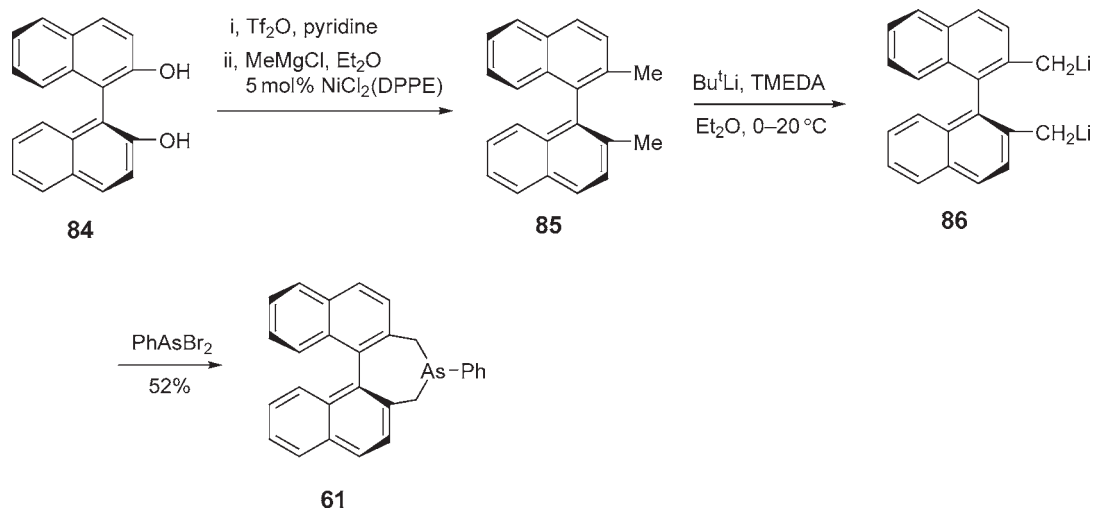


Scheme 6

<1996ICA31> were used to prepare the oxa- and thiaarsocanes with bidentate dithiocarbamate, dithiophosphate, and phosphorodithioate ligands on the arsenic atom (see Section 14.18.8).

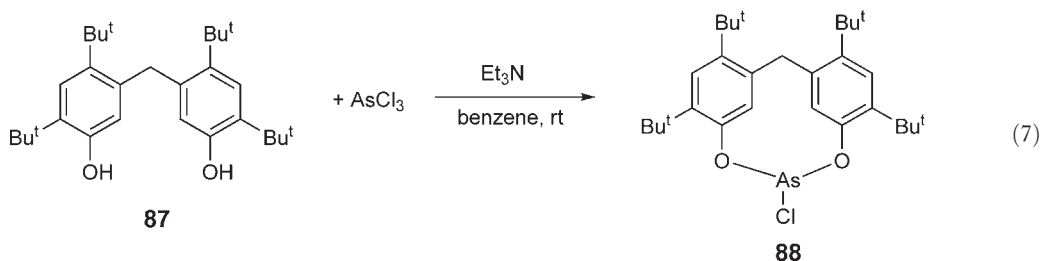
14.18.9.1.3 Macrocyclic esters of arsenic(III) acids and thioacids

Extensive studies on synthesis of cyclic esters of arsenic(III) and arsenic(V) acids and thioacids have been reviewed <1996CHEC-II(9)971>. The majority of these reported syntheses started from arsenic(III) dihalides of the type XAsCl_2 and diols or dithiols. Thus, methylenebis(4,6-di-*tert*-butylphenol) **87** reacted with AsCl_3 in the presence of triethylamine to give 1,3,2-dioxarsenocine **88** in 94% yield, m.p. $225\text{--}227^\circ\text{C}$ (Equation 7) <1995J(P1)2945>. Bis- and tris(amino)arsines $\text{XAs}(\text{NR}_2)_2$ ($\text{X} = \text{Alk}$, Ar , R_2N) were also convenient starting materials for the preparation of seven-membered and larger cyclic arsenites. For example, Davis and Verkade prepared the arsenic compounds **40–42** by



Scheme 7

condensation of $\text{As}(\text{NMe}_2)_3$ with the appropriate alcohol [<1990IC4983>](#). These compounds reacted with base to give NMR spectra that are consistent with the formation of fluxional square pyramidal arsorane anions in solution (see [Section 14.18.3.2](#)).



Further studies of the chemistry of 1,3,2-dioxarsepanes have appeared. 3-Chloro-1,3,2-dioxarsepan [67](#) (obtained from AsCl_3 and the corresponding diol) has been used for the synthesis of mixed aryloxy–glycolate and glycolate–salicylaldimine derivatives ([Equations 3 and 4](#)) [<2002SRI1319, 2003PS1653>](#). A convenient route to eight-membered arsoxanes $(\text{RAsO})_4$ ($\text{R} = \text{Bu}^t$, $m\text{-F}_3\text{CC}_6\text{H}_4$) has been offered using bis(dimethylamino)chloroarsines. The reaction of RLi ($\text{R} = \text{Bu}^t$, $m\text{-CF}_3\text{C}_6\text{H}_4$) with $(\text{Me}_2\text{N})_2\text{AsCl}$ in diethyl ether resulted in the formation of *tert*-butyl(dimethylamino)arsine and *m*-trifluoromethylphenyl-bis(dimethylamino)arsine, which was hydrolyzed in aqueous solution in the presence of sodium carbonate to give the arsoxanes $(\text{Bu}^t\text{AsO})_4$ and $(m\text{-F}_3\text{CC}_6\text{H}_4\text{AsO})_4$, respectively [<2005AOM129>](#).

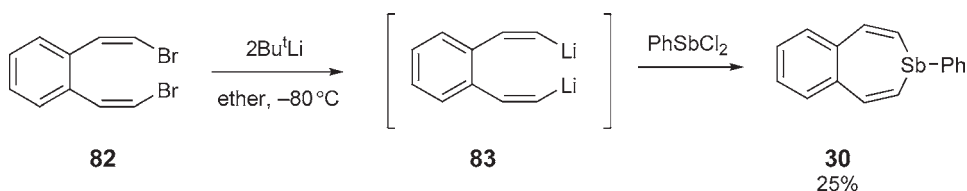
14.18.9.2 Rings Containing Antimony

14.18.9.2.1 Benzostibepins and related fused heterocyclic systems

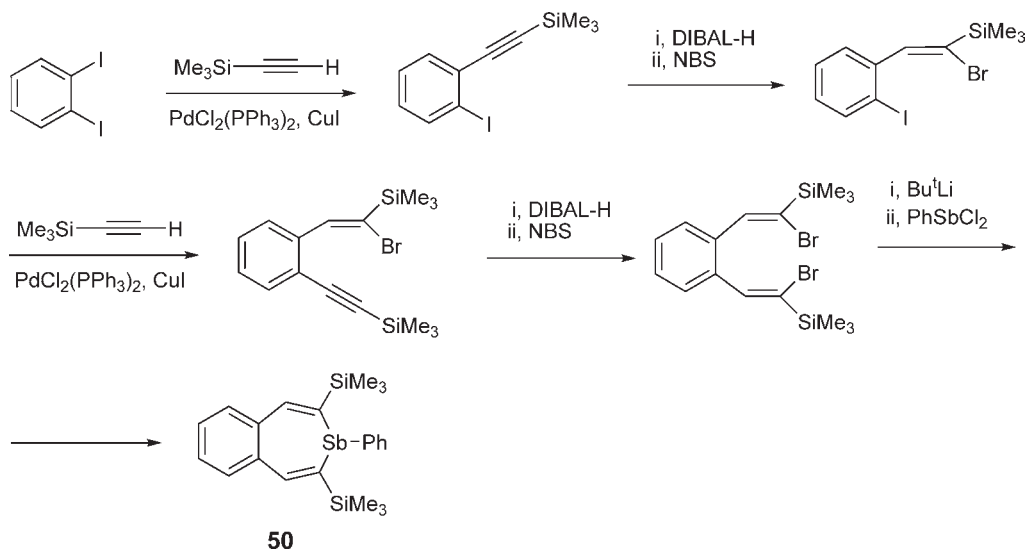
As was mentioned in CHEC-II(1996) [<1996CHEC-II\(9\)971>](#), 1-benzostibepin [26](#) was prepared by desilylation of [48](#), which in turn can be obtained from the appropriate 1,6-dibromohexatriene precursors [79](#) (for its synthesis, see [Scheme 3](#)). Dibenzo[*b,f*]stibepin [38](#) was obtained from *cis-o,o'*-dibromostilbene by lithiation and the addition of dichlorophenylstibine [<1999CPB1108, 1993CC1817>](#).

In a reaction analogous to the synthesis of 3-benzarsepin [29](#) described in [Section 14.18.9.1](#), treatment of (*Z,Z*)-*o*-bis(β -lithiovinyl)benzene with PhSbCl_2 afforded the C-unsubstituted 3-benzostibepin [30](#) ([Scheme 8](#)) [<2003CPB1283>](#).

The 2,4-bis(trimethylsilyl)benzo[*d*]stibepin [50](#) was prepared in 7% yield from *o*-diiodobenzene in six steps of which the key step was the treatment of the 1,6-dilithium compound, generated *in situ*, with dichlorophenylstibine ([Scheme 9](#)) [<2003CPB1283>](#).



Scheme 8

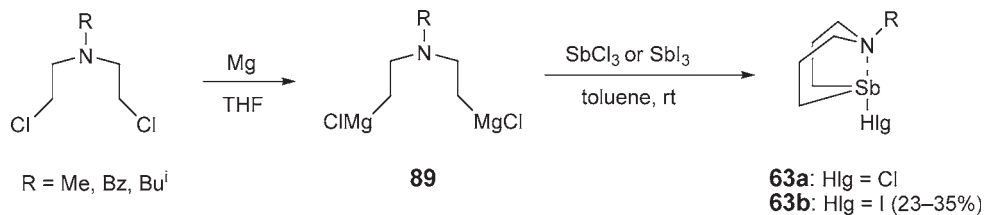


Scheme 9

The dithieno[2,3-*b*;3',2'-*f*]- **54** and dithieno[3,4-*b*;3',4'-*f*]stibepins **58** have been prepared in a similar manner to the analogous arsenic compounds (see [Scheme 5](#)) <1997H(45)1899>.

14.18.9.2.2 Stibocanes and stibatranes

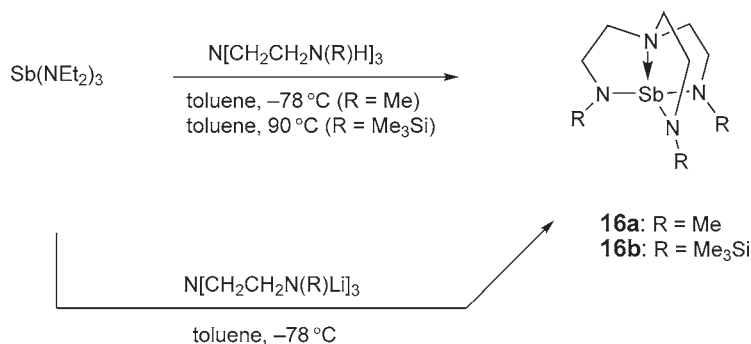
A series of eight-membered chloro- and iodo-substituted stibocanes **63a** and **63b** have been synthesized by reactions of the di-Grignard reagents with **89** with SbCl₃ or SbI₃ ([Scheme 10](#)). Structural, spectroscopic, and electrochemical data as well as semi-empirical MO calculations have been compared to the analogous data of the rings, which contain Sn(IV), As(III), and Bi(III) as central atoms <1998POL2655>.



Scheme 10

The first structurally characterized antimony derivatives of tripodal ligands such as tris(aminoethyl)amines, N[CH₂CH₂N(R)H]₃, named azastibatranes, were obtained from the reaction between tetramines and tris(dialkylamino)stibine. Thus, treatment of [N(CH₂CH₂N(Me)H)] with Sb(NEt₂)₃ led to **16a** isolated as a colorless oil in 95% yield.

A similar metathetical reaction occurred between $\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{Me})\text{Li}]_3$ and SbCl_3 to give *N,N',N''*-trimethylazastibatrane **16a** in 87% yield. Reaction of $\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{SiMe}_3)\text{Li}]_3$ with SbCl_3 afforded *N,N',N''*-tris(trimethylsilyl)azastibatrane **16b**, which was isolated in 61% yield (Scheme 11) <2002IC6147>.

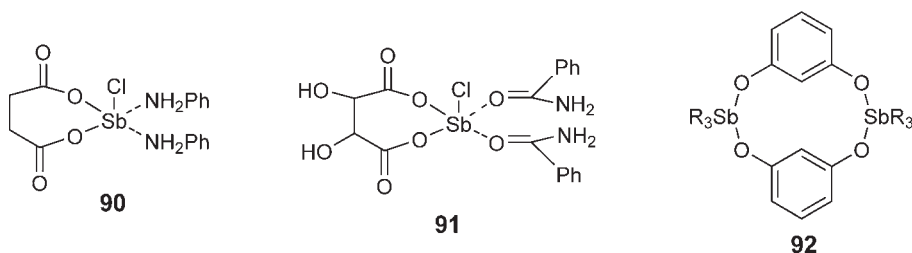


Scheme 11

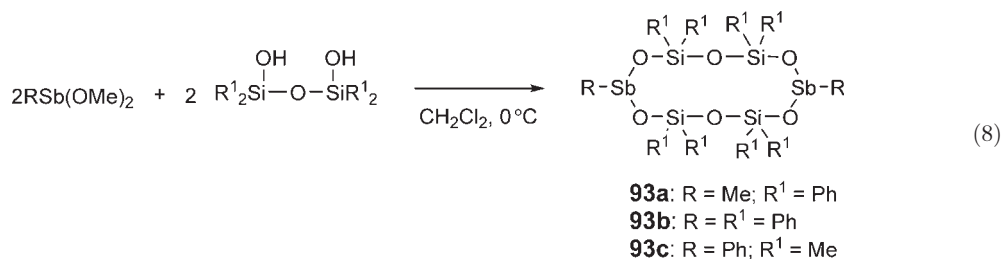
Reaction of SbF_3 with triethanolamine and NaOMe gave 2-fluoro-6-(2-hydroxyethyl)-1,3-dioxo-6-aza-2-stibacyclooctane, $\text{HOCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{O})_2\text{SbF}$ (83% yield) <2001DOK502>.

14.18.9.2.3 Macrocyclic esters of antimony acids

The seven-membered cyclic antimony(III) esters, such as **90** and **91**, were prepared by the reaction of the disodium salts of succinic, tartaric, and phthalic acids and adducts of SbCl_3 with aniline, benzamide, pyridine, and thioureas. The nature of the metal-carboxyl group linkage was discussed <1997MI630>. Reactions in the 1:1 molar ratio of $(\text{OGO})\text{SbOPr}^i$ ($\text{G} = \text{CMe}_2\text{CH}_2\text{CH}_2\text{CMe}_2$) with *N*-arylsalicylaldimines $2\text{-HOC}_6\text{H}_4\text{CH}=\text{NR}$ ($\text{Ar} = \text{Ph}$, 2,6-Me₂C₆H₃, 2,4,6-Me₃C₆H₂, etc.) in benzene afforded the cyclic derivatives of antimony(III) **71** (see Equation 5). Their characterization was conducted by the molecular weight determinations, IR, and ¹H NMR spectroscopic studies <2002SRI1319>. The 12-membered cyclic antimony(v) esters **92** were obtained in 79–83% yield from the reaction of R_3Sb ($\text{R} = \text{Me}$, Ph), resorcinol, and *tert*-butyl hydroperoxide <1995IZV748>.



A ring-closure reaction has been performed using $\text{RSb}(\text{OMe})_2$ ($\text{R} = \text{Me}$, Ph) and 1,1',3,3'-tetraorganodisiloxane-1,3-diols. The products appeared to be 12-membered macrocycles **93** (Equation 8) <1995PS215>.

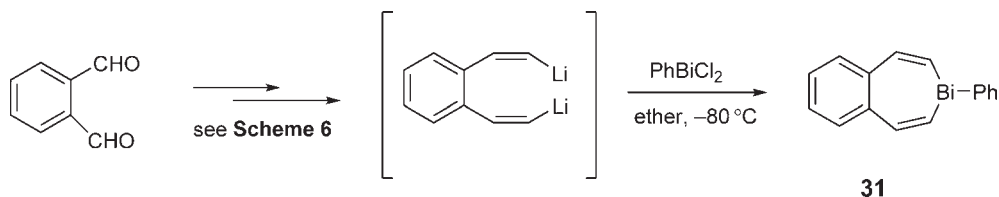


14.18.9.3 Rings Containing Bismuth

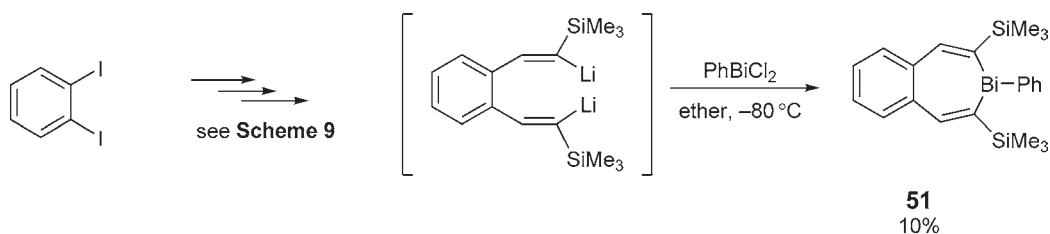
14.18.9.3.1 Benzobismepins and related fused heterocyclic systems

As for analogous arsenic and antimony compounds, the 1-phenyl-2-trimethylsilyl-1*H*-1-benzobismepin **49** has been prepared by the reaction of PhBiCl_2 with the corresponding 1,6-dilithium intermediate, generated from the common (*Z,Z*)-1-bromo-4-(2-bromophenyl)-1-trimethylsilyl-1,3-butadiene (cf. [Scheme 3](#)). The trimethylsilyl group in **49** was readily removed by treatment with tetrabutylammonium fluoride to give the C-unsubstituted benzo[*b*]bismepin **27** <1999CPB1108>.

The 3-benzobismepin **31** obtained by the reaction between (*Z,Z*)-*o*-bis(β -lithiovinyl)benzene and PhBiCl_2 was thermally unstable and could not be isolated, although it was detected at -20°C by ^1H NMR spectroscopy ([Scheme 12](#)). The related 2,4-bis(trimethylsilyl)-substituted 3-benzobismepin **51** resulting from the reaction of silylated 1,6-dilithium intermediate with PhBiCl_2 is much more stable and could be isolated at room temperature ([Scheme 13](#)) <2003CPB1283>.



Scheme 12



Scheme 13

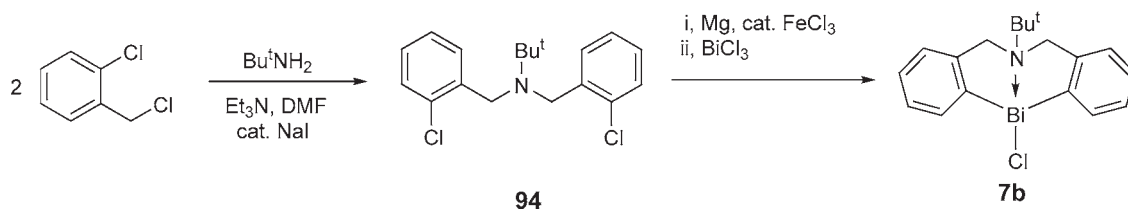
Synthesis of novel dithieno[2,3-*b*,3',2'-*f*]- and dithieno[3,4-*b*,3',4'-*f*]bismepins **55** and **59** was achieved starting from 2-bromo-3-iodothiophene and 3-bromo-4-iodothiophene by analogy with the preparation of arsenic analogous (see [Scheme 5](#)) <1997H(45)1899>.

14.18.9.3.2 Bismocanes and bismatranes

The hypervalent azabismocanes were first synthesized from bis(2-bromobenzyl)-methylamine in two steps by the treatment of $(2\text{-ClC}_6\text{H}_4\text{CH}_2)_2\text{NMe}$ with *n*-butyllithium and the addition of bismuth(III) chloride <1996CHEC-II(9)971>. More recently, a new synthetic procedure for the construction of the 5,6,7,12-tetrahydrodibenz[*c,f*][1,5]-azabismocine structure using the cheaper 2-chlorobenzyl chloride has been developed <2004JOM3012>. The required bis(2-chlorobenzyl)-*t*-butylamine **94** was obtained from $2\text{-ClC}_6\text{H}_4\text{CH}_2\text{Cl}$ and Bu^tNH_2 in 70–84% isolated yields using Et_3N as a base in the presence of a catalytic amount of NaI . Preparation of di-Grignard reagent from **94** was accomplished in a high yield by using a catalytic amount of FeCl_2 . Subsequent reaction with BiCl_3 afforded **7b** in 41–62% isolated yields ([Scheme 14](#)). Synthesis of 5,6,7,12-tetrahydrodibenz[*c,f*][1,5]azabismocines with other substituents on the bismuth atom including alkyl, alkenyl, alkynyl, aryl, or phenylthio groups has been accomplished by the halogen exchange reactions (see [Section 14.18.8](#)) <1999CL861, 2004JOM3012>.

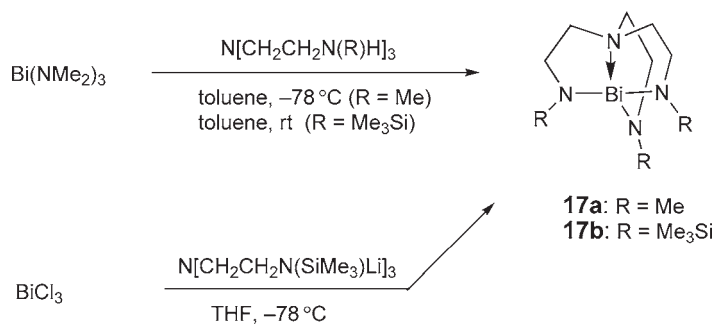
A general approach to dithiabismuth(III) heterocycles **10–12** involved a high-yield metathesis reaction of bismuth chloride or bismuth nitrate pentahydrate with the dithiol at appropriate stoichiometry (1:1 or 3:2) in ethanol.

Bis[[(1,3,6-trithia-2-bismocan-2-yl)thio]ethyl]sulfide **12** was also formed by the reaction of 2-chloro-1,3,6-trithia-2-bismocane **11** with 2-mercaptoethyl sulfide in aqueous NaNO_3 <1996JA3225>.



Scheme 14

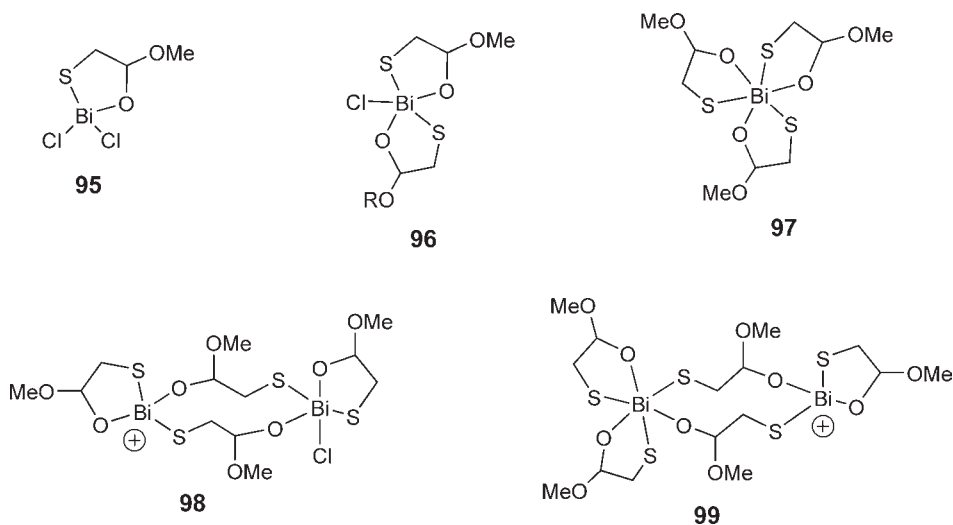
Transamination reactions of $\text{Bi}(\text{NR}_2)_3$ with tetramines $\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{R})\text{H}]_3$ afforded the azabismatranes **17a** and **17b** in 76% and 54% yields, respectively (**Scheme 15**). The metathetical exchange reaction between BiCl_3 and lithiated amine $\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{Me})\text{Li}]_3$ did not yield the expected product **17a**, although treatment of BiCl_3 with $\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{SiMe}_3)\text{Li}]_3$ provided a 46% yield of the corresponding bismatrane **17b** <2002IC6147>.



Scheme 15

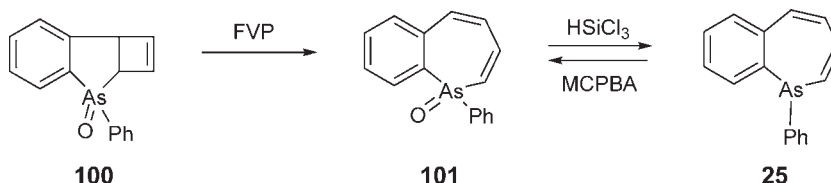
14.18.9.3.3 Macrocyclic esters of bismuth(III) and bismuth(V) acids and thioacids

Electrospray ionization mass spectrometry (ESI-MS) of the reactions between methyl thioglycolate and bismuth(III) chloride in absolute ethanol, 95% ethanol, or methanol revealed the presence of mono-, bis-, and tris-ester complexes **95–97** as well as ‘ligand-bridged’ dibismuth species **98** and **99** <2003IC3136>.



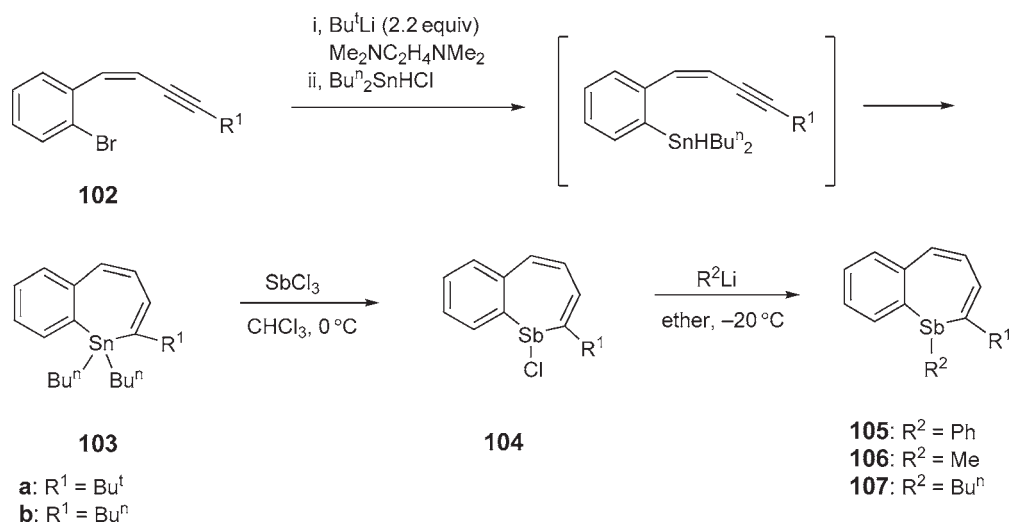
14.18.10 Ring Syntheses by Transformations of Another Ring

FVP of dihydrocyclobut[*b*]arsindole **100** resulted in valence isomerization with ring opening to give 1-phenyl-1-benzarsepin-1-oxide **101**. This oxide **101**, on treatment with trichlorosilane, underwent deoxygenation to afford 1-phenyl-1-benzarsepin **25**; *m*-chloroperbenzoic acid (MCPBA) reconverted the arsine into the oxide (Scheme 16) <1994CPB2441>.



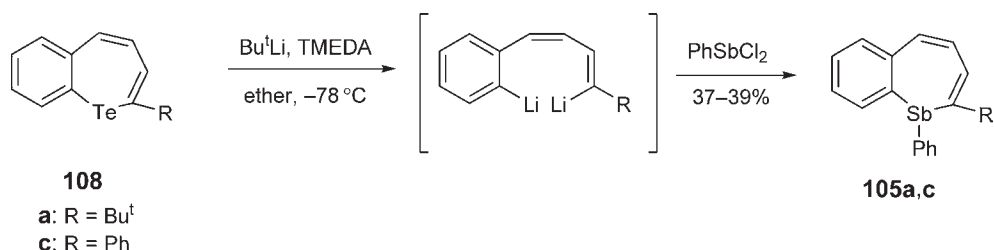
Scheme 16

The typical approach to arsepins and stibepins involved transmetalation of the corresponding stannepins by dichloroarsines or dichlorostibines <2004SOS825, 1996CHEC-II(9)971>. Scheme 17 demonstrated the utility of this route in preparing 2-alkyl-1-benzostibepins. 2-Alkyl-1-benzostannepins **103** were obtained in one pot from (*Z*)-1-(*o*-bromophenyl)but-1-en-3-ynes **102** via the tin hydride intermediates. The stannepins **103** readily reacted with antimony trichloride in CHCl_3 at 0°C to afford the corresponding 1-chloro-2-alkyl-1-benzostibepins **104**, but these compounds were too unstable to be isolated. Treatment of the latter with PhLi in ether at -20°C afforded the 1-phenyl-2-alkyl-1-benzostibepins **105** in moderate yields. The 1-methyl-**106** and 1-*n*-butyl derivatives **107** were obtained in a similar manner by using MeLi and Bu^nLi , respectively. Compounds **105–107** could easily be purified by silica gel chromatography <2000J(P1)1965, 1998CC767>.



Scheme 17

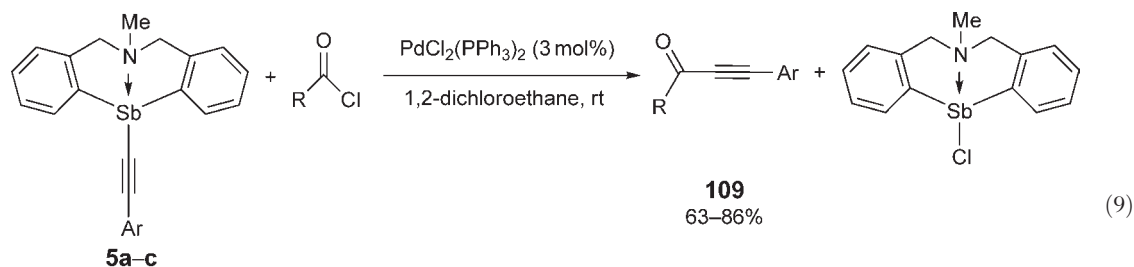
An alternative route for the preparation of 1-benzostibepins **105** involved the treatment of 1-benzotellurepins **108** with *tert*-butyllithium in the presence of tetramethylethylenediamine (TMEDA) in ether followed by addition of PhSbCl_2 (Scheme 18) <2000H(53)49>.



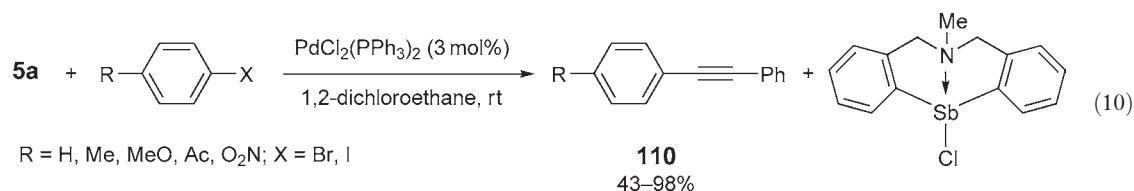
Scheme 18

14.18.11 Important Compounds and Applications

The ability of the ethynyl-1,5-azastibocines **5**, to be used as alkynylation agents, has recently been demonstrated by Kakusawa *et al.* <2003TL8589>. The reaction of **5** with organic halides, such as acyl halides and aryl halides, in the presence of PdCl₂(PPh₃)₂, as a catalyst, led to the formation of cross-coupling products, alkynyl ketones **109** and diaryl acetylenes **110**, in good yields (Equations 9 and 10).



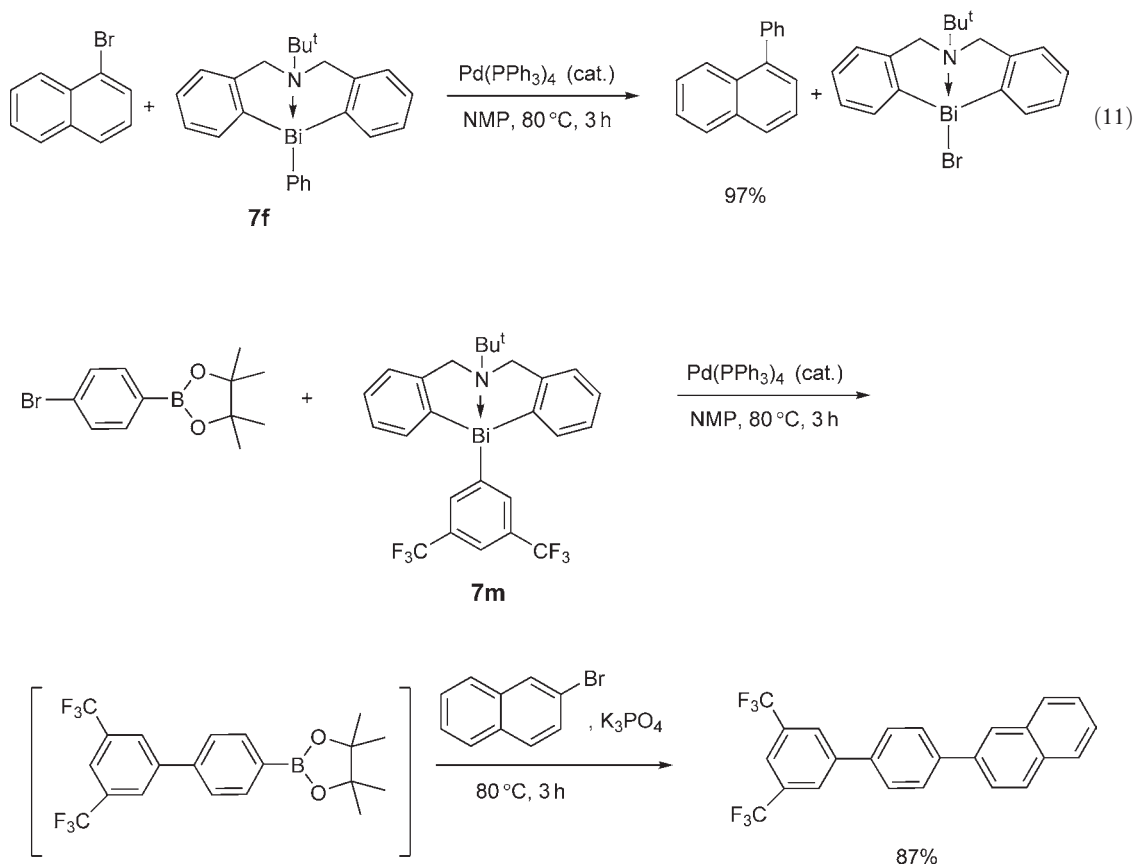
a: Ar = Ph
b: Ar = 4-MeC₆H₄
c: Ar = 4-F-C₆H₄
 R = Et, Hexⁿ, Bu^t, PhCH₂, Ph



R = H, Me, MeO, Ac, O₂N; X = Br, I

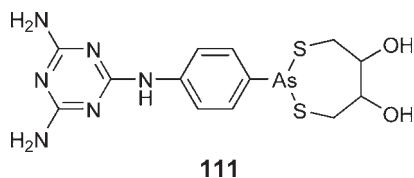
Shimada *et al.* have demonstrated that the organobismuth 2,6-Py(CR₂O)₂BiR¹ (R = alkyl, R¹ = Ph or Me) can be utilized for the transition metal-catalyzed cross-coupling reactions with organic electrophiles such as bromides, iodides, and triflates <2002JOM117, 2001OL4103, 1999OL1271>. In particular, when a toluene solution of 2,6-Py(CEt₂O)₂BiPh, 1-naphthyl trifluoromethanesulfonate, and Pd(PPh₃)₄ was heated at 60 °C for 18 h, 1-phenyl-naphthalene was obtained in 55% yield <2000JPP2000026335>.

5,6,7,12-Tetrahydridibenz[*c,f*][1,5]azabismocines efficiently couples with electron-deficient, -neutral, and -rich aryl bromides in the absence of additional activator by using Pd(PPh₃)₄, as catalyst. For example, the cross-coupling reaction of **7f** with 1-bromonaphthalene afforded 1-phenylnaphthalene in almost quantitative yield (Equation 11). The same reaction of Ph₃Bi with 1-bromonaphthalene produced 1-phenylnaphthalene in only 2% yield. Also, one-pot multicoupling reactions were possible by using a combination of 5,6,7,12-tetrahydridibenz[*c,f*][1,5]azabismocines, bromophenylboronic esters, and aryl bromide. An illustrative example is described by Scheme 19 <2003AGE1845>. Cross-coupling reactions of 6-*tert*-butyl-5,6,7,12-tetrahydridibenz[*c,f*][1,5]azabismocines **7** with aryl and alkenyl chlorides are efficiently catalyzed by the Pd(OAc)₂/DPPF (DPPF = 1,1'-bis(diphenylphosphino)ferrocene) system <2004SL1921>.



Scheme 19

A new drug molecule IMOL 881 **111** was reported to show interesting trypanocidal properties. The test results on animal models indicated activity against several trypanosome species, both in the veterinary and in the human medicine application fields <1993MI261>.



5,6,7,12-Tetrahydridibenz[*c,f*][1,5]azabismocines **7** and related cyclic organobismuth(III) compounds were reported to be antibacterial agents <2005AAC2729>. The eight-membered ring compounds exhibited minimum inhibitory concentrations (MICs) of $<0.5 \mu\text{g ml}^{-1}$ against *Staphylococcus aureus* and were more active than the six-membered compounds (MICs $4.0\text{--}16 \mu\text{g ml}^{-1}$). Azabismocines **6** were also reported to act as fungicides, algacides, and antifouling agents in a patent <2000JPP200035511>. The polyester PETG 6763 containing azabismocines as additives gave a $100 \mu\text{m}$ film with lasting antibacterial and antifungal effects <1999JPP11335487>. In addition, dibenz[*c,f*][1,5]-azabismocines displayed the corrosion-resistant property as antifungal agents or living thing adhesion inhibitors <2000JPP200035511>.

14.18.12 Further Developments

Synthesis and X-ray crystal structures of the first antimony and bismuth calixarene complexes have been described. The reaction of the monosodium salt of *p*-*tert*-butylcalix[4]arene (Bu^tC4) with 2 equiv of SbCl₃ provided Bu^tC4(SbCl)₂. Bismuth calixarene complex was prepared by treatment of *p*-*tert*-butylcalix[8]arene with Bi[N(SiMe₃)₂]₃ <2004CC1472>.

An X-ray analysis has been performed for 1,4,8,11-tetraazacyclotetradecane antimony(III) sulfide. Poly{1,4,8,11-tetraazacyclotetradecane(2+)[hepta- μ -sulfido-trisulfido-hexaantimony(III)]}, {(C₁₀H₂₆N₄) [Sb₆S₁₀]}_n, consists of novel [Sb₆S₁₀]²⁻ layers containing Sb₂S₂, Sb₄S₄, and Sb₇S₇ hetero-rings, which are separated by macrocyclic amine molecules <2007ACC27>.

Periodic terpolymerization of cyclooligoarsine, cyclooligostibine and dimethyl acetylenedicarboxylate provided a periodic terpolymer containing both antimony atom and arsenic atom in the polymer chain <2007MM1372>.

References

- 1990IC4983 R. V. Davis and J. G. Verkade, *Inorg. Chem.*, 1990, **29**, 4983.
 1990ZFA51 E. Nietzschmann, O. Boege, M. Dargatz, J. Heinicke, R. Kadyrov, and A. Tzschach, *Z. Anorg. Allg. Chem.*, 1990, **581**, 51.
 1992OM3748 D. V. Khasnis, H. Zhang, and M. Lattman, *Organometallics*, 1992, **11**, 3748.
 1993MI261 L. Maes, E. B. Songa, and R. Hamers, *Acta Tropica*, 1993, **54**, 261 (*Chem. Abstr.*, 1994, **120**, 235492).
 1993CC1817 S. Yasuike, H. Ohta, S. Shiratori, J. Kurita, and T. Tsuchiya, *Chem. Commun.*, 1993, 1817.
 1994CPB2441 S.-I. Shiratori, S. Yasuike, J. Kurita, and T. Tsuchiya, *Chem. Pharm. Bull.*, 1994, **42**, 2441.
 1994JPR421 F. Kober and P. Aslanidis, *J. Prakt. Chem.*, 1994, **336**, 421.
 B-1994MI725 S. Maeda; in 'The Chemistry of Arsenic, Antimony, and Bismuth Compounds', S. Patai, Ed.; Wiley, New York, 1994, p. 725.
 1994POL365 E. Bräu, R. Falke, A. Ellner, M. Beuter, U. Kolb, and M. Dräger, *Polyhedron*, 1994, **13**, 365.
 1994ZOB1998 V. S. Gamayurova, N. V. Shabrukova, N. V. Chechetkina, T. A. Zyablikova, I. P. Lipatova, and Yu. V. Chugunov, *Zh. Obshch. Khim.*, 1994, **64**, 1998 (*Chem. Abstr.*, 1995, **123**, 198963).
 1995IC3610 S. Shang, D. V. Khasnis, H. Zhang, A. C. Small, M. Fan, and M. Lattman, *Inorg. Chem.*, 1995, **34**, 3610.
 1995ICA31 R. Cea-Olivares, M. A. Muñoz-Hernández, S. Hernández-Ortega, and C. Silvestru, *Inorg. Chim. Acta*, 1995, **236**, 31.
 1995IZV748 V. A. Dodonov, A. Yu. Fedorov, R. I. Ustyatskii, S. N. Zaburdaeva, and A. V. Gushchin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1995, 748.
 1995J(P1)2945 M. A. Said, K. C. Kumara Swamy, M. Veith, and V. Huch, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2945.
 1995MGC159 R. Cea-Olivares, M. R. Estrada, G. Espinosa-Pérez, I. Haiduc, P. Garcia, Y. Garcia, M. Lopez-Cardoso, M. Lopez-Vaca, and A.-M. Coterio-Villegas, *Main Group Chem.*, 1995, **1**, 159.
 1995PS215 M. Wieber, M. Schroepef, and U. Simonis, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1995, **104**, 215.
 1996CC2183 S. Yasuike, T. Kihara, J. Kurita, and T. Tsuchiya, *Chem. Commun.*, 1996, 2183.
 1996CHEC-II(9)971 M. Pabel and S. B. Wild; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 971.
 1996ICA31 M.-G. Muñoz-Hernández, R. Cea-Olivares, and S. Hernández-Ortega, *Inorg. Chim. Acta*, 1996, **253**, 31.
 1996JA3225 L. Agocs, N. Burford, T. S. Cameron, J. M. Curtis, J. F. Richardson, K. N. Robertson, and G. B. Yhard, *J. Am. Chem. Soc.*, 1996, **118**, 3225.
 1996JCD4135 M.-G. Muñoz-Hernández, R. Cea-Olivares, G. Espinosa-Pérez, and S. Hernández-Ortega, *J. Chem. Soc., Dalton Trans.*, 1996, 4135.
 1997H(45)1899 S. Yasuike, F. Nakashima, J. Kurita, and T. Tsuchiya, *Heterocycles*, 1997, **45**, 1899.
 1997MI630 P. Dabas and M. K. Rastogi, *Asian J. Chem.*, 1997, **9**, 630 (*Chem. Abstr.*, 1998, **128**, 96894).
 1998CC767 H. Sashida, A. Kuroda, and T. Tsuchiya, *Chem. Commun.*, 1998, 767.
 B-1998MI403 J. Reglinski; in 'Chemistry of Arsenic, Antimony and Bismuth', N. C. Norman, Ed.; Blackie Academic and Professional, London, 1998, p. 403.
 1998POL2655 E. Bräu, A. Zickgraf, M. Dräger, E. Mocellin, M. Maeda, M. Takahashi, M. Takeda, and C. Mealli, *Polyhedron*, 1998, **17**, 2655.
 1998SAA85 A. Zickgraf, E. Bräu, and M. Dräger, *Spectrochim. Acta, Part A*, 1998, **54**, 85.
 1999CCL1011 X. Y. Chen, Y. Q. Yang, and W. T. Tao, *Chinese Chem. Lett.*, 1999, **10**, 1011 (*Chem. Abstr.*, 2000, **132**, 137548).
 1999CL861 M. Minoura, Y. Kanamori, A. Miyake, and K. Akiba, *Chem. Lett.*, 1999, 861.
 1999CPB1108 S. Yasuike, S.-I. Shiratori, J. Kurita, and T. Tsuchiya, *Chem. Pharm. Bull.*, 1999, **47**, 1108.
 1999JPP11335487 K. Terada, H. Suzuki, and T. Ikegami, *Jpn. Pat.* 11335487 (1999) (*Chem. Abstr.*, 2000, **132**, 12808).
 1999MI45 S. S. Garje and V. K. Jain, *Main Group Met. Chem.*, 1999, **22**, 45.
 1999PS191 K. C. Kumara Swamy, M. A. Said, M. Veith, and V. Huch, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1999, **152**, 191.
 1999OL1271 M. L. N. Rao, S. Shimada, and M. Tanaka, *Org. Lett.*, 1999, **1**, 1271.
 2000CSR403 H. J. Breunig and R. Rösler, *Chem. Soc. Rev.*, 2000, **29**, 403.
 2000H(53)49 H. Sashida, *Heterocycles*, 2000, **53**, 49.
 2000(P1)1965 H. Sashida and A. Kuroda, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1965.
 2000JPP2000026335 S. Shimada and M. Tanaka, *Jpn. Pat.* 2000026335 (2000) (*Chem. Abstr.*, 2000, **132**, 107789).
 2000JPP2000355511 K. Akiba, S. Igarashi, and T. Nishino, *Jpn. Pat.* 2000355511 (2000) (*Chem. Abstr.*, 2001, **134**, 42267).
 2000MI930 X.-Y. Chen and W.-T. Tao, *Youji Huaxue*, 2000, **20**, 930 (*Chem. Abstr.*, 2001, **134**, 207902).
 2001DOK502 M. G. Voronkov, V. A. Pestunovich, E. A. Zel'bst, A. A. Kashaev, V. S. Fundamentalskii, A. I. Albanov, G. A. Kuznetsova, and V. P. Baryshok, *Dokl. Akad. Nauk SSSR*, 2001, **381**, 502 (*Chem. Abstr.*, 2002, **137**, 14790).
 2001IC856 M. B. Dinger and M. J. Scott, *Inorg. Chem.*, 2001, **40**, 856.
 2001JA1302 S. Goyal and A. Singh, *Indian J. Chem., Sect. A*, 2001, **40**, 1302.
 2001MI1 H. Suzuki and Y. Matano; 'Organobismuth Chemistry', Elsevier: Amsterdam, 2001.

- 2001OL4103 M. L. N. Rao, O. Yamazaki, S. Shimada, T. Tanaka, Y. Suzuki, and M. Tanaka, *Org. Lett.*, 2001, **3**, 4103.
- 2002IC6147 P. L. Shutov, S. S. Karlov, K. Harms, D. A. Tyurin, A. V. Churakov, J. Lorberth, and G. S. Zaitseva, *Inorg. Chem.*, 2002, **41**, 6147.
- 2002JOM117 M. L. N. Rao, S. Shimada, O. Yamazaki, and M. Tanaka, *J. Organomet. Chem.*, 2002, **659**, 117.
- 2002SRI1319 S. Goyal and A. Singh, *Synth. React. Inorg. Metal-Org. Chem., Nano-Met. Chem.*, 2002, **32**, 1319.
- 2002TA2187 W.-M. Dai, A. Wu, and H. Wu, *Tetrahedron Asymmetry*, 2002, **13**, 2187.
- 2003AGE1845 S. Shimada, O. Yamazaki, T. Tanaka, M. L. N. Rao, Y. Suzuki, and M. Tanaka, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 1845.
- 2003CCC-II475 W. Levason and G. Reid; in 'Comprehensive Coordination Chemistry II', A. B. P. Lever, Ed.; Elsevier Science, Amsterdam, 2003, vol. 1, p. 475.
- 2003CPB1283 S. Yasuike, T. Kiharada, T. Tsuchiya, and J. Kurita, *Chem. Pharm. Bull.*, 2003, **51**, 1283.
- 2003IC3136 G. G. Briand, N. Burford, M. D. Eelman, T. S. Cameron, and K. N. Robertson, *Inorg. Chem.*, 2003, **42**, 3136.
- 2003PS1653 S. Goyal and A. Singh, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 1653.
- 2003TL8589 Kakusawa, Y. Tobiyasu, S. Yasuike, K. Yamaguchi, H. Seki, and J. Kurita, *Tetrahedron Lett.*, 2003, **44**, 8589.
- 2004CC1472 L. Liu, L. N. Zakharov, A. L. Rheingold, and T. A. Hanna, *Chem. Commun.*, 2004, 1472.
- 2004JOM3012 S. Shimada, O. Yamazaki, T. Tanaka, Y. Suzuki, and M. Tanaka, *J. Organomet. Chem.*, 2004, **689**, 3012.
- 2004SL1921 O. Yamazaki, T. Tanaka, S. Shimada, Y. Suzuki, and M. Tanaka, *Synlett*, 2004, 1921.
- 2004SOS825 J.-P. K. Meigh; in 'Science of Synthesis', S. M. Weinreb, Ed.; Georg Thieme Verlag, Stuttgart, 2004, vol. 17, p. 825.
- 2005AAC2729 T. Kotani, D. Nagai, K. Asahi, H. Suzuki, F. Yamao, N. Kataoka, and T. Yagura, *Antimicrob. Agents Chemother.*, 2005, **49**, 2729.
- 2005AOM129 H. Sun, B. O. Patrick, and W. R. Cullen, *Appl. Organomet. Chem.*, 2005, **19**, 129.
- 2007ACC27 R. J. E. Lees, A. V. Powell, D. J. Watkin, and A. M. Chippindale, *Acta Cryst.*, 2007, **C63**, m27.
- 2007MM1372 K. Naka, A. Nakahashi, and Y. Chujo, *Macromolecules*, 2007, **40**, 1372.

Biographical Sketch



Vadim D. Romanenko was born in Alchevsk, Ukraine, in 1946. He studied at Dnepropetrovsk Institute of Chemical Technology and received his Ph.D. degree there under the supervision of Professor S. I. Burmistrov. Since 1975, he has been working at the National Academy of Sciences of Ukraine from which he earned his Doctor of Chemistry degree in 1988. He became a full professor in 1991. He has been a visiting scientist at the Centre of Molecular and Macromolecular Studies in Lodz (Poland), the University of Pau & des Pays de l'Adour (France), the University Paul Sabatier (France), and the University of California Riverside (USA). His research interests include mainly synthetic aspects of heavy main group elements. He is the author of approximately 300 papers on organoelement chemistry. He is also author of numerous reviews and two monographs on low-coordinated phosphorus compounds.



Jean-Marc Sotiropoulos (born 1963) received his Ph.D. degree in chemistry from the University Paul Sabatier – Toulouse in 1991 under the direction of Dr. Guy Bertrand. After a postdoctoral training with Prof. Dr. K. Seppelt at the FU Berlin as A.v. Humbolt Fellow, he joined the CNRS at the Université de Pau et des Pays de l'Adour. His main research interests concern reactive species from the main group elements and transition metals. He contributes to the development of new photoelectron systems which are used to characterize and understand unusual compounds in combination with modern theoretical methods.

14.19

Rings containing Silicon to Lead

F. Sączewski and A. Kornicka

Medical University of Gdańsk, Gdańsk, Poland

© 2008 Elsevier Ltd. All rights reserved.

14.19.1	Introduction	979
14.19.2	Parent Rings with One Group 14 Heteroatom	979
14.19.2.1	Seven-Membered Rings	979
14.19.2.1.1	Monocyclic derivatives	979
14.19.2.1.2	Fused benzo derivatives	983
14.19.2.2	Larger Rings	986
14.19.3	Rings with Two or More Heteroatoms	987
14.19.3.1	Rings Containing E-(CH₂)_n-E and Related Units	987
14.19.3.2	Rings Containing E-C≡C-E and Related Units	990
14.19.3.3	Insertion into Si-Si and Ge-Ge Bonds	995
14.19.3.4	Rings Containing C-E-O and Related Units	999
14.19.3.5	Rings Containing O-E-O and Related Units	1005
14.19.3.6	Silacrown Ethers, Calixarenes, Cyclophanes, and Metallacenes	1011
14.19.3.7	Atranenes and Related Compounds	1019
14.19.4	Reactivity and Transformations of Heterocyclic Rings	1021
14.19.5	Applications of Computational Methods	1027
14.19.6	Further Developments	1028
	References	1033

14.19.1 Introduction

This subject was covered previously in pages 993–1022 in CHEC-II(1996) (volume 9, chapter 36). This chapter is intended to update the previous work on major preparative and structural aspects of various types of rings containing silicon to lead that have been reported since 1995. As compared to previous work, two novel topics are covered: reactivity and transformations of heterocyclic rings in [Section 14.19.4](#) and application of computational methods in [Section 14.19.5](#). Moreover, silacrown ethers and related compounds such as calixarenes, cyclophanes, and metallacenes are covered in [Section 14.19.3.6](#).

During the past decade, the chemistry of heterocycles containing group 14 heteroatoms has been studied widely and many books and review articles have been published on this subject. Readers are advised to consult the monograph, *The Chemistry of Silicon Compounds* <B-2001MI1> and following reviews: <2004CR5847, 2003COR691, 1999EJI373, 1995CCR157, 1999CRV3463, 2001T7237, 2004AGE4704, 1997AGE2426, 1996POL4311, 2002CCR47, 1995CRV813, 1998T2289, 2005AOM440, 2002AOM481, 2006T7951, 1997CSR453>.

14.19.2 Parent Rings with One Group 14 Heteroatom

14.19.2.1 Seven-Membered Rings

14.19.2.1.1 Monocyclic derivatives

Over the last decade, the synthesis and characterization of trivalent silyl cations (silylium ions), including silatropylium ion **1** ([Figure 1](#)), have remained as a major challenge in organosilicon chemistry, and, therefore, was the subject of intensive studies. The earlier suggestion that silatropylium ion **1** is more stable than silabenzyl cation **2** and may

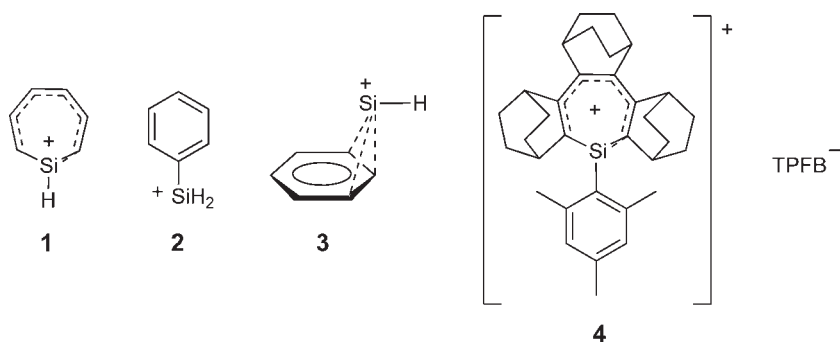
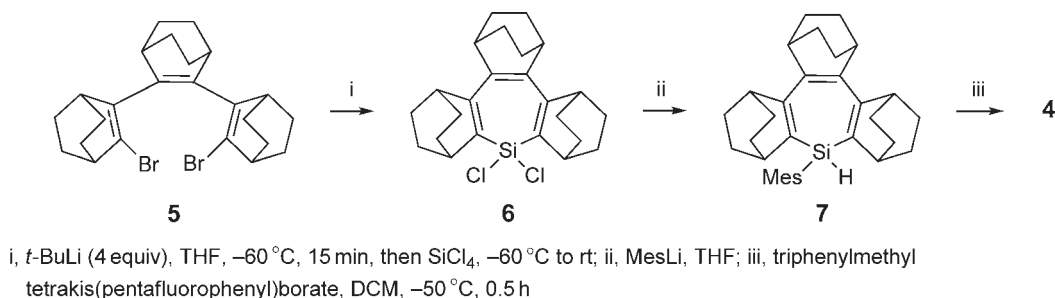


Figure 1

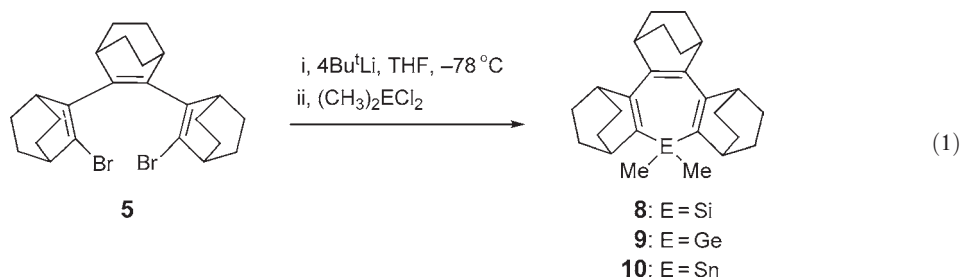
exist in the gas phase [<1993JA10805>](#) was disapproved by both the *ab initio* molecular orbital calculations [<1994JA9769>](#) and experimental study showing that actually it was a rearranged adduct $C_6H_5SiH^+$ of type **3** [<1997JA6376>](#). However, the first silatropylium ion **4** stabilized by rigid σ -frameworks has recently been prepared [<2000JA9312, 2001T3645>](#) having in mind the previously established guideline for the possible generation of silylium ions in condensed phase [<1992JA7737, 1999JA5001>](#), which include (1) the silylium ion center should be surrounded by bulky substituents, (2) the cation should be prepared in the presence of a low-coordinating counter-anion, and (3) a low-coordinating solvent should be used for the synthesis.

The cyclic π -conjugated tropylsilylium ion **4** synthesized from dibromo derivative **5** according to the procedure described in [Scheme 1](#) was found to be stable at temperatures below -50°C and was characterized by ^1H , ^{13}C , and ^{29}Si nuclear magnetic resonance (NMR) spectral data. As a clear evidence for the silylium ion, character of **4** was assumed by the presence of a signal at 142.9 ppm in ^{29}Si NMR spectrum run in CH_2Cl_2 solution. For comparison, the corresponding signal in the spectrum of the precursor silepin **7**, structure of which was determined by X-ray crystallography, was found at -49.3 ppm.

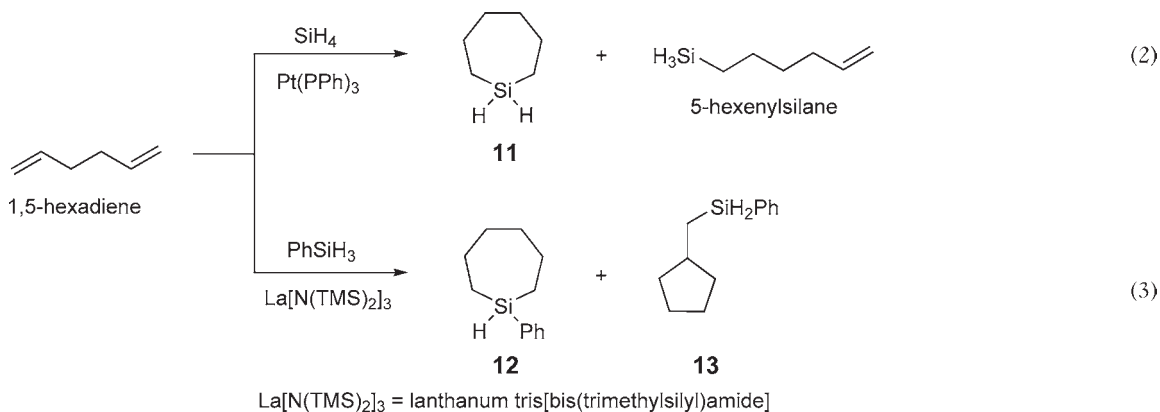


Scheme 1

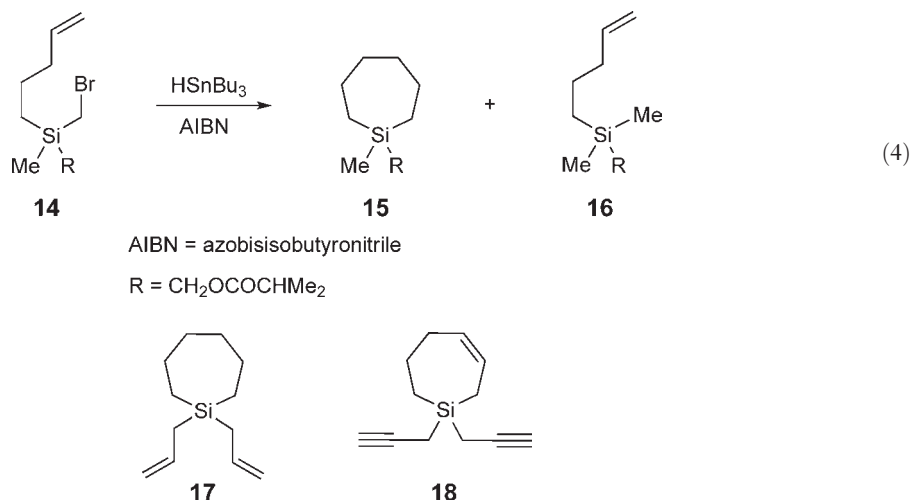
The fully unsaturated seven-membered rings containing group 14 elements (1,1-dimethylmetallepins) **8–10** were also obtained ([Equation 1](#)) and characterized by ultraviolet (UV) and NMR spectroscopic data as well as X-ray crystallographic analysis. All of these compounds were found to have the central seven-membered ring in a boat form. Metallepins **8–10** are stable in the solid state but readily decompose under acidic conditions even during elution from a silica-gel column [<1995JOC1309>](#).



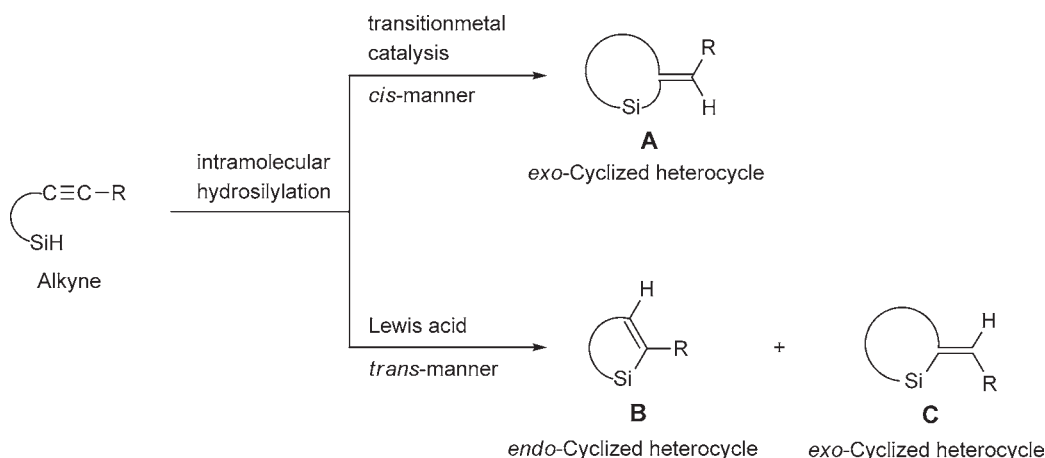
The transition metal-catalyzed hydrosilylation of olefins, which is one of the most versatile methods for the synthesis of alkylsilanes, has been known for many years <B-1992MI1>. The reaction of 1,5-hexadiene with monosilane (SiH_4) was carried out in an autoclave in the presence of a catalytic amount of $\text{Pt}(\text{PPh}_3)_4$ forming a 1:1 mixture of 5-hexenylsilane and silacycloheptane **11** in 31% yield (Equation 2). Product **11** was separated by distillation under reduced pressure and its structure was confirmed by ^1H NMR, infrared (IR) and mass spectrometry (MS) spectral data <1999JOM241>. Hydrosilylation of 1,5-hexadiene with phenylsilane (PhSiH_3) catalyzed by commercially available lanthanum tris[bis(trimethylsilyl)amide] led to the formation of silacycloheptane **12** and silamethylcyclopentane **13** as a 1:4 mixture in 95% yield (Equation 3) <2004OM12>.



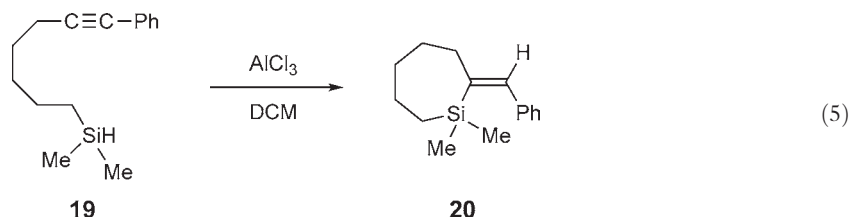
Regioselective synthesis of silacycloalkanes can also be achieved under radical conditions. Thus, upon treatment of 2-(bromomethyl)-2-methyl-silahept-6-enyl-isobutyrate **14** with tributylstannane (HSnBu_3) in the presence of azobisisobutyronitrile (AIBN) in boiling benzene for 48 h, a 56/44 mixture of 2,2-dimethyl-2-silahept-6-enyl isobutyrate **15** and (1-methyl-1-silacycloheptyl)methyl isobutyrate **16** was formed in 73% yield as shown in Equation (4) <2001MGM363>. In similar reactions of triallyl(3-bromopropyl)silane and (3-bromopropyl)tripropargylsilane, corresponding silacycloheptane **17** and silacycloheptene **18** were obtained in 48% and 28% yields, respectively <2001JOM160>.



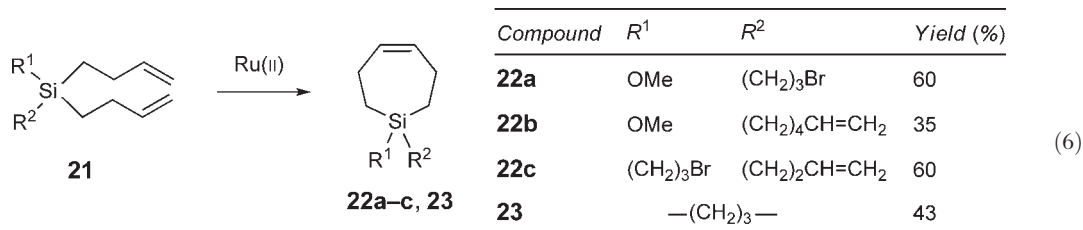
Intramolecular hydrosilylation of alkynes is a widely used method for the synthesis of various silacycles with a vinylsilane framework. As shown in Scheme 2, the reaction provides three different types of silacycles, depending on the mode of the cyclization and addition of SiH bond. The transition metal-catalyzed reaction proceeds in a *cis*-manner leading to *exo*-silacycles of general formula **A** <1999S921>. On the other hand, the Lewis acid-catalyzed hydrosilylation could produce the *endo*- (**B**) or *exo*- (**C**) silacycles depending on the substrates, to give five-, six-, seven-, or eight-membered rings (Scheme 2) <2000JOC8919>. Thus, the AlCl_3 -catalyzed reaction of the phenyl-substituted alkyne **19** having a tether of five methylene groups gave the seven-membered silacycle **20** as a result of the *exo*-mode intramolecular hydrosilylation (Equation 5) <2000JOC8919>.



Scheme 2

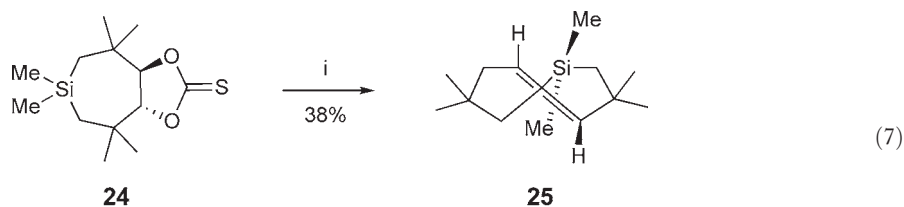


Another method for the synthesis of silacycloalkenes involves carbon–carbon bond formation by a Ru(II)-catalyzed ring-closing metathesis (RCM). As shown in Equation (6), cyclization of dieny silanes **21** conducted in benzene afforded the corresponding 1-silacyclohept-4-enes **22a–c** and silaspirene **23** in 35–60% yield [\[2001JOM160\]](#). The above procedure has also been applied to the preparation of cyclic siloxanes from appropriately functionalized alkoxy silanes [\[1997TL4757, 1997TL7861, 1998JOC6768\]](#).



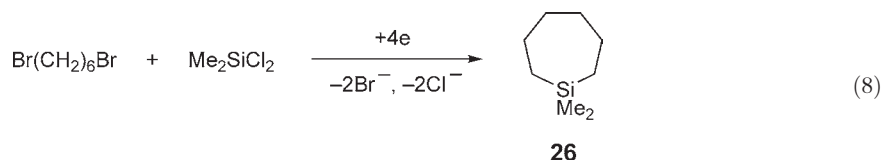
Ru(II) = bis(tricyclohexylphosphine)benzylidene ruthenium dichloride

Enantiomerically pure (*E*)-1,1,3,3,6,6-hexamethyl-1-sila-4-cycloheptene **25**, the smallest nonbridged (*E*)-cycloalkene which can be isolated in a pure form at room temperature, was synthesized by the Corey–Winter elimination of hexamethyl-1-sila-*trans*-4,5-cycloheptanethiocarbonate **24** with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (Equation 7) [\[1997AGE159, 1999TA3483\]](#).

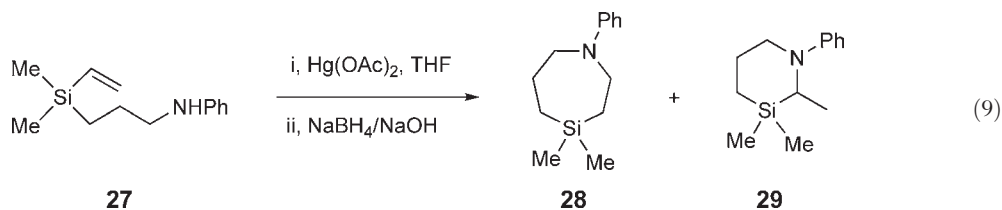


i, 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, 40 °C, 48 h

A facile synthesis of cyclic alkylsilanes consisting in the electrochemical reduction of aliphatic dibromides in the presence of polychlorosilanes of the formula $R_n\text{SiCl}_4$ ($n=0, 2$) affords heterocyclic compounds in good yields <1995JOM213>. According to the procedure described in Equation (8), the compound **26** was obtained in 57% yield. In contrast to nonelectrochemical methods, which are based on the ring closure of terminal unsaturated compounds, the electrochemical route is claimed to be more efficient and selective.

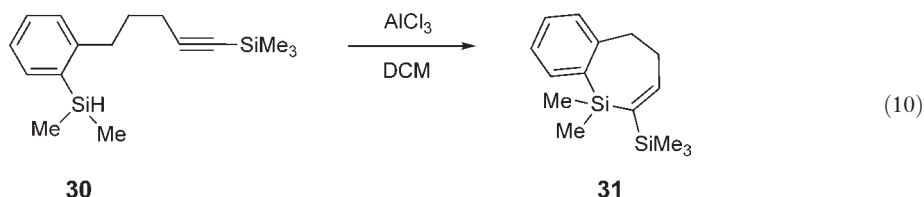


Reaction of vinyl(3-phenylaminopropyl)dimethylsilane **27** with $\text{Hg}(\text{OAc})_2$ followed by the treatment with NaBH_4 afforded 4-silaazepane **28** and 3-silapiperidine **29** as a 2.7:1 mixture in 49% yield (Equation 9). Structures of these products were confirmed by ^1H , ^{13}C , and ^{29}Si NMR spectroscopic data <2001ZOB1979>.

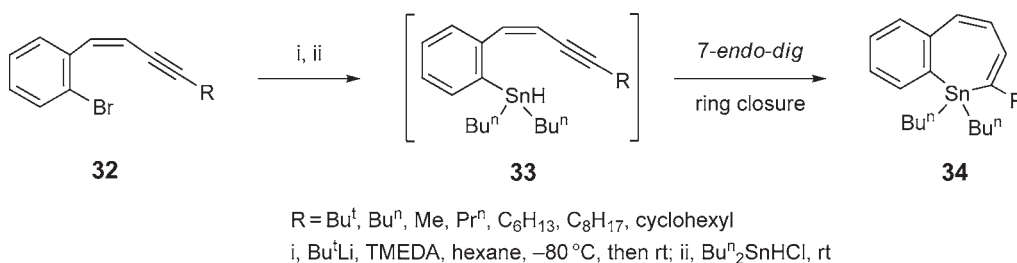


14.19.2.1.2 Fused benzo derivatives

As noted in Section 14.19.2.1.1, the Lewis acid-catalyzed hydrosilylation of unactivated acetylenes provided a general method for the synthesis of alkenylsilanes. Hence, intramolecular *trans*-hydrosilylation of TMS-substituted alkyne **30** bearing a benzene ring spacer led to the formation of *endo*-cyclization product **31** (Equation 10) <2000JOC8919>.

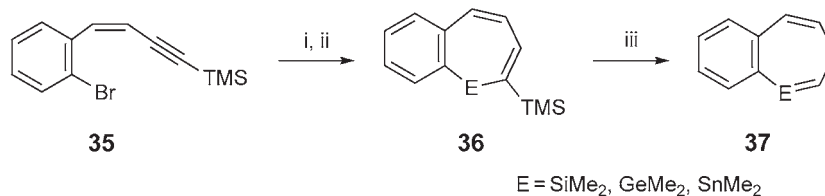


It should be pointed out that intermolecular hydrostannation of acetylene compounds which can be induced by radical initiators, transition metal catalysts, base catalysts, or Lewis acids to form vinylstannanes has also been known for many years. However, the first synthesis of 1-benzostannepines **34** was described in 1998 from (*Z*)-1-(*o*-bromophenyl)but-1-en-3-yne **32** via the tin hydride intermediate **33** by the intramolecular 7-*endo-dig*-ring closure at the sp carbon atom of ethynyl moiety (Scheme 3) <1998CC767, 2000J(PI)1965>. 2-Alkyl-1-benzostannepines thus obtained are stable (not sensitive to air, light and moisture, and colorless oils).



Scheme 3

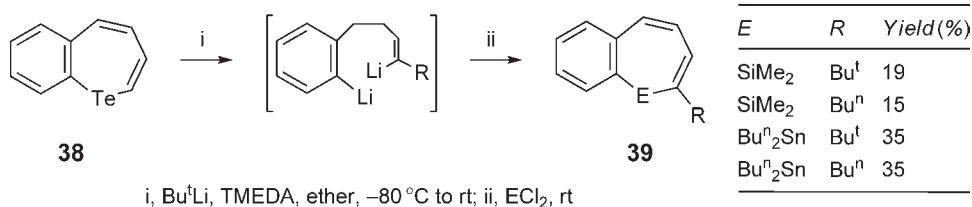
Fully unsaturated group 14 2-trimethylsilyl-1-heteropines **36** and C-unsubstituted parent rings **37** were obtained from the common starting compound (Z)-1-(bromophenyl)-4-trimethylsilyl-1-butyne-3-ene **35**, as shown in **Scheme 4** <1999CPB1108>. Structures of the newly prepared compounds **36** and **37** were confirmed by ^1H NMR and MS spectral data.



i, DIBAL-H, hexane, rt, 50 h, then NBS, -20°C , 6 h; ii, Bu^tLi, ethyl ether, -80 to -20°C , then EC₂; iii, tetrabutylammonium fluoride, THF/H₂O, ice bath, 1–1.5 h

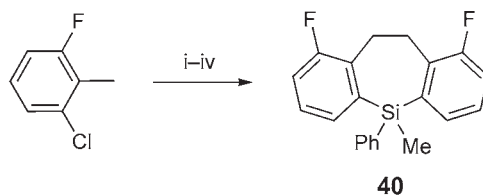
Scheme 4

An alternative route for the preparation of 1-benzosilepines and 1-benzostannepines of type **39** utilized the conversion of 1-benzotellurepins **38** via the Te–Li exchange and successive coupling of dilithium intermediate with silicon or tin reagent <2000H(53)49>. Thus, tellurepines **38** were lithiated with 2.2 equiv of Bu^tLi in the presence of tetramethylethylenediamine (TMEDA) followed by addition of dibutyltin or dichlorodimethylsilane to give corresponding products **39** in 15–35% yield (**Scheme 5**).



Scheme 5

Synthesis of 1,9-difluoro-5-methyl-5-phenyl-10,11-dihydro-5*H*-dibenzo[*b,f*]silepin **40**, the first silepin isolated with substituents adjacent to the ethano bridge, has been achieved starting from 2-chloro-6-fluorotoluene, as depicted in **Scheme 6**. The compound **40** was characterized in the solid state by X-ray crystallography and in solution by ^1H , ^{13}C , ^{29}Si , and ^{19}F NMR spectroscopy. The effect of substituents adjacent to the ethano bridge was found to produce a heterocycle with a smaller butterfly angle (bend angle) than any other tricyclic silepin characterized crystallographically thus far <1995JOM113>.

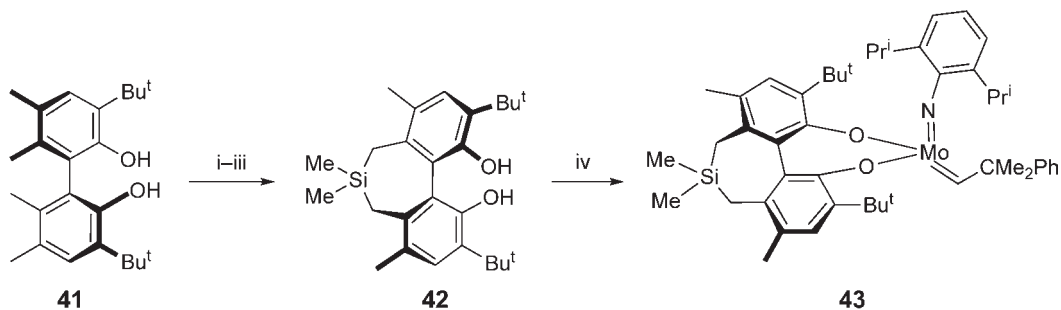


i, NBS, benzoyl peroxide, CCl₄, reflux; ii, PhLi, ether, rt, overnight; iii, Mg or MgCl₂, Li and naphthalene as magnesium source, THF, dibromoethane, rt, 28 h; iv, PhMeSiCl₂, reflux, overnight, then aqueous NH₄Cl

Scheme 6

It has been known that enantiometrically pure complexes of biphenolate **43** (H₂[Biphen]) serve as catalysts for efficient asymmetric metathesis reactions. A method of derivatizing the biphenolate ligand found in these catalysts

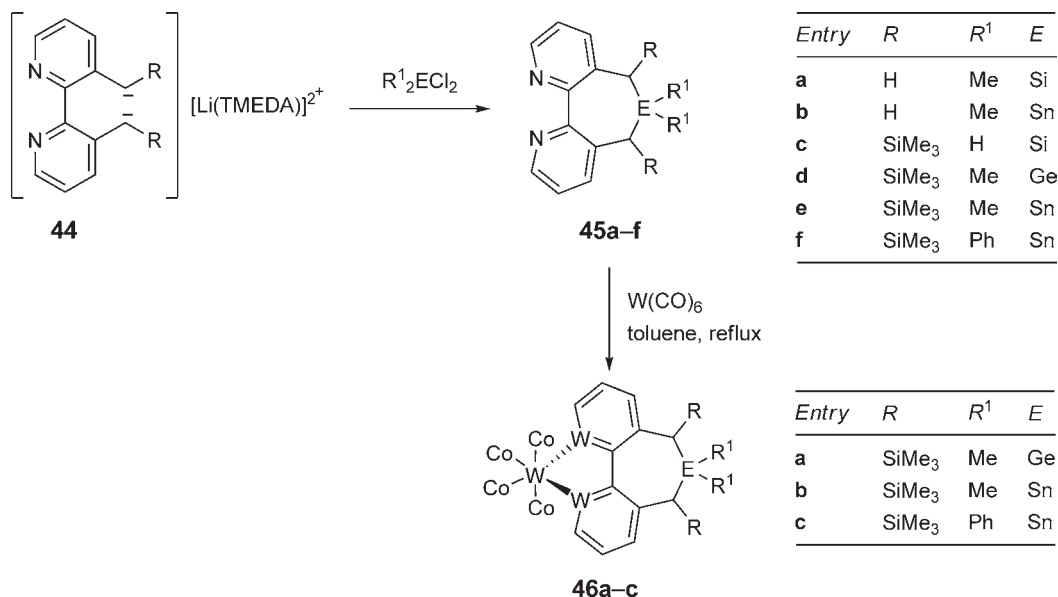
has been developed <2001OM4705>. First, the readily available enantiopure ligand **41** was transformed using a three-step procedure into the ligand $\text{H}_2[\text{Me}_2\text{SiBiphen}]$ **42**. Then, optically pure molybdenum complex **43** was prepared by a standard procedure involving deprotonation of the ligand with benzyl potassium followed by addition of $\text{Mo}(\text{NAr})(\text{CHCMe}_2\text{Ph})(\text{OTf})_2(\text{DME})$ (Scheme 7).



i, 2KH, THF, then MeI; ii, 2KOBu^t, then 2BuⁿLi, pentane, rt; iii, Me₂SiCl₂, then BBr₃, DCM, 0 °C, 24 h; iv, 2PhCH₂K, then Mo(NAr)(CHCMe₂Ph)(OTf)₂(DME)

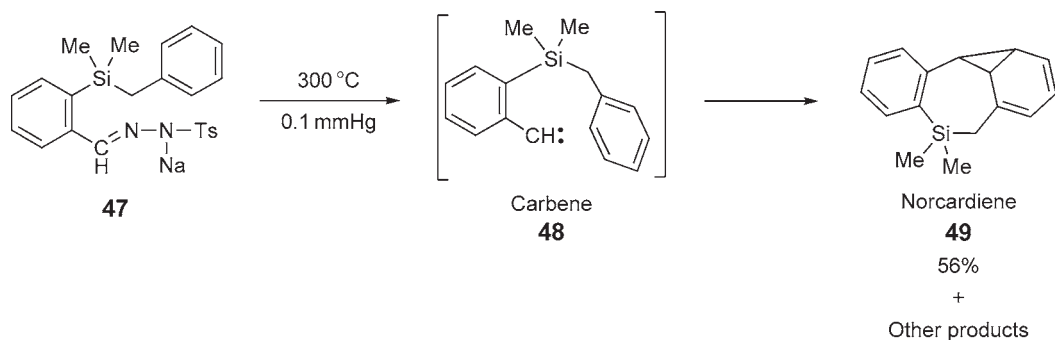
Scheme 7

The reaction of dilithium dialkyl bipyridines **44** derived from dilithiation of 3,3'-dimethyl-2,2'-bipyridine with $(\text{R}^1)_2\text{ECl}_2$ ($\text{R}^1 = \text{Me}$ or Ph; $\text{E} = \text{Si}$, Ge, or Sn) afforded the axially symmetric seven-membered metallacycles **45**, which were purified by column chromatography and characterized by their MS and NMR spectra and for **45c** and **45e** the X-ray structure has been determined. Subsequent reaction of **45d-f** with $\text{W}(\text{CO})_6$ in toluene gave the corresponding bimetallic complexes **46a-c** (Scheme 8) <1997OM4839>.



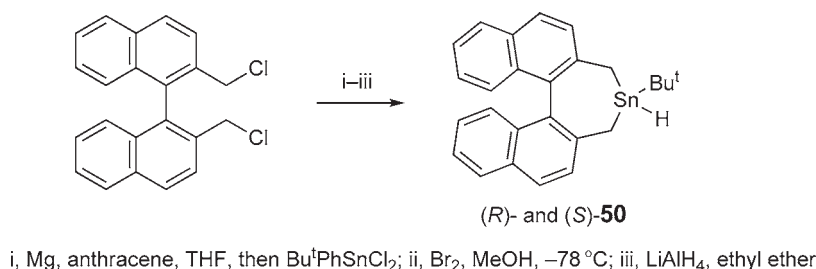
Scheme 8

Reactivity of functionalized arylcarbenes with the $\text{CH}_2\text{-X-Ph}$ ($\text{X} = \text{CH}_2$, O, SiMe₂) group in the *ortho*-position was studied in terms of both the rate and regioselectivity of intramolecular carbene addition to the terminal phenyl group <1997T9935>. Phenylcarbene **48** with the Si(Me)₂CH₂Ph group in the *ortho*-position, generated thermally from tosylhydrazone precursor **47**, underwent an insertion reaction into the 2',3'-bond of the terminal phenyl group to give a norcardiene derivative **49** in 56% yield as a result of the unique donating effect of R₃SiCH₂ substituent (Scheme 9).



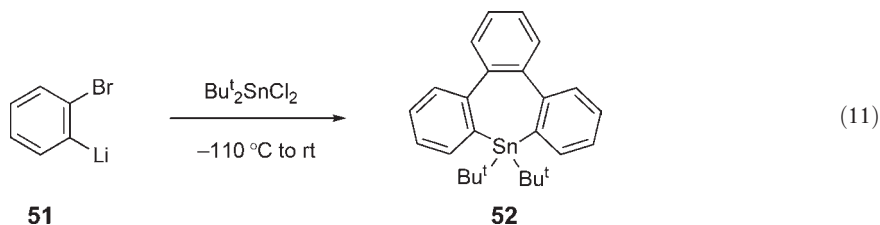
Scheme 9

Tin hydrides (*R*)-**50** and (*S*)-**50** were prepared in three steps starting from (*R*)- and (*S*)-2,2'-bis(chloromethyl)-1,1'-binaphthyl, respectively, in an overall yield of 46% (Scheme 10). This sequence can be used for a wide variety of different alkyl substituents at the tin atom <2003TA3069>.



Scheme 10

When (2-bromophenyl)lithium **51**, generated by the reaction of 1,2-dibromobenzene with *n*-butyllithium at -110 °C, was treated with di-*t*-butyldichlorostannane and then the reaction was warmed to room temperature, an unexpected product tribenzostannepin **52** was obtained in 16% yield together with 9-stannafluorene (Equation 11). Although the mechanism of this reaction was not investigated in detail, the tribenzo skeleton of **52** was reasonably assumed to be formed by successive couplings of benzyne generated from 2-bromophenyllithium with 1,2-dibromobenzene. The structure of **52**, which is the first example of a tribenzo-fused stannepin, was established by X-ray crystallographic analysis. The central seven-membered ring has a boat conformation <2001OM749>.



14.19.2.2 Larger Rings

5,5-Dimethyl-6-(trimethylsilyl)-5,8,9,10-tetrahydro-5-silabenzocyclooctane **53** (Figure 2) was obtained in 48% yield via the Lewis acid-catalyzed intramolecular *trans*-hydrosilylation of 1-(dimethylsilanyl)-2-[5-(trimethylsilyl)-pent-4-enyl]-benzene according to the procedure discussed above for its seven-membered ring analogue **31** <2000JOC8919>.

Metallaacetylenes of general structure **54** represent an interesting class of derivatives because they are expected to show carbene-like character perturbed electronically by a neighboring divalent heavy group 14 element through the resonance forms shown in Scheme 11. The first successful generation of stannaacetylene **54** (E = Sn) consisted in the reaction of arylchlorostannylene **55** with silyldiazomethyl lithium (formation of aryl diazostannylene **56**) followed

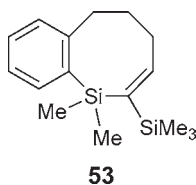
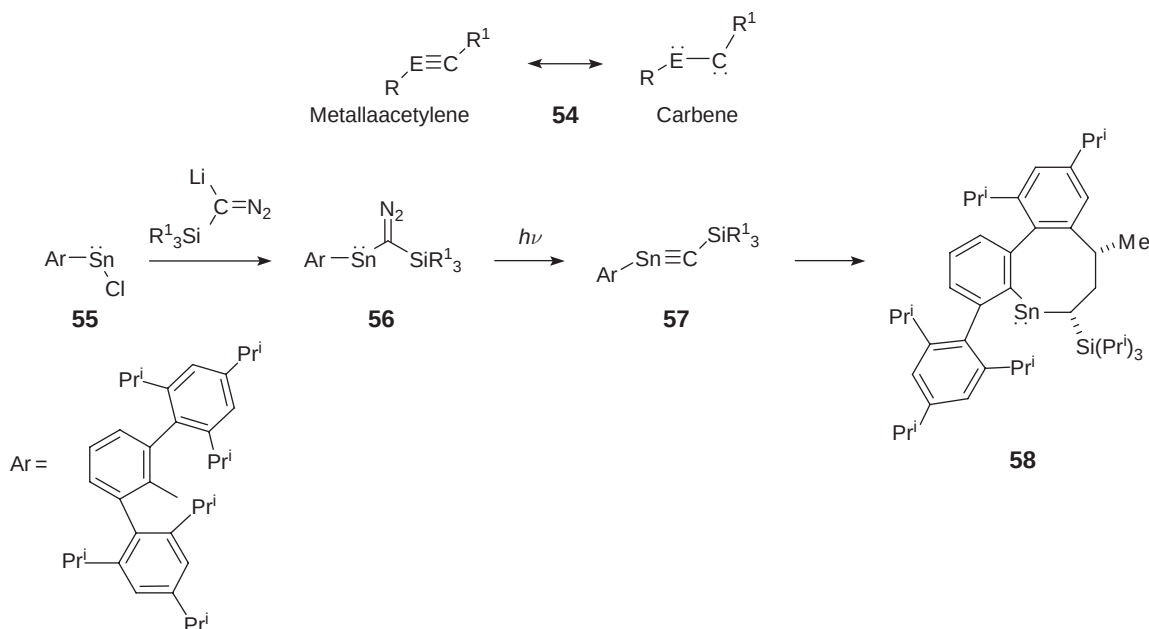


Figure 2



Scheme 11

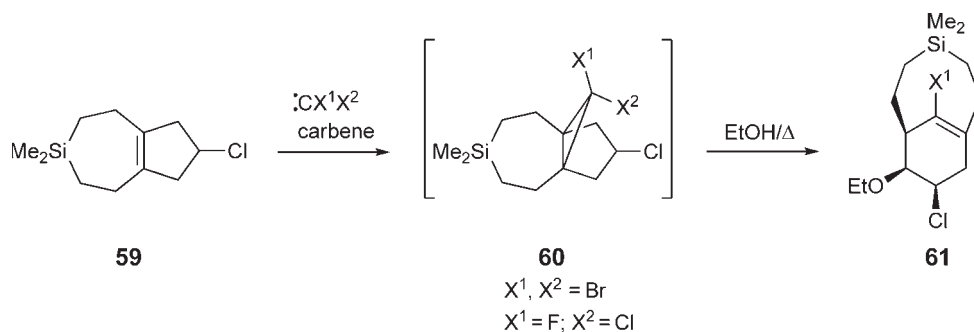
by the photolysis of a benzene solution of **56** using a 500 W high-pressure mercury arc lamp at room temperature. Diazomethylstannylene **56** was obtained in 18% yield as thermally stable but air- and moisture-sensitive red crystals and its structure was confirmed by X-ray crystallography. The photolysis of **56** led to the formation of stannaacetylene **57**, which showed singlet carbene character and underwent the intramolecular insertion of the carbene moiety to a proximate methyl C–H bond in an isopropyl group with the formation of stannacyclooctane **58** in 70% yield. Interestingly, the photocyclization proceeded stereoselectively and gave **58** with a *cis*-arrangement between methyl and triisopropylsilyl substituents on the heterocyclic ring [<2004JA2696>](#).

The sila-*anti*-Bredt olefins (olefins with bridgehead double bond) were obtained starting from **59**, as a key intermediate. Thus, addition of dibromo- or chlorofluorocarbene to **59** gave the crude **60**, which was converted in ethanol to 4-silabicyclo[5.3.1]undec-1(11)-ene **61** (Scheme 12). Molecular structure of **61** was confirmed by X-ray crystallographic studies [<2001JOC1216>](#).

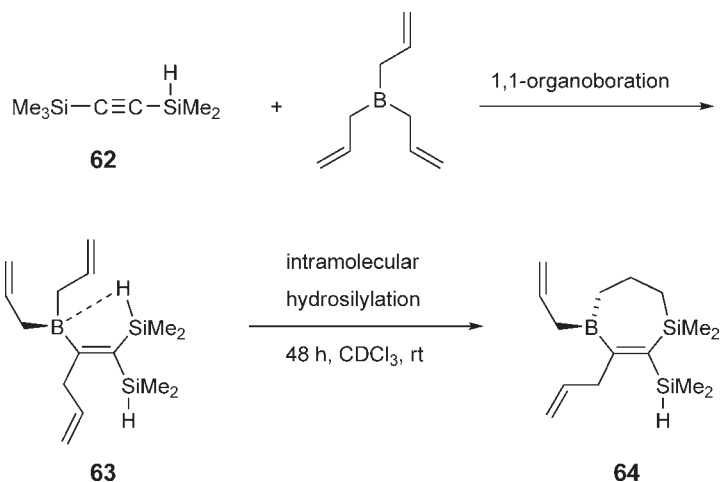
14.19.3 Rings with Two or More Heteroatoms

14.19.3.1 Rings Containing E–(CH₂)_n–E and Related Units

Upon treatment of bis(dimethylsilyl)ethyne **62** with trialkylborane, 1,1-organoboration took place with formation of **63**, which by hydrosilylation of the C=C bond of the alkyl group resulted in the formation of the new seven-membered heterocycle **64** (Scheme 13). The presence of the SiH–B bridge in **63** was confirmed unequivocally by IR, ¹H, ¹³C, and ²⁹Si NMR spectroscopic evidence [<1999AGE124>](#). Compound **64** was isolated by distillation as a colorless, extremely air-sensitive liquid.

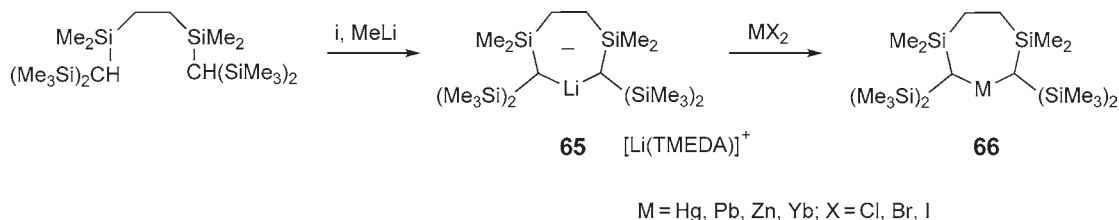


Scheme 12

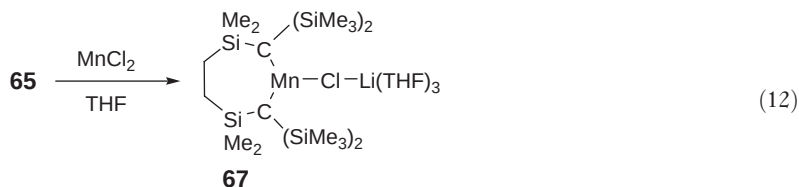


Scheme 13

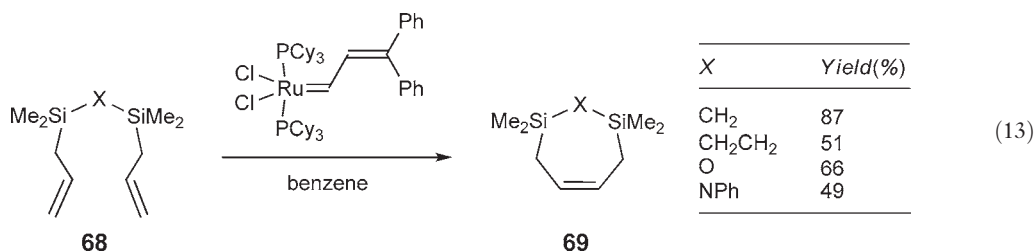
Chelated diorganolithiate ion **65** was prepared and isolated as its $[\text{Li}(\text{TMEDA})]^+$ salt (Scheme 14). It was then transformed into the highly crowded neutral metallacycles **66**: organomercury compound <1996OM1651>, plumbacycloalkane <1997OM5621>, and the chelated compounds of Zn and Yb <1999OM2342> (Scheme 14). On the other hand, the reaction of **65** with MnCl_2 in tetrahydrofuran (THF) afforded complex **67** (Equation 12) <2000OM1190>. Structures of these compounds were confirmed by X-ray crystallographic studies.



Scheme 14



A series of seven- and eight-membered disilacycloalkenes **69** was prepared in 49–87% yield under mild reaction conditions using ruthenium-catalyzed ring-closing metathesis (RCM) of various α,ω -bis(allyldimethylsilyl)-substituted compounds **68** (Equation 13). Interestingly, 5-oxa-4,6-disilacycloheptane and 5-aza-4,6-disilacycloheptane also could be obtained in this manner. The method failed, however, when the ring size was increased to a nine-membered disilaalkene. In order to deepen the understanding of the reaction mechanism and of the accessible ring size, the semiempirical PM3 conformational analyses were carried out <1999BCJ821>.



Reactivity of the highly crowded silicon-substituted cyclic stannylene **70** was investigated in detail <2002OM2430>. Upon treatment with iodoalkanes, enones, and diones, the derivatives **71**, **72**, and **73** were obtained (Figure 3) and their structure was confirmed by ¹H, ¹³C, ²⁹Si, and ¹¹⁹Sn NMR spectroscopy as well as X-ray crystallographic studies.

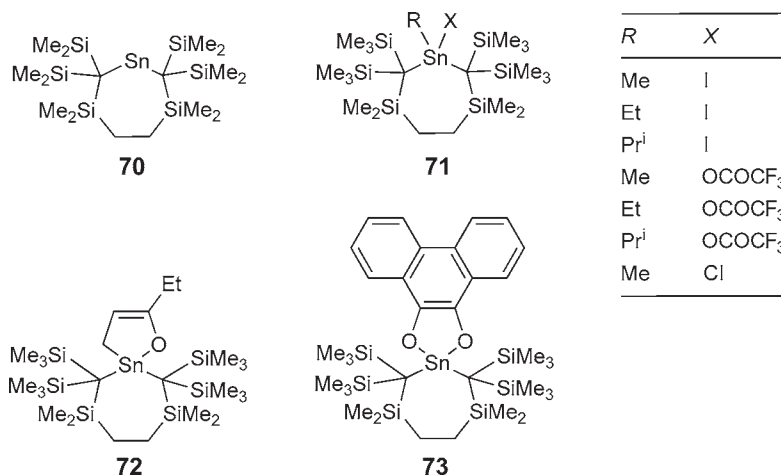
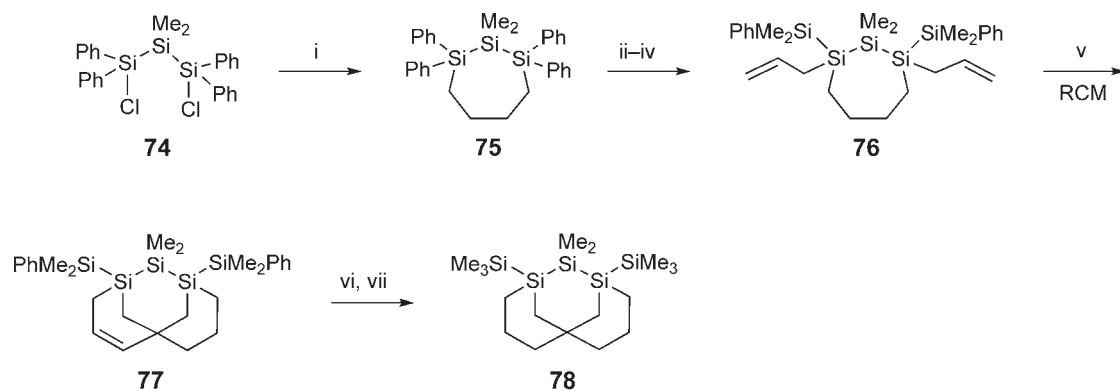


Figure 3

The *anti*-pentasilane **78** was prepared starting from 1,3-dichlorosilane according to Scheme 15. First, the monocyclic structure **75** was constructed by the reaction of **74** with a di-Grignard reagent and after successive introduction of allyl and dimethylphenylsilyl groups at positions 1 and 3 via exhaustive dephenylchlorination and partial amination, RCM of **76** catalyzed by benzylidene ruthenium complex afforded the bicyclic **77**. Hydrogenation at the unsaturated bond in the 'tether', followed by replacement of the phenyl groups in the termini by methyl groups, afforded pentasilane **78**. The structure of **78** with its conformation rigidly constrained to all-*anti* on the basis of the bis(tetramethylene)-tethered bicyclic trisilane unit was confirmed by X-ray crystallographic studies <2004OM3375>.

A series of cyclic diynes of type **79–81** with common dimethylsilyl or dimethylgermyl units in the propargylic position of the ring were synthesized (Figure 4). Based on their photoelectron (PE) spectra, a strong interaction between the plane π -linear combinations of the triple bonds and the bridges has been postulated <1997CB1807, 1997TL8679, 1999(P2)2093, 1999OM3615>.

Reductive lithiation of trisilapentane **82** with lithium 4,4'-di-*tert*-butylbiphenylide (LDBB) and silylation with 1,2-dichloro-1,1,2,2-tetramethyldisilane at -78°C gave pentasilacycloheptane **83** in 69% yield (Scheme 16). A similar cyclization proceeded with dichlorodimethylsilane, while no cyclization occurred with 1,3-dichloro-1,1,2,2,3,3-hexamethyltrisilane due to steric hindrance <2000JOM12>.



i, $\text{ClMg}(\text{CH}_2)_4\text{MeCl}$, 83%; ii, gaseous HCl , AlCl_3 , 93%; iii, Et_2NH , Et_3N , then allylmagnesium bromide and $\text{HCl}(\text{g})$, 70%; iv, PhMe_2SiLi , 48%; v, $\text{IMesRuCl}_2(\text{PCy}_3)(=\text{CHPh})$, 74%; vi, H_2 , $\text{RhCl}(\text{PPh})_3$, 95%; vii, TfOH , then MeMgBr , 79%

$\text{IMes} = 1,3\text{-dimesityl-4,5-dihydroimidazol-2-ylidene}$

Scheme 15

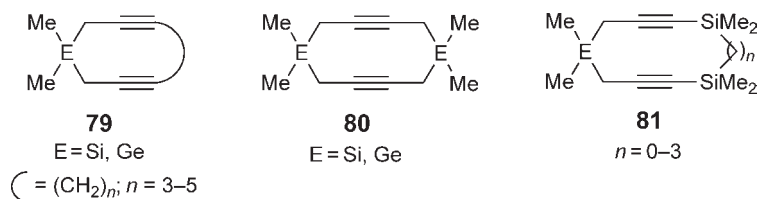
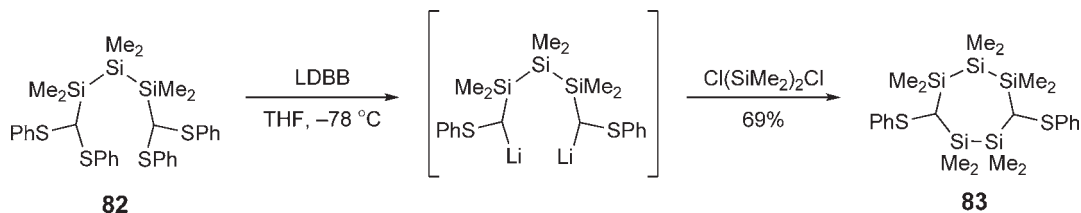


Figure 4

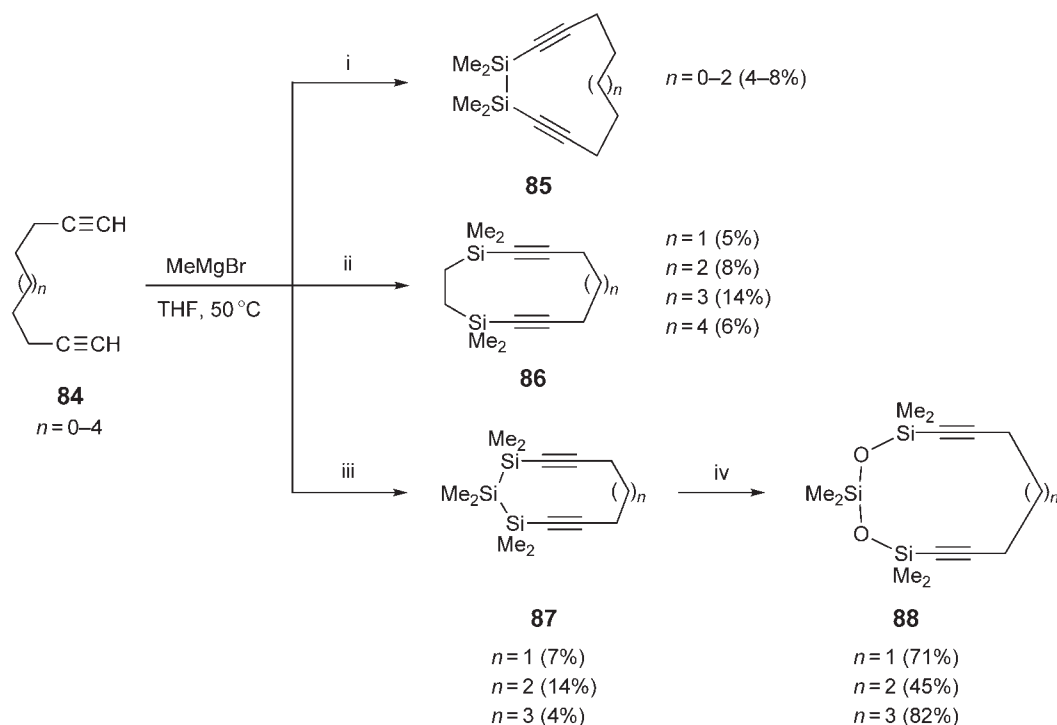


Scheme 16

14.19.3.2 Rings Containing $\text{E}-\text{C}\equiv\text{C}-\text{E}$ and Related Units

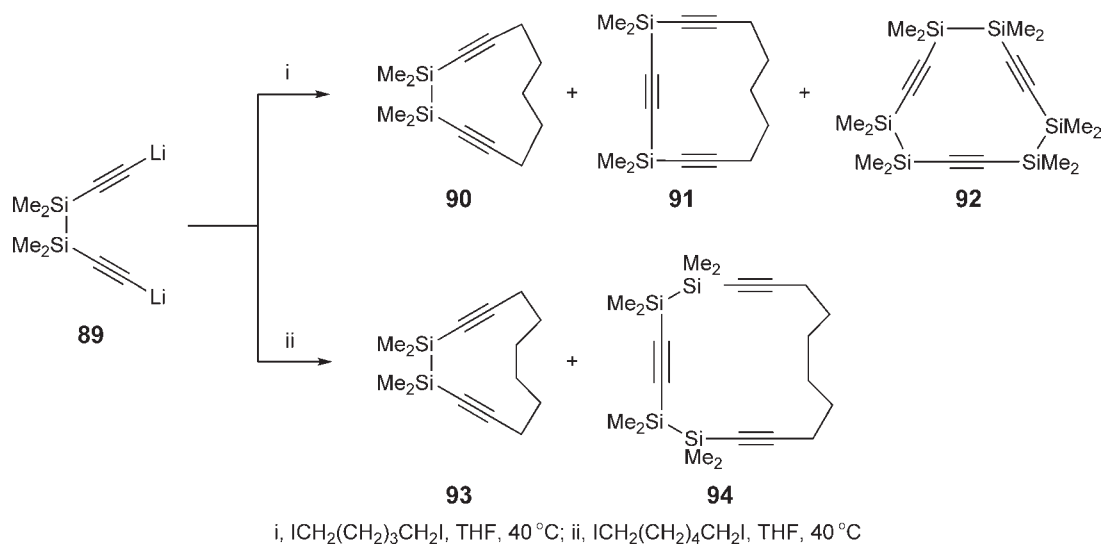
One-sided sterically congested cyclic siladiynes were prepared according to two different protocols. Terminal diynes **84** were transformed into the corresponding Grignard derivatives with MeMgBr , which upon treatment with 1,2-dichloro-1,1,2,2-tetramethyldisilane, 1,4-dichloro-1,1,4,4-tetramethyl-1,4-disilane, or 1,3-dichloro-1,1,2,2,3,3-hexamethyl-1,4-disilane at 25°C in THF were converted into cyclic siladiynes **85**, **86**, and **87**, respectively (Scheme 17) <1995TL4603, 1997OM646>. Structure of **85** ($n = 1$) was confirmed by X-ray crystallographic studies. Compounds **87** 1,2,3-trisilacyclodeca-4,9-diyne ($n = 1$), 1,2,3-trisilacycloundeca-4,10-diyne ($n = 2$), and 1,2,3-trisilacyclododeca-4,11-diyne ($n = 3$) were further treated with trimethylamine oxide in refluxing benzene to afford 2,4-dioxo-1,3,5-trisilacyclodeca-6,11-diyne, 2,4-dioxo-1,3,5-trisilacyclotrideca-6,12-diyne, and 2,4-dioxo-1,3,5-trisilacyclotetradeca-6,13-diyne **88**, respectively.

Synthesis of **90** and **93** was realized by reaction of the dilithium salt of 3,3,4,4-tetramethyl-3,4-disilahexa-1,5-diyne **89** with corresponding diiodides at 40°C in THF. The yields of isolated products **90** and **93** were low (1% and 4%, respectively; Scheme 18) <1995TL4603>. Formation of side products **91**, **92**, and **94** was explained by the previously described <1988CC1079> fragmentation of **89** into $(\text{CH}_3)_2\text{SiLi}(\text{C}\equiv\text{C})\text{Li}$ as an intermediate.



i, $\text{ClSiMe}_2\text{SiMe}_2\text{Cl}$, THF, rt; ii, $\text{ClMe}_2\text{Si}(\text{C}_2\text{H}_4)\text{SiMe}_2\text{Cl}$, THF, rt; iii, $\text{Cl}(\text{Me}_2\text{Si})_3\text{Cl}$, THF, rt; iv, Me_3NO , benzene, reflux

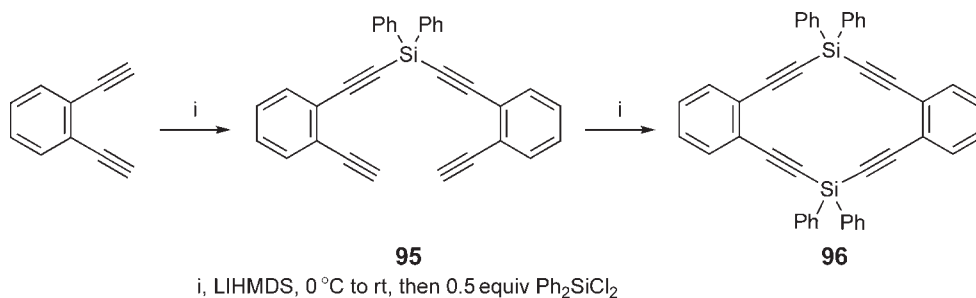
Scheme 17



Scheme 18

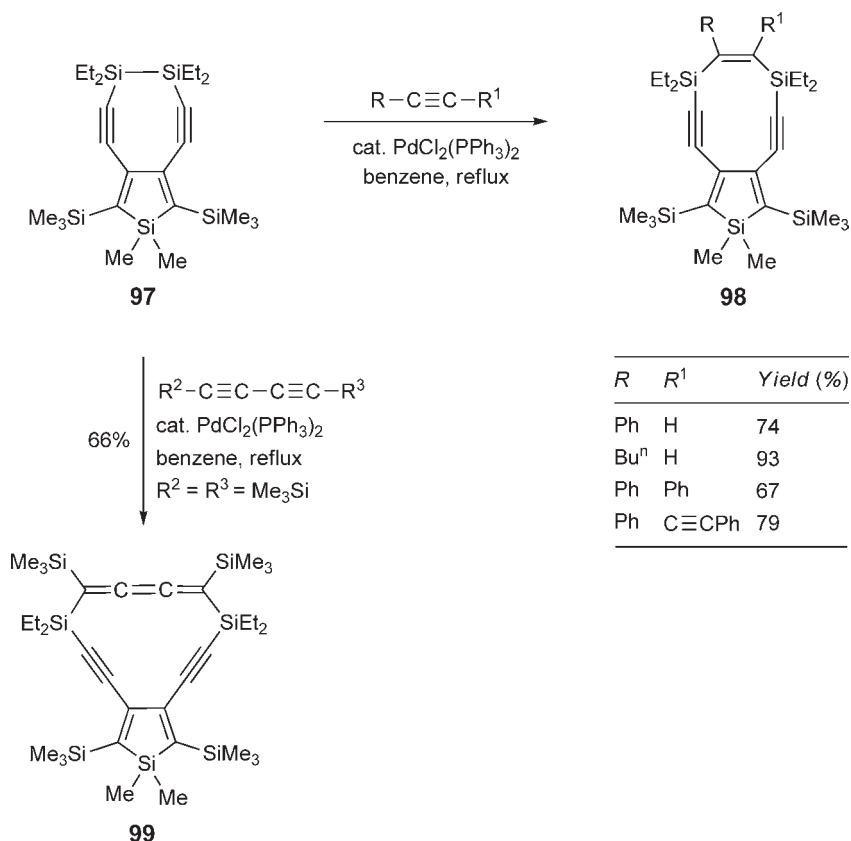
The dibenzo derivative of a cyclic acetylenic silane **96** was synthesized by mono-deprotonation of 1,2-diethynylbenzene with 1 equiv of lithium hexamethyldisilazide (LiHMDS) followed by treatment with 0.5 equiv of dichlorodiphenylsilane (formation of **95**). A repeat of the deprotonation step, followed by silylation cycle, gave **96** in 77% yield after column chromatography (Scheme 19). One-step preparation of **96** using 2 equiv of base and 2 equiv of the silylation agent also yielded the desired product, however, the yield was 50% of those of the previous method

<2000TL2079>. Structure of **96** was fully characterized by MS, IR, and ^1H and ^{13}C NMR spectroscopic methods as well as X-ray crystallography. It should be pointed out that this macrocyclic compound was also mentioned in the patent literature <1995JPP07126394>.



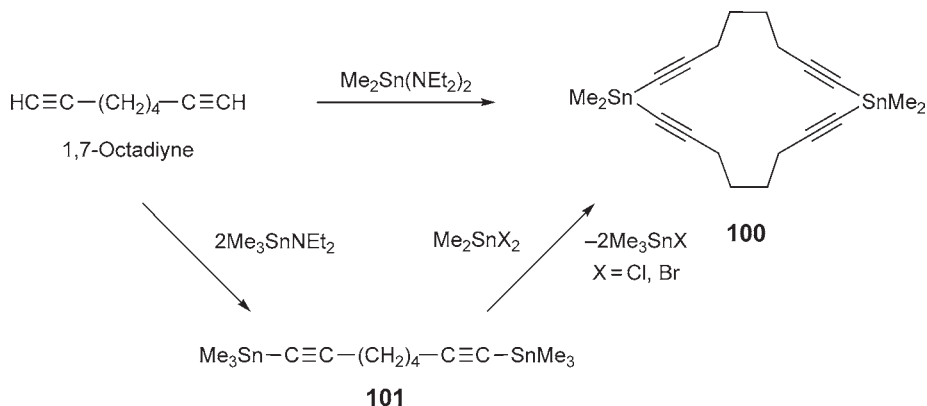
Scheme 19

Dissociative addition of a silicon–silicon linkage to unsaturated carbon units is well known as the bis-silylation reaction. Silole-containing cyclic disilanes, such as 4,5,10-trisilabicyclo[6.3.0]undeca-1(11),8-diene-2,6-diyne **97**, underwent the Pd-catalyzed bis-silylation reactions with acetylenes and 1,3-diynes producing cyclic adducts <1995OM1089>. Addition of butadiyne units occurred regiospecifically, depending on the nature of substituents on the triple bonds. As shown in **Scheme 20**, in this manner 4,7,12-trisilabicyclo[8.3.0]trideca-1(13),5,10-triene-2,8-diyne **98** and 4,9,14-trisilabicyclo[10.3.0]pentadeca-1(15),5,6,7,12-pentaene-2,10-diyne **99** were prepared. Structure of the latter was confirmed by X-ray crystallographic analysis <1999OM3792>.



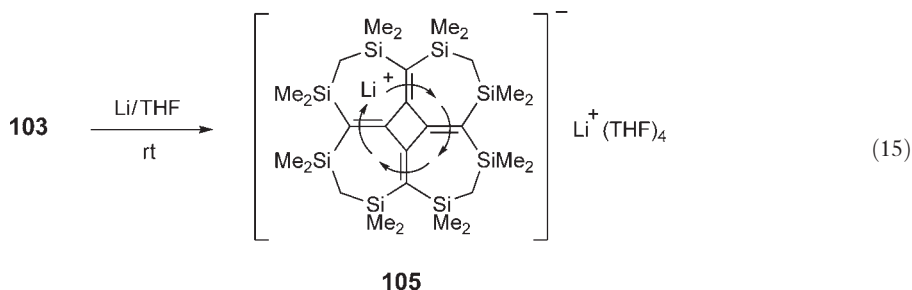
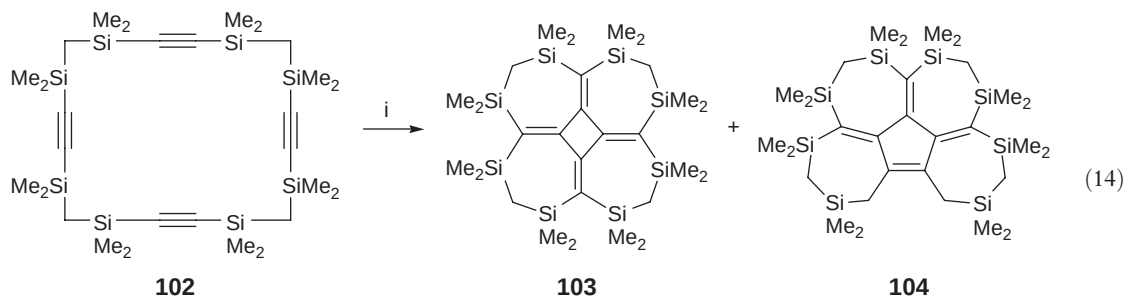
Scheme 20

1,10-Distanna-cyclo-octadeca-2,8,11,17-tetrayne **100** was obtained in 84% yield from the reaction of 1,7-octadiyne with bis(diethylamino)dimethyltin or by reacting 1,8-bis(trimethylstannyl)-1,7-octadiyne **101** with dimethyltin dichloride or bromide in 75% and 80%, respectively (Scheme 21). Structure of **100** was confirmed by MS, IR, ^1H and ^{119}Sn NMR spectroscopic data <1997MGM573>.



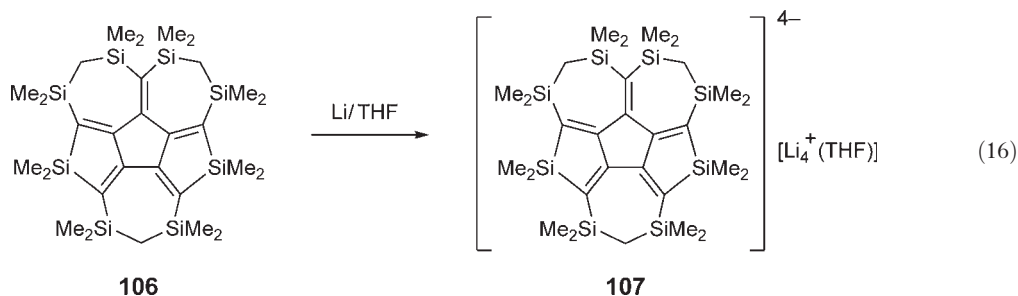
Scheme 21

The first silyl-substituted radialene **103** was obtained in 11% yield from the macrocyclic tetrayne **102** by irradiation with a 500 W high-pressure mercury lamp under the reflux temperature in THF in the presence of 3 molar excess of $[\text{Mn}(\text{CO})_3(\text{Me}-\text{Cp})]$ (Equation 14) <1998BCJ1705>. From the reaction mixture, the trimethylenecyclopentene derivative **104** was also isolated in 17% yield. The octasilyl[4]radialene **103** was then reduced to the lithium salt **105** upon treatment with excess lithium in THF at room temperature (Equation 15). The octasilyl[4]radialene anion has an eight-centered, 10-electron π -system, which was characterized by means of X-ray crystallography, ^1H , ^{13}C , ^{29}Si , and ^6Li NMR spectroscopic data <1998AGE1662>. Variable-temperature ^{13}C NMR experiment revealed that in the temperature range between 173 and 298 K Li^+ ions underwent a walk on the [4]radialene framework, as shown in Equation (15). At 173 K, however, the Li^+ ion walk is suppressed so that Li^+ is fixed at one site of the framework.

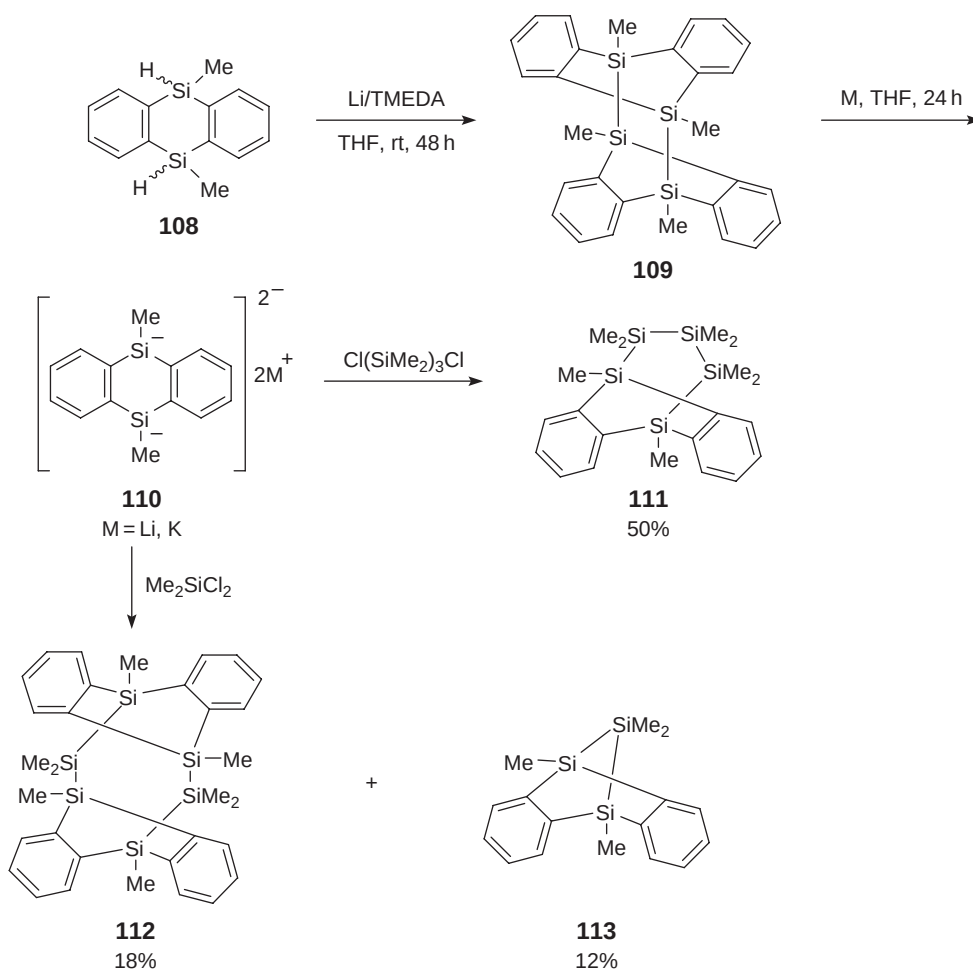


Persilylated [5]radialene **106** was obtained analogously by the intramolecular reaction of hexadecamethyl-3,6,8,11,14,16,19,21-octasilylcycloicos-1,4,9,12,17-pentayne with an excess of $[\text{Mn}(\text{CO})_3(\text{C}_5\text{H}_4\text{Me})]$ by irradiation in

refluxing THF <1998CL1101>. Subsequent reaction of **106** with lithium metal in THF gave air- and moisture-sensitive dark red crystals of the tetralithium salt **107** with 10-centered, 14- π -electron system stabilized by silyl groups (Equation 16) <1999CC1981, 2000BCJ2129>.

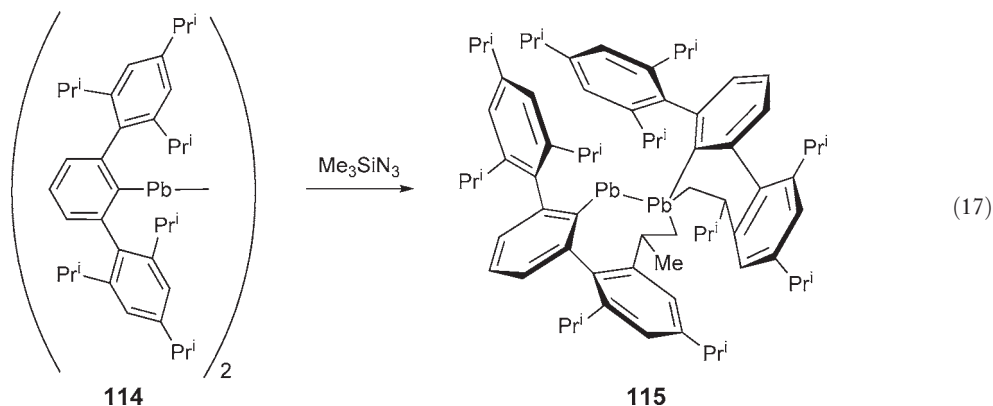


Synthesis of 9,10-disilaanthracene **109** was performed by the treatment of a *cis/trans*-mixture of **108** with 2 equiv of Li in THF containing TMEDA at room temperature for 48 h. The structure of dimer **109** was confirmed by MS, and ^1H , ^{13}C , and ^{29}Si NMR spectroscopy as well as X-ray crystallographic analysis. Upon reduction of **109** with an excess of lithium or potassium in THF solution, the dianions **110** were formed (Scheme 22). Subsequent reaction of **110** with α,ω -dichloropolysilane or dichlorodimethylsilane led to the formation of corresponding cyclic **111–113** <1995OM3625>.



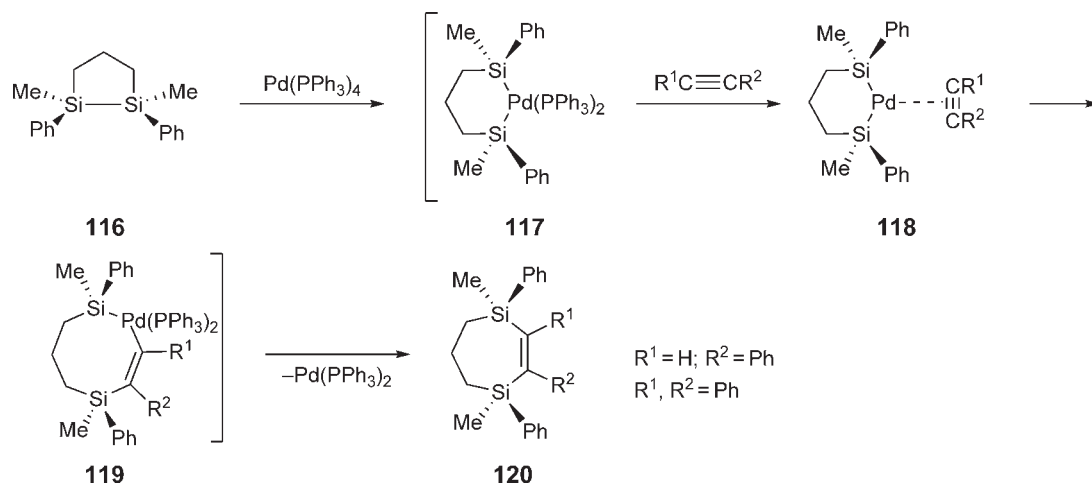
Scheme 22

The first example of stable plumbylplumbylene **115** was obtained and its structure was confirmed by X-ray crystallographic analysis <2005OM5484>. Compound **115**, which can be regarded as an isomeric form of a ‘diplymbene’, was synthesized by reacting terphenyl ‘diplymbene’ [PbAr^{Trip}₂]₂ **114**, where Ar^{Trip}₂ = -C₆H₃(C₆H₂-2,4,6-Prⁱ)₂ with N₃SiMe₃, as shown in Equation (17). The activation of the Prⁱ-CH₃ groups resulted in the incorporation of the Pb(1)–Pb(2) unit into a Pb₂C₆ eight-membered ring, which along with steric factors is responsible for the stability of **115**. The most prominent structural feature is the Pb(1)–Pb(2) bond, which links two-coordinate Pb(1) and four-coordinate Pb(2) lead centers with the formal oxidation states of +1 and +3, respectively. The ¹H NMR spectrum of **115** was consistent with the determined structure. However, ²⁰⁷Pb NMR signal was not observed, apparently due to the large anisotropy associated with the lead environment and poor solubility of **115** in hydrocarbons.



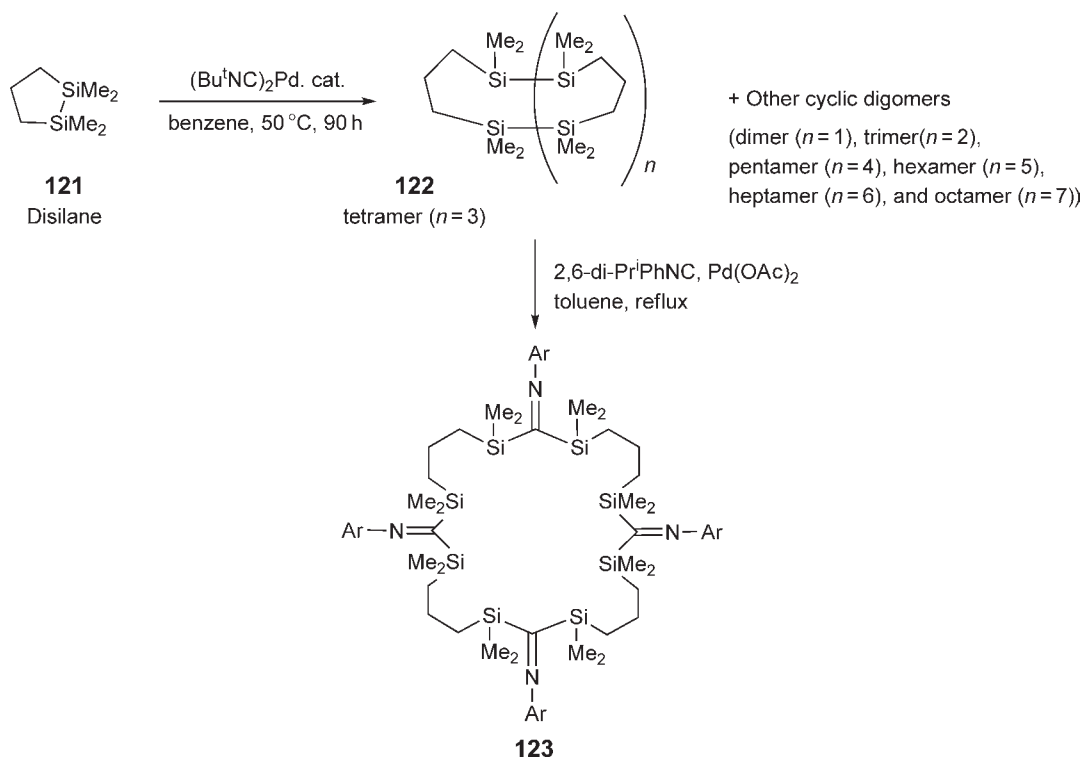
14.19.3.3 Insertion into Si–Si and Ge–Ge Bonds

Palladium-catalyzed reactions of *cis*- and *trans*-1,2-diphenyl-1,2-disilacyclopentanes **116** with phenylacetylene and diphenylacetylene were carried out in a sealed glass tube at 200 °C resulted in the formation of corresponding 1,4-disilacyclohept-2-enes **120** (Scheme 23). The stereospecific formation of **120** was explained in terms of the insertion of a palladium species into a silicon–silicon bond in disilacyclopentanes to give a 2-pallada-1,3-disilacyclohexane **117** with retention of the configuration, followed by coordination of an alkyne to the palladium atom in the intermediate **118**. Then, insertion of the alkyne on the palladium afforded stereospecifically the 2-pallada-1,5-disilacyclooct-3-ene **119**. This process was completed by reductive elimination of the palladium species to give 1,4-disilacyclohept-2-ene **120** with retention of the configuration <2001OM1204>.



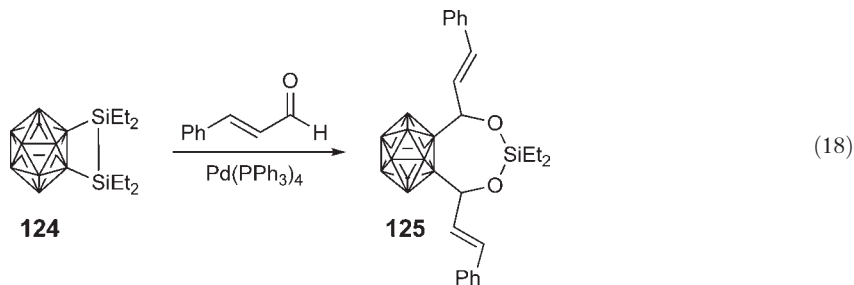
Scheme 23

It is well known that bis(*tert*-butyl isocyanide)–palladium(0) catalyzes a selective intramolecular Si–Si σ -bond metathesis of some bis(silanyl)methanes <1994OM4148>. The same catalyst induced an oligomerization of 1,1,2,2-tetramethyl-1,2-disilacyclopentane **121** via a formal insertion of an $-\text{Me}_2\text{Si}(\text{CH}_2)_3\text{SiMe}_2-$ unit of **121** into the Si–Si bonds of oligomers produced. Cyclic oligomers up to the 40-membered octamer could be obtained according to this method. Structure of 20-membered tetramer **122** (Scheme 24) was confirmed by single crystal X-ray diffraction. Compound **122** was further elaborated by transition metal complex-catalyzed isocyanide insertion into all Si–Si bonds to give **123** <1995JA1665>.

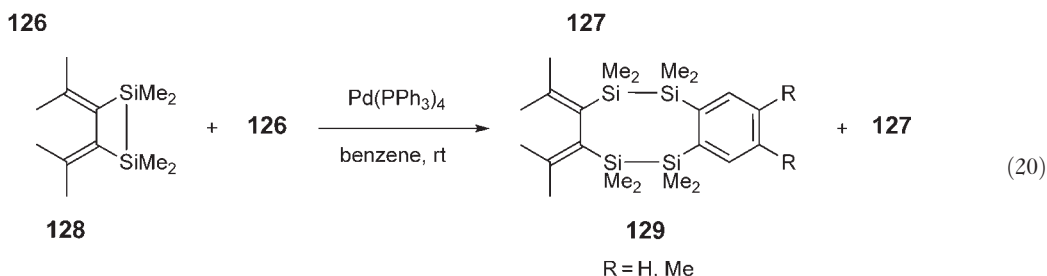
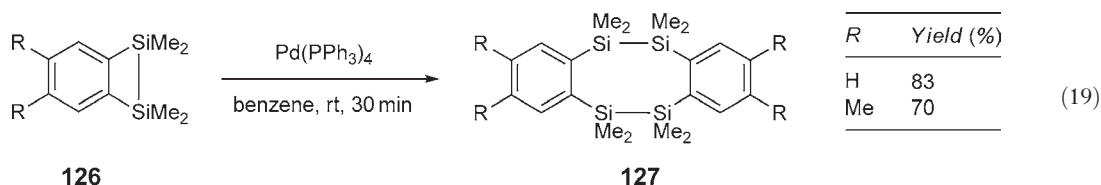


Scheme 24

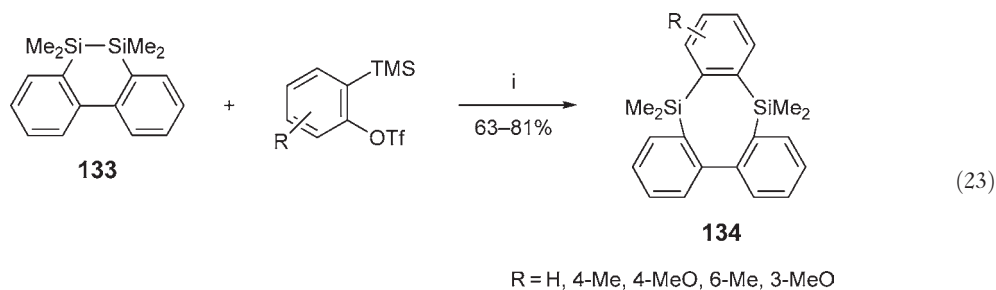
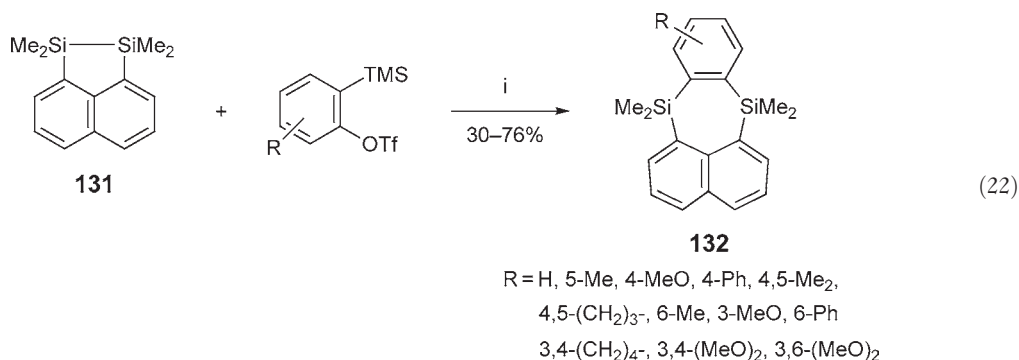
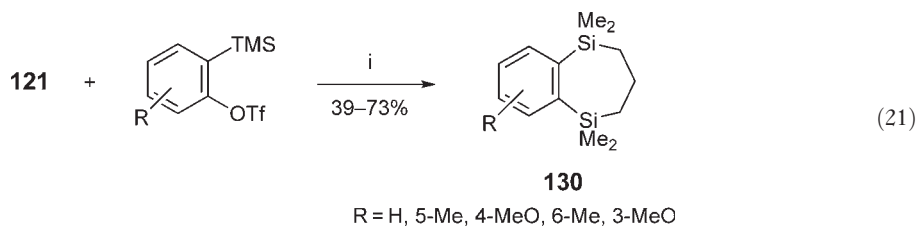
Palladium-catalyzed double-silylation reactions of 3,4-carboranylene-1,1,2,2-tetraethyl-1,2-disilacyclobut-3-ene **124**, obtained from the reaction of 1,2-dilithiated *o*-carborane with 1,2-dichlorotetraethyldisilane, have been described <2001OM5537>. Thus, the reaction of **124** with *trans*-cinnamaldehyde in the presence of $\text{Pd}(\text{PPh}_3)_4$ yielded the insertion compound **125**, whose structure was determined by single crystal X-ray crystallography (Equation 18).



In a similar way, **126** was converted into the corresponding disilane metathesis product **127** (Equation 19) <1995OM2556>. The reaction of equimolar amounts of bis(isopropylidene)disilacyclobutane **128** and 3,4-benzo-1,2-disilacyclobutane **126** in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ gave the cross-metathesis product **129** accompanied by a minor amount of homo-metathesis product **127**. The structure of **129** was assigned by X-ray structure analysis (Equation 20) <1996JOM335>.



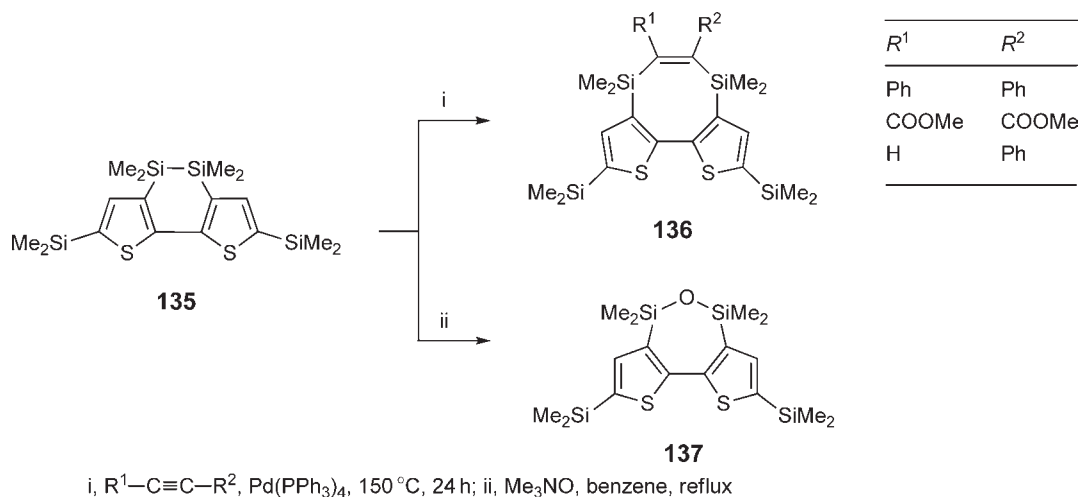
Addition reactions of the Si-Si σ -bonds of disilanes **121**, **131**, and **133** to the $\text{C}\equiv\text{C}$ bonds of various arynes were found to be promoted by a palladium-1,1,3,3-tetramethylbutyl isocyanide complex. Diverse 1,2-disilylated arenes **130**, **132**, and **134** were obtained from five-membered and benzo-condensed six-membered cyclic disilanes (Equations 21–23). The ^1H , ^{13}C , and ^{29}Si NMR spectroscopic data as well as X-ray crystallographic analysis were used to confirm the above structures <2005OM156>.



i, KF/18-crown-6, $\text{Pd}(\text{OAc})_3$ (2 mol%), Oct^tNC (30 mol%), THF, 20 °C

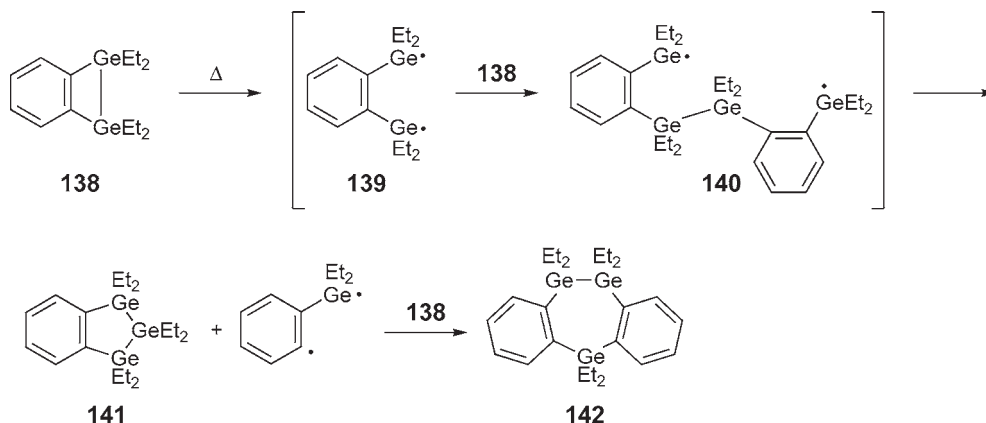
The reactions of dithienodisilacyclohexadiene derivative **135** with acetylenes, such as diphenylacetylene, dimethyl acetylenedicarboxylate, and phenylacetylene, were carried out at 150 °C for 24 h in the presence of a palladium

catalyst to afford respective adducts **136**, resulting from the insertion of a triple bond of the alkynes into the Si–Si bond of **135**. The main product was accompanied by a small amount of the oxygen-insertion product **137**, derived from oxidation of the Si–Si bond of **135** by molecular oxygen (Scheme 25). Compound **137** was obtained in 91% yield by the oxidation of **135** with trimethylamine oxide. The crystal structure as well as optical and electrochemical properties of these products were determined <2006OM48>.



Scheme 25

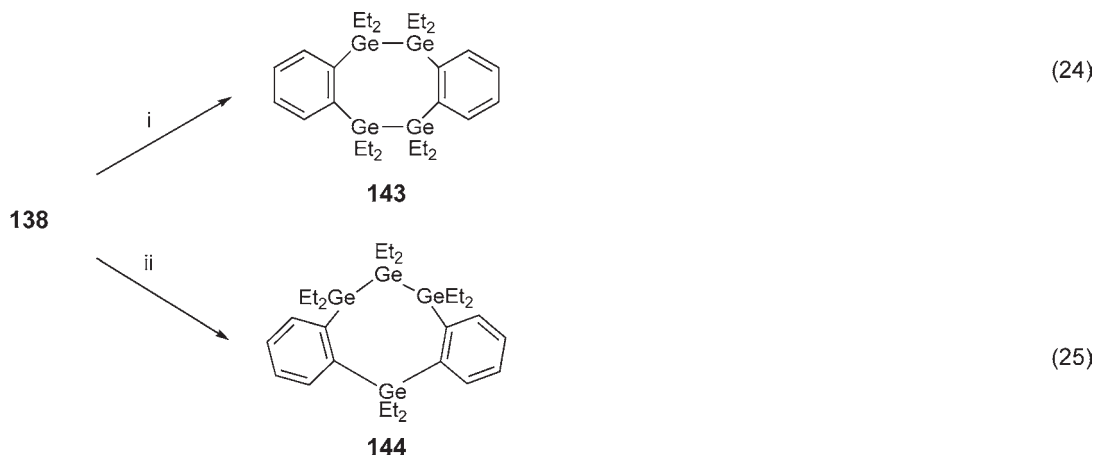
In contradistinction to the chemical and physical properties of the Si–Si bond, which have been studied extensively, the chemistry of its higher analogue Ge–Ge σ -bond has attracted much less attention. It is well recognized that the group 14 dimetalloid σ -bond is reactive as the corresponding C=C π -bond. However, to study reactivity of E–E bond (E = Si, Ge), it should be activated by, for example, ring strain. Thus, a strained germacycle, 3,4-benzo-1,1,2,2-tetramethyl-1,2-germacyclobut-3-ene **138**, was obtained by the treatment of 1,2-bis(chlorodiethylgermyl)benzene with sodium in toluene <1996OM2014>. Compound **138** proved to be thermally labile and, upon thermolysis, conducted in an evacuated sealed tube at 160 °C for 20 h, gave 3,4:6,7-dibenzo-1,1,2,2,5,5-hexaethyl-1,2,5-trigerma-cyclohepta-3,6-diene **142** in 53% yield together with 1,2,3-trigerma-cyclopent-4-ene **141** (Scheme 26). The reaction presumably proceeded via germyl diradical **139** resulting from homolytic scission of the activated Ge–Ge bond and the intermolecular attack on the Ge–Ge bond of a second molecule **138** (formation of **140**) <1996OM2014>.



Scheme 26

Compound **138** underwent palladium-catalyzed Ge–Ge σ -metathesis at room temperature to give the dimeric germacycloocta-1,5-diene **143** (Equation 24). Moreover, at 160 °C in a sealed tube containing a catalytic amount of

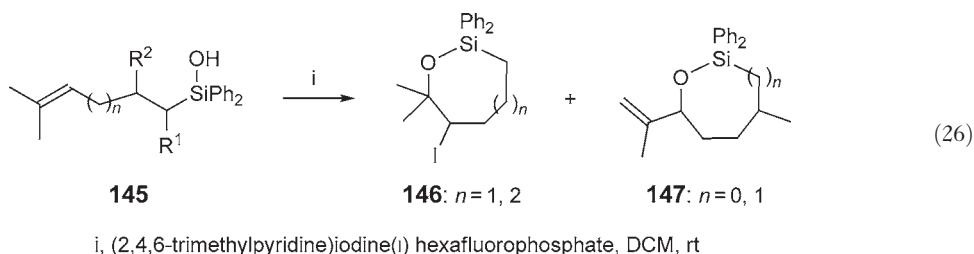
$\text{Pd}(\text{PPh}_3)_4$, **138** gave the unsymmetrical dimer, dibenzo-3,6,7,8-tetragermacycloocta-1,4-diene **144**, in 24% yield (Equation 25) <2000JOM420>.



i, $\text{Pd}(\text{PPh}_3)_4$, toluene, rt, 16 h; ii, $\text{Pd}(\text{PPh}_3)_4$, C_6D_6 , rt, 30 min, then **138**, rt, 16 h

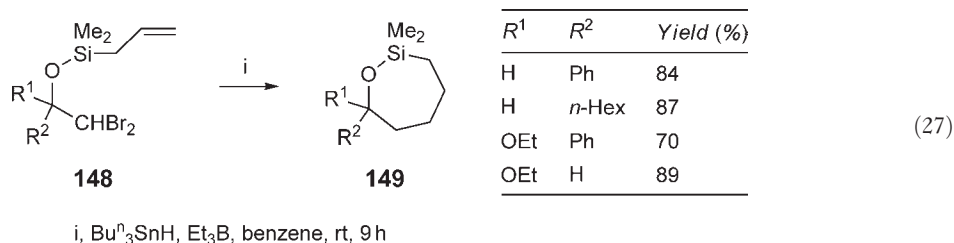
14.19.3.4 Rings Containing C–E–O and Related Units

Intramolecular iodosilyletherization of alkenylsilanols **145** with bis(2,4,6-trimethylpyridine) iodine(i) hexafluorophosphate afforded a mixture of *exo*-ring mode cyclization **146** and *endo*-mode cyclization products **147** in 35–74% combined yields (Equation 26) <1996TL6781>.

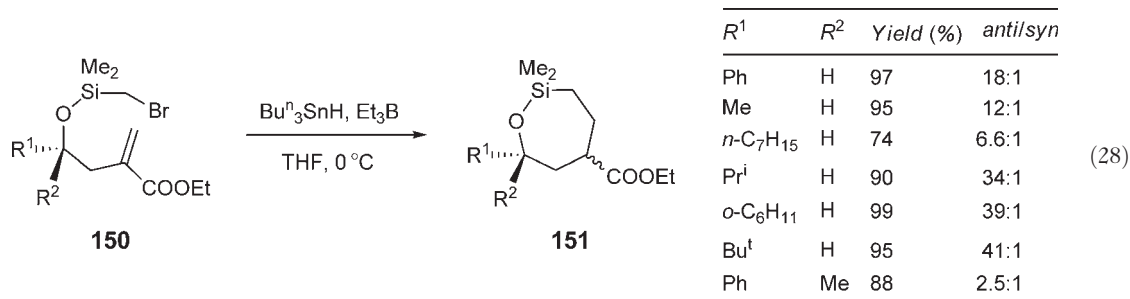


Free radical conjugate additions of carbon radicals onto alkenes which results in formation of carbon–carbon bonds have been important reactions in organic chemistry. This type of reaction was first explored in an intramolecular fashion, but quickly gained attention of heterocyclic chemists and a plethora of novel ring systems have been synthesized by this methodology <2001T7237>.

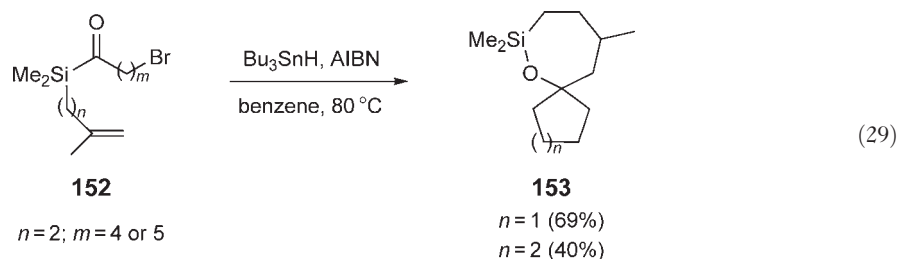
Radical cyclization of allylsiloxy derivatives **148** to 1-oxa-2-silacycloheptanes **149** was achieved by treatment of 2-(allyldimethylsiloxy)-1,1-dibromoalkanes with Bu^n_3SnH in the presence of a catalytic amount of triethylborane in benzene (Equation 27). An interesting stereochemical outcome was observed in the cyclization of 1-allyldimethylsiloxy-2,2-dibromo-1-phenylpropane ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$) which gave a stereoisomeric mixture of 2,2,6-trimethyl-7-phenyl-1-oxa-2-silacycloheptane (*cis/trans* = 87/13). These seven-membered cyclic silyl ethers and acetals were stable and could be isolated by silica-gel column chromatography <1997BCJ2255>.



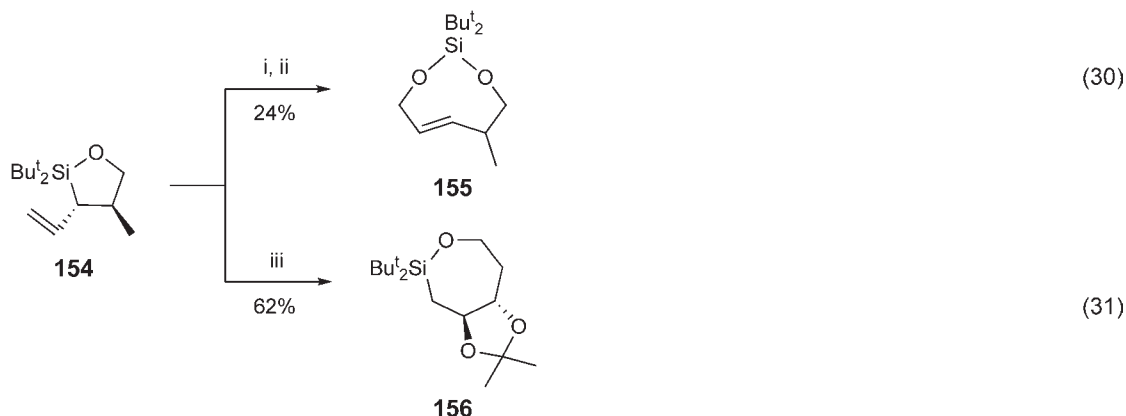
Highly diastereoselective 7-*endo*-radical cyclization of (bromomethyl)dimethylsilyl ethers **150**, derived from ethyl γ -hydroxy- α -methylenecarboxylates, bearing a bulky γ -substituent such as isopropyl, cyclohexyl, and *tert*-butyl in THF gave cyclic silyl ethers **151** bearing preferentially the ethoxycarbonyl group *anti* to the γ -substituent (Equation 28) <2004TL4329>.



Acylsilanes of type **152** with radicalphiles attached to the silicon atom underwent tandem radical cyclization to give 7,7,10-trimethyl-6-oxa-7-silaspiro[4.6]undecane (**153**; $n = 1$) and 8,8,11-trimethyl-7-oxo-8-sila-spiro[5.6]dodecane (**153**; $n = 2$) (Equation 29) <2005T2037>.



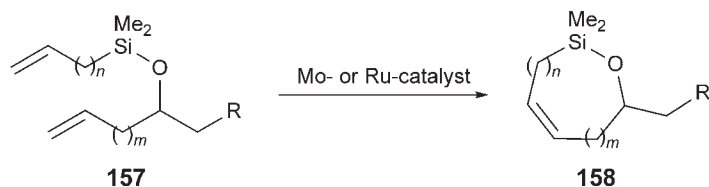
1-Oxa-2-silacyclopentane derivative **154** subjected to the oxidation reaction with Oxone at room temperature followed by treatment with silica gel gave the eight-membered product **155** (Equation 30). On the other hand, seven-membered silyl ether **156** was formed in diastereometrically pure form by the reaction of **154** with *N*-bromosuccinimide (NBS) in acetone–water solution (Equation 31) <1997JOC4206>.



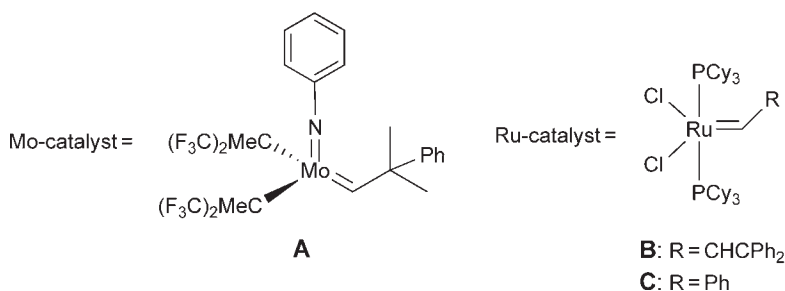
i, oxone, NaHCO₃, acetone/H₂O, rt; ii, SiO₂; iii, NBS, acetone/H₂O, -23 °C to 0 °C
oxone = 2KHSO₅·KHSO₄·H₂SO₄

RCM of acyclic silicon connected dienes **157** using molybdenum and ruthenium alkylidene catalyst afforded the corresponding cyclic silyloxy olefins **158** in good to excellent yields (Scheme 27). Interestingly, the formation of the cyclized eight-membered products (**158f** and **158g**) did not require high dilution conditions commonly used for the formation of eight-membered rings <1997TL4757>.

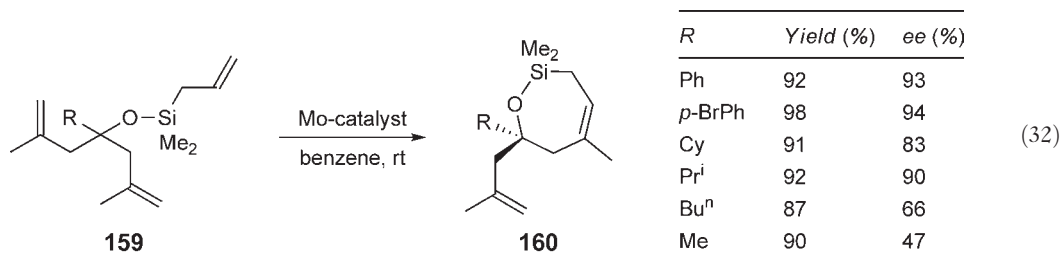
Molybdenum-catalyzed asymmetric ring-closure metathesis (ARCM) has been successfully applied for the synthesis of seven-membered siloxanes **160** bearing tertiary ether centers from trienes **159** (Equation 32). In effecting the ARCM, it performed especially well with siloxanes bearing bulky substituents at α -carbon atom ($R = \text{Ph, Cy, Pr}^i$) <2002JA2868>.



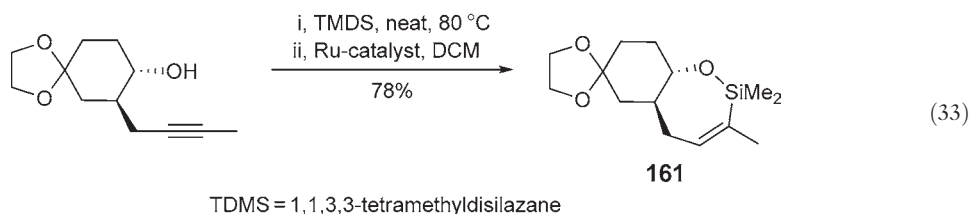
Entry	Diene (m, n, R)	Catalyst	Reaction time (h)	Yield (%)
a	0, 1, Me	C	1	95
b	1, 0, OCH ₂ Ph	A	0.5	84
c	1, 1, OCH ₂ Ph	C	3	88
d	1, 2, OCH ₂ Ph	C	3	93
e	2, 0, OCH ₂ Ph	A	5	91
f	2, 1, Cl	B or C	1	90
g	2, 1, OCH ₂ Ph	C	3	96
h	4, 1, OCH ₂ Ph	A	1	73

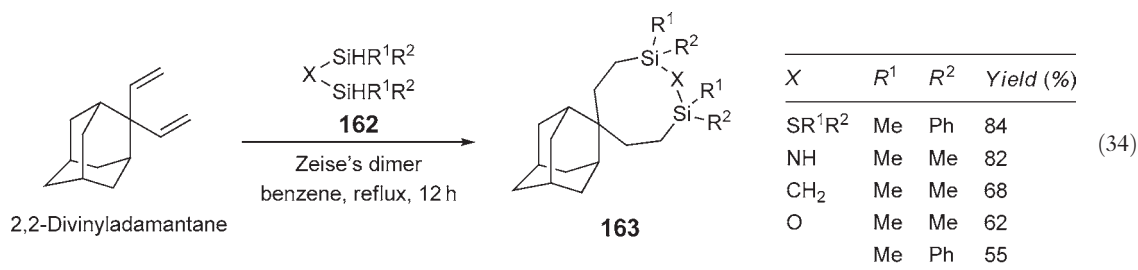


Scheme 27

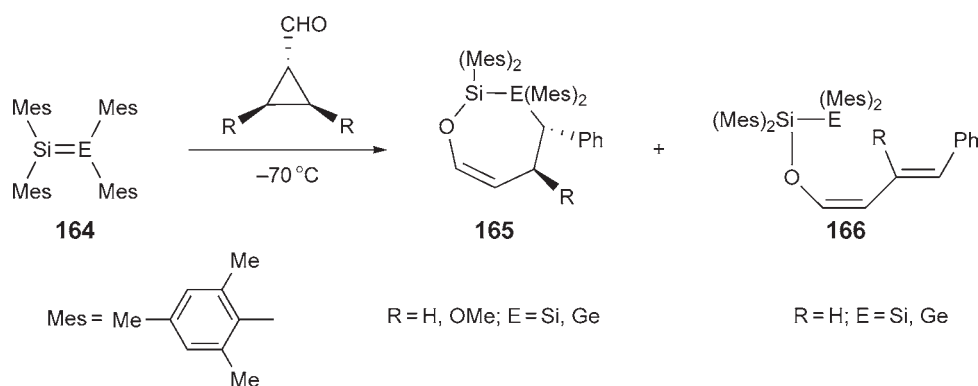


Cyclic seven-membered vinyl silanes **161** were obtained by regio- and stereoselective hydrosilylation of internal alkynes catalyzed by the ruthenium complex [Cp^{*}Ru(MeCN)₃]PF₆, as shown in Equation (33) <2005JA10028>. Hydrosilylation of 2,2-divinyladamantane with bis(hydrosilane) species **162** in the presence of Zeise's dimer [Pt₂Cl₄(CH₂CH₂)₂] gave the disilacyclic **163** in high yields (Equation 34) <1998OM4267>.



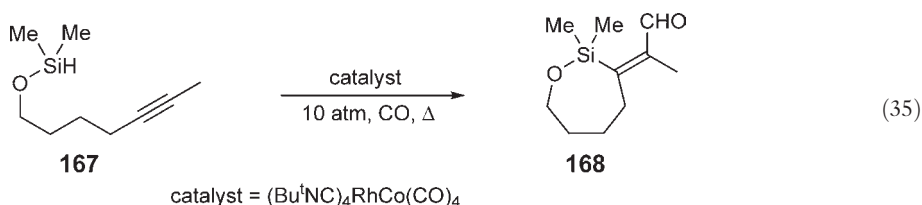


Although many syntheses and reactions of group 14 doubly bonded compounds are well recognized, little is known about the reaction mechanisms. However, elegant mechanistic studies of the addition of carbonyl compounds to disilenes and germasilenes **164** have recently been described [<2003OM1603>](#). Thus, when tetramesityldisilene and tetramesitylgermasilene were subjected to the reaction with *trans*-2-phenylcyclopropane carbaldehydes, a 1:1 mixture of oxasilametallacycloheptanes **165** (E = Si, Ge) and oxapentadienylsilylmetallanes **166** was obtained ([Scheme 28](#)). Unequivocal evidence was obtained for the presence of diradical intermediates in this addition reaction. The structure of 5-methoxyoxa-2,3-disilacyclohept-6-ene **165** (R = OMe) was confirmed by X-ray crystallography.

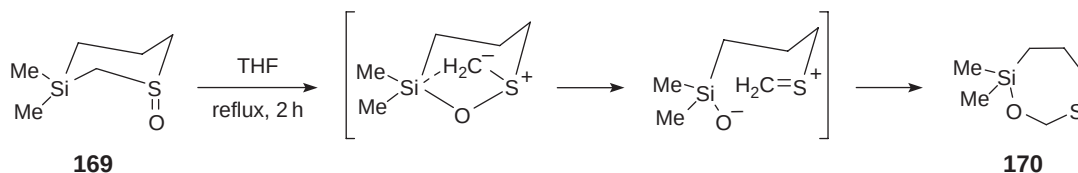


Scheme 28

Functionalized oxasilacycloheptane **168** was obtained by silylformylation of alkynol **167**, in which the catalytic intermediate of an intramolecular hydrosilylation is intercepted by carbon monoxide ([Equation 35](#)) [<1995JA6797>](#).

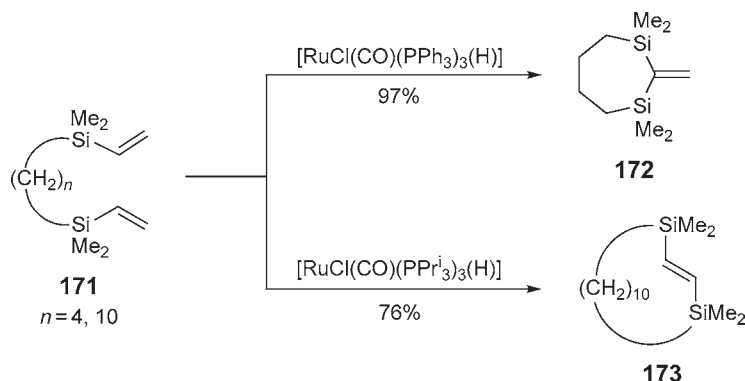


The first example of the sila-Pummerer rearrangement, which consists in the thermal conversion of sulfoxide **169** into O-silylated cyclic *O,S*-acetal **170**, has been described [<1999TL185>](#). As shown in [Scheme 29](#), a 1,3-migration of silicon atom to a sulfoxide oxygen resulted in ring expansion.



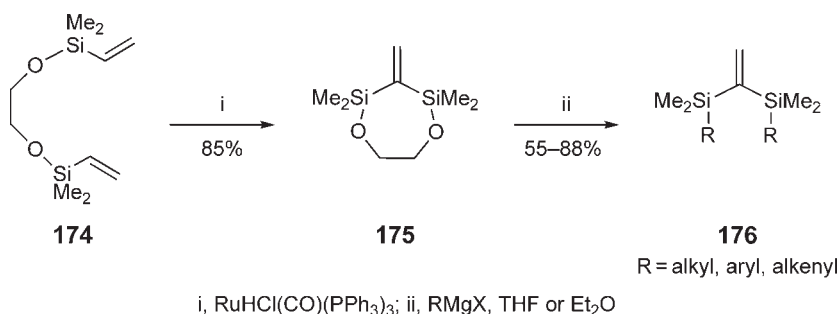
Scheme 29

During the last 15 years, the silylative coupling reactions of vinylsilane derivatives in the presence of ruthenium, rhodium, cobalt, and iridium complexes have been developed [<2003COR691>](#). The mechanism of this reaction involving β -silyl elimination and insertion of a C=C bond into the resulting M–Si bond has been proven by insertion of ethylene and vinylsilane into M–Si bonds (where M = Ru, Rh, Co). Intramolecular disproportionation of α,ω -bis(vinylsilyl) compounds **171** gave disilacycles of various ring sizes **172** and **173** (Scheme 30) [<1998CC699>](#).

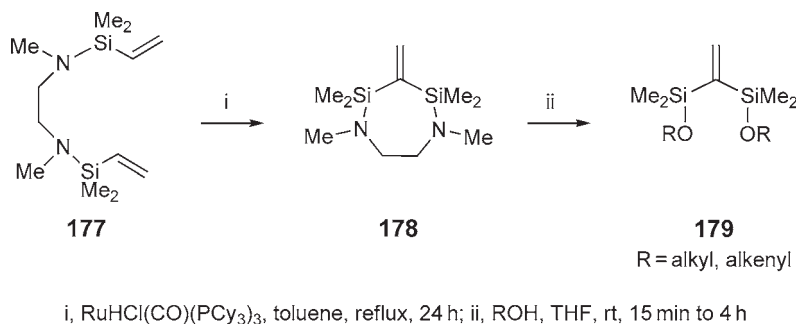


Scheme 30

A facile and efficient method for the synthesis of cyclic silyl ethers **175** consisted of the ruthenium-catalyzed silylative coupling cyclization of 1,2-bis(dimethylvinylsilyloxy)ethane **174** [<2005JOC370>](#). Upon treatment with Grignard reagents, these compounds were converted into alkyl-, aryl-, or alkenyl-substituted 1,1-bis(silyl)ethenes **176** (Scheme 31). Similarly, silylative coupling cyclization of N,N' -dimethyl- N,N' -(dimethylvinylsilyl)ethane-1,2-diamine **177** catalyzed by $[Ru-HCl(CO)(PCy_3)_2]$ in toluene under argon atmosphere gave 1,2,2,4,4,5-hexamethyl-3-methylene-1,5-diaza-2,4-disilacycloheptane **178**, which upon subsequent treatment with alcohols afforded 1,1-bis(alkoxydimethylsilyl)ethanes **179** (Scheme 32) [<2005SL1105>](#).



Scheme 31



Scheme 32

1,1'-Binaphthyl derivatives bearing chlorosilyl or chlorogermanyl substituents at the 2,2' positions have been prepared and converted into oxadisilepin (E = Si) and digermepin (E = Ge) **180** upon treatment with NaOH or Et₂O/H₂O (Figure 5) <1996JOM15, 1997CB923>. 2,2-Dimethyl-4-methyl-1-oxa-4-aza-silabenzocycloheptan-5-one **181** was obtained (Figure 5) by treatment of salicylic acid *N*-ethylamide with hexamethyldisilazane ((Me₃Si)₂NH) and dimethylchloromethylchlorosilane (ClCH₂SiMe₂Cl) in boiling *o*-xylene <2002KGS127>.

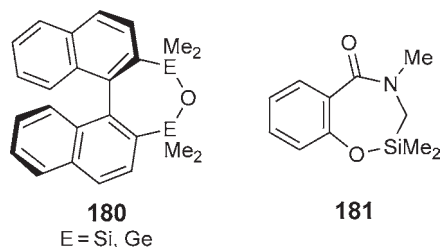
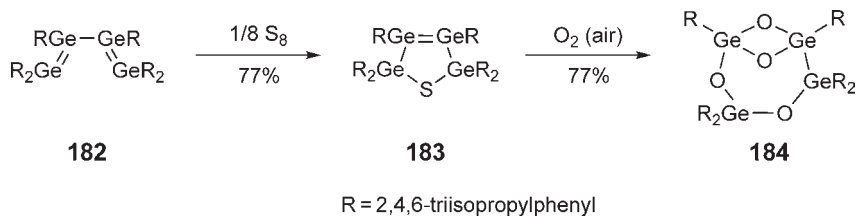


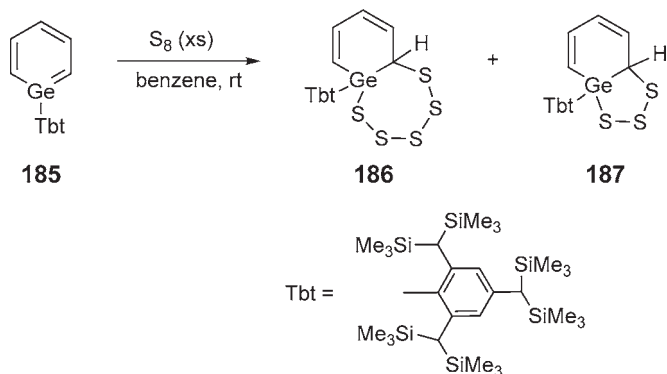
Figure 5

Hexakis(2,4,6-triisopropylphenyl)tetragermabuta-1,3-diene **182** was obtained and converted upon treatment with sulfur into thiatetragermacyclopentene **183** with an endocyclic Ge=Ge bond. The reaction of **183** with dry air furnished a 2,4,7,8-tetraoxa-1,3,5,6-tetragermabicyclo[4.1.1]octane derivative **184** (Scheme 33). Structures of **183** and **184** were confirmed by X-ray crystallographic analysis <2003OM1302>.



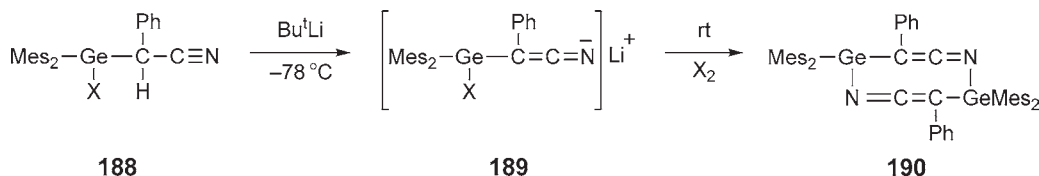
Scheme 33

1,2,3,4,5,6-Pentathiagermepane **186** was obtained by reacting germabenzene **185** with elemental sulfur in benzene at room temperature, together with 1,2,3,4-tetrathiagermolane **187** (Equation 36). Structure of **186**, which was separated by gel permeation liquid chromatography and subsequent preparative thin-layer chromatography, was confirmed by X-ray crystallography <2003JOM66>.



(36)

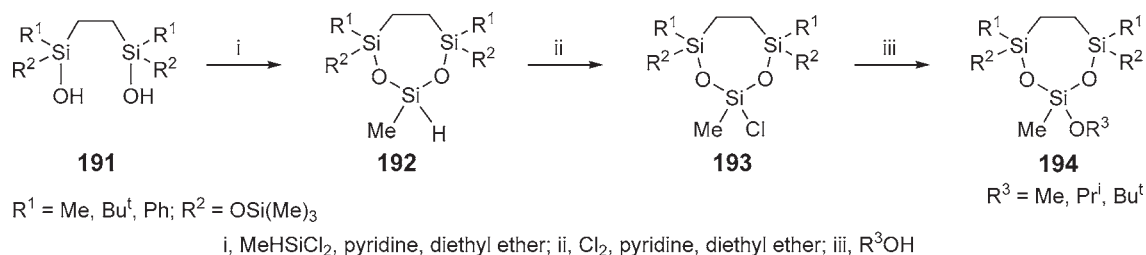
An eight-membered cyclic *C,N*-bis(germadiyl)bis(ketenimine) **190** was prepared by the reaction of *tert*-butyllithium with (fluorodimesitylgermyl)phenylacetonitrile **188** leading to the lithium salt **189**, which then underwent an elimination of lithium halide. Compound **190**, the first ring containing two ketenimine moieties, was characterized by IR and ^{13}C NMR spectroscopy as well as X-ray structure determination (Scheme 34) <1998OM1517>.



Scheme 34

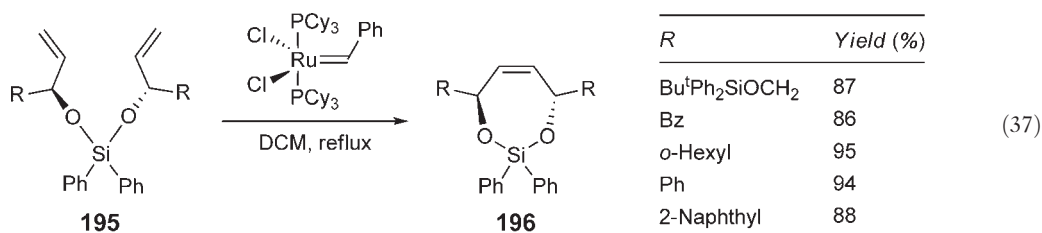
14.19.3.5 Rings Containing O–E–O and Related Units

2-Functional 1,3-dioxa-2,4,7-trisilacycloheptanes **192** were prepared by the reaction of corresponding silane diols **191** with methylchlorosilane in the presence of pyridine, as an HCl acceptor, and diethyl ether, as solvent (Scheme 35). The subsequent reaction of **192** ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{OSi}(\text{Me})_3$) with chlorine in the presence of pyridine afforded chlorosilane **193**, which upon treatment with an alcohol gave alkoxide **194**. Siloxanes **192–194** were characterized by ^1H , ^{13}C , and ^{29}Si NMR spectroscopic data <1995JOM29, 1996KGS1590>.



Scheme 35

Treatment of the allylic alcohols with diphenyldichlorosilane and 2,6-lutidine afforded the bis-alkoxysilanes **195** in excellent yield. These silicon-tethered compounds were treated with Grubbs' catalyst to induce RCM reaction, furnishing the seven-membered silacycles **196** in 87–95% yield (Equation 37) <1998JOC6768>.



The wide applicability of the RCM and its remarkable tolerance to functional groups allowed the preparation of unsymmetrical eight-membered silaketals in the form of a 1:1 mixture of diastereoisomers **197** (*S*) and **197** (*R*) (Figure 6). Compound **197** was further used for the synthesis of spiroketals which constitute the C₂₈–C₃₈ portion of okadaic acid <2001TL239>. A new approach to long-range asymmetric induction using the diastereoselective temporary silicon-tethered (TST) RCM reaction of mixed bisalkoxy silanes derived from an allylic prochiral alcohol was applied to the construction of *cis*-1,4-silaketals **198** <2003AGE1734>. Analogous cyclic silaketals **199** and **200** with ring sizes from 9 to 11 members were also obtained by RCM cyclization of symmetrical silaketals (Figure 6) <1999TL1429>.

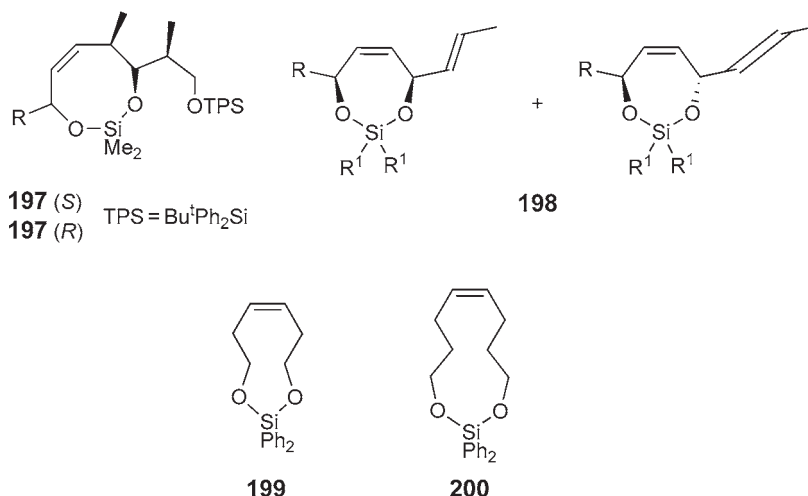
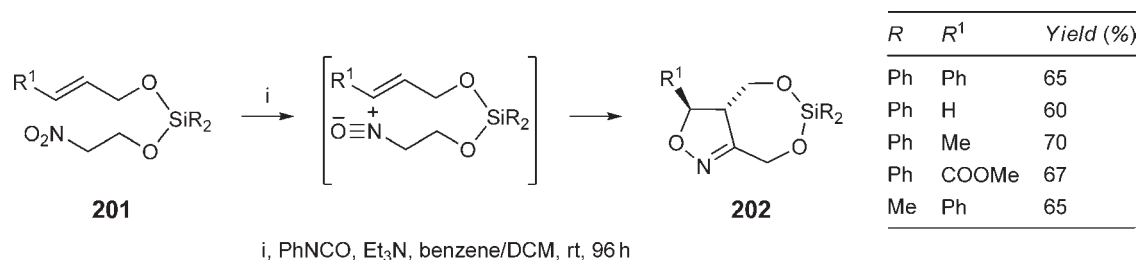


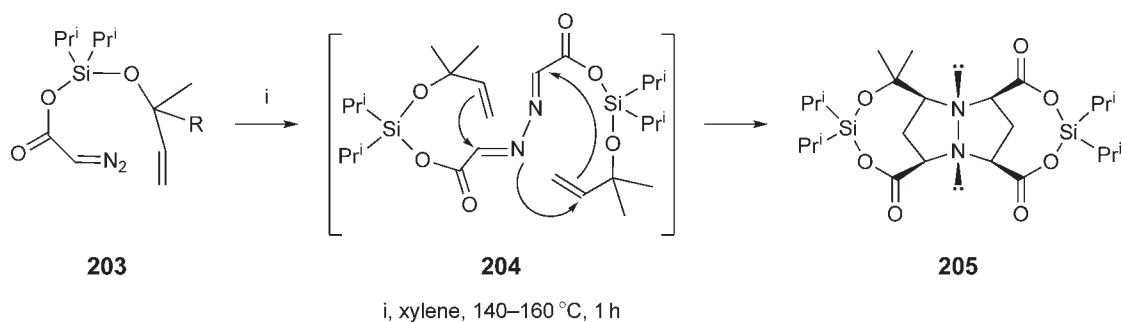
Figure 6

Unsymmetrical silaketals **201** having a 1,2-disubstituted double bond and a nitro group were prepared and transformed upon treatment with phenyl isocyanate in the presence of Et₃N under mild reaction conditions into 2-oxazoline derivatives **202** by a regiospecific intramolecular 1,3-dipolar cycloaddition, as shown in Scheme 36 <1997SL1208>. The *trans*-stereochemistry of the alkene **201** was transported to the 2-isoxazoline product **202**, which was confirmed by the ¹H NMR spectroscopic data.

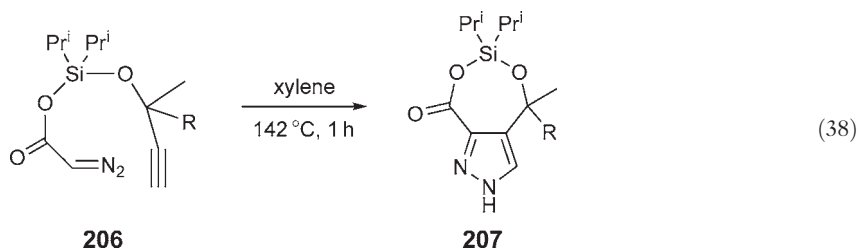


Scheme 36

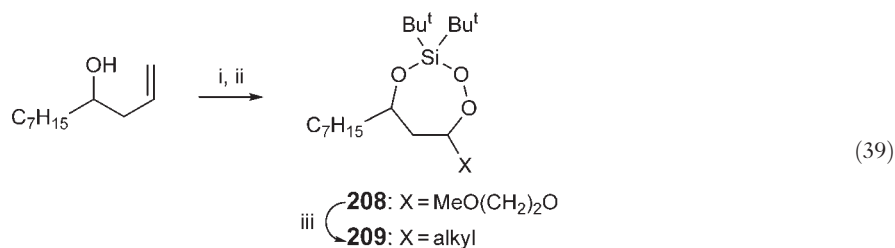
Diazoacetic acid silyl esters can be prepared by *trans*-esterification of *tert*-butyl diazoacetate with trialkylsilyl triflate <1985JOM33>. Analogously prepared (alkenyloxy)silyl **203** and (alkynyloxy)silyl diazoacetates **206** underwent silicon-tethered 1,3-dipolar cycloaddition reactions as shown in Scheme 37 and Equation (38). Compound **205** resulted from a lateral criss-cross cycloaddition of the intermediate azine **204**, which was formed from two molecules of **203** by diazo + diazo or diazo + carbene reaction <2000T4139>. On the other hand, when silyl diazoacetates **206** were kept in xylene at 142 °C for 1 h, bicyclic pyrazoles **207** were obtained (Equation 38).



Scheme 37

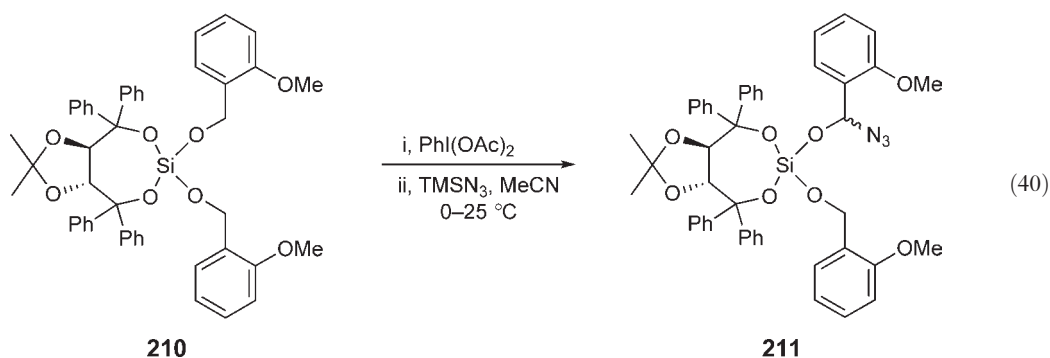


The first synthesis of 3-sila-1,2,4-trioxepane **208** was achieved by a two-step procedure involving initial ozonolysis of undecen-4-ol followed by bissilylation with $\text{Bu}^t_2\text{Si}(\text{OTf})_2$ in the presence of imidazole (Equation 39). Compound **208** was separated by flash chromatography in 45% yield. Alkylation of **208** with alkyltrimethylsilane in the presence of SnCl_4 gave alkylated silatrioxepane **209** in 5% yield <2005T4657>.

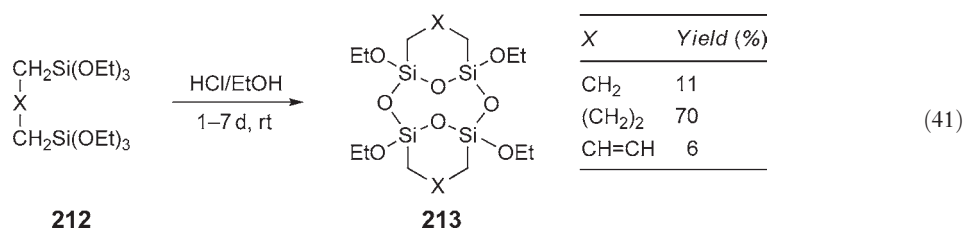


i, O_3 , 2-methoxyethanol; ii, $\text{Bu}^t_2\text{Si}(\text{OTf})_2$, DMF, imidazole, 15 min, rt; iii, alkyltrimethylsilane, SnCl_4 , 0 °C

Chiral silyl ether **210** was prepared and subjected to azidation with trimethylsilyl azide (TMSN_3) and iodobenzene diacetate [$\text{PhI}(\text{OAc})_2$], which served as a substitute of IN_3 , to give α -azido-dioxasilepine **211** as a colorless oil, in diastereoselective ratio 1:3 (Equation 40) <2005OBC816>.

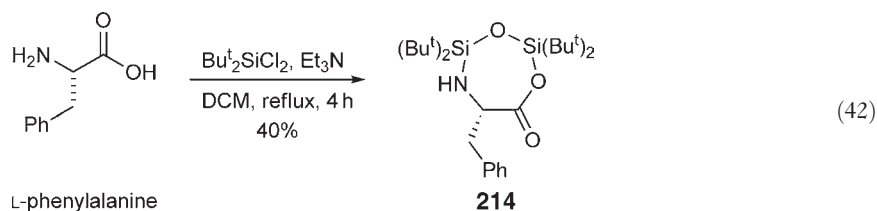


A new class of hydride organic/silica compounds such as organically bridged polysilsesquioxanes **213** were prepared from the hydrolysis and condensation of triethoxysilanes **212** linked by a hydrocarbon spacer, as shown in Equation (41).

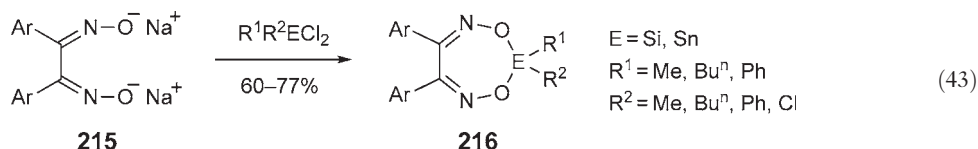


Previously, it has been shown that acid- or base-catalyzed polymerization of α,ω -bis(triethoxysilyl)alkanes proceeds to highly condensed rigid gels within a few hours <1993CM943>. However, when the alkyne bridge is ethylene, propylene, or butylene, as in **212**, gelation under acidic conditions requires 2–6 months to form seven-membered rings **213**, that are designated as ‘cyclic disilsesquioxanes’ <1999JA5413, 1996JA8501>.

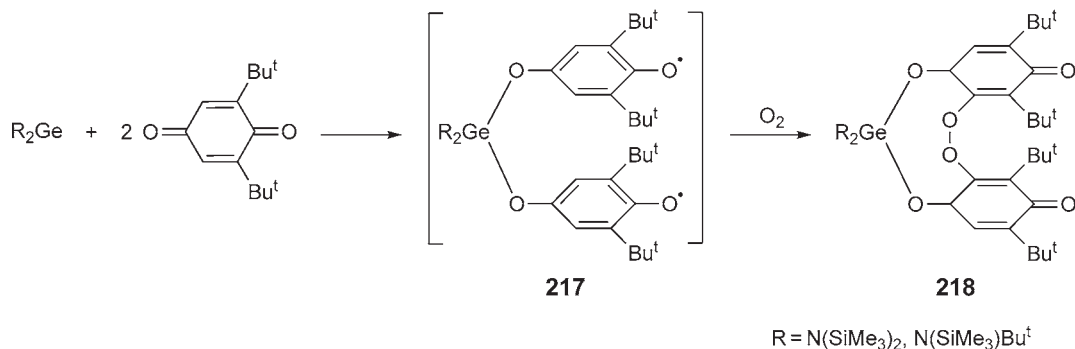
Dichlorodimethylsilane was used for the synthesis of amides from unprotected amino acids by a simultaneous protection–activation strategy <2002TL9203>. However, sterically crowded di-*tert*-butyldichlorosilane reacted with phenylalanine in the presence of Et₃N to give 5-aza-1,3-dioxo-2,4-disilacycloheptan-7-one **214** in 40% yield (Equation 42), whose structure was confirmed by MS, ¹H, and ¹³C NMR spectral data.



Stable dioxadiazasilepines and dioxadiazastannapines **216** were prepared in 60–77% yields from vicinal oximes **215** via dianion intermediates, which are intramolecularly trapped with dielectrophilic diorganodichlorosilanes and diorganodichlorostannanes, respectively (Equation 43) <2005TL315>.

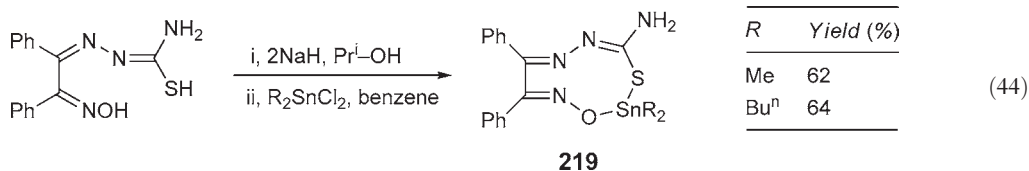


The reaction of germylenes GeR₂ bearing the bulky amide group (R = N(SiMe₃)₂, N(SiMe₃)Bu^t) with *p*-benzoquinone in *n*-hexane at 0 °C followed by exposing to air for 12 h afforded cyclic peroxides **218** in 69% and 50%, respectively. The reaction proceeded via the semiquinone radicals **217** which are trapped by an oxygen molecule. The molecular structure of **218** was definitively determined by X-ray crystallographic analysis (Scheme 38) <1995JA2187>.



Scheme 38

When the disodium salt of benzilmonoxime thiosemicarbazone was treated with $R_2\text{SnCl}_2$ in a 1:1 molar ratio, the nine-membered cyclic compounds **219** were obtained (Equation 44); their ^{119}Sn NMR spectra exhibited a sharp ^{119}Sn resonances at 136.72 ($R = \text{Me}$) and 134.86 ppm ($R = \text{Bu}^n$) confirming the presence of tetracoordinated tin <2002IJB419>.



The addition of 1 equiv of the dilithio salt of *rac*-1,1'-bi-2-naphthol to an equivalent amount of 1,1-dichloro-1-silacyclobutane in ethyl ether at -78°C led to the formation of 1,1-(*rac*-1,1'-bi-2-naphthoxy)-1-silacyclobutane **220** as a white solid in 71% yield (Figure 7). The structure of **220** was confirmed by ^1H , ^{13}C , and ^{29}Si NMR spectroscopy and X-ray crystallographic studies <2005JOM2272>.

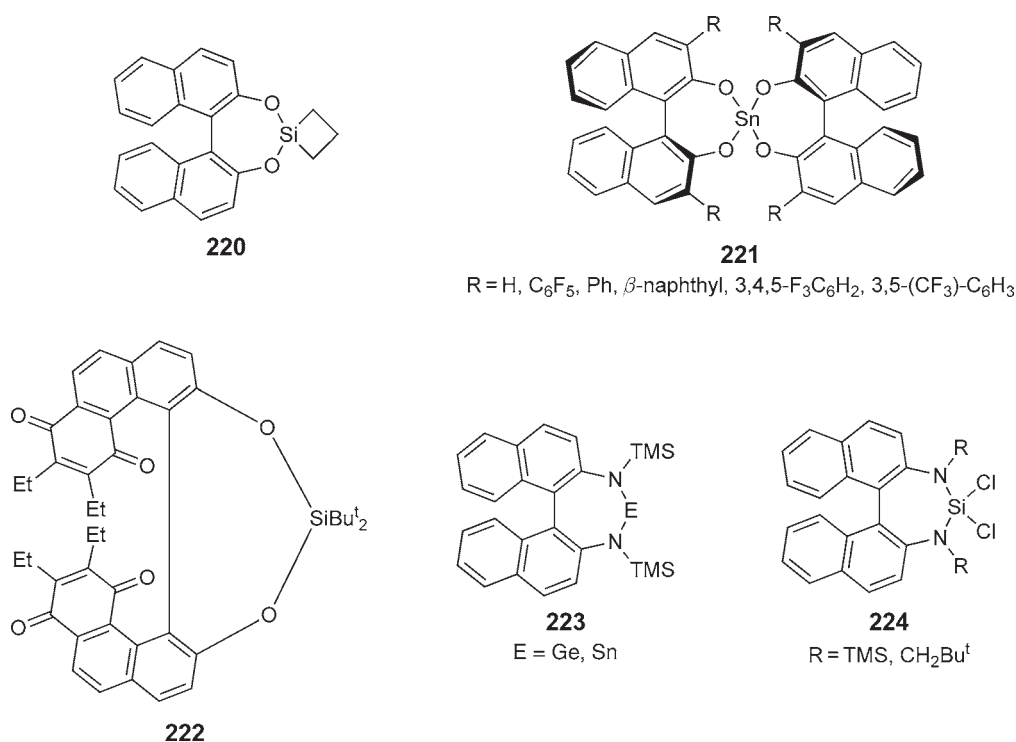


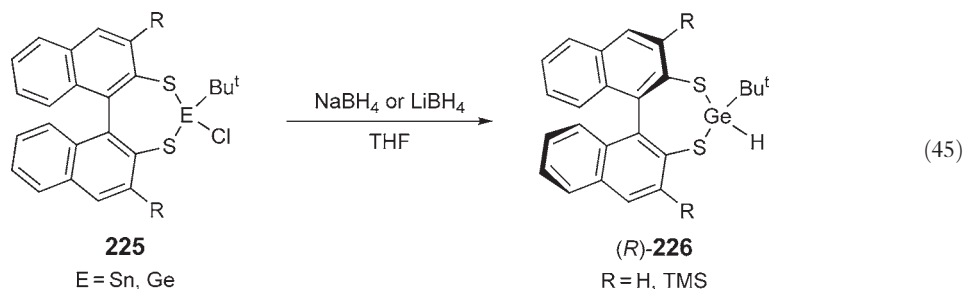
Figure 7

Chiral metal alkoxides $\text{M}(\text{OR})_4$ have been developed as asymmetric variants of ordinary Lewis acids, such as AlCl_3 and ZrCl_4 , and are used as catalysts for selective carbon–carbon bond formation. Thus, starting from bidentate 1,1'-bi-2-naphthol derivatives (BINOL) and SnCl_4 , a series of chiral tin(IV) aryloxides **221** (Figure 7) was prepared and successfully applied to the enantioselective Diels–Alder reaction <2006TL873>. Similar silocanes obtained from menthone- or camphor-derived 2,2'-biphenols have been obtained and their configuration was analyzed by NOE differential spectroscopy (NOEDS) <1997JOC7156>.

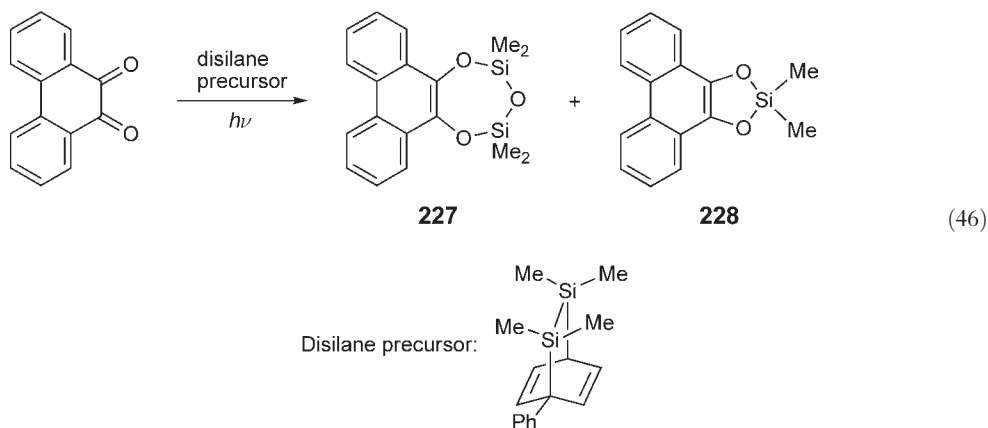
Novel helicene-like quinones **222** were prepared from silylene-tethered binaphthols based on the newly developed chromium-templated [3+2+1] benzannulation reaction (Figure 7) <2005EJO1541>.

The tin(II) and germanium(II) amides **223** were obtained from corresponding dilithio diamide and SnCl_2 or GeCl_2 -diox (diox = dioxane). Analogous reaction with SiCl_4 afforded the appropriate cyclic diaminodichlorosilane **224** (Figure 7) <1996JCD3595>.

The racemic dithiobinap was reacted with either BuSnCl_3 or $\text{BuSn(OPr}^i)_2\text{Cl}$ to produce dithiotin chloride (*rac*)-**225** ($\text{E} = \text{Sn}$) (Equation 45). Similarly, upon treatment of (*rac*)-dithiobinap and (*R*)-dithiobinap with Bu^tGeCl_3 in the presence of Et_3N in THF solution, (*rac*)-**225** and (*R*)-**225** ($\text{E} = \text{Ge}$) were obtained <2001SL1038>. Dithiogerman chlorides ($\text{E} = \text{Ge}$), but not dithiotin chloride ($\text{E} = \text{Sn}$), could be reduced to the hydrides **226** with sodium or lithium borohydride under carefully controlled conditions (Equation 45). Structures of the germanium chloride **225** and hydride **226** were confirmed by X-ray crystallographic analysis <2003JOC5013>.



Photolysis of phenanthraquinone (PQ) in the presence of disilane precursors such as 7,8-disilabicyclo[2.2.2]octa-2,5-diene using two 500 W tungsten-halogen lamps led to the formation of **227** and **228** as silylene-transfer products (Equation 46) <2001JOM63>.



The synthesis and conformation of the sterically congested seven-membered ring containing tetracoordinate germanium(IV) have been described <2001IC3830>. Thus, new dibenzo[*d,f*][1,3,2]dioxagermapin **229** and bis(1,1'-biphenyl-2,2'-dioxy)germanium **230** were obtained from the reaction of tetra-*tert*-butyl-substituted biphenyldiol with dimethyl(diphenyl)germanium dichloride and germanium tetrachloride, respectively (Figure 8). Using variable-temperature ^1H NMR spectroscopy, the free energy of activation ($\Delta G_{288}^\ddagger$) for ring inversion was determined.

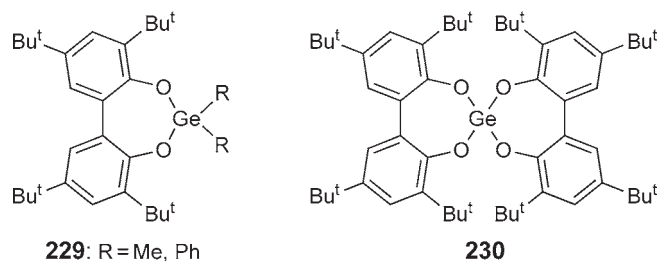
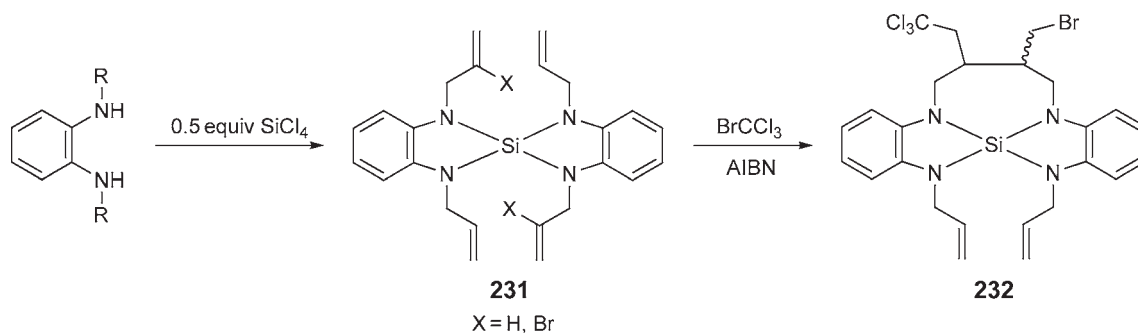


Figure 8

The spiroetraaza silane **231** was prepared by treatment of the corresponding *o*-phenylenediamine derivative with SiCl_4 . When **231** ($\text{X} = \text{H}$) was treated with bromotrichloromethane and AIBN, the monocyclization product **232** was isolated in low yield as a mixture of stereoisomers (Scheme 39). This radical-induced cyclization process was explored with respect to the impact of Si on the chemo- and regioselectivity <2002JOC8906>.



Scheme 39

Diorganotin(IV) derivatives of diphenic acid **233** were prepared by reaction of dialkyltin(IV) oxide with diphenic acid and its sodium salt in 1:1 molar ratio (Figure 9). Structure of these compounds was confirmed by IR, ^1H , and ^{13}C NMR spectroscopic data <1995AOM121>.

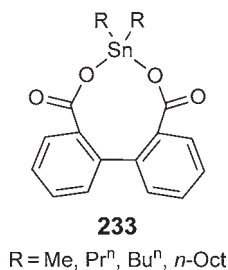


Figure 9

14.19.3.6 Silacrown Ethers, Calixarenes, Cyclophanes, and Metallacenes

[5.5][2.6]Pyridinophanes and cyclophanes **234a–d** containing silylene units (Figure 10) were prepared by sonication of pyridine- or benzenemethanol with dichlorosilanes R_2SiCl_2 ($\text{R} = \text{Me}, \text{Ph}$) in benzene at room temperature for 3 h. As evidenced from X-ray crystallographic studies, in the solid state diphenylsilylene pyridinophane **234b** ($\text{X} = \text{N}$, $\text{R} = \text{Ph}$) and dimethylsilane cyclophane **234c** ($\text{X} = \text{CH}$, $\text{R} = \text{Me}$) were found to adopt an *anti*-conformation, while their congener **234a** ($\text{X} = \text{N}$, $\text{R} = \text{Me}$) exhibited a *syn*-arrangement <1998OM2656>. A polymorphic form of **234a** was claimed to be obtained by other authors <1996IC4342>.

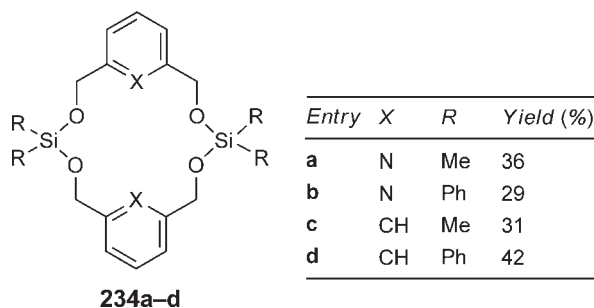
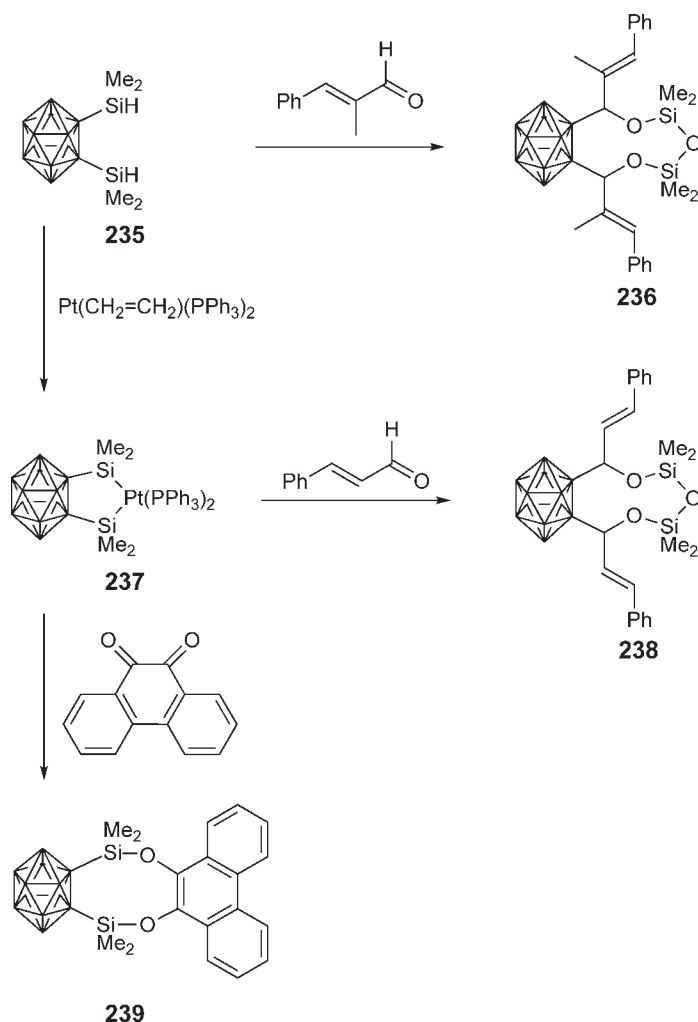


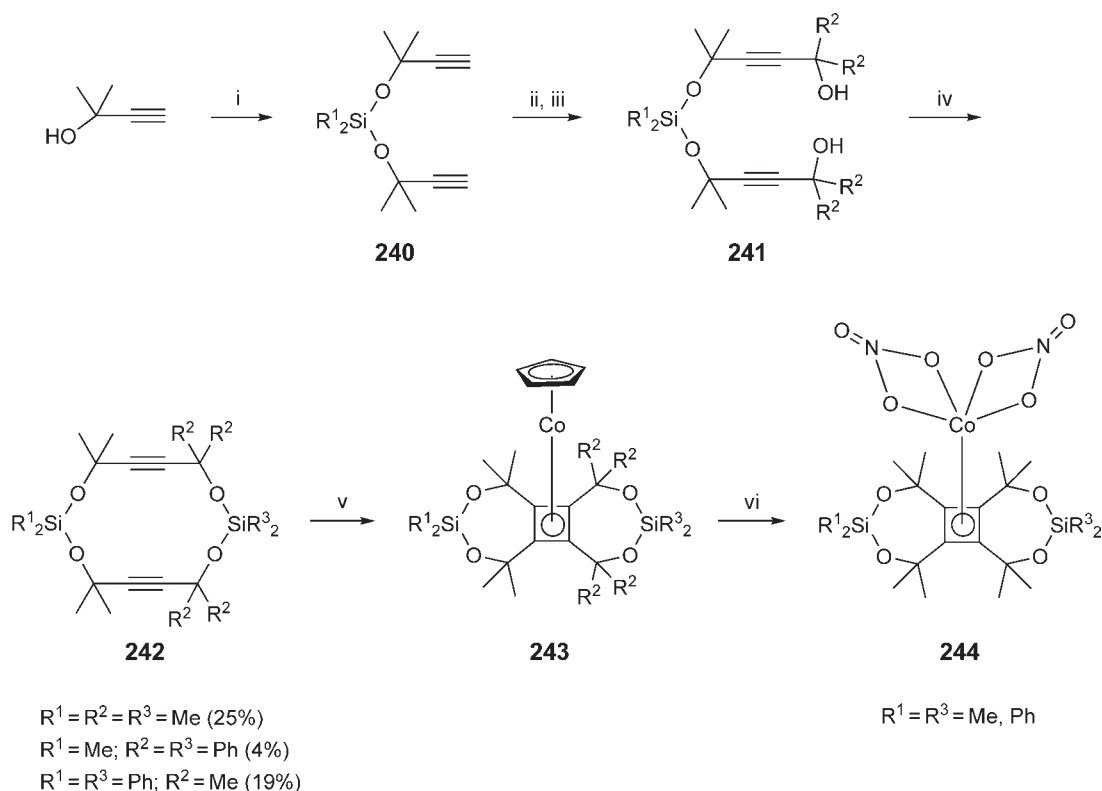
Figure 10

The transition metal-catalyzed 1,4-double silylation of α,β -unsaturated ketones and aldehydes with 1,2-bis-(dimethylsilyl)carborane **235** gave the di-insertion product **236** of a carbonyl group into each of the C–Si bonds <1988JA5579, 1991OM3173>. A similar reaction of **235** with $\text{Pt}(\text{CH}_2=\text{CH}_2)(\text{PPh}_3)_2$ gave the cyclic bis(silyl)platinum complex **237**, which reacted with a variety of substrates such as alkyne, dione, and nitrile to give heterocyclic compounds incorporating an alkene, ketonate, imine, or amine moiety (Scheme 40). Thus, *trans*-cinnamaldehyde reacted with **237** to give the disilylation product **238** in 56% yield and insertion of phenanthrenequinone into **237** produced the eight-membered ring **239** <1999OM1818>.



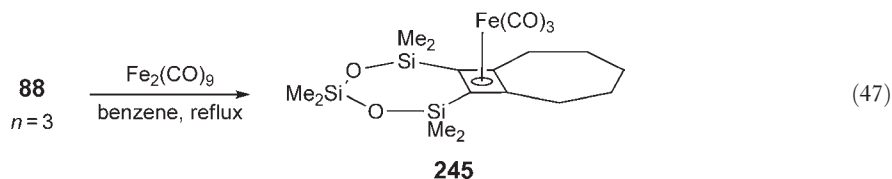
Scheme 40

Sterically hindered cyclotetradeca-1,8-diynes **242** were prepared in a straightforward manner as shown in Scheme 41. First, the reaction of 2-methyl-3-butyne-2-ol with either dimethyldichlorosilane or diphenyldichlorosilane yielded the dialkynes **240**. Then, the bis(lithium) salt of **240** was converted into the bis(alcohols) **241** by reaction with acetone or benzophenone. Finally, condensation of **241** with $\text{R}^3_2\text{SiCl}_2$ afforded the products **242** in 4–25% yield <2003EJOC3051>. Ring conformations of **242** in the solid state were determined by the rigid and linear 1,1,4,4-tetrasubstituted 2-butyne units. The geometry of 14-membered ring was determined by X-ray crystallographic studies. Cyclic diynes **242** were converted into the hexacarbonyldicobalt complexes **243** by refluxing with $\text{CpCo}(\text{CO})_2$ in decalin <2004OM2225>. Reaction of **243** with ceric ammonium nitrate (CAN) gave the dinitrato cobalt-stabilized cyclobutadienes **244** <2004JCD4146>. Similarly, the reaction of **88** with $\text{Fe}_2(\text{CO})_9$ gave the tricyclic complex **245** in low yield (Equation 47). Structures of cyclobutadienes **244** and **245** were established by X-ray crystallographic studies <1997OM646>.



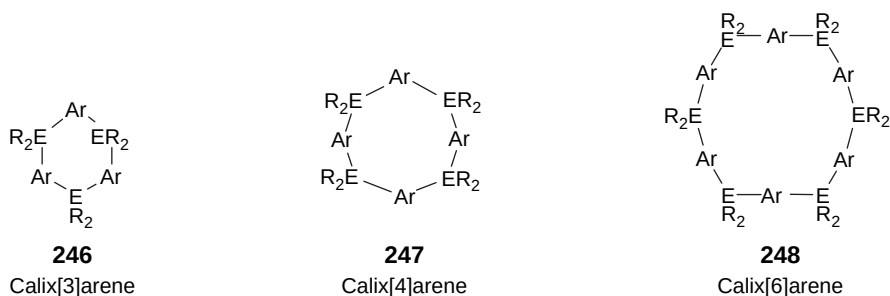
i, $R^1_2\text{SiCl}_2$, DMAP, DMC, 0 °C to rt; ii, Bu^nLi , THF, -40 °C to rt; iii, $R^2_2\text{CO}$, rt; iv, $R^3_2\text{SiCl}_2$, DMAP, DMC, 0 °C to rt; v, $\text{CpCo}(\text{CO})_2$, decalin, reflux, 5 d; vi, $(\text{NH}_4)_2\text{Co}(\text{NO}_3)_6$, MeCN, -40 °C to rt

Scheme 41



Chemistry of compounds in which metal group 14 atoms are joined by organic groups with delocalized π -systems represent an area of considerable interest as a result of their unusual physical and chemical properties. The trisilacalix[3]arenes **246** and tetrasilacalix[4]arenes **247** (Figure 11) were prepared using a one-pot procedure consisting in the condensation of 1,3-dibromobenzene and dimethyldichlorosilane with magnesium in refluxing THF. Due to the formation of linear oligomers, yields of the above products were low. Their structures were confirmed by MS, ^1H , ^{13}C , and ^{29}Si NMR spectra as well as by X-ray crystallography. Compounds **246** and **247a** exhibited π -cryptand character since the cation- π -interactions between the silacalixarenes and a silver cation were observed by FAB mass spectrometry <1999OM1465>. Macrocyclic tetramers of type **247** and hexamers **248** were obtained by deprotonation of furan, thiophene, and *N*-methylpyrrole in the 2- and 5-position with 2 equiv of Bu^nLi /TMEDA/ KOBu^t (1:1:1) in hexane, followed by addition of a solution of R_2ECl_2 in hexane ($\text{R} = \text{Me}, \text{Ph}$, $\text{E} = \text{Si}, \text{Ge}, \text{Sn}$) <1995JOC7406, 1997ICA11, 1997MGM775>.

Moreover, methoxy-directed *ortho*-lithiation of 1,2-dimethoxybenzene followed by addition of Me_2GeCl_2 afforded GeMe_2 -bridged arene **249** in good yield. Subsequent reaction of lithiated **249** with an equimolar amount of Me_2GeCl_2 furnished octamethoxy[14]dimethylgerma-1,4-calixarene **247g**, as a white solid (Scheme 42) <1997CB421>.



Compound	E	Ar	R	Yield (%)	Reference
246a	Si	A	Me	12	1999OM1465
247a	Si	A	Me	2.3	1999OM1465
247b	Si	B	Me	12	1995JOC7406
247c	Si	C	Me	16	1995JOC7406
247d	Si	D	Me	16	1995JOC7406
247e	Si	E	Me	18	1995JOC7406
247f	Si	F	Me	12	1997CB421
247g	Ge	B	Me	3	1997CB421
247h	Ge	D	Me	48	1997ICA11

Compound	E	Ar	R	Yield (%)	Reference
247i	Ge	E	Me	53	1997ICA11
247j	Ge	E	2-Thiophenyl	51	1997ICA11
247k	Ge	F	Me	4	1997MGM775
247l	Ge	F	Ph	9	1997MGM775
247m	Ge	G	Ph	47	1997MGM775
247n	Sn	G	Bu ⁿ	31	1997MGM775
248a	Si	D	Me	10	1995JOC7406
248b	Si	E	Me	17	1995JOC7406

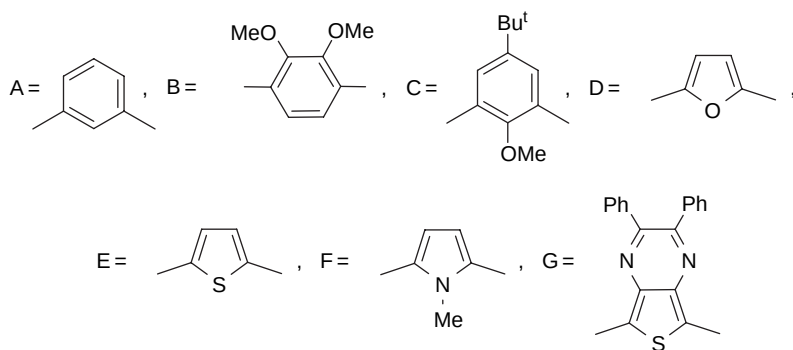
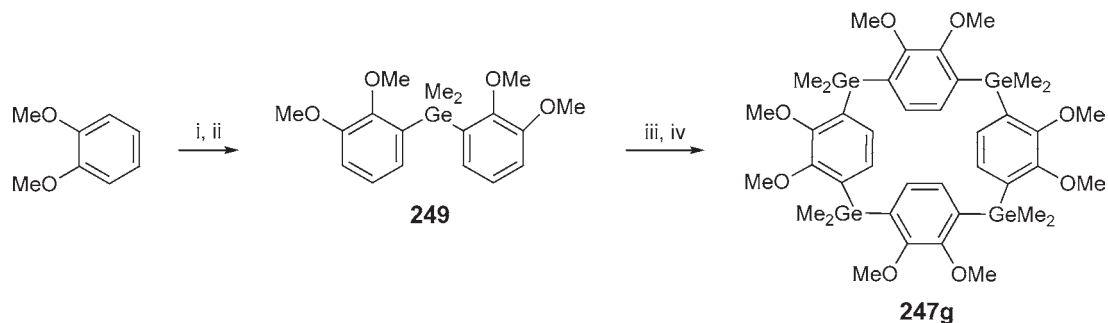


Figure 11



i, BuⁿLi, TMEDA, hexane, rt, 12 h; ii, Me₂GeCl₂, 2 h; iii, BuⁿLi, TMEDA, hexane, rt, 12 h; iv, Me₂GeCl₂, 6 h

Scheme 42

In search for an electronic equivalent of the CO ligand, which could be incorporated into sophisticated structures such as polydentate or macrocyclic ligands, it was found that dicoordinate phosphinine would be a highly advantageous alternative <1998SCI1587>. Thus, silacalix[3]phosphinine **250** and silacalix[4]phosphinine **251** shown in Figure 12 were prepared starting from 1,3,2-diazaphosphinines, and their structures were confirmed by X-ray crystallography <1999CEJ2109>. In the solid state, **250** adopted a partial cone-type structure. Two phosphorus atom lone pairs point toward the top of the cavity and are located above the plane defined by the three silicon atoms, and the third one points below this plane. Macrocycle **251** adopted an opened-out partial cone conformation. Two opposing phosphinine subunits lie almost in the plane defined by the four silicon atoms, whereas the other two subunits are located in two roughly parallel planes that are perpendicular to the first, and their phosphorus atoms point in opposite directions. The strategy devised for the synthesis of **251** was then extended to derivatives containing furan and thiophene (Figure 12, Ar = 2,5-furyl, 2,5-thienyl).

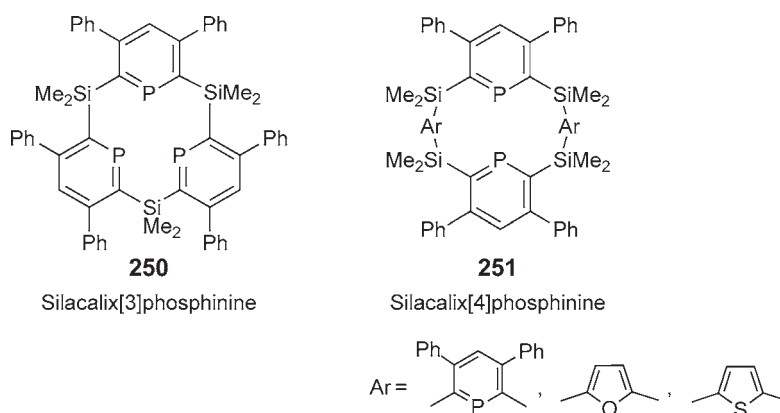
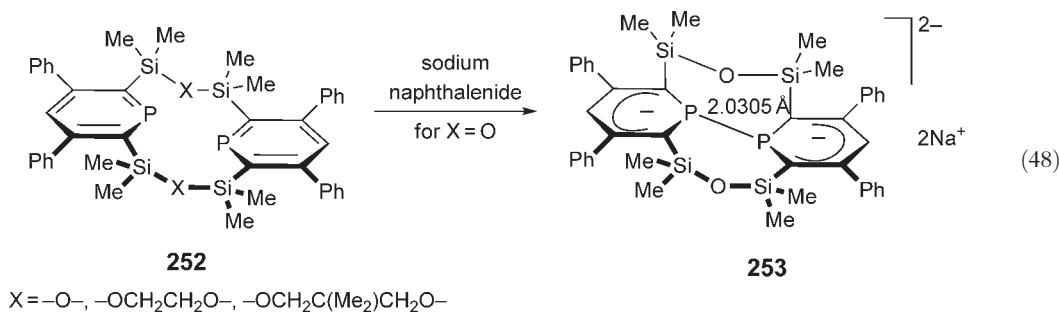
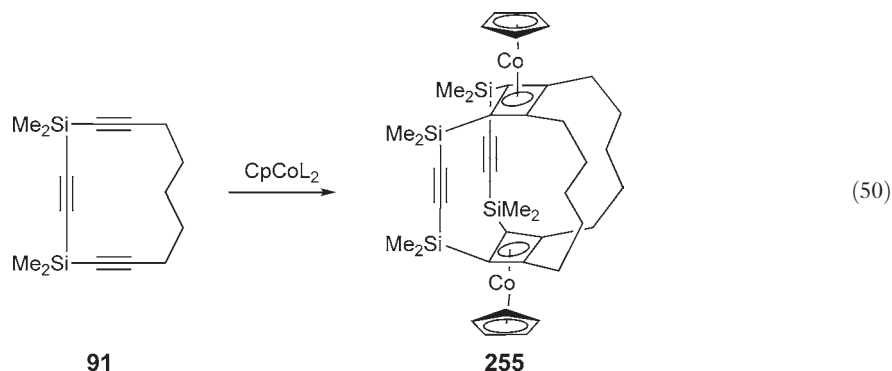
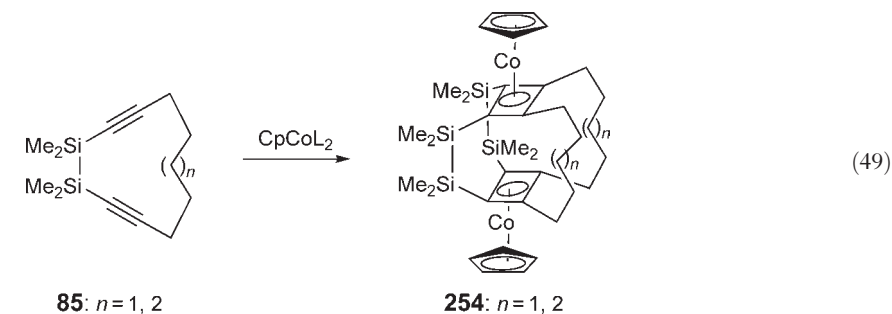


Figure 12

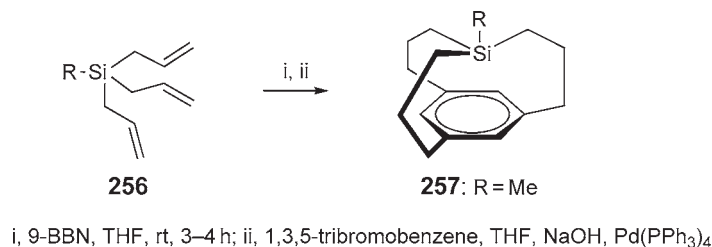
As shown in Equation (48), mixed phosphinine–ether macrocycles **252** were also prepared in 50% (X = O) and 25% (X = OCH₂CH₂O, OCH₂C(Me₂)CH₂O) by reacting diynes (PhC≡CSiO)₂X with 4,6-bis(*tert*-butyl)-1,3,2-diazaphosphinine <2001JOC1054>. Reduction of **252** (X = O) with sodium naphthalenide afforded diamagnetic dianion **253** with a new type of phosphorus–phosphorus bond <2001JA6654>.



Silabridged cyclobutadiene superphanes **254** and **255** were obtained in good yields and high stereoselectivity by reacting unsymmetrically bridged disiladiynes **85** and **91** <1995TL4603> with (η^5 -cyclopentadienyl)cobalt complexes (Equations 49 and 50) <1995TL4607>. The molecular structure of **254** ($n = 1$) was confirmed by X-ray crystallography.



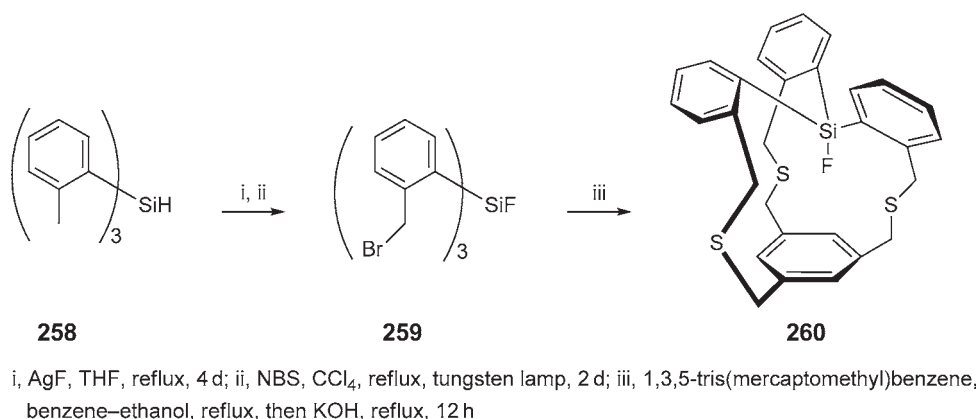
The synthesis of small strained cyclophanes attracted the attention of chemists for many years because the forced proximity of atoms leads to unusual chemical and physical properties. Using the Suzuki reaction to couple a three-legged borane intermediate derived from a triallylsilane **256** to 1,3,5-tribromobenzene, the analogue of Pascal's hydrocarbon was obtained in a single step <1994OM3728>. This strategy has been applied to the synthesis of **257** (4% yield) from trisborabicyclo[3.3.1]nonane (9-BBN) adduct of methyltriallylsilane **256** and 1,3,5-tribromobenzene (Scheme 43).



Scheme 43

An *in* stereoisomer of fluorosilaphane **260** was obtained as depicted in Scheme 44 in overall 0.4% yield. First, tri(*o*-tolyl)fluorosilane **258** was fluorinated at silicon with AgF and then brominated with NBS to give tris[2-(bromomethyl)phenyl]fluorosilane **259**. Condensation of **259** with 1,3,5-tris(mercaptomethyl)benzene yielded the final product **260** <1998JA6421, 1999JOC5626>. The inside location of the fluorine atom was established by X-ray crystallographic analysis. The Si–F bond distance is very short (1.591 Å) compared to the mean Si–F distance for all tetracoordinate tris[(alkyl(aryl)]fluorosilanes found in the Cambridge Structural Database. The ¹⁹F NMR resonance for **260** appears at $\sigma = 5.3$ ppm, that is, 155 ppm upfield from that of tri(*o*-tolyl)fluorosilane **258**.

5,5,6,6,21,21,22,22-Octamethyl-5,6,21,22-tetragerma[10.10]paracyclophane **261** ($R^1 = R^2 = \text{Me}$) was obtained in 0.8% yield by a double Wurtz coupling of 1,4-bis[4(bromodimethylgermyl)butyl]benzene using Na in toluene at reflux (Figure 13). The structure of **261** ($R^1 = R^2 = \text{Me}$) was confirmed by EIMS spectrum, which contained molecular ion peak at $m/z = 786$ accompanied by peaks that form a characteristic pattern that is associated with species containing four germanium atoms. Attempts made to prepare trace amounts of congeners with $R^1 = R^2 = \text{Ph}$ and $R^1 = \text{Ph}$, $R^2 = \text{Me}$ were also successful; however, this method was impractical since analytically pure samples were not obtained <2003JOM61>.



Scheme 44

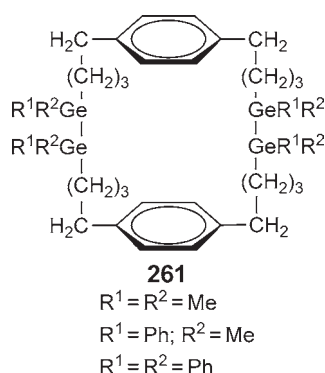


Figure 13

The metallamacrocycles have attracted attention due to their potential applications such as catalysis, sensing, molecular electronics, and host-guest chemistry. The first silicon-bridged [1.1]ferrocenophane [$\{\text{Fe}(\eta\text{-C}_5\text{H}_4)_2\text{SiMe}_2\}_2$] **262** has been obtained from disilylated ferrocene [$\text{Fe}\{\eta\text{-C}_5\text{H}_4\text{SiMe}_2(\text{C}_5\text{H}_5)\}_2$] upon treatment with 2 equiv of BuⁿLi in THF at -5°C followed by the reaction of the resulting $\text{Li}_2[\text{Fe}\{\eta\text{-C}_5\text{H}_4\text{SiMe}_2(\text{Ph})\}_2]$ with FeCl_2 in THF (Figure 14) <1995JCD1893>.

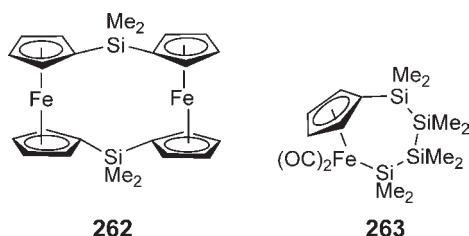
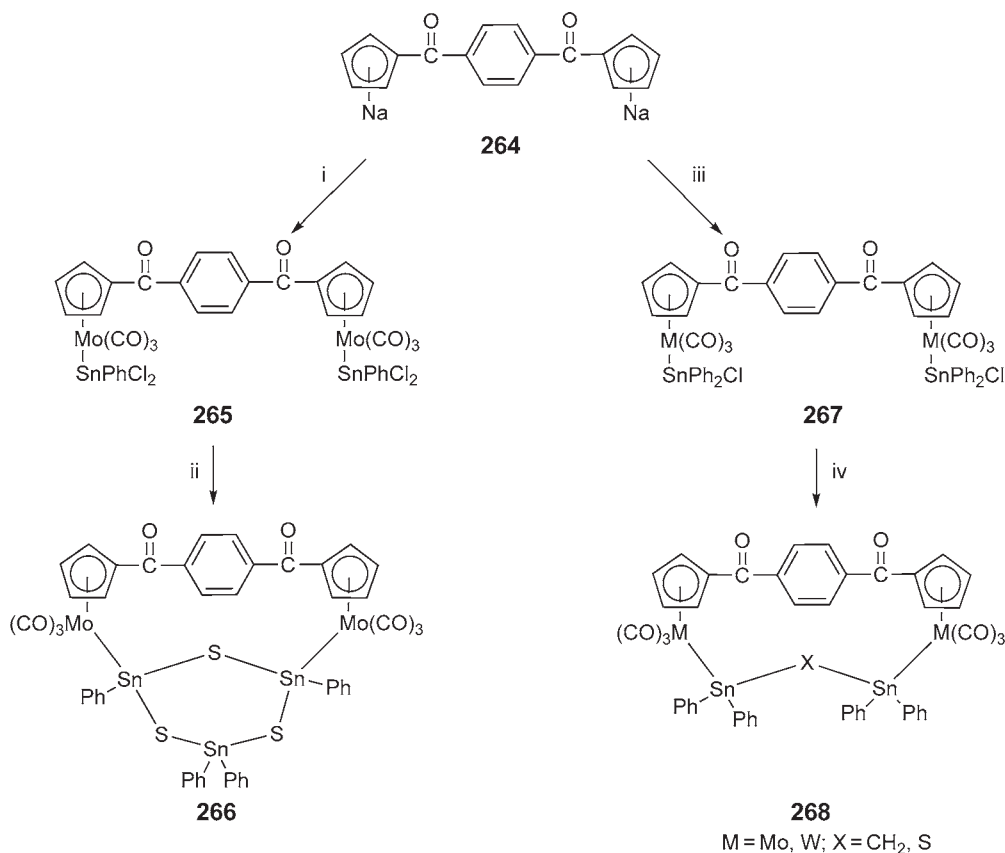


Figure 14

Tetrasilaferrocenophane **263** (Figure 14) was prepared in 24% yield by treatment of tetrasilaferrocene $\text{Fp}(\text{SiMe}_2)_4\text{Cl}$ ($\text{Fp} = [(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2]_2$) with lithium diisopropylamide (LDA) in THF at 0°C . Structure of **263** was confirmed by IR and ^1H , ^{13}C , and ^{29}Si NMR spectral data <2006OM3969>.

A novel pentanuclear heterodimetallic metallamacrocyclic **266** was prepared in three steps starting from $\text{Na}_2[\text{p-C}_5\text{H}_4\text{C}(\text{O})_2\text{-C}_6\text{H}_4]$ **264**, as shown in Scheme 45. First, **264** reacted with $\text{Mo}(\text{CO})_6$ followed by addition of PhSnCl_3 to yield the tetranuclear heterodimetallic complex **265**. Reaction of the latter with $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ in boiling ethanol resulted in the formation of **266**, which was characterized by IR and NMR spectra as well as X-ray structural analysis

<2002OM3675>. The formation of the SnPh_2 unit was attributed to the redistribution reaction of the organotin moiety from the partial decomposition or reductive elimination of complex **265** under reductive conditions. The average bond distances (2.799 Å) and average Sn–S distance (2.417 Å) are within normal range. The structure of **266** is a rare example of an organotin metallamacrocycle involving the molecular architecture and simultaneously fusing a small heterocycle. A similar procedure was applied for preparation of metallamacrocycles **268** via **267** (Scheme 45) <2003JOM57>.



i, $\text{Mo}(\text{CO})_6$ then PhSnCl_2 ; ii, $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$, EtOH, reflux; iii, $\text{M}(\text{CO})_6$ (M = Mo or W), then Ph_2SnBr_2 ; iv, $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$, EtOH, reflux, 2 h

Scheme 45

When the dianion $[(\text{CH}_2(\eta^5\text{-C}_5\text{H}_4)\text{Fe}(\text{CO})_2)_2]^{2-}$, obtained by the reductive cleavage of Fe–Fe bond in the dimer $\text{CH}_2[(\eta^5\text{-C}_5\text{H}_4)\text{Fe}(\text{CO})_2]_2$ with 1% Na/Hg amalgam in THF, was subjected to the reaction with Ph_2SnCl_2 at -78°C for 2 h, the complex **269**, which is soluble in hexane and diethyl ether, was obtained in 80% yield. Structure of **269** was confirmed by ^1H NMR spectrum and X-ray crystallographic studies (Figure 15) <1999ICA252>.

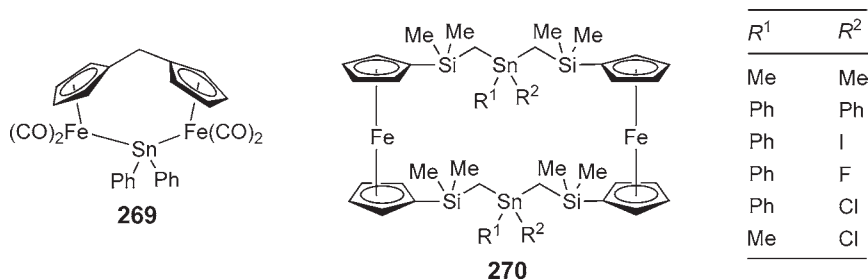


Figure 15

A series of silicon- and tin-containing ferrocenophanes **270** such as 1,1,3,3,14,14,16,16,18,18,29,29-dodecamethyl-3,14,18,29-tetrasil-1,16-distanna[5.5]ferrocenophane were obtained as novel Lewis acids (**Figure 15**) <2000OM430, 1998AXC1425>. The molecular structure of these compounds was confirmed by ^1H , ^{13}C , ^{29}Si , and ^{119}Sn NMR spectroscopy as well as X-ray crystallographic studies of congeners with $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Cl}$, and $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Cl}$. In solution the halogen-substituted ferrocenophanes undergo *cis-trans*-isomerism, the rate of which was enhanced by addition of halide ions.

Compounds **271a** and **271b** (**Figure 16**), containing 10-membered rings, were obtained by reacting $\text{Li}(\text{THF})\{\text{C}(\text{SiMe}_3)_2\text{SiMe}_2\text{C}_5\text{HN}\}^{-2}$ with CuI and AuClSiMe_2 , respectively. Structures of these compounds were confirmed by X-ray crystallographic studies <2002JCD2467>.

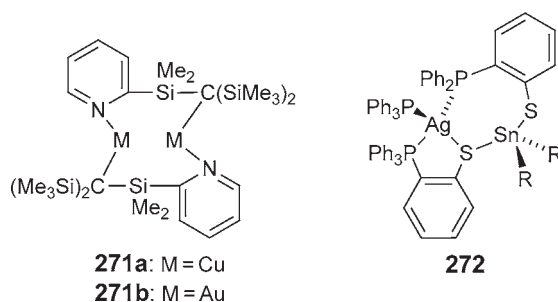


Figure 16

Heteronuclear tin(IV)–silver(I) complexes **272** with phosphinothiolate ligands (**Figure 16**) were obtained in good yields by the reaction of $[\text{SnR}_2(\text{SC}_6\text{H}_4\text{PPh}_2)_2]$ ($\text{R} = \text{Me}, \text{Ph}$) with $\text{Ag}(\text{CF}_3\text{SO}_3)(\text{PR}_3)$ ($\text{PR}_3 = \text{PPh}_3, \text{PPh}_2\text{Me}$) as a result of the coordination of $[\text{AgPR}_3]^+$ units to the starting material. The molecular structure of **272** ($\text{R} = \text{PPh}_2\text{Me}$) has been established by X-ray diffraction of its dichloromethane solvate <2001JOM274>.

14.19.3.7 Atranes and Related Compounds

Atranes as a special class of compounds with $\text{N} \rightarrow \text{E}$ transannular bond have attracted a considerable amount of attention due to their intriguing molecular structure, biological activities, and patterns of chemical reactivity. In contrast, germocanes, closely related analogues of germatranes, have been little studied. Therefore, 1,6-diaza-2,2-dimethoxy-2-silacyclooctane **273** was prepared in 90% yield by heating of 1,4-diaza-8,8,8-trimethoxy-8-silaoctane at reflux, and its structure was confirmed by X-ray crystallographic studies (**Figure 17**) <1996JOM29>. Dichalogermocanes $\text{MeN}(\text{CH}_2\text{CH}_2\text{O})\text{GeX}_2$ ($\text{X} = \text{Cl}, \text{Br}$) were obtained by the reaction of GeX_4 with $\text{N}(\text{CH}_2\text{CH}_2\text{OSiMe}_3)_2$, while dimethylgermocane $\text{MeN}(\text{CH}_2\text{CH}_2\text{O})\text{GeMe}_2$ was formed upon treatment of $\text{Me}_2\text{Ge}(\text{NMe}_2)_2$ with $\text{MeN}(\text{CH}_2\text{CH}_2\text{OH})_2$ <2003ZNB1165>.

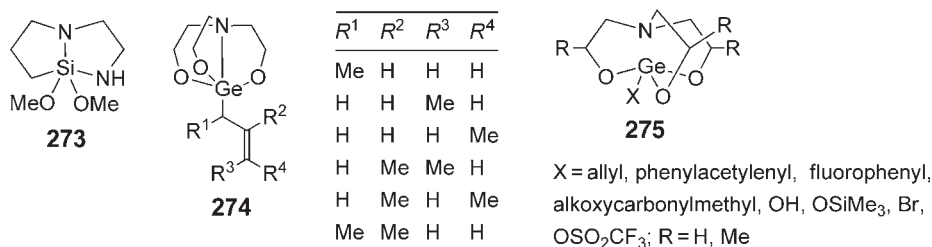
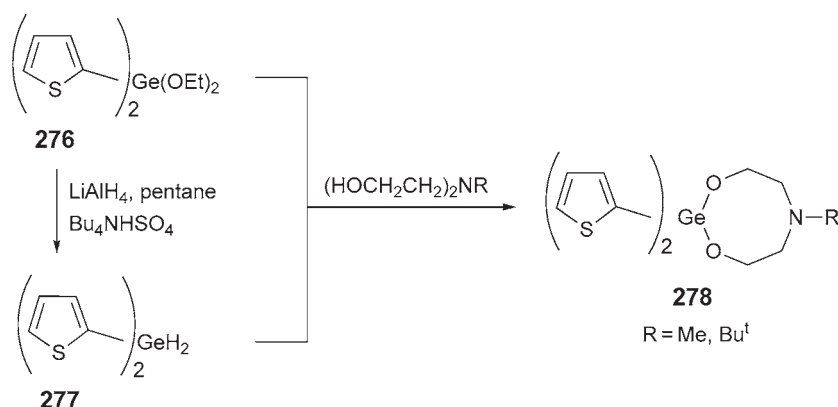


Figure 17

Synthesis of allylic germatranes **274** (**Figure 17**) has been achieved by two complementary routes. The first of these consists in the preparation of the precursor germanium trichlorides by a transmetalation reaction between germanium(IV) chloride and the corresponding tributylstannanes, followed by alcoholysis and reaction with triethanolamine. The second route is through the palladium-catalyzed hydrogermylation of a suitable diene using germatrane

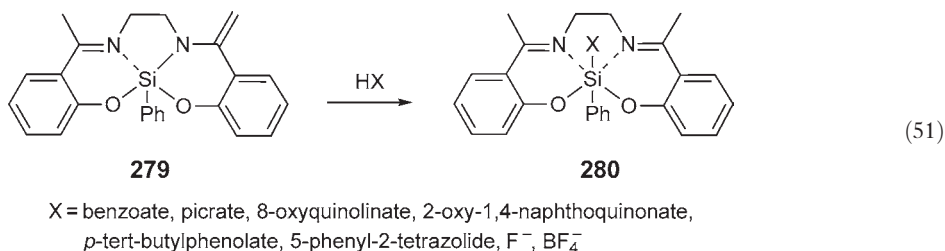
<2004JOM2565>. Germatranes **275** with germanium–carbon bonds containing functional groups neighboring to the germanium atom – allyl <1997ZNB30>, phenylacetylenyl <1997ZFA1144, 2001ZFA1>, fluorenyl <1997ZFA1144, 1998ZNB1247, 1999ZFA655>, benzyl <1999ZOB518>, alkoxy carbonylmethyl <1997CB739>, and 1-trimethylsilyloxy <2000JOM387> – were also prepared. The reactions of germatranyltriflates and 1-trimethylsilyloxygermatranes, which are even more reactive than 1-bromogermatrane, with lithium reagents such as $(\text{Me}_3)_2\text{NLi}$, cyclopentadienyllithium, indenyllithium, and fluorenyllithium were studied in detail <2000JOM387>. Synthesis and characterization of 3- and 4-phenylgermatranes by X-ray crystallography were also described <2003JOM8>.

A new route for the synthesis of 5-coordinated germanium compounds such as (1,3-dioxo-6-aza-2-germoctanes **278** consisted of the reaction of diethanolamine with di(2-thienyl)germane **277** prepared by the reduction of di(2-thienyl)-diethoxygermane **276** with lithium chloride in pentane under phase-transfer conditions (Scheme 46). Germocane **278** ($\text{R} = \text{Me}$) was also obtained by transesterification of **276** with *N*-methyldiethanolamine. Molecular structure of **278** was confirmed by X-ray crystallography. In the solid state, the eight-membered ring has a crown conformation. In contrast to germatranes, germocane **278** is characterized by a considerable lengthening of the $\text{N} \rightarrow \text{Ge}$ transannular bond (2.446 Å). The coordination polyhedron of the germanium atom is a strongly distorted trigonal bipyramid <1996JOM41>.



Scheme 46

The chemistry of hypercoordinate silicon compounds has stimulated the synthesis of novel compounds for applications such as rodenticides and anticancer drugs. A novel approach to switch between penta- and hexacoordination of the silicon atom by adding Brønsted acid to Si-complexes with enamine-functionalized salen-type ligands has been extensively explored <2002AG1825, 2003AGE1732, B-2003MI317>. Silicon complexes **279** with enamine-functionalized salen-type ligands reacted with Brønsted acid in 1,4-addition reaction to yield hexacoordinate silicon complexes **280** (Equation 51). The Si-compounds were characterized by multinuclear NMR spectroscopy and the structures of **280** ($\text{X} = \text{benzoate}$, picrate, 8-oxyquinolate, 2-oxy-1,4-naphthoquinonate, *p*-tert-butylphenolate, 5-phenyl-2-tetrazolide, F^- , BF_4^-) were confirmed by X-ray crystallographic studies <2005ICA4270>.



The new stable formal metallanimines, matallanethiones, and -selones **281** were prepared by the reactions of the divalent species L^2E ($\text{L}^2 = \text{tetradentate Schiff base}$; $\text{E} = \text{Ge, Sn}$) with Me_3SiN_3 , elemental S_8 , or Se (Figure 18) <1999MGM703>.

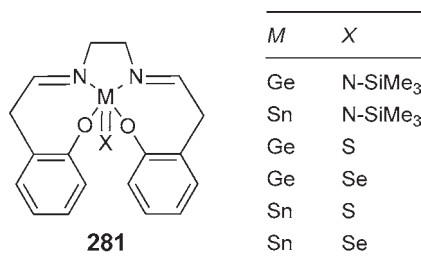
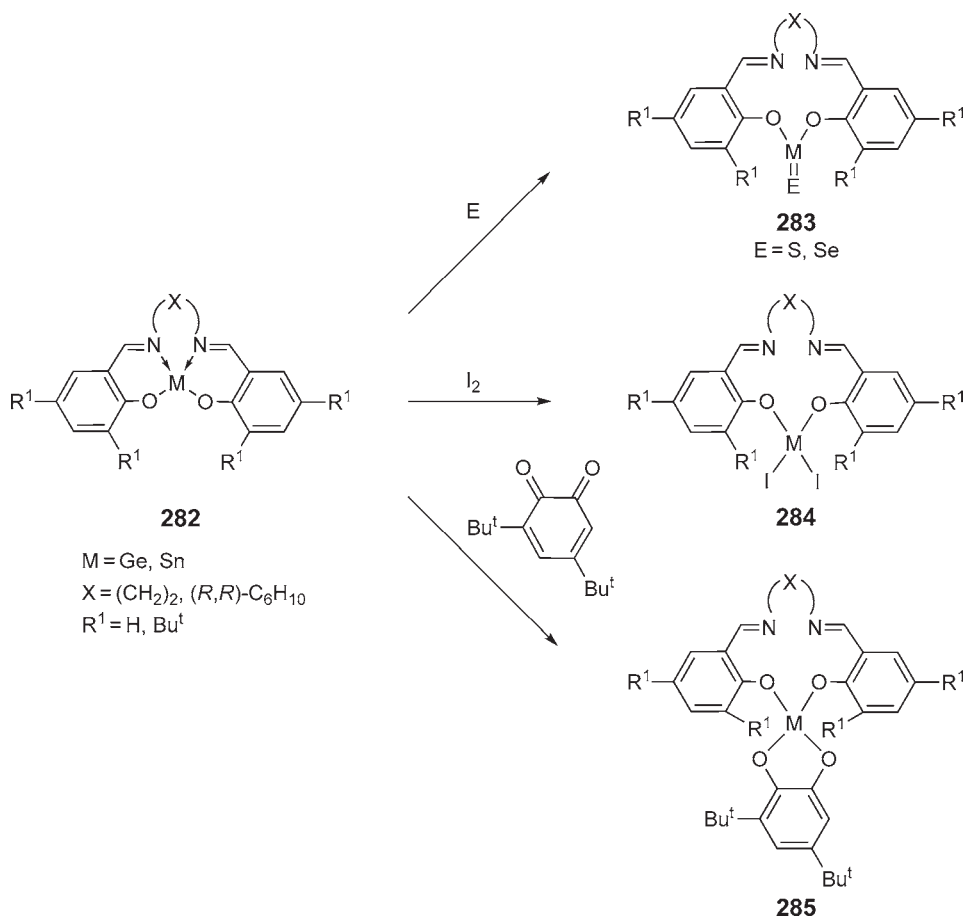


Figure 18

Starting from new bivalent germylenes and stannylenes **282**, various stable cyclic organometallic compounds **283–285** were obtained as shown in [Scheme 47](#) <1997MGM791>.

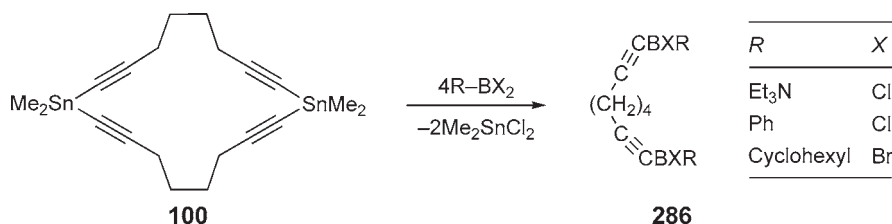


Scheme 47

14.19.4 Reactivity and Transformations of Heterocyclic Rings

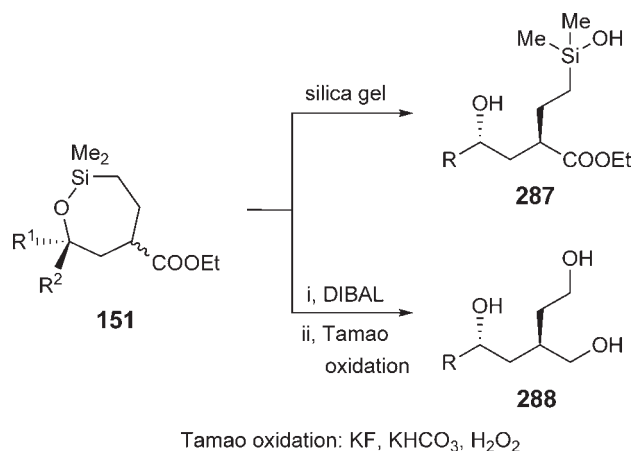
Organometallic compounds with group 14 heteroatoms enjoy a wide range of applications in the synthesis of diverse open-chain organic products.

Treatment of 1,10-distannacyclodeca-2,8,11,17-tetrayne **100** with electrophiles leads to cleavage of the Sn–C bonds. The reaction of **100** with three different boron halides giving rise to the formation of acetylene derivatives **286** is summarized in [Scheme 48](#) <1997MGM573>.



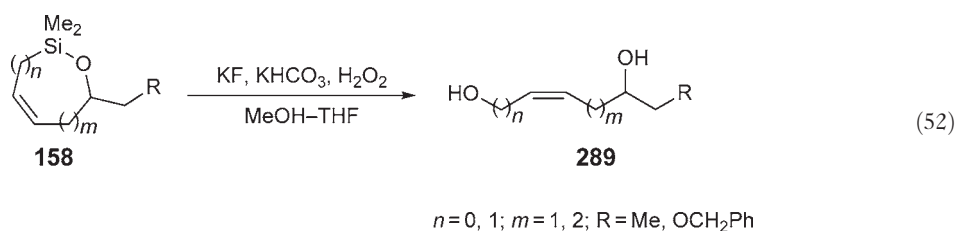
Scheme 48

As shown in [Scheme 49](#), cyclic silyl ethers bearing the ethoxycarbonyl group *anti* to the γ -substituents **151** upon treatment with silica gel gave acyclic ethyl γ -hydroxy- α -[2-(hydroxydimethylsilyl)]carboxylates **287**, and the subsequent reduction with diisobutylaluminium (DIBAL) followed by Tamao oxidation [<1990OS96>](#) gave the corresponding acyclic triols **288** [<2004TL4329>](#).



Scheme 49

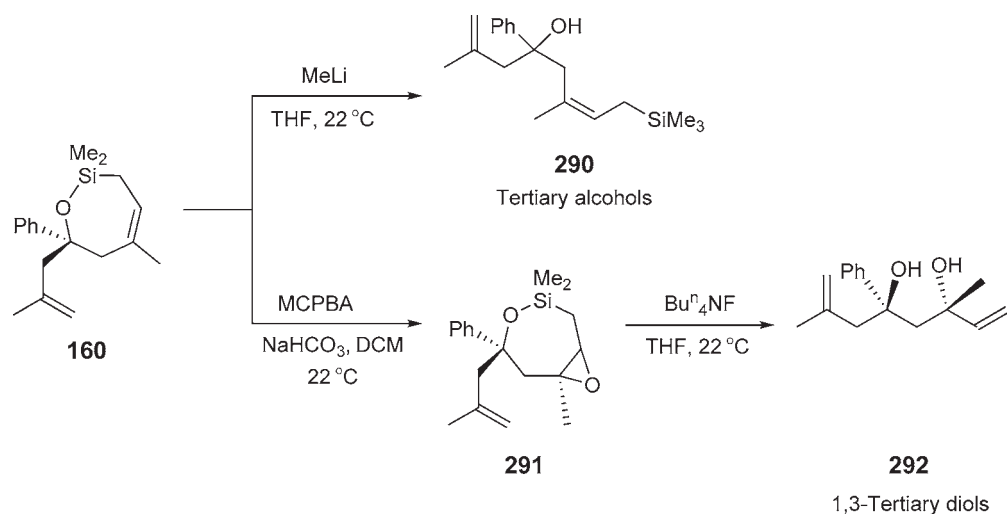
Ring cleavage of cyclic silyloxy olefins **158** using the oxidative conditions developed by Tamao efficiently afforded the corresponding *cis*-olefinic dihydroxy compounds **289** in good to excellent yield ([Equation 52](#)) [<1997TL4757>](#).



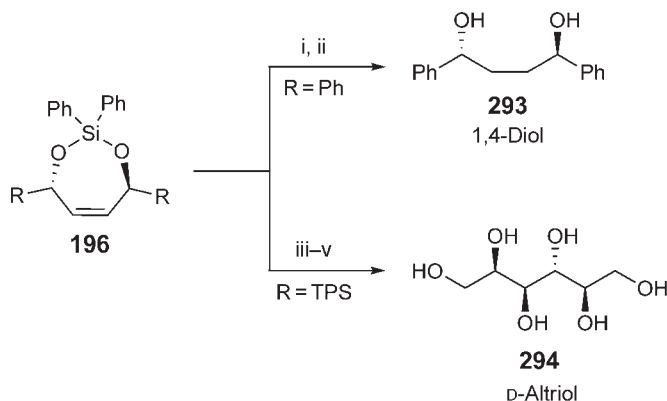
The nonracemic chiral seven-membered ring siloxanes **160** were employed to prepare numerous difficult-to-attain tertiary alcohols. Thus, on treatment with MeLi in THF at 22 °C, tertiary alcohol **290** was obtained (93% ee). Subjection of the siloxane **160** to *m*-chloroperbenzoic acid (MCPBA) led to the diastereoselective formation of epoxide **291**, which reacts further with tetrabutylammonium fluoride (Buⁿ₄NF = TBAF) to give 1,3-tertiary diol **292** ([Scheme 50](#)) [<2002JA2868>](#).

Diphenyl silaketals **196** can be readily converted to the C₂-symmetrical 1,4-diol **293** by reduction with Raney-Ni, followed by desilylation with TBAF in 65% yield. Another potentially powerful application of cyclic alkoxy silanes **196** consists in dihydroxylation with catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMO), followed by treatment with TBAF which gives D-altriol **294** ([Scheme 51](#)) [<1998JOC6768>](#).

The parallel synthesis of an exhaustively stereodiversified library of *cis*-1,5-enediols by silyl-tethered RCM has also been described [<2001OL2157>](#).



Scheme 50



$\text{TPS} = \text{Bu}^t\text{Ph}_2\text{Si}$

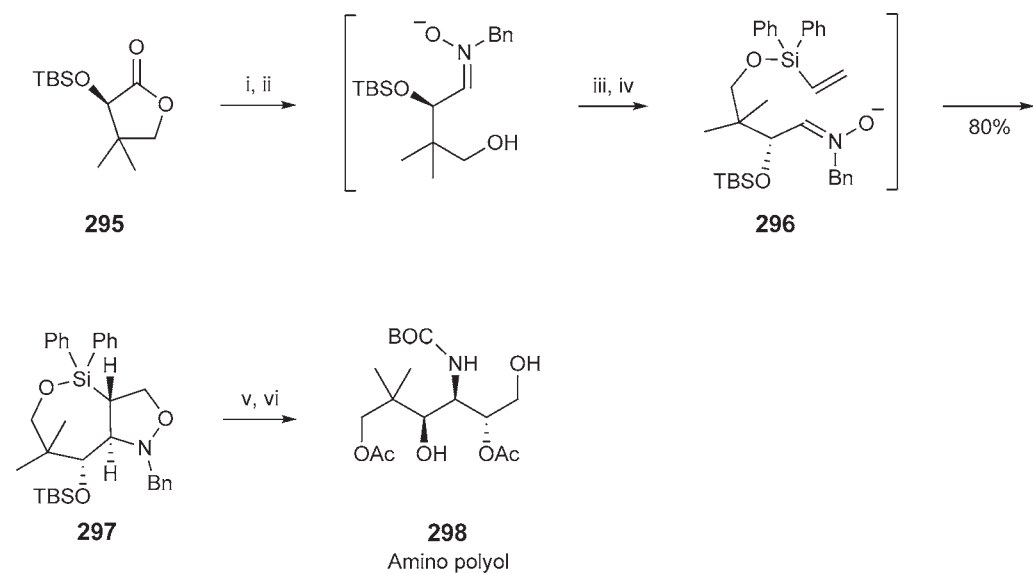
i, H_2 , Raney Ni; ii, TBAF, THF; iii, OsO_4 , NMO, rt; iv, TBAF, then Ac_2O , pyridine; v, cat. NaOMe, MeOH, rt

Scheme 51

A general method for the synthesis of stereodefined amino polyols consists of highly regioselective and diastereoselective intramolecular chiral nitron cycloaddition reactions with a vinyl group tethered by a silicon atom. The reaction sequence is shown in [Scheme 52](#) <2000JA7633>. This strategy features a series of one-pot reactions involving (1) diisobutylaluminium hydride (DIBAH) reduction of the carbonyl group of chiral α -hydroxy carbonyl compounds **295**, in which the hydroxyl group is protected as diphenylvinyl silyl ethers, to give an aldehyde; (2) condensation of the aldehyde with *N*-benzylhydroxylamine to furnish nitron **296**; and (3) intramolecular [3+2] dipolar cyclization reaction between the nitron and the silicon-tethered vinyl group to give isoxazoline derivative **297** as direct precursor of amino polyols **298**.

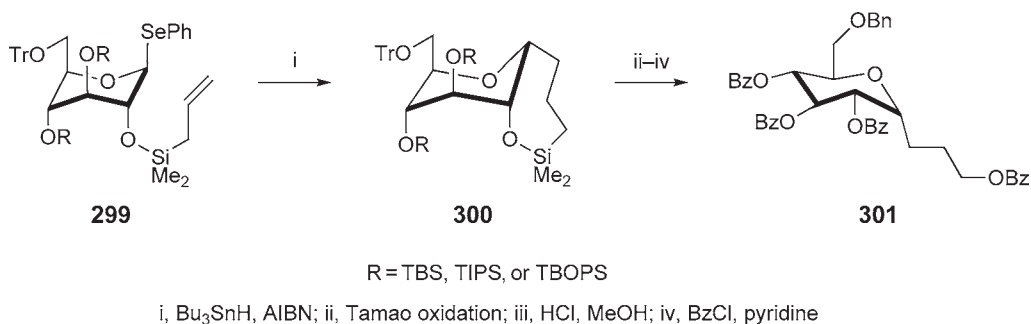
Novel IP_3 receptor ligands having an α -C-glycosidic structure were synthesized via a radical cyclization reaction with a temporary connecting allylsilyl group as the key step ([Scheme 53](#)). Thus, phenyl 2-*O*-allyldimethylsilyl-3,4-bis-*O*-TBS-1-seleno- β -D-glucopyranoside **299** was treated with $\text{Bu}_3\text{SnH/AIBN}$ to form the α -cyclization product **300** in almost quantitative yield. The latter was converted into the corresponding penta-*O*-benzoate **301** by successive treatment under Tamao oxidation conditions, HCl/MeOH , and BzCl/pyridine <2005T3697>.

An effective cross-coupling of alkynes using 'silicon-tethered' $\text{Fe}(\text{CO})_5$ -promoted cyclocarbonylation was shown to provide a seven-membered ring dialkoxysilane **302**, which subsequently upon treatment with Me_3NO in acetone at 0°C was converted to cyclopentadienones **303** with variable substituents ([Scheme 54](#)) <2002OL2837>.

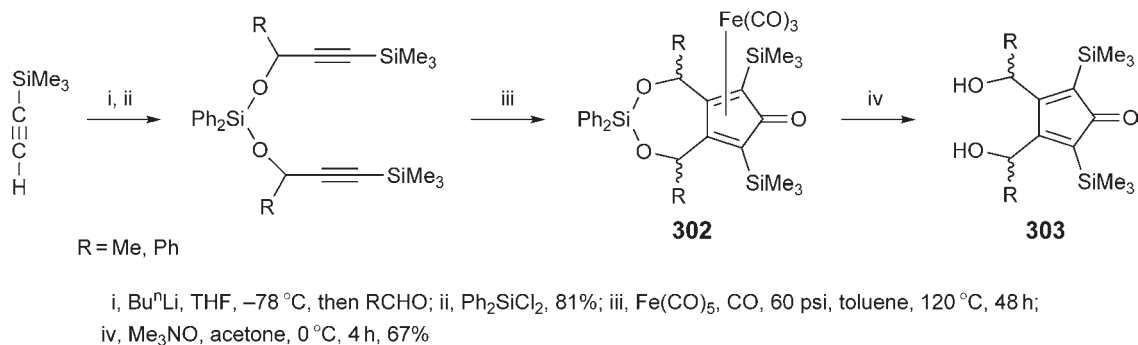


i, DIBALH, -78°C , 30 min; ii, BnNHOH, -78°C to rt; iii, $\text{ClPh}_2\text{SiCH=CH}_2$, rt, 1 h; iv, toluene, 105°C , 53 h; v, H_2O_2 , KHCO_3 , KF, MeOH-THF, rt, 2 h, then Ac_2O , THF, Et_3N , DMAP, rt, 2.5 h; vi, H_2 , $\text{Pd}(\text{OH})_2\text{-C}$, BOC_2O , EtOH, rt, 11 h

Scheme 52

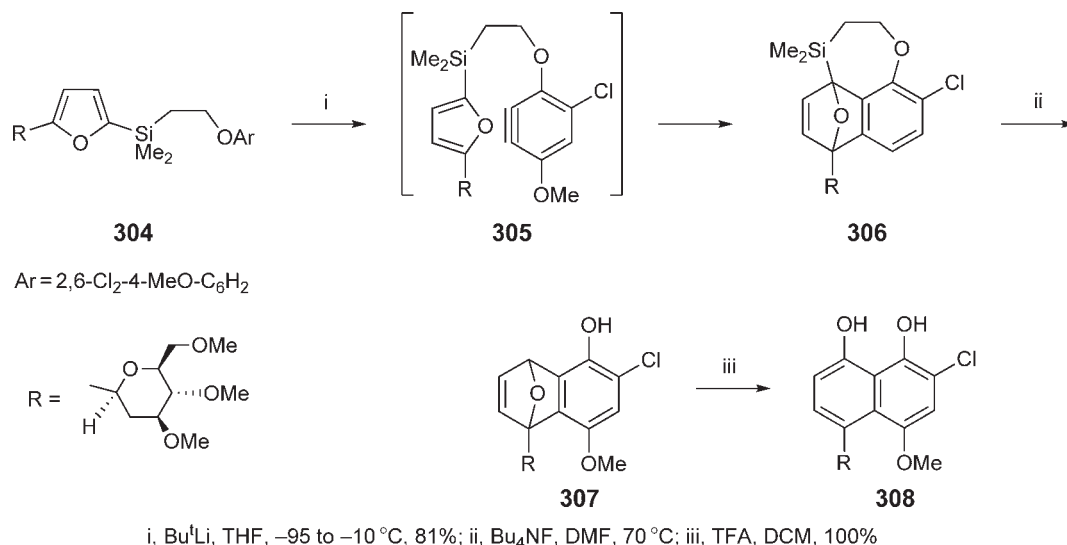


Scheme 53



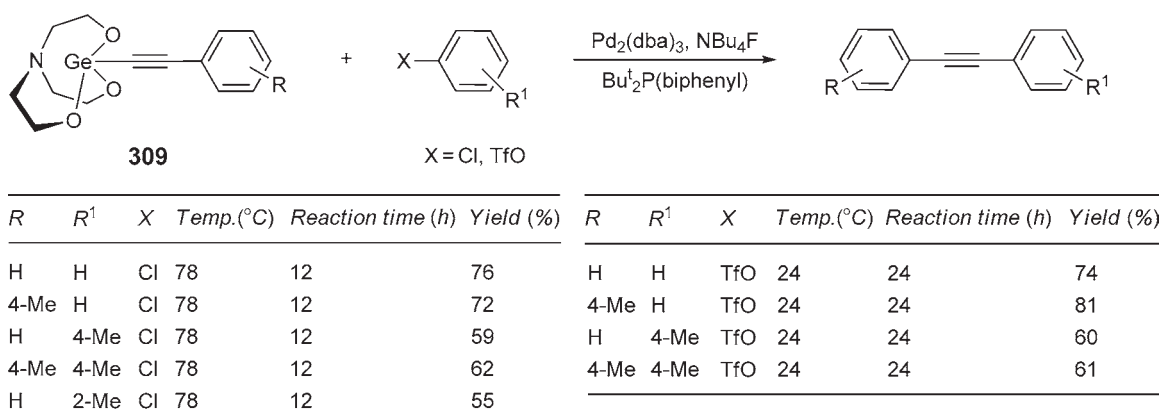
Scheme 54

Regioselective synthesis of unsymmetrical *C*-aryl glycosides using silicon tethers, as disposable linkers, has been developed (Scheme 55). Deprotonation of **304** with Bu^tLi led to the formation of an intermediate benzyne **305** that underwent cycloaddition to deliver **306**. When **306** was treated with TBAF in DMF at 70 °C, the tether was cleaved and **307** was obtained in 80% yield. The acid-catalyzed opening of the oxabicycloheptadiene ring afforded the glycosyl naphthols **308** in quantitative yield <2003JA12994>.



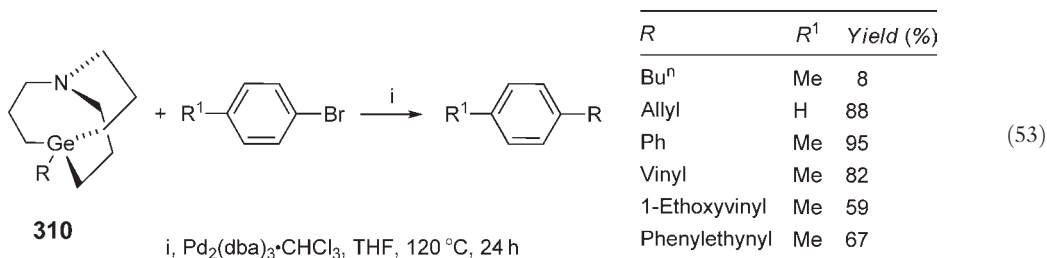
Scheme 55

The Sonogashira reaction is a powerful tool in synthesis for the preparation of arylethynyl compounds. On the other hand, organosilicon and organotin compounds can be successfully applied in cross-coupling reactions. The reactions were extended on the utility of arylalkynyl germatranes **309** as reagents for the Sonogashira-type coupling reaction using aryl chlorides and triflates as substrates (Scheme 56) <2003TL451>. In comparison with other Sonogashira-type reactions, germatrane reagents enable the reaction to proceed at lower temperatures than are required for the related reactions using triorganosilicon compounds.

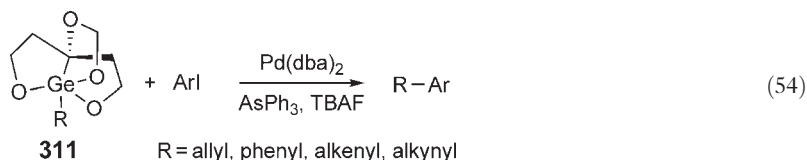


Scheme 56

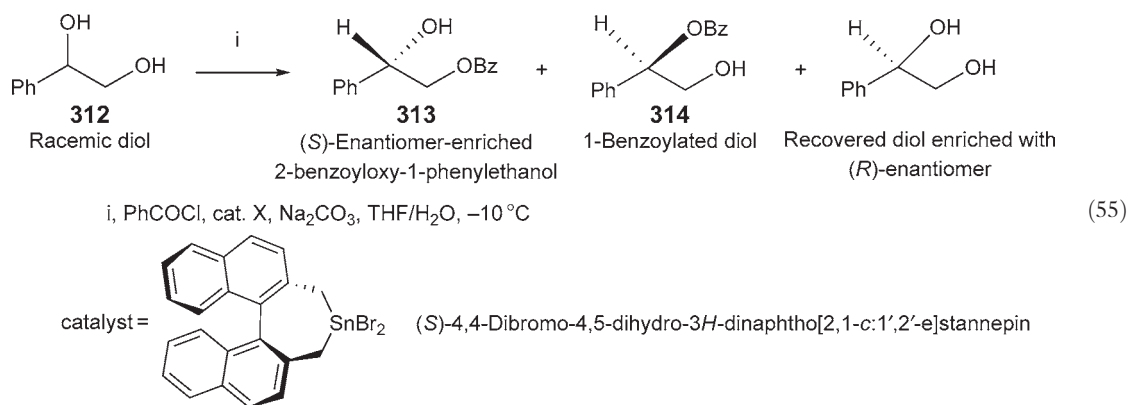
The first example of the coupling of germatranes **310** with aryl bromide has been described (Equation 53) <1996JOM255>. The cross-coupling reaction is possible due to transannular coordination of nitrogen to germanium, which enhances the reactivity of the carbon–germanium bond <2005ICC131>.



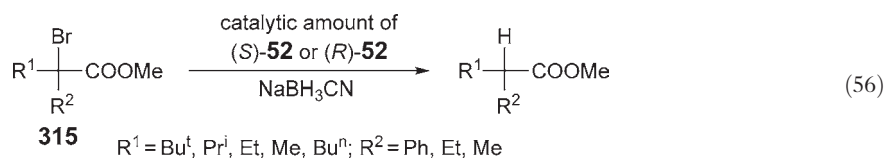
It is well known that stannanes are useful reagents in palladium-catalyzed cross-coupling reactions with aryl iodides. The potential of using organogermatranes in this analogue of Stille–Migita–Kasugi coupling [<2002ACR835, 2002CPB1531, 2006CEJ4954>](#) has been investigated [<2002OM5911>](#). The hypervalent germanium species produced from the germatranes **311** was found to provide a more efficient and more easily handled reagents than trialkylgermanium analogues ([Equation 54](#)).



The 1,1-binaphthyl ring system is a key component of a number of chiral ligands that have been used as catalysts for asymmetric synthesis [<1992S503>](#). Chemo- and stereoselective (*S*)-stannepin-catalyzed monobenzylation of terminal 1,2-diols **312** afforded (*S*)-enantiomer-enriched 2-benzoylated diols **313** in moderate selectivity. Only a trace of 1-benzoylated diols **314** was observed ([Equation 55](#)). Thus, the method was successfully applied to kinetic resolution of racemic 1-phenyl-1,2-ethanol using a chiral organotin catalyst [<2000JOC996>](#).



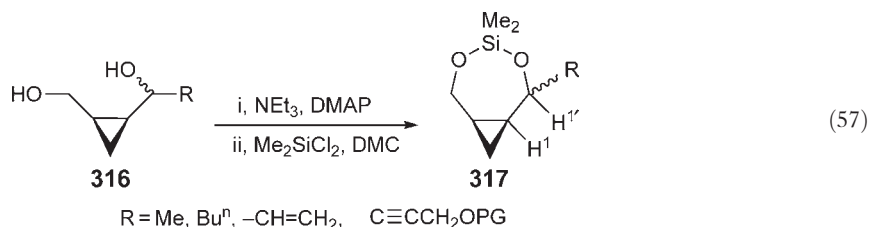
Both enantiomers of 4-*tert*-butyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]stannepin **52** were synthesized and used for the enantioselective reduction of α-bromo esters **315**. By using the achiral hydride sodium cyanoborohydride (NaBH₃CN), the radical reductions proceeded enantioselectively with only catalytic amount of chiral tin hydride ([Equation 56](#)) [<2003TA3069>](#).



The molybdenum complex Mo(NAr)(CHCMe₂Ph)[(*S*)-Me₂SiBiphen] **43** was used for catalytic asymmetric olefin metathesis reactions such as desymmetrization of trienes, kinetic resolution of allylic ethers, tandem catalytic asymmetric ring-opening metathesis/cross-metathesis. Interestingly, tandem catalytic asymmetric ring-opening

metathesis/ring-closing metathesis proceeded with an enantioselectivity comparable to that of catalyzed by $\text{Mo}(\text{NAr})(\text{CHMe}_2\text{Ph})[(S)\text{-Biphen}]$ <2001OM4705>.

A simple and reliable method, based on derivatization and NMR, for stereochemical assignment of 1,4-diols having a *cis*-2,3-methano bridge **316** has been described (Equation 57). The two protons H^1 and $\text{H}^{1'}$ always have a quasi-*trans*-diaxial relationship in the *trans*- (*anti*-)isomers of silicon derivatives **317**, and thus exhibit a larger coupling constant than the *cis*- (*syn*-)isomers <2001NJC676>.



14.19.5 Applications of Computational Methods

Computational methods have been widely used as valuable tools for structure elucidation, investigation of reaction mechanisms, and interpretation of spectroscopic data. The representative applications in the area of heterocyclic compounds described in this chapter with group 14 heteroatom are presented in Table 1.

Table 1 Applications of computational methods

Compound	Method	Problem	Reference
3	DFT, HF, ROHF, MP2, RMP2	Total energy from the optimized geometry of C_6SiH_7^+ and $\text{C}_6\text{SiH}_8^{++}$ radical cation, hydride affinity	1997JA6376
4	B3LYP/6-31G(d)	Structure optimization	2001T3645
8, 9, 10	PM3	Activation parameters for ring inversion and calculation of $\Delta\Delta H_f$	1995JOC1309
24	Combination of DFT and single excitation configuration interaction approach (DFT/SCI)	Theoretical calculation of CD spectrum, i.e., excitation energies ΔE and rotatory strengths R	1999TA3483
40	MM2 (Macromodel v. 3.0)	Conformational analysis, steric strain energy	1995JOM113
50	PM3, <i>ab initio</i> HF-default options available within the MOPAC 93	Structure optimization of the chiral tin hydride	1997AGE235
56	QCISD/3-21G*	Total energy of a singlet carbene-like structure	2003TA3069
69	PM3	Conformational analysis of the RCM reaction	2004JA2696
81	RHF/3-21G*	Calculation of orbital energies based on the optimized geometries	1999BCJ821
136, 137	B3LYP/6-31+G(dp)	Geometry optimization, electronic structure – HOMO, LUMO energy levels	1999OM3615
151	CONFLEC+PM3	Conformational analysis	2006OM48
213	MM2	Conformational analysis	2004TL4329
234	Monte Carlo style conformational search (MC), MM3	Calculation of steric energies	1999JA5413
247 (E = Si)	MM3	Conformational analysis	1998OM2656
253	B3LYP/6-31G* B3LYP/6-31+G*	Conformational analysis, electronic structure, calculation of EPR parameters	1995JOC7406
257 (R = H)	AM1 RHF/6-31G(d)	Examination of the factors that control the preference of the hydrogen for ‘inside’ vs. ‘outside’ orientation	2001JA6654
260	AM1, HF/3-21G*	Geometry optimization, conformational analysis	1994OM3728
317	AM1, PM3	Conformational analysis	1999JOC5626 2001NJC676

Perhaps the most spectacular application of quantum-chemical calculations dealt with clarification of the nature of trialkylsilicenium ion, the first long-lived chiral and highly Lewis-acidic silyl cationic catalyst claimed to be prepared in the condensed state <1998JA7637>. Initially, the ion prepared in acetonitrile solution was characterized as a nitrile-coordinated trialkylsilicenium ion **318** with the reported ^{29}Si NMR chemical shift 34.0 ppm. However, very soon this finding proved to be incorrect <1999JA9615>. Based on optimized geometries obtained at the B3LYP/6-31G* level, NMR calculations were performed using individual gauge for localized orbital (IGLO) method. The calculated ^{29}Si NMR shifts were 334.4 and 44.2 ppm for silenium ion **318** and silanitrilium ion **319**, respectively (Figure 19). The almost 300 ppm difference between the calculated and the experimentally obtained values clearly exclude the observation of a free tertiary alkylsilicenium ion **318**.

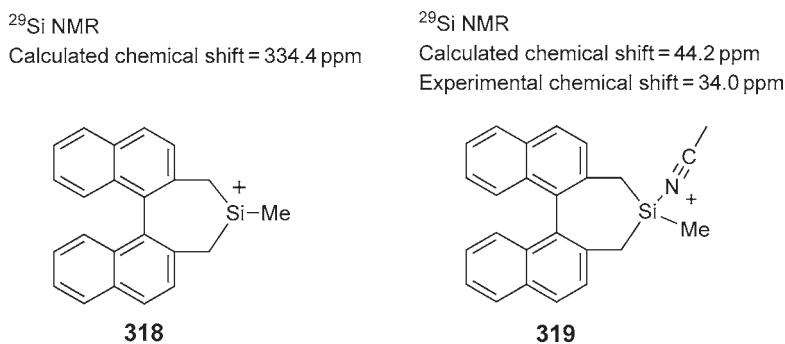
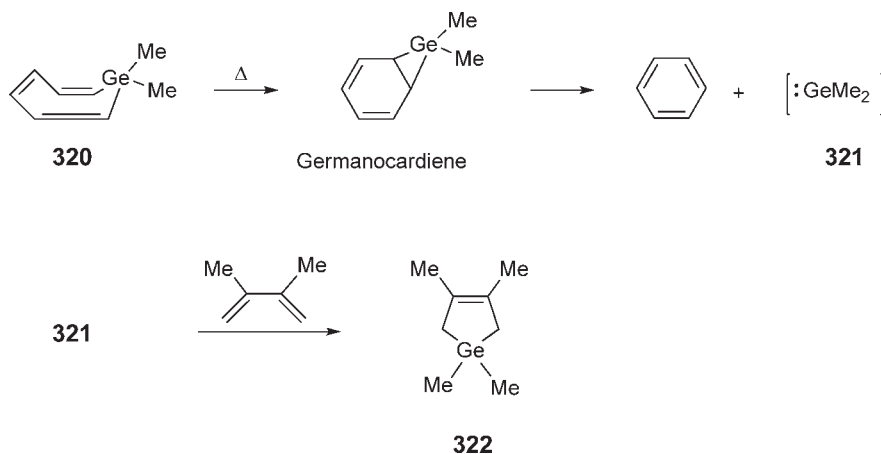


Figure 19

Computational studies have also been focused on the nature of the transannular $\text{N} \rightarrow \text{E}$ bond observed in altranenes. These studies include density functional calculations of geometrical parameters of metallatranes, where $\text{E} = \text{Si}$, Ge , Sn , and Pb <2005JMT31>, *ab initio* and DFT studies of silatranes <1996JMT199>, quantum-chemical study of silatranes and germatranes using modified neglect of diatomic overlap (MNDO), AM1, and *ab initio* methods <1999JOM205>, DFT calculations of 1-phenylethynylgermatranes <2005JST1>, DFT calculations of azametallatranes <2004JST261>, conformational analysis of silatranyl carboxylic acids <1995JST249>, and DFT calculations of *N*-methylgermocanes <2003ZNB1165>.

14.19.6 Further Developments

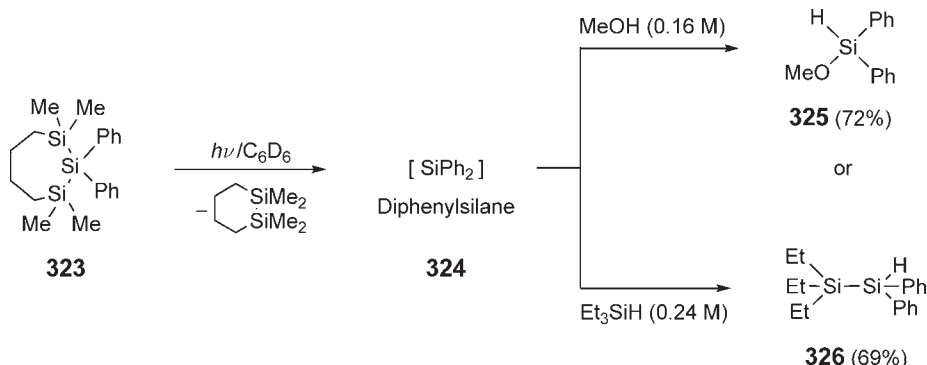
The first kinetics and mechanistic study of the thermolysis of 1,1-dimethylgermacycloheptatriene **320** (Scheme 57) was described and the relationship between the reactivity and the group 14 elements in this type of compounds was discussed <2006OM4231>. Compound **320** underwent thermolytic extrusion of divalent dimethylgermylene **321**



Scheme 57

which could be trapped with 2,3-dimethylbuta-1,3-diene to give 1,1,3,4-tetramethyl-1-germacyclopent-3-ene **322**. The progress of the thermolysis was monitored by ^1H NMR spectral measurements. The pyrolysis was observed to follow first-order kinetics. From Arrhenius plots, the activation energy of the germylene extrusion was estimated to be 21.2 ± 0.1 kcal/mol. The values of activation enthalpy ($\Delta H^\ddagger$) and the activation entropy ($\Delta S^\ddagger$) were determined to be 20.5 ± 0.1 kcal/mol and -8.1 ± 0.1 cal/(mol K), respectively. These data indicate that germacycloheptatriene **320** is the most thermally labile among metallepins containing group 14 elements.

Cyclic trisilane **323** upon steady-state photolysis (245 nm) was used for preparation of diphenylsilylene **324**, the silicon analogue of singlet diphenylcarbene <2006JA14442>. Diphenylsilylene **324** was trapped by MeOH or triethylsilane to give diphenylmethoxysilane **325** and 1,1,1-triethyl-2,2-diphenyldisilane **326** in 72 and 69% yield, respectively.



Scheme 58

All-anti-octasilane **327** (Figure 20) composed of two bicyclic trisilane units with trimethylsilyl groups at the termini was prepared and its structure was confirmed by X-ray crystal structure. The spectroscopic data demonstrated the effective σ -delocalization over the silicon framework <2006JA6800>.

Bridgehead allylsilanes **328** (Figure 20) were prepared and used for the synthesis of a variety of polyhalogenated monoterpene natural products isolated from marine algae *Plocaminium* sp. <1997JOC8962>.

Synthesis of 1-aza-5-silabicyclo[5.2.0]nonan-9-one, a silylated bicyclic lactam **329** (Figure 20) which shows antimicrobial activity against Gram positive bacteria was also achieved <1995JOC8403>.

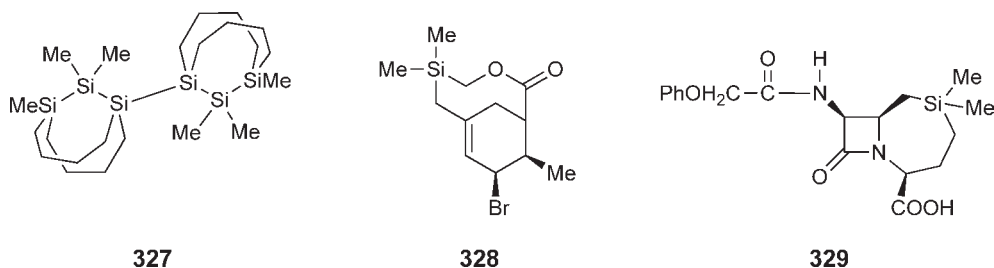
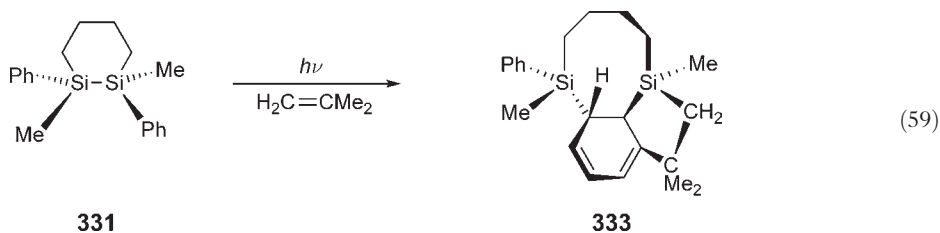
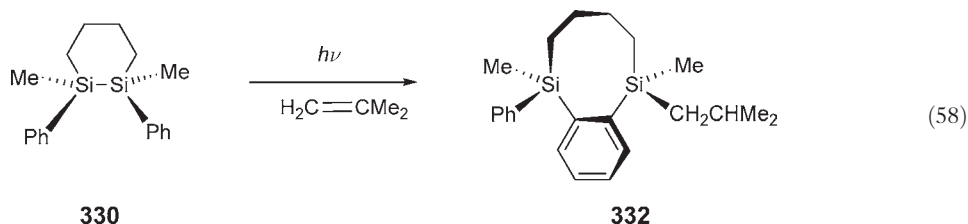
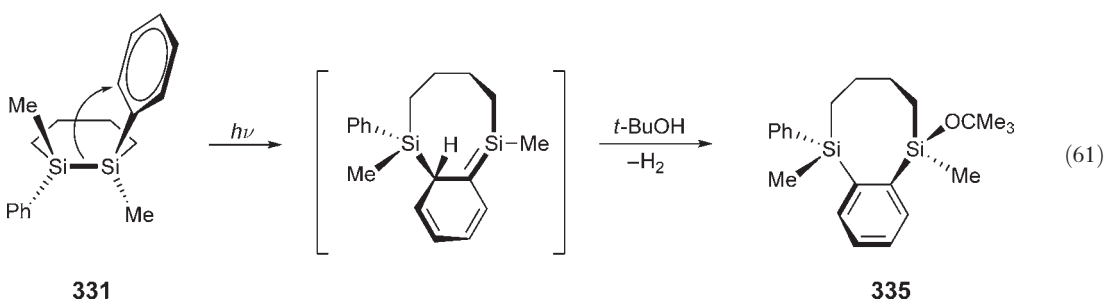
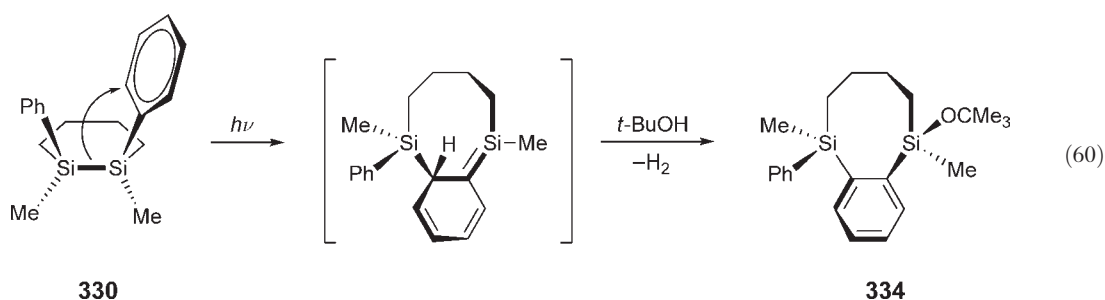


Figure 20

The photolysis of *cis*-1,2-dimethyl-1,2-diphenyl-1,2-disilacyclohexane **330** (Equation 58) affords the rearranged silene which reacts stereospecifically with isobutylene to give the ene-type adduct, *cis*-2,3-benzo-1-isobutyl-1,4-dimethyl-4-phenyl-1,4-disilaoc-2-ene **332**, while *trans*-1,2-dimethyl-1,2-diphenyl-1,2-disilacyclohexane **331** (Equation 59) gives formal [2+2] cycloadduct **333** with *trans*-configuration <2002OM4206>.



Irradiation of **330** in the presence of *tert*-butyl alcohol with low-pressure mercury lamp bearing a Vycor filter gave *cis*-2,3-benzo-1-*tert*-butoxy-1,4-dimethyl-4-phenyl-1,4-disilacyclooct-2-ene **334** in 33% yield (Equation 60), while a similar reaction of **331** led to the formation of *trans*-2,3-benzo-1-*tert*-butoxy-1,4-dimethyl-4-phenyl-1,4-disilacyclooct-2-ene **335** in 41% yield (Equation 61) <2006JOM2440>.



A new synthetic approach to functional eight-membered silicon-containing heterocycles **336** (Figure 21) have been developed. It was found that intramolecular coordination of the aminoaryl ligand enhances the reactivity of at least one of the two functionalities at the silicon atom <1997OM3878>. Reactivity and the influence of substituents on transannular interaction germanium–nitrogen in germocanes **337** (Figure 21) have also been investigated in detail <2006JOM5710>.

As shown in Equation (62), 1,2-*bis*(methylthio)benzene **338** was dimetallated using butyllithium or superbasic mixture of butyllithium/potassium *tert*-butoxide (LICKOR), and then quenched with dichlorodimethylsilane to obtain 1,5,3-benzodithiasilepin **339** <1999T14069>.

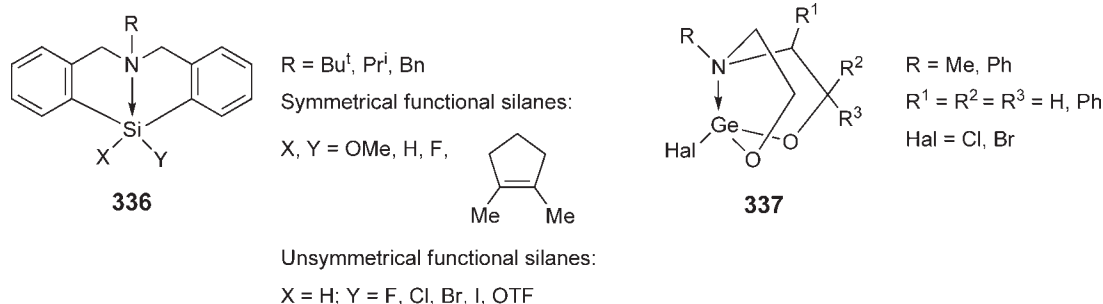
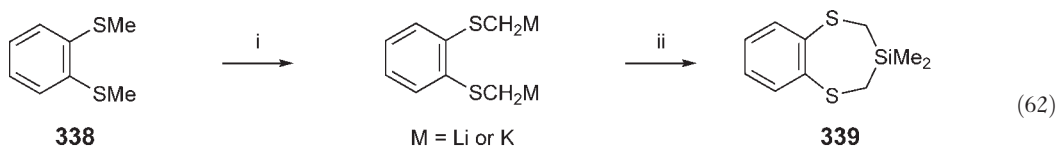
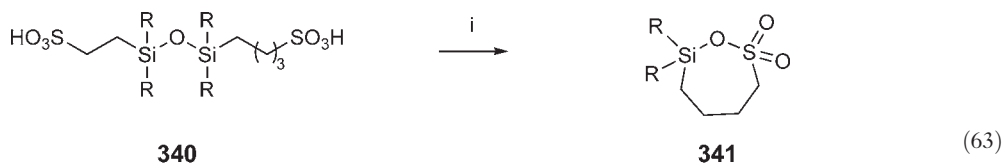


Figure 21



i, BuLi or LICKOR/hexane, -60°C , 2 h to -20°C , 1 h; ii, Cl_2SiMe_2 , -10°C , 1 h to rt, 12 h, then H_3O^+

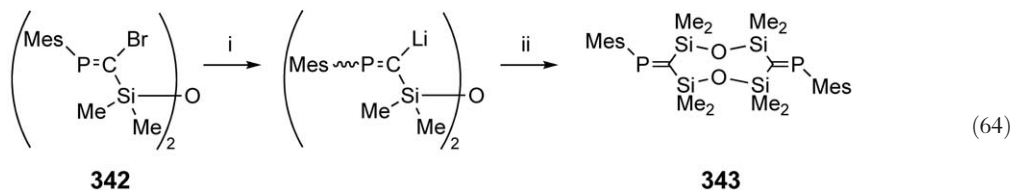
Seven-membered silasultones **341** were synthesized in good-to-moderate yields by dehydrative cyclization of disulfonic acid siloxanes **340**, carried out via vacuum sublimation (Equation 63). This method was found to be superior to attempted dehydrative cyclization of the disulfonic acids by azeotropic removal of water in refluxing toluene <2005T7233>.



$\text{R} = \text{Me}$ (48%); $\text{R} = \text{Bn}$ (45%)

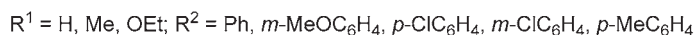
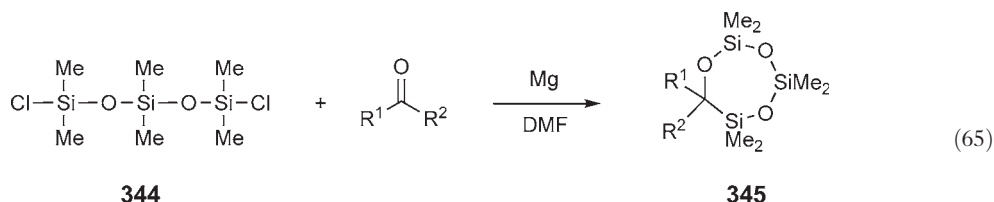
i, 0.02 mmHg, up to 250°C

Siloxane-bridged 8-membered cyclic phosphathene **343** was prepared by the reaction of bis(1-bromo-2-phosphaethenyl)disiloxane **342** with butyllithium (2 equiv) followed by treatment with 1,1,3,3-tetramethyl-1,3-dichlorosiloxane (Equation 64). Structure of **343** was confirmed by ^1H , ^{13}C (^1H) and ^{31}P (^1H) NMR spectra as well as X-ray crystallographic studies. The two $\text{MesP}=\text{C}$ groups take a *trans* configuration in the crystalline state, alleviating steric congestion <2007JOM243>.



i, 2 equiv n-BuLi, THF, -78°C ; ii, $(\text{ClSiMe}_2)_2\text{O}$, -78°C to rt, 10 min

1,5-Dichlorohexamethyltrisiloxane **344** undergoes Mg-promoted reductive coupling with aromatic carbonyl compounds such as benzaldehyde, ketones and esters to give cyclic siloxanes **345** in moderate to good yields (Equation 65). The above reaction represents an interesting example of one-pot selective formation of carbon–silicon and oxygen–silicon bonds initiated by electron transfer from Mg metal <2006T3103>.



Three series of new 8–12-membered heterocycles (Figure 22) such as 1,5-dichalcogena-3,7-siloxanes **346**, 1,6-dichalcogena-3,4,8,9-tetrasiloxanes **347** and 1,5,9-triseleno-3,7,11-trisilacyclodecanes **348** that include mixed Si–S, Sn–S, Si–Se, Sn–Se and Si–Te systems were synthesized and characterized by ^1H , ^{13}C , ^{77}Se and ^{125}Te NMR as well as X-ray crystallography. Oxidation of mixed S(Se, Te)/Si eight membered mesocycles **346** with one electron oxidant nitrosyl hexafluorophosphate (NOPF_6) or Br_2 gave dications and bicyclic dibromides, respectively, structure of which was confirmed by NMR methods <2006JA12685, 2006JA14949>.

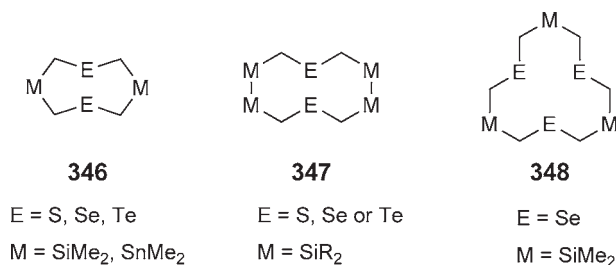
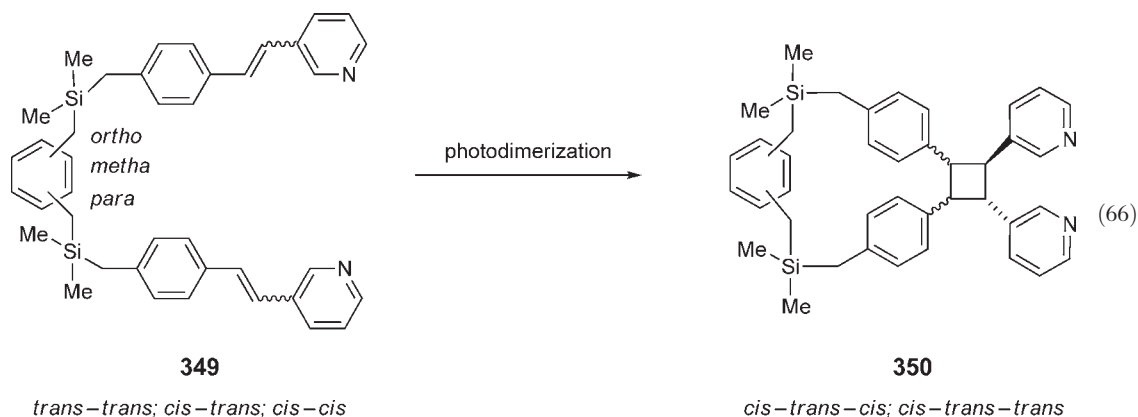


Figure 22

Silyl-tethered stilbazole derivatives **349** were synthesized and subjected to intramolecular photocycloaddition in benzene at room temperature to give compounds of type **350** with stereochemistry *cis-trans-cis* and *cis-trans-trans* (Equation 66). It was shown that complexation of pyridine-containing stilbazoles **349** with dicarboxylic acid or catechol enhanced both the efficiency and stereoselectivity of the photocycloaddition <2006TL7865>.



Acyclic disilane-containing oligoether terminated by two vinyl groups undergo ring-closure metathesis reaction (RCM) in the presence of catalytic amount of $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$ at room temperature to give 32-membered macrocycle **351** (Figure 23) in the isolated yield of 31% (*trans/cis* = 84:16) <2006JOM5260>. A double ring closure metathesis approach was also applied to the synthesis of macrocycles **352** <2006JOM5517>.

A series of axially-disubstituted silicon-phthalocyanines **353** (silicon-Pcs, **Figure 23**) was obtained by the nucleophilic displacement of one or two chlorine leaving groups from either PhSi(Pc)Cl or Si(Pc)Cl_2 , respectively, by reaction with the acid or alkoxide derivative of the ligand. Structure of these compounds was confirmed by ^1H and ^{13}C NMR, UV-vis absorption and emission spectra, electrospray or MALDI-ToF mass spectrometry as well as X-ray crystallography <2006T9433>.

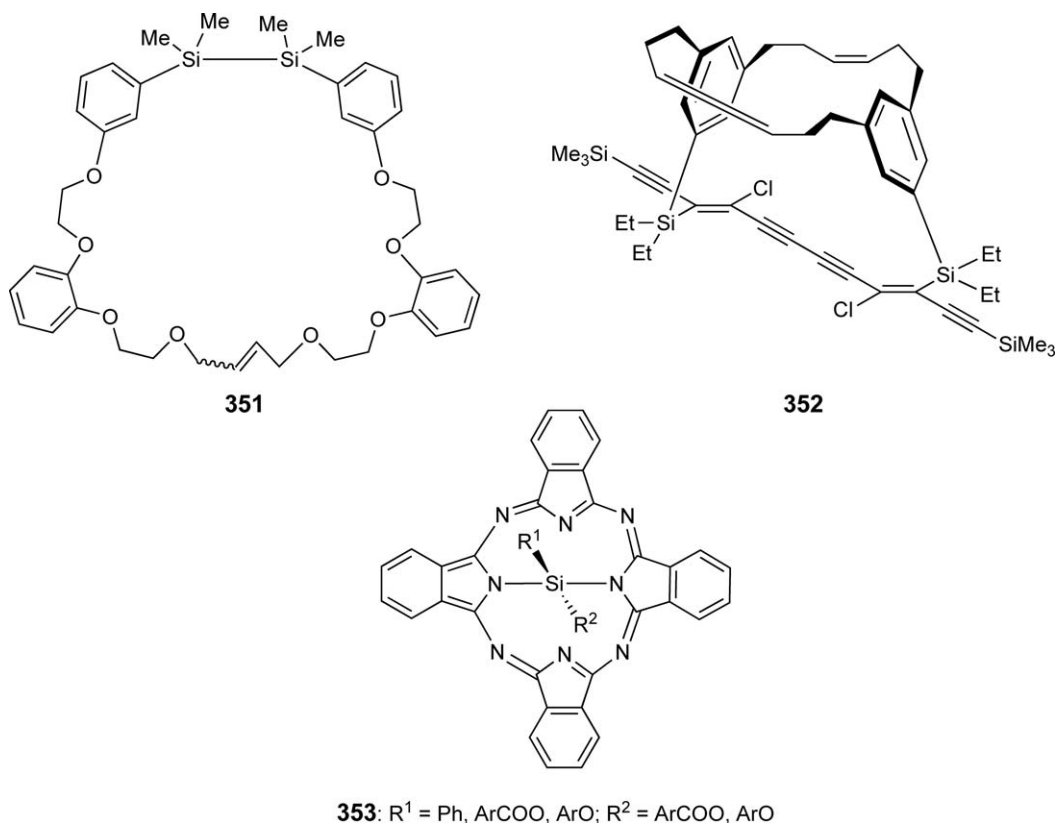


Figure 23

References

- 1985JOM33 T. Allspach, H. Gümbel, and M. Regitz, *J. Organomet. Chem.*, 1985, **290**, 33.
 1988CC1079 R. Bortolin, B. Parbhoo, and S. S. D. Brown, *J. Chem. Soc., Chem. Commun.*, 1988, 1079.
 1988JA5579 T. Hayashi, Y. Motsumoto, and Y. Ito, *J. Am. Chem. Soc.*, 1988, **110**, 5579.
 1990OS96 K. Tamao, N. Ishida, Y. Ito, and M. Kumada, *Org. Synth.*, 1990, **69**, 96.
 1991OM3173 M. Ishikawa, H. Sakamoto, and T. Tabuchi, *Organometallics*, 1991, **10**, 3173.
 1992JA7737 G. A. Olah, G. Rasul, L. Helliger, J. Baush, and G. K. S. Prakash, *J. Am. Chem. Soc.*, 1992, **114**, 7737.
 B-1992MI1 B. Marciniak, J. Guliński, W. Urbaniak, and Z. W. Korntka; in 'Comprehensive Handbook on Hydrosilylation', B. Marciniak, Ed.; Pergamon Press, Tokyo, 1992, p. 99.
 1992S503 C. Rosini, L. Franzini, A. Raffaelli, and P. Salvadori, *Synthesis*, 1992, 503.
 1993CM943 H. W. Oviatt, K. J. Shea, and J. H. Small, *Chem. Mater.*, 1993, **19**, 943.
 1993JA10805 Y. Nagano, S. Murthy, and J. L. Beauchamp, *J. Am. Chem. Soc.*, 1993, **115**, 10805.
 1994JA9769 A. Nicolaides and L. Radom, *J. Am. Chem. Soc.*, 1994, **116**, 9769.
 1994OM3728 W. R. Kwochka, R. Damrauer, M. W. Schmidt, and M. S. Gordon, *Organometallics*, 1994, **13**, 3728.
 1994OM4148 M. Sugimoto, H. Oike, and Y. Ito, *Organometallics*, 1994, **13**, 4148.
 1995AOM121 G. K. Sandhu and R. Hundal, *Appl. Organomet. Chem.*, 1995, **9**, 121.
 1995CCR157 K. M. Baines and W. G. Stibbs, *Coord. Chem. Rev.*, 1995, **145**, 157.
 1995CRV813 L. Fensterbank, M. Malacria, and S. McN. Sieburth, *Chem. Rev.*, 1995, **95**, 813.
 1995JA1665 M. Sugimoto, H. Oike, and Y. Ito, *J. Am. Chem. Soc.*, 1995, **117**, 1665.
 1995JA2187 S. Kobayashi, S. Iwata, M. Abe, and S. Shoda, *J. Am. Chem. Soc.*, 1995, **117**, 2187.
 1995JA6797 T. Oijima, E. Vidal, M. Tzamarioudaki, and I. Matsuda, *J. Am. Chem. Soc.*, 1995, **117**, 6797.

- 1995JCD1893 D. L. Zechel, D. A. Foucher, J. K. Pudelski, G. P. A. Yap, A. L. Rheingold, and I. Manners, *J. Chem. Soc., Dalton Trans.*, 1995, 1893.
- 1995JOC1309 T. Nishinaga, K. Komatsu, and N. Suita, *J. Org. Chem.*, 1995, **60**, 1309.
- 1995JOC7406 B. König, M. Rödel, and P. Bubenitschek, *J. Org. Chem.*, 1995, **60**, 7406.
- 1995JOC8403 M. Altamura, M. Giammaruco, M. Taddei, and P. Ulivi, *J. Org. Chem.*, 1995, **60**, 8403.
- 1995JOM113 J. Y. Corey, A. J. Pitts, R. E. K. Winter, and N. P. Rath, *J. Organomet. Chem.*, 1995, **499**, 113.
- 1995JOM213 V. Jouikov and V. Krasnov, *J. Organomet. Chem.*, 1995, **498**, 213.
- 1995JOM29 K. Rühlmann, S. Jähnichen, U. Scheim, D. Scheller, and F. Keidel, *J. Organomet. Chem.*, 1995, **505**, 29.
- 1995JPP07126394 K. Okada, T. Fujisaka, and B. Yamaguchi (Sekisui Chemical Co. Ltd.), *Jpn Pat.* 07 126 394 (*Chem. Abstr.*, 1995, **123**, 84375).
- 1995JST249 X. Zhang, S. Mao, L. Shen, C. Ye, R. Zhou, Z. Lu, and G. A. Webb, *J. Mol. Struct.*, 1995, **372**, 249.
- 1995OM1089 E. Toyoda, A. Kunani, and M. Ishikawa, *Organometallics*, 1995, **14**, 1089.
- 1995OM2556 T. Kusukawa, Y. Kabe, B. Nestler, and W. Ando, *Organometallics*, 1995, **14**, 2556.
- 1995OM3625 W. Ando, K. Hatano, and R. Urisaka, *Organometallics*, 1995, **14**, 3625.
- 1995TL4603 R. Gleiter, H. Stahr, F. Stadtmüller, H. Imgartinger, and H. Pritzkow, *Tetrahedron Lett.*, 1995, **36**, 4603.
- 1995TL4607 R. Gleiter, H. Stahr, and B. Nuber, *Tetrahedron Lett.*, 1995, **36**, 4607.
- 1996IC4342 T. K. Prakasha, A. Chandrasekaran, R. O. Day, and R. R. Holmes, *Inorg. Chem.*, 1996, **35**, 4342.
- 1996JA501 D. A. Loy, J.-P. Carpenter, S. A. Myers, R. A. Assink, J. H. Small, and J. Greaves, *J. Am. Chem. Soc.*, 1996, **118**, 8501.
- 1996JCD3595 Ch. Dorst, P. B. Hitchcock, and M. F. Lappert, *J. Chem. Soc., Dalton Trans.*, 1996, 3595.
- 1996JMT199 G. I. Csonka and P. Hencsei, *J. Mol. Struct. Theochem*, 1996, **362**, 199.
- 1996JOM255 M. Kosugi, T. Tanji, Y. Tanaka, A. Yoshida, K. Fugami, M. Kameyama, and T. Migita, *J. Organomet. Chem.*, 1996, **508**, 255.
- 1996JOM15 F. Fabris and O. De Lucchi, *J. Organomet. Chem.*, 1996, **509**, 15.
- 1996JOM29 W. Zeiche, B. Ziemer, P. John, J. Weis, and N. Auner, *J. Organomet. Chem.*, 1996, **521**, 29.
- 1996JOM335 Y. Uchimaru and M. Tanaka, *J. Organomet. Chem.*, 1996, **521**, 335.
- 1996JOM41 E. Lukevics, S. Belyakov, and O. Pudova, *J. Organomet. Chem.*, 1996, **523**, 41.
- 1996KGS1590 K. Rühlmann, S. Jähnichen, U. Scheim, and D. Scheller, *Khim. Geterotsikl. Soedin.*, 1996, 1590.
- 1996OM1651 C. Eaborn, Z. R. Lu, P. B. Hitchcock, and J. D. Smith, *Organometallics*, 1996, **15**, 1651.
- 1996OM2014 H. Komoriya, M. Kako, and Y. Nakadaira, *Organometallics*, 1996, **15**, 2014.
- 1996POL4311 J. Manners, *Polyhedron*, 1996, **15**, 4311.
- 1996TL6781 K. Takaku, H. Shinokube, and K. Oshima, *Tetrahedron Lett.*, 1996, **37**, 6781.
- 1997AGE159 A. Krebs, K.-I. Pförr, W. Raffay, B. Thölke, W. A. König, and R. Boesse, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 159.
- 1997AGE235 M. Blumenstein, K. Schwarzkopf, and J. O. Metzger, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 235.
- 1997AGE2426 R. Gleiter and M. Merger, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2426.
- 1997BCJ2255 H. Shinokubo, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 2255.
- 1997CB421 B. König and M. Rödel, *Chem. Ber.*, 1997, **130**, 421.
- 1997CB739 G. S. Zaitseva, L. I. Livantsova, M. Nasim, E. V. Avtomonov, and J. Lorberth, *Chem. Ber.*, 1997, **130**, 739.
- 1997CB923 B. Schilling, V. Kaiser, and D. E. Kaufmann, *Chem. Ber.*, 1997, **130**, 923.
- 1997CB1807 H. Stahr, R. Gleiter, G. Haberhauer, H. Imgartinger, and T. Oeser, *Chem. Ber.*, 1997, **130**, 1807.
- 1997CSR453 G. Rousseau and F. Homs, *Chem. Soc. Rev.*, 1997, **26**, 453.
- 1997ICA11 J. Barrau, G. Rima, A. Akkari, and J. Satgé, *Inorg. Chim. Acta*, 1997, **260**, 11.
- 1997JA6376 R. J. Jarek and S. K. Shin, *J. Am. Chem. Soc.*, 1997, **119**, 6376.
- 1997JOC4206 K. Tanino, N. Yoshitani, F. Moriyama, and I. Kuwajima, *J. Org. Chem.*, 1997, **62**, 4206.
- 1997JOC7156 F. Fabris and O. De Lucchi, *J. Org. Chem.*, 1997, **62**, 7156.
- 1997JOC8962 J. M. Whitney, J. S. Parnes, and K. J. Shea, *J. Org. Chem.*, 1997, **62**, 8962.
- 1997MGM573 B. Wrackmeyer, G. Kehr, and D. Wöttinger, *Main Group Met. Chem.*, 1997, **20**, 573.
- 1997MGM775 J. Hockenmeyer, B. Valentin, A. Castel, P. Rivère, J. Sagté, C. J. Cardin, and S. Teixeira, *Main Group Met. Chem.*, 1997, **20**, 775.
- 1997MGM791 D. Augustin, G. Rima, and J. Barrau, *Main Group Met. Chem.*, 1997, **20**, 791.
- 1997OM646 R. Gleiter, H. Stahr, and B. Nuber, *Organometallics*, 1997, **16**, 646.
- 1997OM3878 F. H. Carre, R. J. P. Corriu, G. F. Lanneau, P. Merle, F. Soulaire, and J. Yao, *Organometallics*, 1997, **16**, 3878.
- 1997OM4839 W. P. Leung, K. S. M. Poon, T. C. W. Mak, R. J. Wang, and Z. Y. Zhou, *Organometallics*, 1997, **16**, 4839.
- 1997OM5621 C. Eaborn, T. Ganicz, P. B. Hitchcock, D. J. Smith, and S. E. Sözerli, *Organometallics*, 1997, **16**, 5621.
- 1997SL1208 R. Dogbeva and L. Breau, *Synlett*, 1997, 1208.
- 1997T9935 W. Kirmse, W. Konrad, and I. S. Özkir, *Tetrahedron*, 1997, **53**, 9935.
- 1997TL4757 C. Chang and R. H. Grubbs, *Tetrahedron Lett.*, 1997, **38**, 4757.
- 1997TL7861 C. Meyer and J. Cosby, *Tetrahedron Lett.*, 1997, **38**, 7861.
- 1997TL8679 G. Haberhauer, R. Roers, and R. Gleiter, *Tetrahedron Lett.*, 1997, **38**, 8679.
- 1997ZFA1144 G. S. Zaitseva, A. V. Avtomonov, and J. Lorberth, *Z. Anorg. Allg. Chem.*, 1997, **623**, 1144.
- 1997ZNB30 G. S. Zaitseva, S. S. Karlov, E. S. Alekseyeva, L. A. Aslanov, E. V. Avtomotov, and J. Lorberth, *Z. Naturforsch., B.*, 1997, **52**, 30.
- 1998AGE1662 A. Sekiguchi, T. Matsuo, and H. Sakurai, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1662.
- 1998AXC1425 O. Gausset, G. Delpon-Loaze, M. Schurmann, and K. Juckchat, *Acta Crystallogr., Sect. C*, 1998, **54**, 1425.
- 1998BCJ1705 T. Matsuo, A. Sekiguchi, M. Ichinohe, K. Ebata, and H. Sakurai, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1705.
- 1998CC699 T. Mise, Y. Takaguchi, T. Umemiya, S. Shimizu, and Y. Wakatsuki, *Chem. Commun.*, 1998, 699.
- 1998CC767 H. Sashida, A. Kuroda, and T. Tsuchiya, *Chem. Commun.*, 1998, 767.
- 1998CL1101 T. Matsuo, H. Fure, and A. Sekiguchi, *Chem. Lett.*, 1998, 1101.
- 1998JA6421 S. Dell, N. J. Vogelaar, D. M. Ho, and R. A. Pascal, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 6421.
- 1998JA7637 M. Johansen, K. A. Jorgensen, and G. Helmchen, *J. Am. Chem. Soc.*, 1998, **120**, 7637.
- 1998JOC6768 P. A. Evans and V. S. Murthy, *J. Org. Chem.*, 1998, **63**, 6768.
- 1998OM1517 V. Y. Lee, H. Ranaivonjatovo, J. Escudie, J. Satge, A. Dubourg, J.-P. Declercq, M. P. Egorov, and O. M. Nefedov, *Organometallics*, 1998, **17**, 1517.
- 1998OM2656 B. Rezzonico, M. Grignon-Dubois, M. Laguerre, and J.-M. Léger, *Organometallics*, 1998, **17**, 2656.

- 1998OM4267 L. Giraud and T. Jenny, *Organometallics*, 1998, **17**, 4267.
- 1998SCI1587 N. Avarvari, N. Mezaillies, L. Ricard, P. Le Floch, and F. Mathey, *Science*, 1998, **280**, 1587.
- 1998T2289 D. R. Gauthier, K. S. Zandi, and K. J. Shea, *Tetrahedron*, 1998, **54**, 2289.
- 1998ZNB1247 G. S. Zaitseva, S. S. Karlov, B. A. Siggelkov, E. V. Avtomonov, A. V. Churakov, J. A. K. Howard, and J. Lorbeth, *Z. Naturforsch., B*, 1998, **53**, 1247.
- 1999AGE124 B. Wrackmeyer, O. L. Tok, and Y. N. Bubnov, *Angew. Chem., Int. Ed.*, 1999, **38**, 124.
- 1999BCJ821 T. Hoshi, H. Yasuda, T. Sanji, and H. Sakurai, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 821.
- 1999CC1981 T. Matsuo, H. Fure, and A. Sekiguchi, *Chem. Commun.*, 1999, 1981.
- 1999CEJ2109 N. Avarvari, N. Maigrot, L. Ricard, F. Mathey, and P. Le Floch, *Chem. Eur. J.*, 1999, **5**, 2109.
- 1999CPB1108 S. Yasuike, S. Shiratori, J. Kurita, and T. Tsuchiya, *Chem. Pharm. Bull.*, 1999, **47**, 1108.
- 1999CRV3463 P. P. Power, *Chem. Rev.*, 1999, **99**, 3463.
- 1999EJI373 M. Weidenbruch, *Eur. J. Inorg. Chem.*, 1999, 373.
- 1999ICA252 P. McArdle, L. O'Neill, and D. Cunningham, *Inorg. Chim. Acta*, 1999, **291**, 252.
- 1999JA5001 J. B. Lambert, Y. Zhao, H. Wu, W. C. Tse, and B. Kuhlmann, *J. Am. Chem. Soc.*, 1999, **121**, 5001.
- 1999JA5413 D. A. Loy, J.-P. Carpenter, T. M. Alam, R. Shaltout, P. K. Dorhout, J. Greaves, J. H. Small, and K. J. Shea, *J. Am. Chem. Soc.*, 1999, **121**, 5413.
- 1999JA9615 G. A. Olah, G. Rasul, and G. K. S. Prakash, *J. Am. Chem. Soc.*, 1999, **121**, 9615.
- 1999JOC5626 S. Dell, D. M. Ho, and R. A. Pascal, Jr., *J. Org. Chem.*, 1999, **64**, 5626.
- 1999JOM205 S. Belyakov, L. Ignatovich, and E. Lukevics, *J. Organomet. Chem.*, 1999, **377**, 205.
- 1999JOM241 M. Itoh, K. Iwata, and M. Kobayashi, *J. Organomet. Chem.*, 1999, **574**, 241.
- 1999(P2)2093 G. Haberhauer, R. Gleiter, H. Irngartinger, T. Oesner, and F. Rominger, *J. Chem. Soc., Perkin Trans. 2*, 1999, 2093.
- 1999MGM703 D. Augustin, G. Rima, H. Gomitzka, and J. Barrau, *Main Group Met. Chem.*, 1999, **22**, 703.
- 1999OM1465 M. Yoshida, M. Goto, and F. Nakanishi, *Organometallics*, 1999, **18**, 1465.
- 1999OM1818 Y. Kang, S. O. Kang, and J. Ko, *Organometallics*, 1999, **18**, 1818.
- 1999OM2342 E. Eaborn, M. S. Hill, P. B. Hitchcock, D. J. Smith, and S. Zhang, *Organometallics*, 1999, **18**, 2342.
- 1999OM3615 R. Gleiter, G. Haberhauer, H. Irngartinger, T. Oeser, and F. Rominger, *Organometallics*, 1999, **18**, 3615.
- 1999OM3792 S. Tsutsui, E. Toyoda, T. Hamaguchi, J. Ohshita, F. Kanetani, and A. Kunai, *Organometallics*, 1999, **18**, 3792.
- 1999S921 H. Sashida and A. Kudoda, *Synthesis*, 1999, 921.
- 1999T14069 M. G. Cabiddu, S. Cabiddu, E. Cadoni, S. De Montis, C. Fattuoni, S. Melis, and F. Sotgiu, *Tetrahedron*, 1999, **55**, 14069.
- 1999TA3483 A. W. Krebs, B. Thölke, K.-I. Pförr, W. A. König, K. Schwarwächter, S. Grimme, F. Vögtle, A. Sobanski, J. Schramm, and J. Hormes, *Tetrahedron Asymmetry*, 1999, **10**, 3483.
- 1999TL185 S. V. Kirpichenko, E. N. Suslova, A. I. Albanov, and B. A. Shinyan, *Tetrahedron Lett.*, 1999, **40**, 185.
- 1999TL1429 T. R. Hoye and M. A. Promo, *Tetrahedron Lett.*, 1999, **40**, 1429.
- 1999ZFA655 G. S. Zaitseva, S. S. Karlov, G. V. Peñkovoy, A. V. Churakov, J. A. K. Howard, B. A. Siggelkov, E. V. Avtomonov, and J. Lorbeth, *Z. Anorg. Allg. Chem.*, 1999, **625**, 655.
- 1999ZOB518 G. S. Zaitseva, S. S. Karlov, P. L. Shutov, B. A. Siggelkov, and J. Lorbeth, *Zh. Obshch. Khim.*, 1999, **69**, 518.
- 2000BCJ2129 T. Matsuo, H. Fure, and A. Sekiguchi, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 2129.
- 2000H(53)49 H. Sashida, *Heterocycles*, 2000, **53**, 49.
- 2000JA7633 T. Ishikawa, T. Kudo, K. Shigemori, and S. Saito, *J. Am. Chem. Soc.*, 2000, **122**, 7633.
- 2000JA9312 T. Nishinaga, Y. Izukawa, and K. Komatsu, *J. Am. Chem. Soc.*, 2000, **122**, 9312.
- 2000JOC996 F. Iwasaki, T. Maki, O. Onomura, W. Nakashima, and Y. Matsumura, *J. Org. Chem.*, 2000, **65**, 996.
- 2000JOC8919 T. Sudo, N. Asao, and Y. Yamamoto, *J. Org. Chem.*, 2000, **65**, 8919.
- 2000JOM387 S. S. Karlov, P. L. Shutov, and G. S. Zaitseva, *J. Organomet. Chem.*, 2000, **598**, 387.
- 2000JOM12 M. Shimizu, T. Hiyama, T. Matsubara, and T. Yamabe, *J. Organomet. Chem.*, 2000, **611**, 12.
- 2000JOM420 H. Komoriya, M. Kako, Y. Nakadaira, and K. Mochida, *J. Organomet. Chem.*, 2000, **611**, 420.
- 2000(JPI)1965 H. Sashida and A. Kuroda, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1965.
- 2000OM430 R. Altmann, O. Gausset, D. Horn, K. Jurkschat, and M. Schurmann, *Organometallics*, 2000, **19**, 430.
- 2000OM1190 C. Eaborn, P. B. Hitchcock, D. J. Smith, and S. Zhang, *Organometallics*, 2000, **19**, 1190.
- 2000T4139 G. Mass and V. Gettwert, *Tetrahedron*, 2000, **56**, 4139.
- 2000TL2079 H. Zhang, K. T. Lam, Y. L. Chen, T. Mo, C. C. Kwok, W. Y. Wong, M. S. Wong, and A. W. M. Lee, *Tetrahedron Lett.*, 2002, **43**, 2079.
- 2001IC3830 S. T. Pastor, A. Carinci, N. Khoury, and D. N. Rahni, *Inorganic Chem.*, 2001, **40**, 3830.
- 2001JA6654 L. Cataldo, S. Choua, T. Berclaz, M. Geoffroy, N. Mezaillies, L. Ricard, F. Mathey, and P. La Floch, *J. Am. Chem. Soc.*, 2001, **123**, 6654.
- 2001JOC1054 N. Mezaillies, N. Maigrot, S. Hamon, L. Ricard, F. Mathey, and P. Le Floch, *J. Org. Chem.*, 2001, **66**, 1054.
- 2001JOC1216 G. W. Wijsman, G. A. Iglesias, M. C. Beekman, W. H. de Wolf, F. Bickelhaupt, H. Kooijman, and A. L. Spek, *J. Org. Chem.*, 2001, **66**, 1216.
- 2001JOM274 J. Aznar, E. Cerrada, M. B. Hursthouse, M. Laguna, C. Pozo, and M. P. Romero, *J. Organomet. Chem.*, 2001, **622**, 274.
- 2001JOM160 I. Ahmad, M. L. Falck-Pedersen, and K. Undheim, *J. Organomet. Chem.*, 2001, **625**, 160.
- 2001JOM63 M. Kako, M. Ninomiya, M. Gu, Y. Nakadaira, M. Wakasa, H. Hayashi, T. Akasaka, and T. Wakahara, *J. Organomet. Chem.*, 2001, **636**, 63.
- 2001MGM363 P. Coelho and L. Blanco, *Main Group Met. Chem.*, 2001, **24**, 363.
- B-2001MI1 In 'The Chemistry of Silicon Compounds', Z. Rapoport and Y. Apeloig, Eds.; Wiley, Chichester, 2001.
- 2001NJC676 A. Benkouider, J. Bouquant, and P. Pale, *New J. Chem.*, 2001, **25**, 676.
- 2001OL2157 B. A. Harrison and G. L. Verdine, *Org. Lett.*, 2001, **3**, 2157.
- 2001OM749 M. Saito, M. Nitta, and M. Yoshioka, *Organometallics*, 2001, **20**, 749.
- 2001OM1204 A. Naka, K. Yoshida, M. Ishikawa, I. Miyahara, K. Hirotsu, S.-H. Cha, K. K. Lee, and Y. W. Kwak, *Organometallics*, 2001, **20**, 1204.
- 2001OM4705 K. C. Haltzsch, P. J. Bonitatebus, J. Jernelius, R. R. Schrock, and A. H. Hoveyda, *Organometallics*, 2001, **20**, 4705.

- 2001OM5537 K. H. Song, I. Jung, S. S. Lee, K.-M. Park, M. Ishikawa, S. O. Kang, and J. Ko, *Organometallics*, 2001, **20**, 5537.
- 2001SL1038 D. P. Curran and G. Gualtieri, *Synlett*, 2001, 1038.
- 2001T3645 T. Nishinaga, Y. Izukawa, and K. Komatsu, *Tetrahedron*, 2001, **57**, 3645.
- 2001T7237 W. Zhang, *Tetrahedron*, 2001, **57**, 7237.
- 2001TL239 J.-G. Boiteau, P. Van de Weghe, and J. Eustache, *Tetrahedron Lett.*, 2001, **42**, 239.
- 2001ZFA1 S. S. Karlov, P. L. Shutov, A. V. Churakov, J. Lorberth, and G. S. Zaitseva, *Z. Anorg. Allg. Chem.*, 2001, **627**, 1.
- 2001ZOB1979 S. W. Kirpichenko, A. T. Abrosimova, A. I. Albanov, and M. G. Woronkov, *Zh. Obshch. Khim.*, 2001, **71**, 1979.
- 2002ACR835 S. E. Denmark and R. F. Sweis, *Acc. Chem. Res.*, 2002, **35**, 835.
- 2002AG1825 J. Wagler, U. Böhme, and G. Roewer, *Angew. Chem.*, 2002, **114**, 1825.
- 2002AOM481 M. Gielen, *Appl. Organomet. Chem.*, 2002, **16**, 481.
- 2002CCR47 S. O. Kang, J. Lee, and J. Ko, *Coord. Chem. Rev.*, 2002, **231**, 47.
- 2002CPB1531 S. E. Denmark and R. F. Sweis, *Chem. Pharm. Bull.*, 2002, **50**, 1531.
- 2002IJB419 M. S. Singh and K. Tawade, *Indian. J. Chem., Sect. B*, 2002, **41**, 419.
- 2002JA2868 A. F. Kiely, J. A. Jernelius, R. R. Schrock, and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2002, **124**, 2868.
- 2002JCD2467 C. Eaborn, M. S. Hill, P. B. Hitchcock, and J. D. Smith, *J. Chem. Soc., Dalton Trans.*, 2002, 2467.
- 2002JOC8906 B. Ding, Z. Teng, and R. Keese, *J. Org. Chem.*, 2002, **67**, 8906.
- 2002KGS127 O. A. Zamyshlaeva, A. G. Shipov, E. P. Kramarova, W. W. Negrebeckiy, S. N. Tandura, S. Y. Bylkin, Y. E. Shumskiy, S. A. Pogozhik, and Y. I. Baukov, *Khim. Geterotsikl. Soedin.*, 2002, 127.
- 2002OL2837 A. J. Pearson and J. B. Kim, *Org. Lett.*, 2002, **4**, 2837.
- 2002OM2430 A. Asadi, C. Eaborn, M. S. Hill, P. B. Hitchcock, M. M. Meehan, and J. D. Smith, *Organometallics*, 2002, **21**, 2430.
- 2002OM3675 L. F. Tang, J. F. Chai, Z.-H. Wang, W.-L. Jia, and J.-T. Wang, *Organometallics*, 2002, **21**, 3675.
- 2002OM4206 M. Ishikawa, S. Shirai, A. Naka, H. Kobayashi, J. Ohshita, A. Kunai, Y. Yamamoto, S.-H. Cha, K. K. Lee, and Y.-W. Kwak, *Organometallics*, 2002, **21**, 4206.
- 2002OM5911 J. W. Faller and R. G. Kulytshev, *Organometallics*, 2002, **21**, 5911.
- 2002TL9203 H. van Leeuwen, P. J. L. M. Quaedfleig, Q. B. Broxterman, and R. M. J. Liskamp, *Tetrahedron Lett.*, 2002, **43**, 9203.
- 2003AGE1732 J. Wagler, U. Böhme, and G. Roewer, *Angew. Chem. Int. Ed.*, 2003, **41**, 1732.
- 2003AGE1734 P. A. Evans, J. Cui, and G. P. Buffone, *Angew. Chem., Int. Ed.*, 2003, **42**, 1734.
- 2003COR691 B. Marciniak and C. Pietraszuk, *Curr. Org. Chem.*, 2003, **7**, 691.
- 2003EJOC3051 C. Schaefer, R. Gleiter, and F. Rominger, *Eur. J. Org. Chem.*, 2003, 3051.
- 2003JA12994 D. E. Kaelin, Jr., S. M. Sparks, H. R. Plake, and S. F. Martin, *J. Am. Chem. Soc.*, 2003, **125**, 12994.
- 2003JOC5013 G. Gualtieri, S. J. Geib, and D. P. Curran, *J. Org. Chem.*, 2003, **68**, 5013.
- 2003JOM8 E. V. Gauchenova, S. S. Karlov, A. A. Selina, E. S. Cherenyshova, A. V. Churakov, J. A. K. Howard, N. A. Troitsky, S. N. Tandura, J. Lorberth, and G. S. Zaitseva, *J. Organomet. Chem.*, 2003, **676**, 8.
- 2003JOM57 L.-F. Tang, J.-F. Chai, S.-B. Zhao, and J.-T. Wang, *J. Organomet. Chem.*, 2003, **669**, 57.
- 2003JOM66 N. Nakata, N. Takeda, and N. Tokitoh, *J. Organomet. Chem.*, 2003, **672**, 66.
- 2003JOM61 Y. Takeuchi, Y. Suzuki, F. Ono, and K. Manabe, *J. Organomet. Chem.*, 2003, **678**, 61.
- B-2003MI317 J. Wagler, U. Böhme, and G. Roewer, in 'Organosilicon Chemistry V: From Molecules to Materials', N. Auner and J. Weis, Eds.; Wiley-VCH, Weinheim, 2003, p. 317.
- 2003OM1302 G. Ramaker, A. Schäfer, W. Saak, and M. Weidenbruch, *Organometallics*, 2003, **22**, 1302.
- 2003OM1603 M. S. Samuel, H. A. Jenkins, D. W. Hughes, and K. M. Baines, *Organometallics*, 2003, **22**, 1603.
- 2003TA3069 M. Blumenstein, M. Lemmler, A. Hayen, and J. O. Metzger, *Tetrahedron Asymmetry*, 2003, **14**, 3069.
- 2003TL451 J. W. Faller, R. G. Kulytshev, and J. Parr, *Tetrahedron Lett.*, 2003, **44**, 451.
- 2003ZNB1165 S. S. Karlov, E. Kh. Yakubova, E. V. Gauchenova, A. A. Selina, A. V. Churakov, J. A. K. Howard, S. A. Tyuria, J. Lorberth, and G. S. Zaitseva, *Z. Naturforsch. B*, 2003, **58**, 1165.
- 2004AGE4704 P. Espinet and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2004, **43**, 4704.
- 2004CR5847 V. Chandrasekhar, R. Boomishankar, and S. Nagendran, *Chem. Rev.*, 2004, **104**, 5847.
- 2004JA2696 W. Setaka, K. Hirai, H. Tomioka, K. Sakamoto, and M. Kira, *J. Am. Chem. Soc.*, 2004, **126**, 2696.
- 2004JCD4146 C. Schaefer, R. Gleiter, and F. Rominger, *J. Chem. Soc., Dalton Trans.*, 2004, 4146.
- 2004JOM2565 J. W. Faller, R. G. Kulytshev, and J. Parr, *J. Organomet. Chem.*, 2004, **689**, 2565.
- 2004JST261 P. L. Shutov, S. S. Karlov, K. Harms, D. A. Tyurin, M. V. Zablov, A. V. Churakov, J. A. K. Howard, J. Lorberth, and G. S. Zaitseva, *J. Mol. Struct.*, 2004, **689**, 261.
- 2004OM12 Y. Horino and T. Livinghouse, *Organometallics*, 2004, **23**, 12.
- 2004OM2225 C. Schaefer, R. Gleiter, and F. Rominger, *Organometallics*, 2004, **23**, 2225.
- 2004OM3375 H. Tsuji, A. Fukazawa, S. Yamaguchi, A. Toshimitsu, and K. Tamao, *Organometallics*, 2004, **23**, 3375.
- 2004TL4329 H. Nagano and S. Hara, *Tetrahedron Lett.*, 2004, **45**, 4329.
- 2005AOM440 M. Gielen, M. Biesemans, and R. Willem, *Appl. Organomet. Chem.*, 2005, **19**, 440.
- 2005EJO1541 J. F. Schneider, M. Nieger, K. Nättinen, B. Lewall, E. Niecke, and K. H. Dötz, *Eur. J. Org. Chem.*, 2005, 1541.
- 2005ICA4270 J. Wagler, U. Böhme, E. Brendler, B. Thomas, S. Goutal, H. Mayr, B. Kempf, G. Ya. Remmennikov, and G. Roewer, *Inorg. Chim. Acta*, 2005, **358**, 4270.
- 2005ICC131 H. Yorimitsu and K. Oshima, *Inorg. Chem. Commun.*, 2005, **8**, 131.
- 2005JA10028 B. M. Trost, Z. T. Ball, and K. M. Laemmerhold, *J. Am. Chem. Soc.*, 2005, **127**, 10028.
- 2005JMT31 S. S. Karlov, D. A. Tyurin, M. V. Zablov, A. V. Churakov, and G. S. Zaitseva, *J. Mol. Struct. Theochem*, 2005, **724**, 31.
- 2005JOC370 P. Pawluć, B. Marciniak, G. Hreczycho, B. Gaczewska, and Y. Itami, *J. Org. Chem.*, 2005, **70**, 370.
- 2005JOM2272 R. Jain, A. P. J. Brunskill, J. B. Sheridan, and R. A. Lalancette, *J. Organomet. Chem.*, 2005, **690**, 2272.
- 2005JST1 S. S. Karlov, A. A. Selina, E. S. Chernyschova, M. V. Zablov, A. V. Churakov, J. A. K. Howard, V. A. Tafeenko, and G. S. Zaitseva, *J. Mol. Struct.*, 2005, **740**, 1.
- 2005OBC816 Ch. M. Pedersen, L. G. Marinescu, and M. Bols, *Org. Biomol. Chem.*, 2005, **3**, 816.
- 2005OM156 H. Yoshida, J. Ikada, M. Shudo, J. Ohshita, and A. Kunai, *Organometallics*, 2005, **24**, 156.
- 2005OM5484 S. Hino, M. M. Olmstead, and P. P. Power, *Organometallics*, 2005, **24**, 5484.

- 2005SL1105 P. Pawluć, G. Hreczycho, and B. Marciniak, *Synlett*, 2005, 1105.
- 2005T2037 K.-H. Tang, F.-Y. Liao, and Y.-M. Tsai, *Tetrahedron*, 2005, **61**, 2037.
- 2005T3697 M. Terauchi, Y. Yahiro, H. Abe, S. Ichikawa, S. C. Tovey, S. G. Dedos, C. W. Taylor, B. V. L. Potter, A. Matsuda, and S. Shuto, *Tetrahedron*, 2005, **61**, 3697.
- 2005T4657 A. Ahmed and P. H. Dussault, *Tetrahedron*, 2005, **61**, 4657.
- 2005T7233 D. C. Braddock and J. J.-P. Peyralans, *Tetrahedron*, 2005, **61**, 7233.
- 2005TL315 M. S. Singh and A. K. Singh, *Tetrahedron Lett.*, 2005, **46**, 315.
- 2006CEJ4954 S. E. Denmark and J. D. Baird, *Chem. Eur. J.*, 2006, **12**, 4954.
- 2006JA6800 A. Fukazawa, H. Tsuji, and K. Tamao, *J. Am. Chem. Soc.*, 2006, **128**, 6800.
- 2006JA12685 R. S. Glass, E. Bloch, E. Lorance, U. I. Zakai, N. G. Gruhn, J. Jin, and S.-Z. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 12685.
- 2006JA14442 A. G. Moiseev and W. J. Leigh, *J. Am. Chem. Soc.*, 2006, **128**, 14442.
- 2006JA14949 E. Block, E. V. Dikarev, R. S. Glass, X. Li, and S.-Z. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 14949.
- 2006JOM2440 A. Naka, K. Nakano, M. Ishikawa, and Y.-W. Kwak, *J. Organomet. Chem.*, 2006, **691**, 2440.
- 2006JOM5260 T. Umemiya, D. Takeuchi, and K. Osakada, *J. Organomet. Chem.*, 2006, **691**, 5260.
- 2006JOM5517 S. M. E. Simpkins, B. M. Kariuki, and L. R. Cox, *J. Organomet. Chem.*, 2006, **691**, 5517.
- 2006JOM5710 E. Kh. Lermontova, A. A. Selina, S. S. Karlov, A. V. Churakov, J. A. K. Howard, Y. F. Oprunenko, M. Yu. Antipin, J. Sundermeyer, and G. S. Zaitseva, *J. Organomet. Chem.*, 2006, **691**, 5710.
- 2006OM48 Y.-W. Kwak, I.-S. Lee, M.-K. Baek, U. Lee, H.-J. Choi, M. Ishikawa, A. Naka, J. Ohshita, K.-H. Lee, and A. Kunai, *Organometallics*, 2006, **25**, 48.
- 2006OM3969 H. K. Sharma, F. Cervantes-Lee, and K. H. Pannell, *Organometallics*, 2006, **25**, 3969.
- 2006OM4231 K. Mochida, N. Matsuhisa, R. Sato, and Y. Nakadaira, *Organometallics*, 2006, **25**, 4231.
- 2006T3103 T. Uchida, Y. Kita, H. Maekawa, and I. Nishiguchi, *Tetrahedron*, 2006, **62**, 3103.
- 2006T7951 G. Rousseau and L. Blanko, *Tetrahedron*, 2006, **62**, 7951.
- 2006T9433 C. A. Baker, K. S. Findlay, S. Bettington, A. S. Batsanov, I. F. Perepichka, M. R. Bryce, and A. Beeby, *Tetrahedron*, 2006, **62**, 9433.
- 2006TL7865 H. Maeda, R. Hiranabe, and K. Mizuno, *Tetrahedron Lett.*, 2006, **47**, 7865.
- 2006TL873 T. Kano, T. Konishi, S. Konishi, and K. Maroka, *Tetrahedron Lett.*, 2006, **47**, 873.
- 2007JOM243 S. Ito, H. Jin, and M. Yoshifuji, *J. Organomet. Chem.*, 2007, **692**, 243.

Biographical Sketch



Franciszek Sączewski was born in Sopot, Poland, in 1951. He graduated from Medical University of Gdańsk in 1974 with M.S. degree in pharmacy and that same year began his career at the Department of Organic Chemistry. In 1981 he received his Ph.D. and in 1988 D.Sc. degree in pharmaceutical chemistry. In 1999 he was promoted to full professor. During 1983–1984 and 1988–1989 he was working with Prof. Alan Roy Katritzky at the Department of Chemistry, University of Florida, USA. He is a member of the Royal Society of Chemistry, International Society of Heterocyclic Chemistry and Polish Pharmaceutical Society.

Prof. F. Sączewski is currently the head of the Department of Chemical Technology of Drugs, Medical University of Gdańsk, Poland. His research interests are focused on the design and synthesis of nitrogen-containing heterocyclic compounds with potential circulatory, anticancer and anti-HIV activities.



Anita Kornicka was born in Gdańsk, Poland on February 15, 1966. She graduated from Medicinal University of Gdańsk in 1990 with M.S. degree in pharmacy. Since 1990 she has been working at the Department of Chemical Technology of Drugs, Medical University of Gdańsk. In 2000 she received her Ph.D. degree in pharmaceutical sciences. For many years she has been conducting studies on chemical and biological properties of 2-mercaptobenzenesulfonamide derivatives. Nowadays, her research interests include the design and synthesis of imidazoline-containing compounds with potential circulatory and anticancer activities. Anita Kornicka is a member of the Polish Pharmaceutical Society.

14.20

Rings containing Boron

G. W. Morrow

University of Dayton, Dayton, OH, USA

© 2008 Elsevier Ltd. All rights reserved.

14.20.1	Introduction	1039
14.20.2	Theoretical Methods	1040
14.20.3	Experimental Structural Methods	1041
14.20.3.1	Ultraviolet and Infrared Spectra	1041
14.20.3.2	NMR Spectra	1041
14.20.3.3	Microwave Spectra	1041
14.20.3.4	X-Ray Analysis	1042
14.20.4	Thermodynamic Aspects	1042
14.20.5	Reactivity of Fully Conjugated Rings	1042
14.20.5.1	Formation of Molybdenum Tricarbonyl Complexes	1042
14.20.5.2	Protonolysis	1043
14.20.5.3	Oxidation–Reduction	1043
14.20.6	Reactivity of Nonconjugated Rings	1043
14.20.6.1	Polyhomologation of Boracyclanes	1044
14.20.6.2	Ring Enlargement of Boracyclanes	1044
14.20.7	Reactivity of Substituents Attached to Ring Carbon Atoms	1045
14.20.7.1	Reactions of 2-Haloborocanes	1045
14.20.8	Reactivity of Substituents Attached to Ring Heteroatoms	1045
14.20.8.1	Reactions of <i>B</i> -Substituted Borepin Molybdenum Tricarbonyl Complexes	1045
14.20.8.2	Reactions of <i>B</i> -Substituted Borocanes	1046
14.20.9	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	1046
14.20.9.1	[6+1] Synthesis of Dihydrodibenzoborepins	1046
14.20.10	Ring Syntheses by Transformations of Other Rings	1047
14.20.10.1	Benzo- and Other Fused Ring Borepins from Stannepins	1047
14.20.11	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	1047
14.20.12	Important Compounds and Applications	1047
References		1048

14.20.1 Introduction

Boron heterocycles of seven atoms or more were covered previously in pages 1023–1031 of CHEC-II(1996), Volume 9, Chapter 37, which is currently available online. This chapter, as the previous one, focuses mainly on borepins and their analogues, providing a brief update of earlier work with special emphasis on the increased number of theoretical studies now available as well as information on several new reactions and rings systems that have recently appeared. A limited amount of information is also presented on the chemistry of some saturated boracycloheptanes and boracyclooctanes. The main sections provide a brief introduction to major advances, if any, since publication of CHEC-II(1996), with detailed subsections following.

14.20.2 Theoretical Methods

Computational power and methodologies have grown significantly over the last decade, so borepins, such as **1**, and its various benzo analogues, such as **2** and **3** (Figure 1), have been targets of numerous theoretical studies designed to establish the interrelationships among stability, geometry, energy, and magnetic properties, mainly as criteria of aromaticity.

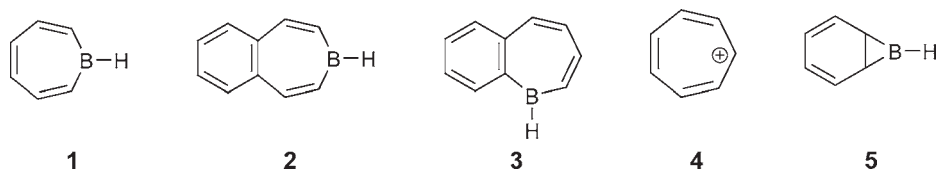


Figure 1

Early *ab initio* calculations using STO-3G basis set suggested that 1H-borepin **1** should be planar and about 37 kcal mol⁻¹ more stable than boranorcaradiene **5** <1982JA3785, 1983TL1863, 1984JA7696>. More recently calculated energies, optimized geometries, magnetic susceptibility anisotropies, nuclear independent chemical shift (NICS) values and ¹H NMR (NMR – nuclear magnetic resonance) chemical shifts determined at the B3LYP/6-311+G** density-functional level suggested that **1** is only weakly aromatic, with a computed aromatic stabilization energy of 5.1 kcal mol⁻¹ versus 16.8 kcal mol⁻¹ for tropylium ion **4** <1997OM2362>. For **1**, this is considerably less than the 12.8 kcal mol⁻¹ reported in an earlier computational study <1989OM733>. Additional theoretical studies on a series of *B*-substituted borepins at the MP2/6-31G level suggested planar structures with weak out-of-plane bending modes, often leading to boat-shaped structures <1996MP213>.

Calculations at the CBS-4 compound level of theory gave homolytic bond dissociation energies (BDEs) for a series of B–H and B–C bonds in numerous cyclic boranes, among which were **1** and its 1-methyl analogue. The BDEs at 298 K were calculated to be 105.8 kcal mol⁻¹ for B–H in 1H-borepin and 104.9 kcal mol⁻¹ for B–CH₃ in 1-methyl-1H-borepin <1996JA4648>. Data on the potential intermediacy of the *B*-centered radical of **1** are also found in a computational study on reaction of benzene with atomic boron to form benzoborirene <2004JPC4576>.

Detailed *ab initio* work on thienoborepins **6** and **7** (Figure 2), which are isoelectronic with azulene, used the 3-21G basis set and showed planar structures to be the most stable geometry, since all calculated vibrational frequencies were positive <1994T6495>. Both were determined to be aromatic, but calculated B–C bond lengths were 0.012 Å shorter for **6** than for **7**, supporting an expected increase in B–C π-bond order for **6**. Later calculations on **9** using the same basis set gave a B–C bond length intermediate between that of **6** and **7** <1995CC1249>. By contrast, B–C bond lengths for **6** and **7** differed by only 0.007 Å using B3LYP/6-311+G** optimized geometries <1997OM2362>. This extensive study suggested that although **6** and **7** are only weakly aromatic, each should have significant ring current in both rings, though weaker in **7** than **6**. These results remained consistent for the series of heterole-fused borepins **8–11** in the same study.

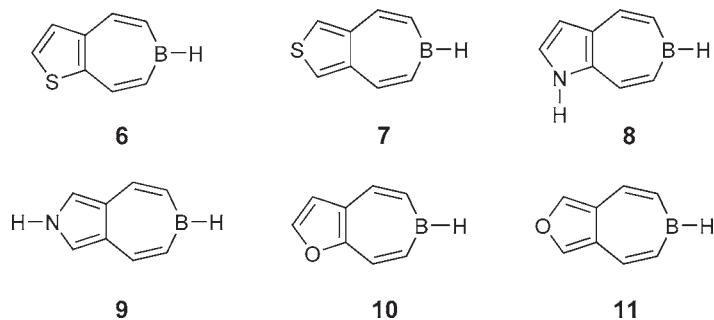
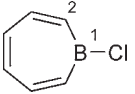
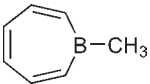
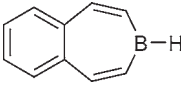
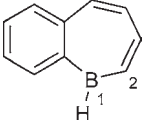


Figure 2

Steric hindrance leading to significant nonplanarity of the seven-membered ring in various substituted borepin derivatives examined at the B3LYP/6-311+G** level resulted in substantially reduced aromatic character. Molecular geometries, ^{13}C and ^{11}B chemical shifts, and magnetic susceptibilities were calculated for several 1-substituted borepins and benzoborepins in these studies; tribenzoborepin and two dibenzoborepins were also predicted to be nonplanar <2000OM2932>. Calculated ^{13}C NMR data from these and related studies are given in Table 1 (also see Section 14.20.3.2).

Table 1 HF/6-31G**/B3LYP/6-311+G** ^{13}C NMR chemical shifts for selected borepins

Borepin	C-2	C-3	C-4	C-5	References
	146.2 (150) ^a	148.3 (148.3) ^a	133.8 (135.4) ^a		2000OM2932
	149.3 (151) ^a	146.7 (146.3) ^a	133.2 (136.4) ^a		2000OM2932
	154.6 (154) ^b	136.0 (140.2) ^b			1997OM2362
	137.2 ^c	150.8 ^c	125.0 ^c	140.1 ^c	1997OM2362

^aExperimental values in parentheses from 1993OM3225.

^bExperimental values in parentheses from 1990OM2944.

^cFor some experimental values not identified by carbon number, see 2000J(P1)1965.

14.20.3 Experimental Structural Methods

14.20.3.1 Ultraviolet and Infrared Spectra

The longest wavelength band in the ultraviolet (UV) spectrum of the 1-phenyl-*N*-methyl derivative of **9** was reported to occur at 356 nm in cyclohexane and displayed only slight solvatochromism, while the fluorescence spectrum ($\Phi = 0.13$, cyclohexane) showed marked solvatochromism, for example, 87 nm with a change from cyclohexane to dimethylformamide (DMF) <1995CC1249>. No infrared (IR) data have been reported recently for borepins or their analogues.

14.20.3.2 NMR Spectra

Early ^1H NMR studies established that when compared to other heteropins, the olefinic protons of borepins appear at the lower field strengths normally associated with diamagnetic ring currents in aromatic systems <1990OM2944, 1987CL1879, 1992AGE1255>. More recently, 1-chloro and 1-phenylbenzoborepins were prepared and their borepin ring protons showed signals shifted downfield by 0.25–0.64 ppm relative to the 1-benzostannepins from which they were prepared <2000J(P1)1965>. As shown previously in Table 1, both theoretical and experimental ^{13}C NMR chemical shifts were likewise consistent with those typical of aromatic sp^2 carbons.

14.20.3.3 Microwave Spectra

The question of ring planarity has always been closely associated with the assignment of aromatic character to borepins, and a recently obtained microwave spectrum of 1-chloroborepin has allowed the derivation of its ground-state rotational constants. Calculation of the inertia defect ($\Delta = -0.19 \text{ u}\text{\AA}^2$) from these data led to the conclusion that

1-chloroborepin is a planar molecule <2006JST317>. This was in good agreement with an earlier X-ray analysis <1993AG(E)1065> as well as a theoretical geometry study of the compound at the MP2/6-31G level of theory <1996MP213>.

14.20.3.4 X-Ray Analysis

Aside from the structure obtained for 1-chloroborepin referred to in Section 14.20.3.3, no other X-ray studies of simple borepins or benzoborepins have been reported; however, an X-ray structure for molybdenum carbonyl complex **12** has been obtained <1997OM1884> and was compared to previously reported structures for **13** and **14** <1992AGE1255> shown in Figure 3.

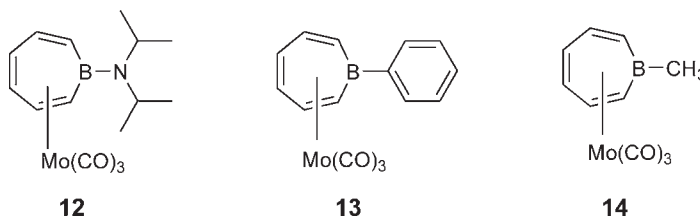


Figure 3

The borepin rings of **13** and **14** were found to be essentially planar and served as η^7 donors to the metal, consistent with their role as aromatic ligands. However, **12** was found to be only η^6 -coordinated to the six ring carbon atoms, with a B–Mo distance about 1/4 Å longer than in either **13** or **14**, a distance apparently too long for significant metal–boron bonding to occur. As in the structure of the molybdenum carbonyl complex of cycloheptatriene <1993JOM107>, the six carbon atoms of **12** were close to coplanar, while the B atom was tipped above-the-plane. As expected, the strong donor character of nitrogen gave rise to a short B–N bond distance (1.39 Å) for **12**, indicative of significant B–N π -bonding, while C–C bond distances alternated between 1.35 and 1.46 Å, which are values typical of cycloheptatriene metal complexes.

14.20.4 Thermodynamic Aspects

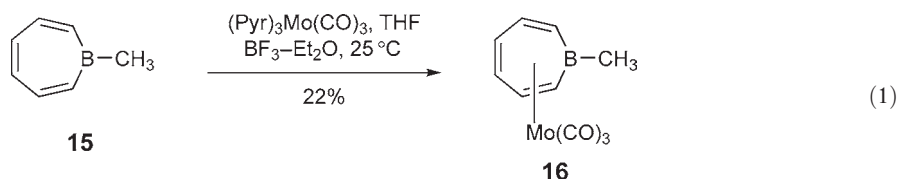
Borepin systems, being aromatic, are often thermally stable, distillable liquids. 2-*t*-Butyl-1-chloro-1-benzoborepin was reportedly a pale yellow oil with a boiling point of 90–100 °C/2.0 mmHg, while 2-*t*-butyl-1-phenyl-1-benzoborepin was distillable at 80–100 °C/ 4.0×10^{-6} mmHg <2000J(P1)1965>. Beyond this meager information, little beyond solubility in common solvents for reactions or NMR spectra (THF, CDCl₃) is available for borepins and benzoborepins. Some data for saturated borepanes (boracycloheptanes) and borocanes (boracyclooctanes) have been recently reported. 1-Azidoboracycloheptane was obtained as a colorless oil at 25 °C/1.5 mmHg and 1-chloroboracyclooctane was distilled at 70 °C/15 mmHg <2004ZFA2641>.

14.20.5 Reactivity of Fully Conjugated Rings

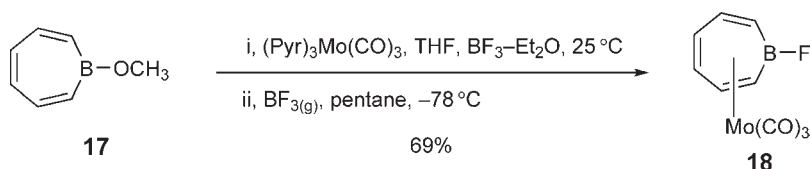
The following brief sections update some of the ring chemistry of borepins, but the reader is referred to Section 9.37.5 in CHEC-II(1996) for more detail, since much of the more recent work on these systems has been of a theoretical rather than an experimental nature.

14.20.5.1 Formation of Molybdenum Tricarbonyl Complexes

As indicated in Section 14.20.3.4, borepins can react with organometallics to form complexes in which the borepin ring serves as an η^7 ligand to the metal. Thus, 1-methylborepin **15** reacted with tris(pyridine)molybdenum tricarbonyl to afford the corresponding molybdenum complex **16** as a red, air-sensitive oil, as in Equation (1) <1997OM1884>.



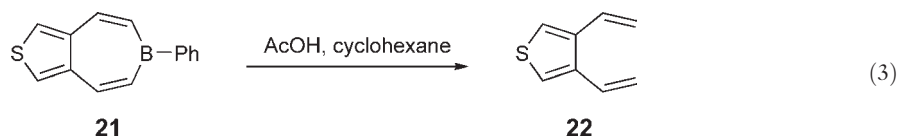
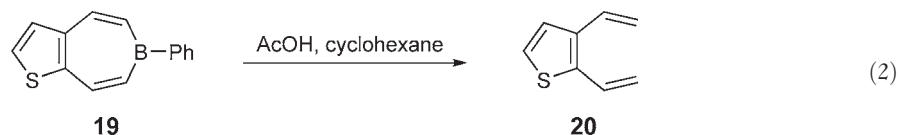
Similarly, orange-red needles (mp 53°C) of 1-fluoroborepin molybdenum carbonyl complex **18** were obtained by conversion of 1-methoxyborepin **17** to the corresponding Mo(CO)_3 complex followed by immediate treatment of the crude complex with boron trifluoride in pentane, as in **Scheme 1**. The intermediate molybdenum complex of **17** could be isolated as air- and moisture-sensitive crystals (mp $110\text{--}115^\circ\text{C}$) but prolonged manipulation led to contamination by the corresponding 1-hydroxyborepin complex [<1997OM1884>](#).



Scheme 1

14.20.5.2 Protonolysis

Cleavage of the carbon–boron bond of thienoborepins **19** and **21** occurred readily in acetic acid–cyclohexane to give the corresponding divinylthiophenes **20** and **22**, as shown in **Equations (2) and (3)**. Rate data indicated that **19** reacted 210 times faster than **21**, suggesting that protonation of carbons α to boron was more important in **19**, while protonolysis of **21** was presumably facilitated by oxo coordination of the acid to the boron atom, as had been suggested for protonolysis of simple 1-phenylborepin and similar monocyclic derivatives [<1994T6495>](#).



14.20.5.3 Oxidation–Reduction

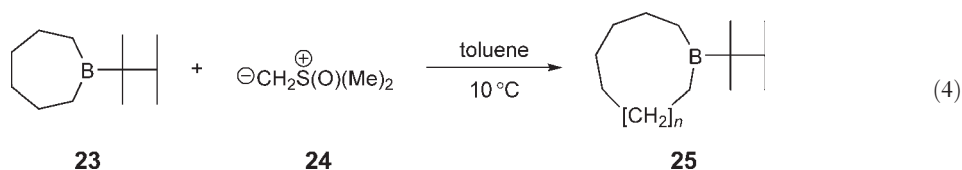
Cyclic voltammetry studies on **19** and **21** gave single reduction waves at -1.70 and -1.66 V, respectively, while two oxidation waves were observed for each at 1.14 versus 0.90 for the first wave and 1.56 versus 1.25 for the second (vs. SCE) [<1994T6495>](#). These redox potentials were comparable to those of both triarylboranes and thiophenes.

14.20.6 Reactivity of Nonconjugated Rings

No new information on dihydroborepins or dihydrobenzoborepins is available (see Section 9.37.5.5 in CHEC-II(1996) for previous information). The following sections briefly describe some reactions of saturated borepanes and similar boracyclane systems.

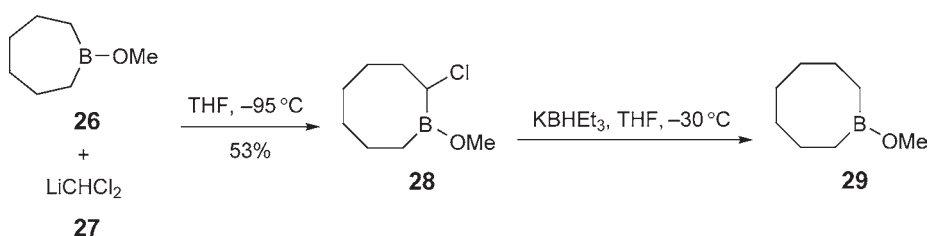
14.20.6.1 Polyhomologation of Boracyclanes

B-Thexylborepane **23**, prepared by hydroboration of 1,5-hexadiene with thexylborane, was found to undergo polyhomologation to a mixture of macrocyclic organoboranes **25** when treated with dimethylsulfoxonium methylide **24** in toluene, as shown in Equation (4). The distribution of molecular weights of the resulting macrocycles was found to be a function of the mole ratio of **23** to **24**, allowing some control over ring size of the resultant boracycles <1998JOC5746>.



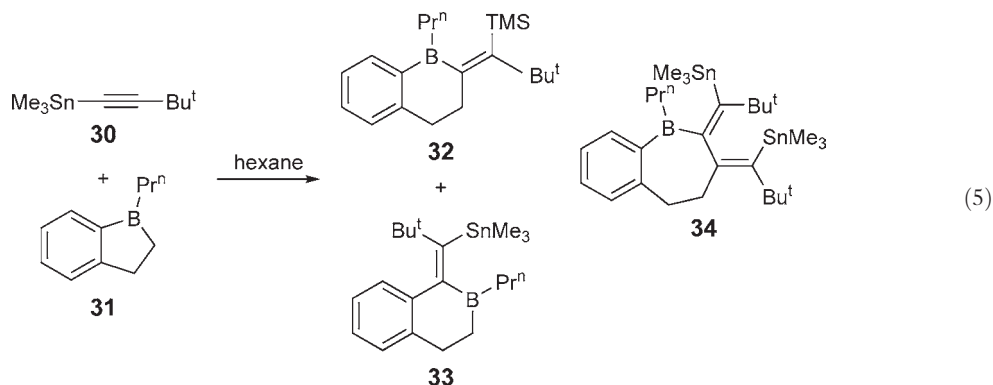
14.20.6.2 Ring Enlargement of Boracyclanes

Selective ring enlargement of 1-methoxyborepane **26** to 1-methoxyborocane **29** was achieved by treatment of **26** with dichloromethyl lithium **27**, followed by reduction of intermediate **28** with KBHET₃ as shown in Scheme 2. Similar one-carbon ring expansions of **26** were achieved by treatment with LiCCl₃ and other reagents of the type LiCR₂Cl <2004ZFA2641>.

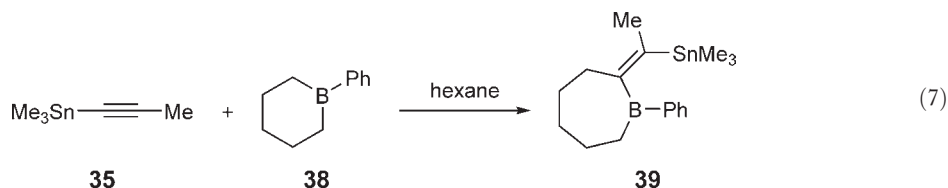
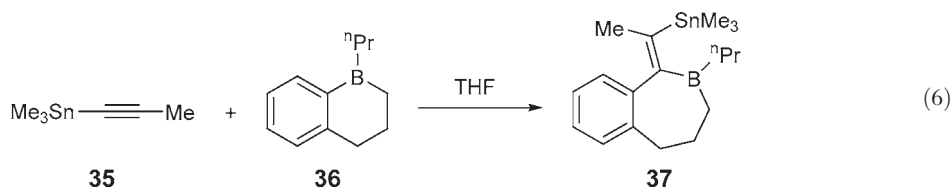


Scheme 2

1,1-Organoboration of 1-alkyl-1-boraindane derivatives with an excess of 1-alkynyltrimethyl tin compounds led to kinetically controlled ring-expansion reactions. Thus, reaction of *t*-butylethynyltrimethylstannane **30** with 1-propylboraindane **31** gave a mixture of boratetralins **32** and **33** as well as benzoborepane **34** (Equation 5) <1998MI515, 1996MI215>.



Similarly, reaction of propynyltrimethylstannane **35** with either *n*-propylboratetralin **36** or 1-phenylborinane **38** exclusively gave benzoborepane **37** (Equation 6) or borepane **39** (Equation 7) respectively.

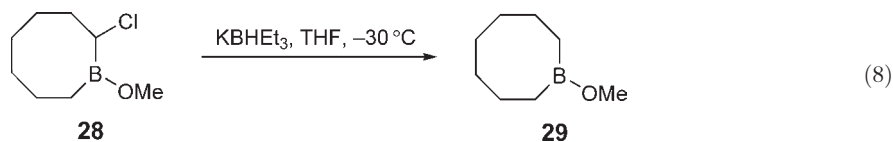


14.20.7 Reactivity of Substituents Attached to Ring Carbon Atoms

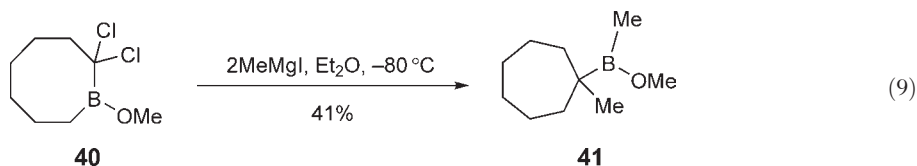
There is little in the way of recent experimental information on ring-carbon substituent reactivity of borepins and the reader is referred to Section 9.37.5.5 in CHEC-II(1996) for some earlier details. Selected recent examples involving other large ring boron heterocycles are given below.

14.20.7.1 Reactions of 2-Haloborocanes

As shown previously in [Scheme 2](#), 2-chloro-1-methoxyborocane **28** was readily reduced to borocane **29** with KBHET_3 in THF, as in [Equation \(8\)](#).



By contrast, dichloroborocane **40**, when treated with 2 equiv of CH_3MgI , gave the ring-contracted cycloheptylborene derivative **41** ([Equation 9](#)) [<2004ZFA2641>](#).

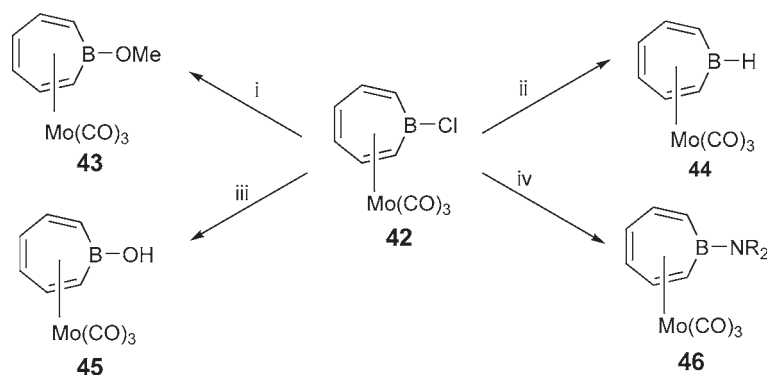


14.20.8 Reactivity of Substituents Attached to Ring Heteroatoms

No new studies of reactivity of substituents on boron have been reported for borepins themselves. A few selected examples of *B*-substituent reactivity of borepin metal carbonyl complexes and of borepanes and borocanes follow. Section 9.37.5.4 in CHEC-II(1996) provides some additional relevant examples.

14.20.8.1 Reactions of *B*-Substituted Borepin Molybdenum Tricarbonyl Complexes

Some replacement reactions of 1-chloroborepin(tricarbonyl)molybdenum **42** are summarized in [Scheme 3](#), illustrating its utility as a precursor to certain derivatives **43–46**, which may be unavailable directly from the corresponding borepin. Subsequent treatment of **45** with MgSO_4 in ether gave the corresponding 1,1'-bis[tricarbonyl(borepin)molybdenum] oxide [<1997OM1884>](#).

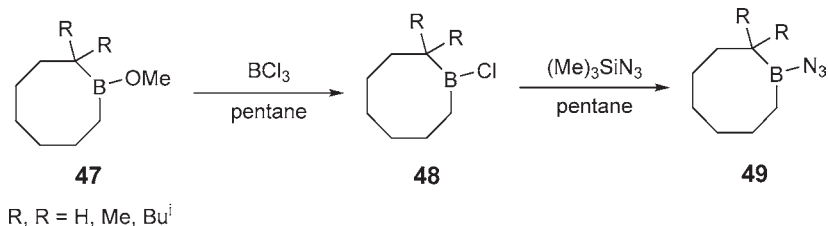


i, MeOH, MgSO₄; ii, LiAlEt₃H, THF; iii, H₂O, Al₂O₃, Et₂O; iv, 2HNR₂, solvent;
 R = ⁱPr, hexane; R = Et, hexane; R = *c*-C₆H₁₁, pentane; R = Bn, Me, benzene

Scheme 3

14.20.8.2 Reactions of *B*-Substituted Borocanes

As shown in [Scheme 4](#), sequential treatment of a series of 1-methoxyborocane derivatives **47** with BCl₃ gave the corresponding 1-chloroborocanes **48**, which in turn were smoothly converted to 1-azidoborocanes **49**, though the chemistry of these compounds was not explored further [<2004ZFA2641>](#).



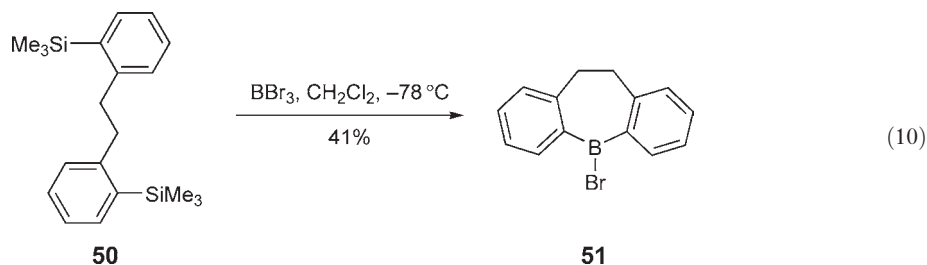
Scheme 4

14.20.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

Only a single example of preparation of a large ring boracycle from acyclic precursors has appeared since CHEC-II(1996) for inclusion in this section.

14.20.9.1 [6+1] Synthesis of Dihydrodibenzoborepins

In a study of the synthesis and chemistry of naphthalene-1,8-diboranes, dihydrodibenzoborepin **51** was prepared by reaction of boron tribromide with 1,2-bis(2-trimethylsilylphenyl)ethane **50**, as shown in [Equation \(10\)](#) [<2004JCD1254>](#).

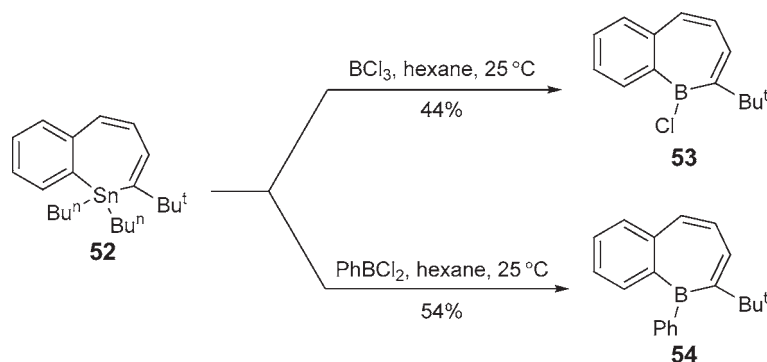


14.20.10 Ring Syntheses by Transformations of Other Rings

This section briefly covers some recent examples of conversion of a benzostannepin to corresponding benzoborepin systems. The reader is also referred to [Section 14.20.6.2](#) for examples of formation of larger ring borepanes and benzoborepanes via some recently reported ring-expansion reactions. No recent examples of synthesis of simple borepin ring systems have been reported.

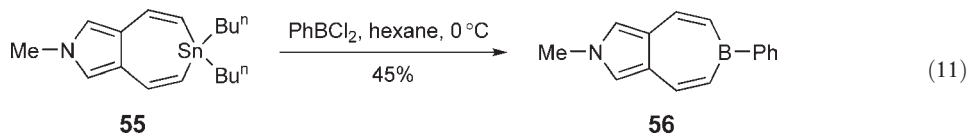
14.20.10.1 Benzo- and Other Fused Ring Borepins from Stannepins

3-Benzoborepins **2** have been known for over 30 years, but the corresponding 1-benzoborepins **3** have only recently been synthesized. Thus, reaction of 1-benzostannepin **52** with either BCl_3 or PhBCl_2 gave the corresponding 1-benzoborepins **53** and **54** in modest yield ([Scheme 5](#)). The ^1H NMR signals for the benzoborepin ring protons were found to be shifted downfield relative to those of the precursor benzostannepin, indicating the aromatic character expected for these new boracycles [<1998CC767, 2000J\(P1\)1965>](#).



Scheme 5

As shown in [Equation \(11\)](#), a similar approach was used to prepare *N*-methylpyrrole-fused borepin **56** from stannepin **55** [<1995CC1249>](#).



14.20.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

The method of choice for the synthesis of borepins, benzoborepins, and heterole-fused borepins is reaction of the corresponding stannepins with boron trihalides or aryl dihaloboron compounds (see [Section 14.20.10](#)). A dibenzodihydroborepin has been prepared by a [6+1]-type cyclization of a naphthalene-1,8-diborane with BCl_3 (see [Section 14.20.9.1](#)). Yields of these methods are comparable. The saturated systems are typically prepared by reaction of 1,6-heptadienes with monoalkyl boranes such as *tert*-hexyl borane (see [Section 14.20.6.1](#)).

14.20.12 Important Compounds and Applications

The aromatic borepins and benzoborepins have been prepared primarily as compounds of theoretical interest and no significant applications have been reported to date. Saturated 1-alkylborepanes, such as **23** and similar large ring boron compounds, are of use primarily as precursors in the synthesis of cyclic ketones by treatment with carbon monoxide followed by alkaline hydrogen peroxide [<1982JOC1792>](#).

References

- 1982JA3785 J. M. Schulman, R. L. Disch, and M. L. Sabio, *J. Am. Chem. Soc.*, 1982, **104**, 3785.
1982JOC1792 D. Basavaiah and H. C. Brown, *J. Org. Chem.*, 1982, **47**, 1792.
1983TL1863 R. L. Disch, M. L. Sabio, and J. M. Schulman, *Tetrahedron Lett.*, 1983, 1863.
1984JA7696 J. M. Schulman, R. L. Disch, and M. L. Sabio, *J. Am. Chem. Soc.*, 1984, **106**, 7696.
1989OM733 J. M. Schulman and R. L. Disch, *Organometallics*, 1989, **8**, 733.
1992AGE1255 A. J. Ashe, III, J. W. Kampf, Y. Nakadaira, and J. M. Pace, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1255.
1993JOM107 F. J. Hadley, T. M. Gilbert, and R. D. Rogers, *J. Organomet. Chem.*, 1993, **455**, 107.
1994T6495 Y. Sugihara, R. Miyatake, T. Yagi, and I. Murata, *Tetrahedron*, 1994, **50**, 6495.
1995CC1249 Y. Sugihara, R. Miyatake, I. Murata, and A. Imamura, *J. Chem. Soc., Chem. Commun.*, 1995, 1249.
1996JA4648 P. R. Rablen and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 4648.
1996MI215 B. Wrackmeyer and V. Hendrick, *Main Group Met. Chem.*, 1996, **19**, 215.
1996MP213 J. M. Schulman and R. L. Disch, *Mol. Phys.*, 1996, **88**, 213.
1997OM1884 A. J. Ashe, III, S. M. Al-Taweel, C. Drescher, J. W. Kampf, and W. Klein, *Organometallics*, 1997, **16**, 1884.
1997OM2362 G. Subramanian, P. von Ragué Schleyer, and H. Jiao, *Organometallics*, 1997, **16**, 2362.
1998CC767 H. Sashida, A. Kuroda, and T. Tsuchiya, *J. Chem. Soc., Chem. Commun.*, 1998, 767.
1998JOC5746 K. J. Shea, S. Y. Lee, and B. B. Busch, *J. Org. Chem.*, 1998, **63**, 5746.
1998MI515 B. Wrackmeyer and V. Hendrick, *Main Group Met. Chem.*, 1998, **21**, 515.
2000J(P1)1965 H. Sashida and A. Kuroda, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1965.
2000OM2932 J. M. Schulman and R. L. Disch, *Organometallics*, 2000, **19**, 2932.
2004JCD1254 J. D. Hoefelmeyer, S. Solé, and F. P. Gabbaï, *J. Chem. Soc., Dalton Trans.*, 2004, 1254.
2004JPC4576 H. F. Bettinger and R. I. Kaiser, *J. Phys. Chem.*, 2004, **108**, 4576.
2004ZFA2641 J. Münster, P. Paetzold, E. Schröder, H. Schwan, and T. von Bennisgen-Mackiewicz, *Z. Anorg. Allg. Chem.*, 2004, 2641.
2006JST317 N. W. Larsen, S. R. Hansen, and T. Pedersen, *J. Mol. Struct.*, 2006, **780–781**, 317.

Biographical Sketch



Dr. Gary W. Morrow earned his B.A. and Ph.D. degrees at the Ohio State University and is presently professor of chemistry at the University of Dayton. His research interests include organic synthesis and organic electrochemistry.

14.21

Rings containing Other Elements

T. P. Meagher

TEKA Consulting, Indianapolis, IN, USA

© 2008 Elsevier Ltd. All rights reserved.

14.21.1	Introduction	1051
14.21.2	Metallomacrocycles with Mercury Atoms	1052
14.21.2.1	Mercuracarborands	1052
14.21.2.1.1	Synthesis	1053
14.21.2.1.2	Structure elucidation	1055
14.21.2.1.3	Physical properties	1056
14.21.2.1.4	Chemical properties	1056
14.21.2.1.5	Important compounds and applications	1057
14.21.2.2	Miscellaneous Polymercuramacrocycles	1057
14.21.3	Metallomacrocycles with Platinum and Palladium Atoms	1058
14.21.3.1	Synthesis	1059
14.21.3.2	Structure Elucidation	1065
14.21.3.3	Physical Properties	1066
14.21.3.4	Chemical Properties	1066
References		1066

This chapter deals with ring systems containing seven atoms or more and possessing one or more heteroatoms other than oxygen, sulfur, selenium, tellurium, nitrogen, phosphorus, arsenic, antimony, bismuth, silicon, germanium, tin, lead, or boron. The remaining heteroatoms, therefore, are group 1 metals, alkaline earth metals (group 2), transition metals, and group 13 metals. There is abundant literature dealing with larger ring system containing metals; however, they mainly involve coordinated complexes comprising metal–oxygen and/or metal–nitrogen bonding. To limit the scope to a manageable amount of material, this chapter covers ring systems containing at least one metal–carbon σ -bond. Studies in this area have been concentrated on rings containing mercury, platinum, and palladium. Since these types of macrocycles are relatively new, research efforts have mainly focused on their preparation and characterization as well as the chemistry of their complexes. Thus, this chapter follows a different organization than most of the others in this volume. Emphasis will mainly be on synthesis, structure elucidation, physical properties, and chemical properties.

14.21.1 Introduction

Larger ring systems under the classifications of crown ethers, cryptands, heterophanes, and metallomacrocycles were previously reviewed in CHEC(1984) and CHEC-II(1996) <[1984CHEC\(7\)709](#), [1984CHEC\(7\)731](#), [1984CHEC\(7\)763](#), [1996CHEC-II\(9\)1033](#)>. Metallo cycles have been studied under the discipline of supermolecular chemistry, which is concerned with the molecular interactions through noncovalent bonds <[1997ACR267](#), [1997CRV1609](#), [1997PIC\(46\)1](#), [1997ACR502](#), [1998CSR289](#), [1998JCD1707](#), [2000CRV3483](#), [2000CRV853](#), [2001AGE2022](#), [2001AGE486](#)>. This is an extremely diverse area encompassing biological systems, molecular recognition, catalysis, macromolecular synthesis, and nanoscale materials, to name but a few. The roots of supermolecular chemistry began in the late 1960s with the synthesis and study of macrocycles such as crown ethers, cryptands, cyclophanes, and calixanes. These covalently bonded compounds have been used to study host–guest interactions between themselves as hosts and smaller cation species, as guests.

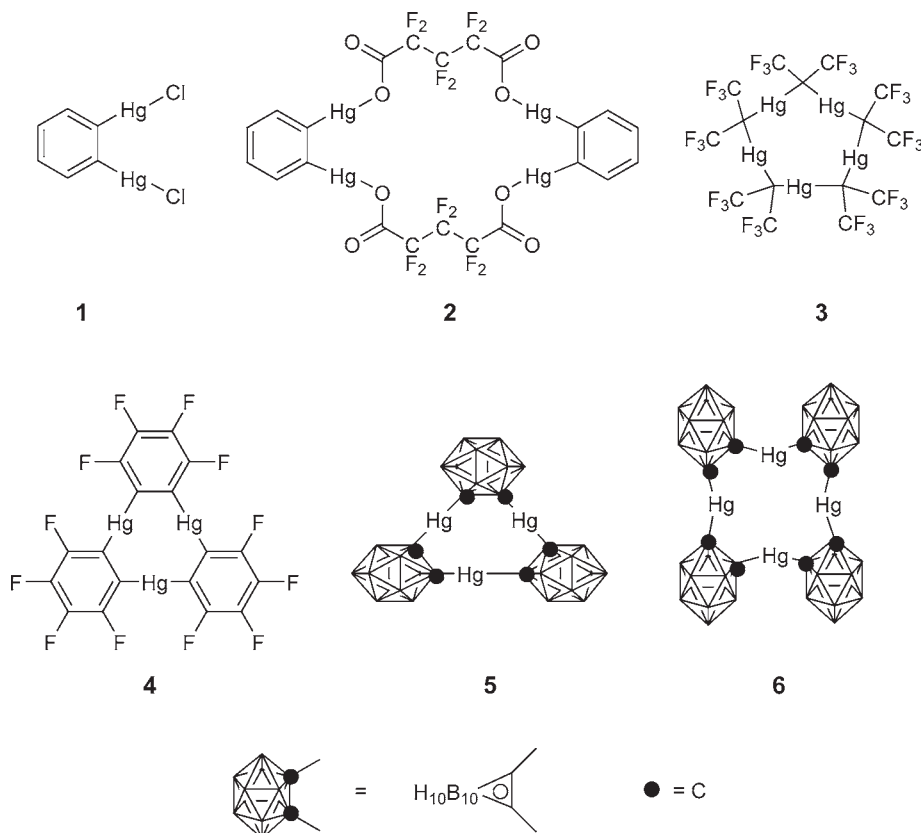
Incorporation of metal sites into rings, in contrast, has allowed the development of ‘anti-crown’ systems, which act as anion hosts <[1993JA193](#), [1997CRV1609](#)>. Although these metallo cycles were first reported about the same time as

crown ethers, they have had limited attention until the 1990s. The delayed effort in this area is mainly due to the difficulty in designing effective and robust anion hosts. Compared to cations, anions are more demanding of host molecules because they are larger, exist in a limited pH range, have varying geometries, and require larger free energies of solvation. The areas utilizing anion host–guest chemistry include catalysis, complexation, molecular recognition, and anion transport <1997CRV1609, 2001AGE486>. Metallocycles have also peaked interest because of their diverse and unique physical properties – electrical, optical, and magnetic, to name but a few.

14.21.2 Metallomacrocycles with Mercury Atoms

Certain bidentate Lewis acids can effectively bind anions and basic sites on molecules. One of the early examples is 1,2-phenylenedichloridimercury **1**, which forms a 2:1 host–guest complex with chloride <1997CRV1609>. This discovery led to interest in developing macrocycles containing mercury and studying their anion-complexing behavior <1993JA193>.

To date, parent ring systems containing mercury are still fairly limited. The first reported synthesis and characterization of a macrocyclic multidentate Lewis acid is **2** <1987JA4714>. More recent examples include 10-membered pentamercuramacrocycle **3** <1994IZV2047> and nine-membered trimercuramacrocycle **4** <2001CEJ3783>; however, the largest efforts reported in the literature have been directed toward mercuracarborands **5** and **6** as well as their derivatives. The nomenclature of mercuracarborands has been adopted from its charged-reversed crown ether analogs <1991AGE1507>. Thus, **5**, the analog of [9]-crown-3 ether, is coined [9]-mercuracarband-3 and **6** is named [12]-mercuracarband-4.



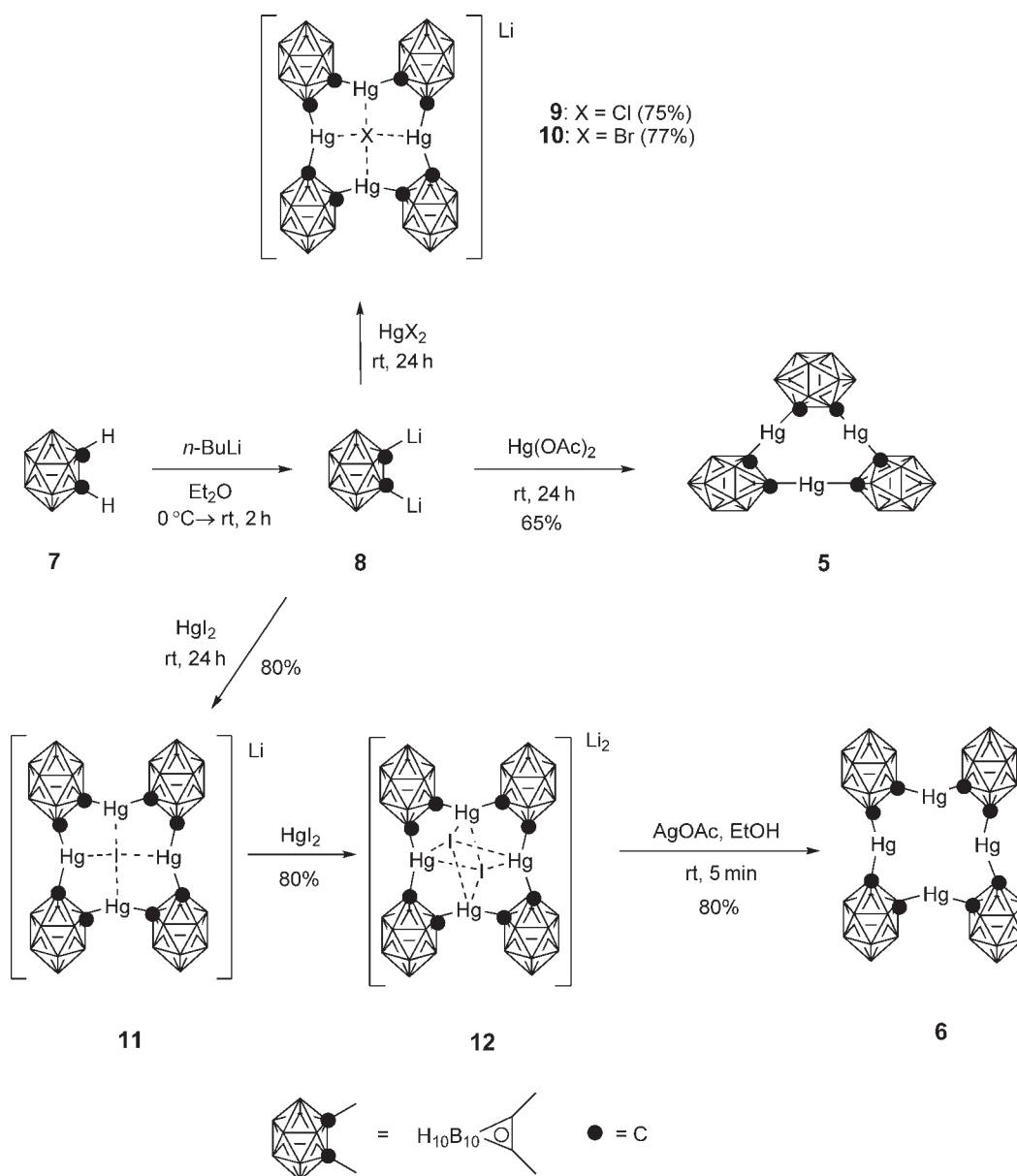
14.21.2.1 Mercuracarborands

Mercuracarborands are macrocycles consisting of three or more mercury atoms arranged in a ring with alternating icosahedral 1,2-carborane cages (1,2-C₂B₁₀H₁₀) <1997ACR267, 1997CRV1609, 1997PIC(46)1, 2001AGE486>. The

carborane elements are rigid and linked via carbon to the mercury atoms to make the macrocyclic ring. Compared to other possible Lewis acid sites (such as silicon, tin, or boron) mercury offers certain advantages. Disubstituted organomercury compounds form nearly collinear Hg–C σ -bonds permitting the preparation of large cyclic structures. The large cavity is an ideal host for various size anions. The metal site also retains its Lewis acid character. Importantly, mercuracarborands are stable to air and water, thus making their study and utility more general.

14.21.2.1.1 Synthesis

Synthesis of unsubstituted mercuracarborands, as illustrated in **Scheme 1**, is a two-step process involving deprotonation of the acidic CH vertices of 1,2-carborane **7** followed by treatment with the appropriate mercury salt [<1994JA7142, 1997ACR267>](#). Thus, *n*-butyllithium efficiently deprotonates 1,2-carborane **7** giving *closo*-1,2-Li₂-1,2-C₂B₁₀H₁₀ **8**, the pivotal intermediate. If treated with mercury acetate, neutral trimer **5** is formed. Using mercury chloride or bromide, however, leads to the formation of tetramer **9** and **10**, respectively, as 1:1 anion–host complexes.

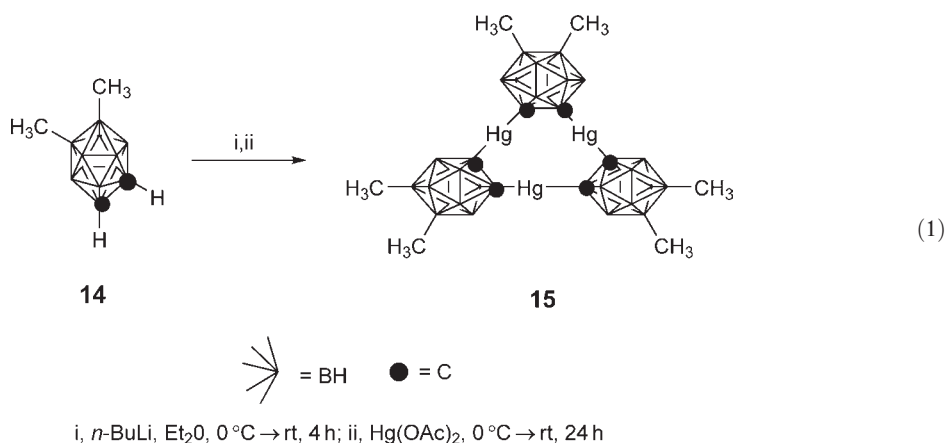


Scheme 1

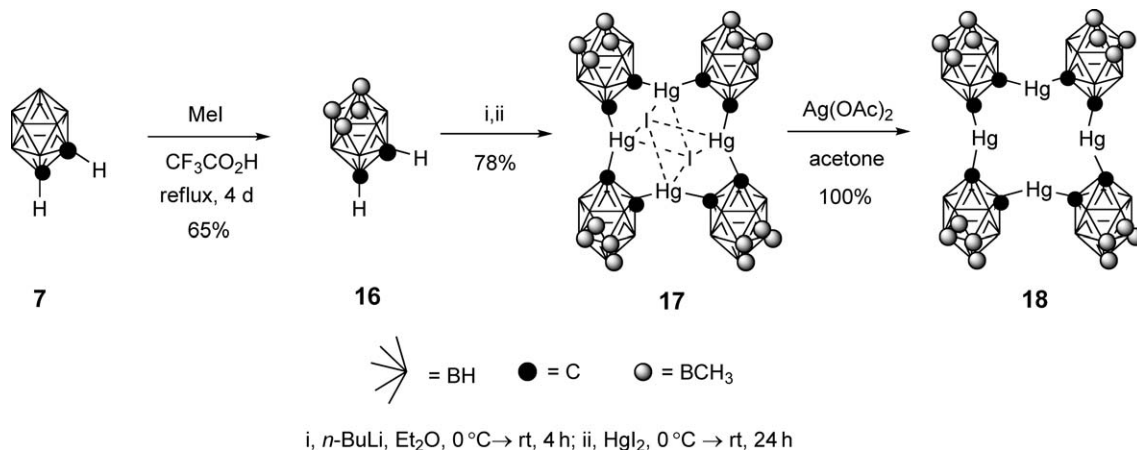
Dilithio **8** reacts with mercury iodide to give tetramer **11**, as a 1:1 complex, in 80% yield. Longer reaction times and additional mercury iodide produces the 2:1 complex **12**. Synthesis of neutral tetramer **6** is achieved by using silver acetate to decomplex diiodide **12**.

Since ring formation is greatly favored over oligomerization in the previous examples, the synthesis of mercuracarborand occurs via a preferred self-assembly process, and it is clear that the ring size is dictated by the associated mercury anion. The noncoordinating acetate anion leads to the less-strained and presumably more-preferred trimeric macrocycle **5**. In contrast, halide anions produce the tetramer macrocycles **9–11**. It is postulated that the halide ions act as kinetic template by stabilizing a trimer intermediate, which subsequently reacts further to form the tetrameric macrocycles <1997ACR267>.

The above approaches can be extended to 1,2-carboranes in which the BH vertices are substituted with alkyl groups <1996IC1235, 1996JA70>. The 9- and 12-boron vertices are the furthest from the carbon atoms in 1,2-carborane **7**. Methyl substitution of **7** at these positions is accomplished by iodine substitution to form 9,12-diiodo-1,2-carborane **13**; then treatment with alkyl Grignard reagent in the presence of a palladium catalyst affords 9,12-Me₂-1,2-carborane **14**, which can be deprotonated at the carbon vertices in the same manner as the parent **7**. Using the same strategy to prepare cyclic trimer **5**, dimethyl **14** is deprotonated and treated with mercuric acetate to form *B*-hexamethyl-[9]-mercuracarborand-3 **15** in 60% yield (Equation 1).



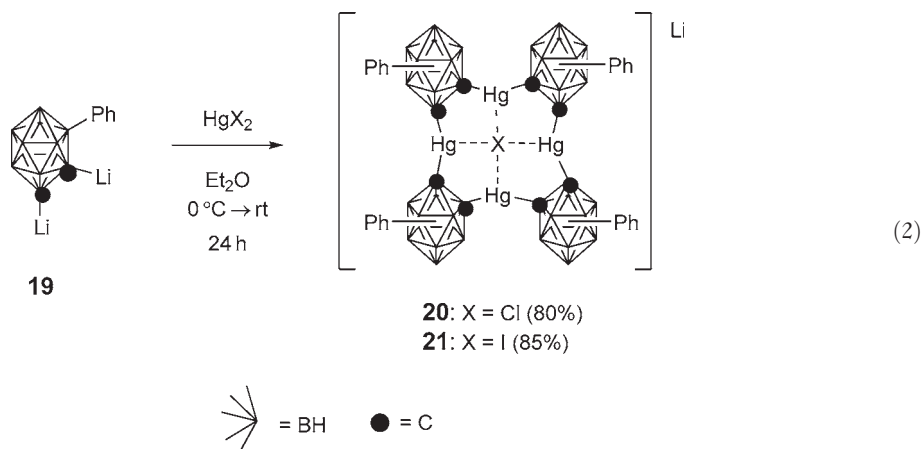
The vertices adjacent to the 9- and 12-positions in 1,2-carborane **7** are the 8- and 10-positions. Methyl substitution at the 8-, 9-, 10-, and 12-boron vertices is done by reacting *closo*-1,2-C₂B₁₀H₁₂ **7** with excess methyl iodide in triflic acid giving *closo*-8,9,10,12-Me₄-1,2-C₂B₁₀H₈ **16** in 65% yield (Scheme 2). This reaction shows great selectivity since only the boron vertices, furthest from the carbon vertices, are substituted. Deprotonation of tetramethyl carborane **16** followed by



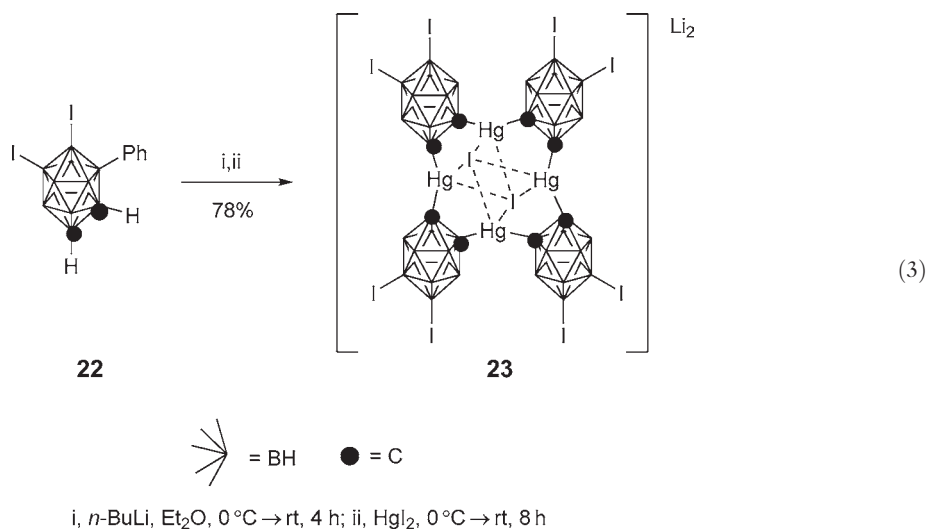
Scheme 2

treatment with mercuric iodide gives diiodide complex **17** in 78% yield. Quantitative decomplexation of **17** is achieved by treatment with silver acetate in acetone at room temperature to give *B*-hexadecamethyl-[12]-mercuracarborand-4 **18**. An alternative method of decomplexation uses silver tetrafluoroborate in acetone <2004AGE1854>.

Phenyl-substituted mercuracarborands can be prepared from their corresponding phenyl-substituted carboranes <1995JA5105> (Equation 2). By using the same methodology to prepare parent tetramer chloride **9** and iodide **11**, *closo*-3-Ph-1,2-Li₂-1,2-C₂B₁₀H₉ **19** is converted to tetramer [3-PhC₂B₁₀H₉Hg]₄·ClLi **20** in 80% yield by treatment with mercuric chloride and [3-PhC₂B₁₀H₉Hg]₄·ILi **21** by treatment with mercuric iodide in 85% yield. Reaction of with mercuric acetate does not produce the expected cyclic trimer but produces an acyclic oligmer instead. It is interesting to note that **20** and **21** have four possible stereoisomers. Only one isomer is formed by treatment with mercuric iodide, whereas mercuric chloride produced a mixture of isomers. Thus, halides are acting as templates to control the cyclization process and effect the product distribution. This is the first reported example of an anion demonstrating simultaneous stereochemical and template control in a cyclization reaction.



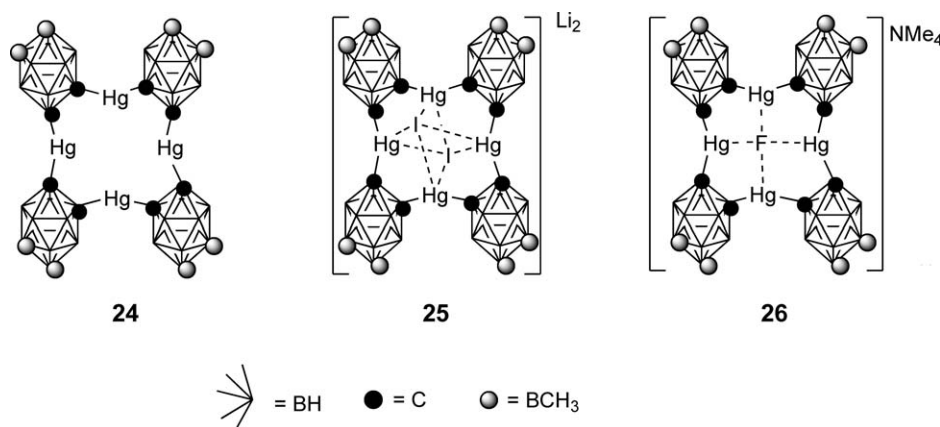
Halogen-substituted mercuracarborands can be prepared from their halogenated substituted carborands <2001AGE2124>. *closo*-9,12-I₂-1,2-C₂B₈H₁₀ **22** can be deprotonated and treated with mercuric iodide to give the bis-iodo-tetramer **23** in 78% yield (Equation 3). The starting bis-iodo-carborane **22** is prepared by electrophilic iodination of the 9,12-vertices of 1,2-carborane.



14.21.2.1.2 Structure elucidation

Although ¹H, ¹³C, and ¹¹B nuclear magnetic resonance (NMR) spectroscopy is routinely used to characterize mercuracarborands and their complexes, it has been proved to be of little value in studying their guest–host

interactions. Strong anion–mercury interactions make ^{199}Hg NMR analysis a more sensitive tool for studying the environment within the macrocycle cavity. Uncomplexed *B*-octamethyl-[12]-mercuracarborand-4 **24** show ^{199}Hg NMR resonances at -1280 ppm (in acetone- d_6) and -1213 ppm (in CH_2Cl_2). Halide complexes of this macrocycle show significant ^{199}Hg signal shifts at -667 ppm (in acetone- d_6) for its diiodide complex **25** and at -1181 ppm (in CH_2Cl_2) for its fluoride complex **26** <2004AGE1854>.



X-Ray crystallographic analysis of fluoride anion complex of *B*-octamethyl-[12]-mercuracarborand-4 **26** shows that the fluoride ion is located at the center of the four coplanar mercury atoms. In comparison, chloride and bromide complexes have halide ions located above the mercury array while the diiodide complex has iodide ions positioned one above and one below the ring <2004AGE1854>. Nitrate ion complexes with [12]-mercuracarbonad-4 **6** to form a bent-butterfly-type structure <1999IC2227>. Comparison of iodide complexes of parent [12]-mercuracarborand-4 **12** with *B*-hexadecamethyl-[12]-mercuracarborand-4 **17**, by X-ray diffraction studies, shows that methyl-substituted complex has longer Hg–I distances than complex **12** <1996IC1235>. The Hg–I distances are equal in **17**, but **12** has three short Hg–I bonds and one longer bond. Apparently iodine–iodine interaction in the tightly bound complex **12** causes asymmetrical Hg–I binding.

14.21.2.1.3 Physical properties

The parent unsubstituted mercuracarborands **5** and **6** are only soluble in electron-donor solvents, which coordinate with the mercury atoms and reduces their potential as homogenous catalysts <1997ACR267>. Modification of the carborane cages with lipophilic substituents (aryl and alkyl) increases the solubility in hydrocarbon solvents (e.g., dichloromethane (DCM) and toluene). Fluoride complex **26** is a moisture- and air-stable solid <2004AGE1854>.

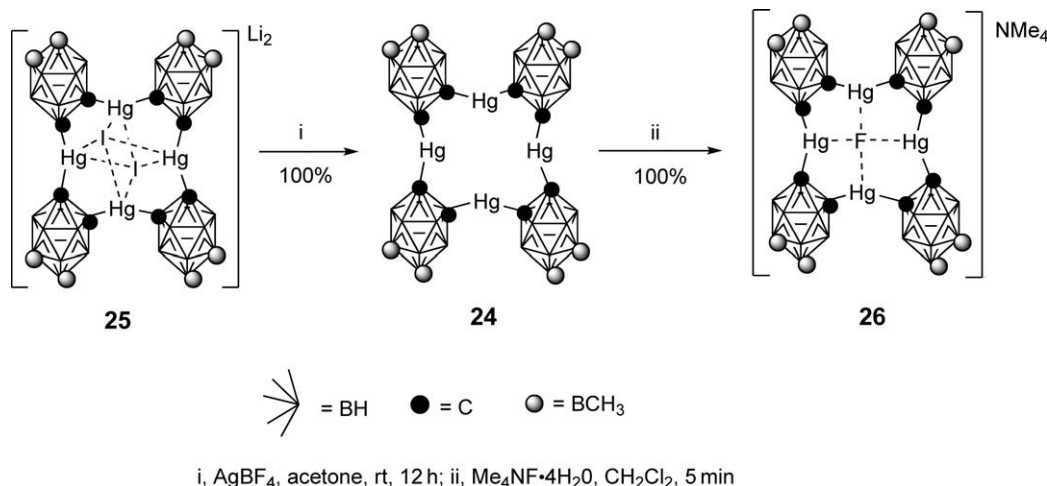
14.21.2.1.4 Chemical properties

Organomercury compounds have Lewis acid character stemming from two empty *p* orbitals situated perpendicular to the metal–carbon bond <1997ACR267>. The mercury carbon bond is especially strong, and the two ligands are collinear making them configurationally very stable. These features allow for the construction of nearly flat ring systems having the ability to bind well with Lewis bases. One of the advantages of Lewis acid hosts is electroneutrality, which allows them to selectively bind with desired anions and reduce ever-present internal competitive binding with counteranions. In particular, mercury is uniquely suited to act as the Lewis acid site and is the reason of rapid progress in this area.

By choosing the proper ring size and carborane substituents of the macrocycle, the cavity size and Lewis acidity can be adjusted to the requirements of a particular anion. Mercuracarborands form complexes with various electron-donating species such as halides, nitrate ion, tetrahydrofuran, MeCN, polyhedral borane, and benzene/water <1999IC2227, 2001AGE3058>. *B*-Hexamethyl-[9]-mercuracarborand-3 **15** forms octahedral coordinated 2:1 host–guest complexes with bromide, iodide, and chloride anions <2000AGE776, 2001JA8543>. The halide ion is sandwiched between two mercuracarborand rings. Macrocycle **15** complexes with benzene and water to form a π -sandwich structure, $[(\mathbf{15} \cdot \text{H}_2\text{O})_2 \cdot \text{C}_6\text{H}_6]$, with benzene located between the two rings <2001AGE3058>.

14.21.2.1.5 Important compounds and applications

The fluoride ion complex of *B*-octamethyl-[12]-mercuracarborand-4 **26** is an effective source of ‘naked fluoride’ <2004AGE1854>. Treatment of a tosylated sugar with fluoride **26**, in the presence of tetra-*n*-butyl ammonium iodide **27**, leads to 49% tosylate replacement. The reaction does not occur without co-reagent **27**, so presumably its role is to help release fluoride ion from complex **24**. Scheme 3 illustrates the preparation of fluoride reagent **26** by decomplexation of diiodide **25** with AgBF₄ forming neutral tetramer **24**, followed by treatment with tetramethylammonium fluoride.



Scheme 3

The ability of mercuracarborands to selectively bind anions has potential applications for anion sensing. An ion-selective electrode, containing ionophore [9]-mercuracarborand-3 **5**, shows selectivity for chloride in the presence of other anions. This type of electrode has the potential for analysis of chloride in physiological fluids <1999ANC1371, 1999USP5985117, 2000ANC4249, 2003MI1244>. Mercuracarborands containing alkyl substitution, such as *B*-hexamethyl-[9]-mercuracarborand-3 **15**, are less selective toward chloride due to decreased Lewis acidity <2003MI1244>.

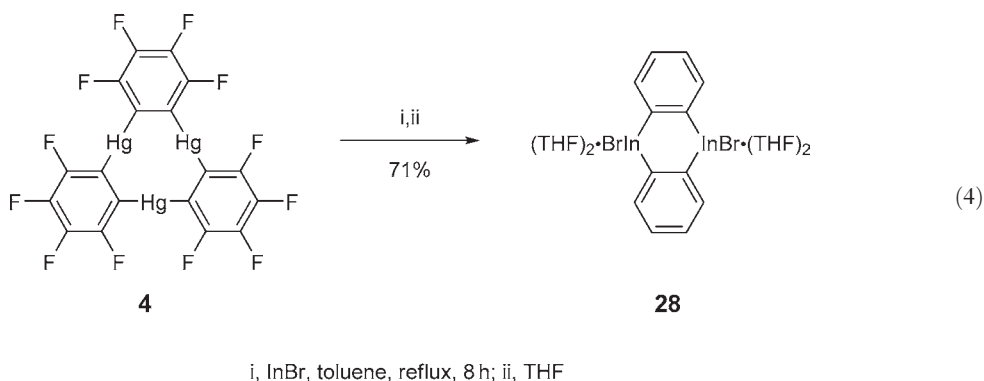
Unsubstituted mercuracarborands have poor solubility in noncoordinating solvents, and, therefore, are poor candidates as homogenous catalysts. This problem was overcome with the development of alkyl-substituted mercuracarborands, such as *B*-hexamethyl-[9]-mercuracarborand-3 **15**, which catalyzes the Diels–Alder reaction of *O*-methyl *trans*-2-butenthioate and cyclopentadiene giving the *endo*-isomer in 99% selectivity and 83% yield <1999TL7651>.

14.21.2.2 Miscellaneous Polymercuramacrocycles

Pentamercuramacrocycle **3** is planar and can host various anions. It complexes two halide anions (Cl[−], Br[−], I[−]) bound above and below the ring structure <1997CRV1609>. This macrocycle is an effective phase-transfer agent <1994IZV2047>. A two-phase solution (benzene/nitrobenzene and nitric acid) containing NaNO₂ and NaCl converts acenaphthene to 5-nitro- and 3-nitroacenaphthenes in ca. 9:1 ratio, respectively, in near quantitative yield. This reaction occurs at room temperature in 10 min. Kinetic studies show that **3** increases the initial nitration rate by a factor of 3300. Sodium chloride also plays a key role in the reaction, since its absence reduces the nitration rate.

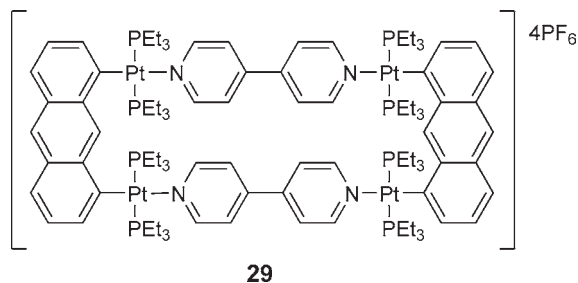
Trimeric perfluoro-*o*-phenylenemercury **4** forms complexes with borohydride [(*o*-C₆F₄Hg)₃](BH₄)[−], [(*o*-C₆F₄Hg)₃](BH₄)₂^{2−}, and [(*o*-C₆F₄Hg)₃](BH₄)[−]. Theoretical calculations show that these complexes have half-sandwich, bipyrimidal, and sandwich structures, respectively <2001CEJ3783>. Polyhedral borane anion *closo*-[B₁₀H₁₀]^{2−} reacts with **4** giving two complexes [(*o*-C₆F₄Hg)₃](B₁₀H₁₀)^{2−} and [(*o*-C₆F₄Hg)₃]₂(B₁₀H₁₀)^{2−} as half-sandwich and sandwich structures, respectively. Reaction of polyhedral *closo*-[B₁₂H₁₂]^{2−} with **4** forms complexes [(*o*-C₆F₄Hg)₃](B₁₂H₁₂)^{2−} and [(*o*-C₆F₄Hg)₃]₂(B₁₂H₁₂)^{2−}, also having half-sandwich and sandwich structures, respectively <2001CEJ3783>.

Macrocycle **4** can be converted into diindacycle **28**, in 71% yield, by treating **4** with InBr in refluxing toluene; then addition of THF leads to **28** (Equation 4) <1998IC5097>.



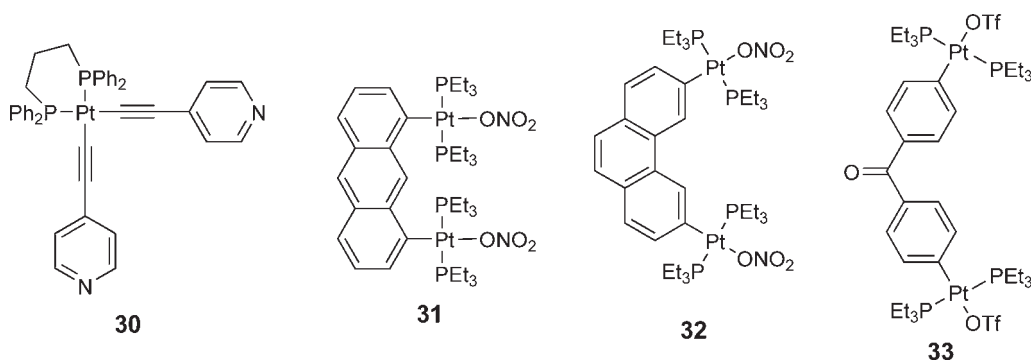
14.21.3 Metallomacrocycles with Platinum and Palladium Atoms

Advances in macrocycles containing platinum and palladium have grown considerably in the past decade. This is due to recent developments in the field of molecular architecture, which has dramatically improved preparation of large-membered rings. Traditional methods of synthesis using multistep linear reaction sequences have inherent disadvantages for these systems. It can be a time-consuming process generating numerous reaction by-products resulting in lower yields and separation challenges. If the product and intermediates contain only covalent bonds, the undesired by-products are not easily transformed to intended molecules. In comparison, nature forms highly complex structures through a process of self-assembly, by which covalent substructures are combined using non-covalent bonding. These weaker bonds (hydrogen bonding, π - π -stacking, and other weak forces) are reversible and allow the most thermodynamically stable configuration to exist. Therefore, natural systems are self-correcting and form essentially defect-free structures. Recent developments in coordination chemistry have allowed mimicking of nature by using metal-ligand bonds to assemble supermolecular architectures <1996BCJ1471, 1997ACR502, 1998CEJ19, 1998CSR289, 1998JCD1707, 2000CRV3483, 2000CRV853>. Moderate-strength coordinate bonds offer certain advantages over weaker natural bonds. They are stronger (10–30 kcal) so fewer bonds are required to hold the structure together, but not so strong as to prevent thermodynamic processes from correcting mistakes. Metal-ligand bonds are also highly directional, so the correct choice of substructures can allow precise molecular construction. The intelligent design of large molecules, therefore, is achieved by the use of discrete building blocks containing the correct bond geometry that directs the course of the self-assembly and contains the desired shape and functionality. Employing a directional-bonding approach using a combinatorial library of different building blocks, referred to as tectons, has allowed numerous ring systems to be prepared. Broadly classified, rings containing two-dimensional (2-D) geometries (square, triangle, rectangle, pentagon, and rhomboid) and 3-D shapes (cages, tetrahedral, cubic) have been prepared this way. Macrocycle **29** illustrates an example of a rectangular metallocycle. More specifically, Pt–C and Pd–C σ -bonded complexes have been prepared that contain unique functionality and nano-architecture; examples include: chirality <2006OL1701>; crown ether incorporation <2006JOC6623>; various geometric shapes (square, triangle, rectangle, rhomboid, and hexagon) <1997JA4777, 1997PAC1979, 2004OM4382, 2004JA2464, 2005JOC797, 2006JOC6644>; bowl-shaped (cavitands) <2006JOC4155>; dendrimer elements <2006JA10014>; carborane-containing <2005JOC10440, 2005JA12131>; oxocarbon dianions, oxalate, and carboxylate linkers <2005IC7130>; ferrocene <2005IC5798>; diaza-crown ether <2004JOC2910>; 3-D cages and prisms <2002PNA4932, 2002OL913, 2003JA9647, 2004JOC964>; bipyridyl, pyridyl-carboxylate ligands <2003JOC9798, 2004JA16569>; and self-recognition <2004IC5335>.

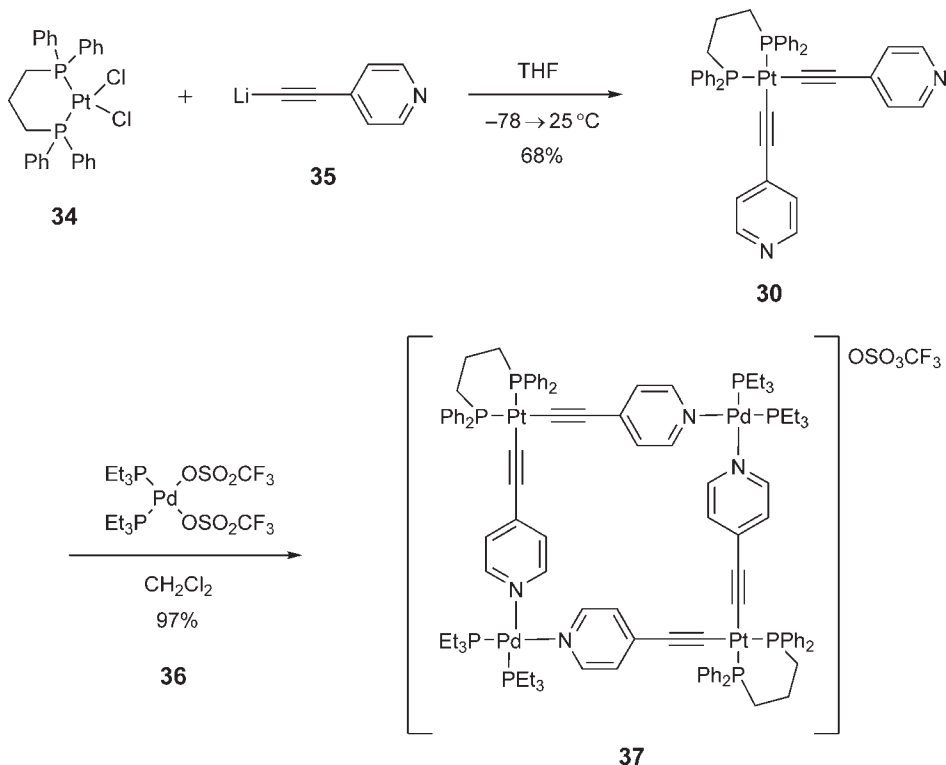


14.21.3.1 Synthesis

The design and preparation of subunits that constitute the desired macrocycle are at the core of the directional-bonding method of synthesis. This is achieved by using acceptor subunits containing transition metals with coordination sites that bind with donor building blocks. The acceptor and donor groups need at least two coordination sites and the correct geometry to form a cyclic structure. This ideally occurs through a spontaneous self-assembly process. Platinum-based tectons **30–33** have been used to prepare numerous metallomacrocycles.

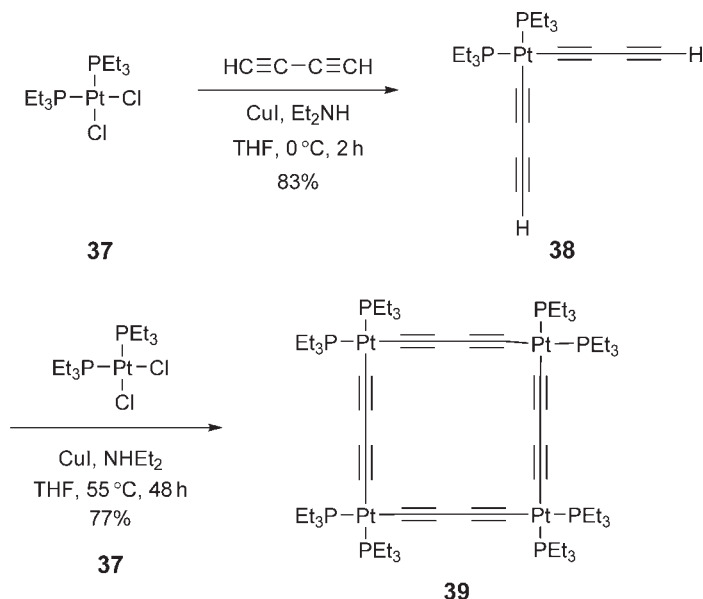


Square structures are prepared from metal complexes containing the required 90° angle. Shown in **Scheme 4**, neutral-charged molecular square **37** is prepared by spontaneous self-assembly of complex **30** and **36** <1997JA2524>. Synthesis of precursor complex **30** is accomplished by coupling of Pt(II) chloride **34** and ethynylpyridine anion **35**.



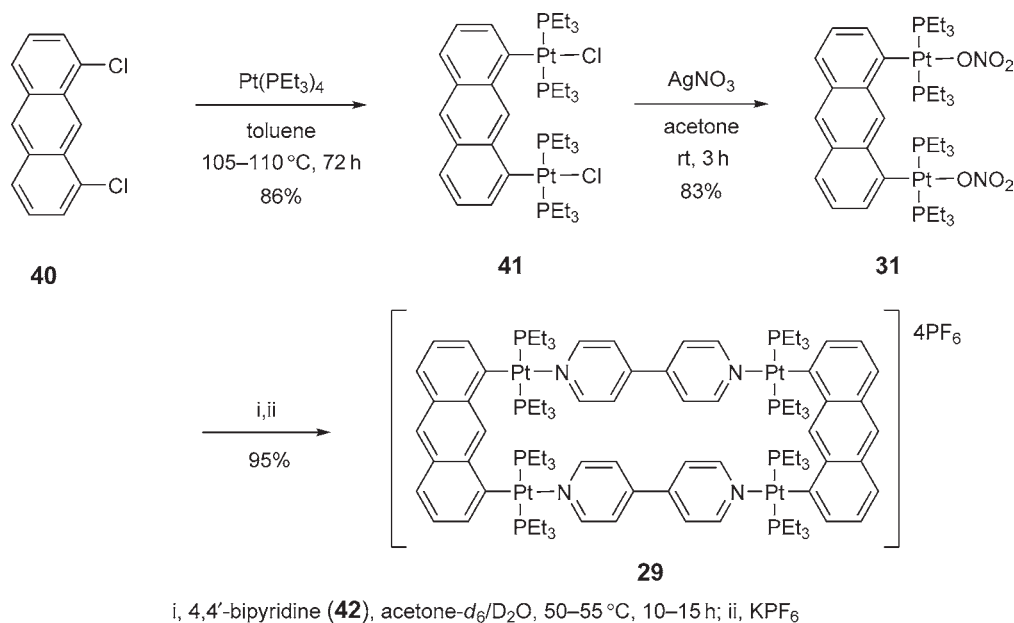
Scheme 4

Molecular square **39** is prepared by consecutive copper-catalyzed reactions (Scheme 5). The first corner unit **38** is prepared by reaction of *cis*-[PtCl₂(PEt₃)₂] **37** with butadiyne in tetrahydrofuran (THF) in the presence of CuI/Et₃N. Further coupling of the platinum complex **38**, in the presence of additional **37** and higher temperatures, affords air-stable square **39** in 77% yield. It is interesting to note that attempts to prepare squares using shorter ethynyl ligands failed presumably due to steric crowding of the smaller target square <2004OM4382>.



Scheme 5

Synthesis of rectangular macrocycles requires a building unit containing two parallel metal coordination sites facing in the same direction <2001JA9634, 2000OL3727>. Scheme 6 illustrates the self-assembly reaction of 4,4'-bipyridine **42** with tecton **31** to form rectangle **29**. Preparation of **31** begins with a double oxidative addition of 1,8-dichloroanthracene

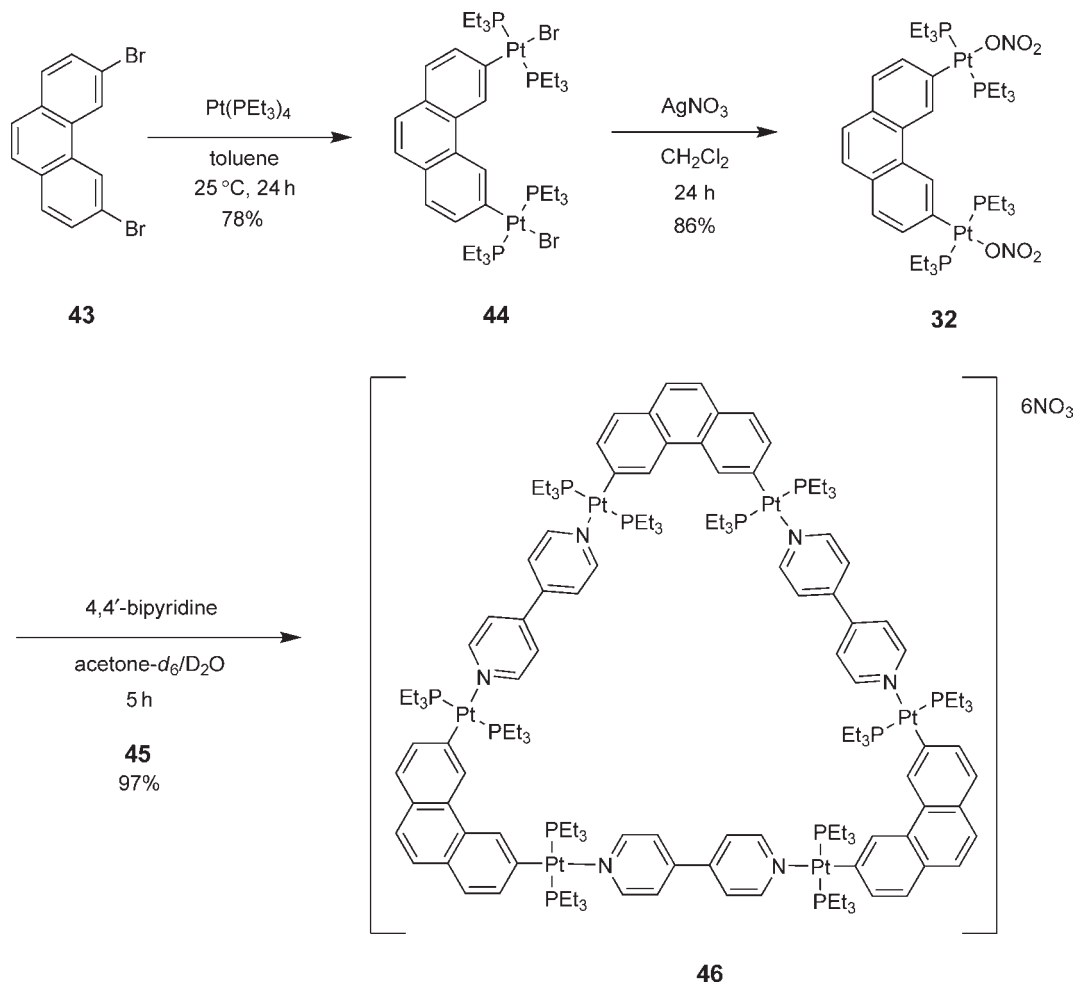


Scheme 6

with $\text{Pt}(\text{PEt}_3)_4$. Chloride replacement with the more labile nitrate ligand is achieved with silver nitrate in acetone. This two-step process gives nitrate **31** as an air- and moisture- stable solid in 71% overall yield. The self-assembly is accomplished in near-quantitative yield by simply heating platinum acceptor **31** with 4,4'-bipyridine **42** in an aqueous acetone solution. Upon complexation, the product is precipitated from a solution with KPF_6 .

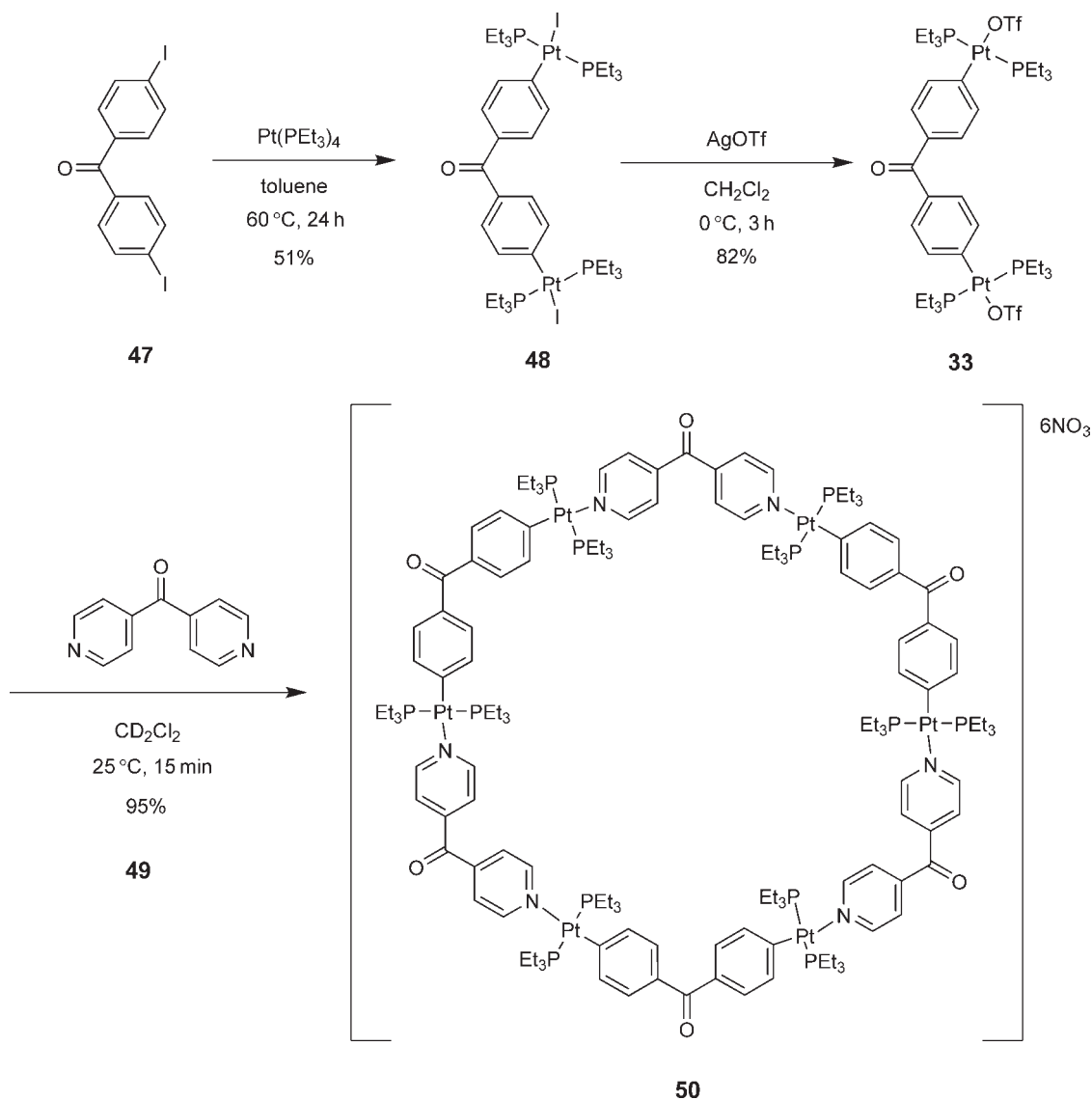
Building unit **31** is considered a molecular clip due to its rigid and parallel bonding geometry. These are important features since less rigid metal centers (e.g., 4,4'-biphenyl platinum complexes) form polymers instead of macrocycles. Early attempts using organic solvents (pure acetone, DCM, etc.) failed to self-assemble, so the reaction solvent needs to possess polar character. Nitrate plays an important role in the process as well by acting as a nucleophile that promotes a thermodynamic self-correcting process. This was shown by addition of a large excess of a weaker nucleophile (NH_4PF_6), which competes for nitrate, predominately resulting in oligomer formation (~70%). The strong nucleophilic character of nitrate is a detriment to isolating the product; however, this can be overcome through ion exchange (PF_6 for nitrate) in the final step.

Until recently, triangular macrocycles were difficult to prepare and consequently rarely reported. This is due to the fact subunits containing the requisite 60° were uncommon. Scheme 7 illustrates the synthesis of such a corner unit **32** and its use in preparing triangle **46** <2003JA5193>. Double oxidative addition of tetrakis(triethylphosphine)-platinum(0) with 2,9-dibromophenanthrene **43** provides dibromide intermediate **44**. Halide replacement using silver nitrate affords the corner tecton **32**, as an air-stable solid. Synthesis of triangle **46** is accomplished by self-assembly of corner unit **32** and linear linker 4,4'-bipyridyl **45** in aqueous acetone. After 5 h, **32** is completely dissolved and triangle **46** is produced in near-quantitative yield. The generality of this method is demonstrated since a variety of longer-length and different-shaped linear linkers react with **32** to form triangles in high yield.



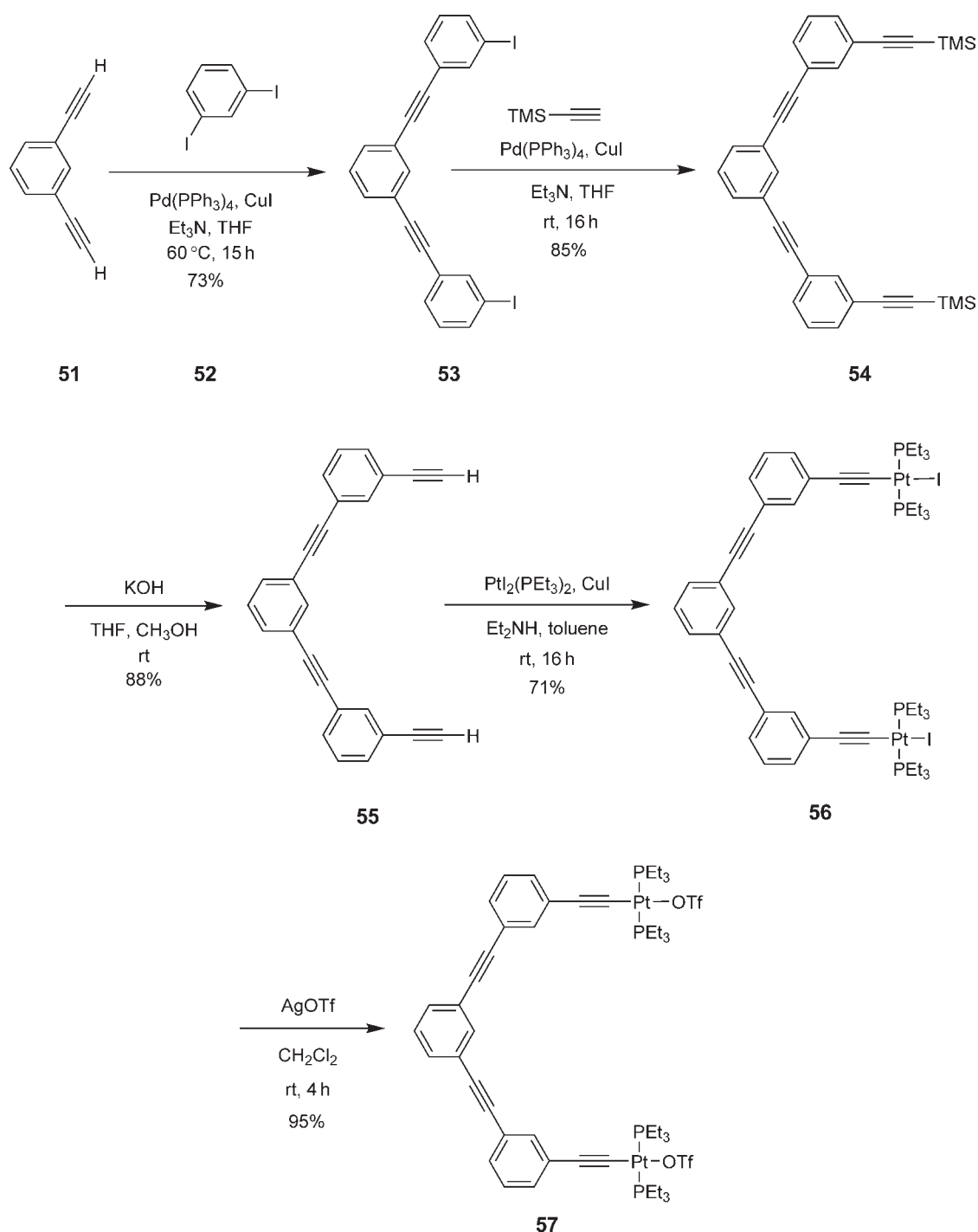
Scheme 7

Hexagonal macrocycle **50** is produced from a 120°-angle-tecton **33** and 120°-angle-linker **49** <1999OL1921> (Scheme 8). Tecton **33** is prepared by double oxidative addition of 4,4'-diiodobenzophenone **47** with tetrakis(triethylphosphine)platinum(II) followed by treatment with AgOTf. Bis(4-pyridyl)ketone **49** combines spontaneously with **33** at room temperature to form metallocycle **50**.



Scheme 8

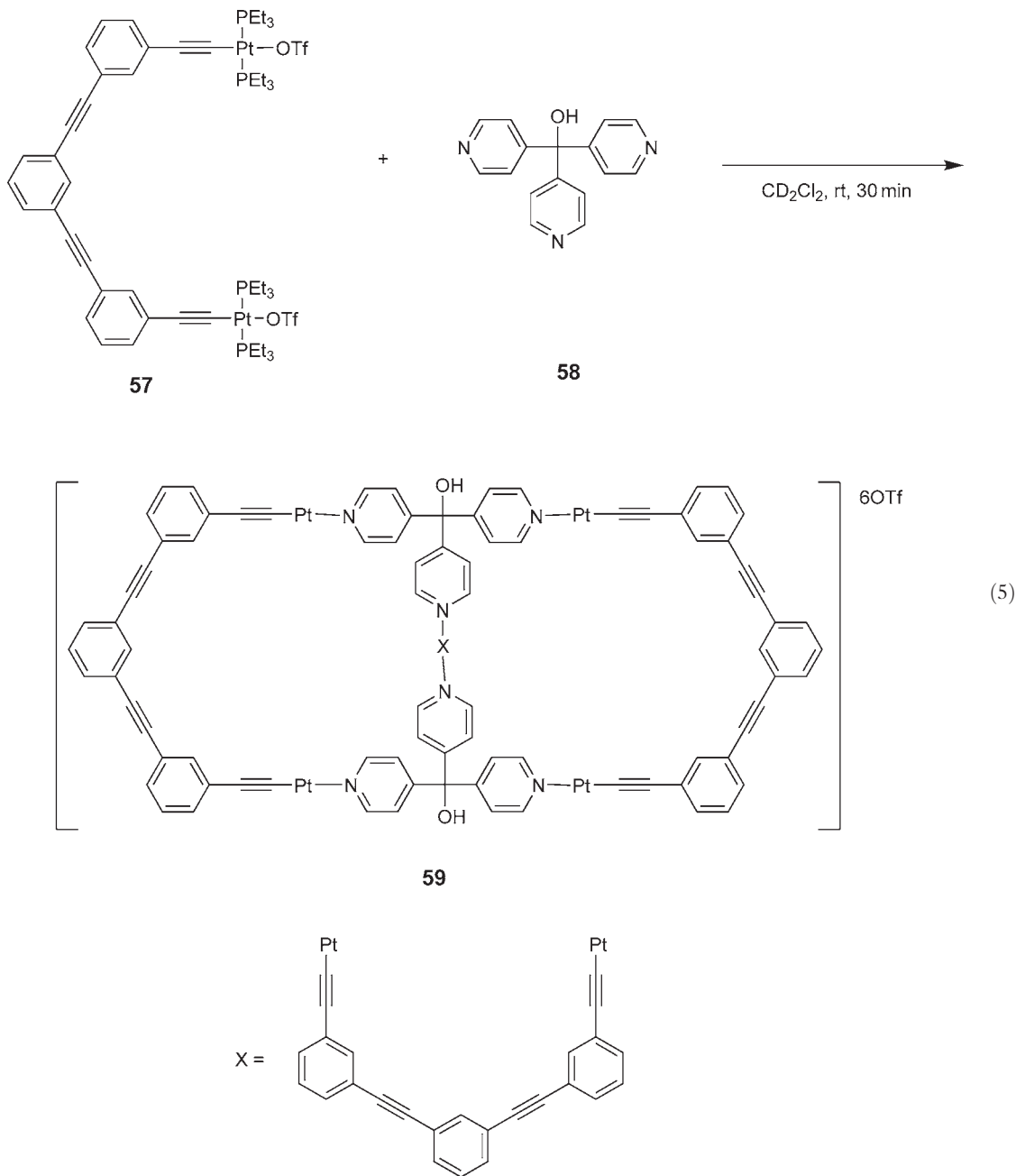
Three-dimensional cage structures can be prepared from the reaction of two tritopic donor ligands with three bidentate acceptors <2006OL3991>. The self-assembly approach allows the cavity size to be adjusted by using different size linkers. For example, cage structure **59** is prepared by the reaction of triflate **57** with tripod **58** (Equation 5). Synthesis of linker **57**, containing Pt σ -bonded acetylene units, begins with two Pd/Cu-catalyzed coupling reactions (Scheme 9). First, 1,3-diethynylbenzene **51** is coupled with 1,3-diiodobenzene **52** affording 1,3-bis(1-iodo-3-ethylphenyl)benzene **53**. A second coupling of **53** with (trimethylsilyl)acetylene followed by desilylation produces 1,3-bis(1,3-diethynylphenyl)benzene **55**. Reaction of **55** with *trans*- $\text{PtI}_2(\text{Et}_3)_2$ affords diiodoplatinum **56**, and finally iodide–triflate exchange using AgOTf produces tecton **57**.



Scheme 9

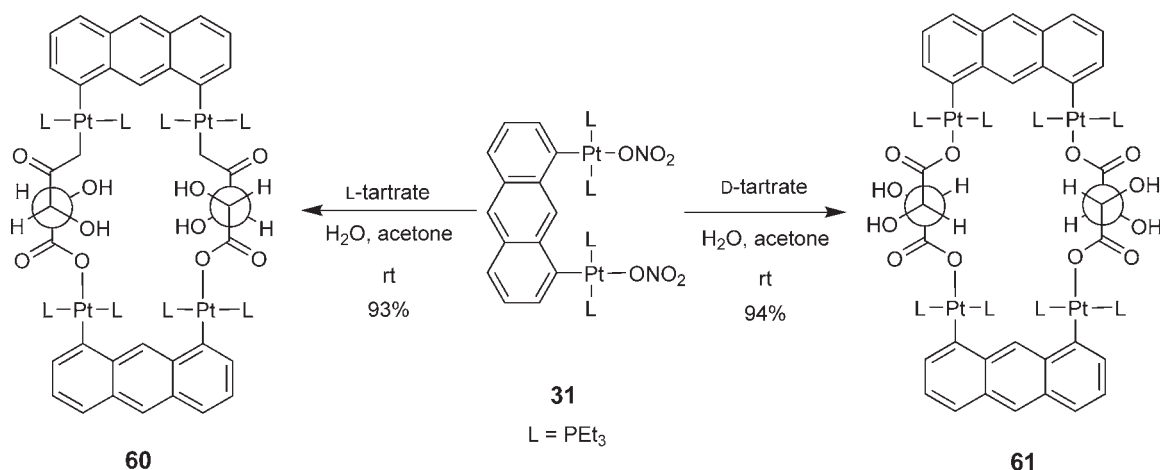
The parallel alignment of the metal coordination sites of **57** suggests that it would behave as a molecular clip similar to tecton **31**. However, the acetylene linkage in **57** provides greater flexibility by allowing the Pt-centers to rotate freely between 0° and 120° . As noted earlier in the preparation of rectangle **29**, flexible components are generally expected to make poor connectors for macrocycle synthesis because they allow noncyclic pathways to occur leading to oligomer by-products. Despite this, molecular clip **57** self-assembles nicely with tripod donor **58**, at room

temperature in 30 min, in 97% yield (Equation 5). Three other tripods also self-assembled to cages smoothly with **58**. These tripods vary in size and shape, demonstrating the general nature of this approach and allows for fine tuning of the cavity size.

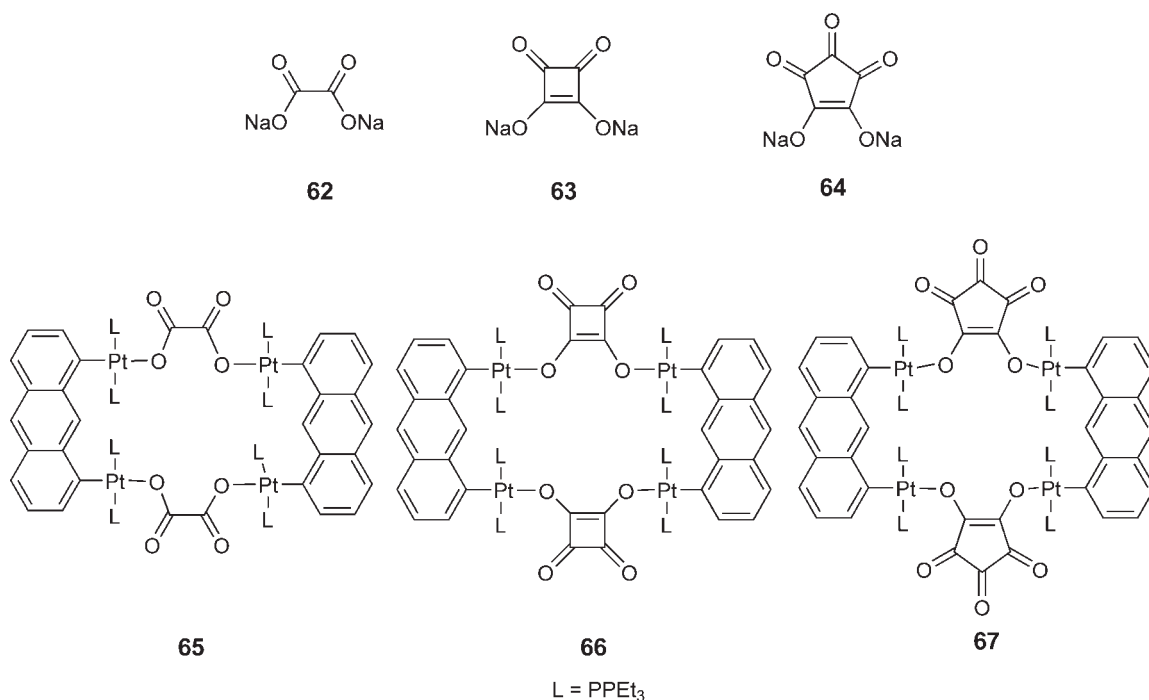


Chiral macrocycles are of interest in the area of enantioselective sensing and asymmetric catalysis. **Scheme 10** illustrates the use of tartrate anions to form chiral molecular rectangles **60** and **61** [<2006OL1701>](#). This strategy uses a self-assembly approach utilizing tartrates, as chiral bridging ligands, and diplatinum **31**, as molecular clips. Thus, disodium L-(+)-tartrate reacts with **31** rapidly in acetone to precipitate **60** in 93% yield. Reaction of disodium D-(–)-tartrate with **31** gives **61** in 94% yield.

The self-assembly methodology can be extended to linkers containing oxygen. Oxalate **62** and oxocarbon dianions **63** and **64** are rigid molecules that react immediately with tecton **31** in water/acetone to form neutral metallomacrocycles **65**, **66**, and **67**, respectively, in 90–98% yields <2005IC7130>.



Scheme 10



14.21.3.2 Structure Elucidation

These self-assembly reactions are easily monitored by multinuclear NMR techniques (^1H and $^{31}\text{P}\{^1\text{H}\}$) [<2000OL3727>](#). For example, the quantitative assembly of rectangle **29** is evident by $^{31}\text{P}\{^1\text{H}\}$ NMR analysis, which shows the formation of a single highly symmetrical molecule. The pyridyl proton signals of **29** have notable downfield shifts ($\Delta\delta \sim 0.5\text{ ppm}$) in the ^1H NMR, reflecting the reduced electron density caused by nitrogen complexation. The normally equivalent set of protons in 4,4'-bipyridine becomes nonequivalent in **29**, demonstrating the different environments inside versus outside the cavity. The reaction mixture of triangle **46** shows a sharp singlet at 14 ppm in the $^{31}\text{P}\{^1\text{H}\}$ NMR indicating the formation of essentially one product [<2003JA5193>](#). Similar to rectangle **29**, two sets of doublets in the ^1H NMR of **46**, corresponding to the α and β -pyridine protons, implies a

different environment inside the ring compared to outside the ring. Variable-temperature NMR analysis (25–120 °C) was used to determine the activation parameters for the rotation about the hindered Pt–N bond of rectangle **29** and triangle **46** <2005OL4971>. As mentioned earlier, the hindered rotation is characterized by the nonequivalent α - and β -pyridyl protons, which display two sets of doublets (A, B, C, and D) in **29** and **46**. The resonances of **29** coalesce at higher temperatures and reappear upon cooling. Interestingly, the resonances of **46** do not coalesce upon heating and actually separate more, indicating that **46** is more stable than **29**. Rectangle **29** has enthalpy of activation ($\Delta H^\ddagger$) = +52.2 kJ mol⁻¹ and entropy ($\Delta S^\ddagger$) = -58.2 J mol⁻¹ K⁻¹ compared to triangle **29** ($\Delta H^\ddagger$ = +59.1 kJ mol⁻¹, $\Delta S^\ddagger$ = -71.8 J mol⁻¹ K⁻¹). The greater number of Pt–N bonds in **46** possibly explains the higher rotational barrier for triangle **46** versus the rectangle **29**. NMR experiments revealed that the nitrate salt of **29** undergoes exchange with clip **31** and 4,4'-bipyridine at 26 °C in solution. The exchange is reduced by using the hexafluorophosphate salt and dropping the temperature to -40 °C <2001JA9634>.

X-Ray analysis of clip **31** reveals that it is rigid and the Pt centers are separated by 5.6 Å and parallel with a dihedral angle of 0° <2001JA9634>. The crystal structure of macrocycle **29** reveals that it is a slightly bowed rectangle <2000OL3727>. The structure is nearly planar with the pyridyl groups having only a small dihedral angle ($\theta \approx 9^\circ$). Wide-angle X-ray diffraction shows that triangle **46** and rectangle **29** in nitromethane solution maintain their general structure and shape but are less rigid when compared to single crystal data <2005JA10731>. Single crystal X-ray analysis of **46** shows a slightly distorted triangle with side dimensions of 2.7 nm and a cavity diameter of 1.4 nm. The triangles are layered in sheets in a head-to-tail fashion <2003JA5193>.

The chirality of tartrates **60** and **61** are confirmed by circular dichroism (CD) spectroscopy <2006OL1701>. Multiple bands in the CD spectra of **60** and **61** are due to tartrate dianions inducing CD in the anthracene rings. This is the first reported case of induced circular dichroism (ICD) observed in a chiral macrocycle.

Formation of a single cage species is confirmed by a single sharp peak at ca. 18.5 ppm in the ³¹P{¹H} NMR of **59**. MM2 force-field simulation shows the inner cavity of **59** to be about 3.2 nm. This is quite a bit larger than the inner cavity size (2.0 nm) of the cage generated from linker **31** with tripod **58** <2006OL3991>.

14.21.3.3 Physical Properties

The molecular rectangle **29** can behave as an electron reservoir by undergoing stepwise reversible oxidation or reduction <2002IC4025>. The anthracene functionality is believed to be involved in the oxidation while the bipyridyl ligand is responsible for the reduction.

14.21.3.4 Chemical Properties

The acetylene corners of molecular square **37** can bind with cations in a 'tweezer' fashion. Silver cations added to these corners (using silver triflate) form modified macrocycles which host a variety of neutral bases (pyridine, pyrazine, phenazine, and dipyridyl ketone) <1998IC5595, 1998JA9827>. The reaction by-product (diethylammonium chloride) of molecular square **39** is difficult to remove and is always detected in the ¹H NMR. This strong affinity is attributed to a 'tweezer' interaction between the corner acetylene groups and the ammonium cation <2004OM4382>.

Relevant Websites

<http://www.chem.ucla.edu/> – Hawthorne Lab, UCLA Department of Chemistry & Biochemistry.

<http://www.chem.utah.edu/> – Peter J. Stang (Faculty), Department of Chemistry, The University of Utah.

<http://www.ineos.ac.ru/> – Laboratory of Metal Complex Activation of Small Molecules, A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences.

<http://en.wikipedia.org/> – Supramolecular Chemistry, Wikipedia.

<http://nobelprize.org/> – Interview with Jean-Marie Lehn, The Nobel Prize Winner in Chemistry 1987, The Official Web Site of the Nobel Foundation.

References

- 1984CHEC(7)709 A. G. Anastassiou; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 7, p. 709.
- 1984CHEC(7)731 A. D. Hamilton; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 7, p. 731.

- 1984CHEC(7)763 G. R. Newkome, J. G. Traynham, and G. R. Baker; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, p. 763.
- 1987JA4714 J. D. Wuest and B. Zacharie, *J. Am. Chem. Soc.*, 1987, **109**, 4714.
- 1991AGE1507 X. Yang, C. B. Knobler, and M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1507.
- 1993JA193 X. Yang, Z. Zheng, C. B. Knobler, and M. F. Hawthorne, *J. Am. Chem. Soc.*, 1993, **115**, 193.
- 1994IZV2047 A. P. Zaisky, O. I. Kachurin, L. I. Velichko, I. A. Tikhonova, A. Y. Volkonsky, and V. B. Shur, *Izv. Akad. Nauk. SSSR Ser. Khim.*, 1994, 2047 (*Russ. Chem. Bull. (Engl.)*, 1994, **43**, 1936).
- 1994JA7142 X. Yang, C. B. Knobler, Z. Zheng, and M. F. Hawthorne, *J. Am. Chem. Soc.*, 1994, **116**, 7142.
- 1995JA5105 Z. Zheng, C. B. Knobler, and M. F. Hawthorne, *J. Am. Chem. Soc.*, 1995, **117**, 5105.
- 1996BCJ1471 M. Fujita and K. Ogura, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1471.
- 1996CHEC-II(9)1033 R. Murugan and M. Sutharchanadevi; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 1033.
- 1996IC1235 Z. Zheng, C. B. Knobler, M. D. Mortimer, G. Kong, and M. F. Hawthorne, *Inorg. Chem.*, 1996, **35**, 1235.
- 1996JA70 A. A. Zinn, Z. Zheng, C. B. Knobler, and M. F. Hawthorne, *J. Am. Chem. Soc.*, 1996, **118**, 70.
- 1996JOM(508)271 I. A. Tikhonova, F. M. Dolgushin, A. I. Yanovsky, Yu. T. Struchkov, A. N. Govrilova, L. N. Saitkulova, E. S. Shubina, L. M. Epstein, G. G. Furin, and V. B. Shur, *J. Organomet. Chem.*, 1996, **508**, 271.
- 1997ACR267 M. F. Hawthorne and Z. Zheng, *Acc. Chem. Res.*, 1997, **30**, 267.
- 1997ACR502 P. J. Stang and B. Olenyuk, *Acc. Chem. Res.*, 1997, **30**, 502.
- 1997CRV1609 F. P. Schmidtchen and M. Berger, *Chem. Rev.*, 1997, **97**, 1609.
- 1997JA2524 J. A. Whiteford, C. V. Lu, and P. J. Stang, *J. Am. Chem. Soc.*, 1997, **119**, 2524.
- 1997JA4777 P. J. Stang, N. E. Persky, and J. Manna, *J. Am. Chem. Soc.*, 1997, **119**, 4777.
- B-1997MI1 A. Bianchi, K. Bowman-James, and E. Garcia-España, Eds.; 'Supramolecular Chemistry of Anions', Wiley-VCH, New York, 1997.
- 1997PAC1979 D. H. Cao, K. Chen, J. Fan, J. Manna, B. Olenyuk, J. A. Whiteford, and P. J. Stang, *Pure Appl. Chem.*, 1997, **69**, 1979.
- 1997PIC(46)1 P. D. Beer and D. K. Smith; in 'Progress in Inorganic Chemistry', K. D. Karlin, Ed.; Wiley, New York, 1997, vol. 46, p. 1.
- 1998CEJ19 P. J. Stang, *Chem. Eur. J.*, 1998, **4**, 19.
- 1998CSR289 C. J. Jones, *Chem. Soc. Rev.*, 1998, **27**, 289.
- 1998CSR417 M. Fujita, *Chem. Soc. Rev.*, 1998, **27**, 417.
- 1998IC5097 M. Tschinkel, A. Schier, J. Riede, and F. P. Gabbai, *Inorg. Chem.*, 1998, **37**, 5097.
- 1998IC5595 J. A. Whiteford and P. J. Stang, *Inorg. Chem.*, 1998, **37**, 5595.
- 1998JA9827 C. Müller, J. A. Whiteford, and P. J. Stang, *J. Am. Chem. Soc.*, 1998, **120**, 9827.
- 1998JCD1707 B. Olenyuk, A. Fechtenkötter, and P. J. Stang, *J. Chem. Soc., Dalton Trans.*, 1998, 1707.
- 1999ACR975 D. L. Caulder and K. N. Raymond, *Acc. Chem. Res.*, 1999, **32**, 975.
- 1999ANC1371 I. H. A. Badr, M. Diaz, M. F. Hawthorne, and L. G. Bachas, *Anal. Chem.*, 1999, **71**, 1371.
- 1999IC2227 A. A. Zinn, C. B. Knobler, D. E. Harwell, and M. F. Hawthorne, *Inorg. Chem.*, 1999, **38**, 2227.
- 1999OL1921 S. Leininger, M. Schmitz, and P. J. Stang, *Org. Lett.*, 1999, **1**, 1921.
- 1999TL7651 H. Lee, M. Diaz, and M. F. Hawthorne, *Tetrahedron Lett.*, 1999, **40**, 7651.
- 1999USP5985117 L. G. Bachas, M. F. Hawthorne, and I. H. A. Badr, *US Pat. 5 985 117* (1999) (*Chem. Abstr.*, **131**, 343458).
- 2000AGE776 H. Lee, M. Diaz, C. B. Knobler, and M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 776.
- 2000ANC4249 I. H. A. Badr, R. D. Johnson, M. Diaz, M. F. Hawthorne, and L. G. Bachas, *Anal. Chem.*, 2000, **72**, 4249.
- 2000CRV853 S. Leininger, B. Olenyuk, and P. J. Stang, *Chem. Rev.*, 2000, **100**, 853.
- 2000CRV3483 G. F. Swiegers and T. J. Malefeste, *Chem. Rev.*, 2000, **100**, 3483.
- 2000OL3727 C. J. Kuehl, C. L. Mayne, A. M. Arif, and P. J. Stang, *Org. Lett.*, 2000, **2**, 3727.
- 2001AGE486 P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 486.
- 2001AGE2022 B. J. Holliday and C. A. Mirkin, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 2022.
- 2001AGE2124 H. Lee, C. B. Knobler, and M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 2124.
- 2001AGE3058 H. Lee, C. B. Knobler, and M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3058.
- 2001CEJ3783 E. S. Shubina, I. A. Tikhonova, E. V. Bakhmutova, F. M. Dolgushin, M. Y. Antipin, V. I. Bakhmutov, I. B. Sivaev, L. N. Teplitskaya, I. T. Chizhevsky, I. V. Pisareva, V. I. Bregadze, L. M. Epstein, and V. B. Shur, *Chem. Eur. J.*, 2001, **7**, 3783.
- 2001JA8543 H. Lee, C. B. Knobler, and M. F. Hawthorne, *J. Am. Chem. Soc.*, 2001, **123**, 8543.
- 2001JA9634 C. J. Kuehl, S. D. Huang, and P. J. Stang, *J. Am. Chem. Soc.*, 2001, **123**, 9634.
- 2002ACR972 S. R. Seidel and P. J. Stang, *Acc. Chem. Res.*, 2002, **35**, 972.
- 2002IC4025 W. Kaim, B. Schwederski, A. Dogan, J. Fiedler, C. J. Kuehl, and P. J. Stang, *Inorg. Chem.*, 2002, **41**, 4025.
- 2002OL913 C. J. Kuehl, T. Yamamoto, S. R. Seidel, and P. J. Stang, *Org. Lett.*, 2002, **4**, 913.
- 2002PNA4932 C. J. Kuehl, Y. K. Kryschenko, U. Radhakrishnan, S. R. Seidel, S. D. Huang, and P. S. Stang, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 4932.
- 2003JA5193 Y. K. Kryschenko, S. R. Seidel, A. M. Arif, and P. J. Stang, *J. Am. Chem. Soc.*, 2003, **125**, 5193.
- 2003JA9647 Y. K. Kryschenko, S. R. Seidel, D. C. Muddiman, A. I. Nepomuceno, and P. J. Stang, *J. Am. Chem. Soc.*, 2003, **125**, 9647.
- 2003JOC9798 K-W. Chi, C. Addicott, A. M. Arif, N. Das, and P. J. Stang, *J. Org. Chem.*, 2003, **68**, 9798.
- 2003MI1244 R. D. Johnson, I. H. A. Badr, M. Diaz, T. J. Wedge, M. F. Hawthorne, and L. G. Bachas, *Electroanalysis*, 2003, **15**, 1244.
- 2004AGE1854 M. J. Bayer, S. S. Jalisatgi, B. Smart, A. Herzog, C. B. Knobler, and M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 1854.
- 2004IC5335 C. Addicott, N. Das, and P. J. Stang, *Inorg. Chem.*, 2004, **43**, 5335.
- 2004JA16569 K-W. Chi, C. Addicott, A. M. Arif, and P. J. Stang, *J. Am. Chem. Soc.*, 2004, **126**, 16569.
- 2004JA2464 P. S. Mukherjee, N. Das, Y. K. Kryschenko, A. M. Arif, and P. J. Stang, *J. Am. Chem. Soc.*, 2004, **126**, 2464.
- 2004JOC964 K-W. Chi, C. Addicott, Y. K. Kryschenko, and P. J. Stang, *J. Org. Chem.*, 2004, **69**, 964.
- 2004JOC2910 K-W. Chi, C. Addicott, and P. J. Stang, *J. Org. Chem.*, 2004, **69**, 2910.
- 2004OM4382 M. Janka, G. K. Anderson, and N. P. Rath, *Organometallics*, 2004, **23**, 4382.
- 2005ACR369 M. Fujita, M. Tominaga, A. Hori, and B. Therrien, *Acc. Chem. Res.*, 2005, **38**, 369.

- 2005IC5798 N. Das, A. M. Arif, P. J. Stang, M. Sieger, B. Sarkar, W. Kaim, and J. Fiedler, *Inorg. Chem.*, 2005, **44**, 5798.
- 2005IC7130 N. Das, A. Ghosh, A. M. Arif, and P. J. Stang, *Inorg. Chem.*, 2005, **44**, 7130.
- 2005JA10731 T. Megyes, H. Jude, T. Grósz, I. Bakó, T. Radnai, G. Tárkányi, G. Pálincás, and P. J. Stang, *J. Am. Chem. Soc.*, 2005, **127**, 10731.
- 2005JA12131 H. Jude, H. Disteldorf, S. Fischer, T. Wedge, A. M. Hawkrige, A. M. Arif, M. F. Hawthorne, D. C. Muddiman, and P. J. Stang, *J. Am. Chem. Soc.*, 2005, **127**, 12131.
- 2005JOC797 C. Addicott, I. Oesterling, T. Yamamoto, K. Müllen, and P. J. Stang, *J. Org. Chem.*, 2005, **70**, 797.
- 2005JOC10440 N. Das, P. J. Stang, A. M. Arif, and C. F. Campana, *J. Org. Chem.*, 2005, **70**, 10440.
- 2005OL4971 G. Tárkányi, H. Jude, G. Pálincás, and P. J. Stang, *Org. Lett.*, 2005, **7**, 4971.
- 2006JA10014 H.-B. Yang, N. Das, F. Huang, A. M. Hawkrige, D. C. Muddiman, and P. J. Stang, *J. Am. Chem. Soc.*, 2006, **128**, 10014.
- 2006JOC4155 H. Jude, D. J. Sinclair, N. Das, M. S. Sherburn, and P. J. Stang, *J. Org. Chem.*, 2006, **71**, 4155.
- 2006JOC6623 F. Huang, H.-B. Yang, N. Das, U. Maran, A. M. Arif, H. W. Gibson, and P. J. Stang, *J. Org. Chem.*, 2006, **71**, 6623.
- 2006JOC6644 H.-B. Yang, N. Das, F. Huang, A. M. Hawkrige, D. D. Diaz, A. M. Arif, M. G. Finn, D. C. Muddiman, and P. J. Stang, *J. Org. Chem.*, 2006, **71**, 6444.
- 2006OL1701 N. Das, A. Ghosh, O. M. Singh, and P. J. Stang, *Org. Lett.*, 2006, **8**, 1701.
- 2006OL3991 H.-B. Yang, K. Ghosh, N. Das, and P. J. Stang, *Org. Lett.*, 2006, **8**, 3991.

Biographical Sketch



A native of Long Island, New York, Timothy P. Meagher received his B.A. from SUNY Potsdam, Potsdam, New York, in 1981. Following a brief stint in industry, he earned his Ph.D. at Ohio State University in 1988. He joined the research department at Reilly Industries, Inc. in 1988. During his tenure there he worked in the area of pyridine chemistry. In particular, projects involved gas phase synthesis, ammoxidation, chlorination, and hydrogenation of pyridine compounds. Publications include contribution to Chemistry of Heterocyclic Compounds II and a patent on hydrogenation of 2-ethanol pyridine. He left Reilly Industries, Inc. in 2001 and is currently a consultant for TEKA Consulting.

14.22

Multiple Macroheterocyclic Rings

A. M.-P. Pederson and H. W. Gibson

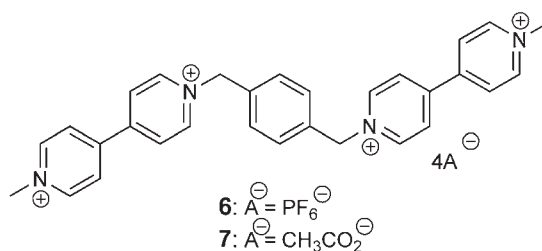
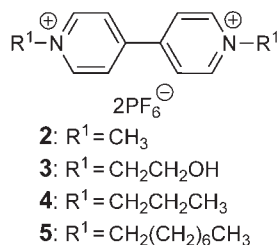
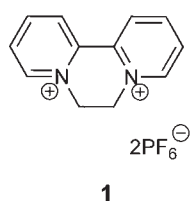
Virginia Polytechnic Institute and State University, Blacksburg, VA, USA

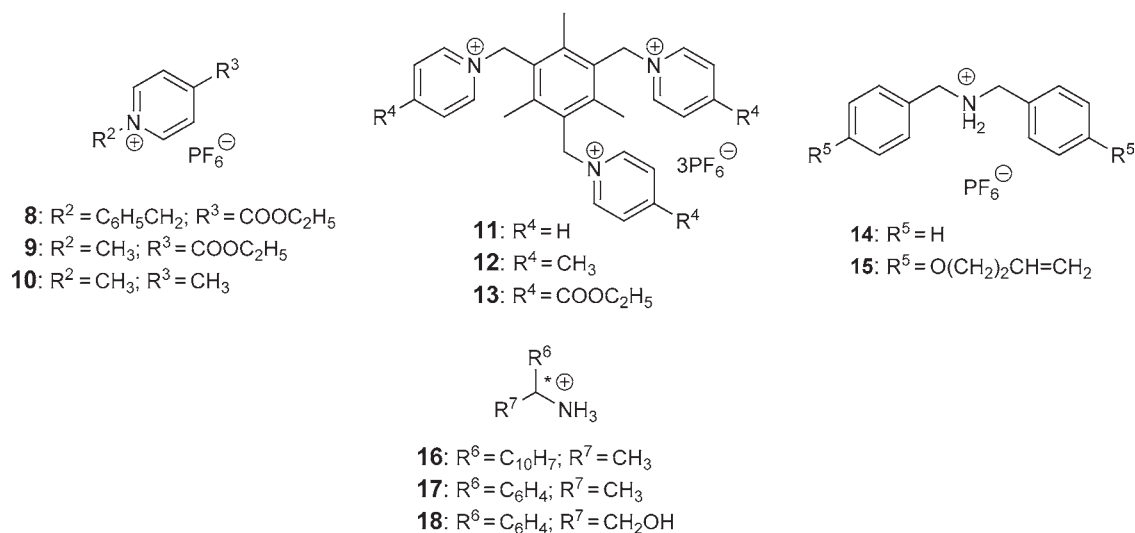
© 2008 Elsevier Ltd. All rights reserved.

14.22.1	Introduction	1071
14.22.2	Theoretical Methods	1072
14.22.3	Experimental Structural Methods	1073
14.22.3.1	X-Ray Crystallography	1074
14.22.3.2	NMR Spectroscopy	1077
14.22.3.3	Mass Spectrometry	1080
14.22.3.4	Other Structural Methods	1081
14.22.4	Thermodynamic Aspects	1081
14.22.4.1	Melting Point Data	1081
14.22.4.2	Solubility and Chromatographic Behavior	1082
14.22.5	Reactivity	1082
14.22.5.1	Complexation	1082
14.22.6	Macrocycle Synthesis	1084
14.22.7	Further Developments	1084
References		1084

14.22.1 Introduction

Previous chapters in CHEC(1984) and CHEC-II(1996) have been devoted to crown ethers (CEs) and CE-like species <1984CHEC(5)531, 1996CHEC-II(9)809, 1996CHEC-II(9)893>; however, none summarize multiple macroheterocycles. Due to the space limitations this chapter summarizes the field of CE-based phenylene cryptands; it does not review the rich fields of aza, calixarene, or metallo-cryptands. The multiple macroheterocycles will be referred to as hosts or cryptands because of their function as hosts for large electron-deficient guests **1–18**. The remainder of this chapter will discuss synthesis, properties, and guest-binding reactions of these macromulticyclic, CE-containing hosts. CE nomenclature is summarized in CHEC-II(1996) <1996CHEC-II(9)893> and is used in the remainder of this chapter.





The exploration of these cryptands precipitated from Colquhoun and Stoddart's work showing that the interaction of the simple CE species, dibenzo-30-crown-10 (DB30C10), with 'diquat' **1** formed a 'hotdog complex' (aka cradled barbell or taco complex), not a threaded pseudorotaxane (**Figure 1**) <1983CC1140>. Gibson *et al.* have also shown that some hosts fold around guest paraquat **2** in either a taco complex <1999OL47> or a supramolecular cryptand formed with the anion <2002JA13378> or water <2003CC2212>. Stoddart proposed that hosts could be preorganized to better accommodate guests by tying the ends of the host together <1985CC311>. Addition of the third arm can affect both entropy through preorganization and enthalpy by introduction of additional hydrogen bond acceptors. These enthalpic and entropic driving forces yield stronger host-guest complexes (aka cryptates). Although, simple CEs are three-dimensional (3-D), cryptands can never be confined to 2-D; this makes cryptands impressive hosts for a vast number of guests. The design and synthetic accessibility of the host are the only limitations.

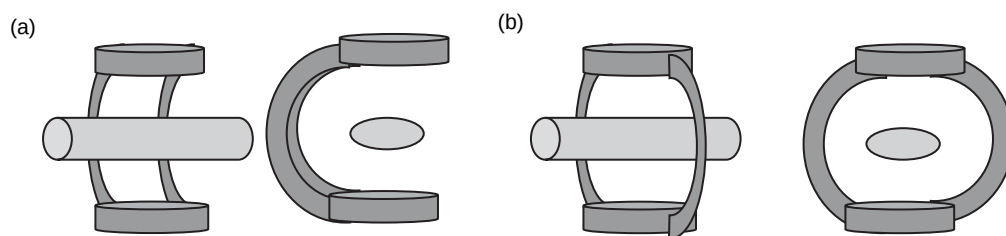


Figure 1 Side and head-on views of a cartoon (a) hotdog complex and (b) pseudorotaxane.

14.22.2 Theoretical Methods

Likely due to macrobicycles' sheer sizes, there are few useful theoretical data for these large molecules. It is expected that this fact should change soon, because the biomimetic utility of cryptands should allow for study of selective synthetic enzymes and for highly selective formation of supramolecular polymers. The Gibson group finds Corey-Pauling-Koltun (CPK) molecular models to be the quickest, most satisfying method to explore new chemistries; nothing else shows the fit and interaction as clearly.

Gibson *et al.* did report AM1 level calculations from the program CAChe on four of their cryptands shown in **Figure 2** <2005JOC3231>. As expected, the cryptands were electron rich and contain strong hydrogen bond acceptors.

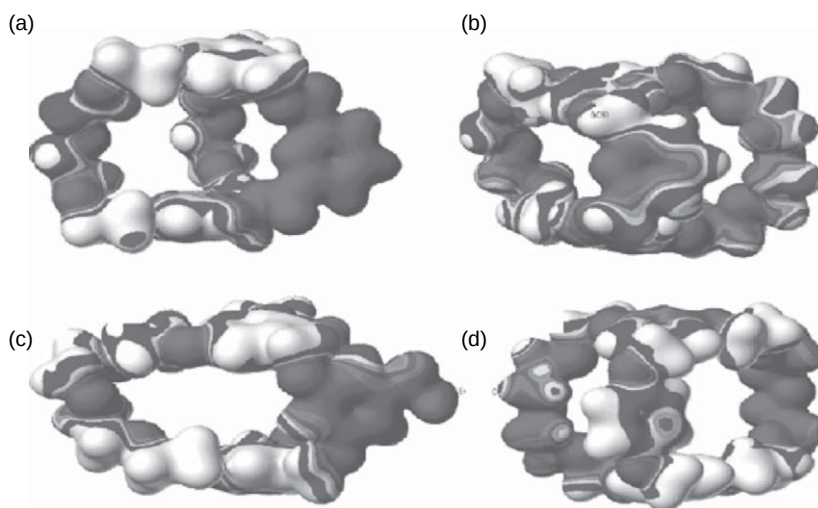
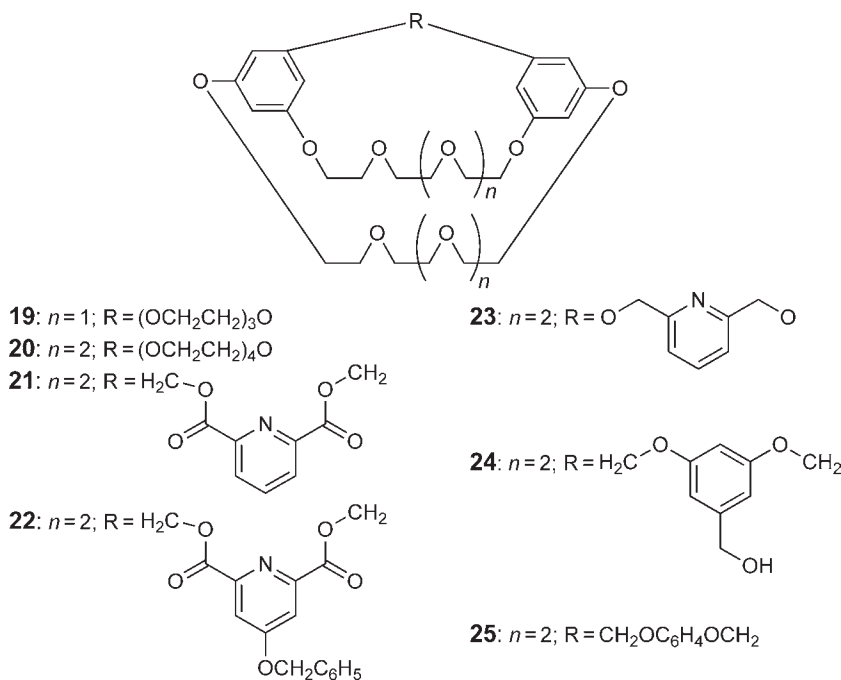


Figure 2 Electrostatic potential energy maps, determined by AM1 level calculations using the program CAChe, of (a) **21**, (b) **22**, (c) **24**, and (d) **25**. Black regions are of high electron density and whites are areas of low electron density.



14.22.3 Experimental Structural Methods

This section deals with the proof of structure of cryptands and cryptates. Especially for cryptates, a combination of many of the following techniques is necessary. X-Ray crystallography, nuclear magnetic resonance (NMR), and mass spectrometry (MS) are typically used. It is important to point out that conflicting results can be produced for solid-state and solution structural determinations of cryptates; in solution, separately **19** and **20** complex **2** in a 1:1 fashion, but X-ray crystallography showed a 2:1 stoichiometry for each [\[2003JA9367\]](#). The explanation is that the solvent used, acetone, can also stabilize the guest by taking up hydrogen bonds, but as the complex crystallizes the solvent is excluded and the hydrogen atoms become available for bonding to a second cryptand, even when the crystals are grown in a guest-rich environment. Due to the size and flexibility of the cryptands, it is sometimes challenging to

obtain X-ray crystal data from uncomplexed hosts. Normally the complexes are easier because the guest occupies the cavity, which holds the hosts in a more rigid fashion and excludes solvent molecules that occupy a cryptand's free space.

14.22.3.1 X-Ray Crystallography

X-Ray crystallography is the definitive proof for cryptand structure and cryptate formation. Using what he and Colquhoun found previously, Stoddart showed cryptate formation in the DB30C10-based cryptand **26** holding **1** (Figure 3) <1985CC311>. The cryptate solution and crystals were deep red in color due to charge transfer between the host and guest. Stoddart reported virtually no change in the structure, determined by X-ray crystallography, of the DB30C10 portion of **26** as compared to the DB30C10 complex previously made. Relying solely on NMR data, Stoddart would not have known that the DB30C10 complex was a 'hotdog' complex and that tying the phenyl groups with a third arm would achieve higher degrees of complexation.

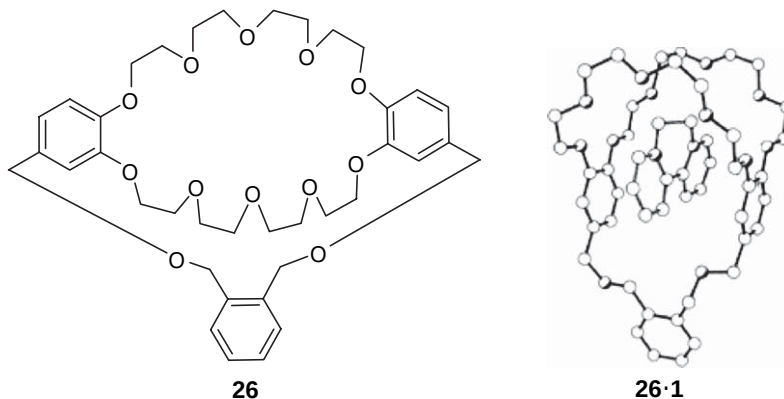


Figure 3 Crystal structure of the cryptate **26·1**. Hydrogen atoms are not shown.

Gibson and co-workers similarly obtained X-ray crystallographic results with the complex of dimethyl paraquat [*N,N'*-dimethyl-4,4'-bipyridinium bis(hexafluorophosphate)] **2** and 3,5-di(hydroxymethylene)BMP32C10, as a taco complex <1999OL1001>. The association constant for the complex was reported to be $5.7 \times 10^2 \text{ M}^{-1}$ ($\Delta G = -53 \text{ kJ mol}^{-1}$) in acetone at 23 °C. Similar to Stoddart, Gibson and co-workers attached a third arm, but this arm contained hydrogen bond acceptors. This new cryptand **20** bound the same guest **2** 100-fold stronger in the same environment ($K_a = 6.1 \times 10^4 \text{ M}^{-1}$, $\Delta G = -92 \text{ kJ mol}^{-1}$), but with identical change in molar enthalpy <1999OL1001>. The crystal structure of the complex is shown in Figure 4.

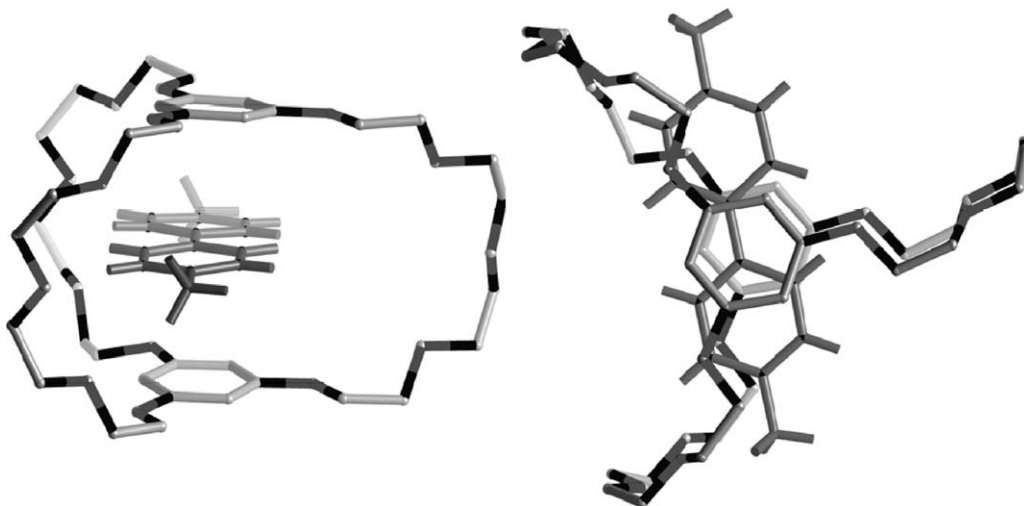


Figure 4 Crystal structure of the cryptate **20·2**: side and top views. Hydrogen atoms of **20** are not shown.

Gibson and co-workers used crystallography to examine numerous cryptand-based complexes in the solid state (summarized in [Table 1](#)).

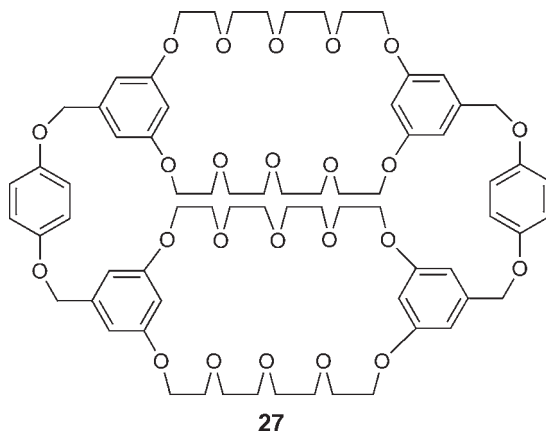
Table 1 X-Ray crystallographic data of cryptands and cryptates

<i>Host</i>	<i>Guest</i>	<i>H:G stoichiometry</i>	<i>Space group</i>	<i>Reference</i>
19			<i>P-1</i>	2005T10242
19	2	2:1	<i>P-1</i>	2003JA9367
19	8	1:1	<i>P2₁/n</i>	2005T10242
20			<i>Pnma</i>	2005JOC3231
20	1	1:1	<i>Pna2₁</i>	2006CC1929
20	2	1:1	<i>P2₁/c</i>	1999OL1001
20	2	2:1	<i>P-1</i>	2003JA9367
20	8	1:1	<i>Pna2₁</i>	2006CC1929
20	6	2:1	<i>P-1</i>	2003JA9272
20	7	2:1	<i>P-1</i>	2005CC1693
20	8	1:1	<i>P-1</i>	2005T10242
20	11	1:1	<i>P-1</i>	2005TL6765
21			<i>C2/c</i>	2005JOC3231
21	2	1:1	<i>P2₁/c</i>	2005JOC3231
21	8	1:1	<i>P2₁/n</i>	2005T10242
22	2	(1:1) ₂	<i>P-1</i>	2004CC2670
23	2	2:1	<i>P-1</i>	2005JOC3231
23	8	1:1	<i>P2₁/c</i>	2005T10242
24	2	1:1	<i>P2₁/c</i>	2005JOC3231
24	8	1:1	Crystallized separately in both <i>P-1</i> and <i>P2₁/c</i>	2005T10242
25			<i>P-1</i>	2005JOC3231
25	8	1:1	<i>P2₁/c</i>	2005T10242
26	1	1:1	<i>P-1</i>	1985CC311
27			<i>P2₁/c</i>	2005JOC809
27	2	2:1	<i>P2₁/c</i>	2005JOC809
30	2	1:1	<i>P2₁/n</i>	2006OL211
30	5	1:1	<i>P-1</i>	2006OL211
32	15	1:3	<i>P-1</i>	2005JA13158
34			<i>P-1</i>	1993JOC7694

The 2:1 result found in the cryptate [19·2](#) was surprising and contradicted NMR results discussed below. Gibson and co-workers regrew crystals in the presence of an excess of [2](#) and still only the 2:1 complex was formed. The cryptate [20·2](#) is a 1:1 complex in solution and can be crystallized in both 1:1 [\[1999OL1001\]](#) and 2:1 [\[2003JA9367\]](#) complexes; the crystallization methods were reportedly similar.

The cryptate [22·2](#) showed 1:1 gaseous (MS), solution, and solid-state behavior, but it was determined, via electrospray ionization mass spectrometry (ESI-MS) and X-ray crystallography, that the cryptate also dimerizes in the gaseous and solid states due to efficient π – π stacking of the substituted pyridyl arm [\[2004CC2670\]](#).

Gibson and co-workers synthesized the bis(BMP32C10) [27](#) that accommodates two guest molecules [\[2005JOC809\]](#). The CE rings are preorganized in a folded conformation.



The Smith group synthesized macrobicyclic species that bound neutral and both constituents of alkali halide salt species by installing both Lewis-acidic and -basic sites <2000JA6201>. The crystal structures of the salt and neutral guest complexes are shown in **Figure 5**. In the salt binding, the Na^+ cation interacts with DB18C6 portion of the host **28** and axially with a water molecule. Prior to this work, no group had shown a host that selectively bound dimethyl sulfoxide (DMSO); the association constant of this complex was reported to be 125 M^{-1} in CDCl_3 at 295 K.

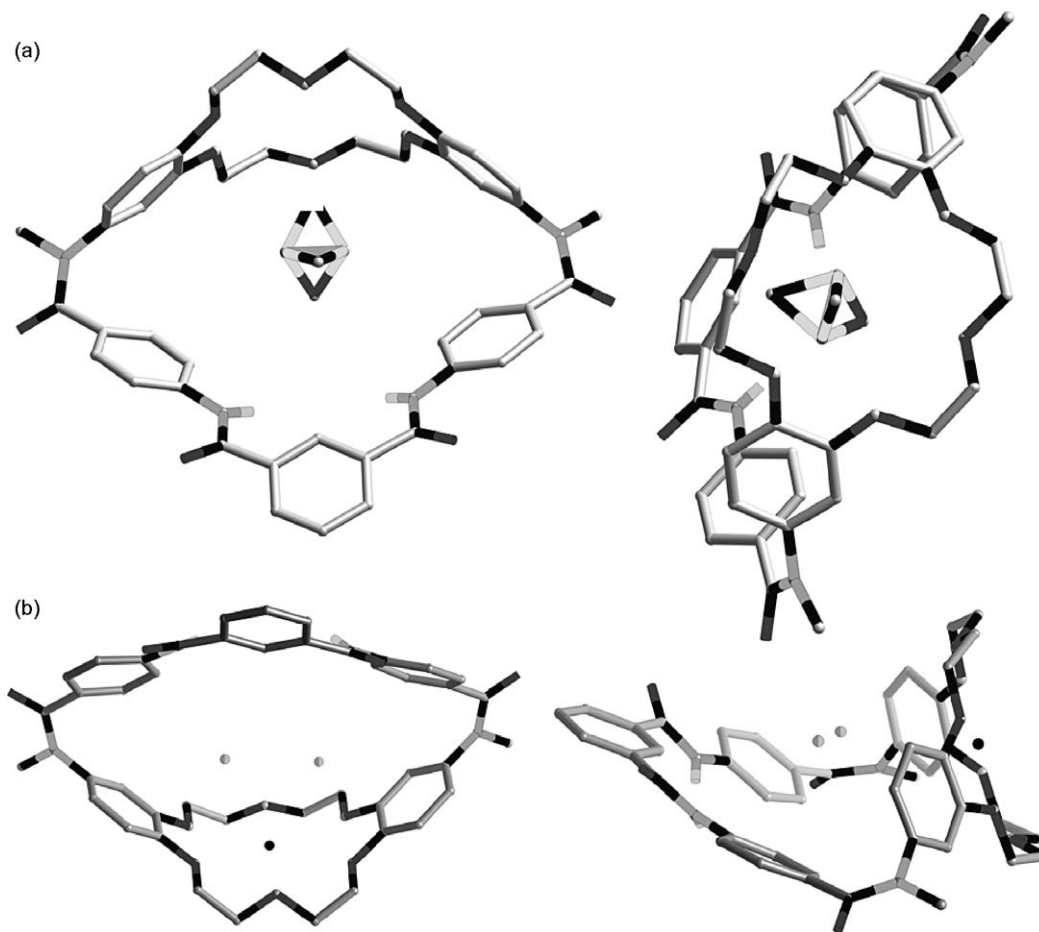
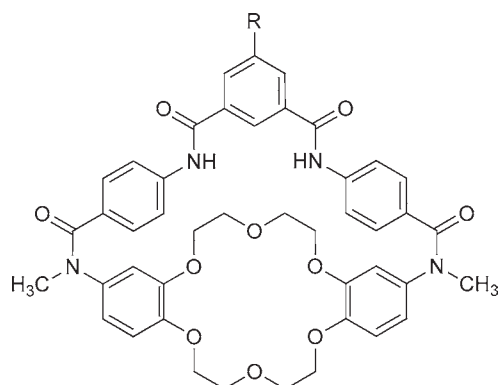


Figure 5 Cryptand **28** is shown binding (a) a disordered DMSO and (b) Na^+ and Cl^- (disordered) simultaneously. Solvent molecules and non-hydrogen-bonded hydrogens are omitted.



28a: $\text{R} = \text{H}$

28b: $\text{R} = t\text{-Bu}$

Kim and co-workers explored synthetic receptors for ammonium ions. They utilized cation– π interactions and ethereal H-bonding <2001AGE2116>. They synthesized cryptand **29**, which they found binds ammonium ions (Figure 6) more strongly than nonactin, a nature antibiotic and a strong host for ammonium ions.

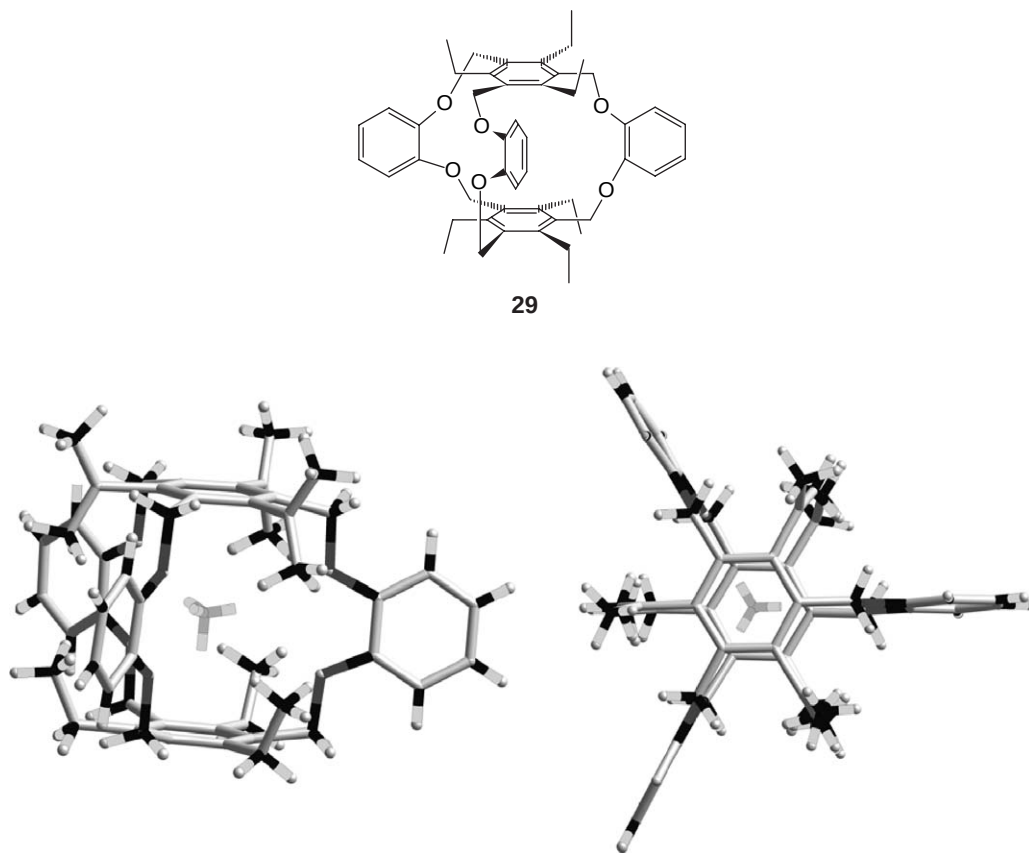


Figure 6 **29** binding NH_4^+ ; counterion and solvent molecules not shown. The ethyl groups appear disordered.

Chen *et al.* proved **30** separately binds both **5** and **14** in 1:1 and 1:2 stoichiometries <2006OL211, 2006OL1859>. Chen *et al.* used X-ray crystallography for definitive proof of their high-yielding synthesis of the [4]catenane of **32** with 3 equiv of **15** (Figure 7). A catenane is a set of mechanically linked macrocycles.

14.22.3.2 NMR Spectroscopy

Due to its facility yielding abundant data, NMR is the most often used technique to reveal structural information on cryptands and cryptates. NMR determination structure is straightforward, but does not give as much structural detail as X-ray crystallography.

NMR is heavily used in the analysis of cryptates. However, cryptate signals often shift up- or downfield; sometimes signals are split between complexed and uncomplexed species (called slow exchange), and sometimes show up as the average of complexed and uncomplexed species (called fast exchange or time-averaged signals). The terms slow and fast exchange only describe the speed of binding as compared to the NMR timescale; they do not describe the strength of complexation. Figure 8 shows a representation of both slow and fast exchange regimes. Host:guest stoichiometry, in slow exchange systems, is determined by ratioing the amount of complexed host to complexed guest. Host:guest stoichiometry in fast exchange systems is analyzed by either continuous variation (aka the Job plot method, shown in Figure 9) <1928LA113> or mole ratio methods <1957JA49>. Both methods work well and are used by all of the groups in the field. The strength of complexation, in fast exchange systems, is estimated by determination of the association constant and the Δ_o value; Δ_o is the change in signal position (in ppm) from completely complexed to completely uncomplexed. Analysis of the association constant has been achieved by Benisi–Hildebrand

<1949JA2703>, Scatchard <1949ANY660>, Creswell–Allred <1959JPC1469>, or Rose–Drago <1959JA798> multi-point methods. All of these methods are useful; however, Gibson and co-workers produced iterative method based on these analyses that more precisely define K_a <1998MM5278>.

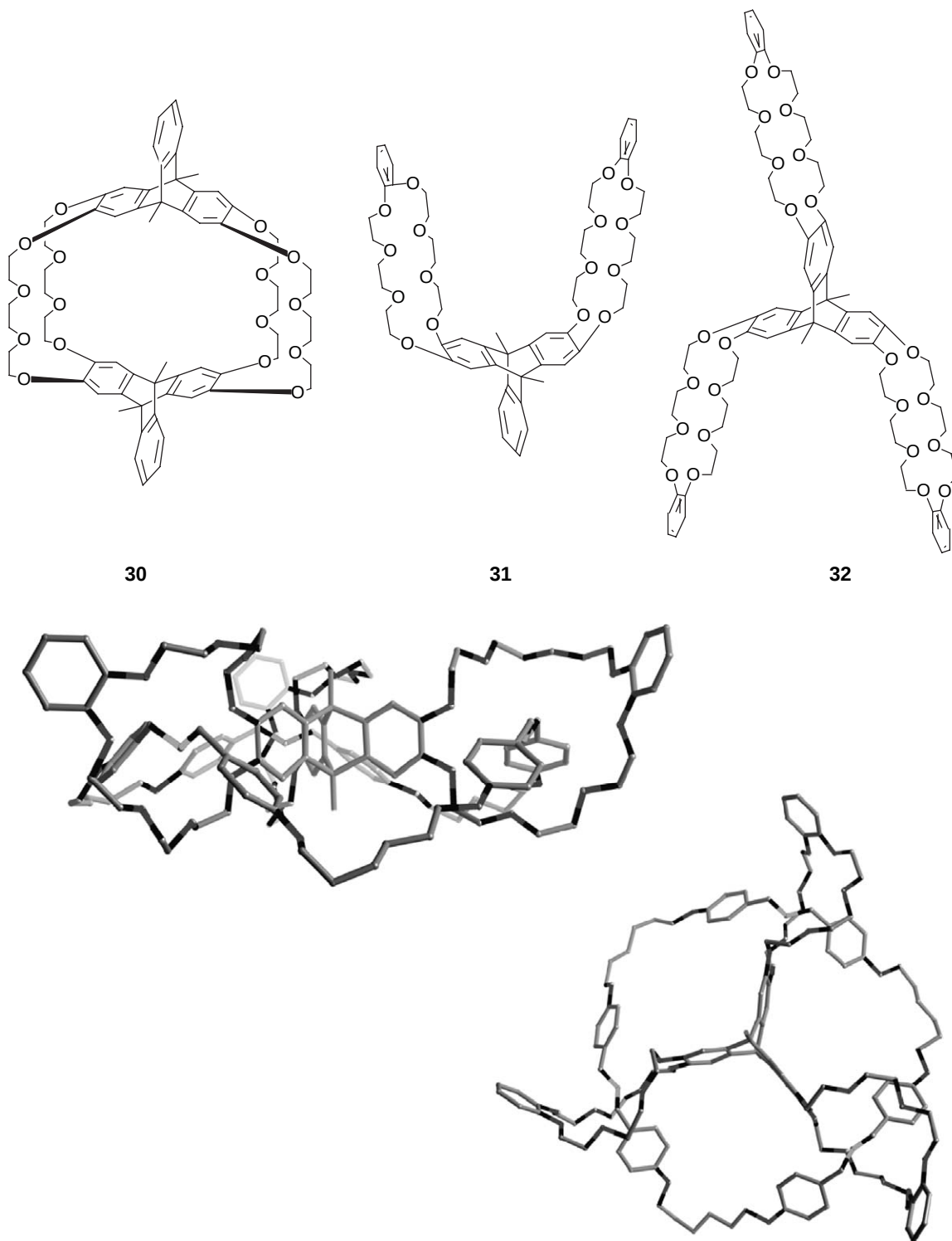


Figure 7 Chen's [4]catenane **32-15₃** in which the guests were converted to a macrocycle via alkene metathesis: through-ring and top views. Hydrogen atoms and counterions are omitted.

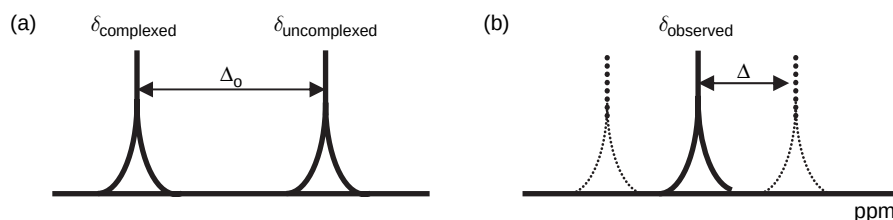


Figure 8 (a) A slow exchange system. (b) A fast exchange system (the broken lines represent where the uncomplexed and complexed signals would be in a slow exchange system).

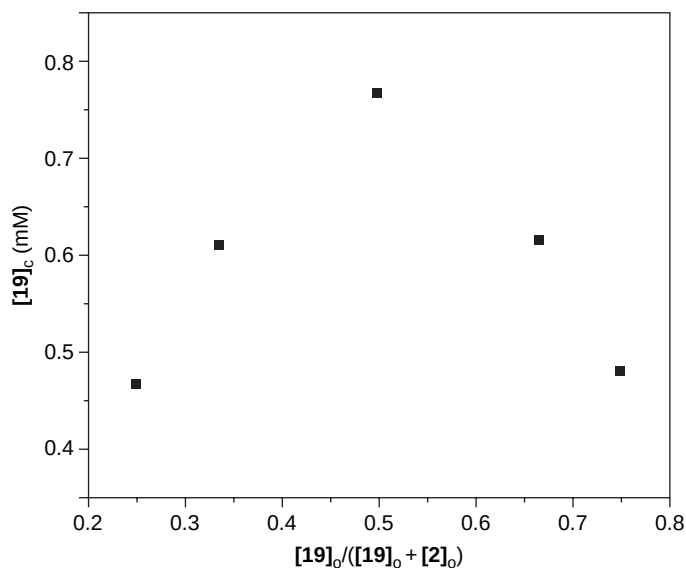


Figure 9 Job plot of **19** binding **2** in a 1:1 fashion: $[19]_o$ was constant.

The errors in producing an NMR sample and the NMR measurement make it difficult to measure association constants greater than 10^4 M^{-1} . Using a competitive complexation method, developed by the Smith group <2003CEJ850>, Gibson *et al.* were able to estimate K_a on the order of $5.0 \times 10^6 \text{ M}^{-1}$ in acetone for **21·2** <2005JOC3231>.

Two-dimensional NMR techniques are often used for characterization of cryptands and cryptates. In combination with crystallography, nuclear Overhauser effect spectroscopy (NOESY) is used to show interactions through space between non-covalently bonded species. Using NOESY, Gibson *et al.* determined **11** was threaded through **20** because there were through-space interactions between the protons of **20**'s ethyleneoxy arms and the methyl and 2-, 3-, 5-, and 6-pyridinium protons of **11**, but not the benzylic or 4-pyridinium protons <2005TL6765>. Zhu and Chen also used NOESY NMR to show that the tris[2]pseudorotaxane **32·15₃** was formed and after metathesis the catenane was synthesized <2005JA13158>.

Gibson and co-workers showed that **19** binds **2** in a 1:1 stoichiometry in solution; Figure 9 shows the Job plot <2003JA9367>, which contradicted X-ray crystallographic results showing the stoichiometry was 2:1 in the solid state. They explained the difference in stoichiometry as being due to interaction with solvent, which stabilizes **2**, but in the solid state only another equivalent of **19** is available to stabilize **2** and involve more of the guest's protons in H-bonding.

Gibson and co-workers produced the first chemically active, switchable host, **23**, for **2** in nonacidic environments <2005CC3655>. Complexation was quenched with addition of trifluoroacetic acid, but re-established with addition of triethylamine.

The bis(CE) **27** accommodates 2 equiv of **2** in a statistical manner. Interestingly, the binding was 3 times stronger than the simple CE BMP23C10, but still much lower than most of the enthalpically active cryptands **21–23** <2005JOC809>.

14.22.3.3 Mass Spectrometry

Soft ionization MS techniques, such as matrix-assisted laser desorption ionization (MALDI), ESI, and fast atom bombardment (FAB), allow cryptand and cryptate molecular ions to be seen. The choice of matrix is important because many of the cryptands easily bind alkali metals, even displacing a cryptate's guest species.

ESI-MS of **22·2** and also **22·3** showed the expected cryptates, but also peaks corresponding to cryptand dimers <2004CC2670>; Table 2 summarizes the reported data. Further exploration with X-ray crystallography of the cryptates showed strong hydrogen bonding and π – π stacking between the substituted pyridyl units.

Table 2 ESI-MS data of cryptate dimers

Peak assignment	m/z	Intensity (%)
$[(22\cdot2) - PF_6]^+$	1164.5	51
$[(22\cdot2) - 2PF_6]^{+2}$	509.9	100
$[(22\cdot2)_2 - HPF_6 - C_6H_6 - H]^{+2}$	1196.5	4
$[(22\cdot2)_2 - 3PF_6 - C_7H_7 - CH_3 + H_2O]^{+2}$	1120.6	3
$[(22\cdot2)_2 - 3PF_6 - C_7H_7 - CH_3 + Na]^{+2}$	1057.5	2
$[(22\cdot2)_2 - 2PF_6 - 2HPF_6 - C_7H_7 - 2CH_3 + Na]^{+2}$	969.5	3
$[(22\cdot2)_2 - PF_6 - 2HPF_6 - C_6H_5]^{+4}$	526.2	7
$[(22\cdot3) - PF_6]^+$	1224	87
$[(22\cdot3) - PF_6 - HPF_6 - CH_3CH_2OH - OCH_2C_6H_5]^+$	927	100
$[(22\cdot3) - OH - CH_2OH]^{+2}$	661	41
$[(22\cdot3)_2 - 4PF_6 - H_2O]^{+3}$	714	7.6
$[(22\cdot3)_2 - 4PF_6 - 2H_2O]^{+3}$	708	17

Gibson and co-workers used ESI-MS to confirm the complex **27·2** and at the same time the 1:1 complex was also observed <2005JOC809>.

Although ‘monopyridinium ions’ **8–10** are relatively small guests for cryptands, Gibson and co-workers only observed their 1:1 complexes with hosts **19–21** and **23–25** in the gas phase using ESI-MS <2005T10242>; see Table 3.

Table 3 ESI-MS data of monopyridinium cryptates

Complex	m/z (intensity (%))		
	$[H\cdot G + Na]^+$	$[H\cdot G + Li - HOCH_2CH_2OH]^+$	$[H\cdot G - PF_6]^+$
20·8	1136.4 (10)	1058.8 (10)	968.6 (100)
20·9	1060.5 (6)	982.6 (7)	892.6 (100)
20·10	1002.6 (1)	924.8 (8)	834.6 (100)
21·8	1137.4 (5)		969.3 (64)
23·8			913.4 (28)
24·8			942.5 (43)

Using the triptycene-based homotritopic host **32**, Chen *et al.* observed the tris[2] pseudorotaxane with **15** using ESI-MS <2005JA13158>. After metathesis, MALDI-TOF (TOF = time of flight) MS, X-ray crystallography (summarized in Section 14.22.3.1), and ^1H and ^{13}C NMR were used in concert to prove synthesis of the [4]catenane.

14.22.3.4 Other Structural Methods

Bradshaw and co-workers reported infrared (IR) vibrational modes of the cryptands, shown in [Table 4](#) <1993JOC7694, 1996JOC7270>, and they determined the optical activity of cryptands [36](#) and [37](#); they gave $[\alpha]_D^{25} = 11.2$ and -307.8 , respectively <1996JOC7270>. Via NMR, [36](#) and [37](#) were shown to have some chiral selectivity for binding [16–18](#).

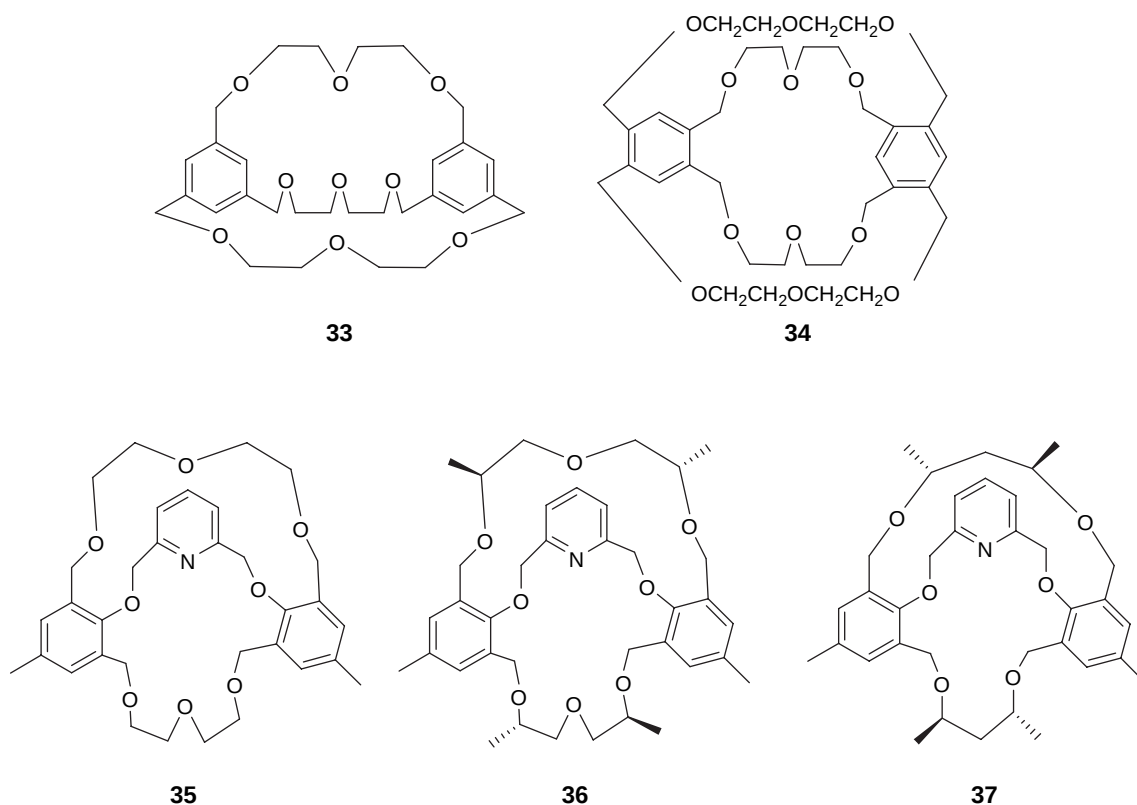


Table 4 Cryptand IR data

<i>Species</i>	<i>IR (KBr, cm⁻¹)</i>
33	2859, 1607, 1453, 1354, 1250, 1114
35	2919, 1596, 1452, 1242, 1097, 697
36	2922, 1529, 1453, 1372, 1207, 1108
37	2928, 1591, 1458, 1372, 1287, 1204, 1153, 1093, 1029

14.22.4 Thermodynamic Aspects

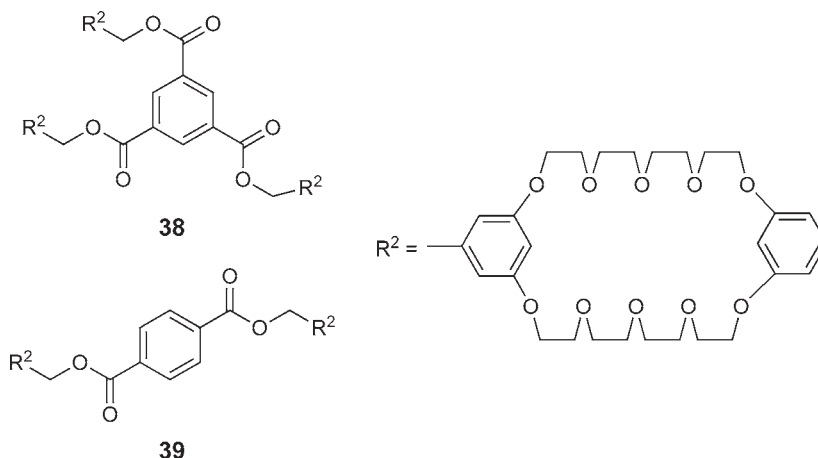
14.22.4.1 Melting Point Data

The physical properties of large macrocycles have not been extensively investigated in lieu of molecular characterization and host–guest complexation ability. No group has explored m.p. behavior in relation to ‘intermolecular forces’. [Table 5](#) summarizes cryptand melting points.

Table 5 Reported cryptand melting points^a

<i>Species</i>	<i>m.p.</i> (°C)	<i>Reference</i>
19	81.2–81.9	2003JA9367
20	77.5–78.0	1999OL1001
21	153.5–155.3	2005JOC3231
23	129–131	2004CC2670
24	120.3–122.2	2005JOC3231
25	98.1–99.0	2005JOC3231
27	69.1–70.0	2005JOC809
28a	>260	2000JA6201
30	>300	2006OL211
31	41–42	2006OL1069
32	32–35	2005JA13158
35	57	1996JOC7270
36	131–132	1996JOC7270
37	62–65	1996JOC7270
39	75.7–77.9	2005JA484

^aThe melting points are uncorrected. **22**, **26**, and **38** were isolated as oils. Although **33** and **34** are solids, m.p. data were not reported.



14.22.4.2 Solubility and Chromatographic Behavior

Solubility has not been analytically explored. Solubility has been explored for purification, separation, or complexation. In general, good solvents for CE cryptands are polar organic solvents such as acetone, chloroform, methylene chloride, MeCN, dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP), ethyl acetate, and alcohols. **Table 6** summarizes the column chromatographic conditions used for cryptand purification.

14.22.5 Reactivity

There are no further chemical reactions that have been reported on the cryptands reported in this chapter. Cryptands have been explored primarily for their ability to bind guest species (noncovalent reactivity).

14.22.5.1 Complexation

Complexation is a measure of how strongly cryptates are formed. There is no assumption that the solution species are identical to the solid state entities. The association constant (K_a) is a measure of the strength of a host's ability to complex a guest in a specific solvent at a specific temperature. As explained in **Section 14.22.2**, under fast exchange Δ is an estimation of the signal position of the fully complexed species in a fast exchange system. Δ_o must be estimated to determine K_a (see **Table 7**).

Table 6 Column Chromatographic Conditions Used to Purify Cryptands (Stationary phase: silica gel)

<i>Species</i>	<i>Eluent</i>	<i>Reference</i>
19	Gradient from pure ethyl ether to pure ethyl acetate (EA)	2003JA9367
20	EA	1999OL1001
22	25:1 CH ₂ Cl ₂ /CH ₃ OH	2004CC2670
21	9:1 CHCl ₃ /acetone	2005JOC3231
23	Gradient from pure ethyl ether to pure EA	2005JOC3231
24	9:1 EA/CH ₃ OH	2005JOC3231
25	EA	2005JOC3231
26	C ₆ H ₅ CH ₃ /CHCl ₃ /CH ₃ OH	1985CC311
27	Gradient from pure EA to EA/CH ₃ OH	2005JOC809
28a	Gradient from 190:9:1 to 90:9:1 CHCl ₃ /CH ₃ OH/H ₂ O	2000JA6201
28b	90:9:1 CHCl ₃ /CH ₃ OH/H ₂ O	2000JA6201
30	100:1 CHCl ₃ /CH ₃ OH	2006OL211
31	100:1 then 60:1 CH ₂ Cl ₂ /CH ₃ OH	2006OL1069
32	100:1 then 60:1 CH ₂ Cl ₂ /CH ₃ OH	2005JA13158
33	60:1 CH ₃ OH/30% NH ₄ OH	1993JOC7694
34	70:1 CH ₃ OH/30% NH ₄ OH	1993JOC7694
35	20:1 CH ₃ OH/30% NH ₄ OH	1996JOC7270
36	20:1 C ₆ H ₅ CH ₃ /EA	1996JOC7270
37	40:1 C ₆ H ₅ CH ₃ /EA	1996JOC7270
38	EA then ethanol	2005JA484
39	EA	2005JA484

Table 7 K_a and Δ_o values determined via ¹H NMR

<i>Cryptate</i>	<i>Reported K_a value (M^{-1}) (Δ_o, ppm)</i>	<i>Reference</i>
19.8	141 ± 21^a	2005T10242
20.1	$2.0 (\pm 0.2) \times 10^{4b}$	2006CC1929
20.2	6.1×10^{4b}	1999OL1001
20.8	588 ± 60^a	2005T10242
	182 ± 20^b	2005T10242
20.9	426 ± 59^a	2005T10242
	173 ± 40^b	2005T10242
20.10	536 ± 48^a	2005T10242
	193 ± 31^b	2005T10242
21.1	$3.30 (\pm 0.66) \times 10^{5b,c}$	2006CC1929
21.2	$5.0 (\pm 2.0) \times 10^{6b,c}$	2005JOC3231
21.8	$1.86 (\pm 0.2) \times 10^{4a}$	2005T10242
22.2	$9.4 (\pm 0.9) \times 10^{3b}$ $\Delta_o = 0.599$	2005JOC323
23.8	423 ± 42^a	2005T10242
24.2	$6.3 (\pm 0.6) \times 10^{3b}$ $\Delta_o = 0.604$	2005JOC3231
24.8	332 ± 33^a	2005T10242
25.2	$2.2 (\pm 0.2) \times 10^{4b}$ $\Delta_o = 0.701$	2005JOC3231
25.8	$1.31 (\pm 0.12) \times 10^{3a}$	2005T10242
27.2 ₂	$K_{a1} 6.4 (\pm 0.6) \times 10^{3d}$ $\Delta_o = 0.399$	2005JOC809
	$K_{a2} 1.6 (\pm 0.2) \times 10^{3d}$	
	$K_{a1} 2.7 (\pm 0.3) \times 10^{3b}$ $\Delta_o = 0.388$	2005JOC809
	$K_{a2} 6.8 (\pm 0.7) \times 10^{2b}$	
30.2	4×10^{5c}	2006OL211
30.5	2×10^{3c}	2006OL211

^aMeasured in 1:1 acetone/chloroform at 22 °C.^bMeasured in acetone at 22 °C.^cDetermined by competitive complexation methods.^dMeasured in 5:1 acetone-*d*₆:chloroform-*d*.^eMeasured in 1:1 MeCN/chloroform at 23 °C.

14.22.6 Macrocyclic Synthesis

Synthetic techniques for monocyclic cyclizations are similar to multicyclic cyclizations as described in <1984CHEC(7)763> and <1996CHEC-II(9)917>. The preferred method is ultrahigh dilution [2+2] additions; these reactions require protection and deprotection reactions. Cyclizations are normally S_N2 reactions, forming ether or ester bonds. It is possible, in a single reaction, to perform multiple [2+2] reactions, but only **32** <2005JA13158> and **34** <1993JOC7694> have been prepared by this route; however, these reactions suffer from poor selectivity, oligomerization, difficult product isolation, and overall low yields.

Cryptand syntheses require ultrahigh purity reagents, water-free conditions, and highly dilute reaction conditions in order to quell partial reactions and polymerizations. Also, a template species such as metal ions or nonreactive guest species is useful.

14.22.7 Further Developments

Since the writing of this chapter Gibson *et al.* have published three papers about cryptands. The smaller DB24C8-based cryptands yielded were produced in higher yields, but were found to be weaker hosts for **3** than the BMP32C10-based cryptands <2007JOC3381>. The association of **25** with dimers of **8** was investigated <2007T2875>. The association of **19–25** with **1** was explored using NMR, ESI-MS, and X-ray crystallography <2007T2829>.

References

- 1928LA113 A. Job, *Liebigs Ann. Chem.*, 1928, **9**, 113.
 1949JA2703 H. Benisi and J. H. Hildebrand, *J. Am. Chem. Soc.*, 1949, **71**, 2703.
 1949ANY660 G. Scatchard, *Ann. NY Acad. Sci.*, 1949, **51**, 660.
 1957JA49 A. S. Meyer, Jr. and G. H. Ayres, *J. Am. Chem. Soc.*, 1957, **79**, 49.
 1959JA798 N. J. Rose and R. S. Drago, *J. Am. Chem. Soc.*, 1959, **81**, 798.
 1959JPC1469 C. J. Creswell and M. L. Allred, *J. Phys. Chem.*, 1962, **66**, 1469.
 1983CC1140 H. M. Colquhoun, E. P. Goodings, J. M. Maud, J. F. Stoddart, D. J. Williams, and J. B. Wolstenholme, *J. Chem. Soc., Chem. Commun.*, 1983, 1140.
 1984CHEC(7)531 A. D. Hamilton; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 7, p. 531.
 1984CHEC(7)763 A. D. Hamilton; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 7, p. 763.
 1985CC311 B. L. Allwood, F. H. Kohnke, A. M. Z. Slawin, J. F. Stoddart, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1985, 311.
 1993JOC7694 H. An, J. S. Bradshaw, K. E. Krakowiak, B. J. Tarbet, N. K. Dalley, X. Kou, C. Zhu, and R. M. Izatt, *J. Org. Chem.*, 1993, **58**, 7694.
 1996CHEC-II(9)809 B. Dietrich; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 809.
 1996CHEC-II(9)893 J. T. Redd, J. S. Bradshaw, and R. M. Izatt; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 893.
 1996CHEC-II(9)917 J. T. Redd, J. S. Bradshaw, and R. M. Izatt; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 9, p. 917.
 1996JOC7270 P. C. Hellier, J. S. Bradshaw, J. J. Young, X. X. Zhang, and R. M. Izatt, *J. Org. Chem.*, 1996, **61**, 7270.
 1998MM5278 C. Gong, P. B. Balanda, and H. W. Gibson, *Macromolecules*, 1998, **31**, 5278.
 1999OL47 W. S. Bryant, I. A. Guzei, A. L. Rheingold, and H. W. Gibson, *Organic Lett.*, 1999, **1**, 47.
 1999OL1001 W. S. Bryant, J. W. Jones, P. E. Mason, I. A. Guzei, A. L. Rheingold, F. R. Fronczek, D. S. Nagvekar, and H. W. Gibson, *Org. Lett.*, 1999, **1**, 1001.
 2000JA6201 M. J. Deetz, M. Shang, and B. D. Smith, *J. Am. Chem. Soc.*, 2000, **122**, 6201.
 2001AGE2116 S. Y. Jon, J. Kim, M. Kim, S.-H. Park, W. S. Jeon, J. Heo, and K. Kim, *Angew. Chem., Int. Ed.*, 2001, **40**, 2116.
 2002JA13378 J. W. Jones, L. N. Zakharov, A. L. Rheingold, and H. W. Gibson, *J. Am. Chem. Soc.*, 2002, **124**, 13378.
 2003CC2212 F. Huang, L. N. Zakharov, A. L. Rheingold, J. W. Jones, and H. W. Gibson, *Chem. Commun.*, 2003, 2212.
 2003CEJ850 R. E. Heath, G. M. Dykes, H. Fish, and D. K. Smith, *Chem. Eur. J.*, 2003, **9**, 850.
 2003JA9272 F. Huang, F. R. Fronczek, and H. W. Gibson, *J. Am. Chem. Soc.*, 2003, 9272.
 2003JA9367 F. Huang, H. W. Gibson, W. S. Bryant, D. S. Nagvekar, and F. R. Fronczek, *J. Am. Chem. Soc.*, 2003, **125**, 9367.
 2004CC2670 F. Huang, L. Zhou, J. W. Jones, H. W. Gibson, and M. Ashraf-Khorassani, *Chem. Commun.*, 2004, 2670.
 2005CC1693 F. Huang, I. A. Guzei, J. W. Jones, and H. W. Gibson, *Chem. Commun.*, 2005, 1693.
 2005CC3655 F. Huang, K. A. Switek, and H. W. Gibson, *Chem. Commun.*, 2005, 3655.
 2005JA484 F. Huang, D. S. Nagvekar, C. Slebodnick, and H. W. Gibson, *J. Am. Chem. Soc.*, 2005, **127**, 484.
 2005JA13158 X.-Z. Zhu and C.-F. Chen, *J. Am. Chem. Soc.*, 2005, **127**, 13158.
 2005JOC809 F. Huang, L. N. Zakharov, A. L. Rheingold, M. Ashraf-Khorassani, and H. W. Gibson, *J. Org. Chem.*, 2005, **70**, 809.
 2005JOC3231 F. Huang, K. A. Switek, L. N. Zakharov, F. R. Fronczek, C. Slebodnick, M. Lam, J. A. Golen, W. S. Bryant, P. E. Mason, A. L. Rheingold, M. Ashraf-Khorassani, and H. W. Gibson, *J. Org. Chem.*, 2005, **70**, 3231.

- 2005T10242 F. Huang, A. L. Rheingold, C. Slebodnick, A. Ohs, K. A. Switek, and H. W. Gibson, *Tetrahedron*, 2005, **61**, 10242.
2005TL6765 F. Huang, F. R. Fronczek, M. Ashraf-Khorassani, and H. W. Gibson, *Tetrahedron Lett.*, 2005, **46**, 6765.
2006CC1929 F. Huang, C. Slebodnick, K. A. Switek, and H. W. Gibson, *Chem. Commun.*, 2006, 1929.
2006OL211 Q.-S. Zong and C.-F. Chen, *Org. Lett.*, 2006, **8**, 211.
2006OL1069 T. Han and C.-F. Chen, *Org. Lett.*, 2006, **8**, 1069.
2006OL1859 Q.-S. Zong, C. Zhang, and C.-F. Chen, *Org. Lett.*, 2006, **8**, 1859.
2007JOC3381 H. W. Gibson, H. Wang, C. Slebodnick, J. Merola, W. S. Kassel, and A. L. Rheingold, *J. Org. Chem.*, 2007, **72**, 3381.
2007T2829 F. Huang, C. Slebodnick, K. A. Switek, and H. W. Gibson, *Tetrahedron*, 2007, **63**, 2829.
2007T2875 F. Huang, C. Slebodnick, E. J. Mahan, and H. W. Gibson, *Tetrahedron*, 2007, **63**, 2875.

Biographical Sketch



Harry W. Gibson, who grew up in the foothills of the Adirondack Mountains of northern New York State in the USA, received his B.S. (1962) and Ph.D. degrees (1965) from Clarkson University, the latter under the direction of Prof. Frank D. Popp in the area of alkaloid synthesis. After a postdoctoral stint studying stereochemistry with Prof. Ernest L. Eliel at the University of Notre Dame, in 1966 he joined Union Carbide Corporation's Chemicals and Plastics Division in Tarrytown, NY, where he carried out mechanistic studies of epoxide/alcohol reactions. In 1969, he joined the Xerox Corporation Research Laboratories in Webster, NY, and contributed to efforts on photoconductors, conductors, and toners. He remained there until 1984 when he joined the Signal Corporate Laboratory in Des Plaines, IL; at Signal, he worked on materials for printed wiring boards. In the fall of 1986, he was appointed professor of chemistry at Virginia Polytechnic Institute and State University, where he has been continuously engaged in research on supramolecular chemistry of crown ethers and related cryptands.



Adam M.-P. Pederson, who grew up in Minneapolis, MN, in the USA, received his B.S. (2000) from the University of Minnesota's Institute of Technology. From 2000 to 2003, he worked as a membrane chemist at Osmonics (later GE Osmonics) in the area of water purification and solvent-based separations. He is currently a chemistry graduate student at Virginia Polytechnic Institute and State University under Harry W. Gibson in the field of supramolecular polymer synthesis.