

13.01

Azepines and their Fused-ring Derivatives

J. B. Bremner

University of Wollongong, Wollongong, NSW, Australia

S. Samosorn

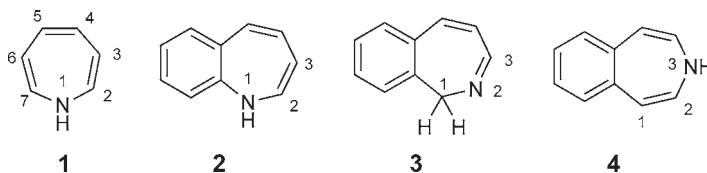
Srinakharinwirot University, Bangkok, Thailand

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13.01.1 Introduction

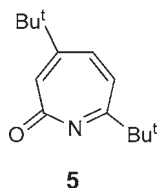
The azepine ring system has continued to attract considerable attention since the publication of CHEC-II(1996) <1996CHEC-II(9)1>. Several reviews of this system have also appeared <B-1996MI(56)1, 2002PAC1317>, and an account of an efficient ring construction strategy for seven-membered rings, including dihydroazepines, has been published <2004SL933>. A reference series has also reviewed seven-membered heterocycles including azepines <2004SOS(17)749> and benzazepines <2004SOS(17)825>, while annual synopses of these systems are covered in the series *Progress in Heterocyclic Chemistry*. Most of the chemistry has centered on reduced or oxidized forms of the ring system, since the parent 1*H*-azepine **1** is not stable, although N-substituted derivatives are known. Considerable chemistry has been described for benz-fused azepines and other fused derivatives. Chemical aspects of the former, of which the parents are 1*H*-1-benzazepine **2**, 1*H*-2-benzazepine **3**, and 3*H*-3-benzazepine **4**, and their tautomers, are also covered in this chapter.



13.01.2 Experimental Structural Methods

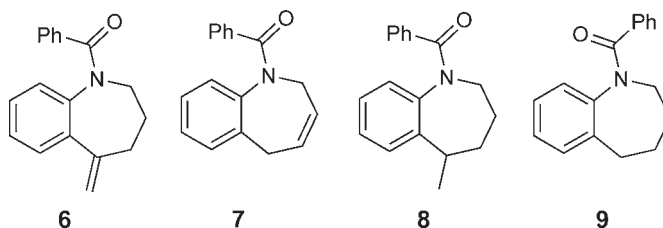
13.01.2.1 Spectroscopic Data

The ^1H NMR, ^{13}C NMR (NMR – nuclear magnetic resonance), infrared (IR), ultraviolet (UV), and mass spectrometry (MS) data have been reported for the first example **5** of a 2*H*-azepin-2-one (2-azatropone). The carbonyl group stretching frequency appeared at 1682 cm^{-1} in the IR spectrum of the neat material <2000JOC6093>. Further ^1H and ^{13}C NMR spectroscopic data on azepine derivatives have been summarized by Smalley <1997HOU(E9d)108>.



A conformational study of novel polyhydroxylated azepanes has been reported in which the ^1H NMR spectroscopy and molecular modeling (molecular mechanics, molecular dynamics, and Monte Carlo methods) afforded insights into aspects of the conformational analysis <2004EJO4119>.

Because of the medicinal chemical significance of 1-benzoyl-1*H*-1-benzazepines, as highly potent and selective nonpeptidic agonists for the arginine vasopressin (AVP) V_2 receptor, some fundamental structural studies of the *N*-substituted 1-benzazepine derivatives **6–9** have been assessed. Dynamic ^1H NMR spectroscopy was used to investigate solution state conformational structures in association with molecular mechanics studies. In the case of **8**, an axial conformer (with the 5-methyl group axial) was shown to be preferred over the equatorial conformer; the energy difference between the two was calculated to be 1.2 kcal mol^{-1} by molecular mechanics calculations and 0.9 kcal mol^{-1} experimentally from the equilibrium constant at 298 K <2005JOC1545>. Also, as the amide bond distortion becomes more marked, a greater reluctance to undergo conformational changes was observed.

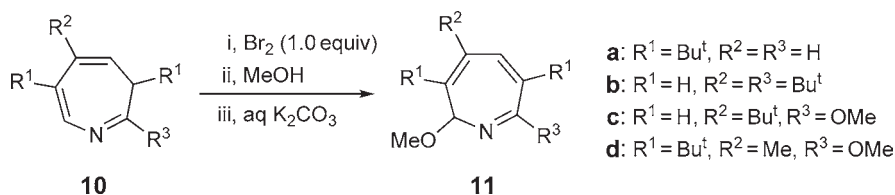


13.01.2.2 X-Ray Studies

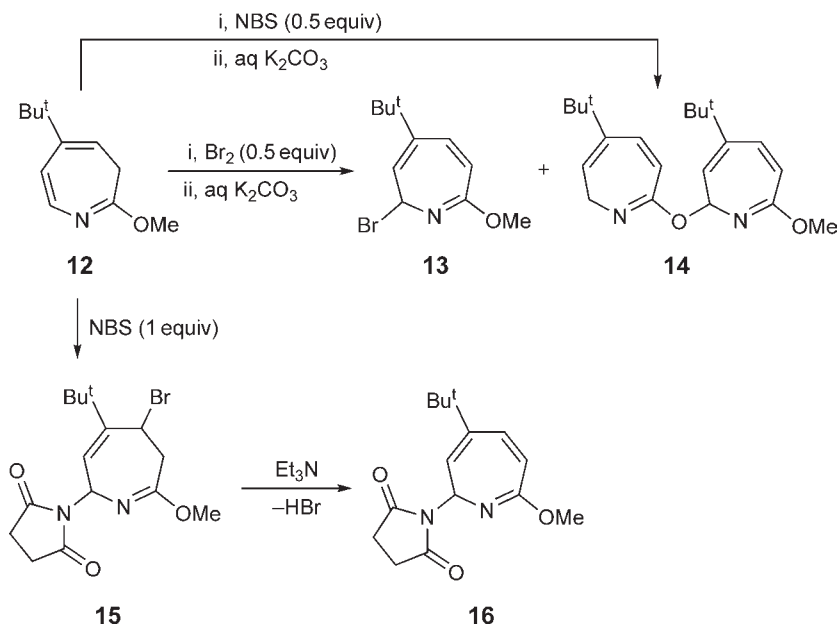
The single crystal X-ray structure of the first reported 2-azatropone has been described by Kimura *et al.*, in which the ring was shown to have a twist-boat-like conformation <2000JOC6093>. Single crystal X-ray data were also used to confirm the structure of a number of 3*H*-azepines <1996LA887>, 3*H*-1-benzazepine <1997HOU(E9d)336>, and a series of 1*H*-1-benzazepine derivatives **6–9**, where the exocyclic double bond, present in **6**, showed the expected flattening of the seven-membered ring to favor a half-chair conformation. The carbonyl group was oriented *anti* to the fused benzene ring in each of the solid-state structures of **6–8** <2005JOC1545>.

13.01.3 Reactivity of Fully Conjugated Rings

Satake *et al.* have described the mechanistic aspects of the formation of 2-methoxy-2*H*-azepine derivatives **11a–d** from 3*H*-azepines **10a–d** upon reaction with bromine <2003H(60)2211> (Scheme 1). Unlike the situation observed with cycloheptatrienes, delocalized azatropylum salts were not formed from the reaction of 3*H*-azepines with bromine in the absence of an alcoholic solvent. Reaction of **12** with bromine gave **13** plus the bis-ether **14** and bromomethane. The product **14** was also observed in the reaction of **12** with NBS (0.5 equiv); with 1 equiv of *N*-bromosuccinimide (NBS) **12** afforded the succinimido-substituted derivative **15**, which upon elimination of HBr in the presence of base gave the 2*H*-azepine **16** (Scheme 2) <2003H(60)2211>.

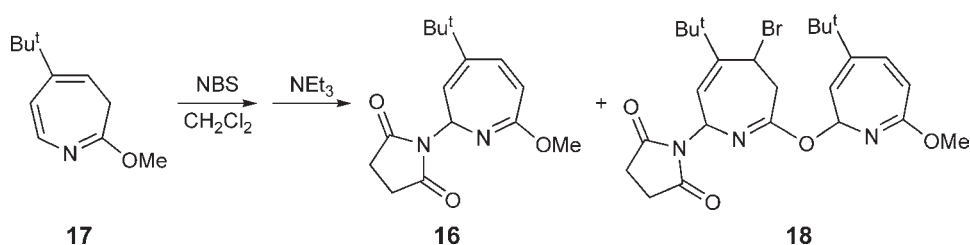


Scheme 1



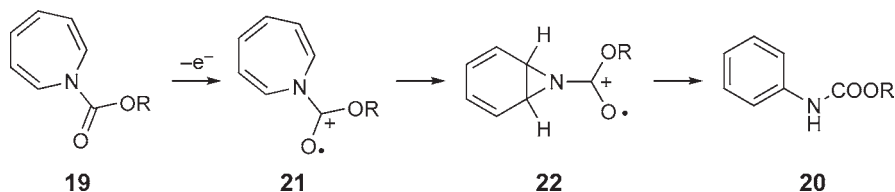
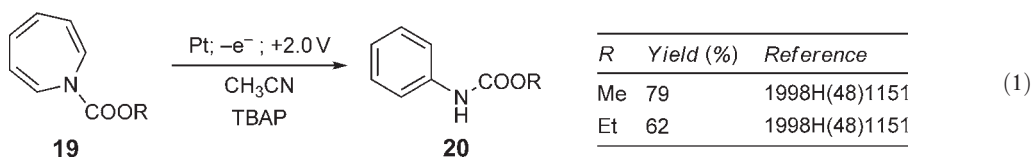
Scheme 2

In an extension of the above work on reactions of 3*H*-azepines, **17** with NBS at very low temperature (-98°C) followed by treatment with base gave mainly the substituted azepine **16**. At 25°C , bisazepinyl ethers were obtained, including **18** (43%), plus some **16** (10%) (Scheme 3) <2005JOC3425>.

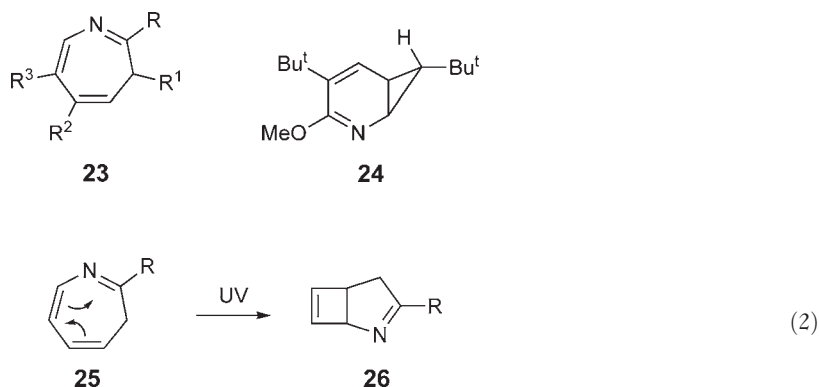


Scheme 3

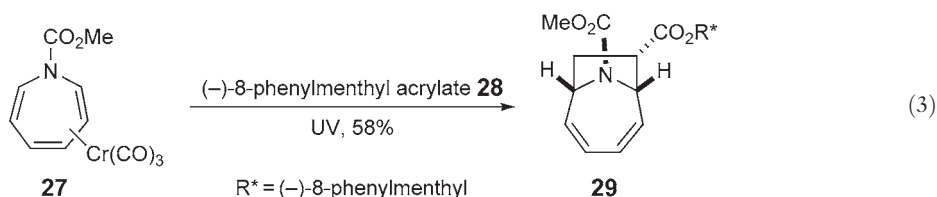
An electrochemical reaction on the azepine carbamates **19** resulted in a ring contraction to give the *N*-substituted anilines **20** in moderate yield (Equation 1). Mechanistically, initial oxidation of the carbamate to give the radical cation **21**, followed by electrocyclic rearrangement to **22**, C–N cleavage, and then reduction was proposed <1998H(48)1151>.



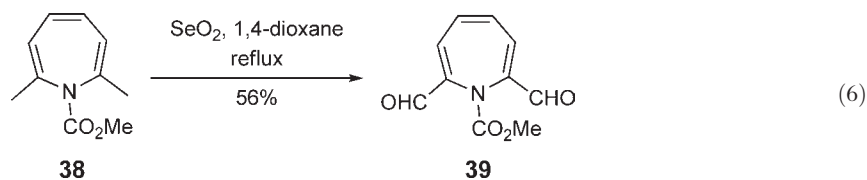
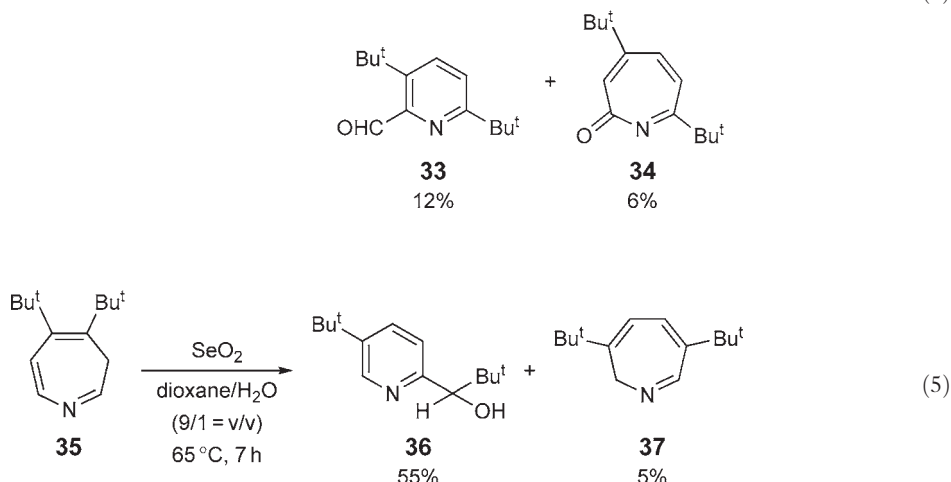
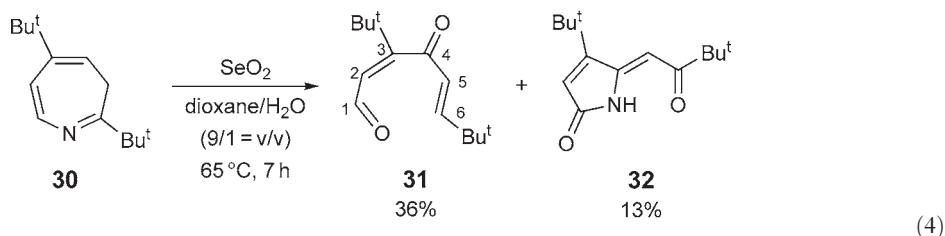
Reaction of the 3*H*-azepines **23** ($R = R^2 = \text{Bu}^t$, $R^1 = R^3 = \text{H}$) and **23** ($R = R^2 = \text{H}$, $R^1 = R^3 = \text{Bu}^t$) with bromine and quenching with MeOH afforded the respective 2-methoxy-2*H*-azepine derivatives, which formed the more stable 3*H*-tautomers at 25 °C. In the latter, tautomerization proceeded further to produce the stable 2-azabicyclo[4.1.0]-heptadiene analogue **24** <1997J(P1)2015>. The 3*H*-azepines **25** with a 2-methoxy, 2-amino, or 2-dimethylamino substituent underwent valence tautomerization under UV light irradiation to give 3-substituted 2-azabicyclo[3.2.0]-hepta-2,6-dienes **26** (Equation 2) <1997JCM276>; no 5-substituted derivatives were observed.



A photo-induced [6+2] cycloaddition of the chiral acrylate **28** with the chromium carbonyl complex **27** afforded the *endo*-adduct **29** in high diastereomeric excess (Equation 3) <1995JOC7392>.

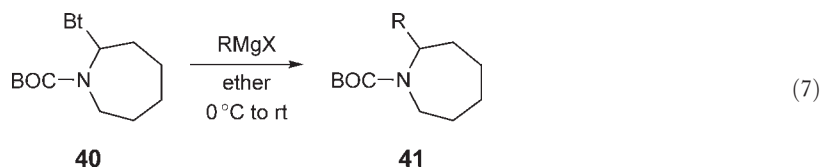


A new oxidative ring cleavage of the dialkyl-3*H*-azepine **30** on treatment with selenium dioxide afforded 4-oxo-octa-2,5-dienal **31** together with minor amounts of the pyrrolone **32** and pyridine **33** plus the first report of the 2-azatropone **34** (Equation 4). The isomeric di-*t*-butylazepine **35** afforded mainly the pyridine derivative **36**, plus the isomeric azepine **37**, although in very low yield (Equation 5) <2000JOC6093>. In contrast, selenium dioxide oxidation of the methyl groups in the 1*H*-azepine derivative **38** afforded dialdehyde **39** in moderate yield (Equation 6) <1999JOC1849>.



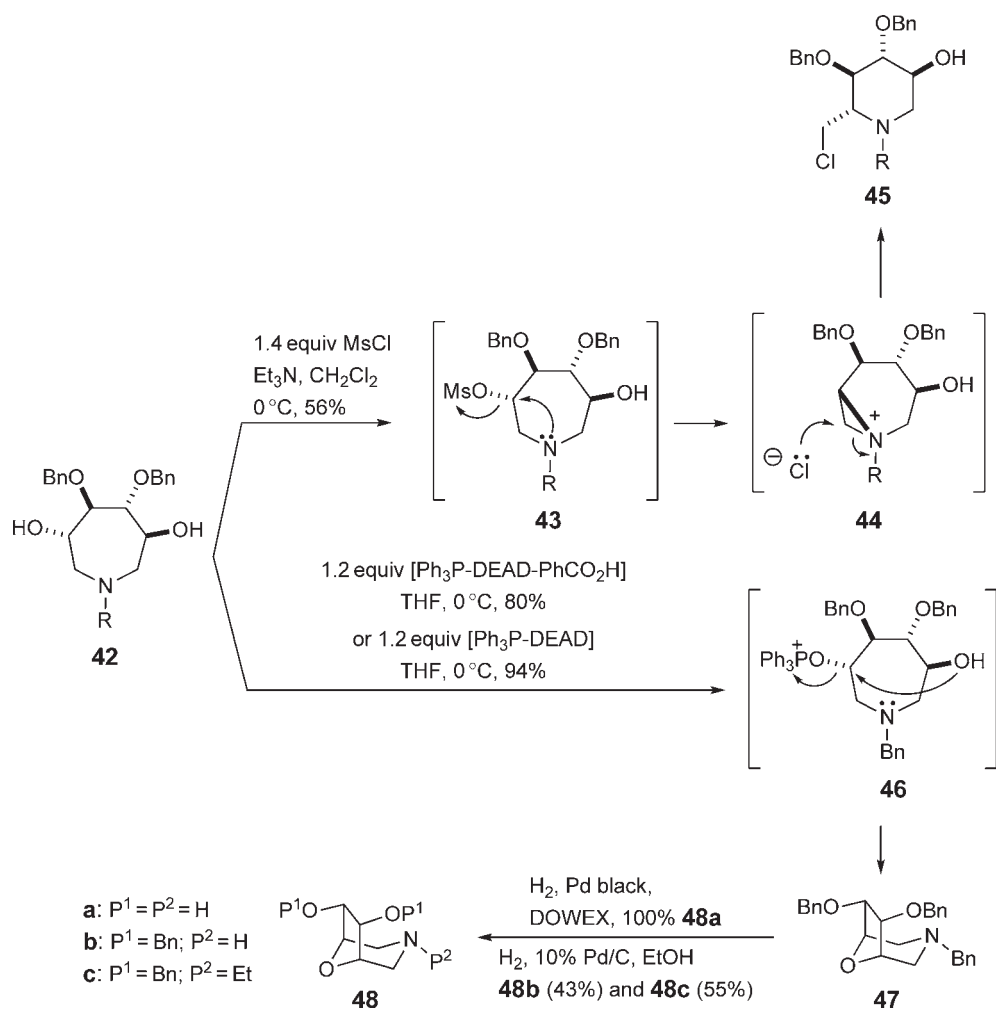
13.01.4 Reactivity of Nonconjugated Rings

An alternative route to racemic 2-substituted azepanes **41**, R = Bu (65%), Ph (59%), involved addition of the appropriate Grignard reagent to the *N*-acyliminium ion species generated *in situ* from **40** upon elimination of the benzotriazolyl moiety (Equation 7) <2005JOC3066>.

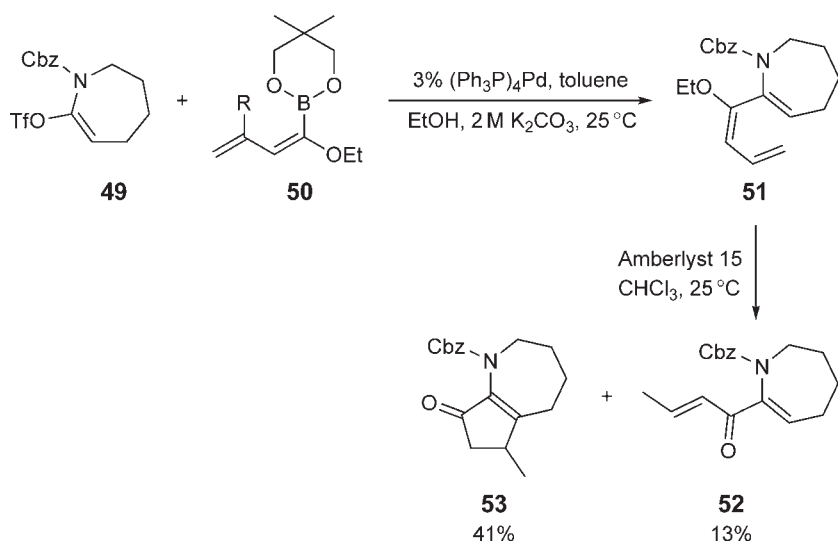


Isomerization of the enantiopure hydroxylated azepane **42**, after hydroxyl group activation, afforded either the ring-contracted piperidine derivative **45** (on *O*-mesylation to **43** followed by internal displacement to the aziridinium ion intermediate **44** and subsequent chloride ion induced ring opening) or the chiral ethylene-bridged morpholines **48** via **47** and an intramolecular Mitsunobu reaction of **46** (Scheme 4) <1996TL1613>.

A different approach to azepine derivatives involved a Pd-catalyzed cross-coupling reaction of the vinyl triflate **49** with the α -alkoxyboronate **50** (R = H) to give **51** in 45% yield; acid-catalyzed hydrolysis then gave the azepine derivative **52** and the fused azepine **53**, although yields were modest (Scheme 5) <2002JOC7144>.



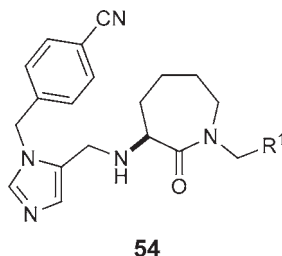
Scheme 4



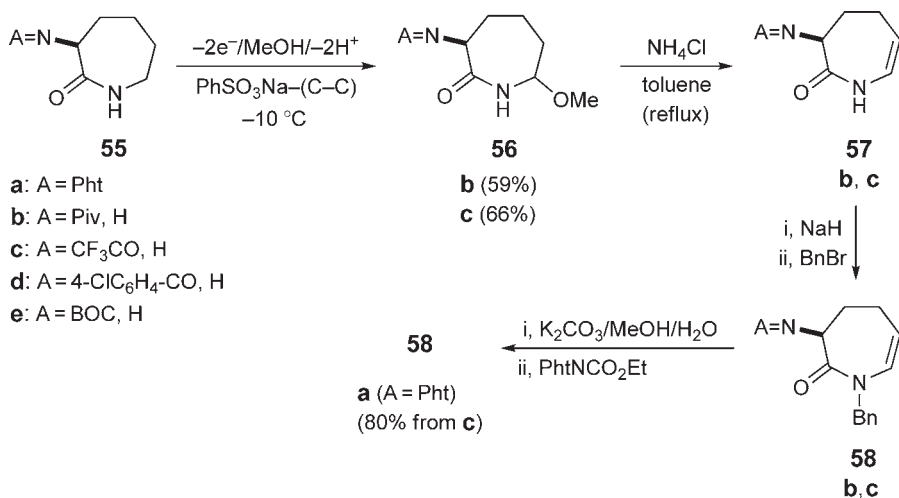
Scheme 5

13.01.5 Reactivity of Substituents Attached to Ring Carbon Atoms

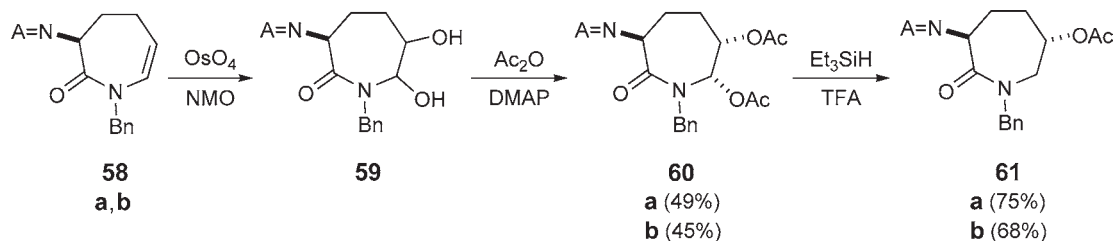
Parallel liquid synthesis has been applied to the preparation of a variety of *N,N'*-disubstituted 3-aminoazepin-2-ones **54** (e.g., $R^1 = m\text{-BrC}_6\text{H}_4$) starting from 1-substituted 3-aminoazepin-2-ones <2003BMC3193>.



Substituted 3-aminoazepanones also formed the core of a number of cyclolysine-based bioactive natural products. A facile approach to these derivatives was based on electrooxidation of **55** to give the methoxy derivatives **56** in moderate yields <2004SL1029>. These latter derivatives in turn could then be converted via **57** to the enamides **58** (Scheme 6). Oxidation of these enamides with OsO_4/NMO then gave, after two further functional group modification steps, the 6-acetoxyazepanones **61**, via **59** and **60** (Scheme 7).

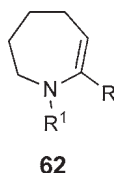


Scheme 6

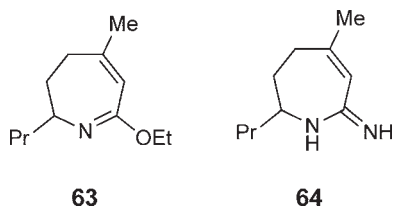


Scheme 7

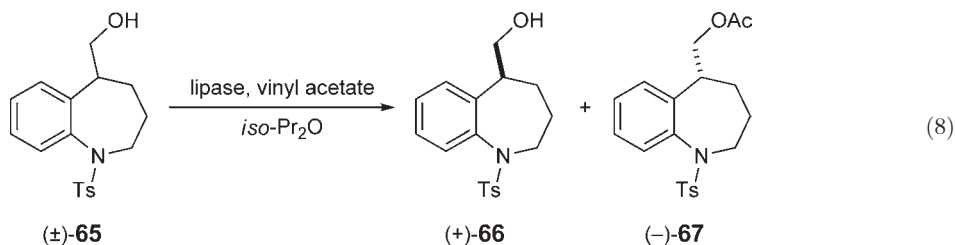
The tetrahydroazepine diphenylphosphates **62** ($R = \text{OPO}(\text{OPh})_2$, $R^1 = \text{CO}_2\text{Ph}$) underwent a Stille coupling and carbonylation to form **62** ($R = \text{CH}=\text{CH}_2$, $R^1 = \text{CO}_2\text{Ph}$) and **62** ($R = \text{CO}_2\text{Me}$, $R^1 = \text{CO}_2\text{Ph}$), respectively <1998CC1757>.



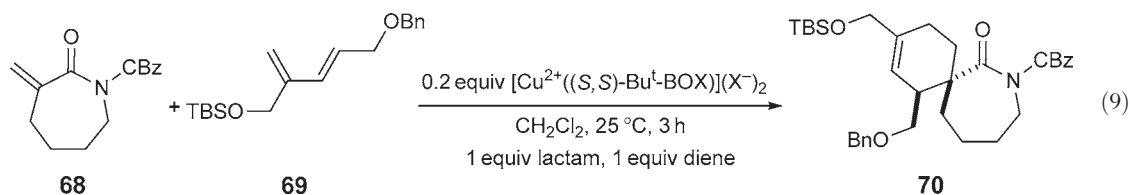
The synthesis of the reduced 2*H*-azepin-2-imine **64** (as its hydrochloride salt) via **63** with ammonia in EtOH followed by treatment with hydrochloric acid in dioxane has also been described [\[2003BMC689\]](#); **64** is notably an inhibitor of inducible nitric oxide synthase.



Enzymatic reactions now have a sound place in contemporary synthetic methodology. Illustrative of this, lipase-catalyzed transesterification of the racemic alcohol **65** has been used effectively to produce (*S*)-(+)-**66** (LipaseQL, 0–5 °C, 4 h; 47% yield; >99% ee), plus the (*R*)-(–)-acetoxy derivative **67** (Equation 8). The 1-benzazepine derivative **66** was then converted to a chiral precursor required for the synthesis of the nonpeptide vasopressin V₂ receptor agonist, OPC-51803 [\[2002H\(58\)635\]](#). The synthesis of a 1-benzazepine-based antagonist (OPC-41061) at this receptor has also been reported [\[2002H\(56\)123\]](#).



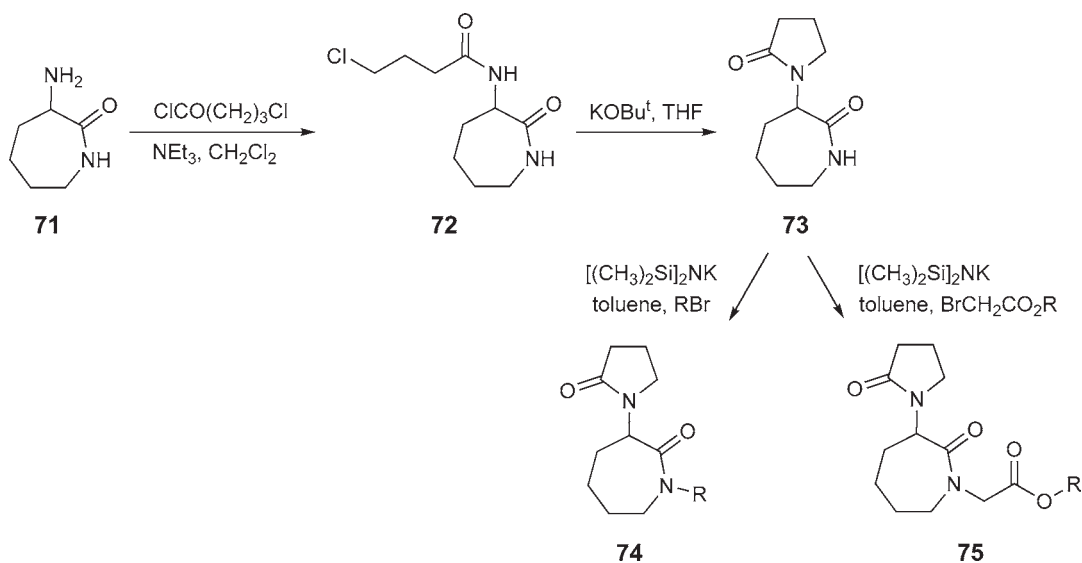
The asymmetric synthesis of the spiroazepinone skeleton present in certain marine toxins was reported by Murai *et al.* A Diels–Alder reaction was key to the synthetic approach. For example, **70** was accessed in 82% yield (96% ee; 99:1 *exo/endo* ratio) from **68** and the diene **69** with X = AsF₆ in the chiral copper complex (Equation 9) [\[2002SL403\]](#).



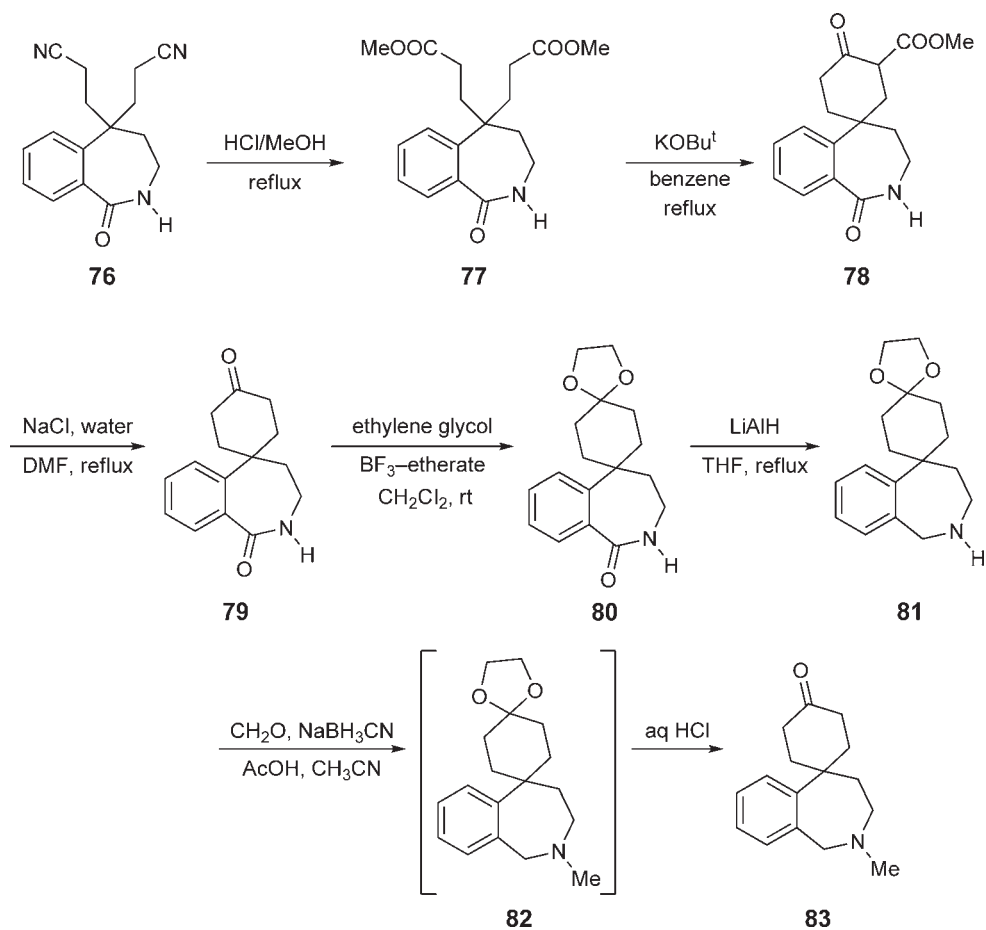
In connection with studies on structure–property relationships with dermal penetration enhancers, substituted azepinone derivatives (e.g., **74**, R = Me and **75**, R = Me) were made by Kim *et al.* from the 3-aminoazepanone **71** via **72** and **73** using standard functional group manipulations (Scheme 8) [\[2001MI183\]](#).

Reactions of a 2-benzazepin-1-one derivative involving a spiroannellation procedure from **76** to afford the spirocyclic 3-benzazepine derivative **83** via **77–82** have been reported (Scheme 9) [\[2005H\(65\)1359\]](#), while other chiral substituted 2-benzazepines have been prepared from D-glucose via furo[3,2-*c*][2]benzazepine derivatives [\[2005S2307\]](#).

Lactim ether formation from 2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one on reaction with dimethyl sulfate and triethyloxonium tetrafluoroborate has been described, and reactions of the lactim ether with a number of primary amines were reported [\[2003CHE344\]](#).



Scheme 8

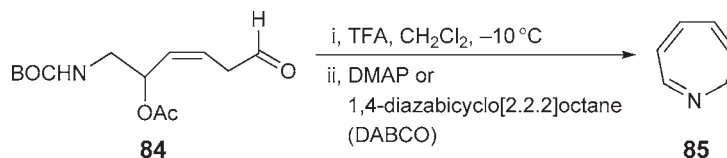


Scheme 9

13.01.6 Ring Synthesis by Ring Construction

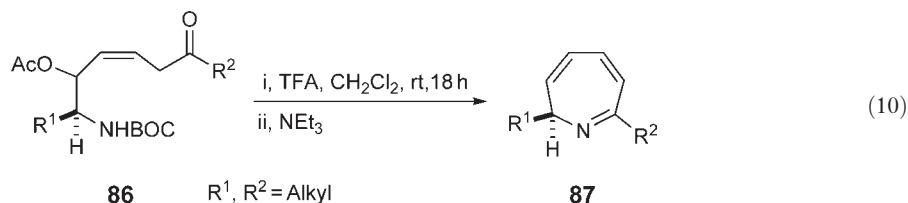
13.01.6.1 Type a (N-C-C-C-C-C-C)

In a very significant development, the parent 2*H*-azepine **85** was prepared for the first time (Scheme 10) <1995AGE1469>. A ring construction was adopted involving *N*-BOC deprotection of **84** followed by treatment with strong base to afford **85** after intramolecular imine formation and base-induced elimination of acetate. While the yield was only 1%, the azepine was sufficiently stable at 25 °C for 48 h to allow for ¹H and ¹³C NMR spectroscopic characterization.

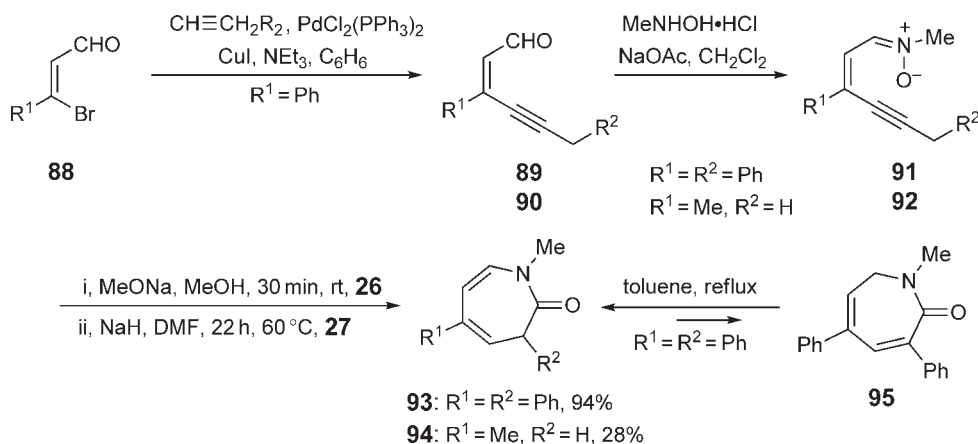


Scheme 10

An extension of the above work to *N*-BOC deprotection of the amino ketones **86** gave the optically active 2*H*-azepines **87** (e.g., **87**, R¹ = Me, R² = Me; 56%). Ready isomerization of **87** by a [1,5]-H shift to the corresponding 3*H*-azepines was observed when the former were left in solution in organic solvents at 25 °C or on warming in CHCl₃ solution (Equation 10) <1996T10883>.



A novel route to the azepinone system in **93** and **94**, based on an intramolecular nitrone–eneallene cycloaddition (in **91** and **92**, which were accessed in turn from **88** via **89** and **90**) and subsequent rearrangement via N–O bond homolysis and an electrocyclic recyclization step) has been described (Scheme 11) <2005EJO2715>. On heating **93** in toluene, equilibrium with the isomeric azepinone **95** was established, although comprising less than 3% of **95**. The general synthetic approach was applied to the synthesis of an analogue of the alkaloid astrocasine.

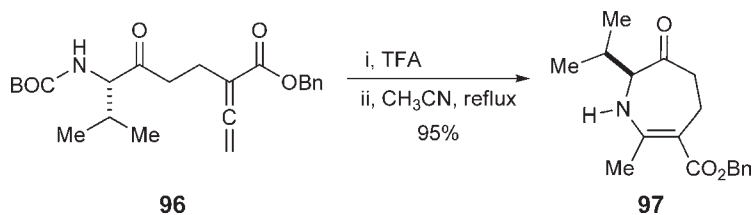


Scheme 11

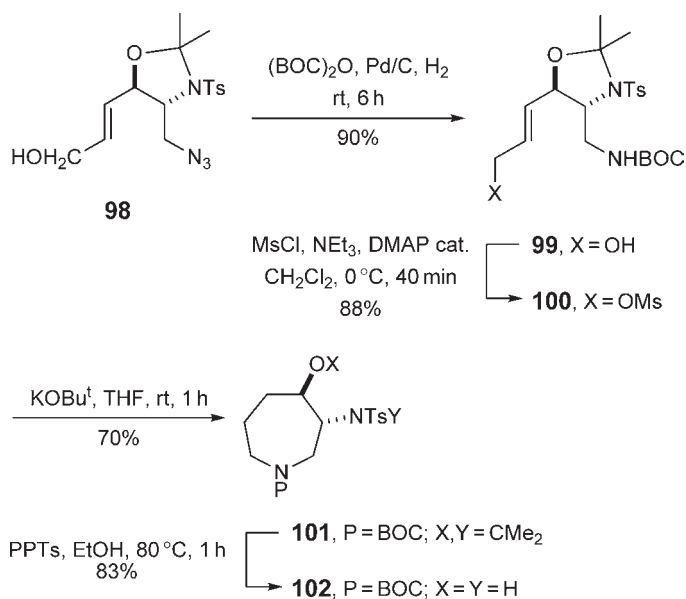
Azepinones, for example, **97**, can also be accessed in high yield from an allene precursor (e.g., **96**) by BOC-group removal and then intramolecular amine addition to the allene (Scheme 12) <2005T6309>.

A stereoselective synthesis of the azepane core of the protein kinase C inhibitor and fungal metabolite, (–)-balanol, and involving C–N bond formation in the ring forming step, has been described (Scheme 13) <2006TL1585>. The

key steps involved azide reduction in **98** with concomitant amine product protection to give **99**, followed by conversion to the mesylate **100** and cyclization to the azepane **101**; removal of the *N,O*-protecting group was then achieved through acid-mediated reactions to give **102**.

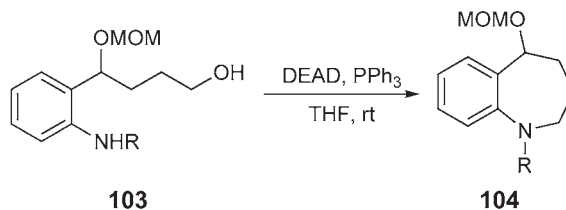


Scheme 12



Scheme 13

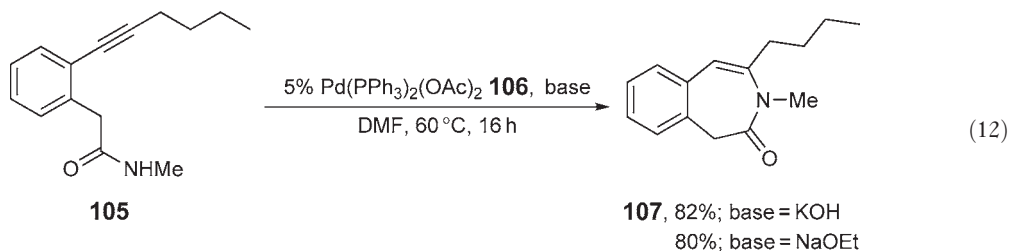
An intramolecular Mitsunobu reaction has been used to prepare a range of substituted 1-benzazepines **104** from **103** in generally very good yields (Equation 11) <2005H(66)481>.



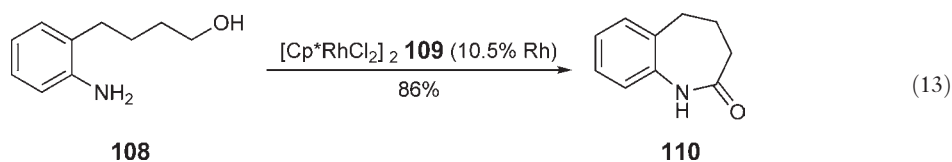
<i>R</i>	Time	Yield (%)	Reference
Ts	2 h	100	2005H(66)481
CF ₃ CO	3 h	85	2005H(66)481
4-O ₂ NC ₆ H ₄ CO	1 d	88	2005H(66)481
4-IC ₆ H ₄ CO	1 d	85	2005H(66)481
4-(2-MeC ₆ H ₄ CONH)C ₆ H ₄ CO	1 d	36	2005H(66)481
BOC	1 d	58	2005H(66)481

(11)

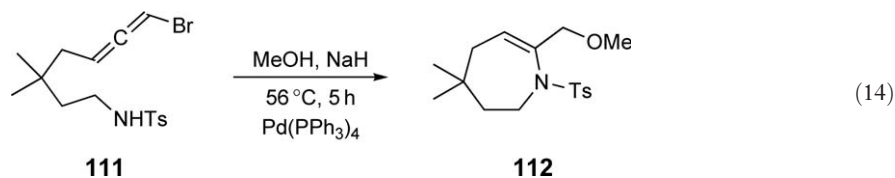
A palladium-catalyzed intramolecular hydroamidation (using **106** as the catalyst) with the alkyne **105** has been shown to proceed regioselectively to provide access to the 3-benzazepinone **107**; either KOH or NaOEt can be used, as the base. Other alkynes can also be used in this reaction (Equation 12) <2006TL3811>.



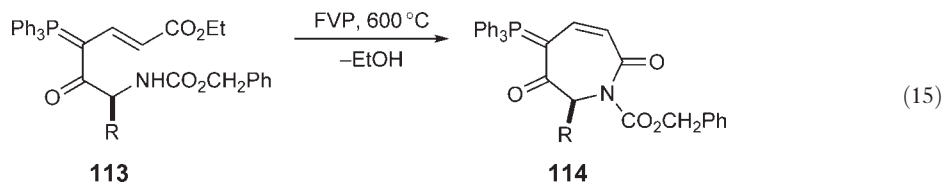
Reaction of the *o*-aminophenylbutanol **108** with a new rhodium-based catalytic system (Cp^* = pentamethylcyclopentadienyl) **109** in the presence of K_2CO_3 gave the tetrahydro-1-benzazepinone **110** in 86% yield (Equation 13). This represents one of the few methods for direct catalytic cyclization to this system <2004OL2785>.



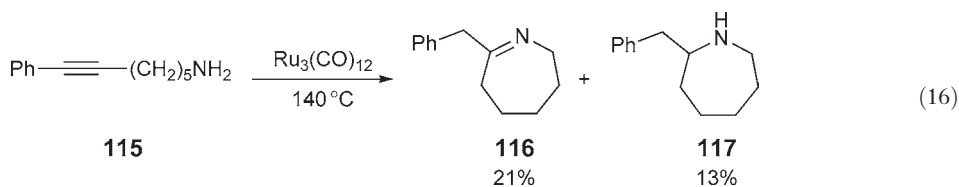
Ohno *et al.* have described an alternative to a ring-closing metathesis to access seven-membered rings <2003H(61)65>. Thus, reaction of the bromoallene **111** containing a nucleophilic entity and $\text{Pd}(\text{PPh}_3)_4$ in the presence of MeOH gave the azepine derivative **112** in good yield (76%) (Equation 14).



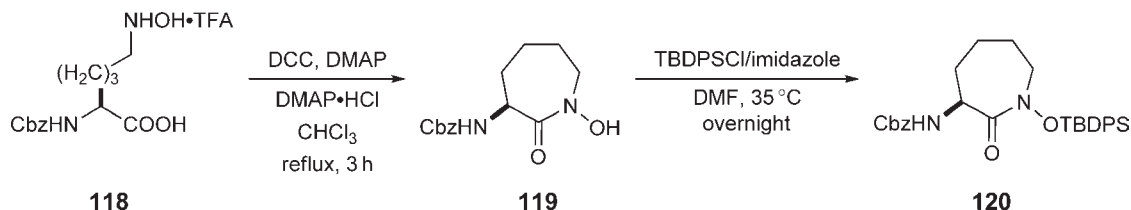
Heterocyclic phosphorus ylides (e.g., **114**, $\text{R} = \text{Me}$) containing an azepinedione nucleus have been prepared, although in low yield (13–26%), by flash vacuum pyrolysis (FVP) of the corresponding open-chain ylide precursor **113** (Equation 15) <2001TL141>. The authors noted, however, that the azepinediones were isolated from the inlet residue rather than from the cold trap after the pyrolysis tube.



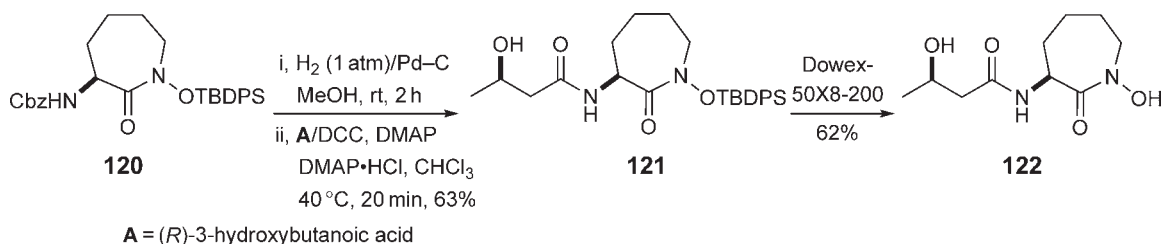
Access to more simply substituted azepine derivatives **116** and **117** has also been realized by ruthenium-catalyzed intramolecular hydroamination of the aminoalkyne **115** (Equation 16) <2001JOM(622)149>. The isolated yield of **116** was 21% and of **117** was only 13%.



Reaction of the acid **118** in CHCl_3 with a mixture of dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), and DMAP·HCl then heating at reflux for 3 h gave the azepane **119**, which was converted to the more readily isolable *t*-butyldiphenylsilyl (TBDPS) ether **120** (Scheme 14). Hydrogenolytic deprotection of the Cbz group in **120** to give **121**, then DCC-mediated coupling with (*R*)-3-hydroxybutanoic acid, and reformation of the azepine *N*-hydroxyl functionality resulted in Cobactin T **122** (Scheme 15), a key component of mycobactins <1995TL6379>.

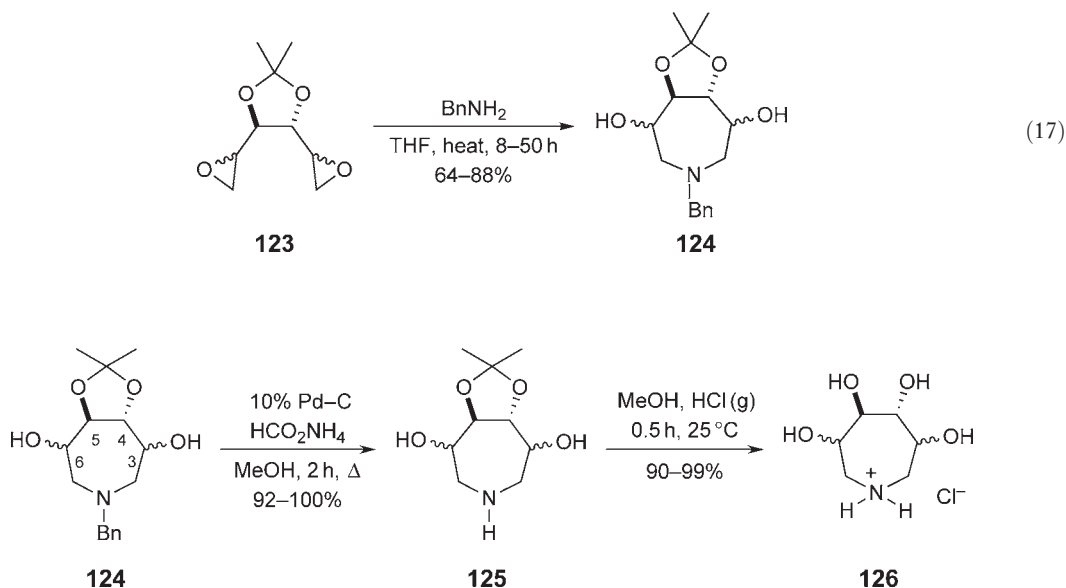


Scheme 14



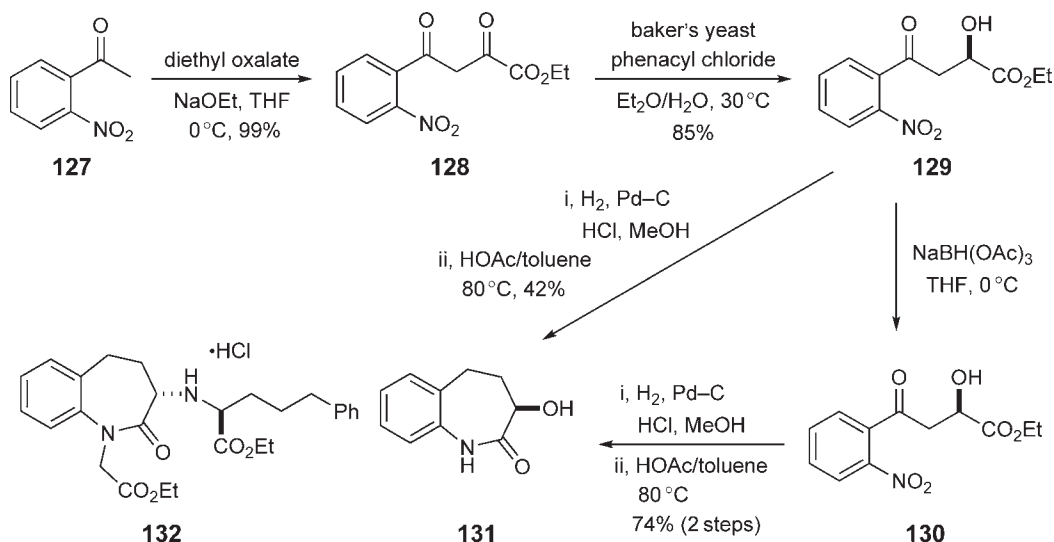
Scheme 15

Cyclization of the bis-epoxides **123** (mixtures of diastereomers) with benzylamine afforded the azepanes **124** in a preferential 7-*endo-tet* methodology (Equation 17) <1995JOC5958>; however, with the corresponding 3,4-benzyl ethers of the bis-epoxides rather than the *trans*-acetonide protecting group, no cyclization to six-membered ring species was observed. The azepanes **124** were then converted in two steps to the amino sugar hydrochloride salts **126** via the *N*-debenzylated intermediates **125** (Scheme 16).



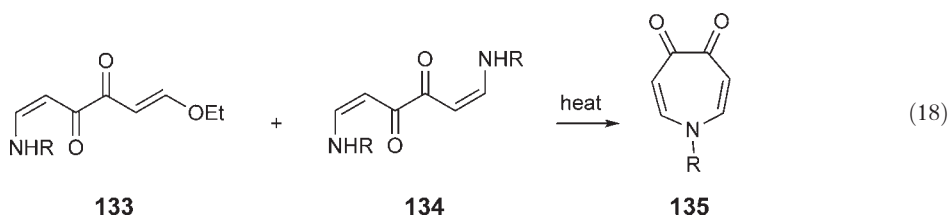
Scheme 16

An important step in the asymmetric synthesis of the angiotensin-converting enzyme inhibitor, benazepril HCl **132**, was the reduction of the ketoester **128** (obtained from **127** by condensation with diethyl oxalate) with baker's yeast to give the chiral α -hydroxy ester **129** in high yield and ee (Scheme 17). Direct formation of the 1*H*-1-benzazepin-2-one **131** from **129** proceeded in 42% yield (without racemization at C-3) or in 74% yield in two steps via **130**, again with no racemization <2003TA2239>.



Scheme 17

The compound 1,6-diethoxy-1,5-hexadiene-3,4-dione has been shown to react with ammonia and primary amines to give a mixture of the aminoalkyl- and bis(aminoalkyl)-dienes **133** and **134**, which on heating in *o*-dichlorobenzene resulted in the formation of 1*H*-azepine-4,5-diones **135** (R = H, alkyl) (Equation 18) <1995JHC57>.

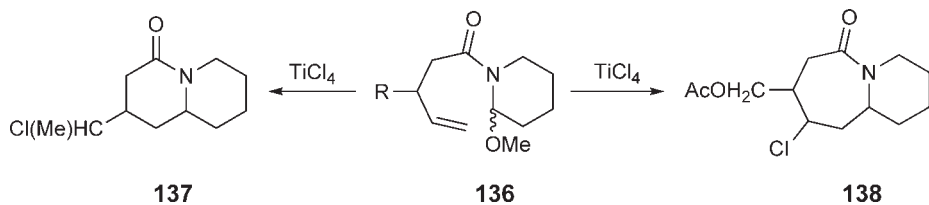


13.01.6.2 Type b (C–N–C–C–C–C–C)

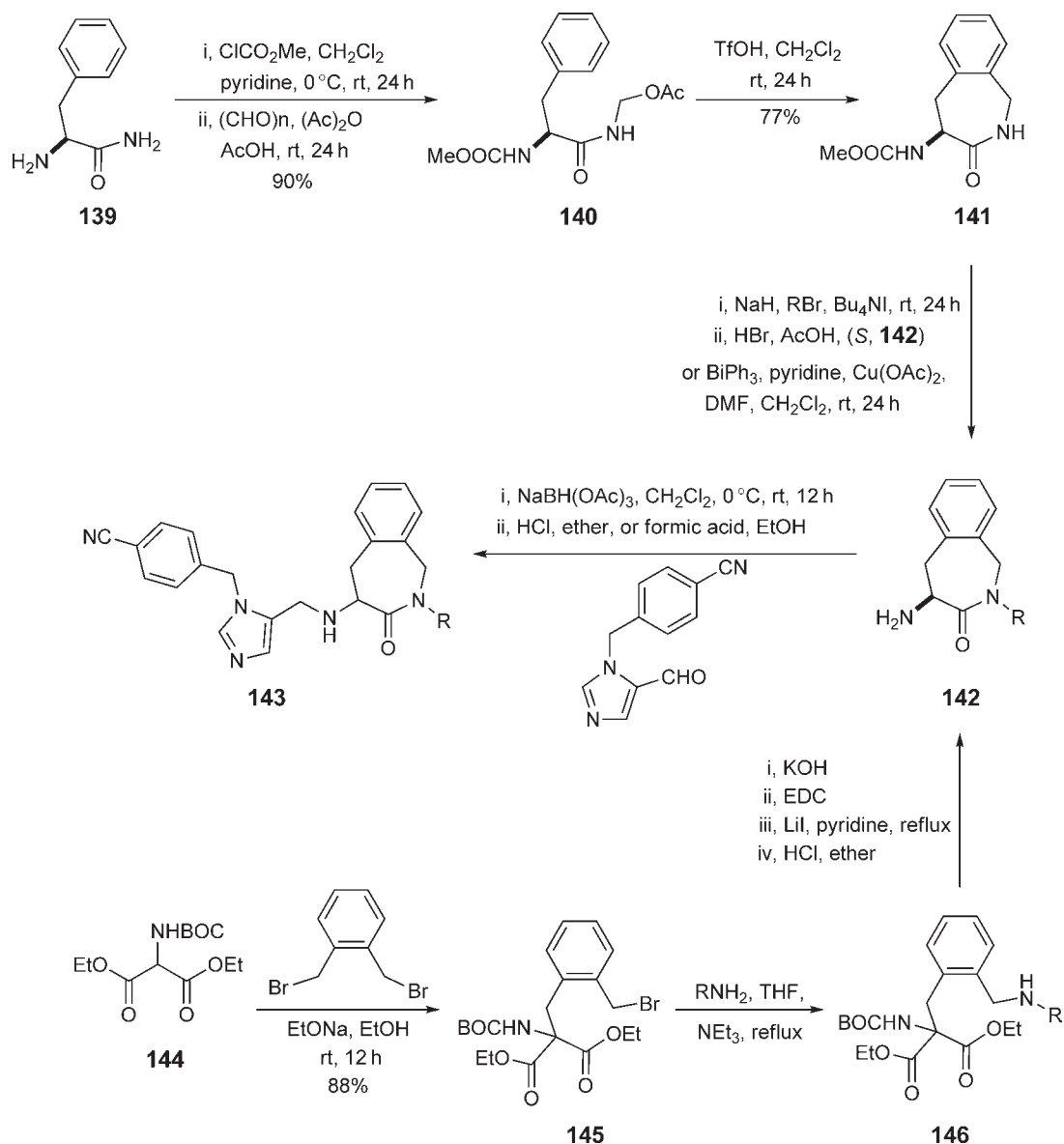
The *N*-acylaminals **136** can serve as substrates for the formation of fused azepinone derivatives on treatment with a catalytic amount of TiCl₄, although the reaction is sensitive to the nature of the R group. Thus, **138** was obtained from **136** (R = CH₂OAc), but with R = Me in **136**, the 6,6-fused system **137** resulted (Scheme 18) <1999TL7939>.

Two approaches to the 2-benzazepine system, in particular the 2-benzazepinone **142**, have been reported by Le Diguarher *et al.* The first started from (*S*)-phenylalanine carboxamide **139** and proceeded via the protected acetoxy derivative **140** and acid-catalyzed cyclization to **141**; N-alkylation and carbamate deprotection then afforded **142**. The second route was based on *N*-BOC aminomalonate **144** and 2,2'-dibromo-*o*-xylene, and then steps via **145** and

146. Although this second route is a type *a* ring construction, it is included here for convenience and comparison with the type *b* approach. The benzazepinone **142** was converted into the N-substituted derivatives **143**, which were potent and specific farnesyl transferase inhibitors (Scheme 19) <2004BML767>.

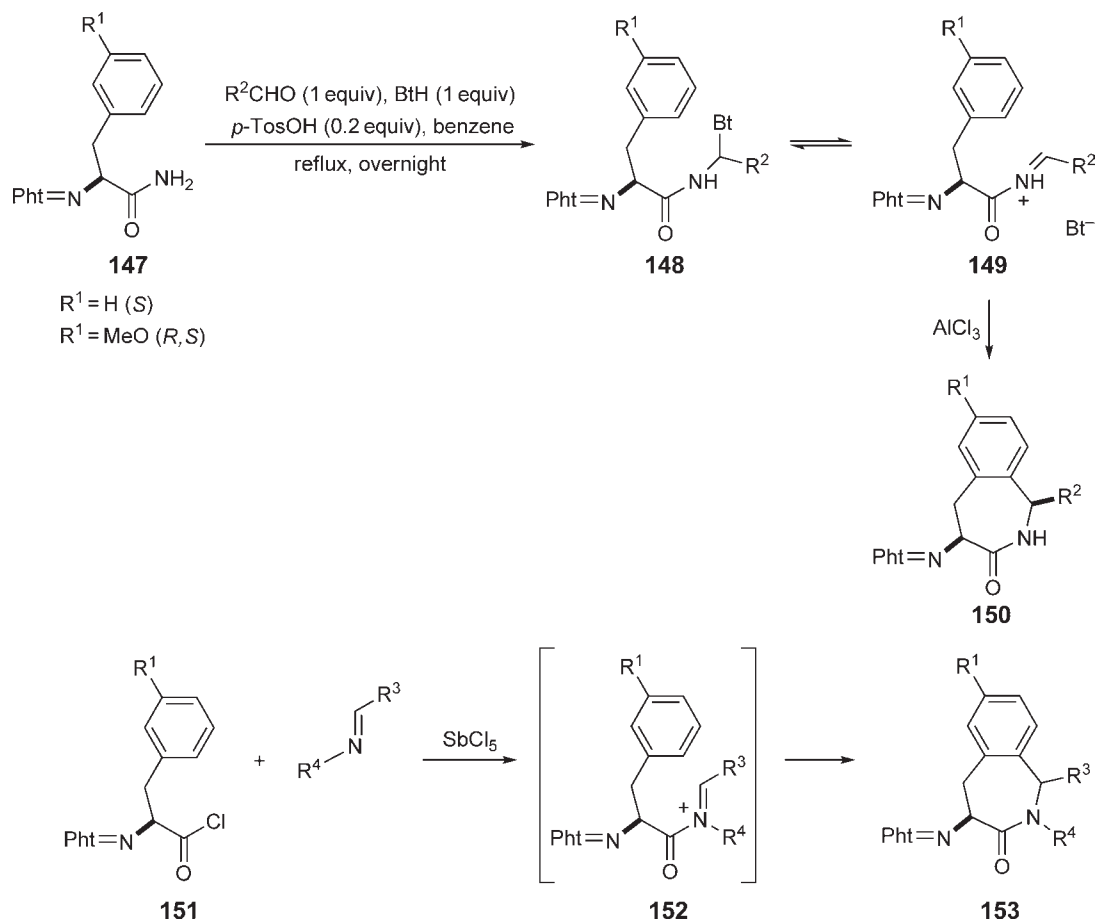


Scheme 18



Scheme 19

The high reactivity of the *N*-acyliminium ion intermediate **149** (generated from **147** via **148**) was used to access the 2-benzazepine-3-ones **150** (e.g., $R^1 = \text{H}$, $R^2 = \text{Ph}$, 31%) in moderate yields [<2005SL2791>](#). The *N*-substituted analogues **153** (e.g., $R^1 = \text{H}$, $R^3 = \text{Ph}$, $R^4 = \text{Bn}$) could be realized via the analogous reactive intermediate **152** but produced in this latter case by SbCl_5 -mediated addition of the acid chlorides **151** to the imines **153** (**Scheme 20**) [<2005SL2791>](#).

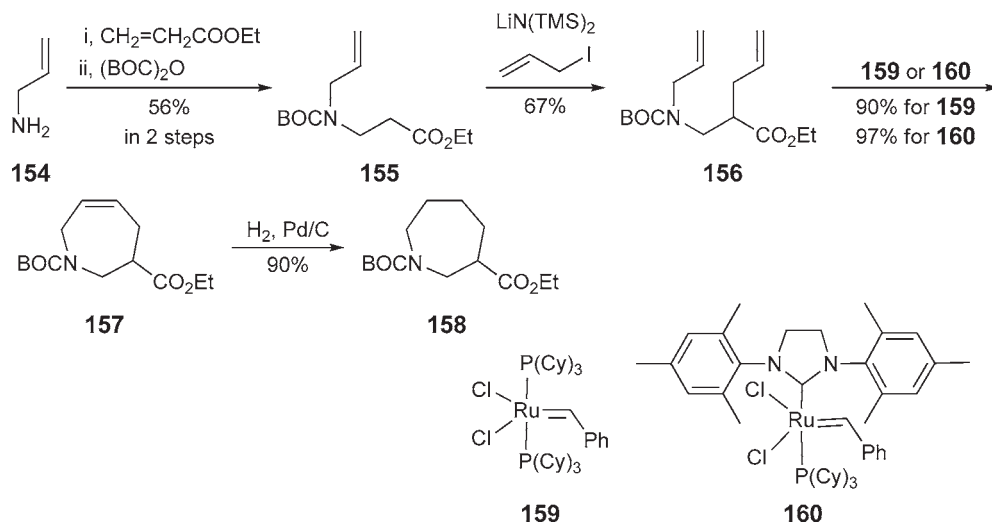


Scheme 20

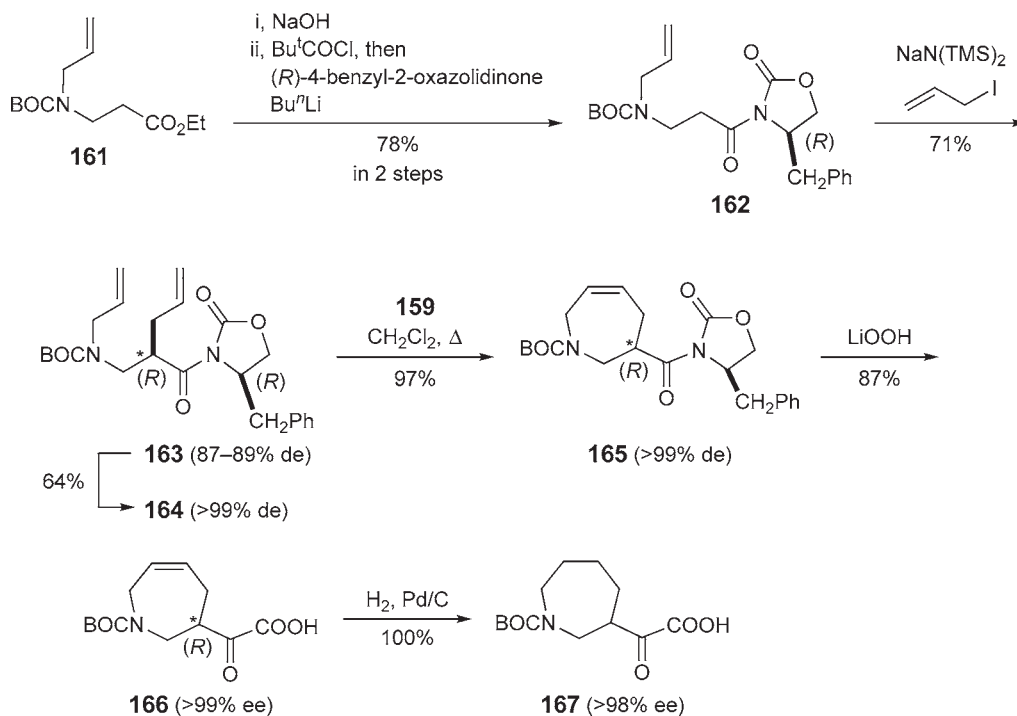
13.01.6.3 Type c (C–C–N–C–C–C–C)

A dominant feature of the type *c* ring-construction approach to azepine systems has been ruthenium-catalyzed ring-closing metathesis reactions. Examples include the synthesis of the azepine derivative **157** from **156** using either the Grubbs type I catalyst **159** or type II **160**. The diene precursor **156** was prepared in turn from **154** via **155**, as shown in **Scheme 21**. Hydrogenation of the C–C double bond in **157** afforded the azepane **158** [<2005SL631>](#).

In a like manner, the chiral keto acid **166** was obtained in good yield (**Scheme 22**) from ring-closing metathesis on **164**, which was obtained via **162** and **163** from **161**; acid **166** resulted from hydrolysis of the initial ring-closing metathesis (RCM) product **165**. Reduction of the double bond in **166** gave azepane **167** in excellent yield [<2005SL631>](#).



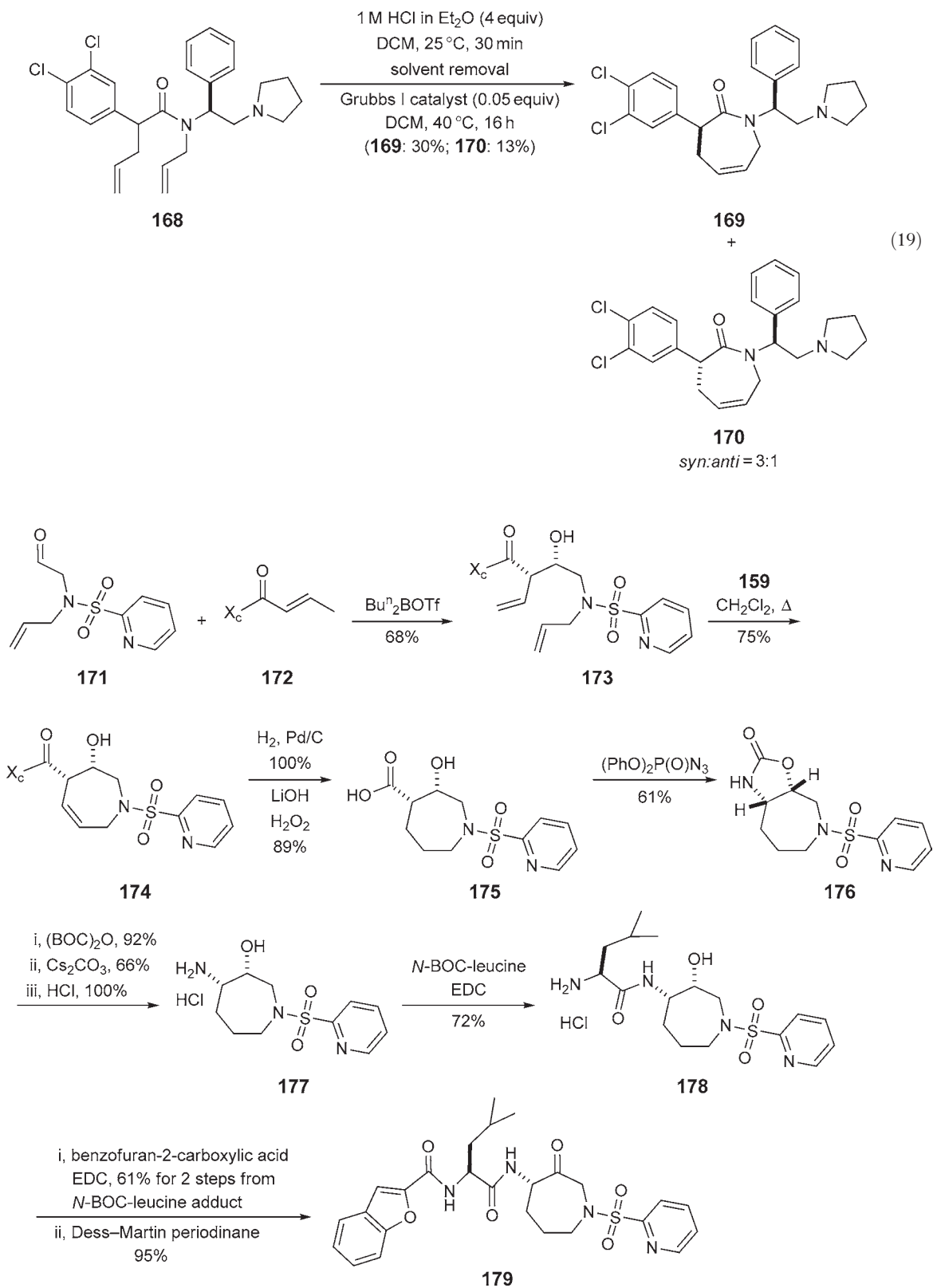
Scheme 21



Scheme 22

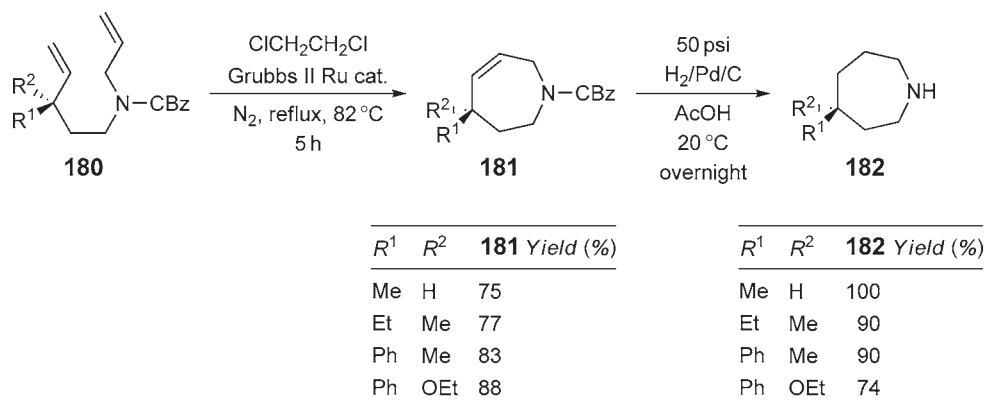
In a further application of a ring-closing metathesis, the preparation of the *syn*- and *anti*-azepinones **169** and **170**, respectively, was achieved from the hydrochloride salt of the precursor **168** using Grubbs I catalyst (Equation 19). The *syn*-isomer **169** showed particularly strong (subnanomolar) *in vitro* binding to the κ -opioid receptor <2004BML5693>.

An azepanone-based inhibitor, **179**, of the cysteine protease inhibitor, cathepsin K, was prepared via an asymmetric synthesis from **171** and **172** (Xc = a 4(*S*)-benzyloxazolidin-2-one moiety) with ring-closing metathesis of **173** then being used to complete the seven-membered ring in the intermediate **174** with a very high de (Scheme 23). Further functional group manipulations via **175**–**178** then resulted in **179** <2005TL2799>.



Scheme 23

The 4,4'-disubstituted azepines **182** can also be accessed in good yield by ring-closing metathesis on diene **180** using the Grubbs II catalyst; the dienes **180** in turn could be made in racemic or optically enriched form from α,α' -disubstituted lactone precursors (Scheme 24) <2006S1437>. Removal of the N-protecting group and double bond in **181** by hydrogenolysis/hydrogenation then afforded the 4,4'-disubstituted azepanes **182**.



Scheme 24

The exploitation of ring-closing metathesis of seven-membered rings is further illustrated by the preparation of the tetrahydroazepines **184** ($X = \text{CH}_2$) or 2-azepinones **184** ($X = \text{CO}$) from the appropriately substituted and readily available precursors **183** (Equation 20). Yields were generally good to high (particularly with Grubbs II ruthenium catalyst) (Table 1); however, as noted in other reactions of this type, amine functionality (**183**; $R_1 = \text{Bn}$; $R_2 = \text{H}$, $X = \text{CH}_2$) prejudiced the metathesis process, and a very low yield of **184** was obtained with Grubbs I catalyst and no product at all with the second generation Grubbs catalyst. Starting material **183** was reisolated in both cases <2006T1777>.

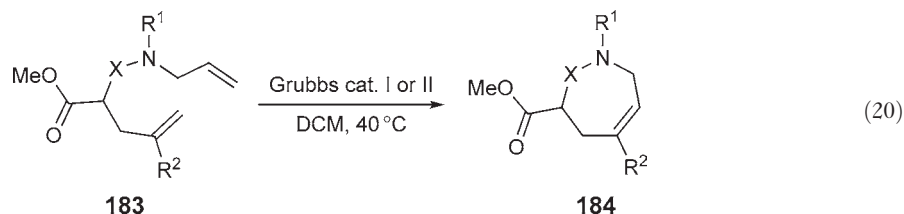
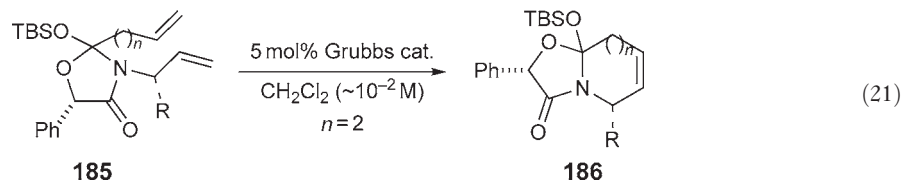


Table 1 Yields of Compounds **184**

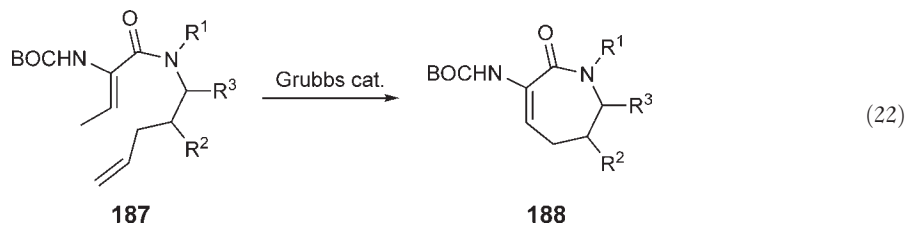
Substrate	R^1	R^2	X	Grubbs I cat. 184 yield (%)	Grubbs II cat. 184 yield (%)	Reference
183	Bn	H	CH_2	8	0	2006T1777
183	Bn	H	$\text{C}=\text{O}$	88	90	2006T1777
183	Bn	CH_2OH	$\text{C}=\text{O}$	16	81	2006T1777
183	Bn	CH_2OTBS	$\text{C}=\text{O}$	23	74	2006T1777
183	BOC	H	CH_2	87	86	2006T1777
183	BOC	CH_2OH	CH_2	37	95	2006T1777
183	BOC	CH_2OTBS	CH_2	44	87	2006T1777

On some occasions, having the amide functionality in the area of the diene precursor to be subjected to the metathesis reaction can mitigate against facile ring closure because of steric disposition issues associated with the amide rotamer. Incorporation of the amide in oxazolidinone functionality can be used to overcome this problem, for example, in the conversion of **185**–**186** (Equation 21); yields of **186** were generally high (Table 2). Ring opening of the oxazolidine moiety with or without loss of the mandelic acid moiety then gave the corresponding azepin-2-ones <2006TL3625>.

**Table 2** Yields of Compounds **186a–d**

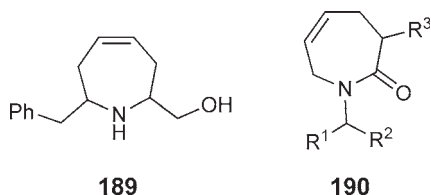
185	<i>R</i>	Catalyst	186 , Yield (%)	Reference
185a	H	159	186a , 91	2006TL3625
185b	Pr ⁱ	159	186b , 79	2006TL3625
185c	Bu ⁱ	160	186c , 78	2006TL3625
185d	Ph	160	186d , 66	2006TL3625

Further N-substituted and reduced 2-azepinone derivatives **188** can also be accessed in high yields (Equation 22 and Table 3) by a ring-closing metathesis on the precursors **187** using Grubbs II catalyst **160**. Various *N*-heteroaryl-substituent groups were tolerated in this reaction <2006TL3295>.

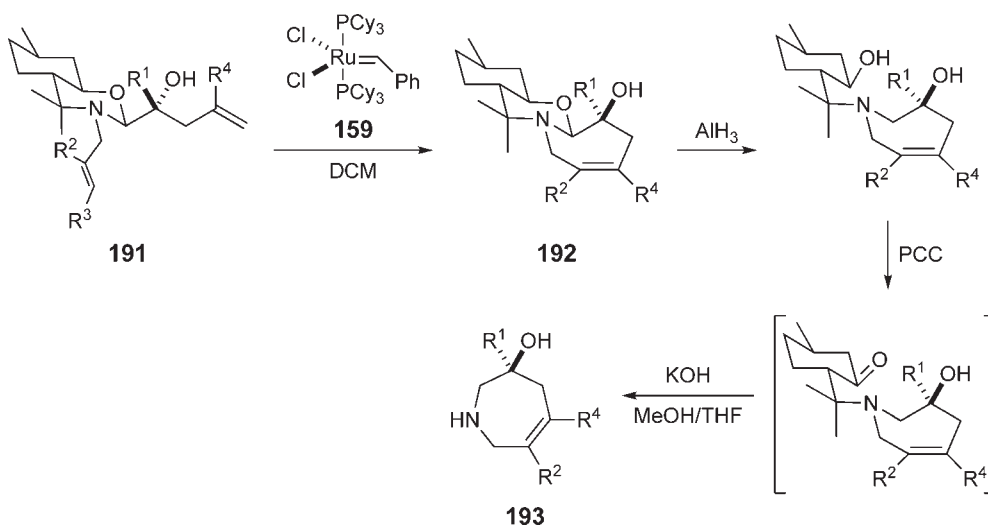
**Table 3** Yields of Compounds **188**

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	Grubbs II cat. (mol%)	Yield (%)	Reference
	H	H	5	86	2006TL3295
	H	H	10	78	2006TL3295
	H	H	10	45	2006TL3295
	H	H	5	90	2006TL3295
	H	H	10	88	2006TL3295
	H	H	10	92	2006TL3295

A solid-state modification of the ring-closing metathesis reaction has also been reported in the preparation of the tetrahydroazepine derivative **189** <1999S138> and of the lactams **190** (e.g., **190**, $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{NHBOC}$; 36% overall yield) <1998TL2667>.

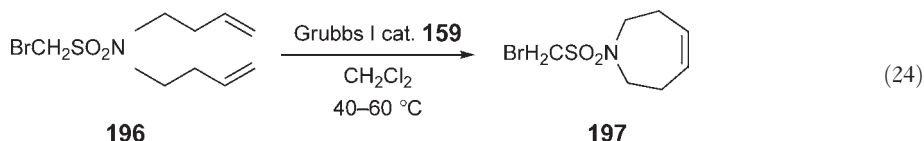
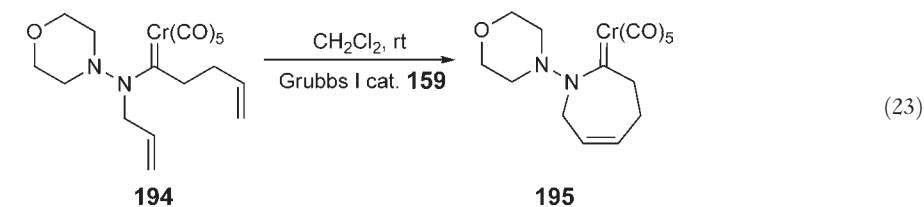


An asymmetric route to the fused azepine derivatives **192** has been reported by Pedrosa *et al.* <2005EJO2449> involving conversion of **191** to **192** (e.g., with $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^4 = \text{H}$; 90% yield) (Scheme 25). Compounds of type **192** could then be readily converted to the reduced azepin-3-ol derivatives **193** (Scheme 25).

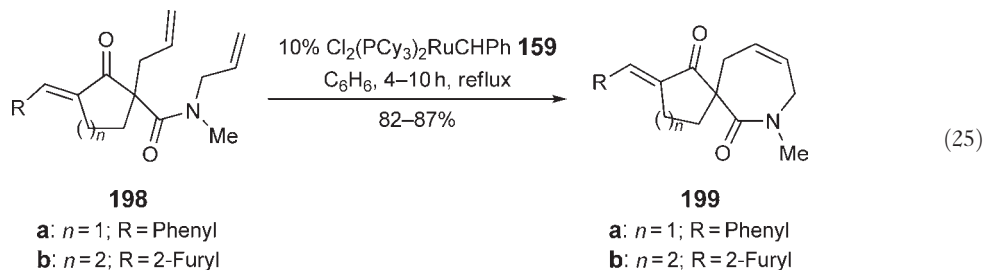


Scheme 25

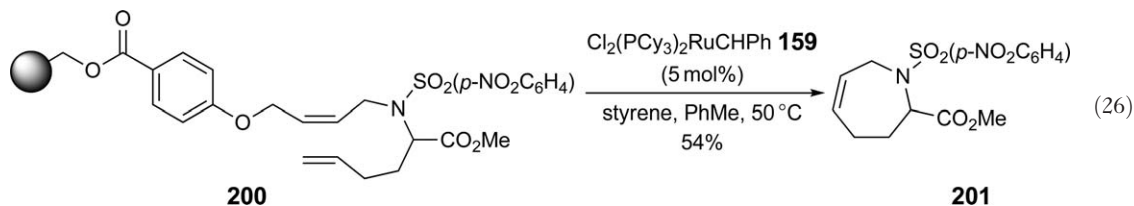
Ring-closing metathesis using Grubbs I ruthenium catalyst **159** (2 mol%) has also been used in the preparation of the Fischer-type chromium carbene complex **195** from the precursor **194** in near quantitative yield (Equation 23) <2001SL757>. The N-substituted tetrahydroazepine **197** could be prepared similarly in excellent yield from **196** (Equation 24) <2001JOC564>.



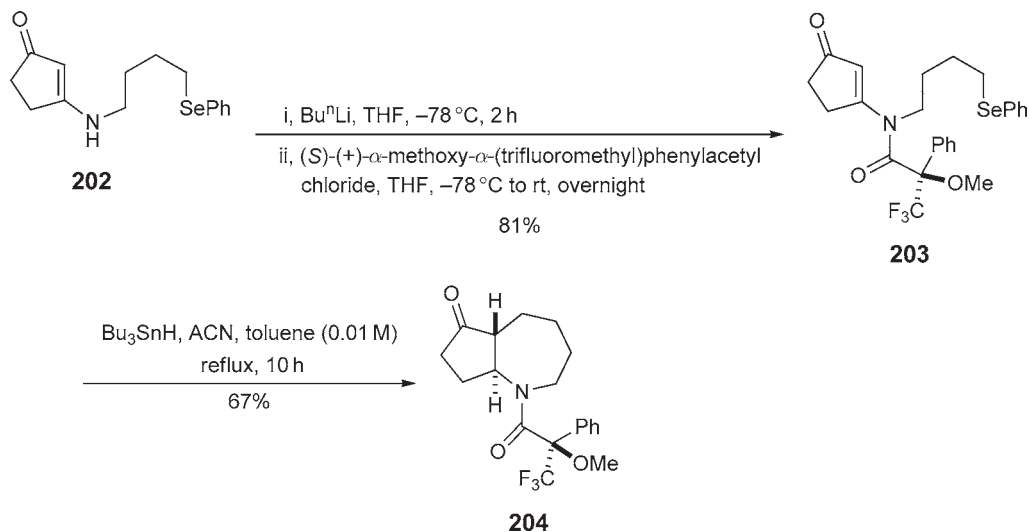
A neat alternative approach to spiro-azepinones involved a ring-closing metathesis of **198** to give **199** in good yields using Grubbs I catalyst (Equation 25) <2002SL1827>.



An elegant traceless linker variation on the ring-closing metathesis strategy resulted in the preparation of the tetrahydroazepine **201** from the immobilized diene **200**, although the yield of **201** was only moderate (Equation 26) <1998EJO2583>.

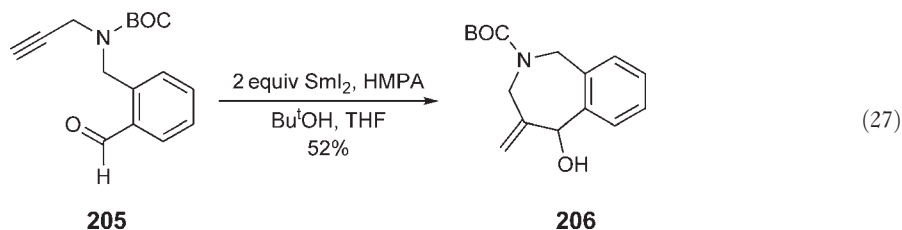


A concise free radical cyclization process has been applied to the synthesis of new cyclopentanone-annulated azepines **204** from chiral vinylogous amides (Scheme 26). The free radical was generated from the phenylselenide group in **203** (made in turn by N-acylation of **202**) using Bu_3SnH and 1,1'-azobis(cyclohexanecarbonitrile) (ACN), as the initiator <2004SL1917>.

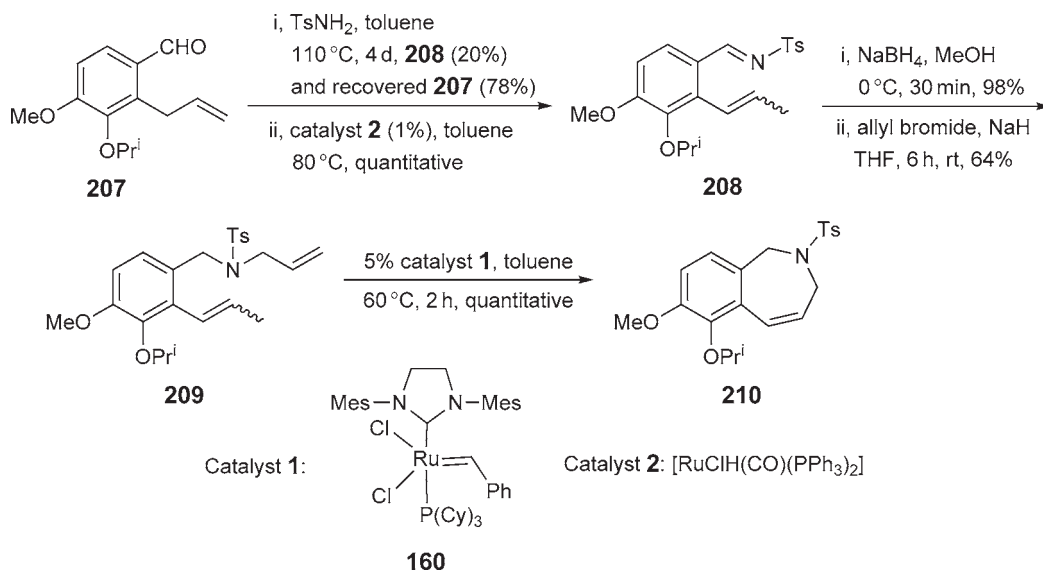


Scheme 26

In a further exploitation of samarium diiodide-induced ketyl couplings, Reissig *et al.* have reported an elegantly designed application in the case of the aldehyde **205**. A 7-*exo-dig* cyclization of the ketyl radical from **205**, formed on treatment with 2 equiv of SmI_2 and hexamethylphosphoramide (HMPA), gave the 2-benzazepine **206** (Equation 27). A disadvantage of this approach is the use of the carcinogen HMPA, and further studies to replace it would be worthwhile <2004SL422>.

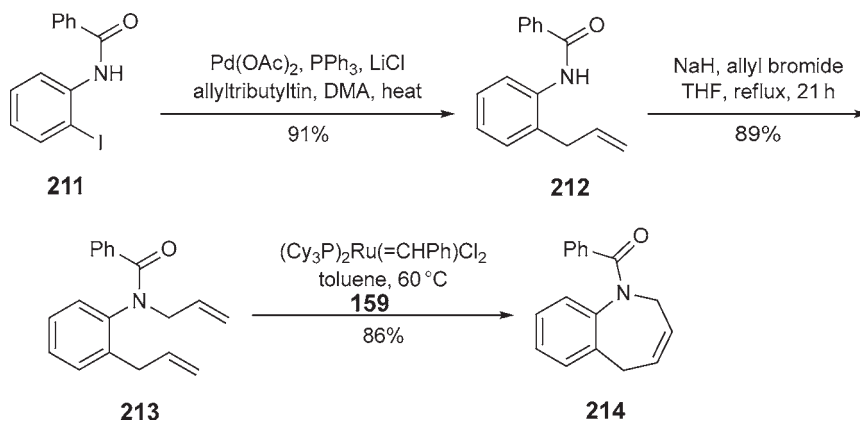


A conceptually neat ruthenium-mediated isomerization and ring-closing metathesis was used in the synthesis of the 1*H*-2-benzazepine derivative **210** in moderate yield from **207** via **208** and **209** (Scheme 27) <2003SL1859>.



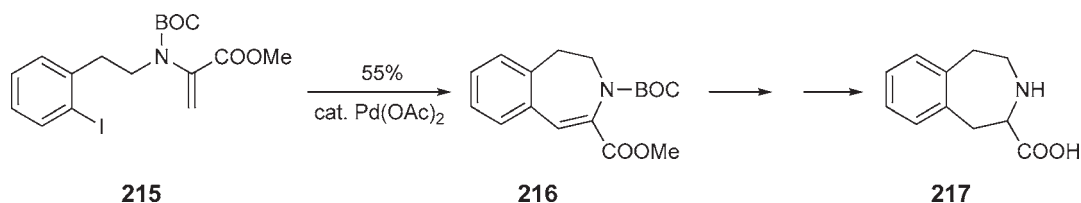
Scheme 27

The Pd-catalyzed reaction of **211** with allyltributyltin to give **212**, followed by N-alkylation to **213**, afforded the 1-benzazepine derivative **214** in high yield on Ru-catalyzed ring-closing metathesis with Grubbs I catalyst **159** (Scheme 28) <2005JOC1545>.



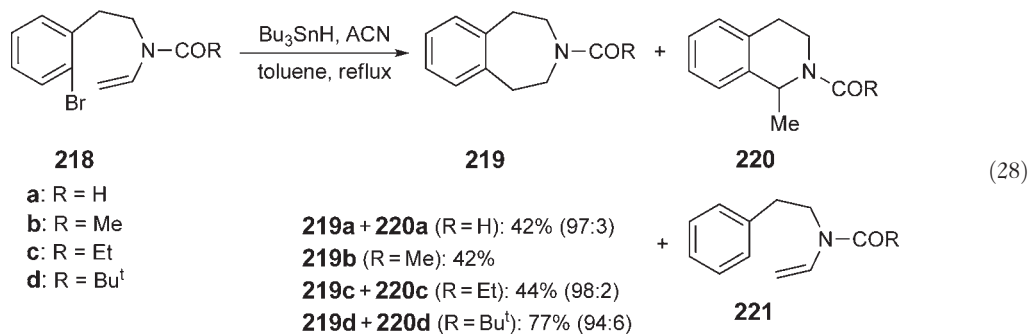
Scheme 28

Cyclization of the iodoaromatic precursor **215** via Heck methodology to afford the 1*H*-3-benzazepine-2-carboxylic ester **216** has been described (Scheme 29) <1997J(P1)447>. The ester **216** was then converted to the conformationally restricted phenylalanine analogue **217** by hydrogenation and ester hydrolysis with concomitant BOC group removal under acidic conditions (HCl), followed by reaction with propene oxide.

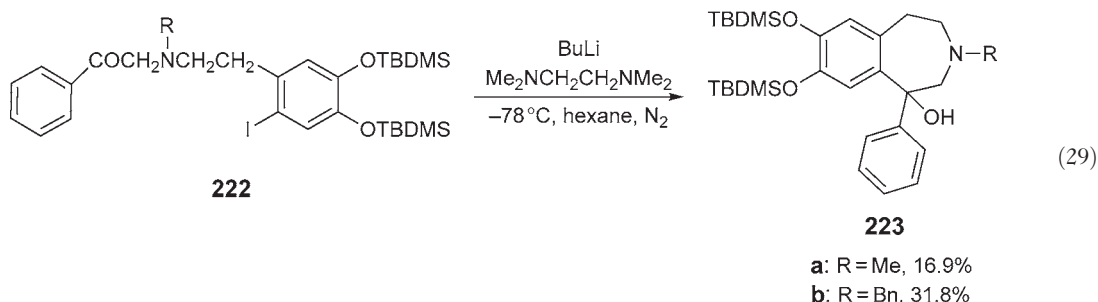


Scheme 29

In a study of the aryl radical cyclization of the enamides **218** mediated by Bu_3SnH , it was found that 7-*endo-trig* cyclization to give the 3-benzazepines **219** was highly favored over the 6-*exo-trig* process to afford the isoquinoline derivatives **220**; low yields of the reduction products **221** were also obtained (Equation 28). The positioning of the amide functionality, external to the cyclizing chain, was an important factor in favoring seven-membered ring formation and this knowledge was then employed in a neat synthesis of a cephalotaxine skeleton <2005JOC1922>.

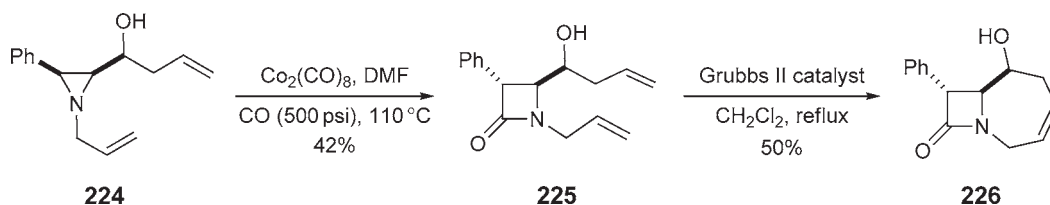


An alternative, low-yielding route to the tetrahydro-1*H*-3-benzazepines **223** from the amides **222** via an intramolecular Barbier reaction has been reported (Equation 29) <2005H(65)2925>. The other significant products from this reaction were the deiodinated noncyclized compounds.

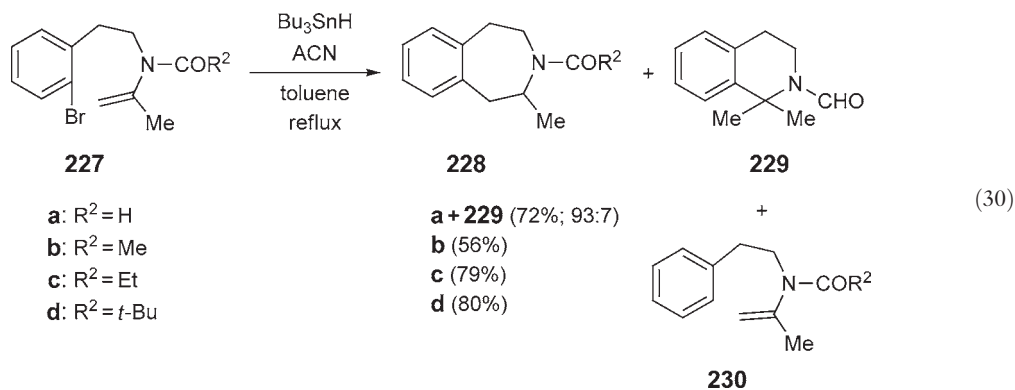


Inclusion of the nitrogen in both the seven-membered ring and another fused ring has also been reported. Ring expansion of the *cis*-aziridine **224** by CO insertion to the azetidinone **225** provided the basis for a ring-closing metathesis using Grubbs II catalyst to give the fused azepine **226** (Scheme 30) <2004H(63)2495>. A simpler analogue of **226** has also been accessed by ring-closing metathesis <1999J(P1)1695>.

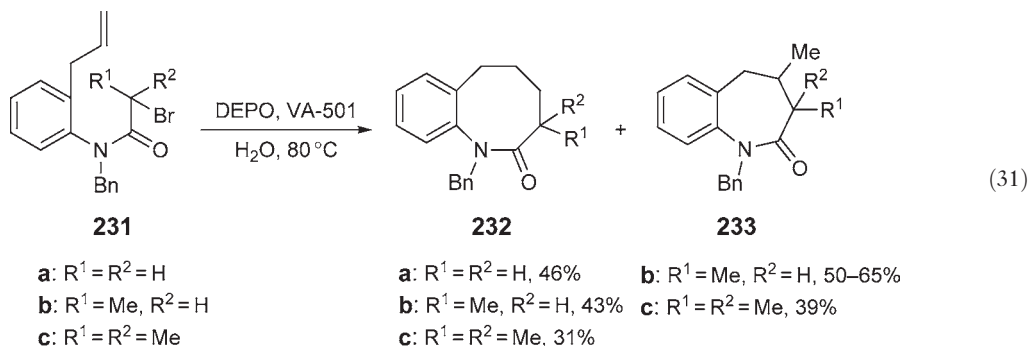
Tributyltin hydride-induced free radical cyclization of **227a–d** gave mainly the 7-*endo* products **228a–d** with some 6-*exo* product **229** (from **227a**) together with low yields of the reduction products **230b** and **230c** (Equation 30) <2005JOC1922>. The precursors **227** are closely related to those described in Equation (28), but include a methyl substituent on the alkenyl group and the 7-*endo* cyclization preference is maintained in both series.



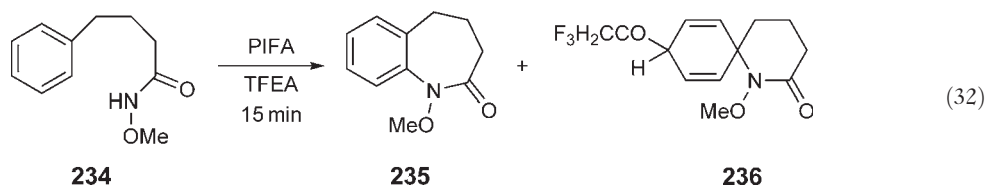
Scheme 30



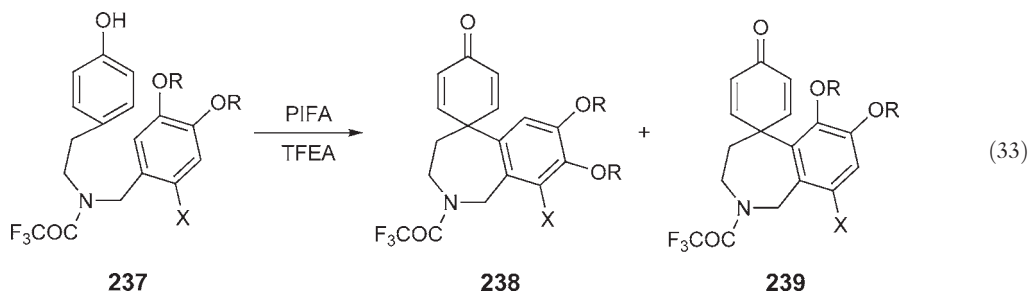
1-Benzazepinones **233b** and **233c** can also be made by free radical cyclization from the 2-bromoacetamides **231b** and **231c** <2005TL4027>; unexpectedly, none of **233a** (R¹ = R² = H) could be isolated from radical cyclization of **231a** (using DEPO – diethylphosphine oxide) and only the eight-membered ring 8-*endo-trig* product **232a** was noted (Equation 31).



Reaction of **234** with phenyliodine(III)bis(trifluoroacetate) (PIFA) afforded the 1*H*-1-benzazepin-2-one **235** in moderate yield (52%) in hexafluoroisopropanol (HFIP) as solvent together with the spiro-cyclized **236** in 48% yield (Equation 32) <2003H(59)149>.



Cyclization of the diarylamine **237** with hypervalent iodine (PIFA) afforded the two spiro systems **238** and **239** formed by *p*-*p'* and *p*-*o'* coupling, respectively (Equation 33) <1998JOC6625>. Substituents influenced the nature of the product and yields (up to 60%) were best when X = H, R and R = -CPh₂- (only product, **238**; 60%) or X = TMS, R and R = -CMe₂-, which gave predominantly **239** (46%), with only 12% of the corresponding cyclized **238**. These products act as precursors of galanthamine-type alkaloids.



13.01.6.4 Type d (C–C–C–N–C–C–C)

A concise alternative synthesis of the azepinones **241** has been developed based on the key ring-closing metathesis of the α -amino enones **240** (Equation 34) <2006H(67)549>. The substrate concentration was 5×10^{-3} M and yields of products are given in Table 4. The azepinone **241c** was then converted to a known cathepsin K inhibitor.

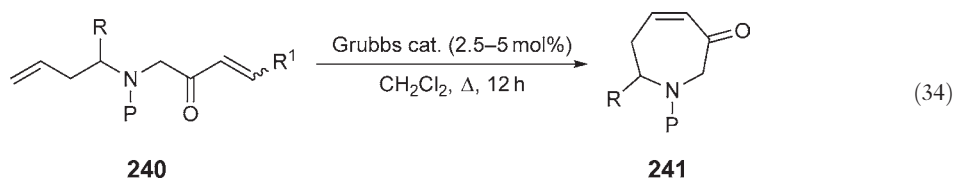
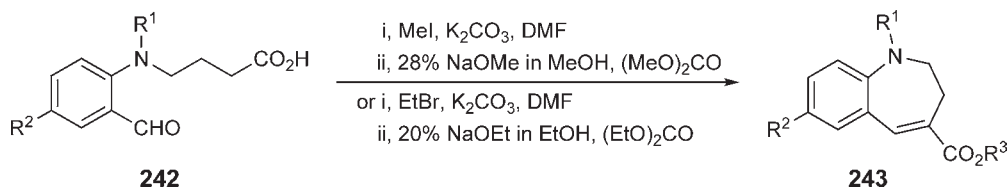


Table 4 Yields of the azepinones **241**

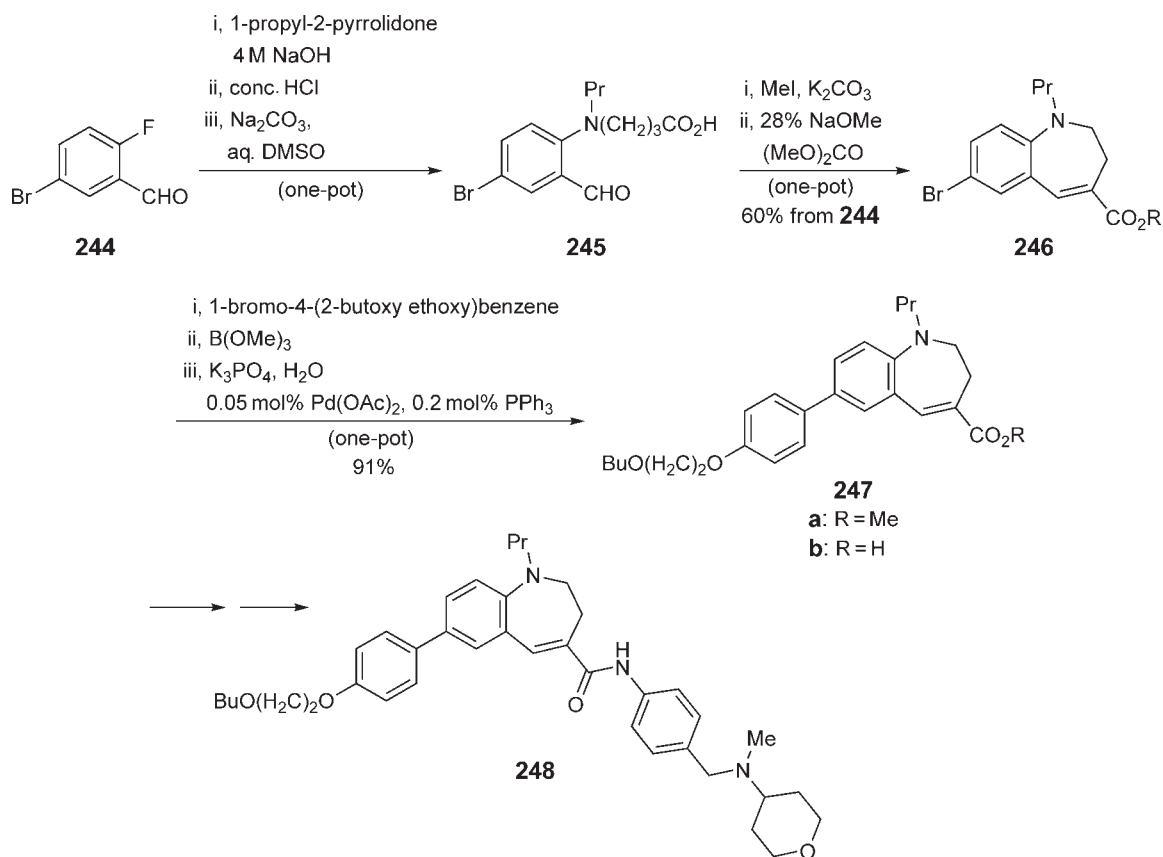
Compound 241	Yield (%)	Reference
a: P = BOC, R = H, R ¹ = Me	90	2006H(67)549
b: P = Cbz, R = H, R ¹ = Me	97	2006H(67)549
c: P = (2-Pyr)SO ₂ -, R = H, R ¹ = Me	96	2006H(67)549
d: P = Ts, R = Ph, R ¹ = H	99	2006H(67)549

In a different type *d* ring-construction process, base-induced intramolecular cyclization of the ester derived from the acids **242** gave the 1-benzazepines **243** in moderate to excellent yields (Scheme 31). The yields were affected by the nature of the substituent group R¹ on nitrogen, with the best yield being obtained with an *N*-benzyl derivative (**243**: R¹ = CH₂Ph, R² = Br, R³ = Et) <2004TL9335>.



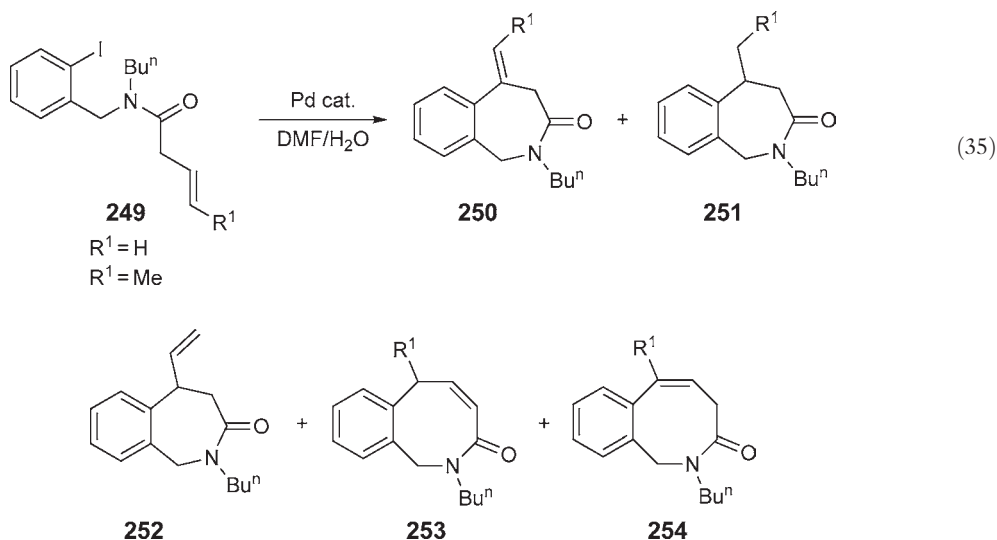
Scheme 31

Based on the above work, a new, practical, chromatography-free method for the preparation of the orally active CCR5 antagonist **248** has been reported by Ito *et al.* <2005OPD168>. Two one-pot sequences were used to prepare **246** from **244** via **245** (Scheme 32). A Suzuki–Miyaura reaction of **246** to give **247**, followed by hydrolysis and an amidation, generated **248** in good overall yield in six steps.

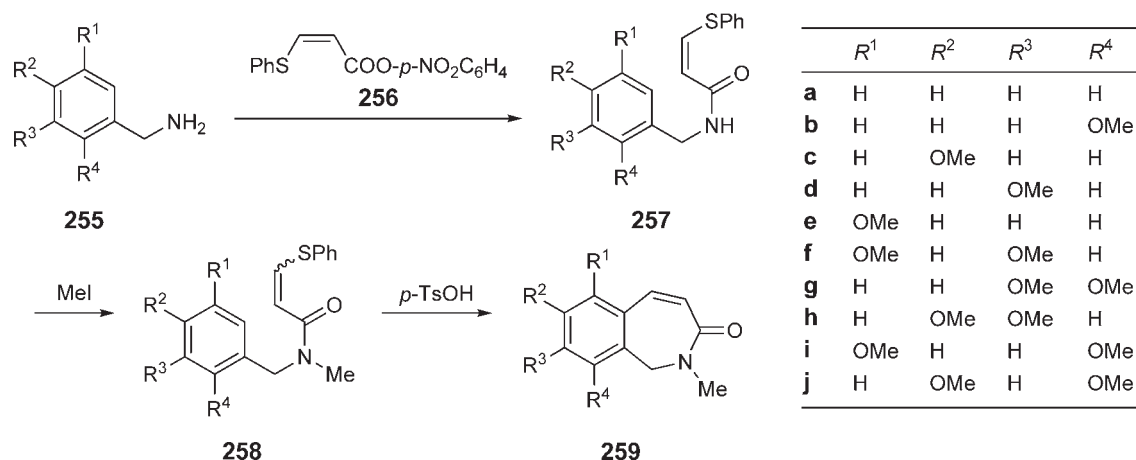


Scheme 32

A marked solvent effect was observed in the palladium-catalyzed cyclization (10 mol% PPh₃, 2.5 equiv Buⁿ₄NOAc, 85 °C) of the butenamides **249** (Equation 35). In anhydrous dimethylformamide (DMF), six-membered ring formation was preferred, while in DMF/H₂O the 2-benzazepinones **250–252** were formed, as well as the eight-membered ring analogues **253** and **254** (all with R¹ = H, Me). A decreased propensity for isomerization of the double bond in the side chain into conjugation with the amide carbonyl group may be a result of the basicity decrease of the medium with water present; this conjugated isomer is the progenitor of the six-membered ring products <2002SL1860>.

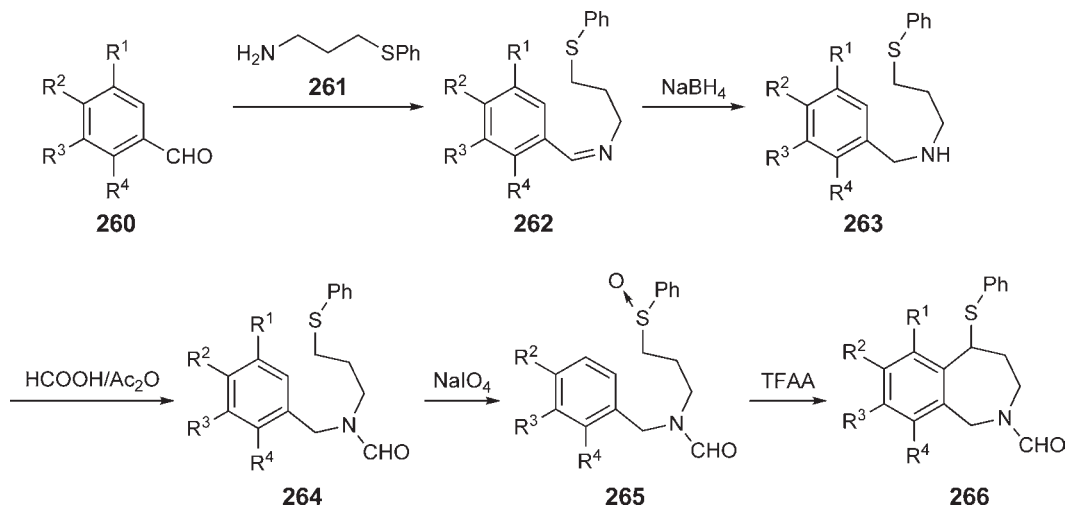


The 2-benzazepin-3-ones **259** have been made in moderate yields by sequential intramolecular acid-catalyzed addition followed by thiol elimination from the precursor phenylsulfanylacrylamides **258** (Scheme 33). The acrylamides **258** were prepared from reaction of the benzylamines **255** with the PNB-ester **256** to give the amides **257**, and then N-methylation with MeI in the presence of potassium hydroxide and tetraethylammonium bromide, as a phase-transfer catalyst. Other noncyclized products were also observed depending on the structure of the *N*-aryl methyl group in **258** and on the nature of the solvent <2002H(57)1063>.



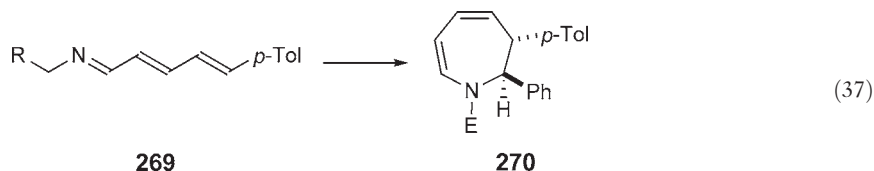
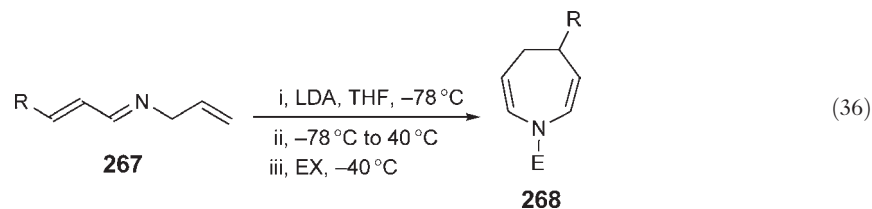
Scheme 33

Sano *et al.* have reported the synthesis of the 2-benzazepines **266**. The steps involved reaction of the aromatic aldehydes **260** with the amine **261** to give the imines **262**, followed by reduction to the amines **263**, N-formylation to **264**, and oxidation to the corresponding sulfoxides **265** (Scheme 34). The seven-membered ring was then formed by a modified Pummerer reaction on **265**, which was then used to complete the seven-membered ring in yields ranging from 45% to 78% (e.g., **266**: $R^1 = R^2 = \text{H}$, $R^3 = \text{OMe}$, $R^4 = \text{H}$; 78%) <2001H(54)967>.

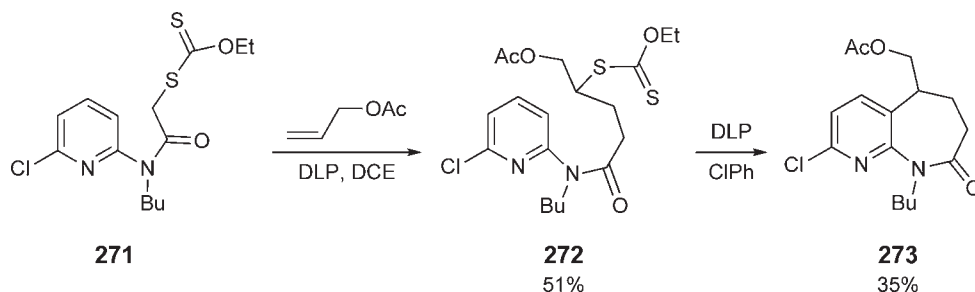


Scheme 34

A lithium-induced cyclization of the imine-diene **267**, followed by N-alkylation (e.g., with EX = EtBr) or N-acylation (e.g. with EX = PhCOCl), to form the 4,5-dihydroazepines **268** in poor to fair yields has been reported (Equation 36) <1995TL7065>. By using the different imine-dienes **269** but the same conditions as for **267** to form the anionic intermediate for the 1,7-electrocyclization, the N-substituted 2,3-dihydroazepines **270** were obtained (Equation 37) <1996T14801>. NMR spectroscopy was used to monitor the progress of these reactions.

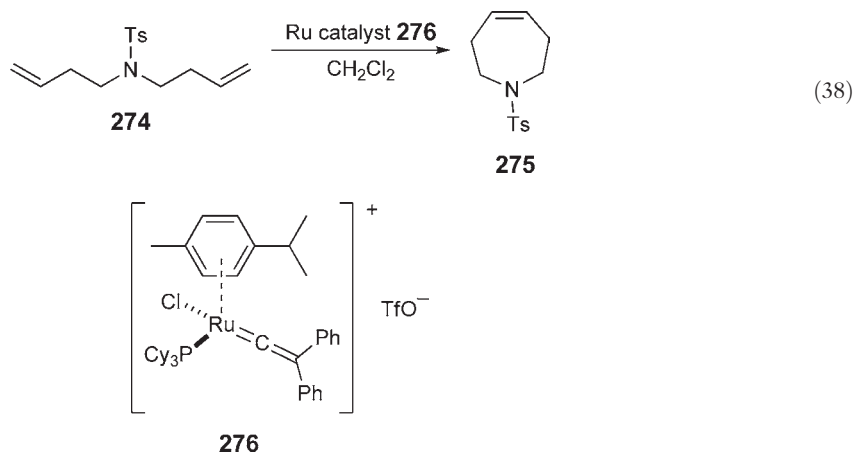


A tin-free radical cyclization of the xanthate **272** using dilauroyl peroxide (DLP), as the radical initiator, in chlorobenzene was used to give the 5*H*-pyrido[2,3-*b*]azepin-8-one **273** (Scheme 35) <2004OL3671>. The xanthate **272** was also made by an intermolecular free radical addition to allyl acetate, using the xanthate **271**, as the radical precursor. Somewhat surprisingly in this latter case, intramolecular free radical attack on the pyridine ring did not take place.



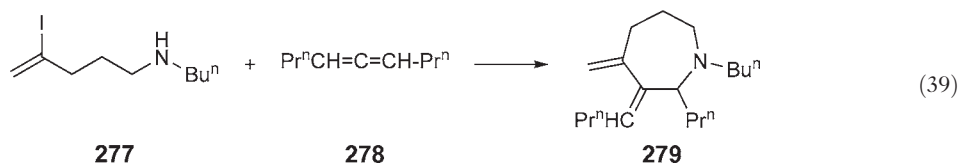
Scheme 35

While microwave-assisted reactions are well established in current synthetic methodology, nonthermal microwave effects have been shown not to be a factor in the observed rate enhancement with the ring-closing metathesis of **274** to form the azepine **275** (88% conversion; 20 min, 100 °C); in this case the ruthenium catalyst **276** was used (Equation 38) <2003JOC9136>.

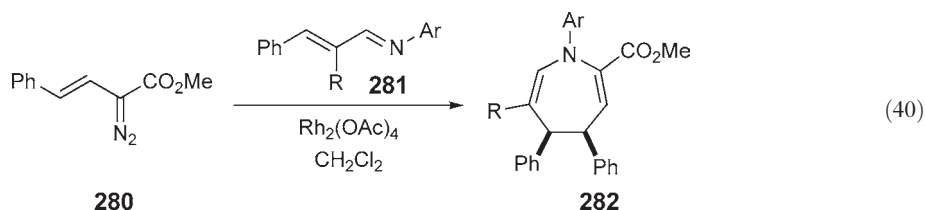


13.01.6.5 Reaction Involving the Formation of Two Bonds

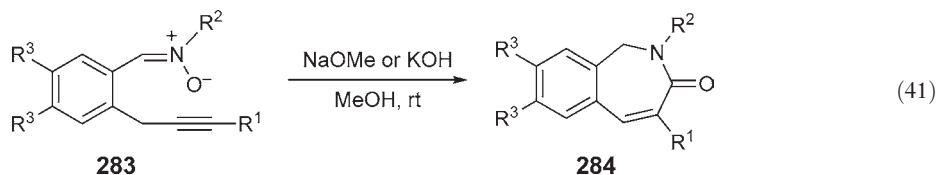
The palladium-catalyzed ring heteroannulation of allenes **278** by tosyl amide and amine-containing allyl and vinyl halides (e.g., **277**) provided a facile route to a variety of azepanes (e.g., **279**) (Equation 39) <2003JOC6859>; in the case of *N*-tosyl-(2-iodophenyl)ethylamine, benzazepines are formed.



An approach to substituted dihydroazepines **282** has been reported based on the reaction of ylides, generated *in situ* from styryldiazoacetates (e.g., **280**), with the imines **281** (Equation 40). In the case of **280** and the imine **281** (Ar = Ph, R = Me), the dihydroazepine **282** (Ar = Ph, R = Me) was obtained in 73% yield <2001OL3741>.

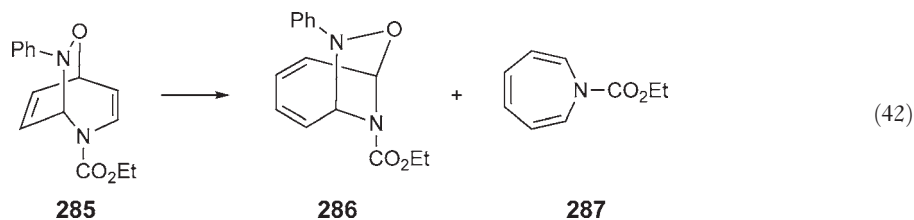


A facile approach to the benzazepinones **284** from the nitrone precursors **283** was reported by Eberbach *et al.* (Equation 41) <2001EJO3313> (see also Scheme 11). Reaction of **283** with base under mild conditions gave **284** in generally high yields, for example, **284** (R¹ = R³ = H, R² = Ph; 84%). A complex series of steps was proposed in the formation of **284** involving allene formation, 1,7-dipolar cyclization, and a series of bond cleavage and formation steps via a cyclopropanone intermediate.

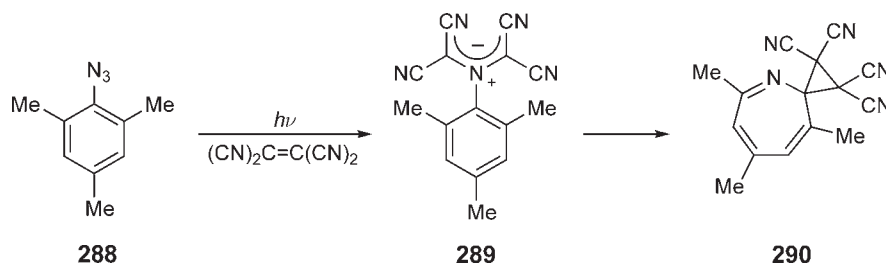


13.01.7 Ring Synthesis by Ring Transformation

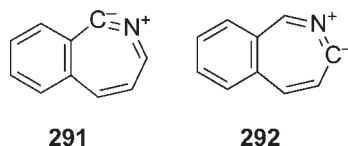
Photolysis of the oxadiazabicyclo[2.2.3]nonadiene **285** gave a rearranged bicyclic system **286** plus 1-ethoxycarbonyl-1*H*-azepine **287** (Equation 42) <1999H(51)141>. The latter was shown to form on photolysis of **285**, but it was suggested on the basis of kinetic evidence, that some may also be formed directly from **285** by what is formally a retro-Diels–Alder type reaction.



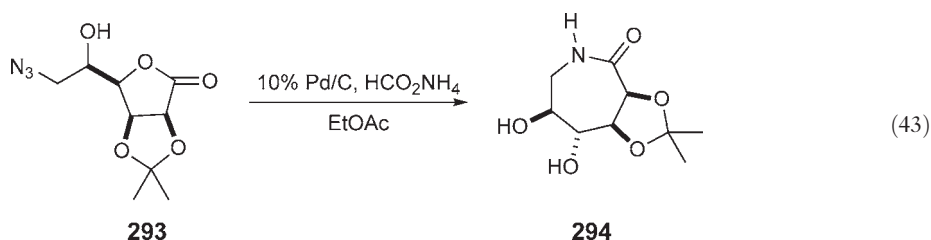
Ultraviolet irradiation of mesityl azide **288** in the presence of tetracyanoethylene has resulted in the isolation of the intermediate azomethine ylide **289** (from trapping of the aryl nitrene) together with its rearrangement product, the spiroazepine **290** (Scheme 36) <1997JOC3055>. Photolysis (at 313 nm) at low temperature of 1- and 2-azido-naphthalenes in an Ar matrix provided access to the novel seven-membered cyclic ketenimines **291** and **292**, respectively <2004JA237>.



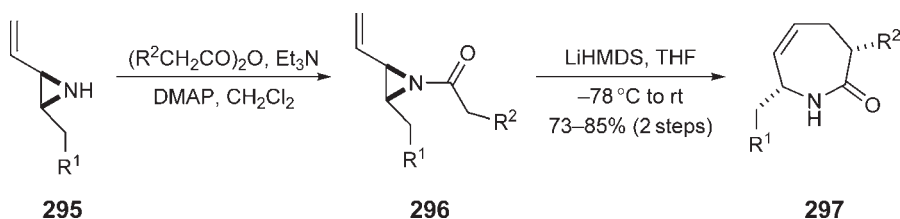
Scheme 36



The synthesis of the *D*-gulonolactam **294** has been described, based on an intramolecular cyclization with ring-enlargement strategy involving reduction of the azido group in **293**, followed by intramolecular nucleophilic attack on the lactone moiety to give **294** in high yield (Equation 43) <2006T7455>.



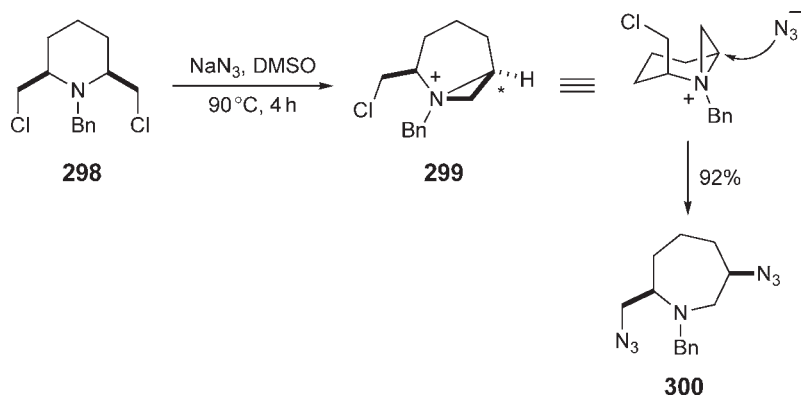
Concerted rearrangement reactions constitute a powerful, and perhaps somewhat under utilized, approach to seven-membered and larger ring systems. Illustrative of this is the conversion of the vinylaziridines **296** (formed from **295**) to the tetrahydroazepin-2-ones **297** via a base-induced stereoselective aza-[3,3]-Claisen rearrangement (Scheme 37). Yields of **297** from the precursor aziridines **296** were generally good to high (e.g., **297**: $\text{R}^1 = \text{CH}_2\text{Ph}$, $\text{R}^2 = \text{Me}$, 85%) <1997JA8385>.



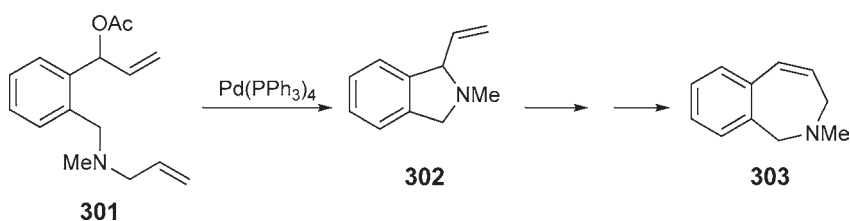
Scheme 37

Piperidine ring-expansion methodology and aziridinium ion intermediate formation has been demonstrated to provide good regio- and stereochemical control in the synthesis of substituted azepanes. Reaction of **298** with azide ion afforded **300** from preferential attack from behind by the azide ion at the methine carbon in the intermediate **299** (Scheme 38) <2002J(P1)2080>.

Reaction of the bis-olefin **301** with $\text{Pd}(\text{PPh}_3)_4$ afforded the isoindoline **302** together with the 1*H*-2-benzazepine **303**; the former was shown to rearrange to **303** in the presence of the palladium complex (Scheme 39) <1996CC2257>.

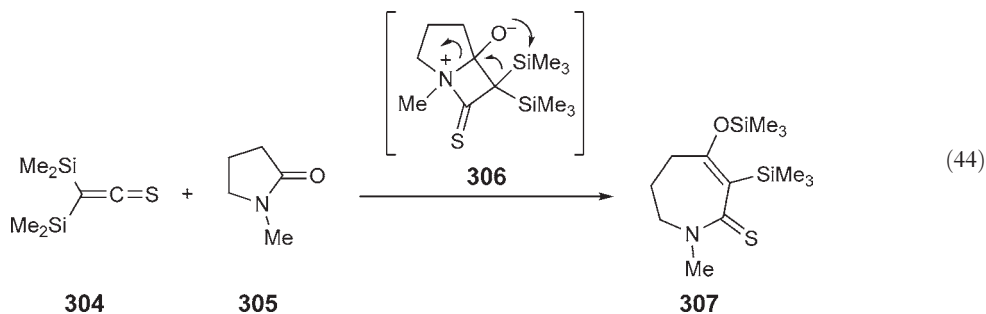


Scheme 38

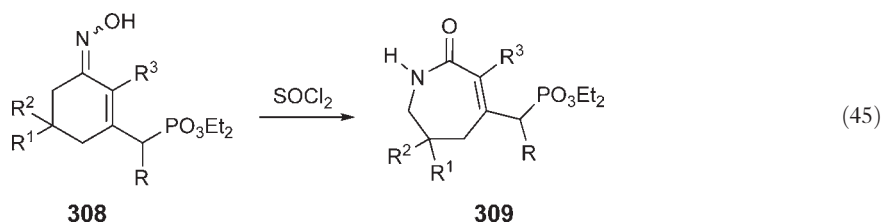


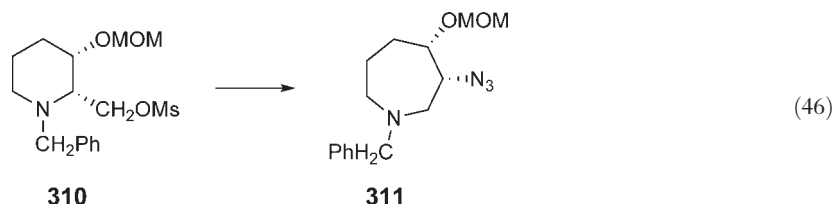
Scheme 39

An unusual ring expansion of the pyrrolidin-2-one **305** has been reported to afford the azepine-2-thione derivative **307** on reaction with the bis silyl-substituted thioketene **304** (Equation 44) <1996CC1621>. It is probable that the process proceeds via rearrangement of the cycloadduct **306**.

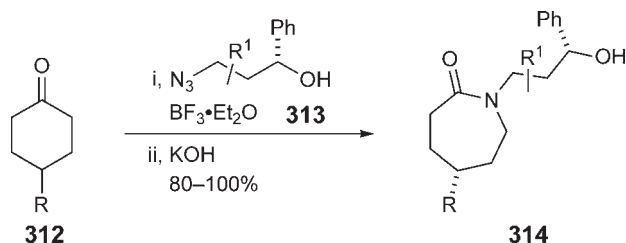


Six-membered rings can also serve as precursors to seven-membered rings by ring-transformation processes. Thus, Beckmann rearrangement of **308** selectively afforded the azepinones **309** (e.g., $R = R^1 = R^2 = \text{H}$, $R^3 = \text{Me}$; 50%) (Equation 45) <1998JCM198>, while reaction of **310** with azide gave the azido azepine **311** (Equation 46) <1998H(48)427>.



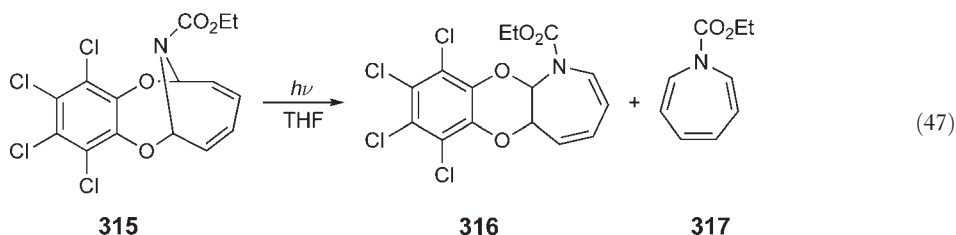


An asymmetric Schmidt ring expansion of the 4-substituted cyclohexanones **312** using chiral azido alcohols **313** gave the azepan-2-ones **314** in high yields and good diastereomeric ratios depending on the nature and position of R^1 (Scheme 40) <2003JA7914>.

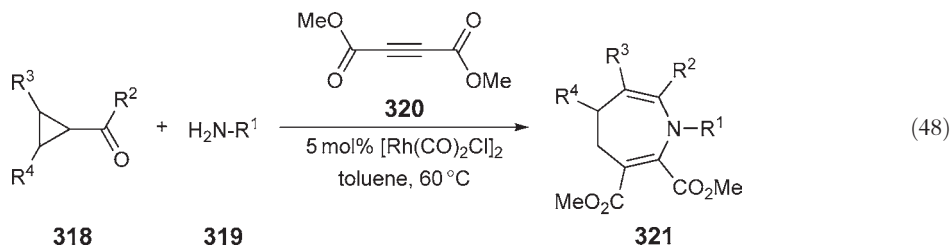


Scheme 40

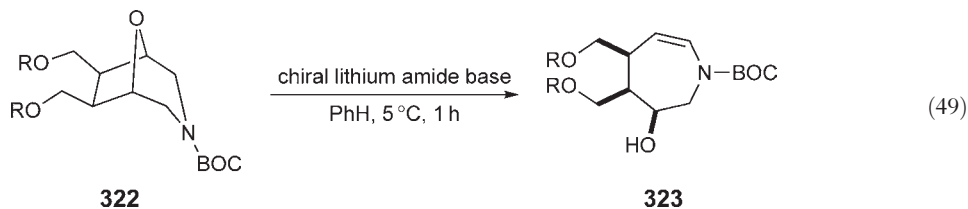
In an unusual alternative approach to the azepine system, photolysis of **315** gave **317** in 14% yield, plus the fused compound **316** (Equation 47) <2001H(54)567>.



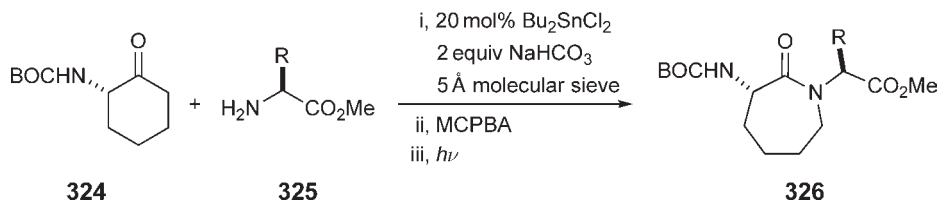
Substituted 4,5-dihydroazepines **321** (e.g., $R^1 = \text{Bn}$, $R^2 = R^3 = \text{H}$, $R^4 = \text{Me}$; 82% yield) may be prepared in high yield by a rhodium-mediated hetero-[5+2]-cycloaddition of the cyclopropyl imines derived from **318** on reaction with the primary amines **319**, with dimethyl acetylenedicarboxylate **320** (Equation 48) <2002JA15154>.



An enantioselective synthesis of the substituted tetrahydroazepines **323** was achieved on treatment of **322** with a chiral lithium amide base (Equation 49) <1997JOC7080>.

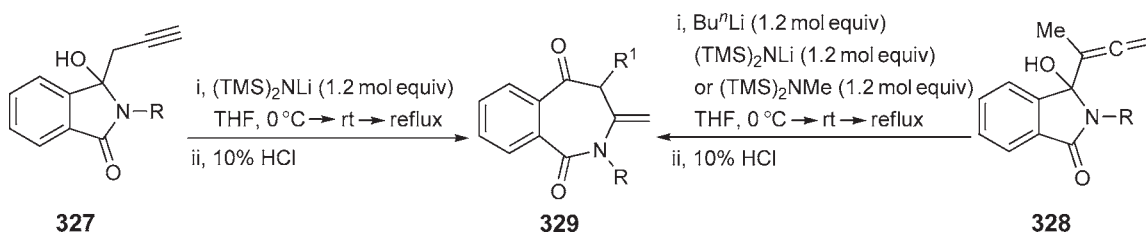


Photolytic ring expansion of a spirooxaziridine intermediate was central to the ring expansion of the cyclohexanone **324** to **326** (e.g., R = Bn) after initial imine formation from reaction of **324** with **325**; the oxaziridine was then generated by oxidation of the imine with *m*-chloroperoxybenzoic acid (Scheme 41) <1997JOC654>.



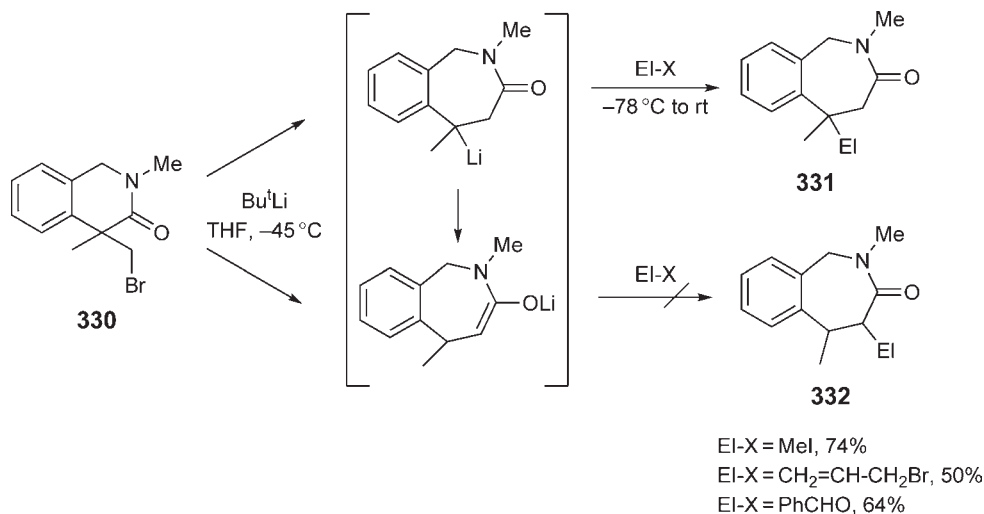
Scheme 41

The 2-benzazepine-1,5-diones **329** can be accessed in two ways from the alcohols **327** and **328**, which were prepared by Grignard reactions on the corresponding *N*-alkylphthalimides (Scheme 42). Reaction of **327** or **328** with base $[(\text{TMS})_2\text{N}]\text{Li}$ initiated a two-carbon ring expansion resulting in **329**; better yields of the seven-membered ring system **329** were obtained from the allenic alcohols **328** (e.g., **329**: R = Et, R^1 = Me; 73%) compared to those from the acetylenic precursors **327** (e.g., **329**: R = Et, R^1 = Me; 34%). Ring cleavage following alkoxide ion formation with subsequent ring closure to give the fused seven-membered ring has been proposed as the mechanistic pathway <1998T14437>.



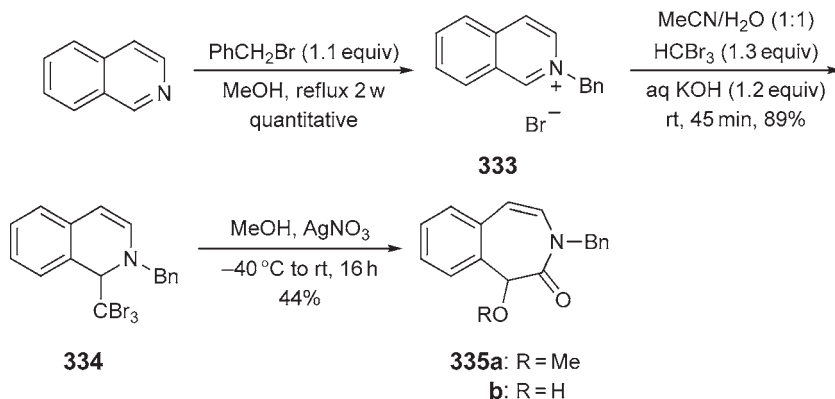
Scheme 42

A ring-interconversion approach has been used to access the functionalized 2-benzazepin-3-ones **331** from the bromo lactam **330** (Scheme 43). The critical ring expansion was initiated by lithium–bromine exchange in **330** followed by intramolecular carbanion attack on the lactam carbonyl group. Electrophilic capture of the ring-expanded lactam intermediate then afforded **331** in moderate to good yields <2003SL2025>. None of the isomeric 2-benzazepin-3-ones **332** expected from the lithium enolate intermediate were observed.



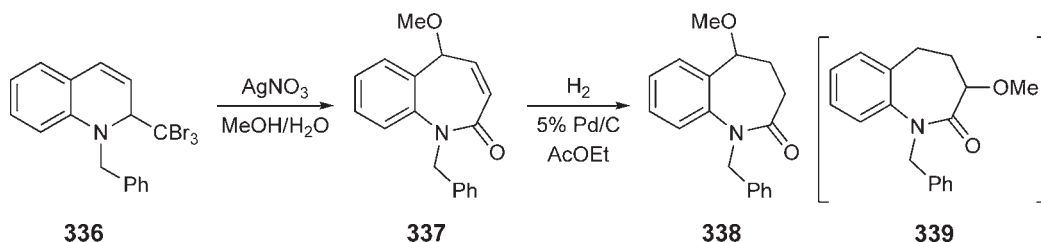
Scheme 43

Silver ion-promoted ring enlargement of the 1-tribromomethyl-1,2-dihydroisoquinoline **334** (prepared from **333**, which was accessed in turn from isoquinoline) resulted in a compact approach to the 3-benzazepin-2-ones **335** (Scheme 44) <2003TL4203>.



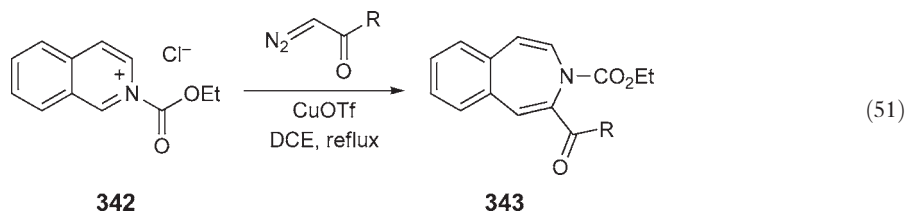
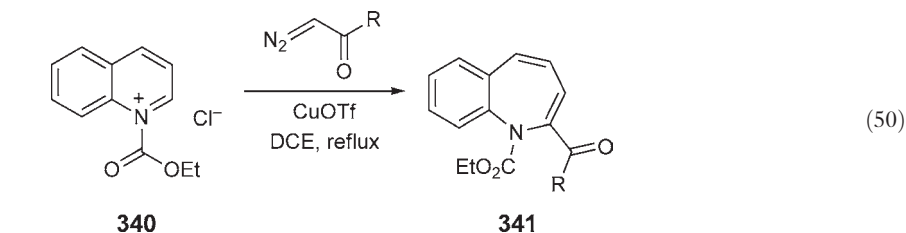
Scheme 44

The 1-benzazepin-2-one system continues to be a target for synthesis because of the pharmacological activities of compounds with this skeletal unit. In this context, a ring-enlargement route to **337** on treatment of **336** with silver nitrate has been reported (Scheme 45). This reaction presumably proceeds via an aziridinium ion intermediate. The structure of the product was confirmed by reduction of **337** to **338**. The possible isomeric product **339** was made separately and shown to be different <2002SL1350>.

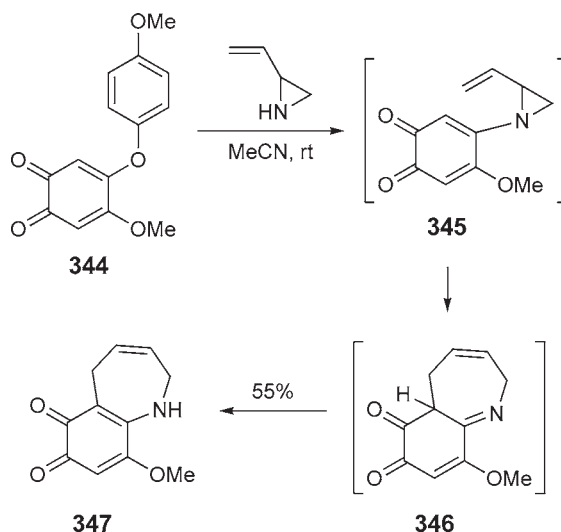


Scheme 45

An unusual ring expansion of the quinoline derivative **340** to 1-benzazepines **341** has been reported by Yadav (Equation 50) <2004CC2466>. This ring expansion is likely to be mediated by ketocarbene addition to **340**. An analogous procedure using the isoquinolinium salt **342**, as the substrate, led to a high yield of the isomeric 3-benzazepines **343** (Equation 51).



Reaction of the quinone **344** with 2-vinylaziridine gave the dihydroazepinoquinone **347** in good yield under very mild conditions [<1995TL4787>](#). An aza-Claisen rearrangement of the intermediate **345**, presumably assisted by strain relief on aziridine ring opening, followed by a sigmatropic rearrangement to give **346** has been proposed for this conversion ([Scheme 46](#)).



Scheme 46

13.01.8 Synthetic Comparisons

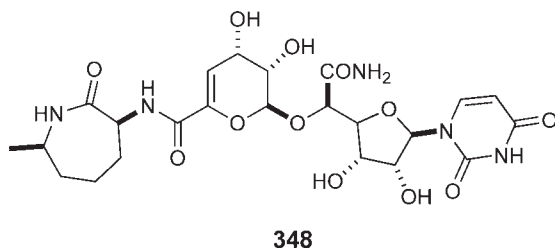
It is noted that, while numerous type *c* ([Section 13.01.6.3](#)) and type *d* ([Section 13.01.6.4](#)) ring-construction manifestations of the ruthenium-catalyzed ring-closing metathesis reaction for the azepine ring formation have been reported, the corresponding type *b* possibility, with an *N*-vinyl component, has not as yet been reported.

Also, while there are some more recent examples of synthetic approaches to spirocyclic systems incorporating azepine or benzazepine structural moieties, the scope to devise new and versatile approaches is still significant. Spirocyclic systems continue to hold considerable promise as scaffolds for the design of new pharmaceutical agents and new synthetic strategies would be of benefit in this area.

13.01.9 Important Compounds and Applications

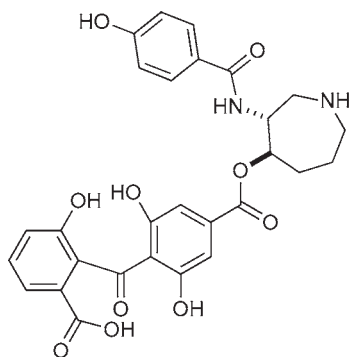
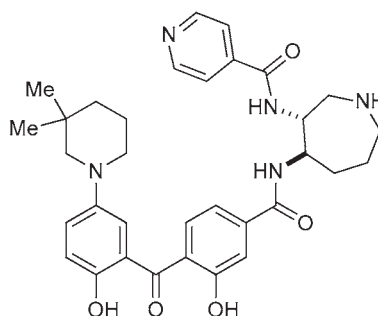
A series of *N,N'*-disubstituted 3-aminoazepin-2-ones with potent and specific farnesyl transferase inhibitory activity have been prepared [<2003BMC3193>](#).

The bacterial translocase 1 inhibitor, A-500359C, **348** (and a methoxy analogue A-500359A), isolated from *Streptomyces griseus* SANK 50196, includes a tetrahydroazepin-2-one unit in its structure [<2003JAN243>](#).



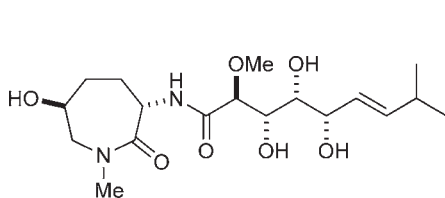
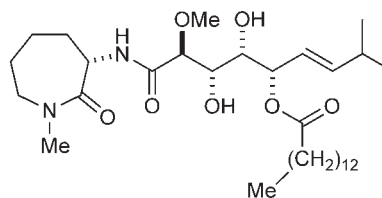
The azepane-ring containing metabolite (–)-balanol, **349**, from the fungus *Verticillium balanoides* [<1993JA6452, 1994JAN639>](#), was found to be a potent ATP-competitive inhibitor of the protein kinase A (PKA) ($K_i = 3.9$ nM).

<1999MPH370>. This compound has since served as a template for the development of a series of analogues as potential antitumor agents, including the substituted azepane **350**, which showed good selectivity for the inhibition of the protein kinase B (IC_{50} = 20 nM) over PKA (IC_{50} = 1900 nM) <2005JME163>.

**349****350**

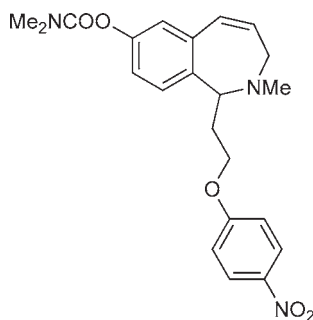
The azepane (*S*)-3-methyl-1-[3-oxo-1-[2-(3-pyridin-2-ylphenyl)ethenoyl]azepane-4-ylcarbamoyl]butylamide <SB 331750> is a potent nonpeptide inhibitor of rat cathepsin K (and thus of potential value in the control of osteoclast-mediated bone resorption) <2002MI746>, and an N-substituted azepane-isatin derivative was reported to be a nonpeptide inhibitor of caspase 3 <2001JME2015>; another N-substituted azepane-indole derivative was shown to act as an estrogen <2001JME1654>.

The naturally occurring azepinone, bengamide Z **351**, has been prepared in chiral form by Boeckman *et al.* <2002OL2109>, and the related ester, bengamide Q **352** together with other bengamides, has been isolated from a *Jaspis* species <2001JOC1733>.

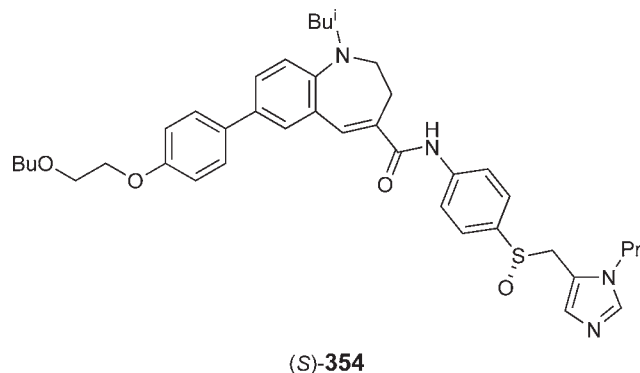
**351****352**

Other azepane derivatives of interest include some protein kinase B inhibitors <2004JME1375>, and 3-(acylamino)-azepan-2-ones as metabolically-resistant broad spectrum chemokine inhibitors <2005JME867>.

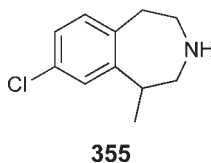
The conformationally restricted 1*H*-2-benzazepine derivative **353**, which is a dual inhibitor of acetylcholinesterase (IC_{50} = 14 nM) and the serotonin transporter (IC_{50} = 6 nM), is a potential agent for the treatment of Alzheimer's disease <2003BMC4389>.

**353**

The chiral sulfoxide **354** was shown to be one of a number of potent CC chemokine receptor 5 antagonists (IC_{50} 1.9 nM) and a potent inhibitor (IC_{50} 1.0 nM) in the HIV-1 envelope mediated membrane fusion assay. This compound also exhibited favorable oral absorption characteristics in rats making it a promising lead for further development as an anti-HIV agent <2005BMC363>.



An interesting series of 3-benzazepine derivatives (including **355**) have been reported to be potent and selective (over 5-HT_{2A} and 5-HT_{2B} receptors) 5-HT_{2C} receptor agonists, of potential use for the treatment of obesity <2005BML1467>.



13.01.10 Further Developments

A comparison of computed properties for twelve 64-electron isoelectronic tropolonoid states, including 5-azatropolone and 1*H*-azepinedione and their ions has been reported <2006JPC(A)1600>. A novel electrophilic substitution reaction involving benzene and the 2-methoxyazepinium ion, prepared *in situ* from treatment of 2-*isopropoxy*-7-methoxy-2*H*-azepine with TiCl₄, afforded a mixture of 7-methoxy-2-phenyl-2*H*-azepine, 2-methoxy-3-phenyl-3*H*-azepine, and 7-methoxy-4-phenyl-4*H*-azepine in 49%, 3%, and 43% yield respectively; kinetic studies on the two step isomerization of the last compound to 2-methoxy-5-phenyl-3*H*-azepine were also reported <2006EJO3803>. Competitive [1,5] sigmatropic H- and propylthio-group shifts have been observed on heating 2-propylthio-2*H*-azepine in various solvents <2006OL5469>.

An asymmetric synthesis of 3,4,5-trisubstituted-tetrahydro-1-benzazepines has been reported based on a type α ring construction process mediated by triethylaluminium with a chiral amino ester followed by lactam reduction with borane <2006OL2667>. Dynamic thermodynamic resolution in a lithiation-substitution sequence was integral to the preparation of the amino ester. An acid-catalyzed ring construction approach to the asymmetric synthesis of 4,5,6-trisubstituted- and 3,4,5,6-tetrasubstituted azepanes based on chiral acyclic precursors has also been described <2006JA2178>.

Access to chiral 1-substituted tetrahydro-3-benzazepines by asymmetric synthesis has been reported <2007EJO462>. The synthesis began with *o*-phenylenediacetic acid and (*R*)-phenylglycinol, and proceeded via an acid catalyzed type α ring construction to afford an intermediate oxazolobenzazepinone. This intermediate in turn was then subjected to lactam reduction followed by hydrogenolytic removal of the N-substituent to afford the chiral reduced 3-benzazepines, which were evaluated as NMDA receptor antagonists.

A more classical type α cyclization approach has been described to substituted 3*H*-1-benzazepines and 1*H*-1-benzazepines, based on intramolecular attack of an aromatic amino group on an oxime <2007EJO2970> with both groups being generated *in situ* following nitro group reductions (SnCl₂·2H₂O). Preferential formation of the

3*H*-1-benzazepine was seen with electron releasing groups being present in the aryl ring precursor. The 1*H*-1-benzazepine products were unstable and underwent a previously unobserved ring contraction to isoquinoline derivatives; one ring carbon is lost in this process and the mechanism is unresolved.

The synthesis of two 3,4-disubstituted 3*H*-2-benzazepines in moderate to good yields has been described. This synthesis involved a copper-mediated intramolecular cyclization of a benz-fused imino-ynyl anion system featuring C–C bond formation in a type *b* cyclization process <2007OL1049>.

Another type *b* cyclization route to substituted tetrahydroazepines involved a new and potentially versatile TBSOTf-mediated attack (using excess TBSOTf in DCM) on an acyclic *N*-formamido precursor; further functional group modifications then provided access to an azepinol and azepinone derivative <2007SL497>.

A type *c* ring construction strategy mediated via a ruthenium catalyzed (Grubbs II catalyst) ring closing metathesis reaction on an ene-yne precursor, followed *in situ* by a cross metathesis reaction, afforded a series of 1-phosphonylated 2-benzazepines in generally good yields <2006SL2771>.

Further application of the powerful intramolecular reductive Heck reaction has been realized in the efficient microwave-assisted synthesis (Pd(PPh₃)₄, 3 mol%, HCOONa, 1.5 equiv, DMF : H₂O 3:1, 110 °C) of the important 3-benzazepine system. The precursors were *N*-ethynoyl derivatives of *N*-substituted *o*-bromophenethylamines, which afforded, via a type *c* ring construction, 3-benzazepin-2-ones with a substituted exocyclic methylene group at the C1 position <2007OL3017>.

Ring closing metathesis mediated by Grubbs II catalyst in a type *c* ring construction process has been used to access stereoisomeric 1,2-disubstituted tetrahydroazepine-3-ol derivatives; preparation of the required diene precursor started from an optically pure substituted aziridine carboxylate ester <2007T3321>.

The intramolecular Heck reaction (type *d* cyclization) has been used to access 3-benzazepine derivatives from *o*-bromobenzyl substituted β -amino ester precursors in excellent yields. A key feature though was the use of microwave irradiation in the poly(ethylene glycol), PEG3400, as the solvent <2007EJO201>.

The use of a zirconium complex (dibutylzirconocene, –78 °C to rt, 2 h) to induce intramolecular co-cyclization of *N*-methyl-5-azanona-1,8-diene to an intermediate zirconacycle was a key step in a new azepane synthetic route; hydrolysis (MeOH, aq. NaHCO₃) of this intermediate then realized the *trans*-1,4,5-trimethylazepane in 75% yield; the active reagent for the initial cyclization was zirconocene (1-butene). The overall transformation represents a type *d* ring construction process <2006SL3439>. This synthetically versatile process is also applicable to aza eneyne and aza diyne precursors as well as benz-fused analogues.

A library of di- and trisubstituted 5-amino-1*H*-1-benzazepine derivatives was assembled through attachment of a preformed 1-benzazepine unit to an aminomethylated polystyrene resin. The initial solution phase synthesis of the 1-benzazepine moiety was based on an intramolecular Dieckmann cyclization (type *d*) followed by a ketone to primary amino group transformation via reduction (NaBH₃CN) of an imine intermediate <2007JCO487>.

A TBAF-induced elimination/rearrangement of certain 4-*tert*-butyldimethylsilyloxy-2-amino-1-aza-bicyclo[4.1.0]-hept-3-enes led to substituted 1*H*-azepin-4(7*H*)-one derivatives in low to fair yields; rearrangement to *N*-substituted pyrid-1(*H*)-ones was a substituent-dependent competing process <2007T11167>.

Further studies on the one-carbon ring enlargement approach to 7-membered rings have been described <2007T11250>. Using reduced 1-tribromomethylisoquinoline and 2-tribromomethylquinoline derivatives, ring enlargement on reaction with silver nitrate in aqueous solution and in the presence of other nucleophiles (methanol; and ethylamine in the case of an isoquinoline derivative) afforded the respective 2*H*-3-benzazepin-2-one (from the isoquinoline) and 2*H*-1-benzazepin-2-one (from the quinoline) derivatives in low to moderate yields.

The synthetic power of one-pot sequential reactions was demonstrated through an elegant route involving an amino-Claisen rearrangement, then intramolecular 1,3-dipolar cycloaddition, and finally reductive N–O bond cleavage to afford *cis*-4-hydroxy-2-aryl-2,3,4,5-tetrahydro-1(*H*)-benzazepines <2006SL2275>.

A Beckmann rearrangement-reduction sequence has been used to access a number of substituted 1*H*-1-benzazepine derivatives, with the required substituted α -tetralone precursors being prepared by a xanthate-based free radical cyclization process <2006BMC6165>.

Further 1,4-disubstituted 1-benzazepin-2-one derivatives have been evaluated as blockers of a voltage-gated sodium channel; one compound in this series showed highly potent activity and, encouragingly, was also active in a rat model of neuropathic pain after oral administration <2007BML4630>. A range of compounds based on a 4,4-difluoro-1-benzazepine core system, and with substituents at positions 1 and 5, have been synthesized and evaluated as selective antagonists of the arginine vasopressin V_{1A} receptor <2006BMC1827>. Potent and selective dopamine D₃-receptor antagonists have also been reported based on 1*H*-1-benzazepin-2-one (and analogous 2,5-dione) derivatives <2006BML658>. Detailed structure-activity relationships have been developed for a series of 5-, 6-, and 7-methyl substituted azepan-3-ones with cathepsin K inhibitory activity <2006JMC1597>.

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Biographical Sketch



Prof. John Bremner is Professor of Organic Chemistry in the Department of Chemistry, University of Wollongong, Australia. He is a graduate of the University of Western Australia and the Australian National University. After being a Research Fellow at Harvard University, he returned to Australia in 1968 to an academic appointment in Chemistry at the University of Tasmania, and then moved in 1991 to the University of Wollongong. At Wollongong he was Head of Department for seven years and then was Director of the newly formed Institute for Biomolecular Science from 2001–2004. His research interests cover heterocyclic chemistry, natural products, and medicinal chemistry, including more recently the design, synthesis and evaluation of new types of anti-infective agents for the potential treatment of bacterial disease and malaria.



Dr Siritron Samosorn received a Bachelors degree in Chemistry in 1990 and a Masters degree in Applied Chemistry in 1994, both from Ramkhamhaeng University, Thailand, under the supervision of Prof. Apichart Suksamrarn. In 1994, she joined the Department of Chemistry at Huachewchalermprikiet University in Thailand as a lecturer, and later moved to a staff position at Srinakharinwirot University (SWU) in 1997. She obtained her PhD from the University of Wollongong in 2005, working with Prof. John Bremner on a new approach to heterocyclic dual-action antibacterial agents to combat the problem of antibiotic resistance by drug efflux. Her research and teaching areas include the related areas of Natural Product Chemistry and Drug Design and Development, and she is a member of 'The Center for the Development of Value-Added Natural Products' at SWU.

13.02

Oxepanes and Oxepines

L. I. Belen'kii

Russian Academy of Sciences, Moscow, Russia

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13.02.1 Introduction

The subject of this chapter was covered previously in ca. 30 pages in CHEC(1984), vol. 7, chapter 5.17 <1984CHEC(5)547>, and in 21 pages in CHEC-II(1996) (vol. 9, chapter 2) <1996CHEC-II(9)45>. The goal of this chapter is to update the previous work concentrating on major new preparations, reactions, and concepts. We have provided at the beginning of each main section a sentence or short paragraph explaining the major advances

since the publication of the earlier chapters and also any major deficiencies in CHEC-II(1996) that we have now attempted to address.

In this chapter, the literature published from 1994 until 2006 (taken from *Chemical Abstracts*) is reviewed. Information concerning chemistry of oxepines and oxepanes from *Progress in Heterocyclic Chemistry* <1995PHC(7)294, 1996PHC(8)298, 1997PHC(9)318, 1998PHC(10)320, 1999PHC(11)319, 2000PHC(12)339, 2001PHC(13)340, 2003PHC(15)385, 2004PHC(16)431, 2005PHC(17)389, 2007PHC(18)402> is also taken into account. Several reviews were published between 1994 and 2006 that were devoted to individual problems of oxepine chemistry, such as synthesis of oxepines and oxepanes <1998ACR603, 1998T12631>, in particular, those using ring enlargement <1996SL1029>, synthesis, and application of dibenzo[*b,f*]oxepines <2004OPP297>.

This chapter does not contain a special section devoted to reactivity of substituents. Data of this kind are considered in Sections 13.02.5–13.02.9, since they are of little importance compared to other reactions of oxepines and oxepanes. Syntheses of ϵ -caprolactone are omitted; its reactivity is included only to demonstrate transformations leading to other oxepanes and hydrooxepines.

13.02.2 Theoretical Methods

The content of Section 9.02.3 in CHEC-II(1996) should be augmented with some new data. Some new data that appeared after the publication of CHEC-II(1996) are given below.

Valence tautomers, benzene oxide **1** and oxepine **2** (Equation 1), as well as relative tautomeric systems, benzene sulfide–thieline and *o*-xylene–2,7-dimethyloxepine, have been studied by a post-Hartree–Fock (HF) *ab initio* QCISD(r)/6-31G^{*}//MP2/6-31G^{*} method. In particular, the enthalpy calculated for a benzene oxide–oxepine system is 0.59 kJ mol^{−1} <1997PCA3371>. The calculated molecular orbital (MO) energies are in linear relationship to those from the photoelectron (PE) spectra <1996JCF1447>. Barrier to tautomerization for a benzene oxide–oxepine system is 29.4 kJ mol^{−1}. Protonation stabilizes the oxide form versus the oxepine <1997PCA3371>.



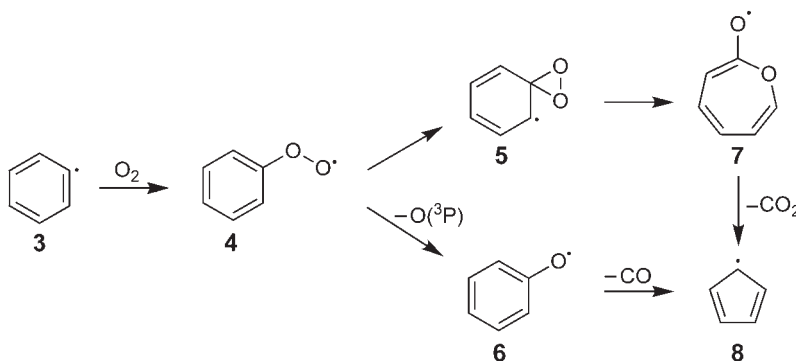
Thermodynamic parameters for the benzene oxide–oxepine system are calculated at MP4(SDQ)/6-31+G^{**}//HF/6-31G^{**} level of theory. The effect of solvent polarity on the above equilibrium is studied using the isodensity polarized continuum method. Low polar solvents favor the oxepine formation, whereas medium to high polar solvents lead to benzene oxide formation. The transition state for the tautomerization is fully characterized and the activation energies for the forward and reverse reaction are estimated to be ca. 9.5 and 11.0 kcal mol^{−1}, respectively. The solvent polarity exerts a reasonable effect decreasing the activation energies up to 4 kcal mol^{−1} <2001MI471>.

Substituent effects on the oxepine-to-benzene oxide tautomerization were found by a Hammett study via quantum-chemical calculations at HF, density functional theory (DFT) (B3LYP), and MP2 levels of theory using the 6-31G^{*} basis set. Equilibrium constants are calculated for conversion of 3-*X*- and 4-*X*-oxepines to their corresponding 2-*X*- and 3-*X*-benzene oxides. Hammett ρ values of 0.8 and 0.6 are obtained for 3- and 4-substituted oxepines, respectively, suggesting that electron-withdrawing groups slightly shift the equilibrium in favor of benzene oxide. All rate constants (k_t), activation electronic energies (ΔE^G), enthalpies (ΔH^G), and Gibbs free energies (ΔG^G) for the tautomerizations are calculated <2005JMT107>.

Using DFT (B3LYP/6-31G^{*}) calculations, it was determined whether the addition of O₂(³ Σ_g^-) to 2-oxepinoxy radical, a proposed intermediate in the unimolecular decomposition of phenylperoxy radical, followed by unimolecular rearrangement and decomposition results in the formation of experimentally detected C₁–C₅ products via oxidative combustion of benzene <2004PCA8419>. Geometries for possible pathways resulting from the initial formation of 1,2-dioxetanyl, 1,3-peroxy, 1,4-peroxy, hydroperoxy, and peroxy moiety scission intermediates were calculated. Energies were determined by B3LYP/6-311+G^{**} single-point energy calculations using the B3LYP/6-31G^{*} geometries. The energetic parameters were used to generate the free energy profiles for all pathways at 298, 500, 750, 1000, and 1250 K. For temperatures between 298 and 750 K, the formation of peroxyoxepinone radicals and their decomposition pathways as well as products are competitive with those proposed for the unimolecular decomposition of 2-oxepinoxy radical. However, a large entropic factor associated with the step for O₂ addition to 2-oxepinoxy radical makes these pathways less competitive with increased temperatures. At temperatures <1250 K, the

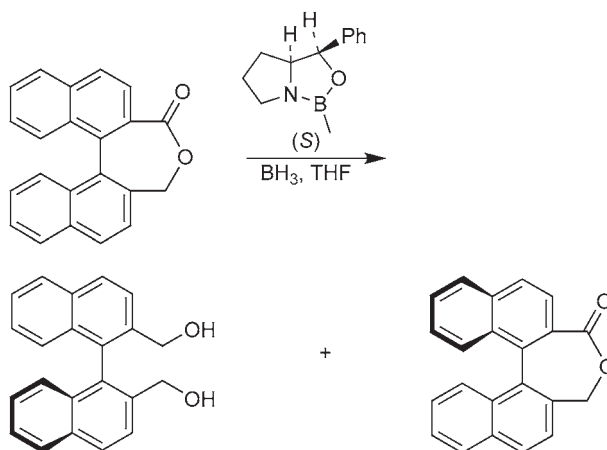
lowest overall free energy profile corresponds to rearrangement of 6-peroxyoxepinone to form a 1,4-peroxy intermediate, followed by release of CO_2 to form 5-oxapentenal radical, which then cyclizes and releases formyl radical, thereby generating furan, CO_2 , and formyl radical, as the final products. At 1250 K, all pathways proceeding from 2-peroxyoxepinone and through the peroxy bond scission intermediate have the lowest free energy profile.

The *ab initio* G2M calculations are performed to investigate the potential energy surface for the reaction of phenyl radical with O_2 . The reaction is shown (Scheme 1) to start with an exothermic barrierless addition of O_2 to the radical site of C_6H_5 **3** to produce phenylperoxy **4** and, possibly, 1,2-dioxaspiro[2.5]octadienyl radicals **5**. Next, **4** loses the terminal oxygen atom to yield the phenoxy **6** or rearranges to **5**. The latter can further isomerize to 2-oxepinyloxy radical **7**, which can give rise to various products including $\text{C}_5\text{H}_5 + \text{CO}_2$, pyranyl + CO , *o*-benzoquinone + H , and 2-oxo-2,3-dihydrofuran-4-yl + C_2H_2 . Since $\text{C}_6\text{H}_5\text{O} + \text{O}$ and $\text{C}_5\text{H}_5 + \text{CO}_2$ are expected to be the major primary products of the $\text{C}_6\text{H}_5 + \text{O}_2$ reaction and thermal decomposition of $\text{C}_6\text{H}_5\text{O}$ leads to $\text{C}_5\text{H}_5 + \text{CO}$, cyclopentadienyl radicals **8** are likely to be the major product of Ph radical oxidation <2005PCA6114>.



Scheme 1

The mechanism of the atroposelective ring opening of a lactone-bridged biaryl, dinaphtho[2,1-*c*:1',2'-*e*]oxepin-3(5*H*)-one, with a chiral oxazaborolidine- BH_3 complex (Scheme 2) was studied using semi-empirical AM1 calculations <2000JOC2517>.



Scheme 2

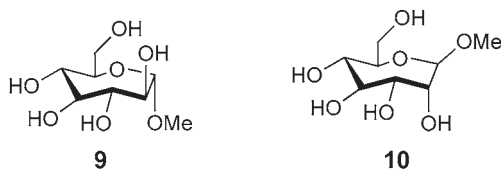
The conformational analysis of oxepane conducted within the MM2 and MM3 force fields shows a preference for the twist-chair conformation, which can be explained based on nonbonding interactions between hydrogen atoms <1994JST247>.

13.02.3 Experimental Structural Methods

After the publication of CHEC-II(1996), considerable experimental data appeared concerning the structure elucidation of natural and synthetically prepared oxepines and oxepanes. In this section, only individual data are considered, which is devoted especially to structural investigations. Most of them deal with the structures of fused systems including oxepine fragments, for example, oxepino[2,3-*b*]indolizine <1994AXC139> and oxepino-[3',4':4,5]isoxazolo[2,3-*a*]-pyridine <1995AXC1314> derivatives.

A systematic conformational analysis of saturated seven-membered compounds including oxepane, ϵ -caprolactone, as well as azepane and ϵ -caprolactam fragments (based on crystallographic results derived from the Cambridge Structural Database) shows that the ring conformations in these fragments fall almost exclusively on the chair/twist-chair pseudorotational pathway. There is a good qualitative agreement between the conformations observed in crystal state and the calculated features of the potential energy hypersurface, despite the wide variety of substitution patterns covered by the X-ray data <1994AXB382>. Determination of the X-ray structures, dipole moments, and *ab initio* calculations of tropones annulated with furan, benzene, and oxepine make it evident that polar structures of 3-oxapentalen-8(*H*)-ones are based not only on the local dipoles but also on the partial intramolecular charge-transfer interaction from the olefinic oxepine ring to the penta-1,4-dien-3-one moiety <2006BCJ1240>.

The conformational study of two septanose carbohydrates <2005JOC24> is of general interest. On the base of comparison of experimentally observed ^1H nuclear magnetic resonance (NMR) $^3J_{\text{H,H}}$ coupling constant with those calculated by quantum-chemical methods for methyl α -D-glycero-D-idoseptanoside **9** and methyl β -D-glycero-D-guloseptanoside **10**, the authors suggest that septanose carbohydrates are not so flexible and should generally prefer one twist-chair conformation.



13.02.4 Thermodynamic Aspects

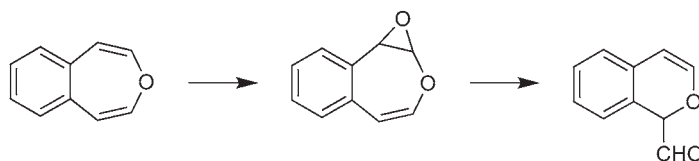
The first of three experiments necessary to establish the heat of formation of 2-oxepinoxy radical **7** was the determination of gas-phase acidity of 2(3*H*)-oxepinone <2005JA7466>. The radical **7** is believed to be formed during the combustion of benzene, in particular, within internal combustion engines. The work is a contribution to the evaluation and substantiation of the two proposed pathways of the phenyl radical oxidation (see Scheme 1), the first (**3** $\rightarrow$ **4** $\rightarrow$ **5** $\rightarrow$ **7** $\rightarrow$ **8**) being thermodynamically and kinetically more accessible at $T < 432$ K whereas above 432 K, the latter (**3** $\rightarrow$ **4** $\rightarrow$ **6** $\rightarrow$ **8**) is thermodynamically favored.

13.02.5 Reactivity of Fully Conjugated Rings

Considered in this section are two groups of oxepine reactions: (1) addition and cycloaddition reactions peculiar to their conjugated carbon chain, and (2) those characteristic of vinyl ethers, particularly, beginning from an attack on ring oxygen. Both reaction types are discussed in detail in CHEC(1984) and CHEC-II(1996); therefore, only several important new examples are given here.

13.02.5.1 Addition and Cycloaddition Reactions

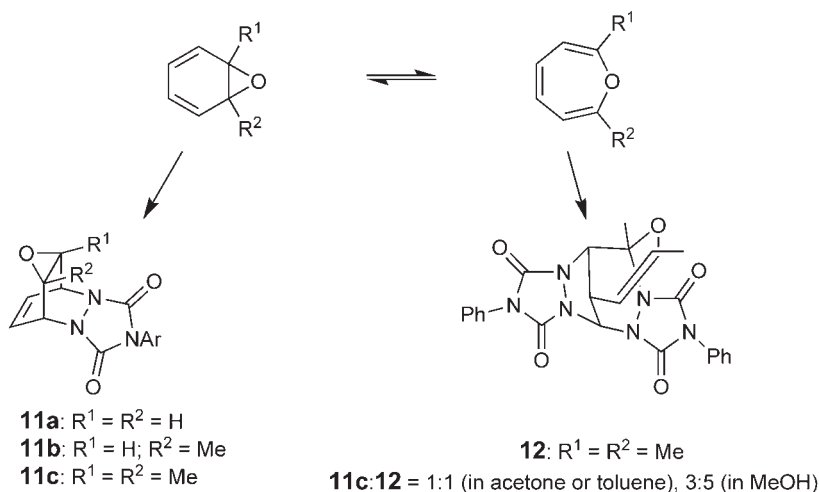
2,3-Epoxyoxepine and its derivatives are supposed to be generated on the epoxidation of oxepines; however, only ring-opened products, such as *trans,trans*-, *cis,trans*-, and *cis,cis*-muconaldehydes, could be observed. The first unambiguous observation of a 2,3-epoxyoxepine using ^1H NMR is reported <2004TL4789>. 3-Benzoxepine reacts (Scheme 3) with deuterated dimethyldioxirane at -50°C in acetone- d_6 to give respective 2,3-oxide, which between 5 and 10°C undergoes rapid ring-opening rearrangement to its isomer, 1*H*-2-benzopyran-1-carbaldehyde.



Scheme 3

By ^1H NMR monitoring of the oxidation of benzene oxide–oxepine with dimethyldioxirane (DMDO), a significant by-product, oxepine 4,5-dioxide, was identified <1997CRT1314>. This fact supports the hypothesis that the route from oxepine to muconaldehyde proceeds via oxepine 2,3-oxide with a minor pathway leading to symmetrical oxepine 4,5-oxide. The DMDO oxidations provide model systems for the cytochrome P450-dependent metabolism of benzene and atmospheric photooxidation of benzenoid hydrocarbons.

In contrast to ‘slow’ dienophiles, such as maleic anhydride, *N*-phenylmaleimides, and 4-methyl-1,2,4-triazoline-3,5-dione, which trap both components of oxepine–benzene oxide tautomeric mixtures, ‘fast’ 4-aryl-1,2,4-triazoline-3,5-diones react more selectively (Scheme 4). At -80°C , unsubstituted oxepine and 2-methyloxepine give 1:1 cycloadducts **11a** and **11b** originated from benzene oxide tautomers. However, 2,7-dimethyloxepine with 4-phenyl-1,2,4-triazoline-3,5-dione gives mixtures of **11c** and 1:2 cycloadduct **12**, the latter arising from oxepine tautomer (**12** does not form from **11c**). Formation of **12** requires molecular rearrangement. Structures of both **11c** and **12** are determined by X-ray diffraction <2002CC1956>.



Scheme 4

13.02.5.2 Cleavage of the Oxepine Ring

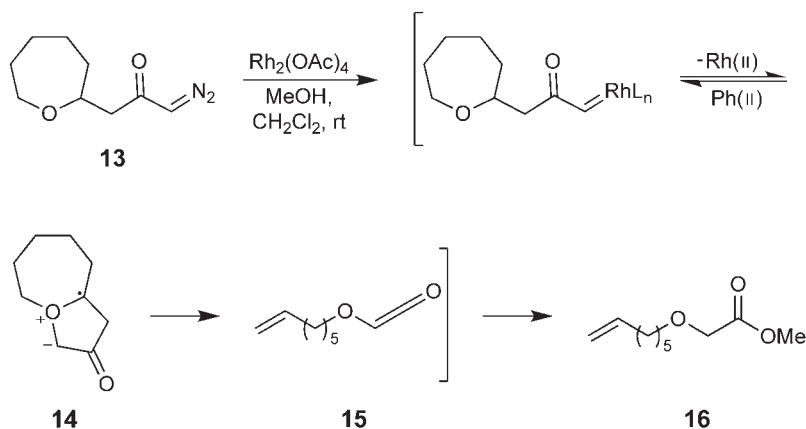
The first catalytic enantioselective trapping of benzene oxide–oxepine equilibrium mixture with an organometallic reagent is reported. The catalyst system included copper ditriflate and (11*bR*)-*N,N*-bis[(1*R*)-1-phenylethyl]dinaphtho[2,1-*a*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine. The products of the reaction with dimethylzinc were (1*S*,6*S*)-6-methyl-2,4-cyclohexadien-1-ol in 93% ee and 4-methyl-2,5-cyclohexadien-1-ol <2001CC2606>.

The gas-phase reaction of triplet oxygen atoms with benzene (a flow system, 50–100 mb, $295 \pm 2\text{ K}$) gives as primary stable products phenol, benzene oxide/oxepine, and an unidentified compound with the probable composition $\text{C}_5\text{H}_6\text{O}$. For benzene oxide/oxepine, a rapid consecutive reaction with $\text{O}(^3\text{P})$ atoms gives a substance $\text{C}_6\text{H}_6\text{O}_2$ (likely oxepine 4,5-epoxide or 2,3-epoxide), the isomers of muconaldehyde, as well as formic acid, acrolein, and *trans*-butenedial <2004MI391>.

The reaction of intracellular glutathione with benzene oxide–oxepin, the initial metabolite of benzene, is presumed to give 1-(*S*-glutathionyl)-cyclohexa-3,5-dien-2-ol, which undergoes dehydration to *S*-phenylglutathione, the precursor of *S*-phenylmercapturic acid. To validate the proposed route to *S*-phenylglutathione, reactions of benzene

oxide–oxepin with glutathione and other sulfur nucleophiles (sodium sulfide, dimethyl sulfoxide (DMSO), *N*-acetyl-L-cysteine) are studied. The data obtained validate the premise that benzene oxide–oxepin can be captured by glutathione to give (1*R*,2*R*)- and/or (1*S*,2*S*)-1-(*S*-glutathionyl)-cyclohexa-3,5-dien-2-ol, which dehydrates to form *S*-phenylglutathione. The capture is a relatively inefficient process at pH 7 that is accelerated at higher pH. These studies account for the observation that the metabolism of benzene is dominated by the formation of phenol. The pathway leading to *S*-phenylmercapturic acid is necessarily minor on account of the low efficiency of benzene oxide capture by glutathione at pH 7 versus spontaneous rearrangement to phenol <2005CRT265>.

The [3+2] cycloreversion of bicyclo[*m*.3.0]alkan-3-on-2-yl-1-oxonium ylides (*m* = 3–6) to alkenyloxyketenes is observed and extensively studied <2004JOC1331>. In particular, rhodium(II)-catalyzed intramolecular reaction of diazomethyl oxepan-2-yl ketone **13** generates a bicyclo[5.3.0]decan-3-one-1-oxonium-2-ylide **14**, which undergoes sigmatropic and stereospecific [3+2] cycloreversion to form hept-6-enyloxyketene **15**. The latter is trapped by MeOH to form the corresponding ester **16** (Scheme 5).



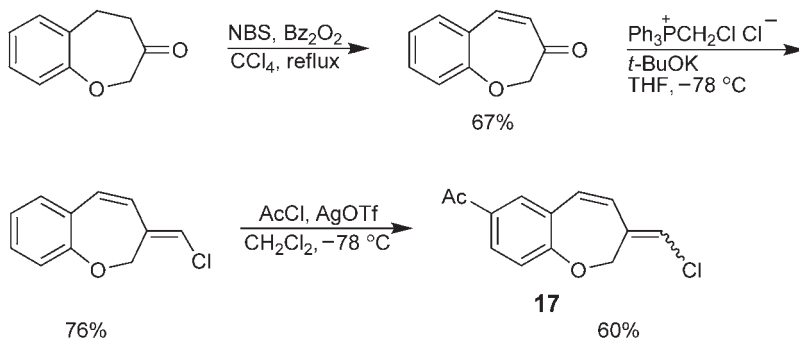
Scheme 5

13.02.6 Reactivity of Non Conjugated Rings

This section retains the same subsections covering reactivity of partially saturated oxepines as in Section 9.02.6 of CHEC-II(1996). Some reactions of highly unsaturated compounds with conjugated systems that, in contrast to oxepines, cannot be even formally regarded as closed ones, namely oxepinones, oxepinediones, and oxepine oxides, are also considered.

13.02.6.1 Dihydrooxepines

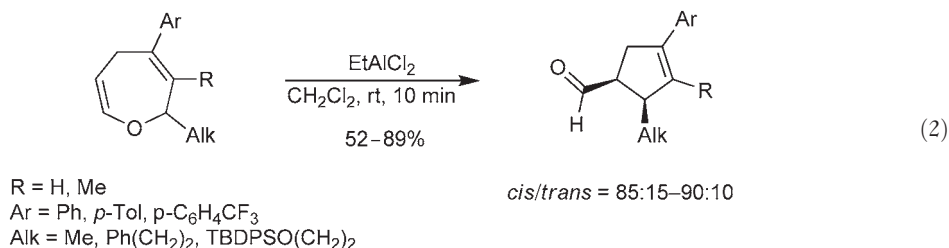
Synthesis of an antifungal natural benzo[*b*]oxepine derivative, pterulone **17** (Scheme 6), demonstrates some reactions of dihydrooxepines. The target product is formed as a mixture of (*E*)- and (*Z*)-isomers (1:3); however, the latter



Scheme 6

can be transformed (rt, 4 h) upon the action of I_2 (cat.) and blue light (300 nm) to give 3:1 mixture, the natural (*E*)-isomer being possible to be isolated by chromatography <2001T7181>.

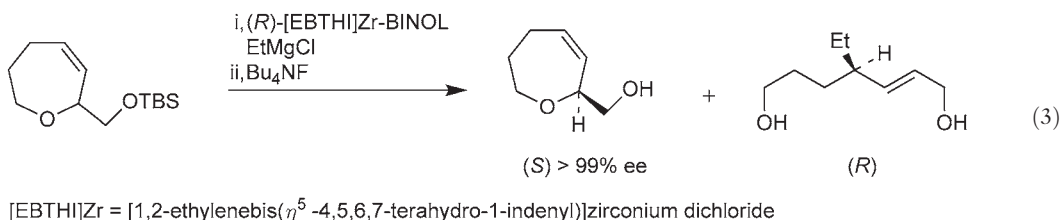
2,5-Dihydrooxepines undergo diastereoselective [1,3] rearrangement (Equation 2) under the action of ethylaluminum dichloride at room temperature <2005AG(E)3264>.



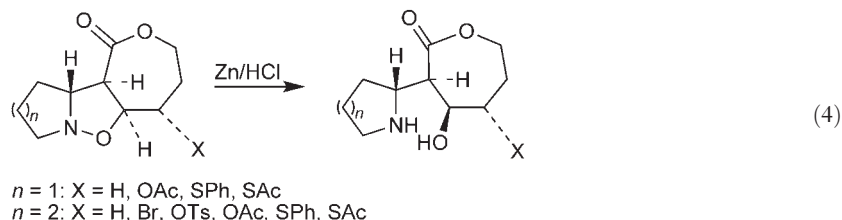
Catalytic rearrangement of 2-(1-hexynyl)-7-(dichloromethylene)oxepane, promoted by the reaction of $Co_2(CO)_8$ with the triple bond and catalyzed by Lewis acid ($BF_3 \cdot OEt_2$ or $TiCl_4$), afforded the corresponding $Co_2(CO)_6$ complex of 2,2-dichloro-3-(1-hexynyl)cycloheptanone <2002AGE2584>.

13.02.6.2 Tetrahydrooxepines

Stereoselective chelate-controlled addition of Grignard reagents to tetrahydrooxepine derivatives (Equation 3) involves Zr-catalyzed kinetic resolution with (*R*)-[EBTHI]Zr-BINOL (BINOL = 1,1'-bi-2-naphthol) <1996JA4291, 1997JA6205, 1999JOC854>.



Several isoxazolidines or their quaternary salts derived from the 1,3-dipolar cycloaddition of α,β -hexenolides (6,7-dihydrooxepin-2(5*H*)-ones) to cyclic nitrones, were converted into the corresponding piperidyl- and pyrrolidyloxepinones by reduction of the nitrogen–oxygen bond (Equation 4). These amino alcohols provide a new access to the 1-azabicyclo[5.3.0]decane core of the *Stemona* alkaloids <2004EJO4215>.

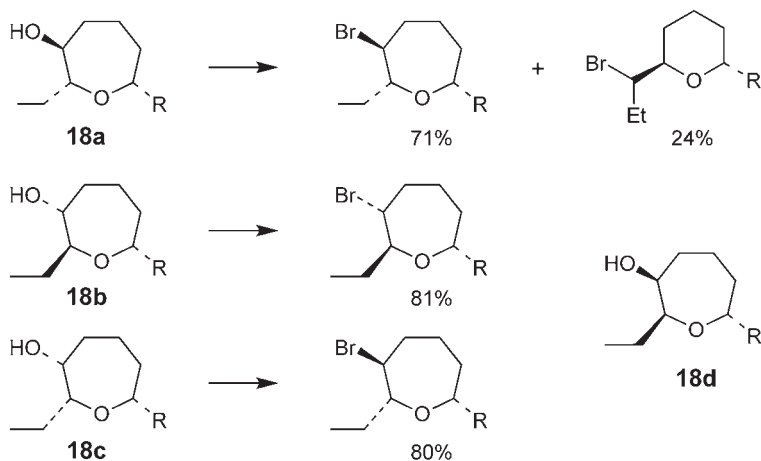


6,7-Dihydro-2(3*H*)-oxepinone undergoes copolymerization with ϵ -caprolactone initiated by aluminium isopropoxide at 0 °C as an easy way to produce unsaturated aliphatic polyesters with nonconjugated C=C double bonds in a controlled manner. The homopolymerization of the dihydrooxepinone is, however, not controlled because of fast intramolecular transesterification <2002PSA2286>.

1,6-Anhydro-3,4,5-tri-*O*-benzyl-2-deoxy-D-xylosept-1-enitol (4,5,6,7-tetrahydrooxepine obtained from 2,3,4-tri-*O*-benzyl-D-xylose) on epoxidation with dimethyldioxirane gives 1,2-anhydro- β -D-idoseptanose, which on trapping by a number of nucleophiles affords α -idoseptanosides. In particular, the product of methanolysis is methyl 2,3,4,5-tetra-*O*-acetyl- α -D-idoseptanoside <2004CAR1163>.

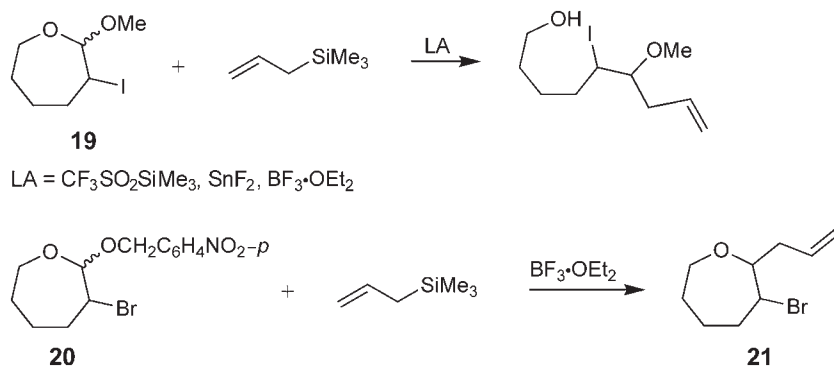
13.02.6.3 Oxepanes, ϵ -Caprolactone, and Adipic Anhydride

The character and stereochemistry of products obtained from 2,7-dialkyl-3-hydroxyoxepanes under the action of phosphine complexes of Br_2 (e.g., DPPE- 2Br_2) depend on the stereochemistry of initial oxepane derivatives (DPPE = bis(diphenylphosphino)ethane; [Scheme 7](#)). Thus, of 2-ethyl-3-hydroxy-7-phenethyloxepanes, *r*-2, *t*-3, *c*-7- and *r*-2, *t*-3, *t*-7-isomers (**18a** and **18b**, respectively) undergo replacement of hydroxy group by a bromine atom with retention of configuration at C-3. However, for *r*-2, *c*-3, *c*-7-isomer **18c**, the configuration is changed and *r*-2, *c*-3, *t*-7-isomer **18d** gives only traces of products; **18a** gives a considerable amount of 2-(2-bromopropyl)-7-phenethyltetrahydropyran as a by-product. Steric inhibition of the attack of O-1 on the C-3 center, which prevents formation of corresponding oxonium ions, may be the origin of the absence of either ring contraction or retention of configuration on the bromination of **18c** and **18d** [<2000SL1187>](#).



Scheme 7

Lewis acid-catalyzed reaction of allyltrimethylsilane with 3-iodo-2-methoxyoxepane **19** leads to the ring opening; however, under similar conditions, 3-bromo-2-(*p*-nitrobenzyloxy)oxepane **20** gives 2-allyl-3-bromooxepane **21**, as the single diastereomer of unknown configuration in 74% yield ([Scheme 8](#)) [<1998TL2759>](#).

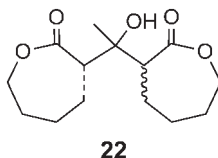


Scheme 8

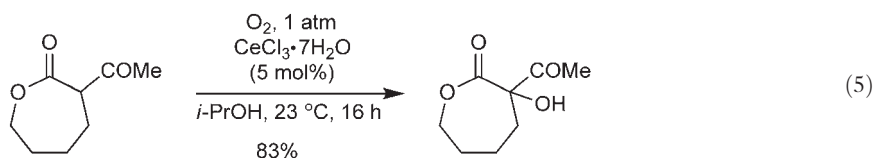
Cyclic bis-hemiacetals, highly fluorinated oxepane-2,7-diols, obtained by reduction of dimethyl perfluoroadipate with Vitride or by dehydration of 1*H*,6*H*-perfluorohexane-1,1,6,6-tetraol, undergo ring opening upon treatment with ethanolic HCl to give 1*H*,6*H*-1,6-diethoxyperfluorohexane-1,6-diol and dehydration with P_4O_{10} giving perfluorohexanedial [<2002CCCC1486>](#).

Reductive alkylation of ϵ -caprolactone (1 equiv) with a 2:0.25 mixture of Grignard reagent and $\text{Zn}(\text{BH}_4)_2$ affords monoalkylated diols, which can be further selectively oxidized with tetrapropylammonium perruthenate (TPAP) into the expected monoalkylated lactones <2002CR571>.

A Mukaiyama-type Claisen reaction gives α -acetyl- ϵ -caprolactone in good yield when ϵ -caprolactone silylenol ether undergoes reaction with acetic anhydride in the presence of TiCl_4 as catalyst. However, the reaction outcome depends on the addition sequence of starting materials: if the mixture of $\text{Ac}_2\text{O}/\text{TiCl}_4$ is added to silylenol ether then the acetylated lactone further converts to bis(oxooxepanyl)ethanols **22**. Both diastereoisomers of the latter were characterized by X-ray crystallography and NMR <2003T3769>.



Cerium-catalyzed, direct α -hydroxylation of a variety of cyclic and acyclic β -dicarbonyl compounds with molecular oxygen is described <2003EJO425>. 3-Acetyloxepan-2-one is among the studied substrates (Equation 5).



13.02.7 Ring Syntheses from Acyclic Compounds

This section includes only the new data appearing after the publication of CHEC-II(1996), though the system is retained the same as in CHEC-II(1996). Cyclization reactions giving oxepines and oxepanes are classified here according to the nature of bonds formed and the number of atoms in the starting compounds used for building the seven-membered ring. In some cases, acyclic precursors are prepared from cyclic starting compounds. If such precursors are isolated before cyclization, the respective reactions are considered here; in other cases, they are discussed in Section 13.02.8. Syntheses of annulated oxepines are also included if the existing ring remained unchanged.

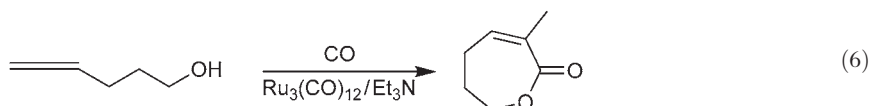
13.02.7.1 Intramolecular Cyclizations

13.02.7.1.1 Cyclizations with formation of ester C–O bonds

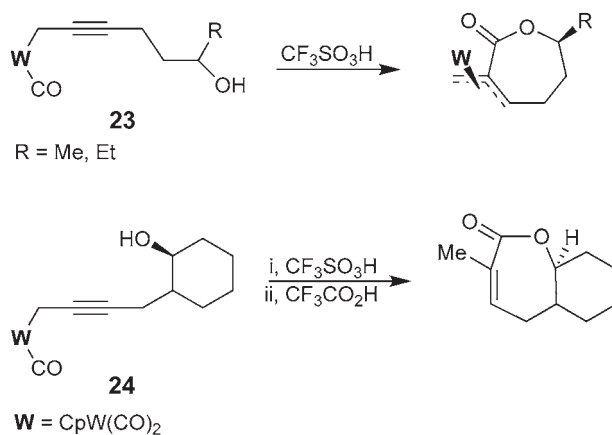
The $\text{CpW}(\text{CO})_3$ complexes **23** and **24** (obtained from $\text{CpW}(\text{CO})_3\text{Na}$ and propargyl halides) undergo cyclization in the presence of trifluoromethanesulfonic acid (Scheme 9), followed by removal of the metal with trifluoroacetic acid to yield corresponding mono- and bicyclic lactones <1995JA2933>.

2-Alkyl- ϵ -caprolactones are formed (Scheme 10) in good overall yields (up to 75%) and with high enantiomeric purity (ee = 90%, 94%) by alkylation of SAMP-hydrazones **25** (SAMP = (*S*)-1-amino-2-methoxymethylpyrrolidine) and subsequent oxidative cleavage of the hydrazone **26** with ozone <1995S947>.

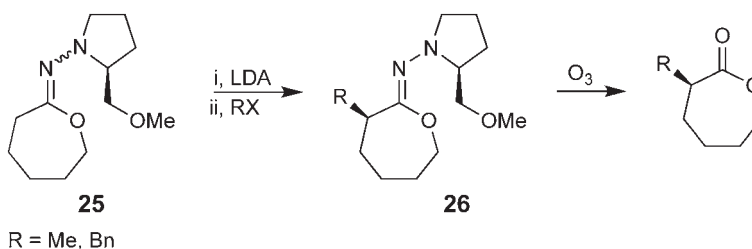
Ruthenium-catalyzed cyclocarbonylation of unsaturated alcohols gives seven-membered lactones in good yields (Equation 6), both ester C–O and C–C bonds being formed <2001TL5459>.



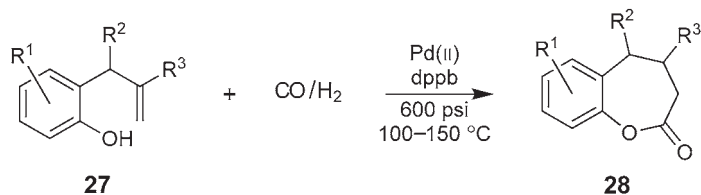
The palladium(II)-catalyzed reaction of 2-allylphenols **27** with carbon monoxide and hydrogen (Equation 7) leads to mixtures of five-, six-, and seven-membered lactones, the content of the latter **28** in the mixture being up to 90–100% <1996JA4264>.



Scheme 9



Scheme 10



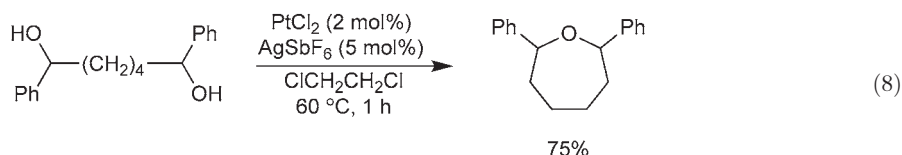
$R^1 = R^2 = R^3 = \text{H}$
 $R^1 = 6\text{-Me}; R^2 = R^3 = \text{H}$
 $R^1 = 4\text{-Cl}; R^2 = R^3 = \text{H}$
 $R^1 = 4\text{-Bu}^t; R^2 = \text{Me}; R^3 = \text{H}$
 $R^2 = \text{Me}; R^1 = R^3 = \text{H}$
 $R^3 = \text{Me}; R^1 = R^2 = \text{H}$
 dppb = 1,4-bis(diphenylphosphino)butane

(7)

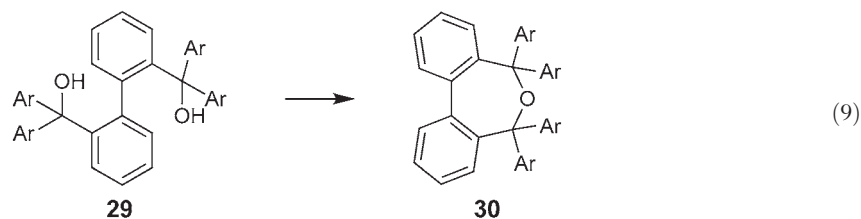
13.02.7.1.2 Cyclizations with formation of ether C–O bonds

Cyclodehydration of hexane-1,6-diol with tin phosphate as a catalyst (230 °C) gives oxepane in 32% yield <2001GC143>. Acid-catalyzed dehydration of 2,2'-bis(hydroxydiphenylmethyl)biphenyl by an ion-exchange resin allows one to prepare a sterically hindered 2,2',7,7'-tetraphenyldibenzo[*c,e*]oxepine in 70% yield under mild conditions (CH₂Cl₂, rt) <2002J(P1)2673>.

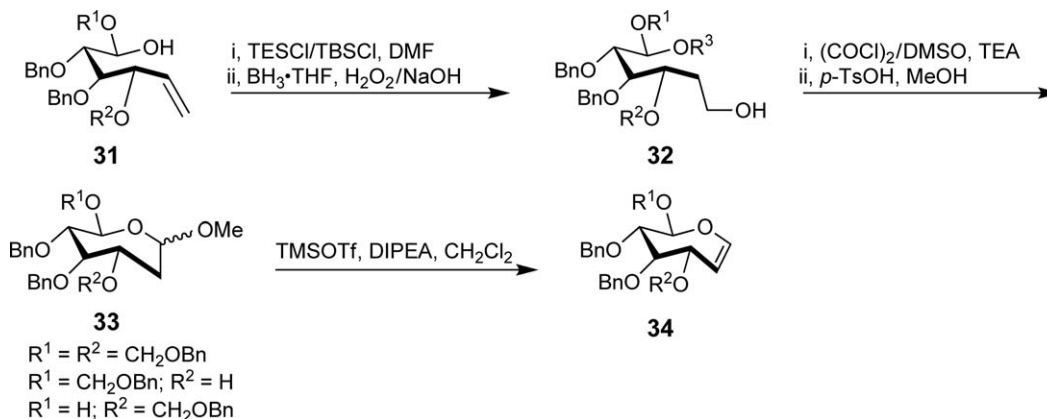
Intramolecular platinum-catalyzed etherification of 1,6-diphenylhexane-1,6-diol to give corresponding oxepane (Equation 8) smoothly proceeds in the presence of platinum hexafluoroantimonate *in situ* prepared from PtCl₂ and AgSbF₆ <2005SL152>.



The first examples of acid-catalyzed cyclizations of 2,2'-bis(diarylhydroxymethyl)biphenyls to 5,5,7,7-tetraaryl-5,7-dihydrodibenzo[*c,e*]oxepines in the solid state are described (Equation 9). Thus, crystals of the 2:1 inclusion compounds of 2,2'-bis(hydroxydiphenylmethyl)biphenyl **29** (Ar=Ph) and formic acid give on heating dihydrodibenzo[*c,e*]oxepine **30** (Ar=Ph) in 89% yield; crystals of the 2:1 inclusion complex of **29** (Ar=4-FC₆H₄) and formic acid undergo an analogous reaction to give **30** (Ar=4-FC₆H₄). Biphenyl **29** (Ar=4-MeOC₆H₄) and *p*-toluenesulfonic acid yield **30** (Ar=4-MeOC₆H₄) upon heating under solvent-free conditions; only a catalytic amount of acid is required to mediate the reaction, and the amount of acid catalyst present serves only to change the rate of reaction <2004H(62)749>.

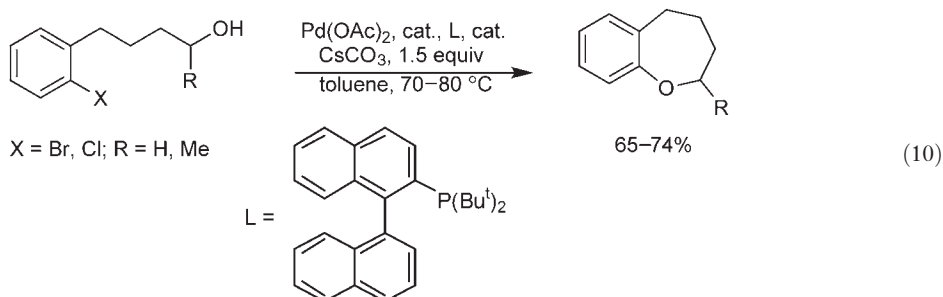


Recently, a cyclization–elimination route to carbohydrate-based oxepines is proposed (Scheme 11). After silyl protection and hydroboration/oxidation, starting hept-1-enitols **31** give the protected heptan-1-itols **32**. Swern oxidation of the latter followed by sequential acetal formation/cyclization provide methyl 2-deoxyseptanosides **33** that undergo elimination reactions to give the carbohydrate-based oxepines **34** <2005JOC3312>.

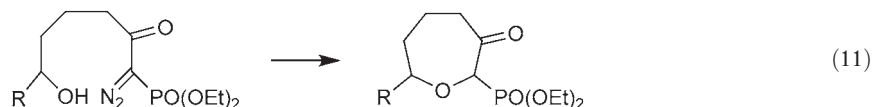


Scheme 11

The Pd-catalyzed cyclization of 2-halogen-substituted δ -hydroxyalkylbenzenes (Equation 10) is a useful method for the synthesis of 1-benzoxepanes <2000JA12907>.

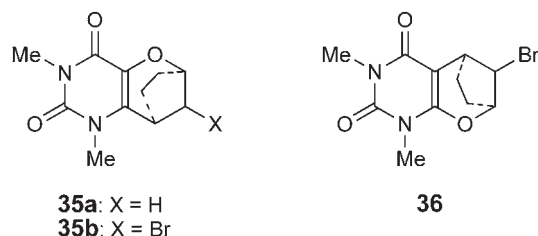


Intramolecular carbene insertion into the O–H bond (Equation 11), which proceeds after the treatment of diethyl 6-hydroxy-2-oxo-1-diazoalkylphosphonates with rhodium(II) diacetate, leads to the respective oxepanes <1994J(P1)501>.

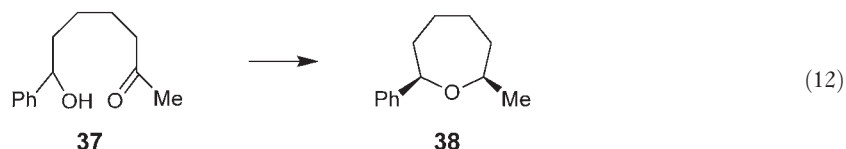


2,7-Dihydrooxepines are formed from (*Z,Z*)-1,6-dihydroxyhexa-2,6-dienes and *p*-toluenesulfonyl chloride <1994CC67, 2000H(53)897>.

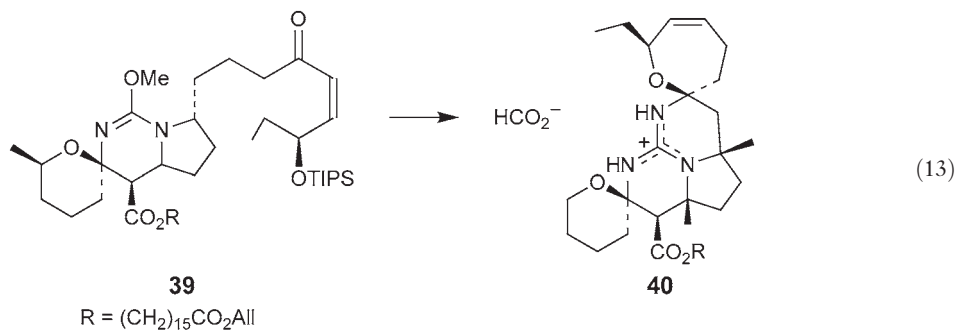
Pyrimidine-annulated methanooxepene **35a** is formed via regioselective heterocyclization of 6-cyclopent-2-enyl-5-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione in the presence of concentrated sulfuric acid. The above-mentioned pyrimidinedione and 5-cyclopent-2-enyl-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione give similar annulated bromomethanooxepenes **35b** and **36**, respectively, when cyclization is performed with pyridine hydrotribromide or hexamethylenetetramine hydrotribromide <2003M1137>.



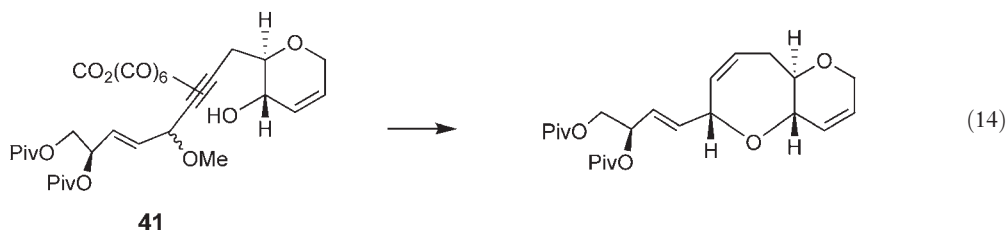
In their prominent synthesis of brevetoxin B, Nicolaou *et al.* have investigated, among some other methods for construction of oxepine ring system, the reductive cyclization of keto alcohol **37** with triethylsilane and trimethylsilyl triflate giving oxepane **38** (Equation 12) <1995JA1173>.



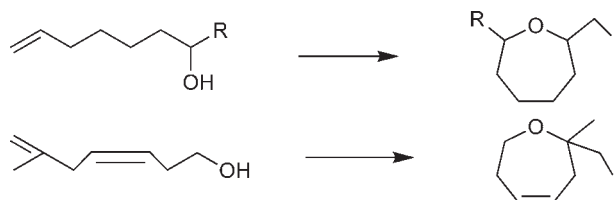
The 1,1,3,3-tetraisopropyldisiloxane (TIPS)-protected alcohol **39** undergoes cyclization (Equation 13) to the spirooxepine **40**, a key intermediate in the synthesis of (–)-ptilomycalin A <1995JA2657>.



The A/B ring system of ciguatoxin is formed stereoselectively from alkyne cobalt complex **41** (Equation 14) using the action of boron trifluoride followed by hydrogenation in the presence of Wilkinson catalyst under high pressure <1995SL1179>. A similar approach works well in the construction of ABC ring system of ciguatoxin <1996SL351, 1999TL1911> as well as of AB fragments of ciguatoxin and gambierotoxin <1999JOC37>.

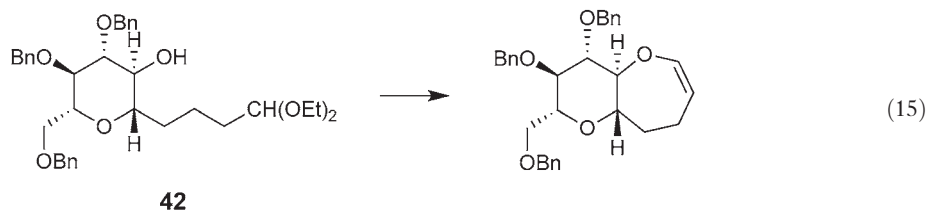


Hept-6-en-1-ols undergo iodoetherification with bis(*sym*-collidine)iodine(I) hexafluorophosphate in CH_2Cl_2 (**Scheme 12**) to give 2-iodomethyloxepanes in high yields <1995SL323, 1996JOC5793>.



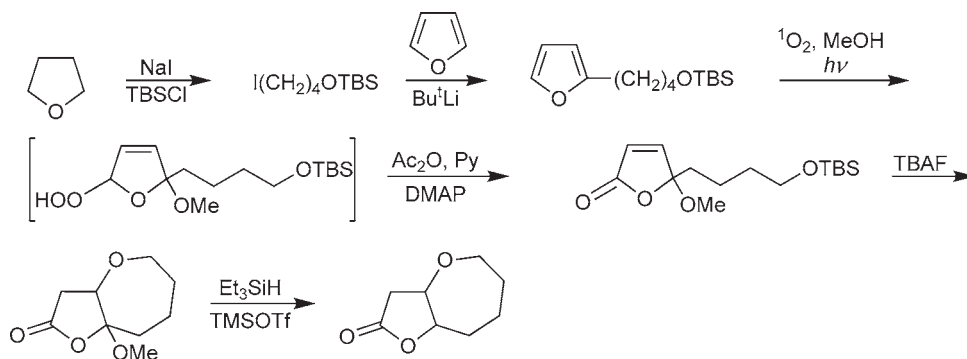
Scheme 12

Acid-catalyzed cyclization of **42** (Equation 15) is a simple and useful method for construction of the oxepane ring <1998TL9601>.



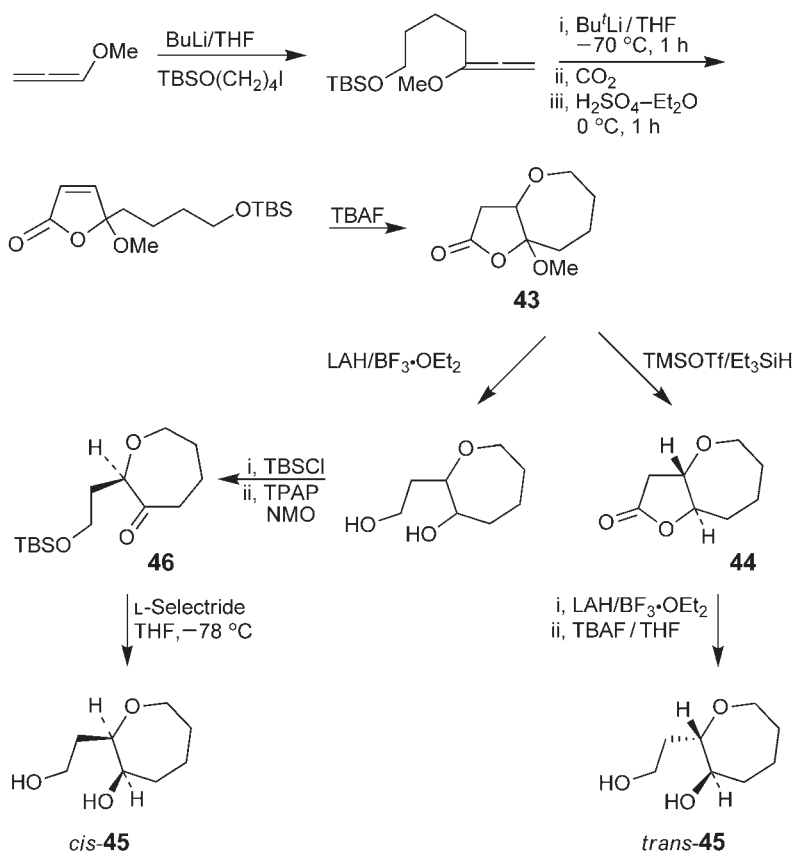
The highly stereoselective synthesis of 2,3-*trans*-3-hydroxytetrahydropyran and 2,3-*trans*-3-hydroxyoxepane was achieved by the SmI_2 -induced reductive intramolecular cyclization from acyclic compounds having an aldehyde and a β -alkoxyacrylate fragments <2002CL148>. Based on this reaction, new effective iterative syntheses of *trans*-fused 6,6,6-tricyclic, 6,7,6-tricyclic, and 6,7,7,6-tetracyclic ethers were developed <2002T1853>.

A six-step synthesis of hexahydrofuro[3,2-*b*]oxepin-2(3*H*)-one involves cyclization with the formation of an etheral C–O bond (**Scheme 13**). However, its specific peculiarities are that the product skeleton is built from tetrahydrofuran (THF) and furan, the key reactions being the oxidation of a furan ring with singlet oxygen, followed by an intramolecular Michael addition to 2(5*H*)-furanone C=C bond <2003TL4467, 2004TL5207>.



Scheme 13

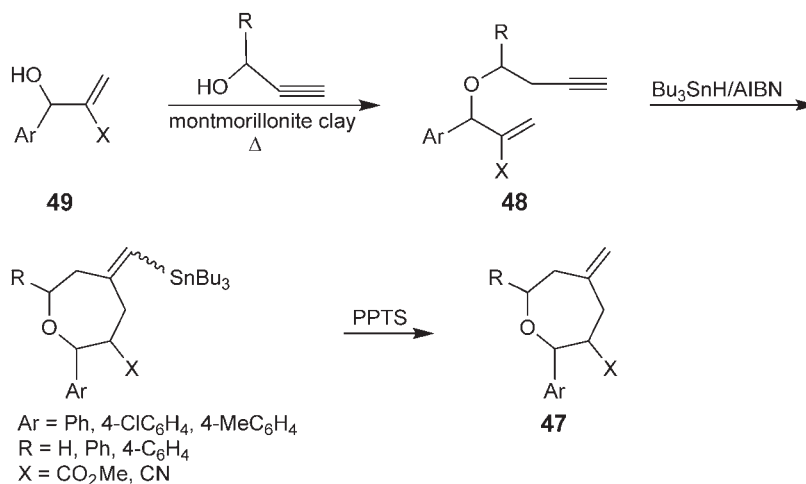
A similar synthesis, using methoxyallene as a building block (**Scheme 14**), was developed by the same group <1999TL8307>. The reaction of 9a-methoxyhexahydrofuro[3,2-*b*]oxepin-2(3*H*)-one **43** (obtained by both furan and methoxyallene approaches) with TMSOTf and Et₃SiH presumably proceeds via oxonium ion intermediate and gives therefore the more stable hexahydrofuro[3,2-*b*]oxepin-2(3*H*)-one **44** with *trans*-ring junction irrespective of *cis*- or *trans*-junction of starting acetal **43**. Lactone **44** gives *trans*-3-hydroxy-2-hydroxyethyloxepane (*trans*-**45**) by the reductive ring opening (BF₃·OEt₂/LiAlH₄). Analogous reaction of **43** results in a mixture of diastereoisomeric diols, which after selective protection of hydroxy group in position 2 followed by oxidation with TPAP and *N*-methylmorpholine *N*-oxide gives the *t*-butyldimethylsilyl (TBS)-protected 2-hydroxyethyloxepan-3-one **46**. The latter produces *cis*-3-hydroxy-2-hydroxyethyloxepane (*cis*-**45**) on successive treatment with the highly diastereoselective reducing agent L-Selectride and tetrabutylammonium fluoride, as deprotecting agent <2005S411>.



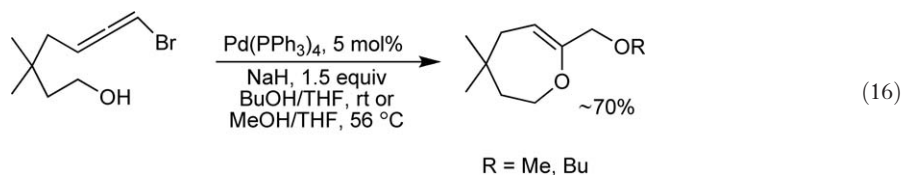
Scheme 14

Tri- and tetrasubstituted oxepanes **47** can be obtained in 50–60% overall yield (**Scheme 15**) using vinyl radical cyclization of homopropargyl and arylhomopropargyl derivatives **48** of Baylis–Hillman adducts **49**, followed by methylidene group deprotection using pyridinium *p*-toluenesulfonate (PPTS) <2005TL3369>.

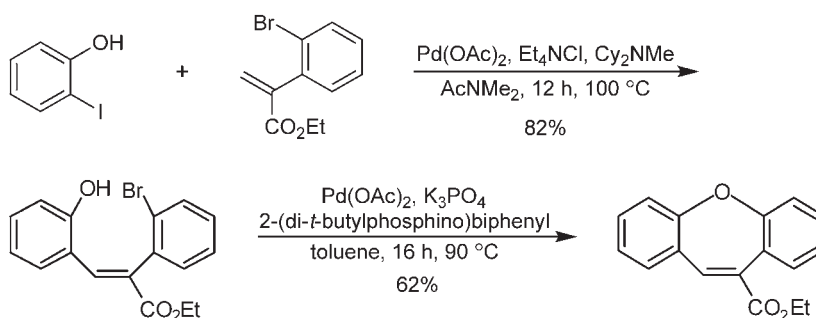
A highly regio- and stereoselective synthesis of oxepine derivatives via cyclization of bromoallenes bound with hydroxy group by a four-carbon atom tether in the presence of a palladium(0) catalyst and alcohol is developed (**Equation 16**). In this reaction, the bromoallenes act as an allyl dication equivalent, and the intramolecular nucleophilic attack takes place exclusively at the central carbon atom of the allene moiety <2004JA8744>.



Scheme 15



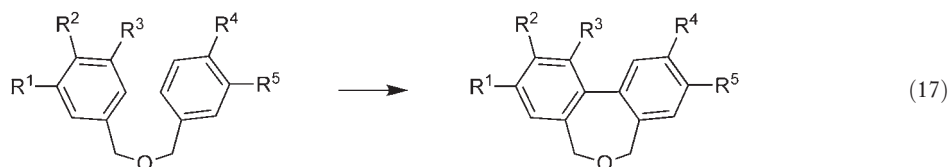
Two-step synthesis of a dihydrodibenz[*b,f*]oxepine derivative by Heck arylation reaction followed by intramolecular O-arylation (Scheme 16) is described <2004OL3005>.



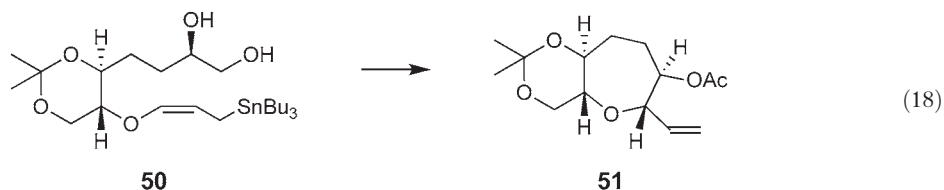
Scheme 16

13.02.7.1.3 Cyclizations with formation of carbon–carbon bond

Oxidative coupling of substituted bibenzyl ethers with phenyliodine(III) bis(trifluoroacetate) affords 6,7-dihydro-5*H*-dibenz[*c,e*]oxepines (Equation 17) <1998JOC7698>.

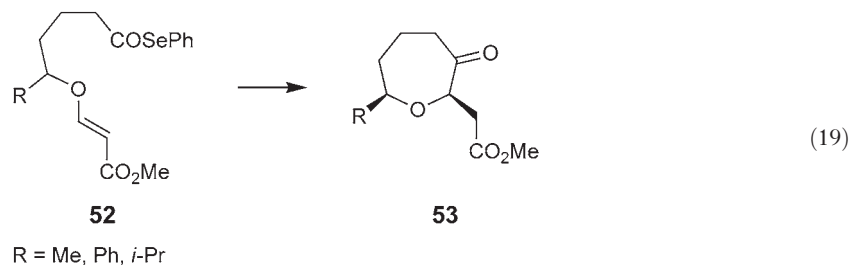


In connection with a ciguatoxin synthesis, a cyclization (Equation 18) of stannane derivatives like **50** with tetrabutylammonium periodate followed by boron trifluoride etherate to give oxepanes, for example, **51**, are described <1996TL2869>.

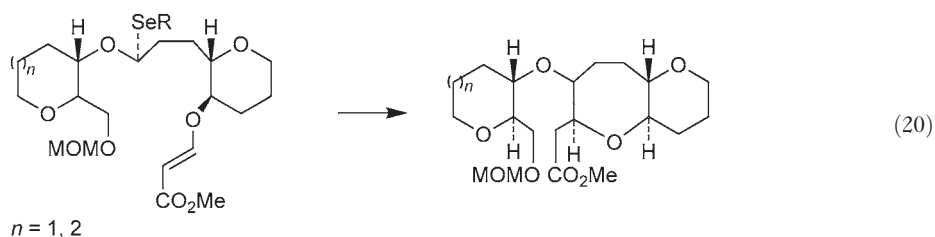


A similar strategy is used in syntheses of hemibrevetoxin B <1998JOC6597>, gambierol <1998TL6369, 1998TL6373>, and ciguatoxin <1998AGE965>.

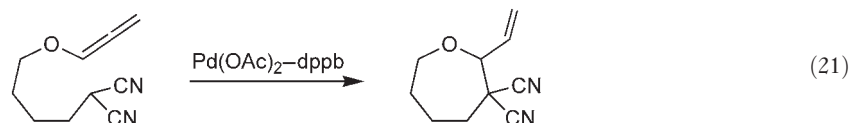
Radical cyclization of acyl selenides **52** (Equation 19) leads to oxepanones **53**, the main product (>95% in the mixture) being *cis*-isomer and the best yields being obtained with (TMS)₃SiH <1996JOC2252>.



Stereoselective radical cyclization (Equation 20) initiated by Bu₃SnH/AIBN or Bu₃SnH/Et₃B is suggested as a method for the synthesis of O-linked oxepane ring systems (AIBN = 2,2'-azobisisobutyronitrile) <1998TL2783>.

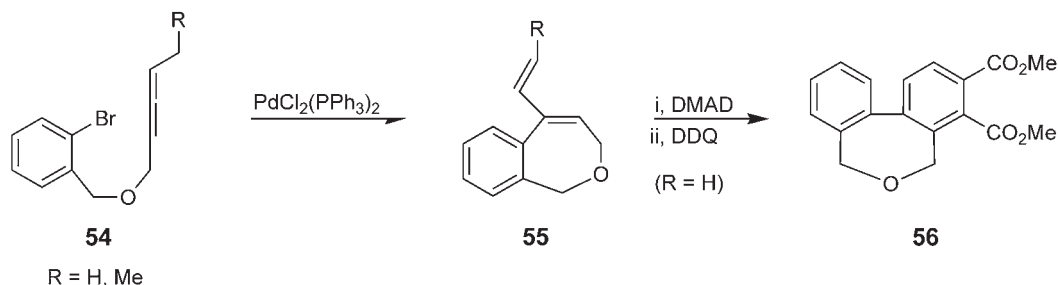


A Pd-catalyzed Michael-type cyclization (Equation 21) is described as a method for construction of a substituted oxepane system <1999TL1747>.



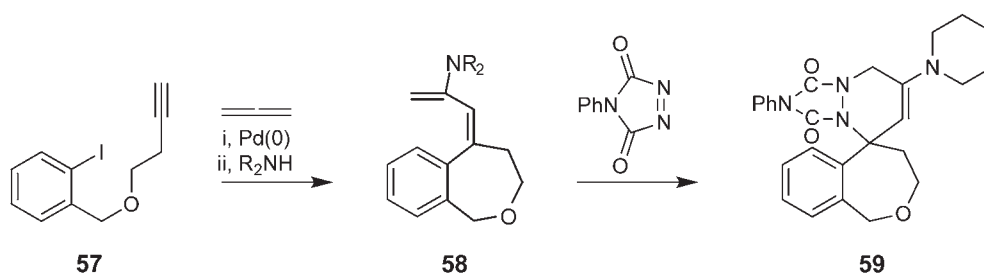
A similar cyclization is also used in the synthesis of a modified estron with ring A fused to a seven-membered lactone fragment <1999TL1771>.

On treatment with a Pd–phosphine complex, allene ethers **54** undergo cyclization (Scheme 17) to the benzoxepines **55**, which can be transformed to a dibenzoxepine derivative **56** via Diels–Alder reaction and aromatization <1994JOC4730>.



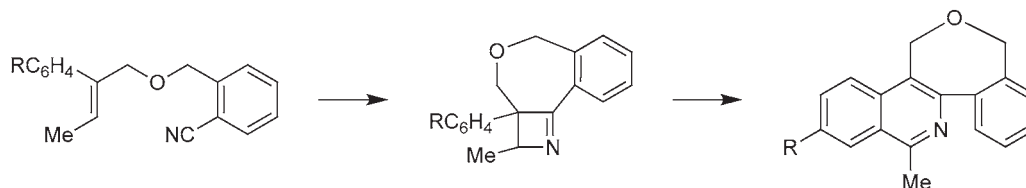
Scheme 17

2-Iodobenzyl propargyl ether **57** cyclizes with π -allylpalladium (Scheme 18) to form after trapping by a secondary amine tetrahydro-2-benzoxepines **58** in ~70% yield. The piperidino derivative **58** ($\text{R}_2 = (\text{CH}_2)_5$) undergoes Diels–Alder reaction with 4-phenyl-1,2,4-triazole-3,5-dione as dienophile to give a spiro derivative **59** in 44% yield <1996TL6565>.



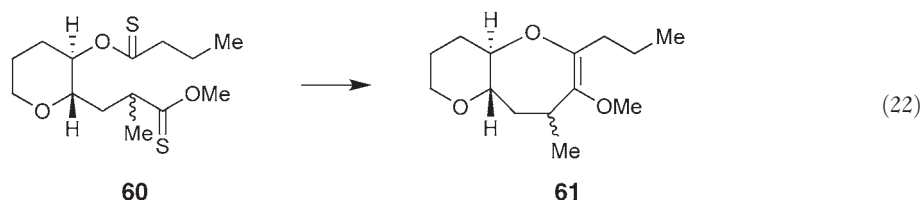
Scheme 18

Irradiation (254 nm) of 1-(*o*-cyanobenzyloxy)-2-arylbut-2-enes (Ar = Ph, *p*-Tol, *p*-anisyl) leads via a [2+2] cycloaddition, followed by the cleavage of the azetidine ring and recyclization (Scheme 19), to the annulated 2,7-dihydrooxepine derivatives <1994BCJ1769>.

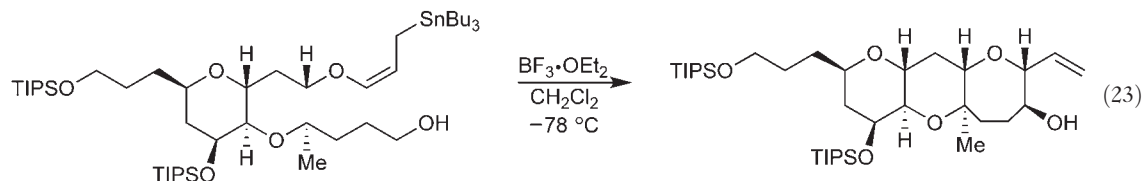


Scheme 19

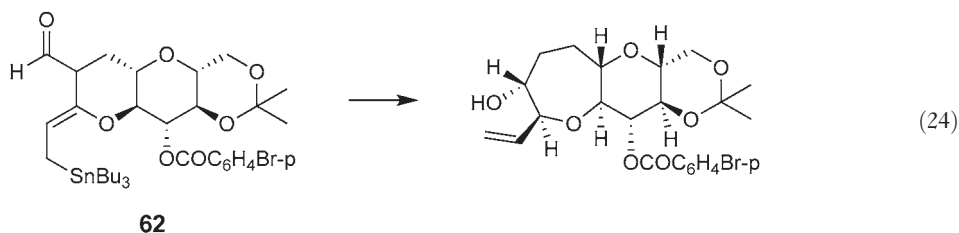
Photolysis of bis-thioester **60** (Equation 22) affords the enol ether **61**, which undergoes equilibration to a single enantiomer upon hydrolysis <1995JA10252>.



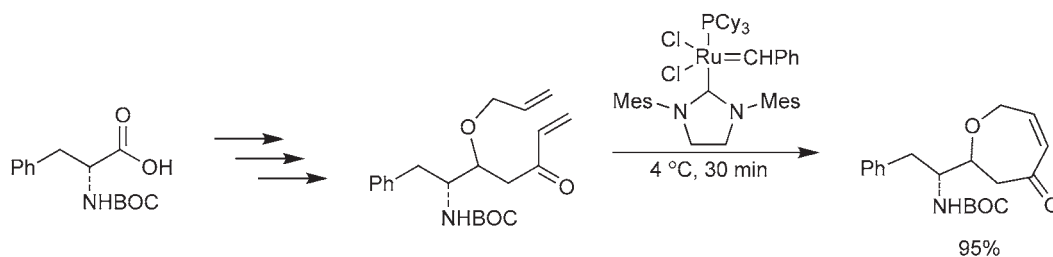
In a synthesis of hemibrevetoxin B, electrophilic addition to a double bond (Equation 23) was successfully used to form the oxepane ring <1995TL5777>.



Boron trifluoride etherate-mediated cyclization (Equation 24) of the pyran derivative **62** (prepared from D-glucose) is used in the synthesis of AB ring system of ciguatoxine <1997T3057>.

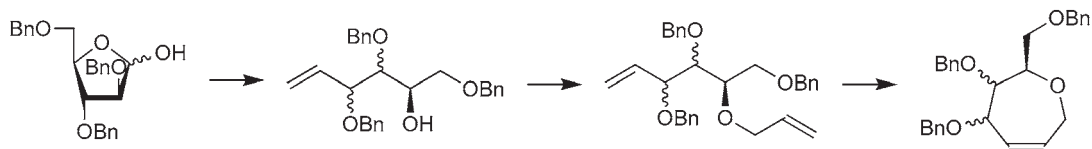


Partially hydrogenated oxepin-4-one system is convenient as a starting material for the synthesis of diverse oxepane-based compounds, such as peptidomimetics. A simple, five-step synthesis of one of the oxepin-4-ones from BOC-D-phenylalanine (Scheme 20) is developed using olefin ring-closing metathesis (RCM), as the final step (BOC = *t*-butoxycarbonyl) <2003TL5511>.



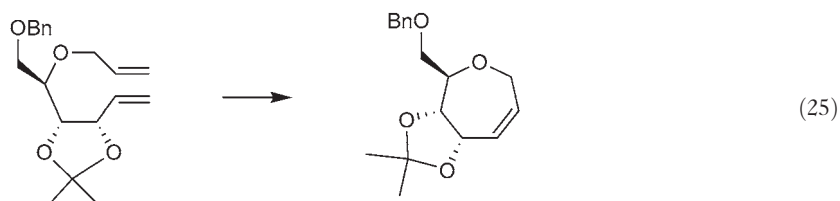
Scheme 20

RCM is now an important method for the building of oxepines. It should be noted that chiral functionalized precursors can be readily prepared from natural monosaccharides. Thus, glucofuranose derivatives can be transformed to tetrahydrooxepines (Scheme 21) in only three steps: olefination, O-allylation, and RCM <1998TL3025>.



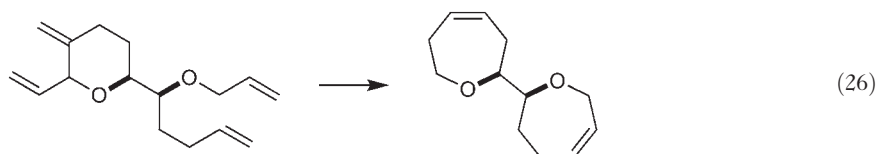
Scheme 21

Similarly, the oxygenated oxepine derivative was prepared (Equation 25) from another precursor, also using RCM <1999TL8751>.

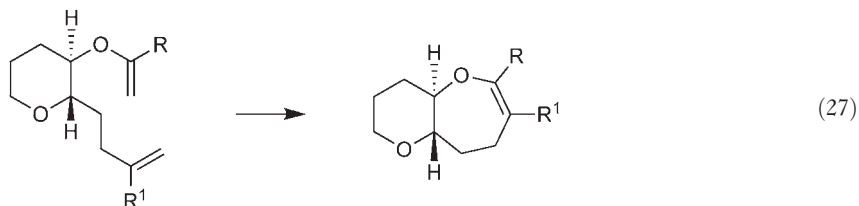


In the synthesis of an oxepine from 2,3,4-tri-*O*-benzyl-D-xylose, 1,6-anhydro-3,4,5-tri-*O*-benzyl-2-deoxy-D-xylosept-1-enitol, the three-step sequence (Wittig olefination, vinyl ether formation, and RCM) was used <2004CAR1163>.

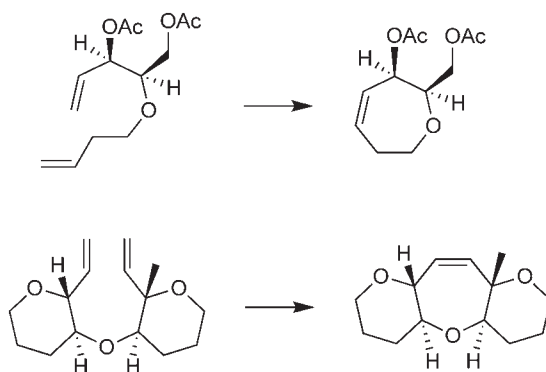
The use of RCM allows one to prepare oxepine ring assemblies (Equation 26) in one step <1999JOC3354>.



The RCM (Equation 27) is a useful method for constructing brevetoxin subunits <1997TL123>.



Other examples of the same kind are syntheses of monocyclic <1997JOC7548> and 6,7,6-membered tricyclic <1997SL980> ethers (Scheme 22), Grubbs' ruthenium catalyst $[(C_6H_{11})_3P]_2Cl_2Ru=CHPh$ being used in both cases.

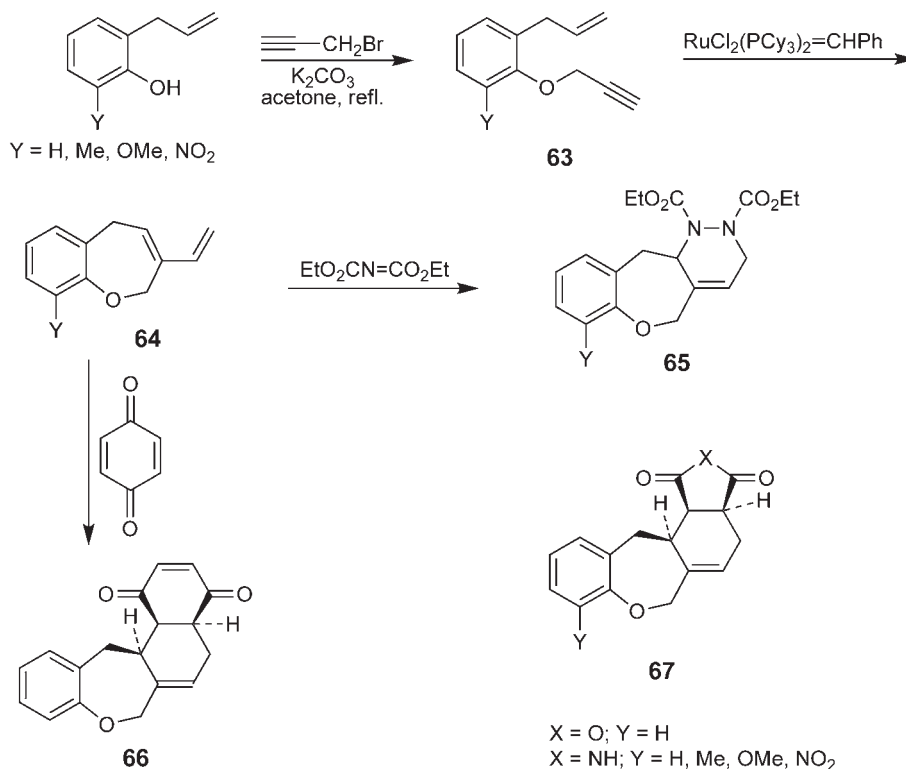


Scheme 22

The general character of RCM is demonstrated by syntheses of 7–10-membered <1998CC1041> and seven- and eight-membered <1998CC2629, 1998TL8321> cyclic ethers, seven-membered lactones <2002H(56)85>, and various annulated oxepines <2001SL1784, 2002H(57)1997, 2002SL1987, 2002TL7781, 2003SL2089, 2006T8830, 2006TL6235>. RCM is used in the synthesis of some natural products and related compounds: oxepanose as analogue of natural furanoses and pyranoses <2005JOC5599>, radulanin A <1998JOC2808>, an analogue of zoapatanol <2001TL5749>, CDEF rings of yessotoxin <2003TL7315>, and rings A <1999CC1063, 1999JOC8396, 1999TL5405> and D <1999CC1063> of ciguatoxin.

Tandem RCM/allylstannane–aldehyde cyclizations are successfully used for the iterative synthesis of *trans*-fused oxepane systems, particularly, three tricycles modeling different fragments in brevetoxins and ciguatoxins <2000S883>. Grubbs' catalyst <1996JA100> was used on RCM step of the tandem while the procedure similar to that proposed by Yamamoto *et al.* <1991TL7069> was applied on the second step.

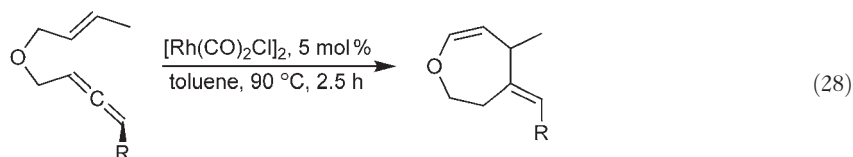
Metathesis of enynes **63** with Grubbs' catalyst (Scheme 23) affords 3-vinyl-2,5-dihydrobenzo[*b*]oxepines **64**. Subsequent dienophile addition gives Diels–Alder adducts **65–67** in 50–80% yields <2001SL1784>.

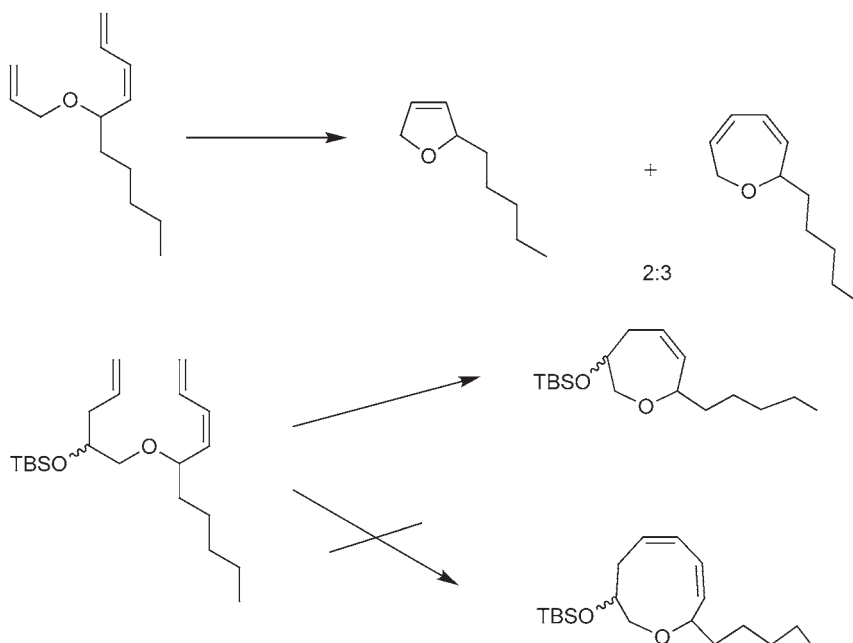


Scheme 23

In the preparation of cyclic ethers by diene–ene RCM, there is a competition between the formation of cyclic allyl ether with a smaller ring size and of cyclic pentadienyl ether with a larger ring size (Scheme 24). In particular, in the competition between five- and seven-membered ring formation, both dihydrofuran and dihydrooxepine derivatives are formed in comparable amounts, whereas in the competition between seven- and nine-membered rings, a dihydrooxepine forms exclusively <2006JOC3977>.

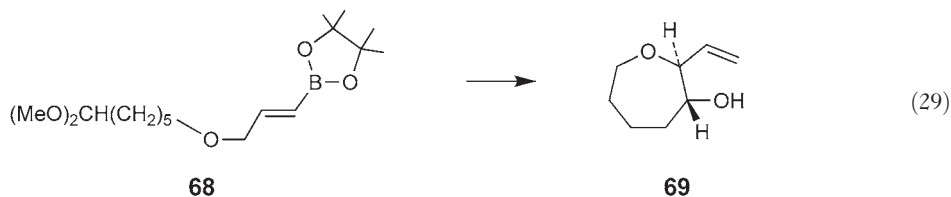
Rhodium(I)-catalyzed ene–allene carbocyclization strategy is suggested for the formation of seven-membered heterocycles, azepines and oxepines. In particular, treatment of an allenyl allyl ether with a catalytic quantity of chlorodi(carbonyl)rhodium dimer affords 4-alkylidene-5-alkyl-2,3,4,5-tetrahydrooxepines (Equation 28) in 40–55% yields <2004OL2161>.





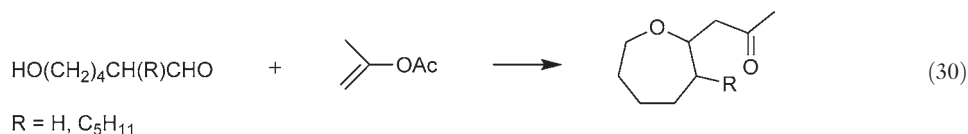
Scheme 24

Intramolecular allylboration of γ -(ω -formylhexyloxy)allylboronate for the syntheses of *trans*- or *cis*-2-(ethenyl)-oxepan-3-ols is described. 3-(6,6-Dimethoxyhexyl)-1-propenylboronate **68** (obtained by hydroboration of corresponding 3-alkoxy-1-propyne with pinacolborane) gives (*E*)- or (*Z*)-3-alkoxyallylboronates by Ir- or Ni-catalyzed isomerization of the double bond, respectively. Both allyl boronates undergo intramolecular allylboration leading to the formation of *trans*-2-(ethenyl)oxepan-3-ol **69** (Equation 29) and the corresponding *cis*-isomer in the presence of Yb(OTf)₃ <2003T537>.



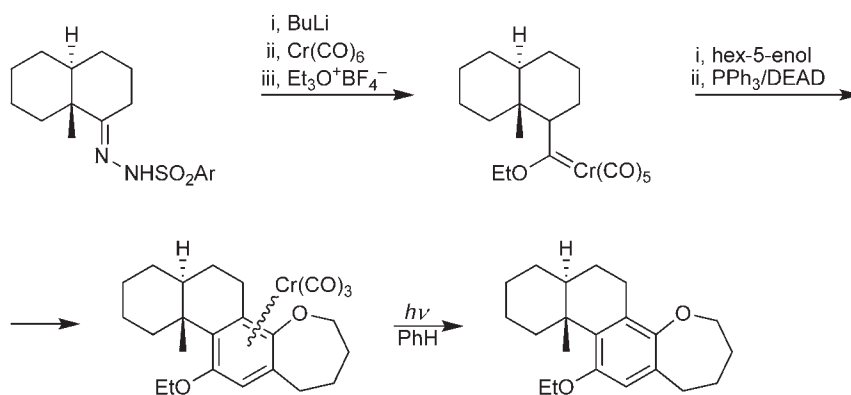
13.02.7.2 Intermolecular Ring Formation

6-Hydroxyhexanal undergoes a Claisen reaction with isopropenyl acetate in the presence of *N*-chlorosuccinimide and tin(II) chloride as catalyst to afford 2-acetyloxepane. In the case of 6-hydroxy-2-pentylhexanal, 2-acetyl-3-pentylloxepane is obtained with 95% diastereoselectivity (Equation 30) <1994CC1123>.

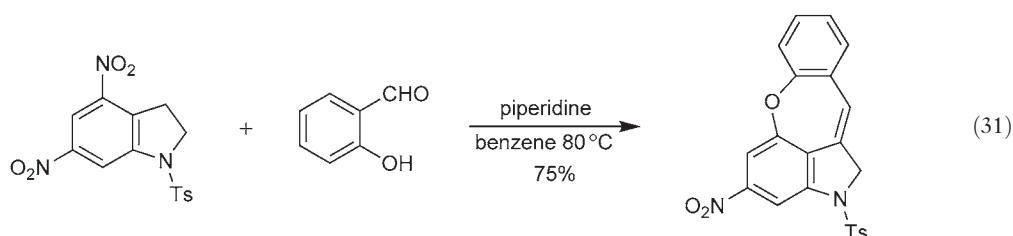


The formation of two rings by chromium catalysis (Scheme 25) is demonstrated <1995TL3027>.

Base-catalyzed condensation (Equation 31) of 4,6-dinitro-1-tosylindoline with salicylaldehyde or 2-hydroxy-naphthalene-1-carbaldehyde is accompanied by intramolecular nucleophilic substitution for one of the nitro groups to give benzo- and naphthooxepino[4,3,2-*cd*]indoles, respectively <2003IZV725>.



Scheme 25



The reaction of $\text{PhCH}=\text{C}(\text{CN})_2$ with the hydroxy allylic carbonate in the presence of catalytic amounts of Pd_2dba_3 in CHCl_3 and $(o\text{-tolyl})_3\text{P}$ in THF at $\sim 100^\circ\text{C}$ gives the cycloaddition product, the oxepane, in 31% yield with low diastereoselectivity (dba = dibenz[*a,h*] anthracene) <2001JOC7142>.

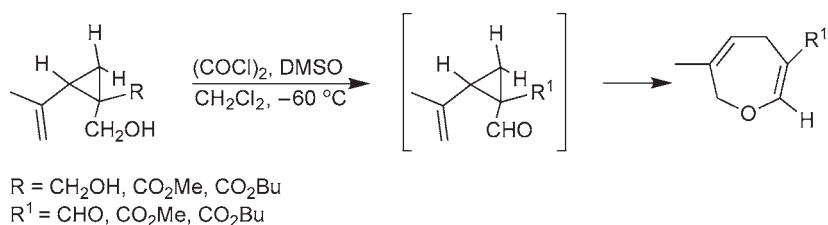
13.02.8 Ring Synthesis by Transformation of Another Ring

This section follows the content of Section 9.02.8 in CHEC-II(1996) without repetition of data presented in the latter but refers to several papers omitted in CHEC-II(1996) along with new publications. Below are presented various synthetic methods, which are classified by the nature and size of the starting ring. Peculiar differences with CHEC-II(1996) should be marked: (1) the absence of paragraphs devoted to formation of oxepine derivatives from four- and five-membered carbocycles because new syntheses of these kinds were not found in the literature; (2) Sections 13.02.8.2.2, 13.02.8.2.5, and 13.02.8.2.6, which are new, appear concerning with formation of oxepine derivatives from four-, (other) seven-, and eight-membered heterocycles, respectively.

13.02.8.1 Synthesis from Carbocyclic Compounds

13.02.8.1.1 By formation of seven- from three-membered rings

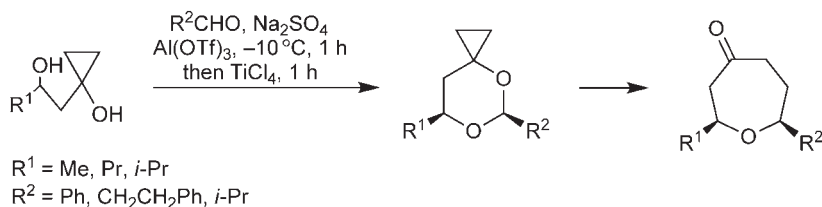
The Swern oxidation of isopropenyl-substituted cyclopropylcarbinols (Scheme 26) results in ring expansion to respective methyldihydrooxepines <1997BCJ2215>. The experimental parameters of the hetero-Cope



Scheme 26

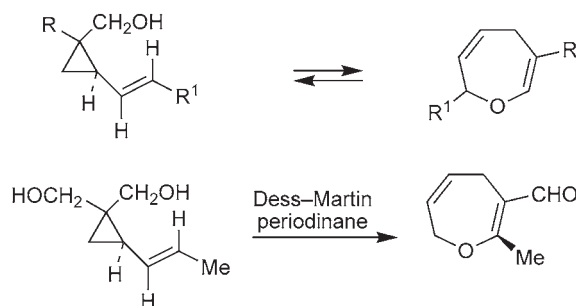
rearrangement of vinylcyclopropanecarbaldehyde, as a model molecule, are well reproduced by MP2/6-31G* *ab initio* and B3LYP/6-31G* DFT quantum-chemical calculations, the aldehyde and oxepin being nearly isoenergetic while the activation energy is $\sim 25 \text{ kcal mol}^{-1}$ <1997LA2443>.

Condensation of β -(hydroxyalkyl)cyclopropanols with aldehydes, followed by rearrangement of acetals formed (Scheme 27), is proposed as simple and convenient method for the synthesis of *cis*-2,7-disubstituted oxepan-4-ones <2005OL515>. Though the intermediate acetal could be isolated in some cases, the reaction is usually carried out as one-pot procedure with sequential addition of two Lewis acids, $\text{Al}(\text{OTf})_2$ and TiCl_4 . The overall yields range from 50% to 70%.



Scheme 27

The 2-(alken-1-yl)cyclopropanecarbaldehyde–1,4-dihydrooxepine equilibrium (Scheme 28) was found to be shifted to the right when alken-1-yl is not vinyl, and this fact was used for the preparation of oxepines from properly substituted cyclopropanes under Dess–Martin oxidation conditions <1993JOC1295>.



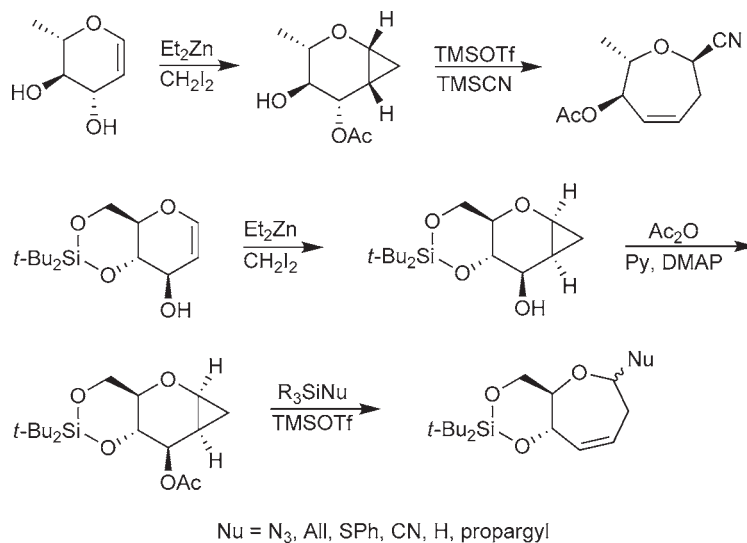
Scheme 28

Cyclopropyl carbinols bearing a (*tert*-butyldiphenylsilyl)methyl substituent undergo silicon-assisted regioselective ring cleavage to generate γ -methylene oxacycles without cleavage of the silane moiety. In particular, the ring opening of 2-(*tert*-butyldiphenylsilyl)methyl-1-hydroxymethyl-1-(3-hydroxypropyl)cyclopropane gives 2-(*tert*-butyldiphenylsilyl)-methyl-5-methyleneoxepanes regioselectively <2002CC514>.

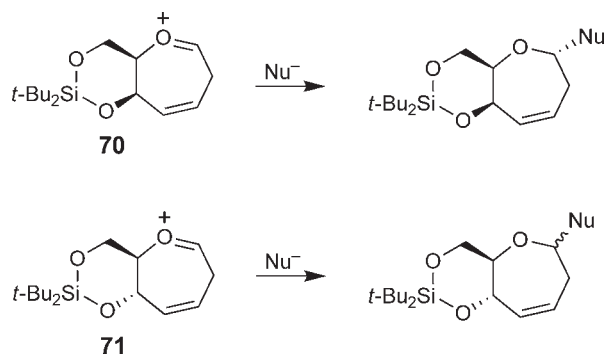
Treatment of 1,2-cyclopropane-annulated carbohydrate derivatives with Lewis acid (Scheme 29) is a convenient route to 2-substituted-2,3,6,7-tetrahydrooxepines <1995TL6831, 1997JOC6615>.

The ring opening of an annulated cyclopropane fragment proceeds through a seven-membered oxonium ion. In galactal-based oxonium ions like **70**, due to their stereochemistry, the ‘upper’ face is hindered and the direct attack of a nucleophile from ‘below’ proceeds in contrast to glucal derivatives, for example, **71** (Scheme 30). This fact provides much higher diastereoselectivity of the ring expansion of cyclopropanated galactal <2003TL9043>.

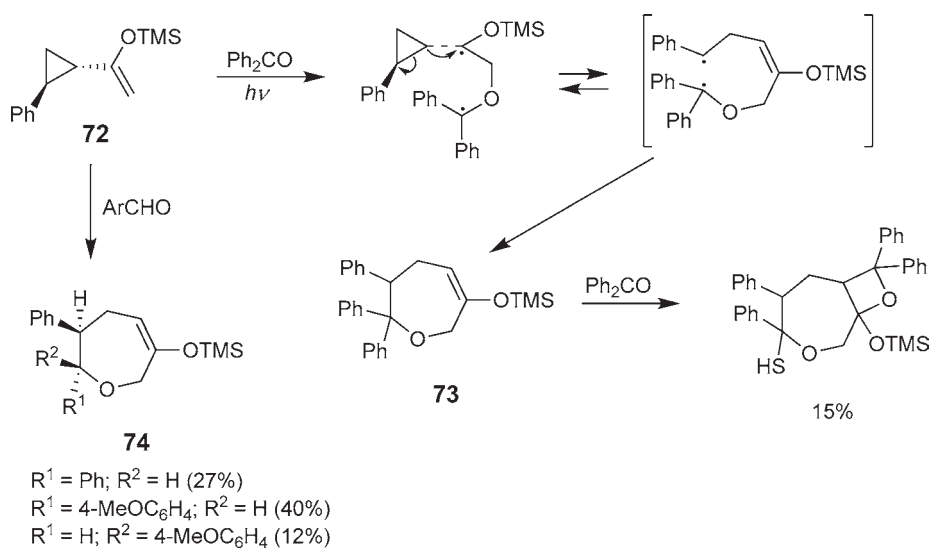
Tandem intermolecular Paterno–Büchi reaction of benzophenone with trimethylsilyl vinylcyclopropyl ether **72** (Scheme 31) leads in its first step to the formation of seven-membered **73** rather than to four-membered heterocycle while its second step proceeds in a normal fashion. With aromatic aldehydes, only tetrahydrooxepine derivatives **74** are formed <1998J(P1)2363>.



Scheme 29



Scheme 30



Scheme 31

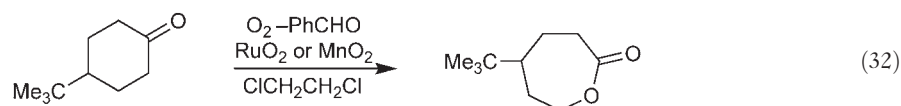
13.02.8.1.2 By formation of seven- from six-membered rings

The Baeyer–Villiger oxidation remains the main route to oxepines from six-membered carbocycles. After publication of CHEC-II(1996), some new oxidative procedures are published.

Optically active 4-alkoxycarbonyl-3-hydroxycyclohexanones (formed in highly enantio- and diastereoselective organocatalytic asymmetric domino Michael aldol reaction of β -keto esters and α,β -unsaturated ketones) are transformed into corresponding chiral oxepanones under the action of urea–hydrogen peroxide and trifluoroacetic anhydride <2004AGE1272>.

A brief review of procedures for asymmetric metal-catalyzed Baeyer–Villiger oxidations is given with asymmetric copper-catalyzed synthesis of 3-phenyl-2-oxepanone as representative of the enantioselective synthesis of lactones from cyclic ketones <B-2001MI147>.

One of the achievements in Baeyer–Villiger oxidation is aerobic catalytic rearrangement of cyclic ketones, for example, *tert*-butylcyclohexanone, in the presence of RuO_2 or MnO_2 (0.05 equiv) and benzaldehyde (3 equiv) at room temperature (Equation 32), giving the respective ε -caprolactones in yields up to 95%, the reaction being accelerated in the presence of lithium perchlorate <1994SL1037>.

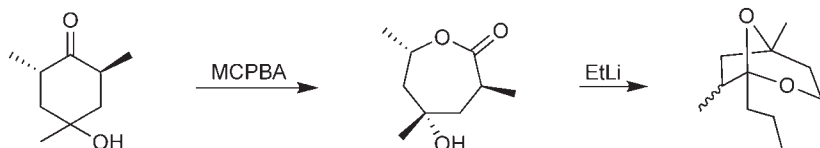


A mixed Ni(II) and Fe(II) form of Dowex 50W catalyzes the oxidation of cyclohexanone with molecular oxygen in the presence of benzaldehyde to ε -caprolactone <2000JCM196>. Chiral nickel and copper complexes are shown to oxidize 2-arylcyclohexanones ($\text{Ar} = \text{Ph}$, 4- ClC_6H_4 , 4- MeOC_6H_4) in rather high yield with ee up to 69%, pivalaldehyde being used as the oxygen acceptor <1994AGE1848>.

The regioselectivity of the Baeyer–Villiger oxidation is studied for a number of O-protected polyhydroxycyclohexanones; the migration ability of the substituted carbon atoms is shown to be in the following order of substituents: benzyloxy > methoxy > ketal oxygen >> acyloxy $\sim$ methyl <1994TL7249>. Magnesium monoprophthalate in MeCN is an effective reagent for Baeyer–Villiger oxidation of cyclic ketones <1996SC4591>. The Baeyer–Villiger oxidation of cyclohexanone to oxepan-2-one can be efficiently carried out using elemental fluorine in continuous-flow gas–liquid thin-film microreactors <2003JFC81>.

For oxidation of a number of cyclohexanones to the corresponding lactones, myristic acid and hydrogen peroxide catalyzed by *Candida antarctica* lipase <1995J(P1)89>, monooxygenase from *Pseudomonas putida* NCIMB 10007 <1995CC1563>, and designer yeast <1996J(P1)755, 1996JOC7652> are used. Cyclohexanones can be also transformed to ε -caprolactones under the action of recombinant baker's yeast <1998JA3541> and lipases <1998J(P1)2625>, the latter process being an autocatalytic Baeyer–Villiger oxidation with urea–hydrogen peroxide as the primary oxidant. Diaryl diselenides <2001JOC2429> and a tin zeolite <2001NAT423> are also used as catalysts in the oxidation of cyclohexanones with aqueous hydrogen peroxide. Cyclopentanone monooxygenase from *Comamonas* sp. NCIMB 9872 expressed in *Escherichia coli* was evaluated as a potential new bioreagent for Baeyer–Villiger oxidations of 4-alkoxy- and halo-substituted cyclohexanones. The results were compared with those obtained in oxidations catalyzed by an engineered *E. coli* strain expressing cyclohexanone monooxygenase(II) from *Acinetobacter* sp. The stereoselectivities of the two enzymes were shown to be opposite <2003JMO211>.

Regioselective oxidation with *m*-chloroperbenzoic acid (MCPBA; Scheme 32) is used in the synthesis of the male pheromone sordidin emitted by the banana weevil *Cosmopolites sordidus* <1995TL1043>.



Scheme 32

The Baeyer–Villiger oxidation is used in diastereoselective synthesis of GH fragment of ciguatoxin starting from 2-bromo-2-cyclohexenone <1997SL307>.

Ozonization of benzo[*e*]pyrene in dodecane/water emulsions (conditions modeling those in contaminated ground-water or industrial wastewater) is shown to yield an ozonide and an oxepinone <2001MI231>.

13.02.8.2 Synthesis from Heterocyclic Compounds

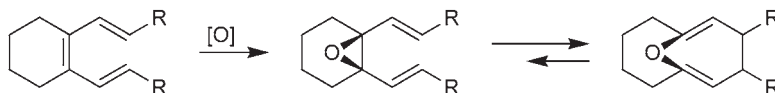
13.02.8.2.1 By formation of seven- from three-membered rings

The Cope rearrangement of *cis*-2,3-divinyloxirane (**Scheme 33**) formed on flash vacuum pyrolysis of 3-oxa-7-thiatricyclo[3.3.0^{2,4}]octane 7,7-dioxide gives 4,5-dihydrooxepine <1999J(P1)605>.



Scheme 33

1,2-Dialkenylcyclohexene epoxides undergo a thermal Cope rearrangement (60–80 °C, in dioxane/Et₃N or CCl₄/Et₃N) to give 2,7-butano-4,5-dihydrooxepines (1,6-epoxycyclodeca-1,5-dienes) in 40–90% yield (**Scheme 34**). These bicyclic compounds are twofold anti-Bredt bridgehead alkenes, one of which (R = Ph) was determined by X-ray diffraction <1999JOC3806>.



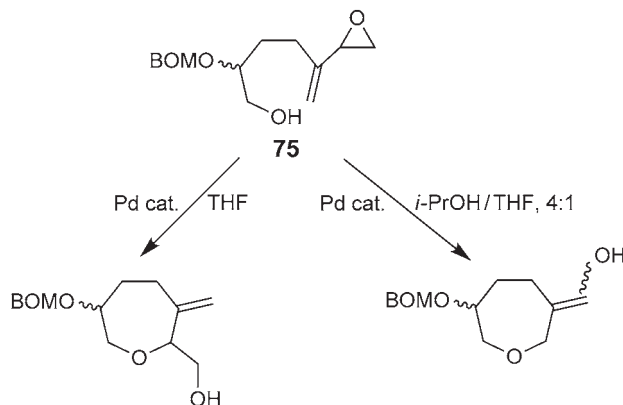
R = Ph, CO₂Me, CO₂Bu-*t*, CO₂Menthyl, 8-phenylmenthyloxycarbonyl

Scheme 34

Stereoselective preparation and Cope rearrangement of 2-CF₃-substituted *cis*-2,3-bis(alkenyl)oxiranes opens a facile approach to diverse 2-trifluoromethyl-4,5-dihydrooxepines. Subsequent reduction or oxidation of the latter provide 2-CF₃-substituted oxepanes or oxepines, respectively <2004CL438>.

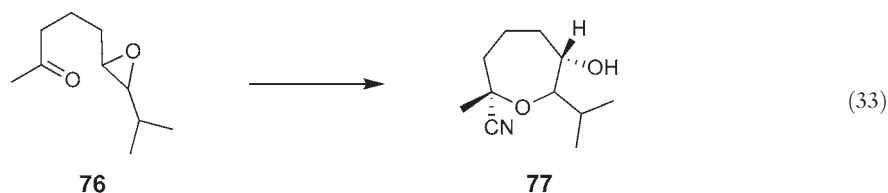
The oxidative ring opening of 3-oxabicyclo[4.1.0]hept-4-enes, formed by the intramolecular Pt(II)-catalyzed cyclopropanation of enol ethers by alkynes, gives oxepane derivatives. Alternatively, the acid-catalyzed opening of the cyclopropane ring leads to dihydrobenzofurans or 3,4-dihydro-2*H*-chromenes <2004OL3191>.

The route of the Pd-catalyzed cyclization of the substituted oxirane **75**, including the involvement of epoxide fragment in the cyclization step (**Scheme 35**), is highly dependent on the hydrogen-bonding properties of the solvent <1994AGE2182>.



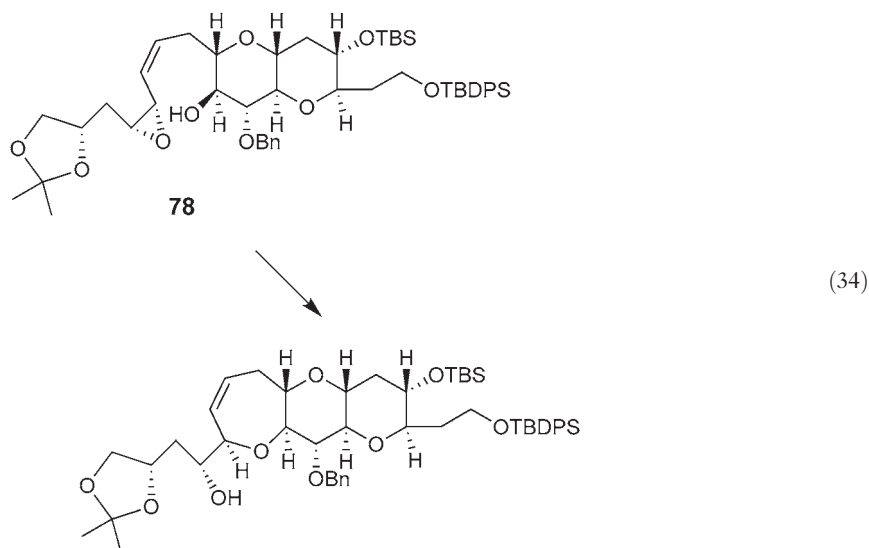
Scheme 35

The epoxide **76** undergoes cyclization with $\text{Et}_2\text{O} \cdot \text{BF}_3$ and TMSCN (Equation 33) to give regio- and stereoselectively oxepane **77** (TMS = trimethylsilyl) <1996TL339>.

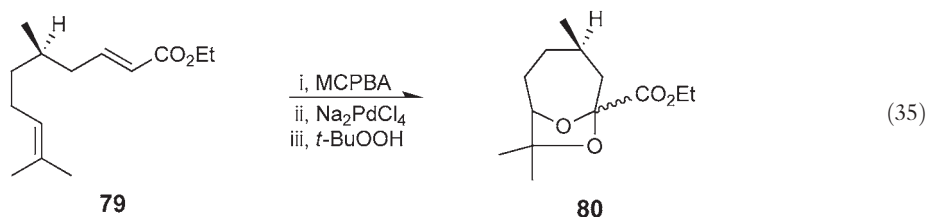


Boron trifluoride etherate promotes the *endo*-selective oxacyclization of polyepoxides derived from various acyclic terpenoid polyalkenes, including geraniol, farnesol, and geranylgeraniol, providing an efficient and stereoselective synthesis of substituted oxepanes and fused polyoxepanes. The oxacyclization transformations may mimic ring-forming steps in the biosynthesis of *trans-syn-trans*-fused polycyclic ether marine natural products <2002JOC2515>.

In the presence of $\text{Eu}(\text{fod})_3$, epoxide **78** transforms (Equation 34) to tricyclic intermediate related to BCD fragment of ciguatoxin <1998T21>.

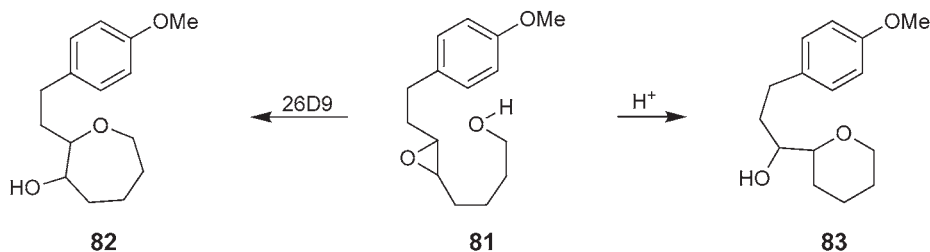


Selective epoxidation of the isolated double bond (Equation 35) in the ester **79**, prepared from citronellal and triphenyl(ethoxycarbonylmethylene)phosphorane, followed by treatment with Na_2PdCl_4 and *tert*-butyl hydroperoxide gives the bis-ether **80** <1994CC903>.

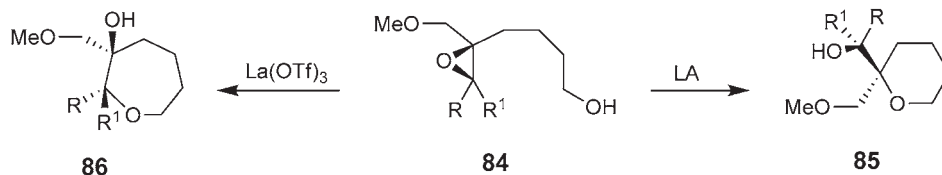


The epoxy alcohol **81** forms oxepane **82** in a 7-*endo*-tet cyclization performed in the presence of antibody 26D9 (Scheme 36), while the acid-catalyzed reaction gives isomeric pyran **83** <1995JA2659>.

Similarly, Lewis acid-catalyzed rearrangement of epoxy alcohols **84** (Scheme 37) gives in most cases the *exo*-cyclized tetrahydropyrans **85** as the main products (80–97%); however, with $\text{La}(\text{OTf})_3$ as the catalyst, the main products (80–90%) are *endo*-cyclized oxepanes **86** <1998TL393>.



Scheme 36



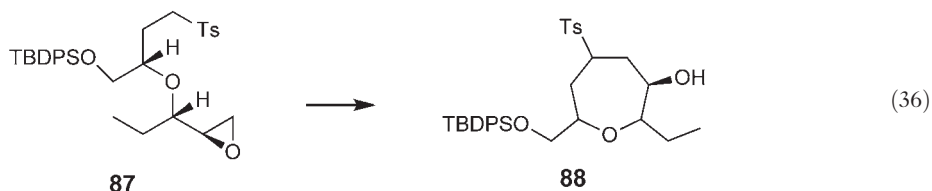
R = H; R¹ = Me

R = Me; R¹ = H

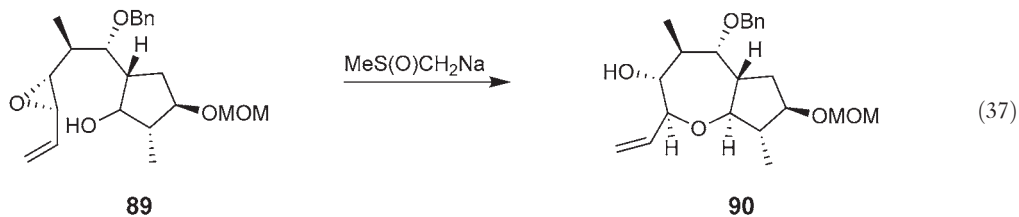
LA = BF₃•OEt₂, TiCl₄, Sn(OTf)₂, Zn(OTf)₂

Scheme 37

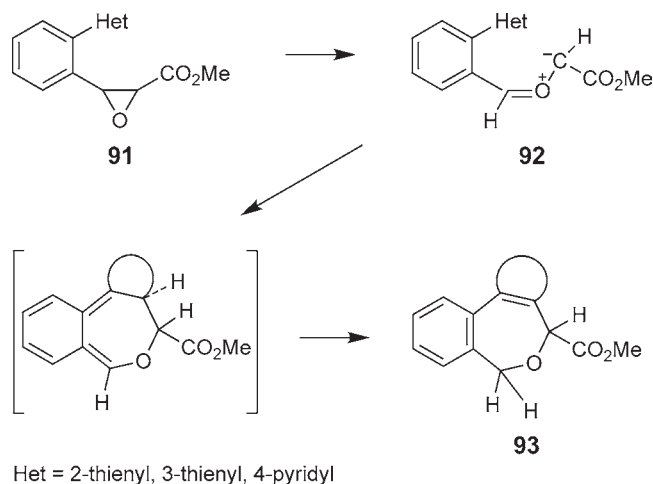
Recyclization of epoxide **87** with lithium diisopropylamide (LDA) in THF at -65°C (Equation 36) gives oxepan **88** <1998JOC9728>.



Nucleophilic ring opening of an epoxide **89** with sodium dimethylsulfate leads to the intramolecular cyclization giving **90** with an annulated oxepane ring (Equation 37), this transformation being a step of stereocontrolled synthesis of the JKLM ring fragment of ciguatoxin <1999JOC9399>.

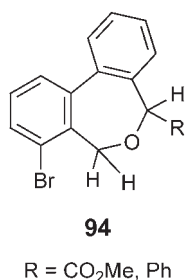


Flash vacuum pyrolysis (625°C , 8×10^{-4} mmHg) of systems like **91** gives diene-conjugated carbonyl ylides **92** with $\alpha,\beta,\gamma,\delta$ -diene system formed by a benzene ring and either a thiophene or pyridine ring (Scheme 38). These carbonyl ylides undergo 1,7-electrocyclization, followed by a [1,5]H shift, to form corresponding thieno- and pyridooxepines **93** in rather high yields <1996J(P1)515>.

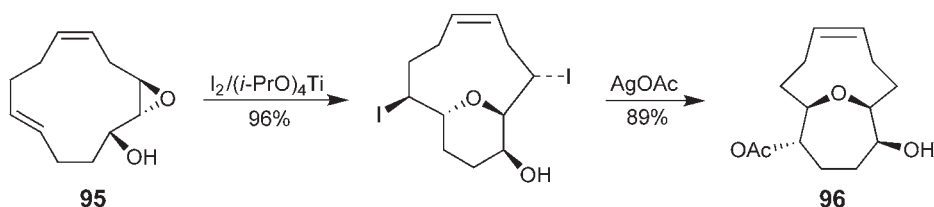


Scheme 38

The same methodology is applicable for the synthesis of dibenzooxepine derivatives **94** <1997J(P1)3025>.



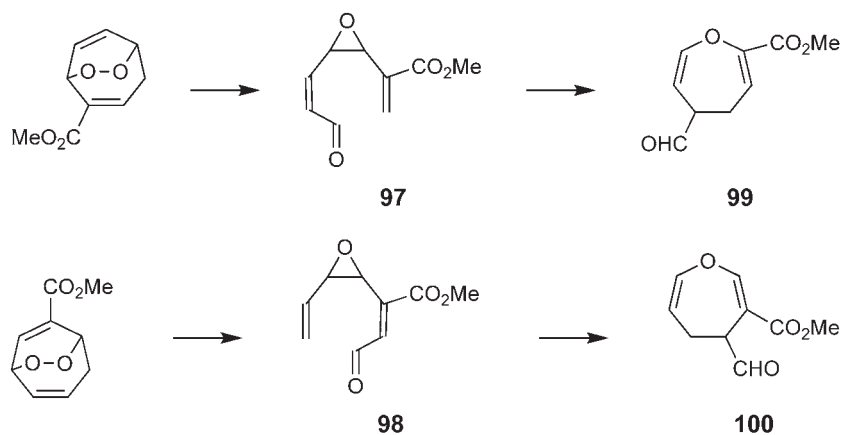
Iodine-promoted transannular epoxide ring expansion of *trans*-1,2-epoxycyclododeca-1,5,9-triene or, better, related 1,2-epoxycyclododeca-1,6,10-trien-3-ol **95** (Scheme 39) leads to specific bridged oxepane derivatives **96** <1997TL5853>.



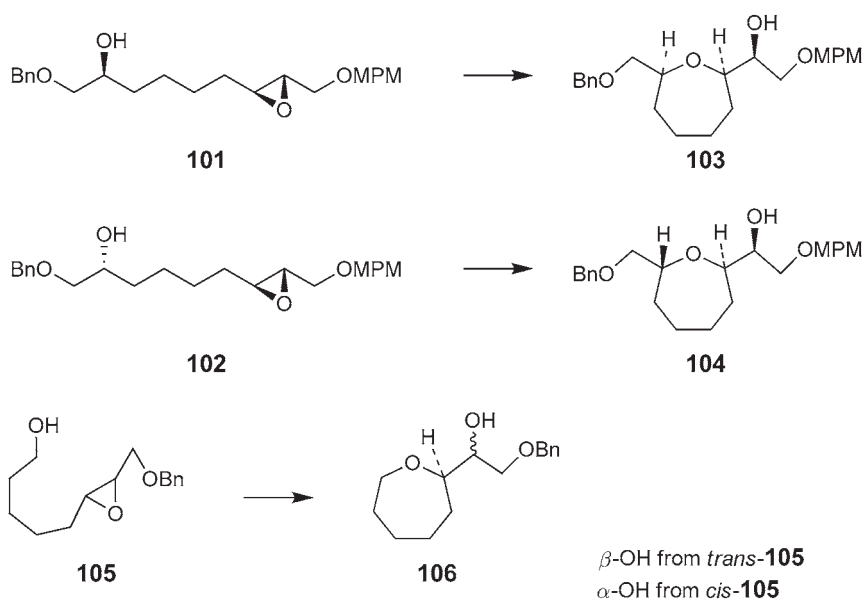
Scheme 39

Substituted cycloheptatriene endoperoxides when treated with Co(II) porphyrin (0 °C, CCl₄) undergo ring opening (Scheme 40) to give corresponding oxiranes **97** and **98** in moderate yields, which are quantitatively converted (45 °C, 1 h) into the substituted 4,5-dihydrooxepine derivatives **99** and **100** <1997J(P1)2071>.

Cyclization of 5-hydroxyalkyloxiranes **101** and **102** promoted by (Bu₃Sn)₂O/Zn(OTf)₂ (Scheme 41) proceeds stereospecifically as an S_N2 process to give the *cis*- or *trans*-2,7-disubstituted oxepanes **103** and **104** in 80–85% yields, respectively <2000TL7697>. 5-Hydroxypentyloxiranes **105** similarly give 2-monosubstituted oxepanes **106** (yields are 83–99%); besides Zn(OTf)₂, other Lewis acids can be used (Sn(OTf)₂, Yb(OTf)₃, La(OTf)₃, Eu(OTf)₃) <2000TL7701>.

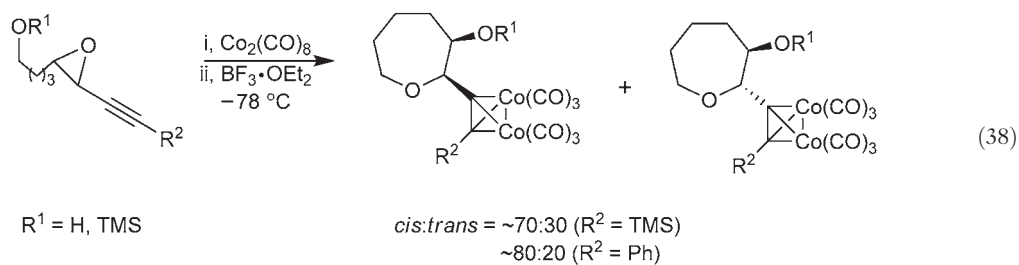


Scheme 40



Scheme 41

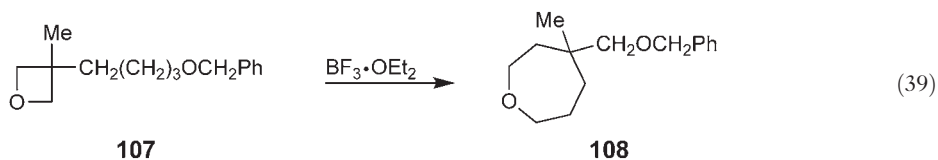
A stereoselective but not stereospecific procedure (Equation 38) for the Co₂(CO)₈-mediated preparation of 2-ethynyl-3-hydroxyoxepane derivatives from 5,6-epoxy-7-octyn-1-ols is described [\[2000JOC6761\]](#).



A similar stereoselective intramolecular reaction involving intramolecular nucleophilic attack of epoxides on *exo*-Co₂(CO)₆-propargylic cations using substrates with stereochemically defined oxirane fragments provides polysubstituted oxepanes with a high degree of stereocontrol. The cyclization is sensitive to the nature of the protecting group used at the primary hydroxyl, and use of *tert*-butyl carbonates highly improves regioselectivity and yields. As above, the hexacarbonyldicobalt complex of a protected epoxyalkynediol undergoes cyclization by treatment with BF₃·OEt₂ in CH₂Cl₂; the final oxidative removal of the Co complex with ceric ammonium nitrate treatment gives ethynyloxepanes in good yields <2004OL565>.

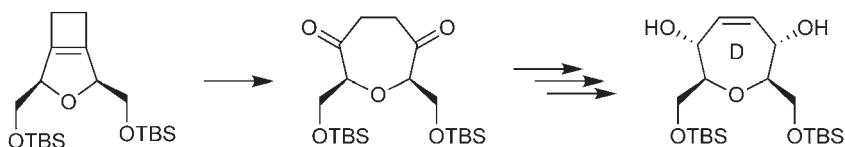
13.02.8.2.2 By formation of seven- from four-membered rings

Oxiranes and oxetanes with ether substituents in side chain undergo ring expansion in the presence of BF₃·OEt₂. Selecting the appropriate side chain, this ring expansion of oxetanes, for example, **107**, gives oxepane **108** (Equation 39) in medium yield <1994H(38)2165>.



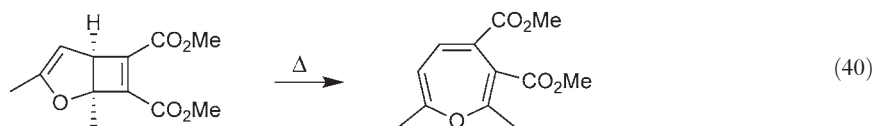
13.02.8.2.3 By formation of seven- from five-membered rings

The cyclobutafuran system is converted to oxepanedione using ozonolysis, followed by reduction with triphenylphosphine <1996SL1165, 1999T7471>. Further transformations allow one to prepare a building block with proper stereochemistry for constructing ring D in ciguatoxin (Scheme 42).



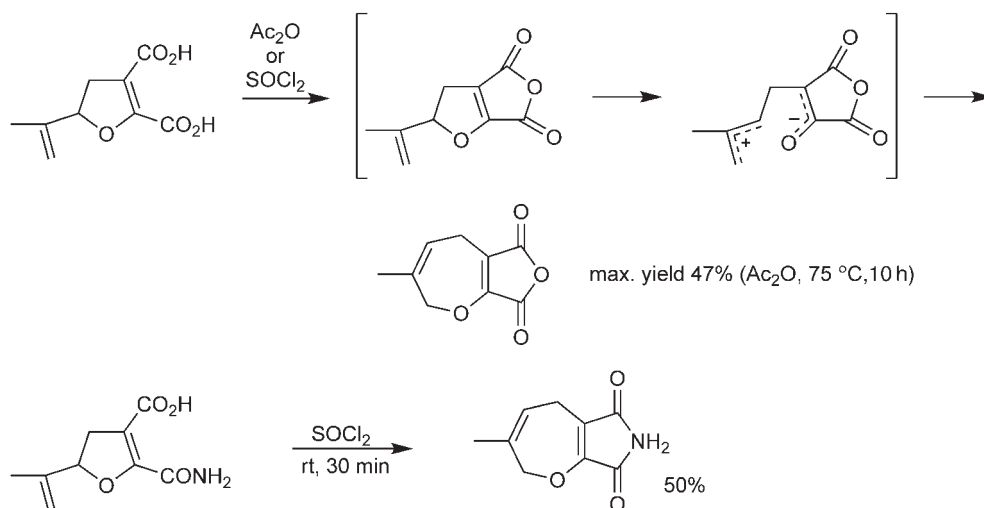
Scheme 42

Thermolysis of another cyclobutafuran derivative (Equation 40) leads to a substituted oxepine <2002JA7395>.

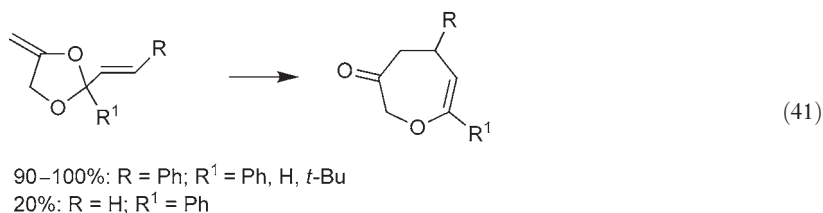


A rearrangement (Scheme 43), similar to that of isopropenyl-substituted cyclopropylcarbinols (see Section 13.02.8.1.1), gives the corresponding 4,7-dihydrooxepine-2,3-dicarboxylic acid derivatives from derivatives of 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylic acid <1997BCJ2777>.

2-Styryl- or 2-vinyl-substituted 4-methylene-1,3-dioxolanes rearrange (Equation 41) simply by heating (80–150 °C, preferably 120 °C, 3–48 h) to 4,5-dihydrooxepin-3(2*H*)-ones <1994TL3111>.

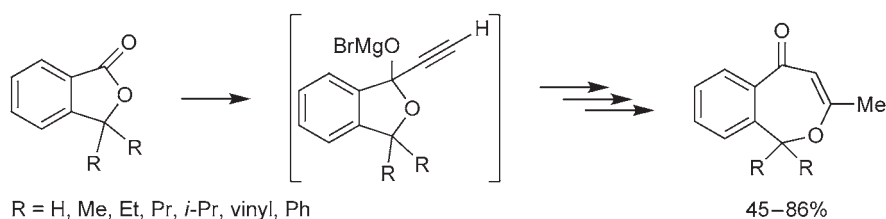


Scheme 43



Chiral pyranooxepine and oxepinooxepine systems are synthesized using 1,3-dipolar cycloaddition of 1,2-isopropylidene furanoside-fused oxepane derivatives and 4-*O*-allyl nitron or nitrile oxides species <2000TL10135>.

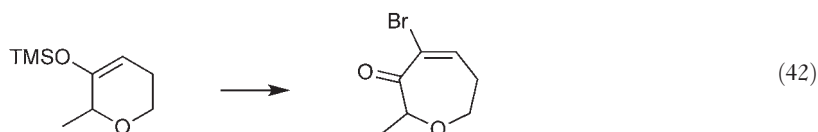
Benzoxepin-5-ones are formed (Scheme 44) by the insertion of a two-carbon fragment into phthalides by reaction with prop-2-ynylmagnesium bromide <1996CC19>.



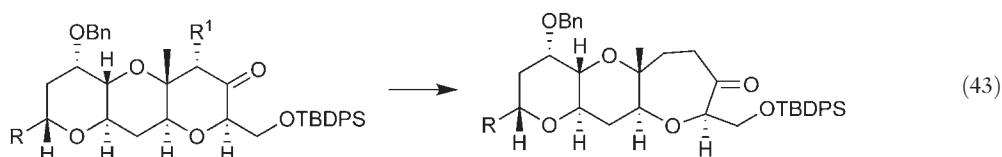
Scheme 44

13.02.8.2.4 By formation of seven- from six-membered rings

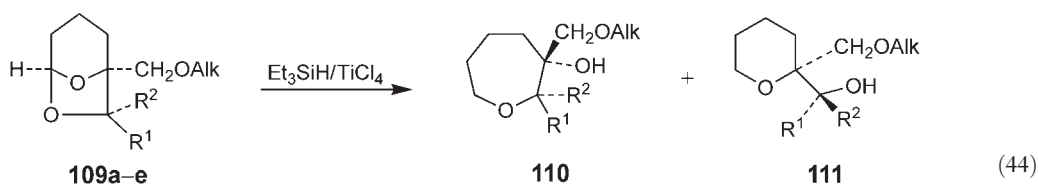
The reaction of 2-methyl-3-trimethylsilyloxy-2*H*-5,6-dihydropyran with dibromocarbene (Equation 42) to give 4-bromo-2-methyl-6,7-dihydrooxepin-3(2*H*)-one and catalytic reduction of the latter ($\text{H}_2\text{-Pd/C}$) to corresponding oxepanone should be mentioned. An analogous transformation is used to prepare an intermediate in the synthesis of zoapatanol <1994TL3085>.



A similar ring expansion with trimethylsilyldiazomethane in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (Equation 43) is used by Mori *et al.* in their syntheses of hemibrevetoxin B <1997JA4557> and brevetoxin B <1997T12917>.



Reductive cleavage of 1-alkoxymethyl-6,8-dioxabicyclo[3.2.1]octanes **109a–e** (Equation 44) can give different products **110** and **111** depending on the nature of hydride reagent and structure of the substrate. With diisobutylaluminum hydride (DIBAH) (rt, 8 days), practically only tetrahydropyran (>98%) is formed as the result of C(5)–O(6) bond scission, while TiCl_4 -catalyzed cleavage with triethylsilane (-78°C , 1 h) preferentially gives an oxepane resulting from a six-membered ring opening <2000T1065>.

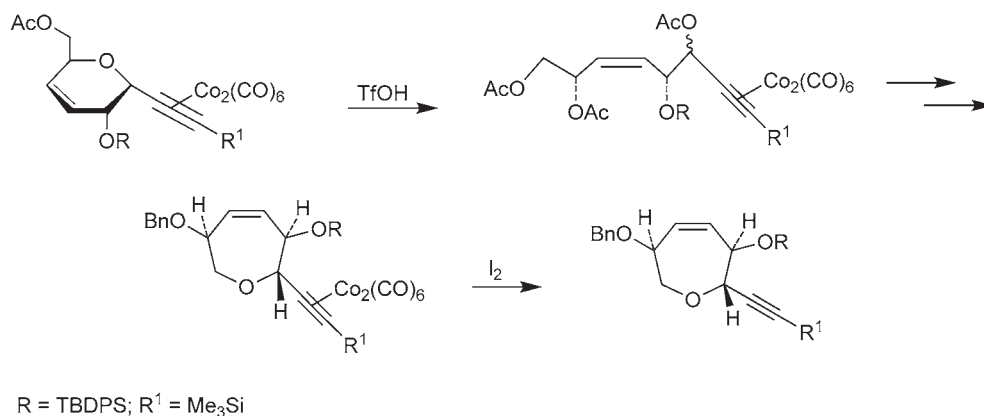


99/100 ratio:		a	b	c	d	e
		54:46	74:26	99:1	49:51	93:7

a–c: Alk = Me; **d,e:** Alk = Bu

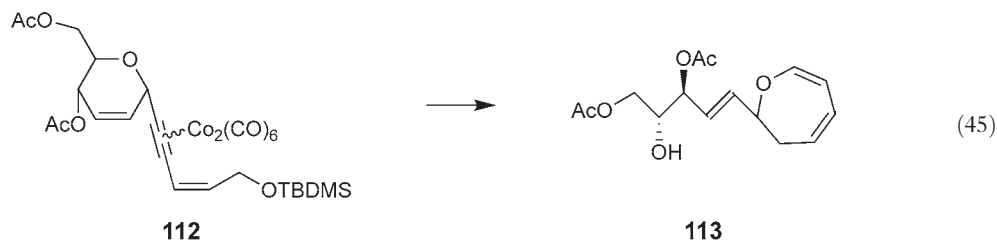
a: $\text{R}^1 = \text{R}^2 = \text{H}$; **b,d:** $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$; **c,e:** $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$

Cobalt complexes of α -alkynylpyranosides undergo TfOH-catalyzed ring cleavage (Scheme 45) to afford the ring-opened products, which cyclize to dehydrooxepanes <1994T12883>.

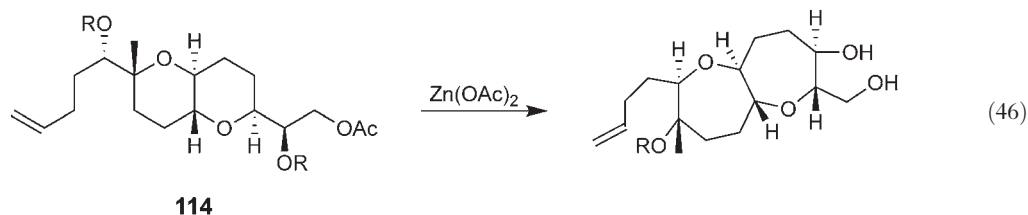


Scheme 45

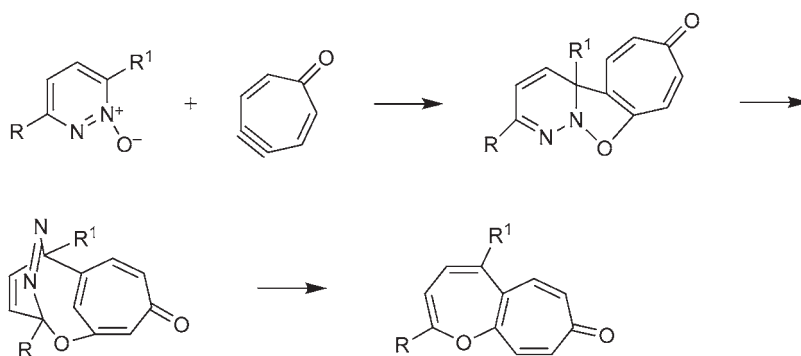
Cyclization of cobalt complex **112** followed by decomplexation with hydrogen over 5% Rh/C in EtOH (Equation 45) affords the dihydrooxepine **113** <1998T2509>.



Wagner–Meerwein-type rearrangement of functionalized tetrahydropyrans proceeds on their heating in aqueous AcOH in the presence of zinc acetate to give oxepane derivatives <1999TL2145, 2002H(56)113>. The same ring expansion is a key step of the total synthesis of 2,3,5,6-tetrahydrooxepine derivative, (+)-rogiooxepane A <2001TL1543>. A zinc-catalyzed ring expansion of the substituted fully hydrogenated pyranopyrans, for example, **114** (Equation 46), is successfully used in a total synthesis of hemibrevetoxin B <1996TL213, 1996TL217, 1996TL6365>.

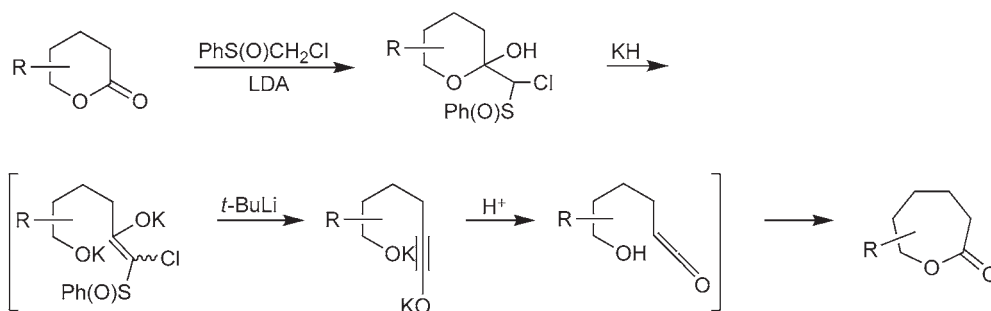


Pyridazine *N*-oxides undergo 1,3-cycloaddition reaction with 4,5-dehydrotropone followed by rearrangement and loss of N₂ molecule (Scheme 46) to give troponooxepines <1994H(38)957>.



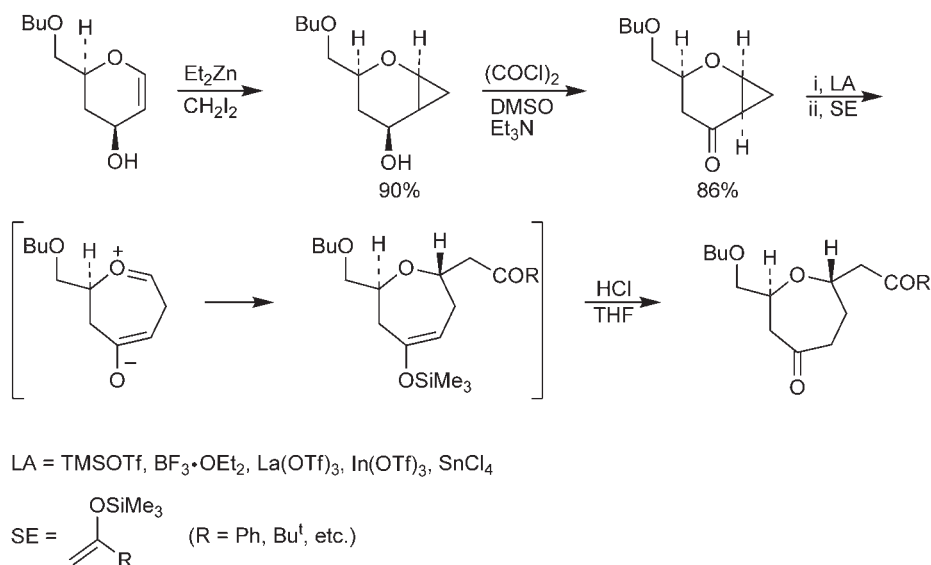
Scheme 46

The one-carbon ring enlargement proceeds in a two-step transformation consisting in LDA-promoted reaction of a lactone with chloromethyl phenyl sulfoxide, followed by one-pot generation and cyclization of an ω -hydroxyalkylketene intermediate (Scheme 47). Both monocyclic and annulated lactones undergo the ring enlargement. The yields are very high at first step but modest at second; for example, for 3,4-dihydrocoumarin and 6-heptyltetrahydropyran-2-one, the yields at the first step are 91% while those at the second step are 36% and 19%, respectively <1998TL9215>.



Scheme 47

A transformation of dihydropyranones to substituted oxepanes is described <2001H(55)855, 2001TL1095>. The key steps are ring-enlargement followed by the action of a silyl enolate (Scheme 48).

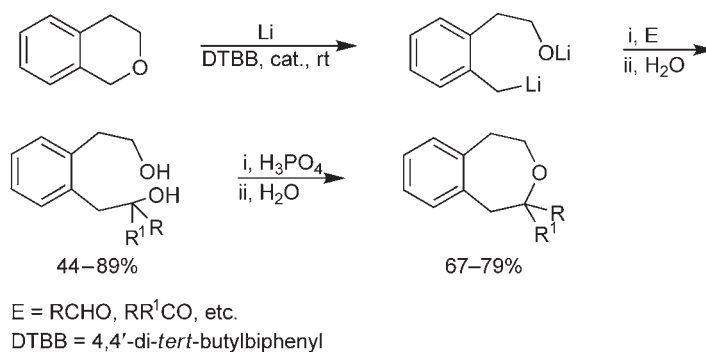


Scheme 48

An efficient approach for the diastereospecific synthesis (>98:2 of diastereoselectivity) of a model of the ABC ring system of hemibrevetoxin B is described [<2006OL4231>](#). One of the key features in the synthesis is a ring expansion to yield the oxepane ring C.

Intramolecular cycloaddition of *N*-benzyl-substituted 3-*O*-allylhexose nitrones furnishes chiral oxepane derivatives. The regioselectivity of the cycloaddition depends on several factors such as: (1) the structural nature of the nitron, (2) substitution and stereochemistry at 3-C of the carbohydrate backbone, and (3) substitution at the terminus of the *O*-allyl moiety. A mixture of an oxepane and a pyran is formed in the intramolecular oxime olefin cycloaddition of a 3-*O*-allyl carbohydrate-derived oxime [<2003T4623>](#). The highly stereoselective synthesis of oxepanes proceeds by intramolecular nitron cycloaddition reactions on sugar-derived methallyl ethers [<2003TA3899>](#).

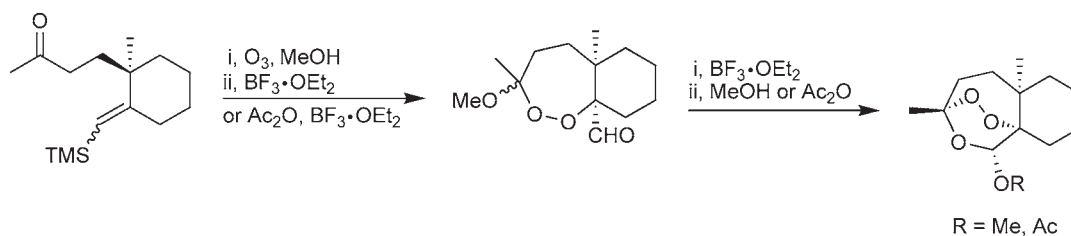
Pyran derivatives, mainly isochromans, undergo homologation to corresponding oxepane derivatives ([Scheme 49](#)) by a sequential reductive opening–lithiation–electrophilic substitution–cyclization [<1995T3365, 2004S1115, 2006AHC135>](#).



Scheme 49

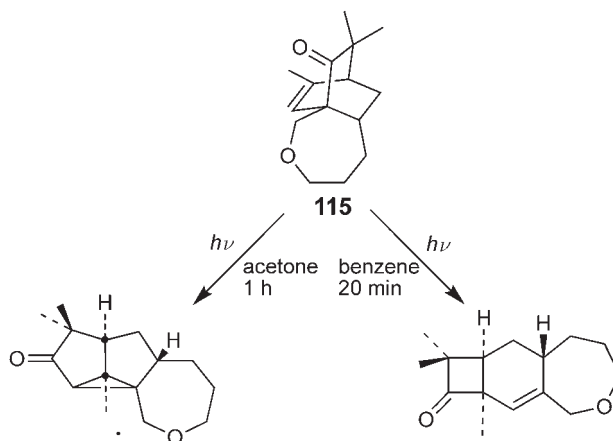
13.02.8.2.5 By formation of seven- from other seven-membered ring

A closure of an additional ring on dioxepine fragment in the synthesis of artemisinin tricyclic analogs ([Scheme 50](#)) can be regarded either as the formation of oxepine ring from other seven-membered ring or as cyclization of a heterocyclic precursor [<1998TL2969>](#).



Scheme 50

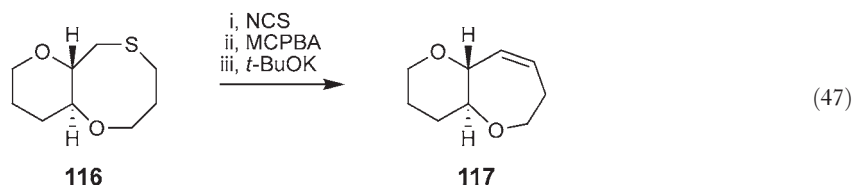
A stereoselective synthesis of compounds possessing an oxepane ring fused to a diquinane or a bicyclo[4.2.0]octane moieties using photochemical reactions of a common precursor **115** (Scheme 51) is developed; the latter compound is related to sterpurane, another class of bioactive sesquiterpenes <2003TL475>.



Scheme 51

13.02.8.2.6 By formation of seven- from eight-membered rings

An efficient strategy for the synthesis of *trans*-fused oxabicyclic systems involving this annulation followed by a Ramberg–Bäcklund olefination (Equation 47) as the key step is used for the ring contraction of **116** to give the oxepane **117** in 41% yield, in which the intermediates formed on α -chlorination and sulfone formation steps were used without purification <1996TL2865>.



13.02.9 Synthesis of Particular Classes of Compounds

Attempts to evaluate the synthetic potential of different preparative methods are made in Sections 13.02.7 and 13.02.8. In Tables 1–3, references are given to synthetic routes to several specific groups of oxepanes and oxepines. Most references are already cited in the previous sections. For completeness, see those from CHEC(1984) and CHEC-II(1996).

Table 1 Synthetic routes to monocyclic oxepanes and oxepines

Type of compound	References
Oxepane	1999T3479, 2001GC143
2-Acetyloxepane	1994CC1123
2-Alkyl-7-aryloxepanes	1995JA1173
2,7-Dialkylloxepanes	1996TL339, 1999TL2145, 2001TL1543, 2002H(56)113
2,7-Diaryloxepanes	2005SL152,
3-Bromo-2,7-dialkylloxepanes	2000SL1187
2-Iodomethylloxepanes	1995SL323, 1996JOC5793
Ring-substituted 3- and 4-methyleneoxepanes	1994AGE2182, 2002CC514, 2005TL3369
Vinyloxepanes	1999TL1747, 2003T537
Allyloxepanes	1998TL2759
Tetrahydrooxepines	1995TL6831, 1997JOC6615, 1997SL980, 1998J(P1)2363, 1998TL3025, 1999TL8751, 2004CAR1163, 2004JA8744, 2004OL2161, 2005JOC3312, 2006JOC3977
Dihydrooxepines	1993JOC1295, 1994CC67, 1997BCJ2215, 1997J(P1)2071, 1998T2509, 1999J(P1)605, 2000H(53)897, 2006JOC3977
Hydroxy-, alkoxy-, and acyloxioxepanes	1994T12883, 1995JA2659, 1996SL1165, 1998JOC9728, 1998TL393, 1999T7471, 2000JOC6761, 2000T1065, 2000TL7701, 2004OL565
Oxepanones and oxepanediones	1994AGE1848, 1994J(P1)501, 1994SL1037, 1994TL3085, 1994TL3111, 1995CC1563, 1995JA2933, 1995J(P1)89, 1995S947, 1995TL1043, 1996J(P1)755, 1996JOC2252, 1996JOC7652, 1996SC4591, 1996SL1165, 1997SL307, 1998JA3541, 1998J(P1)2625, 1998TL9215, 1999T7471, 2000JCM196, 2001H(55)855, 2001JOC2429, B-2001MI147, 2001TL1095, 2001TL5459, 2002CR571, 2002H(56)85, 2003JFC81, 2003JMO211, 2003T3769, 2003TL5511, 2004AGE1272, 2005OL515
4,4-Disubstituted oxepanes	1994H(38)2165
4,7-Dihydrooxepine-2,3-dicarboxylic acid derivatives	1997BCJ2777
Fluorinated and polyfluorinated oxepanes	2002CCC1486, 2004CL438
Polyfluoroalkylloxepanes	
Oxepincarboxylic acids and their esters	2002JA7395

Table 2 Synthetic routes to polycyclic oxepanes

Type of compound	References
Dihydrobenzoxepanes	1994JOC4730, 1997J(P1)3025, 1998JOC7698, 2001SL1784, 2004H(62)749, 2004OL3005
Tetrahydrobenzoxepines	1995T3365, 1996TL6565, 2004S1115, 2006AHC135
Octahydrobioxepine	1999JOC3354
Hexahydrofuro[3,2- <i>b</i>]oxepin-2(3 <i>H</i>)-ones	1999TL8307, 2003TL4467, 2004TL5207, 2005S411
1,3-Dioxolanooxepanes	1996TL2869, 1998AGE965, 1998JOC6597, 1998TL6369, 1998TL6373
1,3,2-Dioxasilolanooxepanes	1997JOC6615, 2003TL9043
Tetrahydro- and hexahydropyranooxepines	1995JA1173, 1995SL1179, 1996SL351, 1997TL123, 1999JOC37, 1999TL1911, 1998TL9601, 1998TL2783
<i>trans</i> -Fused oxepinooxepines, dipyranooxepines, pyranopyranooxepines, and dipyranooxepanooxepines	1995TL5777, 1996TL213, 1996TL217, 1996TL2865, 1996TL6365, 1997JA4557, 1997SL980, 1997T3057, 1997T12917, 1998T21, 2002T1853, 2006OL4231
Spirooxepanes	1995JA2657, 1996TL6565
Annulated hydroxy-, alkoxy-, and acyloxioxepanes	1999JOC9399
Annulated oxepanones	1995JA2933, 1996JA4264
Various annulated oxepanes	1994BCJ1769, 1995TL3027, 1997J(P1)3025, 2000ANY317, 2002H(57)1997, 2002SL1987, 2002TL7781, 2003IZV725, 2003SL2089, 2003TL475, 2006T8830, 2006TL6235
Bridged oxepanes	1994CC903, 1994JPP199492967, 1997TL5853, 1999JOC3806, 2003M1137
Artemisinin analogs	1998TL2969

Table 3 Synthetic routes to polycyclic oxepines

Type of compound	References
Benzoxepines and dibenzoxepines	1994JOC4730, 2002J(P1)2673, 2004H(62)749
Benzoxepin-5-ones	1996CC19
Tropanooxepines	1994H(38)957
Various annulated oxepines	1993JA11418, 1994BML1327, 1996J(P1)515, 1997WO9705270, 2003IZV725

13.02.10 Important Compounds and Applications

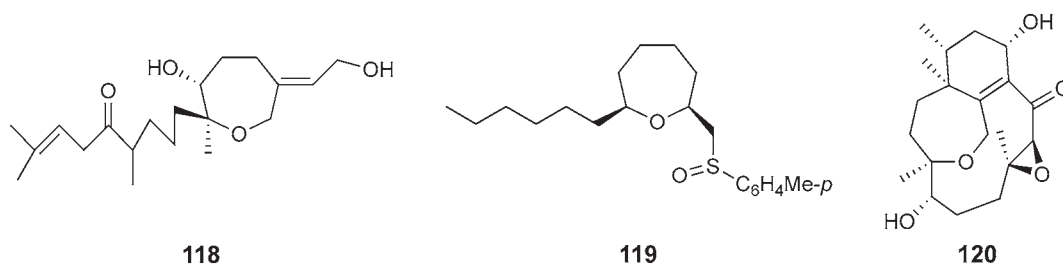
13.02.10.1 Applications and Important Compounds of Oxepanes and Hydrooxepines

The most practically useful compound from oxepanes is ϵ -caprolactone, which is used as an important industrial monomer. Other oxepanes are considered following their structures from rather simple monocyclic to polyheterocyclic systems, the chemistry of the latter being now well developed in connection with investigation of complicated polycyclic natural products of marine origin. Below, only those data are cited that are absent in CHEC-II(1996).

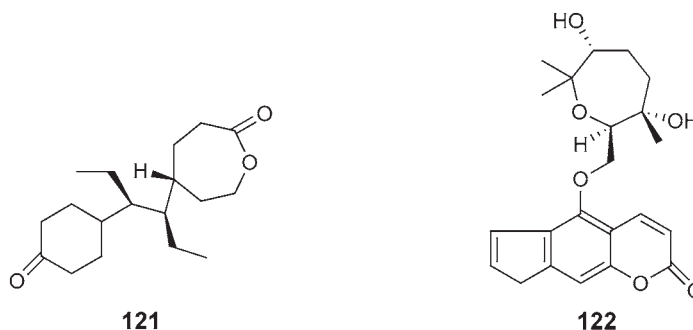
Oxidation of cyclohexane-1,4-dione with MCPBA in dichloromethane (DCM) affords oxepane-2,5-dione, which the authors claim as a precursor of a novel class of versatile semicrystalline biodegradable (co)polyesters <2002MM7857, 2003MM2609>.

The hydrolytic and thermal stability of random copolyesters of ϵ -caprolactone and ca. 30 mol% oxepane-2,5-dione are investigated. Compared with poly(ϵ -caprolactone) of a comparable molecular weight, the hydrolytic degradation of the copolyester is faster in a phosphate buffer (pH = 7.4) at 37 °C as confirmed by the time dependence of water absorption, weight loss, melting temperature, and molecular weight. This difference is a result of the higher hydrophilicity imparted to the copolyester by the ketone moiety of the oxepandione units <2003MAC1191>.

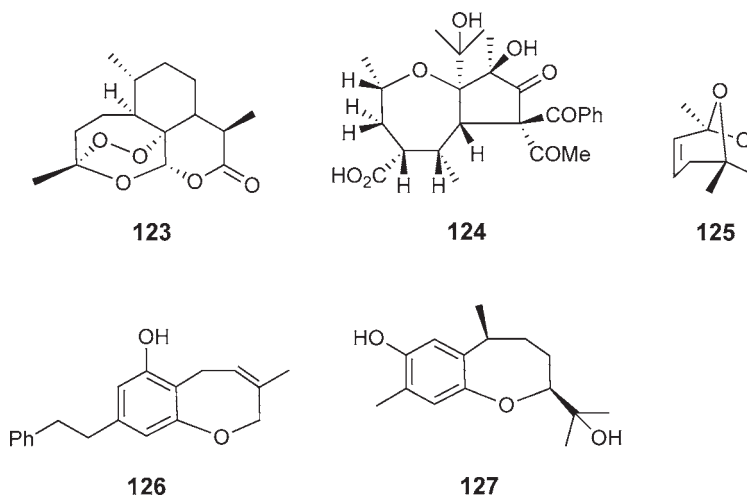
Total syntheses of utero-evacuating oxepanes, zoapatanol **118** and its analogue, are described <2001TL5749, 2004OL2149>. A rather simple five-step asymmetric synthesis of 2,7-disubstituted oxepanes bearing a sulfoxide moiety and closely related to isolaurepan **119** is accomplished <2004OL297>. Phomactin H **120**, a novel diterpene, was isolated from an unidentified marine-derived fungus, and its structure and relative stereochemistry were determined by X-ray diffraction analysis <2004TL6947>.



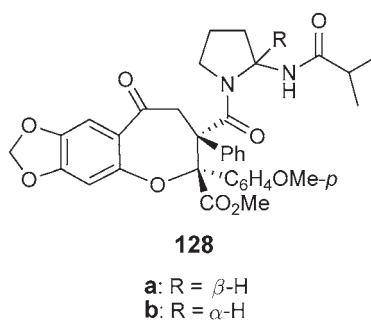
(*R*)-5-[(1*R*,2*R*)-1-Ethyl-2-(4-oxocyclohexyl)butyl]oxepan-2-one **121**, an enantiopure pseudosteroid, that is, perhydrostilbene derivative which mimics steroidal androgens (like hexestrols or stilbestrols serve to substitute natural estrogens), was prepared and fully characterized <2006ZNB111>. Feroniellin C **122**, new cytotoxic furanocoumarin containing oxepane moiety, was isolated from the roots of *Feroniella lucida* <2006TL3685>.



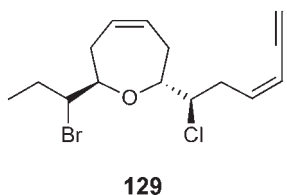
Several groups of other natural products possessing oxepane and hydrogenated oxepine rings are extensively investigated, the most interesting compounds being antimalarial artemisinin **123** and its synthetic analogues <1998JME940, 1998TL2273, 1998TL2969, 1999H(51)1681, 1999J(P1)1827, 1999TL9133, 2000BBR359, 2000BMC1111, 2000BML1601, 2000HCA1239, 2000JME1635, 2000JME4228>. Among other natural products, highly substituted fused oxepane hypertricone **124** isolated from leaves of *Hypericum geminiflorum* <2001HCA1976> and pheromone frontalinalin **125** <1999TL1425>, radulanin A **126** <1998JOC2808>, allelopathic agent from sunflowers heliannuol D **116** as well as its enantiomer and racemate <2000J(P1)1807, 2002CCC634, 2003H(61)125, 2003T1679> can be mentioned. In addition to (+)-, (-)-, and ($\pm$)-heliannuol E, growth-inhibitory activities of four tetrahydrobenzo[*b*]oxepines were examined against oat and cress. All heliannuol E isomers exhibited similar activities against cress, whereas when tested against oat roots, the unnatural optical (+)-isomer showed no inhibitory activity. Two tetrahydrobenzo[*b*]oxepin derivatives also showed apparent inhibition against both cress and oat <2004P1405>.



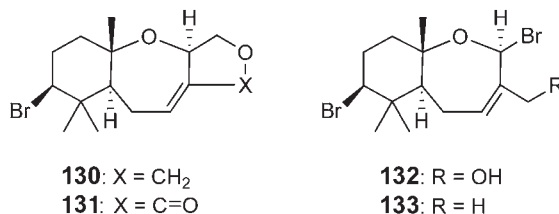
Potential hypotensive agents, substituted oximino-ethers of tetrahydronaphth[1,2-*b*]- and tetrahydronaphth[2,1-*b*]-oxypinones, were synthesized <2004BML3177>. Edulisonones A **128a** and B **128b**, two epimeric benzo[*b*]oxepine derivatives, were isolated from the bark of *Aglaia edulis*, collected in Indonesia. The relative stereochemistry of edulisonone **128a** was determined by X-ray diffraction analysis. Treatment of both edulisonones with lithium hydroxide produced the same hydrolysis products, resulting from the cleavage of the pyrrolidine ring to an alkylated amide mixture, which pointed to the fact that **128a** and **128b** are epimeric at their 2-aminopyrrolidine moiety <2005TL9021>.



The total syntheses of rogioloxepane A **129** closely related to isolaurepinnacin were accomplished <2001TL1543, 2003OL3009>.

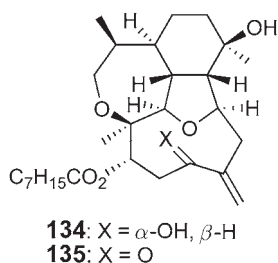


A novel stereocontrolled approach to *syn*- and *anti*-oxepene-cyclogeranyl *trans*-fused polycyclic systems based on stereoselective coupling of a cyclogeranyl tertiary alcohol with a unsymmetrically substituted epoxide and the formation of the highly strained oxepene by the RCM as two key steps make it possible to accomplish asymmetric total synthesis of a series of closely related natural compounds: (–)-aplysistatin **130**, (+)-palisadin A **131**, (+)-palisadin B **132**, (+)-12-hydroxypalisadin B **133**, and the AB ring system of adociasulfate-2 and toxicol A <2004CEJ3822>.



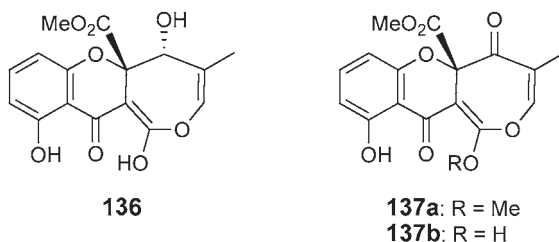
2-Substituted derivatives of 11-aminoalkylidene-6,11-dihydrodibenz[*b,e*]oxepine were prepared and shown to have antiallergic activity <2005WO2005288283>. Klaivanolide (5-acetoxy-7-benzoyloxymethyl-7*H*-oxepin-2-one), a novel antiprotozoal bisunsaturated lactone, was isolated from *Uvaria klaineana* <2002P885>.

Tetracyclic diterpenes briarellins were isolated from Caribbean gorgonian octocorals belonging to the genus *Briarreum* <1995T6869>. The total syntheses of briarellins E **134** and F **135** <2003JA6650>, starting with (*S*)-(+)-carvone and (*S*)-(–)-glycidol, established their absolute configurations and defined a strategy for the total synthesis of briarellin diterpenes, which successfully uses, in particular, pinacol-terminated cationic cyclizations for stereocontrolled synthesis of complex oxacyclic natural products.

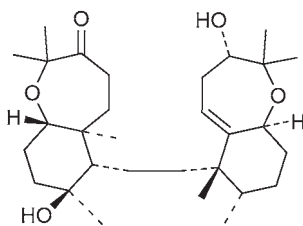


Samaderin B, (1*R*,2*S*,5*R*,5*aR*,7*aS*,11*S*,11*aS*,11*bR*,14*S*)-1,7,7*a*,11,11*a*,11*b*-hexahydro-1,11-dihydroxy-8,11*a*,14-trimethyl-2*H*-5*a*,2,5-(methanoxymetheno)naphth[1,2-*d*]oxepine-4,6,10(5*H*)-trione, and samaderin C, (1*R*,2*S*,5*R*,5*aR*,7*aS*,10*S*,11*S*,11*aS*,11*bR*,14*S*)-7,7*a*,10,11,11*a*,11*b*-hexahydro-1,10,11-trihydroxy-8,11*a*,14-trimethyl-2*H*-5*a*,2,5-(methanoxymetheno)naphth[1,2-*d*]oxepine-4,6(1*H*,5*H*)-dione, were isolated from the seed kernels of *Samadera indica* and exhibit antifeedant activity against *Spodoptera litura* third-instar larvae <2003AXC416>.

Chemical study of a marine-derived *Penicillium brocae*, obtained from a tissue sample of a Fijian *Zyzzya* sp. sponge, resulted in the isolation and characterization of three novel cytotoxic polyketides, brocaenols A–C **136**, **137a**, and **137b**, possessing an unusual enolized oxepine lactone ring system <2003JOC2014>.

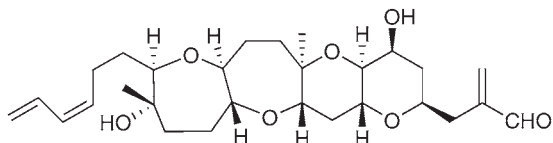


By the bioassay-guided fractionation of the crude extract of the marine sponge *Axinella weltneri*, a new triterpene sodwanone S **138** with an uncommon cyclohexanooxepane system was isolated <2005JNP1284>.

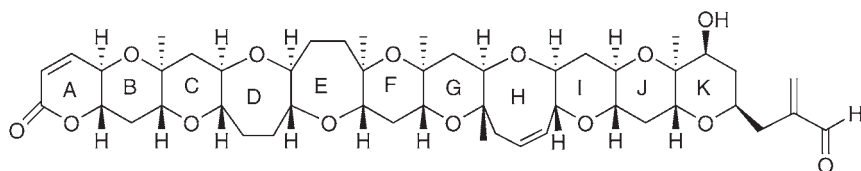


138

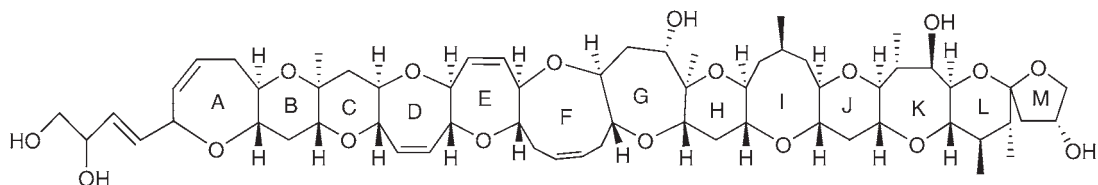
A vast amount of work was devoted to structure elucidation and synthesis of polyether toxins from marine organisms, particularly, of brevetoxins <1995JA1173, 1995TL5777, 1996JA1565, 1996TL213, 1996TL217, 1996TL6365, 1997JA4557, 1997T12917, 1997TL123, 1997TL127, 1998JOC6200, 1998JOC6597, 1998T735, 1999CEJ599, 1999CEJ618, 1999CEJ628, 1999CEJ646, 2002T1853>, for example, hemibrevetoxin B **139** and brevetoxin B **140**, ciguatoxin **141** and its analogues <1995SL1179, 1996SL351, 1997SL307, 1997T3057, 1998TL1197, 1999CC2035, 2000SL587, 2001TL6219, 2002JOC3301>, yessotoxin <1987TL5869, 2003TL7315>, adriatoxin <1998TL8897>, maitotoxin <1994JA7098>, and gambieric acids and related compounds <1992JA1102, 1993JA361, 1998TL6365, 1998TL6369, 1998TL6373, 2006CEJ1736, 2006CEJ1747, 2006MI257>, particularly of gambierol **142**, all of which have oxepane ring as part of their fused polycyclic skeleton. Very important data concerning total synthesis of marine polycyclic ethers are summarized by Yasumoto and Murata <1993CRV1897>, Nicolaou <1996AGE589>, Kadota and Yamamoto <2005ACR423>, and Nakata <2005CRV4314>.



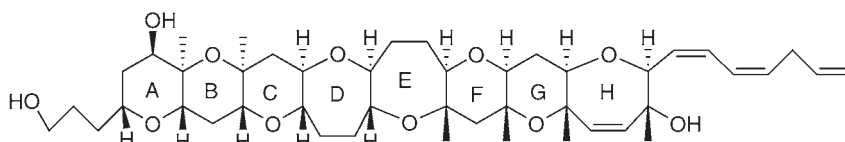
139



140



141



142

Stereoselective synthesis of (2*S*,7*S*)-7-(4-phenoxyethyl)-2-(1-*N*-hydroxyureidyl-3-butyn-4-yl)oxepane, as a potential antiasthmatic drug candidate, is described <2005TA935>.

ϵ -Caproic anhydride (2,7-oxepandione) is suggested as starting compound in the synthesis of perindopril and its pharmaceutically acceptable salts <2003EPP1321471, 2003EPP1323729>.

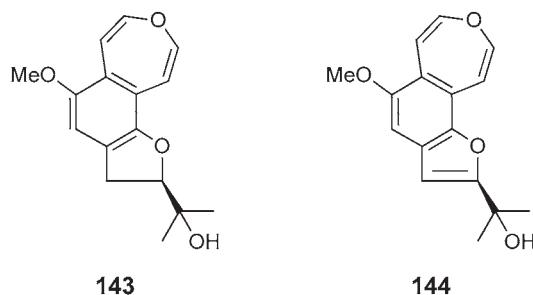
ϵ -Caprolactone is claimed as a component in one-paste-type resin compositions for denture bases <2002JPP2002104912> and ϵ -caprolactone copolymers are suggested as components in polyurethane-based multi-layered artificial leather sheets <2004JPP2004250808, 2004JPP2004250809>.

Oxepan derivatives <2006MI34>, particularly 7-alkenyloxepan-2-ones <2003JPP2003096022>, are known as components of fragrance compositions and cosmetics.

13.02.10.2 Applications and Important Compounds of Oxepines

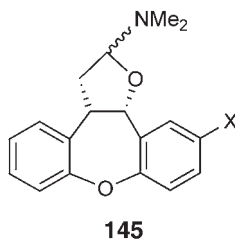
Natural and monocyclic annulated oxepines are not as numerous as their hydrogenated derivatives; however, as mentioned in CHEC(1984) <1984CHEC(7)547> and CHEC-II(1996) <1996CHEC-II(9)45>, they play an important role in biosynthesis and metabolism of monocyclic and polycyclic aromatic compounds. Some new data concerning natural oxepines are presented.

Benzoxepine derivatives, perilloxin **143** and dehydroperilloxin **144**, were isolated from the plant *Perilla frutescens* var. *acuta* <2000JNP403>. Suitably designed mono- and bis-benzo[*b*]oxepines were described as nonsteroidal estrogens <2003BMC5025>.

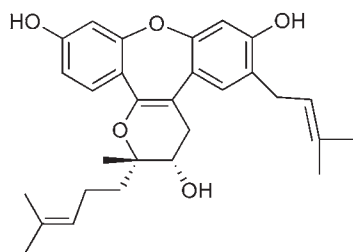


Dibenzoxepine derivatives found a broad application as new prospective drugs. Particularly, a review on the synthesis and applications of naturally occurring dibenzo[*b,f*]oxepines should be seen <2004OPP297>. Some dibenzo[*b,f*]oxepines were claimed as remedies for hyperuricemia and/or gout <2005WO2005079785>; dibenzo[*b,f*]oxepine derivatives and related compounds modulate the activity of L-isopartyl (D-aspartyl) O-methyltransferase and/or glyceraldehyde-3-phosphate dehydrogenase, which enables the prevention treatment or alleviation of type I and/or type II diabetes, autoimmune response and/or diseases, and neurodegenerative diseases <2004WO2004039773>.

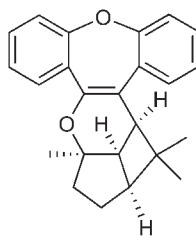
2-*N,N*-Dimethylaminomethyl-2,3,3*a*,12*b*-tetrahydrodibenzo[*b,f*]furo[2,3-*d*]oxepine derivatives, for example, **145** (X = F, Cl, Br, OMe, etc.), are described as potent anxiolytic agents <2004CPB262, 2005BML2898, 2005FA241>, dibenzo[*b,f*]thieno[2,3-*d*]oxepine derivatives are claimed as inhibitors of tumor necrosis factor- α and interleukin-1 production for the treatment of inflammatory diseases <2004WO2004078763>. 8-Oxa-1,2-diazadibenzo[*e,h*]azulene derivatives (dibenzo[*b,f*]pyrazolo[3,4-*d*]oxepines) were synthesized as inhibitors of tumor necrosis factor- α and interleukin-1 production <2003WO2003099822>.



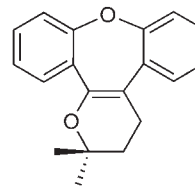
A novel phenolic compound containing dibenzoxepine fragment, artocarpol **146**, was isolated from the root bark of *Artocarpus rigida*. It possesses anti-inflammatory action because of inhibition of the formyl-Met-Leu-Phe/cytochalasin B-stimulated superoxide anion formation in neutrophils <2003HCA2566>. The first synthesis of the polycyclic ring systems of artocarpol A and D was accomplished, and analogues of these compounds, **147** and **148**, respectively, were prepared <2003OL4911>.



146



147

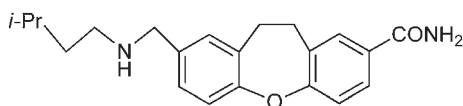


148

Bauhinoxepins A and B, new antimycobacterial dibenzo[*b,f*]oxepines, were isolated from the roots of *Bauhinia saccocalyx* <2004HCA175>.

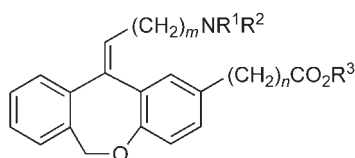
Dibenzoxepines were claimed as medications for the treatment of neurodegenerative disorders, cerebral ischemia, glaucoma, etc. <2005WO2005044255>. In particular, 10-aminoalkyldibenz[*b,f*]oxepines were described as means for the treatment of degenerative ocular disorders, for example, age-related macular degeneration <2004WO2004066993>. Dibenzo[*b,f*]oxepin-10-ylmethyl-prop-2-ynylamine is a novel potential agent in the treatment of chronic neurodegenerative illnesses <2004MIRCM377>.

A preparation of dibenz[*b,f*]oxepinecarboxamide derivatives, useful for the treatment of neurological and vascular disorders related to β -amyloid generation and aggregation, was claimed <2005WO2005014517>. Closely related aminoalkyl-substituted dibenzo[*b,f*]oxepine derivatives, for example, **149**, are opioid receptor antagonists <2005WO2005090337>.



149

Dibenzo[*b,e*]oxepine derivatives of the type **150** (R^1 , R^2 , and R^3 are H or lower alkyl, m and n are same or different and each is an integer in the range 1–4) were claimed as active ingredients for preventing and/or treating chronic sinusitis <2005WO2005102313> and sleep disorder <2006WO2006009093>. Some dibenzo[*b,e*]oxepine derivatives exhibit antidepressant activity <2001FAR11>.

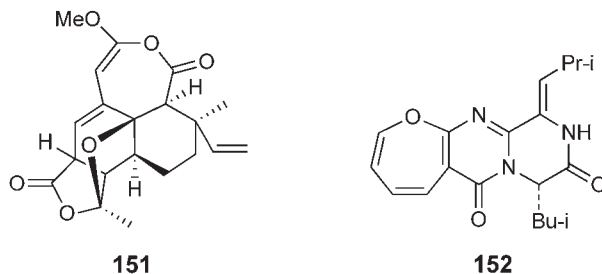


150

The 11-[(*Z*)-3-(dimethylamino)propylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-acetic acid monohydrochloride (olopatadine hydrochloride) is new antiallergic drug acting as a histamine H_1 -receptor antagonist <2002JJP379>. Dihydrodibenz[*b,e*]oxepine-based selective estrogen receptor modulators for treatment of estrogen-related diseases <2004WO2004009603> as well as closely related annelated oxepines possessing benzene and benzothiophene or naphthalene fragments as estrogen receptor ligands <2004WO2004009578> were claimed. Preparation of 6,11-dihydrodibenz[*b,e*]oxepine derivatives as steroid hormone nuclear receptor modulators useful for the treatment of congestive heart disease, hypertension, rheumatoid arthritis, or inflammation was also performed <2005WO2005066161>.

Novel C-19 compounds from *Thapsia transtaganana*, named transtaganolides A–D, were isolated and identified by physical methods, including X-ray analysis of transtaganolides A **151** and B. Structures of these compounds are

unusual, since a 7-methoxy-4,5-dihydro-3*H*-oxepin-2-one fragment is recently found in a natural product for the first time <2005OL881>. Janoxepin **152**, an antiparasitodal metabolite with unusual oxepin-based structure, was isolated from the fungus *Aspergillus janus* <2005T8718>.



Dibenz[*c,e*]oxepine derivatives, particularly 3,9-dibromo-5,7-dihydrodibenz[*c,e*]oxepine, are claimed as key components for semiconductive twisted polymers and copolymers <2002WO2002026856>.

Numerous publications including reviews <B-2003MI(60)1, 2003T8649> are devoted to biological properties and synthesis of pentacyclic anticancer alkaloid camptothecin, 1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline derivative, and its analogues <1997WO9700876, 1998JME5410, 1999WO9911646, 2000ANY317, 2000WO0061146, 2006BMC6202>.

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Biographical Sketch



Leonid Belen'kii was born in Moscow, and he graduated from M. V. Lomonosov Moscow State University in 1953 with Professor A. P. Terentiev as supervisor in organic chemistry. Since 1955, he has worked as junior, senior (since 1966), and leading scientist (since 1988) at N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, where he obtained his Ph.D. degree (1963) under the direction of Professor Ya. L. Gol'dfarb and his Degree of Dr. Chem. Sci. (1974) and rank of Professor in Chemistry (1991). His scientific interests include all aspects of chemistry of heterocyclic and aromatic compounds, particularly electrophilic substitution in benzene, thiophene, furan, and azole series as well as organosulfur chemistry.

13.03

Thiepanes and Thiepines

S. Yamazaki

Nara University of Education, Nara, Japan

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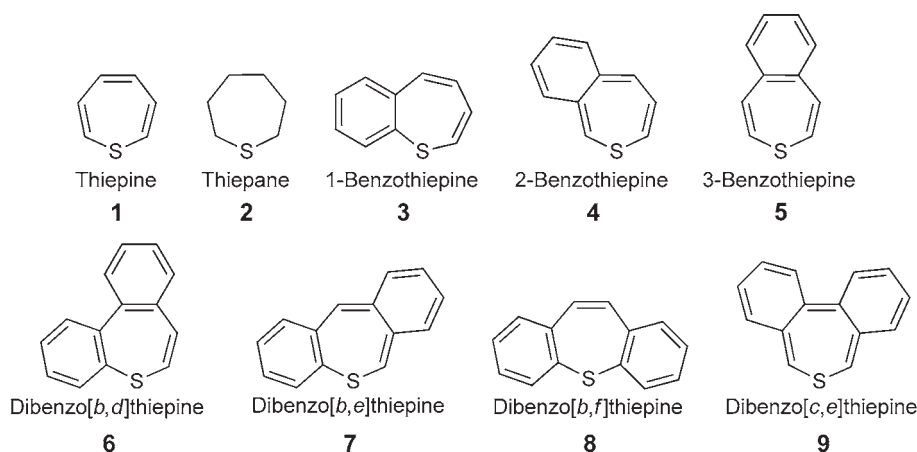
13.03.1 Introduction

Thiepines have been studied extensively due to theoretical and biological interest. The theoretical interest arises from whether thiepines with 8π electrons are nonaromatic or antiaromatic. The subsequent interest is in thiepine–benzene sulfide valence isomerization. Because thiepines are generally thermally unstable and eliminate sulfur, the

This subject was covered previously in CHEC(1984) <1984CHEC(7)547> and in CHEC-II(1996) <1996CHECII(9)67>. The present chapter is intended to update the previous work concentrating on major new preparations, reactions, and concepts, as well as covering the literature published since 1995.

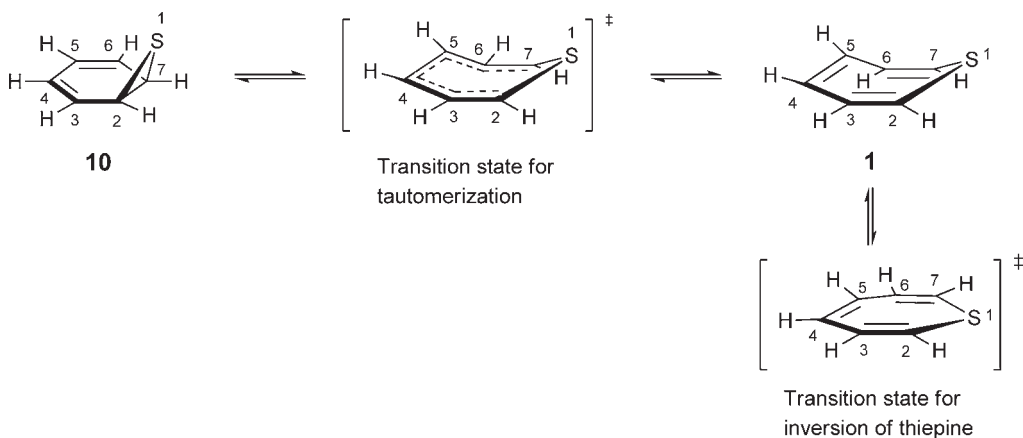
Theoretical studies on thiepine–thianorcaradiene (benzene sulfide) valence isomerization have been of continuous interest. In addition, hypervalency of sulfur in thiepinines has been theoretically studied. The interest in fused systems, such as dibenzo[*b,f*]thiepinines, toward pharmacologically active compounds is growing. In the last decade, many reports on the synthesis, characterization, and utilization of enantiomerically pure dihydro- and tetrahydrothiepinines and thiepanes have appeared.

The following monocyclic, benzo-, and dibenzo-fused ring systems, including dihydro, and tetrahydro derivatives, are treated in this chapter. Further carbocyclic and heterocyclic condensed systems are also described.



13.03.2 Theoretical Methods

Theoretical calculations for the parent thiopine and its valence isomer benzene sulfide were conducted at a high level of theory (**Scheme 1**) ^{<1997PCA3371>}. The enthalpy change of valence isomerization from benzene sulfide **10** to



Scheme 1

thiepine **1** ΔH at 298 K was estimated from QCISD(T)/6-31G^{*}//MP2/6-31G^{*} to be 7.02 kcal mol⁻¹. The high-level computational results are in marked contrast with modified neglect of diatomic overlap (MNDO) studies, which had suggested only a very small preference for **10**. The ΔH value is larger than that of oxepine–benzene oxide and explained as due to a combination of greater stability of the sulfide relative to oxide and relative instability of thiepine compared to oxepine. The entropy change at 298 K was calculated to be 6.68 J mol⁻¹ K⁻¹ (HF/6-31G^{*}).

Bond lengths, angles, and dihedral angles from MP2/6-31G^{*} optimizations are shown in Table 1. Thiepine **1** has a boat conformation, whereas the planar form of thiepine is the transition state for its degenerate conformational inversion.

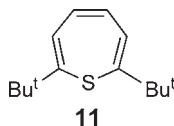
Table 1 Calculated (MP2/6-31G^{*}) bond lengths, angles, and dihedrals of benzene sulfide **10**/thiepine **1**

Coordinate	10	TS ^a	1	Planar ^b
<i>Bond length (atom distance) (Å)</i>				
S(1)–C(2)	1.852 4	1.764 7	1.770 3	1.767 1
C(2)–H	1.087 9	1.088 2	1.087 4	1.088 2
C(2)–C(3)	1.466 7	1.396 1	1.352 8	1.345 8
C(3)–C(4)	1.356 5	1.396 6	1.447 6	1.465 5
C(4)–C(5)	1.447 2	1.404 7	1.364 8	1.351 1
C(2)–C(7)	1.487 8	2.057 6	2.645 8	2.859 5
<i>Bond angle (°)</i>				
S(1)–C(2)–C(3)	118.97	121.80	122.60	134.23
C(2)–S(1)–C(7)	47.69	71.32	96.71	108.01
C(2)–C(3)–C(4)	121.23	124.15	126.32	131.51
C(3)–C(4)–C(5)	121.16	123.01	126.30	130.25
C(3)–C(2)–C(7)	117.47	108.13	99.21	98.23
S–C(2)–C(7)	66.15	54.34	41.64	35.99
<i>Dihedral (°)</i>				
S(1)–C(7)–C(2)–C(3)	111.54	116.58	129.72	180.00
C(3)–C(2)–C(7)–H	145.75	138.74	140.95	180.00
C(4)–C(3)–C(6)–C(7)	175.78	156.52	149.72	180.00

^aTransition state for valence tautomerization.

^bTransition state for inversion of the thiepine.

The calculated molecular orbital (MO) energies are compared to those available from photoelectron spectra. The first four MOs of thiepine **1** are calculated to lie at 8.19, 10.08, 10.32, and 11.64 eV (π'_4 , π'_3 , π''_2 , and n_S , respectively). The basic distribution of these orbitals is in good agreement with the photoelectron spectra of several substituted thiepinines. For example, a linear relationship (slope = 1.36, intercept = –2.33, $R^2 = 0.988$) can be obtained by plotting the experimental ionization energies for 2,7-di-*tert*-butylthiepine **11** versus the calculated orbital energies for thiepine **1** <85JA6874>.



For the benzene sulfide–thiepine system, the rate of valence isomerization is predicted to be much slower than that in the benzene oxide–oxepine system, as the enthalpy of activation for **10** → **1** is 20.5 kcal mol⁻¹ (7.03 kcal mol⁻¹ for benzene oxide–oxepine).

Barriers for ring inversion, shown in Table 2, were obtained in this study <1997PCA3371> and other work, as well as nucleus-independent chemical shifts (NICSs) of thiepine **1** <2000MI177>. From NICS values of thiepine, the planar structure appeared to be antiaromatic and the more stable boat-like structure as nonaromatic. The structure and energies were compared with those of 1,2- and 1,4-dithiins <2000MI177>.

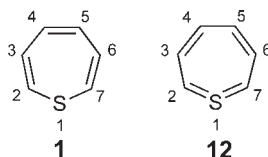
The nonclassical structure of sulfur heterocycles, including thiepine with hypervalency of sulfur, was investigated by MP2(full)/6-31G^{*} and B3LYP/6-31G^{*} calculations <1997JOC1766>. It was shown that both MP2 and DFT methods adequately predict the molecular geometries. The thiepine-1-S^{IV} ($\lambda^4\sigma^2$ -thiepine) **12** with

Table 2 Barriers to ring inversion of thiepine **1** ($\Delta E^\ddagger$) at various levels of theory and nucleus-independent chemical shifts (NICSS) of thiepine

Basis set or property	$\Delta E^\ddagger$ ^a	NICS ^b (boat) (ppm)	NICS ^b (planar) (ppm)	Reference
HF/6-31G*//HF/6-31G*	6.40			1997PCA3371
MP2/6-31G*//HF/6-31G*	9.64			1997PCA3371
MP2/6-31G*//MP2/6-31G*	10.41			1997PCA3371
MP2/6-31+G*//MP2/6-31G*	11.41			1997PCA3371
MP2/6-311G*//MP2/6-31G*	11.33			1997PCA3371
MP3/6-31G*//MP2/6-31G*	7.92			1997PCA3371
MP4/6-31G*//MP2/6-31G*	8.41			1997PCA3371
QCISD(T)/6-31G*//MP2/6-31G*	7.64			1997PCA3371
B3LYP/6-31+G(d,p)	5.8			2000MI177
MP2/6-31G(2df,p)	9.2			2000MI177
GIAO RHF/6-31+G(d)//B3LYP/6-31+G(d)		−1.3	12.6	2000MI177

^aActivation energy in kcal mol^{−1} from thiepine in its preferred boat-like conformer to the planar transition state for its inversion.

hypervalency of sulfur was obtained as a C_2 symmetry structure. Calculated carbon–carbon and carbon–sulfur bond lengths of thiepinines **1** and **12** are listed in Table 3. The calculated CS bonds of **12** are ca. 1.68 Å and consequently contracted by ca. 0.11 Å relative to thiepine **1**. In agreement with the formulas **1** and **12**, the bond alternation is the reverse; however, thiepine **12** is much higher in energy than **1** (MP2: 39.7 kcal mol^{−1}; DFT: 42.4 kcal mol^{−1}; DFT = density functional theory). In view of the high energy of **12**, the planar thiepine (C_{2v} symmetry) was calculated as well. This structure is also a stationary point on the energy surface but proved to be a saddle point of first order. It is of higher energy relative to both minimum structures. According to the calculated internal reaction coordinate (IRC), the saddle point represents another transition structure of inversion of **1** (see Table 1). The barrier is ca. 46 kcal mol^{−1}.

**Table 3** Selected geometric parameters of thiepinines (**1** and **12**) with C_s and C_2 symmetries at the MP2(full)/6-31G* and B3LYP/6-31G* level of theory

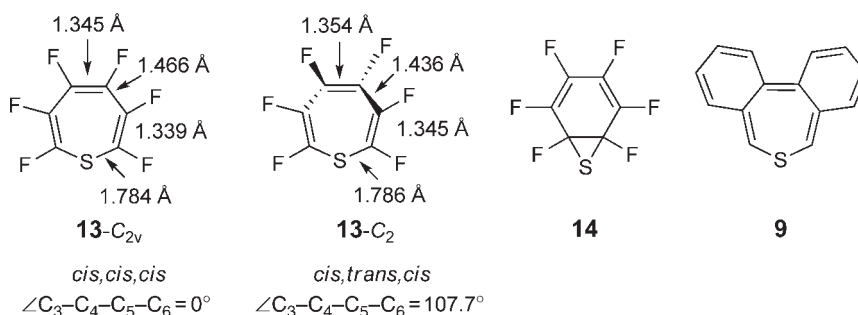
	1 (C_s) ^a		12 (C_2)		12 (C_{2v})	
	MP2(full)	DFT	MP2(full)	DFT	MP2(full) ^b	DFT ^c
<i>Bond lengths</i> (Å)						
S(1)–C(2)	1.768	1.788	1.676	1.662	1.656	1.650
C(2)–C(3)	1.351	1.345	1.451	1.462	1.465	1.471
C(3)–C(4)	1.446	1.455	1.345	1.340	1.346	1.341
C(4)–C(5)	1.363	1.356	1.486	1.496	1.497	1.506
<i>Bond angles</i> (°)						
C(2)–S–C(7)	96.6	99.5	111.8	113.7	116.4	116.8
<i>Dihedrals</i> (°)						
C(3)–C(4)–C(5)–C(6)	0.0	0.0	65.1	49.5	0.0	0.0

^aGeometric parameters for **1** (C_s) at the MP2/6-31G* calculation, see Table 1.

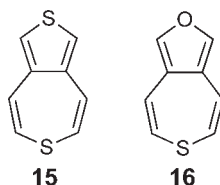
^bOne imaginary frequency 163i cm^{−1}.

^cOne imaginary frequency 131i cm^{−1}.

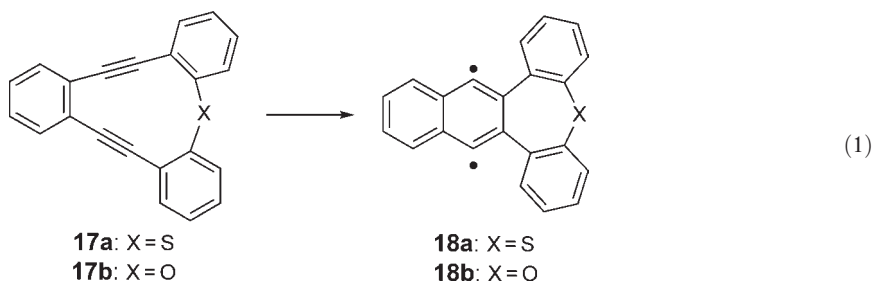
Investigation of Möbius-aromatic systems for planar cyclic compounds with $4n\pi$ -electrons was applied to thiepinines as well as other 8π -electron heteropines <2002J(P2)388>. The reported thiepine structures showed that they have boat-like conformations. The theoretical study by B3LYP/6-31G* calculation was conducted for thiepine **13** with conformations having nonplanar *cis,cis,cis*- C_s symmetry and planar *cis,cis,cis*- C_{2v} and *cis,trans,cis*- C_2 symmetries, and the corresponding valence isomers, benzene sulfide **14**. Perfluorination and biphenyl annelation were introduced in order to examine whether conformations having planar C_{2v} and C_2 symmetries might be energetically accessible. Perfluoro-substituted thiepine of the planar *cis,cis,cis*-system (C_{2v} symmetry) has a single imaginary mode corresponding to a distortion to the lower C_s symmetry. The *cis,trans,cis*-isomer of thiepine **13** with a Möbius-like conformation (C_2 symmetry) was obtained in the location of a minimum, but it is $15.4 \text{ kcal mol}^{-1}$ higher in energy than the planar *cis,cis,cis*-conformation with C_{2v} symmetry. NICS values (7.3 ppm for **13**- C_{2v} , -10.9 ppm for **13**- C_2) and reduced bond alternation suggest that the Möbius conformation **13**- C_2 has the characteristic of increased aromaticity or decreased antiaromaticity. Möbius conformation of dibenzo[*c,e*]thiepine **9** could not be obtained.



The theoretical study of thieno[3,4-*d*]thiepine **15** and furo[3,4-*d*]thiepine **16**, as dienes in thiophene or furan moieties, respectively, in the Diels–Alder reaction was investigated with semi-empirical AM1 calculations <1995JHC1499>. S-Methylation at the thiophene moiety of thieno[3,4-*d*]thiepine **15** was predicted to lower the activation energy and facilitate reaction with less reactive dienophiles, such as ethylene.



The stability of newly synthesized aromatic cyclic enediynes **17a** and **17b** was explained by comparison with the substantially high reaction energies of intermediate biradicals, dibenzonaphthothiepine **18a** ($34.9 \text{ kcal mol}^{-1}$) and dibenzonaphthoxepine **18b** ($32.4 \text{ kcal mol}^{-1}$) and their radical cations, formed via Bergman cyclization, by BLYP/611+G**//BLYP/6-31G* calculations (Equation 1) <2002JOC388>. The formation of the seven-membered ring in the cyclization step increases olefinic strain and destabilizes the intermediates **18a** and **18b**, while cyclic enediynes **17a** and **17b** are at the same time stabilized by conjugation of the triple bond to the aromatic system.



13.03.3 Experimental Structural Methods

13.03.3.1 X-Ray Diffraction

The X-ray crystal structure analyses of fully conjugated thiepinines were described in CHEC-II(1996) <1996CHEC-II(9)67>. In this section, new X-ray data for certain thiepine derivatives are described.

A host molecule, 2,7-di-*p*-chlorobenzoylnaphtho[2',3':4:5]thiepine **19**, exhibited interesting conformational flexibility in its crystalline inclusion compounds <2004MI326>. The structures have been elucidated by single crystal X-ray analysis. Selected bond lengths, bond angles, and dihedral angles of the host molecule in the ruby-red crystals of the 1:1 dioxane adduct of thiepine **19** are shown in Table 4. Both the host **19** and dioxane guest molecules have near-idealized (noncrystallographic) mirror symmetry. The seven-membered ring of thiepine **19** has a boat conformation, and its C=C-C and C=C-S angles in the ring range from 131.26(8)° to 132.96(10)°. The naphthalene C10 unit is essentially planar and shows the expected bond localization pattern. A *cisoid* arrangement was found for the orientation of the aroyl groups and the torsion angles C(3)-C(2)-C(16)-C(17) and C(6)-C(7)-C(23)-C(24) are 31.88(16)° and -28.68(14)°, respectively. A short distance (2.448) Å between an equatorial hydrogen atom on the chair-form dioxane guest and O(30) of a carbonyl group on thiepine **19** may indicate a significant C-H...O interaction. In addition, there are two other short C-H...O interactions of 2.319 and 2.389 Å, where the C-H donor is on the host **19**.

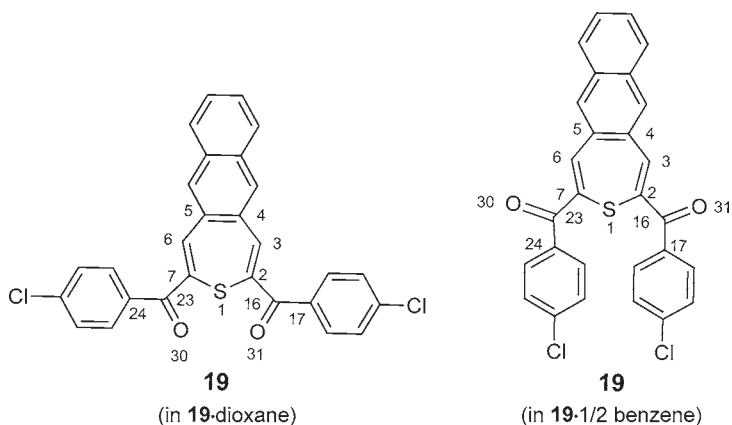


Table 4 Selected bond lengths (Å), bond angles (°), and dihedral angles (°) of thiepine **19** in clathrates **19**·dioxane and **19**·1/2 benzene

	<i>19</i> ·dioxane	<i>19</i> ·1/2 benzene
S(1)-C(2)	1.765 9(11)	1.782 3(13)
S(1)-C(7)	1.764 8(11)	1.774 3(13)
C(2)-C(3)	1.350 6(15)	1.347 8(17)
C(3)-C(4)	1.466 9(15)	1.463 6(17)
C(4)-C(5)	1.438 1(15)	1.439 8(17)
C(5)-C(6)	1.462 3(14)	1.466 8(17)
C(6)-C(7)	1.349 8(14)	1.343 8(17)
S(1)-C(2)-C(3)	131.63(9)	122.16(10)
S(1)-C(7)-C(6)	131.26(8)	121.46(10)
C(2)-C(3)-C(4)	132.80(10)	128.69(12)
C(5)-C(6)-C(7)	132.96(10)	128.81(12)
C(2)-S(1)-C(7)	105.54(5)	100.28(6)
C(3)-C(2)-S(1)-C(7)	-30.49(12)	60.32(12)
C(6)-C(7)-S(1)-C(2)	31.00(12)	-61.47(12)

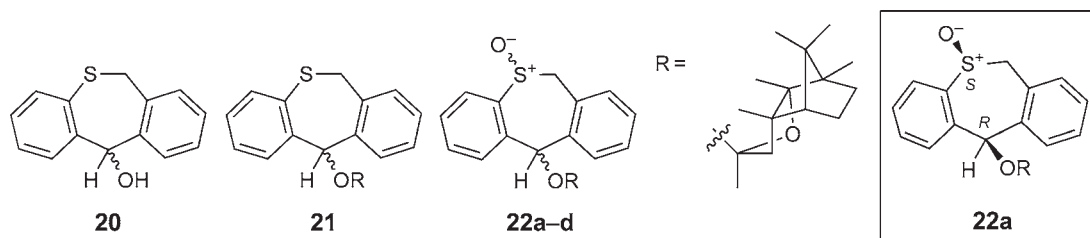
The conformation of the host is very different in the yellow 2:1 (host:guest) benzene clathrate, **19**·1/2 benzene. Structure **19** in benzene clathrate does not have approximate mirror symmetry. The aroyl groups have an asymmetric *transoid* arrangement and the torsion angles C(3)-C(2)-C(16)-C(17) and C(6)-C(7)-C(23)-C(24) are 155.24(12)° and 158.45(12)°,

respectively. While the seven-membered ring still has approximate mirror symmetry, it has a much deeper boat conformation with generally smaller ring angles. For example, the C=C–S angles are 121.46(10)° and 122.16(10)° for benzene clathrate, compared with 131.63(9)° and 131.26(8)° for the dioxane clathrate. The C–S–C angles are 100.28(6)° for benzene clathrate and 105.54(5)° for the dioxane clathrate. The largest changes in the thiepine ring torsion angles are found for C–C–S–C, which are –30.49(12)° and 31.00(12)° for **19**·dioxane and 60.32(12)° and –61.47(12)° for **19**·1/2 benzene.

The crystal packing of the molecules of thiepine **19** in the unsolvated form and the benzene clathrate is very closely related, and the *b*-axial lengths are essentially identical. The packing along the *a*-axis of the unsolvated form is very similar to the *c*-axis packing in the benzene clathrate. A least squares superposition of the molecule of thiepine **19** in its unsolvated and benzene-complexed form showed that their structures and conformations match almost perfectly.

Recent X-ray structural analysis studies have also been performed in order to determine the stereochemistry of chiral dihydro- and tetrahydrothiepinines and thiepanes.

Sulfoxidation of the (+)-Noe-lactol (ROH) ester **21** of racemic 6,11-dihydrodibenzo[*b,e*]thiepin-11-ol **20** gave a separable mixture of four diastereomers **22a–d** <2001TA975>. X-Ray structural analysis of one of these, **22a**, established its relative stereochemistry, and its absolute configuration was established by the known configuration of the Noe-lactol fragment. Subsequent manipulation provided resolved 6,11-dihydrodibenzo[*b,e*]thiepin-11-ol **20** and assigned the configurations of all four sulfoxides **22a–d**.



X-Ray structural analyses of thiepinines incorporated in bridged biaryls have been of interest because of the potential applicability of the chirality. An X-ray crystal structure of (±)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]thiepine **23** was reported (Table 5) <1995TL787>. The X-ray crystal structure of dihydrodinaphthothiepine **23** shows the *cisoid* arrangement around the C(4)–C(5) bond with an interplanar dihedral angle C(15)–C(5)–C(4)–C(16) of 66.1°. The torsion angles C(7)–S(1)–C(2)–C(3) and C(2)–S(1)–C(7)–C(6) were found to be 45.9° and 43.8°, respectively, indicating that the C–S–C–C bonds adopt the *gauche* arrangement.

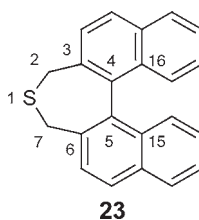
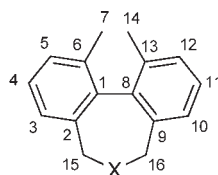


Table 5 Selected bond lengths (Å) and dihedral angles (°) of dihydrodinaphthothiepine **23**

S(1)---C(2)	1.828(3)	C(2)–S(1)–C(7)	99.5(1)
C(2)---C(3)	1.504(3)	C(2)–C(3)–C(4)	120.0(2)
C(4)---C(5)	1.491(3)	C(4)–C(5)–C(6)	119.3(2)
S(1)---C(7)	1.821(2)	S(1)–C(7)–C(6)	113.0(2)
C(3)---C(4)	1.386(3)	S(1)–C(2)–C(3)	112.3(2)
C(6)---C(7)	1.504(3)	C(3)–C(4)–C(5)	118.6(2)
C(5)---C(6)	1.385(3)	C(5)–C(6)–C(7)	119.3(2)

X-Ray structural analysis of bridged biphenyls containing sulfoxide, and sulfone functions in the bridge, 1,11-dimethyl-5,7-dihydrodibenzo[*c,e*]thiepine *S*-oxide **24** and *S,S*-dioxide **25** in racemic form, was undertaken <2000HCA479>. The crystals of both **24** and **25** are centrosymmetric (*R/S*). The crystal structures of **24** and **25** (Table 6) showed similar twisted biphenyl moieties with dihedral angles (θ) C(2)–C(1)–C(8)–C(9) and C(6)–C(1)–C(8)–C(13)) in the range of 62.5–65.0°.

The structures obtained by force-field calculations (MM2-91) showed good agreement with the crystal structures determined for **24** and **25**. In the crystal, the molecule of **25** has C_2 pseudosymmetry. The interaction between the two Me groups at C(6) and C(13) (the C(7)–C(14) distance is 3.311 Å in **24**, 3.426 Å in **25**) led to small deviations from planarity of the benzene rings. The absolute stereochemistries of the enantiomers were assigned by combination of chromatography, circular dichroism (CD) spectroscopy, X-ray crystallography, and empirical force-field and CNDO/S calculations (CNDO = complete neglect of differential overlap).



24: X = SO

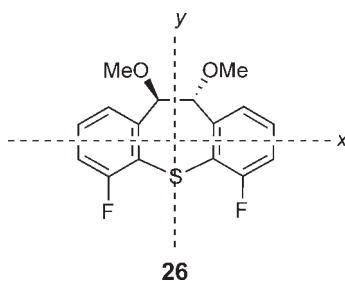
25: X = SO₂

(numbering for X-ray data in Table 6)

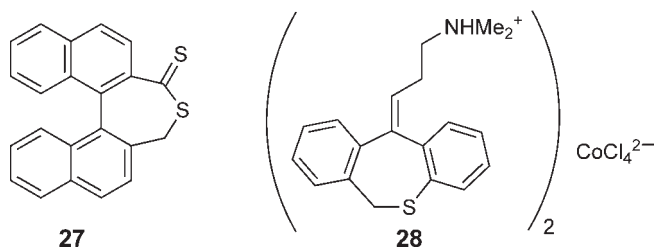
Table 6 Bond lengths (Å), bond angles (°), and dihedral angles (°) in dihydrodibenzothiepinines **24** and **25** by X-ray crystallography

Coordinate	24	25	Coordinate	24	25
<i>Bond length</i>			<i>Bond angle</i>		
S–O(1)	1.500(19)	1.452(4)	C(15)–S–C(16)	97.5(7)	104.3(2)
S–O(2)		1.448(4)	O(1)–S–C(15)	106.0(8)	109.1(2)
S–C(15)	1.832(15)	1.797(4)	O(1)–S–C(16)	107.9(8)	107.4(2)
S–C(16)	1.829(16)	1.787(4)	O(2)–S–C(15)		107.4(2)
C(1)–C(2)	1.396(14)	1.411(5)	O(2)–S–C(16)		109.6(2)
C(1)–C(6)	1.394(15)	1.403(5)	O(2)–S–O(2)		118.1(2)
C(1)–C(8)	1.496(14)	1.498(5)	<i>Dihedral angle</i>		
C(2)–C(16)	1.445(18)	1.513(5)	O(1)–S–C(15)–C(9)	+64.8(1.2)	+70.1(4)
C(6)–C(7)	1.492(17)	1.523(6)	O(1)–S–C(16)–C(2)	–154.6(1.1)	–160.9(3)
C(2)–C(16)	1.445(18)	1.513(5)	O(1)–S–C(15)–C(9)	+64.8(1.2)	+70.1(4)
C(6)–C(7)	1.492(17)	1.523(6)	O(1)–S–C(16)–C(2)	–154.6(1.1)	–160.9(3)
C(8)–C(9)	1.395(15)	1.405(5)	O(2)–S–C(15)–C(9)		–158.8(3)
C(8)–C(13)	1.395(16)	1.411(5)	O(2)–S–C(16)–C(2)		+71.6(3)
C(9)–C(15)	1.498(18)	1.510(5)	C(2)–C(1)–C(8)–C(9)	–63.1(1.3)	–62.6(5)
C(13)–C(14)	1.505(19)	1.521(6)	C(2)–C(1)–C(8)–C(13)	+116.5(1.2)	+116.5(4)
			C(6)–C(1)–C(8)–C(9)	+118.0(1.2)	+115.9(4)
			C(6)–C(1)–C(8)–C(13)	–62.5(1.5)	–65.0(5)
			C(1)–C(8)–C(13)–C(14)	–3.5(1.7)	–7.3(6)
			C(8)–C(1)–C(6)–C(7)	–6.5(1.7)	–6.3(6)

The X-ray crystal structure of chiral dihydrodibenzo[*b,f*]thiepine **26** was reported <1999TL813>. The results showed that thiepine **26** does not adopt a C_2 symmetrical conformation in the crystalline state. The two benzene rings are twisted about the *y*-axis like the wings of a butterfly. The X-ray structure of its corresponding sulfoxide has also been reported <2006OBC2218>.



The X-ray structures of dinaphtho[2,1-*c*:1',2'-*e*]thiepin-3-(5*H*)-thione **27** and 3-(6*H*-dibenzo[*b,e*]thiepin-11-ylidene)-propyldimethylamine hydrochloride cobalt chloride complex **28** have also been reported <2000MI395, 1997MI15>.



13.03.3.2 NMR Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy of monocyclic thiepinines and benzothiepinines was described in CHEC-II(1996) <1996CHEC-II(9)67>. In this section, new data for benzothiepinines are reported.

The ^1H NMR spectra of 2-alkyl- and 2-trimethylsilyl-1-benzothiepinines **29a–g** and 3-benzothiepine **5** at 400 MHz were reported (Table 7) <1995CPB19, 1999CPB1108, 2003CPB1283>. The chemical shifts were compared with those of 1- and 3-benzoheteropine analogs, such as benzosilepine, benzogermepine, benzostannepine, benzophosphopine, benzarsepine, benzoselenepine, benzotellurepine, benzobismepine, and benzostibepine. The chemical shifts of the ring protons are sensitive to change in the heteroatom.

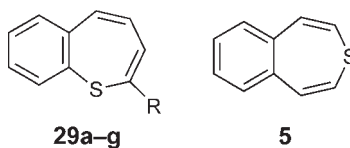


Table 7 ^1H NMR spectra for 2-substituted-1-benzothiepinines **29** and 3-benzothiepine **5** (400 MHz, CDCl_3 , δ)

Compound	R	3- <i>H</i> ^d	4- <i>H</i> (<i>dd</i>) ^{d,e}	5- <i>H</i> (<i>d</i>) ^e	Ar- <i>H</i>	R- <i>H</i>
29a ^a	Me	6.18 (dq)	6.33	6.97	7.24–7.37 (4H, m)	2.14 (3H, d)
29b ^a	Bu ⁿ	6.16 (br d)	6.35	6.98	7.15–7.34 (4H, m)	0.88 (3H, t), 1.20–1.60 (4H, m), 2.36 (3H, d)
29c ^a	Bu ^t	6.26 (d)	6.45	7.04	7.19–7.37 (4H, m)	1.24 (9H, s)
29d ^a	<i>n</i> -Hex	6.17 (d)	6.37	7.00	7.16–7.35 (4H, m)	0.87 (3H, t), 1.29–1.57 (8H, m), 2.35 (2H, t)
29e ^a	<i>c</i> -Hex	6.17 (d)	6.40	7.00	7.14–7.34 (4H, m)	1.19–1.96 (10H, m), 2.14–2.26 (1H, m)
29f ^a	<i>n</i> -Oct	6.19 (d)	6.39	7.01	7.16–7.39 (4H, m)	0.88 (3H, t), 1.20–1.56 (12H, m), 2.36 (2H, t)
29g ^b	TMS	6.65 (d)	6.48	7.08	7.23–7.37 (4H, m)	0.21 (s, 9H)
Compound 5 ^c		1(5)- <i>H</i> 6.72 (2H, d)	2(4)- <i>H</i> 5.89 (2H, d)	$J_{1,2(4,5)}$ (Hz) 9.5	Ar- <i>H</i> 7.10–7.18 (m, 4H)	

^a<1995CPB19>.

^b<1999CPB1108>.

^c<2003CPB1283>.

^d $J_{3,4}$ = 5.1–5.9 Hz.

^e $J_{4,5}$ = 11.5–12.5 Hz.

13.03.3.3 UV and Mass Spectroscopy

Ultraviolet (UV) spectroscopy of fully conjugated thiepinines was discussed in CHEC-II(1996) <1996CHEC-II(9)67>. In this section, the UV spectra of selected chiral thiepinines together with their CD spectra are shown.

The electronic transitions in thiepinines, based on bridged biphenyl structures, have been studied by UV and CD spectra <2000HCA479>. UV and CD spectral data of 5,7-dihydrodibenzo[*c,e*]thiepine derivatives **24**, **25**, and **30** are shown in Table 8. The CD spectra of the enantiomers of thiepinines **24**, **25**, and **30** were resolved into individual bands; the corresponding rotational strengths were calculated. The transitions showed considerable similarity to those of a 1,1'-biphenyl with hydrocarbon bridge (*trans*-5,6,7,8-tetrahydro-6,7-dimethyldibenzo[*a,c*]cyclooctene **30**), though with bathochromic shifts, which permitted the assignment of the absolute configurations of the enantiomers of thiepinines **24**, **25**, **30**. The assignments were supported by comparison of the experimental CD spectra with spectra calculated by the CNDO/S method (see Section 13.03.3.1).

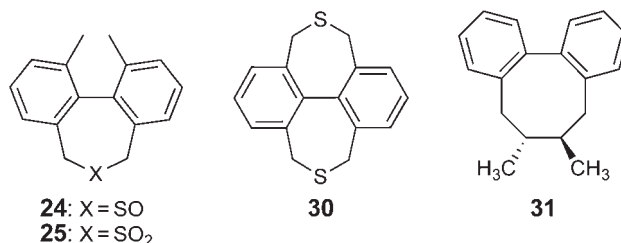


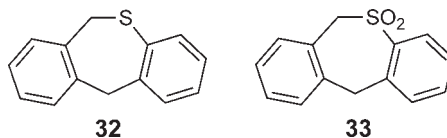
Table 8 UV and CD spectra of thiepinines **24**, **25**, and **30**. CD spectra are of the (S)-enantiomers (solvent, MeCN)

Compound		λ (nm) (ϵ , $\Delta\epsilon$ ($M^{-1} cm^{-1}$))
24	UV	250 (sh ^a) (3300), 219 (42 000), 190 (41 000, end absorption)
	CD	285 (sh) (−2.6), 260 (−27.9), 231 (−34.0), 204 (+102), 200 (+108), 187 (−113)
25	UV	279 (sh) (1300), 27 (2240), 240 (sh) (7500), 217 (39 500), 190 (45 000, end absorption)
	CD	283 (−2.8), 273.5 (−2.3), 241 (−44.6), 222 (−55.0), 209 (sh) (+132), 200 (+227), 188 (−102)
30	UV	287 (sh) (1200), 238 (sh) (6800), 207 (29 500), 190 (43 000, end absorption)
	CD	292 (−6.9), 256 (−39.9 ^b), 229 (+35.3), 206 (+51), 189 (−60)

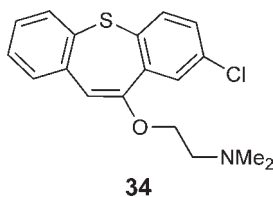
^aShoulder.

^bResolved into two Gaussians with λ_{max} 242 nm ($\Delta\epsilon$ −10.5) and 255 nm ($\Delta\epsilon$ −35.5).

Mass spectra of dibenzo[*b,e*]thiepine **32** and dibenzo[*b,e*]thiepine 5,5'-dioxide **33** were studied via the classical approximation of the quasi-equilibrium theory. A good agreement was achieved between calculated and experimental data <1998RRC849>.



Structure elucidation of 2-(8-chlorodibenzo[*b,f*]thiepin-10-yloxy)-*N,N*-dimethylethanamine (zotepine) **34** and its metabolites has been studied by electrospray ionization (ESI) mass spectra <2002MI316>.



13.03.4 Thermodynamic Aspects

13.03.4.1 Aromaticity and Stability

The theoretical interest in aromaticity and antiaromaticity was described in CHEC-II(1996) <1996CHEC-II(9)67> and Section 13.03.2 in this chapter.

Thermal instability arises from thiepine–benzene sulfide valence isomerization and subsequent irreversible loss of sulfur. There are two main approaches for stabilization. First, thiepinines can be stabilized by electronic effects such as aromatic ring annulations, and, second, thiepinines can also be stabilized by steric effects. These stabilization effects were discussed in CHEC-II <1996CHEC-II(9)67>. Some new results on thermal stability have been reported.

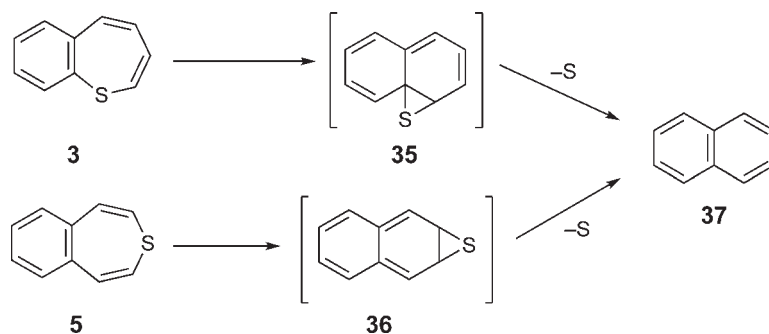
The newly reported half-lives of 1- and 3-benzothiepinines **3** and **5**, respectively, together with the previously reported data for **3**, are shown in Table 9. The half-life ($t_{1/2}$) of 3-benzothiepine **5**, estimated from ^1H NMR, showed that **5** is less stable than 1-benzothiepine **3**. The mechanism of sulfur extrusion in 1- and 3-benzothiepinines **3** and **5** involved isomerization to the corresponding thianorcaradiene intermediates **35** and **36** and subsequent irreversible loss of sulfur, as shown in Scheme 2.

Table 9 Half-lives of 1- and 3-benzothiepinines

1-Benzothiepine 3	Reference	3-Benzothiepine 5	Reference
17 h/25 °C ^a	1978JOC3379, 1973JOC3978		
58 min/47 °C ^a	1975TL2697		
15 min/60 °C ^b	1999CPB1108		
44 min/50 °C ^b	2003CPB1283	1 min at 50 °C ^b	2003CPB1283

^aIn CCl_4 .

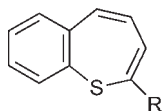
^bIn toluene.



Scheme 2

The thermal stabilities of the group 16 benzoheteropines (S, Se, and Te) were also compared <1999CPB1108, 2003CPB1283>. The stabilities of both 1- and 2-benzoheteropines increased in the order $\text{S} < \text{Se} < \text{Te}$.

2-*tert*-Butyl-1-benzothiepine **29c** is stable and can be kept for several weeks at room temperature without decomposition in solution <1995CPB19>. 2-Trimethylsilyl-1-benzothiepine **29g** gradually decomposed and can be kept for only several days <1999CPB1108>. 2-Methyl-1-benzothiepine **29a** is unstable and gradually decomposed even during isolation <1995CPB19>; its reported half-life is 660 min at 35 °C <1990CE853>.

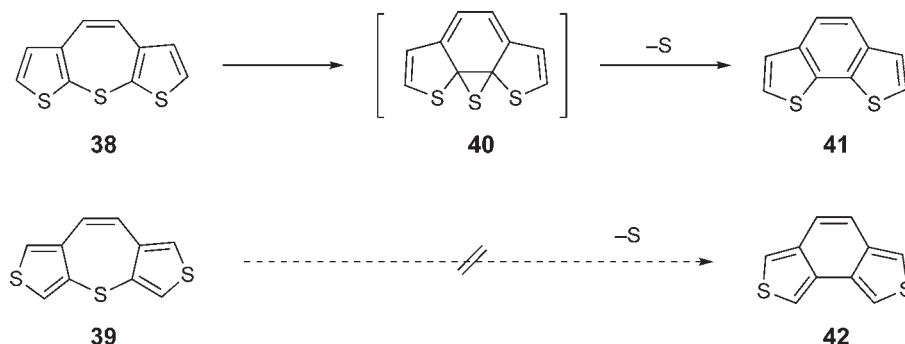


29a: R = Me

29c: R = Bu^t

29g: R = TMS

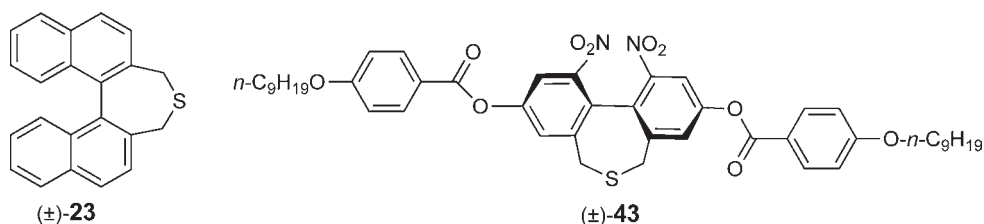
Dithieno[2,3-*b*;3',2'-*f*]thiepine **38** and its heteropine analogs are more stable than the corresponding 1-benzothiepinines, but somewhat less stable than dibenzo[*b,f*]heteropines <1997H(45)1899>. Dithieno[3,4-*b*;3',4'-*f*]thiepine **39** and its heteropine analogs are very stable and remained unchanged even when heated at 180 °C for 24 h, probably because norcaradiene intermediates cannot be formed (e.g., unless hypervalent sulfurs are involved) from **39** and its heteropine analogs, thus giving no dithienobenzene **42** (Scheme 3).



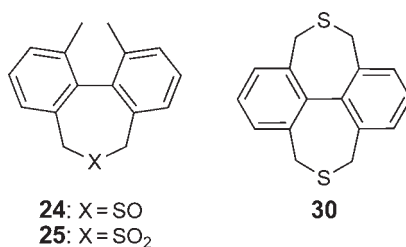
Scheme 3

13.03.4.2 Solubility and Chromatographic Behavior

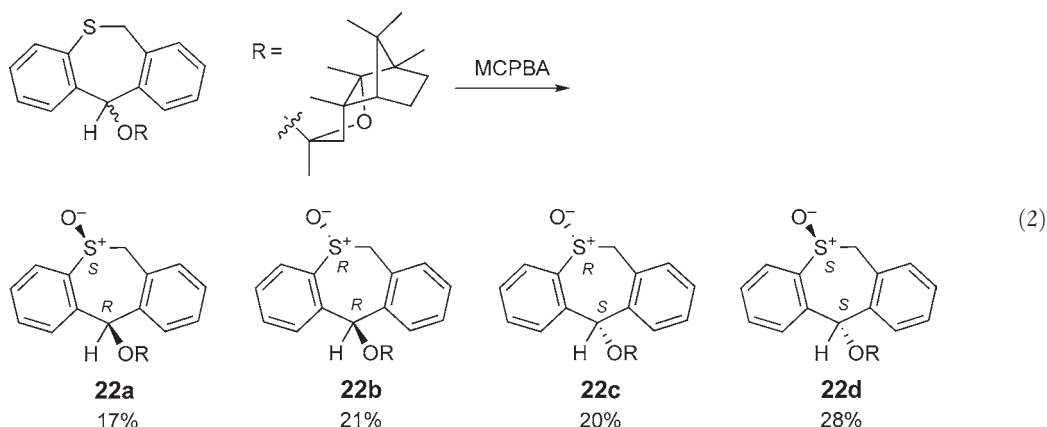
Chromatographic resolution of chiral dihydrothiepinines has been of interest. The chiral thiepinines, shown below, were resolved by chromatography (see Section 13.03.9.2). The racemic thiepine **23** was resolved by chromatography on triacetylcellulose (TAC) on a preparative scale <1994JOC1326>. The absolute configuration (*S*) was assigned to the (+)-enantiomer that eluted first from the TAC column on the basis of comparison of its CD spectrum with those of (*S*)-(+)-4,5-dihydro-4-methyl-3*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine and 2,2'-dimethyl-1,1'-binaphthyl of known absolute configuration. A chemical correlation shown in Section 13.03.9.2 allowed an independent assignment. Racemic thiepine (±)-**43** was resolved by chiral stationary phase (CSP) high-performance liquid chromatography (HPLC) on an (*S,S*)-Whelk-O1 column on a semi-prep scale <2002JMC586>.



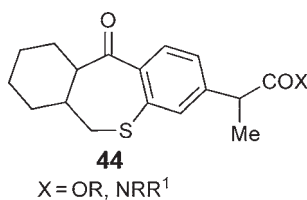
Racemic 1,11-dimethyl-5,7-dihydrodibenzo[*c,e*]thiepine *S*-oxide **24** and *S,S*-dioxide **25** and 10,12-dihydro-4*H*,6*H*-[2]benzothiepinino[6,5,4-*def*][2]benzothiepine **30**, based on bridged biphenyl structures, were resolved into enantiomers by chromatography on swollen microcrystalline TAC <2000HCA479>. The first-eluted enantiomers were assigned to have the (*S*)-configuration by comparison of the experimental CD spectra with spectra calculated by the CNDO/S method (see also Sections 13.03.3.1 and 13.03.3.3).



Racemic 6,11-dihydrodibenzo[*b,e*]thiepin-11-ol (+)-Noc-lactol (ROH) ester **21** is a diastereomixture and not preparatively separable. Oxidation of the mixture of the two sulfides **21** led to a mixture of four diastereoisomeric sulfoxides **22a–d**, which proved to be readily separable analytically by thin-layer chromatography (TLC) or HPLC. Preparative separation was achieved readily by flash chromatography on silica gel, eluting with 2:1 ether/pentane (Equation 2) <2001TA975> (see Section 13.03.3.1).



The chromatographic capacity factor (K_i) for ester and amide derivatives of 6, 6a, 7, 8, 9, 10, 10a, 11-octahydro-11-oxodibenzo[*b,e*]thiepine propionic acid **44**, potent antiinflammatory agents, has been studied, since the parameter was widely used for the interpretation of the activity of drugs <2003RRC795>. K_i was modeled topologically using molecular redundancy index (MRI), equalized electronegativity (χ_{eq}), and van der Waals volume (V_W).



13.03.4.3 Melting and Boiling Points

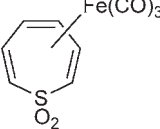
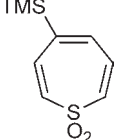
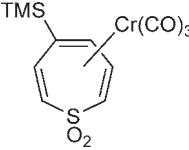
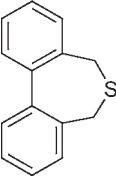
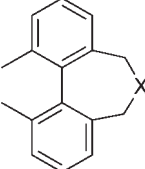
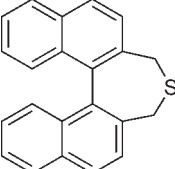
This subject was described in CHEC-II(1996) <1996CHEC-II(9)67>. Selected new melting point data for crystal-line thiepine derivatives are shown in Table 10.

Table 10 Melting points of thiepine derivatives

Compound	<i>m.p.</i> (°C)	Reference
	93–94	1997H(45)1899
	122–123	1997H(45)1899
	54.5–55 (hexane)	1991JA5059

(Continued)

Table 10 (Continued)

Compound	<i>m.p.</i> (°C)	Reference
	169–170	1991JA5059
	132–133	1999JA8237
	188–189	1999JA8237
	(±) 95–96 (hexane) (±) 89–90	2005T9082 1956JA6130
	X = S: (±) 100–101 X = SO: (±) 137–138 (cyclohexane) X = SO ₂ : (±) 221–222 (acetone) X = S: (±) 102–103 X = SO: (±) 137–138 X = SO ₂ : (±) 221–222	2000HCA479 2000HCA479 2000HCA479 1964JA1710 1970CJC633 1970CJC633
	(±) 216–218 (benzene), 212–213 (acetone) (S)-(+ (100% ee) 177–178 (benzene–ether 1:3) (R)-(–) (97% ee) 174–176 (benzene–ether 1:3) (±) 210–212 (hexane)	1994JOC1326 1994JOC1326 1994JOC1326 2005T9082

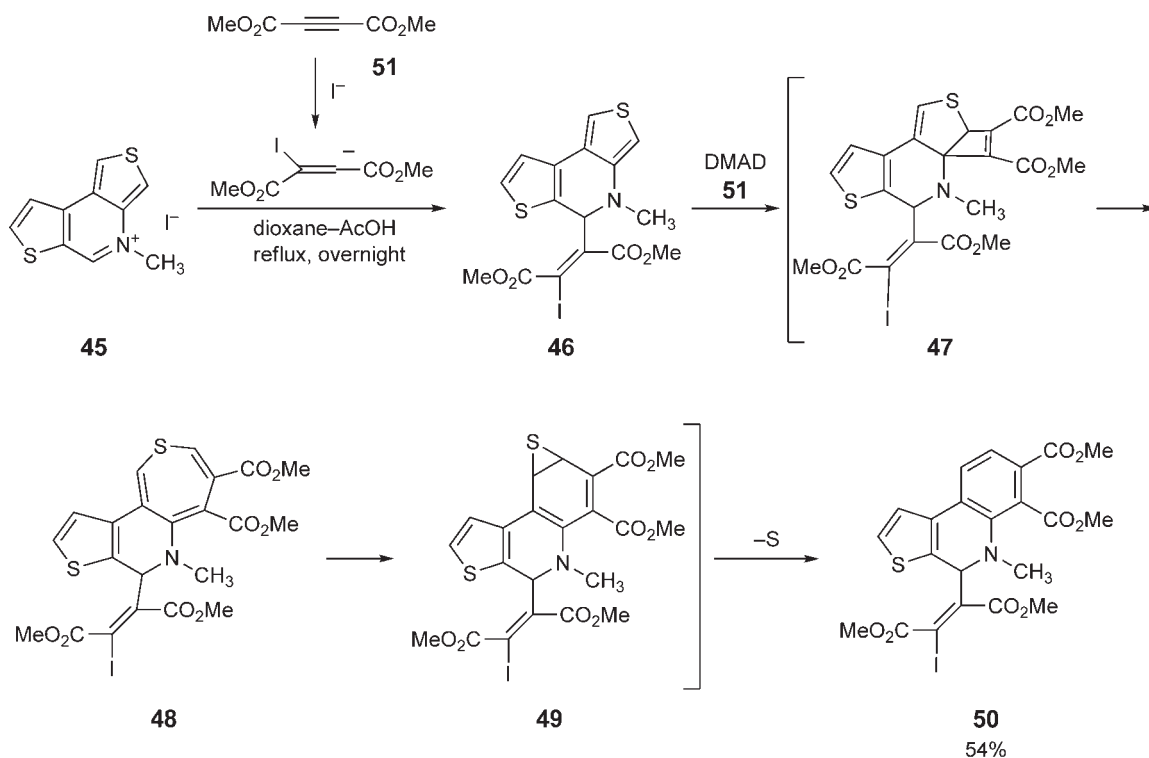
13.03.5 Reactivity of Fully Conjugated Rings (Thiepinines)

13.03.5.1 Unimolecular Thermal and Photochemical Reactions

As described in Section 13.03.1 and CHEC-II(1996) <1996CHEC-II(9)67>, thiepinines are thermally unstable through valence isomerization to the corresponding thianorcaradienes, followed by irreversible cheletropic loss of sulfur. Thiepinines, as unstable intermediates, have been postulated in some stepwise transformations.

For example, reaction of 4-methyldithieno[3,4-*b*:3',2'-*d*]pyridinium iodide **45** with 2 equiv of dimethyl acetylenedicarboxylate (DMAD) **51** gave **50** in 54% yield <1995T13185>. Formation of **50** was explained by a Michael

addition of iodide to DMAD **51**, followed by nucleophilic attack on the positive carbon in **45** which gave **46**; subsequent [2+2] cycloaddition with DMAD **51** led to primary adduct **47**. The adduct **47** rearranges *via* a thiepine **48** by electrocyclic ring opening to episulfide (thianorcaradiene) **49**, which eliminated sulfur to give compound **50**. The intermediacy of the primary adduct **46** was demonstrated by its isolation at shorter reaction time (Scheme 4).

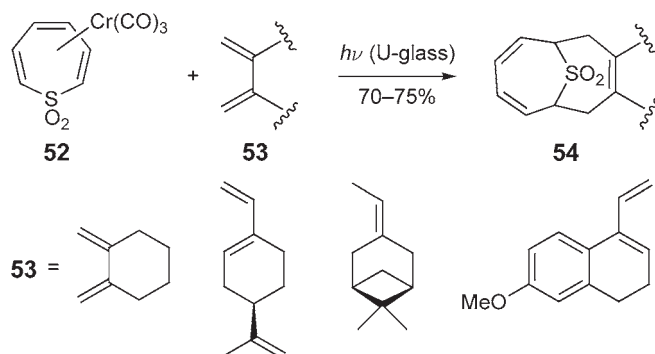


Scheme 4

13.03.5.2 Intermolecular Cyclic Transition State Reactions

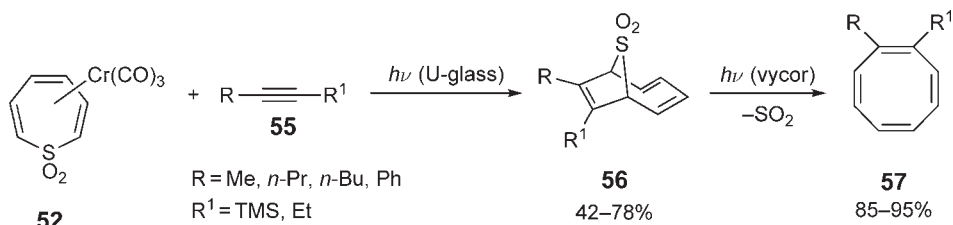
Rigby *et al.* developed higher-order cycloadditions of (η^6 -thiepine 1,1-dioxide)tricarbonylchromium(0) **52** <1992TL5873, 1993JA1382, 1996CHEC-II(9)67> and applied them to various ring systems.

Irradiation (uranium glass filter) of the readily available (η^6 -thiepin-1,1-dioxide)tricarbonylchromium(0) **52** in the presence of various dienes **53** provided the $[6\pi+4\pi]$ cycloadducts **54** (Equation 3) <1996JOC7644, 1999JA8237>. This cycloaddition gave products as single diastereomers and subsequent Ramberg-Bäcklund rearrangement of the cycloadducts **56**, which were utilized to give polycycles (Section 13.03.6.2).



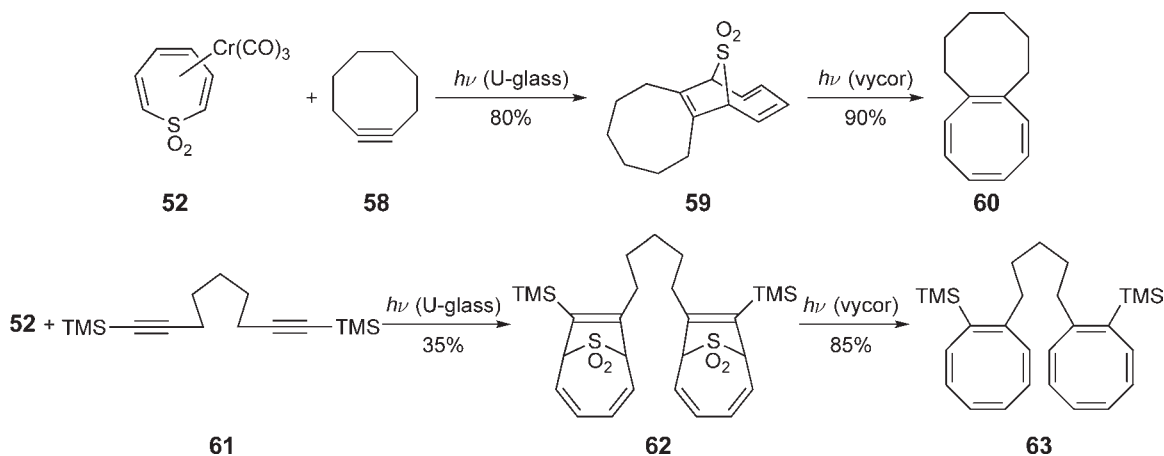
(3)

Irradiation of complex **52** and a small excess of internal alkynes **55** gave $[6\pi+2\pi]$ cycloadducts in 42–78% yield (Scheme 5) <1997TL2049>. A second irradiation (vycor filter) of the cycloadducts **56** afforded cyclooctatetraene derivatives **57** in 85–95% yield, via cheletropic extrusion of sulfur dioxide.



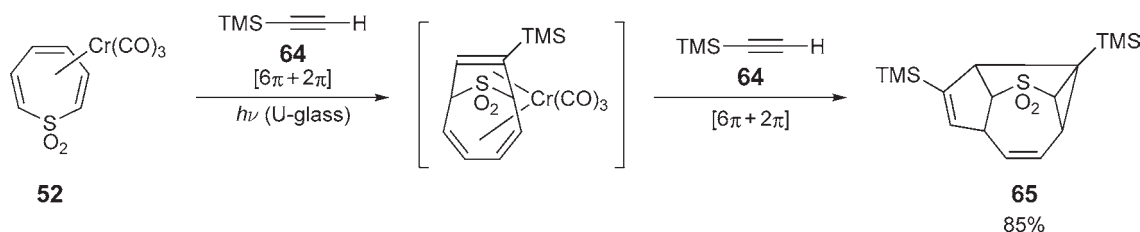
Scheme 5

Various cyclooctatetraenes have been also prepared by this sequential $[6\pi+2\pi]$ cycloaddition and sulfur dioxide extrusion, as shown in Scheme 6.



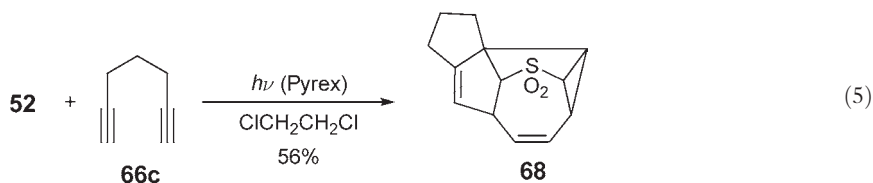
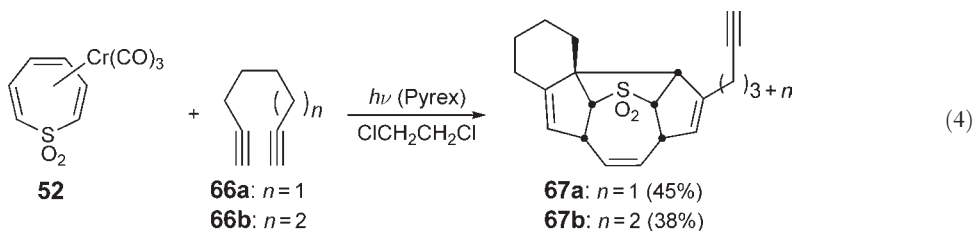
Scheme 6

A three-component, cycloaddition reaction of thiepene 1,1-dioxide chromium complex **52** was reported <1996JA6094>. Irradiation (450 W Canrad–Hanovia medium-pressure Hg-lamp, U-glass filter) of a mixture of (η^6 -thiepene 1,1-dioxide)tricarbonylchromium(0) **52** and excess trimethylsilylacetylene **64** (10 equiv) afforded an 85% isolated yield of the tetracycle **65** (Scheme 7). The process can be viewed formally as two consecutive Cr(0)-mediated $[6\pi+2\pi]$ cycloadditions. A high level of chemical efficiency in a single operation was achieved and only one regioisomer of product was isolated. The regioselectivity exhibited by the second alkyne addition was explained as a result of steric interactions between the trimethylsilyl (TMS) group and the proximate alkene carbon of the seven-membered ring in the alternative regioisomer. The reaction of the thiepene complex **52** and trimethylsilylacetylene **64** can also be effected under thermal activation conditions (160 °C, sealed tube, Bu_2O , 12 h), although the yield is lower than with photoactivation (32%). Other terminal alkynes, such as 3-methyl-3-buten-1-yne ($\text{H}_2\text{C}=\text{CMe}-\text{C}\equiv\text{CH}$) and *t*-butylacetylene ($\text{Bu}^t-\text{C}\equiv\text{CH}$), have been shown to be effective partners in the reaction with the thiepene complex **52**.



Scheme 7

Furthermore, a four-component cycloaddition reaction (η^6 -thiepine 1,1-dioxide)tricarbonylchromium(0) **52** with tethered diynes under photoactivation afforded pentacyclic adducts formally derived from a sequential $[6\pi+2\pi]/[6\pi+2\pi]/[2\sigma+2\pi]$ cycloaddition process [<1999OL507>](#). Photocycloaddition of the complex **52** with excess 1,7-octadiyne **66a** or 1,8-nonadiyne **66b** ($\text{ClCH}_2\text{CH}_2\text{Cl}$, $h\nu$ (Pyrex filter)) afforded the pentacyclic triene sulfones **67a** and **67b** in 45% and 38% yields, respectively (Equation 4). In contrast, 1,6-heptadiyne **66c** afforded only the three-component cycloadduct **68** in 56% yield (Equation 5).

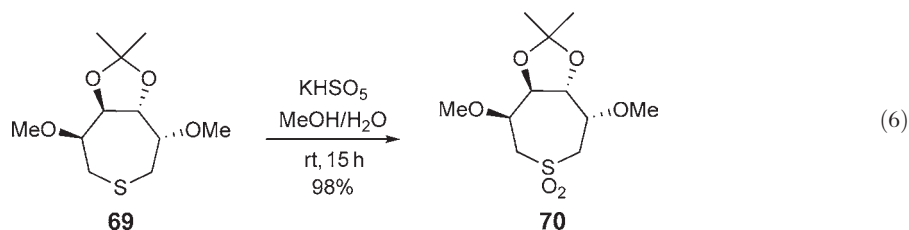


In a mechanism for the $[6\pi+2\pi]/[6\pi+2\pi]/[2\sigma+2\pi]$ process, the first two steps involved in this overall transformation were presumed to parallel the pathway observed for the above described $[6\pi+2\pi]$, $[6\pi+2\pi]$ process. A third cycloaddition of the cyclopropane unit with an additional alkyne component occurred via a $[2\sigma+2\pi]$ cycloaddition; the role of chromium(0) in promoting the critical $[2\sigma+2\pi]$ cycloaddition is not yet clear.

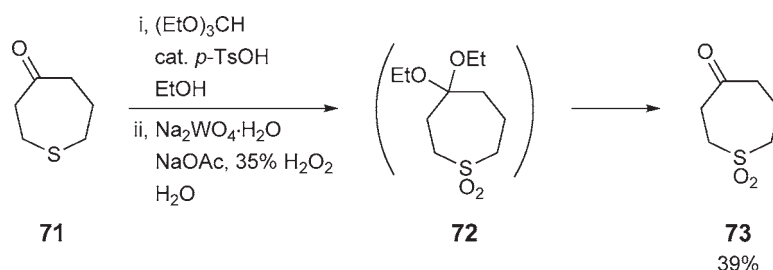
13.03.6 Reactivity of Nonconjugated Rings (Dihydro- and Tetrahydrothiepinines, and Thiepanes)

13.03.6.1 Electrophilic Attack at Sulfur

Various oxidative reactions of thiepinines (thiepanes) to thiepine (thiepane) dioxides have been reported. D-Mannitol-derived chiral thiepane **69** was oxidized to the corresponding thiepane 1,1-dioxide **70** by KHSO_5 in $\text{MeOH}/\text{H}_2\text{O}$ in 98% yield (Equation 6) [<1997TL7797>](#) or by *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 [<1999PS305>](#).

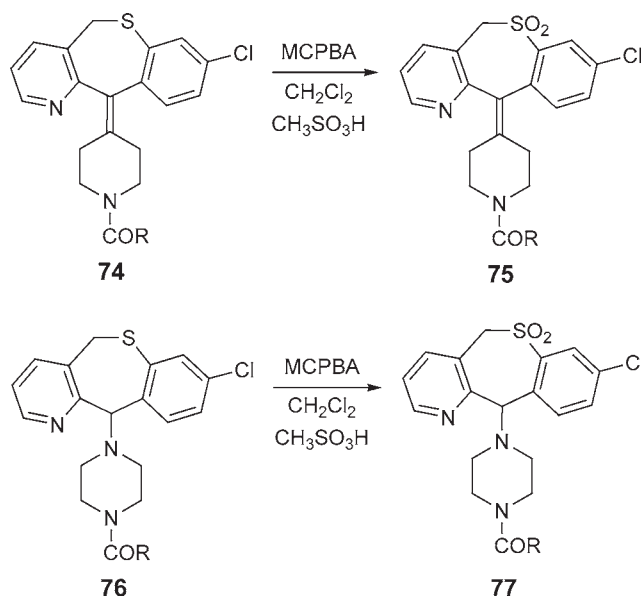


A new synthesis of thiepanone 1,1-dioxide involving sulfur oxidation was reported [<2004SC567>](#). Protection, as the diethyl acetal, using triethyl orthoformate in the presence of *p*-TsOH and subsequent oxidation of thiepan-3-one **71** with aqueous hydrogen peroxide in the presence of catalytic amount of sodium tungstate and sodium acetate gave deprotected thiepan-3-one 1,1-dioxide **73** directly in 39% yield (**Scheme 8**). For the corresponding five- and six-membered rings, tetrahydrothiophene-3-one and thiopyran-3-one, the intermediate acetals were isolated and deprotection of the intermediate acetals in aqueous HCl gave the corresponding 1,1-dioxides in better total yields than that of **73**.



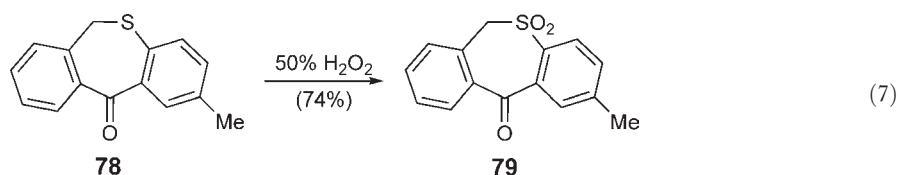
Scheme 8

The 5,11-dihydro-[1]benzothiepine[4,3-*b*]pyridine derivatives **74** and **76** were oxidized to the corresponding sulfones **75** and **77**, respectively, with MCPBA in a CH_2Cl_2 solution containing 3–5 equiv of methanesulfonic acid, which prevented pyridine *N*-oxide formation (**Scheme 9**) [<1998BML2521>](#).

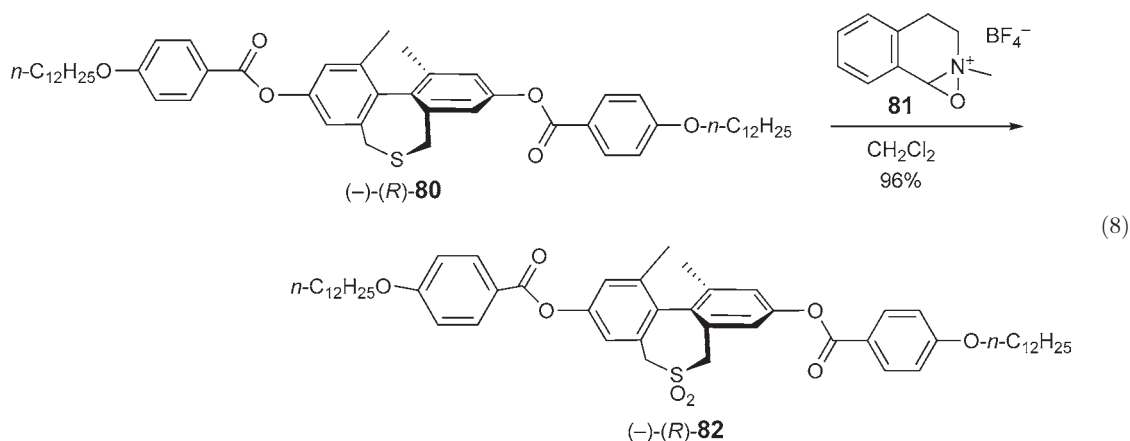


Scheme 9

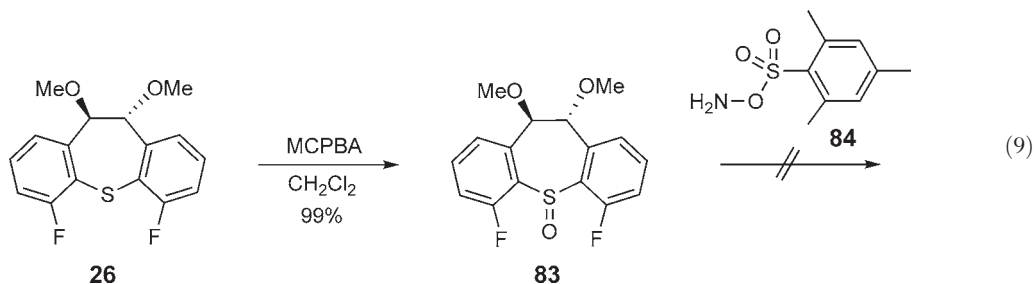
Oxidation of 2-methyldibenzo[*b,e*]thiepin-11(6*H*)-one **78** was oxidized with 50% hydrogen peroxide to give the corresponding sulfone **79** in 74% yield (Equation 7) <2005MI1524>.



The sulfur atom of (–)-(*R*)-3,9-bis[4-(dodecyloxy)benzoyloxy]-5,7-dihydro-1,11-dimethyldibenzo[*c,e*]thiepine **80** was oxidized with *N*-methyl-1,2-epoxy-1,2,3,4-tetrahydroisoquinolinium tetrafluoroborate **81** to the sulfone (–)-(*R*)-**82** (Equation 8) <1998JOC3895>. The oxidation of thiepine **80** failed with most of the usual oxidants.

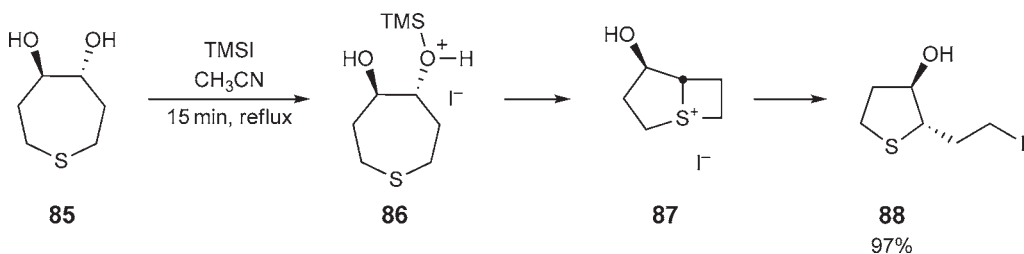


Reaction of thiepine **26** with MCPBA in CH_2Cl_2 gave sulfoxide **83** in 99% yield; however, **83** did not react under various oxidizing conditions including mesitylenesulfonylhydroxylamine **84**, which reacted with diphenyl sulfoxide to give aminated product (Equation 9) <2006OBC2218>.

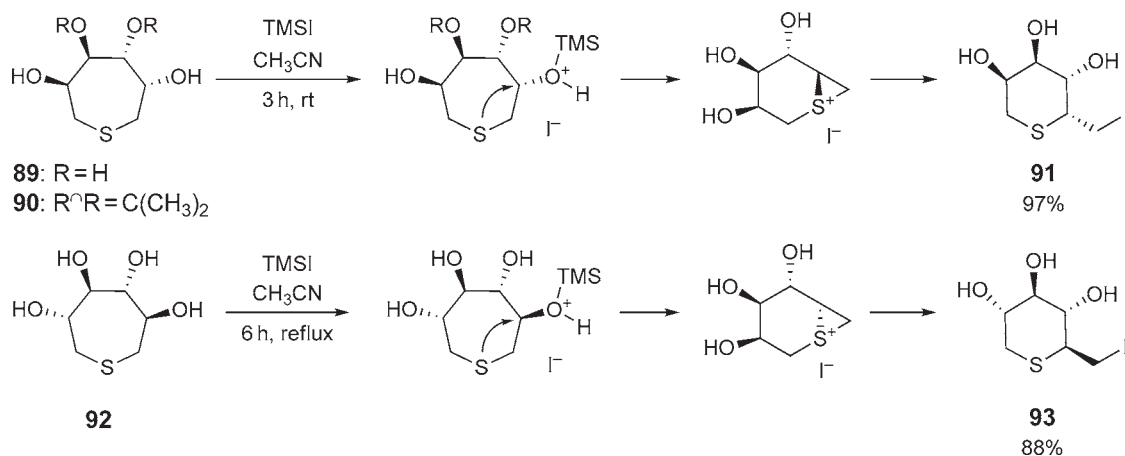


Regio- and stereospecific Me_3SiI -promoted intramolecular displacement of enantiomerically pure hydroxythiepanes in the facile ring contraction to thiolane or thiane derivatives has been studied <1997JOC8572>. The reaction of Me_3SiI with 4(*R*),5(*R*)-dihydroxythiepane **85** proceeded by ring contraction of a seven-membered to a five-membered cyclic sulfide through the oxonium intermediate **86**, which led to the 1-thioniabicyclo[3.2.0]heptane intermediate **87** by transannular sulfide interaction and displacement of the OH group coordinated with the silicon reagent (Scheme 10). The intermediate **87**, via iodide attack at the α -position of the four-membered ring moiety, gave the (2*S*,3*R*)-2-(2-iodoethyl)-3-hydroxytetrahydrothiophene **88** in 97% yield.

In thiepanes **89**, **90**, and **92**, transannular attack at C_3 or C_4 could lead to a mixture of polyhydroxylated tetrahydrothiopyrans or tetrahydrothiophenes. However, by the reaction of substrates **89** (or **90**) and **92** with Me_3SiI , **91** and **93** were obtained exclusively (free of any five-membered cyclic sulfides), respectively, through a seven- to six-membered ring-contraction reaction. In both cases, as predicted for an $\text{S}_{\text{N}}2$ transannular cyclization and due to the presence of a C_2 -symmetric axis (Scheme 11), only one diastereoisomer was obtained. Episulfonium salt was proposed to be formed by a stereo- and regiospecific process, followed by a ring contraction toward the more stable tetrahydrothiopyran derivative.

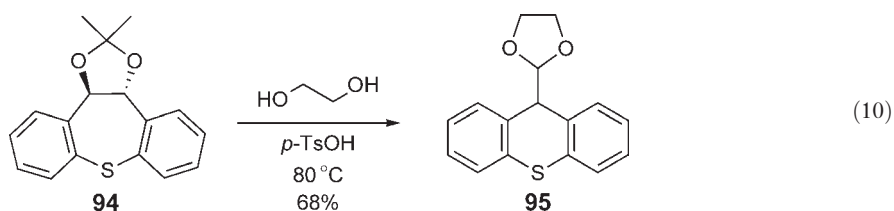


Scheme 10

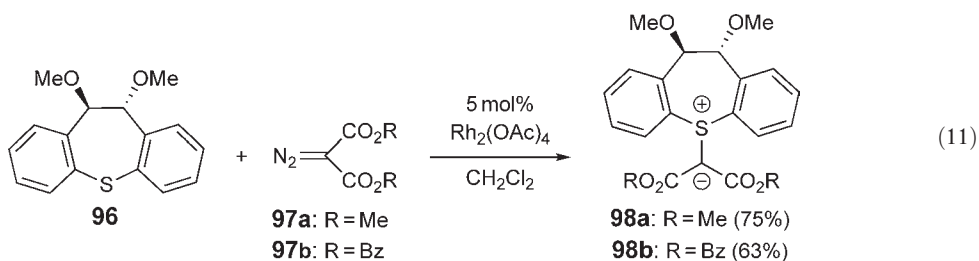


Scheme 11

Related to the ring contraction, another example of transformation of a thiepine seven-membered ring to a six-membered ring is described here. Treatment of thiepine **94** with a combination of ethylene glycol and *p*-toluenesulfonic acid (in an attempt to remove the acetal function) led to thioxanthene ring system **95** in 68% yield (Equation 10) <2006OBC2218>. The mechanism was presumed to involve a 1,2-sigmatropic shift to contract the seven-membered ring with the resulting aldehyde being trapped by the ethylene glycol.



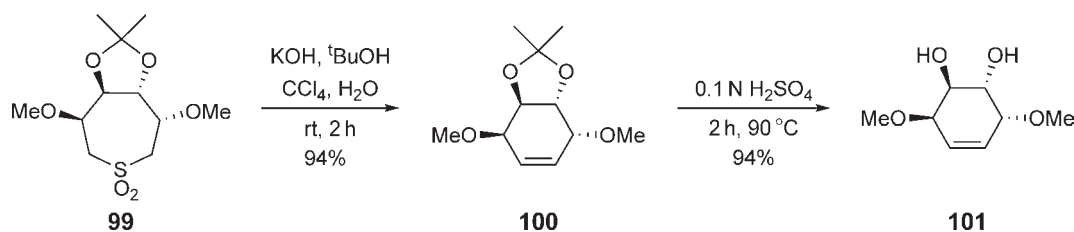
Thiepine **96** was reacted with dimethyl diazomalonate **97a** and dibenzyl diazomalonate **97b** in the presence of 5% [Rh₂(OAc)₄] to give ylides **98a** and **98b** in 75% and 63% yields, respectively (Equation 11) <2006OBC2218>.



13.03.6.2 Nucleophilic Attack at Carbon

Ramberg–Bäcklund rearrangement is the base-induced rearrangement of α -halogenated sulfones via episulfone intermediates to produce alkenes. An α -halogenated sulfone reacted with a base by deprotonation of the sulfone at the α' -position to give a carbanion. An intramolecular nucleophilic substitution reaction on the α -carbon-bearing halogen then gives an episulfone. Loss of sulfur dioxide from the episulfone intermediate gave an alkene. Examples of conversion of dihydro- and tetrahydrothiepine 1,1-dioxide to cyclohexene by Ramberg–Bäcklund rearrangement were shown in CHEC-II(1996) <1996CHECII(9)67>. Some new applications of the Ramberg–Bäcklund rearrangement of dihydro- and tetrahydrothiepine 1,1-dioxides have been reported.

Treatment of tetrahydrothiepine 1,1-dioxide **99** derived from D-mannitol with KOH/CCl₄ at 25 °C for 2 h gave cyclohexene **100** in 94% yield (Scheme 12), which was converted by acid treatment to the enantiopure (–)-conduritol E derivative **101** <1997TL7797, 1999PS305>.



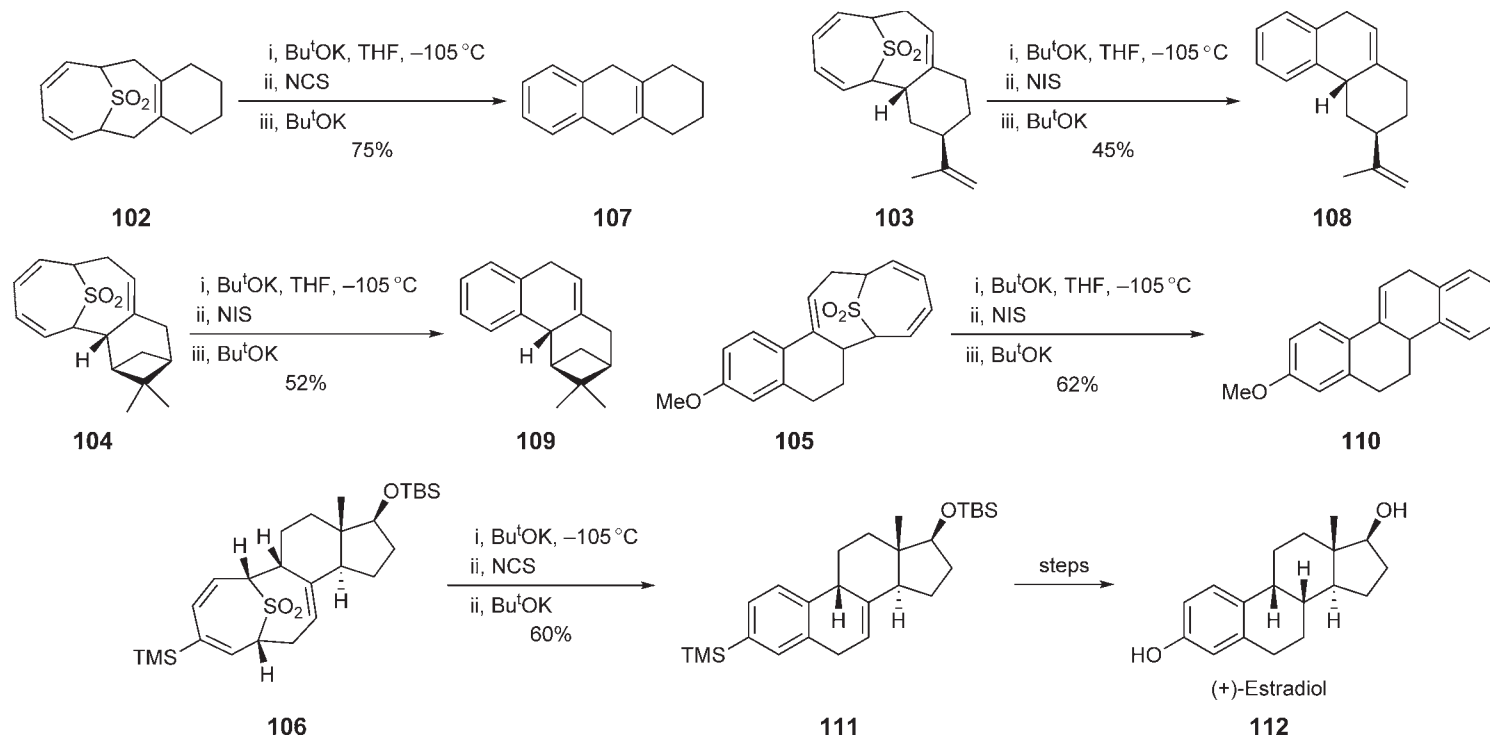
Scheme 12

Ramberg–Bäcklund rearrangement of fused dihydrothiepine 1,1-dioxides obtained via $[6\pi+4\pi]$ cycloaddition (Section 13.03.5.2) led to benzannulated polycycles <1996JOC7644, 1999JA8237>. The rearrangement was conducted by the sequential treatment of dihydrothiepin 1,1-dioxides **102–106** with Bu^tOK and *N*-chlorosuccinimide (NCS) or *N*-iodosuccinimide (NIS) at –105 °C, followed by the addition of another equivalent of the base (Scheme 13). The benzannulated product **111** was transformed to (+)-estradiol **112**.

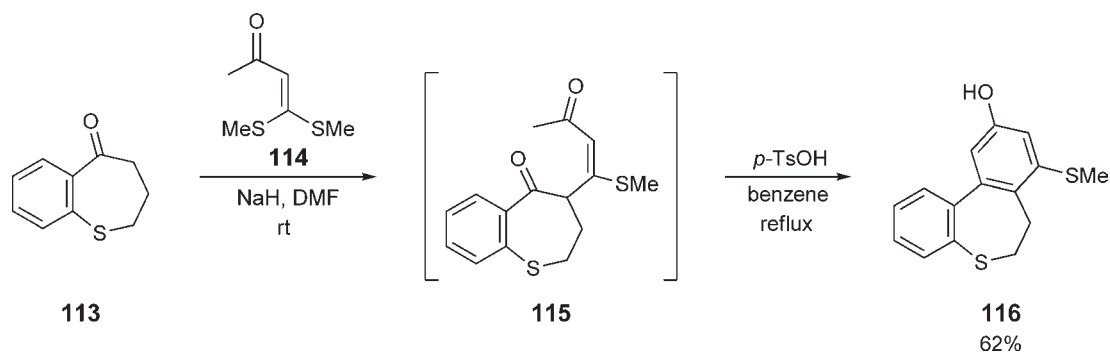
A new method for α -phenol annulation involving base-induced cycloaromatization of readily available 4-bis(methylthio)-3-buten-2-one **114** was applied to 3,4-dihydro-1-benzothiepin-5(2*H*)-one **113** (Scheme 14) <2002JOC5398>. Equimolar quantities of the benzothiepinone **113** and **114** in the presence of sodium hydride were stirred in dimethylformamide (DMF) at 25 °C. Treatment of the reaction mixture with *p*-toluenesulfonic acid in refluxing benzene furnished the phenol-annulated dihydrothiepine **116** in 62% yield. The reaction sequence involved formation of conjugate addition–elimination adduct **115**, followed by intramolecular aldol condensation and cycloaromatization, affording **116**.

13.03.6.3 Reactions with Radicals or Electron-Deficient Species and Reductions

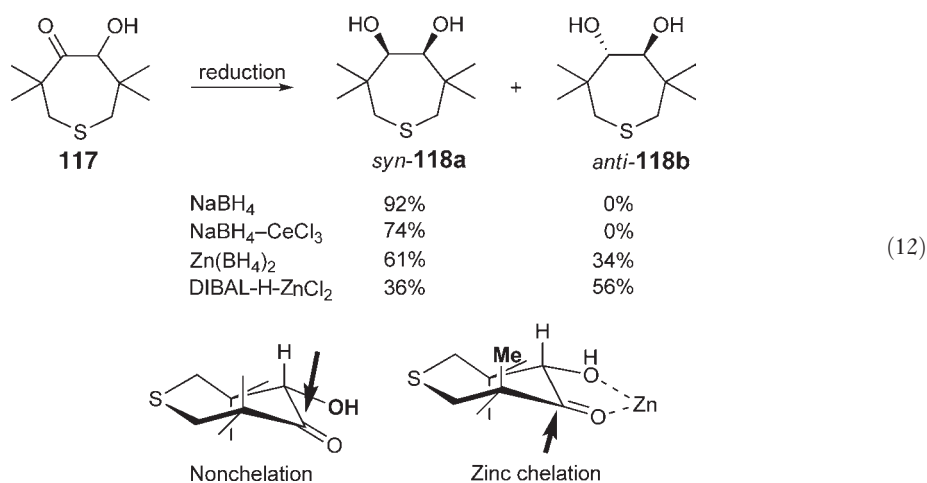
Stereoselective reduction of hydroxythiepanone **117**, which was prepared by intramolecular acyloin condensation, has been studied <1997J(P1)3479>. Reduction of hydroxythiepanone **117** with NaBH₄ or NaBH₄–CeCl₃ gave *syn*-diol **118a** exclusively in 92% and 74% yields (Equation 12). Reduction of thiepanone **117** with Zn(BH₄)₂ gave *syn*-diol **118a** and *anti*-diol **118b**, in 61% and 34% yields, respectively. Reduction of **117** with DIBAL–H–ZnCl₂ gave *anti*-diol **118b** as a major product in 56% yield, accompanied by *syn*-diol **118a** in 36% yield (DIBAL–H = diisobutylaluminium hydride). The formation of *syn*-diol **118a** can be explained by nonchelation control with a Felkin-like conformation of hydroxyketone **117** with the OH group at right angles to the plane of the carbonyl group and attack occurring from the face opposite the OH group. On the other hand, the *anti*-diol **118b** can be formed from the zinc chelate with pseudoaxial attack opposite the nearer pseudoaxial methyl group. Thus, some control of stereoselective reduction by chelation with zinc and nonchelation was achieved. The stereochemistry of *syn*- and *anti*-diols **118a** and **118b** was studied by X-ray crystal structure analysis.



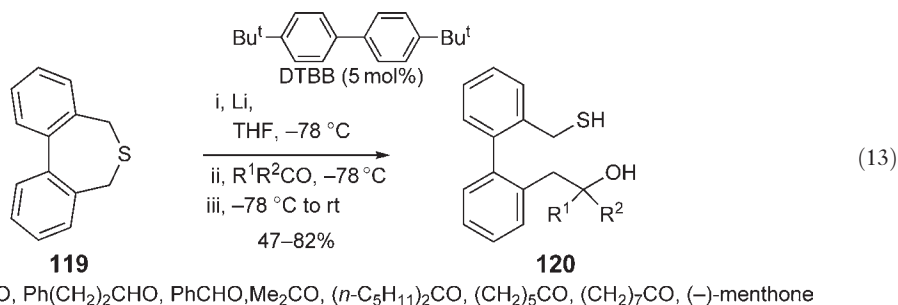
Scheme 13



Scheme 14

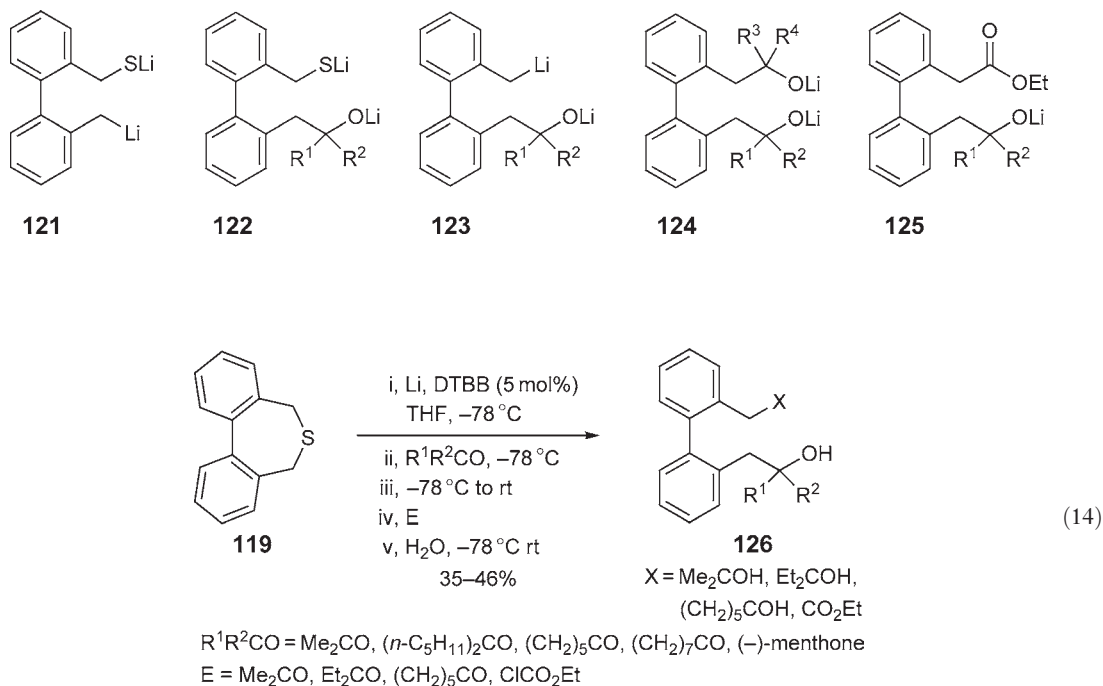


Reductive ring opening of dihydrodibenzothiepinines and dihydrodinaphthothiepinines and subsequent reaction with electrophile have been investigated [<2005T9082, 2001TL2469>](#). The reaction of 5,7-dihydrodibenzo[*c,e*]thiepine **119** with an excess of lithium and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 5 mol%) in tetrahydrofuran (THF) at -78°C , followed by treatment with carbonyl compounds ($\text{R}^1\text{R}^2\text{CO}$) led, after acid hydrolysis at -78 to 25°C , to the corresponding hydroxy thiols **120** in 47–82% yields (Equation 13). For prochiral carbonyl compounds, for example, pivalaldehyde, benzaldehyde, 3-phenylpropanal, and (–)-menthone, the corresponding 1:1 mixture **120** of diastereomers by NMR was obtained.

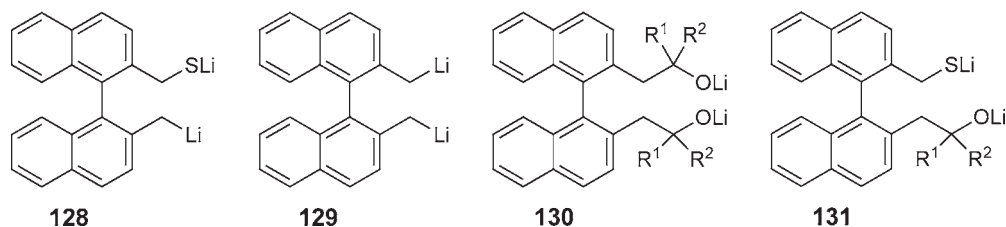
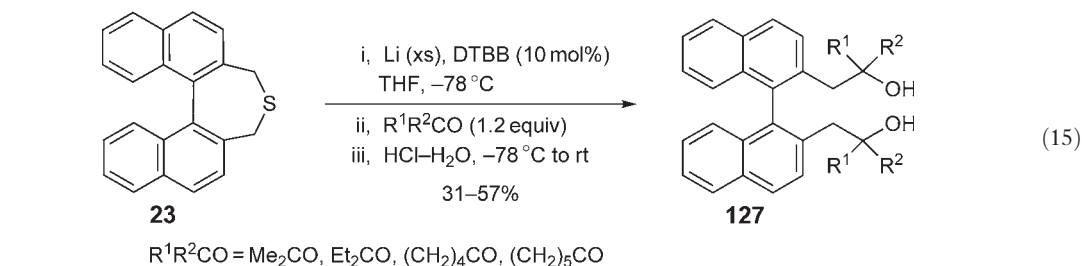


In the lithiation step (Equation 13), a reductive opening of the dihydrothiepine took place giving possible intermediate **121**, which by reaction with the carbonyl compound $\text{R}^1\text{R}^2\text{CO}$ used as electrophile gave the second intermediate **122**, precursor of products **120** by acidic hydrolysis. A variant of the lithiation of the starting material **119** resulted when a second electrophile was introduced in the molecule. After the generation of the intermediate **122**, instead of hydrolysis, a second lithiation took place at temperatures ranging between -78 and

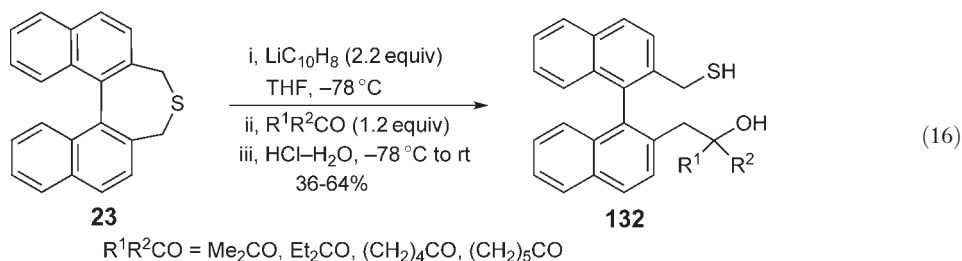
25 °C. Under these reaction conditions, a second carbon–sulfur bond was cleaved to lead to intermediate **123**, which by reaction with a second electrophile at -78°C gave, after hydrolysis, the products **126** in 35–46% yield (Equation 14). Before the final hydrolysis, intermediates **124** (for $\text{R}^3\text{R}^4\text{CO}$) or **125** (for ClCO_2Et) may be involved in the process.



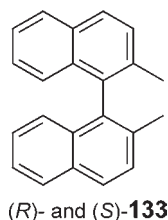
The reaction of 4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]thiepine **23** with an excess of lithium and a catalytic amount of DTBB, under the same reaction conditions as shown in Equation (13) (THF, -78°C), gave, after treatment with a carbonyl compound as electrophile ($\text{R}^1\text{R}^2\text{CO}$) (1.2 equiv to **23**) at -78°C , and hydrolysis, the corresponding **127**, resulting from a double condensation at both benzylic positions in 31–57% yields, based on the starting material **23** (Equation 15). In contrast to the reaction of dibenzothiepine **119**, in the case of dinaphthothiepine **23** after the first reductive ring opening, the organolithium intermediate **128** may suffer a rapid second lithiation to give the dilithium **129**, which reacted with the electrophile to lead to the corresponding dialkoxide **130**, which is a precursor of the products **127**.



Lithiation of dihydrodinaphthothiepine **23** with 2.2 equiv of lithium naphthalenide in THF at -78°C followed by reaction with electrophiles at -78°C led, after hydrolysis, to the unsymmetrically 2,2'-disubstituted binaphthyl **132** in 36–64% yields (Equation 16). Using milder reduction conditions, the first lithiation product **128** reacted with the electrophile giving an intermediate of type **131**, which by hydrolysis afforded thiols **132**.



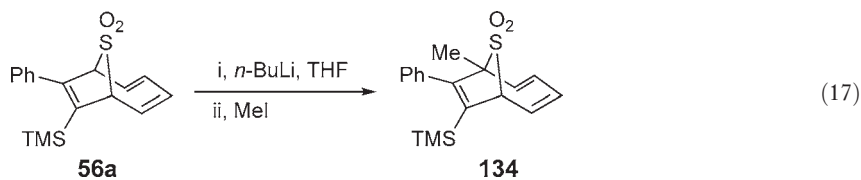
The reaction of (*R*)- or (*S*)-dihydrodinaphthothiepin **23** with an excess of lithium and a catalytic amount of DTBB, under the same reaction conditions shown in Equation (15), after treatment with a carbonyl compound [(Et_2CO or $(\text{CH}_2)_5\text{CO}$] or H_2O as electrophile, gave enantiomerically pure **127** and **133**, respectively. No racemization occurred during the whole process of the tandem reaction.



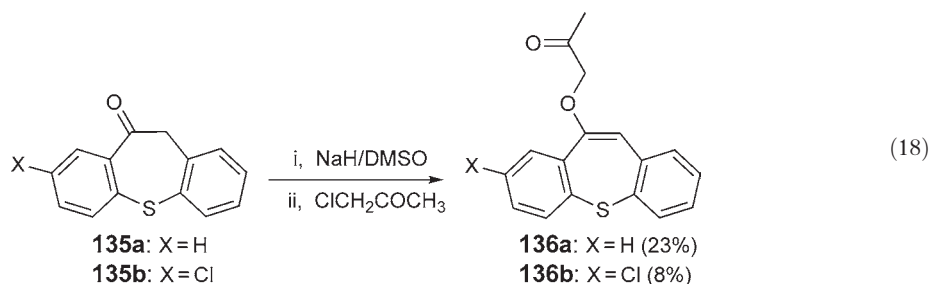
13.03.7 Reactivity of Substituents Attached to Ring Carbon Atoms

13.03.7.1 Attack at Hydrogen

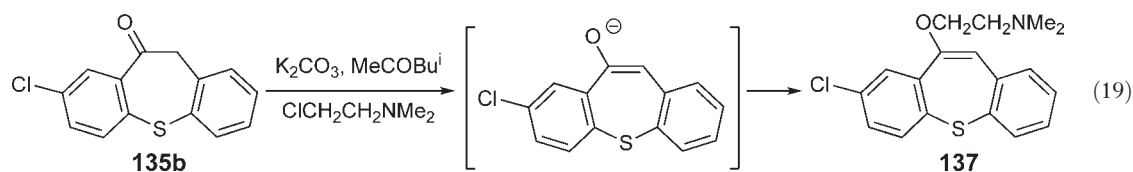
Deprotonation at the bridgehead position in the 9-thiabicyclo[4.2.1]nonatriene-9,9-dioxide **56a** was examined (Equation 17) <1997TL2049>. Thus, treatment of **56a** with excess *n*-BuLi followed by quenching with MeI afforded the monoalkylated bicycle **134**. Metalation occurred only at the position adjacent to the phenyl ring in this substrate, while related compounds without phenyl substituents gave dialkylated products under these conditions. Neighboring phenyl rings are suggested to direct the regiochemical course of metalation. Attempted cheletropic extrusion of SO_2 of the product **134**, described in Section 13.03.5.2, produced many products in low yield.



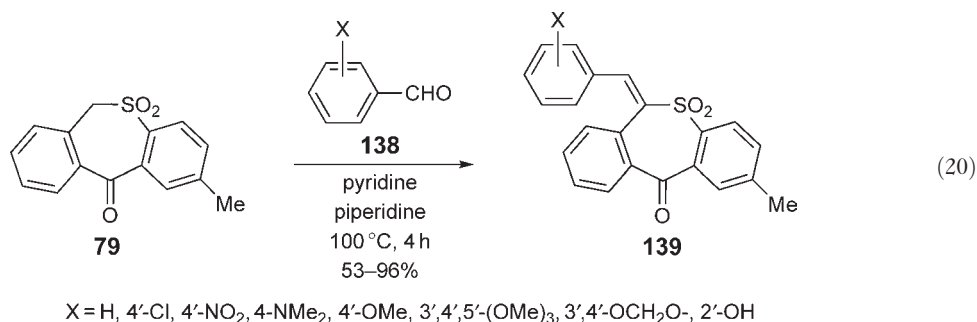
Reaction of 11*H*-dibenzo[*b,f*]thiepin-10-ones **135a** and **135b** with chloroacetone in the presence of base in dimethyl sulfoxide (DMSO) resulted in formation of O-alkylation products **136a** and **136b** in 23% and 8% yields, respectively (Equation 18) <2006JHC749>. On the other hand, oxepine analogs preferentially gave C-alkylation products.



The reaction mechanism of alkylation of 2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-11-one **135b** using potassium carbonate, as a base, to lead to thiepine **137** (zotepine) was studied. Examination of reaction field and reaction rate suggested that the deprotonation of thiepine **135b** and subsequent alkylation took place on the surface of potassium carbonate, and the rate-determining step for the reaction was found to be the deprotonation (Equation 19) <2003MI727>.



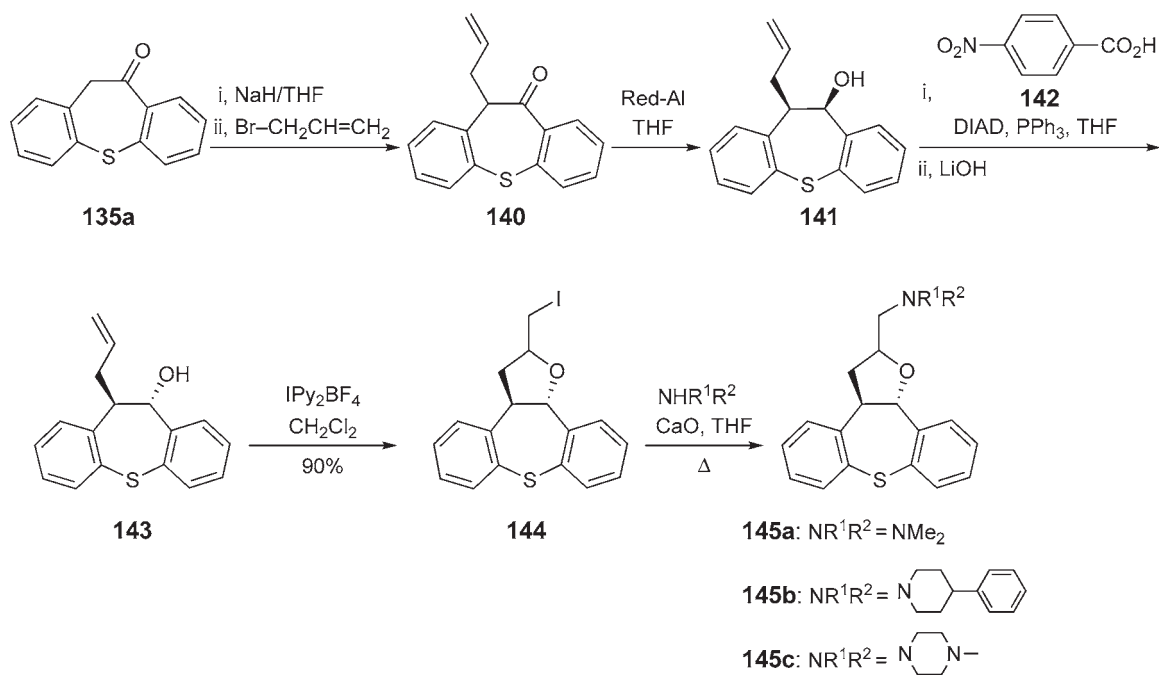
Treatment of 2-methyldibenzo[*b,e*]thiepin-11(6*H*)-one 5,5-dioxide **79** with aromatic aldehydes **138** in pyridine and piperidine produced the Knoevenagel condensation products **139** in 53–96% yields (Equation 20) <2005MI524>.



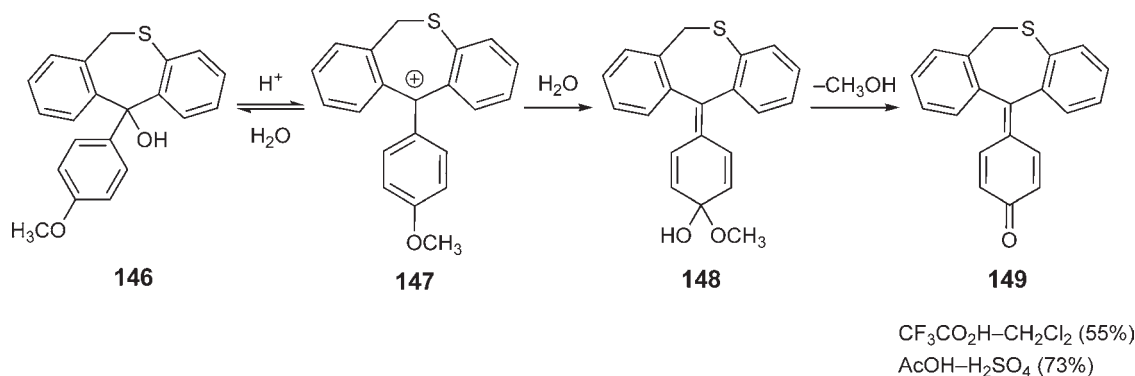
13.03.7.2 Attack at Carbon Functional Groups

Sequential transformation to target molecules **145**, as potential drugs including a thiepine skeleton, was reported <2004BML2765>. First, the reaction of the dihydrodibenzo[*b,f*]thiepinone **135a** with sodium hydride, followed by addition of allyl bromide afforded the α -allylated dihydrodibenzo[*b,f*]thiepinone **140** (Scheme 15) (see Section 13.03.7.1). The reduction of ketone **140** with Red-Al at -30°C in THF gave the *cis*-alcohol **141** with complete diastereoselectivity (see Section 13.03.6.3). Then, the *cis*-alcohol **141** was transformed to the tetrahydrofuran *trans*-fused thiepinines as follows. The required *trans*- β -allylic alcohol **143** was prepared by Mitsunobu inversion reaction of the *cis*-alcohol **141** with *p*-nitrobenzoic acid **142**, followed by ester hydrolysis. The reaction of compound **143** with IPy₂BF₄ [bis(pyridine)iodonium(tetrafluoroborate)] as cyclizing reagent led to the 2-iodomethyltetrahydrofuran **144** in 90% yield, as an equimolar mixture of diastereoisomers. Conversion of **144** into the 2-aminomethyltetrahydrofuran-fused dibenzothiepine derivatives **145a–c** was effected by heating with the amines in THF.

The reaction of 6*H*-dibenzo[*b,e*]thiepin-11-ol **146** in trifluoroacetic acid in CH₂Cl₂ or in glacial acetic acid and conc. H₂SO₄ led to 4-(6*H*-dibenzo[*b,e*]thiepin-11-ylidene)cyclohexa-2,5-dienone **149** in 55% and 73% yields, respectively (Scheme 16) <2002JCM516>. A plausible mechanism involves the formation of stable carbocation **147**, followed by nucleophilic attack of water at methoxy-substituted aryl carbon atom giving a hemiacetal **148**, which subsequently eliminates methanol resulting in quinone methide **149**.

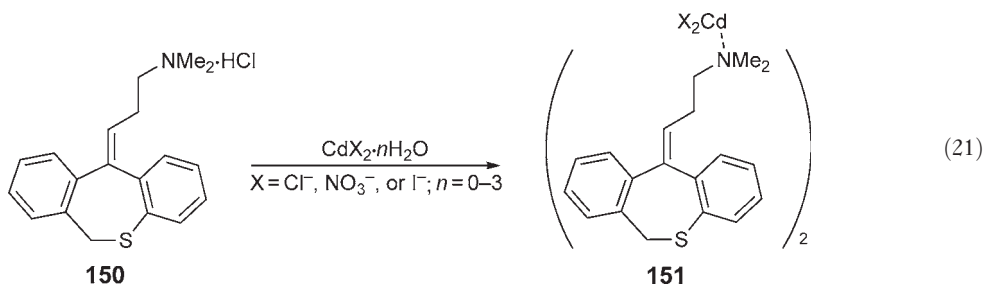


Scheme 15



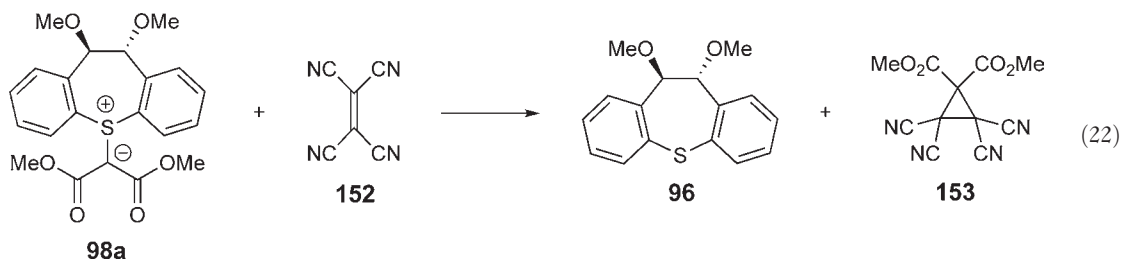
Scheme 16

The reaction of 3-(6*H*-dibenzo[*b,e*]thiepin-11-ylidene)propyldimethylamine chloride **150** and $\text{CdX}_2 \cdot n\text{H}_2\text{O}$ ($\text{X} = \text{Cl}^-$, NO_3^- , or I^- , $n = 0-3$) gave Cd(II) complexes **151** in a 2:1 ratio <2002MI565>. Infrared (IR) and ^1H NMR spectra of Cd(II) complex **151** showed the structure as shown in Equation (21); its thermal degradation kinetics were studied.



13.03.8 Reactivity of Substituents Attached to the Ring Sulfur Atom

Only a limited number of examples have been reported. The reactivity of sulfonium ylide **98a**, prepared by the reaction of thiepine **96** and dimethyl diazomalonate (Section 13.03.6.1), was examined <2006OBC2218>. The reactivity of the stabilized sulfonium ylide **98a** was restricted to the highly reactive Michael acceptor, tetracyanoethylene **152** (the ylide failed to react with benzaldehyde or dicyanoethylene). Reaction of ylide **98a** with tetracyanoethylene **152** led to the consumption of the ylide **98a** (Equation 22). Thiepine **96** was produced in the reaction and the formation of cyclopropane **153** was suggested.

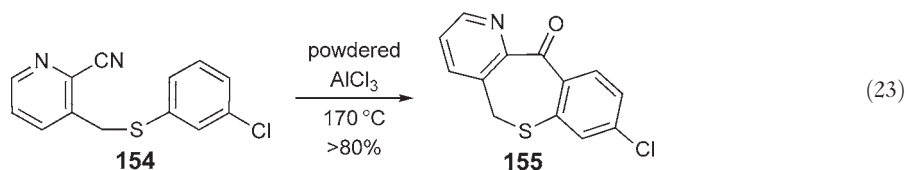


13.03.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

13.03.9.1 By Formation of One Bond

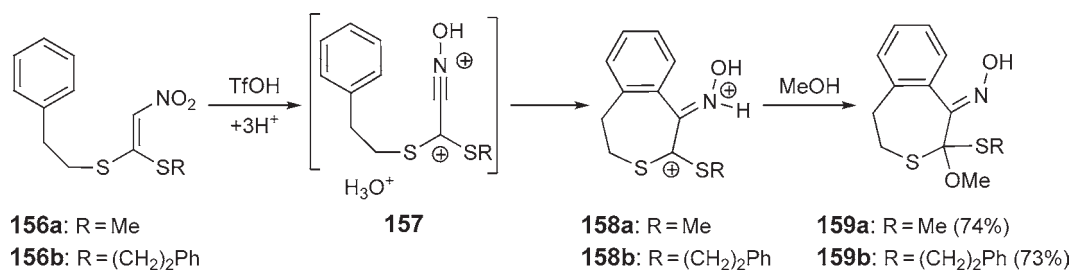
Carbon–carbon bond formation by Friedel–Crafts reactions was a versatile procedure for benzo- and dibenzothiepinines. Some new methods to synthesize thiepine rings by Friedel–Crafts-type reactions have been reported. Carbon–sulfur bond formation has been used for dihydro-, tetrahydrothiepinines, and thiepanes. New cyclization methods involving carbon–sulfur and carbon–carbon bond formation have been added.

An improved method of preparing the 5,11-dihydro[1]benzothiepine[4,3-*b*]pyridine-5-one skeleton **155** was reported (Equation 23) <1998BML2521>. Admixing the precursor **154** with 3–5 equiv of powdered AlCl_3 and melting this mixture at 170°C for <30 min afforded the 8-chloro isomer **155** with high regioselectivity (>97:1) in >80% yield. Preparation of this ring system under conventional Friedel–Crafts conditions (PPA) was previously reported with low yields (5–18%) <1981CPB3515>.

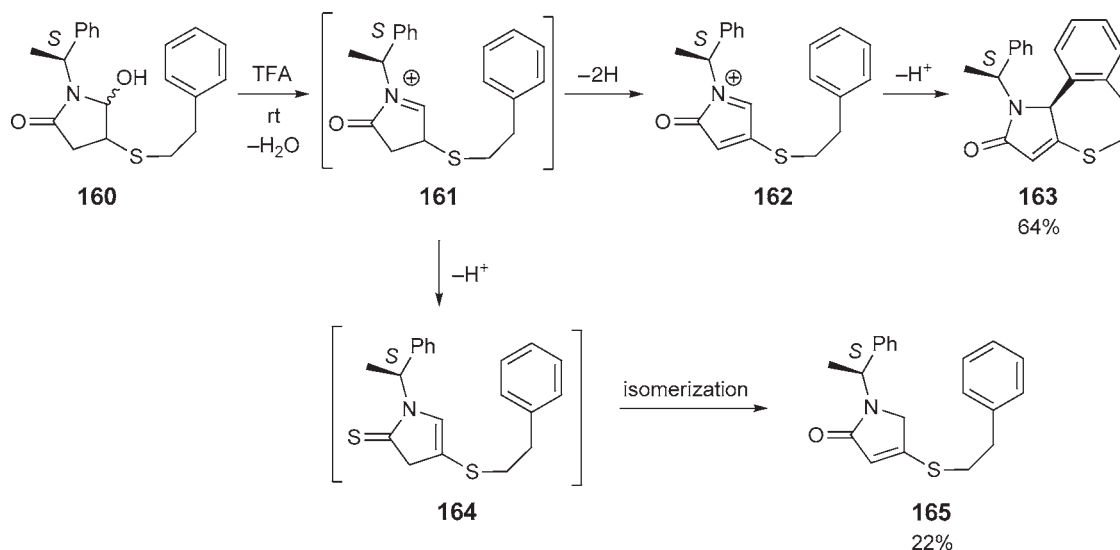


Cyclization of nitroketene *S,S*-acetals **156a** and **156b** in trifluoromethanesulfonic acid led to 4,5-dihydrobenzo[*d*]thiepinines **159a** and **159b** (Scheme 17) <2001EJO1525>. The reactions were conducted in trifluoromethanesulfonic acid at 0°C or at -60 to -80°C . The formation of intermediate dications **158a** and **158b** was detected by NMR spectroscopy. The formation of the cations **158a** and **158b** may be explained as follows: starting **156a** and **156b** underwent multiple protonation, leading quickly to the formation of conjugated hydroxynitrilium cations **157**, which were not observed. As soon as they are formed, the cations **157** reacted with the tethered phenyl ring by means of an electrophilic aromatic substitution mechanism, to afford the observed cations **158a** and **158b**. Addition at the $\text{C}\equiv\text{N}$ bond of the hydroxynitrilium ions occurred with a *cis*-configuration of the aromatic and OH groups, leading to single isomers **158a** and **158b** with (*E*)-configuration. Quenching with MeOH at low temperature afforded thiepinines **159a** and **159b** in 74% and 73% yields, respectively.

Chiral benzo[*d*]thiepine fused to pyrrole ring **163** was obtained via a tandem dehydrogenation/intramolecular arylation <2001TL573>. Treatment of α -hydroxylactam **160** with trifluoroacetic acid (TFA) at 25°C gave a separable mixture of **163** and **165** in 64% and 22% yields, respectively (Scheme 18). Formation of the minor product **165** was a consequence of deprotonation of *N*-acyliminium ion **161**, followed by isomerization of unstable enamide **164**. Formation of benzo[*d*]thiepine **163** can be explained by a π -aromatic intramolecular arylation of



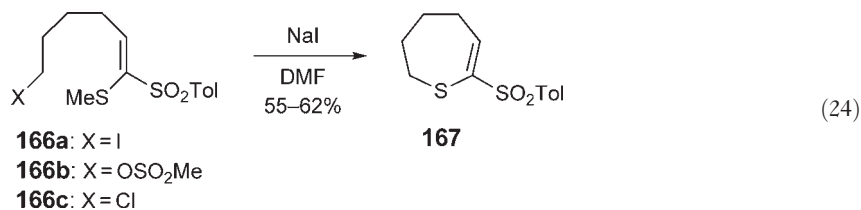
Scheme 17



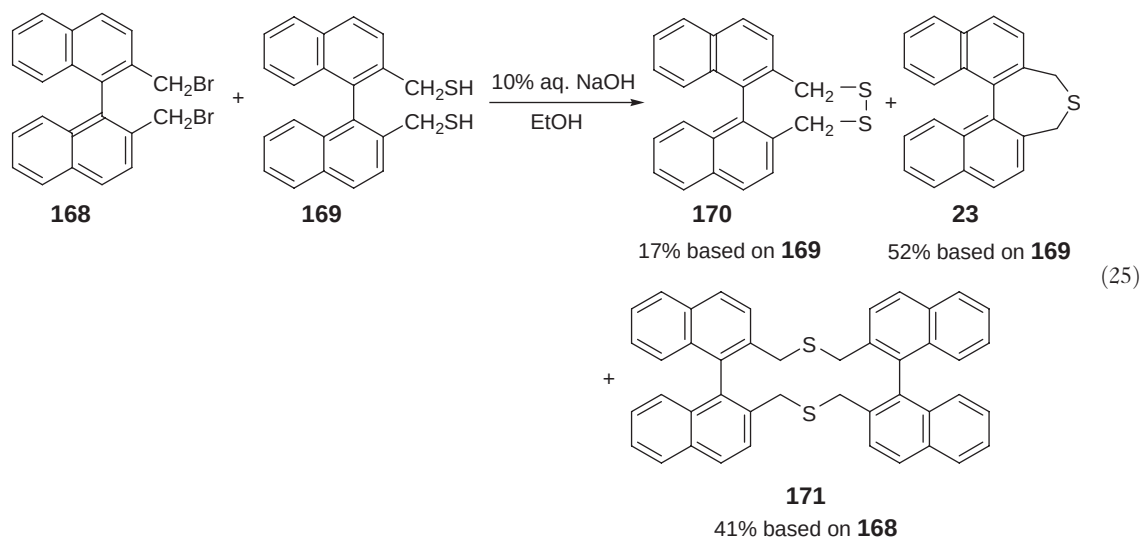
Scheme 18

N-acyliminium ion intermediates **162**, generated from *N*-acyliminium ions **161** by spontaneous loss of two hydrogen atoms. The π -cyclization step seemed to proceed stereoselectively and the thiepine **163** was obtained as a single diastereoisomer.

Refluxing the iodide **166a** derived from a δ -lactol in DMF in the presence of 10 equiv of sodium iodide gave 4,5,6,7-tetrahydrothiepine **167** in 55% yield (Equation 24) <2001JHC579>. The same product **167** was formed directly from the methanesulfonate **166b** and chloride **166c** in 59% and 62% yields, respectively, by refluxing their solutions in DMF in the presence of 10 equiv of sodium iodide. Apparently, the cyclization of **166b** or **166c** proceeds via the iodide **166a**. The sulfide group in **166a** acted as a nucleophile.



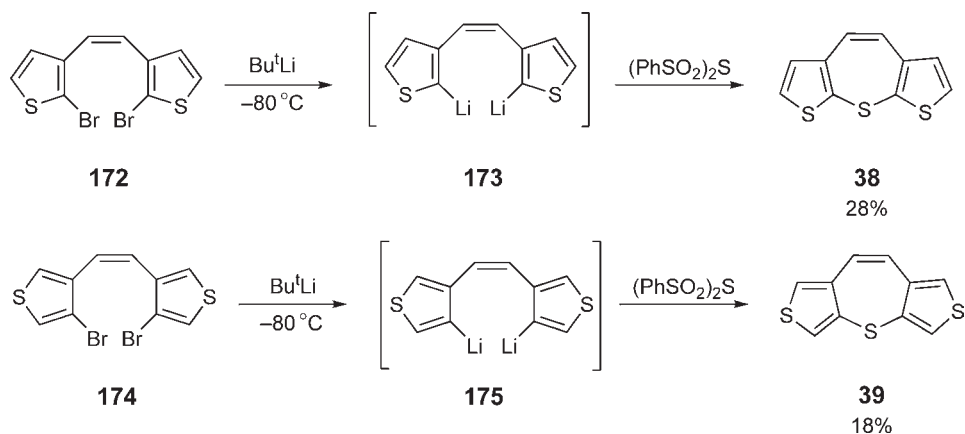
Reaction of dibromide **168** with 1,1'-binaphthalene-2,2'-bis(methylenethiol) **169** gave a mixture containing the disulfide **170** (17% based on **169**), dinaphtho[2,1-*c*:1',2'-*d'*]thiepine **23** (52% based on **169**), and the major **171** isolated from reaction between dibromide **168** and dithiol **169** (41% based on **168**) (Equation 25) <1995T787>. An efficient synthesis of thiepine **23** by treatment of dibromide **168** with sodium sulfide was also reported <1994JOC1326> (see Section 13.03.9.2).



13.03.9.2 By Formation of Two Bonds

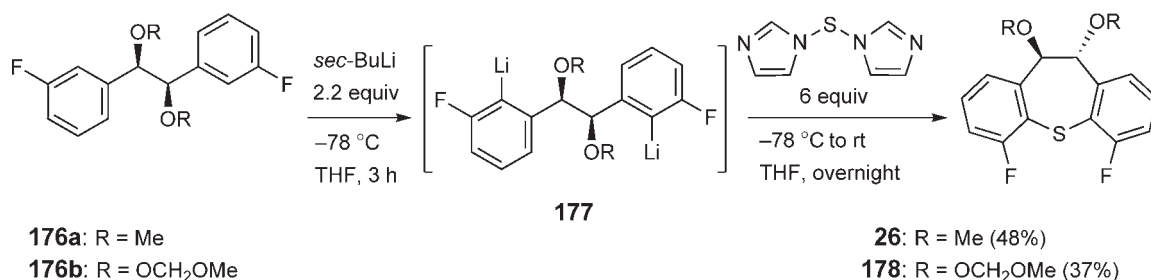
The useful ring closure providing benzothiepinines involved the formation of both S–C bonds by reaction of diaryllithium or divinylolithium organometallic species with S^{2+} equivalents. Another method for formation of both S–C bonds toward dihydro- and tetrahydrothiepinines and thiepinines is the nucleophilic substitution reaction of S^{2-} equivalents (Na_2S or Li_2S) with dibromides. Synthesis of thiepinines by the related stepwise formation of two S–C bonds was also described.

Dibromide **172** was treated with *tert*-butyllithium in ether at -80°C , then with $(PhSO_2)_2S$ to result in ring closure giving dithieno[2,3-*b*;3',2'-*f*]thiepine **38** in 28% yield, presumably via the dilithium intermediate **173**. Dibromide **174** afforded dithieno[3,4-*b*;3',4'-*f*]thiepine **39** in 18% yield (Scheme 19) <1997H(45)1899>.



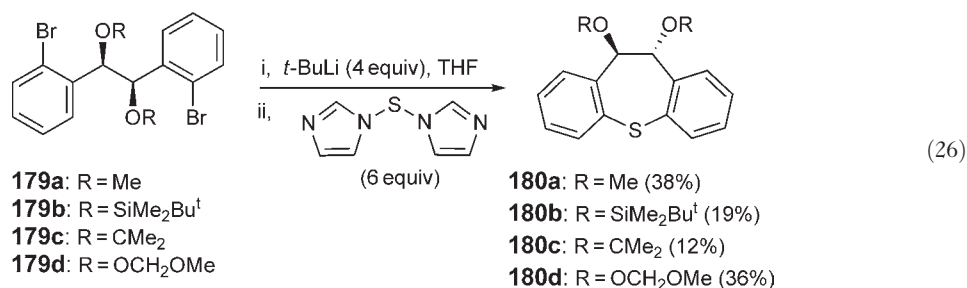
Scheme 19

C_2 Symmetrical and enantiomerically pure thiepinines were prepared <1999TL813, 2006OBC2218>. Diaryl compounds with two chiral centers **176** were lithiated with *sec*-butyl lithium in THF at -78°C to give the bis-*ortho*-lithiated **177**. Reaction of sulfur diimidazole led to thiepinines **26** and **178** in 37–48% yield (Scheme 20). The use of elemental sulfur, thionyl chloride, sulfuryl chloride, SCl_2 , $SO_2(\text{imidazolyl})_2$, $SO(\text{imidazolyl})_2$, sulfur ditriazole, and sulfur bisbenzotriazole, as a sulfur electrophile, gave cyclized products in poor results.

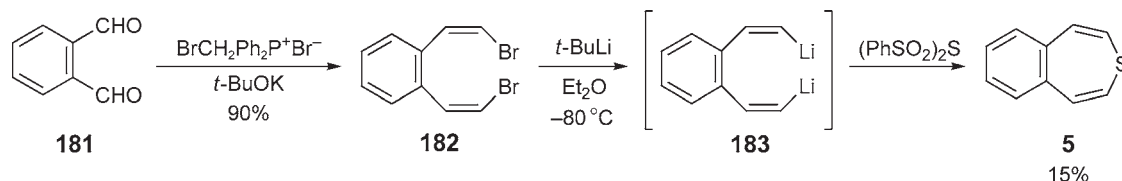


Scheme 20

The thiepinines **180** were prepared via a bromine/lithium exchange for *ortho*-lithiation of **179** (Equation 26). Lithiation was achieved using *t*-BuLi (2 equiv for each bromine) and sulfur diimidazole was used as the sulfur electrophile. Thiepinines **180a–d** were obtained in 12–38% yield.



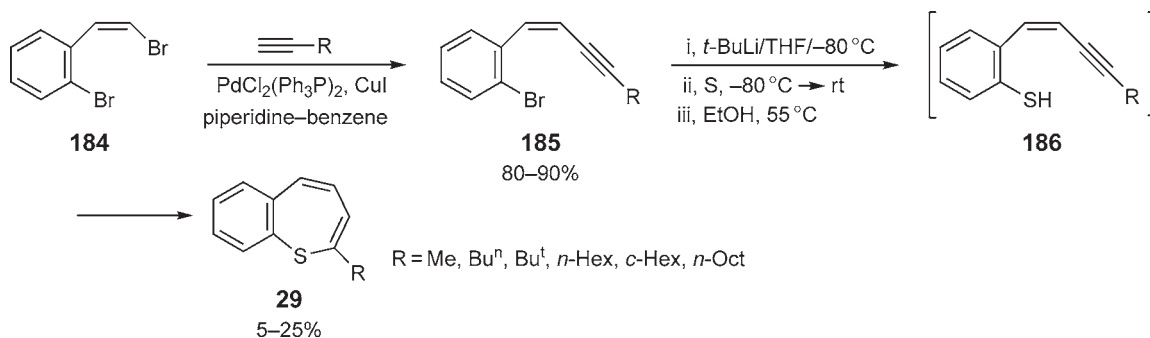
3-Benzothiepine **5** was prepared by the reaction of electrophilic sulfur reagent with (*Z,Z*)-*o*-bis(β -lithiovinyl)benzene **183** which was derived in two steps from common *o*-phthalaldehyde **181** (Scheme 21) <2003CPB1283>. The dibromo **182** was treated with excess *t*-BuLi in diethyl ether at -80°C , and then with (PhSO₂)₂S to result in ring closure, giving rise to 3-benzothiepine **5** in 15% yield. 3-Benzothiepine **5** was thermally labile toward sulfur extrusion and gradually decomposed to naphthalene during isolation by column chromatography, which was thought to be the main reason for its relatively low isolated yield (Section 13.03.4.1).



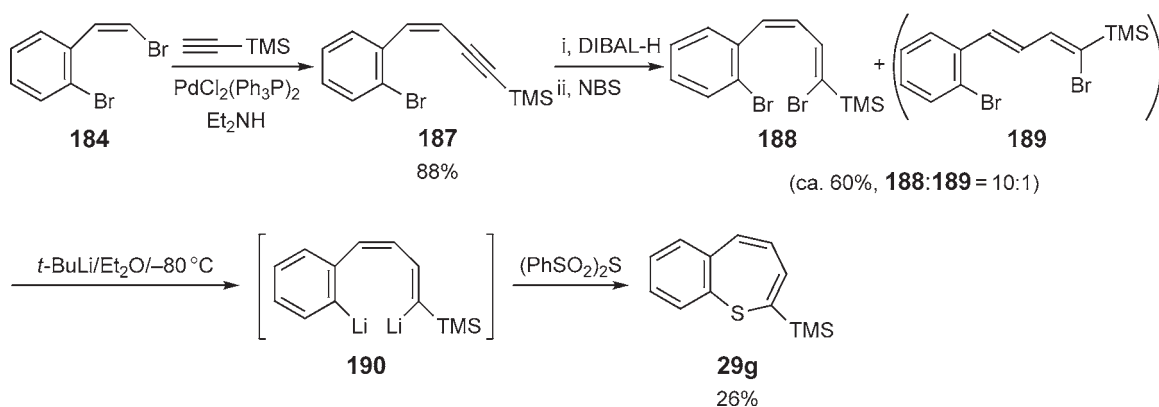
Scheme 21

The 2-alkyl-1-benzothiepinines **29** were obtained from the enynes **186** by successive treatment with *t*-butyllithium, sulfur powder, and ethanol in one pot (Scheme 22) <1995CPB19>. Thus, (*Z*)- β -*o*-dibromostyrene **184** was coupled with various alkylacetylenes in the presence of PdCl₂(Ph₃P)₂-CuI to give the corresponding 4-alkyl-1-(*o*-bromophenyl)-1-buten-3-yne **185** in 80–90% yield. The enynes **185** were lithiated with *t*-butyllithium in THF at -80°C and then treated with sulfur, followed by treatment with ethanol, to give 2-alkyl-1-benzothiepinines **29** in 5–25% yields. The reaction presumably proceeds via thiophenol intermediates **186**.

Similarly, the silicon-substituted precursor **187** was obtained by the reaction of **184** and trimethylsilylacetylene in 88% yield (Scheme 23) <1999CPB1108>. The enyne **187** was hydroaluminated with DIBAL-H, followed by bromination with NBS to give (*Z,Z*)-dibromide **188** and its (*Z,E*)-stereoisomer **189** in a ratio 10:1 in ca. 60% yield. The dibromide **188** containing small amount of isomer **189** was treated with a excess of *t*-butyllithium, followed by (PhSO₂)₂S resulting in ring closure to form the 2-trimethylsilyl-1-benzothiepine **29g** in 26% yield, presumably via the 1,6-dilithium intermediate **190**.

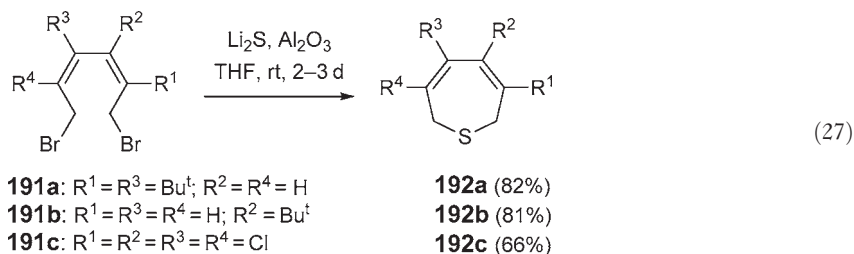


Scheme 22



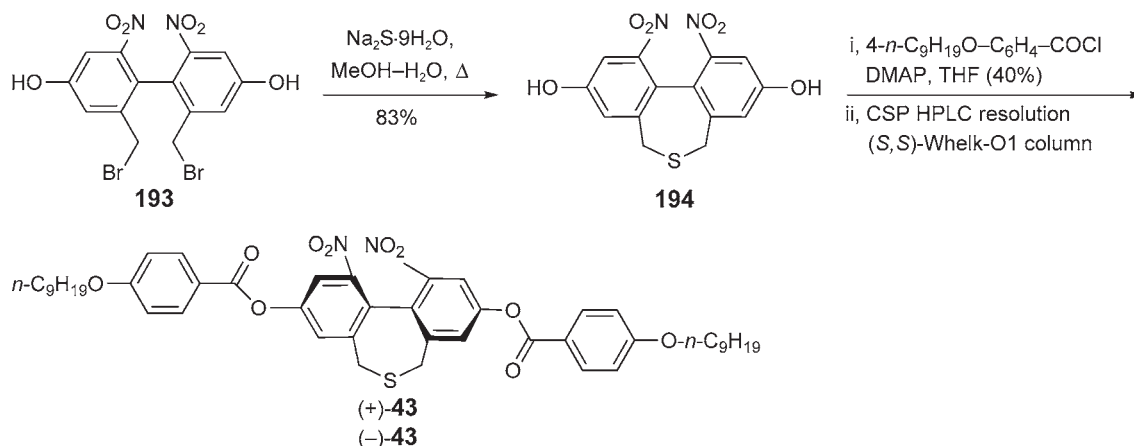
Scheme 23

The reaction of dibromides **191** and Li_2S gave dihydrothiepinines **192** in 66–82% yield (Equation 27) <2000H(53)897>.

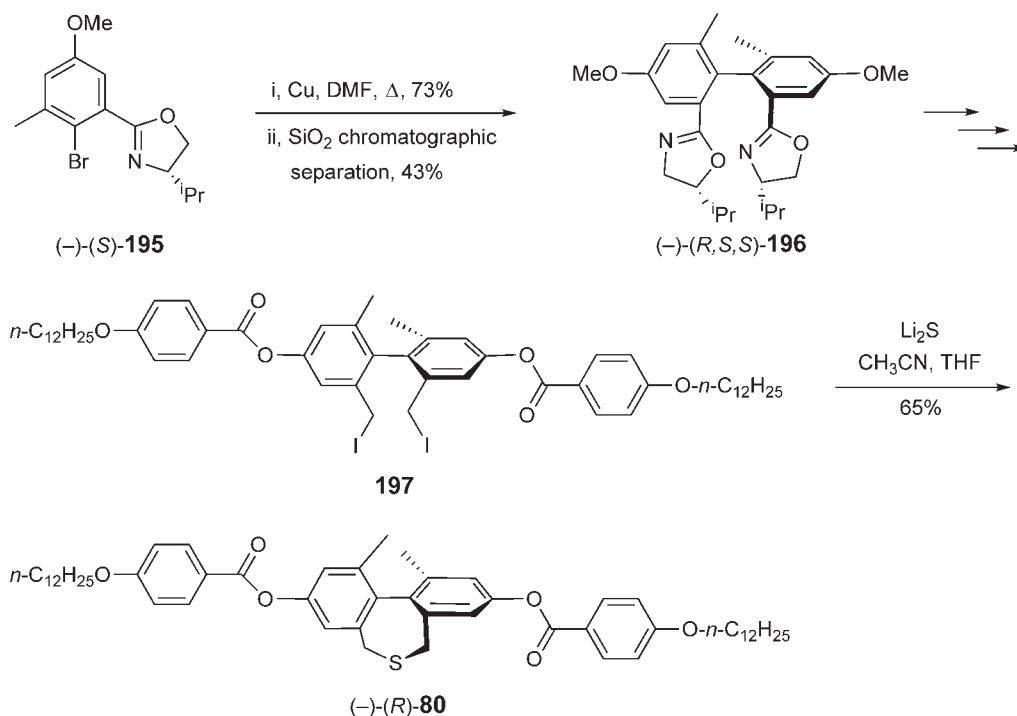


An atropisomeric compound containing a bridged biphenyl core with helical topography, 3,9-bis[(4-nonyloxy)benzoyloxy]-5,7-dihydro-1,11-dinitrodibenzo[*c,e*]thiepine **43**, was obtained in racemic form by treatment of the dibromide precursor **193** with $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ in $\text{MeOH-H}_2\text{O}$, followed by esterification with the corresponding acid chloride (Scheme 24) <2002JMC586>. Resolution of $(\pm)\text{-43}$ was achieved on a semi-prep scale by chiral HPLC (Section 13.03.4.2).

The enantiomerically pure bridged biphenyl, $(-)\text{-}(R)\text{-}3,9\text{-bis}[4\text{-(dodecyloxy)benzoyloxy}]\text{-}5,7\text{-dihydro-}1,11\text{-dimethyl-dibenzo}[c,e]\text{thiepine}$ **80**, was prepared from enantiomerically pure diiodide **197** (Scheme 25) <1998JOC3895>. The synthesis of the precursor **197** was based on Ullmann coupling reaction of the chiral oxazoline $(-)\text{-}(S)\text{-195}$.



Scheme 24

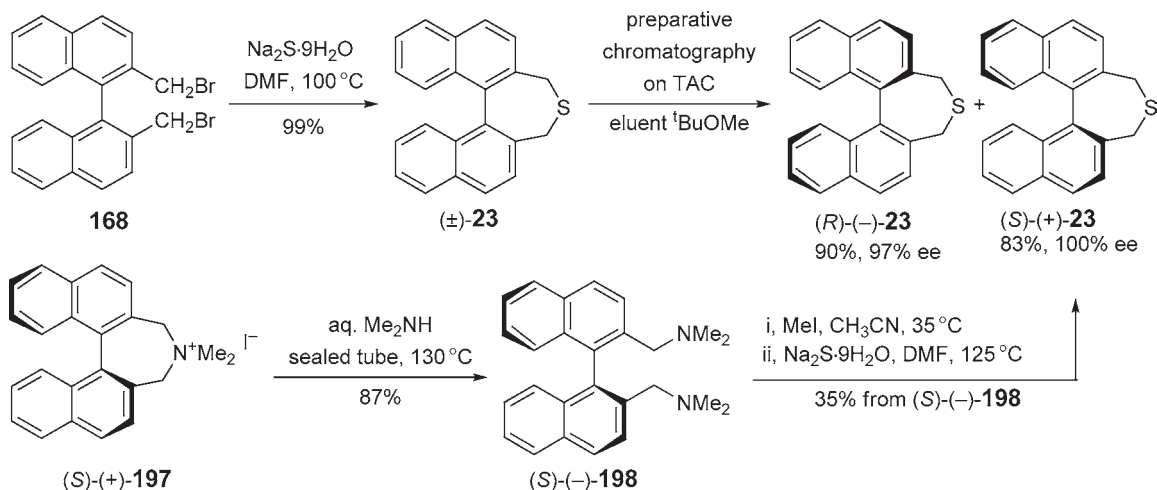


Scheme 25

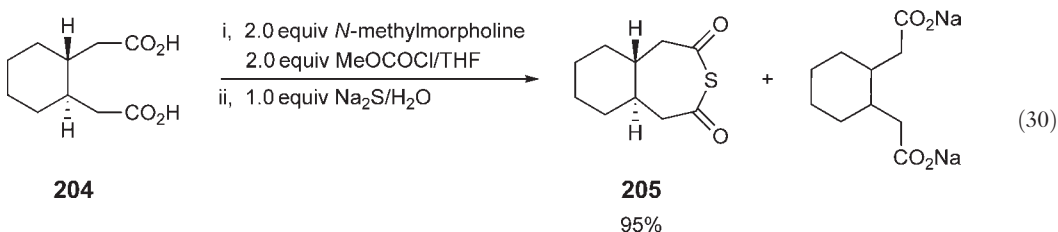
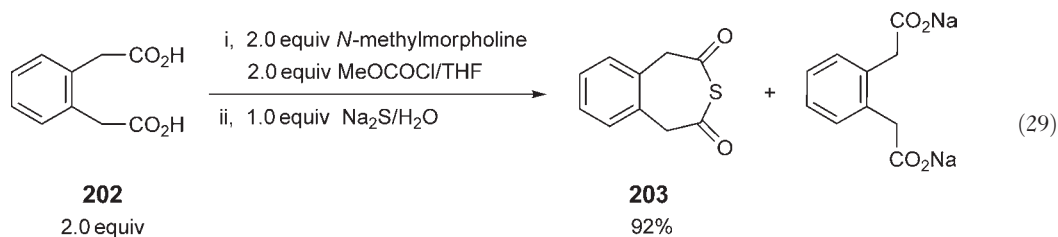
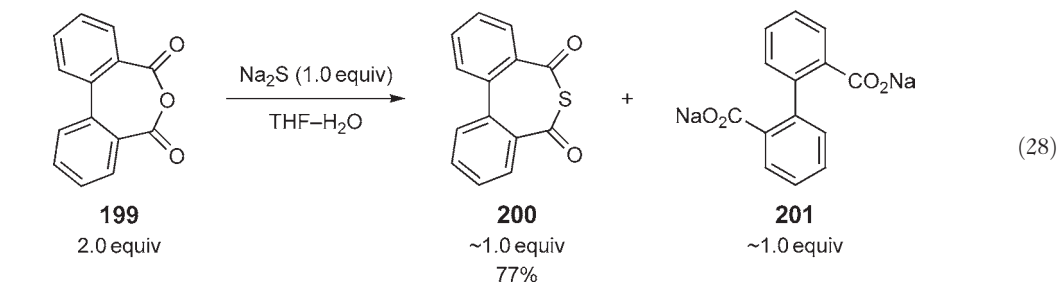
On reaction with sodium sulfide in DMF, easily accessible racemic 2,2'-bis(bromomethyl)-1,1'-binaphthyl **168** afforded dihydrothiepine **23** in 99% yield (Scheme 26) <1994JOC1326>. The racemic thiepine **23** was resolved by liquid chromatography on triacetylcellulose on a preparative scale to give (*R*)-(-)-**23** (90% yield, 97% ee) and (*S*)-(+)-**23** (83% yield, 100% ee) (Section 13.03.4.2). Alternatively, reaction of diamine (*S*)-(-)-**198**, which is derived from an enantiomer (*S*)-(+)-**197**, and methyl iodide in MeCN and subsequent reaction with $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ in DMF gave (*S*)-(+)-**23** in 35% yield.

Chiral thiepine **23** was also prepared from chiral dibromo derivative **168**, which was derived from commercially available (*R*)- or (*S*)-binaphthol <2005T9082>.

Reaction of seven-membered anhydride with sodium sulfide in a 2:1 molar ratio afforded seven-membered thioanhydride and dicarboxylate in a 1:1 molar ratio (Equation 28) <1995JHC971>. The reaction of **199** gave 5,7-dihydrodibenzo[*c,e*]thiepin-5,7-dione **200** in 77% yield. Seven-membered ring anhydrides synthesized *in situ* from the corresponding diacids **202** and **204** using *N*-methylmorpholine and methyl chloroformate were treated with sodium sulfide in THF- H_2O to form thioanhydrides **203** and **205** in 92–95% yield (Equations 29 and 30).

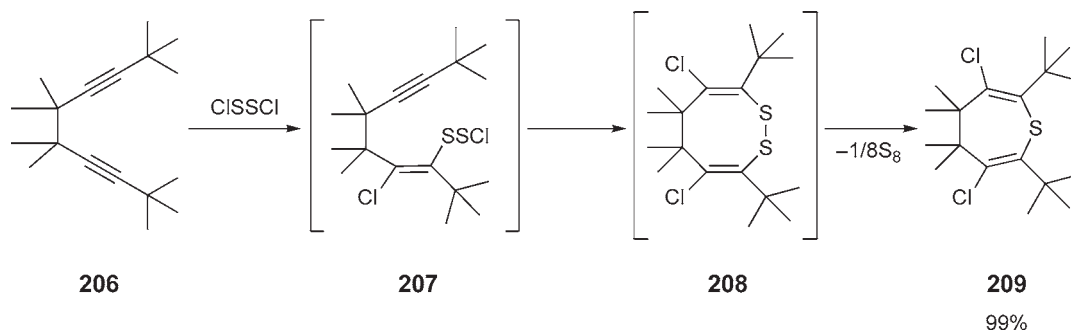


Scheme 26



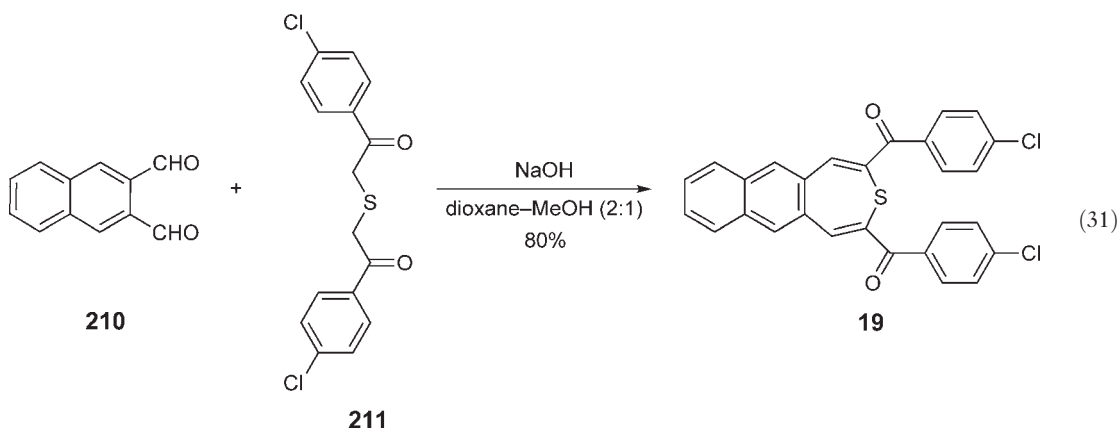
Reaction of α,ω -dibrominated derivatives of *D*-mannitol and *D*-glucitol with $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ gave thiepane derivatives as thiosugars <2001TL3307>. Double substitution of *p*-toluenesulfonate with Na_2S was used to construct 3-thia-8-oxa[3.2.1]bicycles <1997JOC7080>. Ring opening of the resulting thiaoxa[3.2.1]bicycles by chiral base gave substituted tetrahydrothiepinines enantioselectively.

The reaction of 2,2,5,5,6,6,9,9-octamethyl-3,7-decadiyne **206** with S_2Cl_2 gave a 4*H*,5*H*-thiepine **209**, as the sole product, in 99% yield <2000TL8349>. The formation of **209** was explained as shown in Scheme 27. The addition of S_2Cl_2 to one alkyne moiety produced adduct **207**. Intramolecular addition of the intermediate **207** provided cyclic disulfide **208**; then, dihydrothiepine **209** may form from disulfide **208** by loss of sulfur.

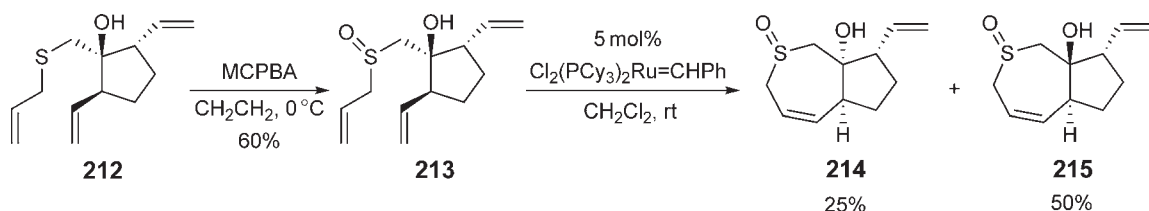


Scheme 27

A few examples of formation of two carbon–carbon bonds were also reported. 2,7-Di-*p*-chlorobenzoylnaphtho[2'3'-4:5]thiepine **19** was prepared by condensation of di-*p*-chlorophenacyl sulfide **211** with naphthalene-2,3-dialdehyde **210** in 2:1 dioxane–MeOH containing a catalytic amount of NaOH in 80% yield (Equation 31) <2004MI326>. The compound **19** exhibited the property as a flexible host molecule (Section 13.03.3.1).

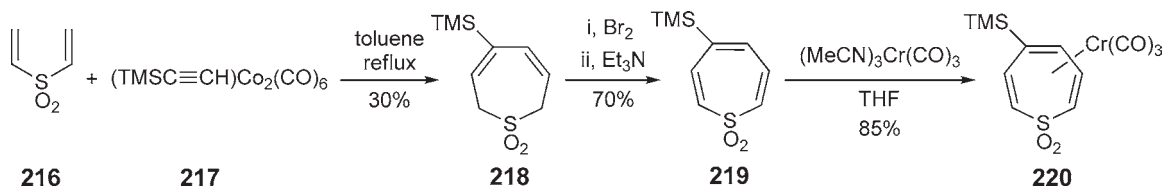


The ring-closing metathesis of sulfoxide **213** using Grubbs' catalyst gave fused dihydrothiepine oxide diastereoisomers **214** and **215** in 25% and 50% yields, respectively (Scheme 28) <2002SL1987>. However, attempts to perform ring-closing metathesis of the sulfide analog **212** failed. The lack of reactivity may be attributed to the formation of a chelate between the sulfur atom and the ruthenium center.



Scheme 28

The reaction of trimethylsilylacetylenedicobalt hexacarbonyl complex and divinyl sulfone in refluxing toluene afforded a dihydrothiepine 1,1-dioxide **218** in 30% yield (Scheme 29) <1999JA8237>. Subsequent bromination–dehydrobromination gave 4-trimethylsilylthiepine 1,1-dioxide **219** in 70% yield. Metalation using $[(\text{MeCN})_3\text{Cr}(\text{CO})_3]$ provided the complex **220** in 85% yield, which was used for $[6\pi+2\pi]$ cycloaddition and subsequent Ramberg–Bäcklund rearrangement (Sections 13.03.5.2 and 13.03.6.2).

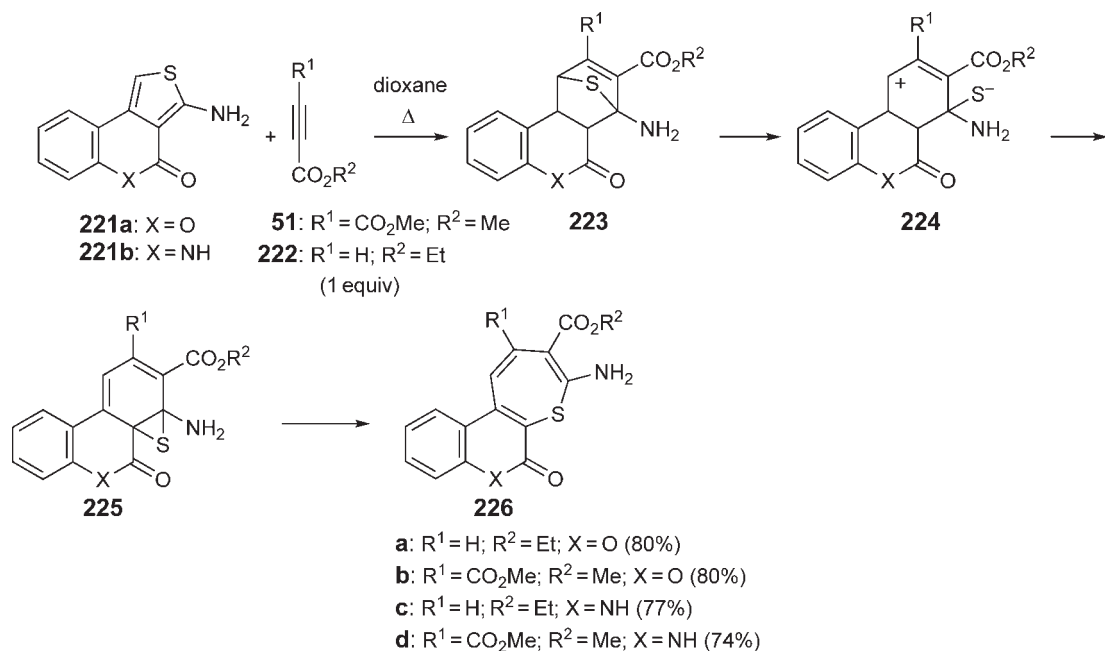


Scheme 29

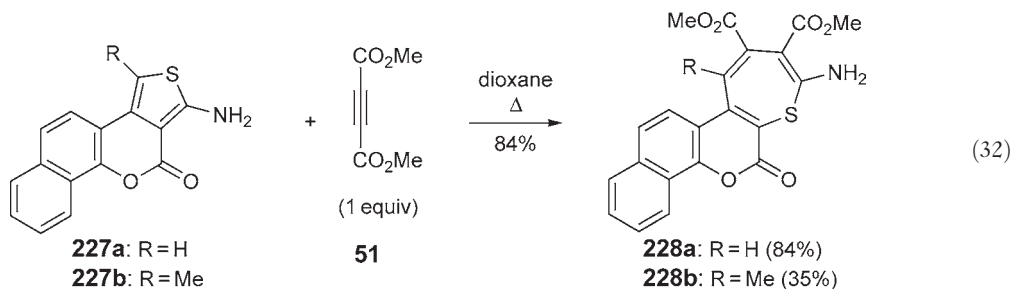
13.03.10 Ring Synthesis by Transformation of Another Ring

A new [4+2] cycloaddition-based strategy from thiophene ring was reported.

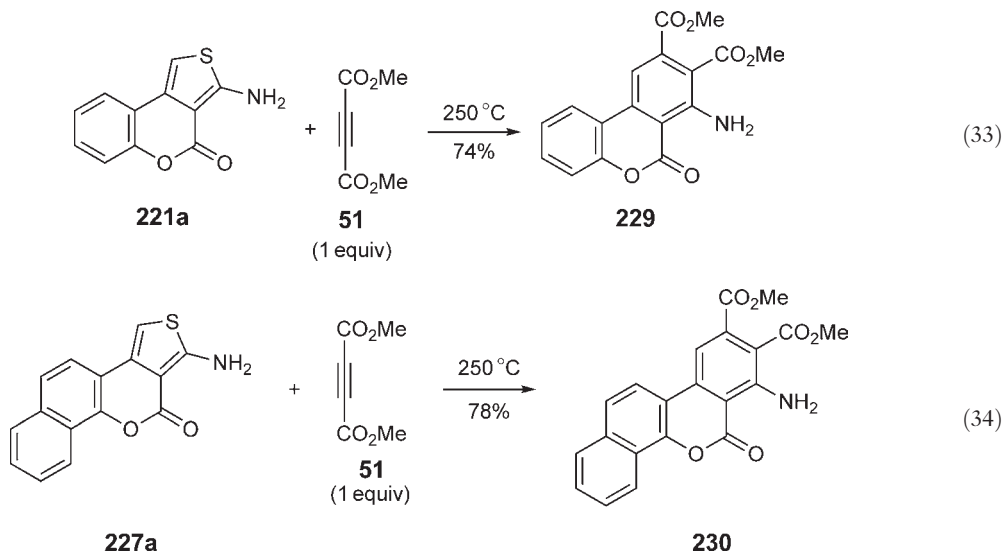
The reaction of annulated thiophenes **221a** and **221b** with DMAD **51** and with ethyl propionate **222** in refluxing dioxane afforded thermally stable condensed thiepinines **226** in 74–80% yield (Scheme 30) <1996T11915>. The reaction of **227a** and **227b** with DMAD **51** in refluxing dioxane afforded the condensed thiepinines **228a** and **228b** in 84% and 35% yields, respectively (Equation 32) <1996T11915, 2000SUL275>. The reaction mechanism for formation of thiepinines **226** was assumed, as shown in Scheme 30. Ring opening of initial [4+2] adduct **223** would lead to a zwitterionic intermediate **224**, which isomerized to thianorcaradiene **225**, then thiepinines **226**. The thermal stability of these thiepinines may be attributed to delocalization of the thiophene π -electrons into the π -electron system of annulated rings.



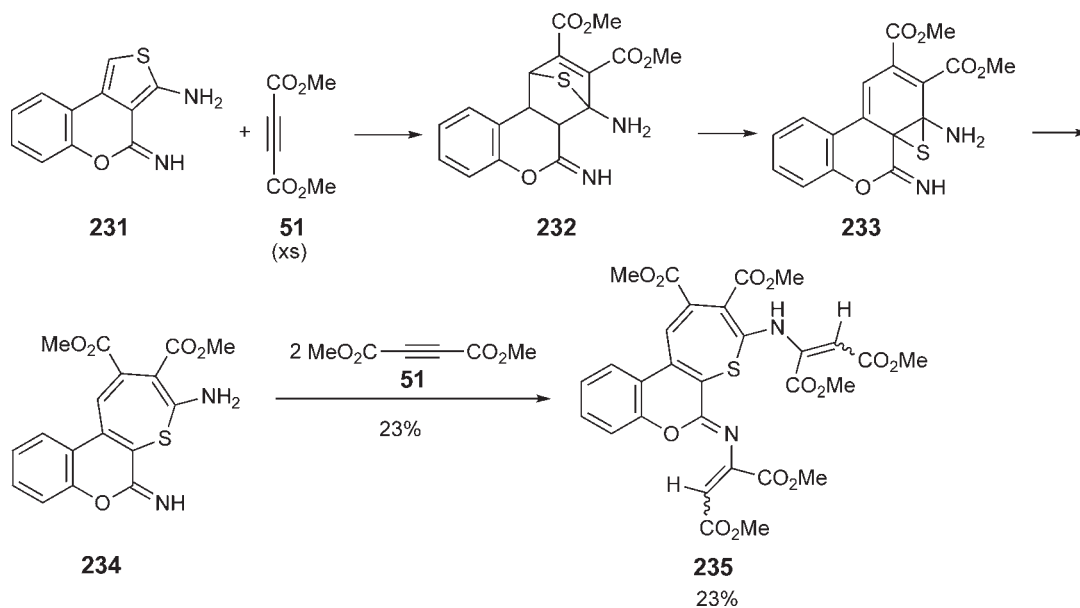
Scheme 30



At 250 °C, the reaction of annulated thiophenes **221a** and **227a** led to products of addition and desulfurization **229** and **230** in 74% and 78% yields, respectively (Equations 33 and 34). Thiepinines **226** (Scheme 30) and **228a** (Equation 32) are believed to be intermediates in the reactions and under the reaction conditions undergo desulfurization via valence isomerization to give isolated products **229** and **230** (see Section 13.03.5.1).



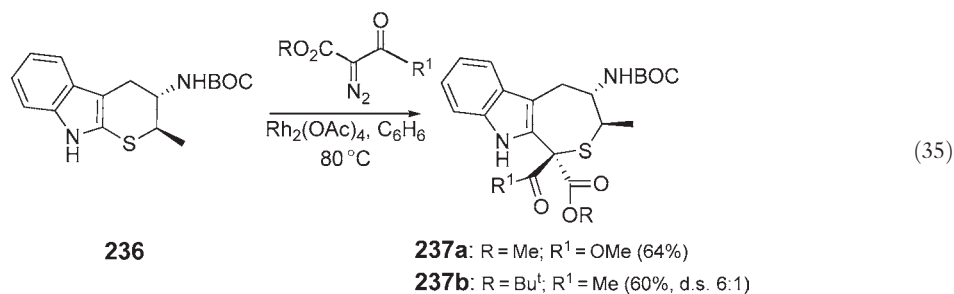
Thiophene **231** reacted with excess DMAD **51** in refluxing MeOH or EtOH to give a thermally stable thiepine **235** (two stereoisomers, ca. 80:20) in 23% yield <1994J(P1)2191>. A plausible reaction mechanism for the early steps was similar to Scheme 30: (1) cycloaddition of thiophene **231** to DMAD **51**, (2) isomerization of the 1:1 cycloadduct **232** to thianocaradiene **233**, and (3) valence isomerization of the latter to thiepine **234**, which might then undergo two Michael additions to DMAD **51** to yield thiepine **235** (Scheme 31).



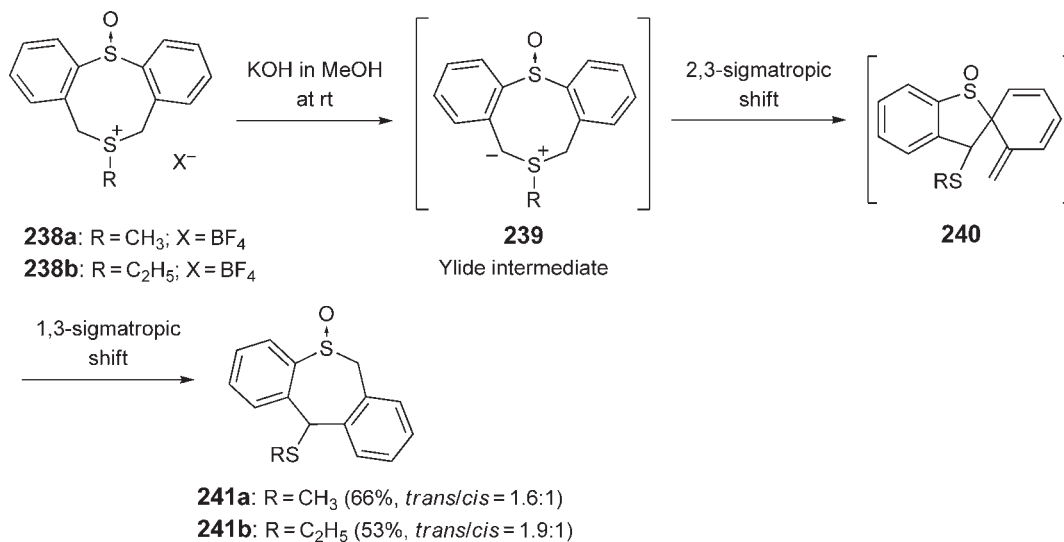
Scheme 31

Thiopyranylindole **236** underwent ylide-derived Stevens' rearrangements when exposed to malonate and α -ketoester carbenoids and resulted in a one-carbon ring expansion reaction to lead to thiepinines <2005JOC746>. Thus, reaction of thiopyranylindole **236** with dimethyl diazomalonate and *t*-butyl diazoacetylacetate in the presence

of $[\text{Rh}_2(\text{OAc})_4]$ at 80°C in benzene gave thiepinines **237a** and **237b** in 64% and 60% yields, respectively (Equation 35). Thiepine **237b** was isolated as a 6:1 mixture of diastereomers.



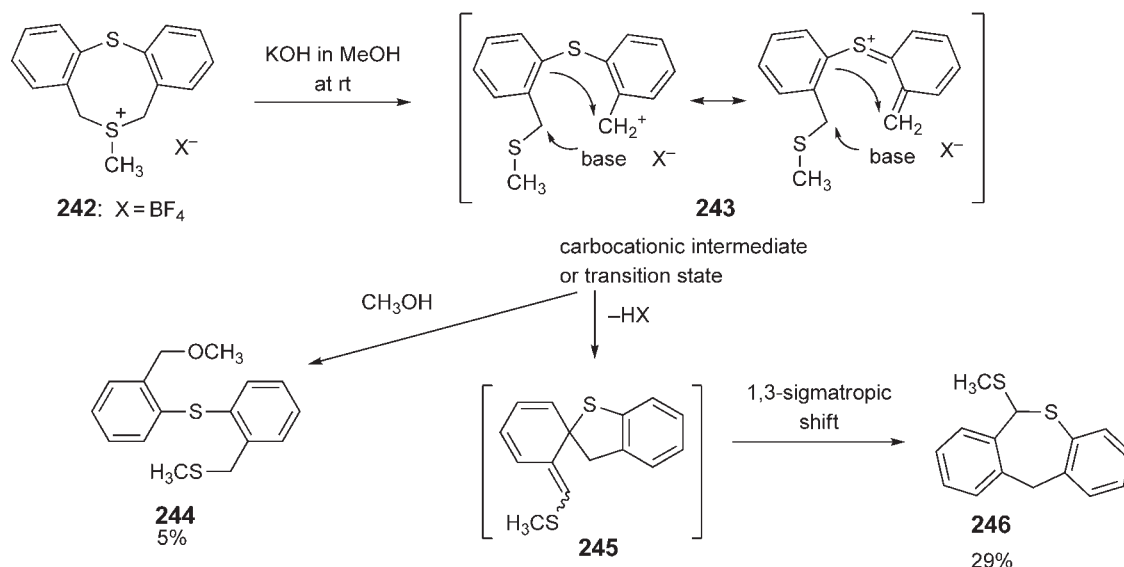
Treatment of 6-methyl-12-oxo-5*H*,7*H*-dibenzo[*b,g*][1,5]dithiocinium salt **238a** with methanolic KOH afforded a mixture of dibenzothiepine derivative **241a** in 66% yield <2002J(P1)2704>. The rearrangements into the dibenzothiepinines **238a** and **238b** are explained in terms of consecutive [2,3]- and [1,3]-sigmatropic shifts (the Sommelet-Hauser rearrangement) via spirocyclic intermediates **240**, as shown in Scheme 32.



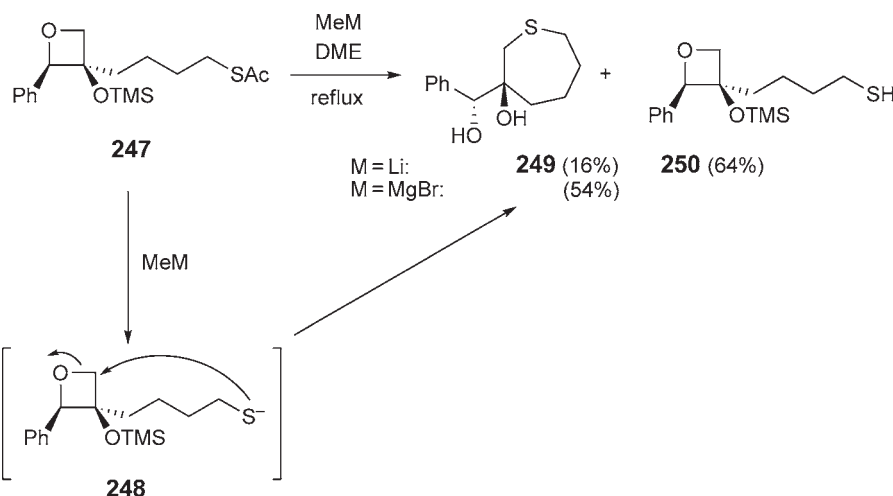
Scheme 32

A unique rearrangement via an alternative spirocyclic intermediate **245** was found in 6-methyl-5*H*,7*H*-dibenzo[*b,g*][1,5]dithiocinium salt **242** to give dibenzothiepine derivative **246** in 29% yield along with a small amount of a ring-opened product **244** in 5% yield under the same reaction conditions (Scheme 33). It was considered that these products resulted from the ring opening of a spirocyclic intermediate **245** analogous to the intermediate **240** from the sulfoxide derivative **238** in Scheme 32. The *ab initio* MO calculations at HF/6-31G* basis set was performed on the possible reaction intermediates and products.

Intramolecular ring-opening reaction of 2-phenyl-3-oxetanol has been studied. Treatment of 2-phenyl-3-oxetanol **247** with MeLi/MeMgBr gave an intermediate thioalkoxide **248**. Subsequent intramolecular attack of the thioalkoxide led to a thiepane **249** (Scheme 34) <1998JOC1910>. Thus, heating oxetane **247** with methyl lithium in 1,2-dimethoxyethane (DME) gave **249** in 16% yield accompanied by the thiol **250** in 64% yield, whereas the reaction with methylmagnesium bromide gave **249** in 54% yield. The counterion (MgBr)⁺ of the thioalkoxide **248** gave a beneficial influence on its nucleophilicity or, alternatively, on the electrophilicity of the oxetane. Thiepane **249** was obtained as a single diastereomer.

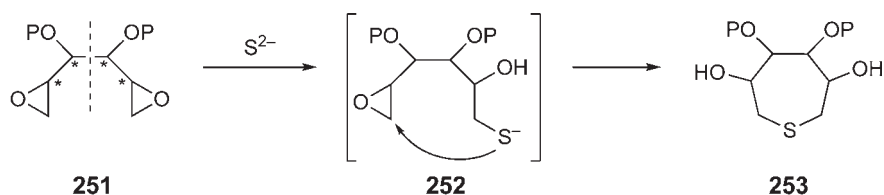


Scheme 33



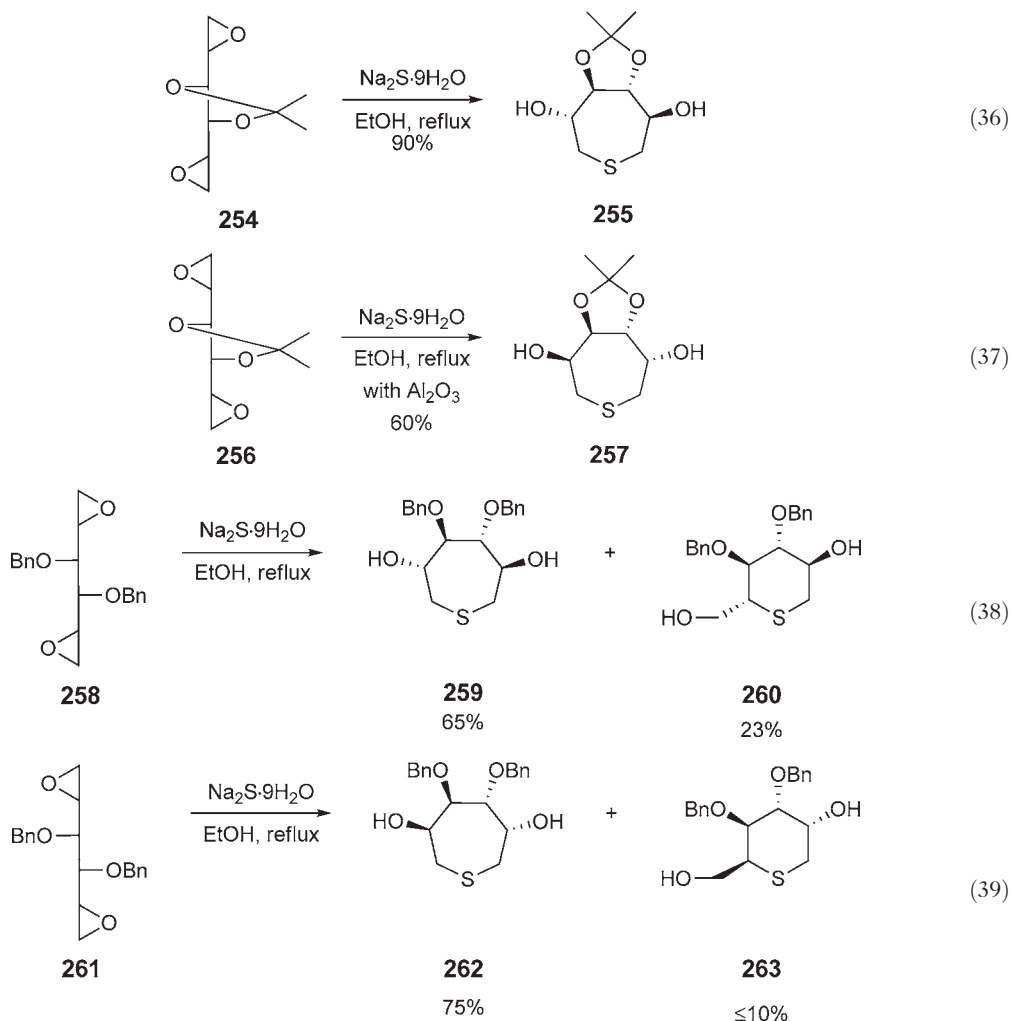
Scheme 34

Enantiomerically pure thiosugars with a thiepane backbone have been synthesized by thio-heterocyclization of enantiopure C_2 -symmetric bis-epoxides [<1995TL6443>](#). This approach involved a regioselective opening of one epoxy function by S^{2-} , followed by cyclization, and arose from the higher nucleophilicity of the thiolate group than that of the liberated hydroxyl group resulting from the opening of the first epoxide **251** ([Scheme 35](#)). The reaction of 1,2:5,6-dianhydro-3,4-di-*O*-isopropylidene-L-*iditol* **254** or D-mannitol **256**, where the 3,4-diol is protected in a *trans*-dioxolane, with 2 equiv of sodium sulfide nonahydrate in refluxing EtOH gave the thiepanes **255** and **257**, in 90% and 60% yields, respectively, as the only products ([Equations 36 and 37](#)) [<1977CAR105, 1995TL6443>](#). The reaction of bis-epoxide **258**, where the 3,4-diol is protected as a dibenzyl ether, with 2 equiv of sodium sulfide nonahydrate in refluxing EtOH afforded the crystalline thiepane **259** and tetrahydrothiopyran **260** in 65% and 23% yield, respectively ([Equation 38](#)) [<1995TL6443>](#). Both **259** and **260** could be easily separated by flash chromatography. Under the same conditions, the diastereomeric bis-epoxide **261** gave the corresponding thiepane **262** (75%) and tetrahydrothiopyran **263** ($\leq 10\%$ yield) ([Equation 39](#)).



C_2 axis of symmetry
P = protecting group

Scheme 35



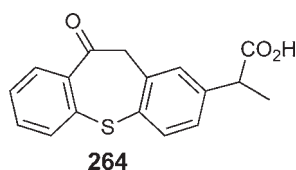
13.03.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Recently, enantiomerically pure dihydro- and tetrahydrothiepinines and thiepanes have been of more interest. In this section, the syntheses of chiral thiepinines by various routes described in [Sections 13.03.9 and 13.03.10](#) are summarized.

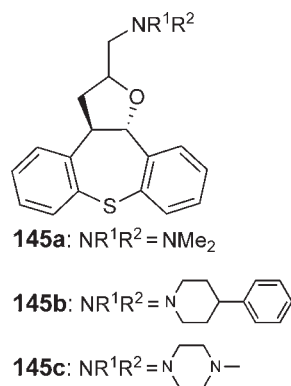
Approaches using chiral starting material are found in **Schemes 18, 20, 25**, and **26**, **Equations (26) and (36)–(39)**, and reference <2001TL3307> in **Section 13.03.9.2**. The easily accessible chiral starting materials were obtained such as by dihydroxylation, from sugar derivatives, or from known binaphthyls. Approach by resolution of racemic thiepinines is found in **Schemes 24 and 26**. Enantioselective transformation of thiaoxa[3.2.1]bicycles to tetrahydrothiepinines by chiral base was also reported <1997JOC7080> (**Section 13.03.9.2**).

13.03.12 Important Compounds and Applications

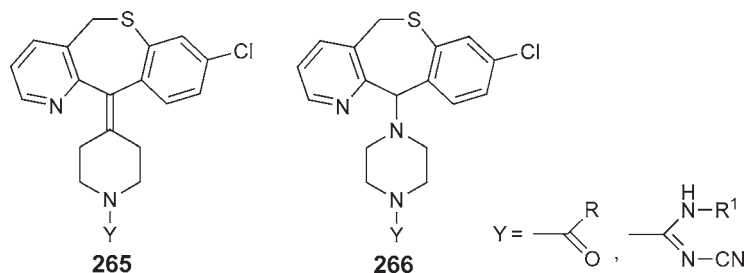
Physiological activity of thiepine derivatives was described previously in CHEC-II(1996) <1996CHEC-II(9)67>, and research has been studied continuously. The activities of dibenzo[*b,f*]thiepine derivatives have been also reviewed <1996JHC497>. 2-(10,11-Dihydro-10-oxo-dibenzo[*b,f*]thiepin-2-yl)propionic acid (zaltoprofen) **264** is known as a nonsteroidal anti-inflammatory drug <1996CHEC-II(9)67>, which prevents the development of inflammation by blocking the synthesis of prostaglandins. Zaltoprofen **264** inhibits cyclooxygenase and exhibits anti-bradykinin activity. A study evaluated the preemptive analgesic effect of zaltoprofen **264** in a postoperative pain model produced by plantar incision <2005MI427>.



Dihydrodibenzo[*b,f*]thiepine derivatives **145a–c** were prepared as 5-HT_{2A/2C} antagonists as potential drugs. A series of substituted 2-(aminomethyl)-3,3a,8,12b-tetrahydro-2*H*-dibenzocyclohepta[1,2-*b*]furan derivatives were synthesized and the 5-HT_{2A}, 5-HT_{2C}, and H₁ receptor affinities were examined <2004BML2765> (see **Section 13.03.7.2**).

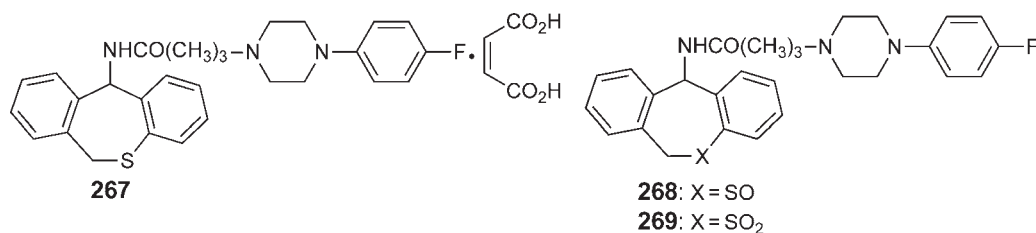


Amide and cyanoguanidine derivatives **265** and **266** containing a 5,11-dihydro[1]benzothiepine[4,3-*b*]pyridine ring system were evaluated *in vitro* and found to be good inhibitors of farnesyl-protein transferase <1998BML2521>.



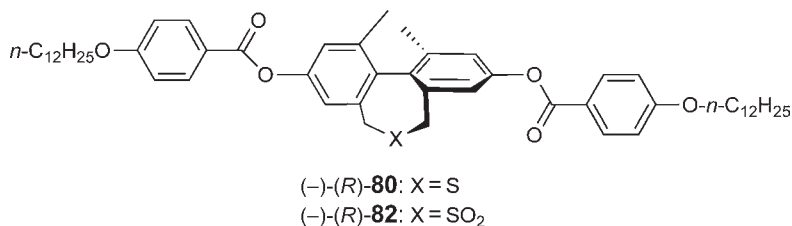
The calcium antagonistic and α_1 -adrenergic receptor blocking activities of monatepil maleate ((±)-*N*-(6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-4-(4-fluorophenyl)-1-piperazinebutanamide monomaleate, AJ-2615 **267**), its metabolites (AJ-2615-sulfoxide A, AJ-2615-sulfoxide B **268**, and AJ-2615-sulfone **269**), and their enantiomers were studied

<1995AF1057>. There was a difference in the calcium antagonistic activities between the enantiomers of monatepil maleate **267** but not in their α_1 -adrenergic receptor blocking activity.

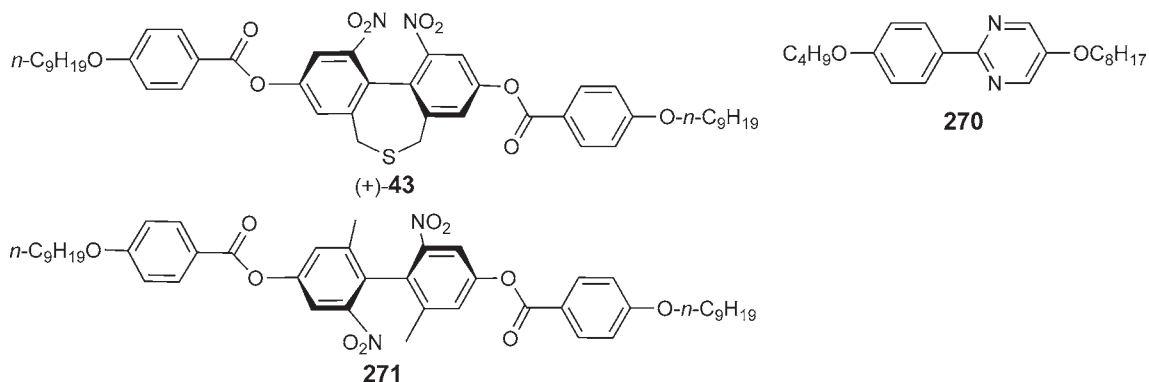


A new method, shape signatures, in the area of computer-aided molecular design has been studied <2003JME5674>. The method has been demonstrated to work well in selecting molecules on the basis of shape and polarity and has been applied to a receptor-based strategy. Dibenzo[*b,f*]thiepine appears in the hit list for 5*H*-benz[*b,f*]azepin.

Research utilizing the thiepine skeleton in material science has been reported. For example, liquid crystals with chiral dihydrodibenzo[*c,e*]thiepinines were studied. The enantiomerically pure (–)-(*R*)-3,9-bis[4-(dodecyloxy)benzoyloxy]-5,7-dihydro-1,11-dimethyldibenzo[*c,e*]thiepine **80** and (–)-(*R*)-3,9-bis[4-(dodecyloxy)benzoyloxy]-5,7-dihydro-1,11-dimethyldibenzo[*c,e*]thiepine dioxide **82** display smectic C* mesophases by a rigid twisted biphenyl core and axial chirality <1998JOC3895>.

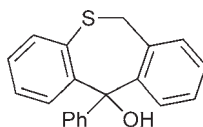


An atropisomeric dopant containing a bridged biphenyl core with helical topography, 3,9-bis[4-(nonyloxy)benzoyloxy]-5,7-dihydro-1,11-dinitrodibenzo[*c,e*]thiepine **43**, was doped in the liquid crystal host 2-(4-butyloxyphenyl)-5-octyloxypyrimidine **270** to produce a ferroelectric smectic C* phase <2002JMC586>. The polarization power of the dopant **43** was compared to that of an analogous unbridged dopant, 2,2'-dimethyl-6,6'-dinitro-4,4'-bis[(4-*n*-nonyloxy)benzoyloxy]biphenyl **271**. The results show that dopant **43** has a greater propensity to undergo chirality transfer with surrounding host molecules via conformational core–core interactions.



The solvent inclusion properties of 11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol **272** were investigated <2004MI44>. DMF and DMSO were both included by host **272** with a host:guest ratio of 2:1; however, the presence

of a sulfur atom in the central seven-membered tricyclic system significantly decreased the solvent inclusion ability relative to the corresponding carbocyclic systems, such as 5-phenyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ol and 5-phenyl-5*H*-dibenzo[*a,d*]cyclohepten-5-ol.



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13.03.13 Further Developments

Some new synthetic methods towards thiepane derivatives have been reported. Reaction of thiafuranone and acrolein derivatives in the presence of K_2CO_3 and MeOH gave tetrahydrothiepinines stereoselectively. This synthetic method involves a base-induced anionic domino reaction <2006OL4819>. [*n*+1] Radical annulation using sulfur dioxide to give cyclic sulfones includes preparation of a thiepane skeleton. [6+1] cyclization of allylic sulfide-substituted 1,6-heptadiene with SO_2 gave a thiepane 1,1-dioxide derivative <2005JOC10854>.

A series of novel benzothiepinines (3*R*,3*R'*-2,3,4,5-tetrahydro-5-aryl-1-benzothiepin-4-ol 1,1-dioxides) were synthesized by cyclization of arylsulfone aldehydes with $KOBu^t$. They are tested for their ability as apical sodium dependent bile acid transporter inhibitors <2005JMC5837, 2005JMC5853>. This class of benzothiepine is one of the most potent classes of inhibitors discovered to date.

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Biographical Sketch



Shoko Yamazaki was born in Osaka, Japan. She studied chemistry at Osaka University and received her Ph.D. in 1986 under the supervision of Prof. Ichiro Murata. From 1985, she was an assistant lecturer at Nara University of Education. She joined the group of Professor Barry M. Trost as a visiting researcher at Stanford University (USA) in 1987–88. She became an assistant professor at Nara University of Education in 1989 and since 2003, a full professor of Nara University of Education. Her current main research interests are the development of new organic synthetic reactions.

13.04

1,2-Diazepines

T. P. Meagher

TEKA Consulting, Indianapolis, IN, USA

R. Murugan

Vertellus Specialties Inc, Indianapolis, IN, USA

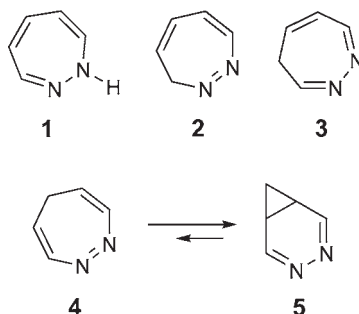
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13.04.1 Introduction

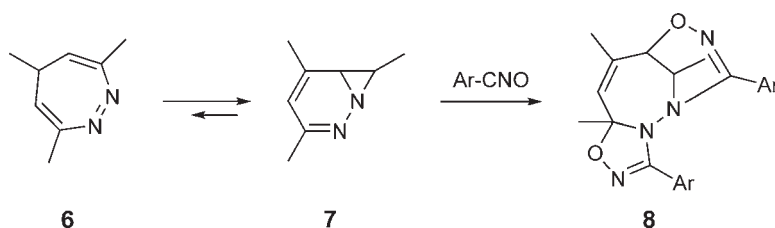
In CHEC(1984), the ring system for the 1,2-diazepines was covered as a part of bigger chapter on seven-membered rings with two or more heteroatoms <1984CHEC(7)593>. The main focus was on the synthesis and reactivity. However, in CHEC-II(1996), in addition to the sections on reactivity and synthesis as seen in CHEC(1984), there are few sections on the structure of 1,2-diazepines, such as theoretical methods, experimental methods and thermodynamics aspects <1996CHEC-II(9)113>. Since CHEC-II(1996), 1,2-diazepines have been extensively studied

<2004SOS(17)929>. Interest in this class of compounds stems mainly from their neuropharmacological properties <2001RMC243, 2000MI309, 2001TH1, 2002FA129>. This chapter, similar to CHEC-II(1996), will cover the structure, reactivity, and synthesis of the parent conjugated 1*H*-1,2-diazepine **1** and nonconjugated 3*H*- and 4*H*-1,2-diazepines **2** and **3**, and 5*H*-1,2-diazepine **4** (in tautomeric equilibrium with 3,4-diazanorcaradiene **5** with the equilibrium far in favoring **5**), and its partially and fully reduced compounds, oxo compounds, and benzo derivatives. There are two new sections in this chapter, one dealing with the critical comparison of the various synthetic routes available for making 1,2-diazepines and the other dealing with important 1,2-diazepines and their applications.



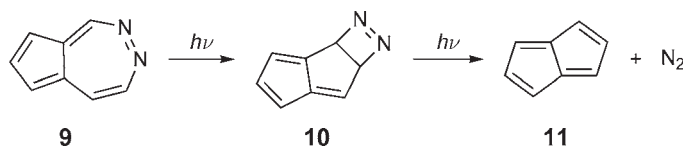
13.04.2 Theoretical Methods

Ab initio and density functional theory (DFT) calculations were used to explain the peri- and regioselectivity of the double cycloaddition reaction of aryl nitrile oxide with norcaradiene tautomer **7** of 3,5,7-trimethyl-5*H*(1,2)diazepine **6** forming cycloadduct **8** <2002JST(580)183> (Scheme 1).



Scheme 1

A semi-empirical method (SIND01) was used to study the reaction pathways for the photochemical transformation of diazaazulene **9** to pentalene **11** <1995JPC5834>. It is proposed that the Dewar diazaazulene **10** would be formed first followed by loss of nitrogen to **11** (Scheme 2).

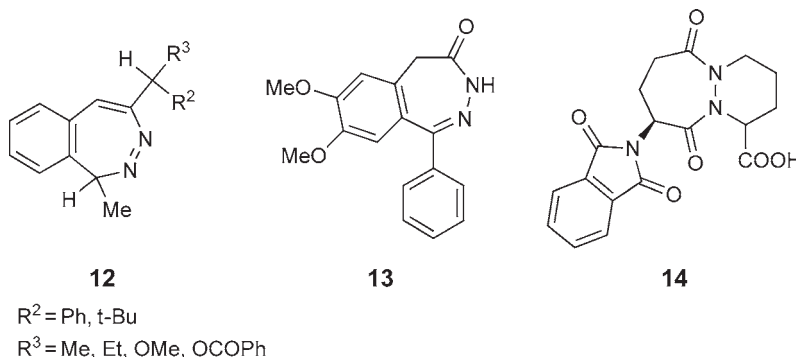


Scheme 2

13.04.3 Experimental Structural Methods

Crystal structures of 1,2- or 2,3-benzodiazepines are relatively rare. Three interesting examples are illustrated. The geometry of diazepine ring of **12** is unaffected by a wide range of substituents at C-4. Two planes (N(2)–N(3)–C(5a)–C(9a) and N(3)–C(4)–C(5)–C(5a)) adequately described all sets of isomers <1995AXC1621>. Benzodiazepine **13**, an

antagonist for AMPA/kainite receptors and an anticonvulsant, adopts a boat conformation <2001AXC1225>. Confirmation of the stereochemistry (*S,S*) of the two chiral centers of **14** was obtained by single crystal X-ray crystallography <1999BML1587>.



13.04.4 Thermodynamic Aspects

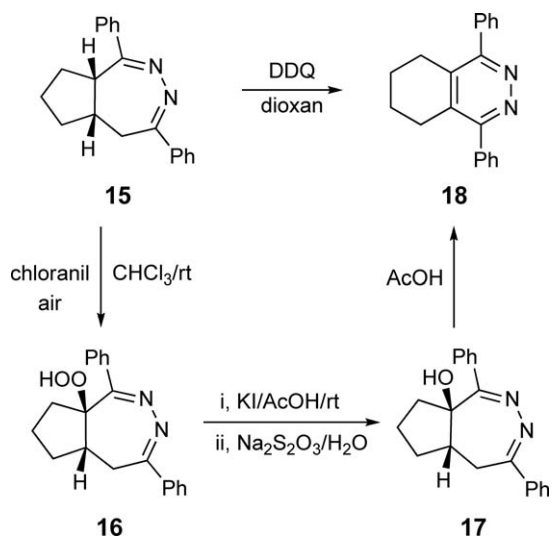
Chromatographic behavior of 1,2-diazepines continues to be of interest due to their unique pharmacological properties. Some of the studies include: enantioselectivity of chiral supercritical fluid chromatography <2001JCH(929)101>; high-performance liquid chromatography (HPLC) of biological fluids <1999JCH(846)165, 1998JCH(705)149, 1996JCH(678)63>; electrochromatography on phenyl silica stationary phase <1999JCH(845)203>; separation and identification of Tofisopam stereoisomers by HPLC <1999JLC713>; reversed-phase liquid chromatography of benzodiazepines <1996ANC2869>; and separation of enantiomers using chiral-AGP column <1995JCH(709)265>.

13.04.5 Reactivity of Fully Conjugated Rings

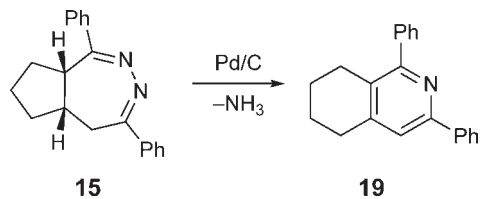
The reactivity of 1,2-diazepines, as covered in CHEC(1984), was categorized by reaction types (photochemical, thermally induced, electrophilic, nucleophilic, reduction, and cycloaddition) in a broad survey of seven-membered rings with two or more heteroatoms. In CHEC-II(1996), a chapter was dedicated exclusively to 1,2-diazepines, and their reactivity was addressed in sections covering the following: fully conjugated rings, nonconjugated rings, substituents attached to the ring carbon atoms, and substituents attached to ring nitrogen heteroatoms. In this chapter, reactivity is divided in a similar fashion except that further subdivisions into reaction types (oxidation, reduction, etc.) or structural types (3*H*-1,2-diazepine, 4*H*-1,2-diazepine, etc.) in the case of nonconjugated rings are not done. This is due, in part, because much of the known chemistry of 1,2-diazepines stems from their preparation of pharmacological analogs which is covered in Sections 13.04.9 and 13.04.10 of this chapter. As shown earlier in Section 13.04.2 (Scheme 2), antiaromatic pentalene **11** is formed via photolysis of 5,6-diazaazulene **9**. The proposed reaction intermediate is Dewar diazaazulene **10** <1995JPC5834>.

13.04.6 Reactivity of Nonconjugated Rings

Attempts to prepare the unknown conjugated π -electron 5,6-diazaazulenes yielded some interesting transformations <2001TH1>. Dehydrogenation of diazepine **15** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) did not lead to the unsaturated 5,6-diazaazulene; but instead caused ring rearrangement to 1,4-diphenylphthalazine **18** in 52% yield. Air oxidation of **15** occurs readily in the presence of chloranil at room temperature to afford peroxide **16** (92% yield). Reduction of **16** with potassium iodide gives alcohol **17** which when heated in acetic acid forms **18** in 72% yield (Scheme 3). Treatment of **15** with palladium on carbon produces pyridine **19** by loss of ammonia and ring contraction (Equation 1).

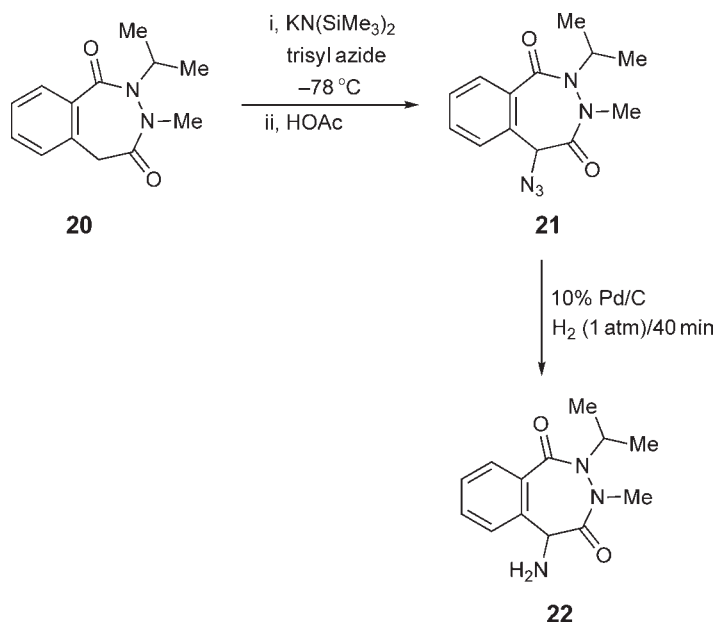


Scheme 3



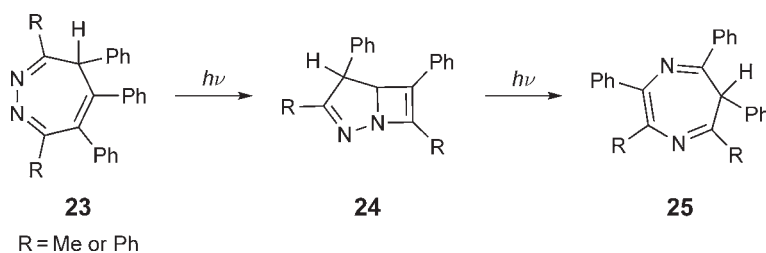
(1)

Benzodiazepin-1,4-dione **22** was a key intermediate for synthesis of a series of peptidomimetic inhibitors [<2004BML3535>](#). The preparation of **22** starts by the reaction of the enolate of diazepine **20** with trisyl azide giving azide **21**. Reduction of **21** under heterogeneous hydrogenation conditions gives amine **22** (Scheme 4).



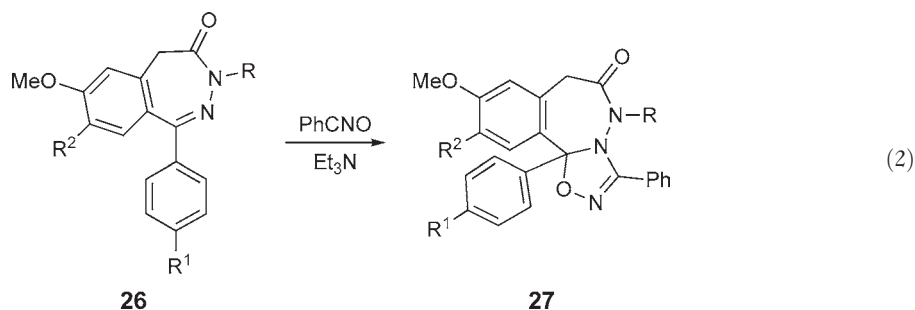
Scheme 4

Scheme 5 illustrates the photochemical rearrangement of 4*H*-1,2-diazepine **23** to 6*H*-1,4-diazepine **25**, which occurs via an aza-di- π -methane reaction with 1,2-diazabicyclo[3.2.0]hepta-2,6-diene **24**, as the intermediate <1996CRV3065>.

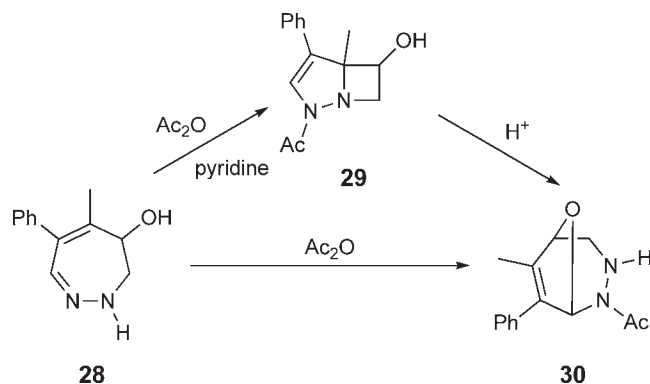


Scheme 5

A series of oxadiazolo-2,3-benzodiazepines **27** were prepared because of their chemical similarity to known therapeutic 2,3-benzodiazepines <1995EPH411>. Their preparation was achieved by 1,3-dipolar cycloaddition of benzonitrile oxide, formed *in situ* from benzohydroxamoyl chloride, with 2,3-benzodiazepines **26** (Equation 2).



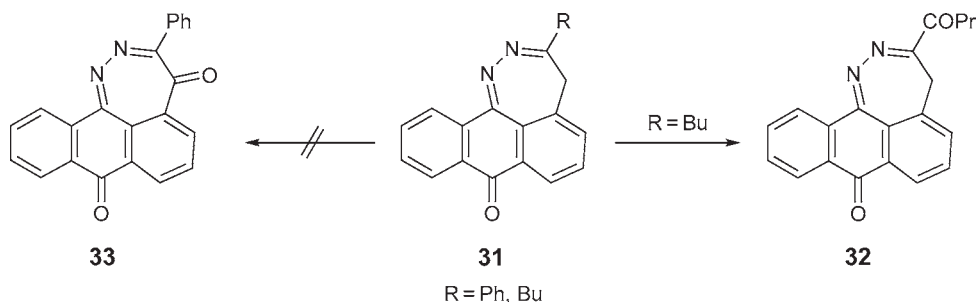
Reaction of 2,3-dihydro-1,2-diazepin-4-ol **28** with acetic anhydride forms 2-acetyl-5-methyl-4-phenyl-1,2-diazabicyclo[3.2.0]heptane-6-ol **29** in the presence of base and forms 2-acetyl-6-methyl-7-phenyl-2,3-diaza-8-oxabicyclo[3.2.1]-6-octene **30** in the absence of base. In addition, bicyclic **29** can be transformed into oxadicyclic **30** by treatment with acid. A study using AM1 semi-empirical calculations offers several different routes for these rearrangements <1999JST(458)239> (**Scheme 6**).



Scheme 6

13.04.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Oxidation of 3-butyryl diazepinanthrone (R = *n*-Bu) **31** with MnO₂ gives the ketone derivative **32**. The relative resistance of the ring carbon to oxidation is shown in 4-phenyl diazepinanthrone (R = Ph) **31**, which does not react to give **33** under identical conditions <2000TL771> (**Scheme 7**).



Scheme 7

13.04.8 Reactivity of Substituents Attached to Ring Heteroatoms

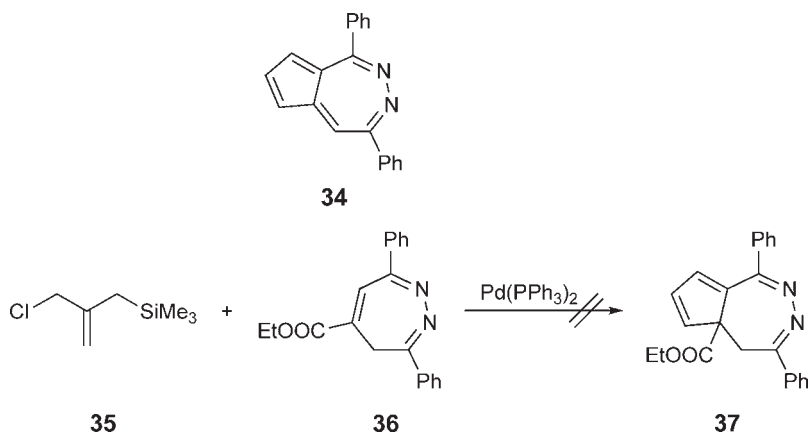
Reports of reactions involving substituents attached to the ring nitrogen of 1,2-diazepines mainly involve acetyl and tosyl groups which are used for protection during their synthesis or selective transformations of the ring. For example, tosylhydrazine condenses and ring-closes with $\alpha,\beta,\gamma,\delta$ -unsaturated ketones to form tosylated 1,2-diazepines, which are detosylated with sodium ethoxide [<2004SOS\(17\)929>](#). Acetic anhydride adds to the 3,4-C–N double bond of 2,3-benzodiazepines forming the *N*-tosylate derivative which undergoes deacylation with sodium borohydride [<2000MI309>](#). This provides a way to selectively saturate the 3,4-C–N double bond of 2,3-benzodiazepines.

13.04.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

The synthesis of diazaazulenes was investigated as mentioned earlier in [Section 13.04.2](#), during the study of the nature of aromaticity of numerous nonbenzenoid carbocyclic and heterocyclic conjugated π -electron systems. The synthetic approaches started with reactions of semicyclic 1,5-diketones with various hydrazines to give partially saturated cyclopenta[*c*]-1,2-diazepines. Then several methods were used to dehydrogenate, as described earlier, the cyclopenta-1,2-diazepines to the respective diazaazulenes without much success [<2001TH1>](#).

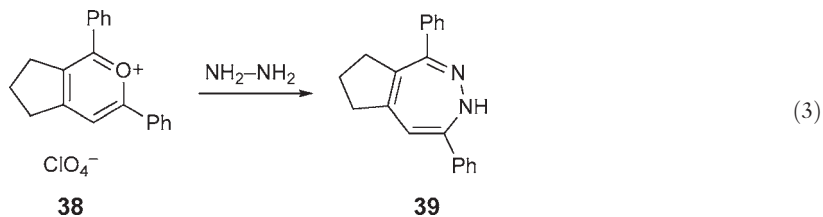
Many attempts were made to synthesize the diazaazulene derivative 4,7-diphenyl-5,6-diazaazulene **34**. A directed synthesis of diazaazulene **34** by [6+4] cycloaddition of fulvenes with 1,2,4,5-tetrazenes when attempted with 2-cyclopentadienyliden-1,3-dioxolane led to the formation of cyclopenta[*d*]pyridazines via a [4+2] cycloaddition pathway [<2001TH1>](#).

After the failure of the direct synthesis of the completely unsaturated heterocycle **34**, an attempt was made to synthesize the partially saturated cyclopenta[*c*]-1,2-diazepine, which then could be dehydrogenated to the 5,6-diazaazulene **34**. However, this approach by starting with a 1,2-diazepine ring **36** (made successfully by following published method) and its [3+2] palladium-catalyzed cycloaddition with allyl chlorosilane **35** to the bicyclic diazepine **37** failed ([Scheme 8](#)).

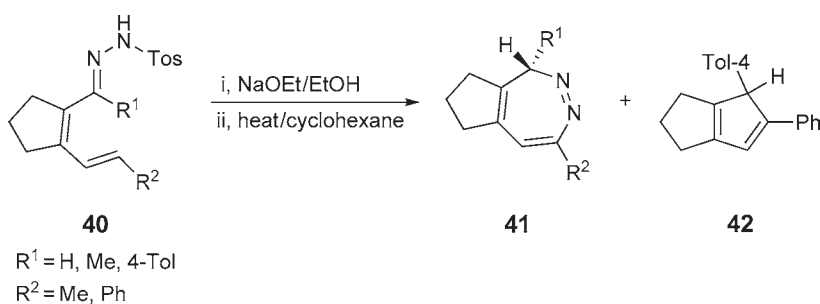


Scheme 8

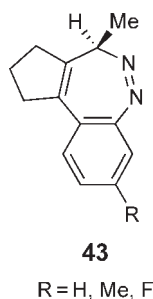
Another approach starting with the cyclopenta[*c*]pyrylium perchlorate **38**, followed by condensation with hydrazine, should have given a hydrogenated precursor of **34**. However, the reaction gave an oil in a very low yield and it could not be completely characterized. Only the peak of $m/z = 286$ in a mass spectrum of the raw product confirmed the existence of the 2,6,7,8-tetrahydro-1,4-diphenylcyclopenta[*d*]-1,2-diazepin **39** (Equation 3).



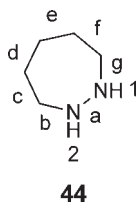
The method using the cyclization of the tosylhydrazone **40**, however, gave diazepine **41** in moderate yield (9%) along with the formation of tetrahydropentalene **42** (in 40% yield) (Scheme 9). The tosylhydrazone **40** was made in a four-step synthesis sequence in moderate yield from cyclopentanone. Benzoannulated, polycyclic and the partly saturated systems are known and have been obtained, for example, the benzo[*c*]cyclopenta[*e*]-1,2-diazepine **43** <2001TH1>.



Scheme 9



The synthetic preparations from acyclic compounds are classified according to the bonds formed using convention described earlier <1984CHEC(7)593, 1996CHEC-II(9)113>, of labeling ring sides by lower case italic letters as shown in structure **44**.

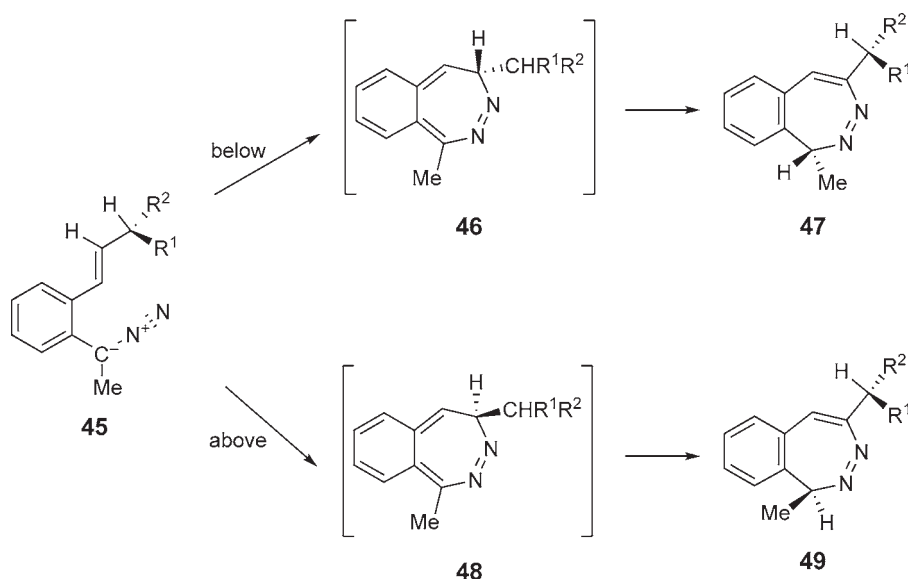


13.04.9.1 Type a (N-C-C-C-C-N)

This is the least common method available to synthesize 1,2-diazepines. The reason for this is that there are fewer methods/reactions to form N-N bond. Reductive cyclization of a 1,5-dinitro compound has been used in the preparation of dibenzo[*c,f*]diazepines <1984CHEC(7)593>. A photochemical approach has been used in making the N-N bond of acetylesters of 2,2'-dinitrodiphenylcarbinols in protic solvents, such as isopropanol, to give dibenzo[*c,f*][1,2]diazepin-11-one 5-oxides <1996CHEC-II(9)113>.

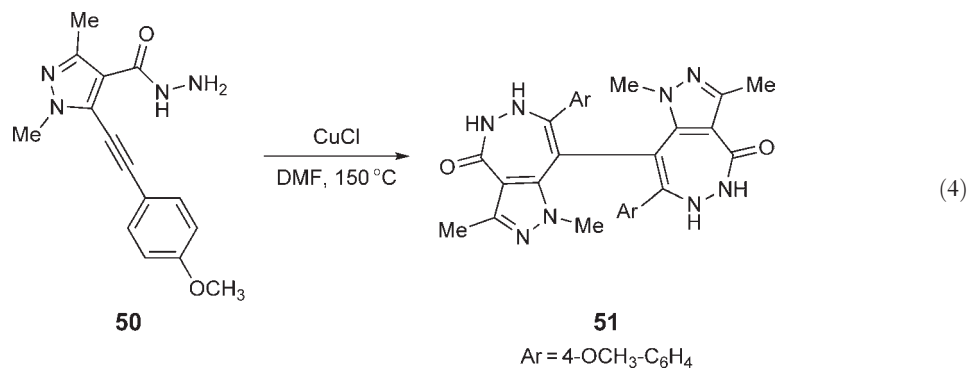
13.04.9.2 Type b (C-C-C-C-C-N-N)

Compounds were prepared in order to study the effect of different chiral groups on an 1,7-electrocyclization (Scheme 10). Cyclization was followed by a [1,5]-sigmatropic shift to produce diastereomers **47** and **49**. Stereochemical effects of different chiral groups on their 1,7-electrocyclization have been investigated <1994J(P1)3149; 1995AXC1621>.



Scheme 10

A simple cyclization of hydrazides of *o*-acetylenylbenzoic and acetylenylpyrazolecarboxylic acid **50** can lead to four different compounds, namely the five-membered *N*-aminolactams, six-membered *N*-amino lactams, and six-membered diazinones and diazepinones, but only the first three have been reported. The unexpected formation of bis(pyrazolo[4,3-*d*][1,2]diazepinone **51** (R = 4-MeOC₆H₄) structure has been established by X-ray crystallography <2005TL4457> (Equation 4).



13.04.9.3 Type *be* (C–C–C + C–C–N–N)

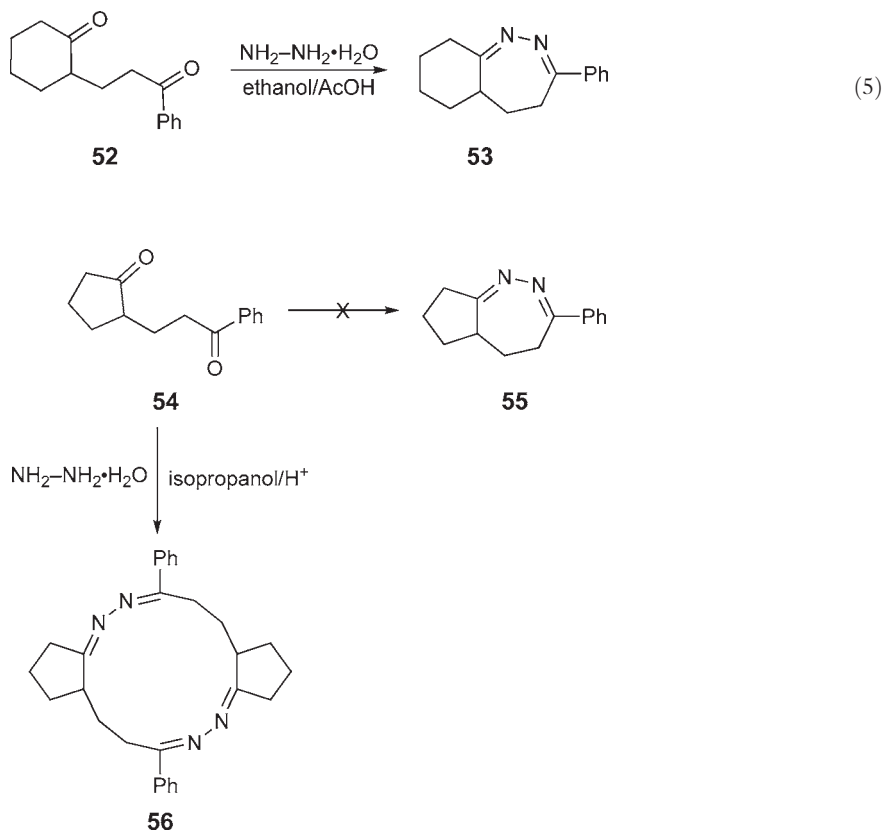
This type of synthesis using acetohydrazides, as the 1,4-dinucleophile, and 1,3-diketones, as the 1,3-dielectrophile, has been reported <1996CHEC-II(9)113>.

13.04.9.4 Type *bf* (C–C–C–C + N–N–C)

This type of preparation of 1,2-diazepines has been reported earlier involving the dipolar cycloaddition of sydnone with benzocyclobutene <1996CHEC-II(9)113>. This method could be further exploited by the use of the correct hydrazone derivative (1,3-electrophile, nucleophile) with α,β -unsaturated ketone (1,4-electrophile, nucleophile) for the synthesis of 1,2-diazepines.

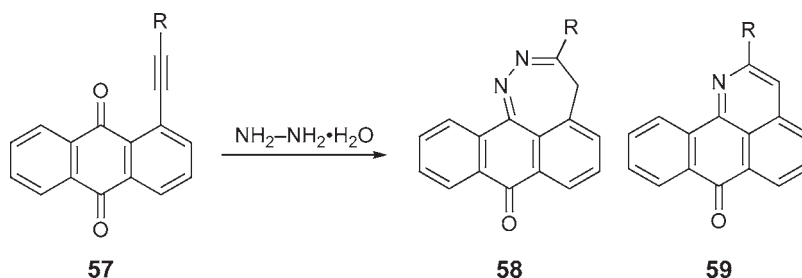
13.04.9.5 Type *bg* (C–C–C–C–C + N–N)

Diazepines **53** (Equation 5) and **55** (Scheme 11) have been made during the studies toward the synthesis of diazaazulenes described earlier. The conversion of 2-(3-oxo-3-phenylpropyl)cyclopentanone **54** with an equivalent hydrazine hydrate and catalytic quantities of *p*-toluenesulfonic acid in refluxing isopropanol gave a light yellow solid with a melting point of 196–198 °C. After detailed mass spectrometry (MS), infrared (IR), and nuclear magnetic resonance (NMR) investigations as well as an elemental analysis, the solid was found to be 6,14-diphenyl-1,2,3,7,8,8a,9,10,11,15,16,16a-dodecahydro-4,5,12,13-tetraazadicyclopenta[*a,h*]cyclotetradecene **56**, which was obtained in 41% yield <1952JA4923, 1991HC(50)1, 2001TH1> (Scheme 11).



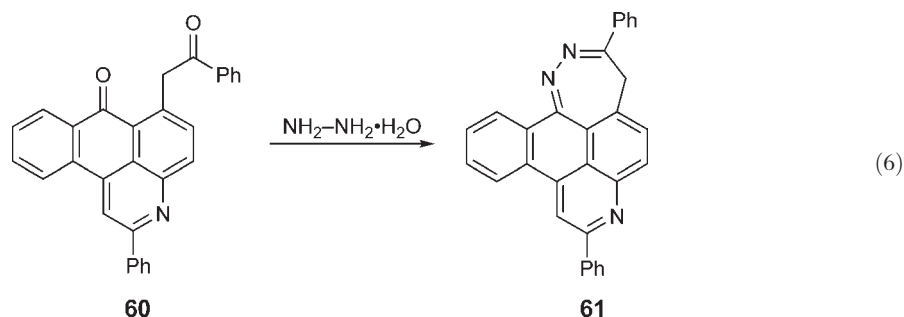
Scheme 11

Reaction of alkynyl-substituted anthraquinones **57** with excess hydrazine in pyridine at 90–115 °C for 20–90 min gave mixtures of diazepineanthrones **58** (45–64%) and pyridineanthrones **59** (17–38%) <2001MI582> (Scheme 12).

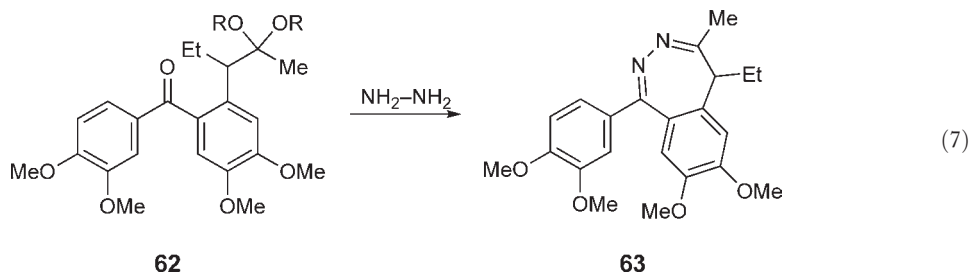


Scheme 12

Cyclization of 6-(arylcarbonyl)methyl-2-aryl-7*H*-naphtho[1,2,3-*de*]quinoline-7-ones **60** with hydrazine hydrate gave 1,2-diazepine derivatives **61** <2003AJC1219> (Equation 6).



The 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5*H*-2,3-benzodiazepine **63**, a known anxiolytic agent, is prepared by the reaction of a monoketal derivative of a 1,5-dicarbonyl compound **62** with hydrazine or its hydrate or its salt <2003WO2003050092A2> (Equation 7).



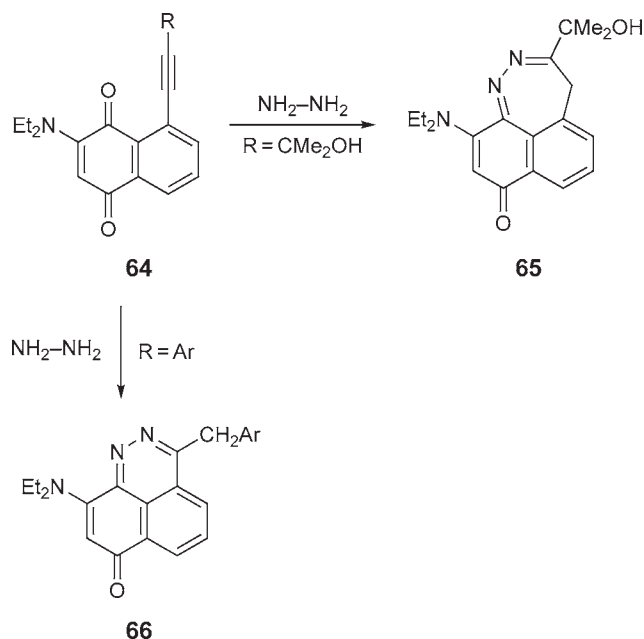
Condensation of 5-(arylethynyl)-3-(diethylamino)naphthoquinones **64** with hydrazine afforded 3-benzyl-9-(diethylamino)benzo[*de*]cinnolin-7-ones **66**. Replacement of the arylethynyl substituent in the starting naphthaquinone by a 3-hydroxyalk-1-ynyl group leads to a change in the direction of cyclization, resulting in substituted naphtha[1,8-*cd*]-1,2-diazepin-8-ones **65**, as condensation products <2001RCB1668> (Scheme 13).

Friedel–Crafts acylation with various acyl chlorides of resin-bound 3,4-dimethoxyphenylacetate afforded resin-bound ketones which, following treatment with hydrazine, were converted into the corresponding 2,3-benzodiazepines in good yields and purities <2001TL7683>.

The reaction of pyrazolone bearing a β -ketoester moiety with aliphatic dibasic functional reagents in EtOH afforded binary ring heterocycles. Whereas when using an excess of a dibasic reagent, dipyrazolo[3,4-*c*3',4'-*f*][1,2]diazepine derivatives were obtained <2001SC1335>.

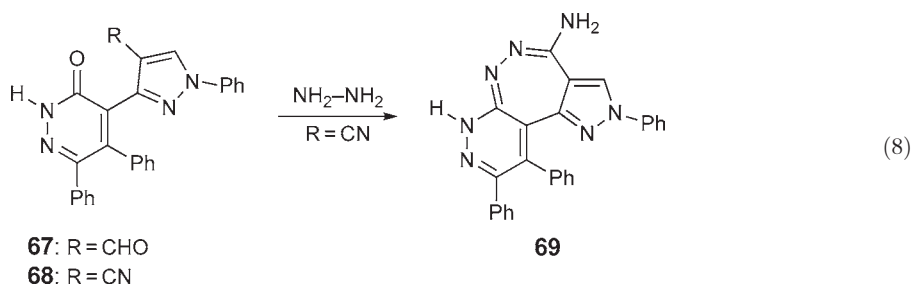
The heterocycle formed in the cyclocondensation reactions of 2-acetylenyl-1-chloro-9,10-anthraquinones or 5-acetylenyl-3-(diethylamino)-1,4-naphthaquinones with hydrazine is influenced by the presence of a heterofunctional OH group in the acetylenic substituent. This directive effect was used in the synthesis of naphtha[2,3-*h*]cinnoline-4,7,12-triones and 4*H*-naphtho[1,8-*cd*]-1,2-diazepin-8-ones <2000MC188>.

Cyclocondensation of 3-diethylamino-5-phenylethynyl-1,4-naphthoquinone with hydrazine resulting in the closure of a pyridazine ring is reported. This hydrazine condensation was unknown for peri-acetylenic derivatives of polycyclic quinones <2000TL771>.



Scheme 13

Compound 4-acetyl-5,6-diphenyl-3(2*H*)-pyridazinone was allowed to react with phenylhydrazine to afford the corresponding hydrazone, which on treatment with $POCl_3/DMF$ gave the formyl pyrazolypyridazine **67**. Conversion of this formyl group into its corresponding nitrile **68** via its oxime, followed by treatment with hydrazine afforded pyrazolopyridazodiazepine **69** <1998PHA839> (Equation 8).



13.04.9.6 Type *c* (C–C–C–C–N–N–C)

This type of synthesis of 1,2-diazepines by forming the *c* bond is uncommon and is supposed to have considerable potential <1996CHEC-II(9)113>. The cyclization of nitrilimines, generated by reaction of hydrazoyl chloride with triethylamine (TEA), to 1,2-diazepines and the $TiCl_4$ catalyzed alkenyl ring-closure to an iminium ion to form 1,2-diazepines has been reported <1984CHEC(7)593, 1996CHEC-II(9)113>.

13.04.9.7 Type *ce* (C–C + C–C–N–N–C)

This type of synthesis has been described earlier in the formation of 2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinolines by 1,5-dipolar cycloaddition of quinoxalin-4-oxides with 2-chloroacrylonitrile <1996CHEC-II(9)113>.

13.04.9.8 Type *d* (C–C–C–N–N–C–C)

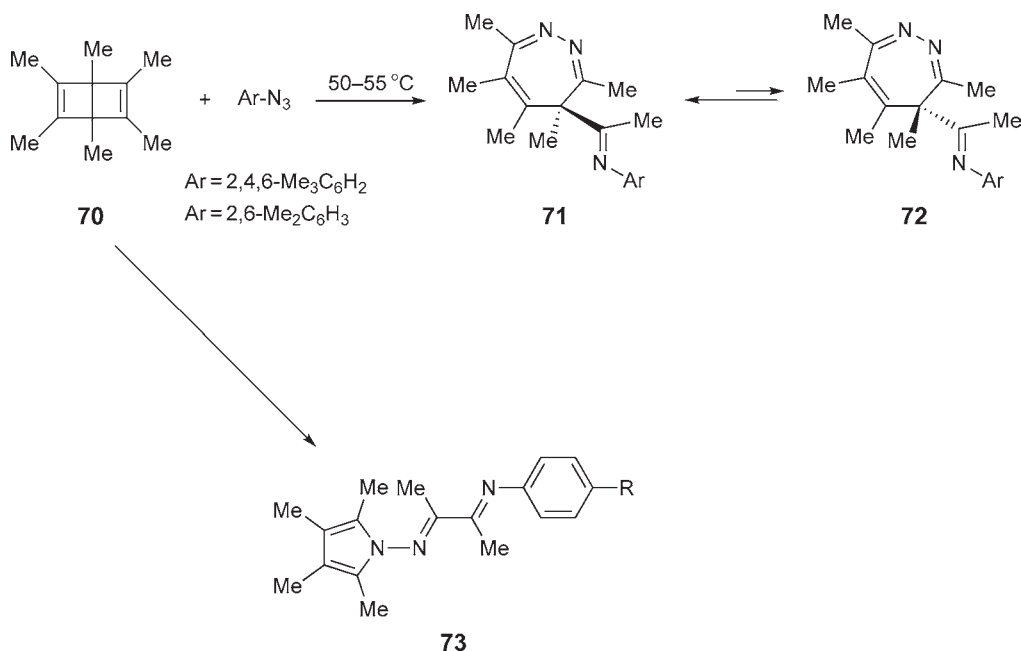
Many examples are reported for this type of synthesis to 1,2-diazepines. For example, cyclization of dihydrazones, Michael adducts between the hydrazines and dimethyl acetylenedicarboxylate (DMAD), and Dieckman cyclization of 1,1'-bipyrrroletetraacetic ester have been used in the synthesis of 1,2-diazepines <1996CHEC-II(9)113>.

13.04.9.9 Type *de* (C + C–C–N–N–C–C)

The azine derivative of α -bromoacetophenones has been used as the 1,6-dielectrophile along with malonate esters as the 1,1-dinucleophile has been used in the synthesis of 1,2-diazepines <1984CHEC(7)593, 1996CHEC-II(9)113>.

13.04.10 Ring Synthesis by Transformation of Another Ring

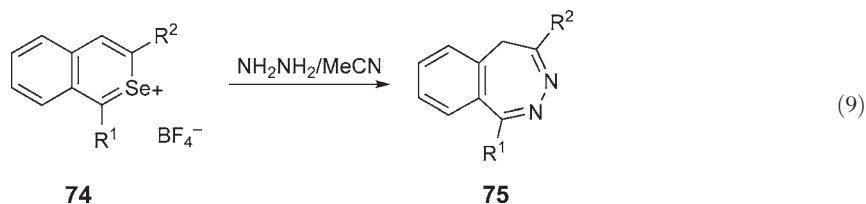
Unexpectedly, substituents on the phenyl group greatly effect the reaction pathway for mild thermolysis of hexamethyl Dewar benzene (HMDb) **70** in the presence of various azidobenzenes (Scheme 14). Thus, 1-azido-2,4,6-trimethyl- and 1-azido-2,6-dimethylbenzene give 1,2-diazepines **71**, whereas azidobenzene and 4-nitroazidobenzene give tetramethylpyrrole **73**.



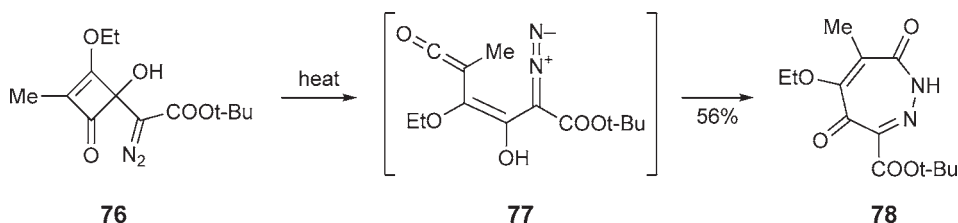
Scheme 14

The X-ray data for **71** confirm its structure. The low-temperature ^{13}C NMR suggests that **71** exists in two boat configurations (**72** being the other). Estimate for the free activation enthalpies for the major conformer of **71** is of *c.* 13–14 kcal mol $^{-1}$ <2005HCA1421>.

Reactions of 2-benzoselenopyrylium salts **74** with methyl- or phenyl-hydrazine afforded the 1-hydrazino-1*H*-isoselenochromenes, while the treatment of the selenopyrylium salts **74** with anhydrous hydrazine in dry MeCN resulted in a ring transformation to give the 5*H*-2,3-diazepines **75** in the one-pot reaction under mild conditions in moderate yields <2005CPB60> (Equation 9).



Ring expansion of diazo-functionalized 4-hydroxycyclobutenone is reported to give 2(5*H*)-furanone, cyclopentanedione, and diazepinedione formed by thermal $4\pi-8\pi$ electrocyclic ring-opening and -closure process. For example, a highly functionalized 4-hydroxy-2-cyclobutenone **76** exclusively gave the diazepinedione **78** in 56% yield upon heating in refluxing xylene <1999JOC707, 2003CRV1485> (Scheme 15).



Scheme 15

13.04.10.1 From Pyridine *N*-Imides

Photochemical conversion of pyridinium *N*-imides to 1*H*-1,2-diazepines is well known and described earlier <1984CHEC(7)593, 1996CHEC-II(9)113>.

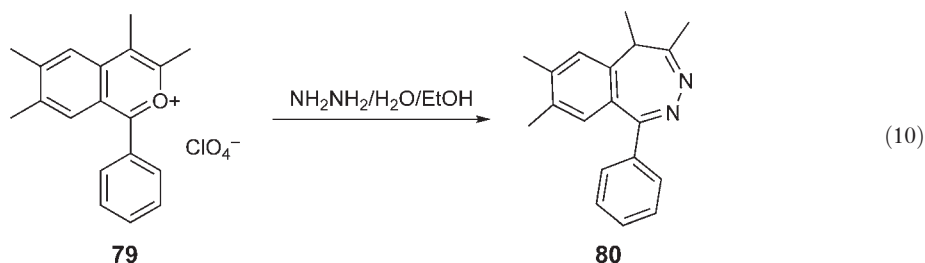
13.04.10.2 From Tetrahydro- γ -Carbolines

This is very similar to the above method of conversion of pyridinium *N*-imides to 1,2-diazepines. Here the tetrahydrocarbolines <1996CHEC-II(9)113> or the tetrahydroisoquinolines <1984CHEC(7)593> are *N*-substituted and *N*-aminated with *O*-sulfonyl hydroxylamine derivatives followed by treatment with base to give the corresponding 1,2-diazepines.

13.04.10.3 From Pirylium Salts

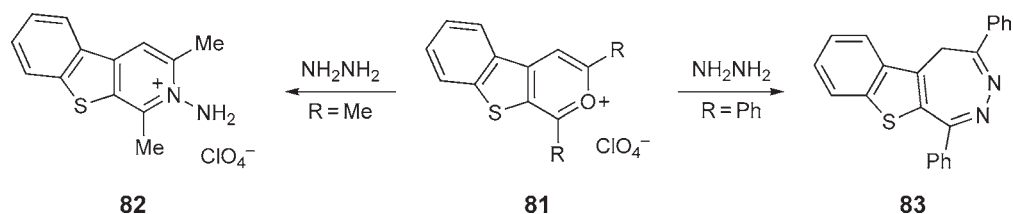
Reactions of pentafluorophenyl-substituted pyrylium perchlorates with hydrazine hydrate are known to give 1,2-diazepines. 2-Pentafluorophenyl-4,6-diphenylpyrylium perchlorate reacts with hydrazine hydrate like the unfluorinated analogue, forming 3,5-diphenyl-7-pentafluorophenyl-4*H*-1,2-diazepine. However, the 2,6-di(pentafluorophenyl)-4-phenylpyrylium perchlorate gives under the same conditions a mixture of 3-pentafluorophenyl-5-phenyl-5-pentafluorophenacyl-2-pyrazoline, 1,5-di(pentafluorophenyl)-3-phenyl-1,5-pentadione, and trace amount of 3,7-di(pentafluorophenyl)-5-phenyl-4*H*-1,2-diazepine <2004MI1>.

Reaction of 2-benzopyrylium perchlorate **79** with hydrazine gives 1-aryl-5*H*-2,3-benzodiazepines **80** <2001RMC243> (Equation 10).



The reaction of 1,3-disubstituted benzothieno[2,3-*c*]pyrylium salts **81** with hydrazine has been studied. It has been shown that these pyrylium salts interact with hydrazine to give *N*-amino-1,3-dialkylbenzothieno[2,3-*c*]pyridines **82**. In contrast, 1,3-diphenylbenzothieno[2,3-*c*]pyrylium perchlorate gives exclusively 5*H*-[2,3]benzothieno[2,3-*c*]diazepine **83** <1998CHE983> (Scheme 16).

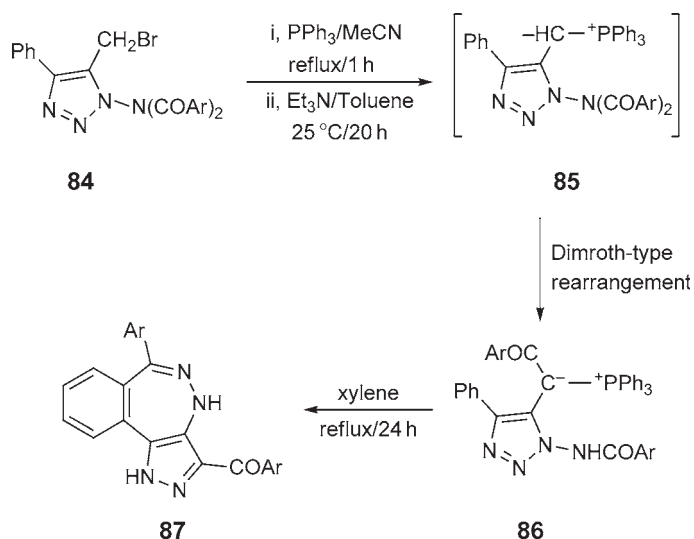
The 1-(hetero)arylvinyl-5*H*-2,3-benzodiazepines, useful for the treatment of central nervous system (CNS) disorders, are prepared by the reaction of 2-benzopyrylium perchlorates with hydrazine hydrate <2001EPP0726257B1>.



Scheme 16

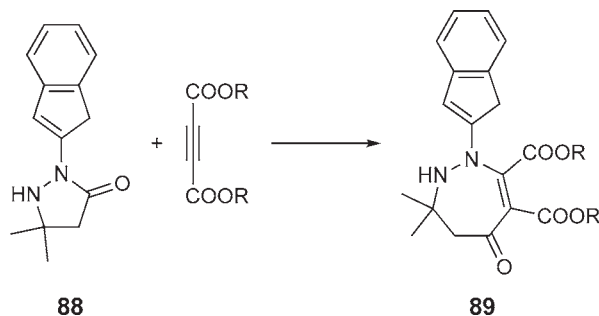
13.04.10.4 From Pyrazoles, Pyrazolines, and Related Species

Unexpected results lead to the discovery of pyrazolo[4,3-*d*][2,3]benzodiazepine **87** preparation from 1-(*N,N*-diaroyl)-amino-4-phenyl-[1,2,3]triazol-5-yl-methyltriphenylphosphonium ylide **85**. Ylide formation was followed by a Dimroth-type rearrangement to **86** and to product **87** <1995TL5637> (Scheme 17).



Scheme 17

Although reaction of 2-substituted 3-pyrazolidinones with acetylenedicarboxylates usually gives ring-expansion products, such as 1,2-diazepines, the treatment of the 2-substituted 3-pyrazolidinone **88** with dialkyl acetylenedicarboxylate resulted in the formation of a tricyclic compound as the major product, along with the formation of the expected 1,2-diazepine **89**, as the minor product <2000OL423> (Scheme 18).



Scheme 18

13.04.10.5 From Isoxazolo[3,4-*d*]pyridazin-7(6*H*)-Ones

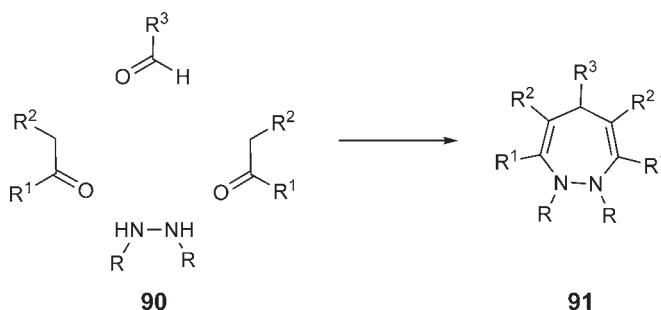
The conversion of certain substituted isoxazolopyridazines to 1,2-diazepines on alkali treatment is described in CHEC-II(1996) <1996CHEC-II(9)113>.

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

From reviewing the literature for the synthesis of 1,2-diazepines, just from the volume of the work it is apparent that the most preferred route to make 1,2-diazepines, starting from fragments, has been the type *bg* approach by using a 1,5-dielectrophile with hydrazine (a 1,2-nucleophile). In the case of ring transformation approach to 1,2-diazepines, the conversion of a pyrylium or a thiapyrylium salt to 1,2-diazepines has been the preferred route. In the end, the preferred method would depend on the nature of substituents and the unsaturation required on the 1,2-diazepine ring.

Of the four single bond-forming synthetic approaches (type *a*, *b*, *c*, and *d*) only type *a* is the least common due to, as mentioned earlier, the lack of availability of reactions forming N–N bonds (compared to C–C bond-forming reactions). Of the five remaining methods of two bond-forming synthetic approaches (type *be*, *bf*, *bg*, *ce*, and *de*), only type *bg* is the most common for the synthesis of 1,2-diazepines. This is due to the ready availability of hydrazine and its derivatives along with 1,5-dielectrophiles. As mentioned earlier, type *c* approach has the potential to be further exploited for the synthesis of 1,2-diazepines.

One other possibility to make 1,2-diazepines by forming four bonds (bonds *b*, *d*, *e*, and *g*) should be explored. This would be a one-pot synthesis from fragments like hydrazine, ketone, and aldehyde as shown in **90**, leading to 1,2-diazepines **91** (Scheme 19).



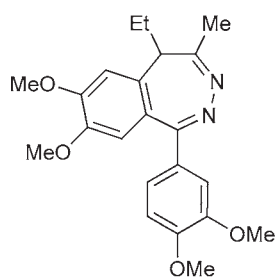
Scheme 19

13.04.12 Important Compounds and Applications

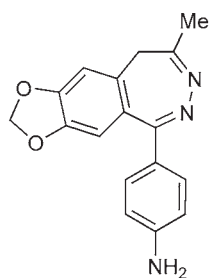
Interest in 2,3-benzodiazepines continues because of their therapeutic potential in CNS disorders <2001RMC243, 2000MI309>. Unlike 1,4-benzodiazepines, such as diazepam (Valium) and chlordiazepoxide (Librium), they have nonsedative character and lack the potential undesirable side effects when combined with other drugs or alcohol.

These 1,2-diazepines, for example, 1-arylvinyl-3,4-dihydro-5*H*-2,3-benzodiazepines <1996EPP0726256A1> and the corresponding 1-heteroarylvinyl derivative <2001EPP0726257B1>, show pharmacological activity and have found use for the treatment of CSN disorders.

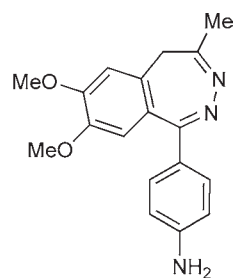
The first therapeutic 2,3-benzodiazepine was Tofisopam (Grandaxin) **92** which contains anxiolytic and antipsychotic properties. Since the success of **92**, other closely related compounds have demonstrated interesting biological activity. GYKI 52466 **93** is an anticonvulsant, and structure-activity relationship (SAR) studies have determined that the 4-aminophenyl group on the diazepine ring produces its antiepileptic properties. The 7,8-methylenedioxy functionality of Nerisopam **94** eliminates anticonvulsive character but produces anxiolytic and antipsychotic properties. The 3-*N*-methylcarbamoyl group in GYKI 5355 **95** increases its potency toward seizures compared to **93** <1995MI185>. Grisopam **96** shows significant anxiolytic and antipsychotic properties. An example of a diazepine showing non-CNS biological activity is PD 194035 **97**, which is a highly active interleukin-1 β -converting enzyme (ICE) inhibitor <1999BML1587>.



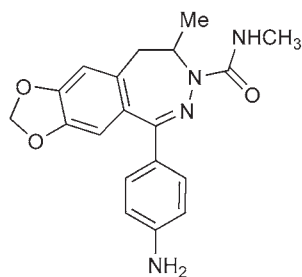
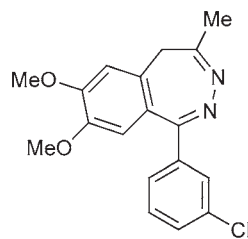
Tofisopam

92

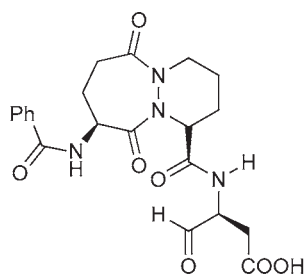
GYKI 52466

93

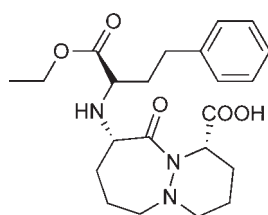
Nerisopam

94Talampanel
(GYKI 53655 or LY 300168)**95**

Girisopam

96**97**

The 1,2-diazepine Cilazapril **98** is an angiotensin-converting enzyme inhibitor and its design and synthesis have been reported [<1986J\(P1\)1011; 1999WO99/55724>](#).



Cilazapril

98

Other derivatives of benzo-2,3-diazepines have been made by forming a five-membered heterocyclic ring like imidazole [<2005JME4618>](#) as well as triazole [<2002FA129, 2003JME3758>](#) ring using the N-3 as one of the nitrogen atoms common to both the diazepine as well as the newly formed five-membered heterocycle (imidazole or triazole). Such compounds were synthesized and studied for their pharmacological properties.

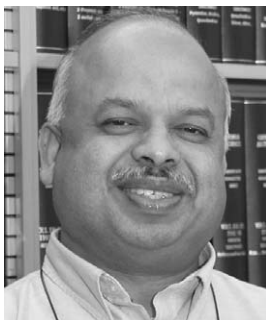
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Biographical Sketch



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.



Ramiah Murugan, born in Madurai, obtained BSc in chemistry from American College and MSc in chemistry from Madurai University. After 4 years working as a junior scientist at Madurai University, he joined Prof. Alan R. Katritzky's group in the Department of Chemistry at University of Florida and obtained his PhD in 1987. He continued in Prof. Katritzky's group for 2 more years doing postdoctoral work in the area of high-temperature aqueous organic chemistry. He joined Reilly Industries in 1989 (currently it is Vertellus Specialties, Inc.) and grew with in the ranks from research chemist to currently senior research associate. His research interests include synthesis of intermediates for pharmaceuticals, agrochemical products, and performance products; mechanistic studies; catalysis; polymer chemistry; and process development. He has many patents and publications to his credit in the above-mentioned areas of interest.

13.05

1,3-Diazepines

W. M. De Borggraeve and A. M. Van den Bogaert

K U Leuven, Leuven, Belgium

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13.05.1 Introduction

The chemistry of 1,3-diazepines **1** (Figure 1) was previously covered by Sharp in 4 pages <1984CHEC(7)605> and by Le Count in 12 pages <1996CHEC-II(9)139> in CHEC(1984) and CHEC-II(1996). Since then, a review by Herr appeared on the synthesis of seven-membered hetarenes with two or more heteroatoms in which 1,3-diazepines are also treated <B-2004SOS929>.

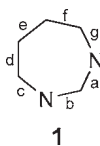


Figure 1

13.05.2 Theoretical Methods

When comparing the experimental structures calculated for diazepine **2** (Figure 2) with the X-ray structure of a benzoylated analogue, it is clearly seen that MP2 geometry calculations are superior in predicting the structure of these compounds (Table 1) <1997J(P2)1851>.

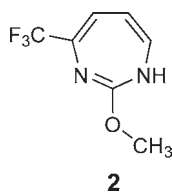


Figure 2

Table 1 Selected geometrical data for 2-methoxy-4-trifluoromethyl-1H-1,3-diazepine **2**

	Experimental	HF/6-31G*	MP2/6-31G*	BLYP/6-31G*
<i>Bond Lengths (pm)</i>				
N(1)–C(2)	142.2	138.5	140.9	142.6
C(2)–N(3)	126.8	125.6	128.2	128.5
N(3)–C(4)	138.8	139.6	139.8	140.8
C(4)–C(5)	134.8	132.5	135.5	136.3
C(5)–C(6)	143.2	146.7	145.1	146.2
C(6)–C(7)	131.4	132.0	134.7	135.5
C(7)–N(1)	142.6	141.2	142.5	143.4
C(2)–O(8)	132.8	132.0	134.6	136.0
O(8)–C(9)	143.7	141.9	144.3	145.6
C(4)–C(10)	148.8	150.7	150.1	151.9
<i>Bond angles (deg)</i>				
N(1)–C(2)–N(3)	125.2	128.3	126.7	128.0
C(2)–N(3)–C(4)	120.5	123.0	119.8	128.1
N(3)–C(4)–C(5)	127.2	129.1	128.1	128.5
C(4)–C(5)–C(6)	124.5	124.2	123.3	124.7
C(5)–C(6)–C(7)	123.9	124.1	123.1	124.9
C(6)–C(7)–N(1)	121.2	124.7	122.1	124.1
C(7)–N(1)–C(2)	113.4	119.5	113.1	116.6

Wentrup *et al.* evaluated *ab initio* and density functional theory (DFT) calculations to predict ^{13}C nuclear magnetic resonance (NMR) chemical shifts of azepines and diazepines <1997J(P2)1851>. Based on the comparison of these results with experimental data, they came to the following conclusions: Becke3LYP/ and HF/6-31G* and /6-31+G** single-point calculations based on MP2 geometries give the lowest average errors. The Becke3LYP calculations are better at predicting the correct order of chemical shifts, and localized orbital methods, such as individual gauge for localized orbitals (IGLO) or localized orbital, localized origin method (LORG), do not improve the quality of the results.

Benassi *et al.* studied the structure, the electronic properties, and barriers of rotation about the exocyclic double bond in 2-*exo*-methylene and 2-cyanoiminobenzodiazepines **3a–d** by means of NMR and a theoretical molecular orbital (MO) *ab initio* study (Figure 3; Table 2) <2000JST273>. For **3b**, in solution, the two (*E/Z*)-isomers were shown to exist with the (*Z*)-isomer predominating (96%). For **3c** and **3d**, at ambient temperature and upon cooling to 200 K, a single set of signals was observed, which means that only one isomer is present. According to calculations, the stability of the hydrogen bond in **3b** and steric effects in **3c** and **3d** explain the preference for one isomer over the other.

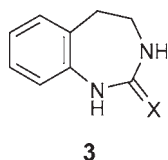


Figure 3

Table 2 Substituents for **3**

Compound	X
3a	C(CN) ₂
3b	C(CN)(COOEt)
3c	N(CN)
3d	NTos

All of the molecules examined show low barriers (of torsional type) for isomer interconversion according to theoretical results. These barriers are lower than in unsubstituted double bond derivatives and in imines. For **3c** and **3d**, the values for the rotational barrier are similar to open-chain derivatives. The calculated values, including solvent effects, are close to the experimental values.

Because of the importance of 1,3-diazepin-2-ones as human immunodeficiency virus 1 (HIV-1) protease inhibitors, considerable computational effort has been devoted to the analysis of the structure <1998JA4570> and binding properties <2004JME6673, 2004BMC5819, 1999JME249> of these compounds.

The conformational behavior of a diastereomeric series **4** (Figure 4) of these inhibitors was examined using the low mode:Monte Carlo conformational search method <2004JME4838>. Force fields were validated by comparing the energetic ordering of the minimum-energy structures on the AMBER*/GBSA(water), OPLSAA/GBSA(water), and HF/6-311G**/SCRF(water) surfaces. The energetic ordering on the OPLSAA/GBSA(water) surface was in better agreement with the quantum calculations than the ordering on the AMBER*/GBSA(water) surface. An ensemble of low-energy structures was generated using OPLSAA/GBSA(water) and used to compare the molecular shape and flexibility of each diastereomer to the experimentally determined binding affinities and crystal structures of related compounds. These results indicate that solution-phase energetic stability, conformational rigidity, and ability to adopt a chair conformation strongly correlate with experimental binding affinities.

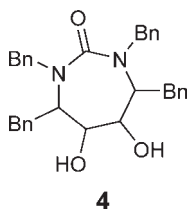


Figure 4

Another significant work in this area entails the modeling of the activity of cyclic urea HIV-1 protease inhibitors using artificial neural networks <2006BMC280>.

13.05.3 Experimental Structural Methods

13.05.3.1 X-Ray Studies

Wentrup and co-workers reported the first X-ray study of a monocyclic N-unsubstituted 1*H*-1,3-diazepine **5** (Figure 5) <2004OBC1227>. The structures of these compounds are boat-like.

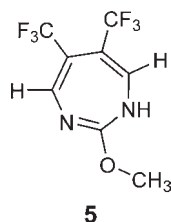


Figure 5

Scarborough *et al.* developed a number of seven-membered N-heterocyclic carbene ligands (based on 2,2'-diaminobiphenyl) and characterized several of the transition metal complexes formed with these ligands via X-ray crystallography <2005JOM6143, 2005AGE5269>. Furthermore, numerous papers presented the X-ray structures as proof for the formation of a type of compound without going into an in-depth discussion of the structural features of the compound itself.

13.05.3.2 NMR Studies

In almost all synthetic papers mentioned in this text, the authors have considered the NMR data of the compounds synthesized or have used NMR to prove or disprove the presence or absence of a certain conformer. Only in a few papers have the authors gone into a more systematic discussion of NMR properties. Of specific interest, the group of Isab has published a series of papers concerning the complexation of 1,3-diazepine-2-thione **6** and its seleno analogue **7** (Figure 6) with different metals such as Au(I) <1996TML553, 2004TML870, 2005TML389>, Ag(I) <2002POL1267, 2004TML400> and Hg(II) <1996POL2397> using ^1H , ^{13}C , ^{15}N , ^{107}Ag , and ^{199}Hg spectroscopy. They also performed a solid-state NMR study of **7** <2003MRC1026>.

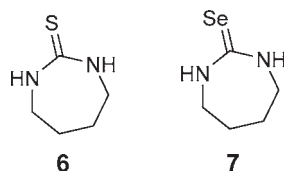


Figure 6

13.05.4 Thermodynamic Aspects

The free energy of activation for the proton shift process in the interconversion between tautomeric forms **8** and **9** was measured by the Forsén–Hoffman double resonance saturation transfer method and determined to be 16.2 kcal mol⁻¹ (Figure 7) <2004OBC1227>. This value was an average over three different structures (R = Me, Et, Prⁱ).

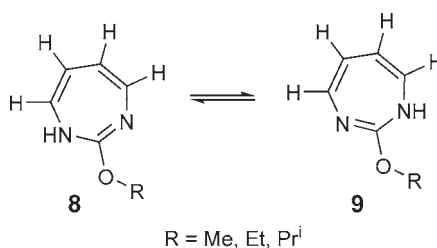


Figure 7

DFT calculations were performed for the double proton transfer in bicyclic 2,2'-bis(4,5,6,7-tetrahydro-1,3-diazepine) (**Figure 8**) <2001CPL591>. Both a concerted and a stepwise mechanism for proton transfer are considered. Though the concerted transition state has two imaginary eigenfrequencies, dynamical calculations have demonstrated that it has to be taken into account in the mechanism of the proton transfer even if it is not a true reaction path.

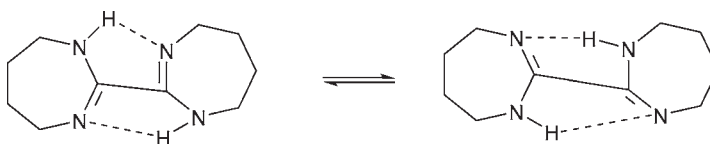


Figure 8

The diazepines **10** (**Figure 9**) are monobases which upon protonation at N-3 lead to a cyclic amidinium ion, which is strongly stabilized by mesomeric effects. The pK_a values determined via the potentiometric method for **10** are given in **Table 3** <2001JHC895>. The diazepines are somewhat stronger bases than the corresponding 4-substituted arylamines. This is easily explained by the formation of the stabilized amidinium ion. Electron-releasing groups at N-1 increase basicity, whereas electron-withdrawing groups at N-1 decrease it.

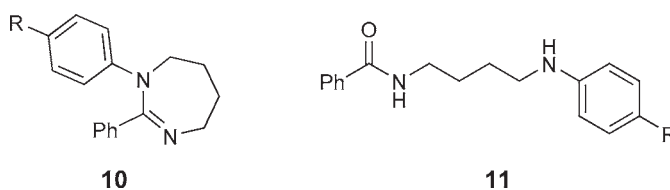


Figure 9

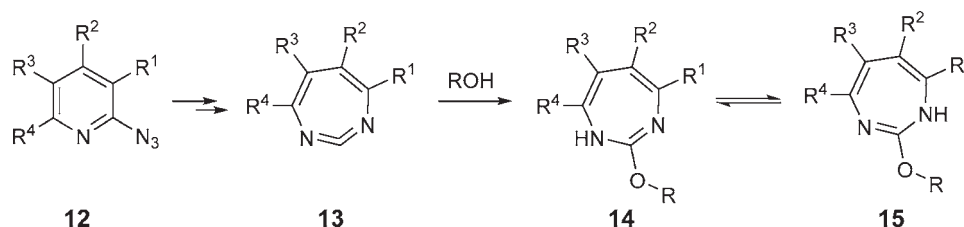
Table 3 pK_a values of **10**

Compound	R	pK_a
10a	H	9.59
10b	CH ₃	9.68
10c	OCH ₃	10.08
10d	Cl	8.58
10e	NO ₂	8.43

Diazepines **10** are completely stable to acid hydrolysis and can be recovered unchanged after prolonged periods of heating at 120°C in 3.8 M sulfuric acid solution. The acid stability of these systems is more pronounced than the stability of the analogous dihydroimidazoles which do hydrolyze in strong acidic media while being stable under mild acid conditions. The alkaline hydrolysis of **10** follows pseudo-first-order kinetics, proving that the rate-determining step in the hydrolysis is the decomposition of the tetrahedral intermediate. The alkaline hydrolysis only gives rise to compounds of type **11** (Figure 9).

13.05.5 Reactivity of Fully Conjugated Rings

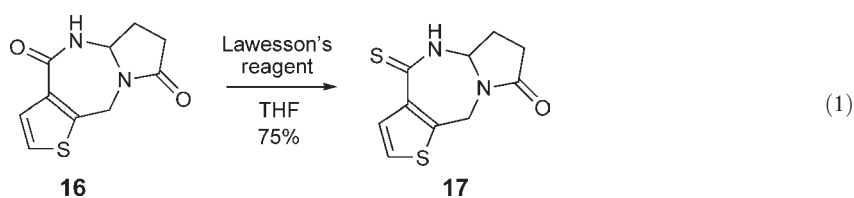
Tetraene intermediates **13** are formed upon irradiation of azidopyridines **12** (Scheme 1). The tetraenes react with alcohols forming products **14** and **15**, which are in tautomeric equilibrium <2004OBC1227, 1998JCS(P1)2247>. Usually, the NH is farthest away from the substituents in unsymmetrical systems.



Scheme 1

13.05.6 Reactivity of Nonconjugated Rings

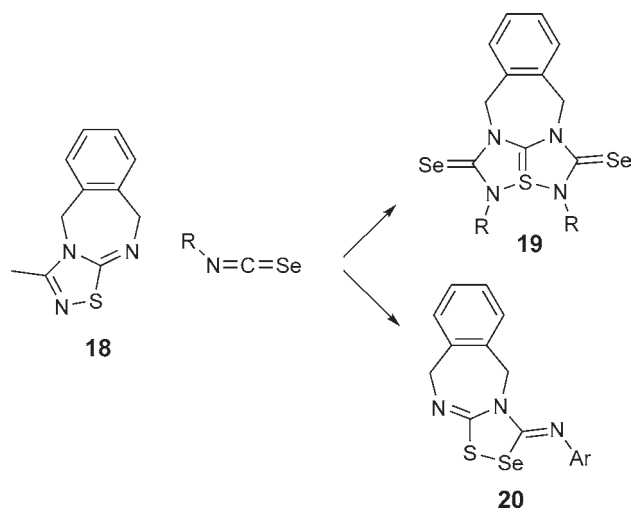
Using Lawesson's reagent in boiling tetrahydrofuran (THF), it is possible to selectively convert the diazepine lactam function in **16** to a thiolactam in 75% yield (Equation 1) <1996PS169>. Further treatment of the product **17** with another equivalent of Lawesson's reagent or treatment of **16** with 2 equiv of this reagent in boiling THF furnished the corresponding dithiolactam in 91% yield.



13.05.7 Reactivity of Substituents Attached to Ring Carbon Atoms

When the thiadiazole derivative **18** is reacted with a series of isoselenocyanates, **19** or **20** form depending on the R group on the isoselenocyanate (Scheme 2; Table 4) <1996HAC97>. Alkyl isoselenocyanates give rise to tetracycles **19**. Compound **19d** formed 1:1 clathrates with benzene, cyclohexane, toluene, and 1,2-dichloroethane, a 3 host:1 guest clathrate with Et₂O, and a 4 host:3 guest clathrate with dichloromethane (DCM). The diazepine **18** also reacted with aryl isoselenocyanates with elimination of MeCN, but with incorporation of only one molecule of the isoselenocyanate to yield **20**. The structures of **19** and **20** were confirmed by X-ray crystallography on representative members of the series.

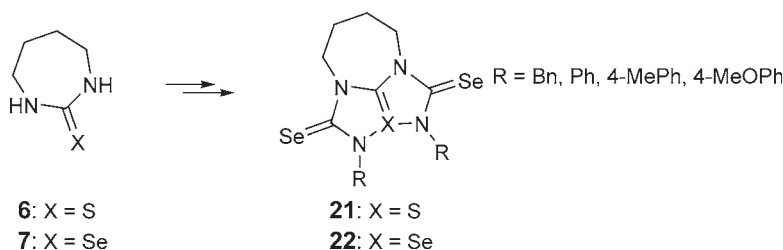
In follow-up work by the group, a general method is described to convert cyclic thio- or selenoureas **6** or **7** to **21** or **22** using isothiocyanates or isoselenocyanates (Scheme 3) <1997HAC13>.



Scheme 2

Table 4 Synthesis of **19** and **20**

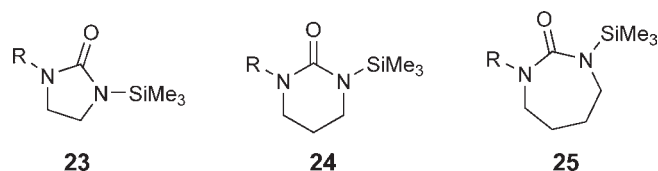
Compound	R	Yield (%)	Compound	R	Yield (%)
19a	Et	88	20a	Ph	71
19b	<i>n</i> -Bu	92–94	20b	4-MePh	75
19c	Cyclopentyl	45	20c	4-MeOPh	68
19d	Cyclohexyl	60	20d	4-BrPh	75
19e	Cycloheptyl	51	20e	3-EtOPh	30
19f	Bn	54	20f	3-ClPh	40
19g	PhCH ₂ CH ₂	87	20g	2-EtOPh	58
19h	Ph ₂ CHCH ₂	71	20h	2-BrPh	66



Scheme 3

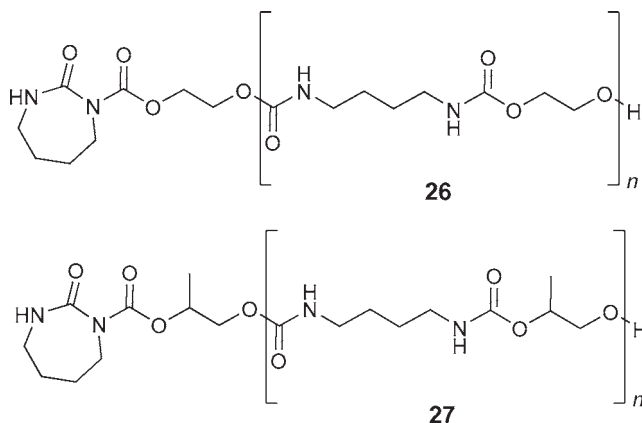
13.05.8 Reactivity of Substituents Attached to Ring Heteroatoms

In a comparative study of the octanololysis of N-trimethylsilylated cyclic urea derivatives (Figure 10) <2005JOM1498>, it was found that the five-membered systems were much more stable than the corresponding six- and seven-membered rings (Figure 10; Table 5). The half-life of these compounds was determined in the presence of an excess of octanol. It is very striking that the six- and seven-membered derivatives **24** and **25** are three orders of magnitude more reactive in the solvolysis than the five-membered ring **23**. The higher reactivity is ascribed to the fact that in the six- and seven-membered structures, there is a slight distortion from the tetrahedral coordination around the silicon atom in favor of a pseudotrigonal bipyramid (where the carbonyl oxygen is the fifth coordinating element). This finding is corroborated by X-ray data and calculations described in the same paper.

**Figure 10****Table 5** Hydrolysis of N-trimethylsilylated ureas **23–25**

<i>Compound</i>	<i>R</i>	<i>t</i> _{1/2}
23	SiMe ₃	35 days
24a	SiMe ₃	17 min
24b	Me	20 min
25	SiMe ₃	16 min

The synthesis of polyurethanes from tetramethylene urea, 1,2-propylene carbonate, and ethylene carbonate shows an interesting alternative route to polyurethanes **26** and **27** (Figure 11). The tetramethylene urea ring is not opened to form an isocyanate under the reaction conditions applied <2004MAC888>.

**Figure 11**

The same authors report the formation of copolymers and terpolymers of tetramethylene urea, γ -butyrolactone, and ethylene carbonate or 1,2-propylene carbonate <2004MM6755>.

Several poly(urea urethane) oligomers **28** (Figure 12) were prepared by one-component polycondensation of *N*-(hydroxyalkyl)-2-oxo-1,3-diazepane-1-carboxamides, which act as intramolecular blocked isocyanates <2005PLM1459>. These oligomers are semicrystalline materials and their melting points show the odd/even effect observed earlier for [*n*]-polyamides, [*n*]-polyurethanes, poly(ester amide)s, and poly (amide urethane)s. Further analysis showed that the polymers are stable up to ca. 205–230 °C, the polymers with the lower number of methylene groups in the amino alcohol decomposing at the lowest temperature.

Reaction of arylidenemalononitriles **29** with some nitroenamines **30** leads to polyfunctionally substituted pyrido[1,2-*a*]-1,3-diazepines **31** (Figure 13) <2005KGS1850>.

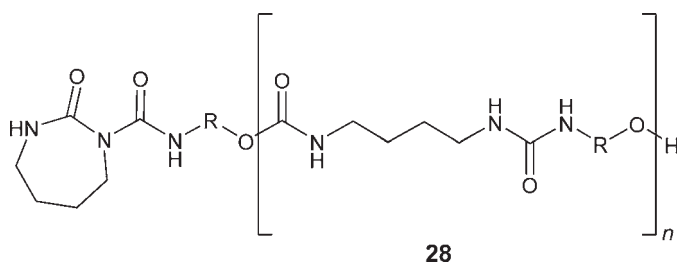


Figure 12

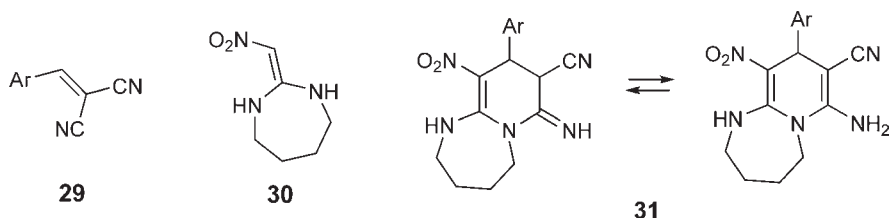


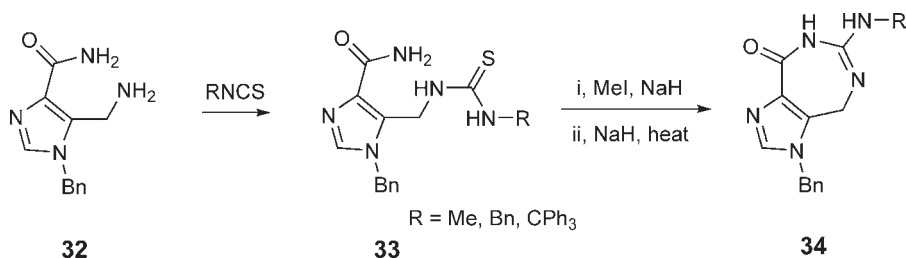
Figure 13

13.05.9 Synthesis of 1,3-Diazepines by Ring Closure

13.05.9.1 Formation of One Bond

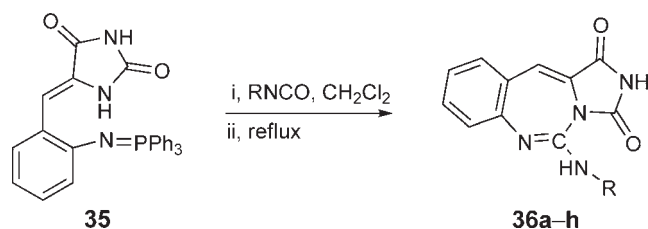
13.05.9.1.1 Type a (N-C-C-C-C-N-C)

Ring expanded analogues **34** of guanidine have been prepared by reacting the benzyl protected imidazole **32** with an isothiocyanate to form a thiourea **33** in 60–90% yields (Scheme 4). Methylation on sulfur with MeI and NaH in dimethylformamide (DMF) allows subsequent ring closure with another equivalent of NaH upon heating <1996J(P1)2257>. In a similar way, an integrin antagonist was prepared by Ishikawa *et al.* <2006BMC2109>.



Scheme 4

Reaction of iminophosphoranes **35** with a variety of aromatic isocyanates gives rise to the formation of imidazo[1,5-*c*][1,3]benzodiazepines **36** in yields ranging from 65% to 85% (Scheme 5; Table 6) <1997T15895>.

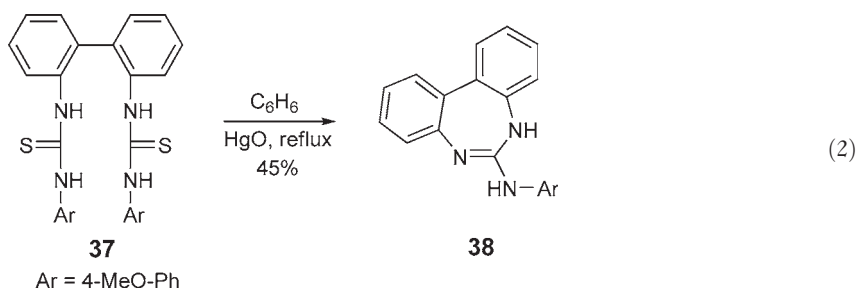


Scheme 5

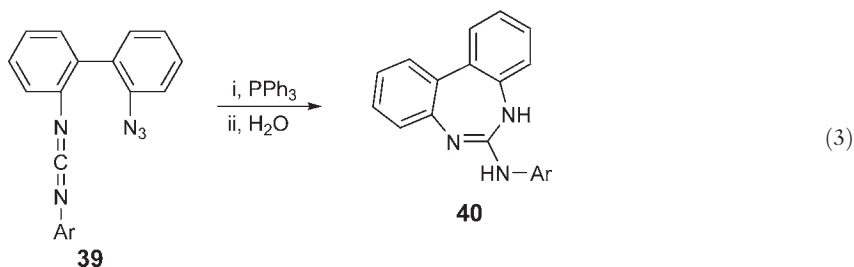
Table 6 Synthesis of imidazobenzodiazepines **36**

Product	R	Yield (%)
36a	Ph	85
36b	<i>p</i> -CH ₃ -Ph	80
36c	<i>o</i> -CH ₃ -Ph	82
36d	<i>p</i> -CH ₃ O-Ph	78
36e	<i>m</i> -CH ₃ O-Ph	83
36f	<i>p</i> -Cl-Ph	69
36g	<i>p</i> -NO ₂ -Ph	65
36h	Bn	79

Dehydrosulfurization of **37** using HgO gives the diazepine **38** in 45% yield (Equation 2) <1999JOC1121>.

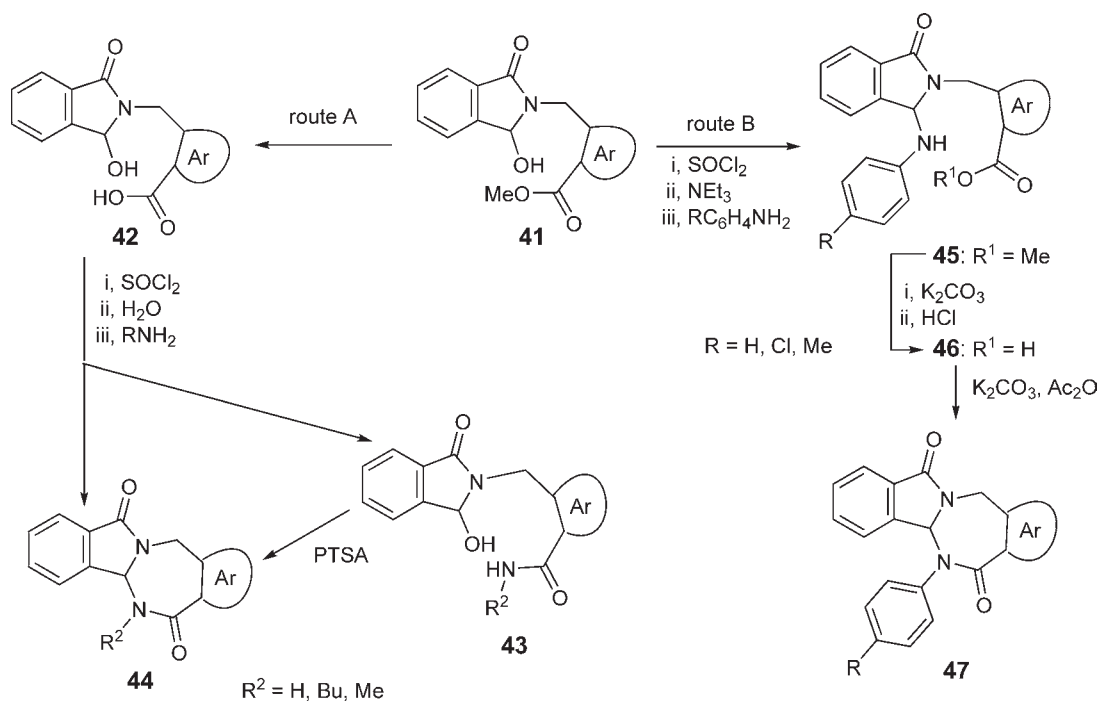


In this same paper, the authors mention that upon treating **39** with PPh₃ followed by aqueous workup (Equation 3), the diazepines **40** are isolated; however, there is no mention of the yields.



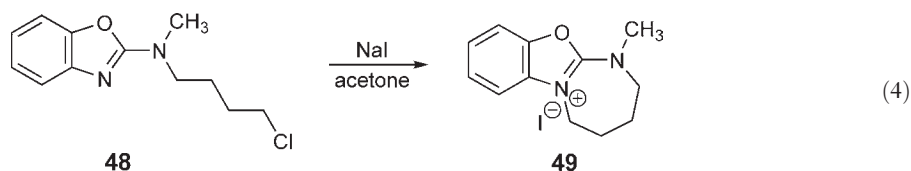
13.05.9.1.2 Type c (N-C-N-C-C-C-C)

The *N*-aryl or *N*-alkyl derivatives of isoindolo[2,1-*b*][2,4]benzo(or thieno)diazepines **44** and **47** <1998T1497> were synthesized via *N*-acyliminium intermediates (Scheme 6). Two routes are reported for their synthesis starting from a similar intermediate **41** (Ar = phenyl or thiophene). The main difference between the routes is the order in which the subsequent steps are performed. For the synthesis of the *N*-alkyl derivatives, route A was followed in which the precursor was first converted into a hydroxylactam acid **42** (Scheme 6). Treating this hydroxylactam acid with SOCl₂, followed by partial hydrolysis furnishes a hydroxylactam acid chloride. Upon addition of an aliphatic amine, this intermediate is directly converted into the desired **44** or into a mixture of the desired **44** and the open form **43**. Treating this mixture with *p*-toluenesulfonic acid (PTSA) converts everything to the desired products. This route was not successful for the synthesis of the *N*-aryl derivatives where numerous side products were formed. For the synthesis of the *N*-aryl derivatives, route B (Scheme 6) proved to be more successful. In this route, the aniline moiety in **45** is introduced via a chlorolactam formed *in situ* by treating the **41** with SOCl₂. This chlorolactam is converted into an *N*-acyliminium ion that can further react with an arylamine. Subsequent hydrolysis of the ester gives the carboxylic acid derivatives **46**, which upon activation allows cyclization to the desired **47**.

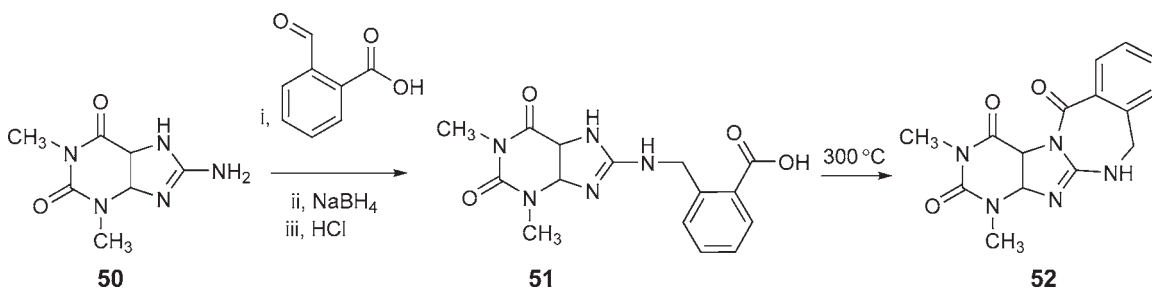


Scheme 6

In the course of the synthesis of substituted benzoxazoles, it was found that upon reacting **48** with NaI in acetone, the stable salt **49** was formed (Equation 4) [<2000T8567>](#).

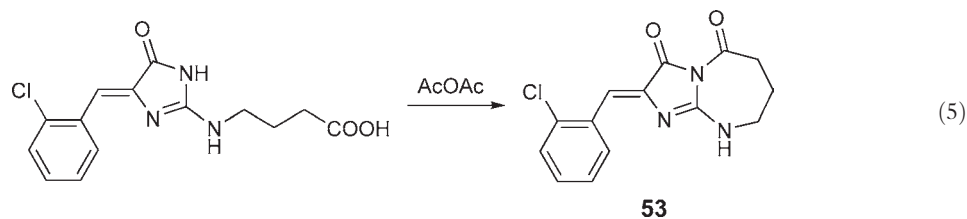


An example of diazepinone formation by lactamization is given by Da Settimo *et al.* [<1999JHC639>](#). After reacting 8-aminotheophylline **50** with 2-carboxybenzaldehyde to form a Schiff base, reduction with NaBH_4 forms precursor **51**, which can be easily cyclized by heating at 300°C in a Pyrex tube to give **52** in 64% yield (Scheme 7). If the overall reaction is considered starting from theophylline, it could also be classified as a type cg bond formation.



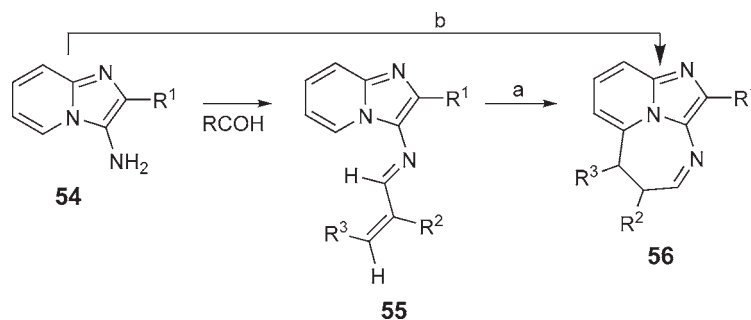
Scheme 7

A similar diazepinone formation was performed for the synthesis of **53**. In this case, however, the cyclization was performed via the formation of a mixed anhydride (Equation 5) <2001EJM407>.



13.05.9.1.3 Type d (C–N–C–N–C–C–C)

Imidazopyridodiazepines **56** are formed by *peri*-annulation of imidazo[1,2-*a*]pyridines **55** (route a; Scheme 8; Table 7) <2002TL9119>. These compounds can alternatively be synthesized directly from the 2-substituted-3-amino imidazopyridines **54** and simple aldehydes or α,β -unsaturated aldehydes in good yields. Products are formed as *cis/trans*-mixtures.



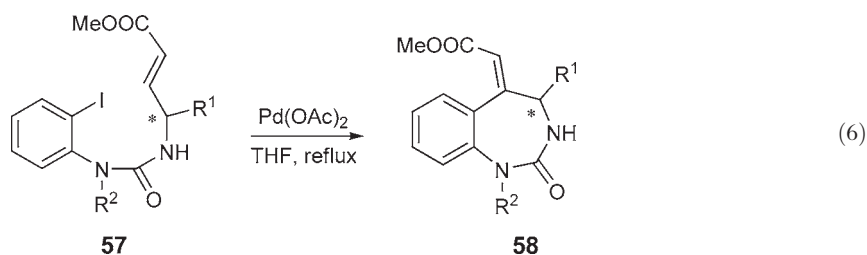
Scheme 8

Table 7 Synthesis of imidazopyridodiazepines **56**

Product	R	R ¹	R ²	R ³	Yield (route a) (%)	Yield (route b) (%)
56a		Ph	CH ₃	CH ₂ CH ₃	61	60
56b		Ph	CH ₃	CH ₂ CH ₃	97	99
56c		Ph	H	H	42	45
56d		Ph	H	CH ₃	98	99
56e		<i>o</i> -CH ₃ OPh	H	CH ₃	90	90
56f		Cl	H	CH ₃	90	91

13.05.9.1.4 Type e (C–C–N–C–N–C–C)

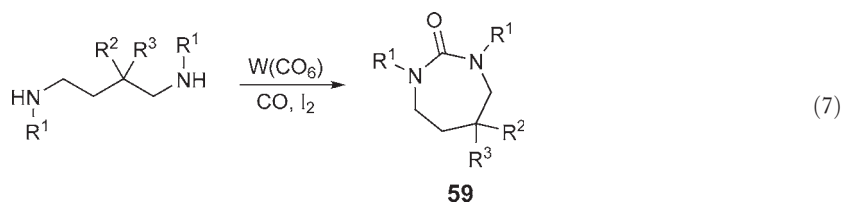
For the synthesis of 1,3-benzodiazepin-2-ones potentially containing a chiral center at C-4, Horikawa *et al.* used an intramolecular Heck reaction as the key step in their synthesis [<1998H\(48\)1331>](#). The direct precursors **57** for the diazepines **58** were made in a few steps from amino acids; Pd(OAc)₂ was used as a catalyst (5 mol%) in the cyclization together with PPh₃ (10 mol%) and Et₃N (1.5 equiv) in refluxing THF ([Equation 6](#)). In the reaction, some olefin isomerized products and deiodinated compound were also observed (up to maximum 20%). The reported yields range from 76% to 100% for the cyclization reaction.



13.05.9.2 Formation of Two Bonds

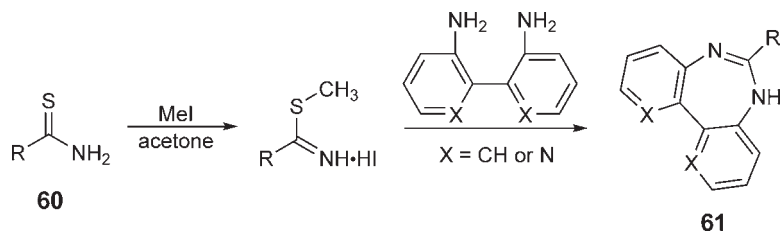
13.05.9.2.1 Type ab (N–C–C–C–C–N + C)

In a systematic study on the catalytic carbonylation of primary and secondary diamines using W(CO)₆ as the catalyst, I₂ as the oxidant, and CO (100 atm) as the carbonyl source, it was found that the ureas **59** are accessible in rather modest yields of ca. 36–38% ([Equation 7](#)) [<1999OL961, 2002JOC4086>](#).



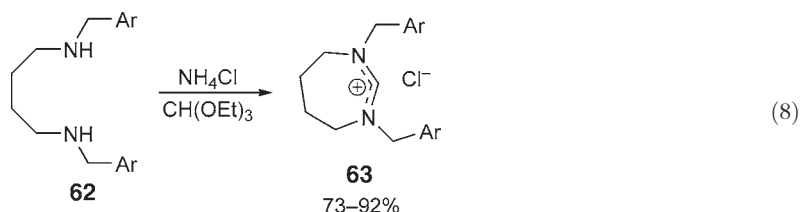
This catalytic carbonylation strategy was further applied to the synthesis of the core structure of HIV protease inhibitors [<2003JOC1615>](#).

Thioamides **60** can be converted into dibenzo- and dipyrro[1,3]diazepines **61** in a reaction with *o,o'*-diaminobiaryl derivatives in yields ranging from 72% to 98% ([Scheme 9](#)) [<1997SC2393>](#). This is an alternative to reactions of *o,o'*-diaminobiaryls with imino ester salts.

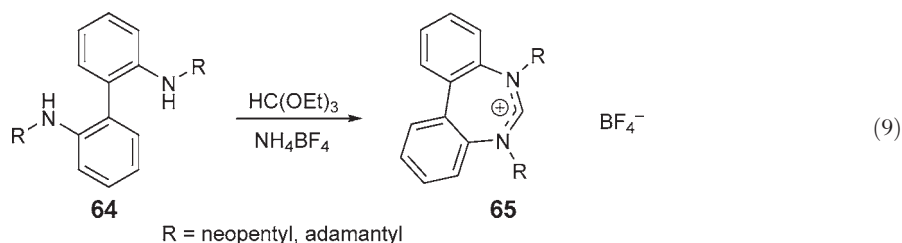


Scheme 9

In a report by Özdemir *et al.* [<2005SL2394>](#), tetrahydrodiazepinium salts **63** ([Equation 8](#)) are used as precursors to carbene ligands to be used in Suzuki reactions with aryl chlorides in an aqueous media. In order to prepare these N-heterocyclic carbene ligands, the diamines **62** were reacted with ammonium chloride and triethyl orthoformate. The catalysts prepared from these ligands are stable to air.



Independently, S. S. Stahl's group prepared a series of chiral N-heterocyclic carbenes based on chiral 2,2'-diaminobiphenyl precursors **64** (Equation 9) <2005JOM6143, 2005AGE5269>. The carbene ligand is formed out of the salts **65** by simple deprotonation.



Also, reactions performed on a solid support can lead to 1,3-diazepin(on)e-containing skeletons. Meldal's group used peptide-derived *N*-acyliminium intermediates, which underwent nucleophilic attack from side-chain functional groups to afford bicyclic skeletons **66** and **67** after cleavage from the resin in >95% and 93% purity, respectively (Figure 14) <2005OL3601>.

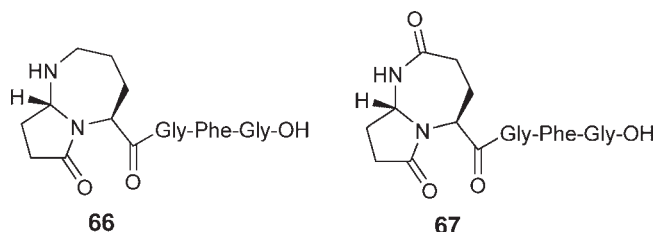
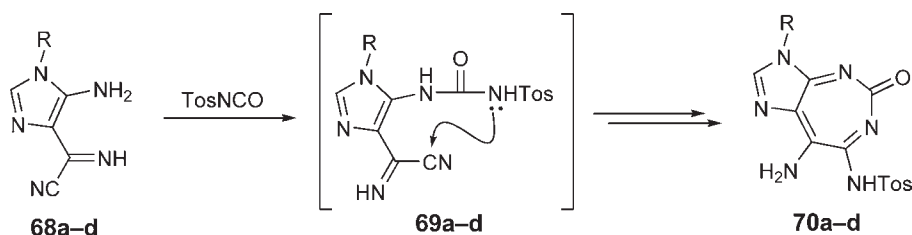


Figure 14

13.05.9.2.2 Type ac (N-C-C-C-C + C-N)

When 5-amino-4-(cyanoformimidoyl)imidazoles **68** are reacted with tosyl isocyanate, **70** are formed (Scheme 10; Table 8) <1996JHC855>. After a 7-*exo-dig*-cyclization of intermediates **69a–d**, a Dimroth rearrangement takes place to give the thermodynamic products **70a–d**.



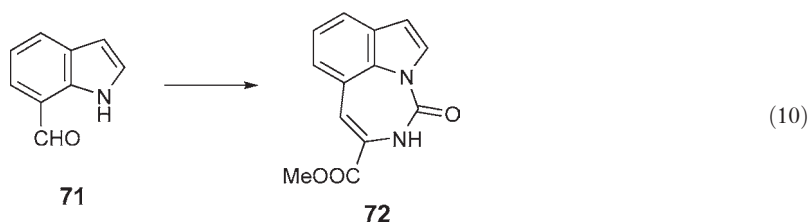
Scheme 10

Table 8 Formation of compounds **70a–d** (Scheme 10)

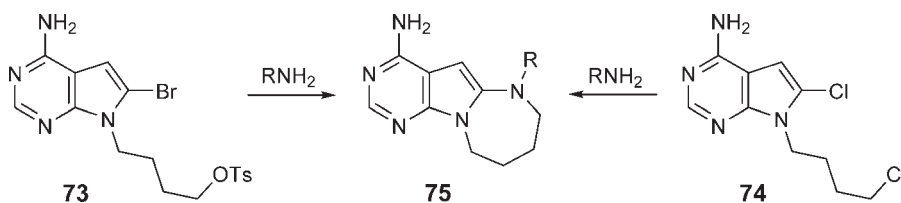
Product	R	Yield (%)
70a	$-\text{CH}_2\text{CH}_2\text{OH}$	37
70b	$p\text{-CH}_3\text{C}_6\text{H}_4-$	96
70c	$p\text{-NCC}_6\text{H}_4-$	99
70d	$p\text{-CH}_3\text{OC}_6\text{H}_4-$	88

13.05.9.2.3 Type ad ($\text{C}-\text{C}-\text{C}-\text{N} + \text{C}-\text{N}-\text{C}$)

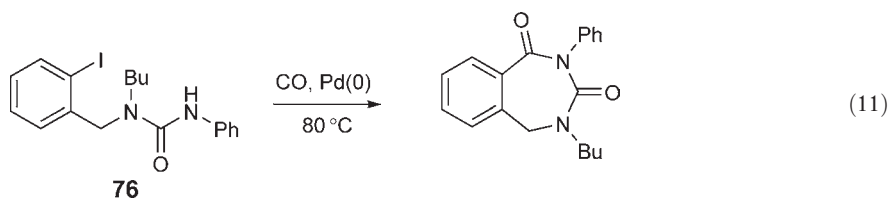
In their work on the synthesis of analogues of the tryptophan amino acid, Carlier *et al.* found that when product **71** is treated with 1.5 equiv of $(\text{MeO})_2\text{P}(\text{O})\text{CH}-(\text{NH}\text{Cbz})\text{CO}_2\text{Me}$ in the presence of a base, **72** is formed after the olefination reaction by extrusion of benzyl alcohol (Equation 10) <2002JOC6256>.

13.05.9.2.4 Type bc ($\text{C}-\text{N}-\text{C}-\text{C}-\text{C} + \text{N}$)

Reaction of **73** and **74** with primary amines, ammonia, or hydrazine at elevated temperature provides access to the corresponding diazepines **75** in good yield (Scheme 11) <2000CCCC1109>.

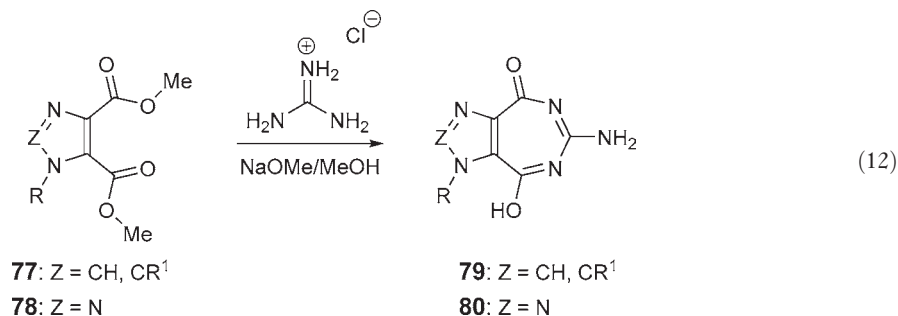
**Scheme 11**13.05.9.2.5 Type cd ($\text{N}-\text{C}-\text{N}-\text{C}-\text{C} + \text{C}$)

Carbonylation of **76** is possible using Pd under CO atmosphere (Equation 11) <1999TL2623>; DMF was the solvent of choice.

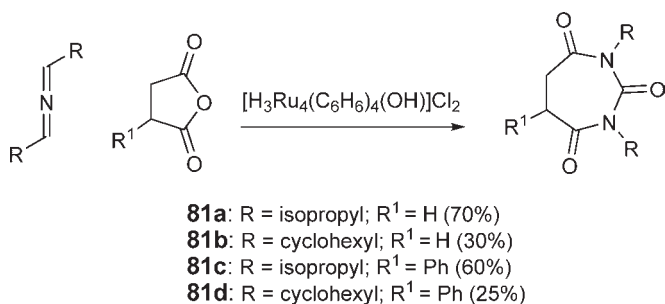
13.05.9.2.6 Type cg ($\text{C}-\text{C}-\text{C}-\text{C} + \text{N}-\text{C}-\text{N}$)

By reacting N-functionalized imidazole-4,5-dicarboxylates **77** with guanidine·HCl and NaOMe/MeOH, Hosmane *et al.* prepared a series of ring-expanded nucleoside analogues **79** ('fat' nucleobase analogues) (Equation 12), which

were tested for their biological activity <1999NN331, 1999BMC2931, 2000JHC951, 2001JHC1313, 2002BML3391, 2003JME4776, 2003JME4149, 2005BML5397>. Using a similar strategy, triazole analogues **80** were synthesized via the corresponding triazole dicarboxylates **78** <2002NN361>.



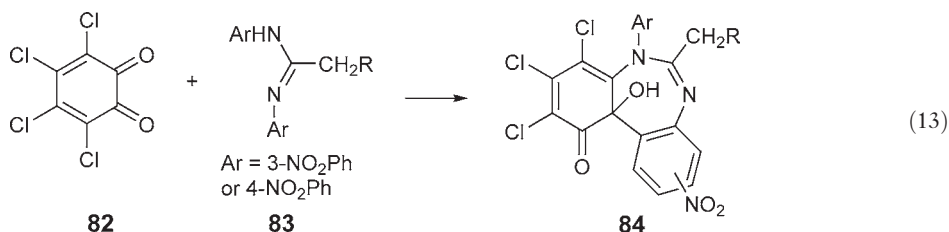
The cationic hydroxo cluster $[H_3Ru_4(C_6H_6)_4(OH)]^{2+}$ is able to catalyze the insertion of carbodiimides into cyclic anhydrides giving rise to seven-membered analogues of barbituric acid (**Scheme 12**). The mechanism for the formation of the derivatives **81** is not yet clear, but according to the authors it seems to involve a triply bridging hydroxo ligand <2002TL6653>.



Scheme 12

13.05.9.2.7 Type eg (N-C-N-C-C + C-C)

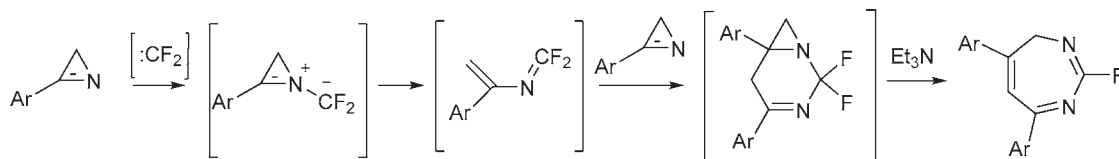
Nitro-substituted *N*¹,*N*²-diarylamidines **83** react with chlorinated derivatives **82** to form mainly dihydrodibenzo-diazepinones **84** (Equation 13) <2003T5887>. With diphenylamidines or di-(4-*tert*-butylphenyl)amidines, 6,7,8,9-tetrachlorodibenzodioxins are obtained instead.



13.05.10 Synthesis of 1,3-Diazepines by Ring Transformation

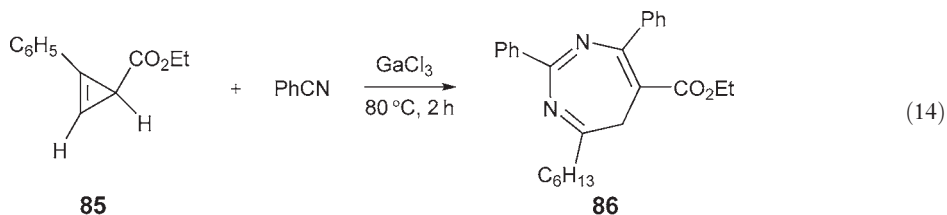
13.05.10.1 Transformation of a Three-membered Ring

The 5,7-diaryl-2-fluoro-4*H*-1,3-diazepines have been synthesized from 3-aryl-substituted 2*H*-azirines and difluorocarbene (**Scheme 13**). The reaction involves isomerization of azirinium ylide into a 2-aza-1,3-diene, which undergoes [4+2] cycloaddition with the starting azirine, followed by ring expansion and dehydrofluorination <2006TL639>.



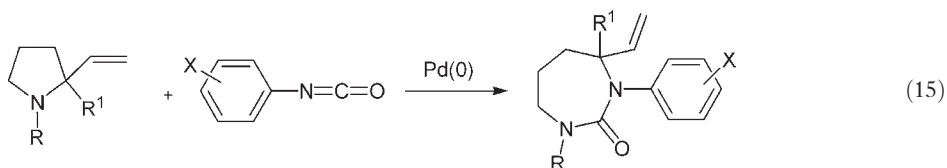
Scheme 13

In a pyrrole synthesis, cyclopropene **85** and a twofold excess of phenylacetonitrile were treated with $GaCl_3$ at $80^\circ C$ for 2 h. The 1,3-diazepine **86** was formed in 10% yield as a by-product in this reaction (Equation 14) <2003OBC4025>.

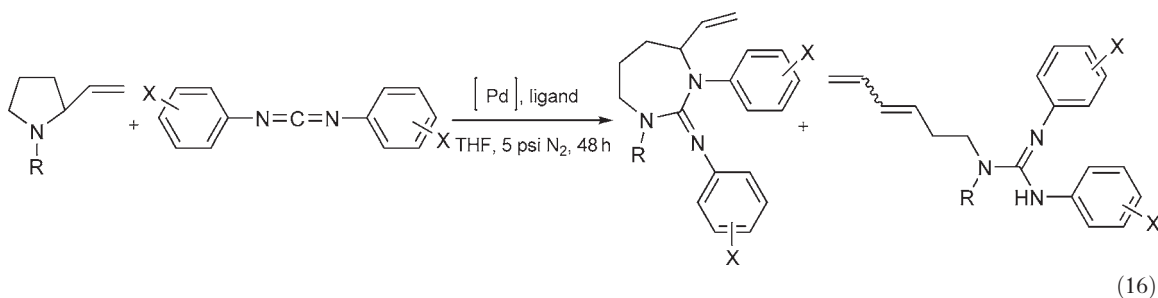


13.05.10.2 Transformation of a Five-membered Ring

The 2-vinylpyrrolidines can undergo a $Pd(0)$ -catalyzed ring expansion upon treating them with aryl isocyanates (Equation 15) <2003JOC3439>.

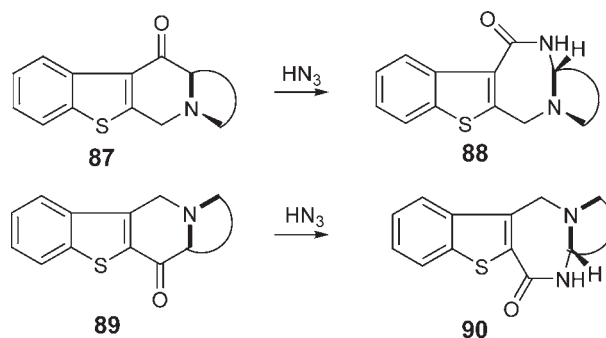


In a similar fashion, cycloaddition reaction of 2-vinylpyrrolidines with carbodiimides in the presence of $Pd(OAc)_2$ and 1,5-bis(diphenylphosphino)pentane affords the seven-membered ring cyclic arylguanidines in acceptable yields and conversions (Equation 16) <2004T73>.



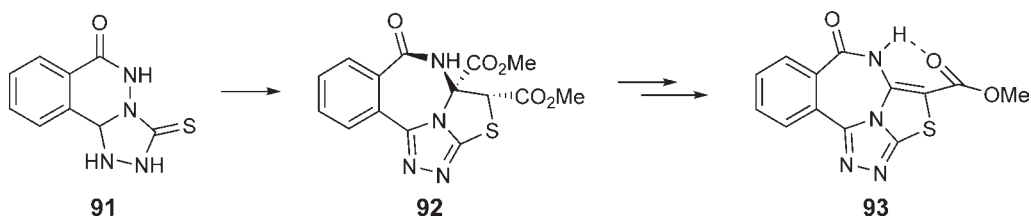
13.05.10.3 Transformation of a Six-membered Ring

The Schmidt rearrangement of [1]benzothienindolizidinones **87** and [1]benzothienoquinolizidinones **89** led exclusively to the [1,3]diazepine derivatives **88** and **90**, respectively (Scheme 14) <1996JHC873>.



Scheme 14

On heating the condensed [1,2,4]-triazolo[4,3-*b*]pyridazine-6(5*H*)-one-3(2*H*)-thione **91** with dialkyl acetylenedicarboxylates in DMF, the subsequent ring transformations yielded the novel tetracyclic 1,3-diazepine *cis*-**92**, which can further be converted to **93** in a number of steps involving elimination, decarboxylation, and cyclization oxidation upon heating (Scheme 15) <2001T7191>.



Scheme 15

Ultraviolet (UV) irradiation of **94** gives the derivatives **95** and **96** (Figure 15) <1997JCM170>.

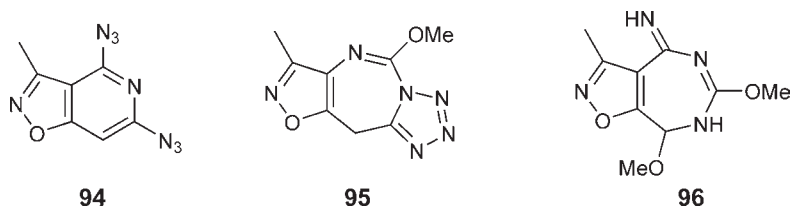


Figure 15

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

One specific class of compounds, which contains the 1,3-diazepine ring as a 'subcaffold', is the class of the molecular clips and capsules. In these compounds, the diazepine ring is a structural feature, which helps to extend the concave shape of a central diphenylglycoluril moiety, for example, **97**, or a central dimethylpropanediurea moiety, for example, **98** (Figure 16). For their synthesis <1998CC121, 2001JOC2643, 2004SL2385>, the previously mentioned bond-forming techniques have been used. Because of the very specific applications in molecular recognition <2003JOC6184, 2002AGE4028>, supramolecular chemistry <2003CC1638, 2001JOC391, 2001JA5213> and host-guest chemistry <2002AGE3793, 2001JOC1538>, these compounds are mentioned in this part of the text only.

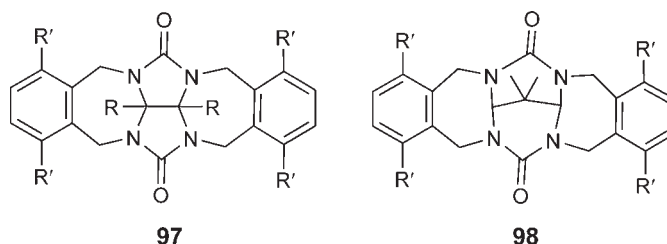


Figure 16

13.05.12 Important Compounds and Applications

In the last decade, the 1,3-diazepine skeleton has also drawn considerable attention of medicinal chemists. Among others, these compounds were tested as protease inhibitors and antiviral compounds. A number of cyclic ureas, for example, **99** (Figure 17), were designed as HIV protease inhibitors. Their design was based on the analysis of X-ray structures of HIV-1 protease with a number of peptidomimetic inhibitors, first principles, and computer-aided design <1996JME3514, 2004JME6673, 2004BMC5819, 1999JME249>.

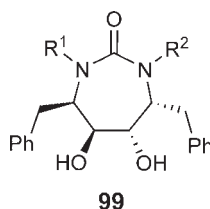


Figure 17

A series of imidazo[4,5-*e*][1,3]diazepines **100** have been synthesized as analogues of nucleosides and nucleotides and they have proven to be potential inhibitors of NTPases/helicases of *Flaviviridae*, including the West Nile virus, Hepatitis C virus, and the Japanese encephalitis virus (Figure 18) <2003JME4149, 1999BMC2931, 2005BML5397, 2003JME4776, 2002BML3391>. Minor modification in their structure has been responsible for major changes in biological activity.

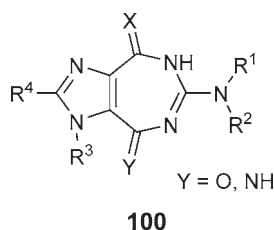


Figure 18

References

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Biographical Sketch



Wim M. De Borggraeve was born in Kortrijk (Belgium) in 1976. He received his licentiate degree in chemistry in 1998 at K. U. Leuven. In 2002, he obtained his Ph.D. under the guidance of Professor G. Hoornaert at the same university with a thesis on the use of cycloaddition chemistry in the development of secondary structure mimics. From 2002 until now, he has been working as a postdoctoral researcher at the FWO-Vlaanderen at K. U. Leuven. During this time, he carried out part of his research in the groups of W. D. Lubell (Université de Montréal) and C. Toniolo (Università degli studi di Padova). His main research interests are heterocycle chemistry and the design of secondary structure mimics.



An M. Van den Bogaert was born in Lier, Belgium (1981). She graduated from Sint-Ursula Lier High School in 1999. She received her licentiate degree in chemistry in 2003 at K. U. Leuven. In 2004, she obtained a teaching certificate at the K. U. Leuven. After this, she started her Ph.D. as a researcher at the FWO-Vlaanderen at the same university in the lab of Molecular Design and Synthesis. Her promotor is Professor Frans Compennolle. She is working on the synthesis of probes for targeted drug delivery and on the application of the 'scaffolding approach' for the development of potential (ant)agonists of short bioactive peptides.

13.06

1,4-Diazepines

N. A. Meanwell and M. A. Walker

Bristol-Myers Squibb Research and Development, Wallingford, CT, USA

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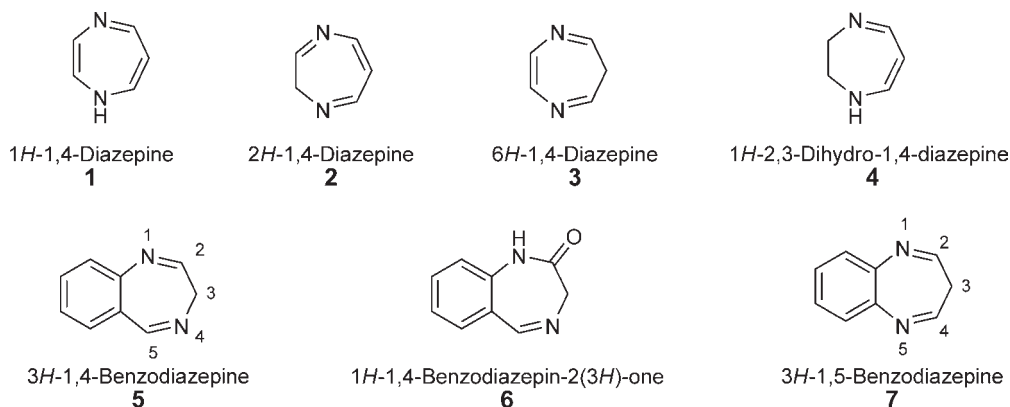
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13.06.1 Introduction

The clinical importance and commercial success associated with the 1,4-benzodiazepine class of central nervous system (CNS)-active agents and the utility of 1,4-diazepines as peptidomimetic scaffolds have led to their recognition by the medicinal chemistry community as privileged structures. This ring system has demonstrated considerable utility in drug design, with derivatives demonstrating a wide range of biological activities. As a consequence, there is an abiding interest in developing a deeper understanding of conformational preferences associated with 1,4-diazepines that permits more effective control of conformer populations with a view to broadening the potential applications. In concert with this, the development of new synthetic approaches to the 1,4-diazepine ring system and their further elaboration have provided access to a broad range of functionalized derivatives that have contributed to advances in understanding the underlying principles of structure and reactivity. In this chapter, the outlines followed by CHEC(1984) <1984CHEC(7)593> and CHEC-II(1996) <1996CHEC-II(9)151> are followed with additional sections as appropriate to reflect developments in the area. This summary augments the literature summarized in CHEC(1984) and CHEC-II(1996), adding examples of new topological ring constructions and updating previously discussed disconnections where new methodology or reagents have been developed that enhance the value of the process. The examples cited are drawn from the literature published between 1995 and the end of 2006 and focus on monocyclic 1,4-diazepines and their benzo-fused homologues. 1,4-Diazepines that incorporate additional fused heterocyclic rings remain an area of considerable interest but are not specifically discussed, although examples are included where such derivatives offer illustrative insights into important and useful aspects of the chemistry.

The ring numbering and nomenclature for 1,4-diazepines used in this chapter are illustrated by structures 1–7.



Reviews of 1,4-diazepines that are of interest include: general reviews <1984CHEC(7)593, 1996CHEC-II(9)151, 2004SOS929, 1997PHC(9)318, 1999PHC(11)319, 2000PHC(12)339, 2001PHC(13)340, 2003PHC(15)385, 2004PHC(16)431, 2005PHC(17)389, 2007PHC(18)402>; combinatorial approaches to benzodiazepine derivatives <1996ACR132, 2006RMC53>; 1,5-benzodiazepines and 1,5-benzodiazepinium salts <1998AHC2>.

13.06.2 Theoretical Methods

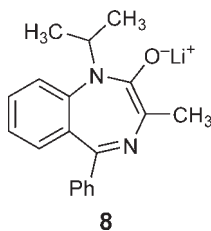
Because 1,4-diazepines have been used extensively in the design of compounds which bind to receptors or enzymes and as templates for modeling protein secondary structure, a large body of computational structural analysis has been published. However, since this material is of a specialized nature and generally limited in scope and application, it will not be discussed. In contrast, numerous studies have appeared which either introduce refinements to existing force fields, reevaluate previous computational analyses using updated, state-of-the-art methodology, or provide additional insights into diazepine conformation and reactivity. Theoretical methods focusing on understanding conformational preferences and transition state geometries in the context of experimental data in addition to the development and understanding of structure–activity relationships are discussed.

A refined set of force field parameters useful for evaluating the preferred conformations of 1,4-benzodiazepines using AMBER or other molecular mechanics programs, particularly those which also include protein and DNA parameters, has been developed <1997JCI951>. The Cambridge Crystallographic Database served as the source of equilibrium parameters while semi-empirical methods (AM1 and PM3) were used for estimating bond stretching and torsion potential force constants. Modeling of representative 1,4-benzodiazepinones accurately predicted their X-ray crystallographic structure to within 0.01 Å for bond lengths, 0.8° for bond angles, and 5° for torsional angles.

There appear to be limited studies that focus on calculating the *M*- to *P*-inversion barrier for 1,4-benzodiazepines using *ab initio* methods rather than molecular mechanics and semi-empirical approaches. To make up for this deficiency and to establish the most appropriate method for treating this ring system, the ring inversion barrier of diazepam, *N*-(1-desmethyl)diazepam, and *N*-(1-desmethyl)-3-methyldiazepam has been examined using Hartree–Fock (HF), unrestricted Hartree–Fock (UHF), and density functional theory (DFT) methods <1999CH651>. DFT appeared to be best able to predict the conformational barriers when compared to experimentally determined values. For diazepam and *N*-(1-desmethyl)diazepam, the calculated transition state energies were 17.6 and 10.9 kcal mol^{−1}, respectively, in close agreement with the experimentally measured values of 17.6 and 12.3 kcal mol^{−1}. The relative energies of the *M*- and *P*-conformations of *C*-(3-methyl)diazepam were also calculated and it was found that the 3-(*S*)-diastereomer preferred the *M*-conformer by 4.3 kcal mol^{−1}. Related to this study, a more extensive analysis of variously substituted 1,4-benzodiazepines has been performed using DFT methods in which the inversion barriers of a series of *N*-(1-substituted)-1,4-benzodiazepinones (N-1 = Me, Bn, *i*-Pr, and CHPh₂) were measured <2005JOC1530>. The calculated $\Delta G^\ddagger$ values (in dimethyl sulfoxide (DMSO)) of 16.9 (Me), 17.8 (Bn), 21.6 (*i*-Pr) and 20.8 (CHPh₂) kcal mol^{−1} were in good agreement with the experimentally (¹H nuclear magnetic resonance (NMR)) determined inversion barriers of 18.0, 19.5, 21.3, and 21.5 kcal mol^{−1}, respectively. Moreover, analysis of the geometry of the ring-inversion process identified two transition state pathways of equal energy, reflecting the maintenance of the *M*- or *P*-configuration at the transition state by the benzodiazepine ring which does not flatten during this process.

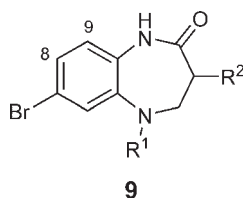
Theoretical treatment of the conformational properties of the related 1,4-benzodiazepin-2,5-dione ring system has received less attention but HF and DFT methods have been applied to examine the relative conformational energies and activation energy for the *M*-to-*P*-isomer interconversion <2004JST37>. The DFT method provided superior prediction of the bond distances and angles that were comparable to those observed by X-ray crystallography.

Ab initio methods also appear to be useful for predicting the *M*- to *P*-conformational transition barrier for reactive species, such as enolate **8**. It is known that the presence of an (*S*)-C3-substituent will favor the *M*-conformer in which the C-3 substituent adopts a pseudoequatorial arrangement. Consequently, deprotonation of C-3 at low temperature of certain benzodiazepines can result in single, conformationally chiral, nonracemic enolates locked in the *M*-configuration. The inversion barrier for enolate **8** at 195 K is calculated by DFT methods to be 17.5 kcal mol^{−1}, which compares with 12.4 kcal mol^{−1} for the derivative where the N-1 group is methyl instead of isopropyl <2003JA11482>. These results were used to explain the enantioselective C-3-alkylation method discussed in Section 13.06.4.3. A similar analysis of a C-3,N-4-pyrrolo-fused derivative calculated an interconversion energy of 12.2 kcal mol^{−1} <2005OL5305>.



The base-mediated alkylation of (*S*)-3-methyl-4,5-dihydro-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one with aminoethyl chlorides occurred at the more acidic amide moiety under conventional heating in dimethylformamide (DMF) for several hours using excess K_2CO_3 as the base <2006TL3357>. However, brief (90 s) microwave heating resulted in the alkylation being redirected to occur with complete regioselectivity at N-4. Rationalization was sought by conducting *ab initio* calculations (MP2/6-31G* and HF/6-31G*) which indicated that deprotonation is the rate-limiting step for alkylation at N-4 while formation of the N(1)–C bond is rate limiting for the reaction at N1. The microwave conditions lead to greater anion production that is slightly biased toward the higher-energy N-4 anion, which reacts more rapidly than the N-1 anion, leading to functionalization specifically at N-4. This is facilitated by the larger change in dipole moment associated with deprotonation at N-4, a pathway known to be favored under microwave irradiation.

The regioselectivity associated with the nitration of the 7-bromo-1,5-benzodiazepinone **9**, which occurred at C-8 and C-9, was examined by considering the relative atomic charge densities, total p_z electron population, and the electron population density of the highest occupied molecular orbital (HOMO) at each site. The π -localization energy of the two C-8 and C-9 nitration transition state σ -complexes was better able to predict the observed ratio of products, which favors nitration at C-9 by 3:1 <2003M1629, 2004HAC263>.



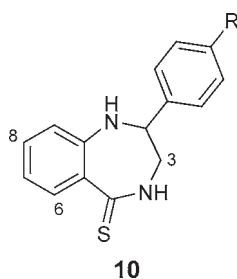
13.06.3 Experimental Structural Methods

The most powerful spectroscopic method for determining structural connectivity and conformational analysis of fused and nonfused 1,4-diazepine rings is NMR, and this technique has been used extensively. Mass spectral data have also been exploited to provide insight into structure based on an analysis of fragmentation patterns. Circular dichroism (CD) is particularly useful for assigning the absolute configuration of 1,4-benzodiazepine *M*- and *P*-atropoisomers since the *P*-isomer typically exhibits a strong negative Cotton effect at 254 nM in the CD spectrum <1997CH495>.

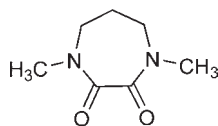
13.06.3.1 NMR Studies

One of the more interesting aspects in the area has been the application of ^1H NMR spectroscopy to evaluate conformational properties of benzodiazepine and diazepine peptidomimetics; these studies are discussed in greater detail in the sections that cover specific heterocycles. Numerous papers have been published which tabulate the NMR of potentially interesting new diazepine derivatives, extending data presented in CHEC(1984) and CHEC-II(1996) <1996JHC1159, 1996JHC271, 1996MRC324, 2002JHC1321>.

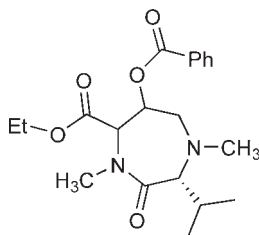
The protons at C-6 and N-4 of thioamide derivatives **10** exhibit a downfield shift in the ^1H NMR spectrum relative to those of the corresponding C-5 amide, indicative of deshielding <2000MRC207>. The protons at C-3 and N-4 of **10** also resonate downfield, while, in contrast, the proton at C-8 is slightly shielded. The observed downfield shifts are attributed to the higher polarizability of the C=S bond leading to an increased magnetic anisotropy of this moiety. The ^{13}C NMR spectra of C-7-substituted compounds reveal a downfield shift of the thiocarbonyl carbon by 30 ppm compared to the corresponding amide while C-2 and C-3 are deshielded by 1.8–2.4 and 3–4 ppm, respectively.



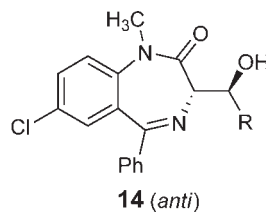
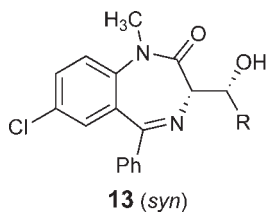
The effect of ring size and nitrogen substitution on the ^{17}O NMR shifts of a series of cyclic α -diamides, including the 1,4-diazepin-2,3-dione **11**, has been examined <1998JPO387>. In MeCN, the ^{17}O NMR shift for **11** resonated at 325.3 ppm, which is similar to the corresponding six-membered ring analogue, 323.0 ppm, but deshielded compared to the five-membered ring derivative, 285.5 ppm. Semi-empirical calculations suggested that the dihedral angle for the dicarbonyl unit is 78° .

**11**

Conformational flexibility has hindered attempts to use NMR spectroscopy to determine the relative and absolute stereochemistry associated with the substituted 1,4-diazepin-2-one ring of liposidomycin. However, stereochemical assignments were made possible by comparing NMR data for the synthetically prepared family of diastereomers of **12**. The results indicated that the relative stereochemistry of liposidomycin is consistent with either the (*R*)-C-3, (*R*)-C-6, (*R*)-C-7 or (*S*)-C-3, (*S*)-C-6, (*S*)-C-7 diastereomer <2001JOC5822>.

**12**

The reaction of diazepam with aldehydes at C-3 yields a mixture of *syn*- and *anti*-aldol derivatives, **13** and **14**, respectively, the relative stereochemistry of which were determined by examining the coupling constant between the C-3 -protons and the exocyclic carbinol proton. In accordance to the standard aldol reaction, the *syn*-diastereomers **13** exhibited coupling constants of ca. 5 Hz, while those for the *anti*-diastereomers **14** were ca. 9 Hz <2000HCA603>. The stereochemical assignments made using ^1H NMR were corroborated through single crystal X-ray analysis of representative compounds.



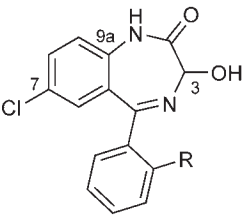
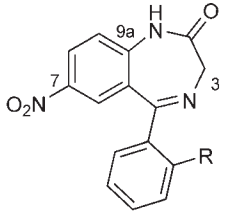
The site of deprotonation of lorazepam and oxazepam (NH vs. OH) was determined by monitoring the change in ^{13}C NMR shifts upon addition of *t*-BuOK to a solution of the compounds in DMSO <2003MI693>. Changes in ^{13}C shifts, summarized in Table 1, occurred mainly in the fused phenyl group rather than in the seven-membered diazepam ring, consistent with deprotonation of the amide NH. Nitrazepam and clonazepam, analogues lacking the C-3 hydroxyl, exhibited the same trend in ^{13}C NMR shifts.

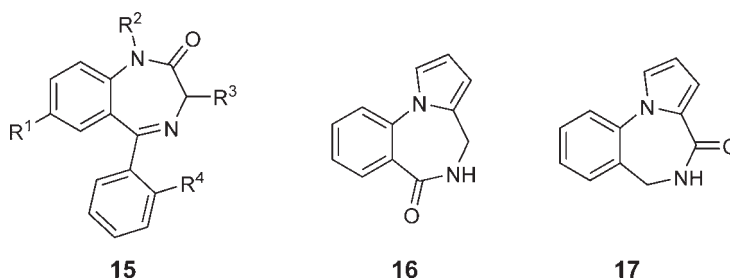
13.06.3.2 Mass Spectrometry

Characteristic trends in the fragmentation patterns of 1,4-benzodiazepines can be observed using ion-trap mass spectrometry (MS). For the 1,4-benzodiazepin-2-one **15**, ion fragmentation was largely dictated by the attached substituents, R^1 , R^2 , R^3 , and R^4 <2000RCM2061>. Using collision-induced ionization (CID) spectrometry, the C-3-unsubstituted analogues were shown to eliminate CO while the hydroxylated compounds predominantly

decomposed by loss of H₂O <2001MI359>. The pyrrolo-benzodiazepine isomers **16** and **17** are difficult to distinguish since they both yield similar fragmentation patterns under low-resolution MS; however, high resolution and tandem MS showed characteristic differences in their corresponding isobaric fragment ions <1996JAM653>.

Table 1 Changes in ¹³C shifts for substituted 1,4-benzodiazepin-2-ones upon treatment with *t*-BuOK in DMSO

 R = H (oxazepam) R = Cl (lorazepam)  R = H (nitrazepam) R = Cl (clonazepam)			
$\Delta^{13}\text{C NMR anion} - \text{parent (ppm)}$			
Compound	C-7	C-9a	C-3
Oxazepam	-5.7	+8.7	+0.2
Lorazepam	-5.5	+8.5	+0.2
Nitrazepam	-4.8	+10.0	+2.0
Clonazepam	-3.5	+7.1	+1.9



13.06.4 Thermodynamic Aspects

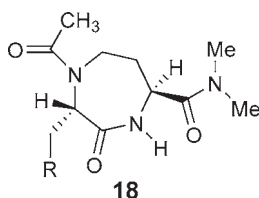
13.06.4.1 General Aspects

Fully unsaturated and conjugated 1,4-diazepines are encountered less often than partially or fully saturated 1,4-diazepines, probably because they contain $4n\pi$ electrons and thus are not as stable as the $4n + 2\pi$ electron systems. Consequently, partially and fully saturated ring systems dominate the literature, and the physical properties that have been of principal interest are associated with the conformational flexibility and tautomeric lability of these heterocycles. Physical chemical properties associated with specific molecules are discussed in the individual sections. Understanding the fundamental underlying principles of the conformation of 1,4-diazepines and 1,4-benzodiazepines is of considerable importance to the medicinal chemistry community where these ring systems enjoy the high profile accorded to a privileged scaffold. 1,4-Diazepines function as topological mimetics of certain structural elements found in peptides and modulation of the topographical disposition of substituents attached to these heterocycles is frequently critical for drug action. While conformational aspects of 1,4-benzodiazepines are well developed, study of the 1,4-diazepine ring system has proven to be far more challenging due to the inherently greater conformational mobility.

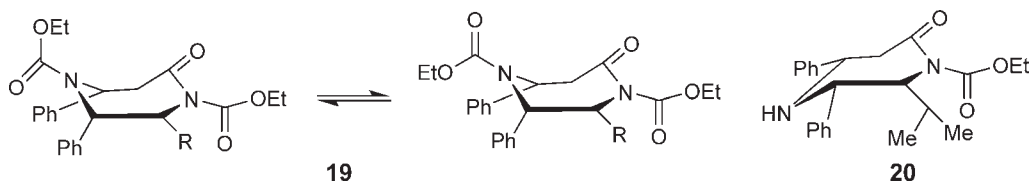
13.06.4.2 Conformation Studies – Monocyclic

The fully saturated 1,4-diazepine heterocycle is composed of sp^3 -hybridized atoms that allow torsional bond flexibility, resulting in a high degree of conformational mobility. Consequently, control of 1,4-diazepine conformation has most frequently been accomplished by annealing additional rings and/or incorporating amide bonds into the heterocyclic ring that are designed to restrict torsional freedom. Conformational bias is also influenced by nonbonded interactions between ring substituents, effects that are beginning to be explored more deeply as part of an effort to broaden the application of 1,4-diazepines in peptide mimicry. However, because the range of conformations available to monocyclic rings is large, spectroscopic analysis is complex and initial studies have been restricted to a somewhat limited set of unique ring systems and patterns of substitution. Nevertheless, these studies are providing new insights into the underlying principles and revealing additional aspects that facilitate some predictivity, although much remains to be understood.

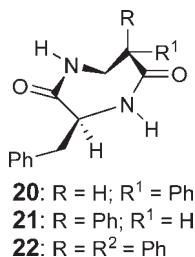
Extensive analysis of ^1H and ^{13}C NMR data combined with computer simulation studies indicate that the trisubstituted 1,4-diazepin-3-one peptidomimetic **18** adopts a boat conformation in which the C-2 substituent, PhCH_2 or CH_3 , adopts a pseudoaxial arrangement to avoid steric interactions with the N-Ac moiety. The limitations in conformational space available to the ring substituents resulted in an opposed alignment of the N-Ac methyl group and the C-2 substituent, which project into complementary planes of the ring in a fashion that is determined by the absolute configuration at C-2 [<1997JA2430>](#).

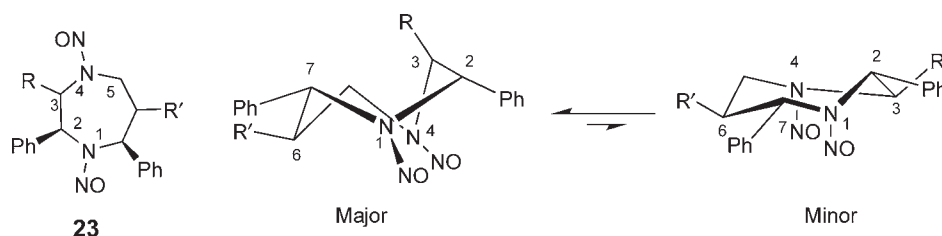


The 1,4-diazepin-5-one derivative **19** with $\text{R} = \text{H}$ or Me adopts a flattened boat conformation that orients the two phenyl groups in a quasi-axial arrangement. This allows the N-1 CO_2Et to undergo rotameric interconversion that is rapid on the NMR timescale, where the barriers were determined to be 11.93 ($\text{R} = \text{H}$) and 13.86 ($\text{R} = \text{Me}$) kcal mol^{-1} , respectively. In contrast, the rotational barrier for the corresponding *N*-nitroso and *N*-formyl derivatives is considerably higher, $>20 \text{ kcal mol}^{-1}$, indicating lower N-C double-bond character for the carbamate **19** [<1997JOC7984>](#). Removal of the N-1 CO_2Et moiety, studied with the 3-isopropyl derivative **20**, relieves steric interactions, allowing the ring to adopt a preferred chair conformation in which the two phenyl groups are equatorial and the C(3)-N(4) bond is partially twisted to relieve allylic 1,3-strain between the *i*-Pr and imidic N-CO₂Et moiety.



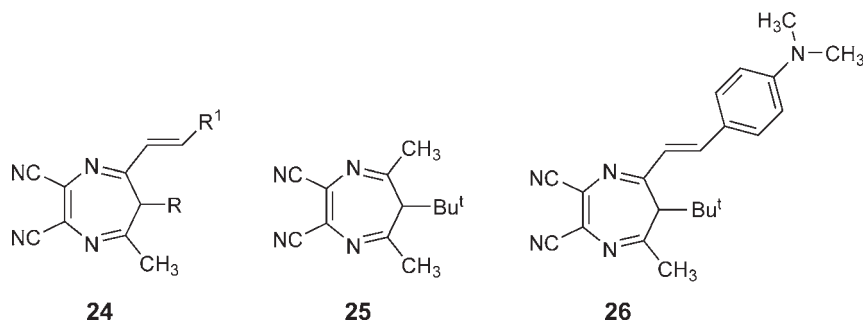
The 3-benzyl-6-phenyl-1,4-diazepine-2,5-diones **21** and **22** exhibited complex NMR spectra indicative of limited conformational mobility in which the ring geometry is dictated by the two *cis*-amide elements, which define individual planes [<2003MI187>](#). Based on an analysis of the nuclear Overhauser effect (NOE) between protons on the ring, the preferred boat conformation in solution projects the 3-benzyl moiety pseudoequatorially with the 6-phenyl substituent disposed axially or equatorially, dependent upon the relative stereochemistry. This conformation is also observed in the solid state for the *cis*-substituted isomer **21** in which the phenyl group is axial. In contrast, the bis-phenyl derivative **23** is conformationally mobile based on the ^1H NMR spectrum where resonances were not resolved.





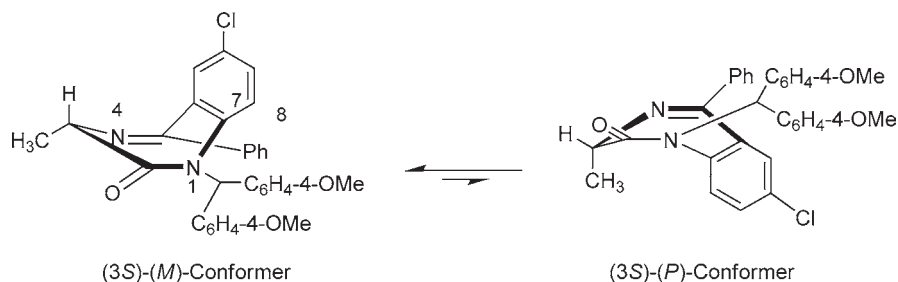
The absence of Bohlmann bands in the infrared (IR) spectrum indicates that the nitrogen lone pairs of the di-*N*-nitroso-1,4-diazepines **23** are delocalized [<1995JOC7461>](#). While the absence of an amide moiety in the ring confers torsional freedom, the *cis*-2,7-di-Ph groups reduce ring flexibility and the ^1H NMR data are consistent with major and minor families of four twist chair conformers that project the C-7 Ph and C-6 R'-substituents equatorially. These interconvert by a pseudorotation that allows the C-2 phenyl and C-3 R substituents to adopt a pseudoaxial orientation in the preferred conformer family.

Conformational aspects of more highly unsaturated 1,4-diazepines have been examined in the context of trisubstituted 1,4-diazepine-2,3-dicarbonitrile **24** [<2005BCJ316, 2005BCJ1167, 2004CL170>](#). Monoethylene derivatives of **24** in which R is an alkyl group exist as a mixture of diastereomers as a consequence of the C-6 chiral center and ring atropoisomerism. These compounds typically prefer a conformation in which the C-6 substituent is in the equatorially disposed position. However, the C-6 *t*-butyl derivative of the 5,7-dimethyl-1,4-diazepine **25** was observed to be a mixture of axial and equatorial isomers in a ratio of 2:3, attributed to unfavorable steric interactions with the C-5 and C-7 methyl groups [<2005BCJ1167>](#). These became more dominant with unsaturated exocyclic substituents, exemplified by the styryl derivative **26** where the *t*-butyl moiety was exclusively in the axial position.



13.06.4.3 Conformation Studies – 1,4-Benzodiazepines

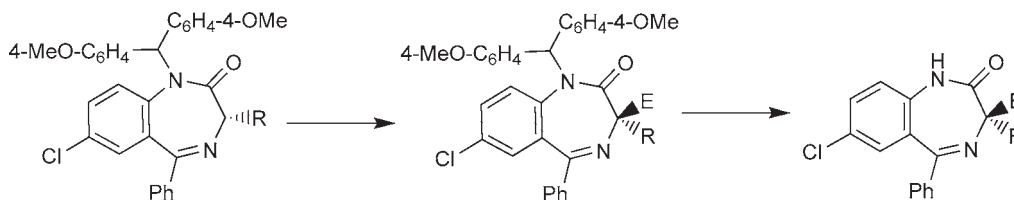
The 2,3-dihydro-1*H*-1,4-benzodiazepin-2-ones exist as an equilibrium mixture of two conformers, designated by the helical descriptors *M* and *P*, that reflect chirality associated with the *R*-N(1)-C(7)-C(8) dihedral angle (**Scheme 1**). The interconversion barrier between the *M*- and *P*- atropoisomers is dependent upon the size of the N-1 substituent with $\Delta G^\ddagger = 12.3, 18.0, 21.1$, and >24 kcal mol $^{-1}$ for H, Me, *i*-propyl, and *t*-butyl, respectively, a function of increasing



Scheme 1

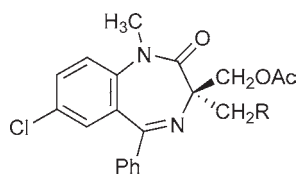
nonbonded *peri*-interactions with the substituent at C-9 <2005JOC1530, 1999CH651, 2005S1>. Atropoisomers with interconversion barriers of $>20 \text{ kcal mol}^{-1}$ can be separated chromatographically and have been shown to be differentiated by both biological receptors and human serum albumin <1997CH495, 2000JA460>.

Substituents at C-3 typically prefer an equatorial disposition with the absolute configuration influencing conformational bias such that a 3-(*S*)-derivative adopts the *M*-conformation. The 3-(*S*)-methyl derivative of an *N*-(1-substituted)-7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one can be deprotonated and alkylated at C-3 with preservation of chirality, the electrophile approaching C-3 *syn* to the aryl ring in a contrasteric fashion <2005S1>. The success of this process, referred to as memory of chirality, depends upon the conformational stability of the nonracemic enolate, which is critically dependent on the size of the N-1 substituent and the temperature at which the reaction is conducted <2003JA11482, 2005TA2998, 2005S1, 2006JA15215>. A di(*p*-anisyl)methyl (DAM) substituent at N-1 combines excellent conformational control of the enolate with high chemical reactivity toward a range of electrophiles (Scheme 2) <2006JA15215>. For the C-3 methyl derivative, potassium hexamethyldisilazane (KHDMS) and hexamethylphosphoramide (HMPA) in tetrahydrofuran (THF) at -78°C were used to generate the enolate, providing products in good yield (65–96%) and with high enantioselectivity, ee ranging from 96% to $>99.5\%$. For the C-3 ethyl, benzyl, and $\text{CH}_2\text{CH}_2\text{SMe}$ homologues, yields were considerably poorer under these conditions; however, the use of 1,2-dimethoxyethane (DME) rather than THF as solvent and conducting the reaction at -42°C gave acceptable chemical yields (33–80%) with ee ranging from 72% to $>99\%$ <2006JA15215>. The N-alkylated quaternary derivatives, which have been the subject of only limited study, are mixtures of conformers that interconvert slowly on the NMR timescale while the *M*- and *P*-forms of the NH derivatives, obtained by removal of the DAM moiety under acidic conditions, exist in rapid equilibrium. The 3-CN derivatives appear to be an exception, with this substituent preferring an axial orientation, apparently for steric reasons.



Scheme 2

The preferred conformation of chiral C-3-disubstituted, 1,4-benzodiazepin-2-ones depends not only on the identity of the substituents but is also influenced by solvent polarity <1999T1407>. The optically pure alcohol (–)-**27** exists in CDCl_3 and $\text{DMSO}-d_6$ as a single isomer that is the same in both solvents and was determined to be the *P*-conformer based on the strong negative Cotton effect at 260 nm in the CD curve, obtained in MeCN. The smaller CH_2OH moiety adopts an axial orientation, since the CH_2 protons resonate at low field, shielded by the ring current associated with the proximal annulated benzene ring, while the CH_2 protons of the CH_2OAc element resonate consistent with an equatorial disposition, derived by comparison with ^1H NMR spectra of the corresponding achiral diol and diacetate. These data allow the absolute configuration of **27** to be designated as the 3-(*R*)-isomer. In contrast, the tosylate **28** and chloride **29** exist as equilibrium mixtures of atropoisomers in both polar and nonpolar solvents. The *P*-isomer of **28**, in which CH_2OTs is axial, is prevalent in both solvents, although somewhat more so in CDCl_3 , while for **29**, the *P*-isomer is favored over the *M*-isomer by 70:30 in CDCl_3 but reversed to 30:70 in $\text{DMSO}-d_6$.

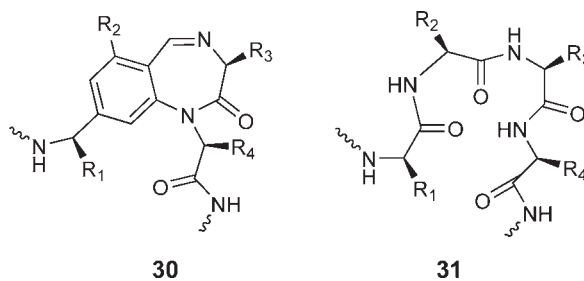


27: R = OH
28: R = O-*p*-Ts
29: R = Cl

The calculated interconversion barriers between the *M*- and *P*-forms of 3,4-dihydro-1*H*-benzo[1,4]diazepin-2,5-diones depend on the size of the N-1 substituent but not the C-3 and N-4 substituents <2004JST37>. The

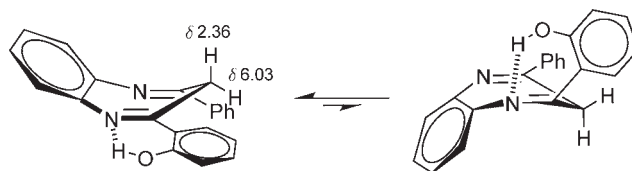
atropoisomers of a N-1 *t*-butyl 1,4-benzodiazepin-2,5-dione derivative, in which the inversion barrier was calculated to be $>23 \text{ kcal mol}^{-1}$, were separated by chromatography but equilibrated over 24 h <1997JMC717>. Atropoisomers of the N-1 Me analogue, predicted to have a $\Delta G^\ddagger = 17 \text{ kcal mol}^{-1}$, could be separated only when a chlorine atom was introduced at C-9, where the calculated inversion barrier was increased to 23 kcal mol^{-1} , confirming the importance of *peri*-interactions in controlling equilibration. However, this compound also racemized over 24 h. The combination of a N-1 *t*-butyl moiety with a C-9 Cl gave stable atropoisomers, with one demonstrating higher binding affinity for the platelet glycoprotein IIb/IIIa receptor <1997JME717>.

The 1,4-benzodiazepines have been classified as type III mimetics of peptide motifs based on their ability to project functional groups important for molecular recognition in a topologically similar fashion to that of structurally defined protein domains (e.g., β - or γ -turns and α -helices). As depicted in the 1,4-benzodiazepin-2-one **30**, the substituents at C-8, C-6, C-3, and N-1 topologically mimic the $C\alpha$ substituents of a four-residue β -turn, represented by **31**. Additionally, C-5 substituents are projected toward the region in space occupied by the C-6 substituent, providing a second vector to access this α -side chain element of the β -turn <1993T3593, 2006MI321>. In order to more fully understand the topographical similarities between the heterocycle scaffold and β -turn structure, the two atropisomeric conformers of the 1,4-benzodiazepin-2-one derivatives **30** and the C-3 enantiomers were modeled in SYBYL 7.1 and fully minimized using the MM3 module. Comparing all of the conformers available to the N-1 and C-8 substituents with experimental and modeled β -turn structures revealed that the side-chain orientations of the four residues of type I, II, III, IV, and VI reverse turns could be readily accessed by the 1,4-benzodiazepin-2-one scaffold with only small root-mean-square deviations. However, a single diastereomer can mimic one or more but not all of the experimental β -turn structures. This observation, which does not take account of the relative energy differences between the conformers, provided a rationale for selecting specific patterns of substitution that approximate unique orientations and might be further optimized by the introduction of additional conformation-influencing elements <2006MI321>.



13.06.4.4 Conformational Studies – 1,5-Benzodiazepines

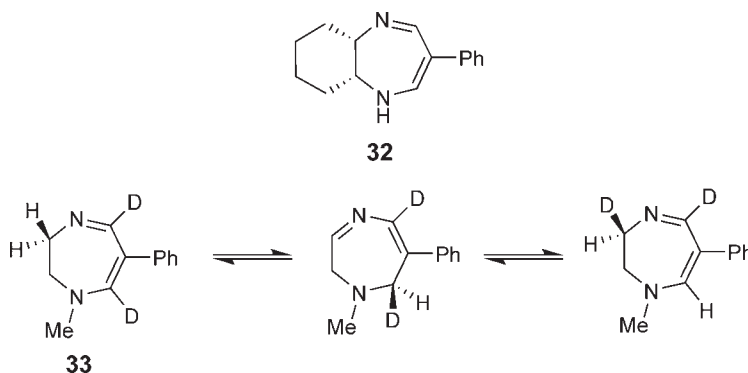
The 2,4-diphenyl-1,5-benzodiazepines interconvert between two boat conformations with the conformer in which the two phenyl groups are pseudoequatorial predominating <1997M633>. The calculated interconversion barrier is $\sim 13 \text{ kcal mol}^{-1}$, rapid on the NMR timescale at 323 K, but slower at 233 K, where the C-3 protons split into doublets, $J_{\text{gem}} \sim 11.5 \text{ Hz}$. The equatorial proton is deshielded by the C-4 aryl ring π -electron current and the axial proton is shielded by the annulated benzene ring <1997M633>. The interconversion barrier between the two phenols depicted in **Scheme 3** was calculated from NMR data to be $12.97 \text{ kcal mol}^{-1}$, similar to the $12.61 \text{ kcal mol}^{-1}$ calculated for the unsubstituted parent, suggesting that the intramolecular hydrogen bond is preserved during the ring inversion.



Scheme 3

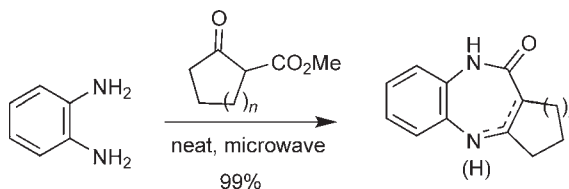
13.06.4.5 Tautomers

Tautomeric rearrangement of unsaturated 1,4-diazepines and benzo-fused homologues occurs under thermal conditions or where extended conjugation lowers the overall energy of the system. Amide and thioamide derivatives of benzodiazepinones have been shown to exist in the oxo and thiono forms with no evidence for the OH or SH tautomers, even in substrates where there exists the potential for conjugation <2000AHC1>. Similarly, 1,5-benzodiazepin-2,4-dione exists as the dioxo form. However, imines, both within and exocyclic to the ring, will tautomerize to allow conjugation or satisfy opportunities to engage in intra- or intermolecular hydrogen bonding. Flash vacuum pyrolysis (FVP) of the *cis*-fused 2,3-dihydro-1,4-diazepine **32** at temperatures above 450 °C produced the *trans*-fused isomer, as detected by ^{13}C NMR, attributed to imine tautomerization <1995CC2337>. FVP of the deuterium-labeled 2,3-dihydro-1,4-diazepine **33** at 450–500 °C resulted in sequential, suprafacial 1,5-sigmatropic shifts that resulted in rearrangement of hydrogen and deuterium atoms (Scheme 4). At higher temperatures, ring contraction to a quinoxaline occurred, presumably via radical intermediates.

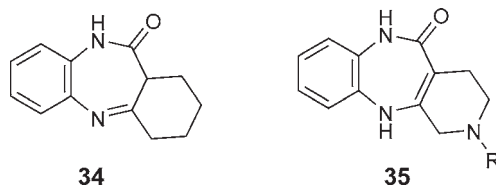


Scheme 4

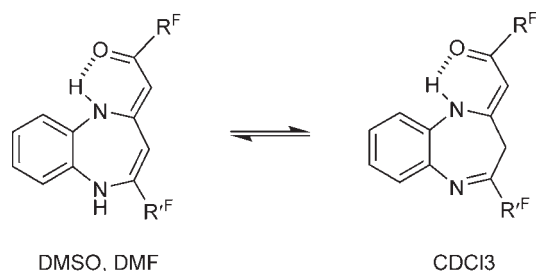
The preferred tautomer of the products derived from the condensation reaction of phenylenediamine with cyclic β -keto esters (Scheme 5) is highly dependent on the structure of the β -ketoester <2005JHC1001>. ^1H and ^{13}C NMR analysis of the 1,5-benzodiazepin-2-one **34**, formed from methyl 2-oxocyclohexanecarboxylate under microwave conditions, indicated the presence of the C(4)–N(5) imine <2005JHC1001>. In contrast, the products arising from condensation with methyl 2-oxocyclopentanecarboxylate and methyl 1-alkyl-4-oxopiperidine-3-carboxylates were found to be in the enamine form **35**.



Scheme 5

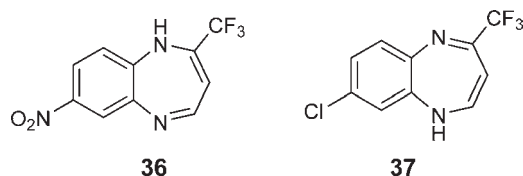


Polyfluoroacyl-containing 1,5-benzodiazepines, prepared from phenylenediamine and fluorinated 1,3,5-triketones, were isolated as mixtures of imine and enamine tautomers based on detailed ^1H , ^{13}C , and ^{19}F NMR analysis <2004M23>. The position of equilibrium was independent of the fluoroalkyl moiety but sensitive to solvent, with the imine tautomer favored to the extent of 85–96% in nonpolar CDCl_3 after 3 weeks of equilibration (Scheme 6). In DMSO and DMF, equilibration was rapid, strongly favoring the enamine tautomer that is stabilized by a hydrogen bond between the enamine NH and solvent <2004M23>. An intramolecular hydrogen bond stabilizes the (Z)-form of the enone moiety, a circumstance similar to that seen with a structurally homologous ester <2001TL3227>.



Scheme 6

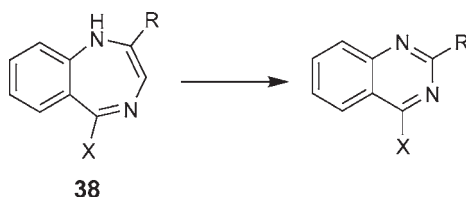
It is known that completely unsaturated 1,5-benzodiazepines favor the bis-imine tautomer due to the $4n\pi$ nature of the completely conjugated seven-member ring. However, tautomer preference in this ring system can also be influenced by substituents on the aromatic ring, with powerful electron-withdrawing NO_2 and PhCO groups at C-7 stabilizing the $1H$ species **36**, while, chlorine and methyl substituents afforded the $5H$ tautomer **37**. The two isomers are readily differentiated by analyzing coupling patterns in the ^1H NMR spectrum and the effects of D_2O on resonance multiplicity <1996TL2845>.



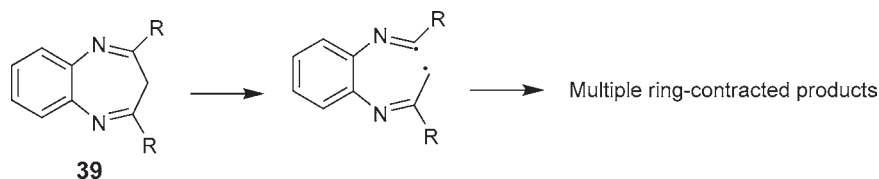
13.06.5 Reactivity of Fully Conjugated Rings (Unsaturated Rings)

With the exception of ring-contraction reactions that are discussed below, new insights into the reactivity of fully unsaturated diazepine ring systems that add to the current level of understanding have been limited.

Ring-contraction studies that have previously been focused on saturated diazepine ring systems have been extended to fully unsaturated templates. The thermal ring contraction of **38** ($\text{X}=\text{OMe}$ or NMe_2), conducted at $\leq 180^\circ\text{C}$, appears to be the first example of this type of reaction for unsaturated diazepines, as depicted in Scheme 7 <1999H(51)2409>. At the much higher temperatures associated with FVP, $>800^\circ\text{C}$, decomposition of 2,4-dimethyl- or 2,4-diphenyl-1,5-benzodiazepines **39** occurred to produce multiple ring-contracted products that can be traced mechanistically to homolysis of the $\text{C}(2)\text{--}\text{C}(3)$ bond (Scheme 8) <1998T9667>; however, subsequent pathways differ for the two compounds, as might be expected.

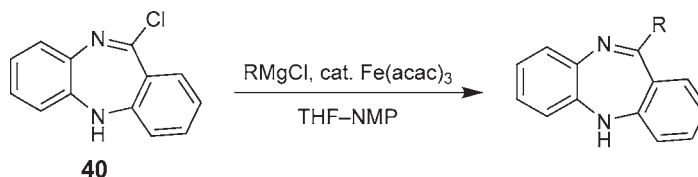


Scheme 7



Scheme 8

The application of transition metal catalysis provided new opportunities to introduce diverse functionality to the diazepine ring system. Iron-catalyzed cross-coupling of Grignard reagents with the imidoyl chloride **40** provided a convenient and efficient method for substituting the heterocyclic ring (Scheme 9) <2006OL1771>.



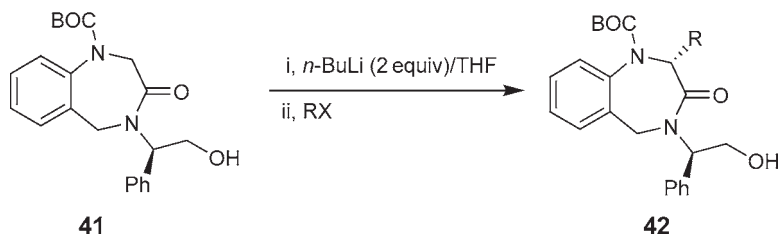
Scheme 9

13.06.6 Reactivity of Nonconjugated Rings (Saturated Rings)

This section is expanded compared to CHEC(1984) and CHEC-II(1996) and is organized according to the ring atom under discussion, starting with the carbon atom at C-2 and proceeding in ascending order before discussing reactivity at the ring nitrogen atoms.

13.06.6.1 Reaction at C-2

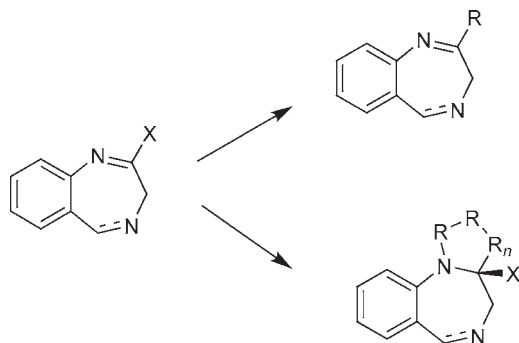
Highly diastereoselective alkylation at C-2 of benzo-1,4-diazepin-3-ones **41** was accomplished in 40–85% chemical yield using an (*R*)-phenylglycinol moiety at N-4, as the chirality-inducing element (Scheme 10) <2005EJO1590>. The optimum conditions involve deprotonation of **41** with 2 equiv of *n*-BuLi at -40°C and alkylation at -78°C to give products **42** with 86–96% de. A single crystal X-ray diffraction analysis of the methylated derivative determined that the major product formed was the 2-(*R*)-isomer, as depicted in the product **42**.



Scheme 10

The C-2 position is readily manipulated when in the oxidized amide form where conversion to an imino chloride, an imino phosphate, or a thioamide allows introduction of a range of nucleophiles at C-2 or promotes cycloaddition reactions across the N(1)–C(2) bond with concomitant loss of the C-2 leaving group (Scheme 11). N(1)–C(2) imines are electrophilic, with reactivity influenced by the size of the substituent at C-2. A hydrogen atom at C-2 provides the basis for the biological activity associated with the pyrrolo[2,1-*c*][1,4]benzodiazepine class of antitumor antibiotic where the N(1)–C(2) imine reacts with N-2 of guanine in the minor groove of DNA <1994CRV433>. A 2-methyl-substituted imine was reduced diastereoselectively to the amine with NaBH₄ or diisobutylaluminum hydride (DIBAL), affording a 3:1 ratio favoring the

(*R*)-isomer in a reaction where chirality was transferred from a (*R*)- α -phenylmethyl substituent at N-4 <2004TA687>. The imine double bond of a 1,4-diazepin-5-one can be introduced by oxidation of the saturated amine using tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO), as the co-oxidant <1997T3223>.

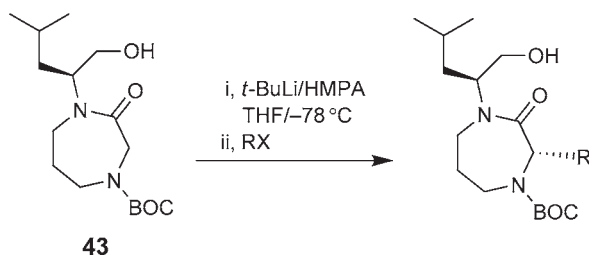


Scheme 11

Relatively simple imino chlorides are quite reactive and, although sensitive to hydrolytic decomposition, structurally novel and synthetically useful examples have been isolated and characterized by single X-ray crystallographic analysis <2001TL5183, 2003TL2425>. A cross-coupling reaction broadens the range of nucleophiles that can be introduced at a C-2 iminoyl chloride to include Grignard reagents in a reaction catalyzed by Fe(acac)₃ (acac = acetylacetonate) <2006OL1771>. An *N*-methyl-*N*-nitroso moiety offers a useful and chemically stable alternative leaving group to chlorine, reacting with tosylmethyl isocyanide (TOSMIC) to introduce a 2,3-fused imidazole ring <2004S2697>.

13.06.6.2 Reaction at C-3

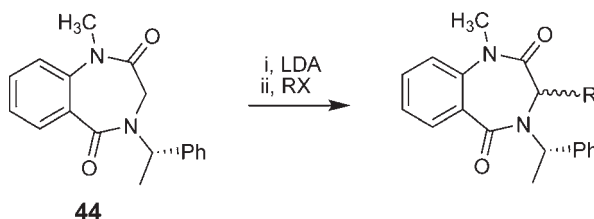
Treatment of the 3-oxo-1,4-diazepane **43** with 2 equiv of *t*-BuLi in THF at -78°C in the presence of HMPA generated a dianion, which was alkylated at the enolate with MeI, benzyl bromide, and allyl bromide to give single diastereomeric products in modest yield (47–53%) (Scheme 12) <1997TL5809>. The absolute configuration of the benzylated compound was established as (*S*) by X-ray crystallographic analysis.



Scheme 12

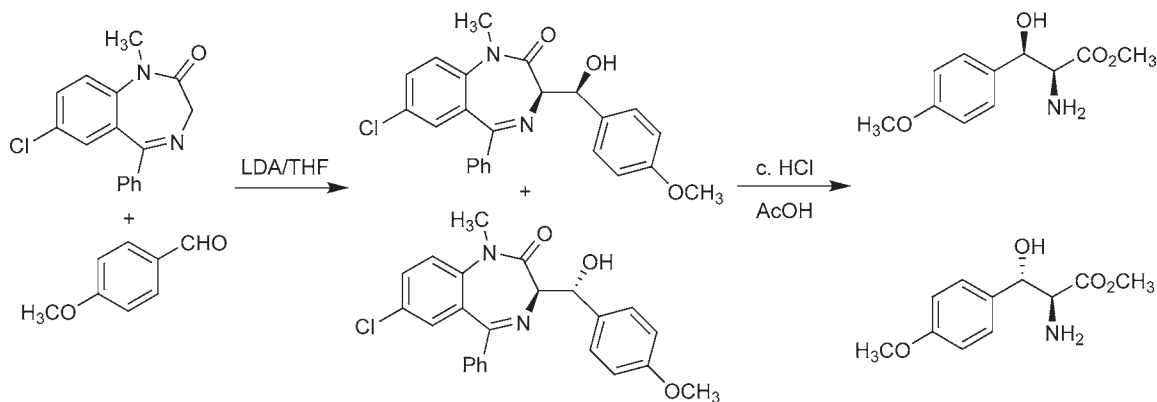
The introduction of electrophiles at C-3 of 1,4-benzodiazepinone derivatives can be accomplished with high diastereoselectivity by taking advantage either of the inherent atropisomeric chirality of the ring or an appended chiral inducing element, processes that have been established for almost all of the amide isomers. 1,2-Dihydro-1,4-benzodiazepin-2-ones were readily deprotonated at C-3 to generate enolates and these species were reacted with a range of electrophiles, providing access to compounds suitable for further elaboration or to amino acid derivatives after hydrolysis. High levels of asymmetry can be introduced on both C-3-unsubstituted and C-3 monoalkylated compounds, which incorporate bulky N-1 substituents, as discussed in Section 13.06.4.2 <2005TA2998, 2003JA11482, 2006JA15215, 2005S1>. The phosphonium ylide (Me₂N)₃PC(Me)₂, easily prepared by alkylation of (Me₂N)₃P with 2-iodopropane followed by deprotonation with *n*-BuLi and extraction into pentane, is an effective base for the C-3 alkylation of *N*-(1-alkylated)-1,4-benzodiazepin-2-ones, providing products, as single diastereomers, under mild conditions <1999JOC3741>.

Alkylation of the benzo-1,4-diazepine-2,5-dione **44** occurred in good chemical yield but with moderate and unpredictable diastereoselection (**Scheme 13**) <1999JOC2914>. Although both the yield and de were improved in the presence of excess HMPA, the inclusion of LiCl, as an additive, led to a significant erosion of de. These results could not be rationalized after theoretical analysis of transition state geometries.



Scheme 13

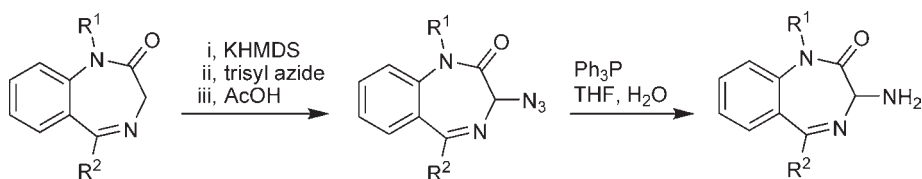
Aldol reactions at C-3 of benzo-1,4-diazepin-2-ones have been examined with both aliphatic and aromatic aldehyde partners and generally proceed in good yield <2000HCA603>. Diastereoselectivity is high for aliphatic aldehydes, affording a racemic mixture of *threo/erythro*-adducts with ratios ranging from 11:89 to 6:94, but considerably poorer for aromatic aldehydes, where ratios ranged from 30:70 to 55:45. The structures of the products were established by ^1H NMR analysis and confirmed by X-ray crystallography. With α -methylcinnamaldehydes, the slower-moving product on reverse-phase high-performance liquid chromatography (HPLC) was determined to be the racemic *erythro*-diastereomer, formed under kinetic control, while the more mobile *threo*-isomer predominated under equilibrating conditions <2003HCA2247>. The HPLC mobility of the *erythro*-isomer was attributed to a strong intramolecular hydrogen bond between the hydroxyl and amide carbonyl that reduces overall polarity. This chemistry was utilized to synthesize β -hydroxyphenylalanine derivatives as precursors to isomers of the naturally occurring cytokine modulator cytotoxazone (**Scheme 14**) <2003S375>.



Scheme 14

A simple and efficient procedure for the direct oxidation of C-3 of 1,4-benzodiazepin-2-ones, applicable to the preparation of the anxiolytic agents oxazepam and lorazepam, has been developed that represents an improvement over the well-established Polonovsky rearrangement of the N-4 oxide <2006OPD1192>. Iodine in AcOH at 65 °C catalyzed acetoxylation in a reaction that involved iodination at C-3 followed by a rapid nucleophilic displacement by KOAc. The liberated HI was recycled to iodine by inclusion of a stoichiometric oxidant, with $\text{K}_2\text{S}_2\text{O}_8$ being the optimal compromise of cost, availability, and efficiency.

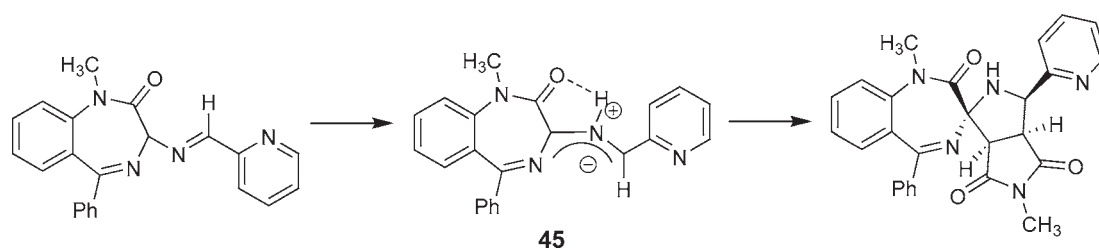
The direct azidation of 1,4-benzodiazepin-2-ones with trisyl azide provided access to 3-amino derivatives after reduction of the intermediate azide in a process that is compatible with a range of N-1 and C-5 substituents (**Scheme 15**) <1996TL6685>. This protocol offers a convenient alternative to the reduction of a C-3 oxime, obtained by reaction of the 1,4-benzodiazepin-2-one with isoamyl nitrite, which requires more vigorous conditions



Scheme 15

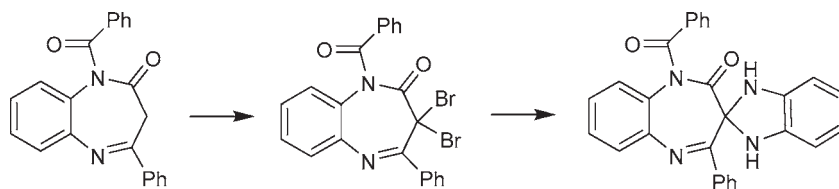
that can lead to over-reduction of the imine. This azidation process was also effective with 5-chloro-1-alkyl-1*H*-benzo-1,4-diazepin-2-ones, providing 3-amino derivatives after azide reduction and capture of the amine *in situ* by BOC anhydride (BOC = *t*-butoxycarbonyl) <2003JOC2844>.

Heating imines derived from 3-amino-1,4-benzodiazepin-2-ones with *N*-methylmaleimide in boiling toluene provided adducts derived from the stereospecific cycloaddition of the resonance-stabilized azo-methine ylide **45**, formed by a 1,2-prototropic rearrangement, in 82–89% yield (Scheme 16) <1996T13455>. The relative stereochemistry was established by analysis of ¹H NMR NOE data and comparison with the single crystal X-ray structure of an analogous compound.



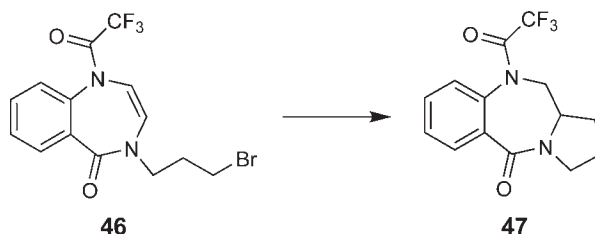
Scheme 16

Reactions occurring at the C-3 position of 3*H*-1,5-benzodiazepines feature prominently in the chemistry of this heterocycle, with bromination providing a particularly useful synthetic intermediate. The C-3 bromine was introduced using standard brominating reagents, such as Br₂ or *N*-bromosuccinimide (NBS), and acts either as an electrophilic or, after metal–halogen exchange, a nucleophilic species. Displacement of the C-3 bromide was facile with a malonate ester while reaction of the derived Grignard reagent with CO₂ introduced a carboxylic acid moiety at C-3 <2001JHC641>. The C-3 bromide of 4-phenyl-1*H*-benzo[1,4]diazepin-2(3*H*)-one reacts with oxygen-, nitrogen-, and sulfur-based nucleophiles <2001SC2523>. Benzoylation of the amide moiety facilitated dibromination at C-3 to give an electrophilic precursor to spiro derivatives, illustrated by the reaction with phenylenediamine, depicted in Scheme 17, which proceeded in 65% yield.



Scheme 17

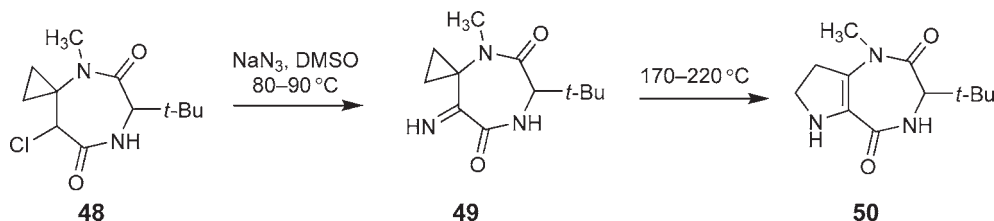
The C(2)–C(3) olefin of a 1,4-benzodiazepin-5-one regioselectively captured an alkyl radical intramolecularly in a 5-*exo-trig*-process that is the critical step in an approach to the construction of the fused tricyclic system found in the pyrrolo[2,1-*c*][1,4]benzodiazepine class of antitumor antibiotic. Treatment of the alkyl bromide **46** with Bu₃SnH afforded the tricyclic product **47** in 90% yield, a reaction that proceeded with equal efficiency with the alkoxy aryl ring substituents found in the naturally occurring (±)DC-81 (Scheme 18) <1999OL1835>.



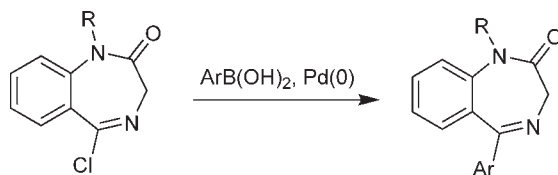
Scheme 18

13.06.6.3 Reaction at C-5

Treatment of 5-chloro-1,4-diazepin-2,5-dione **48** with NaN_3 in DMSO effected a facile conversion directly to the imine **49**, which underwent a Cloke rearrangement upon heating *in vacuo* to give the dihydropyrrolo-fused 1,4-diazepin-2,5-one **50** in good overall yield [<2004OL4249>](#). Alternatively, acidic hydrolysis of the imine provided an α -ketoamide, which rearranged thermally to the dihydrofuran corresponding to **50**. These compounds, which are air sensitive, were readily oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide pyrrole- and furan-fused heterocyclic analogues of benzo-1,4-diazepines.



The imidoyl chloride moiety of 5-chloro-1-alkyl-1,4-benzodiazepin-2-ones participates in Pd-catalyzed, Suzuki cross-coupling reactions, reacting with a range of functionalized aromatic boronic acids to provide an efficient and versatile approach to 5-aryl and 5-heteroaryl compounds ([Scheme 19](#)) [<2003JOC2844>](#). This chemistry readily extends to 3-amino-substituted compounds that are orally bioavailable inhibitors of the aspartyl protease γ -secretase [<2003BML4143>](#).



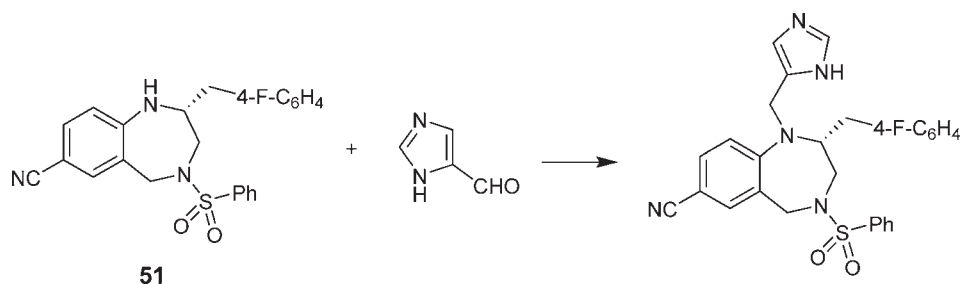
Scheme 19

13.06.6.4 Reaction at N-1

The alkylation at N-1 of the 1,4-benzodiazepine **51** with imidazole-5-carboxaldehyde is readily accomplished in excellent yield via a reductive amination process that involves simply stirring with triethylsilane in a 1:1 mixture of CH_2Cl_2 and $\text{CF}_3\text{CO}_2\text{H}$ at 25°C for 4 h ([Scheme 20](#)) [<2001TL1245>](#). This reaction is notable because of the low reactivity associated with electron-deficient aniline derivatives.

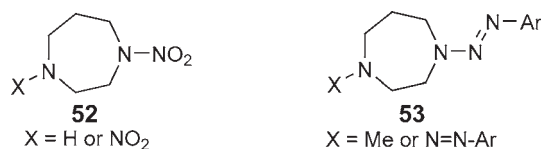
The regioselectivity of alkylation of (*S*)-3-methyl-4,5-dihydro-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one with aminoethyl chlorides is governed by the reaction conditions [<2006TL3357>](#). Under conventional heating in DMF with K_2CO_3 for several hours exclusive N-1 alkylation was observed, while under brief microwave heating alkylation occurred exclusively at N-4. A cyclopropyl ring has been introduced directly to N-1 of a fused 1,5-benzodiazepin-2-one derivative using a cyclopropylbismuth reagent under the influence of a copper additive [<2007JA44>](#).

A convenient method for the monoacylation of homopiperazine and other diamines has been described [<1999JOC7661>](#). Under conventional conditions, the bis-acylated product is favored but treatment of homopiperazine with 2 equiv of *n*-butyllithium to form a dianion followed by reaction with 1 equiv of benzoyl chloride provided a 27:1 ratio of mono- to bisacylated derivatives from which the monoacylated compound was isolated in 91% yield.



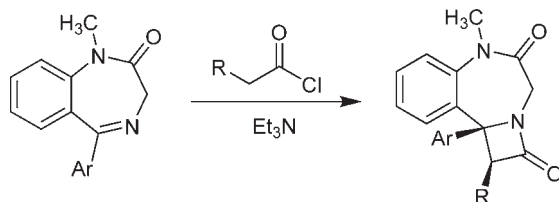
Scheme 20

N-Nitration of homopiperazine using 1 equiv of the new nitrating reagent, 4-chloro-5-methoxy-2-nitropyridazin-3-one, provided the mononitrated product **52** in 86% yield while the use of 2 equiv resulted in nitration of both N atoms <2003JOC9113>. Diazene-substituted 1,4-diazepines are rare, with only one previously reported preparative procedure. Mono- and bis-diazene-substituted homopiperazines **53** were prepared by coupling aryldiazonium salts with homopiperazine or mono-*N*-methyl-homopiperazine <2004CJC1725>.



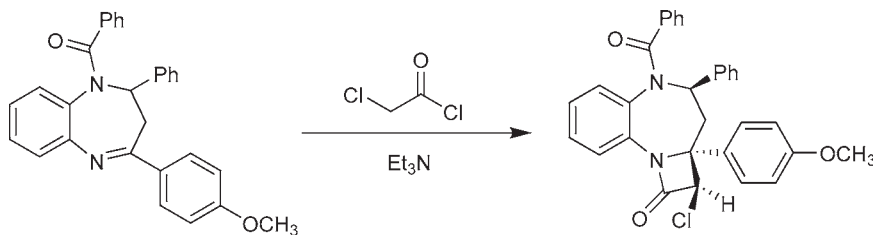
13.06.6.5 Reaction at N-4

The imine moiety of 1*H*-1,4-benzodiazepin-2-(3*H*)ones reacts regio- and stereospecifically with a range of functionalized ketenes to afford substituted, fused β -lactam [2+2] cycloaddition adducts (Scheme 21) <2004EJO535>. The use of [4-(*S*)-2-oxo-4-phenyloxazolidin-3-yl]acetyl chloride, as a homochiral ketene precursor, afforded a single product, the structure of which was established by X-ray crystallography, while the (4*S*,5*R*)-diphenyl analogue provided a 1.8:1 mixture of chromatographically separable diastereomers.



Scheme 21

Chloroketene adds to the imine moiety of substituted 2,3-dihydro-1*H*-benzo-1,4-diazepines with excellent regio- and diastereoselectivity to afford the (2*S*,2*aR*,4*R*)-fused β -lactam adduct and its enantiomer (Scheme 22)



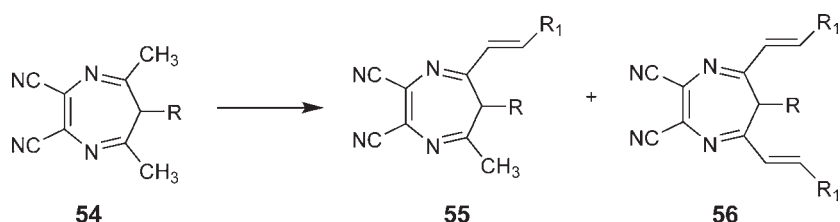
Scheme 22

<2001JHC1031>. This result was rationalized based on stereocontrol originating with the ketene approaching the imine N lone pair from the least hindered side of a boat conformer, opposite the 2-phenyl moiety. In this geometry, the chlorine atom is *exo* to the diazepine ring and a counterclockwise, conrotatory ring closure forms the β -lactam ring.

13.06.7 Reactivity of Substituents Attached to Ring Carbon Atoms

13.06.7.1 Monocyclic 1,4-Diazepines

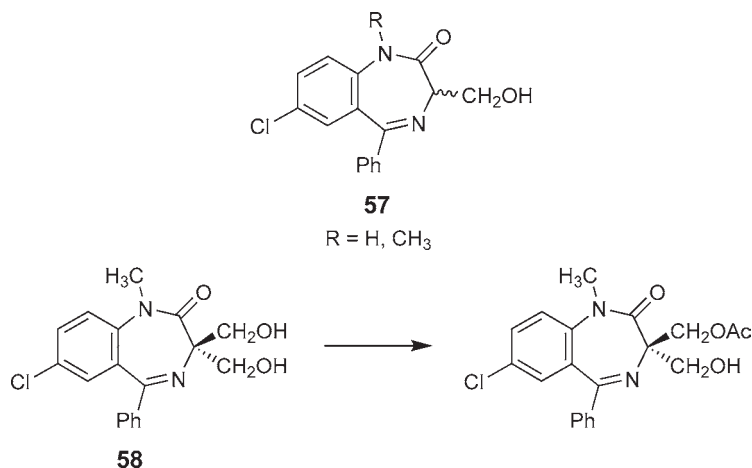
The exocyclic methyl groups of 6-substituted-5,7-dimethyl-6*H*-1,4-diazepine-2,3-dicarbonitrile derivatives **54** condense with aromatic and heteroaromatic aldehydes in a reaction catalyzed by piperidine (Scheme 23) <2005BCJ316, 2005BCJ1167>. Monoethylene derivatives **55** predominated when **54** was condensed with molar equivalents of electron-donating aldehydes but mixtures were obtained with electron-deficient aldehydes, as the coupling partners; however, bis-ethylene derivatives **56** were the major product when excess aldehyde is used. The products fluoresce in the near-IR in the solid state, the intensity of which is dependent on the nature of intermolecular interactions that are a function of crystal packing. Large substituents at C-6 favor increased intensity by reducing molecular stacking and the potential for fluorescence quenching.



Scheme 23

13.06.7.2 Benzodiazepines

Derivatives of C-3 mono- and dihydroxymethyl-substituted 1,4-benzodiazepin-2-one can be resolved in a kinetic fashion by a lipase-mediated selective transfer of the acetyl moiety of vinyl acetate to the alcohol of one enantiomer <1998HCA85, 1998HCA1567, 2003TA2725>. Immobilized *Mucor miehei* lipase (Lipozyme IM) selectively acetylated the (*R*)-enantiomer of alcohol **57**, known to preferentially exist in the *P*-conformation in which the CH₂OH is equatorial <1998HCA85>. The recovered alcohol is the (*S*)-enantiomer, which prefers the *M*-conformation thereby placing the CH₂OH axial, suggesting steric control in enzyme recognition. For the C-3-disubstituted 1,4-benzodiazepin-2-one **58**, the *pro*-(*R*)-hydroxymethyl moiety of the diol is acetylated, thought to occur via reaction with the equatorial CH₂OH in the *P*-conformation (Scheme 24) <1998HCA1567>.



Scheme 24

13.06.8 Reactivity of Substituents Attached to Ring Heteroatoms

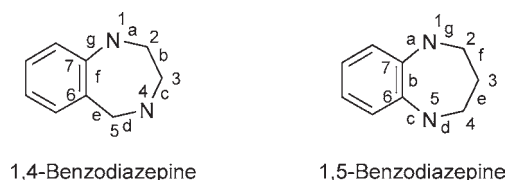
The *N*-4-(benzotriazolylmethyl)-tetrahydro-1,4-benzodiazepine **59** reacted smoothly with Grignard reagents in THF to provide convenient access to substituted homologues in good yield (Scheme 25) <2002J(P1)592>. The benzotriazole moiety can be removed reductively with NaBH₄ to provide the simple *N*-methyl compound, while reaction with triethyl phosphite and ZnBr₂ in dry THF gave the diethylphosphonate derivative.



Scheme 25

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

The system used for defining ring-construction topology from acyclic precursors is the same as that used in CHEC(1984) and CHEC-II(1996), in which the bond(s) being formed are designated by lowercase italicized letters and the precursor fragments are defined by the individual sequences of carbon and nitrogen atoms. Ring syntheses are considered in alphabetical order of the disconnection, with reactions forming two bonds following the single-bond discussion, also in alphabetical order based on the second bond being formed. Thus type *a* is considered first followed by type *ab*, then type *ac*, before type *b* ring closures are discussed. Summaries of monocyclic diazepine and benzodiazepine ring-closure methods are combined under the bond-disconnection designation, whereas 1,5-benzodiazepines are considered in a separate section, following the precedent set by CHEC-II(1996).



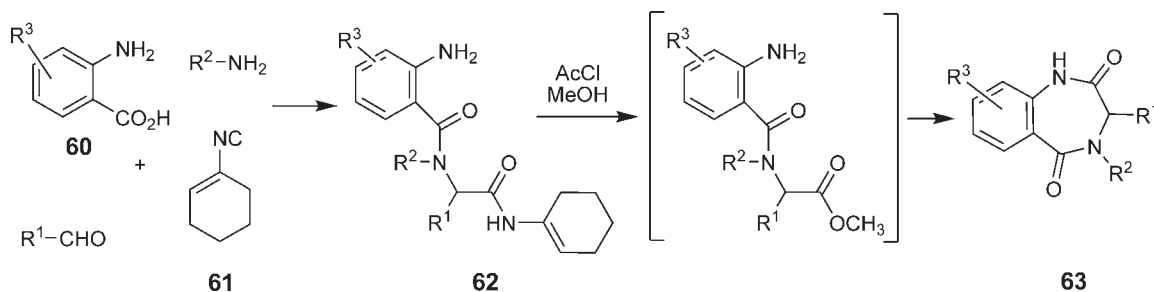
13.06.9.1 Monocyclic 1,4-Diazepines and 1,4-Benzodiazepines

The interest in understanding conformational aspects of monocyclic 1,4-diazepines in the context of peptidomimetics has stimulated the development of new preparative methodologies and procedures designed to improve limitations associated with previously established routes to these compounds. Synthetic approaches to both 1,4- and 1,5-benzodiazepines are generally well described, but the development and application of new methodology, particularly using transition metal catalysis, has resulted in innovative bond-construction strategies that broaden the range and nature of functionality both within the ring and incorporated into substituents. Moreover, the well-established utility of 1,4-diazepines as drug scaffolds in medicinal chemistry has provided a significant impetus to develop combinatorial syntheses that allow access to large numbers of structurally diverse compounds suitable for high-throughput screening campaigns.

13.06.9.1.1 Type *a* (N-C-C-C-C-N-C-C)

The type *a* ring-closure topology is one of the most frequently used methods to synthesize 1,4-benzodiazepin-2,5-diones because of the reliability of amide formation from precursors readily available by acylating α -amino acid derivatives with an activated anthranilic acid or a synthetic surrogate. A particularly useful protocol that relies upon a type *a* ring-closure to synthesize 1,4-benzodiazepin-2,5-diones prepared precursors from anthranilic acids using the Ugi reaction, a four-component process that allowed considerable structural diversity to be introduced in a combinatorial fashion (Scheme 26) <1996JA2574, 1996JOC8935>. The most effective reaction protocol takes advantage of the unique chemical properties of 1-isocyanocyclohexene that allow it to function as a 'universal isocyanide'. As illustrated in

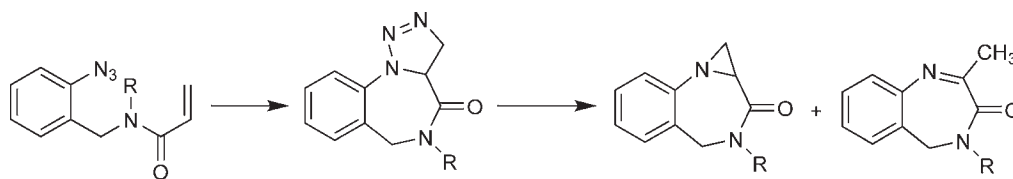
Scheme 26, the combination of an aldehyde, a primary amine, an anthranilic acid **60**, and the isocyanide **61** afforded the acylated amino acid **62** in a process conveniently performed in a single operation. The key step in this process is the conversion of the cyclohexenylamide in **62** to an ester, which occurred under acidic conditions. This step of the sequence was proposed to proceed by way of an intramolecular nucleophilic expulsion of the acylated iminium by the anthranilamide moiety to afford a dipolar münchnone intermediate. This provides a satisfactory explanation for why the ester was formed rather than the primary amide, which would arise from a simple hydrolysis. Cyclization of the intermediate ester to the 1,4-benzodiazepin-2,5-dione **63** was completed by heating. The yield of this reaction can be increased by introducing an *N*-BOC or *N*-Fmoc (Fmoc = 9-fluorenylmethyloxycarbonyl) protecting group onto the anthranilic acid while the use of ethyl glyoxalate led to 3-carboxamide derivatives <1998JOC8021, 1999TL5295>. The convenience of this procedure is further enhanced by using resin-bound isocyanides <2002OL1167, 2002TL4083>.



Scheme 26

A related process, in which 2-aminoacetophenone is coupled with a 2-nitrobenzoic acid, a ketone, and an isocyanide, afforded 2-aryl-4,5-dihydro-1,4-benzodiazepin-5-ones in good to excellent overall yields after Fe-mediated reduction of the nitro group and ring closure <2005TL711>.

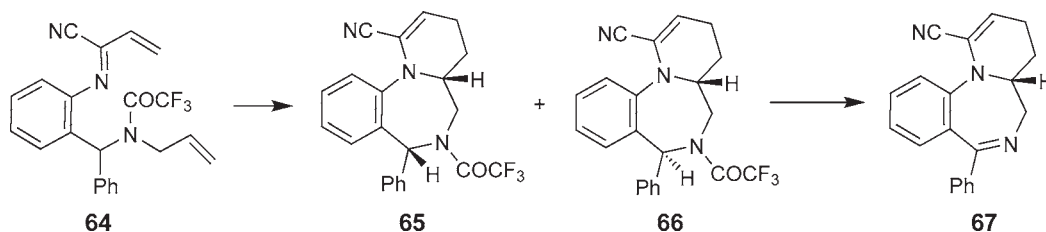
A number of procedures based on a [3+2] intramolecular cycloaddition protocol have been developed, including the intramolecular cycloaddition of an aryl azide to an alkene which provides triazolino-fused diazepine derivatives that extrude N₂ upon heating <2001J(P1)1816, 2001TA1201, 2004TA687>. This process afforded mixtures of two 1,4-benzodiazepin-3-one derivatives in which N-1 is either incorporated into a fused aziridine ring or is part of an imine moiety, as depicted in **Scheme 27**. The outcome of this process depended upon the substitution pattern of the alkene since the cinnamide analogue afforded only the substituted aziridine product upon heating of the azide in toluene. In this case, the product was isolated as a mixture of diastereomers when the R-substituent contains a chiral center. Anthranilamides derived from allyl amine, in which the amide moiety is configured in an alternative topology, form 3-alkyl-1,4-benzodiazepin-5-ones exclusively in good yield, particularly under microwave heating <2001TL2397>.



Scheme 27

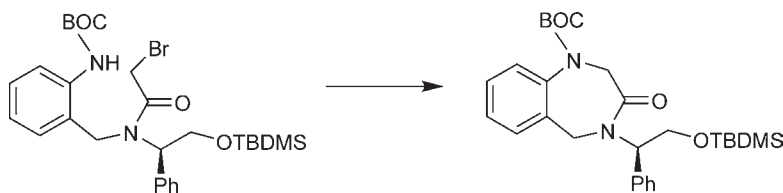
Structurally related nitrile imines, generated *in situ*, add to the pendant alkene to afford fused 1,4-benzodiazepin-3-one and 1,4-benzodiazepin-5-one derivatives depending upon the oxidation state at C-3 and C-5 of the starting material <1999TA2203, 1999TA4447>. The incorporation of chiral elements into the ester moiety or the amide N-substituent is associated with modest diastereoselection <1999TA3873, 2001SC2649>.

A [4+2] cycloaddition strategy involving a hetero-Diels–Alder reaction afforded N-1-, C-2-fused tricyclic 1,4-benzodiazepines <1998TL4283>. Heating the azadiene **64** in toluene at 180 °C afforded a 3:2 mixture of the chromatographically separable *cis*- and *trans*-1,4-benzodiazepines **65** and **66** in 74% yield (**Scheme 28**). The structure of the adducts was determined by ¹H NMR, with an NOE observed between the C-4a and C-7 protons for the *cis*-isomer **65**. Removal of the N-protecting group from the *trans*-isomer using K₂CO₃ in MeOH, followed by oxidation with Pb(OAc)₄ and iodine, provided the fused 2,3-dihydrobenzo-1,4-diazepine **67** in 76% yield.



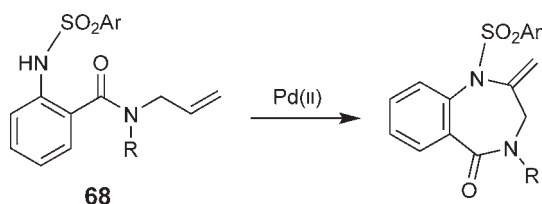
Scheme 28

The intramolecular alkylation of a BOC-protected aniline by an α -bromo amide using NaH in DMF, depicted in [Scheme 29](#), provided an example of a type *a* ring closure to 1,4-benzodiazepin-3-ones, a straightforward and effective procedure that, surprisingly, has not been more broadly exploited [<2005EJO1590>](#).



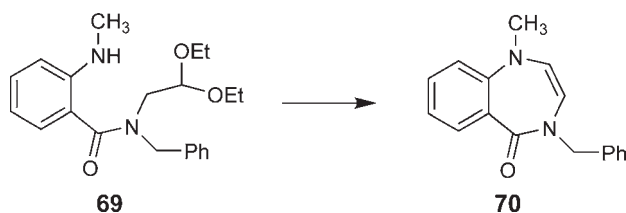
Scheme 29

The Pd-catalyzed cyclization of the allyl anthranilamide **68** to a benzo-1,4-diazepin-5-one was optimized to provide good selectivity for the formation of the seven-membered ring rather than the quinazolin-4-one derivative ([Scheme 30](#)) [<2004JOC5627>](#). Optimal conditions were determined to be 10 mol% $\text{Pd}(\text{OAc})_2$ in xylene at 100 °C with pyridine, as the base, the inclusion of which was essential to the success of this procedure. Notably, the BOC protecting group was unable to substitute for the sulfone moiety, presumably reflecting the requirement for a specific $\text{p}K_a$ range. A Pd(0) catalyst promoted a topologically similar intramolecular cyclization of an unsaturated, bicyclic hydroxamide in a reaction that was dependent on the aniline moiety being protected with the heavily electron deficient 2,4-dinitrobenzenesulfonamide moiety as a means of reducing the $\text{p}K_a$ of the nucleophile precursor [<2002OL139>](#).



Scheme 30

The first example of 1,4-benzodiazepin-5-one that incorporates an unsubstituted 2,3-carbon-bond was obtained by hydrolyzing the acetal **69** in THF in the presence of Amberlyst-15 resin [<2000S265>](#). Subsequent heating of the product in toluene with azeotropic removal of water gave the 1*H*-benzo[*e*][1,4]diazepin-5(4*H*)-one **70** ([Scheme 31](#)).



Scheme 31

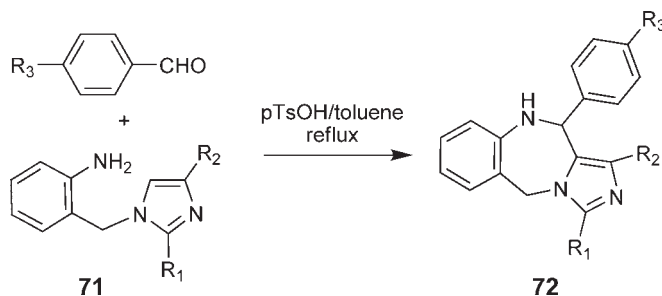
Analysis of ^1H NMR spectra revealed that the two enamide protons resonate as doublets at 5.28–5.36 and 5.55–5.62 ppm with a 5.6 Hz coupling constant.

The Michael-type addition of an aniline to an unsaturated ester, generated *in situ*, provided an example of a type *a* ring closure in which the electrophilic center is sp^2 -hybridized <2004BML4147>. This reaction represents a synthetically useful procedure to access tetrahydro-1,4-benzodiazepines.

Several type *a* ring closures have been developed that use solution- and solid-phase methodology to facilitate the application of high-throughput synthesis technology <2000TL1509, 1996TL8081, 2001TL5141>. These procedures provide the type of diverse array of products preferred for screening campaigns and include a library of substituted 1,4-benzodiazepin-2,3-diones.

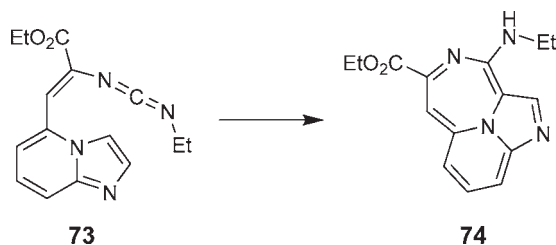
13.06.9.1.2 Type *ab* (N–C–C–C–N–C + C)

Examples of the type *ab* ring closure that have been described involve the *in situ* capture of an imine derived from an aniline by a nucleophilic olefin moiety and are limited to substrates in which the olefin is part of an azole-derived heterocycle, leading to products in which the diazepine moiety is embedded in a fused ring system <1996CHEC-II(9)151>. Heating the aniline **71** with an aromatic aldehyde in toluene at reflux in the presence of a catalytic amount of TsOH effected a Pictet–Spengler ring closure between the imidazole ring and intermediate imine (Scheme 32) <2005JOC4889>. The fused benzo-1,4-diazepine derivatives **72** were isolated in yields ranging from 75% to 88%. This reaction was insensitive to the electronic nature of the 4-substituent on the aldehyde and the steric environment at the 5-position of the imidazole, since the 4-phenyl and 4-methyl derivatives cyclized with equal efficiency.



Scheme 32

The carbodiimide **73**, obtained by reaction of an iminophosphorane with ethyl isocyanate, underwent a thermally induced cyclization in 1,2-dichlorobenzene at reflux to give the azulene **74** in 42% isolated yield (Scheme 33) <2001JOC6576>. This process was regiospecific since products arising from reaction with the six-membered ring were not observed.

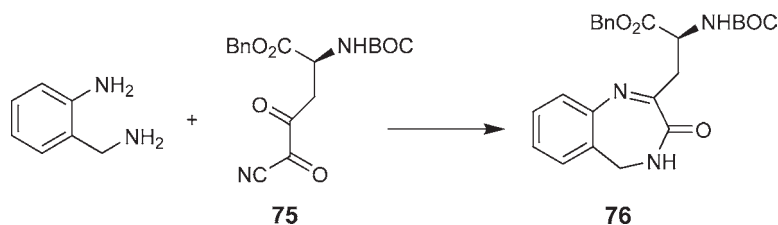


Scheme 33

13.06.9.1.3 Type *ac* (N–C–C–C–N + C–C)

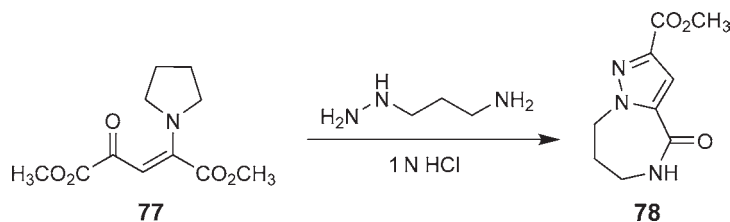
The type *ac* ring-construction process relies upon the reaction of a 1,3-diamine with a two-carbon electrophile, readily available fragments that offer simplicity in reaction design. The reaction of 2-aminobenzylamine with the reactive diketetonitrile **75**, derived from aspartic acid, in CH_2Cl_2 proceeded smoothly to furnish the 1,4-benzodiazepin-3-one **76**

in 64% yield (Scheme 34) <2003TL361>. The structure of **76** was not definitively established but assigned based on the expectation that the more nucleophilic primary amine would react more rapidly at the acyl cyanide carbonyl.



Scheme 34

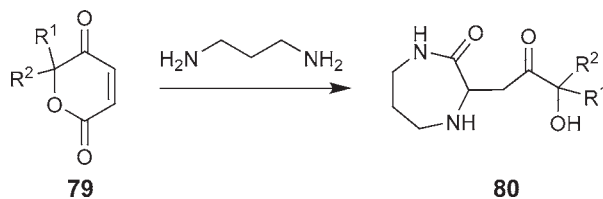
The pyrrolidiny enamino keto-diester **77** reacted with 3-hydrazinylpropan-1-amine in the presence of 1 N HCl to afford the pyrazolodiazepine **78**, a key intermediate in the preparation of a glycoprotein IIb/IIIa antagonist, in 40% yield (Scheme 35) <2003TL5867>. The requirement for the presence of 1 N HCl to promote this process suggested that the diketo diester is the actual intermediate in the process, evaluated by examining the outcome with a mixed methyl/ethyl ester. The product was isolated as a 1:1 mixture of ester isomers, consistent with the intervention of a hydrolytic step that led to symmetrization of the electrophile.



Scheme 35

The reductive amination of a substituted 1,3-diaminopropane with glyoxal provided the saturated 1,4-diazepine derivatives, which have been used as intermediates in the synthesis of a number of biologically active compounds <1998T10671, 2002OPD28>. This process is related to the previously established method for the synthesis of 1,4-diazepin-2-ones that relies upon the combination of glyoxal, or its bis-bisulfite, with a 1,3-diaminopropane derivative under nonreducing conditions <2001JOC5822>.

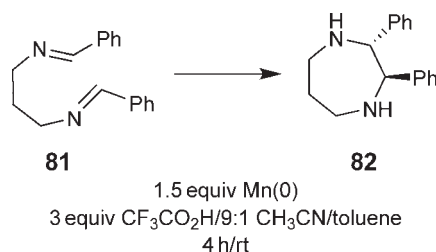
The ketone moiety of unsaturated 5-ketolactones **79** both directs and facilitates the reactivity of diaminopropane toward a Michael reaction at C-3 and amide formation with the lactone carbonyl, yielding 3-substituted diazepinones **80**, as shown in Scheme 36 <1996JHC703>.



Scheme 36

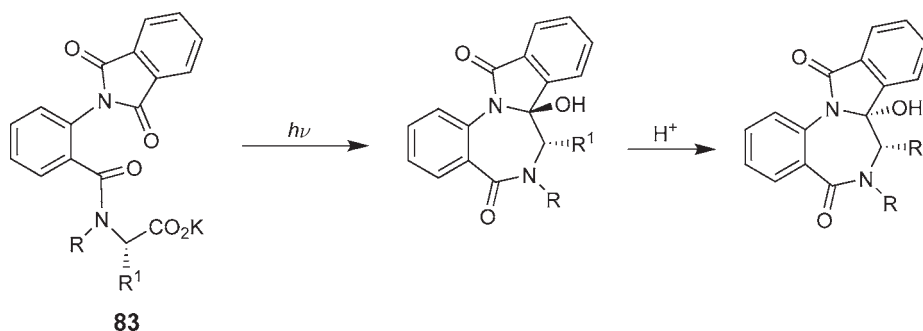
13.06.9.1.4 Type b (C-N-C-C-C-N-C)

A chemical approach to the reductive cyclization of the symmetrical diimine **81** provided the *trans*-substituted 1,4-diazepine **82** in 73% yield, thus providing an alternative to the electrochemical processes that have more commonly been described to effect this transformation (Scheme 37) <2003OL1591>.



Scheme 37

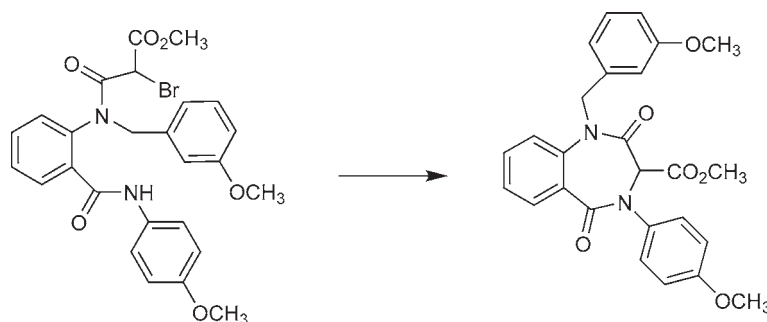
The preparation of 1,4-benzodiazepines using a type *b* ring-closure reaction is rare, restricted to photochemically induced radical cyclizations with uniquely designed substrates <2001AGE577, 2001S1159>. Irradiation of the potassium salts **83** of *N*-phthaloylanthranilamide at 300 nm in aqueous acetone afforded 1,4-benzodiazepin-5-ones in 54–83% yield after a photoinduced decarboxylation that generated a radical, which was trapped by the carbonyl moiety (Scheme 38). On a small scale, the product was produced, as a single diastereomer, in which the OH and R¹ moieties are *trans*, the result of a kinetically controlled process. However, larger-scale reactions produced a mixture of *cis*- and *trans*-products, reflecting thermodynamic equilibration that could also be established by exposure of the kinetic product to a catalytic amount of CF₃CO₂H <2001AGE577>. Substrates in which the anthranilic acid element is replaced by β-alanine follow a similar reaction manifold to give 1,4-diazepin-5-one derivatives, albeit in lower yield <2001OL537>.



Scheme 38

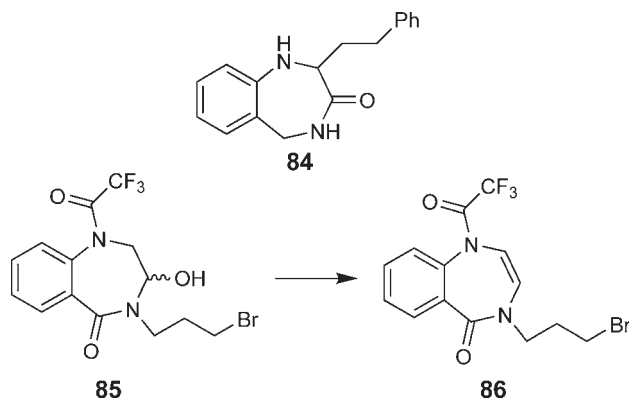
13.06.9.1.5 Type *c* (N–C–C–C–N–C–C)

The intramolecular alkylation of an aryl amide by an activated bromide, readily available by bromination of a malonamide methylene with pyridinium tribromide in the substrate depicted in Scheme 39, provided an example of a type *c* ring closure to furnish 3-carboxymethyl-1,4-benzodiazepin-2,5-diones <2006OBC510, 2002H(56)1501, 1999JOC2914>.



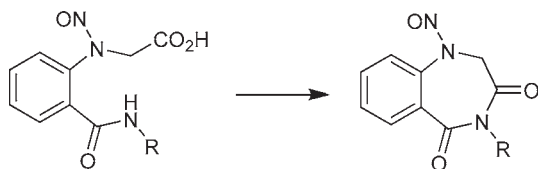
Scheme 39

Type *c* ring closures involving carbonyl-containing electrophiles have been exemplified <1999OL1835, 2004BML1031, 2003OPRD655>. The unmasking of a primary benzylamine from the corresponding nitrile in the presence of an ester resulted in spontaneous cyclization, providing the 1,4-benzodiazepin-3-one **84** in 65% yield <2004BML1031>. 3-Hydroxy-1,4-benzodiazepin-5-ones were produced when an aldehyde was generated in the presence of a secondary amide and the resulting acylated hemiaminals **85** were readily dehydrated to the enamide **86** in good overall yield by heating in toluene in the presence of acid (Scheme 40) <1999OL1835>.



Scheme 40

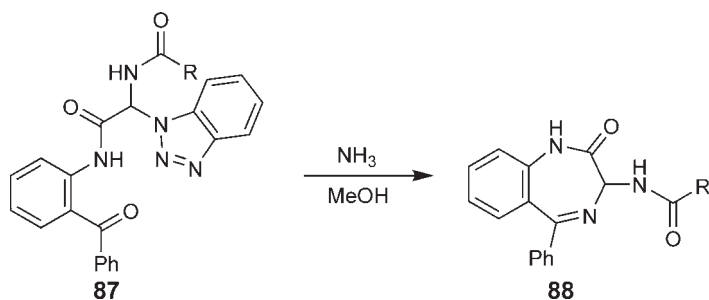
Substituted 1,4-benzodiazepin-3,5-diones can be prepared by capturing an amide with a carboxylic acid that has been activated as the mixed anhydride, as shown in Scheme 41 <2004JOC6371>. An *N*-nitroso protecting element was essential for the success of this procedure, facilitating the reaction by enhancing the anhydride's electrophilicity. Both alkyl and aryl amides participated and the nitroso moiety was readily removed from the product by heating in $\text{CF}_3\text{CO}_2\text{H}$ in the presence of urea, as a scavenger.



Scheme 41

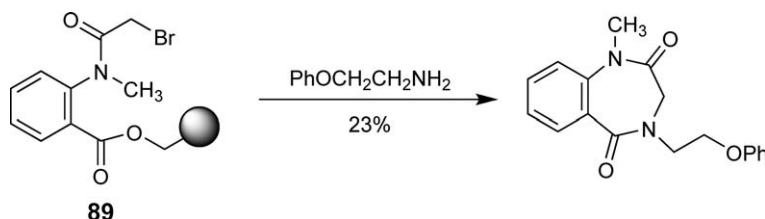
13.06.9.1.6 Type *cd* (C–C–C–N–C–C + N)

The synthetically versatile benzotriazole moiety offers an effective and convenient leaving group that extends the range of substrates that participate in a type *cd* ring-closure. Racemic 3-amino-2,3-dihydrobenzo-1,4-diazepin-2-ones **88** were obtained in 59–77% yield when α -amidobenzotriazoles **87** were exposed to a saturated solution of NH_3 in MeOH (Scheme 42) <1995JOC730, 2001M747, 2003JOC2844>.



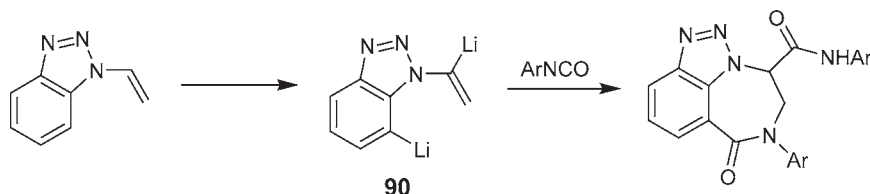
Scheme 42

Heating the Wang resin-bound anthranilic ester **89** at 150 °C with a primary amine in a microwave apparatus effected a tandem N-alkylation–intramolecular cyclization that proceeded with concomitant cleavage of the 1,4-disubstituted-1,4-benzodiazepin-2,5-dione product from the resin (**Scheme 43**) <2005AGE5830>. A topologically similar process provided access to sclerotigenin, a benzodiazepine alkaloid isolated from extracts of sclerotia of *Penicillium sclerotigenum* that is a potential anti-insectant <2002JHC351>.



Scheme 43

Reaction of the dilithio anion of 1-vinylbenzotriazole **90** with 2 equiv of an aryl isocyanate led to a fused 1,4-diazepine ring formation via an intramolecular Michael addition of the intermediate aryl amide to the vinyl moiety, a type *c* ring closure that proceeded in good overall yield (**Scheme 44**) <2003JOC5713>.



Scheme 44

13.06.9.1.7 Type *d* (C–C–C–N–C–C–N)

The type *d* ring closure to access monocyclic 1,4-diazepines is typically accomplished by uniting a nucleophilic nitrogen atom with an electrophilic carbon atom; examples, where the latter is in either an sp^2 or an sp^3 hybridization state, have been described.

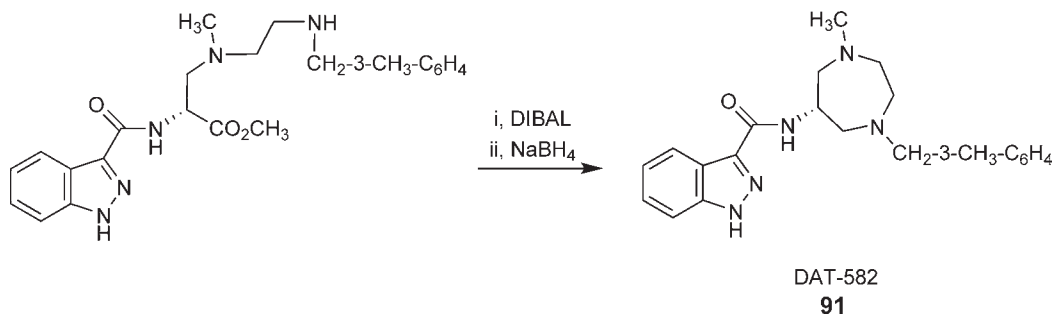
The cyclization of ω -amino acids offers the most logical and straightforward approach to 1,4-diazepines but this process can be problematic and complicated. Low yields have been attributed to dimerization as an alternative reaction pathway, particularly prominent if a secondary amide moiety that favors a transoid geometry intervenes between the reacting termini <2000EJO251>. The use of resin-bound substrates has provided a useful method to isolate reactive intermediates, such that amide bond formation of β -alanine-based dipeptides occurs efficiently, mediated by the base-catalyzed intramolecular reaction of the amine with an ester or activated acid <2001TL5389, 1998BML2273>. ω -Amino acid ester substrates derived from a cyclic β -amino acid cyclized more efficiently in a reaction promoted by the hindered base *N,N*-diisopropylethylamine in CH_2Cl_2 , a process that occurred without racemization of the ω -amino acid chiral center <2006CL86>.

More highly saturated 1,4-diazepine derivatives can be accessed by reductive amination procedures in which the imine is formed by the interaction of an amine with a pendant aldehyde or ketone moiety. This ring-closure topology has been exploited in a total synthesis of caprazol, the core found in both the caprazamycin family of antituberculosis antibiotics and the liposidomycins, lipid-containing nucleoside antibiotics that inhibit peptidoglycan synthesis <2005AGE1854, 2003H(59)107>. A similar strategy allowed the synthesis of the 1,4-diazepine element found in DAT-582 **91**, a potent and selective 5HT_3 receptor antagonist (**Scheme 45**) <1997J(P1)3219, 1997TA2367>.

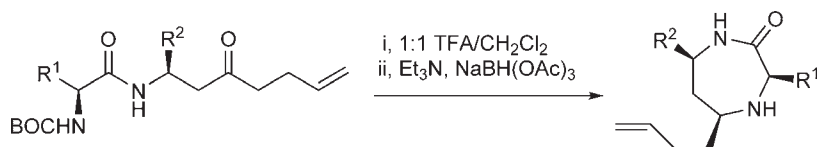
The incorporation of an amide bond in the substrate provided 1,4-diazepin-2-ones as single diastereomers with the stereochemistry at C-5 determined by single crystal X-ray structure analysis, as depicted in **Scheme 46** <2006OL3425>.

The AgOTf-catalyzed, PhSeBr -induced ring closure of the prolinamide-derived cinnamoylamide **92** proceeded via *anti*-addition to the olefin, which afforded the *trans*-substituted pyrrolo[1,2-*a*][1,4]diazepin-1,5(2*H*)-dione **93** in 73%

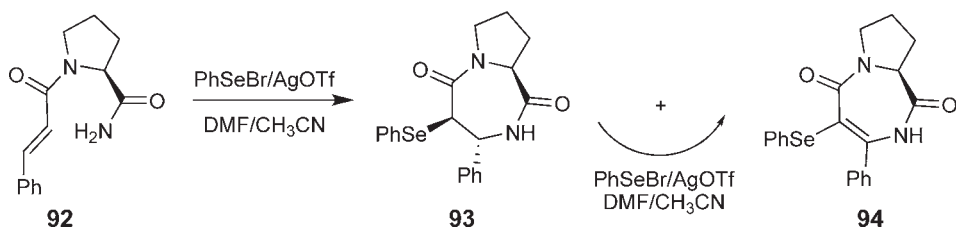
yield (Scheme 47) <1998J(P1)969>. In the presence of excess PhSeBr, the unsaturated selenide **94** is produced in 72% yield and the structure of both products was confirmed by X-ray crystallography. The course of this reaction is dependent upon the identity of the unsaturated amide moiety, in a fashion that appears to reflect the inherent electronic properties of the olefin. The 3,3-dimethylacrylamide analogue provided the corresponding diazepine in 22% yield but the crotonamide derivative engaged an alternative reaction manifold leading to a fused diketopiperazine derivative, a result attributed to the poorer carbenium ion stabilization associated with the single methyl substituent. This procedure has been successfully applied to the synthesis of inhibitors of the binding of the oncogenic protein HDM2 to p53 <2005BML1857>.



Scheme 45

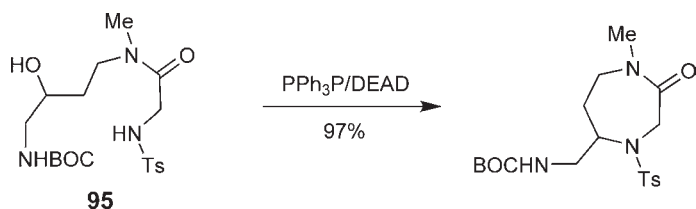


Scheme 46



Scheme 47

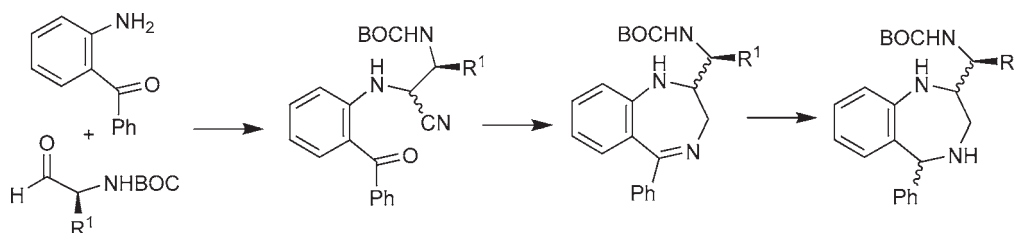
An intramolecular Mitsunobu alkylation applied to 1,7-aminoalcohol derivatives effected ring closure to 1,4-diazepines in a reaction that is only successful if the amine nucleophile is activated by an electron-withdrawing element, that can adjust the pK_a to the range that has been defined as optimal for this reaction <1998TL2099>. The hydroxy sulfonamide **95**, readily derived from glycine, cyclized in high yield to the 1,4-diazepin-2-one, useful as a peptidomimetic scaffold, in a reaction facilitated topologically by the presence of the methylated amide (Scheme 48).



Scheme 48

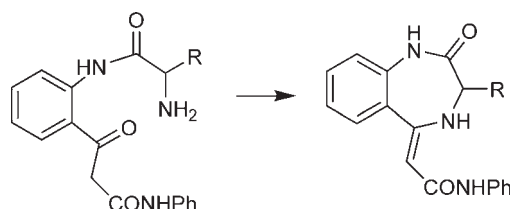
Both an intramolecular alkylation and a Mitsunobu reaction were used to synthesize the [1,4]diazepino[1,2,3-*g,h*]purine heterocyclic fragment of the cytotoxic marine sponge metabolite asmarine A <2001TL5941, 2003T6493>. In this reaction, the nucleophile was a heteroaryl alkoxyamine that conferred the appropriate pK_a on the NH. *O*-Alkyl hydroxamic acids are also useful substrates for Mitsunobu reactions. BOC-Ser-Phe-NHOBn and analogous dipeptides cyclized to give 1,4-diazepin-2,5-ones in modest to good yields under microwave heating, which promoted cyclization by populating the *cisoid*-conformation at the central amide bond <2003JOC7893>. This reaction has been extended to more complex systems using a solid-phase-based approach in which the hydroxamic acid oxygen atom is bound to a resin. Reduction of the N–O bond in the cyclized product with concomitant removal from the resin was accomplished by treatment with SmI_2 in THF <2003JOC7893>.

The preparation of 1,4-benzodiazepines using a type *d* ring-closure strategy is well developed and widely applied because of the ready availability of *ortho*-substituted anilines. However, new substrates for this process that provide access to uniquely substituted ring systems continue to be explored and some of the more interesting examples are summarized. The combination of 2'-aminobenzophenone, an *N*-protected α -aminoaldehyde and trimethylsilyl cyanide (TMSCN) in the presence of ZnCl_2 , as a catalyst, provided the Strecker products as an epimeric mixture at the newly formed chiral center (Scheme 49) <2003JOC4582>. Reduction of the nitrile moiety to the primary amine using Raney nickel in the presence of hydrazine was accompanied by imine formation to give diastereomeric 5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepines. Small amounts of the 2,3,4,5-tetrahydro derivatives were also formed, a transformation that could be completed in a discrete step using NaBH_3CN in AcOH. The identity of the chromatographically separable diastereomeric 2,3-dihydro-1*H*-1,4-benzodiazepines was determined by ^1H NMR spectroscopy and the preservation of the chiral center in the *N*-protected α -aminoaldehyde established by additional experiments. Application of this procedure to an anthranilic ester provided access to structurally less complex 1,2,3,4-tetrahydrobenzodiazepin-5-one derivatives, scaffolds suitable for the synthesis of peptidomimetics <2003T4491>.



Scheme 49

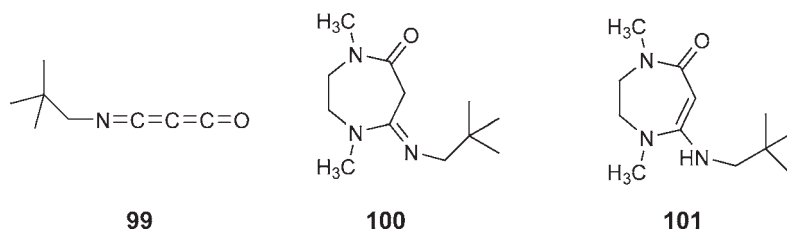
Condensation of an amino acid-derived anilide and a β -ketoamide afforded 1,4-benzodiazepin-2-ones in which the initially formed imine tautomerizes to an exocyclic enamide (Scheme 50) <2001TL3227>. Only the (*Z*)-isomer of the enamide was isolated, assigned based on NOE data, and presumably reflecting stabilization by an intramolecular H-bond between the ring NH and exocyclic amide carbonyl.



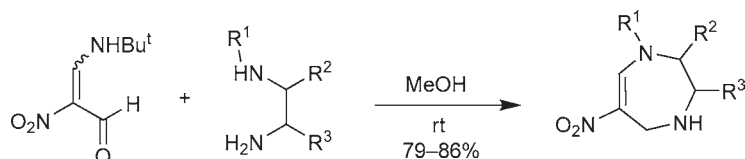
Scheme 50

13.06.9.1.8 Type *de* (C–C–N–C–C–N + C)

The first examples of a type *de* ring closure to 1,4-benzodiazepines that rely upon different sources of the single carbon atom have been described <2005JA14776, 2006T2563>. The carbonylation of *N*¹-(2-iodophenyl)-*N*¹-methylbenzene-1,2-diamine, catalyzed by Pd complexed to a silica-based dendrimer ligand, provided 5-methyl-5*H*-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one in 96% yield after capture of the intermediate acyl palladium species by the aniline nitrogen (Scheme 51) <2005JA14776>. While the generality of this process has been demonstrated by the

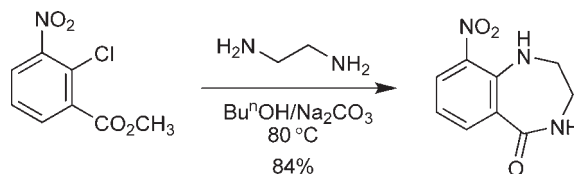


The 3-(*tert*-butylamino)-2-nitroacrylaldehyde is a synthetic equivalent to nitromalonaldehyde that reacts with substituted ethylenediamines in MeOH at 25 °C to provide the first examples of 6-nitro-2,3,4,5-tetrahydro-1*H*-1,4-diazepines in excellent yield (**Scheme 54**) <2004JOC8382, 2002H(56)425>. The slow addition of a solution of the diamine to the nitroenamine was required in order to minimize oligomer formation.



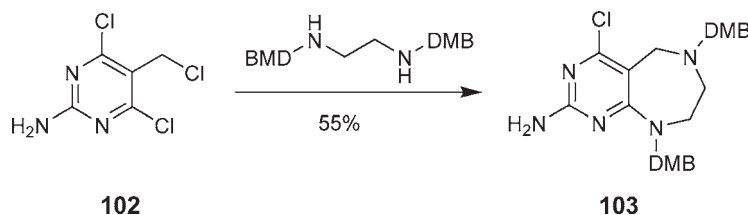
Scheme 54

Heating ethylenediamine with methyl 2-chloro-3-nitrobenzoate and Na₂CO₃ in butanol at 80 °C effected a dual S_N2Ar/acylation reaction to afford 9-nitro-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one, an intermediate in the synthesis of inhibitors of poly(ADP-ribose) polymerase-1, in 84% yield (**Scheme 55**) <2003BMC3695>.



Scheme 55

The dual alkylation/S_N2Ar cyclization of *N*¹,*N*²-bis(2,4-dimethoxybenzyl)ethane-1,2-diamine (bis-DMB-ethylenediamine) with the chloromethyl pyrimidine **102** provided the fused ring diazepine **103**, a transformation that could not be accomplished by simply using unprotected ethylenediamine (**Scheme 56**). The product is an intermediate toward the synthesis of potential folate-related antitumor agents that act as glycinamide ribonucleotide formyltransferase inhibitors <2004HCO405>.

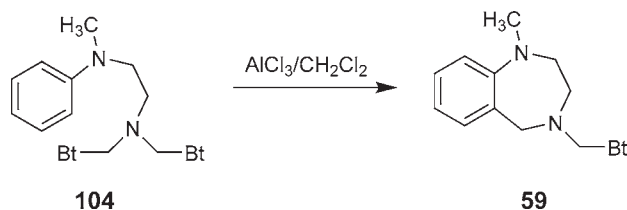


Scheme 56

13.06.9.1.10 Type e (C–C–N–C–C–N–C)

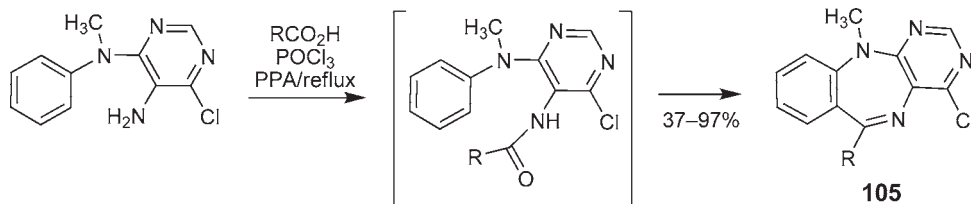
The most common form of the type *e* ring-closure reaction to afford 1,4-benzodiazepines is a 7-*endo-trig*-process in which a substituted iminium derivative, typically generated *in situ*, is captured by the aryl ring. Cyclization of the *N,N'*-(bis-1,2,3-benzotriazol-1-ylmethyl)amine **104** by a Friedel–Crafts-type ring closure afforded the tetrahydro-1,4-

benzodiazepine **59** in 86% yield (**Scheme 57**) <2002J(P1)592>. The starting material was easily obtained by treating the primary amine with 2 molar equiv of benzotriazole and formaldehyde, which afforded the pure N-1 benzotriazole isomer at both heterocycles. Interestingly, the cyclization product was isolated as a 4.4:1 mixture of N-1 and N-2 isomers; however, since benzotriazole isomers are known to have similar stability and reactivity, this observation is inconsequential for subsequent transformations that involve exchange of the heterocycle by a range of nucleophiles, a well-established and versatile synthetic methodology.



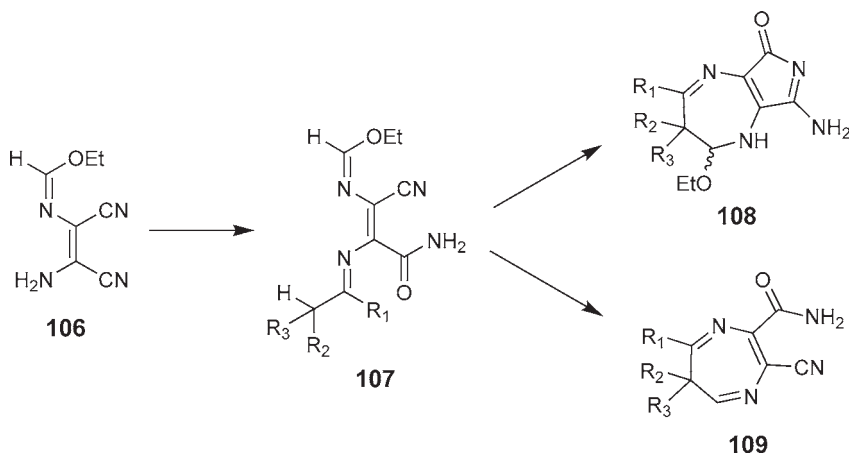
Scheme 57

Heating *N*-[2-(arylamino)phenyl]amides under strongly acidic conditions or with powerful chlorinating agents like phosphoryl chloride effects a Bischler–Napieralski-type cyclization to afford 1,4-benzodiazepine derivatives <2004SOS929>. This process has been demonstrated in the context of an aminopyrimidine substrate and it was subsequently shown that acylation of the primary amine with a benzoic acid and the cyclization reaction could be combined into a single, practical preparative procedure <2005OL1541>. The components are simply heated with polyphosphoric acid or with POCl₃ to provide the tricyclic products **105** in 37–97% yield (**Scheme 58**).



Scheme 58

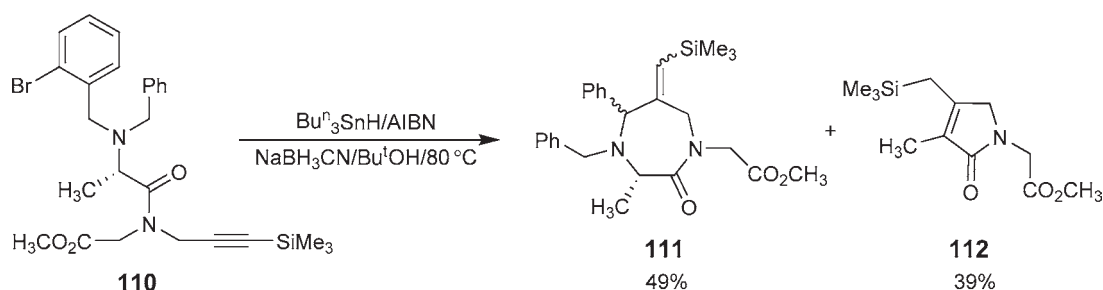
Reaction of the imide **106** with an aldehyde or a ketone in EtOH at 0°C in the presence of Et₃N afforded the Schiff's base **107** in which one of the nitrile groups has been partially hydrolyzed (**Scheme 59**) <2000JHC1041>.



Scheme 59

Prolonged exposure to Et_3N led to a type *e* ring closure, presumably via a 7-*endo-trig*-process, accompanied by a slower cyclization of the amide and nitrile moieties to give the fused pyrrole ring **108**. Imine **107** also cyclized in a similar fashion under the influence of mild acid, PhCO_2H in EtOH , but these conditions led to the elimination of EtOH , affording the fully unsaturated ring system **109** in which the amide and nitrile elements are preserved intact. These processes proceeded much more rapidly when activated carbonyl components were used, exemplified with ethyl pyruvate and diacetal.

A particularly interesting approach to a type *e* ring construction arose when the substituted alanine amide **110** was treated with $n\text{-Bu}_3\text{SnH}$ <2003JOC1552>. This reaction generated an aryl radical that has access to two alternative 1,5-shift modes of rearrangement, the first resulting in the radical moving to the $\text{C}\alpha$ of the amino acid, while the alternative 1,5-shift transferred the radical to the methylene of the adjacent benzyl group. The latter radical is poised to add to the alkyne in a 7-*exo*-fashion, which occurs to provide the diazepine **111** in 49% yield (Scheme 60). The former radical can also add to the alkyne, a 5-*exo*-ring-closure that leads to a pyrrolidinone intermediate which is subject to a second 1,5-shift with subsequent loss of dibenzylamine and allylic rearrangement of the resulting radical to give the lactam **112** in 39% yield. The yield of the diazepine is considerably lower when the benzyl element is replaced by a methyl substituent, consistent with the proposed rearrangement mechanism. The 2-bromobenzyl element is designated as a protecting/radical-transfer (PRT) moiety.

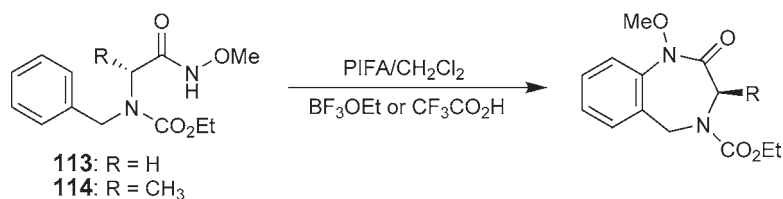


Scheme 60

13.06.9.1.11 Type *g* (N–C–C–N–C–C–C)

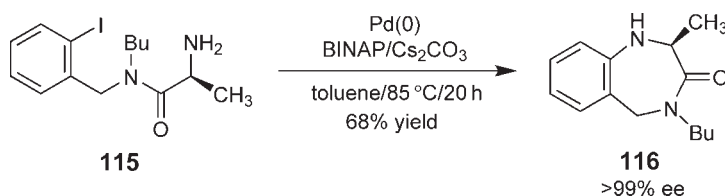
The type *g* ring closure as defined in this section was treated as a type *b* ring closure in both CHEC(1984) and CHEC-II(1996) but is considered here as a discrete topological disconnection. Synthetic methodology that allows facile access to 1,4-benzodiazepines by way of a type *g* ring closure has been expanded considerably and two complementary processes have been described. The first depends upon the nitrogen atom being incorporated into functionality that facilitates its activation to an electrophilic species that engages in a Friedel–Crafts–type reaction with the aromatic ring. In the alternative process, the nitrogen atom functions in the more traditional role of that of a nucleophile.

The oxidation of *N*-alkoxyamides with phenyliodine(III)bis(trifluoroacetate) (PIFA) afforded an acyl nitrenium ion that under acid catalysis was trapped by a pendant phenyl ring, a process that has been used to prepare synthetic precursors to the antitumor antibiotic ($\pm$)-DC-81 <2003T7103, 2005JOC2256>. This process was initially examined with the *N*-benzylglycine-derived substrate **113** for which $\text{BF}_3\cdot\text{OEt}$ in CH_2Cl_2 at -20°C was determined to be the superior catalyst and conditions (Scheme 61). With the alanine analogue **114**, $\text{CF}_3\text{CO}_2\text{H}$ in CH_2Cl_2 at 0°C more effectively promoted the cyclization, which occurred without compromising the integrity of the single chiral center. The methoxy moiety was conveniently removed from the N-1 amide in good yield by treatment with $\text{Mo}(\text{CO})_6$ in aqueous MeCN <2005JOC2256>.



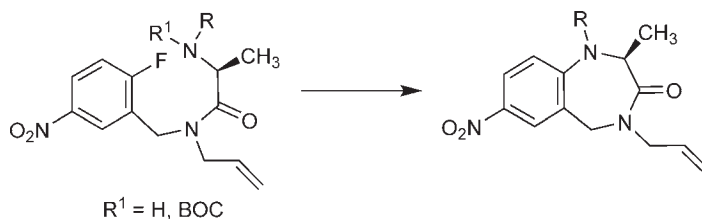
Scheme 61

The scope of type *g* ring-closure processes in which the nitrogen atom functions as a nucleophile has been expanded considerably and synthetically useful procedures that afford 1,4-benzodiazepine derivatives have been developed. The more common process relies upon displacement of a leaving group in an S_NAr process while a second approach takes advantage of the activation of a 1,4-dihydroxybenzene by oxidation to a quinone intermediate that acts as a powerful electrophile toward the amine. The advent of copper- and palladium-catalyzed processes for the arylation of nucleophilic nitrogen species has allowed access to an intramolecular variant to the preparation of 1,4-benzodiazepine derivatives <2001SL803, 2004JA14475, 2001OL2583, 2004JA14475>. Heating a solution of (*S*)-2-amino-*N*-butyl-*N*-(2-iodobenzyl)propanamide **115** in toluene at 85 °C in the presence of 10 mol% $Pd_2(dba)_3 \cdot CHCl_3$, the bidentate phosphine ligand 2,2-bis(diphenylphosphanyl)-1,1'-binaphthyl (BINAP) and Cs_2CO_3 or *t*-BuOK, as base, promoted ring closure to the 1,4-benzodiazepin-2-one **116** (Scheme 62) <2001SL803>. This reaction was quite efficient, proceeding in 68% yield, and the conditions are sufficiently mild that the chirality of the amino acid moiety was completely preserved. A CuI/ K_2CO_3 -mediated process conducted in DMF at 100 °C performed similarly <2001OL2583>. Amides based on a complementary topology are also effective nucleophiles in this process under copper catalysis with optimized conditions involving heating the aryl halide in DMSO at 110 °C in the presence of CuI (10%), thiophene-2-carboxylic acid as ligand (20%), and K_2CO_3 , providing access to 1,4-benzodiazepin-2,5-diones in excellent yields <2004JA14475>.



Scheme 62

Aryl fluorides are suitable substrates for type *g* ring closures in the absence of transition metal catalysis when activated by the presence of a powerful electron-withdrawing substituent <2001TL4963, 2003TL1947, 2002OPD488, 2005TL3633>. With both primary and secondary amine nucleophiles, this process occurs upon exposure to a base or by simply heating the substrate in DMSO at 200 °C, conditions which effect thermolytic removal of a BOC group protecting the nucleophilic amine, allowing the combination of two steps into a single process <2001TL4963, 2003TL1947, 2002OPD488, 2005TL3633>. These reactions typically proceed without significant racemization of chiral centers. In the example depicted in Scheme 63, further elaboration of the product was accomplished by manipulation of the nitro group after reduction and removal of the *N*-4 allyl protecting moiety, which allowed access to more elaborately substituted homologues <2005TL3633>.

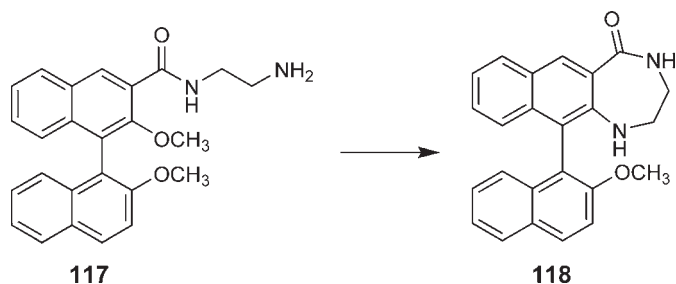


Scheme 63

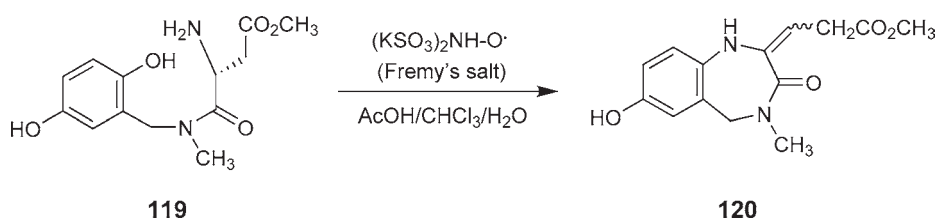
The optically pure bis-naphthalene *ortho*-methoxy amide **117** cyclized to the 1,4-diazepin-5-one **118** in 86% yield and with >95% ee upon refluxing in ethylenediamine for 5 h to provide the first axially chiral 1,4-diazepine derivative (Scheme 64) <2000SL1616>. This example of a type *g* ring closure in which the leaving group is MeOH, proceeded in lower yield with an *ortho*-hydroxy substituent, with product distribution largely redirected toward an imidazolidine derivative in which the ethylenediamine reacted solely with the ester. In the structurally simpler salicylic acid ester series, activation of the phenol as the trifluoromethanesulfonate facilitated the S_NAr reaction <1995TL7595>.

The intramolecular electrophilic capture of an amine by a quinone, accessed by oxidation of a hydroquinone, furnished an intermediate iminoquinone in which tautomerization allowed rearomatization <1999SL865>. The

benzodiazepin-3-one **120**, an intermediate in the synthesis of a glycoprotein IIb/IIIa antagonist, was isolated in 56% yield after oxidation of the substituted hydroquinone **119** using Fremy's salt under acidic conditions (Scheme 65); however, the requirement for olefin tautomerization inevitably sacrificed the chiral integrity of the starting material.



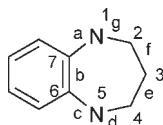
Scheme 64



Scheme 65

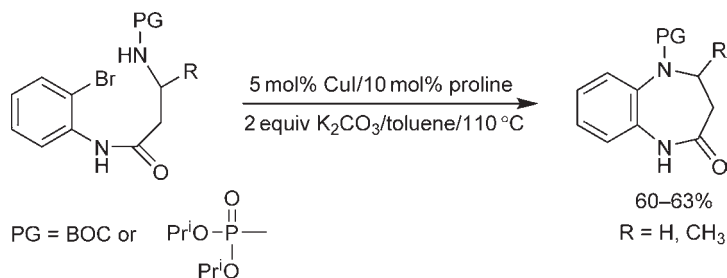
13.06.9.2 1,5-Benzodiazepines

Discussion of preparative methods for 1,5-benzodiazepines is expanded compared to the corresponding sections in CHEC(1984) and CHEC-II(1996), reflecting the development of new synthetic methodology to access these heterocycles. Ring-closure processes are discussed in alphabetical order based on the bond disconnections noted below.



13.06.9.2.1 Type a (C–C–N–C–C–C–N)

A Cu-catalyzed, Ullman-type intramolecular arylation of a protected amine afforded 1,5-benzodiazepin-2-ones in good yield via a type *a* ring closure (Scheme 66) <2005OL4781>. An *N*-BOC or *N*-diisopropylphosphono (DIPP) protecting group was essential for the success of this reaction since unprotected amines failed to cyclize under the same conditions.

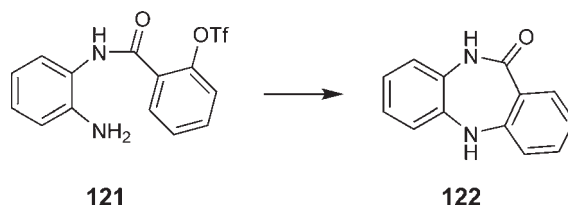


Scheme 66

Aniline nucleophiles readily participate in this type of ring-closure process under palladium catalysis ($\text{Pd}(\text{OAc})_2$, BINAP, and Cs_2CO_3 in hot toluene) without resort to protecting groups when an aryl iodide is used <2005Tf61>.

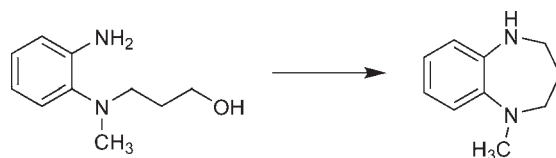
13.06.9.2.2 Type *d* (C–C–C–C–N–C–C–N)

A type *d* $\text{S}_{\text{N}}\text{Ar}$ ring closure of the triflate **121** proceeded smoothly under mild conditions comprising simply heating at reflux in MeCN for 24 h to give **122** in 77% yield (Scheme 67) <1995TL7595>. A fluorine leaving group activated by a *para*- NO_2 substituent functioned similarly in a reaction that was promoted by a resin-bound tertiary amine as base <2001TL4963>. Under acidic conditions, primary amine substrates typically cyclize to benzimidazole derivatives.



Scheme 67

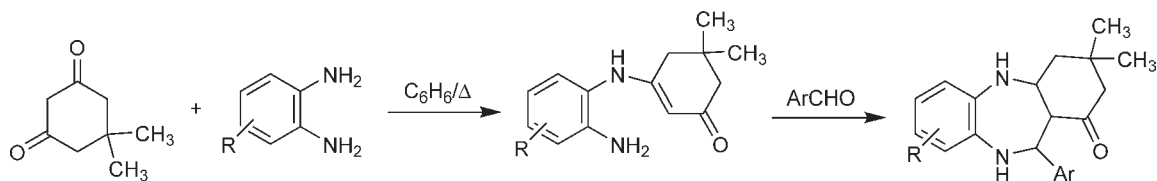
A sequence comprising an Oppenauer-type oxidation, intramolecular imine formation, and reduction, a process mediated by the iridium catalyst $[\text{Cp}^*\text{IrCl}_2]_2$ and K_2CO_3 in toluene at 120°C for several days, afforded the structurally simple 1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[1,4]diazepine in 68% yield from *N*-(2-aminophenyl)-(*N*-methylamino)propan-1-ol (Scheme 68) <2006TL6899>.



Scheme 68

13.06.9.2.3 Type *de* (N–C–C–N–C–C + C)

The acid-catalyzed reaction of enaminones and enamino-esters with aromatic and aliphatic aldehydes produced 1,5-benzodiazepines via a type *de* ring-closure topology, as depicted in Scheme 69 <2002JHC55, 2002JHC277, 2002JHC811>. A substituted phenylenediamine, when condensed with dimedone at reflux in anhydrous benzene, provided an enamine in good yield that engaged in a second condensation with an aromatic or heteroaromatic aldehyde to afford the fused tricyclic 1,5-benzodiazepine <2002JHC55, 2004JHC277, 2004KGS949>. Both *ortho*- and *para*-substituted aldehydes participated and the products were extensively characterized spectroscopically, with the single benzylic proton resonating as a doublet at 5.83–6.22 ppm in the ^1H NMR spectrum <2002JHC55>.



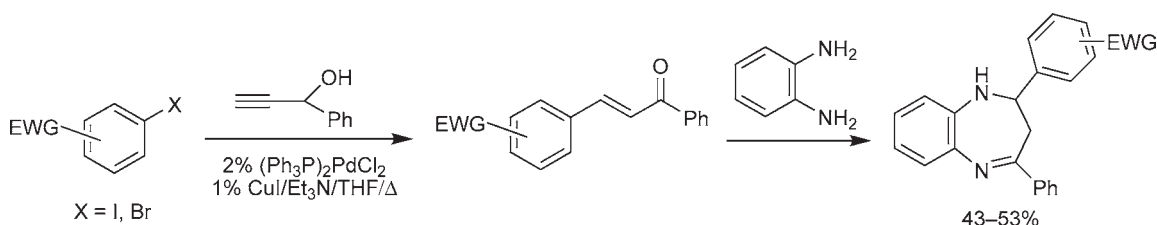
Scheme 69

13.06.9.2.4 Type *dg* (N–C–C–N + C–C–C)

The type *dg* ring disconnection remains the most common and straightforward strategy for accessing the 1,5-benzodiazepine ring system, combining readily available phenylenediamine derivatives with three-carbon components that contain reactive elements at each terminus. Typical electrophiles include acylating agents, carbonyl derivatives that afford imines, optionally as part of a reductive amination protocol, Michael acceptors and alkylating agents, and

combinations thereof. Several new variants that extend the versatility and enhance operational convenience have been described along with new three-carbon fragments and methods of activation.

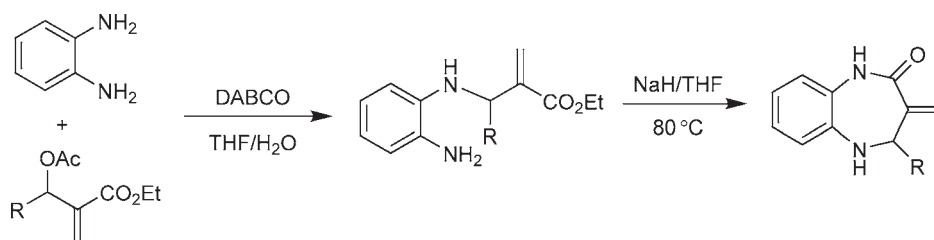
An interesting variant on the reaction of phenylenediamine with an enone relies upon generation of a chalcone *in situ* via the Pd/Cu-catalyzed Sonogashira coupling of an aryl iodide or bromide with a propargylic alcohol, a process that is accompanied by rearrangement to the chalcone (Scheme 70) <2004T9463>. The subsequent addition of phenylenediamine provided 1,5-benzodiazepine derivatives in 39–79% overall yield, constituting a convenient, one-pot synthesis that offers advantage based on the structural diversity available in the aryl halide and propargylic alcohol.



Scheme 70

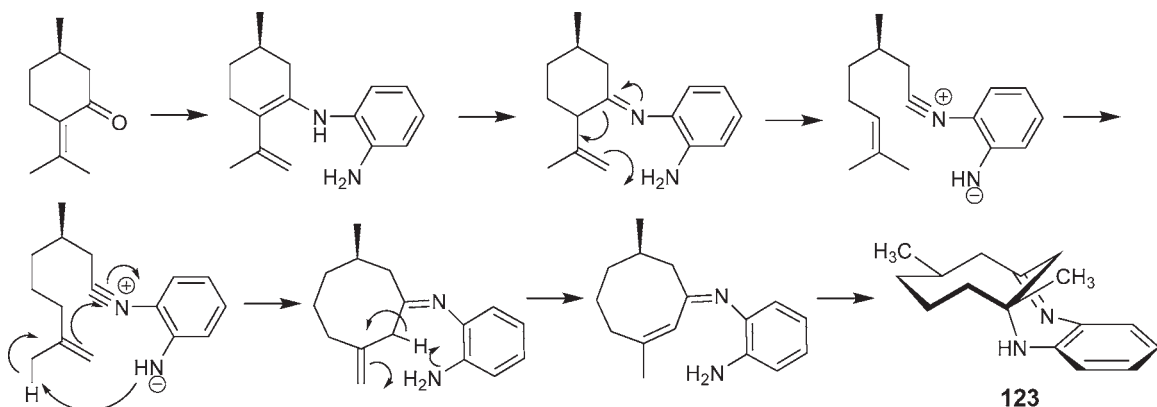
Phenylenediamine reacted with the highly reactive three-carbon electrophile (*N*-mesitylimino)propadienone in THF to afford 4-(mesitylimino)-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-2-one, as a white solid in 55% yield <2002JOC2619>.

Acetylated derivatives of Baylis–Hillman adducts derived from ethyl acrylate and aromatic and heteroaromatic aldehydes are synthetically accessible three-carbon fragments that readily react with phenylenediamine under the influence of base to provide 1,4-benzodiazepin-2-ones in good overall yield, as depicted in Scheme 71 <2006S4205>.



Scheme 71

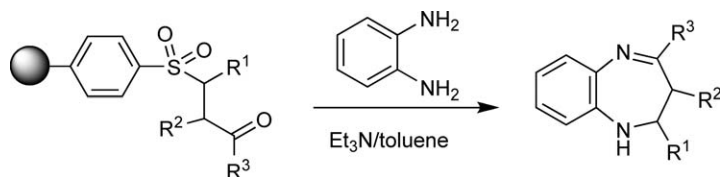
The reaction of phenylenediamine with pulegone in toluene at reflux provided a particularly interesting example of a type *dg* ring construction, producing the bicyclic 1,5-benzodiazepine **123** in 68% yield by the proposed mechanistic pathway outlined in Scheme 72 <1995T2293>. The structure of **123** was determined after extensive



Scheme 72

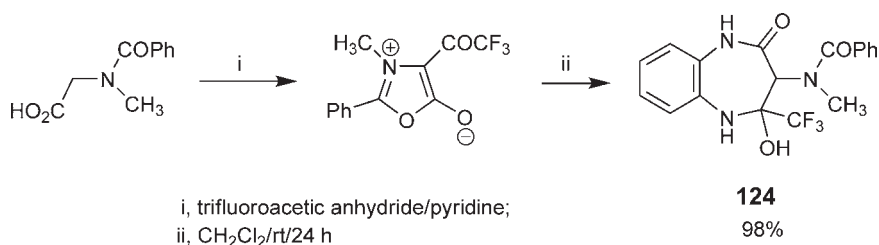
analysis of ^1H and ^{13}C NMR spectra with bond connectivities established from correlation spectroscopy (COSY) experiments and long-range coupling data. The stereo- and regioselectivity of this process is quite remarkable, with a 5-Cl- or 5-methyl-substituted phenylenediamine producing a single product in which the substituent resides *para* to the amine moiety. The pattern of substitution was established by NOE difference experiments involving irradiation of the NH while the disposition of the methyl group adjacent to the NH was determined to be equatorial based on NOE enhancement of both of the protons on the adjacent carbon atoms.

Resin-bound γ -keto sulfones, prepared in a straightforward, three-step process comprising alkylation of a resin-bound sulfinate salt, alkylation of a sulfone-supported anion with an epoxide, and Jones oxidation of the γ -hydroxy sulfone, provided a source of structurally diverse three-carbon fragments <2004JCO928>. Reaction with a phenylenediamine to give the 1,5-benzodiazepine presumably occurs via initial imine formation followed by expulsion of the resin-bound sulfone, which acts as a traceless linker (Scheme 73). Yields for this process are a modest 10–38%.



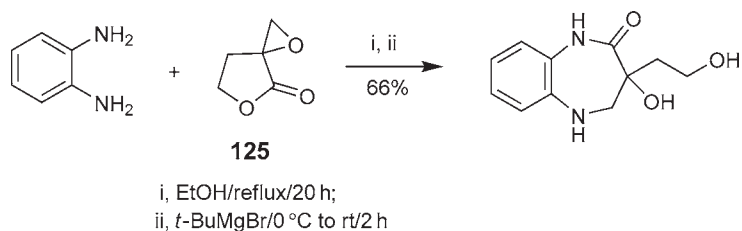
Scheme 73

Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-oloates (münchnones), readily available from glycine, condensed with phenylenediamine at 25°C in CH_2Cl_2 to afford 3-amino-1,5-benzodiazepine derivatives in excellent yield (Scheme 74) <2001H(55)1919>. An *N*-alkyl substituent in the münchnone is essential for success, since the single *N*-phenyl derivative examined gave a complex mixture. The structure of the 1,5-benzodiazepin-2-one **124** was confirmed by X-ray crystallographic analysis, revealing a boat conformation in which the CF_3 and amine moieties are in a *trans*-relationship and occupy equatorial positions.



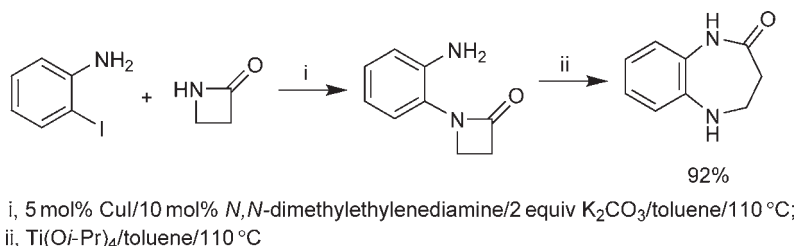
Scheme 74

Reaction of the spiroepoxy lactone **125** with phenylenediamine in EtOH at reflux provided the 1,5-benzodiazepin-2-one after amide formation, mediated by *t*-BuMgBr (Scheme 75) <2003S1209>. The scope of this approach may be limited since the single spiroepoxy lactone substituted on the epoxide ring that was studied was an ineffective partner.



Scheme 75

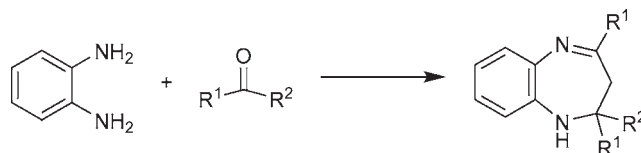
An interesting tandem, Cu-catalyzed arylation of 2-azetidinone with 2-iodoaniline followed by transamidation promoted by 50 mol% $\text{Ti}(\text{OiPr})_4$ in toluene at 110 °C provided the parent 1,5-benzodiazepin-2-one in 92% yield (**Scheme 76**) <2004JA3529>.



Scheme 76

13.06.9.2.5 Type e (C–N–C–C–N–C–C)

The condensation of a phenylenediamine with two molecules of a ketone provided ready access to 2,3-dihydro-1,5-benzodiazepines (**Scheme 77**). Continued interest in this approach has led to further optimization of catalysts and reaction conditions with a view to enhancing convenience and broadening application to a wider range of substrates. The key step in this process is the tautomerization of one of the imines of the intermediate diamine to an enamine which cyclizes via a 7-*endo-trig*-process. A sampling of the effective catalysts that have been developed, many of which are used under heterogeneous, solvent-free conditions, include MgO/POCl_3 <2001TL1127>, $\text{Yb}(\text{OTf})_3$ <2001TL3193>, YbCl_3 <2006SC457>, InBr_3 <2005S480>, $\text{Al}_2\text{O}_3/\text{P}_2\text{O}_5$ <2001H(55)1443>, $\text{Sc}(\text{OTf})_3$ <2005TL1811>, molecular iodine <2005SL1337>, poly-(4-vinylpyridine) (PVP)-supported FeCl_3 under microwave conditions <2005MI67>, $\text{Ag}_3\text{PW}_{12}\text{O}_{40}$ (a heteropoly acid that is recyclable) <2004S901>, AcOH /microwave <2002TL1755>, and superacid sulfated zirconia <2003TL4447>. An ionic liquid reaction medium promoted this reaction in the absence of an added catalyst in less than an hour at 25 °C and in 87–96% yield <2003TL1835>. In the examples described, unsymmetrical alkyl methyl ketones afforded single products resulting from reaction of the less-substituted enamine <2005TL1811, 2005SL1337> while the monosubstituted phenylenediamines afforded products in which the substituent resides *para*- to the imine moiety of the product <2005MI67, 05S480>.

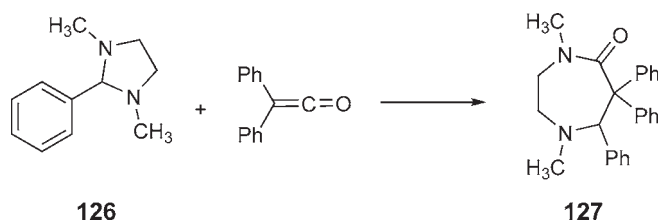


Scheme 77

13.06.10 Ring Syntheses by Transformation of Another Ring

13.06.10.1 Monocyclic

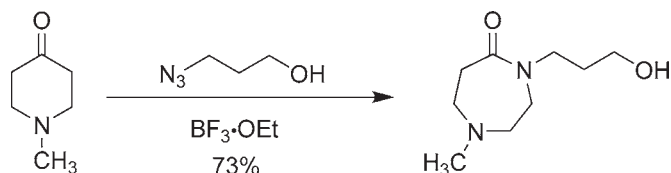
The reaction of diphenylketene with the imidazolidine **126**, catalyzed by ZnCl_2 in Et_2O , provided a single example of a reaction that delivers the 1,4-diazepin-5-one **127** in 64% yield (**Scheme 78**) <1998S653>. This reaction is



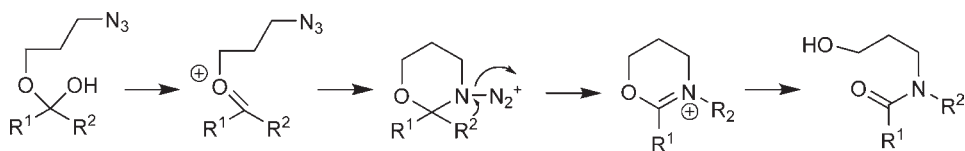
Scheme 78

thought to be initiated by an initial nucleophilic attack of an amination nitrogen atom on the ketene, followed by ring opening of the imidazolidinium and intramolecular capture of the resultant iminium by the enolate, the final step formally being a type *f* ring closure.

The Schmidt reaction of cyclic ketones with hydrazoic acid affords convenient access to ring-expanded N-unsubstituted lactams but extension of this process to alkyl azides to provide *N*-alkyl lactams is capricious in nature. A protocol that takes advantage of a temporary tethering strategy markedly improved this reaction by rendering it functionally intramolecular, and has been applied to piperidinone substrates to provide access to *N*-alkyl-1,4-diazepan-5-ones (Scheme 79) <1997T16241, 2005OL1059>. Basic and nonbasic piperidinones reacted with 3-azidopropanol under Lewis acid catalysis to form ring-expanded lactams in a process postulated to proceed through the intermediacy of a hemiacetal, the precursor to a reactive oxonium intermediate which readily reacts with the tethered azide, as summarized in Scheme 80. The products were isolated in good yield and the inclusion of substituents in the hydroxyl azide moiety provided 1,4-diazepan-5-ones that are useful scaffolds for the synthesis of peptidomimetics.

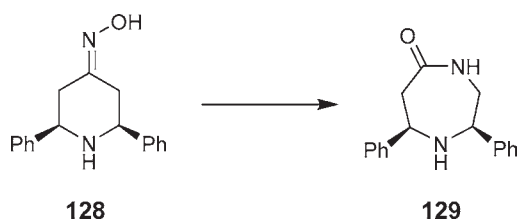


Scheme 79



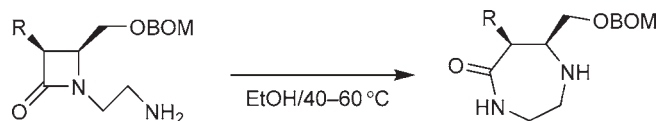
Scheme 80

Improved preparative procedures to promote the Beckmann rearrangement of a piperidinone oxime to afford ring-expanded diazepine derivatives have been described, including the use of silica-supported MoO₃, sulfonation, or the dehydrating agent 2-chloro-1,3-dimethylimidazolinium chloride <1999JOC5832, 2004TL4759, 2005MI48>. An illustrative example is the rearrangement of the oxime of 2,6-diphenylpiperidin-4-one **128** which afforded the diazepin-5-one **129** in 89% yield after exposure to silica-supported MoO₃ in EtOH at reflux for 18 h, (Scheme 81) <2004TL4759>.



Scheme 81

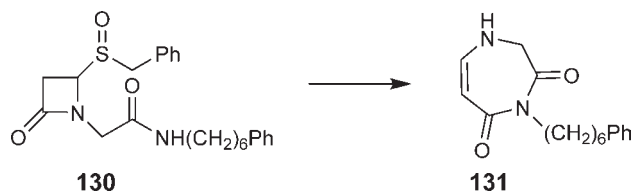
The thermally induced intramolecular transamidation of aminoethyl-substituted β -lactams, readily obtained by the Staudinger reaction of ketenes with imines, offers a useful approach to libraries of monocyclic and fused bicyclic 1,4-diazepin-5-ones (Scheme 82) <2004OL3361, 1998TL9539, 2003EJO1319, 2005T1531>. The transamidation



Scheme 82

reaction is promoted by electron-deficient ring substituents at C-3 of the β -lactam, which contribute to activation of the carbonyl moiety. For example, a C-3 phenoxy derivative in cyclized 10-fold faster than the C-3 unsubstituted β -lactam.

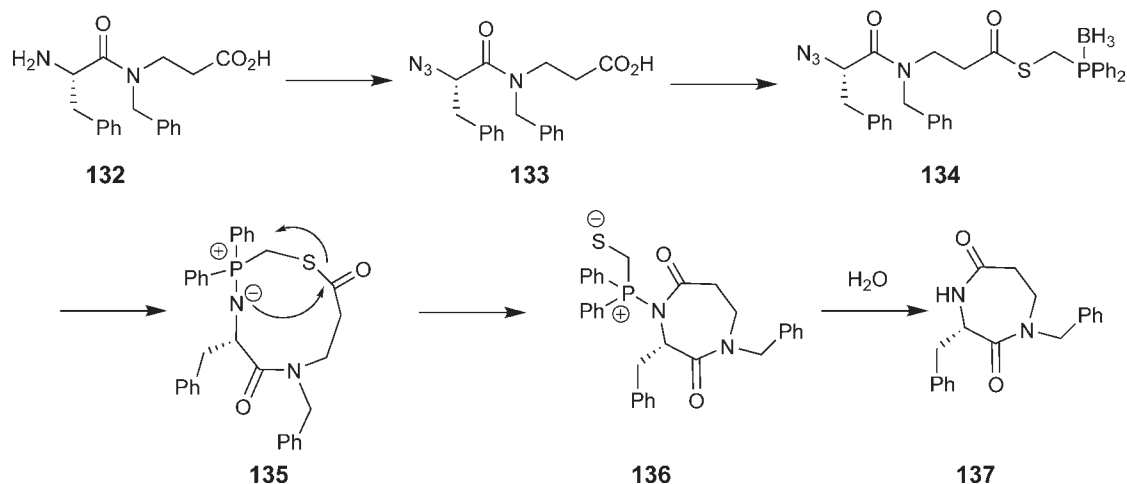
An electron-withdrawing sulfoxide substituent at C4 of a β -lactam was an even more effective activating element, since the β -lactam **130** underwent a ring-expansion reaction by simply stirring at 25 °C in a pH 9 buffer (Scheme 83) <2001SC2713>. In this reaction, the β -lactam is sufficiently activated to react with an amide as the nucleophilic species, affording the N-substituted 3,4-dihydro-1*H*-1,4-diazepin-2,7-dione **131** in 80% yield, as a white solid. The structure was confirmed by both NMR methods and single crystal X-ray analysis.



Scheme 83

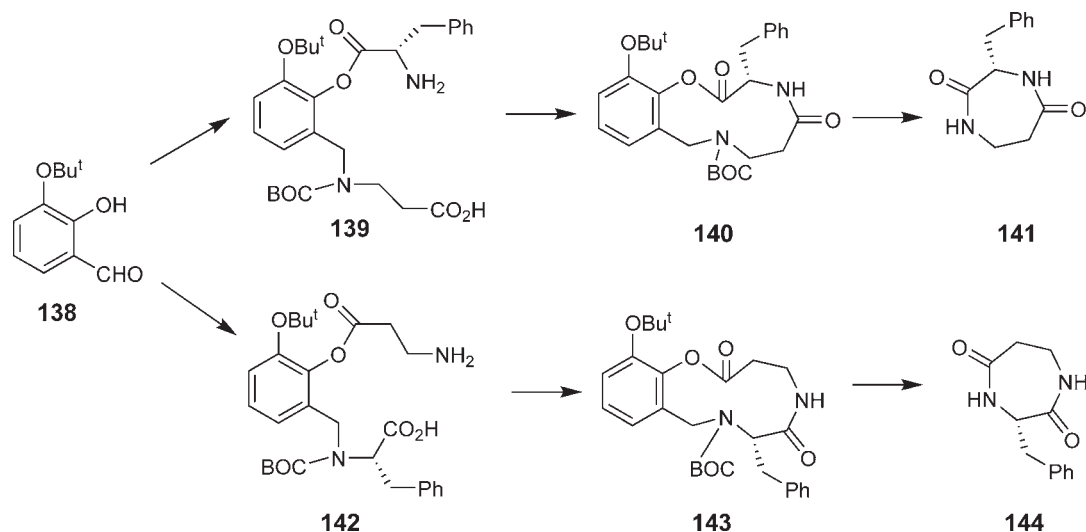
Ring expansion of 2,6-diaryl-4-azidopyridine derivatives occurred upon irradiation for 3 h in a 1:1 mixture of MeOH/dioxane containing NaOMe to afford the 3,5-diaryl-1*H*-1,4-diazepin-7(6*H*)-one in 60–70% yield after hydrolysis of the imino ether intermediate <2000HCA384>. This rearrangement was postulated to be initiated by an intramolecular reaction of the singlet nitrene, generated by extrusion of nitrogen, to give a strained azirine which reacts with methoxide to give an antiaromatic 1,4-diazepine. Tautomerization afforded the more stable imino ether isomer which hydrolyzed to the amide upon exposure to water during isolation. Unsymmetrically substituted 4-azido pyridine derivatives subjected to this process gave mixtures of the two possible diazepine-4-one isomers. Similar ring expansions have been observed under thermal conditions in the gas phase <2001JA7923>.

An innovative application of the Staudinger ligation reaction was developed to cyclize dipeptide-based ω -amino acid derivatives to medium ring lactams, including 1,4-diazepine derivatives (Scheme 84) <2003AGE4373>. In this procedure, the amine of **132** was converted to an azide **133** by diazotransfer from triflyl azide and the acid coupled with the borane adduct of diphenylphosphanylmethanethiol, essential to protect against premature reaction of the phosphane with the azide. The phosphane is released from **134** by treating with 1,4-diazabicyclo[2.2.2]octane (DABCO), promoting a Staudinger reaction with the azide. Elimination of nitrogen furnished an ylide intermediate **135** which reacted intramolecularly with the thioester to provide the 1,4-diazepin-2,5-dione **137** in 80% yield after hydrolytic decomposition of the amidophosphonium salt **136**. The versatility of this process to produce 1,4-diazepines with different substitution patterns was demonstrated with three closely related substrates, which gave cyclic products in yields ranging from 29% to 60%.



Scheme 84

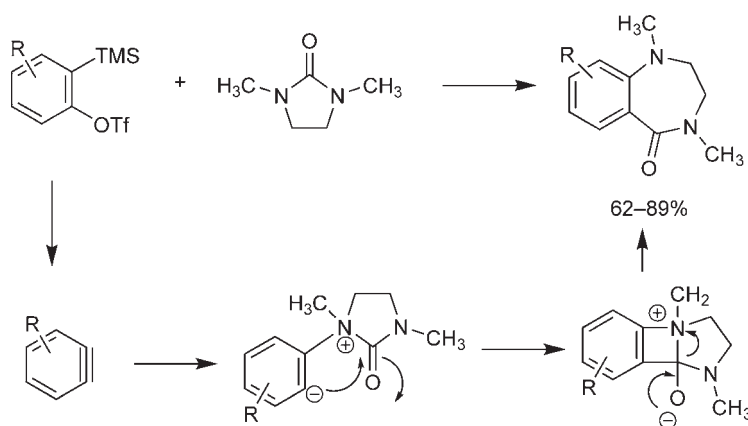
These products were also prepared with similar efficiency by a related strategy that involved a ring contraction mediated by an intramolecular acylation reaction using the benzaldehyde **138** as a templating auxiliary, as summarized in [Scheme 85](#) <2003OBC1830>. The presence of the aryl *O*-*t*-Bu substituent in **138** is essential to temper reactivity of the ester moiety during construction of the macrolactam precursors **139** and **142** but is readily removed concomitantly with the BOC moiety upon exposure to CF₃CO₂H in CH₂Cl₂. Transannular lactam formation occurred in 79% overall yield when the macrocyclic esters **140** and **143** were treated with NaHCO₃ in EtOAc. The vestige of the template moiety was removed from the newly formed amide element by a straightforward, two-step process comprising methylation of the phenols and reduction with Na in liquid NH₃ to give the 1,4-diazepines **141** and **144**.



Scheme 85

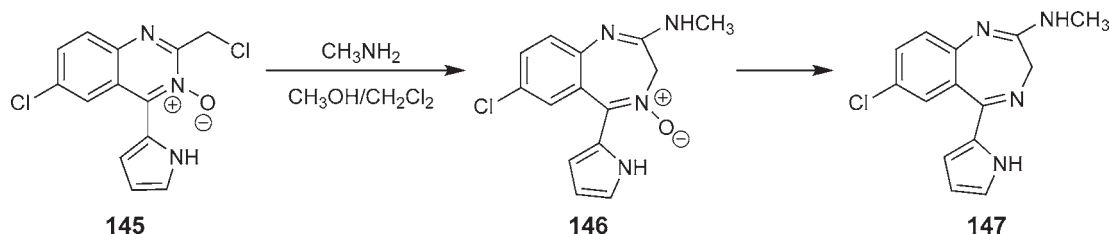
13.06.10.2 1,4-Benzodiazepines

Cyclic ureas add to *in situ*-generated benzyne to give 1,4-benzodiazepin-5-ones in good yield by the mechanism depicted in [Scheme 86](#) <2002AGE3247>. 3-Substituted benzyne react in a regioselective fashion, directing the urea nitrogen to add to the sterically less encumbered atom of the transient cyclic alkyne.



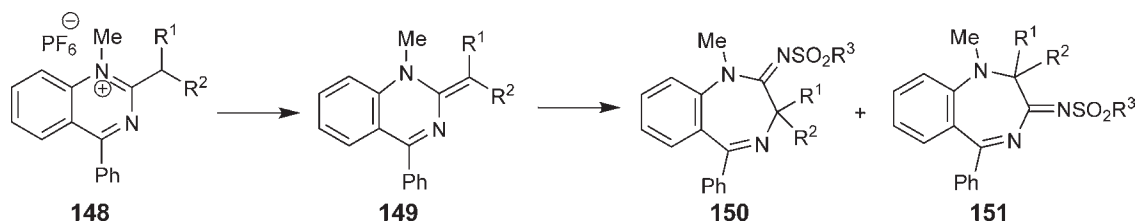
Scheme 86

Addition of methylamine to the 2-position of the quinazoline *N*-oxide **145** resulted in a ring expansion to give the 1,4-benzodiazepine *N*-oxide **146**, which was reduced with Raney nickel to provide an improved synthesis of the human immunodeficiency virus (HIV) Tat antagonist **147**, ([Scheme 87](#)) <1995BMC391>.



Scheme 87

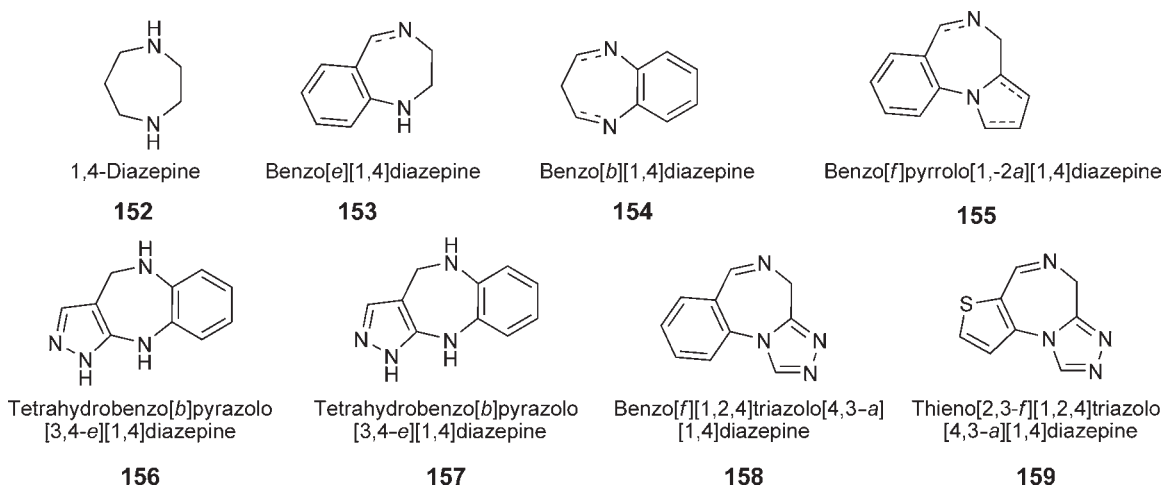
Deprotonation of the quinazolinium salt **148** with NaH or KH gave the dienamine **149** which cycloadds to methylsulfonyl azide or trifluoromethanesulfonyl azide included in the reaction to afford a mixture of two sulfonylimino-substituted benzodiazepine derivatives **150** and **151** after a ring expansion mediated by the expulsion of N₂ (Scheme 88) <2000EJO1577>.



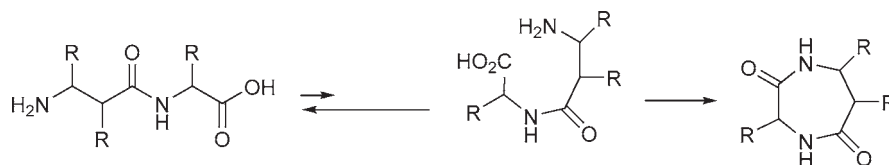
Scheme 88

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

Preparative routes to assemble substituted 1,4-benzodiazepines are well established, a direct result of the synthetic utility, the many applications in drug design, and commercial success of compounds based on this ring system. As a consequence, synthetic strategies that reflect almost all of the possible topological disconnections have been described in the literature and the continued interest in accessing uniquely functionalized molecules provides a strong impetus to develop new methodology. Access to 1,5-benzodiazepines and 1,4-diazepines fused to a wide array of heterocyclic rings is similarly mature. The importance of 1,4-diazepines is reflected in a substructure search conducted in SciFinder®, which yielded over 80 000 compounds representing more than 2000 different ring systems. The most highly represented rings systems include homopiperazine **152**, 1,4-benzodiazepine **153**, 1,5-benzodiazepine **154**, and the more complex fused ring heterocycles **155–159** that are depicted in generic form.



Derivatives of homopiperazine **152** are the most prominent examples of 1,4-diazepines, largely represented by derivatives that are unsubstituted at the ring carbon atoms and reflecting relatively nonspecific applications. However, the burgeoning interest in using this heterocycle, as a peptidomimetic scaffold, is catalyzing the synthesis and evaluation of more highly substituted homologues. To date, the majority of the synthetic approaches that have been developed to access this heterocyclic rely upon standard reactions, including amide bond formation and alkylation procedures involving the ring nitrogen atoms, while the chirality at the ring carbon atoms is most typically derived from acyclic starting materials. The synthesis of nonfused 1,4-diazepine peptidomimetic scaffolds via lactamization is often hampered by the conformational preferences of the dipeptide substrate that slow ring formation, a consequence of the amide bond being reluctant to assume the generally disfavored *s-cis*-conformation (**Scheme 89**).



Scheme 89

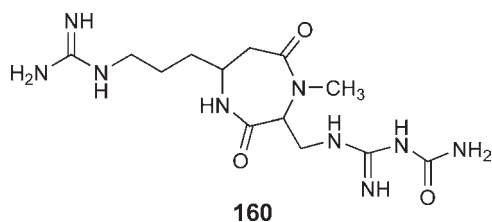
This problem is ameliorated in substrates that afford 1,4-benzodiazepines, a relatively straightforward process that has contributed to these ring systems enjoying a prominent role in medicinal chemistry and producing a wide range of biological activities. The ready availability of aniline and *ortho*-substituted aniline derivatives provides the basis for much of the synthetic methodology that has been developed toward 1,4-benzodiazepine derivatives. The advent of combinatorial strategies and the optimization of the application of procedures such as the Ugi reaction have expanded the utility of these procedures, providing access to molecules incorporating considerably greater structural diversity.

The development of synthetic approaches to 1,4-benzodiazepines that improve on precedented bond disconnections or allow completely new ring-closure topology has grown in concert with the significant expansion in the application of transition metal catalysis to mediate C–N and C–C bond formation. These processes typically proceed under conditions that tolerate a wide range of functionality and have facilitated entry into novel functionalized derivatives by expanding the pool of synthons. Moreover, the advent of improved methods for ring functionalization, including the enantioselective introduction of substituents at C-3 of 1,4-benzodiazepin-2-ones through enolate alkylation or aldol chemistry, has allowed access to a wider range of substitution patterns from preformed diazepine ring systems.

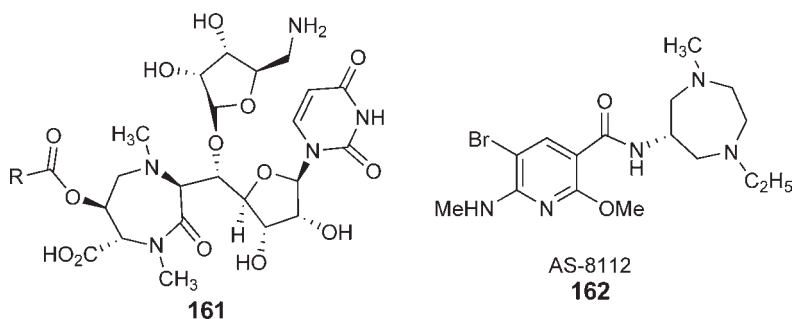
The phenylenediamine moiety embedded in 1,5-benzodiazepines provides a logical synthetic basis for ring formation in which the additional three carbon atoms are installed using 1,3-dicarbonyl or α,β -unsaturated carbonyl synthons. While these synthons are readily made using standard aldol or Claisen condensation chemistry, they can be formed in the presence of phenylenediamine derivatives that allow concomitant diazepine ring formation in a three-component reaction process. The synthesis and elaboration of 1,5-benzodiazepine derivatives have also benefited from the application of transition metal catalysis, processes that most commonly rely upon the formation of the N–C(aryl) bond via nucleophilic substitution. In contrast to developments with the 1,4-benzodiazepine ring system, research into the asymmetric synthesis of 1,5-benzodiazepine derivatives has been limited, possibly a consequence of the tautomeric lability of partially unsaturated ring systems that may lead to racemization of singly substituted chiral carbon atoms.

13.06.12 Important Compounds and Applications

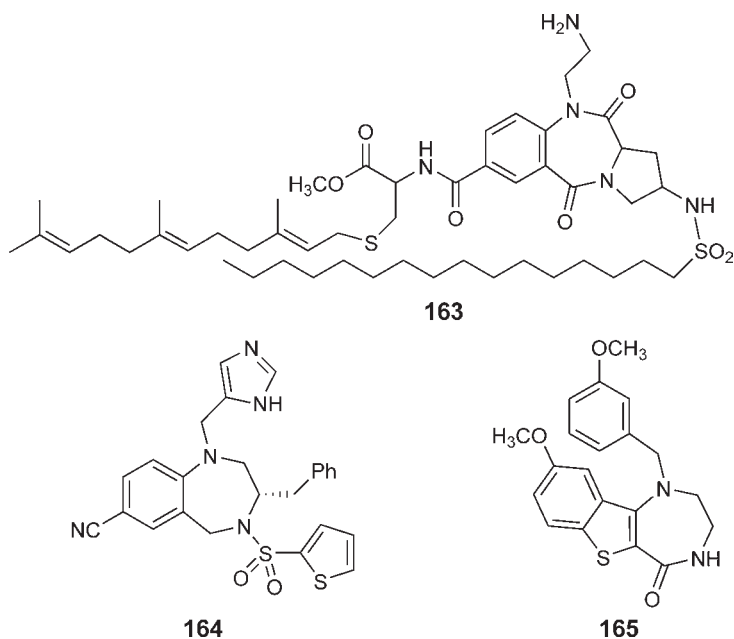
Compounds derived from the 1,4-benzodiazepine heterocycle are a prominent class of CNS drugs that demonstrate a range of clinically important properties and many are well-established commercial successes. As a consequence, fused ring 1,4-diazepines have dominated studies with this class of heterocycles in the several decades since the original discovery. However, the 1,4-diazepine ring system demonstrates considerable versatility as a platform for drug design and a wide range of biological activities have been described for structurally diverse members of the class. Monocyclic 1,4-diazepines are emerging as a medicinally useful chemotype that occurs naturally. For example, TAN-1057A-D **160** is a member of a series of 1,4-diazepin-2,5-dione-containing dipeptides isolated from *Flexibacter* bacteria that demonstrate antibiotic activity toward methicillin-resistant *Staphylococcus aureus* <1997JA11777>. This diazepine core has also been used as a scaffold in the design of inhibitors of lymphocyte function-associated antigen-1 (LFA-1), a leukocyte adhesion receptor involved in inflammation and immune responses <2005BML1217>.



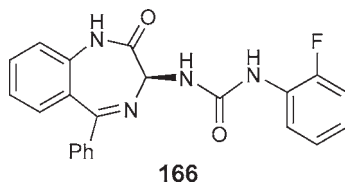
The caprazamycins **161** are a family of liponucleoside antibiotics isolated from a *Streptomyces* strain that contain a 1,4-diazepin-2-one ring system [<2005JAN327, 2005AGE1854>](#). The *N,N*-dialkylated-1,4-diazepane, DAT-582 **91**, is a potent and selective serotonin 5-HT₃ antagonist with antiemetic activity [<1995CPB1912>](#), while AS-8112 **162** combines potent 5-HT₃ and dopamine D₂ antagonism in a single molecule that broadens the antiemetic spectrum [<2003JME702, 2001BJP253>](#).



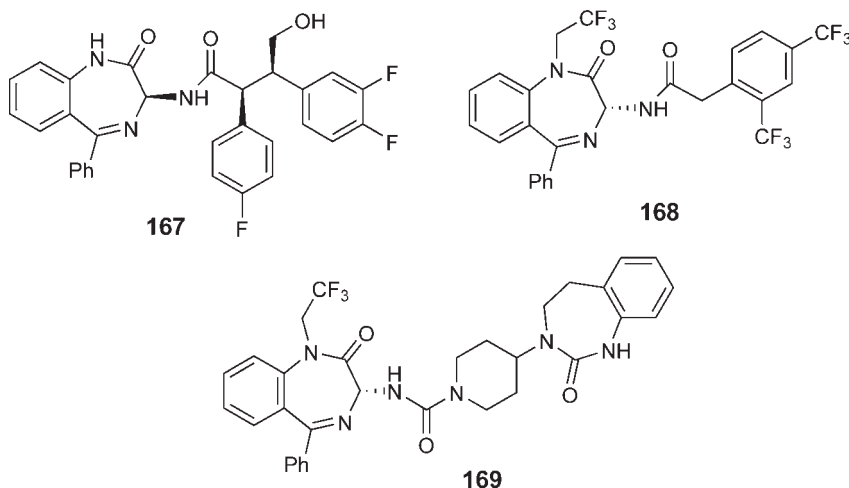
The 1,4-benzodiazepin-2,5-dione **163** is a potent inhibitor of acyl protein thioesterase-1 (APT-1), an enzyme that palmitoylates a range of proteins involved in biological signaling [<2005AGE4975>](#). The design of this compound anticipated peptidomimetic activity based on prior studies that established the value of the parent heterocycle in this role. The tetrahydro-1,4-benzodiazepine **164**, designated as BMS-214662, potently inhibits farnesyltransferase and demonstrates antitumor activity *in vitro* and *in vivo* [<2000JME3587>](#). The benzothieno-1,4-diazepin-5-one **165** is an exquisitely potent inhibitor of herpes simplex virus (HSV) replication in cell culture (EC₅₀ = 400 pM), that appears to interfere with a cellular process involved in the expression of viral immediate early genes [<2002BML2981>](#).



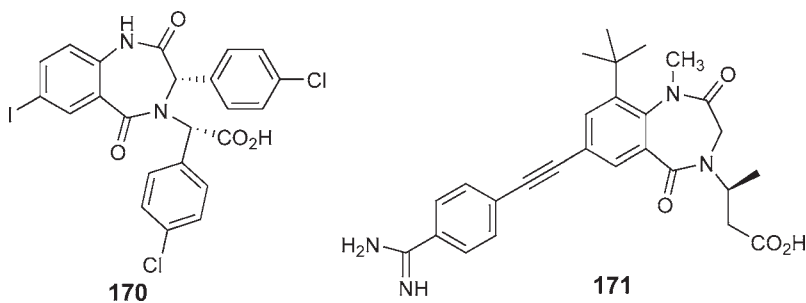
Substituted derivatives of 3-amino-5-phenyl-1,4-benzodiazepin-2-one continue to be a rich source of compounds that display a diverse range of biological properties. The 2-fluorophenylurea **166** is an inhibitor of respiratory syncytial virus (RSV) that appears to act by inhibiting the nucleocapsid (N) protein <2006JME2311, 2007JME1685>. This compound is the first orally active inhibitor of RSV to be advanced into clinical studies.

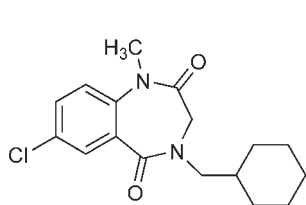


The 2,3-diphenyl-4-hydroxybutyramide **167** is an extremely potent inhibitor of the mammalian aspartyl protease γ -secretase, ($IC_{50} = 60$ pM), that was profiled as an inhibitor of amyloid precursor protein processing with potential utility in the prevention and treatment of Alzheimer's disease <2003JME2275>. The *N*-1-alkylated-3-amido-1,4-benzodiazepin-2-one **168** is a selective blocker of the cardiac slowly activating delayed rectifier potassium current (I_{Ks}), of sufficient interest as a potential class III antiarrhythmic agent that a process suitable for providing clinical grade material was developed <1997JME3865, 1999T909>. Extending the amino substituent to the structurally more complex moiety found in the urea **169** provides a benzodiazepine derivative that is representative of a well-explored series of calcitonin gene-related peptide (CGRP) antagonists <2006BML2595, 2006BML5052>.

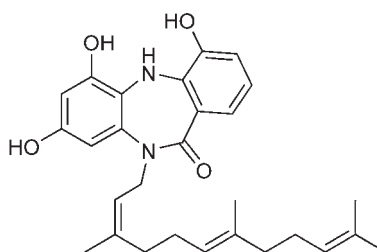


The carboxylic acid **170** is a potent inhibitor of the oncogenic HDM2 protein binding to the tumor suppressor p53 ($IC_{50} = 220$ nM) <2005BML1857, 2005JME909>, while the C-9 *tert*-butyl moiety of the 1,4-benzodiazepin-2,5-dione **171** stabilizes an active atropoisomer recognized by the blood platelet glycoprotein IIb/IIIa receptor <1997JME717>. The 1,4-benzodiazepin-2,5-dione **172** is one of a series of compounds that demonstrate potent antiparasitic activity *in vitro* toward a clinically derived strain of *Leishmania donovani* <2007BML624>. The antibiotic diazepinomicin **173** is a rare example of a 1,5-benzodiazepine-based natural product that was isolated from a marine actinomycete <2004JNP1431>. A 1,5-benzodiazepin-2-one core was used to design potent inhibitors of the cysteine protease caspase-1, also known as interleukin-1 β converting enzyme <2002BML1225>.





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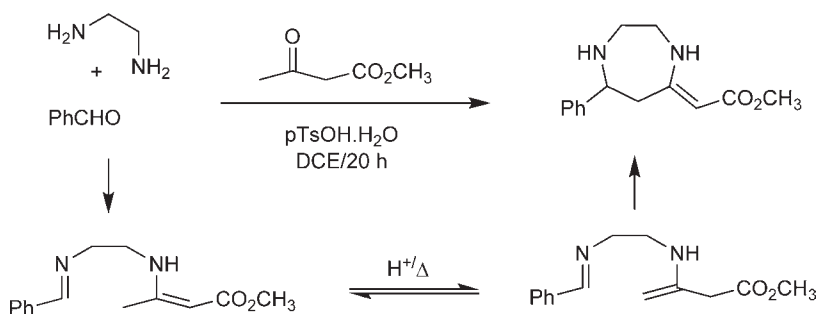


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13.06.13 Further Developments

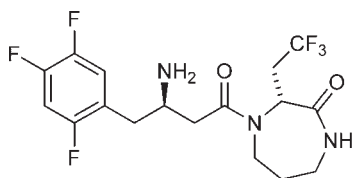
13.06.13.1 Type of Ring Closure

The acid catalyzed reaction of ethylene diamine, benzaldehyde, and methyl acetoacetate in dichloroethane (DCE) provided (*Z*)-methyl 2-(7-phenyl-1,4-diazepan-5-ylidene)acetate in an optimized 59% yield, a reaction thought to proceed via a 7-endo-trig ring closure of an intermediate enamine. The ring closure may be promoted by an intramolecular hydrogen bond with the ester moiety that is preserved in the product and stabilizes the exocyclic olefin geometry [2007OL1687](#). In the absence of benzaldehyde and an acid catalyst, 1,4-diazepin-5-ones are formed in a process enhanced by microwave irradiation [2007TL2583](#).

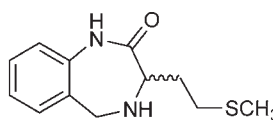


13.06.13.2 Important Compounds and Applications

Merck have described 1,4-diazepine derivatives as potent dipeptidyl peptidase IV inhibitors for the treatment of diabetes with **X** studied extensively preclinically as a potential back-up compound to sitagliptan, marketed by Merck in 2006 as Januvia™ [2007BML49](#), [2007BML1903](#).



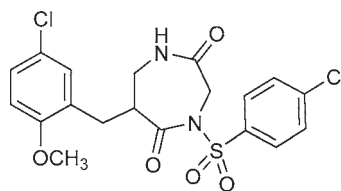
X



Y

Benzodiazepine-2-one **Y** demonstrates anti-ischemic activity *in vitro* protecting neuronal cell from apoptosis and necrosis, with the (*S*)-isomer more active than the (*R*)-isomer [2007BML1326](#).

The racemic 1,4-diazepane-2,5-dione **Z** is a potent inhibitor of the mast cell serine protease chymase, $IC_{50} = 34$ nM with all of the activity residing in the (*S*)-enantiomer [2007BML3432](#), [2007BML3435](#).



Z

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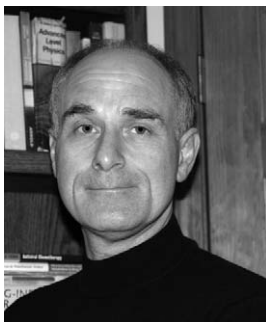
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Biographical Sketch



Nicholas A. Meanwell is currently executive director of chemistry at the Bristol-Myers Squibb Pharmaceutical Research Institute in Wallingford, Connecticut. He received his Ph.D. degree in 1979 from the University of Sheffield for studies conducted under the supervision of Dr. D. Neville Jones that focused on the application of alkenyl sulfoxides as synthetic precursors of prostaglandin analogues. A postdoctoral fellowship (1979–82) with Professor Carl R. Johnson at Wayne State University was devoted to the development of new synthetic methodology based on sulfur chemistry and its application to total synthesis. In 1982, he joined Bristol-Myers Squibb where he designed and synthesized inhibitors of blood platelet aggregation as part of the cardiovascular therapeutic focus before contributing to the identification and development of neuroprotective agents. The large conductance, Ca^{2+} -dependent potassium channel opener Maxipost™ that was advanced into Phase III clinical trials, emerged from those studies. Since 1994, he has been responsible for a team of chemists designing and synthesizing antiviral agents directed toward new developing therapeutic options for the treatment of HIV, HCV, RSV, and influenza.



Michael A. Walker received a B.A. degree in chemistry from the University of Pennsylvania and an M.S. degree in organic chemistry from the University of Florida, where he worked on the total synthesis of forskolin under the supervision of Dr. Merle A. Battiste. His graduate studies were completed at the University of California at Berkeley, where he received a Ph.D. under the direction of Dr. Clayton Heathcock for investigations into novel asymmetric aldol methodology and the total synthesis of the natural product mirabazole. In 1992, he joined Bristol-Myers Squibb as a member of the medicinal chemistry team led by Dr. Raymond Firestone, Distinguished Research Fellow, which developed the antibody-targeted antitumor agent BR96. He is currently a principal scientist at Bristol-Myers Squibb and actively engaged in the discovery of antiviral agents for the potential treatment of HIV.

13.07

1,2-Oxazepines and 1,2-Thiazepines

J. B. Bremner

University of Wollongong, Wollongong, NSW, Australia

S. Samosorn

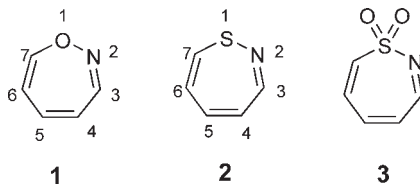
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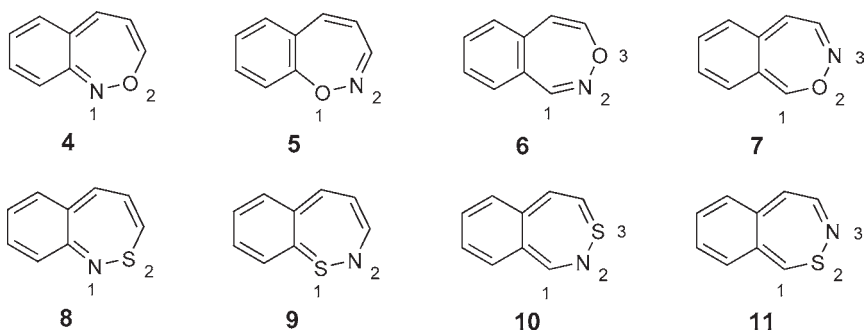
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13.07.1 Introduction

There has been a modest interest in the chemistry of these systems over the past decade. In this chapter, the 1,2-oxazepines and 1,2-thiazepines are grouped together due to their sparseness in the literature. There is a general review of these systems that appeared in CHEC-II(1996) <1996CHEC-II(9)183>. The parent systems **1** and **2**, respectively, are shown below; however, most of the known compounds are based on their reduced derivatives. Oxidized forms of the 1,2-thiazepine system are also treated, in particular derivatives of 1,2-thiazepine 1,1-dioxide **3**.



Benz-fused analogues are also covered in this chapter. The possible benz-fused parent systems are 2,1-benzothiazepine **4**, 1,2-benzoxazepine **5**, 3,2-benzoxazepine **6**, 2,3-benzoxazepine **7**, 2,1-benzothiazepine **8**, 1,2-benzothiazepine **9**, 3,2-benzothiazepine **10**, and 2,3-benzothiazepine **11**; derivatives of some of these systems are included. A major reference series has reviewed seven-membered heteroarenes with two or more heteroatoms <1997HOU(E9d)299>, while the syntheses of benzoxazepines, including 2,3-, 3,2-, and 2,1-skeletons, have also been reviewed <1997MI1>.

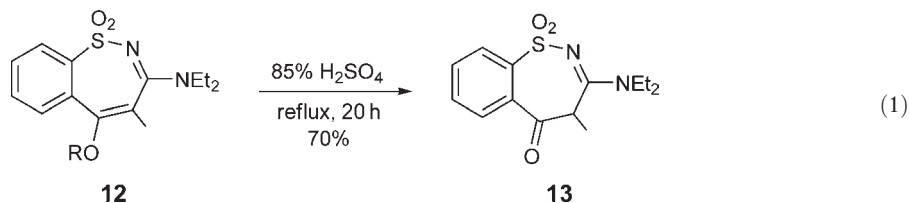


There appears to have been no further reports dealing with experimental structural methods or thermodynamic aspects of these systems.

13.07.2 Reactivity

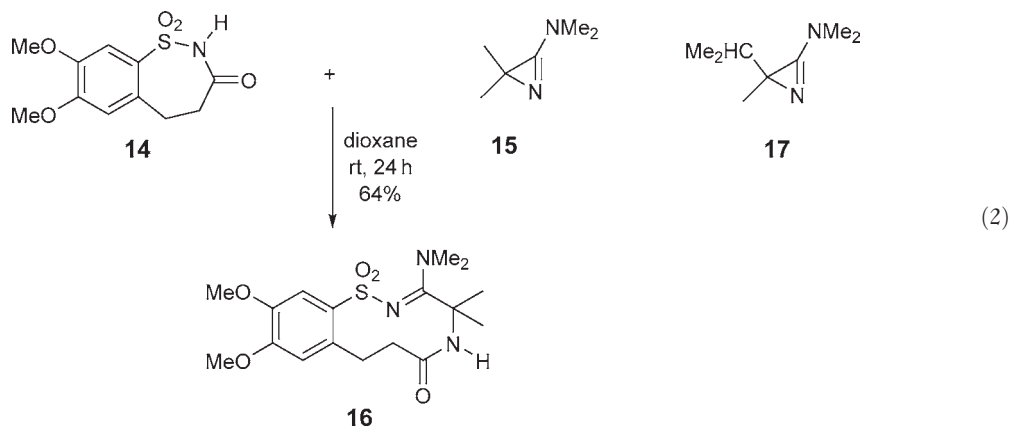
13.07.2.1 Reactivity of Fully Conjugated Rings

Very little further work has been reported in this area. Heating of the 1,2-benzothiazepine 1,1-dioxides **12** in an aqueous sulfuric acid solution gave ketone **13** in good yield (Equation 1) <1996T3339>.



13.07.2.2 Reactivity of Nonconjugated Rings

An interesting ring expansion of the 1,2-benzothiazepine derivative **14** was observed when it was treated with azirine **15** in dioxane to give the benz-fused 10-membered heterocyclic derivative **16** in moderate yield (Equation 2) <1996HCA1121>. With the more sterically hindered azirine **17**, no ring expansion occurred.



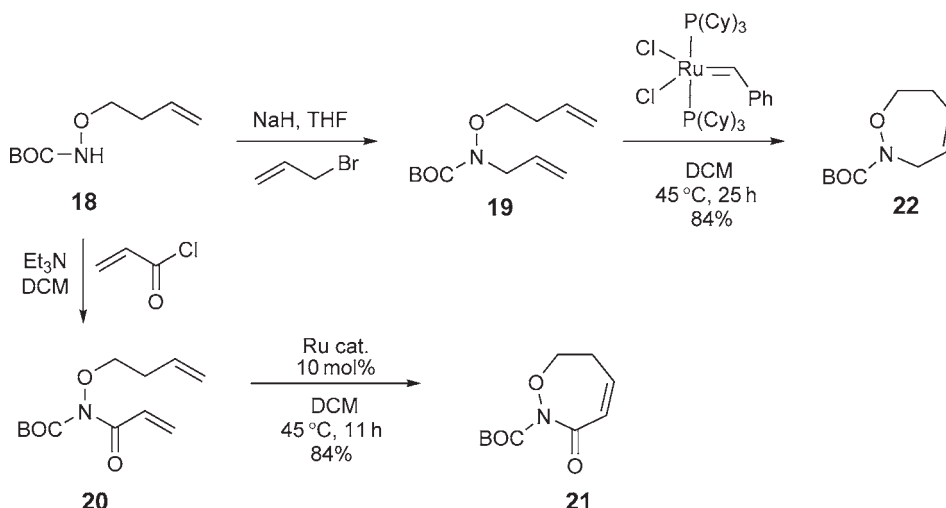
13.07.3 Ring Synthesis by Ring Construction

For the classification of these ring constructions, the same system is used for the non-benz-fused and benz-fused derivatives with the type designation being based on the seven-membered ring skeleton itself.

13.07.3.1 1,2-Oxazepines and Benz-Fused Derivatives

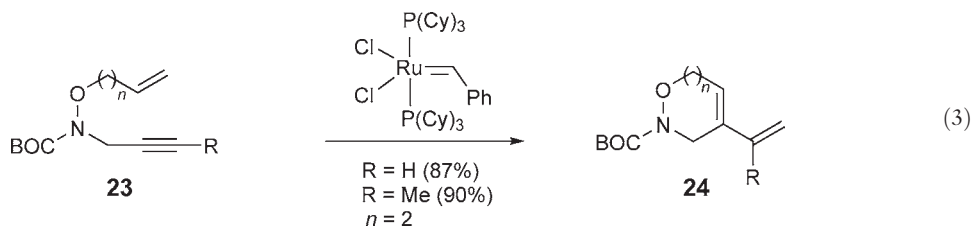
13.07.3.1.1 Type d (C–C–N–O–C–C–C)

Ring-closing metathesis methodology has been used in the synthesis of the 1,2-oxazepine derivatives **21** and **22**. These derivatives were synthesized from the respective diene precursors **20** and **19**, which were derived from **18** by N-acylation or N-alkylation respectively (**Scheme 1**) <2003SL1043>.



Scheme 1

In a similar metathesis process, the 1,2-oxazepines **24** were prepared from *N*-alkynyl analogues **23** (Equation 3) <2003SL2017>. A range of Diels–Alder reactions based on the dienophilic moiety in **24** have also been reported <2003SL2017> to give ring-fused 1,2-oxazepine systems.



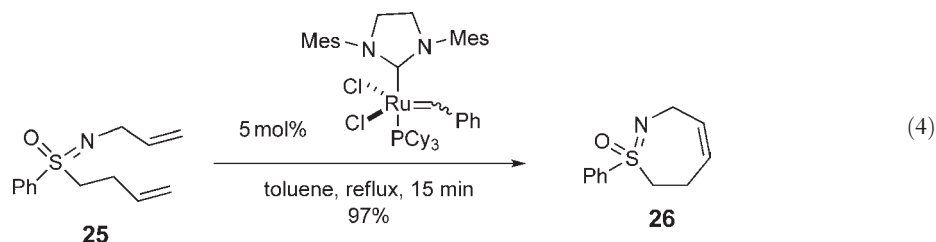
13.07.3.1.2 Type g (O–N–C–C–C–C–C)

Acid-catalyzed seven-membered ring formation to afford the first stable *N*-oxo-2,1-benzoxazepinium ions has been reported, based on reaction of 1-chloro-2-(2-nitrobenzyl)cyclopropane with H_2SO_4 and FSO_3H ; nitro group trapping of an intermediate carbocation was proposed in this process <1996ZOR852>.

13.07.3.2 1,2-Thiazepines and Benz-Fused Derivatives

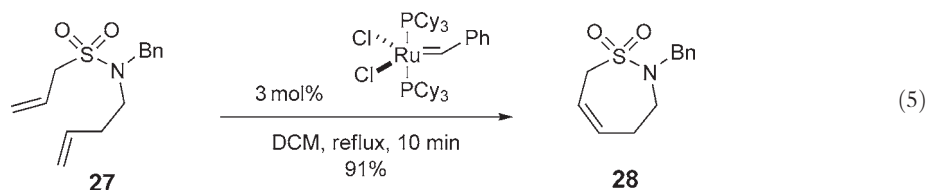
13.07.3.2.1 Type d (C–C–N–S–C–C–C)

Ring-closing metathesis involving a sulfoximine **25** was utilized to access the novel 1,3-thiazepine **26**, which incorporates a sulfoximine moiety (Equation 4) <2005S1421>; the more reactive Grubbs II ruthenium catalyst was utilized.



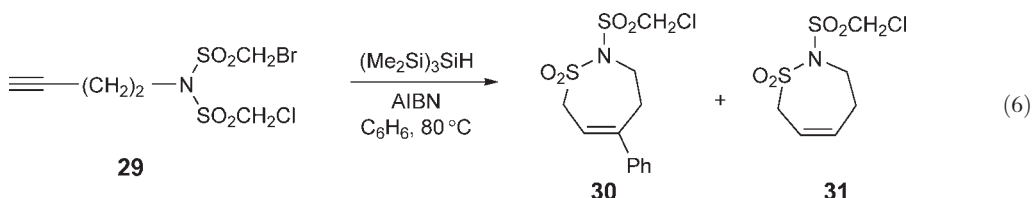
13.07.3.2.2 Type e (C–C–S–N–C–C–C)

The ring-closing metathesis reaction has also been applied to the formation of a seven-membered cyclic sulfonamide [<1999TL4761>](#). Thus, heating **27** at reflux in dichloromethane (DCM) with ruthenium catalysis (Grubbs I catalyst) gave **28** in high yield (Equation 5).



13.07.3.2.3 Type f (C–S–N–C–C–C–C)

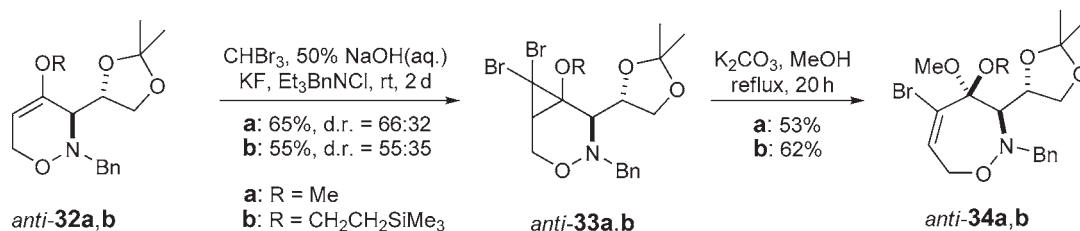
An intramolecular free radical addition was used to prepare the 1,2-thiazepine derivatives **30** and **31** from **29** (Equation 6). A further elegant intramolecular radical cyclization was then used to convert **30** to a new aza-bicyclic system with a bridgehead nitrogen [<2001JOC3564>](#).



13.07.4 Ring Synthesis by Ring Transformation

13.07.4.1 1,2-Oxazepines and Benz-Fused Derivatives

Ring expansion of the enantiopure 1,2-oxazines **32a** and **32b** involving dibromocarbene cycloaddition, followed by methanolysis of the intermediates **33a** and **33b**, provided a convenient route to the 1,2-oxazepines **34a** and **34b** in moderate yields (Scheme 2). The vinylic bromide was then used as a site for the introduction of other functionality via palladium-catalyzed C–C bond-forming reactions [<2005SL2376>](#).

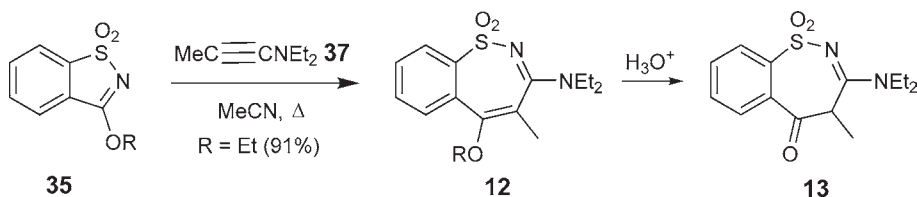


Scheme 2

The Meisenheimer rearrangement of substituted tetrahydroisoquinoline *N*-oxides <1996CHEC-II(9)183> has been further exploited as a convenient approach for the synthesis of 2,3-benzoxazepine derivatives <1997MI13>.

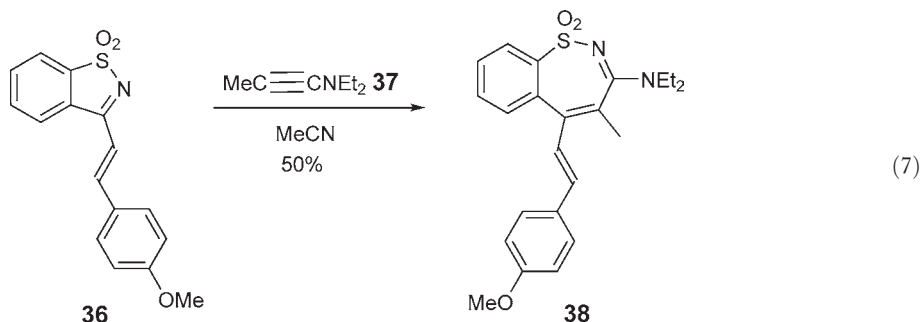
13.07.4.2 1,2-Thiazepines and Benz-Fused Derivatives

Ethers of the 1,2-benzisothiazole 1,1-dioxides (**35**: R = Et, Me₃Si) have been shown to form 1,2-benzothiazepines **12** (R = Et, Me₃Si) when treated with 1-diethylamino-1-propyne **37** <1996T3339>. These ethers **12** may be hydrolyzed to the ketone **13** (see also Section 13.07.2.1), which in the solid state is in equilibrium with the enol **12** (R = H) on the basis of infrared (IR) evidence (Scheme 3). In solution (CDCl₃), only the keto form **13** was detectable by ¹H nuclear magnetic resonance (NMR).

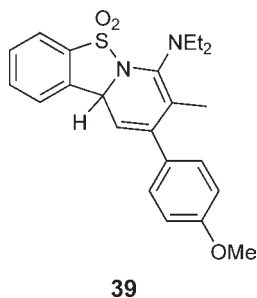


Scheme 3

An analogous ring expansion of the 1,2-benzisothiazole dioxide **36** was also observed on reaction with 1-diethylamino-1-propyne **37** in MeCN to give the seven-membered ring derivative **38** in moderate yield (Equation 7) [\[1996T3339\]](#).



In anhydrous diethyl ether, as solvent, the reaction took a different pathway to afford the pyrido-fused derivative **39** in 37% yield.



The solvent effects on the reaction outcome from **36** with **37** may be rationalized in terms of 1,2-addition to give an initial dipolar intermediate in the polar solvent, MeCN, followed by fused azetine formation and electrocyclic ring opening to afford **38**. In the less polar solvent, Et₂O, 1,4-cycloaddition may proceed without any dipolar intermediate,

followed by 1,3-hydrogen migration to give **39**. Such an initial 1,4-cycloaddition might well occur with an electron-rich dienophile, like **37**, but with electron-deficient dienophiles, this cycloaddition does not proceed <1996T3339>.

13.07.5 Synthetic Comparisons

Compared with azepine derivatives, considerable scope still exists for innovative exploration of ring-closing meta-thesis methodology to access multisubstituted 1,2-oxazepine and 1,3-thiazepine derivatives and benz-fused analogues. Also, the full synthetic potential of the Meisenheimer rearrangement to afford various 1,2-oxazepine derivatives with different types of functionality present is still to be realized.

13.07.6 Important Compounds and Applications

The effects on behavior of two antidepressants with contrary molecular actions, that is, tianeptine (a serotonin reuptake enhancer) and fluoxetine (a serotonin reuptake blocker) were examined. As well as their effects on serotonin reuptake, other mechanisms were also involved in their antidepressant action <2000AF5, 2001PHC340>.

A review on tianeptine, a dibenzo[*c,f*][1,2]thiazepine derivative, has also appeared <2001MI231>. While a number of bis-fused 1,2-thiazepine systems are known, they were outside the scope of this chapter.

13.07.7 Further Developments

A potentially powerful synthetic sequence to access substituted 1,2-benzothiazepine 1,1-dioxides has been described incorporating a Type e (C–C–S–N–C–C–C) ring synthesis by ring construction approach. This sequence was based on an initial aza Baylis–Hillman reaction (with an aromatic sulfonamide, an aromatic aldehyde, methyl acrylate, Ti(*i*-PrO)₄, 2-hydroxyquinuclidine, molecular sieves, and *i*-PrOH) to afford *ortho*-bromobenzenesulfonamide derivatives. These sulfonamides then underwent an intramolecular Heck reaction (Pd(OAc)₂, P(*o*-tolyl)₃, NEt₃, THF, 160 °C, microwave heating, 1 h) in a separate second step to give the benz-fused seven-membered rings in moderate yields <2006TL8591>. This reaction sequence has considerable scope for the controlled introduction of a variety of groups in this ring system.

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Biographical Sketch



Prof. John Bremner is Professor of Organic Chemistry in the Department of Chemistry, University of Wollongong, Australia. He is a graduate of the University of Western Australia and the Australian National University. After being a Research Fellow at Harvard University, he returned to Australia in 1968 to an academic appointment in Chemistry at the University of Tasmania, and then moved in 1991 to the University of Wollongong. At Wollongong he was Head of Department for seven years and then was Director of the newly formed Institute for Biomolecular Science from 2001–2004. His research interests cover heterocyclic chemistry, natural products, and medicinal chemistry, including more recently the design, synthesis and evaluation of new types of anti-infective agents for the potential treatment of bacterial disease and malaria.



Dr Siritron Samosorn received a Bachelors degree in Chemistry in 1990 and a Masters degree in Applied Chemistry in 1994, both from Ramkhamhaeng University, Thailand, under the supervision of Prof. Apichart Suksamrarn. In 1994, she joined the Department of Chemistry at Huachewchalermprakiet University in Thailand as a lecturer, and later moved to a staff position at Srinakharinwirot University (SWU) in 1997. She obtained her PhD from the University of Wollongong in 2005, working with Prof. John Bremner on a new approach to heterocyclic dual-action antibacterial agents to combat the problem of antibiotic resistance by drug efflux. Her research and teaching areas include the related areas of Natural Product Chemistry and Drug Design and Development, and she is a member of 'The Center for the Development of Value-Added Natural Products' at SWU.

13.08

1,3-Oxazepines and 1,3-Thiazepines

J. B. Bremner

University of Wollongong, Wollongong, NSW, Australia

S. Samosorn

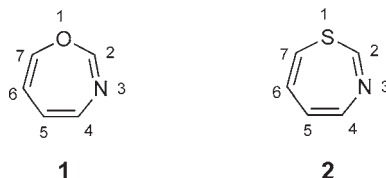
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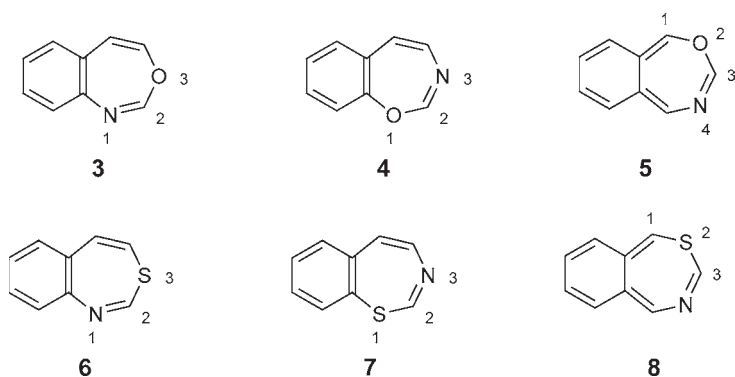
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13.08.1 Introduction

There has been relatively restrained interest in the chemistry of these systems since the publication of CHEC-II(1996). In this chapter, the 1,3-oxazepines and 1,3-thiazepines are grouped together; also included is a treatment of some of their benz-fused analogues. A general review of these systems appeared in CHEC-II(1996) <1996CHEC-II(9)199>. The parent systems considered 1,3-oxazepine **1** and 1,3-thiazepine **2** are shown below. Much of the chemistry has been focused on the 1,3-oxazepine system and its benz-fused derivatives; whereas, the 1,3-thiazepines and its derivatives continue to be less well developed. A major reference series has reviewed seven-membered hetarenes with two or more heteroatoms <2004SOS(17)929>, while the synthesis of benzoxazepines, including 3,1-, 1,3-, and 2,4-skeletons, has been reviewed earlier <1997MI1>.



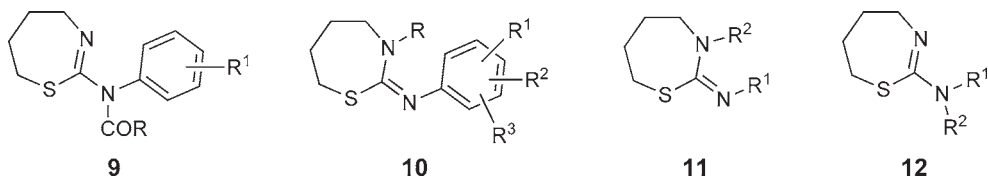
There are three possible benz-fused skeletons each with a 1,3-relationship of the N and O atoms or N and S atoms. These include the 3,1-benzoxazepine **3**, 1,3-benzoxazepine **4**, 2,4-benzoxazepine **5**, 3,1-benzothiazepine **6**, 1,3-benzothiazepine **7**, and 2,4-benzothiazepine **8**.



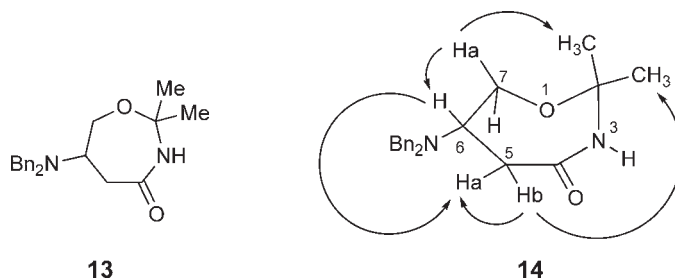
13.08.2 Experimental Structural Methods

13.08.2.1 Spectroscopic Data

A study of the ultraviolet absorption spectra of a series of *N*-acyl-*N*-aryl-2-amino-4,5,6,7-tetrahydro-1,3-thiazepines **9** and *N*-aryl-2-iminohexahydro-1,3-thiazepines **10** has been reported [<2003CHE368>](#). Quantum chemical calculations on the energies and bond orders were also undertaken and a rationalization provided for the weaker basicity of the ring nitrogen in the former series in terms of the electron acceptor properties of the amide carbonyl group. The ^{13}C NMR (NMR – nuclear magnetic resonance) spectra of 2-phenyl- and 2-benzyliminothetrahydro-1,3-thiazepines **11**, and the aminotetrahydrothiazepines **12**, together with their alkyl, acyl, carbamoyl, and thiocarbamoyl derivatives, have been studied. Substituents in the 2- and 3-positions of the thiazepine ring mainly influenced the chemical shifts for the C-4 carbon in the heterocyclic nucleus [<2002CHE612>](#).



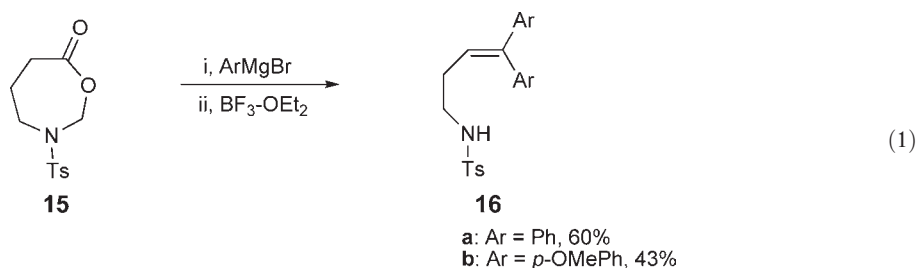
The preferred conformation of the 1,3-oxazepinone derivative **13** was shown to be the twist-boat conformer **14** on the basis of NOE studies and the coupling constants for couplings involving H6. A nuclear Overhauser effect (NOE) was only seen between H6 and H5a and not between H6 and H5b; other NOEs are indicated on **14** [<1999H\(51\)365>](#).



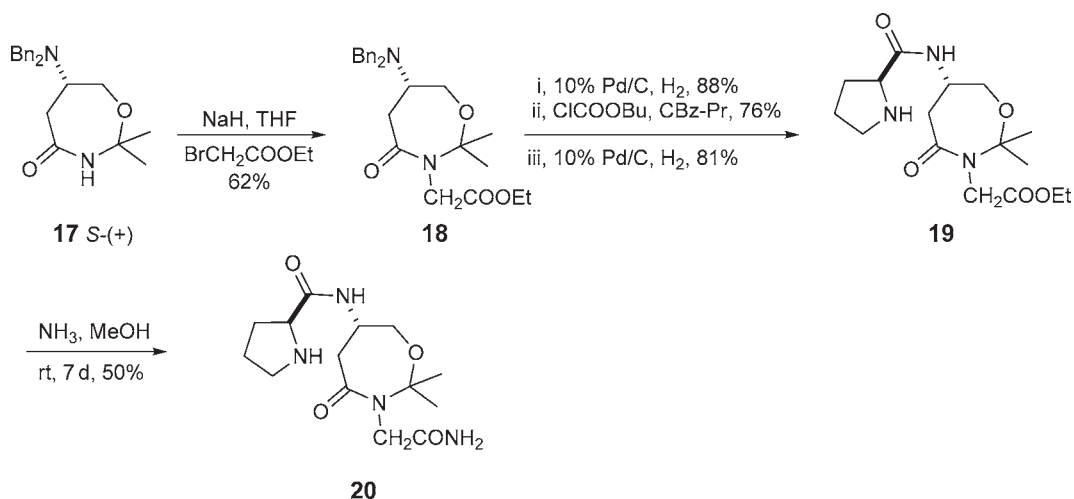
13.08.3 Reactivity

13.08.3.1 Reactivity of Nonconjugated Rings

Ring opening of the 1,3-oxazepinone **15** on treatment with an arylmagnesium bromide, followed by dehydration, gave the substituted alkenes, for example, **16a** and **16b**, in modest yields (Equation 1). Alkene **16a** then served as a precursor for the anticonvulsant SKF 89976A [<2006TL6389>](#).



The ring-constrained β -amino acid analogue **20** of the dopamine receptor-modulating peptide Pro-Leu-Gly-NH₂ has been described. This 1,3-oxazepinone analogue was synthesized in modest overall yield from the (*S*)-asparagine-derived precursor **17** via standard functional group manipulations through **18** and **19** (Scheme 1) <1999H(51)365>.



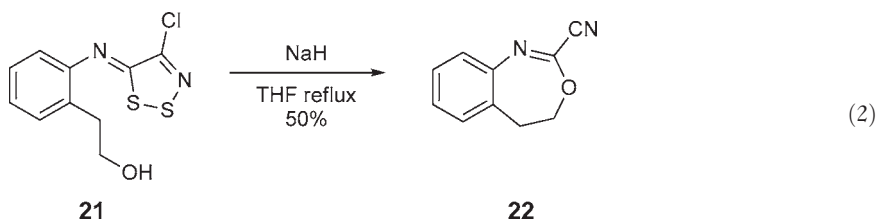
Scheme 1

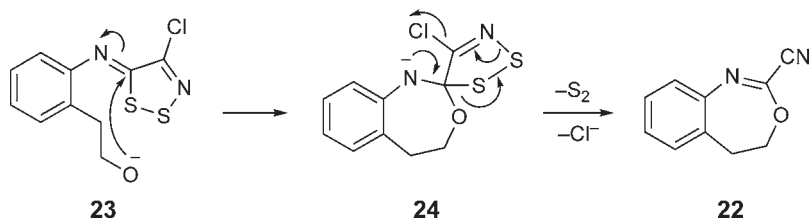
13.08.4 Ring Synthesis by Ring Construction

13.08.4.1 1,3-Oxazepines and Benz-Fused Derivatives

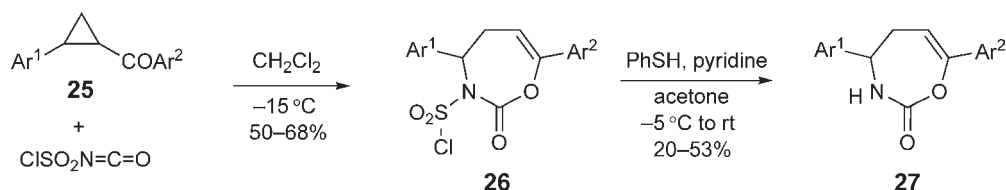
13.08.4.1.1 Type a (C–N–C–C–C–C–O)

Heating the alkoxide, derived from **21** and NaH in tetrahydrofuran (THF), gave the 3,1-benzoxazepine **22** in moderate yield (Equation 2) <1997SL704>. Mechanistically, it was proposed that the reaction proceeded via intramolecular nucleophilic attack by the alkoxide on the exocyclic imino group in **23**, followed by expulsion of S₂ and Cl[−] in the dithiazole intermediate **24** to afford **22**.





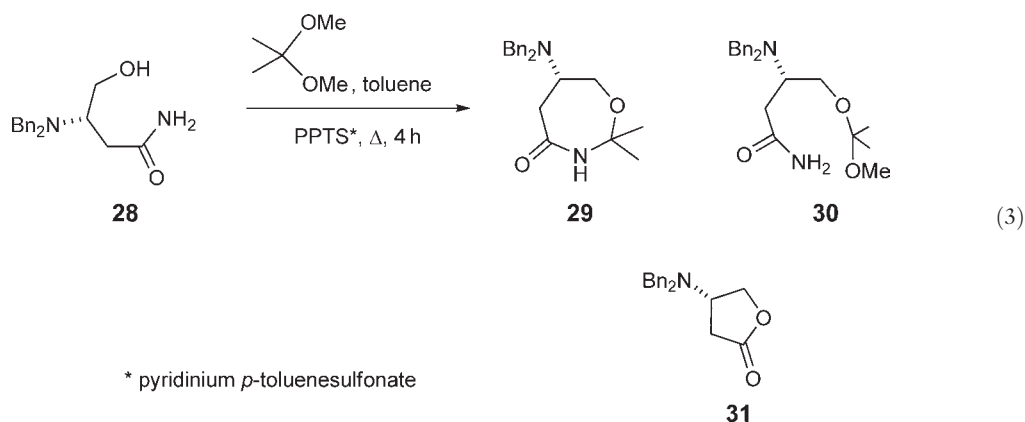
The 4,7-diaryl-4,5-dihydro-1,3-oxazepinones **27** can be accessed from a two-step sequence involving the reaction of 1-aryl-2-arylcyclopropanes **25** with chlorosulfonyl isocyanate, followed by removal of the chlorosulfonyl group from **26** with benzenethiol in pyridine (Scheme 2) <1995SC1939>. Yields in each step were low to moderate, for example, for **27** (Ar¹ = *p*-MeOC₆H₅, Ar² = Ph), the yield was 50%; while for the corresponding intermediate **26**, the yield was 53%.



Scheme 2

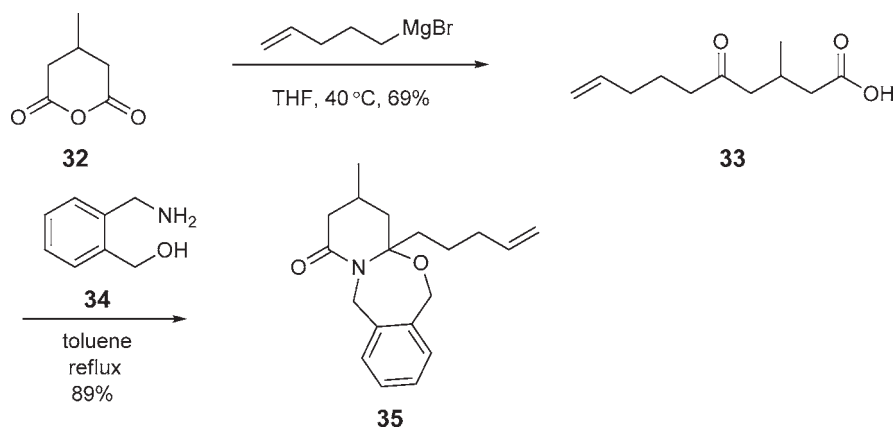
13.08.4.1.2 Type ab (N-C-C-C-C-O+C)

The enantiopure (*S*)-(+)-6-amino-1,3-oxazepan-4-one **29** was obtained in 35% yield by acid-catalyzed condensation of **28** (obtained in two steps from natural asparagine) with dimethoxypropane (Equation (3); see also Section 13.08.3.1). This reaction, which was very sensitive to both reaction conditions and the nature of the acid catalyst, was shown to proceed via the amide **30**. Further reaction of **28** under forcing conditions (heating in toluene with *p*-toluenesulfonic acid) resulted in ring contraction to lactone **31** <1999H(51)365>.

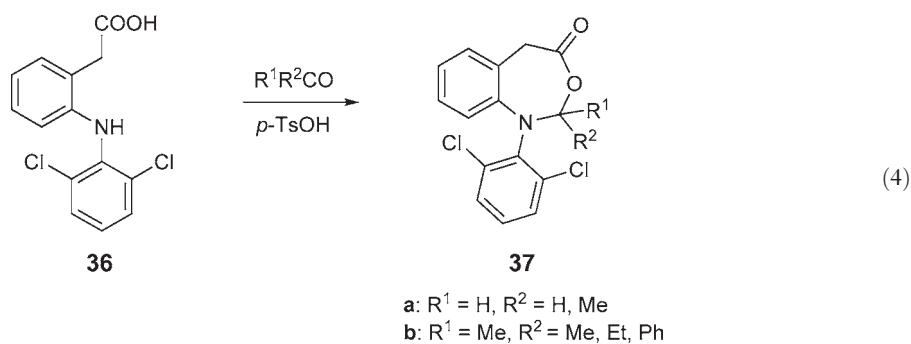


The bis-fused 1,3-oxazepine derivative **35** can be made by treatment of amino alcohol **34** with the keto acid **33**, the latter being prepared from a Grignard reaction with 3-methylglutaric anhydride. A 6:1 *trans:cis* diastereomeric ratio was obtained with **35**, which was then used in a new approach to a spiro heterocyclic system (Scheme 3) <2001SL1506>.

Ring-constrained analogues **37** of the anti-inflammatory drug, diclofenac, have been prepared by acid-catalyzed condensation of aldehydes (or ethylene ketals of ketones) with **36** (Equation 4) <1998MI201>. This reaction presumably proceeds via intramolecular nucleophilic attack by the carboxylic acid group on an iminium ion intermediate from condensation of the secondary amine. Interestingly, the compounds **37** showed comparable activities to diclofenac in the formalin-induced rat paw edema test.

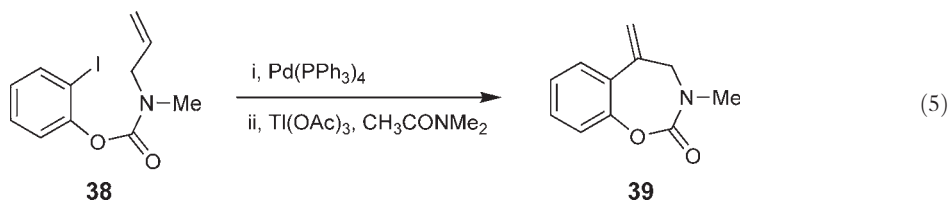


Scheme 3

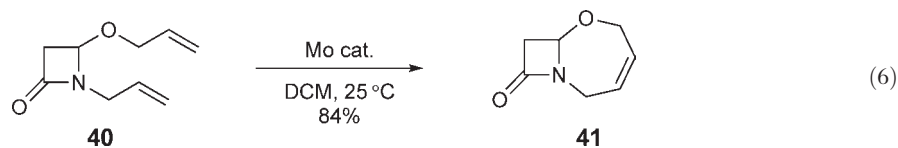


13.08.4.1.3 Type e (C–C–N–C–O–C–C)

Access to the 1,3-benzazepinone **39** has been achieved from aryl iodide **38** with a Pd(0) catalyst, followed by cyclization of the intermediate palladium complex upon reaction with thallium acetate, thus providing a convenient approach to the fused seven-membered ring system (Equation 5) <1998ICA(270)123>.



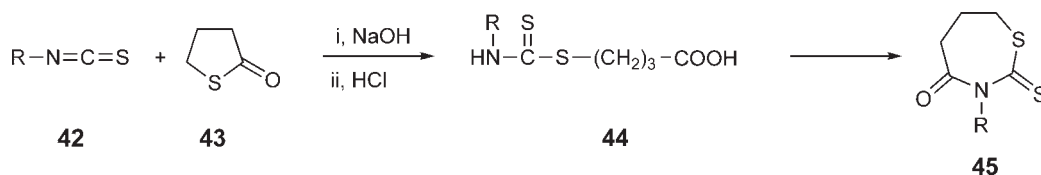
The ring-closing metathesis of the bis-allyl derivative **40** using $Mo(=CHCMe_2Ph)$ ($=NC_6H_3Pr^{i-2,6}$)[OCMe(CF₃)₂]₂ (5 mol%) gave 1,3-oxazepinone **41** in 84% yield (Equation 6) <1996CC2231>.



13.08.4.2 1,3-Thiazepines and Benz-Fused Derivatives

13.08.4.2.1 Type c (N-C-S-C-C-C-C)

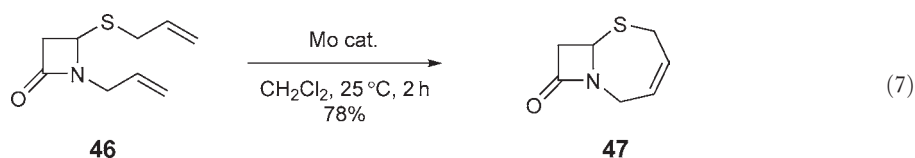
A ring-closure reaction involving the dithiocarbamates **44** was found to provide access to the 2-thioxo-1,3-thiazepan-4-ones **45** in generally fair to moderate yields (Scheme 4) <1999JHC1167>. The precursors **44** were obtained from isothiocyanates **42** with γ -thiobutyrolactone **43** in the presence of sodium hydroxide, followed by acidification. The substituents (R) varied from alkyl groups (Me, Et) to aryl groups (e.g., Ph, *p*-MeO-C₆H₄). In some cases (e.g., **45**, R = *p*-MeO-C₆H₄), the corresponding acid was not isolated prior to cyclization.



Scheme 4

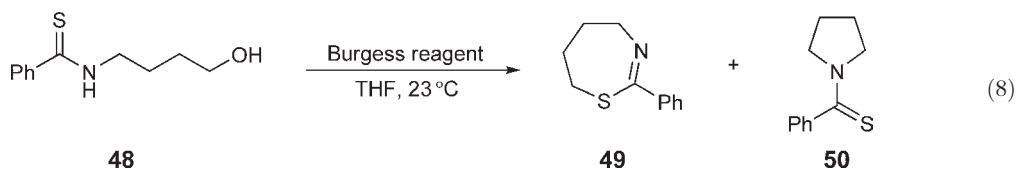
13.08.4.2.2 Type e (C-C-N-C-S-C-C)

As part of a program exploring functionalized bicyclic β -lactams, the ring-closing metathesis of the β -lactam diene **46** in the presence of a molybdenum-based catalyst (5 mol%) was shown to afford access to the fused 1,3-thiazepine **47** in 78% yield (Equation 7) <1997CC155>.

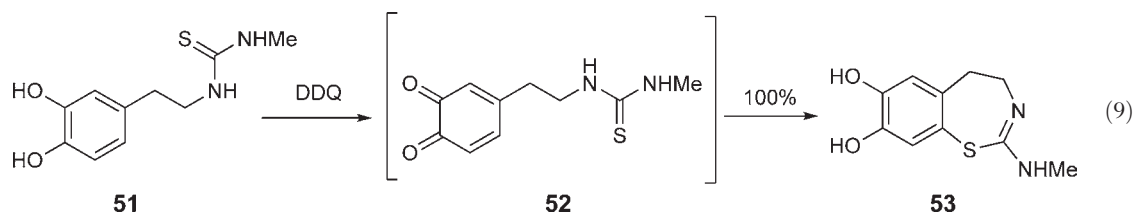


13.08.4.2.3 Type g (S-C-N-C-C-C-C)

Cyclodehydration of hydroxythioamide **48** with standard Burgess reagent gave the 1,3-thiazepine **49** in 58% yield. When, however, a polyethylene glycol (PEG)-linked Burgess reagent was used (in THF, 23 °C), only 17% of **49** was obtained together with the pyrrolidine thioamide product **50** in 40% yield (Equation 8) <1998T6987>.



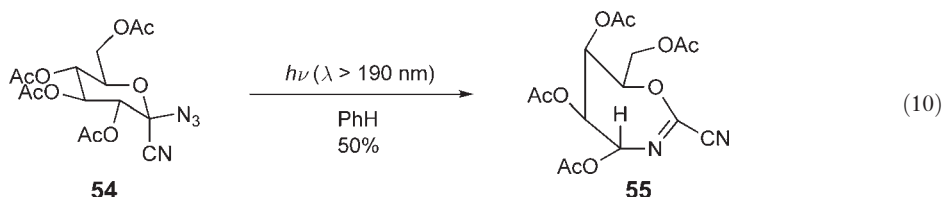
Oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) of the thiourea **51**, derived from dopamine, gave the 1,3-benzothiazepine **53** in quantitative yield via a facile *S*-based nucleophilic intramolecular addition to the intermediate *o*-quinone **52** (Equation 9) <2005OBC2387>.



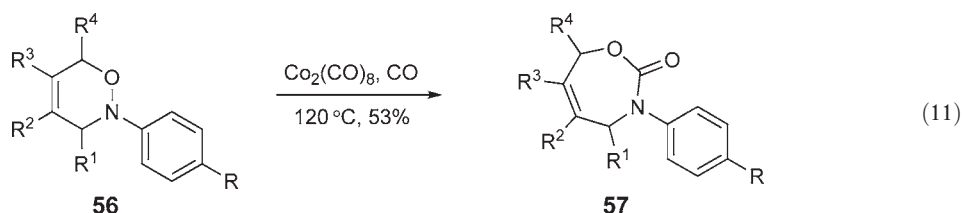
13.08.5 Ring Synthesis by Ring Transformation

13.08.5.1 1,3-Oxazepines and Benz-Fused Derivatives

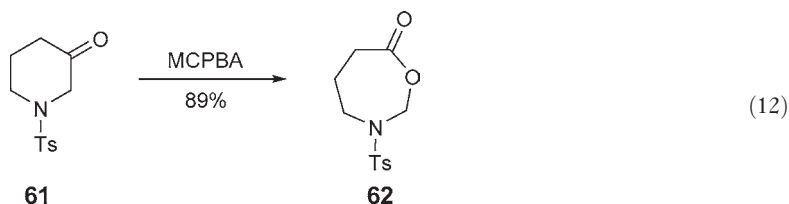
Photolysis of the azide **54** in benzene gave the tetrahydro-1,3-oxazepine **55** in moderate yield. The rearrangement proceeded by migration of the endocyclic carbon atom attached to the anomeric center, independent of the anomeric configuration (Equation 10). Unfortunately, when the nitrile group was replaced either by a carboxamido or a tetrazolyl group, complex mixtures of products resulted <2000TA533>.



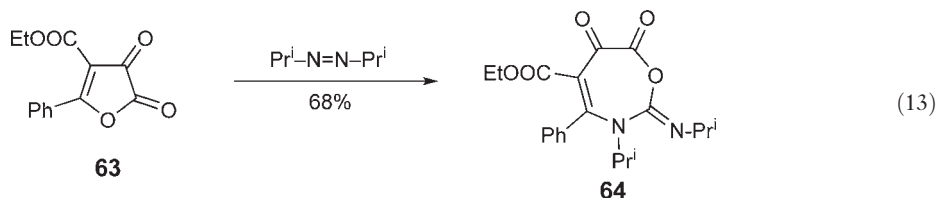
A one-atom cobalt carbonyl-mediated ring expansion of the 3,6-dihydro-2*H*-1,2-oxazines **56** provided access to the 4,7-dihydro-1,3-oxazepin-2(3*H*)-ones **57** in modest yields (Equation 11) <1996TL2713>; however, these conditions were quite severe with carbon monoxide at 1000 psi being required for the cobalt carbonyl used.



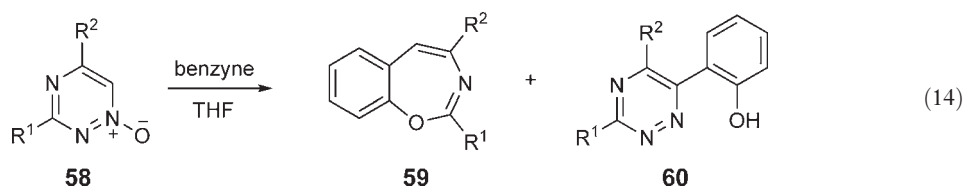
The Baeyer–Villiger ring expansion continues to be a useful methodology for accessing 1,3-oxazepinones, as illustrated by the reaction of **61** with *m*-chloroperbenzoic acid (MCPBA) giving **62** (see also Section 13.08.3.1) in high yield; none of the isomeric 1,4-oxazepan-2-one derivative was observed indicative of some directive influence by the nitrogen (Equation 12). This seven-membered lactone **62** was a key intermediate in the synthesis of the anticonvulsant SKF 89976A <2006TL6389>.



Reaction of the furan-2,3-dione **63** with diisopropylcarbodiimide at 25 °C has been reported to give the ring-expanded 1,3-oxazepine-6,7-dione **64** in moderate yield (Equation 13) <1997M381>.

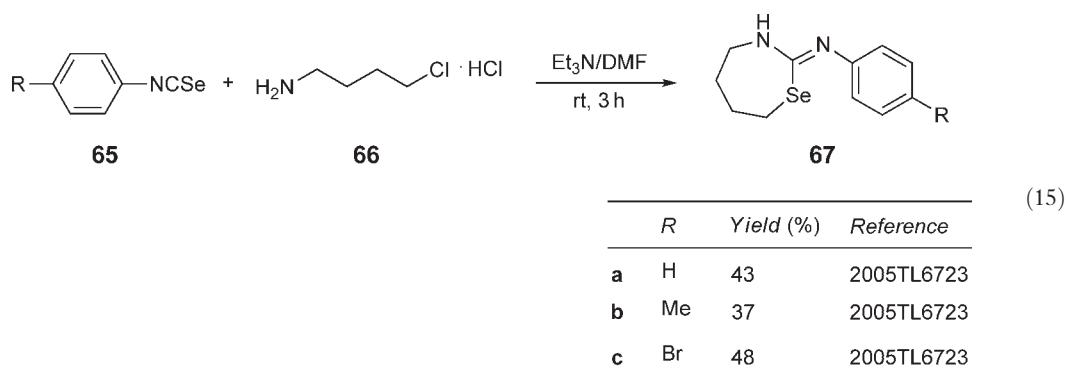


A reaction of benzyne with the 6-unsubstituted 1,2,4-triazine-1-oxides **58** ($R^1 = \text{Ph}$, $R^2 = \text{H}$, Me) gave the 1,3-benzoxazepines **59** ($R^1 = \text{Ph}$, $R^2 = \text{H}$, Me) (15–20% yield) and the 6-(*o*-hydroxyphenyl)-1,2,4-triazines **60** (30–40% yield) via the (C₆NO)-1,3-dipolar cycloadducts (Equation 14) <1996H(43)2091>. From the cycloadduct, sequential N–O bond cleavage, a 1,3-shift, and nitrogen loss provided access to **59**; a competing 1,5-shift, followed by aromatization, led to the alternative products **60**.



13.08.6 Synthetic Comparisons

The first route described to nonfused selenazepanes **67** from the aryl isoselenocyanates **65** and the chloro amine **66** by a stepwise amine addition-ring cyclization strategy (Equation 15) <2005TL6723> also has potential for application to the 1,3-thiazepane and 1,3-oxazepane analogues from the corresponding aryl isothiocyanates and aryl isocyanates.



Considerable synthetic scope exists for the application of diene-based and ene-yne-based ring-closing metathesis reactions to the synthesis of 1,3-oxazepine and 1,3-thiazepine derivatives. Particular emphasis on type *e* reactions is likely to be very fruitful.

Further potential is also seen in the Pd-based methodology described by Ma *et al.* for the synthesis of fused 1,3-oxazepines <2006T9002>. Value would be added to this methodology if it could be adapted to the simpler 1,3-benzazepine system, perhaps via alternative methods for carbinolamine precursor generation.

13.08.7 Important Compounds and Applications

Various 3,1-benzoxazepin-2-ones (described therein as 1,3-benzoxazepin-2-ones), which are mono- or disubstituted at C-5, have been claimed to be useful as HIV reverse transcriptase inhibitors <2001USP6204262>.

13.08.8 Further Developments

On the basis of some detailed reaction co-ordinate calculations with simpler analogues (at the B3LYP/6-31+G* level) a 1,3-thiazepine intermediate was proposed in the conversion of 2-aminothiazoles to a specific substituted pyridine product on reaction with dimethyl acetylenedicarboxylate in acetonitrile at 25 °C <2006JOC5328>. The reaction is proposed to proceed via an initial [2+2] cycloaddition of the acetylene to the 4,5-double bond in the 1,3-thiazole followed by disrotatory ring opening of the 4-membered ring in this intermediate to give the all *cis*-1,3-thiazepine. Electrocyclic rearrangement of the thiazepine to the 7,2-thiazabicyclo[4,1]heptadiene intermediate then thermal extrusion of sulfur with concomitant aromatization would afford the substituted pyridine product.

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Biographical Sketch



Prof. John Bremner is Professor of Organic Chemistry in the Department of Chemistry, University of Wollongong, Australia. He is a graduate of the University of Western Australia and the Australian National University. After being a Research Fellow at Harvard University, he returned to Australia in 1968 to an academic appointment in Chemistry at the University of Tasmania, and then moved in 1991 to the University of Wollongong. At Wollongong he was Head of Department for seven years and then was Director of the newly formed Institute for Biomolecular Science from 2001–2004. His research interests cover heterocyclic chemistry, natural products, and medicinal chemistry, including more recently the design, synthesis and evaluation of new types of anti-infective agents for the potential treatment of bacterial disease and malaria.



Dr Siritron Samosorn received a Bachelors degree in Chemistry in 1990 and a Masters degree in Applied Chemistry in 1994, both from Ramkhamhaeng University, Thailand, under the supervision of Prof. Apichart Suksamrarn. In 1994, she joined the Department of Chemistry at Huachewchalermprakiet University in Thailand as a lecturer, and later moved to a staff position at Srinakharinwirot University (SWU) in 1997. She obtained her PhD from the University of Wollongong in 2005, working with Prof. John Bremner on a new approach to heterocyclic dual-action antibacterial agents to combat the problem of antibiotic resistance by drug efflux. Her research and teaching areas include the related areas of Natural Product Chemistry and Drug Design and Development, and she is a member of 'The Center for the Development of Value-Added Natural Products' at SWU.

13.09

1,4-Oxazepines and 1,4-Thiazepines

W. Dehaen and T. H. Ngo
University of Leuven, Leuven, Belgium
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13.09.1 Introduction

The chemistry of 1,4-oxazepines and 1,4-thiazepines was covered previously in CHEC(1984) <1984CHEC(7)593> in less than 10 pages together with data on all other seven-membered rings with two heteroatoms, and in 15 pages in CHEC-II(1996) <1996CHEC-II(9)217>. The previous chapters in CHEC(1984) and CHEC-II(1996) should be read together with this chapter in order to get a comprehensive view of the field.

Actually, treating the two related ring systems in one chapter makes sense since in many cases they appear side by side in the same article or in a series of follow-up articles by the same author. There has been considerable activity concerning these two ring systems and this is certainly due to the large medicinal interest in 1,4-oxazepines and 1,4-thiazepines and their benzo derivatives. In this chapter, we have compiled the data abstracted from selected recent publications (since 1995) focusing on aspects of synthesis and reactivity as also has been the case in the previous treatments. The most important medicinal applications are mentioned at the end of the text.

13.09.2 Theoretical Methods

Theoretical studies of several classes of the title heterocycles have appeared. A majority of these studies focus on the conformational aspects of partially to completely reduced and/or (di)benzo-fused derivatives.

Solvation energies, logP values, conformational and electronic features of diltiazem **1** (Figure 1), and analogous molecules were determined via molecular mechanics and quantum chemical methods. Furthermore, the molecular electrostatic potentials (MEPs) and common interaction fields derived from the use of the GRID program were compared. This yielded a pharmacophore model with three crucial characteristics: (1) two aromatic systems in a distance of about 6.7 Å, (2) a basic side chain with pK_a in the physiological range, and (3) a 4-methoxy group <1999MI1506>. Molecular modeling (AM1 method), based on X-ray crystallographic coordinates, was used to probe the three-dimensional (3-D) similarities of benzoxazepines to fentanyl <1995BML1177>. Extensive molecular mechanics (MM) studies in concert with X-ray structural data were used by Nacci and co-workers to identify the receptor-bound conformations and mutual alignments of Ro-4864, PK 11195, and three potent benzodiazepines **2** (Figure 1) binding selectively to the mitochondrial benzodiazepine receptors (MBRs) <1995JME4730>. The same group also reported similar studies on the *S*-enantiomer of **3** (Figure 1), as compared to nevirapine. Energies of **3** (X=S) were computed through the MM Tripos force field using Gasteiger–Hückel charges <1996JME2672>.

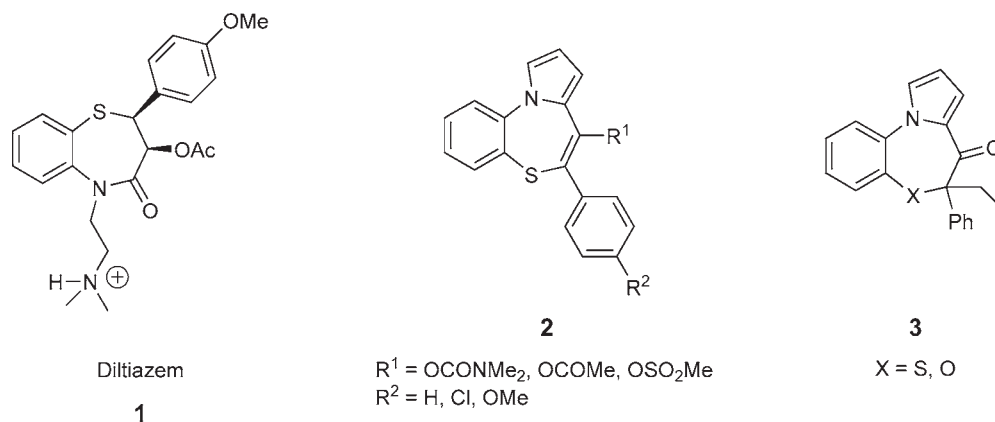
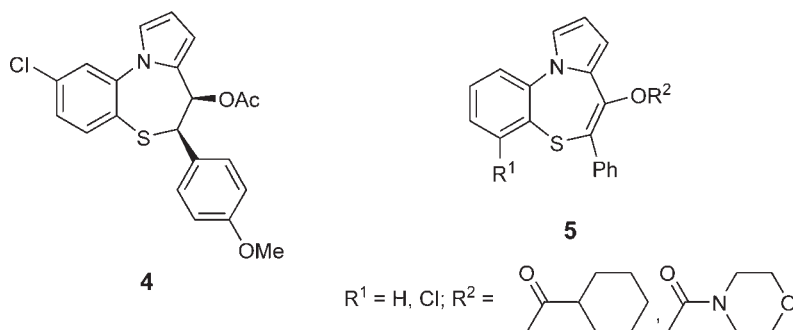


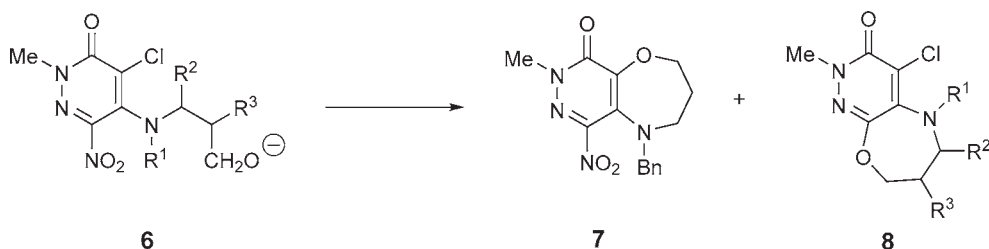
Figure 1

The molecular structure determinations of **4** <1996JME2922> and **5** <1997EJM241> by X-ray diffraction, molecular modeling, and nuclear magnetic resonance (NMR) analysis were reported (Figure 2).

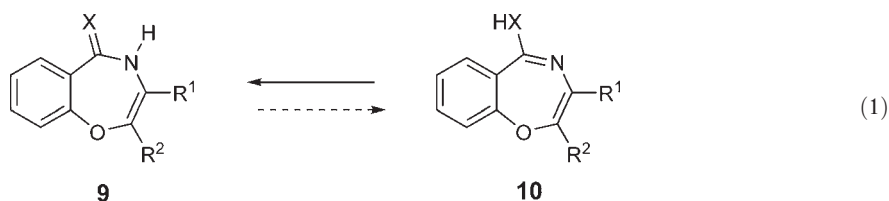
In a more recent continuation of these studies, Campiani and co-workers carried out semi-empirical calculations on a series of active compounds related to **2**. This led to the identification of several structural and conformational features responsible for this activity <2005JME4367>. Docking into the human immunodeficiency virus 1 (HIV-1) reverse transcriptase non-nucleotide binding site (RT NNBS) of a compound of type **3** (X=O) highlighted that one of the phenyl rings of this compound protrudes toward the catalytic site <2005JME7153>.

**Figure 2**

Full geometry optimization of anionic intermediates **6** leading to alternative pyridazino-fused oxazepines **7** (minor product for the unsubstituted benzylamine) and **8** (major product) was carried out at the semi-empirical AM1 level. The theoretical considerations were in agreement with the experimental results in most cases (Scheme 1) <2001JMT(545)75>.

**Scheme 1**

Quantum-chemical (Gaussian 98W package) calculations have been used, together with spectroscopic (^{13}C , ^1H NMR) methods, to investigate the structures and stabilities of the potentially tautomeric 2-phenyl and 3-phenyl benzoxazepinones and their thiolactam analogues. Experimental and computational data indicate the predominance of (thio)lactams **9** in the gas phase and in solution over the imino tautomers **10** (Equation 1) <2004JMT(668)157>.



13.09.3 Experimental Structural Methods

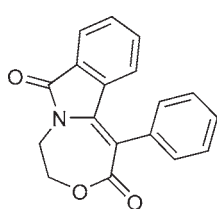
13.09.3.1 Crystal Structures

Numerous X-ray crystallographic studies have been published of the title heterocycles and their (di)benzo derivatives. In many cases, the solid-state characteristics have been used as a starting point for molecular modeling (see Section 13.09.2). Table 1 summarizes some selected data (R value < 0.1) on the bond lengths of 1,4-oxazepine derivatives: **7** <2001JMT(545)75>, **11** <1998JHC33>, **12** <2000JHC287>, **13** <2002JFC(115)91>, **14** <2002BMC401>, **15** <2004JOC280>, **16** <1999JME2235>, **17** <1999TA3873>, **18** <2004OL2281>, **19** <2000TA3449> (structures **11–19** in Figure 3) and Table 2 the corresponding data on 1,4-thiazepines **1**

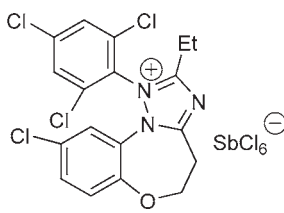
<1984HCA916>, **2** ($R^1 = \text{Me}_2\text{NCOO}$, $R^2 = \text{H}$) <1995JME4730>, **4** <1996JME2922>, **20** <2000S435>, **21** <1996AGE90>, **22** <2002J(P2)1816>, **23** <1996JHC583>, **24** <2000J(P1)1897>, **25** <2002T2861>, and **26** <2001JHC561> (structures **21–26** in Figure 4).

Table 1 Bond lengths of 1,4-oxazepine rings (in Å)

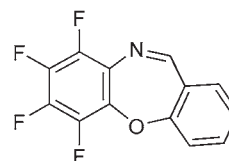
Structure	O(1)–C(2)	C(2)–C(3)	C(3)–N(4)	N(4)–C(5)	C(5)–C(6)	C(6)–C(7)	C(7)–O
7	1.354	1.371	1.394	1.457	1.525	1.490	1.449
11	1.430	1.487	1.452	1.405	1.350	1.497	1.346
12	1.369	1.359	1.428	1.340	1.489	1.514	1.452
13	1.398	1.401	1.405	1.287	1.472	1.387	1.378
14	1.432	1.522	1.363	1.440	1.405	1.518	1.430
15	1.437	1.517	1.452	1.359	1.507	1.384	1.365
16	1.401	1.398	1.401	1.290	1.496	1.397	1.392
17	1.463	1.488	1.365	1.422	1.400	1.494	1.348
18	1.450	1.531	1.476	1.348	1.514	1.492	1.345
19	1.332	1.509	1.463	1.666	1.544	1.537	1.455



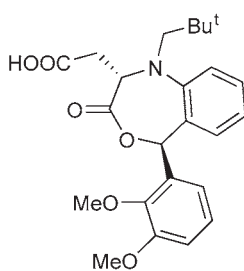
11



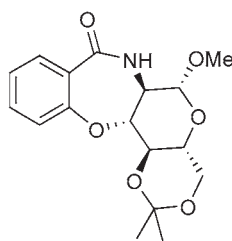
12



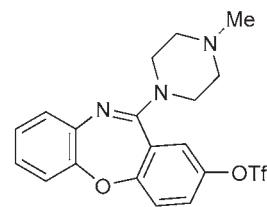
13



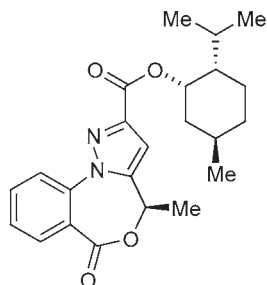
14



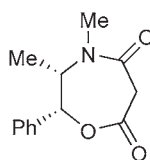
15



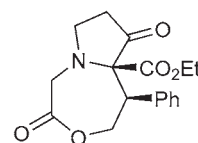
16



17



18

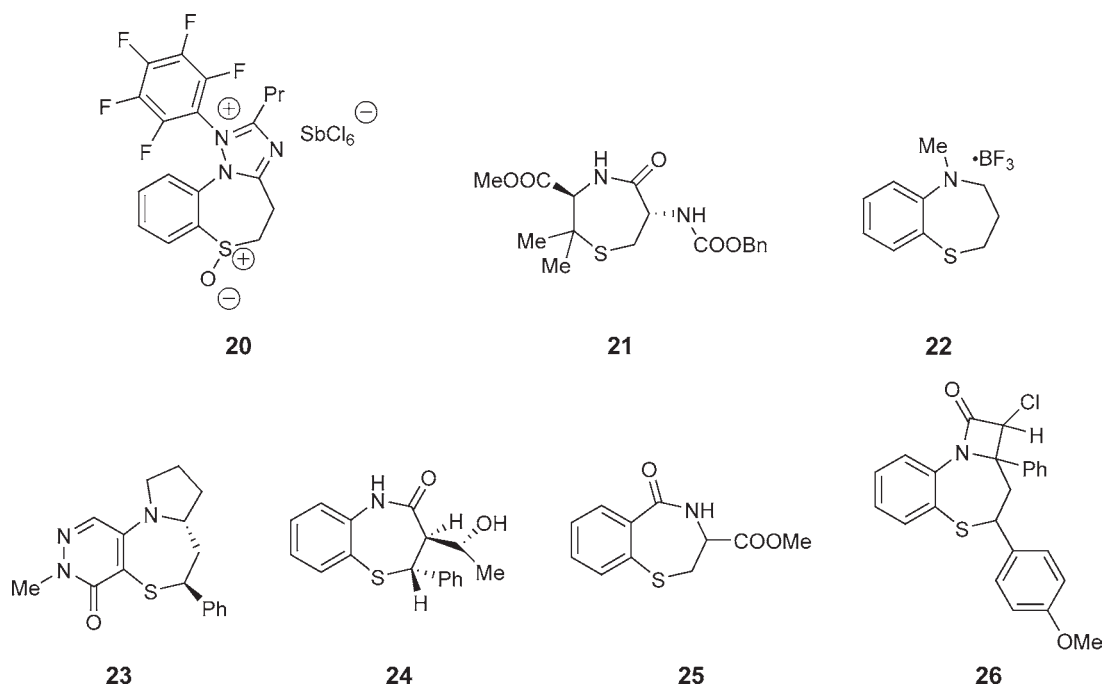


19

Figure 3 Structures **11–19**.

Table 2 Bond lengths of 1,4-thiazepine rings (in Å)

Structure	<i>S</i> (1)– <i>C</i> (2)	<i>C</i> (2)– <i>C</i> (3)	<i>C</i> (3)– <i>N</i> (4)	<i>N</i> (4)– <i>C</i> (5)	<i>C</i> (5)– <i>C</i> (6)	<i>C</i> (6)– <i>C</i> (7)	<i>C</i> (7)– <i>S</i>
1	1.765	1.396	1.434	1.350	1.540	1.532	1.845
2	1.766	1.389	1.415	1.388	1.448	1.338	1.789
4	1.772	1.402	1.424	1.380	1.484	1.525	1.842
20	1.785	1.398	1.432	1.327	1.483	1.511	1.813
21	1.830	1.559	1.455	1.348	1.538	1.537	1.805
22	1.832	1.528	1.506	1.525	1.524	1.411	1.783
23	1.776	1.415	1.331	1.457	1.520	1.534	1.801
24	1.775	1.399	1.412	1.356	1.529	1.542	1.838
25	1.811	1.543	1.448	1.341	1.497	1.406	1.773
26	1.767	1.395	1.423	1.501	1.517	1.525	1.840

**Figure 4** Structures **20–26**.

13.09.3.2 NMR Spectroscopy

Obviously most papers on the title heterocycles also list NMR data as part of the characterization. We will mention only a few articles that are partially or completely dedicated to NMR studies of 1,4-oxazepine and 1,4-thiazepine derivatives.

From the data on ^1H NMR couplings, it was concluded that dibenzoxazepine **27** (Figure 5) adopts a V-form conformation in solution, as was also observed in the solid state (X-ray data) <1996MRC989>.

The spirobenzoxazepine **28** was studied by 2-D and nuclear Overhauser enhancement Spectroscopy (NOESY) NMR and X-ray crystallography, and in both cases the same chair conformation, **28**, was formed (See Figure 5). The authors conclude that this compound **28** is a semirigid scaffold, able to present various substituents without undergoing hydrophobic collapse, and **28** behaves structurally as a privileged structure <2004TL1051>.

Benzoxazepines **9** were shown by NMR spectroscopy to be in the thiolactam structure <2004JMT(668)157>. Oxazepinium and thiazepinium salts **29** (X=O, S) were fully characterized by NMR spectroscopy. The spectral resolution had a substantial temperature dependence, which can be associated with an improvement in conformational averaging (Figure 5) <2003MRC975>.

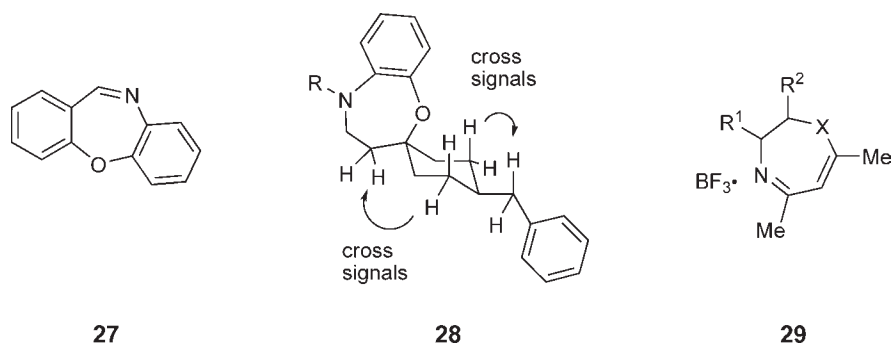


Figure 5

The stereostructures (chair conformations) of *cis*- and *trans*-benzothiazepine isomers **30a** and **30b** were determined from the ^1H and ^{13}C NMR spectra by using data from differential nuclear Overhauser effect (DNOC), and, in the case of **30b**, 2-D heteronuclear shift correlation (HSC) measurements <1995TL753>. The complete assignment of the spectrum of **30** has been made by using ^1H NMR homonuclear (COSY) and ^{13}C - ^1H heteronuclear (HETCOR) shift-correlated 2-D NMR experiments. The relative configuration at the C-6 and C-7 centers has been determined by means of NOE analysis. More information on the conformations was obtained by X-ray crystallographic analysis <1996JME2922>. From the variable-temperature ^1H NMR spectra of tetrahydrobenzothiazepines of type **31** it could be derived by Katritzky *et al.* that the heterocycles exist as two puckered mirror-image (enantiomorphic) conformers, with benzothiazepine ring chair-to-chair interconversion barriers of ca. 10 kcal mol $^{-1}$ in dichloromethane solution. The ^1H and ^{13}C NMR spectral assignments of **31** were determined by COSY, HETCOR, and NOESY experiments. The solid-state structure of the BF_3 complex of **31**, that is, **22**, confirmed the stereochemistry and conformation obtained by NMR in solution <2002J(P2)1816>. Further studies on systems similar to **31** were done with attached proton test (APT), distortionless enhancement by polarization transfer (DEPT), NOE-difference, COSY, HETCOR, gradient heteronuclear multiple quantum correlation (gHMOC), and gradient heteronuclear multiple bond correlation (gHMBC) techniques <2004MRC648>. Benzothiazepines **32** were characterized by the combined use of multinuclear 1-D and 2-D NMR together with GIAO/DFT calculations of ^1H , ^{13}C , and ^{15}N chemical shifts (Figure 6) <2005T6642>.

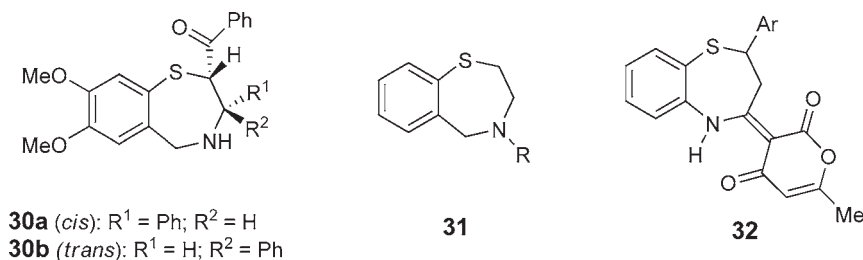


Figure 6

13.09.3.3 Mass Spectrometry

Again we discuss only dedicated papers. The mass spectrometric fragmentation of 2-phenoxyazetidinones fused with benzothiazepine (**33**: $\text{R} = \text{OPh}$) has been investigated using the aid of mass-analyzed ion kinetic energy spectrometry. All compounds of type **33** tend to eliminate a phenoxy, phenol, and phenoxyketene, respectively, from the molecular ions. Further fragments after ketene loss are 2-arylbenzothiazole ions and ions due to the loss of sulfur <2004RCM859>. Also, for the corresponding phthalimido derivatives **33**, similar fragmentations were found (Figure 7) <2000RCM2373>. The fragmentation behavior of tetracyclic benzothiazepine derivatives **34**, cationized with protons and silver cations under post-source decay (PSD) matrix-assisted laser desorption/ionization (MALDI) conditions, was reported. Several fragments are formed from the protonated adduct ions, mostly ring-opened and ring-contracted compounds (Figure 7) <2004RCM1259>.

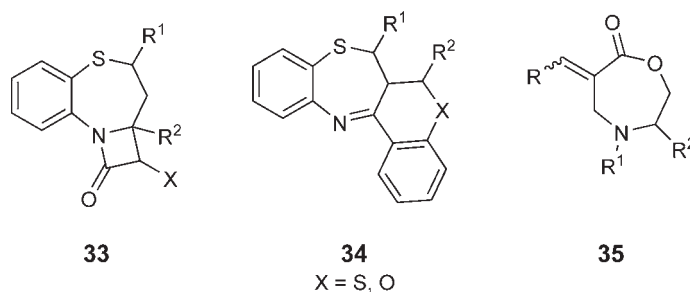


Figure 7

Oxazepine derivatives **35** gave intense molecular peaks and a number of fragments. It was interesting to note that only the (*E*)-isomers of **35** gave $[M^+ - R]$ as major fragments (Figure 7) <2000JOC6932>.

13.09.3.4 Miscellaneous

The two diastereoisomers of optically active 1,4-benzothiazepinones of types **36a** and **36b** were shown to have clearly different circular dichroism (CD) spectra, allowing a fast diagnosis of their structure (Figure 8) <2000J(P1)1897>.

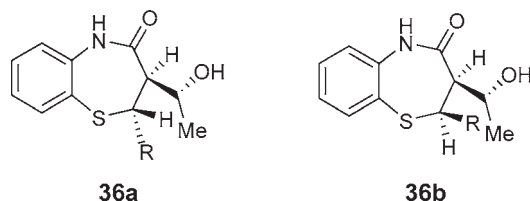


Figure 8

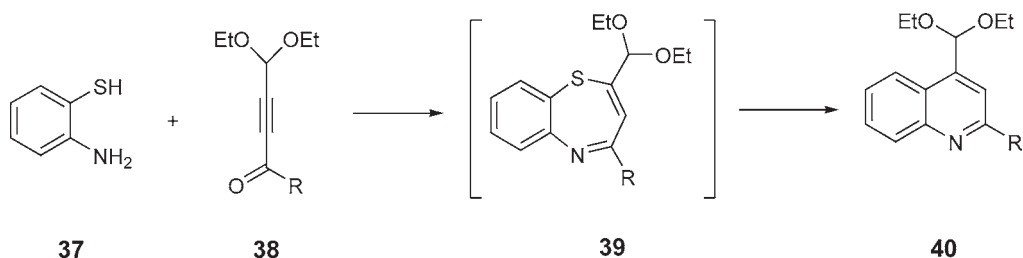
13.09.4 Thermodynamic Aspects

In general, 1,4-oxazepines and 1,4-thiazepine derivatives are stable compounds. Many of the (di)benzo derivatives are crystalline, while some of the more flexible monocyclic derivatives may be liquids. Conjugated (benzo)thiazepine derivatives can lose sulfur on heating, forming (fused) pyridines. This aspect of their reactivity is treated in Section 13.09.5. The completely or partially reduced derivatives of the title heterocycles and the benzo analogues may adopt different conformations, which has already been discussed in Section 13.09.2. The study of the tautomerism of lactams **9** has also been mentioned in Section 13.09.2.

13.09.5 Reactions of Conjugated Rings

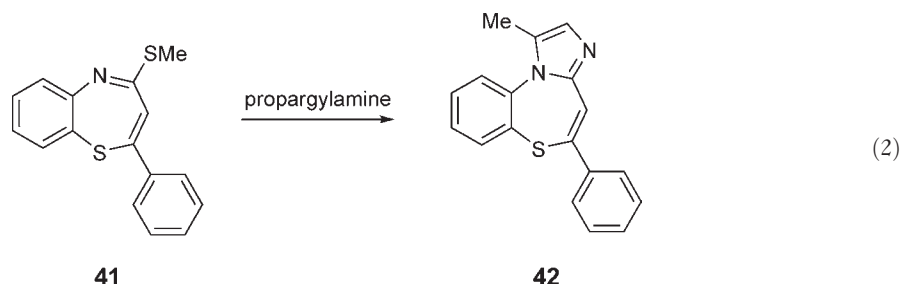
The simple fully conjugated 1,4-oxazepine or 1,4-thiazepine system is rare, and most derivatives described have at least one aromatic or heterocyclic moiety fused to the ring.

The benzo-1,4-thiazepine **39** was generated as an intermediate from the reaction of 2-aminothiophenol **37** with alkyne acetals **38**, leading to 2,4-disubstituted quinolines **40**. The sulfur is smoothly extruded on heating at reflux in toluene <1997T641>. Attempted isolation of the 1,4-thiazepine **39** leads to partial loss of sulfur – thus the sequence was carried out as a one-pot reaction (Scheme 2). The method has been extended to the stereoselective synthesis of novel enantiopure quinolyglycines <2000SL595, 2001TA1851>. Monocyclic thiazepines have been proposed as intermediates in the [2+2] cycloaddition of 2-aminothiazoles and acetylenedicarboxylate, leading to pyridines <2006JOC5328>.

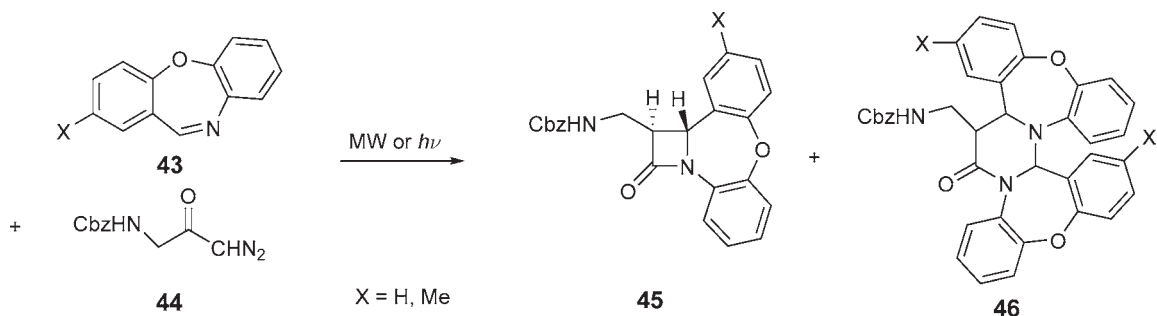


Scheme 2

The benzothiazepine ring **41** could be substituted at C-2 with propargylamine nucleophile, apparently without desulfurization, leading to an imidazole derivative **42** fused with a benzothiazepine (Equation 2) <1995EJM429, 1993FA665>.

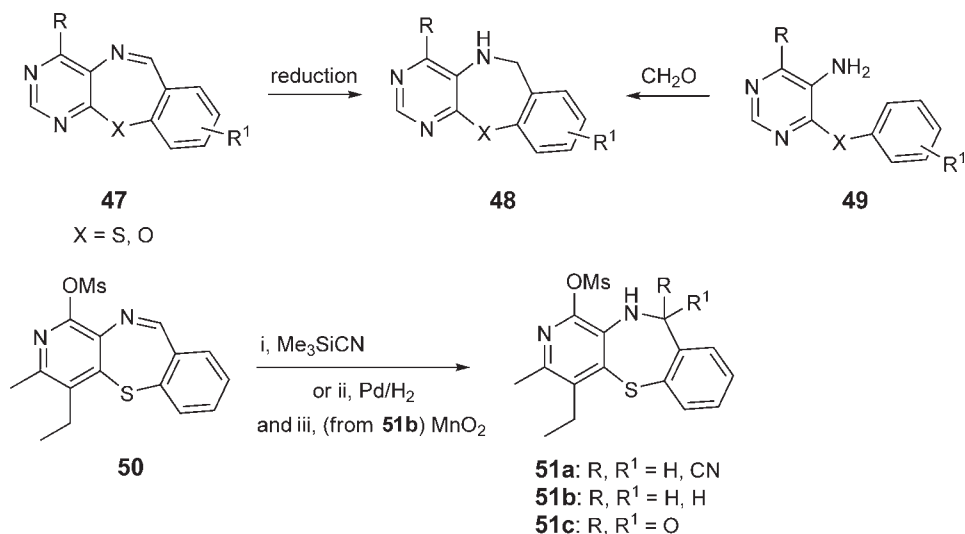


The imine bond of dibenzoxazepine **43** underwent [2+2] cycloaddition (Staudinger reaction) with ketenes, generated *in situ* from diazoketones **44** by microwave or photoirradiation, to afford the fused β -lactams **45**. In the case of photoirradiation, [2+2+2] cycloadducts **46**, containing two dibenzoxazepine rings, were formed as by-products (Scheme 3) <2005JOC334>. Other examples have been described where the ketene component was generated from an acid chloride by dehydrohalogenation <2002HAC276, 2004TA2555>.



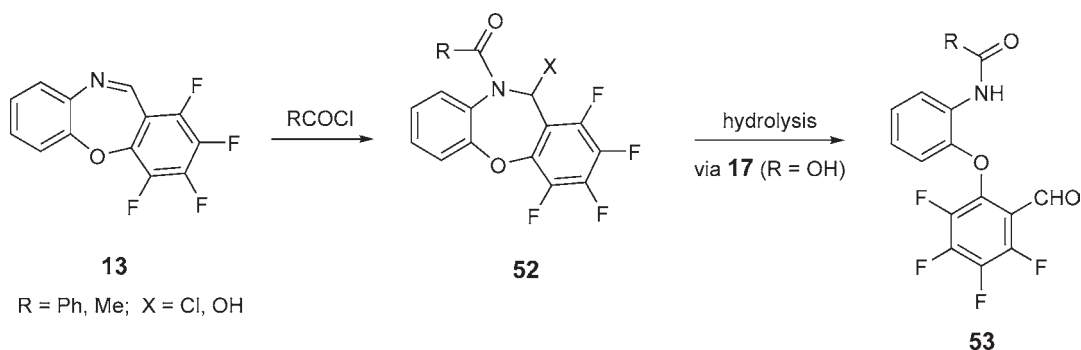
Scheme 3

Reduction of the imine bond of doubly fused 1,4-oxazepines and -thiazepines such as compound **47** can take place with either sodium borohydride <1985KGS122, 2005TL7523>, lithium borohydride <2006BML1643>, sodium cyanoborohydride <2005TL7523>, or catalytic hydrogenation (H_2 /Pd) <2005TL2919>. Similar products **48** can be obtained directly by Pictet–Spengler cyclization, provided the aromatic ring of the open chain precursor **49** is sufficiently electron rich <2005JOC9629>. In the same way, hydrocyanic acid could be added, using the convenient trimethylsilyl cyanide (TMS–CN) reagent, to the imine bond of the 1,4-thiazepine **50** to afford the pyridinone **51** ($R=H$, $R^1=CN$). Catalytic reduction of thiazepine **50** gave amine **51** ($R=R^1=H$) that could be reoxidized with MnO_2 to the amide **51** ($R=R^1=O$) in low yield (Scheme 4) <2005TL2919>. Lithium aluminium hydride reduction of amide or imine derivatives of 1,4-benzothiazepines and 1,4-benzoxazepines gave the corresponding 2,3,4,5-tetrahydro derivatives <2002J(P1)592>.



Scheme 4

Acylation of the ring nitrogen of fluorinated dibenzoxazepine **13** afforded ring-opened products **53** after addition of chloride anion and hydrolysis (Scheme 5). The hydroxy and chloro derivatives **52** could be isolated and characterized by X-ray crystallography <2003JFC(119)15>.



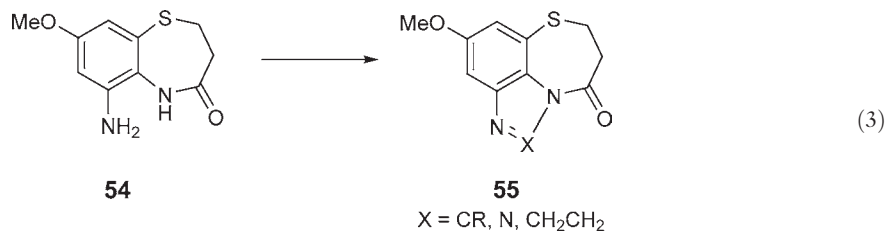
Scheme 5

13.09.6 Reactions of Nonconjugated Rings

13.09.6.1 Reactions at Nitrogen

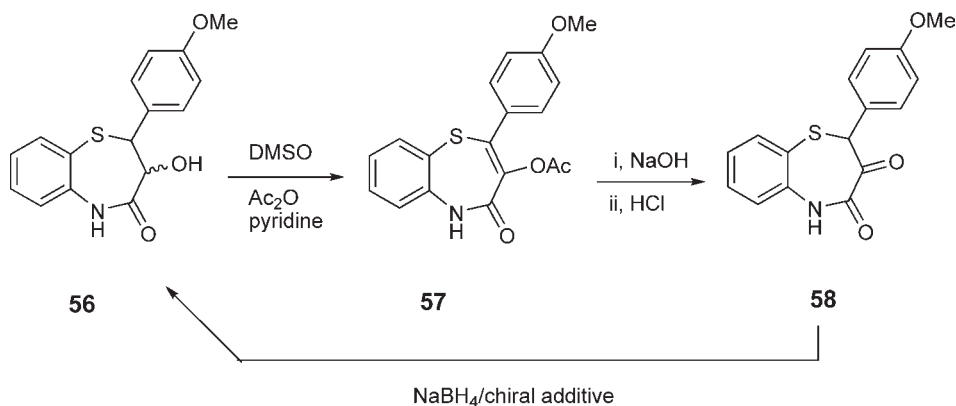
The most obvious way of functionalizing an oxazepine or thiazepine is to use the nitrogen atom in a reaction with an electrophilic reagent. Such reactions are well documented in the literature and not very different from the reactions of open-chain analogues. We limit ourselves to representative recent examples. Thus, alkylation of amine <2000BMC393, 2001BMC1> or amide <1996JME1196, 2001BML595, 2001CR925, 2001JME4082, 2003JOC1736, 2004BML5987, 2004JME4627> functionalities of oxazepine or thiazepine has been very common. On the other hand, N-dealkylation has been described only a few times as deprotection strategy, for example, in solid-phase synthesis of dibenzoxazepinones <1999T2826, 2003TL8169>. Acylation <1996JME609, 2003BML4031, 2004T11547> and sulfonation <1999JME4547> of the nitrogen atom of oxazepines and thiazepines were also described, as well as deacylation <2000BMC393> and desulfonation <2004T11547>.

Different cyclization reactions of *ortho*-amino-substituted benzothiazepinones **54** lead to tricyclic derivatives **55**, containing imidazole ($X = CR$), 1,2,3-triazole ($X = N$), or tetrahydropyrazine ($X = CH_2CH_2$) rings (Equation 3). These compounds are structural analogues of the anti-HIV product thiobenzimidazolone (TIBO) <1999EJM701>.



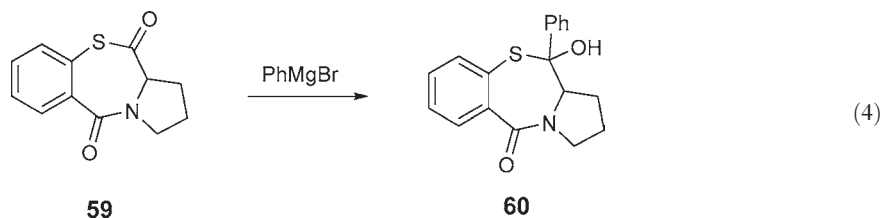
13.09.6.2 Reactions at Carbon

The racemic (2*RS*,3*RS*)-diltiazem analogue **56** could be oxidized and acetylated to the unsaturated derivative **57**. Hydrolysis gave a diketone **58**, which after asymmetric reduction with chirally modified sodium borohydride, gave good *de*'s and *ee*'s for the formation of certain diastereoisomers **56**, depending on the amino acid additive (Scheme 6). The combination $NaBH_4$ /(*S*)-leucine gave the best results <1996JOC8586>.

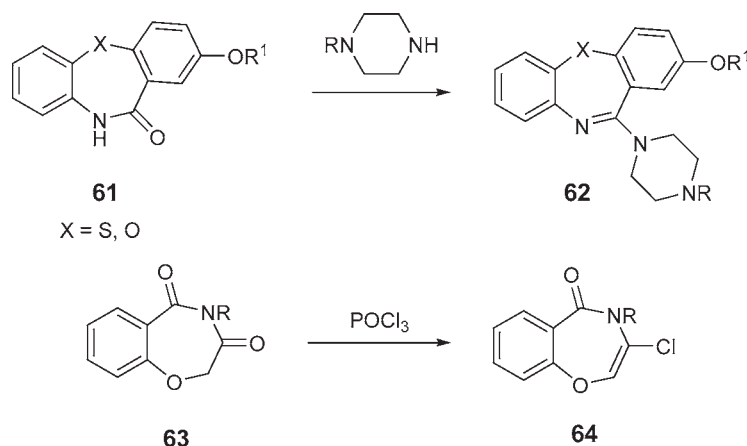


Scheme 6

Addition of Grignard reagents to benzothiazepinediones **59** gave the corresponding monoadducts **60**, involving the thioester function but leaving the amide function intact (Equation 4) <1999JME3334>.



Amide functions of dibenzothiazepinones and dibenzooxazepinones **61** could be aminated at carbon with substituted piperazines to the fully conjugated dibenzo derivatives **62** having an amidine moiety <1999JME2235, 2001JME372>. The 3-carbonyl function of a benzotetrahydrooxazepine-3,5-dione **63** could be transformed into the 3-chlorodihydrooxazepin-5-one **64** with phosphoryl chloride (Scheme 7) <2006BMC1978>.



Scheme 7

α -Chloro-substituted benzothiazepinone **65** (R = Cl), available by chlorination of the unsubstituted derivative **65** (R = H) with sulfonyl chloride, could be arylated to derivative **65** (R = Ph) with benzene and aluminium chloride in a Friedel–Crafts alkylation reaction [\[1997EJM241\]](#). Substitution of the very reactive chloride **65** (R = Cl) with *N*-methylpiperazine to obtain thioaminal **65** (R = 1-methylpiperazin-4-yl) was also possible [\[1999JME3334\]](#).

Potassium enolates, generated from pyrrolobenzothiazepinones **66** (X = S) with potassium hydride, could be alkylated on carbon, giving 57–72% yield of **67** with about 20–30% of O-alkylation **33** (R = alkyl) occurring at the same time. The corresponding benzoxazepinones **66** (X = O) gave similar results [\[1996JME2672, 2005JME7153\]](#). The same enolates are selectively O-functionalized with acetyl chloride or other acylating or sulfonating reagents [\[1995JME4730, 1996JME2922, 1997EJM241\]](#). Other examples of C-alkylation of benzothiazepinones were described in the synthesis of analogues **69** of CP-340868, a potent squalene synthase (SQS) inhibitor. The ester functions of racemic **69** were selectively hydrolyzed by enzymatic resolution with lipases ([Figure 9](#)) [\[2000TA4447\]](#).

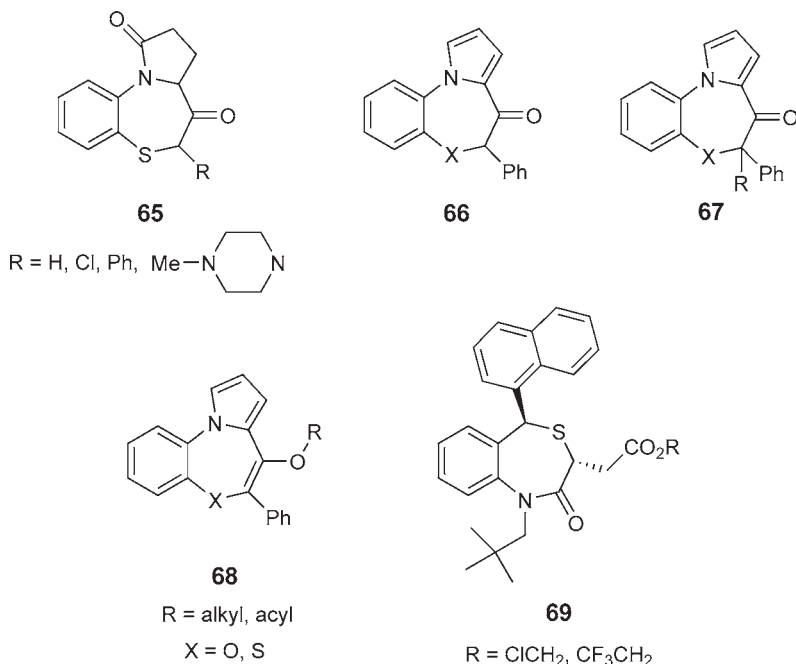


Figure 9

13.09.6.3 Reactions at Sulfur

The most common reaction at sulfur atoms is oxidation of the 1,4-thiazepine derivative, and either sulfoxides or the fully oxidized sulfones may be formed depending on the number of equivalents of oxidant used. Oxidants include *m*-chloroperbenzoic acid (MCPBA) <1996JME2672, 1997TL2775, 1999JOC3019, 2000TL3029, 2002BMC385>, hydrogen peroxide <1995JMC925>, peracetic acid <1999JME4547>, or oxone <2005BML1641>.

The oxidation of 1,4-thiazepinone **70** ($n=0$) to the sulfoxide **70** ($n=1$) was used to prove its enantiomeric purity. The two diastereomeric sulfoxides afforded the same sulfone **70** ($n=2$) by oxidation (Figure 10) <1997TL2775, 1999JOC3019>. In other cases, only one diastereoisomer **71** was obtained, albeit without determination of the stereochemistry (Figure 10) <2002BMC385>.

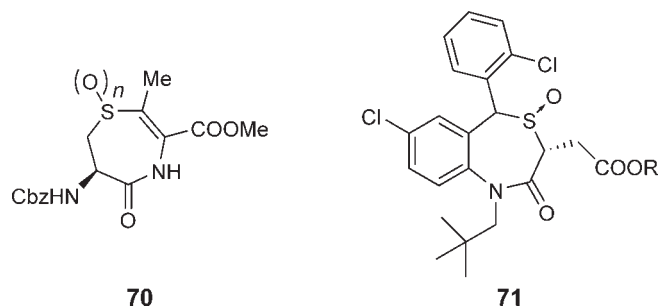
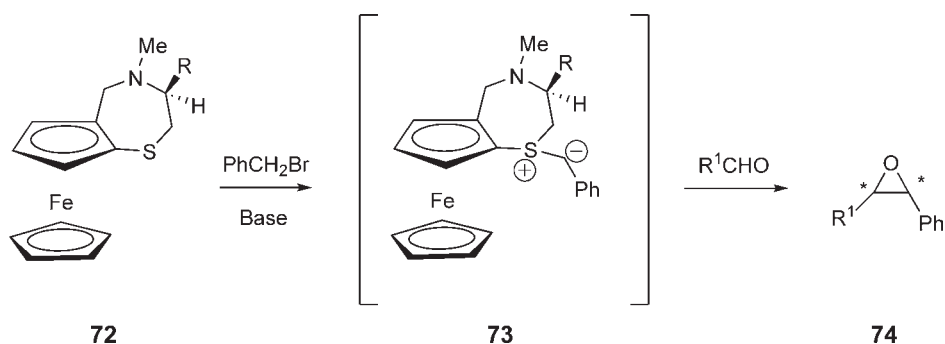


Figure 10

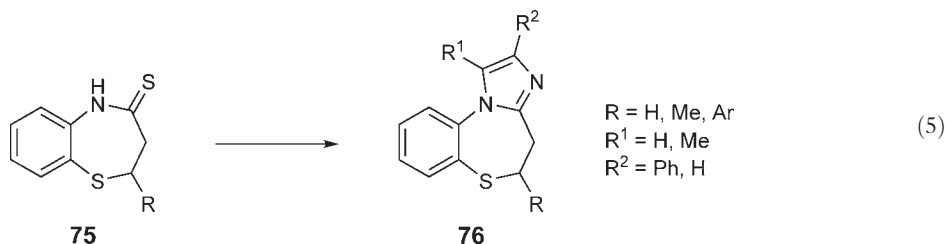
The homochiral ferrocenyl 1,4-thiazepines **72** were used for the asymmetric transformation of aldehydes into epoxides **74**. The reaction involved the formation of an intermediate sulfur ylide **73**. The ee's were up to 94%, although the diastereoselectivity remains to be controlled, being 60:40–82:18 in favor of the *trans*-oxirane **74** (Scheme 8) <2004TA3275>.



Scheme 8

13.09.6.4 Reactions Involving Two or More Ring Atoms

Imidazole rings could be fused to the benzothiazepine ring (e.g., **76**) starting from a thioamide derivative **75** by either (1) addition of ammonia, followed by an α -chlorocarbonyl derivative or (2) methylation at sulfur, addition of propargyl amine, and cyclization (Equation 5) <1995EJM429>. Similar ring fusions (1,2,4-triazole, quinazoline, 1,2,4-triazine) starting from 2,3-substituted thiophene analogues of **75** were described <1997JHC921>.



The 1,3-dipolar cycloaddition reaction of benzonitrile oxide to the imine function of a benzothiazepine yielded the fused 1,2,4-oxadiazoline **77** <1995EJMC925>.

The tricyclic β -lactams **78** that are formed by a [2+2] cycloaddition as described before for the fully conjugated derivatives could be ring-opened with trifluoroacetic acid (TFA) to the benzoxazepines or benzothiazepines **79** with an exocyclic double bond. The (*E*)-stereoisomer was formed in excess. The reaction was thought to involve formation of an azetidinone after loss of thiomethanol, followed by ring opening (Figure 11) <1997T8439>. N-Acetylated 2,5-dihydrobenzo-thiazepines and -oxazepines may be formed as side products <1997JHC823>.

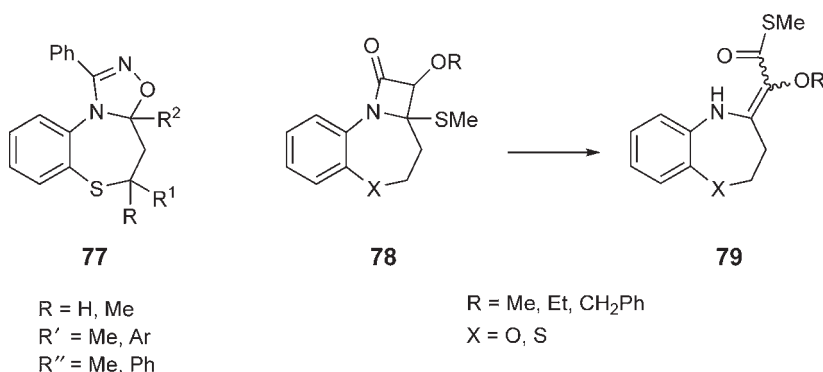
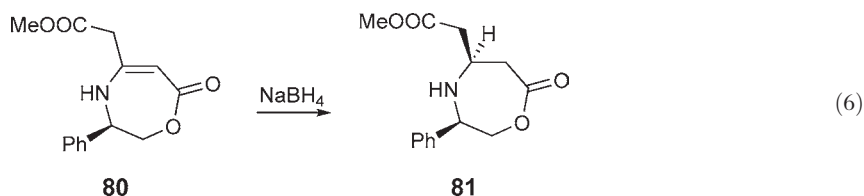
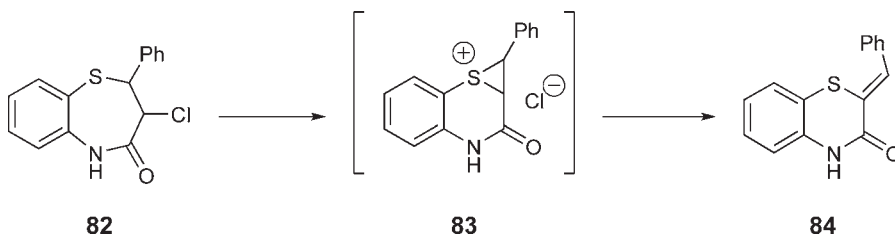


Figure 11

Reduction of a tetrahydrooxazepine **80** with sodium borohydride gave the corresponding hexahydro derivative **81**, an intermediate in the synthesis of β -amino diacids (Equation 6) <2005TL8203>.

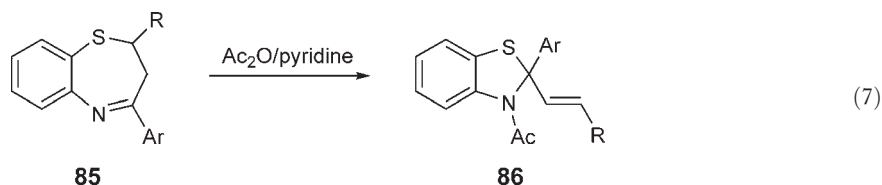


The β -chlorobenzothiazepinone **82** underwent solvolysis in dimethylformamide (DMF) solution, involving a thiiranium intermediate **83**, and affording the ring-contracted benzothiazine derivative **84** (Scheme 9) <2001CR925>.

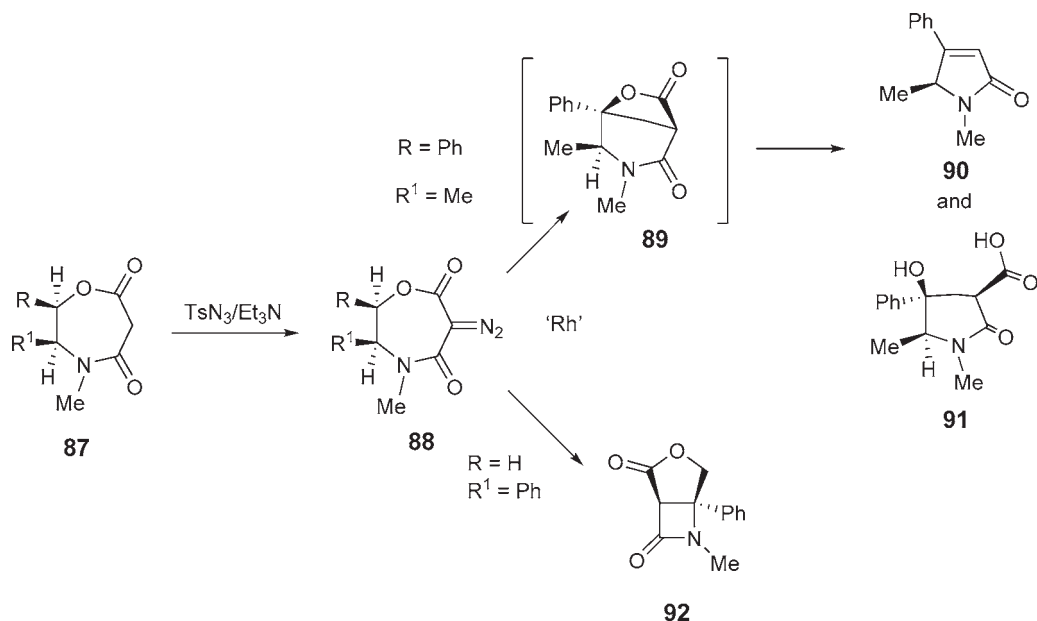


Scheme 9

Acetylation of benzothiazepine **85** (R = aryl, 2'-styryl) in the presence of pyridine caused a ring contraction, affording 2,2-disubstituted-3-acetylated benzothiazoline derivatives **86** (Equation 7) <1997LA995, 2003ARK19, 2004JHC399>.

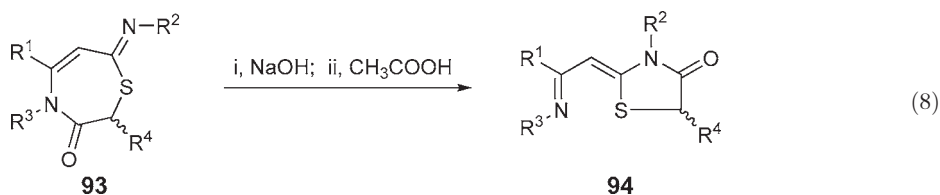


The enantiopure oxazepane diones **87** could be readily transformed by a diazo-transfer reaction with tosyl azide and base to the diazo derivative **88**. Catalytic decomposition of **88** gave different ring-contracted heterocycles, depending on the direction of the carbene insertion. The ephedrine derivative **88** (R = Ph, R¹ = Me) inserted at the benzylic position, generating an intermediate **89** and leading to pyrrole derivatives **90** and **91** <1995AGE78, 1995TA807>. If the position next to oxygen of the oxepane is unsubstituted, the reaction took another course and the stable β -lactams **92** were isolated (Scheme 10) <1997TA699>.

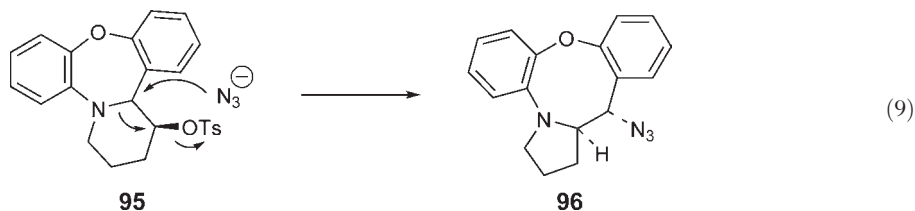


Scheme 10

Ring transformation of 1,4-thiazepine **93** in basic medium afforded ring-contracted thiazolidin-5-one derivative **94** (Equation 8) <1996LA211, 2000SL1831>.



An interesting ring-expansion reaction of the tetracyclic oxazepine derivative **95** occurred to yield a 1,4-oxazocine derivative **96**. The reaction mechanism was thought to involve anchimeric assistance of the nitrogen atom of the heterocycle (Equation 9) <1996J(P1)545>.

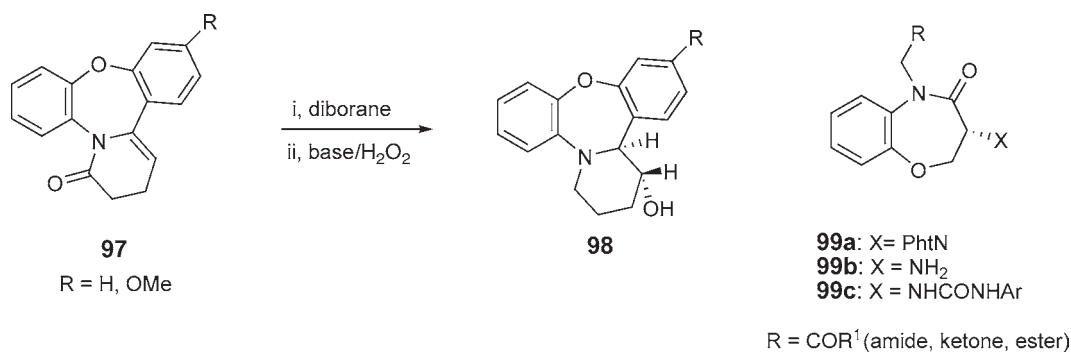


13.09.7 Reactivity of Substituents Attached to Ring Carbon Atoms

13.09.7.1 1,4-Oxazepines

The exocyclic double bond of the enamide **97** was reacted with diborane, followed by alkaline hydrogen peroxide addition, affording the *trans*-alcohol **98** <1996J(P1)545>.

Phthalimide-protected 6-aminobenzoxazepinones **99a** were deprotected with hydrazine hydrate and the resulting amines **99b** have been condensed with isocyanates. The resulting urea derivatives **99c** are dual histamine H2 and gastrin receptor antagonists (Scheme 11) <1997BMC1411>. Similar aminooxazepines have been described <1997JMC1570>.



Scheme 11

Different 3-substituted derivatives **100a–g** of 5-arylbenzoxazepine were prepared starting from the ethoxycarbonyl-substituted **100a**. The acid derivatives **100b** were used to prepare isolable diastereoisomers by amidation reactions with amino acid derivatives. Acid cleavage of the isolated diastereoisomers gave the homochiral **100b**. These benzoxazepines **100** have been found to have potent SQS inhibition activities <2002BMC385, 2002BMC401, 2002JME4571>.

A diastereoselective method for the asymmetric synthesis of monocyclic oxazepines **101** with an ester side group has been described (Figure 12) <2005TL8203>.

Chloropyrimidines fused to benzoxazepines are versatile starting materials for development of inhibitors of specific kinases. Thus, the 1-chloro function of pyrimidooxazepine **102** could be substituted with heterocyclic amines <2005BML5474, 2005TL7523, 2006BML5102>, anilines, arylthiols, and phenols <2005JOC9629> to afford the substituted derivatives **103**. In the same way, the 3-chloro function of pyrimidine **104** could be substituted (Scheme 12) <2005TL7523>.

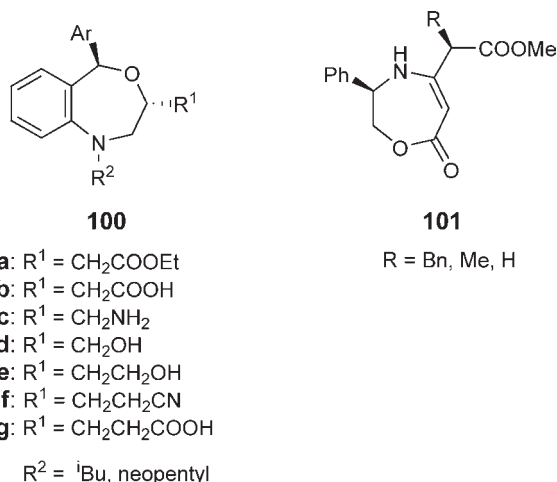
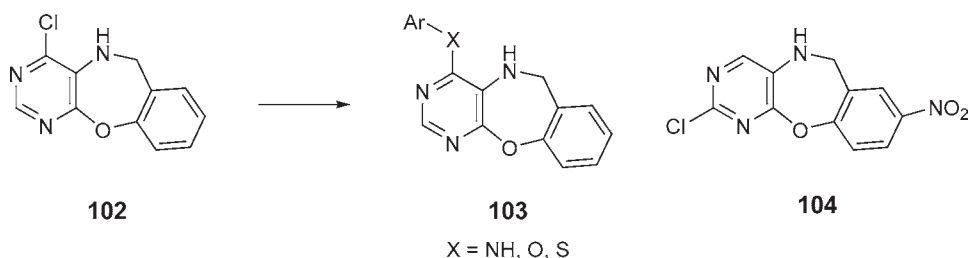


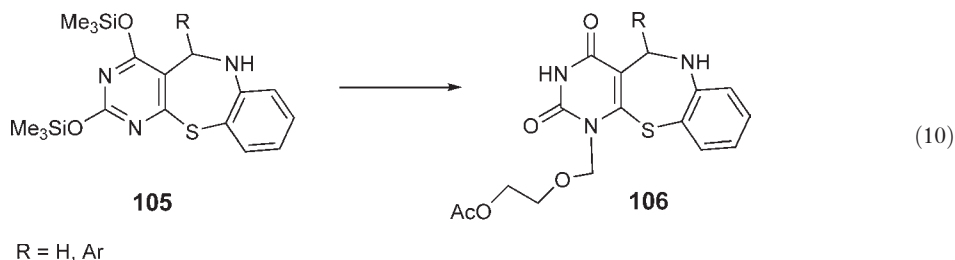
Figure 12



Scheme 12

13.09.7.2 1,4-Thiazepines

Pyrimido[5,4-*f*]benzo[1,4]thiazepines **105** were alkylated by the Vorbruggen reaction at the pyrimidine nitrogen. The resulting uracil derivatives **106** are inhibitors of HIV-1 reverse transcriptase (Equation 10) <1995JME2145>.



Carboxylic acid derivatives of thiazepine were obtained by cyclization of D-penicillamine. The ester derivative **107a** was transformed to the carboxylic acid **107b** and hydroxamic acid **107c**. The latter compound is a matrix metalloproteinase (MMP) inhibitor (Figure 13) <1999JME4547>.

Amide derivatives of benzothiazepinone **108** were prepared by solid-phase synthesis. Cleavage of **108** from the *p*-methylbenzhydryl (MBHA) resin was done with HF/anisole (Figure 13) <1999TL4939>.

The side chain at the 7-position of benzothiazepine **109** was varied starting from the 2-hydroxyaryl derivative **109a**. For instance, homologous acids **109b** and **109c** have been prepared using standard transformations. The acetic acid derivative **109b** showed potent and selective V_2 arginine vasopressine receptor antagonist activity (Figure 13) <2003BML4031>.

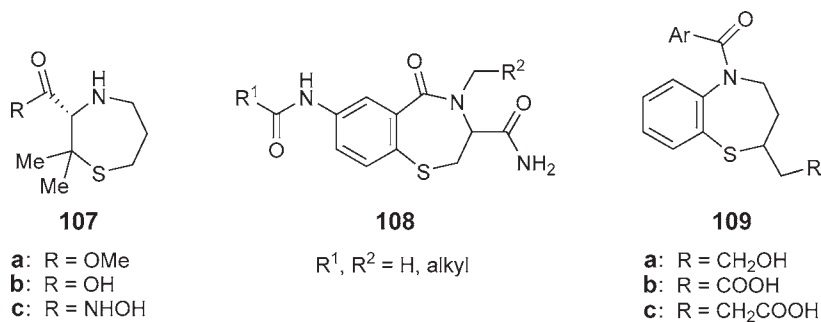


Figure 13

6-Amino-substituted benzothiazepin-5-ones **110** were prepared in optically active form by solid-phase synthesis starting from cysteine. After 9-fluorenylmethoxycarbonyl (Fmoc) deprotection of **110a**, the free amine **110b** could be transformed into the amide, urea, and sulfonamide **110c–e** (Figure 14) <1999JOC2219>. Similar derivatizations were carried out starting from the *t*-butoxycarbonyl (BOC)-protected monocyclic 6-aminothiazepin-5-one **111** (Figure 14) <1999JOC3019, 2002BML1291>. For more examples, see <1997BMC1411, 2000JME2387, 2000TL3029, 2001BML2127>.

Analogous to the oxazepine systems **102** and **103** described in Section 13.09.7.1 pyrimido[4,5-*b*][1,4]benzothiazepines **112** (Figure 14) could be substituted at the pyrimidine ring with S- and N-containing nucleophiles. Nucleophilic substitution may, in fact, take place either before or after the Bischler–Napieralski reaction, leading to the tricyclic ring system <2005JOC10810, 2006BML5102>.

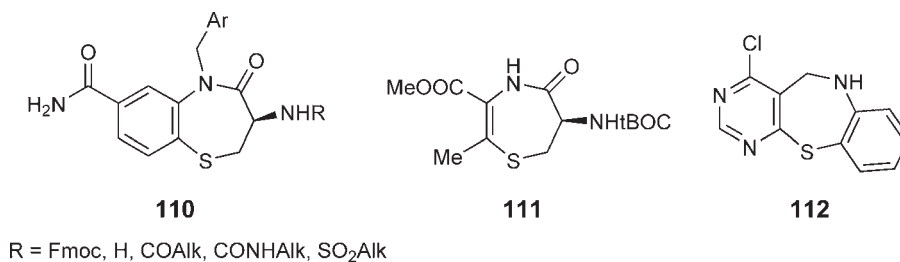


Figure 14

13.09.8 Reactivity of Substituents Attached to Ring Heteroatoms

13.09.8.1 1,4-Oxazepines

Acetamide derivatives of dibenzoxazepine **113** were prepared and amidated with different alkyl and aralkyl side chains in order to function as a potential surrogate for the diacylhydrazine group of SC-51089, a potent PGE₂ antagonist (Figure 15) <1996JME609>.

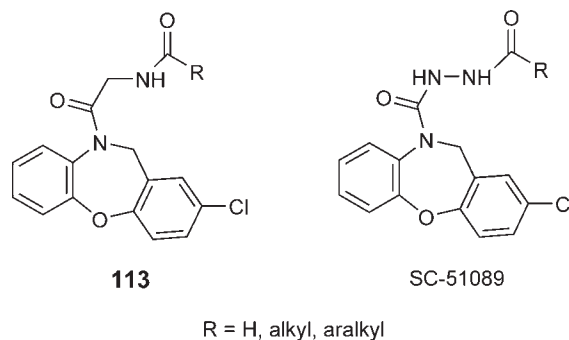


Figure 15

13.09.8.2 1,4-Thiazepines

The *N*-(2-hydroxyethyl)benzothiazepinone derivative **114a**, which is a metabolite of diltiazem, was prepared via alkylation of the unsubstituted benzothiazepinone **114b** with ethyl bromoacetate. This afforded ester **114c** that was saponified to the corresponding carboxylic acid **114d** and then reduced with diborane to **114a** <1996JME1196>. Similarly, a propargyl side chain was attached to **114b** affording an acetylene **114e** that underwent 1,3-dipolar cycloaddition with benzyl azide affording 1,2,3-triazole **114f**. Reaction of **114d** with hydrazine gave hydrazide **114g** <2001CR925>. Related examples of N-functionalization of analogues of **114b** have been described (Figure 16) <2001JME4082, 2005T3753, 2006BML4728>.

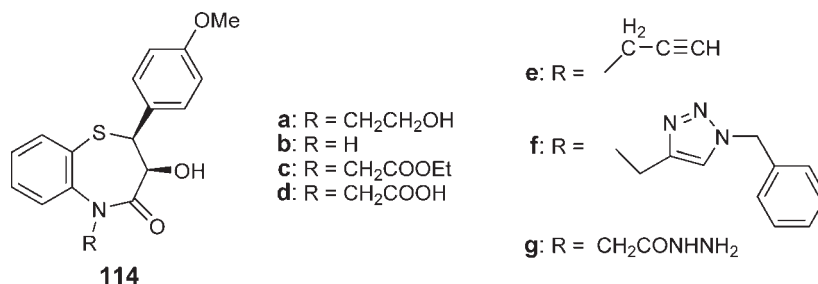


Figure 16

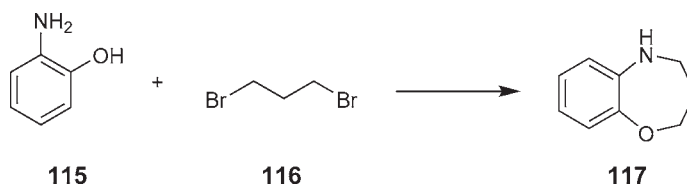
13.09.9 Ring Synthesis of 1,4-Oxazepines and 1,4-Thiazepines, Classified by Number of Ring Atoms in Each Component

Numerous 1,4-oxazepines and 1,4-thiazepines have been synthesized mainly for biological and pharmaceutical purposes. A multitude of synthetic procedures are frequently used and well known by many chemists. In this part, we try to summarize the most important methods for their synthesis. Most of the intermediates during the synthesis are isolated before the cyclization, so these procedures can be classified as occurring via acyclic fragments. These procedures will be discussed in the following section. First, we review the synthesis from two fragments without the isolation of the intermediates.

13.09.9.1 1,4-Oxazepines

13.09.9.1.1 From [4+3] fragments

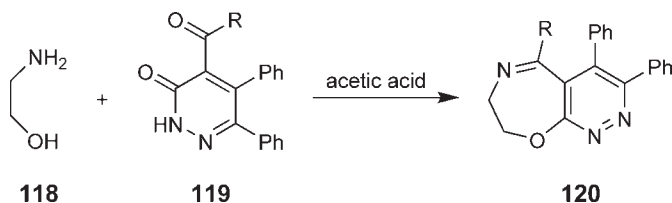
One of the most commonly used procedures is the combination of two fragments containing three and four atoms of the final product. One of these fragments, a bis-electrophile, contains two efficient leaving groups, and the other part is a bis-nucleophile with an amine and hydroxyl group. Normally halogen atoms serve as leaving groups. The most simple example is the reaction of 2-aminophenol **115** with 1,3-dibromopropane **116** to produce 1,4-benzoxazepine **117** (Scheme 13) <1980MI19>.



Scheme 13

Instead of halogen atoms, other functional groups can be attacked by the nitrogen and oxygen atom. The reaction of 2-aminoethanol **118** with β -diketones **119** led to the corresponding enamines, which reacted further with acetic

acid, as catalyst, in ethanol to afford the pyridazino-oxazepine **120** (Scheme 14) <2003PS199>. On the other hand, α,β -unsaturated amides lead to amino-substituted benzoxazepines <2004EJM369>. Further examples have been described <2006T6018>.



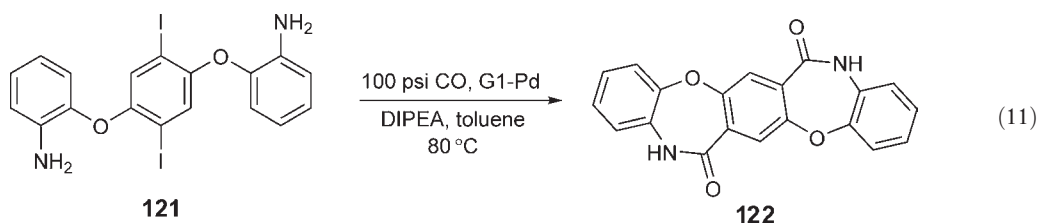
Scheme 14

13.09.9.1.2 From [5+2] fragments

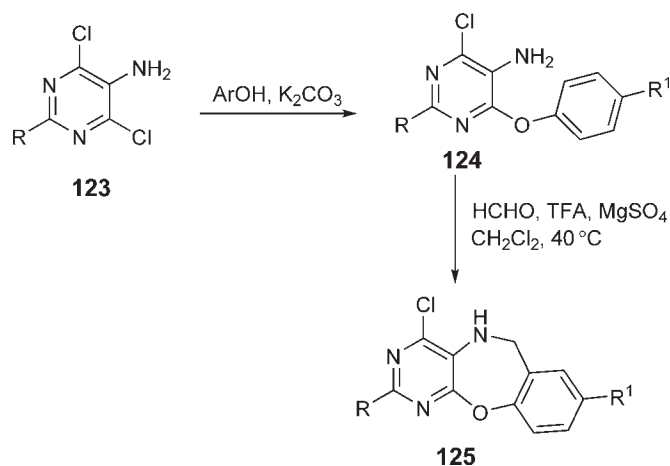
To the best of our knowledge, no procedure has been reported since 1995 for the synthesis of 1,4-oxazepines from [5+2] fragments without isolating the intermediate.

13.09.9.1.3 From [6+1] fragments

The transition metal-catalyzed carbonylation reaction is an important pathway to introduce an extra carbon atom in the heterocyclic ring. Lu and Alper used this reaction with recyclable palladium-complexed dendrimers on silica to synthesize 1,4-oxazepines. Remarkably, starting from iodinated arylamine **121**, as a substrate for the intramolecular carbonylation, quantitative conversion to the pentacyclic heterocycle **122**, containing two oxazepine rings, was achieved (Equation 11) <2005JA14776>.

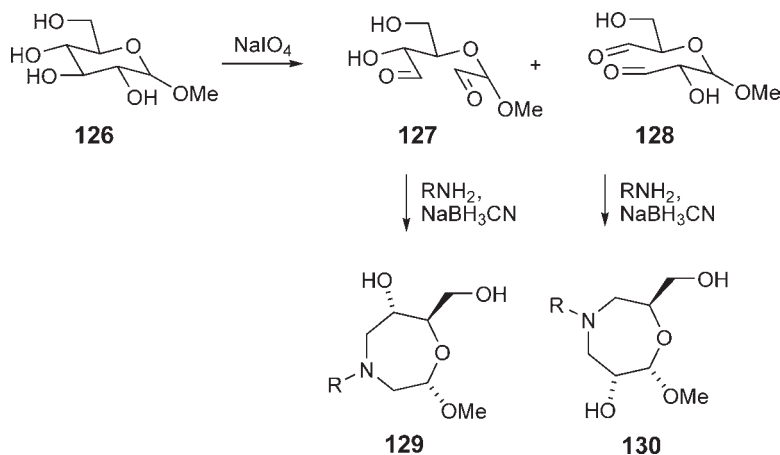


After the nucleophilic aromatic substitution of pyrimidine **123**, the isolated monosubstituted ether product **124** was cyclized with paraformaldehyde in dichloromethane under acidic Pictet–Spengler conditions to form pyrimido[4,5-*b*]-1,4-benzoxazepine **125** in good yield (62%) (Scheme 15) <2005JOC9629>. The same procedure has been used by Xu *et al.* <2005TL7523>.



Scheme 15

Clark and Osborn reported in 2004 the synthesis of 1,4-oxazepanes by a ring cleavage reaction of methyl α -D-glucopyranoside. Using a small amount of sodium periodate (2 equiv), α -D-glucopyranoside **126** was converted to dialdehydes **127** and **128**. Reductive amination of both compounds gave the corresponding oxazepanes **129** and **130** (Scheme 16) <2004TA3643, 2004T4959>. Oxazepines have been prepared from other biscarbonyl electrophiles in an Ugi three-component reaction involving a ketoester, an amine, and an isonitrile <2006TL2649, 2006JOC2811>.

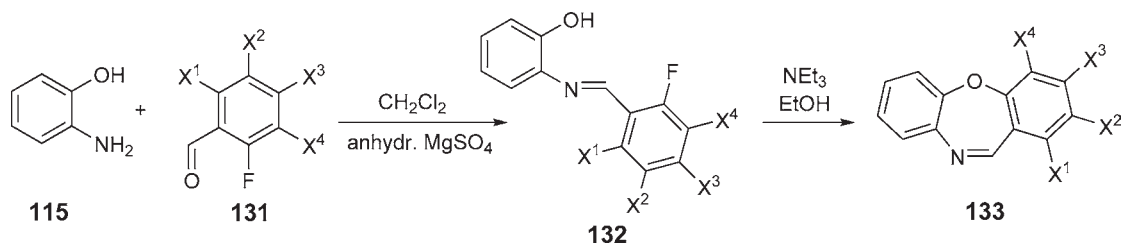


Scheme 16

13.09.9.1.4 From acyclic fragments

13.09.9.1.4(i) O-C-C-N-C-C-C

High yields have been achieved via Schiff base condensation of 2-aminophenol **115** and fluorinated benzaldehyde **131** in dichloromethane over anhydrous magnesium sulfate at room temperature. Cyclization of the resulting imines **132** in the presence of an excess of triethylamine produced a mixture of products. Purification by extraction yielded the expected 1,2,3,4-tetrafluorodibenzo[*b,f*][1,4]oxazepine **133** (Scheme 17) <2002JFC(115)91>.



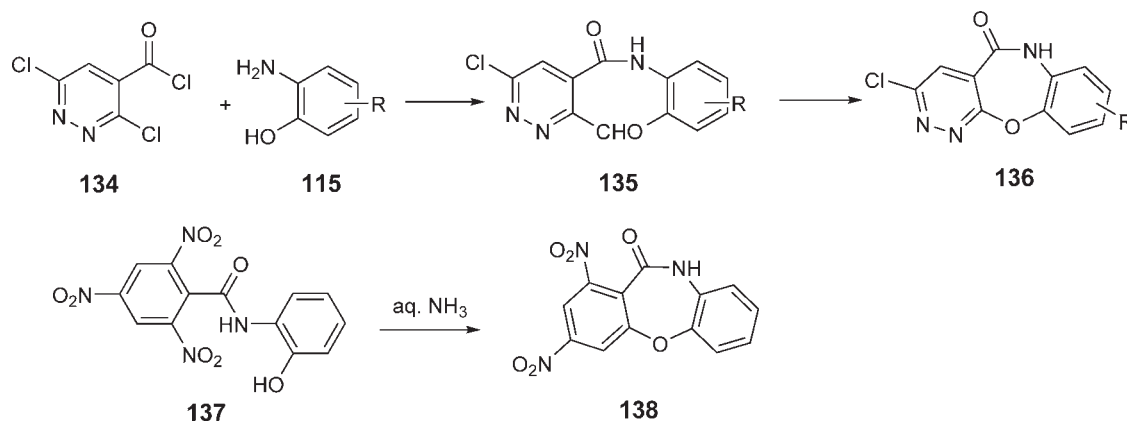
Scheme 17

In the framework of a synthesis of antimycobacterial agents, acid chloride **134** was reacted with 2-aminophenol **115** and base. The isolated product **135** underwent a base-mediated ring closure to form tricyclic benzoxazepines **136** (Scheme 18) <2000AP231>. The same procedure has been used for the synthesis of multidrug resistance modulating agents <2004JME4627>.

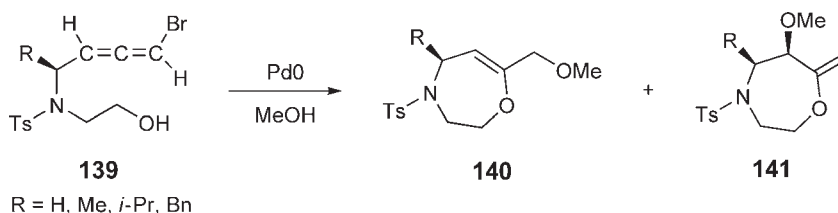
In some cases, as with the very electron poor starting material **137**, a nitro group can serve as the leaving group, leading to dibenzoxazepine **138** (Scheme 18) <2005JOC9371>.

Bromoallene **139** was used as an allyl dication equivalent, and palladium-catalyzed cyclization leads to a mixture of regioisomers **140** (major) and **141** (minor) (Scheme 19) <2004JA8744>.

Several analogous examples of cyclization using oxygen atom as a nucleophile to form the 1,4-oxazepine ring can also be mentioned here <1995BML1177, 1997JHC485, 1999T9205, 2000JOC6932, 2002S2232, 2003HCA726, 2004JOC280, 2004T11547, 2005BML2515, 2005S2549>.



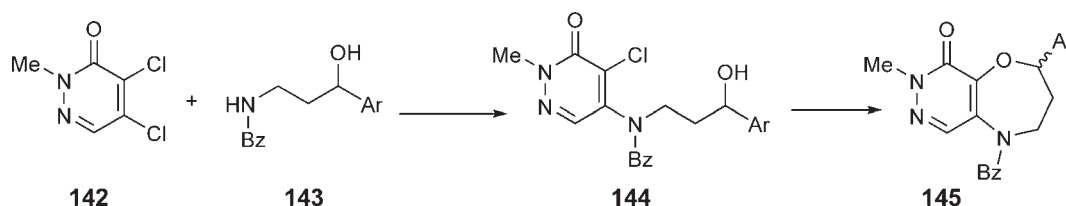
Scheme 18



Scheme 19

13.09.9.1.4(ii) O-C-C-C-N-C-C

This procedure is similar to the previous one, except that the cyclization happens on the carbon at the β -position of the nitrogen atom. The synthesis of oxazepine **145** started with the reaction of 4,4'-dichloro-2-methyl-3-(2*H*)-pyridazinone **142** with 3-benzylamino-1-phenylpropen-1-ol **143**. The obtained product **144** was cyclized in basic conditions to the desired 1,4-oxazepine **145** (Scheme 20) <1996JHC583>.



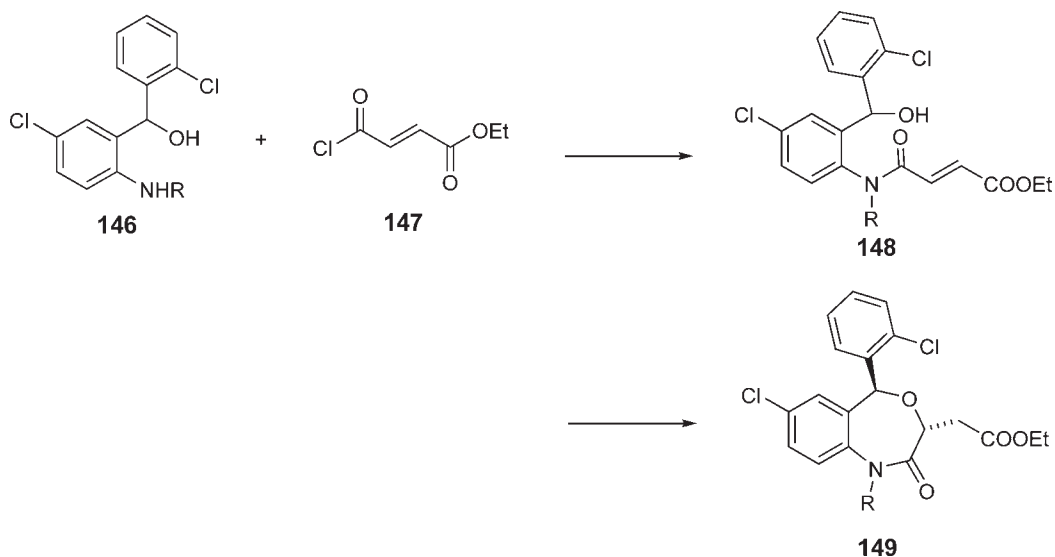
Scheme 20

Condensation of fumaric acid chloride monoethyl ester **147** with aminoalcohol **146**, followed by intramolecular Michael addition of the isolated amide **148**, afforded the 1,4-benzoxazepine-3-acetate **149**. The thermodynamically favored 3,5-*trans*-isomers were obtained (Scheme 21) <2002BMC385, 2002BMC401, 2002JME4571>.

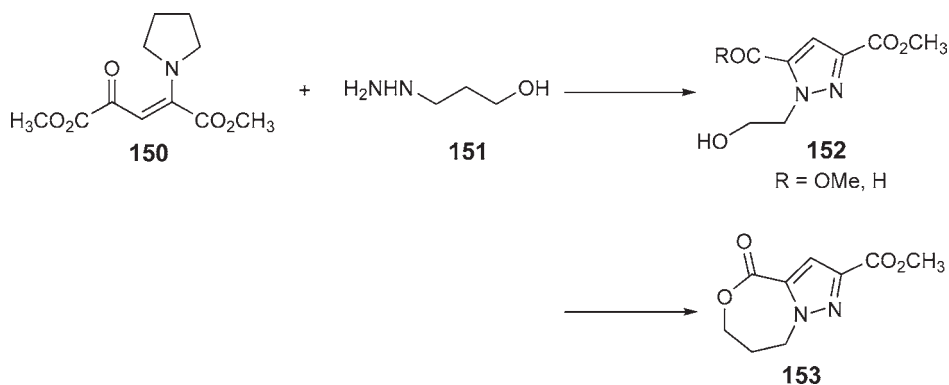
Pyrazolooxazepine **153** was synthesized starting from the condensation of hydrazinol **151** with enaminoketone **150**. When the isolated ester intermediate **152** (R = OMe) was saponified, ester hydrolysis afforded acid **152** (R = H), which cyclized on subsequent treatment with 1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) to form oxazepine **153** (Scheme 22) <2003TL5867>.

13.09.9.1.4(iii) N-C-C-O-C-C-C

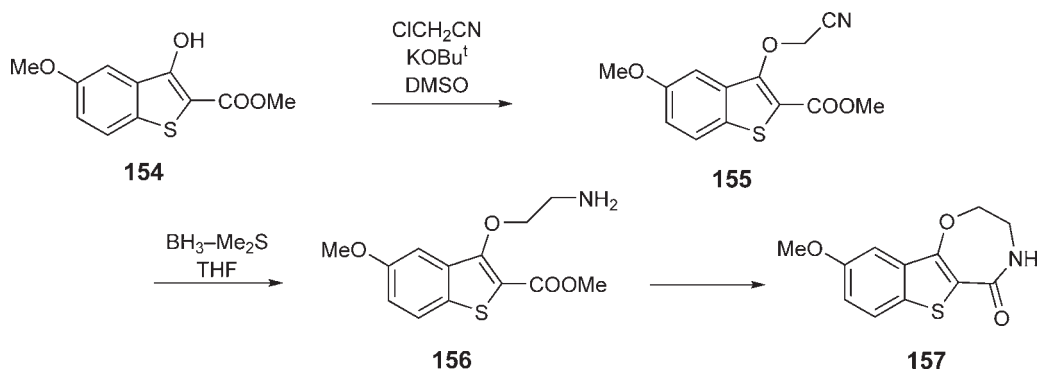
The reaction of **154** with chloroacetonitrile in the presence of potassium *tert*-butoxide afforded **155**. The nitrile group was reduced with borane methyl sulfide to the corresponding amine **156**, which on treatment with sodium methoxide was transformed into the 1,4-oxazepine **157** (Scheme 23) <1996JOC6060>.



Scheme 21

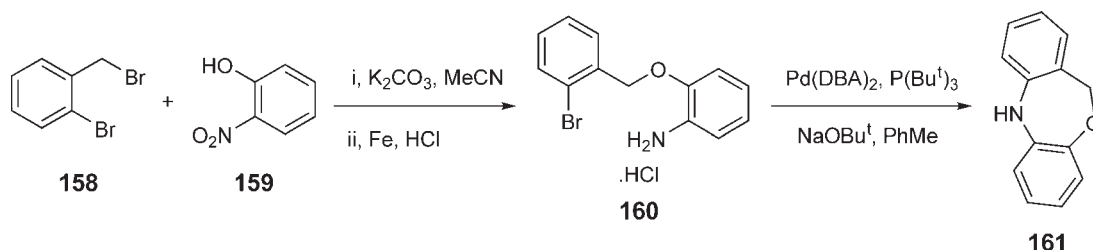


Scheme 22



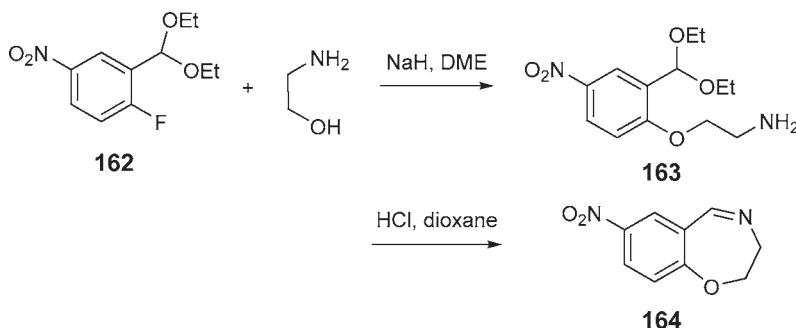
Scheme 23

As an alternative to this procedure, the amino group of **160** can be generated from the corresponding nitro derivative prepared from **158** and **159** by reduction with iron. Palladium-mediated cyclization of **160** produced the desired dibenzoxazepine **161** (Scheme 24) <2003JOC644>. Tandem reduction/reductive amination <2004JHC963> and reduction/lactamization <2006JHC1031> procedures were also described.



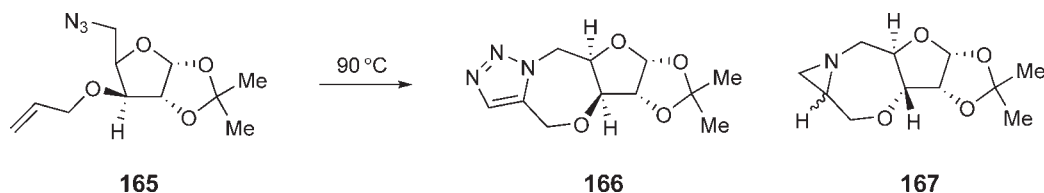
Scheme 24

Compound **164** was readily synthesized in two steps starting from 2-fluoro-5-nitrobenzaldehyde diethyl acetal **162** by nucleophilic substitution. Acidic hydrolysis of the diethylacetal function of **163** restored the aldehyde group, followed by spontaneous cyclization yielding oxazepine **164** (Scheme 25) <2004TA2555>.



Scheme 25

The protected glucose derivative **165** was transformed by an intramolecular 1,3-dipolar cycloaddition of the azide to the allyl function, affording a fused 1,2,3-triazole **166** after *in situ* oxidation. The other stereoisomer gave under the same conditions aziridine **167**, probably after ring opening of the intermediate 1,2,3-triazoline (Scheme 26) <2004T4959>.



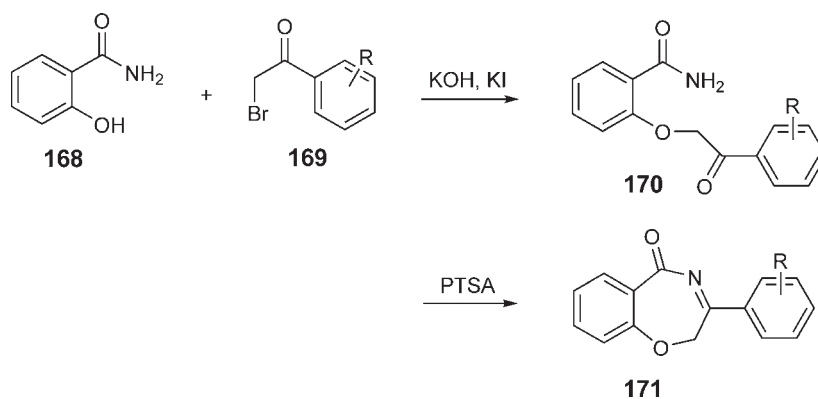
Scheme 26

13.09.9.1.4(iv) N-C-C-C-O-C-C

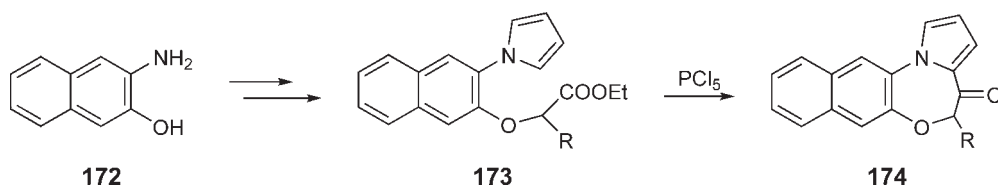
Alkylation of the salicylamide **168** with 2-bromoacetophenone **169**, followed by the acid-mediated (*p*-toluenesulfonic acid, PTSA) cyclocondensation of intermediate **170** under Dean–Stark reflux conditions, gave 55–90% of the oxazepinones **171** (Scheme 27) <2002BML2367>. A related example leading to benzoxazepin-5-ones has been reported <1995T13301>. Tetracyclic benzoxazepinones derived from sugars were prepared by intramolecular nucleophilic substitution of fluorine <2001OL1089>.

13.09.9.1.4(v) C-N-C-C-O-C-C and C-C-O-C-C-N-C

During the research for a novel reverse transcriptase inhibitor, Campiani *et al.* synthesized oxazepines **174**, starting from 3-amino-2-naphthol **172**. After saponification of the ester group of pyrrole derivative **173** (R = OEt), intramolecular Friedel–Crafts acylation occurred after generating the acid chloride **173** (R = Cl) using phosphorus pentachloride, affording the tetracyclic **174** (Scheme 28) <1996JME2672>. There are some more recent reports related to these fused pyrrole derivatives <2002JME4276, 2005JME4367, 2005JME7153>.

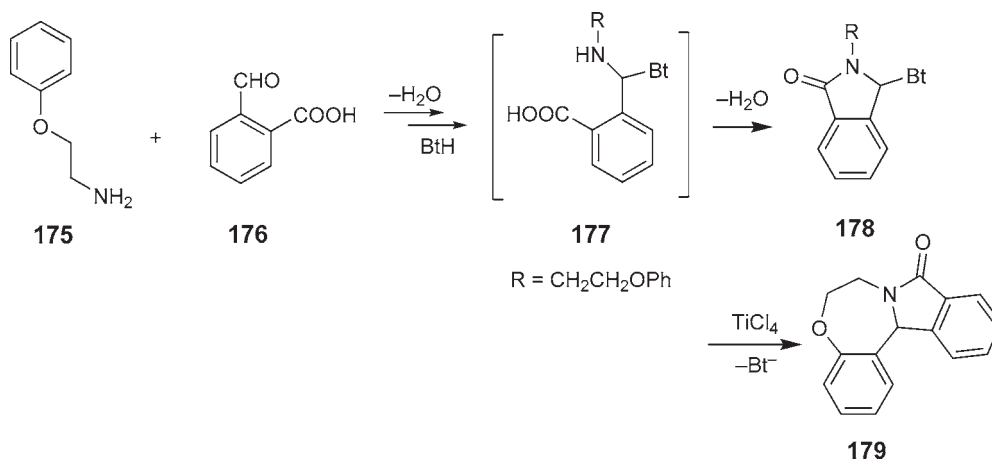


Scheme 27



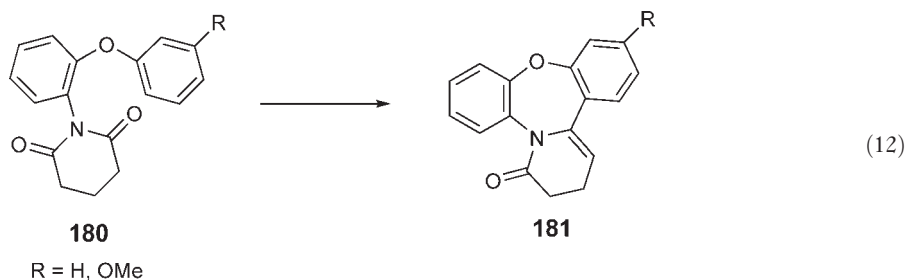
Scheme 28

The synthesis of the 1,4-oxazepine **179** involved the formation of intermediate **178**. The latter has been obtained by the three-component reaction of amine **175**, aldehyde **176**, and benzotriazole, leading to the intermediate **177**, which underwent dehydrative cyclization to generate **178**. Lewis acid-mediated cyclization with the loss of benzotriazole anion produced the interesting 1,4-oxazepine **179** (Scheme 29) <2001JOC5590>. A similar scandium or copper triflate-catalyzed reaction has been reported <1996SL871>.



Scheme 29

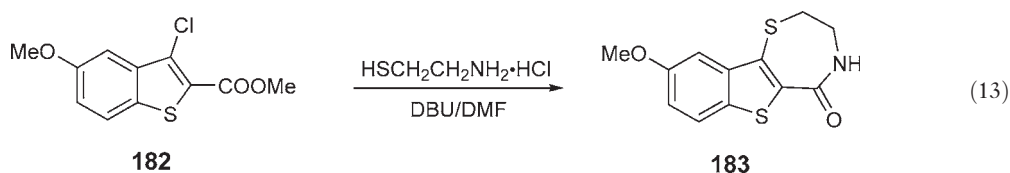
Tetracyclic pyridodibenzothiazepine derivative **181** was prepared via polyphosphoric acid cyclization of glutarimide **180** (Equation 12) <1996J(P1)545>.



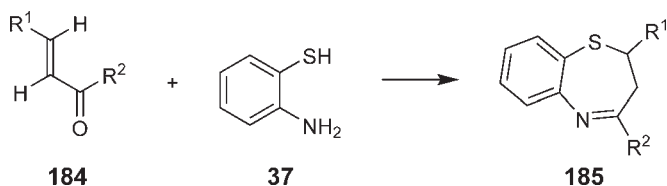
13.09.9.2 1,4-Thiazepines

13.09.9.2.1 From [4+3] fragments

The thiazepine **183** was easily obtained in a one-pot reaction of **182** with cysteamine-HCl and 1,8-diazacyclo[5.4.0]-undec-7-ene (Equation 13) <1996JOC6060>. Monocyclic homochiral thiazepin-5-ones were prepared from a 1,3-diol and protected cysteine <2002OL1235> or from penicillamine and dehydroalanine derivatives <1997LA17110>.



(*E,E*)-Cinnamylideneacetophenone **184** ($R^1 = \text{PhCH}=\text{CH}$, $R^2 = \text{Ar}$) reacted with 2-aminothiophenol **37** in a one-pot reaction to form the corresponding 1,4-benzothiazepine **185**. Lévai has optimized this reaction using mild conditions (Scheme 30). The somewhat lower yields (38–53%) of **185** are due to the decomposition on silica during chromatographic purification. The substituents on the aryl ring of **184** have no influence on the yield <2004JHC399>.

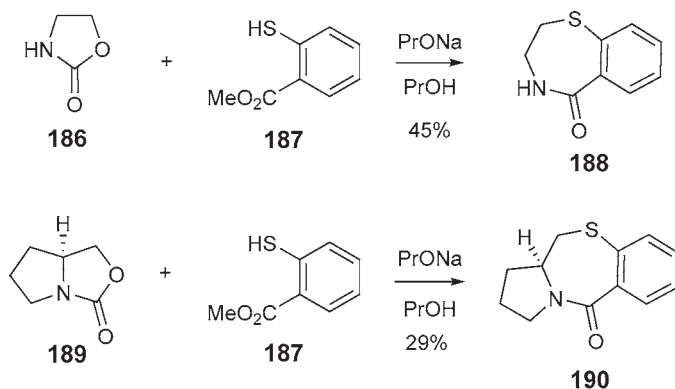


Scheme 30

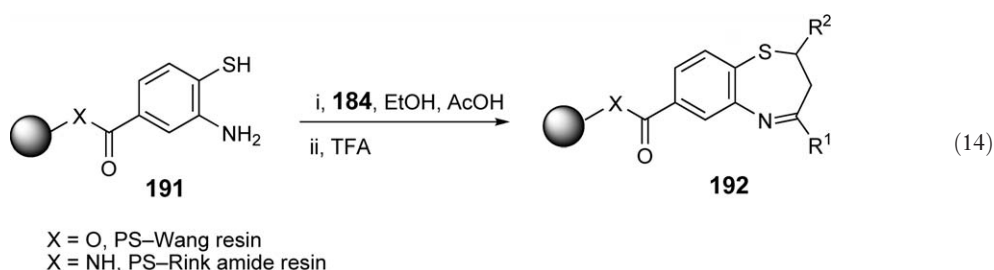
The reaction of chalcones **184** with 2-aminothiophenol **37** and its derivatives is indeed one of the more popular methods toward benzothiazepine derivatives <1998JFC(91)171, 2003CPB1137, 2005T6642>. Reactions of **37** with α,β -unsaturated esters are also possible affording benzothiazepinones <2003BML4031>.

The reaction of methyl thiosalicylate **187** with 2-oxazolidinone **186** yielded 45% of benzothiazepinone **188**. The same procedure has been followed to synthesize chiral thiazepine **190** starting from bicyclic oxazolidinone **189** and methyl thiosalicylate **187** (Scheme 31) <2001T2115>. Related reports about cyclization of amino acid derivatives and analogues of **187** have appeared <2004BMC4459>.

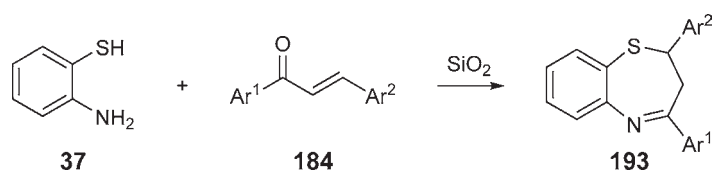
The synthesis of 1,4-thiazepines from chalcones **184** is also possible on solid support. This has been shown by Lee *et al.* In an one-step bis-nucleophilic attack of **75**, loaded on Wang or Rink amide resin, to the α,β -unsaturated ketone **184**, the seven-membered ring **192** is formed. TFA cleavage afforded more than 29% overall yield (Equation 14) <2001TL109>.



Scheme 31



Solvent-free conditions with high yields are reported by Kodomari *et al.* in the synthesis of 1,4-thiazepines **193**. Silica gel, as an inorganic support, gave the best result (87% yield). The reaction in toluene of *o*-aminothiophenol **37** with chalcones **184**, with electron-donating groups, gave only β -phenyl- β -(2-aminophenylmercapto)propiophenones, while with chalcones **184** bearing electron-withdrawing substituents, only 1,4-benzothiazepines were formed. On the other hand, this same reaction under solvent free conditions in the presence of silica gel gave only benzothiazepine **193** in good yield independent of the chalcone substituents, with the exception of nitro and hydroxyl groups (Scheme 32) <2004SC1783>. The chalcone reagent **184** can be generated *in situ* from propargyl alcohols and (het)aryl iodides and bromides by palladium-catalyzed coupling/isomerization reaction <2000OL4181, 2004T9463>.

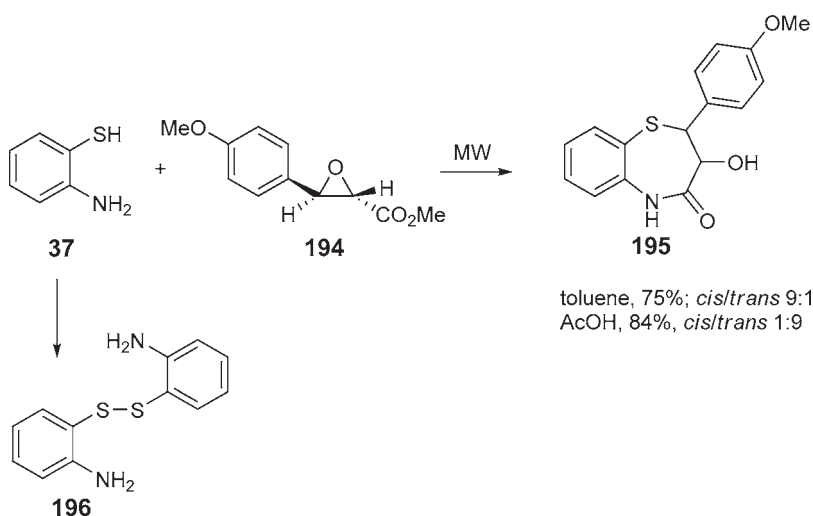


Scheme 32

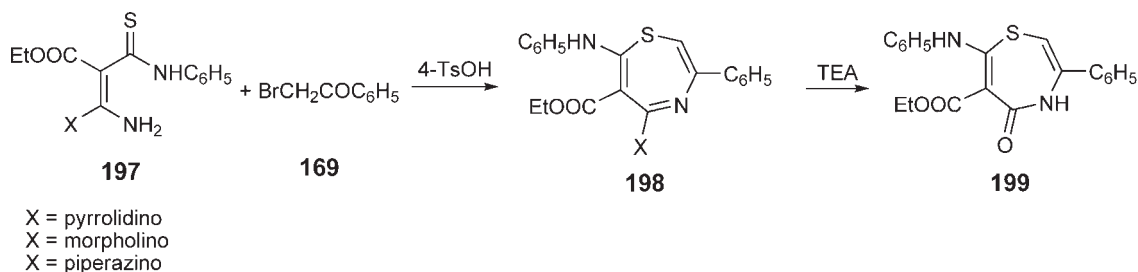
The traditional one-pot preparation of racemic **195** needed for the synthesis of diltiazem and analogues, starting with 2-aminothiophenol **37** and epoxide **194**, is simple but the obtained yields are low because of the prolonged reaction time. This favors the oxidation of **37** to the corresponding disulfide **196**. Vega *et al.* have optimized the reaction by microwave heating and different reaction conditions. The *cis/trans*-ratio is highly dependent on the solvent, and the total yields are raised to 75–84% (Scheme 33) <1996TL6413>. Diltiazem precursor **195** was also prepared from **37** and cyclic sulfites <2003JOC1736>.

13.09.9.2.2 From [5+2] fragments

The one-step reaction of thioamides **197** with 2-bromoacetophenone **169** (R=H) in the presence of a catalytic amount of PTSA in chloroform at reflux temperature yielded thiazepine **198**. The same reaction in the presence of base leads to 1,4-thiazepine-5-one derivative **199** (Scheme 34) <1995JHC463>.

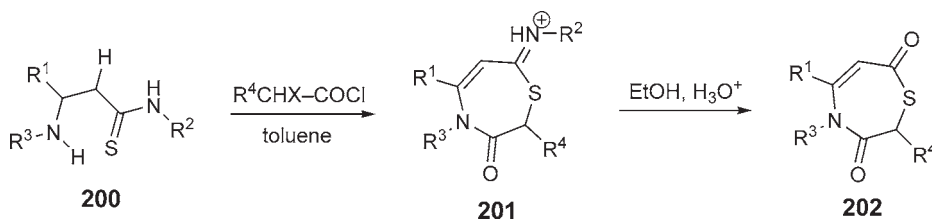


Scheme 33



Scheme 34

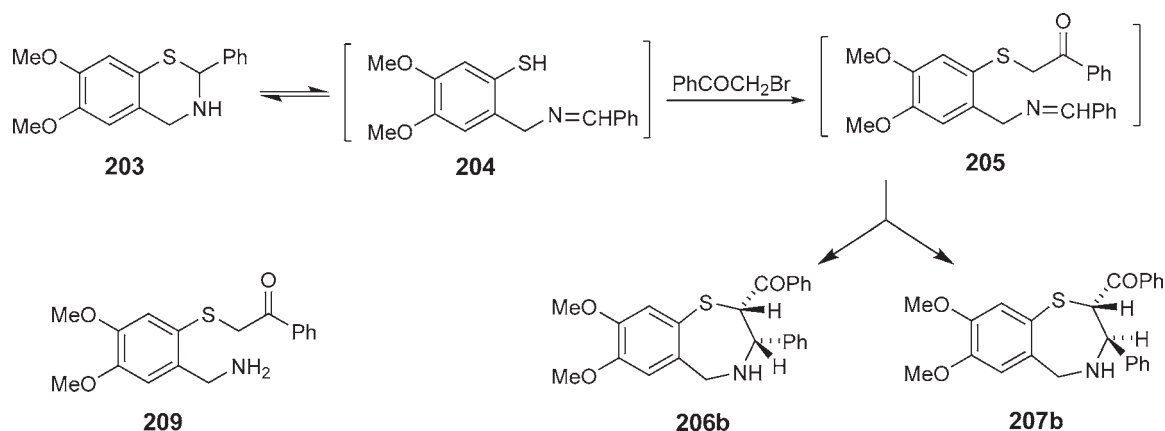
Regiospecific cyclocondensation has been carried out by Zaleska *et al.*, leading to 1,4-thiazepines **201**. After optimization, a 90% yield of thiazepines **201** was achieved from the reaction of thioamide **200** with α -haloacid chloride. After hydrolysis in ethanol with 1% hydrochloric acid, 1,4-thiazepin-3,7-diones **202** were formed (Scheme 35) <1996LA211>.



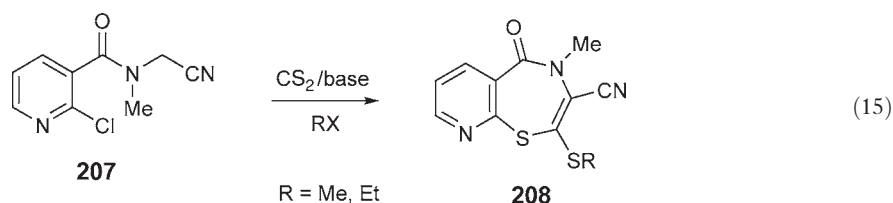
Scheme 35

When dihydro-1,3-benzothiazine **203** was allowed to react with KF in DMF (or NaOMe in MeOH), an open ring tautomeric isomer **204** was formed. When 2-bromoacetophenone **169** ($R = H$) is present in the reaction medium, a mixture of two diastereoisomers of **206** was obtained (75%) after enolate/imine addition of intermediate **205** with a slight excess of the *cis*-isomer **206a** over the *trans*-isomer **206b** (Scheme 35). The same result was obtained by a synthesis from [6+1] fragments, reported in the next section <1995TL753>.

The aminonitrile **207** was condensed with carbon disulfide and base, leading to an intermediate dithiocarboxylate, which underwent intramolecular substitution. After alkylation of the remaining thiolate function, pyridothiazepinones **208** were formed (Equation 15) <1998EJO1237>.



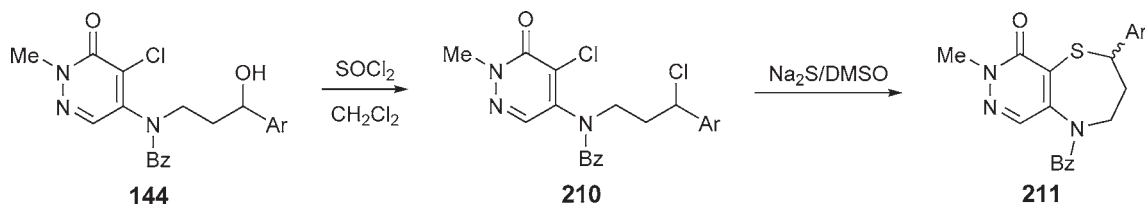
Scheme 36



13.09.9.2.3 From [6+1] fragments

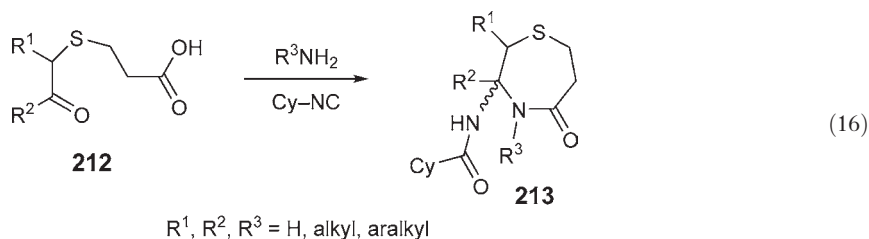
Instead of following the procedure described in Scheme 35, 1,4-benzothiazepine **206** can also be formed by the Mannich reaction of 2-benzoylmethylthio-4,5-dimethoxybenzoylamine hydrochloride **209** with benzaldehyde in the presence of NaOH in methanol. A good yield is observed for the diastereoisomers **92a** and **92b** in a ratio of 6:5 (Scheme 36) <1995TL753>.

Starting from pyridazine **144**, *o*-phenyl thiazepine **211** can be synthesized. The conversion of the hydroxy group of **144** to chloride **210** with thionyl chloride, followed by ring closure with sodium sulfide monohydrate in dimethyl sulfoxide (DMSO), yielded the desired thiazepine **95** (Scheme 37) <1996JHC583>.

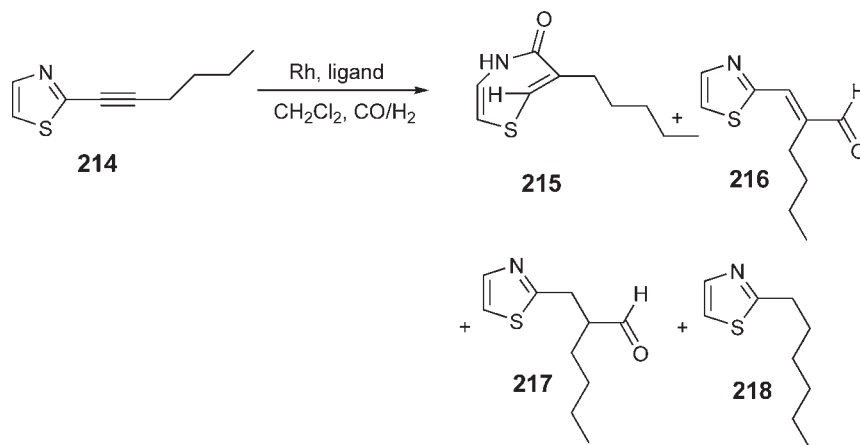


Scheme 37

The intramolecular Ugi reaction of 6-oxo-4-thiacarboxylic acids **212**, benzylamine, and cyclohexyl isonitrile gave hexahydro-1,4-thiazepin-5-ones **213**, in some cases with high stereoselectivity (Equation 16) <2003JOC3315>.

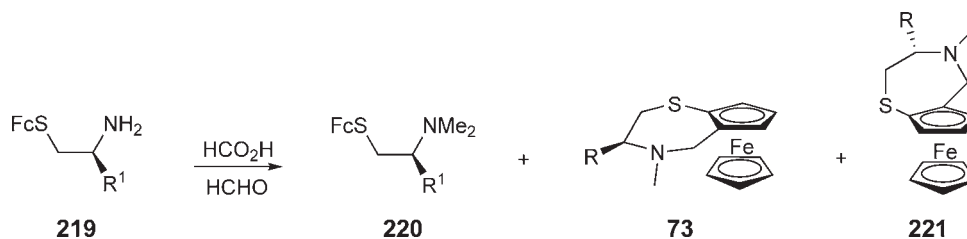


In 2001, Van den Hoven and Alper reported the unexpected 2(*Z*)-6(*E*)-4*H*-[1,4]-thiazepin-5-one **215**, as the major product, from the reaction of acetylenic thiazole **214** with carbon monoxide and hydrogen in presence of a zwitterionic rhodium complex and triphenyl phosphite. After optimization of the reaction condition, the pressure, and the temperature, up to 90% yield is achieved with good selectivity for thiazepine **215** over thiazole side products **216–218** (Scheme 38) <2001JA1017>.



Scheme 38

Attempted *N,N*-dimethylation of the ferrocene derivative **219** with formic acid and formaldehyde gave unexpectedly a mixture of two diastereoisomers **73** and **221**, as major reaction products along with the expected **220** (Scheme 39). The diastereoisomeric excess of **73** over **221** suggested a selectivity of *ortho*-cyclization because of steric and electronic effects. The selectivity increased as the *R*-group became larger, with the phenyl group providing the best result <2002EJO2776>.



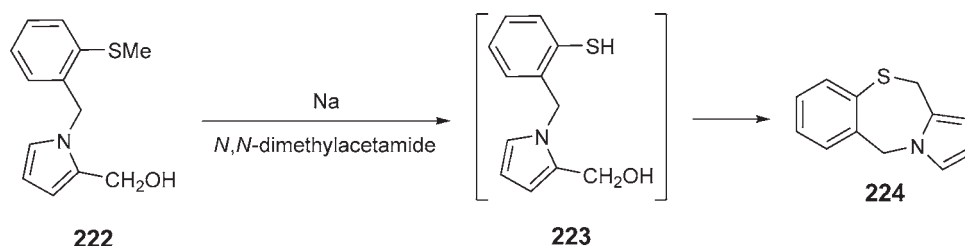
Scheme 39

Tricyclic thiazepine derivatives were analogously prepared via an intramolecular Mannich-type reaction <1995JME2145, 2000JOC4269>.

13.09.9.2.4 From acyclic fragments

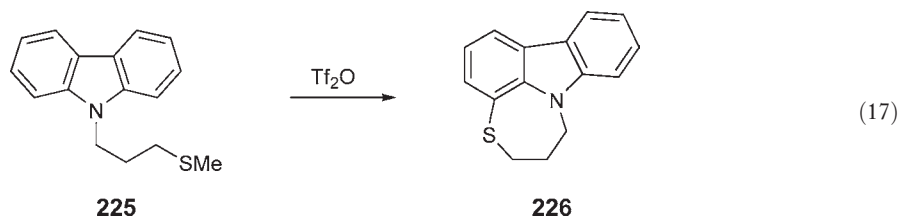
13.09.9.2.4(i) S-C-C-N-C-C-C and S-C-C-C-N-C-C

Cyclization with sulfur, as the nucleophile, is one of the most common pathways to form medium-size rings. The attack may take place on an electrophilic carbon, via Michael addition <1997LA1711, 1999JOC3019> or by displacement of a leaving group such as halogen <1995JOC2597, 1996T7745, 2005TL7977>, triflate <1997TL2775, 1999JOC3019>, or hydroxyl, as described in the following example. After demethylation of **222** with sodium in *N,N*-dimethylacetamide, thiophenol **223** was cyclized immediately without purification, using the Mitsunobu reaction to form tricyclic 1,4-thiazepine **224**. No intermediate purification was done because of the high sensitivity of **223** to air oxidation, which is one of the reasons for the low yield. Another reason is the oxidation of the thiol group due to the redox character of the Mitsunobu reaction (Scheme 40) <1999T1479>.



Scheme 40

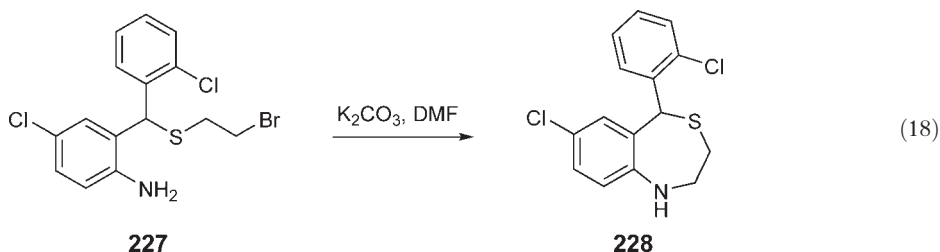
Remarkably, sulfur acted as the electrophile in the conversion of sulfide **225** to the fused carbazole **226** (Equation 17) <2003S1191>. A similar sulfur-mediated radical cyclization of indole derivatives is also known <2004OL819>.



13.09.9.2.4(ii) N-C-C-S-C-C-C and N-C-C-C-S-C-C

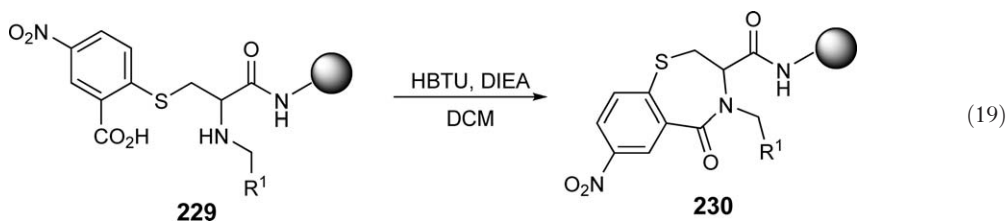
One of the most well known cyclization methods used to form thiazepine from acyclic fragments is the attack of nitrogen on carboxylic acid <2000TA4447, 2001JOC6792>, ester <1997T2421, 1999J(P1)149, 2000J(P1)1897, 2003BML4031, 2003JOC92, 2005FA385>, nitrile <1997JHC465>, α -haloacid groups, or a carbon bearing a leaving group. These leaving groups can be halogens <2003JOC644>, hydroxy 1997LA1711, 1999T1479, 1999JME4547, 2005BML1641>, alkoxy <2001JOC6792>, or nitro groups <1999TL4939>.

In the research of potential therapeutics for type II diabetes, Pei *et al.* synthesized 1,4-thiazepines by performing a nucleophilic substitution to cyclize to the seven-membered ring. Aniline **227** underwent intramolecular ring closure in the presence of potassium carbonate in DMF to form 1,4-thiazepine **228** (Equation 18) <2003JOC92>.



In recent years, solid-phase chemistry has gained more interest because of the possibility to synthesize large combinatorial libraries used for high-throughput screening. Since 1,4-thiazepines are of great importance to the pharmaceutical industry, it was an obvious choice to synthesize these products on a solid phase <1999JOC2219, 2000TL3029>.

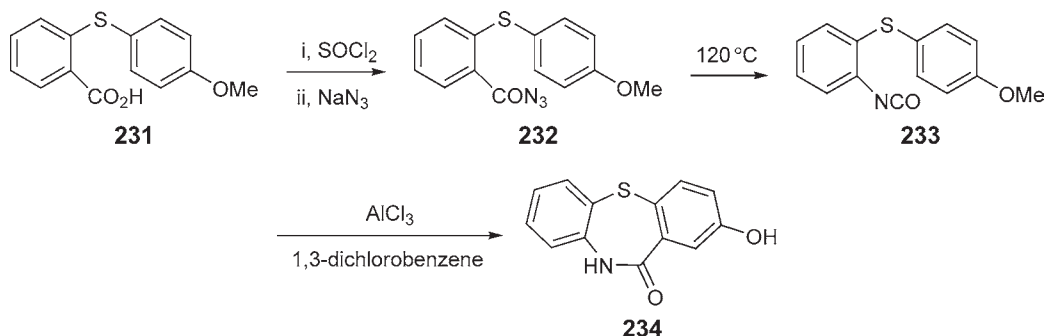
Here we give an example of this method. The resin-bound **229** was treated with *O*-benzotriazolyl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) in anhydrous dichloromethane, and intramolecular amide bond formation occurred to afford resin-bound nitrobenzothiazepine **230** (Equation 19) <1999TL4939>.



13.09.9.2.4(iii) C–N–C–C–S–C–C and C–C–S–C–C–N–C

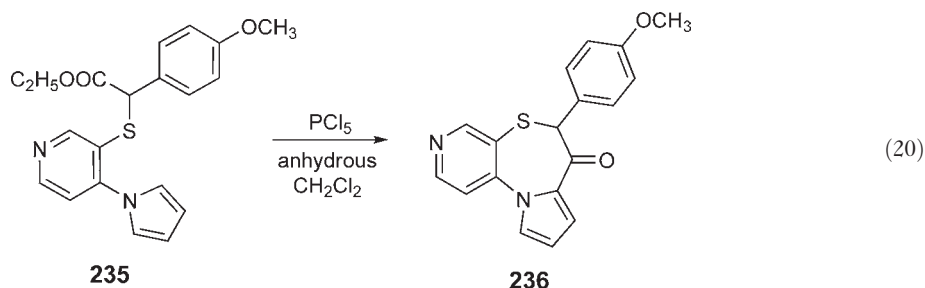
In this case, the seven-membered ring is formed from the reaction of an electrophilic carbon atom with an electron-rich component, such as an aromatic ring to afford di- or tricyclic benzo-1,4-thiazepine derivatives.

After conversion of acid **231** to its azide derivative **232** and heating, isocyanate **233** is generated. Further treatment with aluminium chloride yielded the tricyclic 1,4-thiazepine **234** (Scheme 41) <1999JME2235>.



Scheme 41

Pyrrolo-thiazepine **236** was obtained by connecting the α -carbon of the pyrrole moiety with the carbonyl group of **237** using phosphorus pentachloride in anhydrous dichloromethane (Equation 20) <2003MOL678>. A similar procedure was followed by Campiani *et al.* <1997EJM241>. Petrova *et al.* reported the synthesis of the related imidazothiazepine by polyphosphoric acid-mediated cyclization <2003SC4355>.



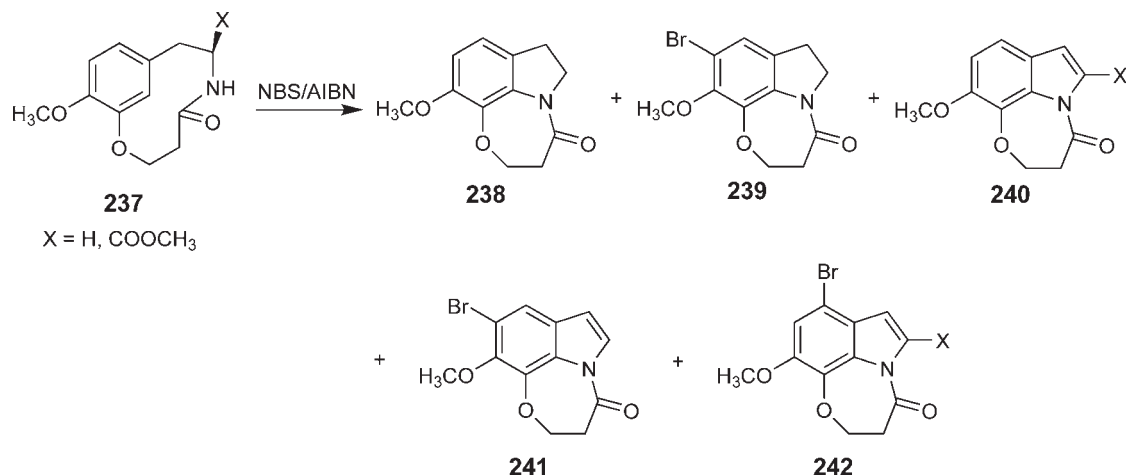
13.09.10 Ring Synthesis of 1,4-Oxazepines and 1,4-Thiazepines by Transformation of Another Ring

In the previous section, the synthesis of 1,4-oxa- and 1,4-thiazepines is described starting from different fragments. In this section, we review several methods to afford these seven-membered rings by transformation from another (heterocyclic) ring. This transformation could be involving a ring contraction or ring expansion, the latter being the most common in the literature.

13.09.10.1 Ring Contraction

Rezaie and Bremner reported the synthesis of tricyclic 1,4-thiazepines by ring contraction. *m*-Cyclophane lactam **237** was treated with *N*-bromosuccinimide and azoisobutyronitrile to yield 47% of dihydroindole derivative **238**, as the major product next to side products **239–242** (Scheme 42). The same reaction condition was applied for the ester derivative of **237** (X = COOCH₃), but with longer reaction time. This resulted in indole analogues **240–242** (X = COOCH₃) without the formation of dihydroindole derivatives. Bromination on the aromatic ring was observed prior to the intramolecular cyclization. The exact mechanism has not been resolved, but a possible reaction sequence could be

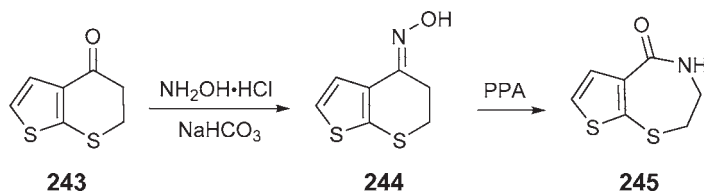
the formation of traces of hypobromous acid from *N*-succinimide or bromine and adventitious water, followed by the formation of *N*-bromolactam and water from the reaction of hypobromous acid with the lactam. The cyclization then happened with the loss of hydrogen bromide or via thermal lactam radical formation (Scheme 42) <1996SL1061>.



Scheme 42

13.09.10.2 Ring Expansion

The reaction of ketone **243** with hydroxyamine resulted in the formation of oxime **244**. Treatment of this oxime with polyphosphoric acid induced the Beckmann rearrangement of oxime **244** to form lactam **245** without detectable formation of isomeric lactam (Scheme 43) <1997JHC921>. Other examples of the Beckmann rearrangement of pyran and thiane derivatives have been reported <2004BML5907, 2004TL1051, 2005JOC10132>.

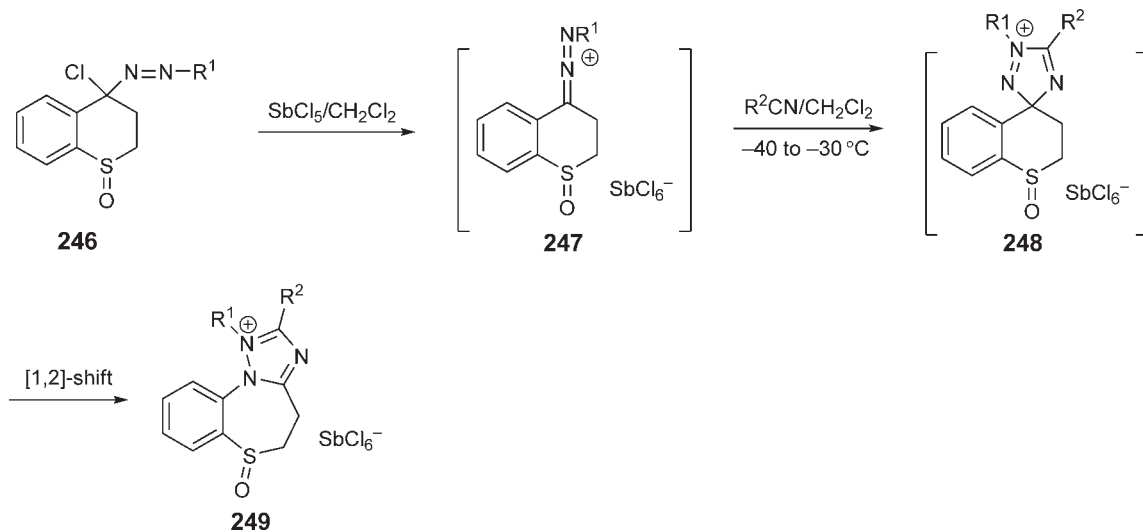


Scheme 43

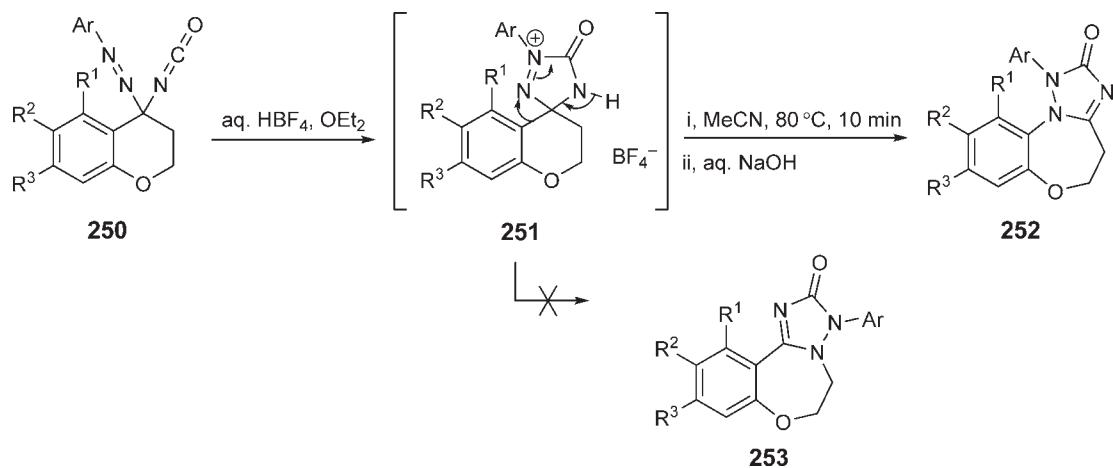
The α -chloroazo **246** reacted with antimony pentachloride in dichloromethane at low temperature to give an allene-like cation **247**. This highly reactive intermediate underwent a [3+2] cycloaddition to the triple bond of acetonitrile. By raising the temperature, **248** spontaneously rearranged with the insertion of the nitrogen atom into the S-containing ring to yield tricyclic thiazepine **249**. Other Lewis acids can be employed; however, silver salts as a Lewis acid did not give the desired final products <2000S435>. The same procedure has also been followed for the rearrangement to synthesize a 1,4-oxazepine derivative (Scheme 44) <2000JHC287>.

Li *et al.* used a similar rearrangement to synthesize 1,4-oxazepine **252**, but instead of antimony pentachloride, tetrafluoroboric acid was employed as the acid. In the solution of bicyclic geminal arylazo isocyanate **250** in diethyl ether, a solution of tetrafluoroboric acid was added to form triazolium tetrafluoroborate salt **251**. The rearrangement of **251** occurred quickly under mild conditions with ring expansion to yield the tricyclic **252** in less than 5 min. The isomeric form **253** is not observed (Scheme 45) <2004SC1691>.

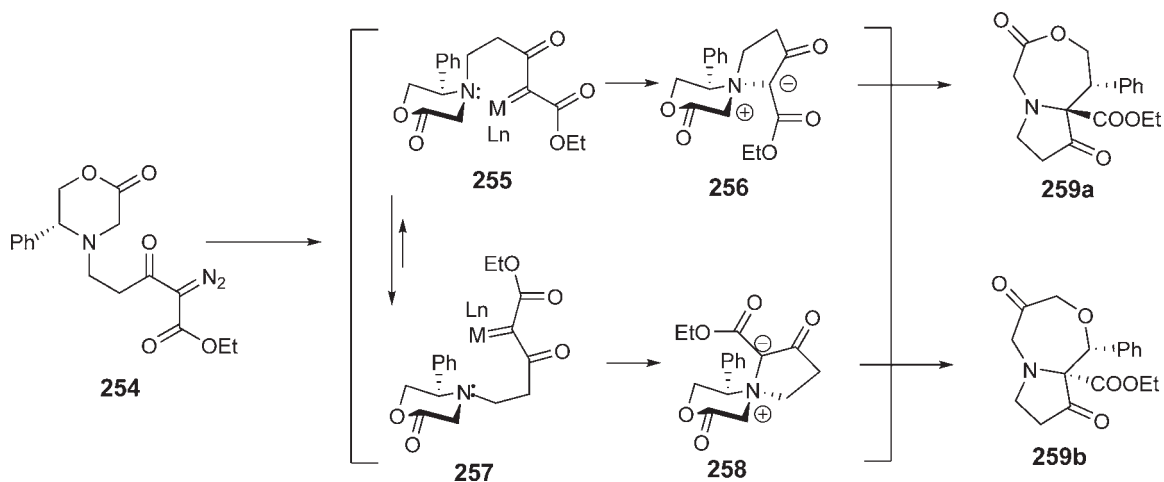
Diastereoisomers **259a** and **259b** were quantitatively obtained in a 1:2 ratio by the copper(II) acetylacetonate-catalyzed decomposition of diazo **254** in boiling toluene. Due to steric hindrance, the isomeric form **138** was favored. Cyclization followed by rearrangement (Stevens-[1,2]-shift) of the intermediates **255–258** yielded the diastereoisomers **259a** and **259b** (Scheme 46) <2000TA3449>.



Scheme 44

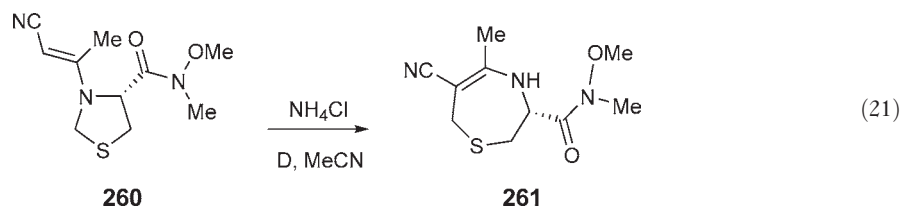


Scheme 45

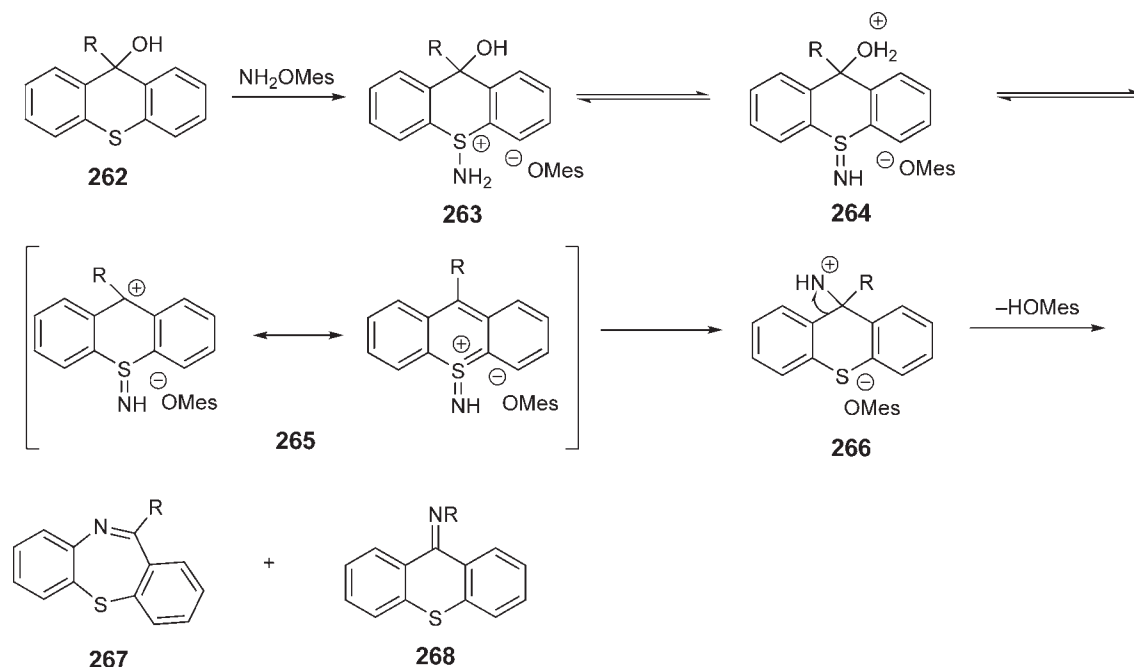


Scheme 46

Thiazoline carboxamide **260** was transformed into thiazepine **261** by simple thermal treatment under the influence of ammonium chloride. This expansive rearrangement involved ring opening of the thioaminal function of **260** (Equation 21) <2005SL239>.

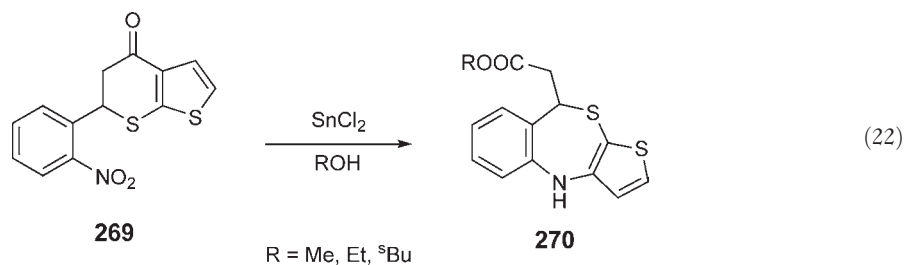


The first step in the procedure reported by Fujii *et al.* was the amination of thioxanthen-9-ols **262** by *O*-mesitylenesulfonyl hydroxylamine (MSH). Loss of water from the obtained products **263** and **264** yielded the corresponding iminothioxanthylum cations **265**, which underwent an intra- or intermolecular migration of the imine nitrogen to the 9-carbon atom to give the intermediate nitrenium ion **266**. Rearrangement of **266** gave the corresponding dibenzothiazines **267**. Migration of the R-substituent results in the formation of a side product, **268** (Scheme 47) <2004HAC246>.

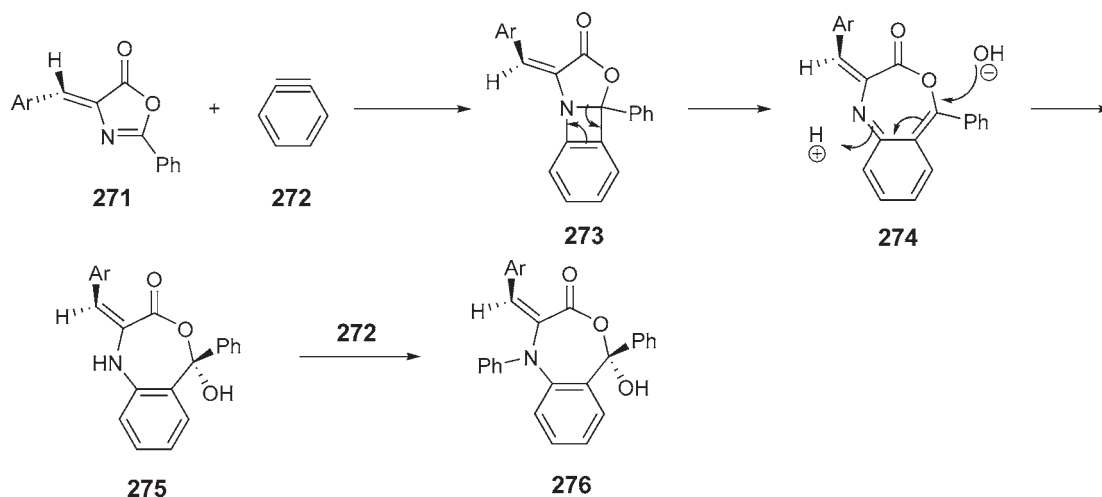


Scheme 47

Reduction of nitro compound **269** with stannous chloride did not give the expected amino compound but rather the tricyclic 1,4-thiazepine derivative **270** after a semi-pinacol-type rearrangement (Equation 22) <2002JOC8662>.



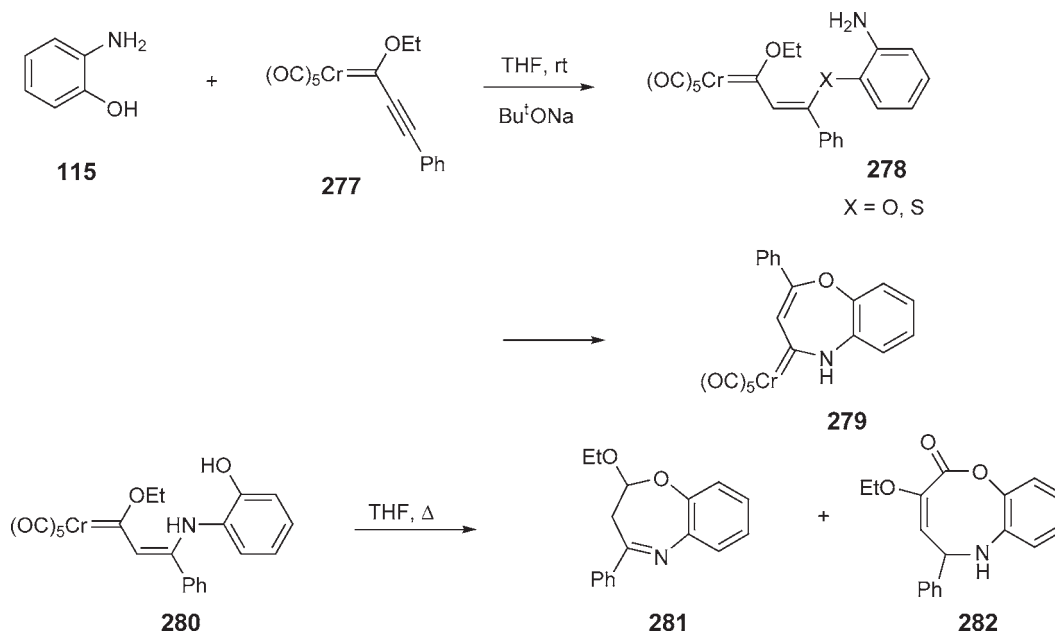
After $[2\pi+2\pi]$ cycloaddition reaction of imine **271** and benzyne **272**, the formed benzazetidine **273** underwent ring opening into its valence tautomer **274**. Moisture attacked the tautomer **274** to give oxazepine **275**. This method yielded 60–68% of the bicyclic 1,4-oxazepine **275**. One extra mole of benzyne led to the formation of N-phenylated **276** (Scheme 48) <2003T6067>.



Scheme 48

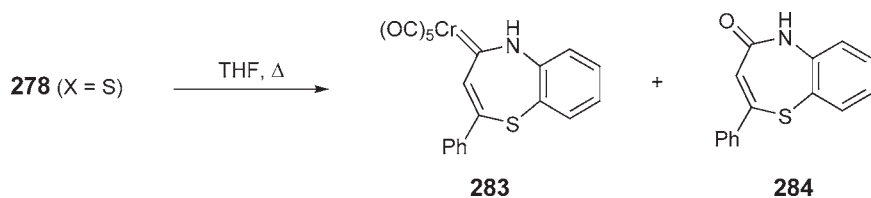
13.09.11 Synthesis of Particular Classes of Compounds

The reaction of deprotonated 2-aminophenol **115** with an alkynyl-substituted Fischer carbene **277** gave a cyclic complex **279** in 40% yield, most probably via an intermediate adduct **278** ($\text{X} = \text{O}$). On the other hand, complex **280**, obtained from **115** and **277** without base, was heated in tetrahydrofuran to afford benzoxazepine derivative **281** (38%) and benzoxacinone **282** (36%) with reverse regiochemistry (Scheme 49) <2003CEJ4943>.



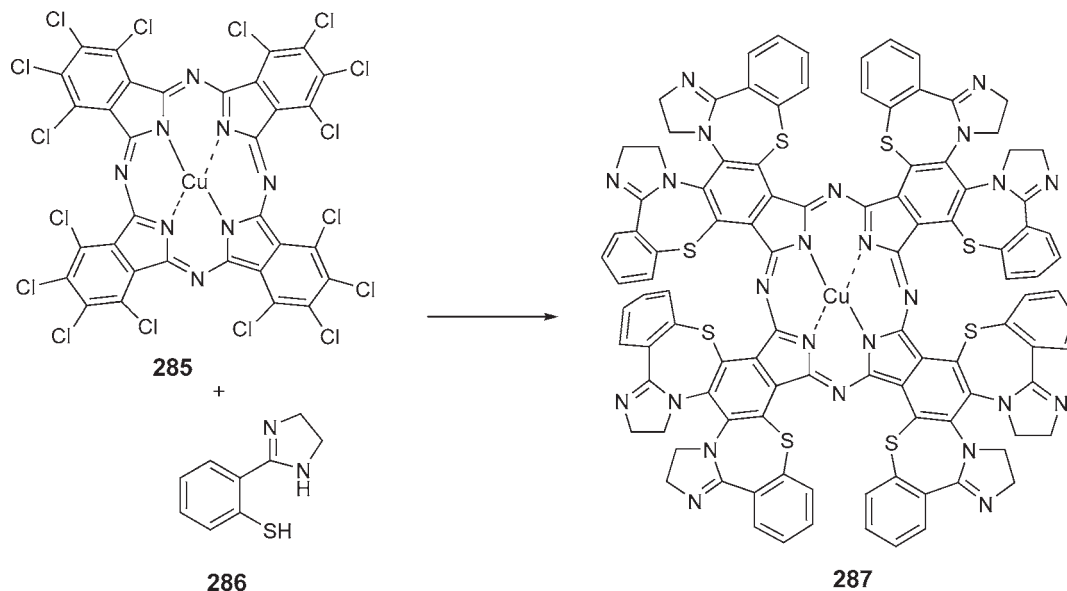
Scheme 49

2-Aminothiophenol **37** and **277** formed an isolable adduct **278** ($X = S$) that on heating was transformed to a mixture of complex **283** (10%) and the demetallated benzothiazepinone **284** (51%) (Scheme 50) <2003CEJ4943>. Similarly, monocyclic 1,4-oxazepinone derivatives of tungsten and chromium have been prepared by a domino [4+2]/[2+2] cycloaddition reaction of 1-alkynyl Fischer carbenes with oxazolines <2005OM302>.



Scheme 50

Remarkable phthalocyanines **287**, bearing eight thiazepine rings, were claimed to be prepared from perchlorinated Cu-phthalocyanine **285** by nucleophilic substitution with *ortho*-(2-imidazolyl)thiophenol **286** at 120 °C (Scheme 51). The pyrimidine homologues were also prepared. Compounds **287** were not completely characterized and it is to be expected since it is a mixture of regioisomers. The resulting phthalocyanines **287** have absorption spectra in the infrared region <1997EP0799831A1>.



Scheme 51

13.09.12 Applications

1,4-(Benzo)oxazepine and 1,4-(benzo)thiazepine derivatives are of considerable pharmacological interest and many articles have appeared since 1995 describing their activities. We only give a limited coverage of this work due to space limitations. Many reports have appeared on the study of benzothiazepinones and benzoxazepinones as potential anti-AIDS drugs (AIDS = acquired immune deficiency syndrome). The pyrrolo[2,1-*d*]benzoxazepine **3** ($X = O$) was found to be more potent as an NNRT inhibitor than nevirapine in the same experimental conditions. <1996JME2672>. Further work on similar pyrrole-fused systems has been reported <2005FA385, 2005JME7153>. The pyridone derived from **51a** by hydrolysis of the mesylate function was found to be a potent inhibitor of wild-type HIV-1 replication <2005TL2919>. The TIBO analogues **55** were found to be only moderately active against HIV <1999EJM701>. Other studies mention inhibition of integrase (IN) by thiazolothiazepines such as **288** and **289** <1999JME3334, 2004BMC4459>.

Diltiazem **1** may be the most known member of a family of calcium antagonists, interacting with the L-type voltage-gated Ca^{2+} channel, and useful as a remedy for angina and hypertension. Pyrrolo[2,1-*d*]benzothiazepines of type **4** have dual 'peripheral-type' benzodiazepine receptor (PBR) affinity and calcium antagonist activity <1996JME2922>. The related **5** and **290** have been used as molecular probes of the PBR binding site <1997EJM241, 2002JME4276>.

Benzothiazepines of type **291** were described as antagonists for the mitochondrial sodium–calcium exchanges and thus are potential therapeutics for type II diabetes (Figure 17) <2003JOC92>.

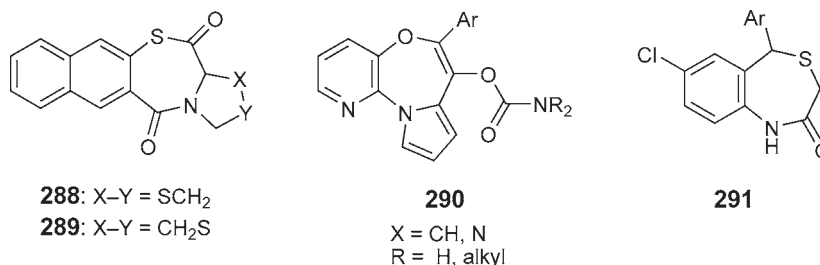


Figure 17

The thiazepane **292** was a potent inhibitor of nitric oxide synthase <2004BML5907>. Thiazepines **293** (together with the corresponding diazepines) have been studied as TNF- α converting enzyme (TACE) and matrix metalloproteinase (MMP) inhibitors in a mouse collagen-induced arthritis model <2005BML1641>. Many of the title compounds have central nervous system (CNS) activity. Pyridobenzoxazepine **294** and similar tricyclic molecules were found to have antipsychotic activity (Figure 18) <1997MI255, 2001JMC769, 1999JME2235>. Related molecules of type **62** that are nondyskinetic dopamine antagonists were reported <2001JME372>.

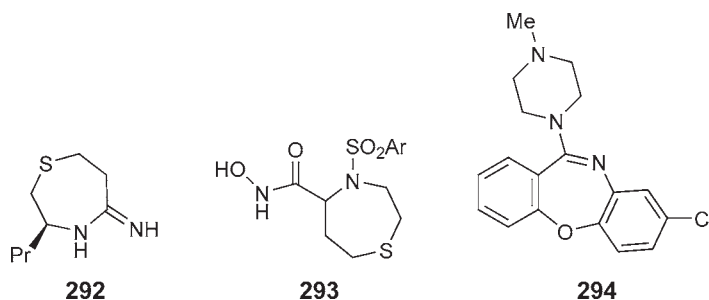


Figure 18

Pyridazino[4,5-*b*]oxazepines **295** are 5-HT_{1A} receptor ligands <1997BML2857>. The 5-HT_{1A} receptor plays a role in psychiatric disorders such as anxiety and depression. 1,4-Benzoxazepine **296** is a 5-HT_{1A} antagonist and exhibits highly potent anti-ischemic effects <2001BML595>.

Molecules of type **70** related to temocapril **297** with cyclic dipeptide structure were prepared as potential anti-hypertensive agents <1997TL2775, 1999JOC3019>. The potent bradykinin B₁ receptor antagonist JMV1640 **298** was prepared (Figure 19) <2000JME2387> and the benzothiazepine unit was shown to induce a β -turn <2005TL3733>.

A series of growth hormone secretagogues were prepared via peptide coupling to acid **299**. These molecules were rationally designed by computational methods <2001JME4082>.

Tyrosine kinases, such as Src, are involved in many pathologies such as cancer, inflammation, or osteoporosis, and thus are important targets. The Src SH2 domain is critical to bone resorption, and thiazepinone ligands based on amine **300** and its monocyclic analogue **301** were found to have specific binding with the protein (Figure 20) <2001BML2127, 2002BML1291>.

Spirobenzothiazepines **302** were reported to have antifungal and antitubercular activity <2003CPB1137>. Oxazepines with antifungal properties are also known <2002BMCL1705, 2002BMCL27570>.

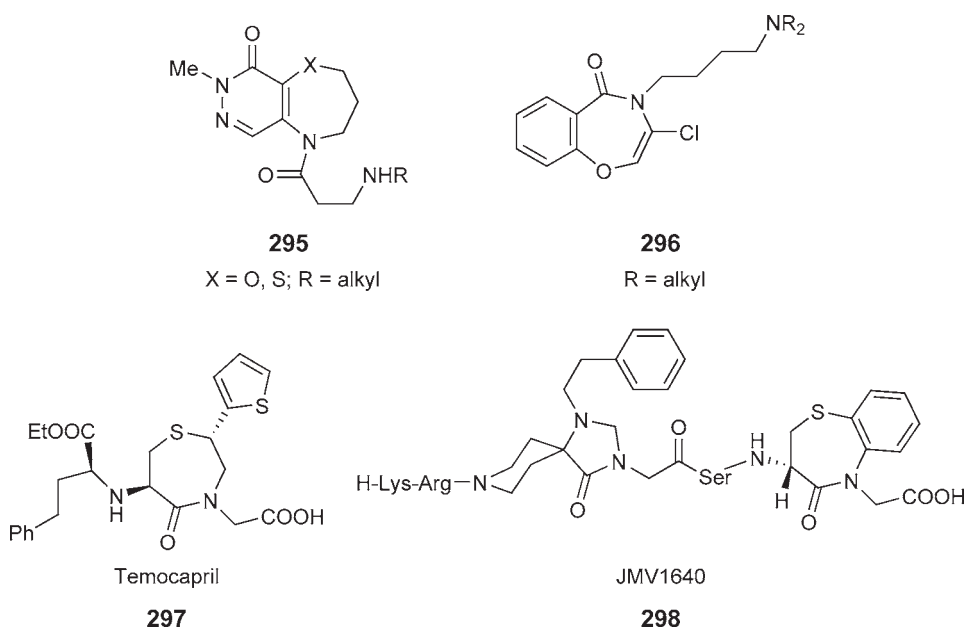


Figure 19

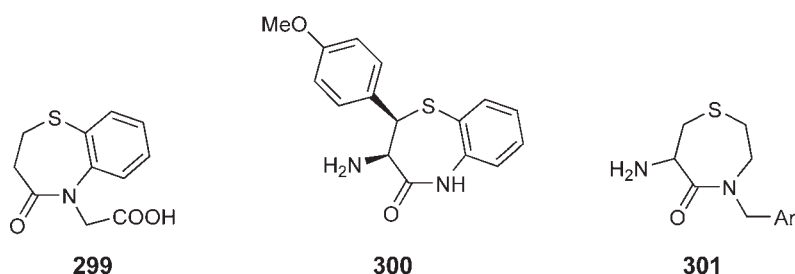


Figure 20

Antiproliferative activity against the MCF-7 breast cancer cell line was unexpectedly found for tetrahydrobenzoxazepine acetals **303** <2004T11547>.

Pyrrolobenzoxa(thia)zepines of type **304** are potent apoptotic agents and have potential as novel anticancer agents <2005JME4367>. Tubulin was identified as the molecular target of these compounds **304** <2006MPH60>. Pyrimidooxazepines of type **103** were versatile templates for the development of inhibitors of specific kinases of importance in kinase-targeted cancer therapy <2005BML5474, 2006BML5102>. Thiazepines of type **305** are of interest as interleukin-1 β -converting enzyme (ICE) inhibitors (Figure 21). The most active **305** (Ar = 2-naphthyl) exhibited an IC₅₀ value of 30 nM in an enzyme inhibition assay <2006BML4728>.

Compounds of type **107** were evaluated as MMP inhibitors <1999JME4547>. MMPs are a structurally related class of enzymes that is responsible for the metabolism of the extracellular matrix proteins and are linked to diseases such as arthritis and multiple sclerosis.

Pyridazino[3,4-*b*]benzoxazepinones with structure of type **136** were described as multidrug-resistance-modulating agents with low toxicity <2004JME4627>. The same compounds **136** were antimycobacterial also <2000AP231>.

Benzoxazepines **100** have been described to have potent SQS inhibitory activities <2002BMC385, 2002BMC401, 2002JME4571> and thus are important in control of serum cholesterol levels and therapy of diseases related to atherosclerosis, such as ischemic cardiopathy and cerebral infarction. Benzothiazepines **69** of similar structure and activity were reported <2000T(A)435>.

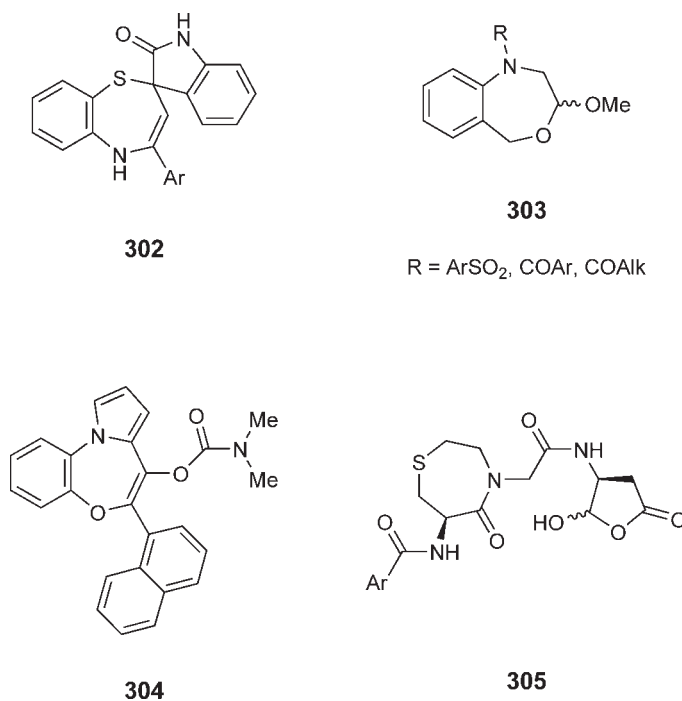


Figure 21

Benzothiazepines were screened for their ability to inhibit arginine vasopressin binding to the human V₂ and V_{1a} receptor subtypes. A V₂ antagonist acts as an aquaretic, increasing water output without promoting the loss of electrolytes. The most potent derivative **109b** had 140-fold greater selectivity for the V₂ over the V_{1a} receptor in the binding assay <2003BML4031>.

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Biographical Sketch



Wim Dehaen was born in Kortrijk, Belgium. He obtained his Ph.D. in 1988 under the guidance of Prof. Gerrit L'abbé on a study concerning the rearrangements of 5-diazoalkyl-1,2,3-triazole derivatives. After postdoctoral stays in Israel (1988–90), Denmark (three months in 1990), the United Kingdom (three months in 1994), and Belgium (most of 1990–98), he was appointed associated professor at the University of Leuven (Belgium) in 1998, becoming a full professor at the same university in 2004. Up to 2006, 220 publications have appeared in international journals about his work on heterocyclic and supramolecular chemistry.



Thien H. Ngo was born in Ho Chi Minh City (Vietnam). Since 1989, he has resided in Belgium, where he received most of his education, and he finished his 'Licentiaat' studies (corresponding to M.Sc.) in chemistry at the University of Leuven in 2004, when he presented a thesis under the joint promotorship of Prof. W. Dehaen and Prof. S. Campagna (University of Messina, Italy). Part of the experimental work for this thesis was carried out in Italy in the framework of the Erasmus exchange program. Currently, Thien H. Ngo is working on a Ph.D. thesis (promotor Prof. W. Dehaen) concerning the synthesis and applications of novel *meso*-pyrimidinyl-substituted corrole derivatives.

13.10

1,2-Dioxepanes, 1,2-Oxathiepanes, and 1,2-Dithiepanes

M. J. Haddadin and C. J. Nachef

American University of Beirut, Beirut, Lebanon

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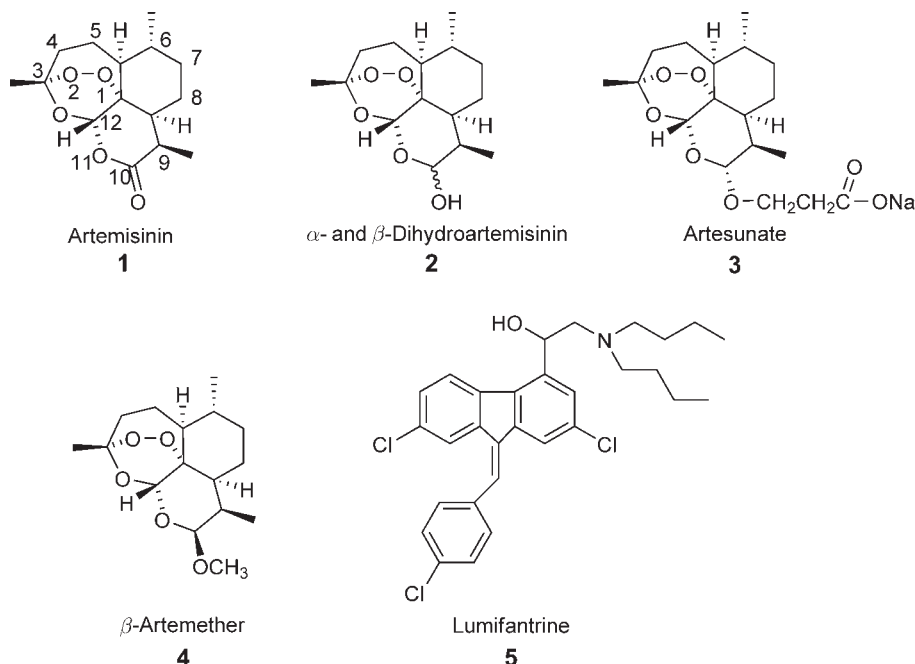
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13.10.1 Introduction

This chapter comprises an update on the chemistry of 1,2-dioxepines, 1,2-oxathiepanes, and 1,2-dithiepanes which appeared in Chapter 9.10 in CHEC-II(1996). It is evident that the structural nature, in terms of construction and/or stability of each of these seven-membered heterorings, which include a relatively weak O–O, O–S, or S–S bond, lies behind the paucity of publications in this area. However, the literature on the effective antimalarial artemisinin **1**, a remarkably stable endoperoxide, and especially its derivatives more than make up for this deficiency.

Artemisinin **1** is named by *Chemical Abstracts* as a pyrano[4,3-*f*]benzodioxepin, specifically: (3*R*,5*aS*,6*R*,8*aS*,9*R*,12*S*,12*aR*)-octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*f*]-1,2-benzodioxepin-10(3*H*)-one with a registry number of 63968-64-9. IUPAC uses a different numbering of this structure <1992CSR85, 1999J(P2)2089>. The leaves of the herb *Artemisia annua* L., from which artemisinin is extracted, have been used by the Chinese to combat fevers since ancient times. Yet, the most effective drugs for the multidrug-resistant parasite *Plasmodium falciparum* are derivatives of artemisinin **1**, artesunate **3** and artemether **4**, which are currently essential ingredients in the

WHO prequalified drugs in what is known as the artemisinin combination therapy (ACT): Coartem is a combination of artemether **4** and lumefantrine **5** <2005CEN69>.

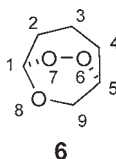


The herb *A. annua* L., which is now cultivated in a number of countries including China, Vietnam, India, Kenya, Tanzania, and Uganda, is the most practicable source of this drug. Semi- or total syntheses are not commercially competitive so far. It was estimated that at 0.5 g of artemether **4** per total dose regimen, the amount of artemisinin required, in 2005, would be 114 tons <2006MI1210-11>. The importance of eradicating malaria as a disease, which becomes pressing when it is realized that 40% of the world population in 90 countries are at risk and 3 million people (mainly African children) are killed per year <1999MI1>, cannot be overemphasized.

13.10.2 Theoretical Methods

The mechanism(s) of action of artemisinin **1** and its derivatives have been the subject of many studies and reviews <2004ACR397, 2006MI1836, 2006OPP3>. A very recent study looked into the proposal that the formation of a carbocation at C₄, via an ionic cleavage of the peroxide moiety, is the source of antimalarial activity of artemisinin and its derivatives. This study used density functional theory (DFT) (B3LYP/6-31+G level) on artemisinin **1** and artemether **4** and concluded that protonation is unlikely to occur on the peroxide bond O₁–O₂ and hence lead to ionic cleavage. Instead, the radical pathway is favored <2006JME6065>. Because the mechanism of action of artemisinin is not well established, a host of theoretical publications tried to explain how artemisinins act. It is generally accepted that ferrous iron, of heme, or iron(II) salts, attacks O₁ of the peroxide moiety and generates an oxygen-centered radical <1996JA3537>, which gives a carbon-centered radical. The formation of those two intermediates has been confirmed by electron paramagnetic resonance (EPR) spin-trapping techniques <2001AGE1954, 2001JME58, 1997JA5968, 1998CSR273, 1998JME952>. Quantum-chemical calculations using IMOMO (B3LYP/6-31G(d,p)): HF/3-21G method was used to differentiate between two possible pathways for the reaction of Fe(II) with the bridged endoperoxide oxygens of artemisinins to produce carbon-centered radical intermediates. One path involves a 1,5-hydrogen shift while the other undergoes C–C cleavage <2005MI366>.

Calculations on an artemisinin molecular model: 6,7,8-trioxybicyclo[3.2.2]nonane **6** using HF/3-21G and B3LYP/6-31G(d,p) found several intermediates and radicals to be relatively stable and could be responsible for the antimalarial action of artemisinin and its derivatives <2006PCA7144, 1999PCA9364>. In an attempt to quantitatively relate structure to activity, the technique of local lazy regression (LLR), which focuses on a query point using its local neighborhood, was applied to three biological data sets, one of which consisted of 179 artemisinin analogs. This technique, in comparison to the global model, led to a few observations being poorly predicted <2006MI509>.



Another study calculated the quadrupole coupling constant (NQCC, x) of ^{17}O in artemisinin and some of its derivatives. These calculations were made at the HF/3-21G level using the Gaussian 98 program. It was concluded that heme iron approaches the endoperoxide O_1 position in preference to O_2 <2005MI366>.

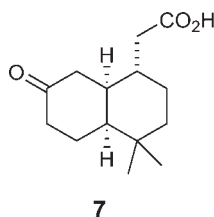
A combination of experimental circular dichroism (CD) and a statistical dynamic Monte Carlo (DMC) treatment showed that complexation of artemisinin **1** with β -cyclodextrin does not affect the functionality of artemisinin <2004CPL566>. DFT calculations showed that the bridged endoperoxide moiety of artemisinin initially formed an Fe–O bond, followed by hemolytic cleavage of the O–O bond. This study concluded that the reactivity of the peroxide functionality is greater with iron hexahydrate for radical-mediated damage as compared to heme, which leads to an unreactive species <2005JMT87>. Semiempirical AM1, PM3 methods and density functional (DFT/ B_3LYP) using 6-31G(d) basis set examined the relative stabilities of radicals arising from endo- and exoperoxide bridges, with the nonperoxide oxygen of the trioxane ring and/or the carbonyl group (C_{10}) of artemisinin, replaced by CH_2 <2005IJQ749>. Furthermore, the role of C-centered radicals on the mechanism of the antimalarial action of artemisinin **1** was explored by AM1 and PM3 semiempirical methods. This study suggested that the C_4 -centered radicals may be responsible for destroying the parasite *P. falciparum* <2002JMT207>.

Automated calculations of docking of artemisinin to heme concluded that the O_1 of the endoperoxide moiety of artemisinin **1** approaches the heme <2001MI26> contrary to an earlier report <1995MI215>. Using computer-aided three-dimensional quantitative structure–activity relationships (3-D QSARs) and comparative molecular field analysis (CoMFA), predicted, to a reasonable extent, the biological activity of new compounds. This study made use of the known X-ray structure of artemisinin and the assumption that antimalarial activity is initiated by the interaction of endoperoxide moiety of artemisinin and the heme (Fe(II)) <2002JME292, 2003JME4244>. Other earlier related studies can be referred to in <2001JMT267>, <2000JCI354>, <1999JMT103>, and <1998JMT87>.

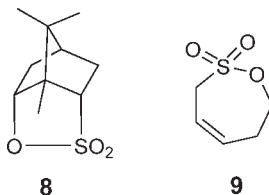
13.10.3 Experimental Structural and Spectroscopic Methods

13.10.3.1 X-Ray Diffraction

X-Ray diffraction techniques were used to help in the study of a QSAR of artemisinin **1** <2002JME292>, as well as in the determination of the structure of the artemisinin intermediate $\alpha,4$ -dimethyl-decahydro-7-oxo-1-naphthaleneacetic acid **7**, where the cyclohexane ring assumes a chair conformation and the cyclohexanone ring a distorted one <1995JCX473>.

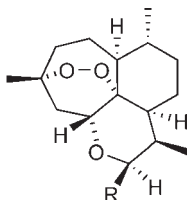


The structure of 1,7,7-trimethyl-2,6-bicyclo[2.2.1]heptane sulfone **8** was confirmed by X-ray <1995SUL71>. X-Ray diffraction analysis was used in the determination of the structure of 3,6,7,8-tetrahydro[1,2]oxathiepine-2,2-dioxide **9** <2004S1696>. Using X-ray and ^1H nuclear magnetic resonance (NMR), the structure of diastereomeric artemisinin derivatives has demonstrated that packing forces are unimportant in this particular case <1995AXB1063>.



13.10.3.2 Molecular Spectra

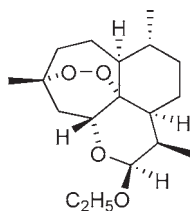
NMR (^1H , ^{13}C), mass spectrometry, infrared (IR), and ultraviolet (UV) were used, especially NMR, in studying the complexation interactions of artemisinins with agents, such as β -cyclodextrin <2004JPS2076> and micellar dispersions of octanoyl-6-*O*-ascorbic acid <2002JPS2265>. Furthermore, the structure–activity relationship of solution structures of deoxyartemisinin **10a** and carboxypropyldeoxyartemisinin **10b**, as antitumor compounds, was studied by ^1H and ^{13}C NMR <2000BBR359>.



10a: R = H

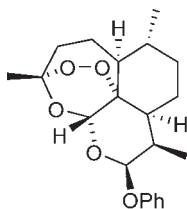
10b: R = $(\text{CH}_2)_3\text{-COOH}$

A conformational study of β -arteether **11**, by ^1H and ^{13}C NMR, showed that the solution of β -arteether **11** is similar to that of its X-ray structure <1999J(P2)2089>. The interaction of artemisinin **1** with manganese tetraphenylporphyrin, in the presence of a reducing agent, was studied by UV–visible (UV–Vis) and ^1H NMR <1997CR59>. A series of rules using 1-D and 2-D NMR spectroscopy for identification of relative stereochemistry of substituted antimalarials, related to artemisinin **1**, were reported <1997SPL241>.



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A recent visible absorption spectroscopic investigation of the reaction, at pH 7, 37 °C, of hemoglobin (HB) (ferrous heme and not the ferric heme) with artemisinin **1**, sodium artesunate **3**, and dihydroartemisinin (DHA) **2** showed that this reaction selectively took place at the heme sites leading to a slow decay of the Soret band as a result of heme alkylation and loss of π -electron delocalization <2006BMC2972, 2001CR85>. In another study, visible, CD, and reverse-phase high-performance liquid chromatography (HPLC) were used to show that the protein-bound heme in Hb reacts with artemisinin **1** much faster than with the free heme. Mono- and dialkylated heme derivatives of artemisinin **1** have been isolated <2005BJ409>. Electron spin resonance (ESR) spin-trapping experiments succeeded to spin-trap both the primary and secondary carbon radicals generated from the Fe(II) reaction with the C_{10} phenoxy analogue **12** of artemether **4** <2001JME58>.



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Correlation spectroscopy (COSY), nuclear overhauser enhancement spectroscopy (NOESY), 1-D NOE, and HPLC techniques were utilized in the identification of three trapped products formed from coupling of the generated C_4 -centered radical of artemisinin with manganese(II) tetraphenylporphyrin <2001AGE1954>.

13.10.4 Thermodynamic Properties and Aromaticity

The peak temperature of the major endotherm (T_m) and the total enthalpy for the melting of crystals of artemisinin **1** were reported <1997P1209>.

13.10.5 Reactivity of Fully Conjugated Ring Systems

There is nothing to report in this area.

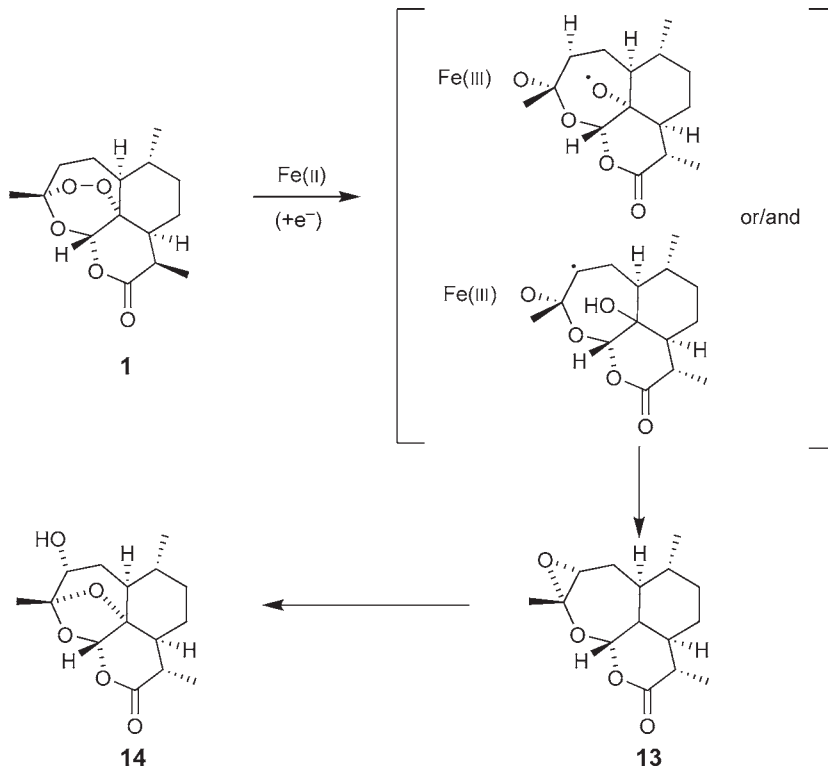
13.10.6 Reactivity of Nonconjugated Ring Systems

13.10.6.1 Reactivity of Artemisinin

Because of the publication of two excellent reviews on artemisinin and its analogue recently, this chapter does not deal with the reactivity of artemisinin and its derivatives exhaustively and therefore refers the reader to those two reviews <2005MI75, 2006OPP1>. It will highlight the most often targeted sites of reactivity in artemisinin: (1) reactivity of the endoperoxide moiety with the heme [Fe(II)], (2) the reduction of the carbonyl group (C_{10}) of the lactone ring C and further elaboration of this lactol, (3) replacement of oxygen atom (O_{11}) of the lactone function by a heteroatom, and (4) reactions of the methyl group (C_{16}) attached to (C_9). It will become evident that reactions of (2), (3), and (4) are integral to the syntheses of artemisinin analogs. Therefore, methods of syntheses of the core structure of artemisinins focus on cyclization reactions. Furthermore, this section discusses the reactivity of 1,2-dioxepanes, 1,2-dioxethiepanes, and 1,2-dithiepanes.

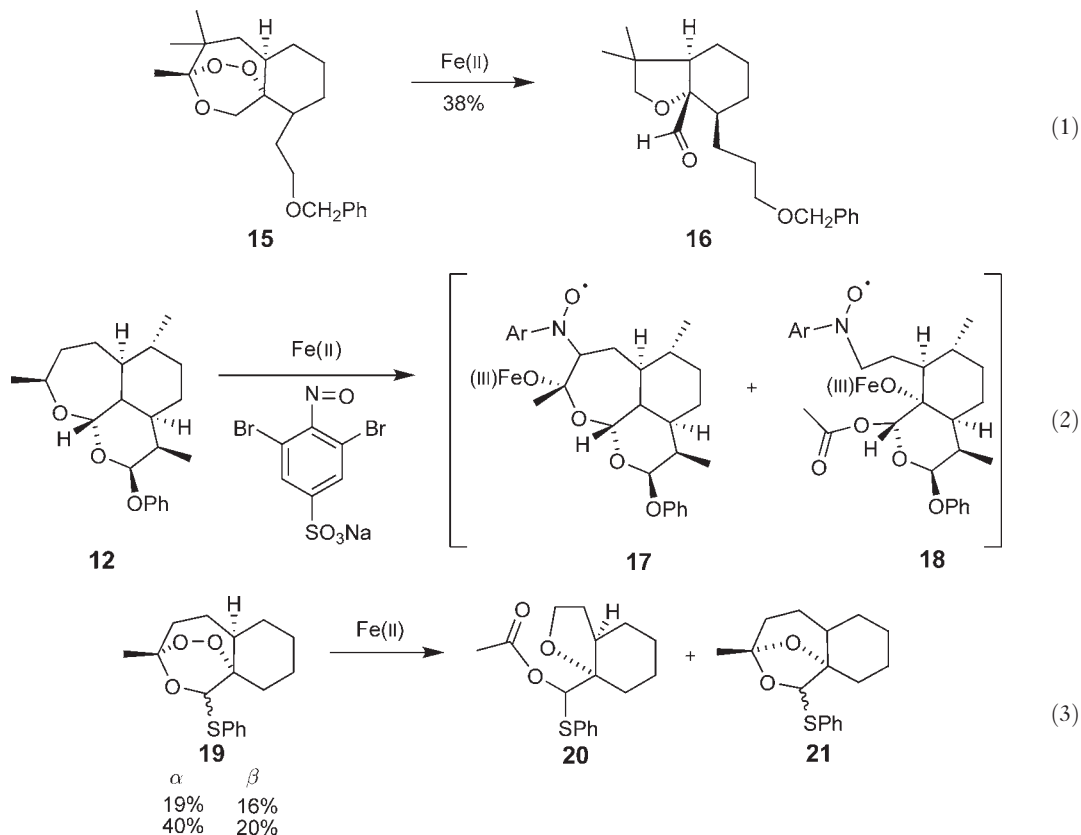
13.10.6.1.1 Reaction of endoperoxide with Fe(II)

It is generally accepted that the endoperoxide moiety of artemisinin **1** and its analogues undergo a reaction with Fe(II) to yield O- and C-centered radicals (Scheme 1).



Scheme 1

Hydroxy-epoxide **13** was isolated, in low yield, when artemisinin was reacted with ferrous salts <1998JA3316>. Hydroxy-dioxolane **14** is a metabolite of artemisinin **1** in the presence of rat liver microsomes <1990MI923>. Other examples of reactions of ferrous with endoperoxides are <1994JME1256, 2001JME58> shown in Equations (1)–(3).



The α -isomer of **19** led to 19% of **20** and 16% of **21**, whereas the β -isomer gave 40% of **20** and 20% of **21**. A carbon-centered radical proposal was used to rationalize these results <1998TL2273>.

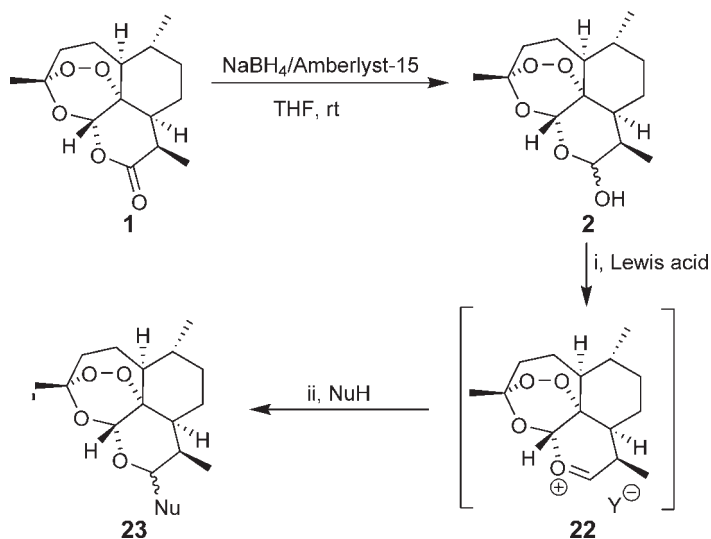
13.10.6.2 Reactions at the C₁₀ Carbonyl Group (of the Lactone) of Artemisinin

The most celebrated reaction, for the preparation of artemisinin analogs, is the reduction of the C₁₀ carbonyl group of ring C of artemisinin to give the lactol derivative referred to as DHA **2**. This reduction (Scheme 2) can be effected by NaBH₄, LiAlH₄, diisobutylaluminium hydride (DIBAL) <1996JME4149>, or NaBH₄/Amberlyst-15.

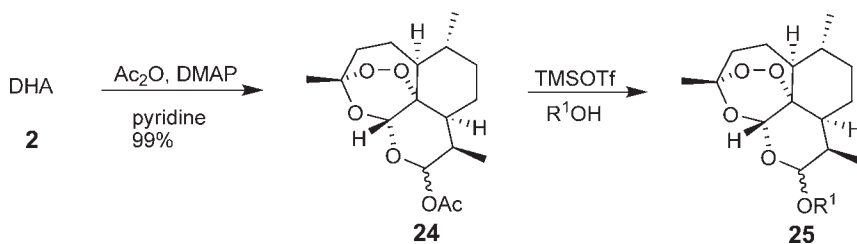
Reaction conditions are critical for better yields; however, the formed DHA was often not isolated. Treatment of DHA **2** with a Lewis acid (BF₃·OEt₂, trimethylsilyl chloride (TMS-Cl), TiCl₄, SnCl₄, etc.), followed by the specific nucleophile, led to the C₁₀ analogs of artemisinin. One recent review <2006OPP1> cited over 100 analogues of this type. This methodology (Scheme 2) was extensively used in the preparation of a large number of C₁₀ substituted analogs of artemisinin <2006AGE2082, 2002TL7535, 2001JME58, 2001BML5, 2001EJMC469, 1997JME1396, 2002JME1052, 1996JME4511, 2003BMC4363, 2000BMC2739, 1997JNP325>.

It should be kept in mind that Lewis acids' reactions with DHA also led to the formation of dimers and/or of anhydroartemisinin (AHA) **23**, often as a major product. To circumvent this problem, DHA was converted to the C₁₂ acetate, which was displaced by ether formation.

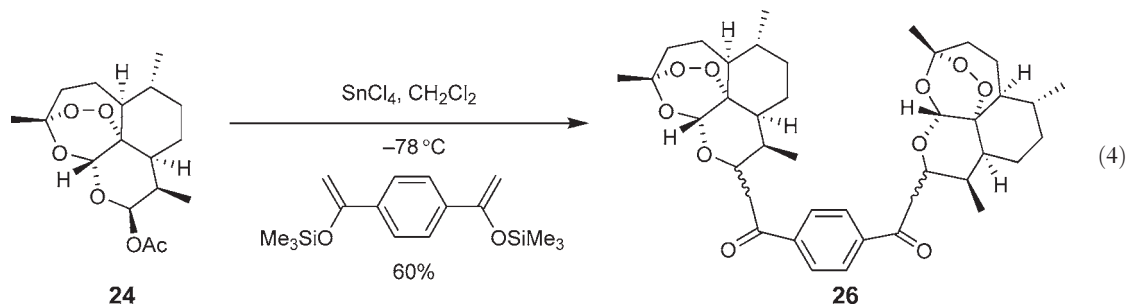
The best yields (65–99%) were obtained using TMSOTf <2004JOC3242> rather than BF₃·OEt₂ (Scheme 3). For cases which failed to form products analogous to **25**, the DHA acetate was converted to the C₁₀ chloride, *in situ*, followed by treatment with the pyridine-based alcohol to give the corresponding C₁₀ ether in high yields <2006OPP1>. Tin tetrachloride treatment of dihydroartemisinin α -acetate **24** facilitated a double coupling with the bisenol trimethylsilyl ether of *p*-diacetylbenzene to produce a mixture of dimers **26** (Equation 4) <2002BMC227>.



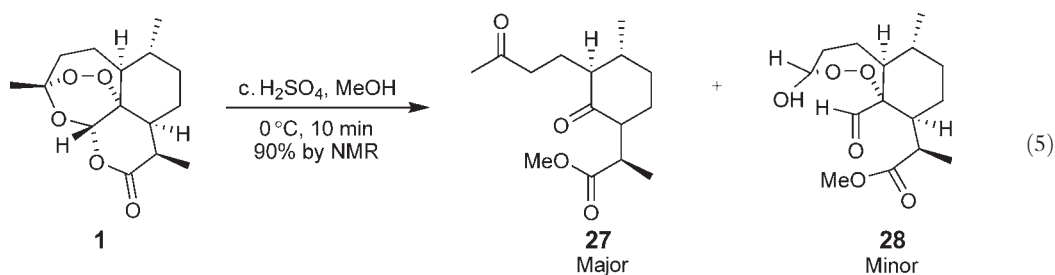
Scheme 2



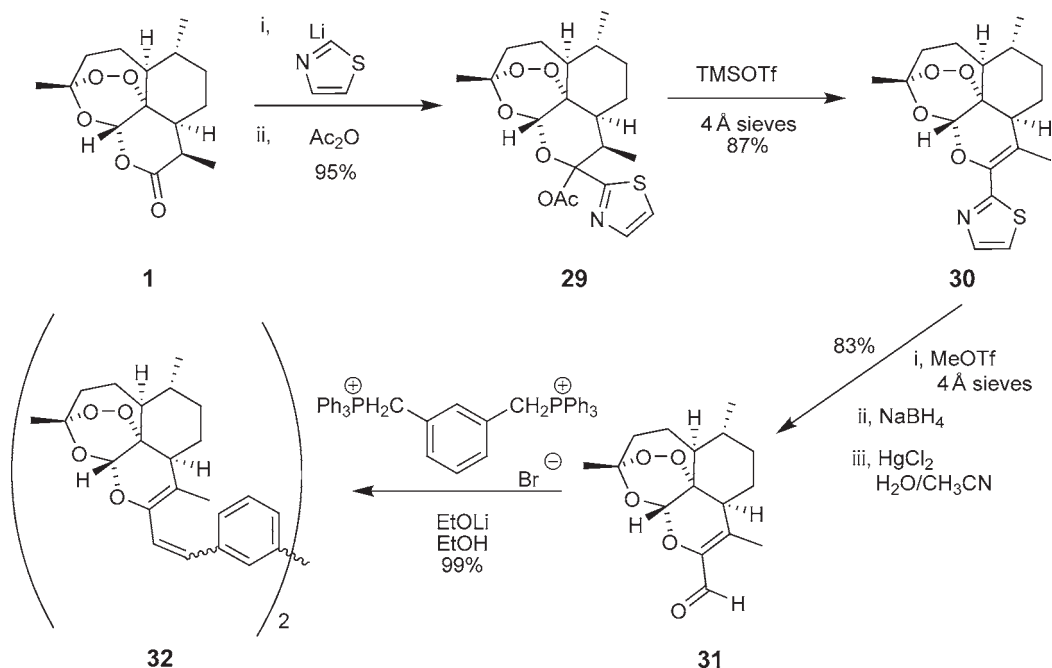
Scheme 3



Treatment of artemisinin with methanol/ H_2SO_4 led to a wide variety of products, including **27** and **28** (Equation 5) <2001T8495>.

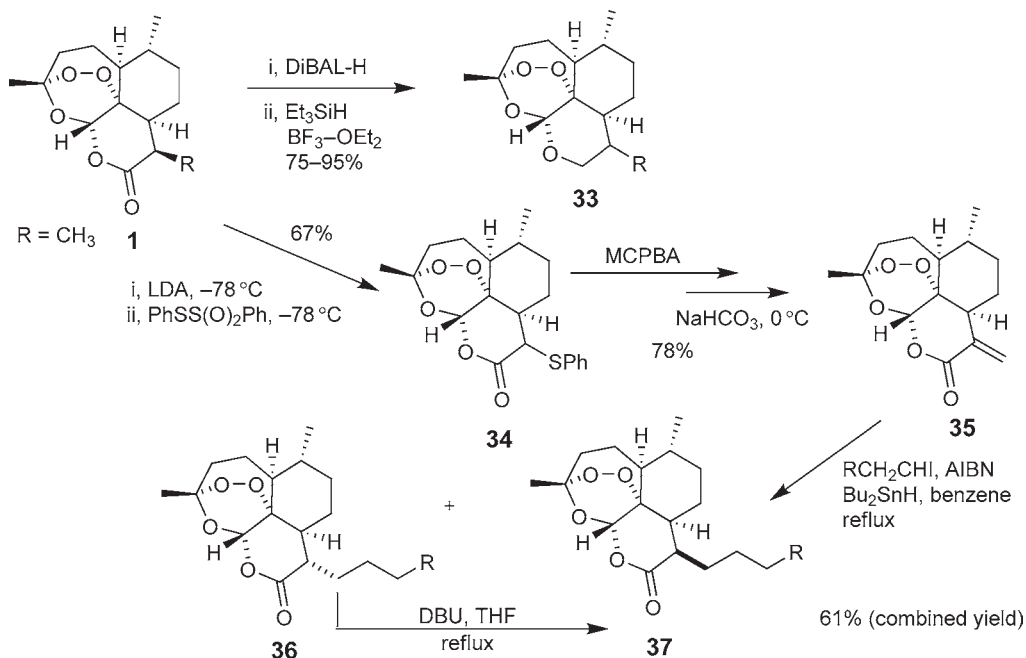


Reactions at C₁₀ carbonyl carbon were utilized effectively to introduce a functional group at this carbon for further elaboration (**Scheme 4**) <1999JME4275>.



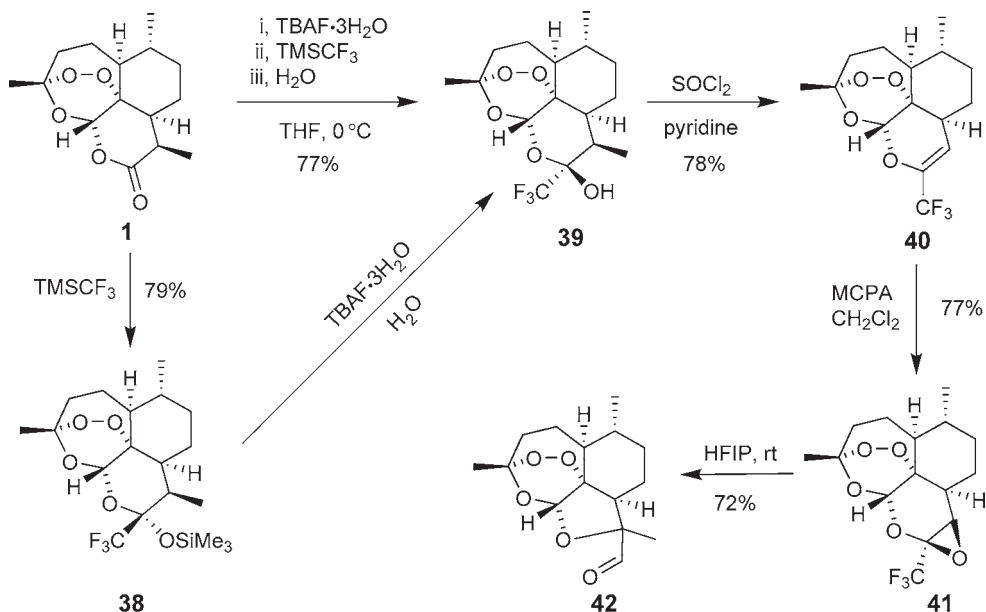
Scheme 4

The C₁₀ lactone carbonyl oxygen was removed by diisobutylaluminum hydride (DIBAL) reduction, followed directly by a second reduction (BF₃·OEt₂/Et₃SiH) to convert ring C into a pyran ring (**Scheme 5**). <2002JME4321>.



Scheme 5

Scheme 6 gave further products and some of their transformations, resulting from reactions of the C₁₀ carbonyl group of artemisinin.

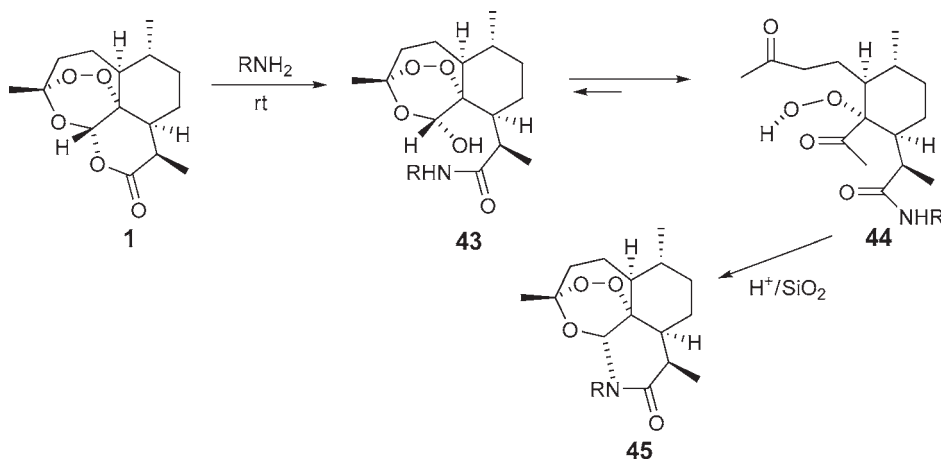


Scheme 6

The reaction leading to hemiketal **39** was stereoselective with the nucleophile attacking from the more hindered α -side; however, the structure of **39** was established by NMR (^1H and ^{13}C), NOE, and X-ray <2002JOC1253>.

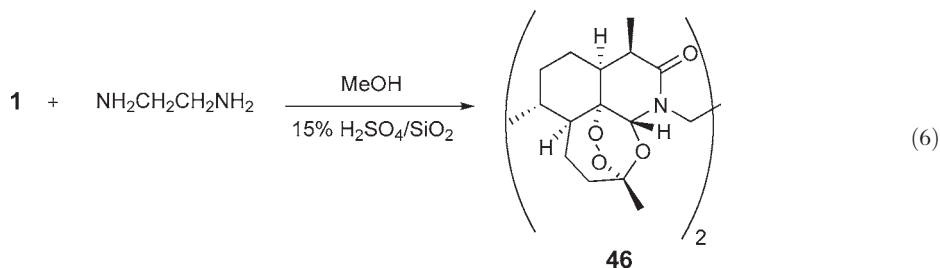
13.10.6.3 Conversion of Lactone (C-Ring) of Artemisinin to a Lactam (Azaartemisinin)

Artemisinin reacted with methanolic ammonia or primary amines and the crude mixture amido-acetal $\rightleftharpoons$ amido-aldehyde **43** $\rightleftharpoons$ **44** is treated with sulfuric acid/silica gel (**Scheme 7**).



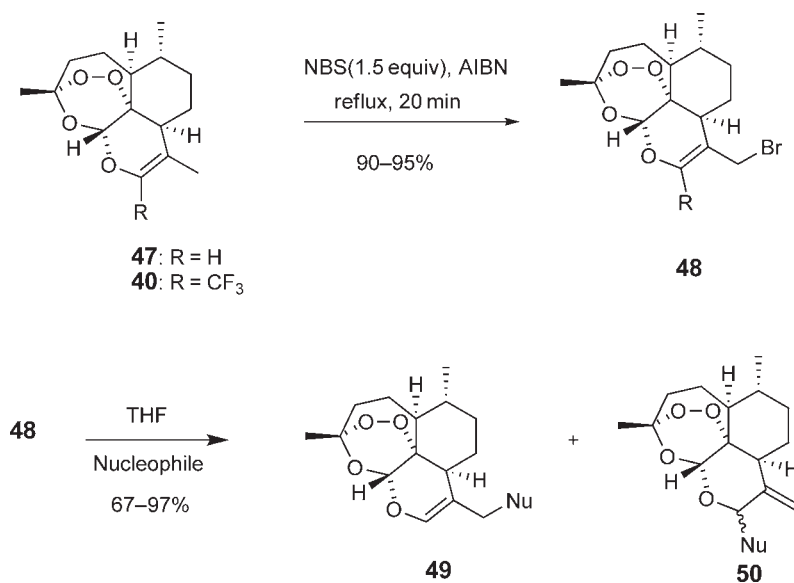
Scheme 7

Lactam **45** (R = H) was used, in base as a nucleophile in Michael addition, to yield *N*-alkyl derivatives in good to high yields (73–90%), <1995TL829, 1995JME5045, 2000BMC1111>; however, when ethylenediamine was reacted with artemisinin, dimer **46** was isolated in low yield (Equation 6) <2003MOL901>.



13.10.6.4 Reactions of the β -CH₃ (C₁₆) Group at C₉ of Artemisinin

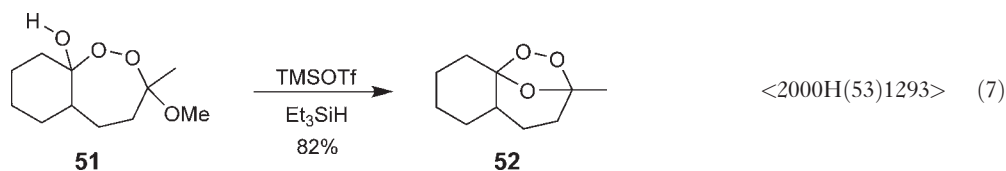
Allylic bromination of AHA **47** (R = H) and AHA **40** (R = CF₃) led to SN and SN' products **48** and **49**, respectively, in varying ratios depending on reaction conditions (Scheme 8) <2006JOC3082, 2002TL7837>.

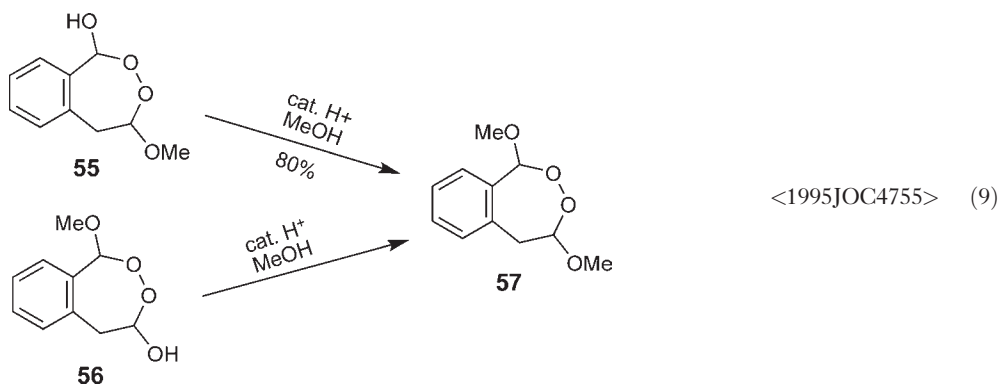
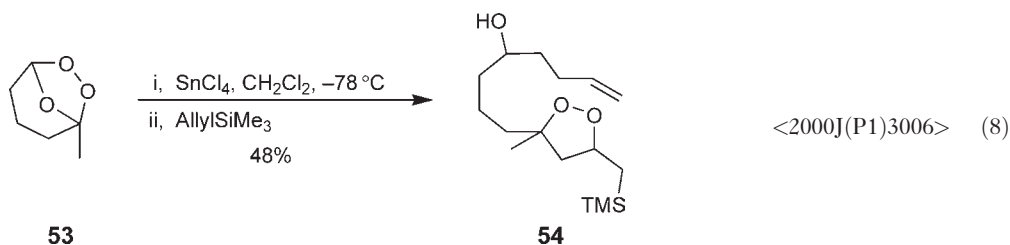


Scheme 8

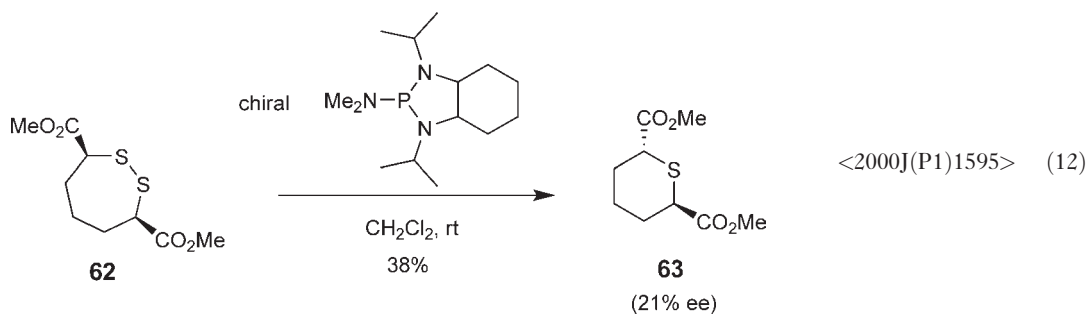
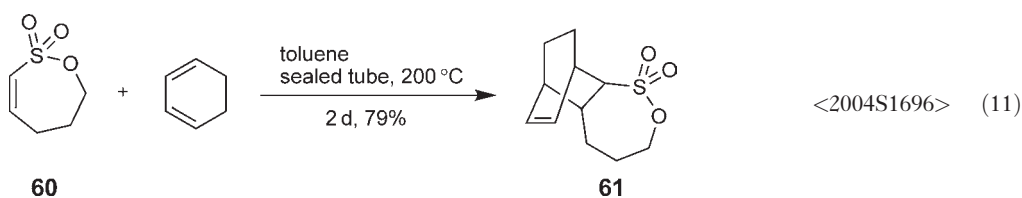
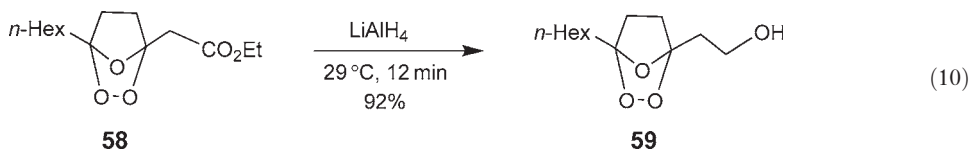
13.10.6.5 Reactivity of (Nonartemisinin) Nonconjugated 1,2-Dioxepanes, 1,2-Oxathiepanes, and 1,2-Dithiepanes

Some examples are shown in Equations (7)–(9).





The peroxide O–O bond is relatively weak; therefore, reactions at another site of a molecule, which bears a peroxide function, are carefully controlled. The tolerance of the peroxy O–O bond to a number of metal hydrides including 1,2-dioxepane derivatives was studied (Equations 10–12). For example, **58** was examined with the targeted reduction site being an ester group. The peroxide bond survived these reduction conditions <2005JOC4240>.



13.10.7 Reactivity of Substituents Attached to Ring Heteroatom

There is nothing to report in this area.

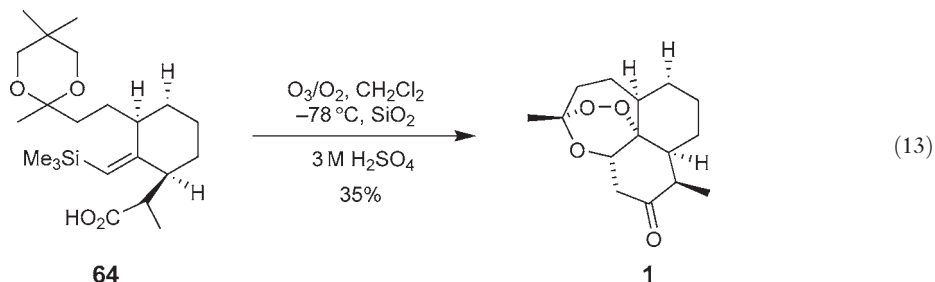
13.10.8 Ring Syntheses

13.10.8.1 Synthesis of the 1,2-Dioxepane Ring and Derivatives Thereof

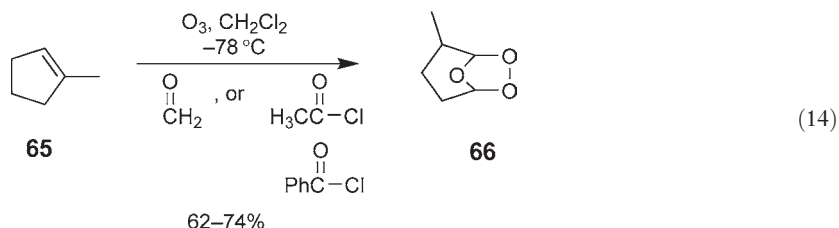
Synthesis of 1,2-dioxepane derivatives can be achieved through mainly four methods, three of which have the potential O–O bond already in one reactant, namely ozone, oxygen gas, or a hydroperoxide moiety. The fourth method involves the linking of two oxygen atoms to form a 1,2-dioxepine bond.

13.10.8.1.1 Ozonolysis

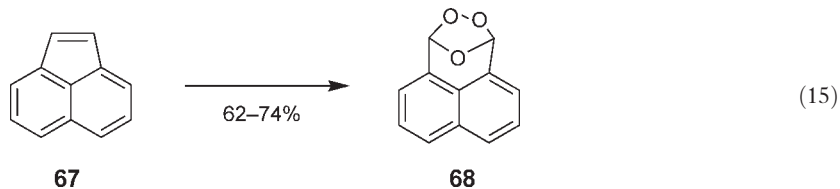
Ozonolysis of a substituted ene function (as part of acyclic or cyclic structure) has been used extensively in the preparation of 1,2-dioxepane derivatives. A classic example of this reaction was the ozonolysis of ene **64** to yield artemisinin **1** in 35% yield (Equation 13) <1992JA974, 1997BML2357, 2002JME4321, 1996JME4149, 1996JME2900>.



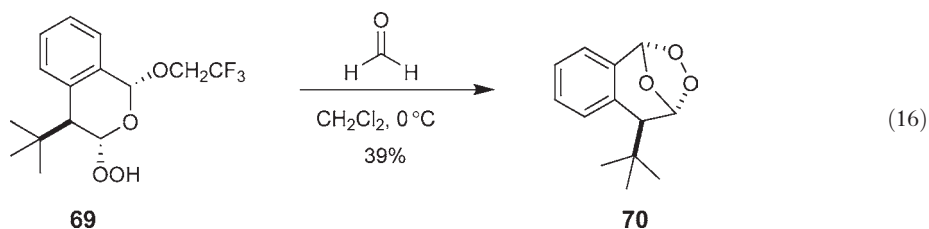
Ozonolysis of 1-methylcyclopentene in the presence of formaldehyde, acetyl chloride or benzoyl chloride gave 1,2-dioxepane (trioxane) **66** (Equation 14).



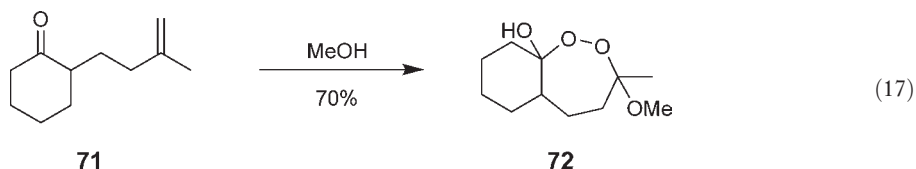
Similarly, the ozonolysis of acenaphthylene **67**, under the above conditions, led to 1,2-dioxepane (trioxane) **68** (Equation 15) <2000EJO335>.



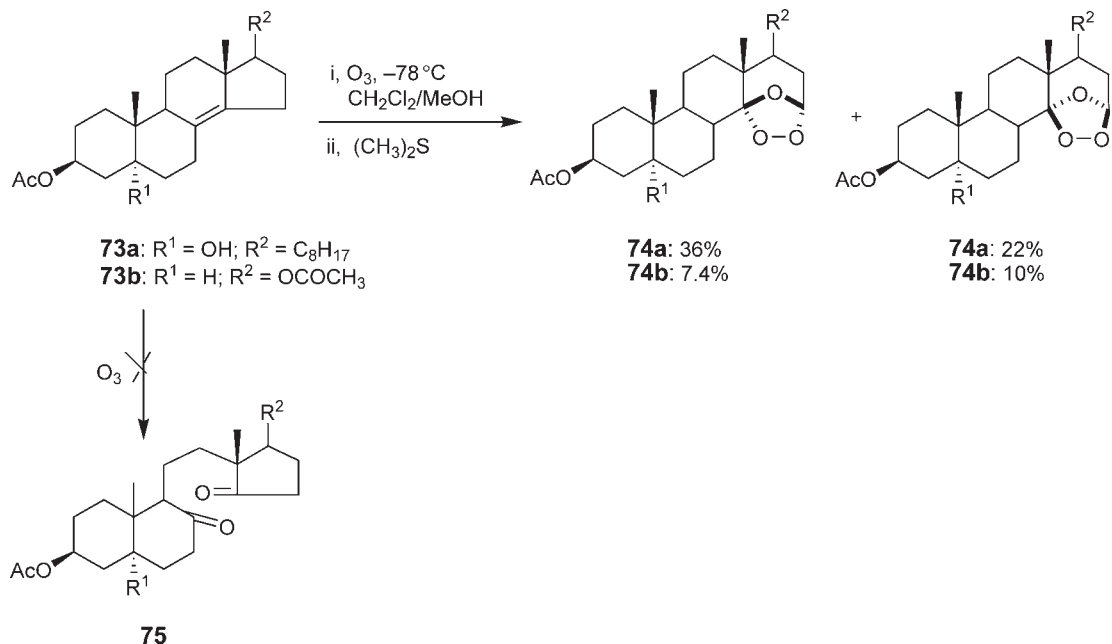
The conversion of α -(2,2,2-trifluoroethoxy)- α' -hydroperoxide ether **69** to 1,2-dioxepane (trioxane) **70** bears resemblance to the above-cited reactions (Equation 16) <1998J(P1)3059>.



The previous protocol was used with the carbonyl group being part of the ene to be ozonized (Equation 17) <2000H(53)1293>.

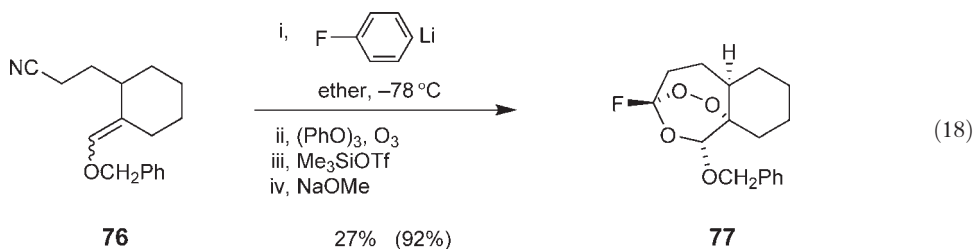


An intriguing reaction was reported in which ozonolysis of $\Delta^{8(14)}$ -unsaturated steroids **73a** and **73b** gave mixtures of 1,2-dioxepanes **74a** ($R^1 = \text{OH}$, $R^2 = \text{C}_8\text{H}_{17}$) and **74b** ($R^1 = \text{H}$, $R^2 = \text{OCOCH}_3$), respectively, and not the expected dione **75** (Scheme 9) <2002JCM392>.



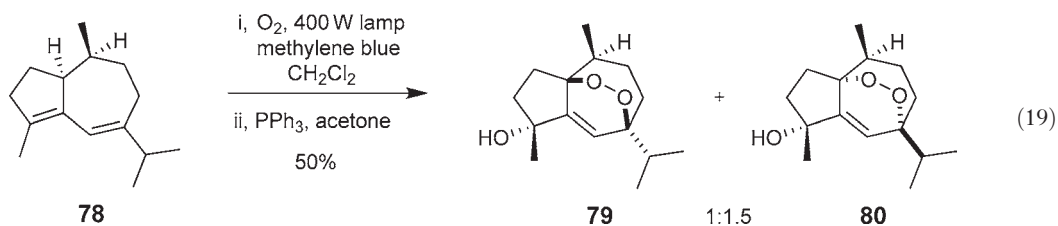
Scheme 9

Another interesting ozonolysis reaction is summarized by the conversion of 2-(2'-cyanoethyl)-1-(benzyloxymethyl)ene)cyclohexane **76** into 1,2-dioxepane (trioxane) **77**; the experimental section cites a 92% yield (Equation 18) <2002JME3824, 2000BMC1361>.

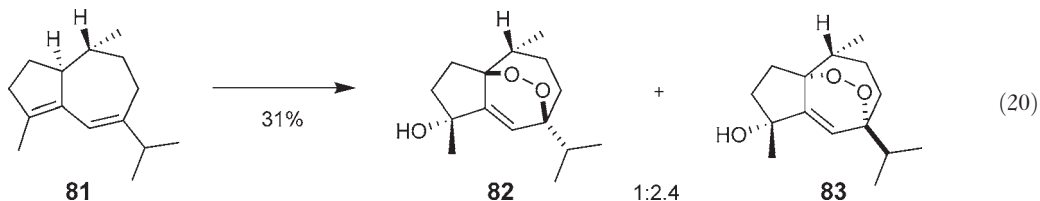


13.10.8.1.2 Addition of oxygen

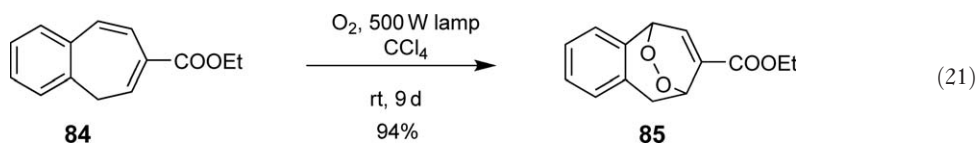
1,2-Dioxepane derivatives were made by the photolytic addition of an ene or 1,3-diene. Recently, an ene hydroperoxylation-[4+2] cycloaddition with O_2 of **78**, followed by selective reduction, led to the formation of a mixture (1:1.5) of 1,2-dioxepanes **79** and **80**, respectively (Equation 19).



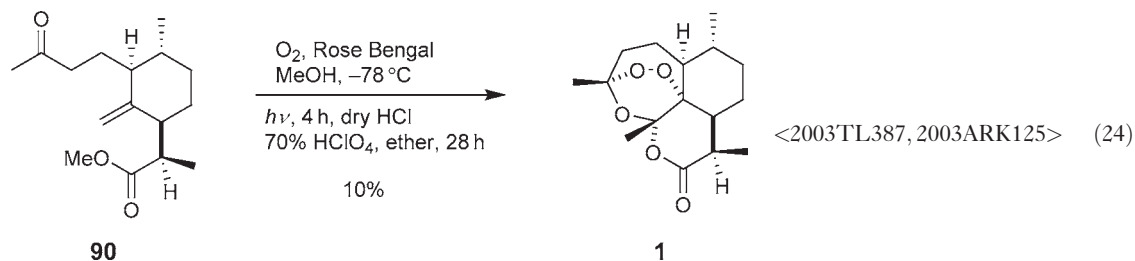
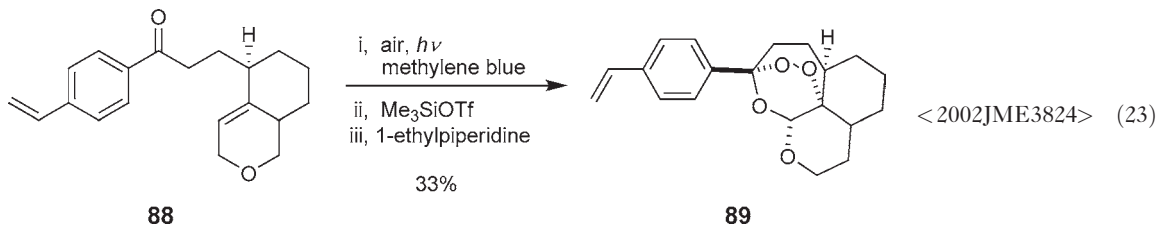
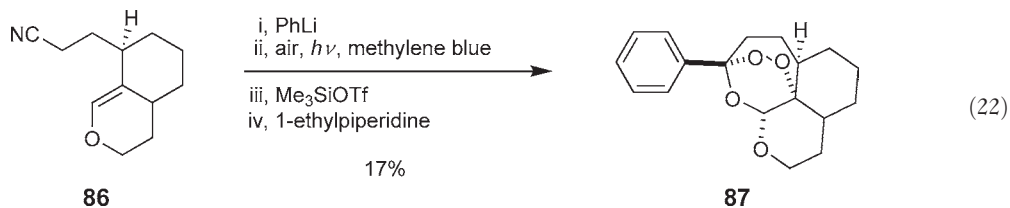
Similarly, diene **81** was converted to a mixture of 1,2-dioxepanes **82** and **83** (1:2.4; Equation 20) <2005OL3291>.

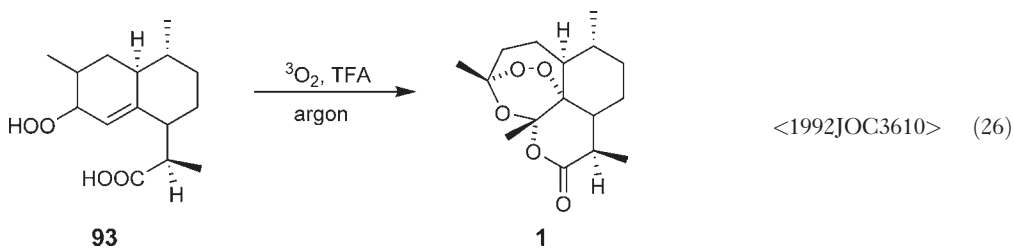
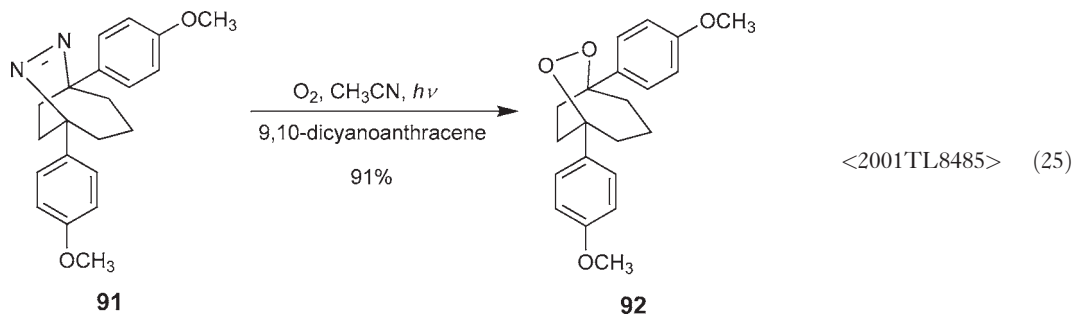


Singlet oxygen addition to 1,3-diene **84** yielded benzo[*d*]-1,2-dioxepine **85** upon bubbling O₂ through a CCl₄ solution of 1,3-diene **84** for 9 days (Equation 21) <2005CJC227>.



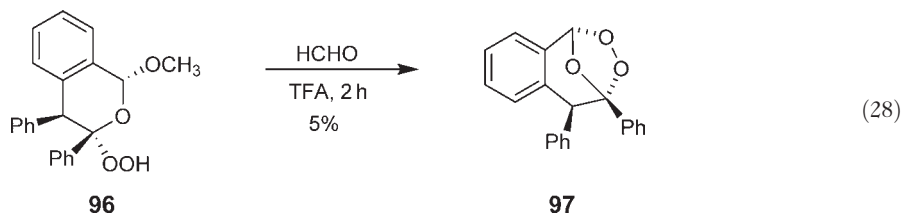
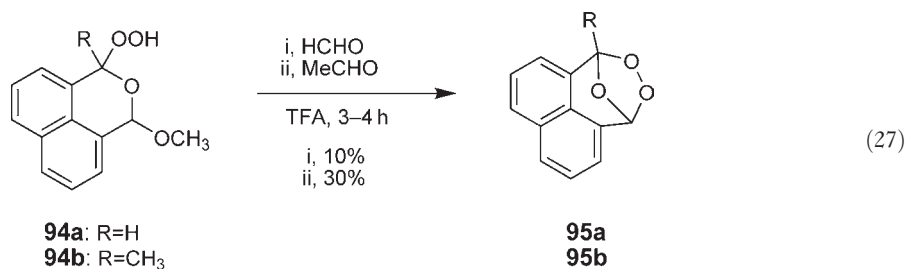
The reactions illustrated in Equations (22)–(26) the general utility of photooxygenation in the formation of 1,2-dioxepane derivatives.





13.10.8.1.3 Via hydroperoxide and O–O linkage

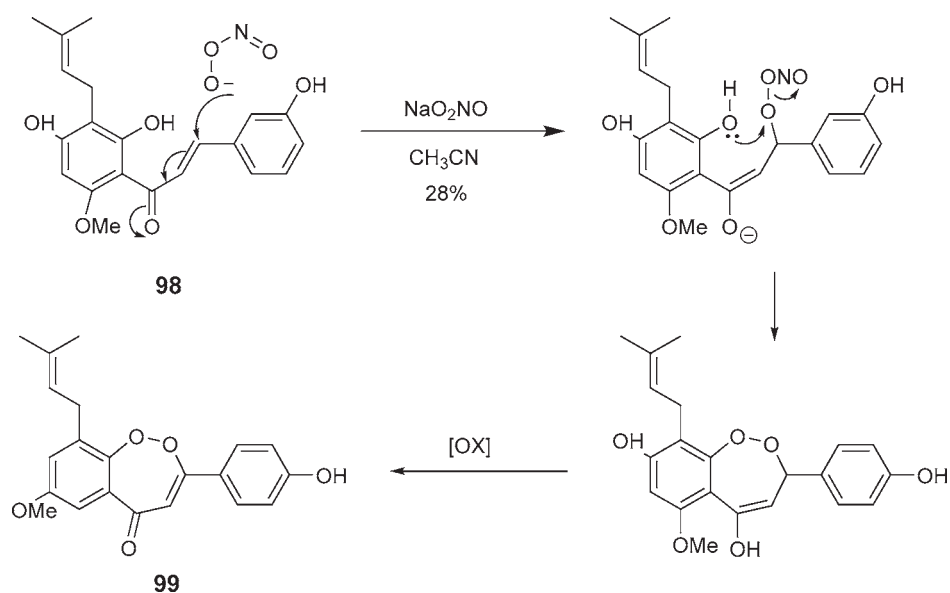
One report made use of the hydroperoxide moiety to prepare 1,2-dioxepanes in moderate to low yields (Equations 27 and 28) <1998J(P1)3053>.



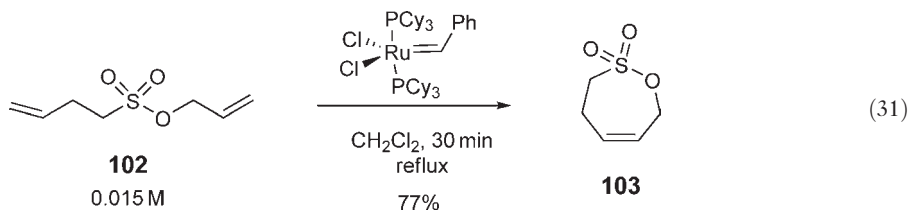
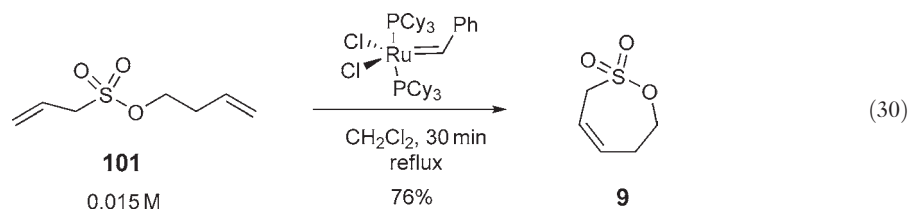
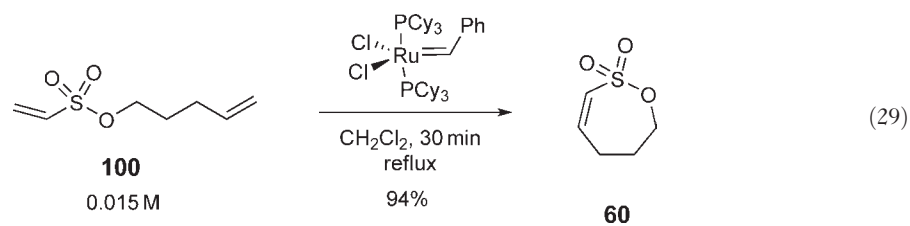
The other report employed peroxynitrite (twofold molar excess), as a nucleophile, in a Michael addition, followed by cyclization and oxidation to deliver endoperoxyzanthohumol **99** (Scheme 10) <2003CRT1277>.

13.10.8.2 Synthesis of 1,2-Oxathiepane Derivatives

A remarkable ring-closing metathesis (RCM) reaction was highly effective in the syntheses of a number of cyclic sulfones, in high to good yields, from sulfonates (Equations 29–31) <2004S1696>.

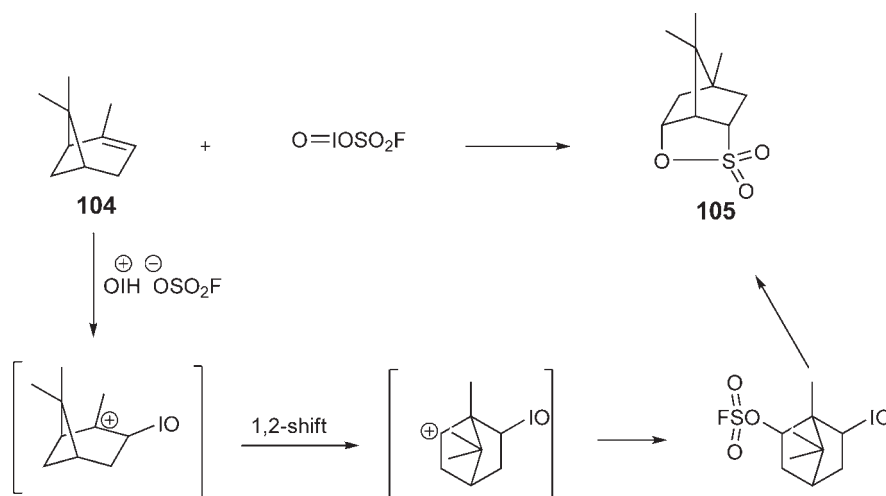


Scheme 10

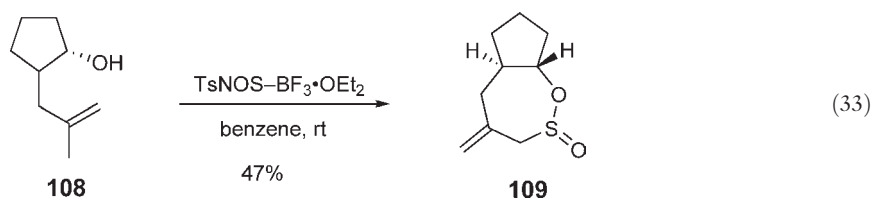
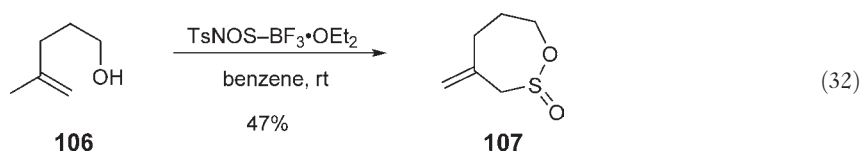


1,7,7-Trimethyl-2,6-bicyclo[2.2.1]heptane sulfone **105** was prepared via the rearrangement shown in [Scheme 11](#) <1995SUL71>.

Sulfines were prepared from the reaction of unsaturated alcohols and *N*-sulfinyl-*p*-toluene sulfonamide (TsNOS)- $\text{BF}_3\text{-OEt}_2$ (Equations 32 and 33) <1995JOC8067>.

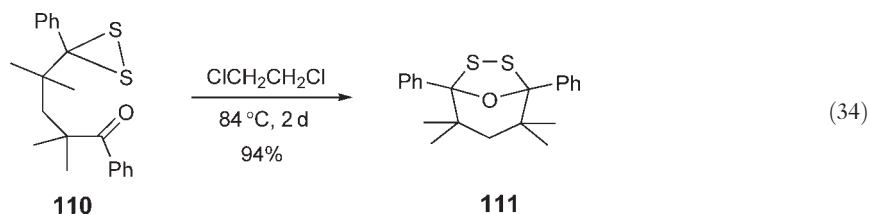


Scheme 11

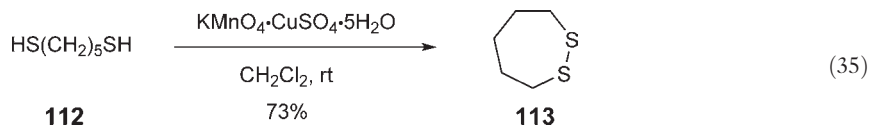


13.10.8.3 Synthesis of 1,2-Dithiepane and Derivatives

Heating of dithiirane **110** at 84°C for 2 days resulted in its rearrangement to 1,2-dithiepane **111** in 94% yield (Equation 34) <1994PS445, 1997BCSJ509>.

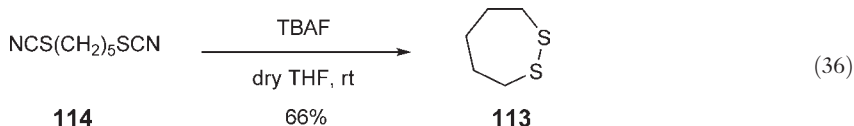


Potassium permanganate adsorbed on copper sulfate pentahydrate oxidizes dithiol **112** into 1,2-dithiepane **113** (Equation 35) <1998S1587>.

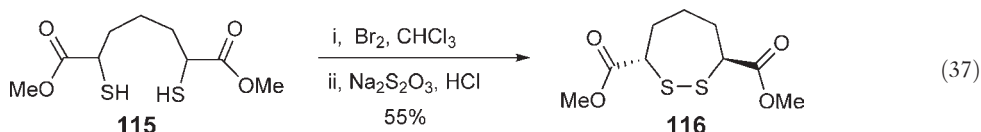


Treatment of acyclic bithiocyanate **114** with tetrabutylammonium fluoride (TBAF) in dry tetrahydrofuran (THF) gave 1,2-dithiepane **113** in 66% yield (Equation 36). It is suggested that the fluoride ion acted as a nucleophile, which

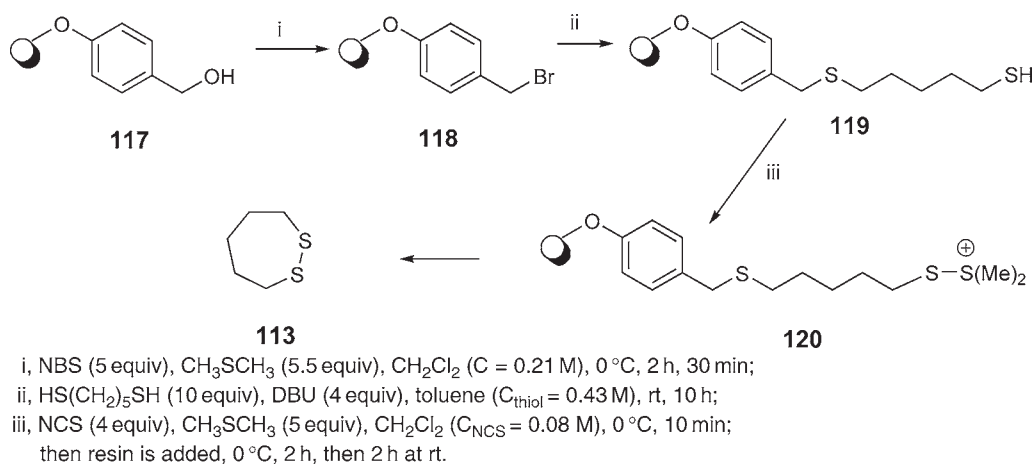
attacked the nitrite carbon of one thiocyanate to generate a sulfide ion which in turn attacked the sulfur atom of the second thiocyanate group to push a cyanide ion, as a leaving group <1999TL6489>.



A dropwise addition of a chloroform solution of iodine to a solution of dimethyl *meso*- α,α' -dimercaptopimelate **115** and triethylamine gave *cis*-3,7-bis(methoxycarbonyl)-1,2-dithiepane **116** in 55% yield (Equation 37) <2000J(P1)1595>.

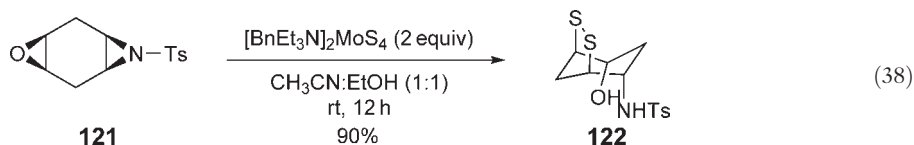


Solid-phase chemistry was employed in the synthesis of cyclic disulfides. Scheme 12 shows a sequence of reactions that led to the formation of 1,2-dithiepane in 75% yield <2000TL9989>.

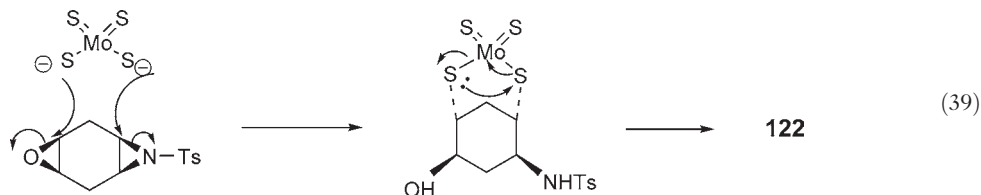


Scheme 12

Various oxidations of dithiols to cyclic sulfides were exemplified further by using bromine on silica gel solid support in CH_2Cl_2 . Under these conditions, 1,5-pentanedithiol was converted to 1,2-dithiepane **113** in 86% yield <2000TL6271>. Probably, the most interesting new development in the synthesis of 1,2-dithiepane was the reaction of benzyltriethylammonium tetrathiomolybdate ($[\text{BnEt}_3\text{N}]_2\text{MoS}_4$) with the *cis*-aziridino epoxide **121** to give the 1,2-dithiepane derivative **122** in 90% yield (Equation 38). This report constitutes the first synthesis of a functionalized 1,2-dithiepane in a locked conformation.



The formation of **122** can be envisaged to proceed via the mechanism shown in Equation (39) <2005JA12760>:



13.10.9 Ring Syntheses by Transformation of Another Bicyclic Ring System

In Section 13.10.8, two cases are already included.

In conclusion, the vast literature and its derivatives, particularly artesunate, artemether, and arteether, point out to the need to make these derivatives in quantities that would reduce their current production cost to make these drugs accessible to the economically underprivileged societies that are often the victims of malaria. A recent promising method in which artemisinic acid, a precursor to artemisinin, has been produced in engineered yeast. Therefore, microbially produced artemisinic acid holds promise to the syntheses of antimalarial drugs at affordable prices <2006N940>. Furthermore, anticancer activities of artemisinin **1** and its derivatives have been reviewed <2005MI995>.

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Biographical Sketch



Makhlu J. Haddadin was born in Main, Jordan. He holds B.S. and M.S. degrees (Professor C. H. Issidorides) from the American University of Beirut and a Ph.D. degree from the University of Colorado, USA (Professor A. Hassner). He was a research fellow at Harvard University (Professor L. F. Fieser). The art of heterocyclic chemistry has been his main hobby as he worked on heterocyclic steroids, isobenzofurans, isoindoles, quinoxaline 1,4-dioxides (the Beirut reaction), pyridazines, tetrazines, *2H*-indazoles, and other heterocycles. He rejoined his alma mater in 1964 and currently serves as professor of chemistry. He was vice-president for academic affairs (1987–99).



Claudia J. Nache was born in Saida, Lebanon. She holds a B.S. degree from the Saint-Joseph University, Lebanon, and a M.S. degree (Doctor Jean-Yves Winum) from the University of Montpellier II, France. She is currently a research assistant at the American University of Beirut (Professor M. J. Haddadin). She worked on sulfonylureas for her M.S. degree and has been working on benzofurazan oxides, quinoxaline 1,4-dioxides, phenazines, and pyocyanins.

13.11

1,3-Dioxepanes, 1,3-Oxathiepanes, and 1,3-Dithiepanes

H. Frauenrath and S. Flock

University of Kassel, Kassel, Germany

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13.11.1 Introduction

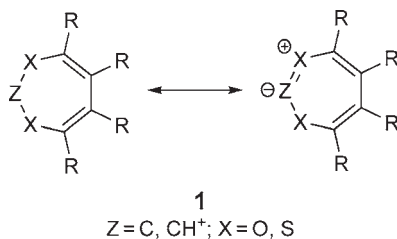
This subject was covered previously in 2 pages in CHEC(1984) (Volume 7, Chapter 5.18.3.2. and 5.18.4.2) and 31 pages in CHEC-II(1996) (Volume 9, Chapter 9.11) both of which are available online. The present chapter is intended to update the previous work concentrating on major new preparations, reactions and concepts, and also to address any major deficiencies in CHEC-II(1996).

In this chapter, the different classes of compounds, that is, 1,3-dioxe-, oxathie-, and dithiepins and their benzo derivatives, are now grouped together, and their chemistry is treated under the common aspects given for this volume. However, it should be pointed out that the classes of compounds described here are not typical hetero-aromatic compounds, and much of the chemistry is concentrated on nonconjugated ring systems.

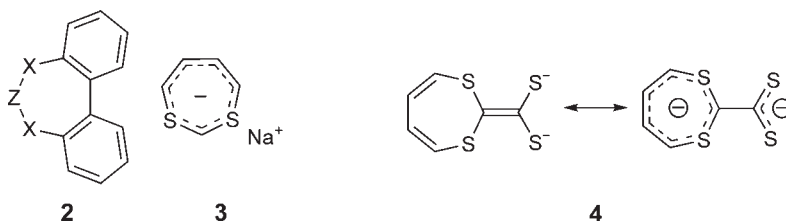
Abundant recent work focused on the chemistry of benzo-fused derivatives, particularly on biaryl systems comprising a short tethered chain. A review on the chemistry of 1,3-dioxepins is available <2005PHC389>.

13.11.2 Theoretical Methods

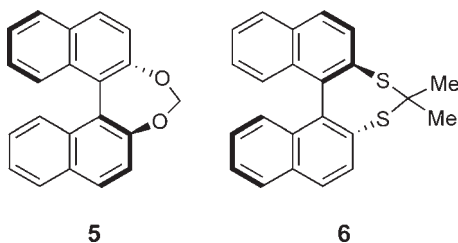
Only a few reports deal with the aromatic character of the fully conjugated rings. Based on calculated diatropic ring currents (quantified as *Nucleus Independent Chemical Shift* or NICS values), <1996JA6317> dioxa and dithia ring systems **1** were predicted to attenuate the Hückel anti-aromaticity expected of a planar $4n$ p_π system with varying degrees of C_2 symmetric distortion toward Möbius aromaticity <2002CC642>.



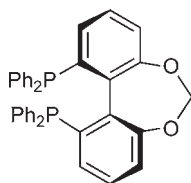
The aromatic character of the dibenzo derivative **2** has also been calculated. Studies on the behavior of the deep red anion **3**, as a potential 10π heteroaromatic system, were described previously <1996CHEC-II(9)268>. ¹H NMR spectra (NMR – nuclear magnetic resonance) of 1,3-dithiepin-2-carbodithiolate **4**, a ligand obtained from the reaction of carbon disulfide with the lithium salt of 1,3-dithiepin, as well as its palladium salt suggest a good deal of Hückel aromatic character in the seven-membered dithiepin ring <1991ICA(185)169>.



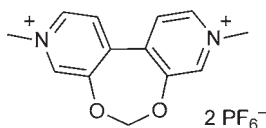
A theoretical study of numerous chiral molecules including bridged biaryls **5** and **6** has been undertaken using a molecular Monte Carlo simulation approach coupled with calculations of molecular chirality based on a chirality order parameter. The method successfully predicts the helical twisting powers <2003JCP10280>.



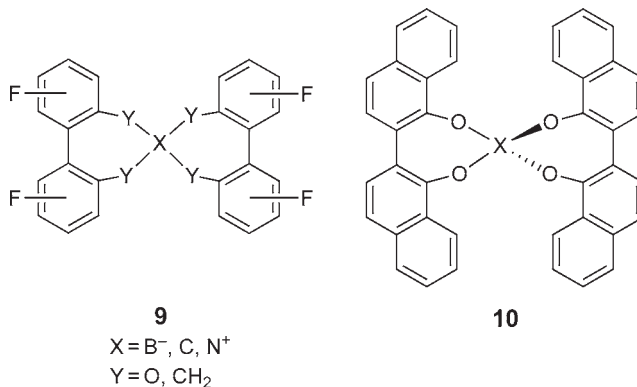
The influence of the dihedral angle on the natural bite angle of Ru complexes bearing biaryl units such as C₁-TunePhos **7**, as chiral ligands, has been studied by MM2 <2000JOC6223, 2003TL823> and density functional theory (DFT) methods <2005CCL1555>.

**7**

Molecular modeling calculations were conducted on the methyl viologen derivative **8** and methyl viologen (MV²⁺) to generate the dihedral angles for the dicationic (fully oxidized) and monocationic (one-electron reduced) species <2005TL7291>.

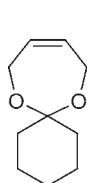
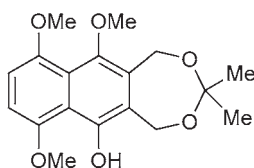
**8**

A DFT study of the geometrical, electronic, and energetic parameters of fluoro derivatives of diphenylborates **9** and **10** and isoelectronic structures where the central atom has been substituted by carbon and nitrogen has also been carried out <2005TA755>. The relative energy of the homochiral versus heterochiral complex has been linearly correlated with the central atom and fluorine substitution on the different positions of the aromatic ring.

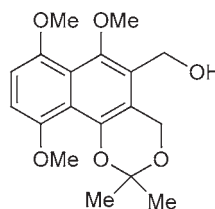
**9****10**

X = B⁻, C, N⁺
Y = O, CH₂

An *ab initio* study of the conformational energy surface of spirodioxepin **11** <2002JST(589)153> and a study of the conformational equilibrium of various 1,3-dithia- and 1,3-dioxa-5,6-benzocyclohexenes have been reported <1995JST59>. For a theoretical study of H complexes of twist and chair conformations of 2-alkyl substituted 4,7-dihydro-1,3-dioxepin using different semiempirical methods (see <2002RJC1107>). Furthermore, the relative energies for structural isomers **12** and **13** have been calculated by MM2 <2001OL2661>.

**11****12**

9.4 kcal mol⁻¹

**13**

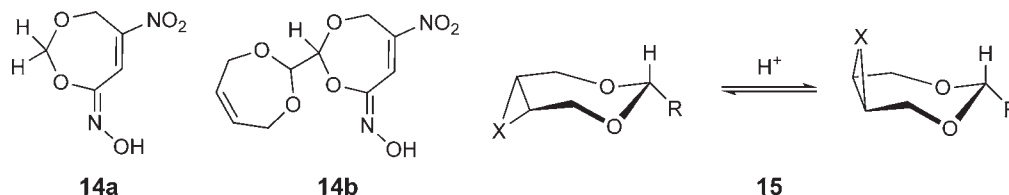
0.0 kcal mol⁻¹

AM1 calculations on blepharismins and oxyblepharismins revealed that the substituents of the natural pigments do not lead to a change of the tautomerism and conformational states of the fundamental system <2000M1115>.

13.11.3 Experimental Structural Methods

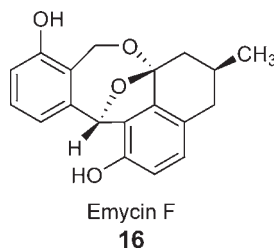
13.11.3.1 NMR Spectroscopy

^1H and ^{13}C NMR techniques have widely been used to determine the configuration of new dioxepins and dithiepins and to elucidate the constitution and conformation of new naturally occurring substances. For example, the configuration of oximes **14a** was determined by ^1H and ^{13}C correlated spectra, correlation spectroscopy (COSY), nuclear Overhauser enhancement spectroscopy (NOESY), heteronuclear correlation (HETCOR) spectroscopy, and heteronuclear multiple bond correlation (HMBC) spectroscopy <1998CCA557>.

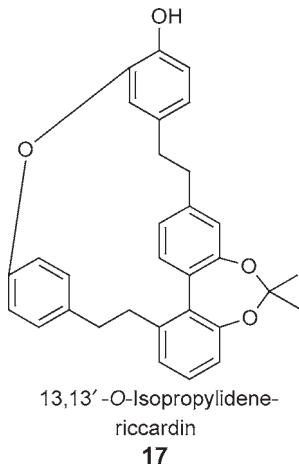


Gradient-selected differential nuclear Overhauser effect (NOE) measurements confirmed that in a dimethylsulfoxide solution oximes **14a** and **14b** exist in (*E*)-configuration. The steric structure of diastereomers of 4-substituted 8,8-dihalogeno-3,5-dioxabicyclo[5.1.0]octanes **15** (X = CCl₂, CBr₂) and carbenodioxepins **15** (X = CH₂) has been studied by ^{13}C NMR spectroscopy <2003RJOC1029, 2005RJO293>.

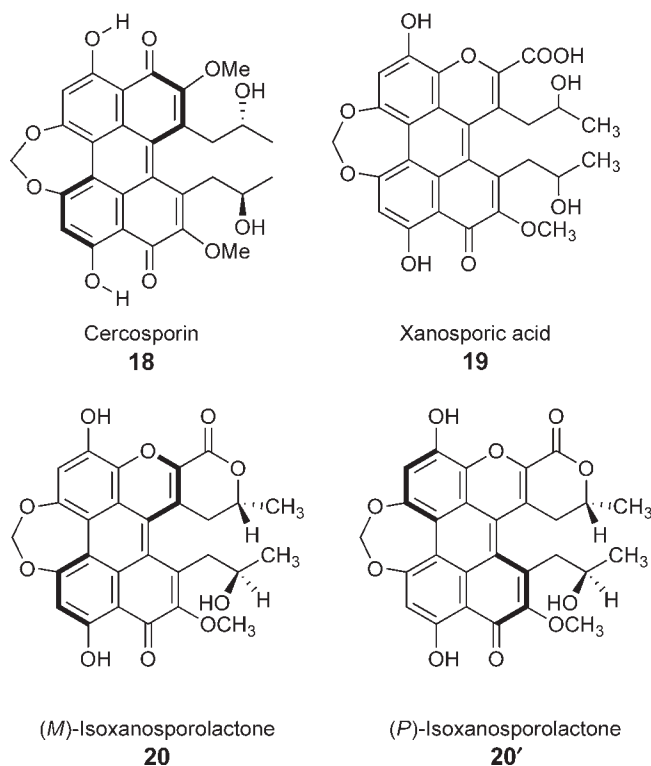
The constitution of the antibiotic emycin F **16** incorporating a benzoannelated dioxepin moiety was mainly established through $^nJ_{\text{C-H}}$ long-range couplings from HMBC and correlation through long-range coupling (COLOC) NMR experiments <1995AGE1617>.



The structure of a compound separated from the antifungal constituents of the Chinese liverwort *Marchantia polymorpha* L. (Marchantiaceae) was identified by ^1H and ^{13}C NMR spectroscopy and established to be 13,13'-*O*-isopropylidene-riccardin **17** <2006MI34>. The acetonide structure of **17** emerged from the ^{13}C NMR spectra and HMBC correlations. For the structural elucidation of a new *ent*-kaurane diterpenoid, hebeirubescensin A, see <2006T4941>.



Deuterium isotope effects on ^1H and ^{13}C NMR chemical shifts of intramolecularly hydrogen-bonded, natural-occurring perylenequinones, such as cercosporin **18**, have been studied <1997J(P2)2013>. HMBC NMR experiments have also been used to elucidate the structure of the biodegradation products of cercosporin **18**, xanosporic acid **19**, and (*P*)- and (*M*)-xanosporolactone **20** <2003P723>. Xanosporolactone was isolated in a 2:1 ratio of (*M*):(*P*) atropisomers.



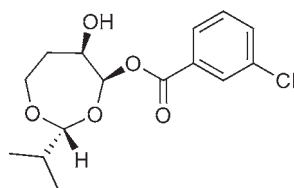
Furthermore, the allohimachalane (see Section 13.11.9.1) <1999T14623> as well as boletunones A and B, highly functionalized sesquiterpenes from the fruit body of the mushroom *Boletus calopus* <2004OL823>, have been characterized by 2D-NMR (heteronuclear single quantum correlation (HSQC), HMBC, and ^1H -COSY). The structure of a drimen-11,12-acetonide, isolated from *Maya's herb*, was deduced by means of ^1H and ^{13}C NMR, distortionless enhancement by polarization transfer (DEPT), COSY, NOESY, HSQC, and HMBC analyses <2005MRC339>.

The structure of copolymers obtained by ATRP copolymerization of 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) with *n*-butyl acrylate (*n*BA) using ethyl 2-bromoisobutyrate and *N,N,N',N',N'*-pentamethyldiethylenetriamine/copper(I) bromide, as the initiator and catalyst, respectively, was studied by 1D and 2D NMR techniques, which revealed a quantitative ring opening of BMDO in the copolymerization <2005PLM11698>. For a similar study of copolymers of BMDO and styrene, see <2003MM6152>, and with methyl methacrylate, <2003MM2397>.

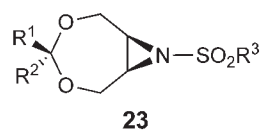
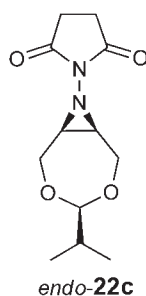
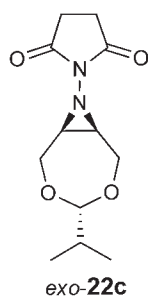
13.11.3.2 X-Ray Diffraction

X-Ray diffraction is the preferred method to establish the relative and absolute configuration of 1,3-dioxe- and 1,3-dithiepins. For example, X-ray analysis afforded the relative configuration of dioxepane *rac*-**21c**, which was

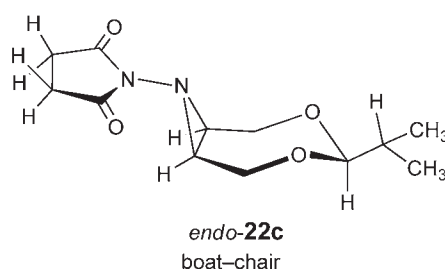
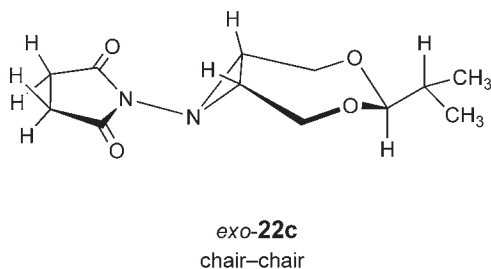
important for establishing the absolute configuration of 2-substituted 4,5-dihydro-1,3-dioxepins obtained by asymmetric double-bond isomerization <2001AGE177>. The asymmetric unit of *rac*-**21c** contains two crystallographically independent molecules.

**21c**

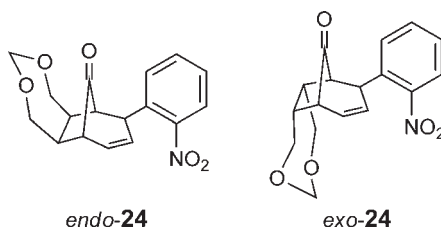
Crystal structures of aziridinodioxepanes **22c** revealed that the isopropyl group in both the *endo*- and *exo*-isomers strongly prefer the *quasi*-equatorial position. Hence, the *exo*-isomer adopts a chair-chair conformation and the *endo*-isomer of a boat-chair conformation. The substituent on the aziridine *N* atom occupies, in both cases, the *anti*-position with respect to the dioxepane ring <2005AXC705>. Similar results have been obtained for *N*-sulfonyldioxepanoaziridines **23**. The asymmetric unit of **23a**, unsubstituted in the 2-position of the dioxepane moiety, contains two crystallographically independent molecules, one having a boat-chair and the other a twist-boat conformation. The *endo*-isomer **23d** adopts a boat-chair, the *exo*-isomer **23b** a chair-chair, and the *exo*-isomer **23c** a boat-twist conformation <1995JME3034>.



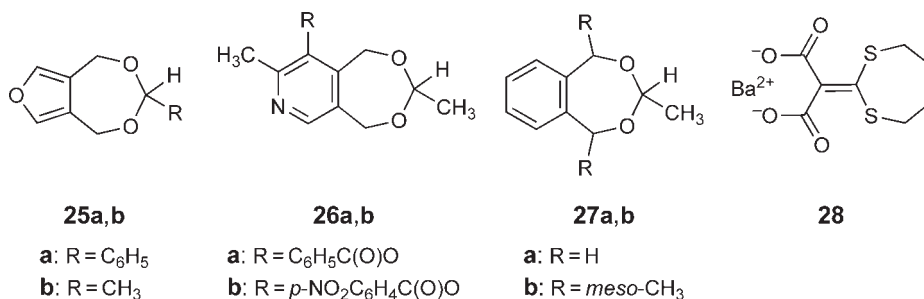
	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³
a	H	H	4-AcNH-C ₆ H ₄
b	H	<i>i</i> -Pr	4-O ₂ N-C ₆ H ₄
c	H	<i>i</i> -Pr	4-AcNH-C ₆ H ₄
d	<i>i</i> -Pr	H	4-AcNH-C ₆ H ₄



The structures of the *endo*- and *exo*-isomers of bridged bicyclodioxepanes **24** were confirmed by X-ray crystallography <2006T3423>.

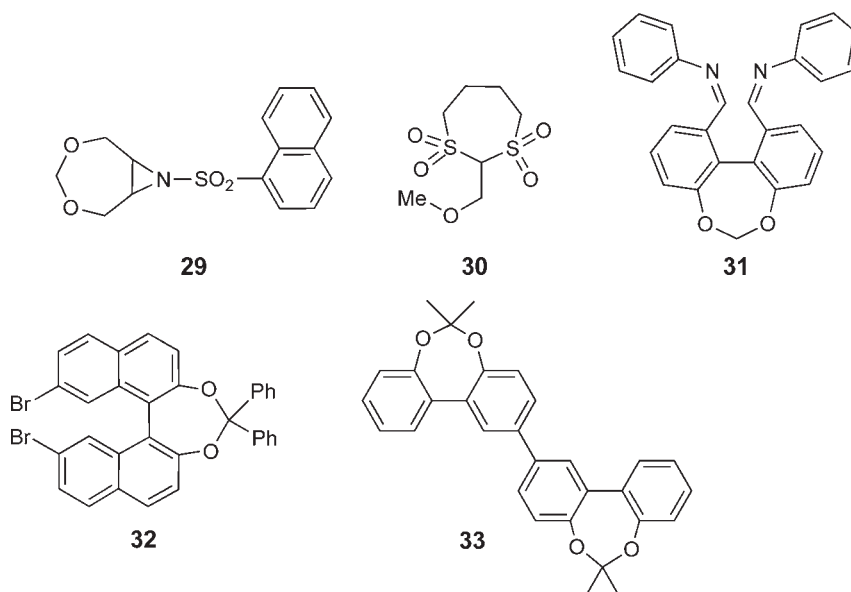


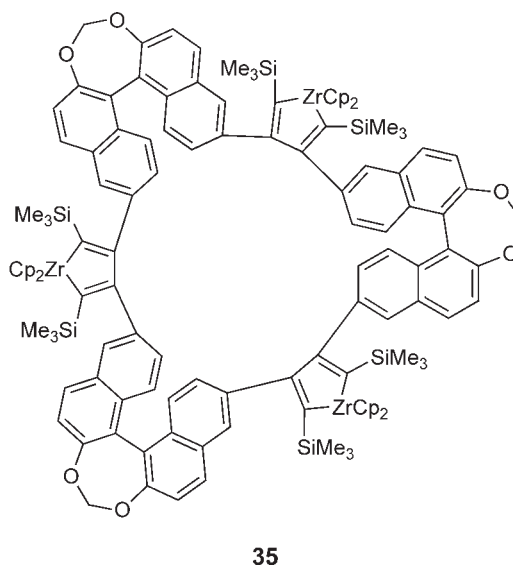
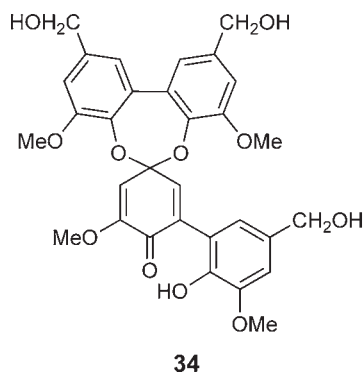
The X-ray structures of a series of seven-membered acetals bearing a planar structural element, such as **25–27** <2003JST(644)89> as well as dithiepane **28** <1996IC3077>, have been investigated.



It has also been shown by X-ray diffraction that the major diastereomer of 9-phenyl-4,8,10-trithiadibenzo[*cd,i*]-azulene 8-oxide (cf. Section 13.11.6.5) is the *trans*-isomer with the phenyl group and the sulfinyl-oxygen atom occupying the equatorial positions (*R_S*, *S_C* and *S_S*, *R_C* configurations) <1996CL655>.

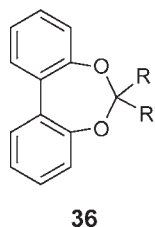
Various other crystal structures incorporating a 1,3-dioxe- or dithiepin ring were described, particularly for biaryl compounds in order to determine the dihedral angle around the biaryl axis and to gain information about the conformational flexibility, for example, aziridinodioxepin **29** <2005AXE2844>, dithiepane tetraoxide **30** <2003AXE1251>, dibenzodioxepins **31** <2005ICC1049> and **32** <2005EJO1541>, the dimer of 6,6-dimethyl-dibenzo[*d,f*][1,3]dioxepin **33** <2004PCB9571>, an oxidation product of dehydrodivanillyl alcohol **34** <1996AX(C)1815>, and the crystal structure of a homochiral (*SSS*), trimeric, zirconium-containing macrocycle **35** <2001JA2683>.





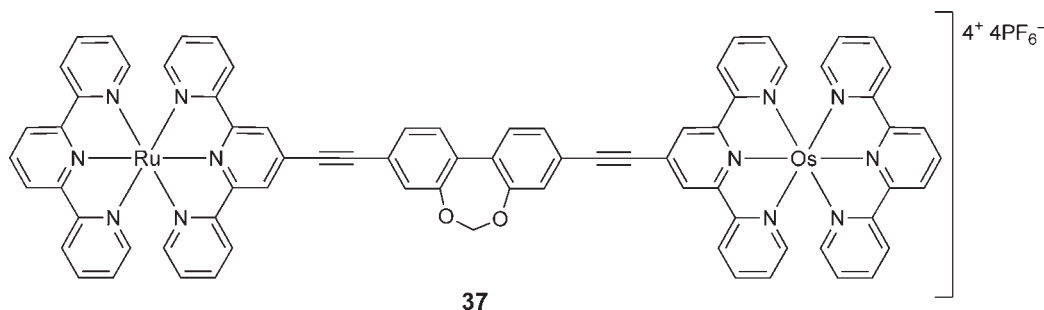
13.11.3.3 Mass Spectrometry

Because of the importance of the biphenyl scaffold, as a structure of pharmaceutical and active therapeutic compounds, the mass spectrometric behavior of a series of 6,6-disubstituted dibenzo[*d,f*][1,3]dioxepins **36** has been studied. The electron ionization-induced fragmentation patterns were discussed based on use of labeled compounds, accurate mass measurements, and collisionally induced dissociation experiments using an ion trap [<2006JMP577>](#).



R	CH ₃	iPr	CH ₂ OCH ₃	C ₄ H ₉	CH ₂ COCH ₃	CH ₂ CO ₂ Me
R'	CH ₃	CH ₃	CH ₃	CH ₃	CH ₃	CH ₃
R	C ₆ H ₅	C ₆ H ₄ CH ₃	CH ₂ Ph	CD ₃	C ₆ H ₅	
R'	CH ₃	CH ₃	CH ₃	CD ₃	CD ₃	

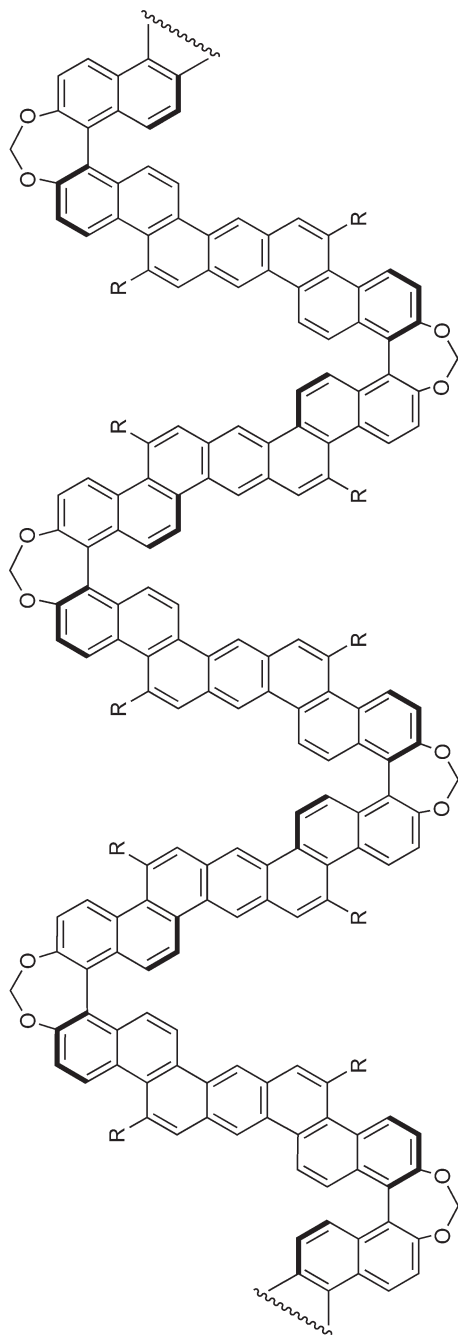
The organometallic **37** bearing a dibenzo-fused dioxepin ring has been characterized by MALDI-TOF mass spectrometry using a 2-[(2*E*)-3-(*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile matrix [<2006ANC199>](#).



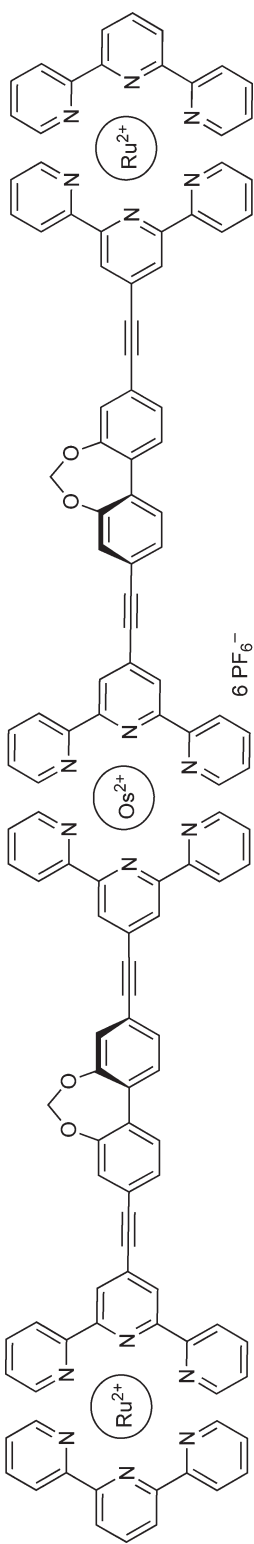
13.11.3.4 Other Methods

Novel helical polybinaphthyls, including **38**, have been synthesized, and their structures were characterized by NMR, UV, FL, and CD. Their optical properties have also been studied, and it was observed that these compounds exhibit a significantly increased fluorescence effect to an amino alcohol quencher over the parent 1,1'-bi-2-naphthol [<2004MM2695>](#).

The electrochemical and photophysical properties of a linear 2,2':6',2''-terpyridine-based trinuclear Ru(II)–Os(II) nanometer-sized array **39** have been studied [<2005JA2553>](#).



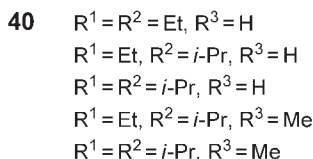
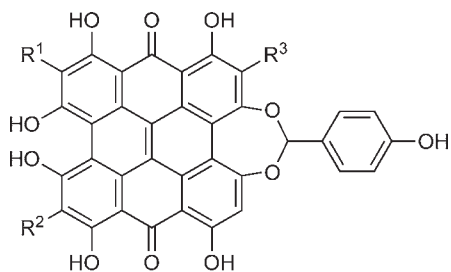
38
 $R = p\text{-}n\text{-C}_6\text{H}_{13}\text{OPh}^-$



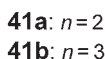
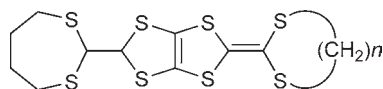
The effect of the torsion angle on the rate of intramolecular triplet energy transfer has been discussed. The magnitude of the electronic coupling between terminal chromophores shows a precise dependence on the dihedral angle around a bridging biphenyl group <2005PCP3677> (see also <2006PCA9880>). The electrochemical behavior of the constrained methyl viologen derivative **8** has also been studied <2005TL7291>.

Adsorptive accumulation on glassy carbon electrodes from 1 M HClO₄ solutions was used to detect the phytotoxin cercosporin **18** (CER; cf. Section 13.11.3.1) from infected leaf tissues, and the adsorptive square wave voltammetry was employed to perform the quantitative determination of CER in naturally infected extracts <2003ELA40, 2005ANA199>.

Circular dichroism was used to study the structure of oxyblepharismine **40**, the photoreceptor chromophore for the photophobic response of the blue form of *Blespharisma japonicum* <2005MI1343>.



Salts of **41** were obtained by the controlled-current electrocrystallization, and their electrical conductivity has been studied <2003SM(135)539>.

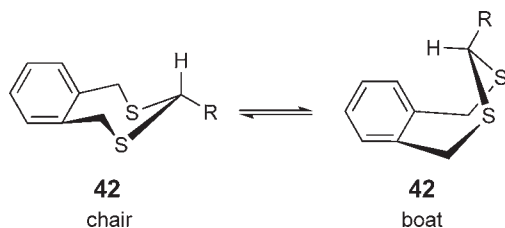


Solvent effects including 2-methyl-1,3-dioxepane (MDOP), as a solvent, on the propagation kinetics of methyl acrylate (MMA) have been investigated using the PLP-SEC technique (PLP = pulse laser polymerization) <2005MI267>, and the composition of dioxolane–dioxepane copolymers has been studied by IR and differential scanning calorimetry (DSC) <2004PB349>.

13.11.4 Thermodynamic Aspects

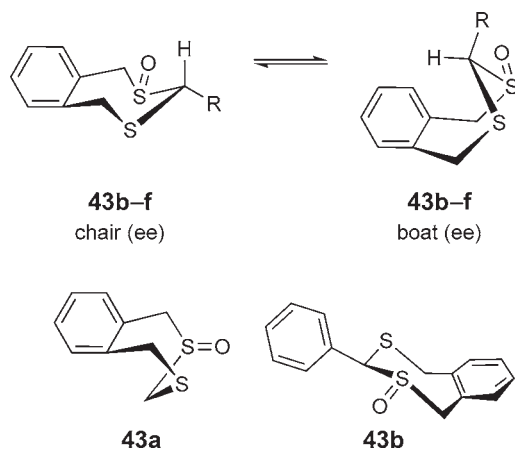
The relative thermodynamic stabilities of 4,7-dihydro- and 4,5-dihydro-1,3-dioxepins as well as a number of their 2-substituted derivatives have been determined by base-catalyzed chemical equilibration in dimethyl sulfoxide (DMSO) <1999STC295>.

As shown by dynamic ¹³C NMR spectroscopy, *trans*-2-substituted 1,3-dithia-5,6-benzocycloheptenes **42** exist as an equilibrium of chair and boat conformations with the substituents in the equatorial positions and preference of the chair. The boat form is characterized by its NMR parameters, namely an upfield shift (10 ppm) of the C2 signal. These results were confirmed by Raman spectroscopy and X-ray diffraction <2004JST(688)191> (see also <2001RJGC960>).



R = H (a); Ph (b); Me (c); Et (d); *i*-Pr (e); *t*-Bu (f)

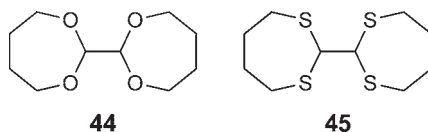
The preferred conformation of related 2-substituted *trans*-1,3-dithia-5,6-benzocycloheptene 1-oxides **43** depends on the substitution pattern. Compounds **43b–f** (R = phenyl, methyl, ethyl, isopropyl) exist in CDCl₃ at –60 °C as an equilibrium of chair and boat conformations with the substituents in the equatorial position. Unsubstituted **43a** (R = H) possesses a boat form with an axial sulfinyl group; whereas, for the butyl derivative the conformational equilibrium is completely shifted to the boat structure. The proton–proton distances for the chair conformer of 2-phenyl-1,3-dithia-5,6-benzocycloheptene 1-oxide **43b** were determined by 2D NOESY experiments in CD₂Cl₂ and CS₂–CDCl₃. It has been shown that solvent effects influence the thermodynamic parameters of the conformational equilibrium [<2001JGU1266>](#).



The thermal inversion of the helix of cercosporin **18** and related compounds was studied by kinetic experiments, by NOESY exchange, and dynamic NMR experiments. The activation parameters $\Delta H^\ddagger$, $\Delta G^\ddagger$, and $\Delta S^\ddagger$ were thus obtained [<2001J\(P2\)2276>](#).

Conformational analyses of C₂ symmetric 1,1'-binaphthyl derivatives comprising a dioxepin unit were performed by CD spectroscopy [<2000JOC5522>](#).

The *gauche/trans* conformational equilibria of 2,2'-bi-(1,3-dioxepanyl) **44** and 2,2'-bi-(1,3-dithiepanyl) **45** in CCl₄ and benzene have been studied by a dipole moment determination. The data revealed that both **44** and **45** favored the *trans*-conformation; however, the X-ray crystallography showed that both compounds prefer the *trans*-conformation in the solid state [<2004PCA6874>](#).



13.11.5 Reactivity of the Fully Conjugated Rings

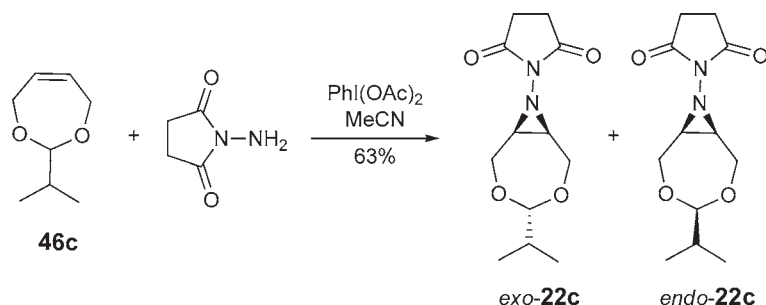
It has been postulated that perfluorinated 1,3-dioxa systems **1** are unlikely to fragment easily and may be therefore thermodynamically stable, because perfluorination induces a negative NICS value (cf. [Section 13.11.2](#)) corresponding

to some mildly aromatic character, and the bond alternation reduces even further. Furthermore, disproportionation to CO_2 and two units of alkyne is only modestly exothermic and perfluorination changes this process to an endothermic value <2002CC642>. The reactivity of the anion **3** has already been described <1996CHEC-II(9)268>.

13.11.6 Reactivity of Nonconjugated Rings

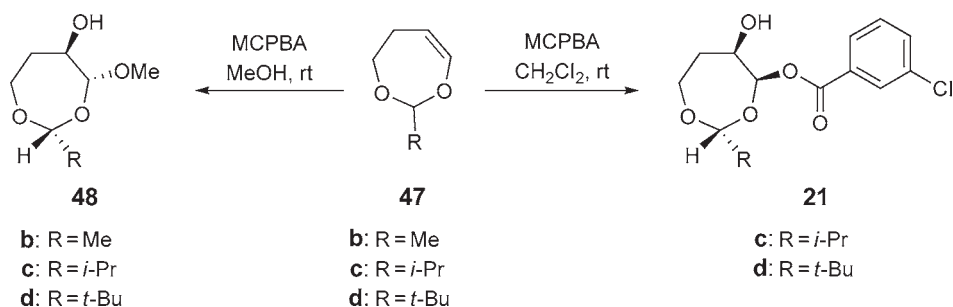
13.11.6.1 Addition Reactions

The addition of chlorine and bromine or the epoxidation of 4,7-dihydro-1,3-dioxepins **46** has already been described in CHEC-II(1996). Treatment of **46c** with iodobenzene diacetate and *N*-aminosuccinimide in MeCN yielded a mixture of *exo*- and *endo*-*N*-amino-substituted aziridinodioxepanes **22c** (Scheme 1) <2005AXC705> (cf. Section 13.11.3.2). The diastereomeric mixture was easily separated by column purification of the crude reaction product.



Scheme 1

4,5-Dihydro-1,3-dioxepins **47** have been oxidized with *m*-chloroperbenzoic acid to give 4,5-dihydroxylated products. The product formation depends on the solvent used for oxidation. In dichloromethane (DCM), 4-acyloxy-5-hydroxydioxepanes **21** were formed; whereas, the same reaction in MeOH afforded 5-hydroxy-4-methoxydioxepanes **48** (Scheme 2) <2001AGE177>.

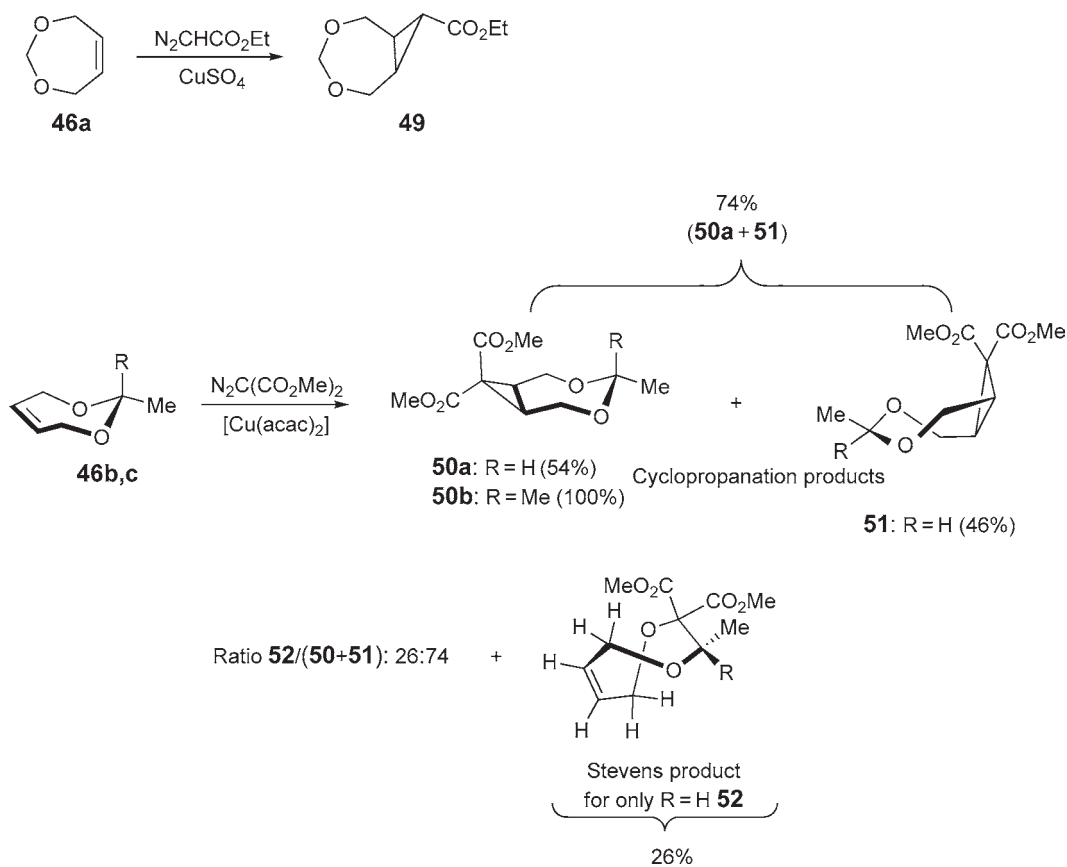


Scheme 2

13.11.6.2 Cycloaddition Reactions

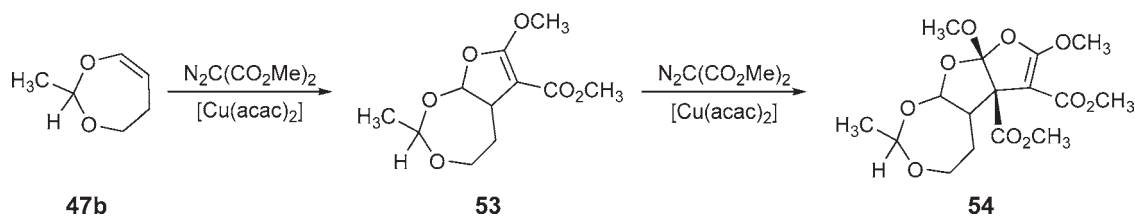
Copper-catalyzed cyclopropanation of 4,7-dihydro-1,3-dioxepin **46a** with ethyl diazoacetate gave cyclopropanodioxepane **49**, as the only product. The product formation of cyclopropanation with dimethyl diazomalonate (dmdm) catalyzed by copper(II) acetylacetonate depends on the substitution pattern of the dioxepin (Scheme 3) <2000HCA966>.

The conformation of cyclopropanoaziridines has been studied by ^1H and ^{13}C NMR spectroscopy; several other cyclopropane derivatives, derived from dioxepins, have also been described <2003HCA2779>.



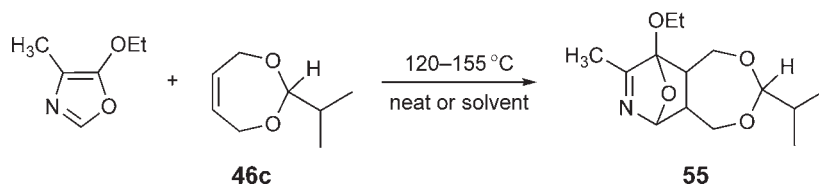
Scheme 3

4,5-Dihydro-1,3-dioxepin **47b** reacted with dimethyl diazomalonate in a double [3+2] cycloaddition reaction to give furofuran derivative **54** as a mixture of stereoisomers (Scheme 4) <2000HCA966>.



Scheme 4

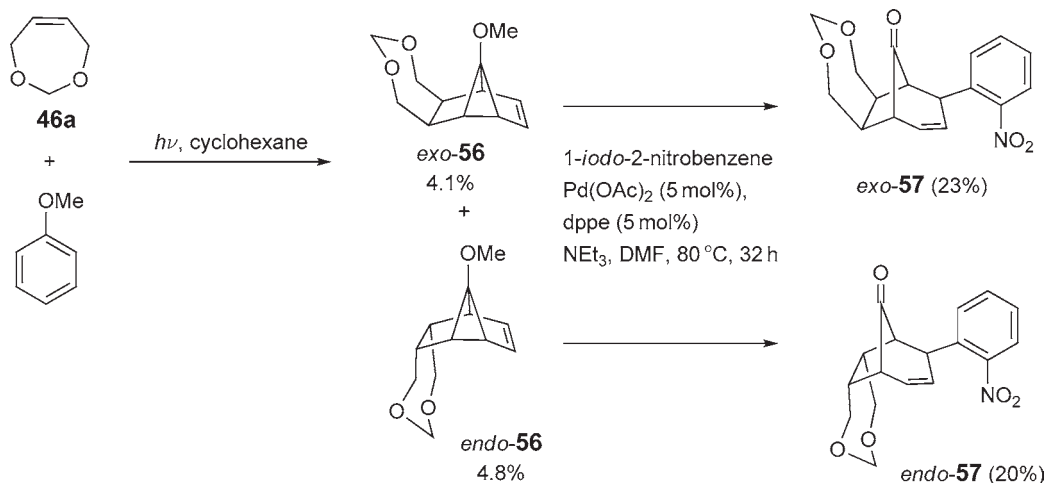
The Diels–Alder reaction of 2-isopropyl-4,7-dihydro-1,3-dioxepin **46** and 5-ethoxy-4-methyl-1,3-oxazol affords adduct **55** (Scheme 5) <2005WO049618A1>.



Scheme 5

The Diels–Alder reaction of 5-ethoxy-4-methyl-1,3-oxazole and **46a** in a sealed tube and microwave heating was also reported (IP165617). Diels–Alder product **54** is an important intermediate in the synthesis of vitamin B₆ (see Section 13.11.12).

Meta-photocycloadducts *exo*- and *endo*-**56** were obtained by irradiation of a solution of 4,7-dihydro-1,3-dioxepin **46a** and anisole, which were fragmented and arylated under Heck conditions to give bridged bicyclo[3.2.1] compounds **57** (Scheme 6) <2006T3423>; however, the yields of the photocycloadducts were low.

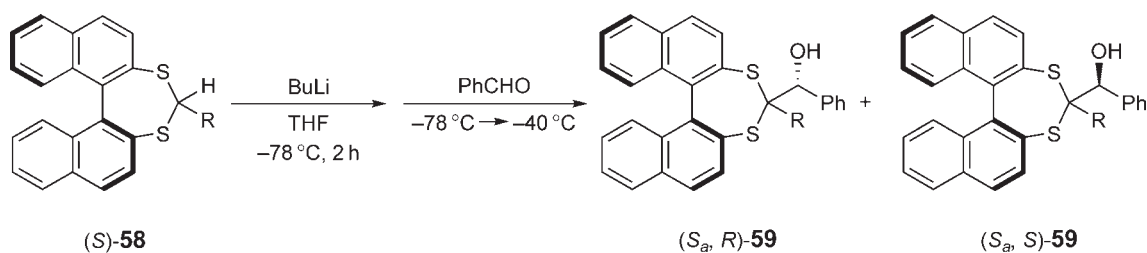


Scheme 6

13.11.6.3 Alkylation

Alkylation reactions in the 2-position are restricted to 1,3-dithiepins and related compounds. The anions behave as an acyl anion equivalent, and treatment with an electrophile affords 2-alkylated products.

Dinaphtho[2,1-*d*:1',2'-*f*]-[1,3]dithiepins **58** are readily lithiated with *n*-butyllithium at −78 °C. Asymmetric nucleophilic addition of the anions to aldehydes afforded **59** with moderate to good diastereoselectivities (Scheme 7) <2002H(57)1487>. For a similar reaction, see <1991JOC4467>.



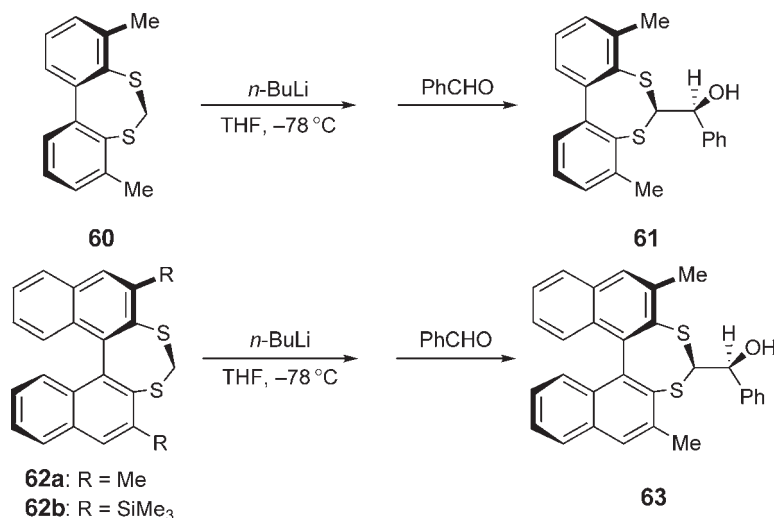
58a: R = Me **58c**: R = Bn

58b: R = Et **58d**: R = Ph

R	Product	Yield (%)	de (%)
Me	59a	82	80
Et	59b	33	88
Bn	59c	27	50
Ph	59d	21	7

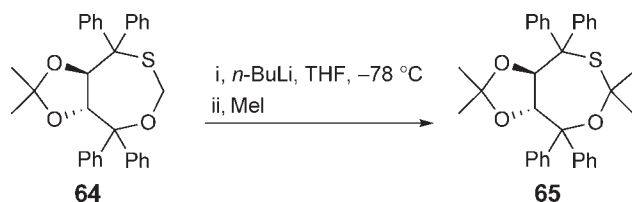
Scheme 7

Alkylation of the anions derived from dithiepins *rac*-**60** and *rac*-**62a**, respectively, gave *rac*-**61** or *rac*-**63a** products, as a single diastereomer <1997T6073>. Dithiepin **62b** proved to be unreactive toward alkylation (Scheme 8).



Scheme 8

Lithiation of oxathiepane **64** with *n*-butyllithium at -78°C and reaction with methyl iodide only gave dimethylated product **65**, even when **64** was used in a large excess with respect to methyl iodide, or when less than 1 equiv of *n*-butyllithium was used (Scheme 9) <1991SL844>.

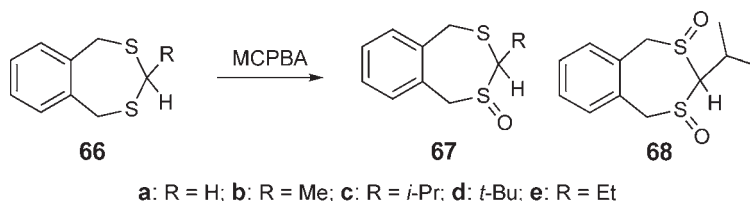


Scheme 9

13.11.6.4 Oxidation

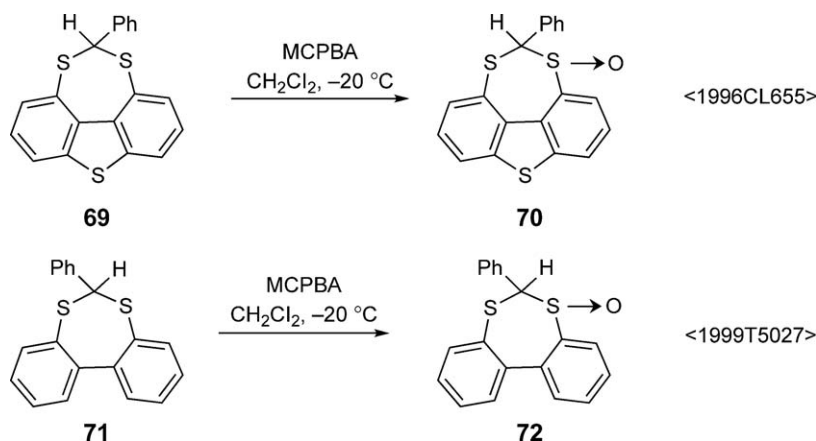
The noncatalytic oxidation of 4,7-dihydro-1,3-dioxepin **46a** with nitrous oxide in liquid phase at 220°C produces 1,3-dioxepan-5-one; however, the conversion is very slow <2004ASC268>.

1,3-Dithiepanes and 1,3-oxathiepanes are readily oxidized to give the corresponding *S*-oxides. For example, oxidation of 1,3-dithia-5,6-benzocycloheptenes **66** with *m*-chloroperbenzoic acid afforded 1,3-dithia-5,6-benzocycloheptene 1-oxides **67** (cf. also compounds 42 and 43, Section 13.11.4). In the oxidation of the isopropyl derivative **66d**, *trans*-2-isopropyl-1,3-dithia-5,6-benzocycloheptene 1,3-dioxide **68** was isolated as a byproduct (Scheme 10) <2001JGU960, 2004JST(688)191>. For the conformation of **67** and **68**, see Section 13.11.4.



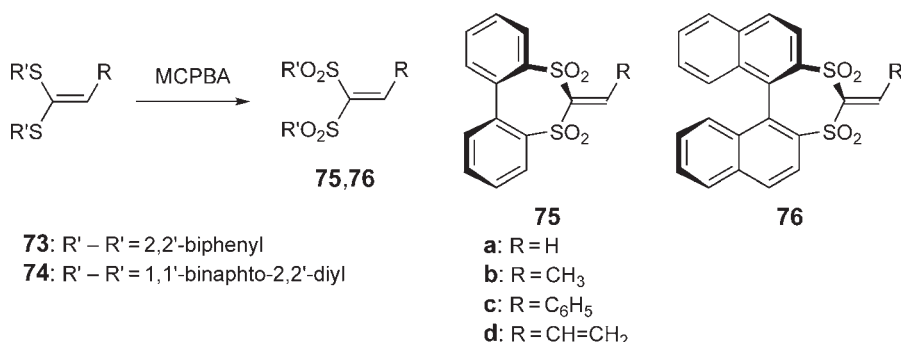
Scheme 10

Further examples are (Scheme 11):



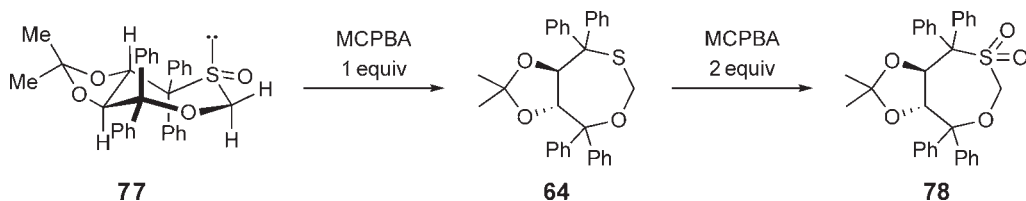
Scheme 11

It has also been reported that *m*-chloroperbenzoic acid oxidation of unsaturated 1,3-dithiepins **73** and **74** led to 1,3-dithiepin *S,S*-tetraoxides **75** and **76** (Scheme 12) <1992T1485>.



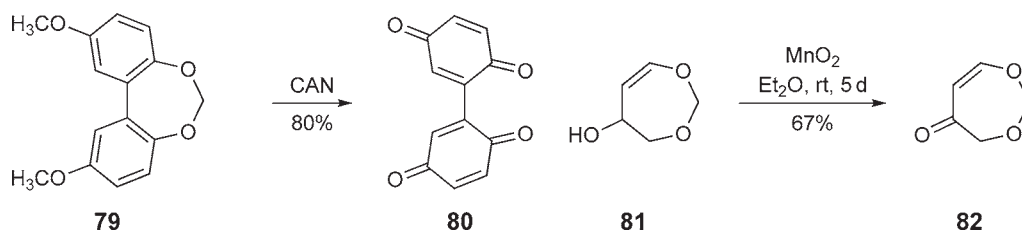
Scheme 12

(-)-*Trans*-4,5-bis(diphenyl-hydroxymethyl)-2,2-dimethyl-1,3-dioxolane (TADDOL)-based sulfoxide **77** and sulfone **78** were obtained by the oxidation of oxathiepane **64** with 1 and 2 equiv *m*-chloroperbenzoic acid, respectively <1991SL844>. Sulfoxide **78** was obtained as a single diastereomer with a pseudoequatorial conformation with respect to the sulfoxide oxygen (Scheme 13).



Scheme 13

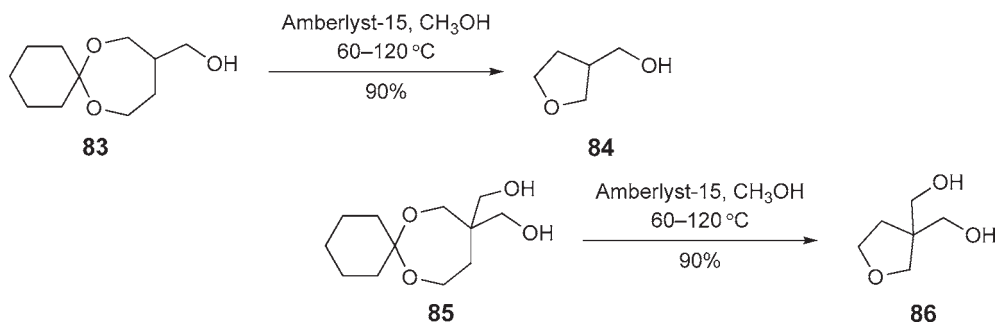
Oxidation of benzo-fused 1,3-dioxepane **79** with cerium ammonium nitrate afforded the *p*-diquinone **80** <2006T635>, and oxidation of 2-hydroxydioxepin **81** with manganese dioxide gave 1,3-dioxo-4-cyclohepten-6-one **82** <2004RJO1830> (Scheme 14).



Scheme 14

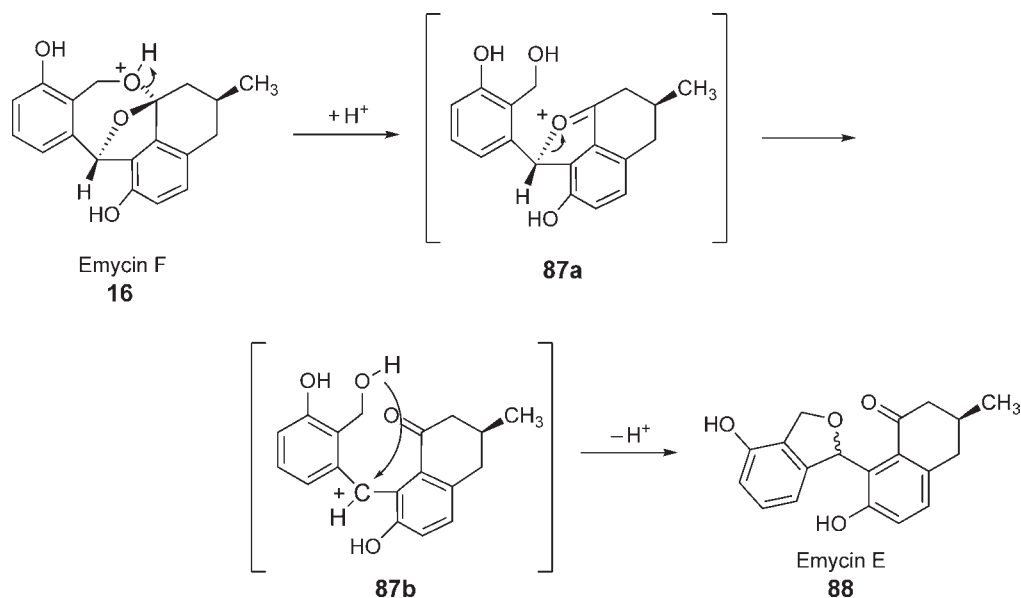
13.11.6.5 Rearrangement

Under acidic conditions 1,3-dioxepanes undergo ring contraction to give tetrahydrofuran derivatives (e.g., [Scheme 15](#)) <2005MI971>.



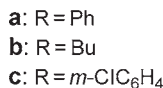
Scheme 15

Ring contraction of 1,3-dioxo-5,6-benzocycloheptenes to dihydroisobenzofurans is only achieved under strong acidic conditions. For example, antibiotic emycin F **16** (cf. [Section 13.11.3.1](#)) was converted into emycin E **88** by stirring of **16** at pH 1 for 24 h ([Scheme 16](#)). It was anticipated that this ring contraction also occurs under the participation of an enzyme <1995AGE1617>.



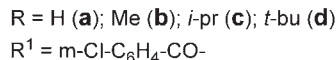
Scheme 16

<2005BCJ2209>.



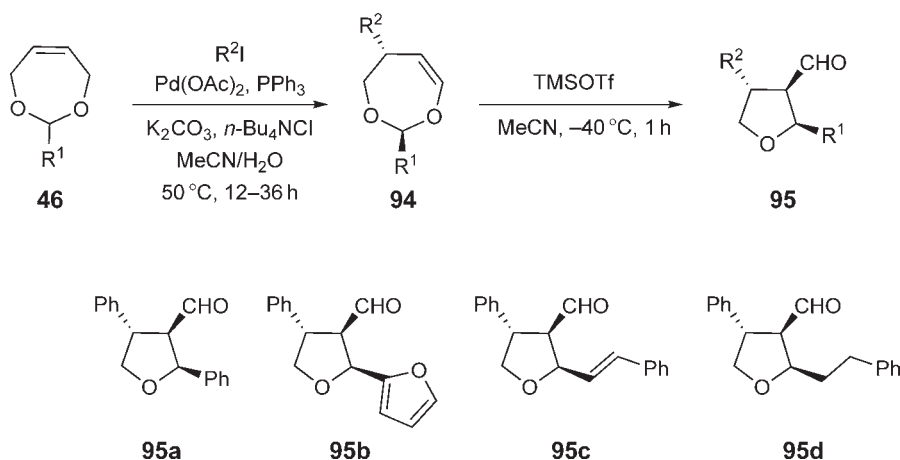
Scheme 17

93b and 93d (Scheme 18) <2001AGE177>.



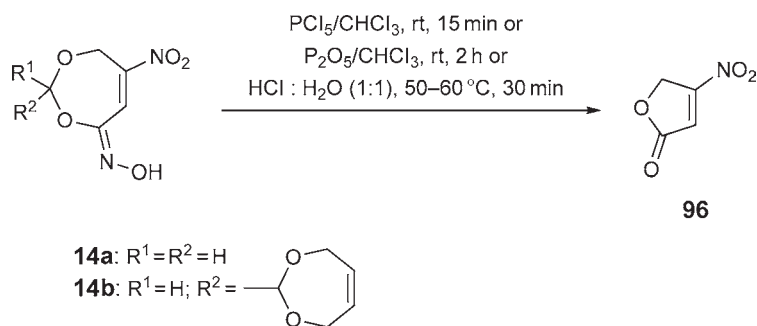
Scheme 18

<2006CC3119>.



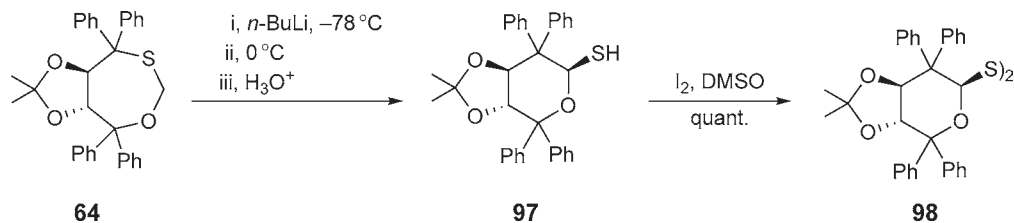
Scheme 19

Treatment of oximes **14** with PCl_5 or P_2O_5 in CHCl_3 and aqueous HCl solution (1:1) afforded 4-nitro-5*H*-furan-2-one **96** (Scheme 20) <1998CCA557>; the Beckmann rearrangement was not observed.



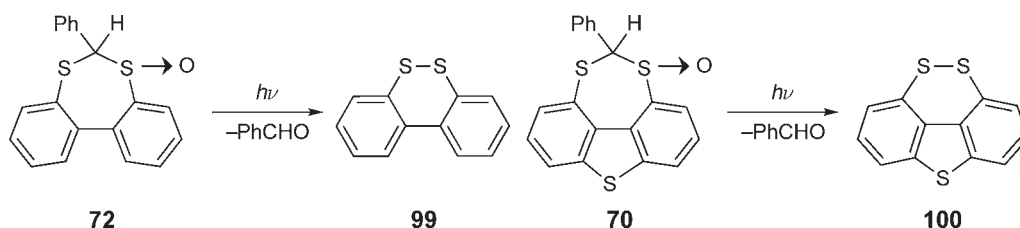
Scheme 20

Oxathiepane **64** rearranged quantitatively on lithiation with *n*-butyllithium at temperatures higher than -50°C into **97**. The structure of **97** was confirmed by conversion into disulfide **98** with iodine in DMSO (Scheme 21) <1991SL844>.



Scheme 21

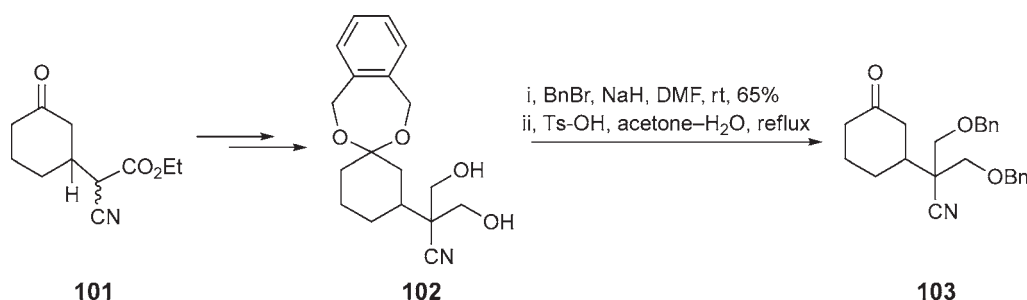
Dibenzo-fused dithiepins undergo photochemically induced ring contractions. Thus, irradiation of 2-phenyldibenzo- $[d,f][1,3]$ dithiepin 1-oxide **72** <1999T5027> and 9-phenyl-4,8,9-trithiadibenzo $[cd,ij]$ azulene 8-oxide **70** <1996CL655> using a high-pressure mercury lamp (400 W) gave disulfides **99** and **100** (Scheme 22).



Scheme 22

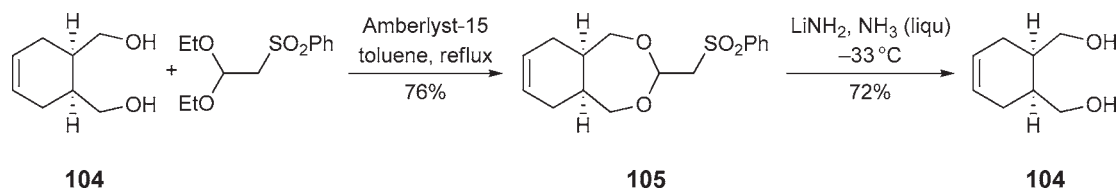
13.11.6.6 Cleavage Reactions

Dioxepanes as well as 5,6-benzo-1,3-dioxepanes have often been synthesized as a protecting group for either a 1,4-diol unit or carbonyl group. Deprotection of acetonides is readily achieved by standard methods (see also Section 13.11.9.2). Cleavage of **102** (an intermediate in the synthesis of the 11-membered ring of madangamine alkaloids), prepared from cyclohexanone derivative **101** and 1,2-bis(hydroxymethyl)benzene, was conducted in acetone–water at reflux using *p*-toluenesulfonic acid, as a catalyst (Scheme 23) <2006TL3489>.



Scheme 23

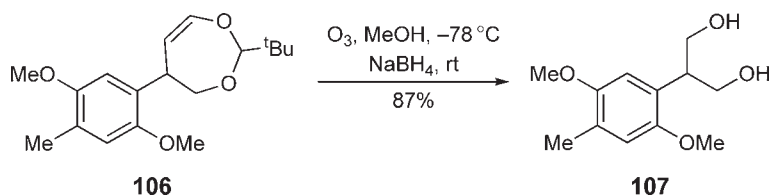
Dioxepins derived from 1,4-diols and α -phenylsulfonylacetaldehyde diethyl acetal have proved to be robust protection groups for 1,4-diols under a variety of reaction conditions. They are stable to 60% AcOH , 6 M HCl , and 0.1 M H_2SO_4 , and they resist β -elimination by reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Cleavage was achieved with either lithium amide in liquid ammonia at -33°C or *n*-butyllithium at 35°C (Scheme 24) <2003SC895>.



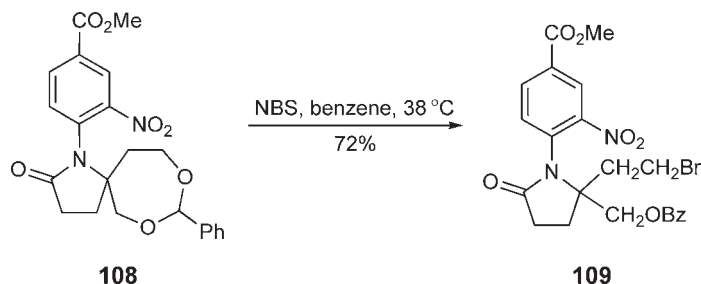
Scheme 24

In the synthesis of the monocyclic bisabolene-type sesquiterpenoids (+)-curcuquinone and (–)-curcuhydroquinone, 1,3-diol **107** was obtained by ozonolysis of 4,5-dihydro-1,3-dioxepin **106** (obtained by Heck reaction, see Section 13.11.10) and reductive workup (Scheme 25) <2003ARK232>.

For the application of this method in the enantioselective total synthesis of heliannuols D and A, see <2000J(P1)1807>. An isomeric mixture of dioxepane **108** was cleaved with *N*-bromosuccinimide to give bromoester **109** (Scheme 26) <2003BMC2739>. For the preparation of **108**, see Section 13.11.9.2. Ring opening of **109** occurred regioselectively on the least hindered carbon.

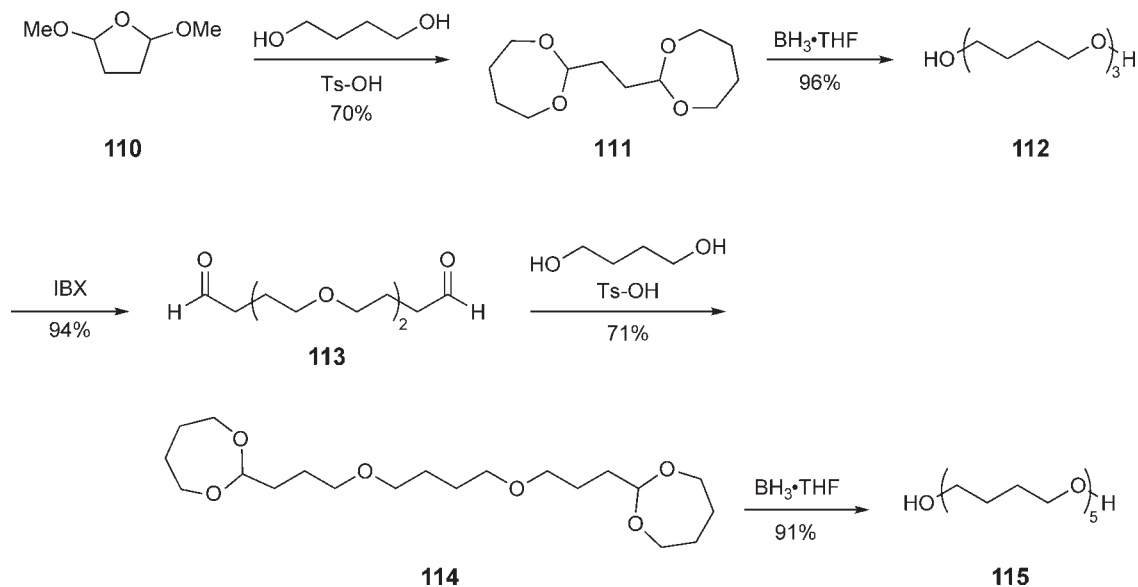


Scheme 25



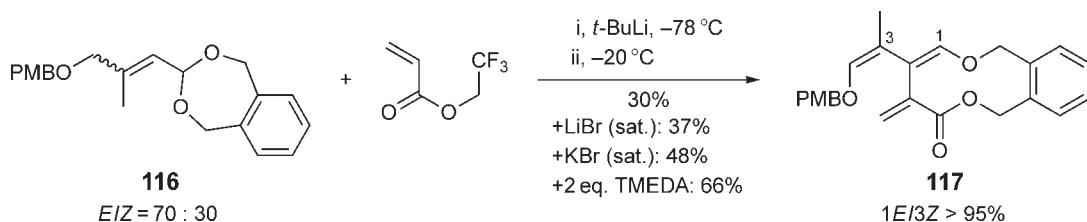
Scheme 26

Reductive cleavage of dioxepanes with borane–THF complex (THF = tetrahydrofuran) leads to 1,4-diols. This procedure has found application in the synthesis of discrete polyethers ([Scheme 27](#) [<2003JOC9166>](#)).



Scheme 27

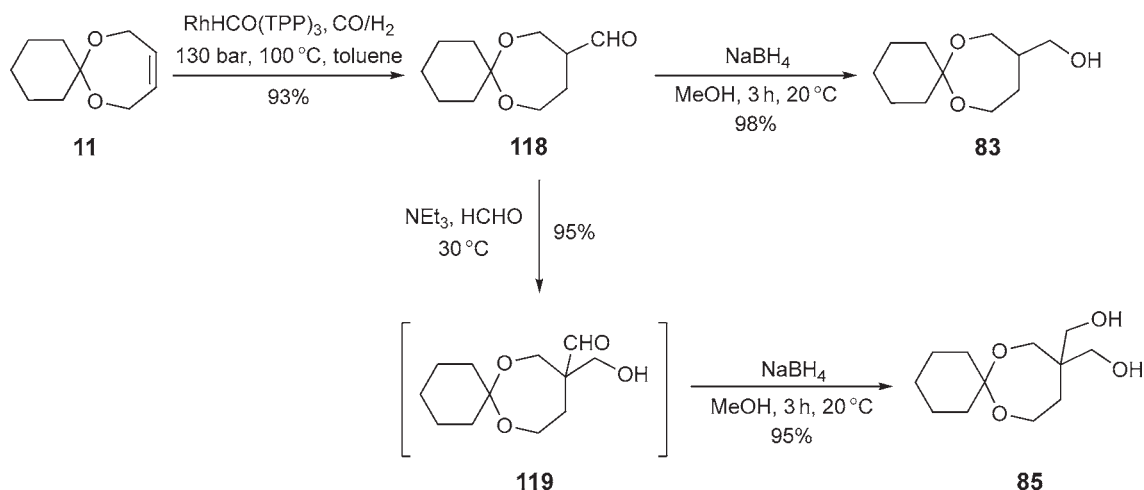
The reaction of α,β -unsaturated benzodioxepin **116** with *tert*-butyllithium in THF at -78°C produced a lithium alkoxide, which was trapped *in situ* with 2,2,2-trifluoroacrylate to give acryloyl (1*Z*,3*E*)-dienyl ether **117** with high diastereoselectivity ([Scheme 28](#) [<2005OBC1308>](#)). The procedure has found application in the synthesis of carbo-sugars via Diels–Alder reaction.



Scheme 28

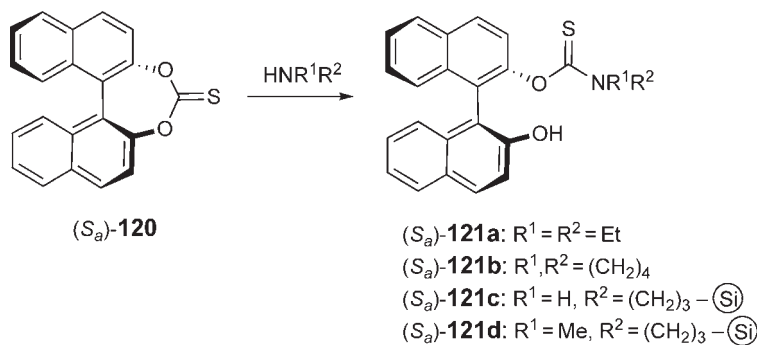
13.11.6.7 Miscellaneous Reactions

7,12-Dioxaspiro[5,6]dodecane **11** was subjected to hydroformylation in the presence of $\text{RhHCO}(\text{TPP})_3$ using syngas to give 9-formyl-7,12-dioxaspiro[5,6]dodecane **118**, which was transformed into dioxepanes **83** and **85** by standard procedures (Scheme 29) <2005SC971>.



Scheme 29

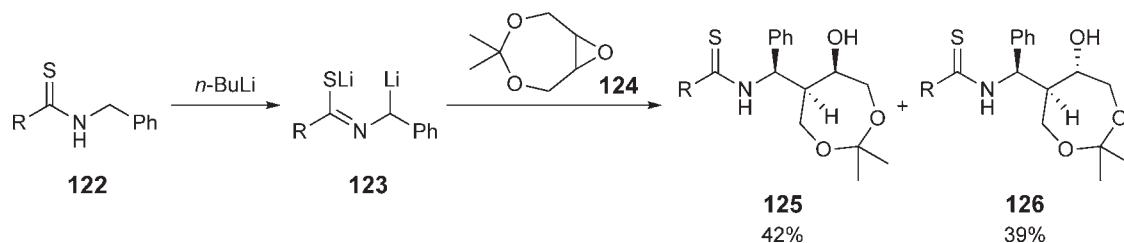
Thiocarbamates, such as **120**, readily undergo ring opening with nucleophiles to give thiocarbamates **121** (Scheme 30) <2004TL39, 2005T51>.



Scheme 30

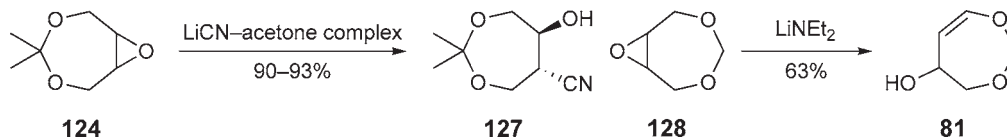
13.11.7 Reactivity of Substituents Attached to Ring Carbon Atoms

5,6-Epoxy-1,3-dioxepanes are readily converted into ring-opening products by reaction with nucleophiles. Thus, addition of **124** with dianions **123** generated from thioamides **122** and 2 equiv of *n*-butyllithium yielded a mixture of diastereomers **125** and **126**, which were separated by column chromatography (Scheme 31) <2005JOC8148>.



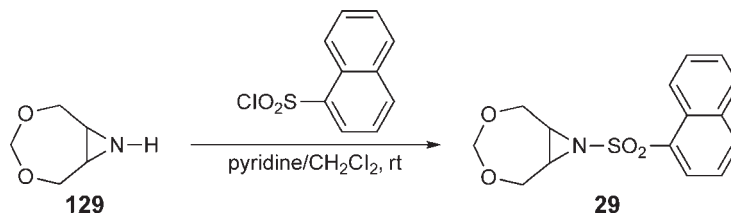
Scheme 31

Epoxydioxepane **124** was converted with a LiCN–acetone complex (prepared from acetone cyanohydrine and methyllithium; CAUTION!) into β -hydroxy nitrile **127** <2004TL7201>, and epoxydioxepane **128** with lithium amide into hydroxydioxepin **81** (Scheme 32) <2004RJOC1830>.



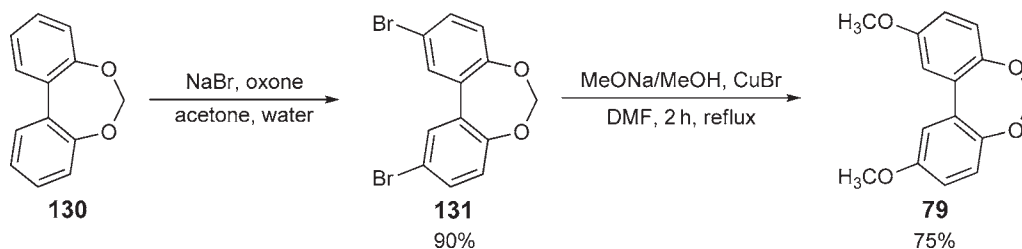
Scheme 32

Reaction of aziridinodioxepane **129** with 1-naphthalenesulfonylchloride in the presence of pyridine yielded 1-naphthylsulfonyl-substituted aziridinodioxepane **29** (Scheme 33) <2005AXE2844>.



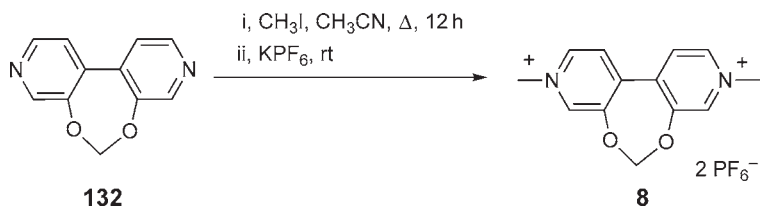
Scheme 33

Several reports describe reactions on the attached rings of benzo-fused dioxepins and dithiepins. For example, biphenyl derivative **79** was prepared in a two-step procedure by halogenation of **130** with NaBr/oxone in aqueous acetone and subsequent substitution of the **131** with a methoxy group (Scheme 34) <2006T635>.



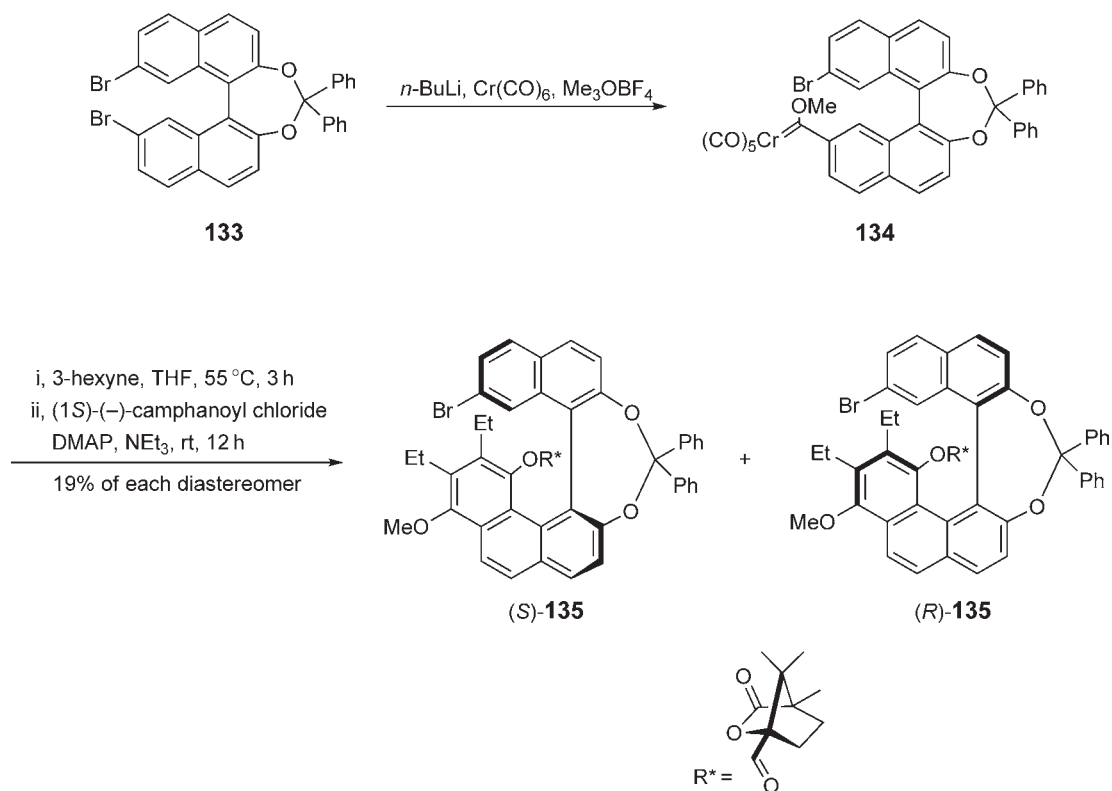
Scheme 34

The biaryl **132** was converted into methyl viologen **8** by treatment with methyl iodide and anion exchange with potassium hexafluorophosphate (**Scheme 35**) <2005TL7291>.



Scheme 35

Biaryl **133** was converted into **135** via a [5]helicene-analogous monocarbene chromium complex **134**. Compound **135** was used for the resolution of the racemic mixture (**Scheme 36**) <2005EJO1541>.

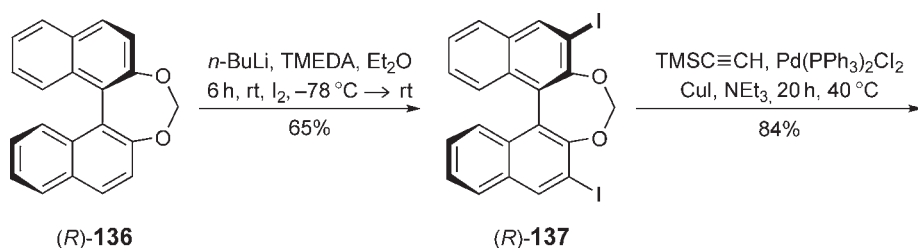


Scheme 36

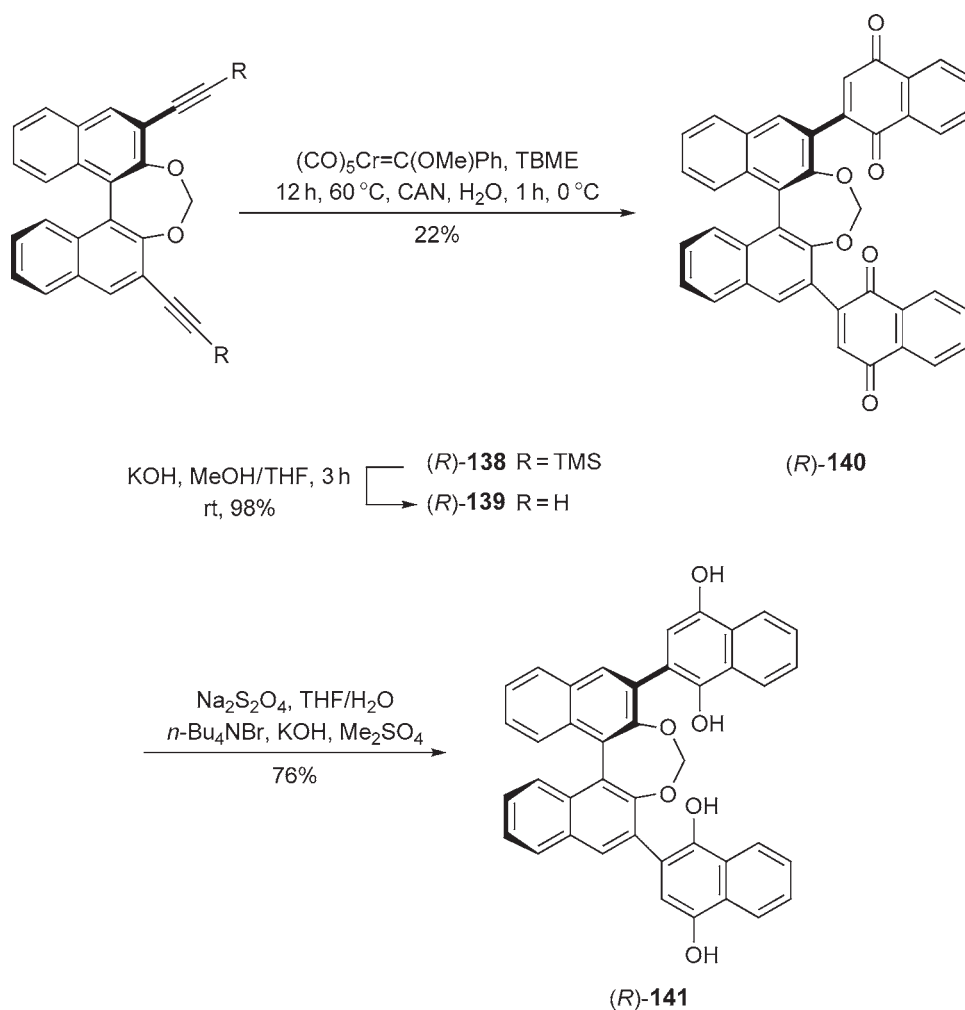
Quinoid BINOL-type compounds (BINOL = 1,1'-bi-2-naphthol) were prepared by the following reaction sequence (**Schemes 37 and 38**) <2005TA3256>.

Only monosubstitution was observed, when dioxepins **142** and **144** were treated with a large excess of phthalimidesulfonyl chloride (**Scheme 39**) <2003T2131>.

For the synthesis of several other biaryl-derived dioxepins for second-order nonlinear optics, see <1996JA6841>.



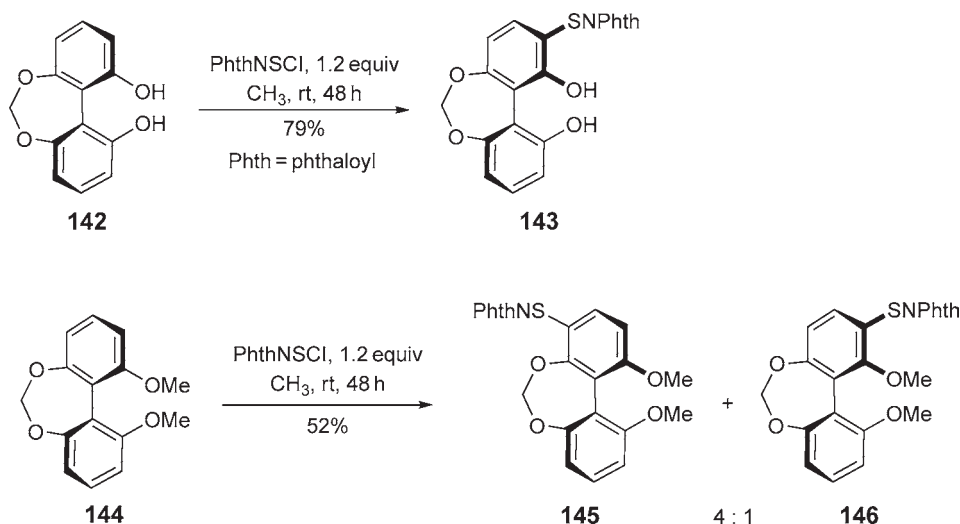
Scheme 37



Scheme 38

13.11.8 Reactivity of Substituents Attached to Ring Heteroatoms

This type of reactivity is not found for these classes of compounds.

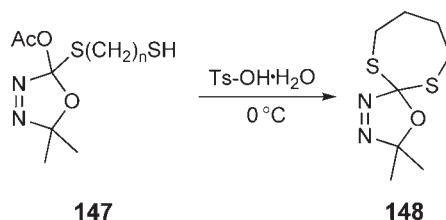


Scheme 39

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

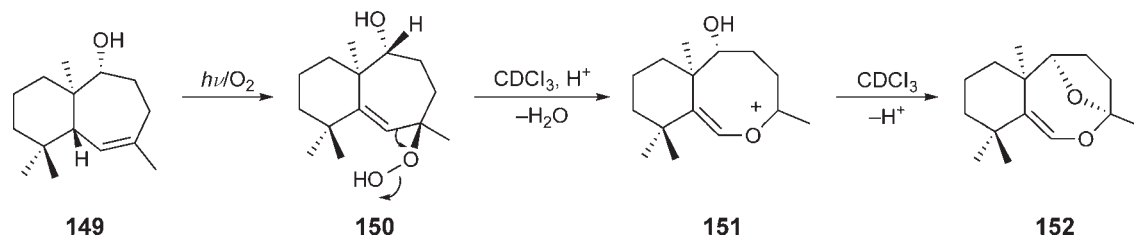
13.11.9.1 Type a (O—C—C—C—C—O—C)

Only a few reports have dealt with this type of synthesis of the 1,3-dioxepin and 1,3-dithiepin moiety. Dithiepane **148** could be obtained by an intramolecular transacetalization of mercaptane **147** (Scheme 40) <2000T10101>.



Scheme 40

A Heck-type rearrangement possibly accounts for the formation of allohimachalane **152**, which was isolated as an autoxidation/rearrangement product of allohimachalol **149** on standing on air in the presence of light (Scheme 41) <1999T14623>. The formation of **152** was also performed *in vitro* by photooxidation of **149** with singlet oxygen (photosensitizer methylene blue) in CDCl₃.



Scheme 41

Dihydromethanobenzodioxepin **155** was obtained by alkylation of benzofuranone **153** and lithium aluminium hydride reduction together with tetrahydrofurobenzofuran **154** (Scheme 42). The ring expansion to **155** probably proceeds *via* hemiacetal **156** <2005JOC6171>.

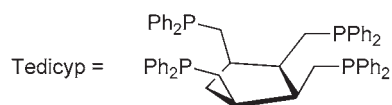


Scheme 43

Reaction scheme for the synthesis of 163a,b and 164a,b:

Starting material **160** (4-allyloxy-1-butanol) reacts with an aryl bromide (Ar-Br) in the presence of Tedicyp (0.4%), $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ (0.2%), and K_2CO_3 in DMF at 130°C for 20 h, achieving 100% conversion.

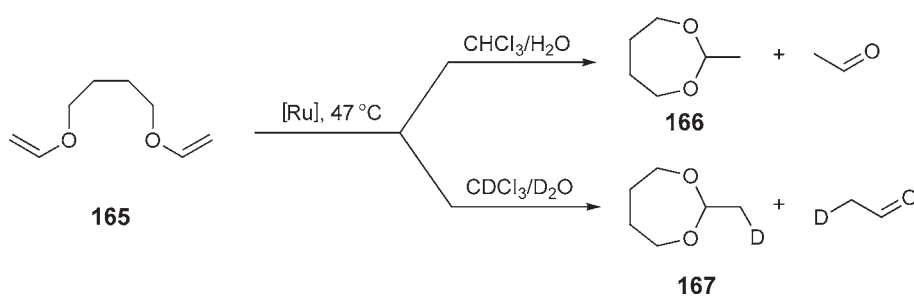
The reaction yields two isomeric intermediates, **161a,b** and **162a,b** (a mixture of *Z* and *E* isomers), which then cyclize to form the final products **163a,b** and **164a,b**.



ArBr— 4-bromacetophenone: **161a**: 18%; **162a**: 19%; **163a**: 48%; **164a**: 15%
1-bromonaphthalene: **161b**: 42%; **162b**: 15%; **163b**: 40%; **164b**: 3%

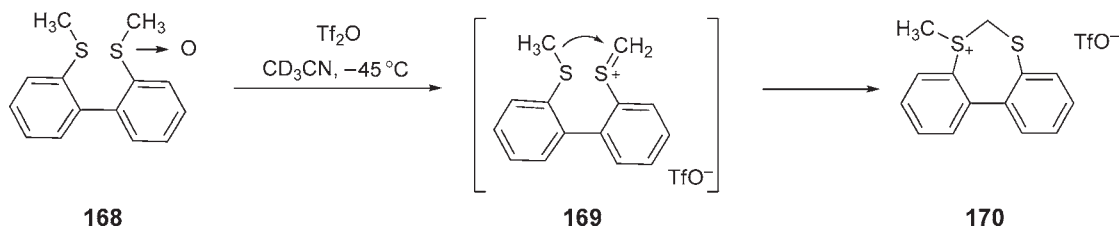
Scheme 44

Treatment of vinyl ether **165** with the water-soluble ruthenium allenylidene complex [(RuCl(μ -Cl)-(C=C=CPh₂)(TPPMS)₂)₂]Na₄ in CHCl₃/water and CDCl₃/D₂O, respectively, afforded dioxepanes **166** and **167** (Scheme 45) [<2003EJ11614>](#); however, this method is of little synthetic interest.



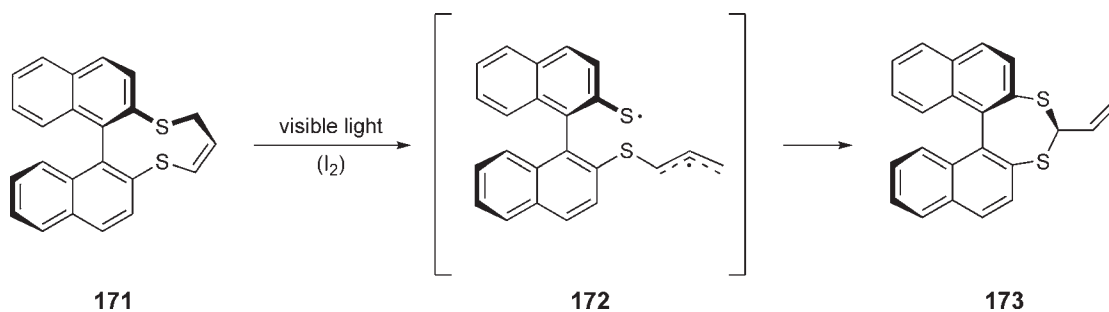
Scheme 45

Methylsulfonium ion **170** was isolated upon treatment of the monosulfoxide **168** with Tf_2O in CD_3CN at -45°C (Scheme 46) <1996TL667>. The structure of the salt was confirmed by ^1H , ^{13}C , ^{19}F , and FAB spectroscopy.



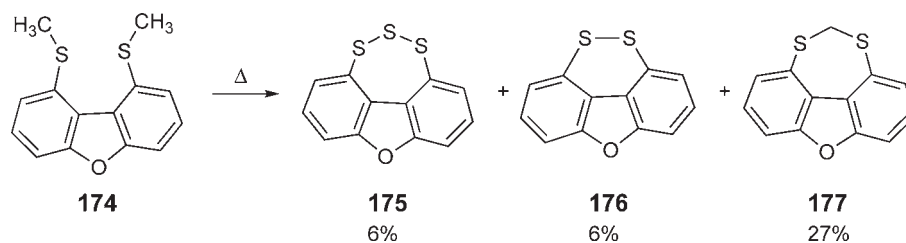
Scheme 46

Binaphthyl **171** rearranged in visible light to give benzo-fused dithiepin **173** in quantitative yield (Scheme 47) <1991TL4771>.



Scheme 47

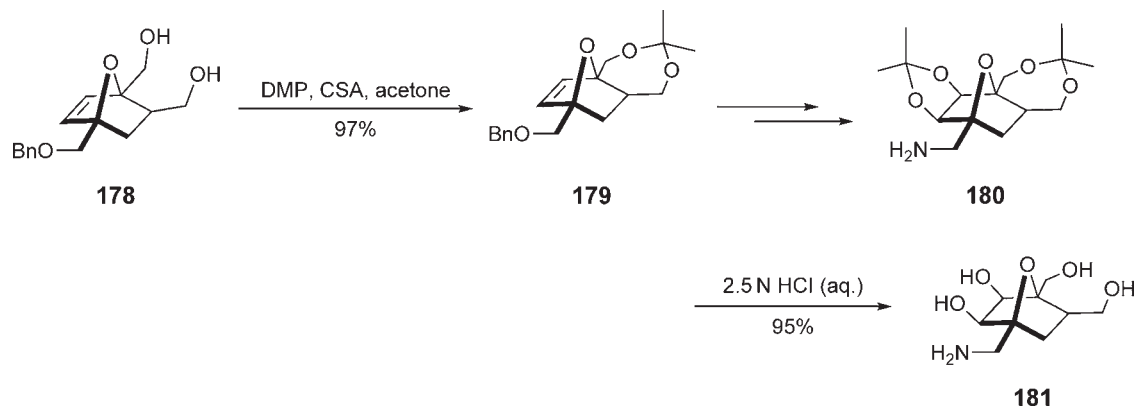
Dibenzo[*bc,hi*]oxa[4,6]dithiaazulene **177** was found as the main product in the thermolysis of **174** (Scheme 48) <1994H(37)541>.



Scheme 48

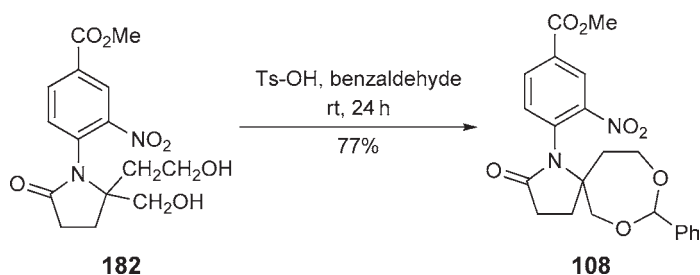
13.11.9.2 Type ab (O–C–C–C–C–O + C)

As already mentioned, 1,3-dioxepanes and their benzo-fused derivatives have often been synthesized as protecting groups for 1,4-diol units and acetals or ketones, respectively (cf. [Section 13.11.6.6](#)). They can be prepared in the usual manner by direct acetalization of the corresponding diol or carbonyl compound, as shown with the following example ([Scheme 49](#)) <2005HCA3151>.



Scheme 49

Acetalization of sterically crowded diols often require modified conditions. For example, benzylidene acetal **108** was obtained in high yield by acetalization of **182** with benzaldehyde (neat) in the presence of an acid. Under standard conditions, acetal **108** was only obtained in poor results ([Scheme 50](#)) <2003MI2739>.



Scheme 50

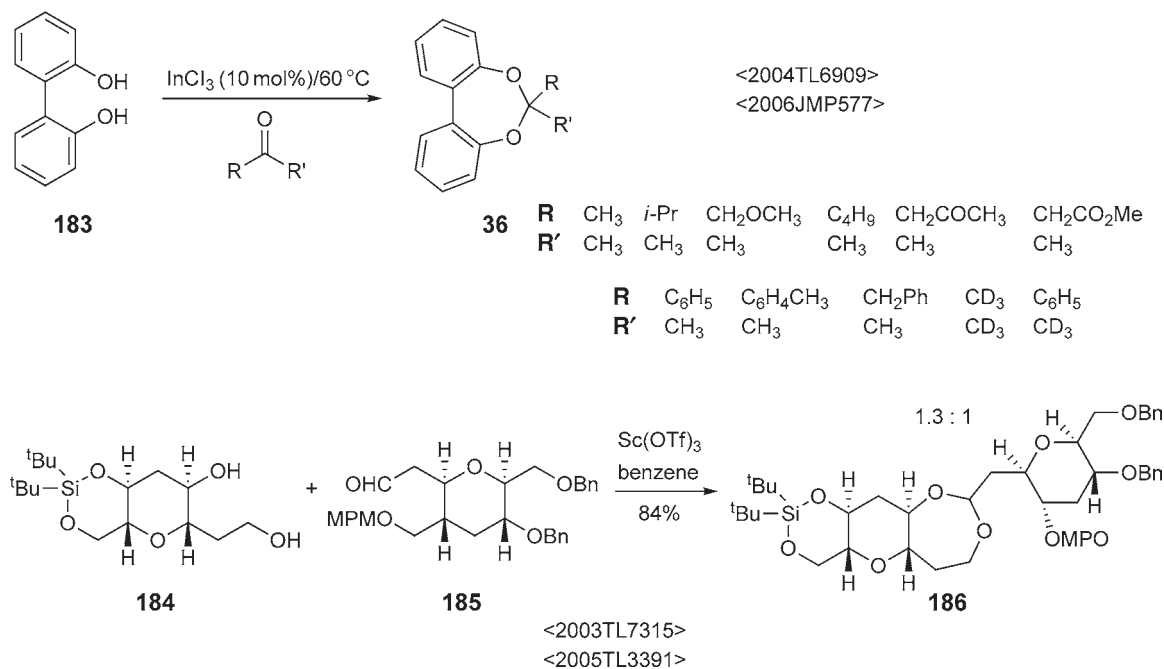
Besides acidic catalysts, several other catalysts have been applied for the direct acetalization, for example, InCl_3 , $\text{Sc}(\text{OTf})_3$, etc. ([Scheme 51](#)).

The acetalization of dimercapto compounds **99** and **100** with benzaldehyde was catalyzed by SiCl_4 ([Scheme 52](#)) <1999T5027>.

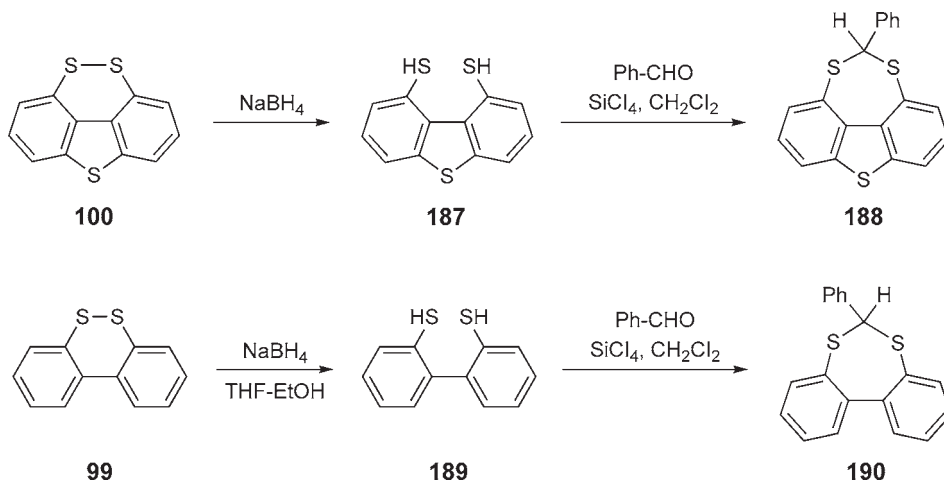
However, the preparation of acetonides under standard conditions often proceeds very sluggishly, for example, the synthesis of 6-fluoropyridoxol derivative **192** ([Scheme 53](#)) <2006JME1991>.

Higher yields of acetonides have been obtained by transesterification of a 1,4-diol unit with dimethoxypropane, as demonstrated with the protection of **193**, an intermediate in the synthesis of a cytotoxic bisabolane sesquiterpene (+)-curcuphenol ([Scheme 54](#)) <1998TA2215>.

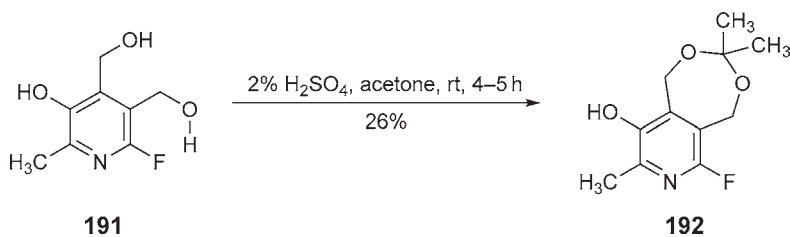
For a further application of this method in the natural product synthesis, see <2003JOC3831, 2004OBC3573, 2005JOC9658>. For the synthesis of 5-chloro-5-deoxy-1,2-*O*-isopropylidene- β -L-idofuranose by this method, see <2004CAR1941>.



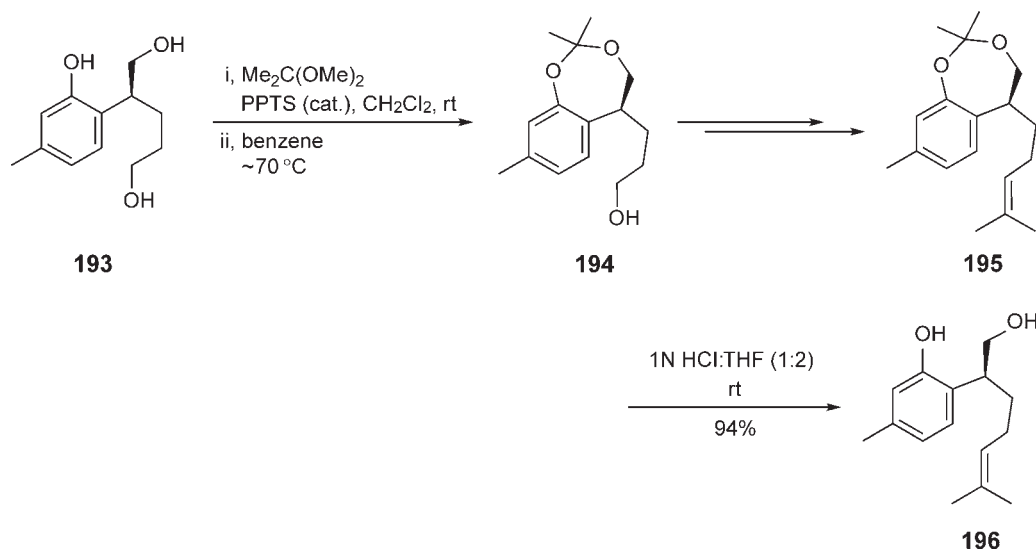
Scheme 51



Scheme 52



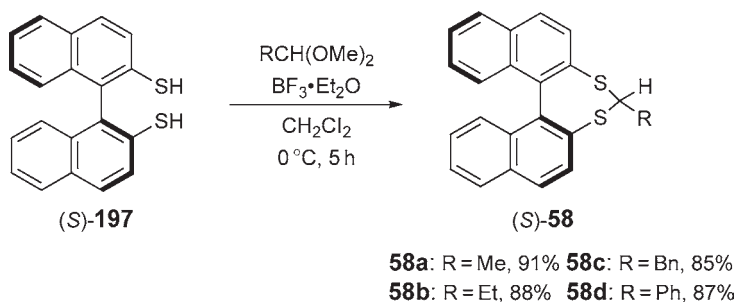
Scheme 53



Scheme 54

The preparation of dibenzo-fused dithiepins was usually catalyzed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$. For example, the synthesis of dibenzo[*d,f*][1,3]dithiepin from 1,1'-binaphthalene-2,2'-dithiol and dibromomethane and diiodomethane, respectively, failed; however, reaction of the dithiol with dimethoxymethane in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ afforded the desired dithiepin in 71% yield [\[1995T787\]](#).

Optically active dithiepins **58** bearing substituents in the 2-position of the dithiepin moiety have been prepared by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ catalyzed transacetalization of **197** (Scheme 55) [\[1991JOC4467, 2002H\(57\)1487\]](#), and even sterically more demanding biaryl-derived dithiepins, such as **60**, **62**, and **201**, have been successfully prepared by using this method (Scheme 56):

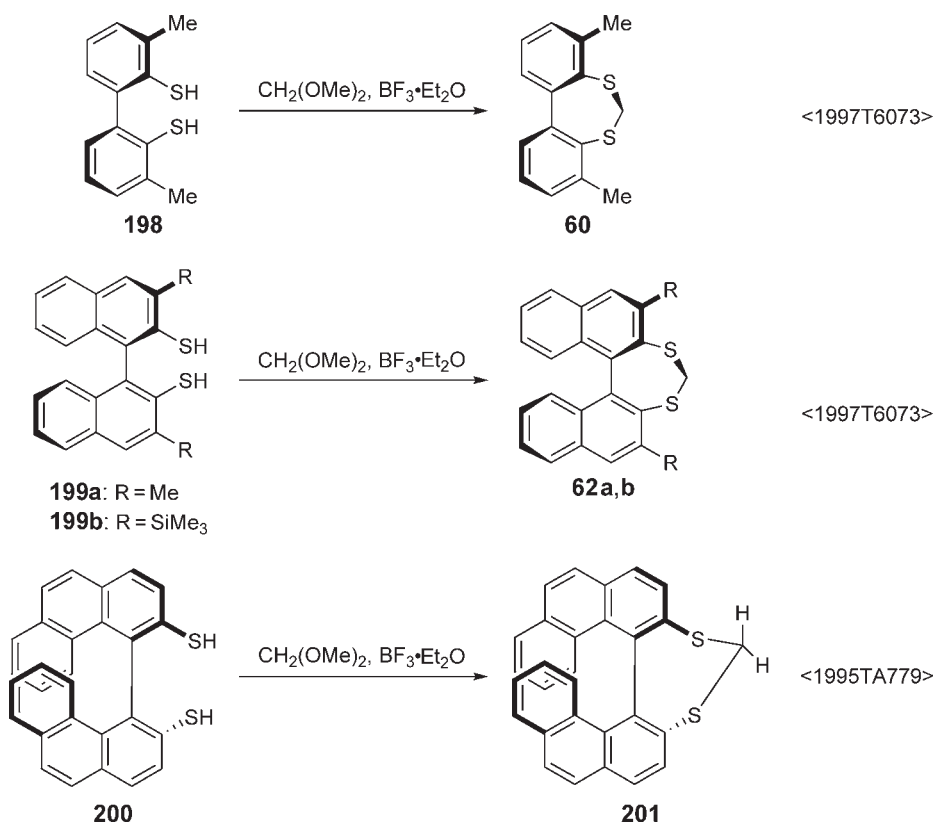


Scheme 55

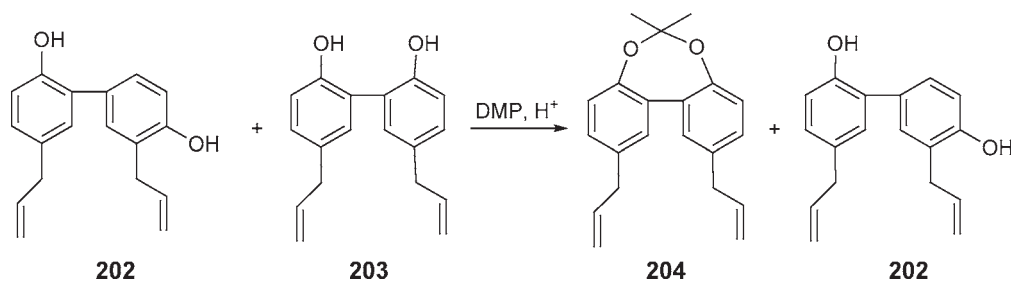
Extracts of a mixture of honiokol **202** and magnolol **203** (the main constituents of the stem bark of *Magnolia abovata* thumb and *Magnolia officinalis rhed*, used in traditional Chinese medicine) have been separated by acid-catalyzed transformation of magnolol with dimethoxypropane into **204** (Scheme 57) [\[2006JME3426\]](#).

Dialdehyde **207** was prepared via acid-catalyzed transacetalization of 1,1-dimethoxycyclohexane and **205** (Scheme 58) [\[2003SM\(135\)209\]](#).

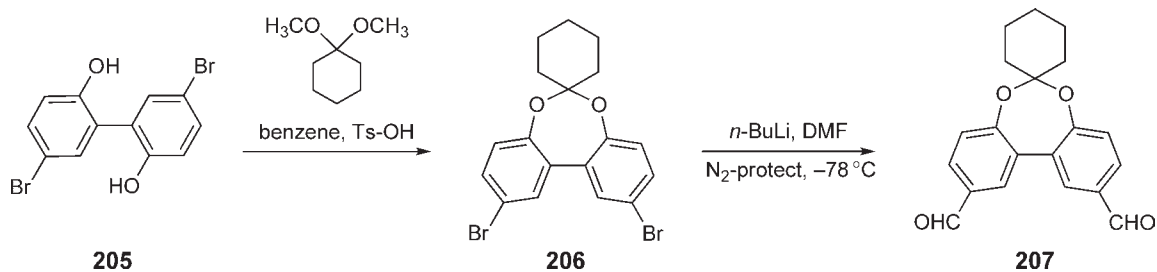
Acid-catalyzed *N,O*-acetal reaction of *N*-BOC protected 2-amino-1,4-butanediol **208** with dimethoxypropane gave only moderate yields of **209** because of concurrent six- and five-membered ring formation (Scheme 59) [\[2005OL1423\]](#).



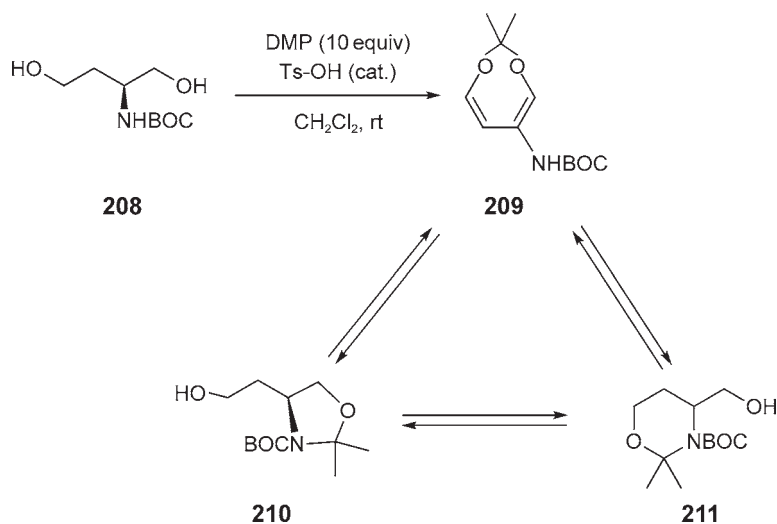
Scheme 56



Scheme 57

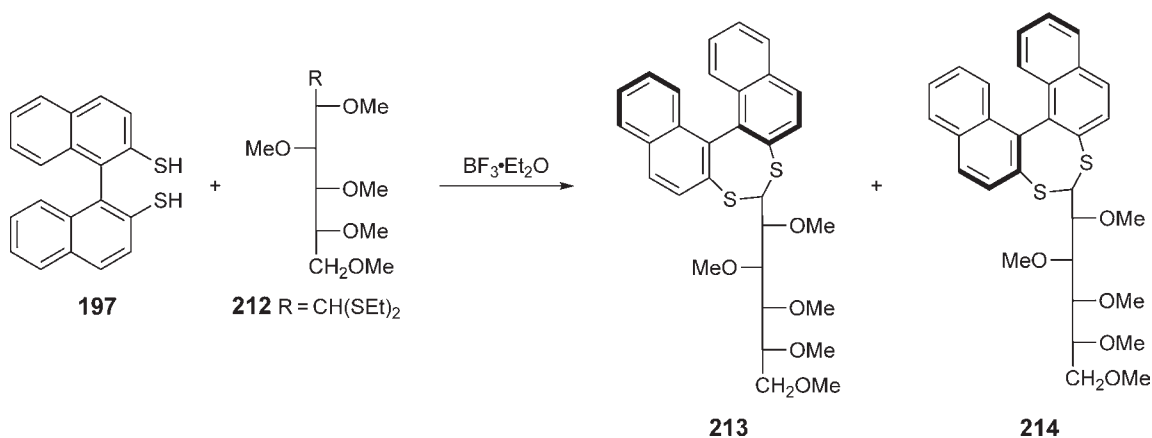


Scheme 58



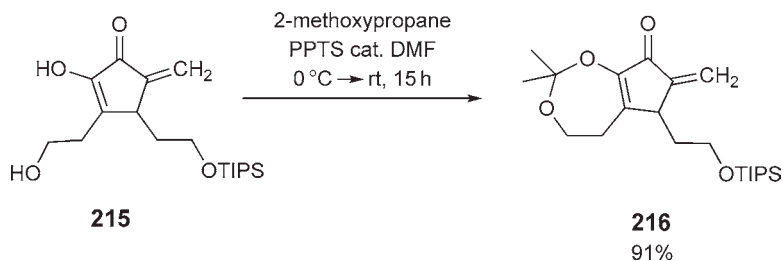
Scheme 59

Dithioacetals have also been used as precursors for the transacetalization. Thus, both diastereomers **213** and **214** have been prepared from glucose-derived dithioacetal **212** and *rac*-**230** and used for the efficient resolution of *rac*-**197** (Scheme 60) <1995TA295>.



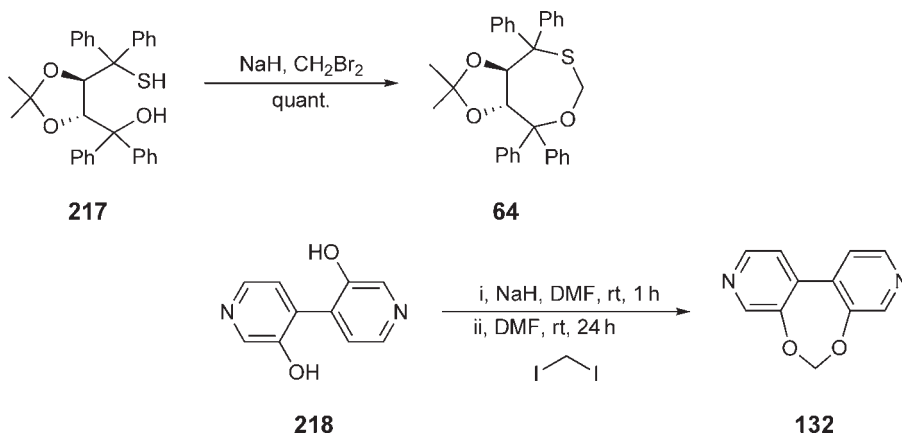
Scheme 60

Synthesis of acetonides can also be performed using 2-methoxypropane instead of 2,2-dimethoxypropane <2005OL5011>; however, 4,5-dihydro-1,3-dioxepins, such as **216** (Scheme 61), can only be obtained by direct acetalization or transacetalization with special substrates.



Scheme 61

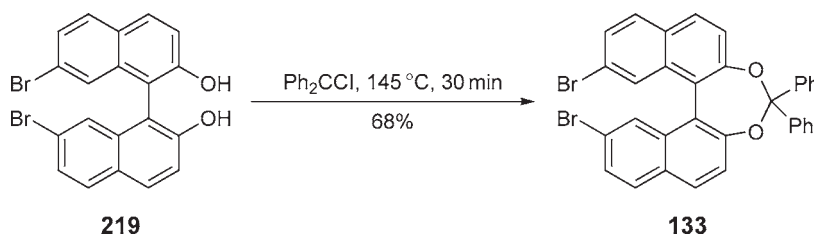
Another useful procedure for the synthesis of dioxepins, oxathiepins, as well as dithiepins under basic conditions involves deprotonation of a diol or dithiol precursor and treatment of the resulting anion with a *gem*-dihalo compound, as demonstrated with the synthesis of the TADDOL-derived oxathiepin **64** <1991SL844> and biaryl derivative **132** <2005TL7291> (Scheme 62):



Scheme 62

For similar syntheses by this method, see <2001TA1451>.

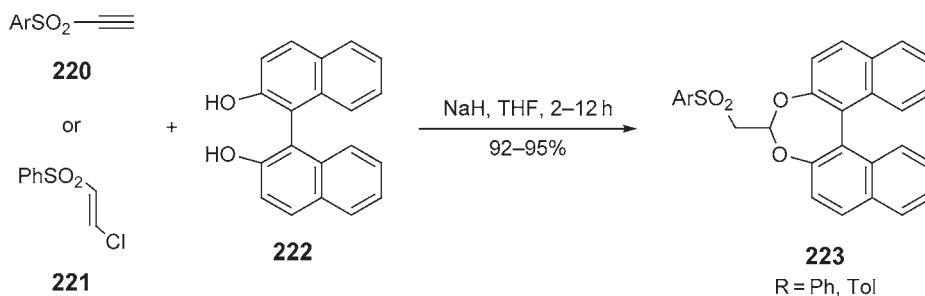
2,2-Diphenyl-substituted dinaphthodioxepin **133**, a precursor for the formation of helicene-like quinones, was prepared directly from binaphthol **219** and dichlorodiphenylmethane at higher temperatures (Scheme 63) <2005EJO1541>.



Scheme 63

For a similar reaction using ditosyloxymethane as reagent, see <2006JOC3481>.

2-Arylsulfonylmethyl-substituted dinaphthodioxepins **223** were obtained from arylsulfonylalkynes via Michael reaction. The procedure engages NaH-supported reaction of 1,1'-binaphthalene-2,2'-diol **222** with **220** (Ar = phenyl, tolyl). The procedure can also be performed using (*Z*)- or (*E*)-1-chloro-2-phenylsulfonyl ethylene and bis(phenylsulfonyl)ethylene, respectively, instead of arylsulfonylalkynes (Scheme 64) <1996SL1481>.

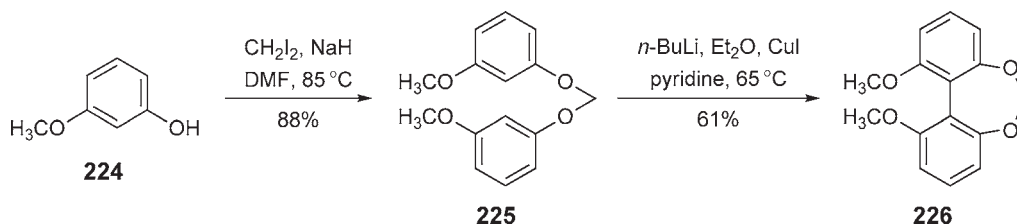


Scheme 64

Similarly, 2-phenylsulfinylmethyl-substituted 4,7-dihydro-1,3-dioxepin was prepared by the reaction of *cis*-butene-2,3-diol with 2.2 equiv of sodium hydride and 1-phenylsulfinyl-2-phenylsulfanylethylene <2005TL1035>.

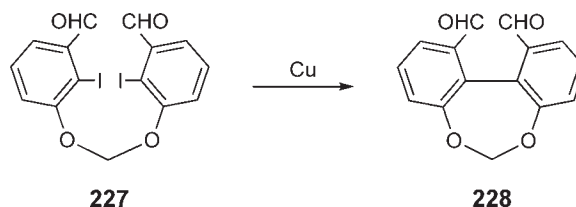
13.11.9.3 Type e (C–C–X–C–X–C–C)

Acetal **225** gave the respective biphenyl derivative **226** in 61% yield by treatment with *n*-butyllithium at room temperature and quenching with activated CuI in the presence of pyridine. The route involves generation of the *ortho*-dilithium derivative and treatment with CuI in the presence of a polar, coordinating solvent such as pyridine (Scheme 65) <1998TA2819>.



Scheme 65

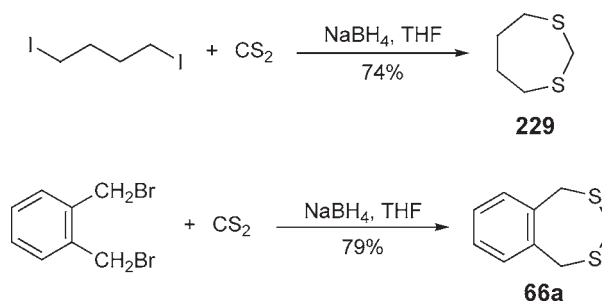
Dialdehyde **227** was prepared by intramolecular coupling of acetal **228** under Ullmann conditions (Scheme 66) <2005ICC1049>.



Scheme 66

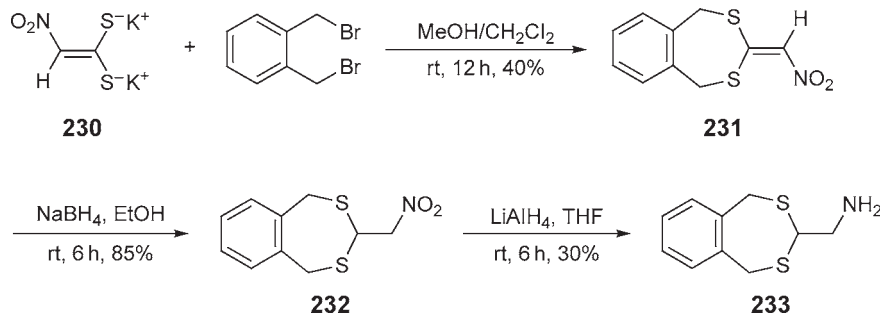
13.11.9.4 Type cg (C–C–C–C + X–C–X)

Only a few samples exist for this type of ring synthesis. Thus, a straightforward synthesis of dithiepanes and benzodithiepanes, for example, **229** and **66a**, was achieved by treatment of a corresponding 1,4-dibromo or diiodo compound with carbon disulfide activated by sodium borohydride (Scheme 67) <2000OL1133>.



Scheme 67

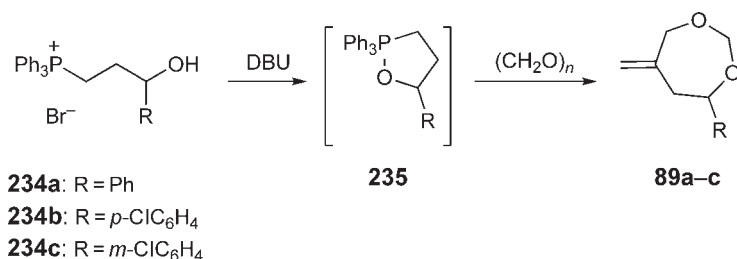
Another example is the reaction of the potassium salt of 2-nitro-1,1-ethanedithiol **230** with *o*-xylenyl dibromide. It was suggested to call the class of compounds, such as **231** nitroethylenophanes (Scheme 68) <2001SC3517> (see also <2002SUL207>).



Scheme 68

13.11.9.5 Type ae (O–C–C–C + C–O–C)

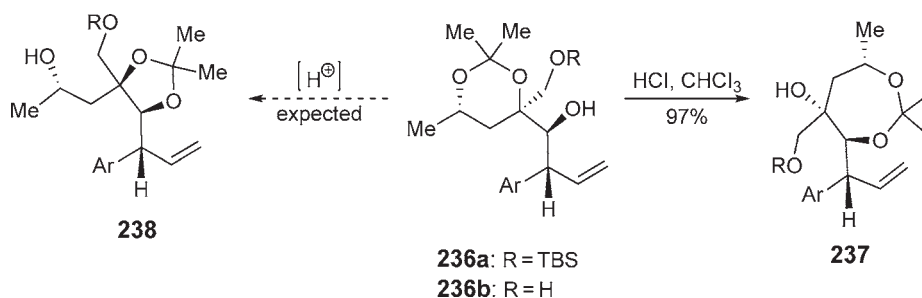
The reaction of oxaphospholanes **235** derived from 3-hydroxy-3-arylphosphonium salts **234** and DBU with para-formaldehyde yielded 4-aryl-6-methylene-1,3-dioxepanes **89** (Scheme 69) <2005BCJ2209>.



Scheme 69

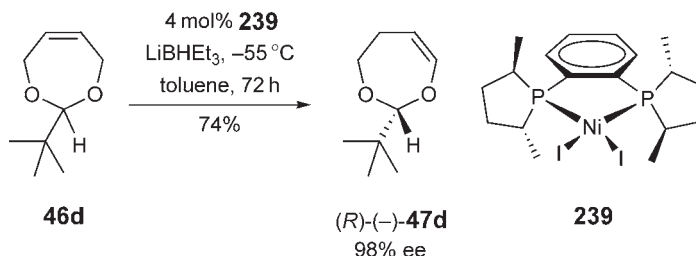
13.11.10 Ring Syntheses by Transformation of Another Ring

In the course of a total synthesis of resiniferatoxin, an unexpected ring extension occurred, when 1,3-dioxane **236a** was treated with an acid in chloroform. The ring extension was confirmed by acid-catalyzed rearrangement of diol **236b** into dioxepane **237** (Scheme 70) <2004OL4371>.



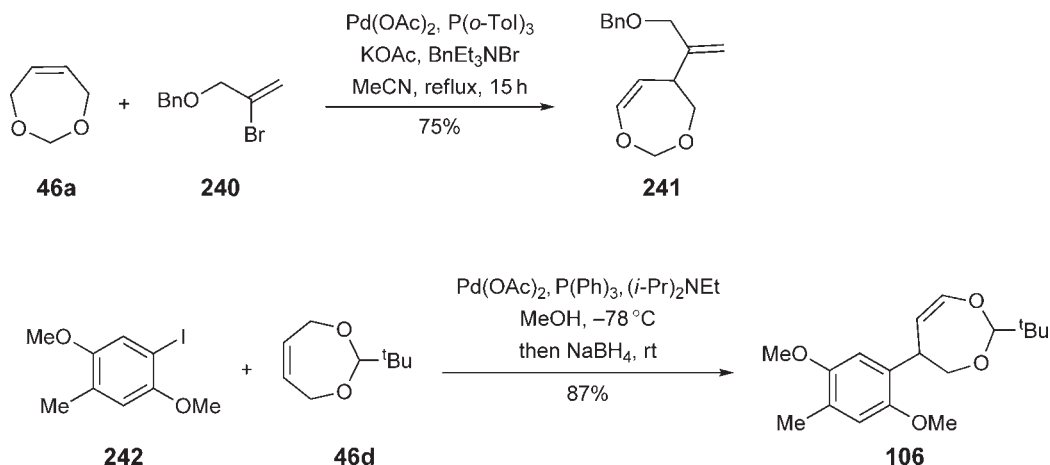
Scheme 70

Two general procedures exist for the synthesis of 4,5-dihydro-1,3-dioxepins, that is, double-bond isomerization and Heck reaction of 4,7-dihydro-1,3-dioxepins. Besides the potassium *tert*-butoxide/DMSO procedure, the transition metal-catalyzed isomerization was effected with rhodium, ruthenium [<1998TA3231>](#), and nickel catalysts [<1998TA1103, 1998T1021>](#). Significant improvements have been achieved in the asymmetric double-bond isomerization using *in situ* generated hydridonickel complexes modified with chiral ligands. Thus, 2-*tert*-butyl-4,5-dihydro-1,3-dioxepin (*R*)-**47d** was obtained with 98% ee by isomerization of 2-*tert*-butyl-4,7-dihydro-1,3-dioxepin **46d** (R = *tert*-Bu) with catalyst precursor **239** and activation with lithium triethylborohydride (**Scheme 71**) [<2001AGE177>](#).



Scheme 71

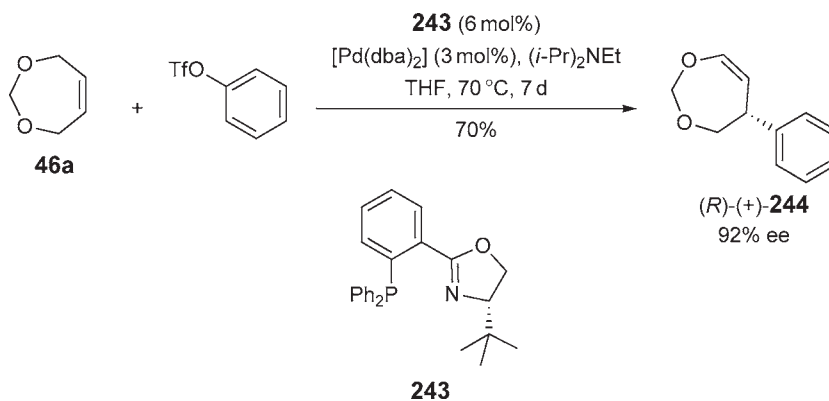
The Heck reaction of 4,7-dihydro-1,3-dioxepins has found further applications in the total synthesis of naturally occurring compounds. For example, 4,5-dihydro-1,3-dioxepin **241** was prepared as an intermediate in the synthesis of Brefeldin A [<1999JOC3800>](#), and the *tert*-butyl derivative of **106** in the synthesis of (+)-curcuquinone and (-)-curcuhydroquinone (**Scheme 72**) [<2003ARK232>](#).



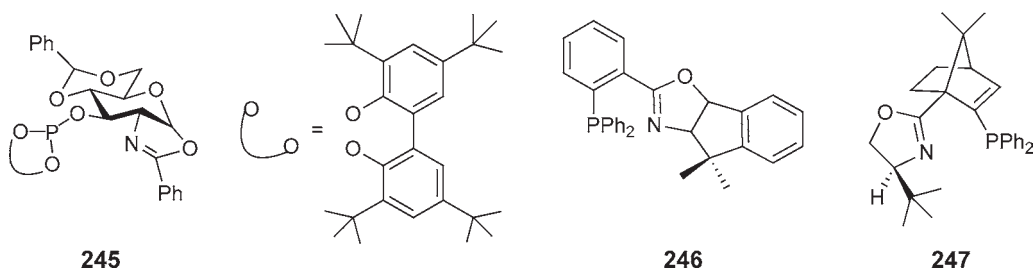
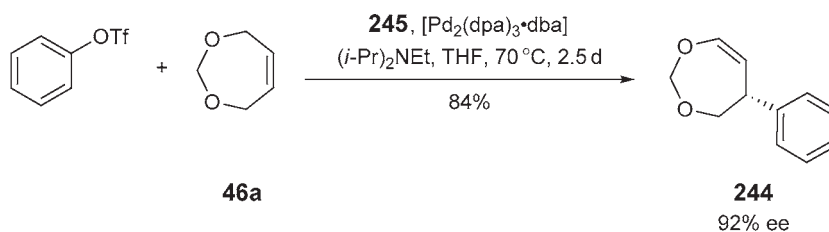
Scheme 72

In the asymmetric Heck reaction, BINAP-modified palladium catalysts gave only moderate enantioselectivities [<1994TL1227>](#). The values greater than 90% have been obtained with several *P,N*-ligands, for example, phosphanyldihydrooxazole **243** (**Scheme 73**) [<1997S1338, 1996AGE200>](#), phosphite oxazoline **245** (**Scheme 74**) [<2005OL5597>](#), 2-[2-(diphenylphosphino)phenyl]oxazoline **246** [<2000TA2205>](#), and ketopinic acid-based phosphine-oxazoline **247** (**Scheme 74**) [<2001OL161>](#); however, the reactions with ligands **246** and **247** proceed very slowly.

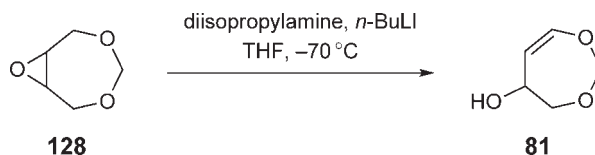
6-Hydroxy-4,5-dihydro-1,3-dioxepin **81** (cf. section 7 of Chapter 13.11) was obtained by ring opening of epoxy-dioxepane **128** with lithium amide (**Scheme 75**) [<2004RJOC1876>](#).



Scheme 73



Scheme 74

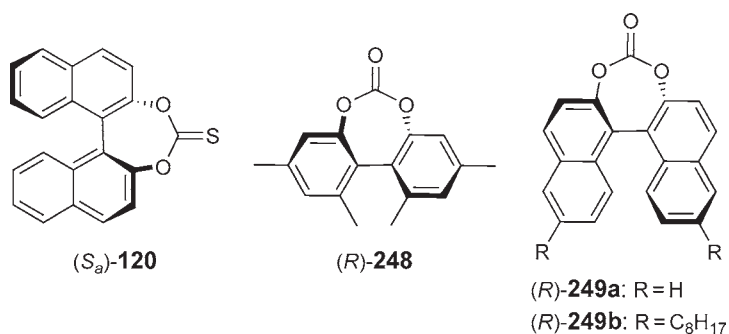


Scheme 75

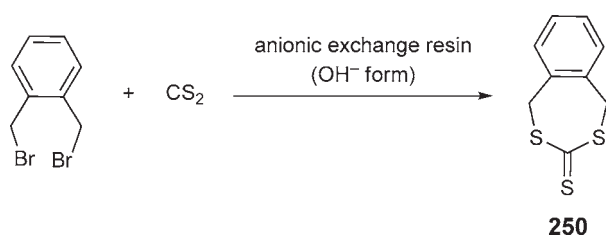
13.11.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

13.11.11.1 Carbonates, Thiocarbonates, and Orthocarbonates

Carbonates as well as thiocarbonates, for example, (S_a) -**120** <2004TL39>, (R) -**248** <1999CL93>, and (R) -**249** <1998JA4530>, were readily prepared by reaction of the corresponding diol with triphosgene and thiophosgene.

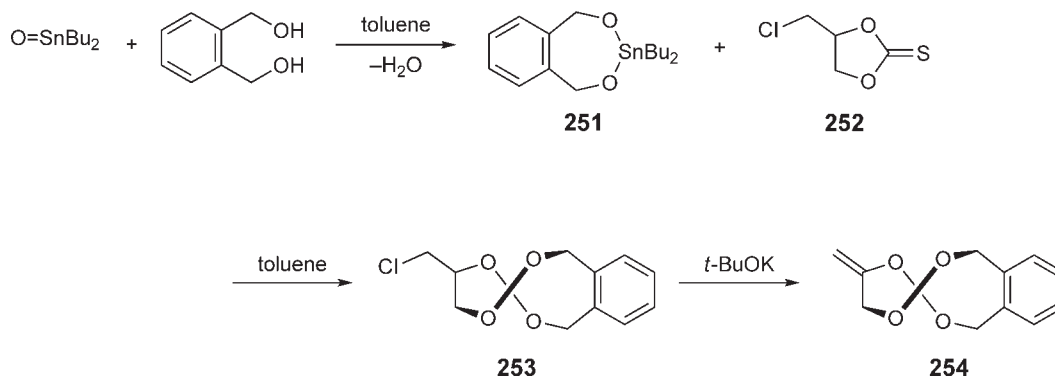


A straightforward procedure of trithiocarbonate **250** involves reaction of carbon disulfide with anion exchange resin (OH[−] form) and reaction with α,α' -dibromo-*o*-xylene (**Scheme 76**) <2005MM2691>.



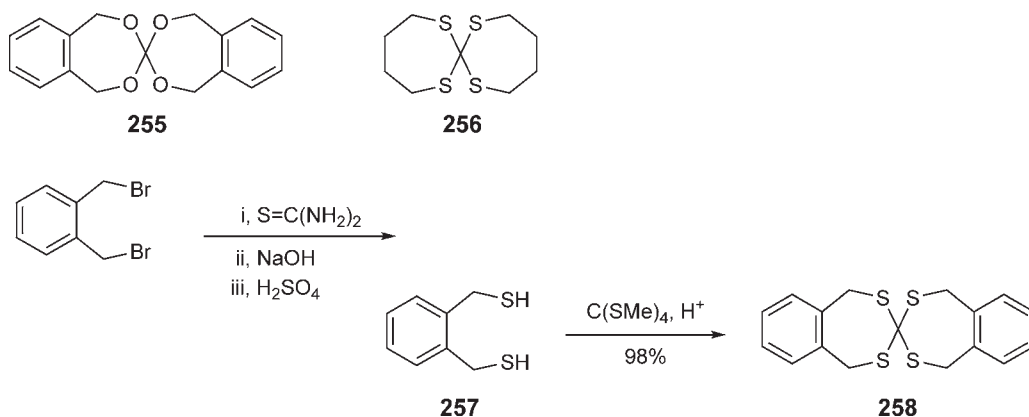
Scheme 76

Spiroorthocarbonates were obtained by coupling of cyclic tin adduct **251**, prepared from 1,2-dihydroxymethylbenzene and dibutyltin oxide, with thiocarbonate **252**. Reaction of the resulting orthocarbonate **253** with potassium *tert*-butoxide in toluene afforded spiroorthocarbonate **254** (**Scheme 77**) <2003BKC1371>.



Scheme 77

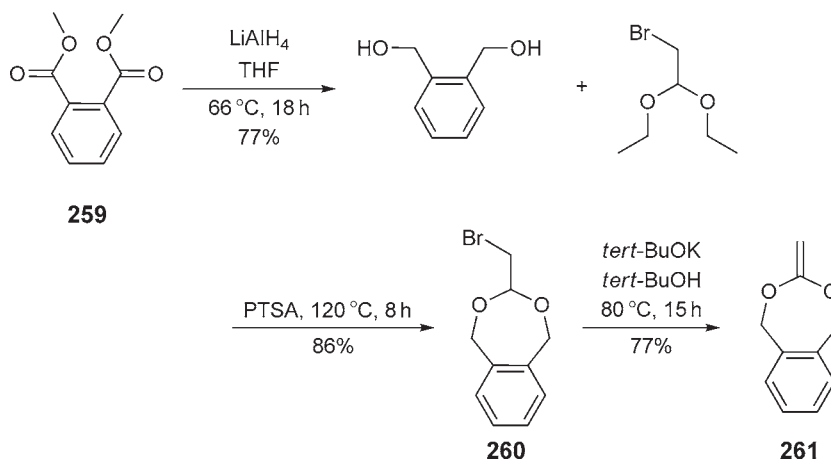
The polymerization of spiroorthocarbonate **255** and spirotrithioorthocarbonate **256** has previously been studied. The synthesis of spirotrithioorthocarbonate **258** was performed by acid-catalyzed transesterification of tetrakis-(methylthio)methane with *o*-xylenedithiol <1997MM6721> (**Scheme 78**).



Scheme 78

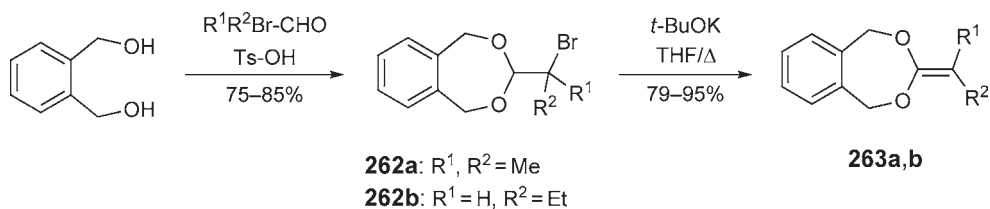
13.11.11.2 Ketene Acetals and Thioketene Acetals

An older procedure for the synthesis of ketene acetal **261** was improved by slight modifications (Scheme 79) <2003MM6152>. It was also reported that dehydrobromination of **260** was achieved without use of a solvent in high yield by microwave <1996TL1695>.



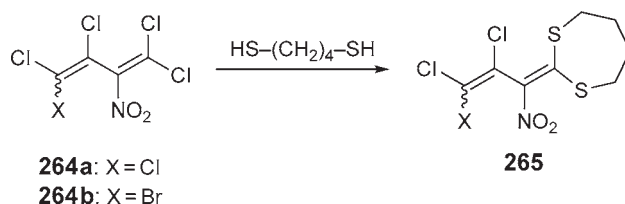
Scheme 79

Disubstituted ketene acetals **263** have been prepared in a similar way (Scheme 80) <2001TL3183>.



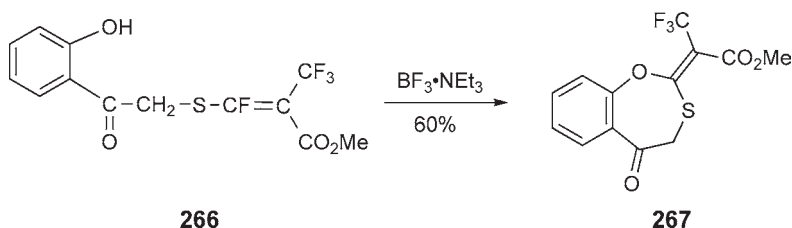
Scheme 80

Dithioketene acetals have been synthesized by stirring of substrates **264** with butane-1,4-dithiol at 30–35 °C (Scheme 81) <2002PS2529>.



Scheme 81

The synthesis of 2-alkylidene-substituted 1,3-benzoxathiepan-5-one **267** possessing a *O,S*-ketene acetal structure was achieved by heterocyclization of **266** in the presence of $\text{BF}_3 \cdot \text{NEt}_3$ (**Scheme 82**) <2001RCB1255>. The reaction corresponds to a formal *type a* ($\text{O}-\text{C}-\text{C}-\text{C}-\text{C}-\text{O}-\text{C}$) synthesis.



Scheme 82

13.11.11.3 Critical Comparison of the Various Routes Available

Various methods have been developed for the synthesis of the different classes of compounds. Their applicability depends on the substrates available and the desired products. Insofar, a comparison of the methods is not possible.

However, it has turned out that there are a few synthetic methods having broad scope, that is, (a) for the synthesis of dioxepins and dithiepins: (i) transacetalization of the corresponding diol or dithiol, respectively, with an open chain acetal; (ii) treatment of the corresponding diol or dithiol with sodium borohydride and reaction of the resulting dianion with a *gem*-dihalogen derivative. The latter method is particularly useful for the synthesis of dioxepins and dithiepins unsubstituted in the 2-position; (b) for the synthesis of 4,5-dihydro-1,3-dioxepins: (i) metal- or base-catalyzed double-bond isomerization; and (ii) Heck vinylation or arylation, respectively, for the synthesis of 6-substituted 4,5-dihydro-1,3-dioxepins.

13.11.12 Important Compounds and Applications

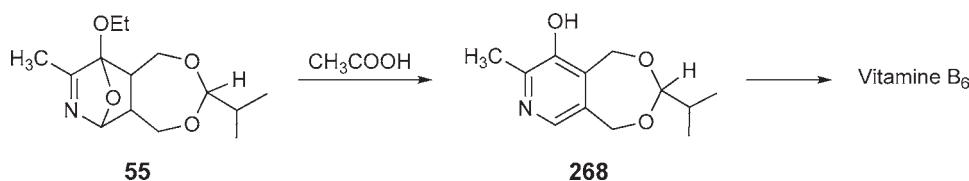
Dioxepanes, carbonates, and thiocarbonates as well as ketene acetals bearing a dioxe- or dithiepane unit have found a lot of applications in polymer chemistry. Particularly, they have found recent interest as biodegradable polymers. For some selected recent applications, see [2003MM2397](#), [2005JPS\(A\)1014](#), [2005MI901](#), [2005PLM11698](#), [2005MM2691](#).

C₁-TunePhos-modified Pd catalysts have found applications in allylic asymmetric alkylations, asymmetric hydrogenations of α - and β -ketoesters [<2006SL1169, 2000JOC6223>](#), allylphthalimides [<2005AGE4933>](#), enol acetates [<2002OL4495>](#), and asymmetric cycloadditions [<2005TL8213>](#).

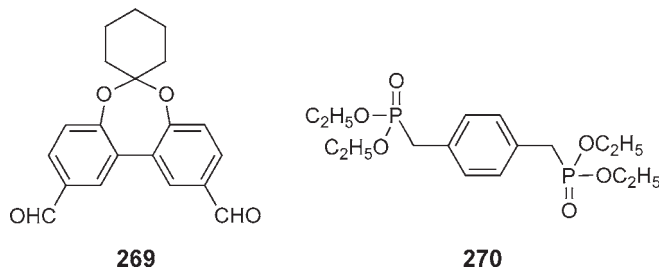
4,5-Dihydro-1,3-dioxepins were used as chiral building blocks [<2001AG\(E\)177>](#) and substrates for the synthesis of naturally occurring compounds [<2003ARK232>](#).

Dioxepane **55** has found application in the manufacturing of vitamin B₆. Cycloadduct **55** was obtained by Diels–Alder reaction of 2-isopropyl-4,7-dihydro-1,3-dioxepin with 4-methyl-5-ethoxy-1,3-oxazol (see [Section 13.11.6.2](#)), and the resulting adduct was rearranged in the presence of an acid to give pyridoxol derivative **268** [\[<2004DE10261271A1, 2005WO049618A1> \(Scheme 83\)](#).

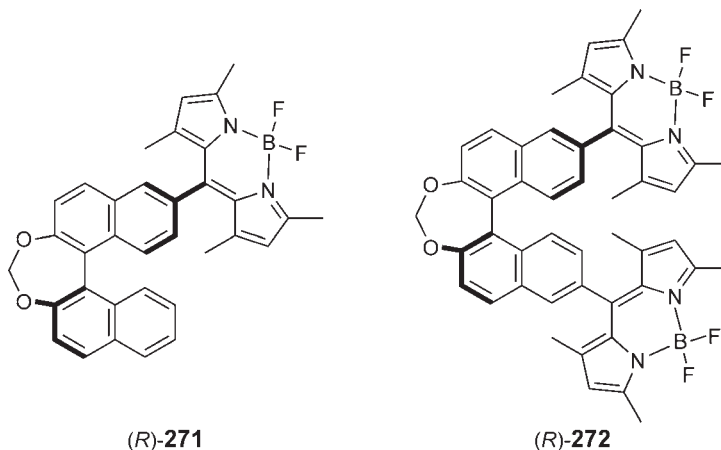
N-(*o*-, *m*-, or *p*-)hydroxylaminobenzenesulfonyl dioxepanoaziridines [<1996US5545659>](#) and *O*-substituted 6-sulfonamido-1,3-dioxepan-5-ols [<1997US5635529>](#) have found application because of their hypoglycemic activity.

**Scheme 83**

Dioxepin and dithiepin derivatives are also of great interest in material sciences. For example, dioxepin **269** was used in the copolymerization with **270** to give blue light emitting PPVs (PPV = poly(1,4-phenylene vinylene)). The polymers are soluble in common organic solvents and exhibit a blue light emission with PL efficiencies as high as 70% in dilute solution <2003SM(135)209>.



Glassy-forming liquid crystals have been modified with (*R*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3]dioxepin to give chiral-nematic systems <1999AM1183>. Because of their optical properties and chirality, binaphthyl boron dipyrromethene (BPD) conjugates, such as (*R*)-**271** and (*R*)-**272**, are of interest for several applications, for example, chiral fluorophores within sensor systems, organic light-emitting diodes (OLEDs) with circular polarized luminescence and light-emitting diodes (LEDs) powered by spin-polarized carriers <2000AG3252>.



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13.12

1,4-Dioxepanes, 1,4-Oxathiepanes, and 1,4-Dithiepanes

H. Frauenrath and S. Flock

Universität GH Kassel, Kassel, Germany

R. Murugan

Vertellus Specialties Inc., Indianapolis, IN, USA

E. F. V. Scriven

University of Florida, Gainesville, FL, USA

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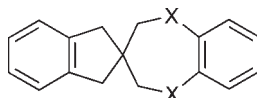
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13.12.1 Introduction

This topic was covered in <1984CHEC> (Volume 7, Chapters 5.18.3.3 and 5.18.4.3) and in <1996CHEC-II> (Volume 9, Chapter 9.12). This chapter presents an update of the literature for the period 1996–2007.

13.12.2 Theoretical Methods

Little theoretical work has been reported on these systems during the review period. Energy calculations were performed on the spirans **1a** and **1b** to determine the preferred conformations. The minimum-energy conformation for the 1,5-dithiepine **1** is virtually identical with that in the solid state, in contrast for the dioxepine system that are different <2004JST(687)79>.



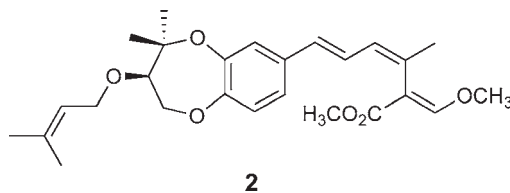
1a: X = S

1b: X = O

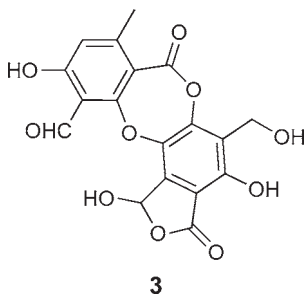
13.12.3 Experimental Structural Methods

13.12.3.1 NMR Spectroscopy

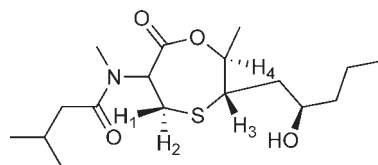
Nuclear magnetic resonance (NMR) spectroscopy, with X-ray analysis, forms the basis for the determination of the structures of most of the compounds discussed in this chapter. ¹H and ¹³C NMR played a key role in the revision of the structure of the antifungal metabolite strobilurin D **2**, which was shown to contain a benzodioxepin moiety rather than epoxide <1999T10101>. 9-Methoxystrobilurin K was also shown to contain a 1,4-benzodioxepin <1997TL7465>.



The ¹H and ¹³C NMR spectra of salazinic acid **3** have been completely assigned <2000MRC472>. Kaye has assigned the ¹³C NMR of a series of benzoaxathiepine derivatives <2005MRC952>. Natural abundance of ¹⁷O for some benzoaxathiepins has also been determined <1996JCM152>. NMR spectroscopy combined with X-ray analysis has been used to study the conformations of 1,5-benzo-dioxepines, -dithiepins, and -oxathiepins that are potential benzodiazepine receptor ligands <2006JCM512>.



A novel cysteine derivative, spongiacysteine, was isolated recently from marine sponge. It was converted to lactone **4** by reaction with 2,4,6-trichlorobenzoyl chloride, 4-dimethylaminopyridine (DMAP), and triethylamine. Selected nuclear Overhauser enhancement spectroscopy (NOESY) correlation and coupling constants are given <2004CL1262>.



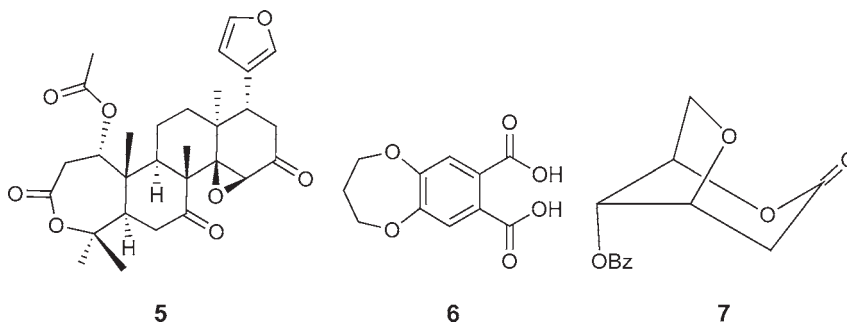
4

$J(\text{H}_3/\text{H}_4) = 9.8 \text{ Hz}$

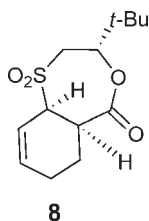
NOESY (H_1/H_3 and H_2/H_4)

13.12.3.2 X-Ray Diffraction

The absolute stereochemistry of **5–7** has been determined from single crystal X-ray diffraction studies <2006AXE2502, 2005ANS81, 2001AXE360>.

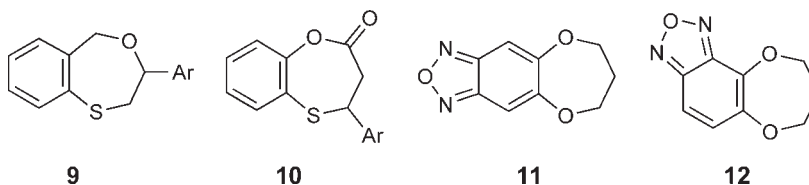


The oxathiapinone **8** prepared by an intramolecular Diels–Alder reaction was found to have a sofa conformation from X-ray analysis <2006AXE370, 2006AXE366>.



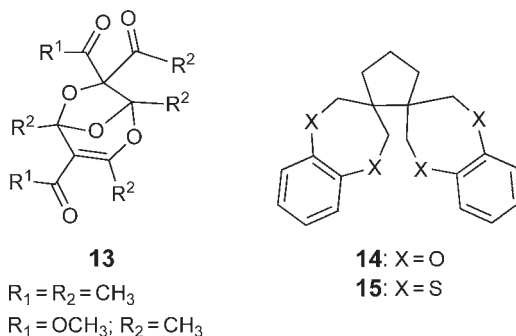
13.12.3.3 Mass Spectrometry

Mass spectral fragmentation pathways for some benzoxathiepins **9** and benzoxathiepinones **10** have been deduced <1999JCM584>. Mass spectrometry allows the distinction between the linear and angular benzofurazans (and furoxans) of the type **11** and **12** <1999JMP1137>.



13.12.4 Thermodynamic Aspects

Structures of five derivatives of **13** were obtained in the solid state by X-ray diffraction analysis; the experimentally determined bond lengths differed from those calculated by the Hartree–Fock method <2001AXB63>. X-ray structures determined for the dispirans **14** and **15** revealed an interesting facet. In the solid state the heterorings of the oxygen dispirane **14** both exist in the twist boat form in accord with calculation. By contrast, in the sulfur analog **15** the heterorings have different conformations (twisted boat and chair) <2004JST(691)39>.



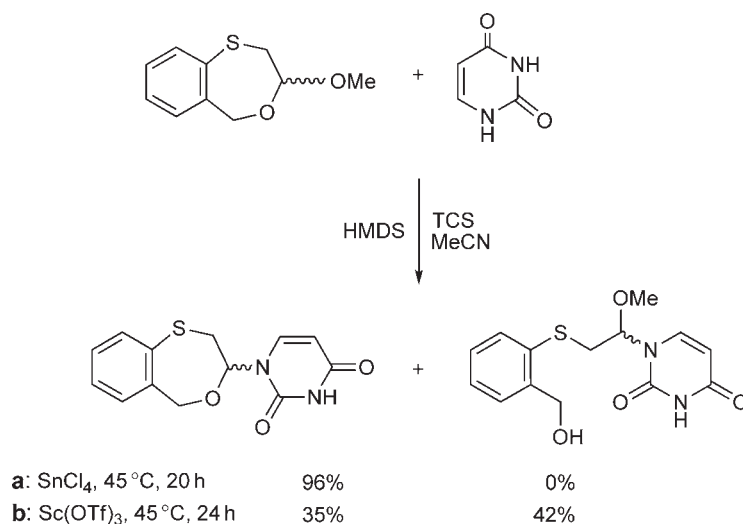
13.12.5 Reactivity of Fully Conjugated Rings

No examples have been found.

13.12.6 Reactivity of Non-conjugated Rings

13.12.6.1 Lewis Acid-Mediated Reactions

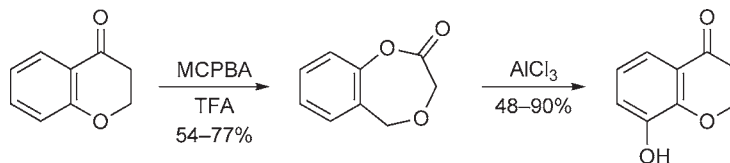
Some dihydrobenzodioxepin-3-ylfluorouracils are good antiproliferative agents against certain cancer cell lines. These and related acyl nucleosides have been made by treatment of a methoxydioxo-, oxathia-, or dithiapiin with a pyrimidine or purine base, hexamethyldisilazide (HMDS), trimethylchlorosilane (TCS), and a Lewis acid in anhydrous acetonitrile (Scheme 1) <1998T13295, 2005T10363, 2007T183>.



Scheme 1

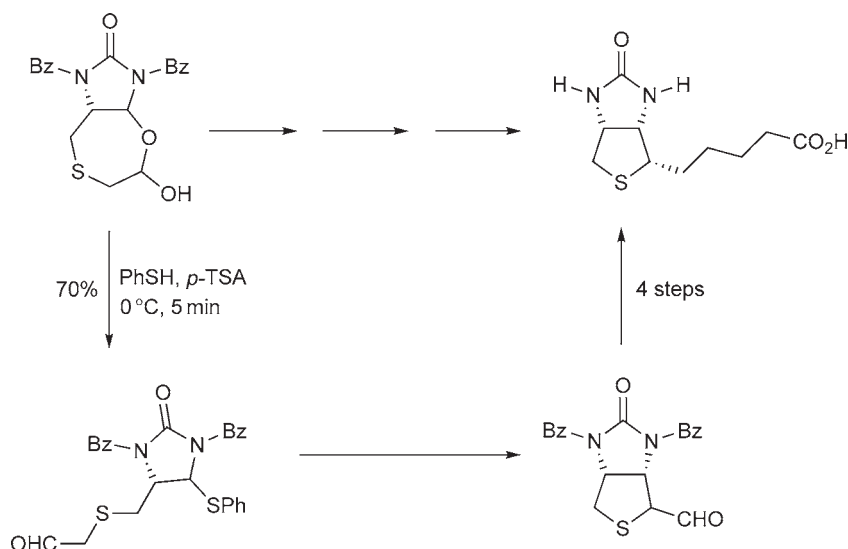
13.12.6.2 Ring Contraction

Benzodiazepin-2-ones, formed by Baeyer–Villiger oxidation, readily underwent ring contraction on treatment with aluminium chloride to offer a useful synthesis of 8-hydroxychromanones ([Scheme 2](#) <1997SC4245>).



Scheme 2

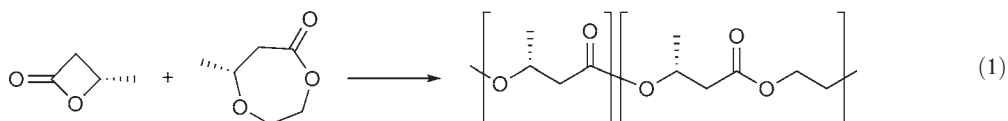
Ring opening of imidazolidone-fused oxathiepin and ring closure affords a useful synthesis of biotin ([Scheme 3](#) <2001JOC6197>).



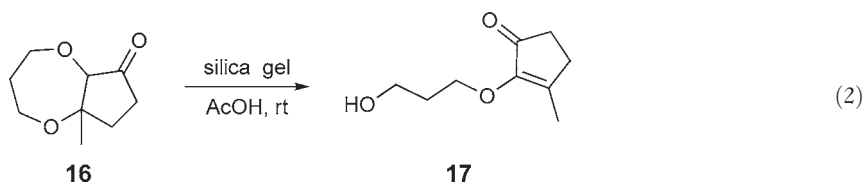
Scheme 3

13.12.6.3 Ring Opening

Ring-opening copolymerization (ROP) of (*R*)- β -butyrolactone with (*R*)-3-methyl-4-oxa-6-hexanolide in the presence of tin(IV) chloride affords a new biodegradable copolymer ([Equation 1](#) <1995MM406>).

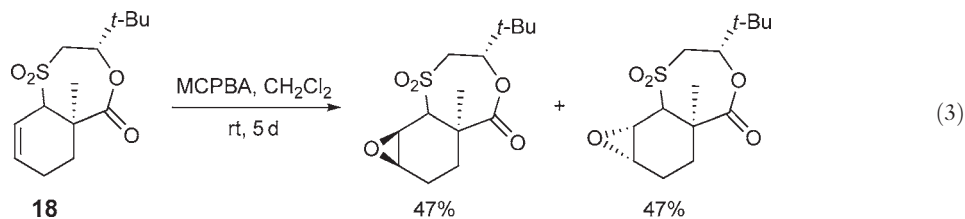


The dioxapin derivative **16** is very labile under acidic conditions and quantitatively gave the ring-opened cyclopentenone **17** ([Equation 2](#) <1997JOC2123>).

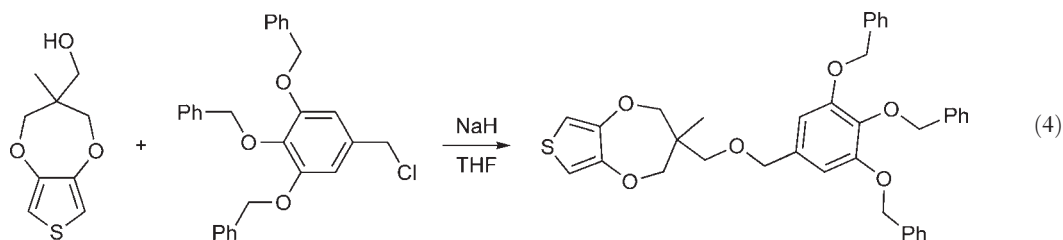


13.12.7 Reactivity of Substituents Attached to Ring Carbon Atoms

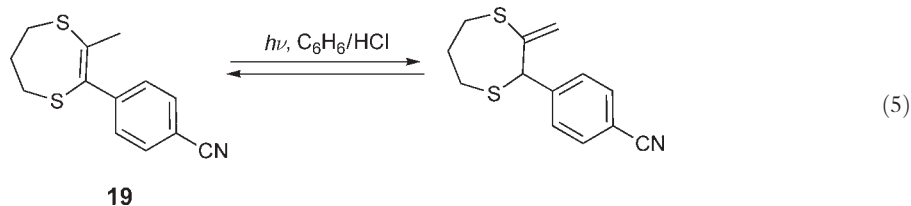
Treatment of **18** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane for 5 days at room temperature gives a 1:1 mixture of diastereomeric epoxides (Equation 3) <2006AXE1411>.



The functionalization of ProDot-OH offers a useful example of a substituent reaction (Equation 4) <2004JMC1896>.



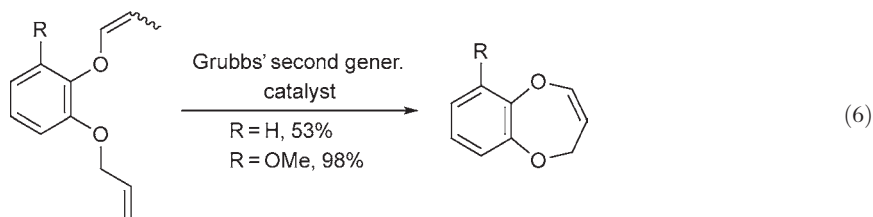
Methyldithiepin **19** undergoes photoinitiated 1,3-proton shift, leading to a change in hyperpolarizability, which is of great importance for organic electronic materials (Equation 5) <2001JOC1894>.



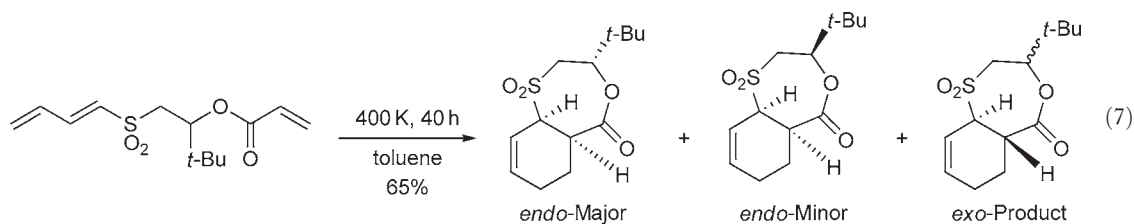
13.12.8 Ring Synthesis from a Single Precursor

13.12.8.1 Ring Closure by C–C Bond making

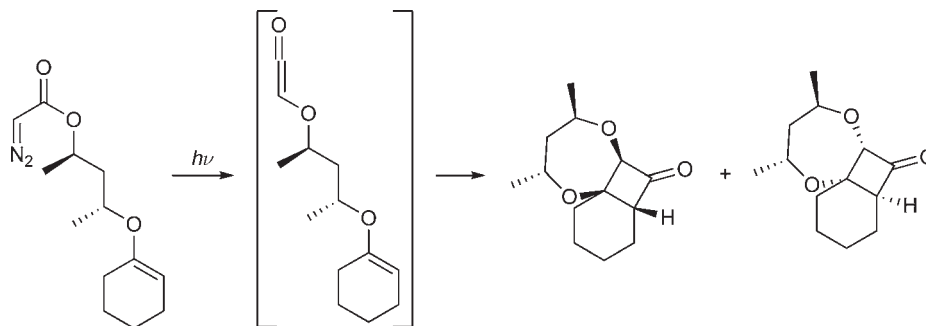
Ring-closing metathesis (RCM) has been employed for the construction of 1,5-benzodioxepine derivatives (Equation 6) <2004TL2631>.



The first use of β -hydroxysulfone-based tethers in an intramolecular Diels–Alder reaction provides a novel route to fused 1,4-oxathiepinone sulfone derivatives; the *endo*-adduct is favored (Equation 7) <2005OL3203>.

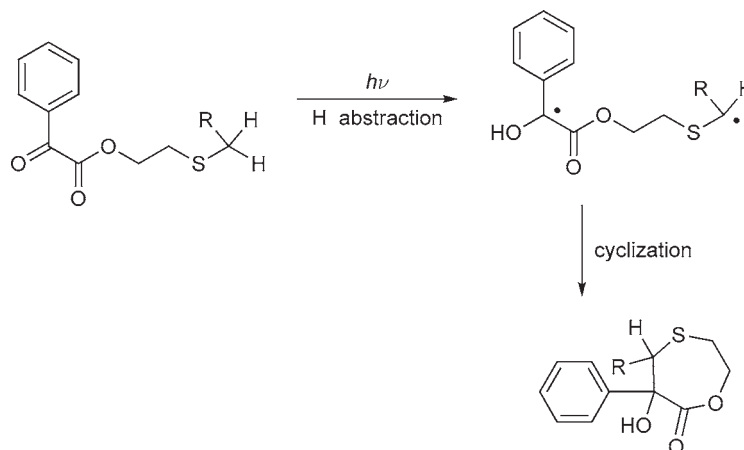


A [2+2] cycloaddition that involves a ketene has been used to make a dioxepane annulated to a cyclobutanone (**Scheme 4**) <2000JA2128>.



Scheme 4

Photolytic ring closure of substituted alkyl phenylglyoxylates has been reported. This ring closure involves a diradical intermediate, formed by H-abstraction, which then cyclizes (**Scheme 5**) <1997T2751>.

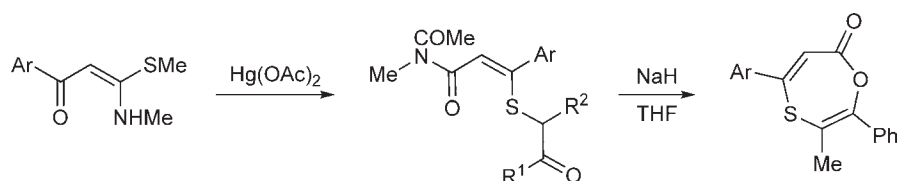


Scheme 5

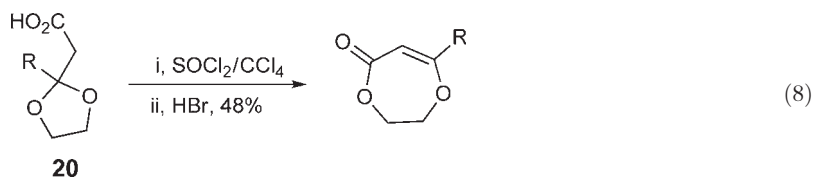
13.12.8.2 Ring Closure by C–O Bond Making

3-Alkyl-2,5-diaryl-1,4-oxathiepin-7-ones have been prepared from propenamides in high yield (**Scheme 6**) <2001TL4637>.

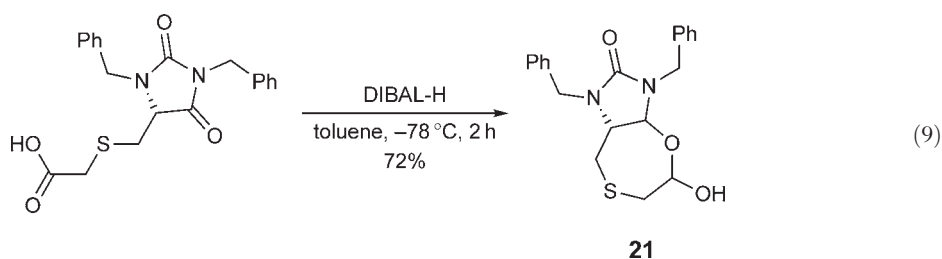
Treatment of 1,3-dioxalanes **20** with thionyl chloride and then 48% hydrobromic acid gave 7-(perfluoroalkyl)-2,3-dihydro-5*H*-1,4-dioxepin-5-ones, 50–95% yield (**Equation 8**) <2001TL2305>.



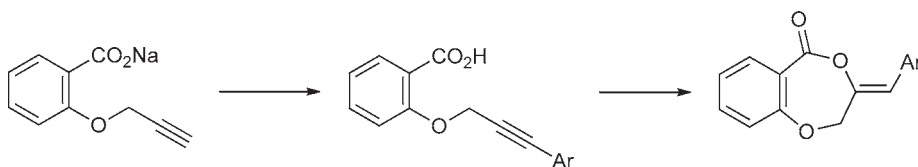
Scheme 6



The hydroxyoxathiapane **21**, a precursor in a new biotin synthesis, is readily obtained by cyclization (Equation 9) <2001JOC6197>.

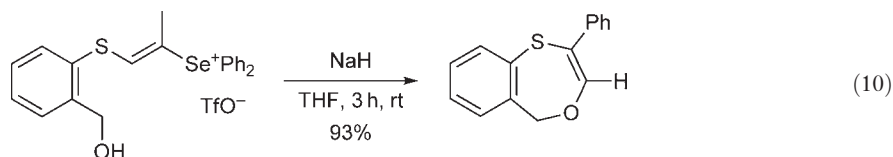


A highly regio- and stereoselective synthesis of 3-arylidene-1,4-benzodioxepin-5-ones has been achieved with palladium–copper catalysis (Scheme 7) <2000J(P1)775>.

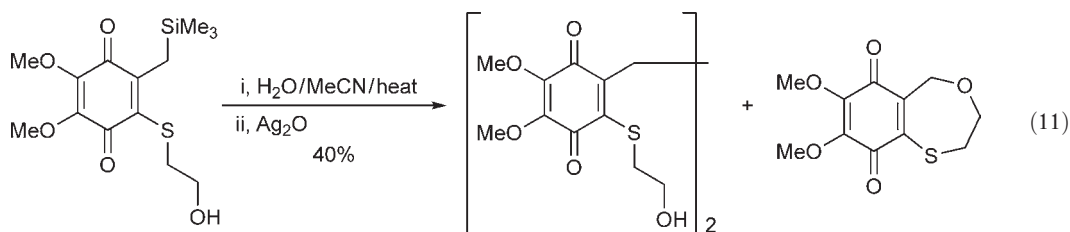


Scheme 7

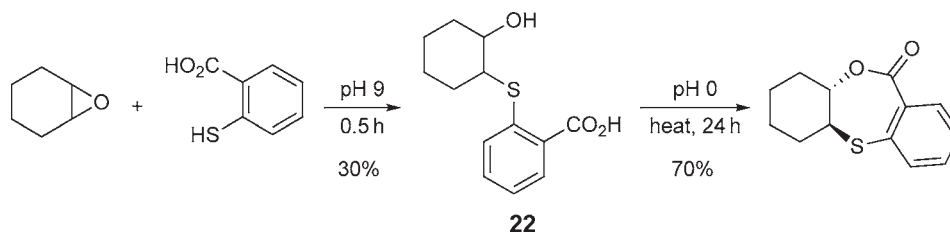
β -Alkylthioalkenylselenonium salts, bearing a hydroxyl group on a β -sidechain, underwent cyclization on treatment with sodium hydride to provide a useful approach to a benzoxathiepins (Equation 10) <2000JOC8893>.



The reaction of *o*-trimethylsilylmethyl-1,4-benzoquinones with silver oxide gave benzoquinoneoxathiepins (Equation 11) <2005T275>.

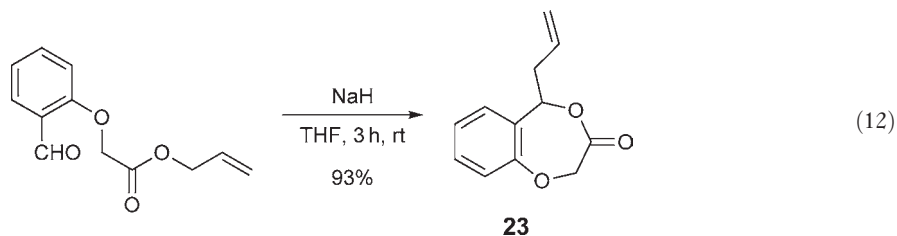


Nucleophilic ring opening of oxiranes gives intermediates of the type **22**, which readily ring-closed (Scheme 8) <2004JOC8780>. A similar reaction can be carried out in one step <2003GC436>.

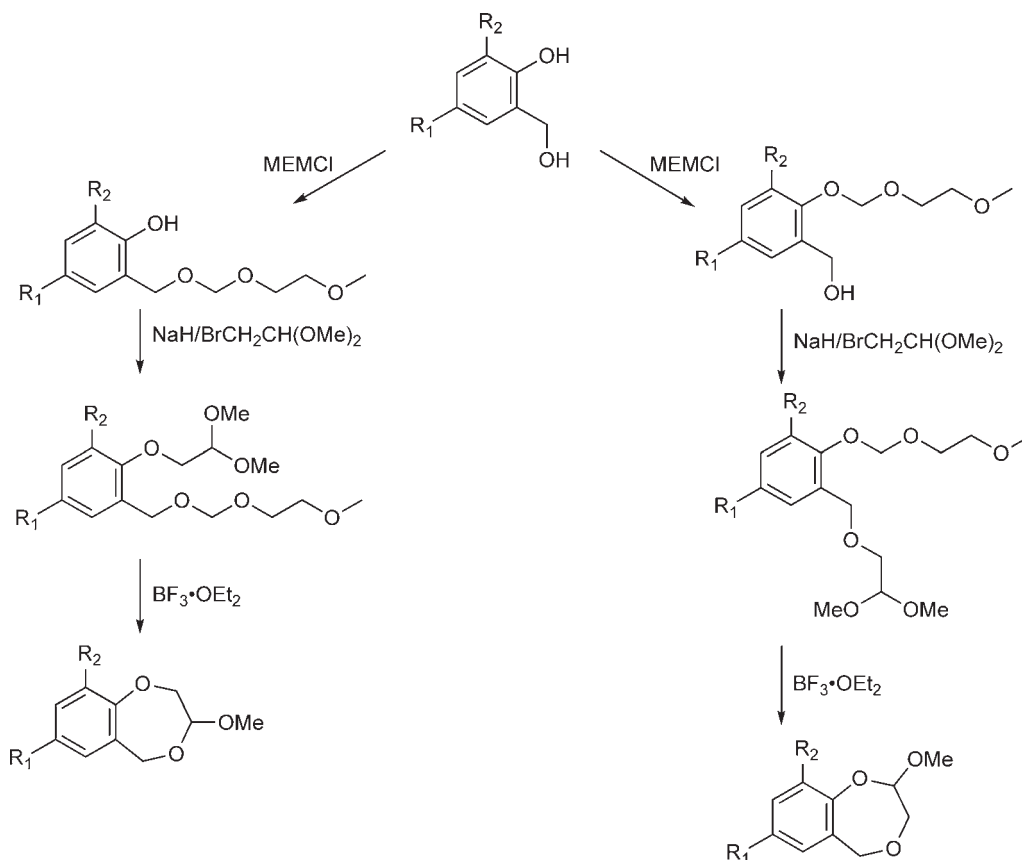


Scheme 8

The benzolactone **23** has been prepared in good yield by an electrochemical process (Equation 12) <2001SL806>.



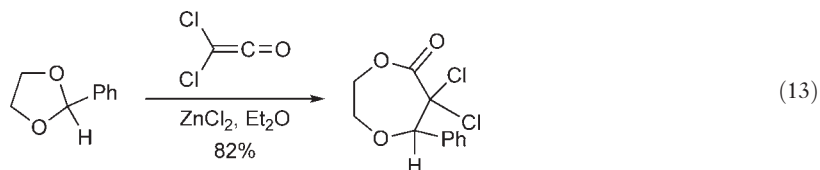
2-Hydroxybenzyl alcohols have been converted to dioxepins, as the major product, by forming methoxyethoxy-methyl (MEM) ethers either on the phenolic $-\text{OH}$ or on the benzylic $-\text{OH}$ and reacting the other $-\text{OH}$ group with bromoacetaldehyde dimethyl acetal, followed by treatment with $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 9) <2004T11453>.



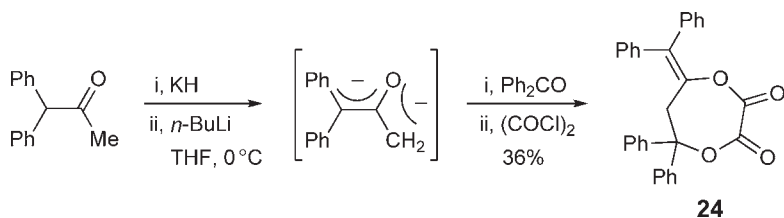
Scheme 9

13.12.9 Ring Synthesis from Two or More Precursors

Mulzer *et al.* have extended the applicability of the insertion reaction of ketene into an acetal, to that of a substituted ketene into a 1,3-dioxalane to provide an elegant synthesis of 6,6-dichloro-1,4-dioxepan-5-ones (Equation 13) <1996AGE1970>.

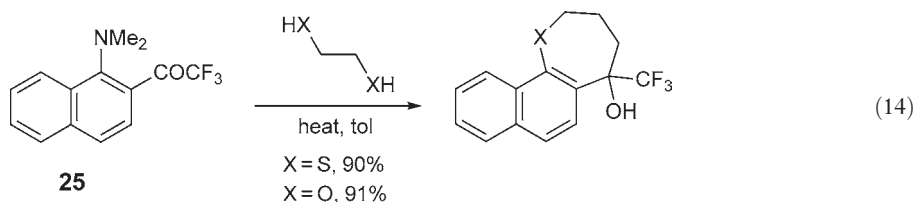


A 1,4-oxepane-2,3-dione **24** has been made by the reaction of a 1,3-dione with oxalyl chloride (Scheme 10) <2001EJO1511>.

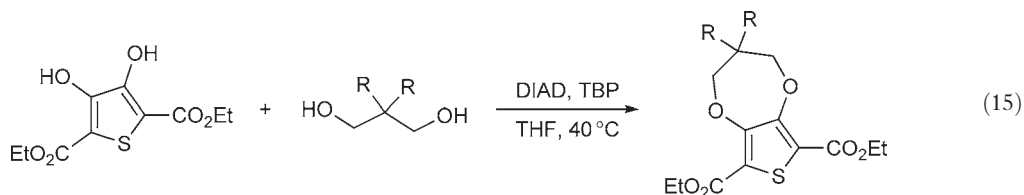


Scheme 10

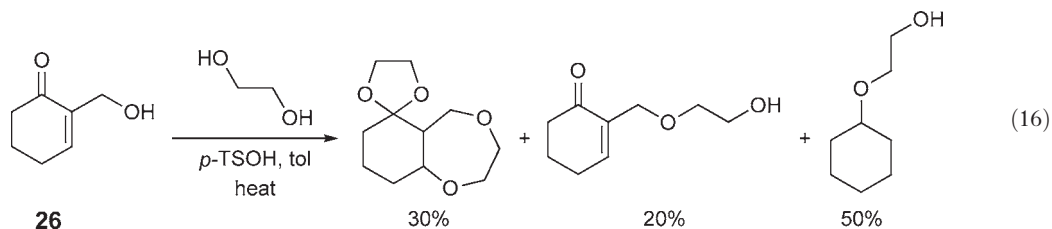
The reaction of trifluoroacetylnaphthylamine **25** with diols and dithiols offers a convenient high yield synthesis of 1,4-dioxepins and dithiepins (Equation 14) <1998H(49)297>.



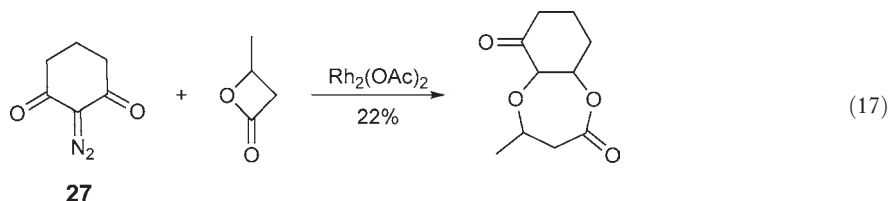
The prepolymer 3,4-ethylenedioxythiophene (EDOT) has been made in good yield from a pair of diols (Equation 15) <2002CC2690>.



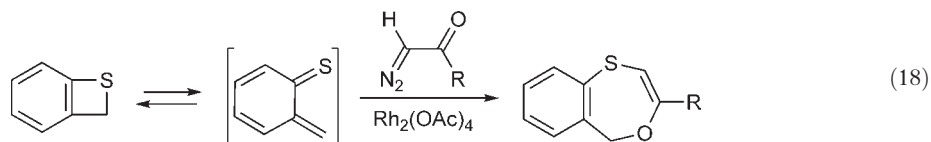
The well-known Baylis–Hillman adduct **26** has been exploited to produce dioxepins and dithiepins (Equation 16) <2002JCM366>.



Rhodium acetate has been used to facilitate the reaction of **27** with a β -lactone to give dioxapinones (Equation 17) <1997CC1>.

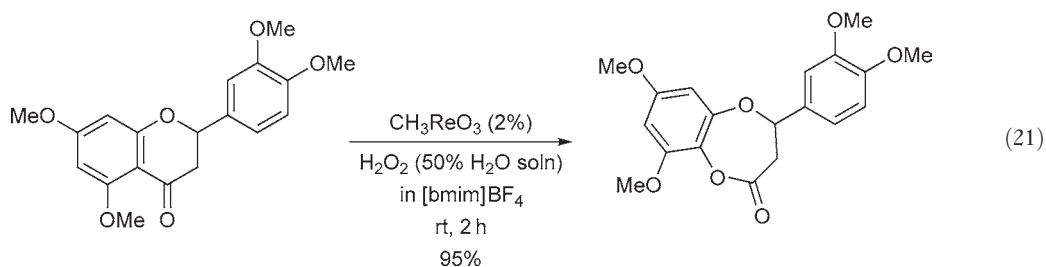
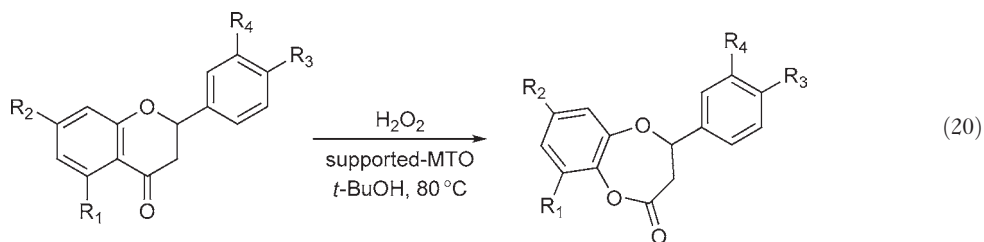
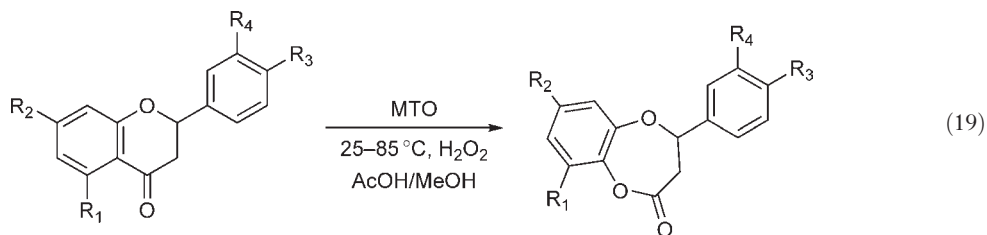


Oxathiepins have been obtained from the reaction of 2*H*-1-benzothiote with diazo compounds in the presence of rhodium acetate (Equation 18) <1995TL6047>.

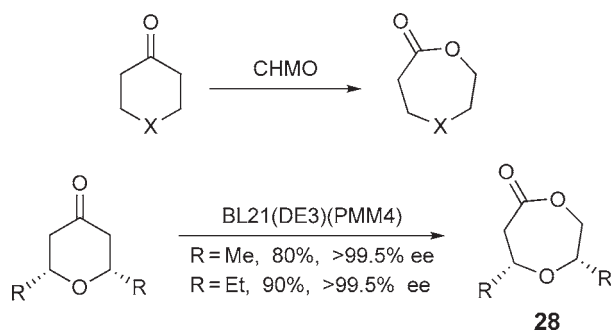


13.12.10 Ring Synthesis by Transformation of Another Ring

The Baeyer–Villiger oxidation of six-membered ring ketones to form dioxepinones was discussed in CHEC-II(1996)(9) p282 is well represented in the literature of the period covered and some interesting developments have taken place. Bernini *et al.* have applied the methyltrioxorhenium (MTO)/hydrogen peroxide system to the oxidation of flavones and this has enabled them to obtain remarkably high yields of 1,5-benzodioxepin-2-ones (Equation 19) <2001TL5401>. They have extended this work to develop a supported MTO catalyst (Equation 20) <2003TL4823> and a recyclable homogeneous catalyst in an ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate) (Equation 21) <2003TL8991>.

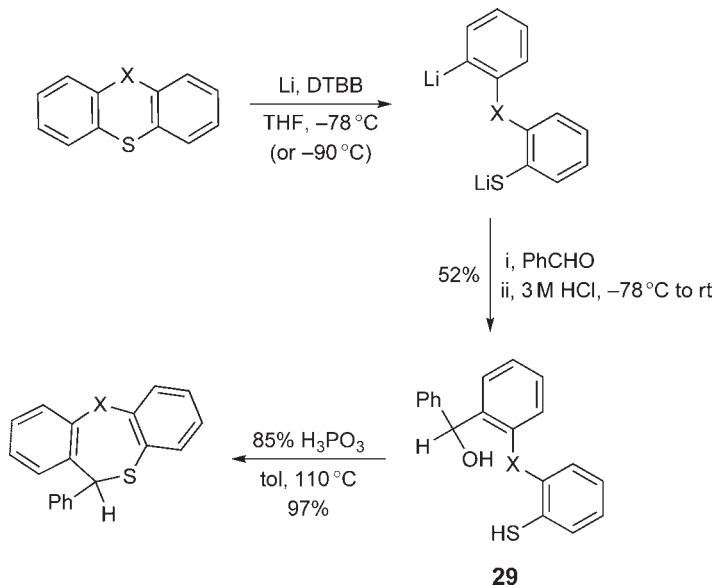


The Baeyer–Villiger enzyme, cyclohexanone monooxygenase (CHMO), has been applied to the oxidative ring expansion of *cis*-2,6-dialkylperhydropyrans to afford **28** with very high yields and ee's, when R = methyl or ethyl (Scheme 11) <2001JMO349, 2003SL1973>.



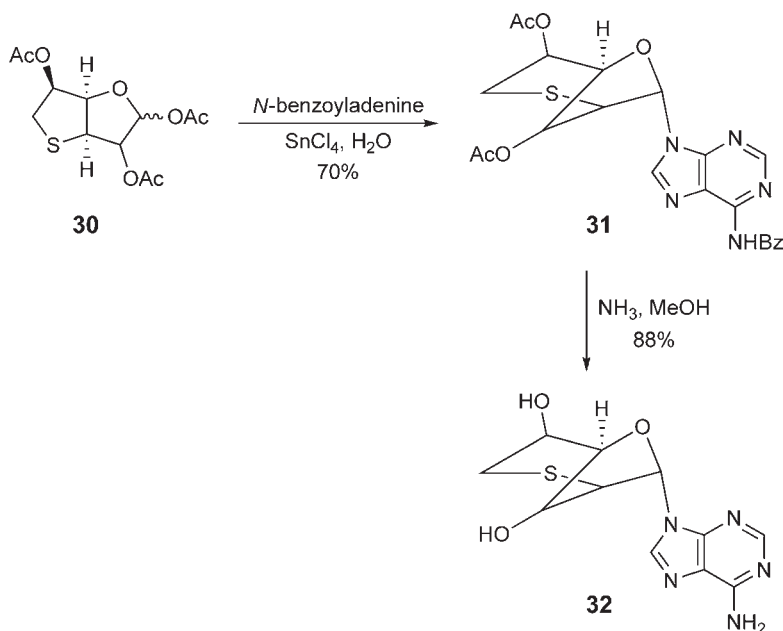
Scheme 11

MCPBA in dichloromethane (DCM) continues to be used as an oxidant for the preparation of benzo-1,5-dioxapins <2001S473, 1996SC4459>. Dibenzothiins and phenoxathiins undergo DTBB-catalyzed lithiation (DTBB – 4,4'-di-*tert*-butylbiphenyl). Reaction of the so-formed lithio intermediates with suitable electrophiles gives **29**, which undergoes cyclization (Scheme 12) <2002CL726>.



Scheme 12

Currently, there is a lot of interest in nucleoside attached to seven-membered ring carbohydrate derivatives. Conversion of **30** to **31** was discovered serendipitously when wet tin tetrachloride was used instead of an anhydrous sample <1998TL3923>. This led to a useful synthesis of **32** (Scheme 13).



Scheme 13

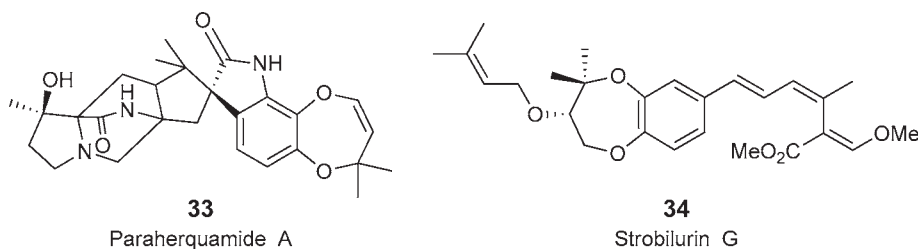
13.12.11 Critical Comparison of the Various Routes Available

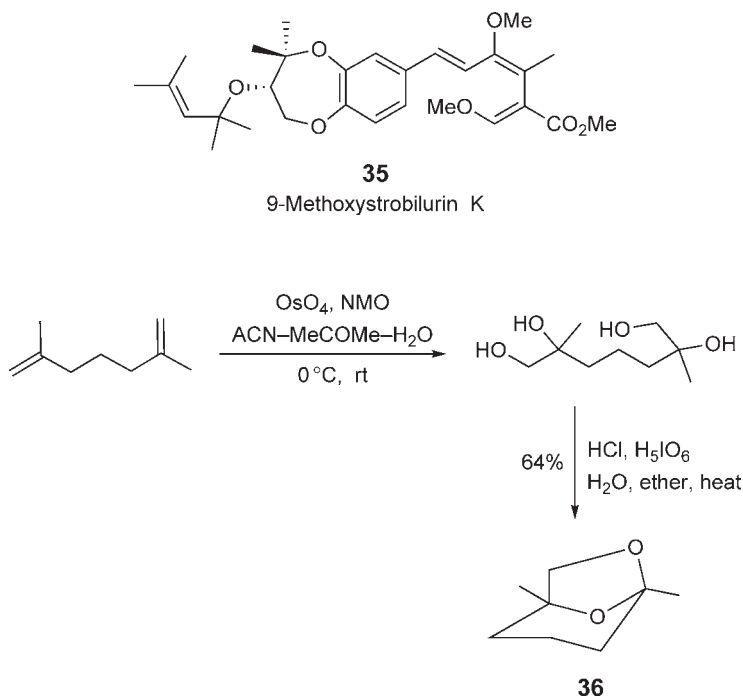
Compounds in this class are usually made from specific precursors with the ultimate functionalities appearing in the starting materials. Syntheses in which one new bond is formed (cyclizations) usually involve substitution or condensation reactions. Two new closures with potentially some generality have been noted in this chapter. One of the intramolecular Diels–Alder reactions (see Section 13.12.8.1) and the other RCM (see Section 13.12.8.1). The Baeyer–Villiger reaction is still very much used for the preparation of lactones. A supported catalyst and a recyclable catalyst carried in an ionic liquid have been introduced for use in Baeyer–Villiger oxidations from other areas.

13.12.12 Important Compounds and Applications

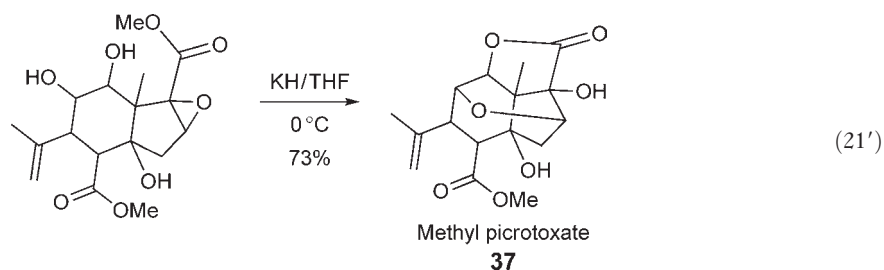
13.12.12.1 Important Compounds

The dioxepin moiety is found in a number of important natural products. A few important ones noted here are **33–35**. Williams *et al.* have reported asymmetric, stereocontrolled syntheses of paraherquamide A **33** <1996JA557, 2003JA12172>. Steglich has reported the total synthesis of strobilurins G **34**, among others. The total synthesis of 9-methoxystrobilurin K has also been achieved **35** <2001TL4531>. Two more natural product syntheses are of interest as the final steps in both cases involve the formation of a dioxapane ring in frontalalin **36** (Scheme 14) and a dioxapinone ring in methyl picrotoxate **37** (Equation 21') <1998T3693>.



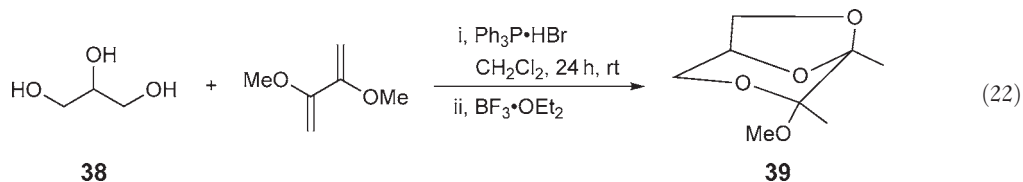


Scheme 14

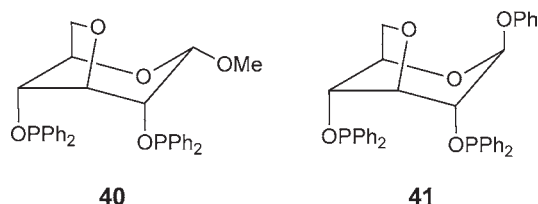


13.12.12.2 Synthetic Methodology

Ley in a continuation of his study of the use of 1,2-diacetals for protection of vicinal diols has synthesized various bis-enol ether derivatives. Treatment of the triol **38** with bis-enol ether gave **39** in good yield after equilibration with $\text{BF}_3 \cdot \text{OEt}_2$ (Equation 22) <2001SL1793>.



The two diphosphinites **40** and **41** obtained from D-glucose by standard procedures proved to be good asymmetric hydrogenation catalysts <2000CCCL587>.

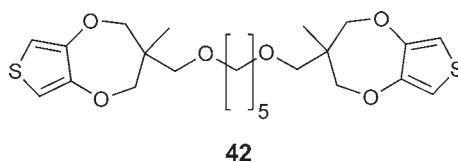


13.12.12.3 Bioactive Compounds

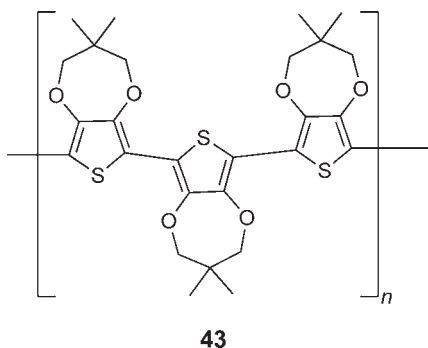
The influence of structural features of benzodioxepine and benzodithiepine derivatives on rat brain benzodiazepine receptors has been studied [\[1996MSR589\]](#). A group at Givaudan has synthesized and studied the conception, characterization, and correlation of new marine odorants based on the benzo[*b*][1,4]dioxepinone system [\[2003EJO3735\]](#). 1,4-Dithiapane was among a data set of 101 hetero sulfamate sodium salts that was tested as potential sweeteners in a structure–taste relationship study [\[2000J\(P2\)1369\]](#).

13.12.12.4 Materials

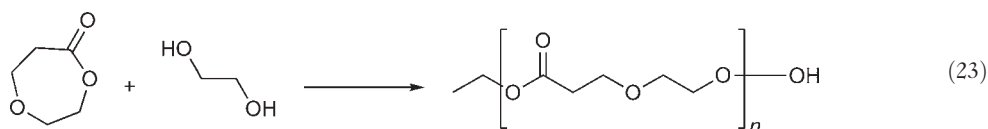
Reynolds *et al.* have made an extensive study of electronic materials based on 3,4-propylenedioxythiophenes [\[2002CC2498, 2005AM422\]](#). They now report that tethered poly(3,4-propylenedioxy)thiophene derivatives, for example, **42**, provided a handle with which to tune the optical and electronic properties of the device [\[2006CC1604\]](#).



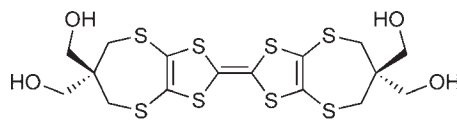
New electrochromic polymers, for example, **43**, have been made that offer a large contrast ratio and rapid switching between two electrodes [\[2004JMR2072\]](#).



Some new star-shaped poly(1,5-dioxapan-2-one) polymers have been prepared by ROP (Equation 23) [\[2002PSA2049\]](#).



A novel 1,4-dithiepine **44** containing four hydroxyl groups has been synthesized [\[2001J\(P1\)407\]](#).



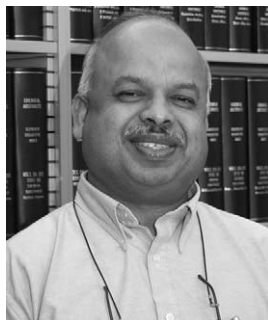
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Biographical Sketch



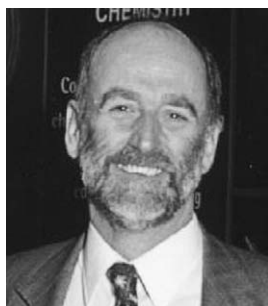
Ramiah Murugan was Born in Madurai, obtained BSc in chemistry from American College and MSc in chemistry from Madurai University. After 4 years working as a junior scientist at Madurai University, he joined Prof. Alan R. Katritzky's group in the Department of Chemistry at the University of Florida and obtained his PhD in 1987. He continued in Prof. Katritzky's group for 2 more years doing postdoctoral work in the area of high-temperature aqueous organic chemistry. He joined Reilly Industries in 1989 (currently it is Vertellus Specialties, Inc.) and grew with in the ranks from research chemist to currently senior research associate. His research interests include synthesis of intermediates for pharmaceuticals, agrochemical products, and performance products; mechanistic studies; catalysis; polymer chemistry; and process development. He has many patents and publications to his credit in the above-mentioned areas of interest.



Alan Katritzky was born in London, U.K. and educated at St. Catherine's College, Oxford, of which he became an Honorary Fellow in 2006. He was a Founder Fellow of Churchill College, Cambridge, and then founding Professor/Dean of the School of Chemical Sciences at the University of East Anglia, before crossing the Atlantic in 1980 to become Kenan Professor and Director of The Center for Heterocyclic Compounds at the University of Florida. He has researched, published, lectured, and consulted widely in heterocyclic chemistry, synthetic methods, and QSPR. He created the non-for-profit foundation ARKAT and since 2000 has organised the annual "Florida Heterocyclic and Synthetic Conferences" (Flohet), and publishes the "Archive for Organic Chemistry" (Arkivoc) completely free on the Internet at arkat-usa.org. His honors from 20 countries include 15 honorary doctorates.



Eric Scriven is a native of Wales, U. K. After working at BISRA and Esso Ltd, he attended the University of Salford and graduated in 1965. He obtained his M. Sc. from the University of Guelph, and his Ph.D. from the University of East Anglia (with Professor Katritzky) in 1969. After postdoctoral years at the University of Alabama and University College London, he was appointed Lecturer in Organic Chemistry at the University of Salford. There, his research interests centered on the reactivity of azides and nitrenes. While at Salford, he spent two semesters at the University of Benin, Nigeria. He joined Reilly Industries, Inc. in 1979 and he was Director of Research & Development from 1991 to 2003. He is currently at the University of Florida. He edited *Azides & Nitrenes* (1984), and he and Professor H. Suschitzky were founding editors of *Progress in Heterocyclic Chemistry*, which has been published annually since 1989 by the International Society of Heterocyclic Chemistry. He collaborated with Professors Katritzky and Rees as Editors-in-Chief of *Comprehensive Heterocyclic Chemistry II* (1996). Currently, he is Publishing editor of *Arkivoc*, an online journal of organic chemistry that is free to readers and authors.

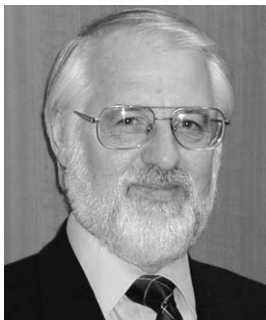


Richard Taylor is currently Professor of Organic Chemistry at the University of York, where his research focuses on the development of novel synthetic methodology and the synthesis of natural products and related compounds of biological/medicinal interest. The methodology is concentrated primarily on organometallic, organosulfur, oxidation and tandem processes, and the targets include amino acids, carbohydrates, prostaglandins and polyene and polyoxygenated natural products, particularly with activity as antibiotics and anti-cancer agents.

He is a graduate and postgraduate of the University of Sheffield (Ph.D. with Dr. D. N. Jones). He then carried out postdoctoral research at Syntex, California (Dr I. T. Harrison) and at University College London (Professor F. Sondheimer). His first academic appointment was at the Open University in Milton Keynes. This post gave Professor Taylor the opportunity to contribute to Open University textbooks, radio programs and television productions on various aspects of organic chemistry. He then moved to UEA, Norwich, where he established his independent research program, before taking up his present position in York in 1993.

Richard Taylor was Chairman of the Royal Society of Chemistry's Heterocyclic Group (2000-2001), President of the Organic Division of the Royal Society of Chemistry (2001-2004), and is currently President-Elect of the International Society of Heterocyclic Chemists. His awards

include the Royal Society of Chemistry's Tilden Lectureship (1999), the RSC Heterocyclic Prize (1999) and the RSC Pedlar Lectureship (2007). He is currently the UK Regional Editor of the international journal *Tetrahedron*.



Chris Ramsden was born in Manchester, UK in 1946. He is a graduate of Sheffield University and received his PhD (W. D. Ollis) in 1970 and DSc in 1990. After post-doctoral work at the University of Texas (M. J. S. Dewar)(1971-3) and University of East Anglia (A. R. Katritzky)(1973-6), he worked in the pharmaceutical industry. He moved to Keele University as Professor of Organic Chemistry in 1992. His research interests are heterocycles, *ortho*-quinones and three-centre bonds, and applications of their chemistry to biological problems.

13.13

Seven-membered Rings with Three Heteroatoms

1,2,3

A. Kiselyov and A. Khvat
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13.13.1 Introduction

The subject of 1,2,3-heterocyclic seven-membered ring system (triheterocepines) has been covered in CHEC(1984) (Volume 7, Chapters 5.18.7–5.18.9) and CHEC(1996) (Volume 9, Chapter 9.13). Both CHEC(1984) and CHEC(1996) can be found on-line. The present work is intended to update previous publications. Herein, we concentrate on the newly published synthetic methodologies, reactivity, and theoretical studies of the title scaffolds. At the beginning of every section, a brief update is presented on what has happened in a particular field since 1995 when CHEC(1996) was published. Additional literature that had not been covered in CHEC(1984) and CHEC(1996) will also be discussed. Where no new work has been reported in the literature since 1995, the relevant section heading has been omitted. Thus, all of the 12 standard headings used in this work do not appear for any of the heterocycles.

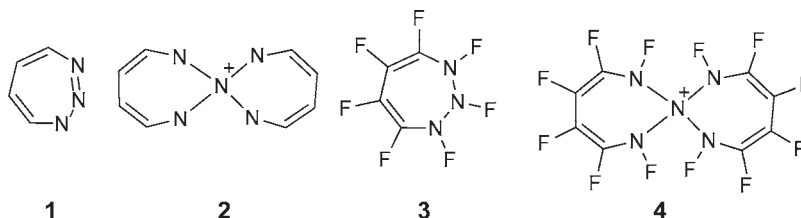
13.13.2 Triazepines

13.13.2.1 Introduction

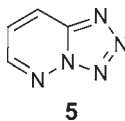
Concerning the theoretically accessible triazepine systems, the respective 1,2,3-analogues are the least studied. Despite several computational studies published since CHEC(1996), the synthesis of both monocyclic and fused 1,2,3-triazepines remains elusive.

13.13.2.2 Theoretical Methods

The Hückel anti-aromaticity versus Möbius aromaticity effects for the seven-membered systems **1** and **2** have been studied computationally using Gaussian98 at the closed shell B3LYP/6-31G(d) level <2003OBC182>. It was shown that Möbius aromaticity was preferred for the respective perfluorinated derivatives **3** and **4**.

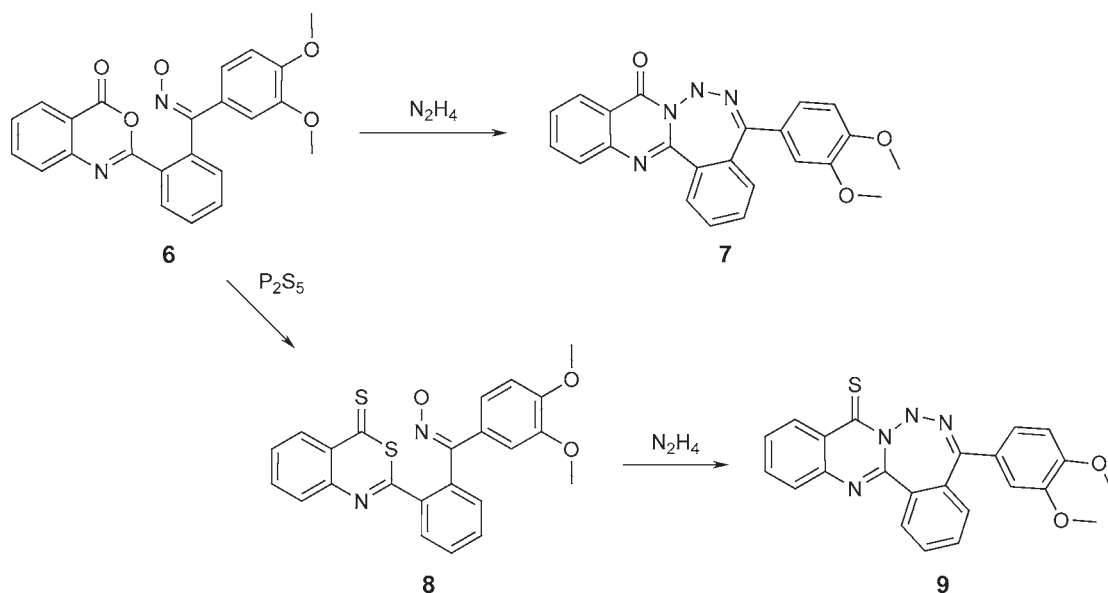


The parent 1,2,3-triazepine **1** was suggested as a possible product of a gas-phase photolysis of tetrazolo[1,5-*b*]-pyridazine **5** <2003PCP1051>; these authors further discussed the geometry of multiple electronic states for **5** under photolytic conditions.



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

Syntheses of several annulated 1,2,3-triazepine structures have been reported recently <2000EJC421>. Compound **7** (m.p. 245 °C, 68% yield) was obtained by reaction of benzoxazinone **6** with hydrazine hydrate in boiling ethanol (Scheme 1). The structure was confirmed by its IR [ν 1670 (C=O), 1620 (C=N), 3250 (NH) cm^{-1}], ^1H NMR (NMR – nuclear magnetic resonance), and combustion data. Furthermore, treatment of **6** with P_2S_5 in dry xylene resulted in the formation of **8**. Subsequent reaction of **8** with hydrazine hydrate in boiling ethanol gave **9** in a 50% overall yield. The reported infrared (IR) data for **9** are as follows: 1240 (C=S), 1640 (C=N), and 3250 (NH) cm^{-1} .

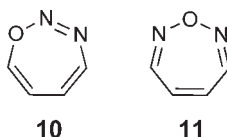


Scheme 1

13.13.3 Oxadiazepines

13.13.3.1 Introduction

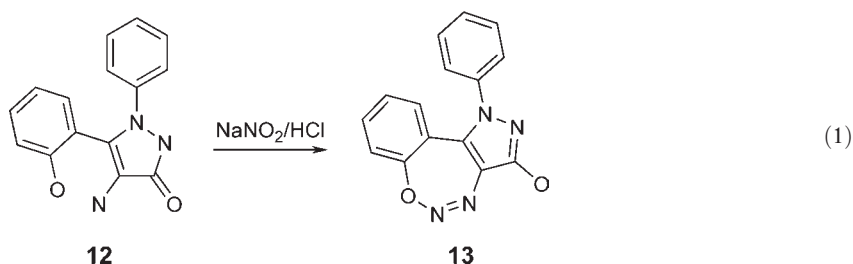
No significant progress toward the synthesis of oxadiazepines has been reported since the publication of CHEC(1996). The title molecules are rather obscure. Two possible structures, namely 1,2,3- **10** and 1,2,7-oxadiazepines **11** were suggested for this template.



13.13.3.2 Ring Syntheses by Transformation of Another Ring

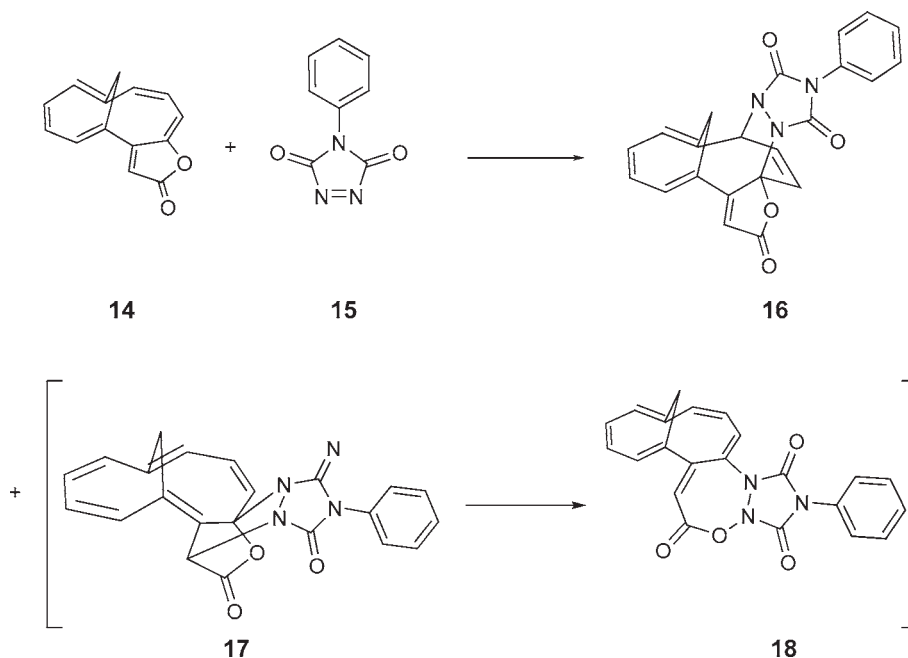
13.13.3.2.1 1,2,3-Oxadiazepines

The fused 1,2,3-oxadiazepine system has been accessed via the reaction of 1-phenyl-4-amino-5-(2-hydroxyphenyl)-3-pyrazolone **12** with hydrochloric acid and sodium nitrite [<1945JA102>](#) to give **13** that was characterized by melting point (245–250 °C) and combustion data ([Equation 1](#)).



The cycloaddition reaction of methanocycloundeca[*b*]furan-2-one **14** with **15** was described to yield 1,2,3-oxadiazepinone derivatives **18** (8% yield, red powder, m.p. 205 °C) [<1994H\(38\)629>](#). Structural assignment for **18** was

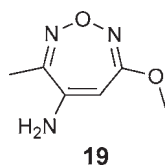
based on similarity of electronic and NMR spectra between **18** and **14** and observed m/z value of 252 [**14** + N=C=O] $^+$. Tentative mechanism of this conversion involved intermediary formation of **17** (Scheme 2).



Scheme 2

13.13.3.3 Important Compounds and Applications

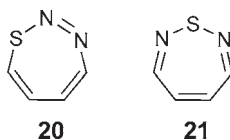
Considering the lack of reliable information on the synthetic approach to 1,2,3- and 1,2,7-oxadiazepine systems, it was surprising that **19** is available commercially from ChemStep. Unfortunately, synthesis of **19** was not described.



13.13.4 Thiadiazepines

13.13.4.1 Introduction

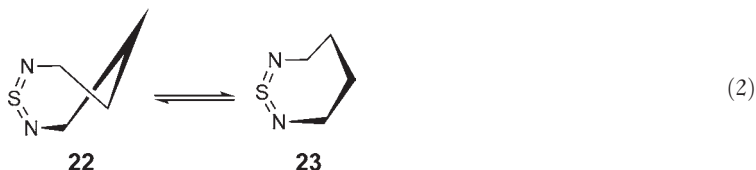
As stated in CHEC(1984) and CHEC(1996), both possible thiadiazepines systems **20** and **21** have been synthesized. The synthesis of 1,2,3-thiadiazepines, described in CHEC(1996), remains to be the only, to the best of our knowledge, publication available on this ring system. In contrast, however, the respective 1,2,7-thiadiazepines attracted significant interest due to their biological activity, particularly as HIV-1 protease inhibitors. This section is dedicated to the discussion of this 1,2,7-thiadiazepine template.



13.13.4.2 Theoretical Methods

13.13.4.2.1 1,2,7-Thiadiazepines

The modified neglect of diatomic overlap (MNDO) semi-empirical SCF MO calculations were used to investigate conformational properties of five-to-eight-membered cyclic sulfur diimides <1996JMT(364)79>. 3,4,5,6-Tetrahydro-1,2,7-thiadiazepine system was found to have two main conformations, namely envelope **22** and half-chair **23**, favoring conformer **22**. The calculated energy barrier for interconversion of **22** to **23** was reported to be 7.5 kJ mol^{-1} (Equation 2).

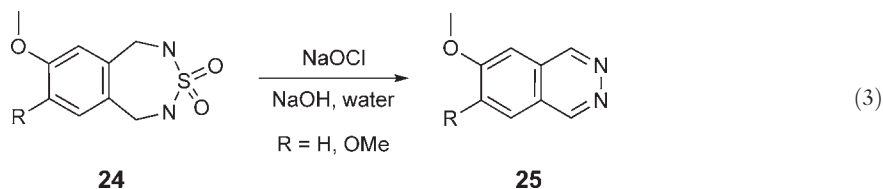


Several conformational studies along with the protein-binding experiments were published for 1,2,7-thiadiazepine HIV-1 protease inhibitors <1997JME885, 1999JME4054, 2001JME155, 2004JME5953, 2006JCI168>.

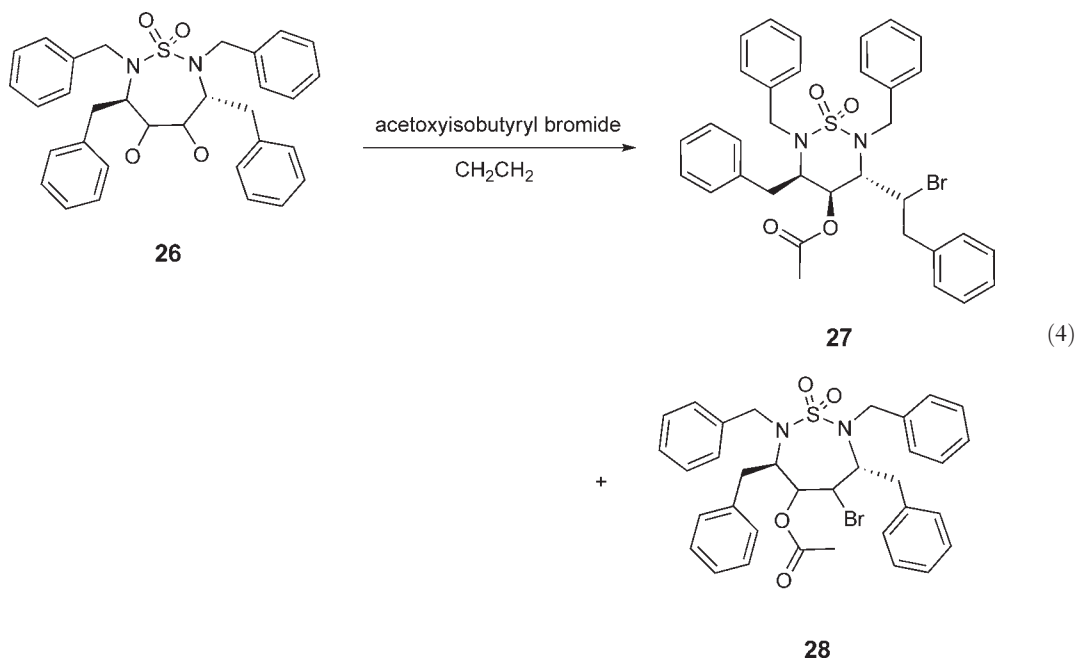
13.13.4.3 Reactivity of Nonconjugated Rings

13.13.4.3.1 1,2,7-Thiadiazepines

3,6-Dihydro-1,1-dioxothiadiazepines **24** were converted into corresponding phthalazines **25** by treatment with NaOCl in aq. NaOH in >90% yields <1997JKC677> (Equation 3).



1,1-Dioxothiadiazepine template **26** was also featured by Lucca <1998JOC4755>; specifically, **26** was converted into a *c.* 50/50 mixture of **27** and **28** by treatment with acetoxyisobutryl bromide (Equation 4).



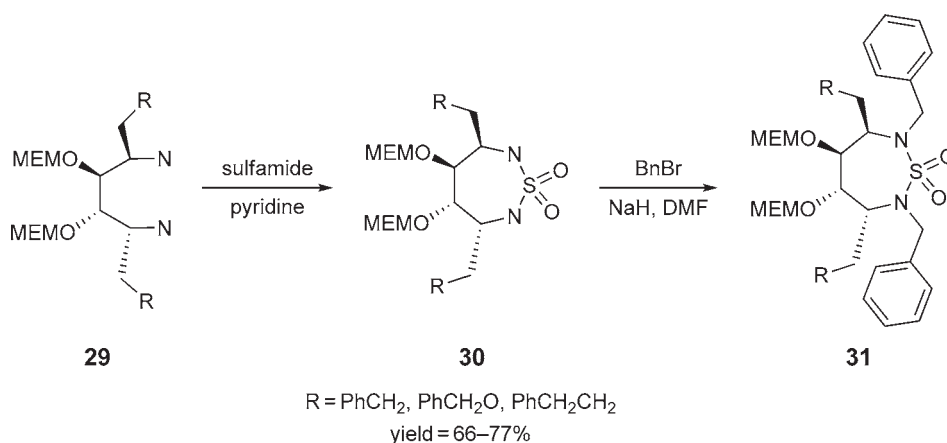
13.13.4.4 Reactivity of Substituents Attached to Ring Carbon or Heteroatoms

Numerous modifications of side chains in 1,2,7-thiazepines have been described [<1997JME885, 1999JME4054, 2000T9781, 2001JME155, 2002OL4673>](#). In general, synthetic protocols applicable to alicyclic sulfonamides were successfully used for the manipulation of substituents at the 1,2,7-thiazepine system. Representative examples include microwave-assisted synthesis and Pd-catalyzed amidation reactions have been described [<2006T4671>](#).

13.13.4.5 Ring Syntheses from Acyclic Compounds

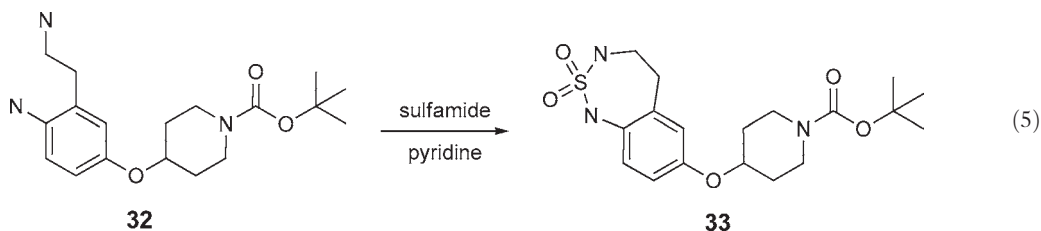
13.13.4.5.1 1,2,7-Thiadiazepines

Unsaturated 1,1-dioxo derivatives **30** were accessed in *c.* 60% yields via cyclization of mannitol derivatives **29** with sulfamide in pyridine [<1997JME885, 1999JME4054, 2001JME155, 2002OL4673>](#). As a part of a medicinal chemistry approach to HIV-1 protease inhibitors, the resulting products **30** were further alkylated with benzyl bromide in >90% yields (**Scheme 3**).

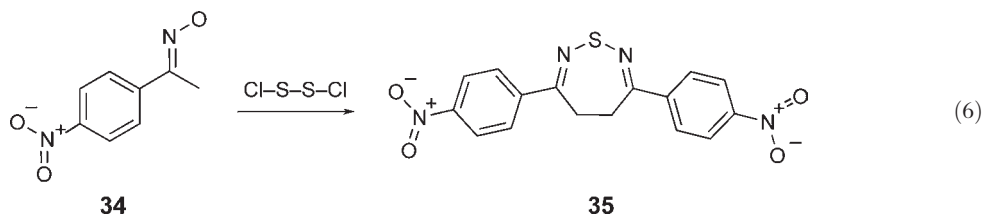


Scheme 3

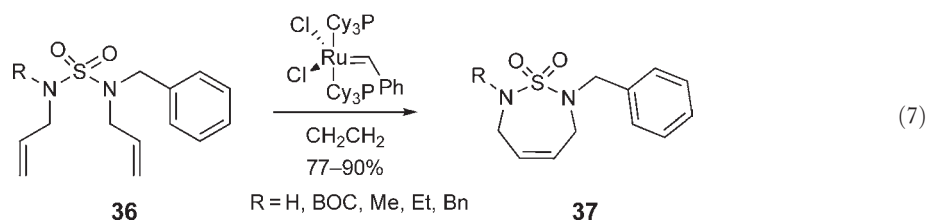
The same strategy was applied for the synthesis of annulated analogues **33** [<2003BMC367>](#) (Equation 5).



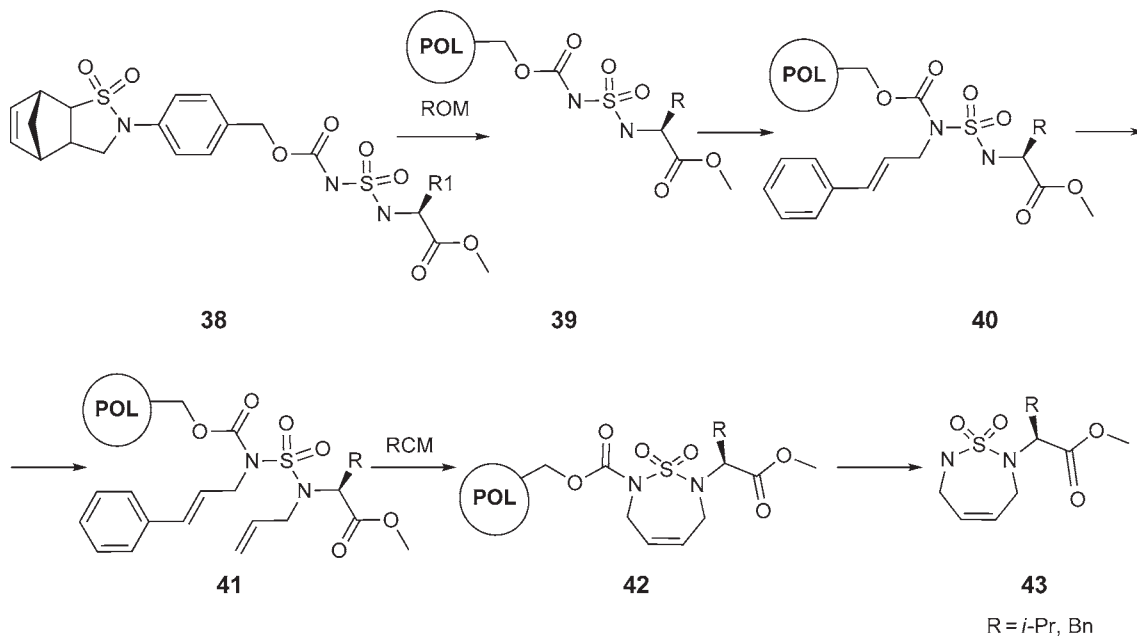
Reaction of oxime **34** with disulfur dichloride yielded **35** [<1997BSB605>](#) which formally was derived from two molecules of oxime and one sulfur atom (Equation 6).



Both the symmetric and unsymmetric derivatives of 1,1-dioxo-3,6-dihydrothiadiazepines **37** were synthesized in *c.* 90% yields from **36** employing a ring-closing metathesis (RCM) strategy (Equation 7) [<2000T9781, 2002OL4673, 2003OL3403, 2003T8901, 2004EJO800>](#).

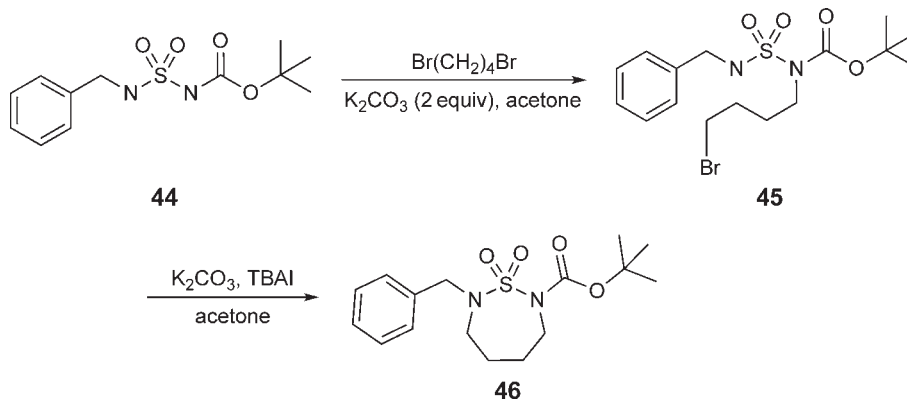


Ring-opening metathesis (ROM) oligomers were used as a soluble support for this reaction sequence [38–43](#) [<2003OL15>](#) with the yield 50–55% ([Scheme 4](#)).



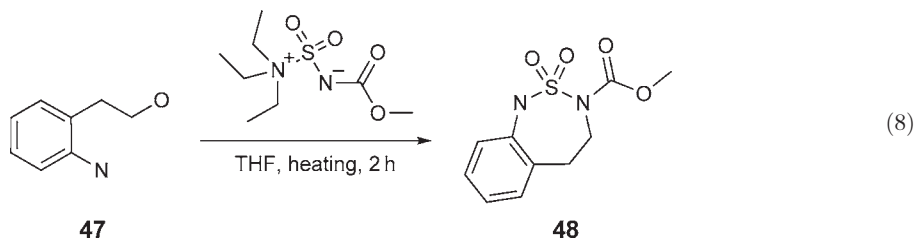
Scheme 4

The general method for the synthesis of cyclic sulfamides including the respective 1,1-dioxo-3,6-dihydro-thiadiazepines [46](#) from [44](#) has been described [<2003T6051>](#) ([Scheme 5](#)) in which the yield of the final step was 75%.



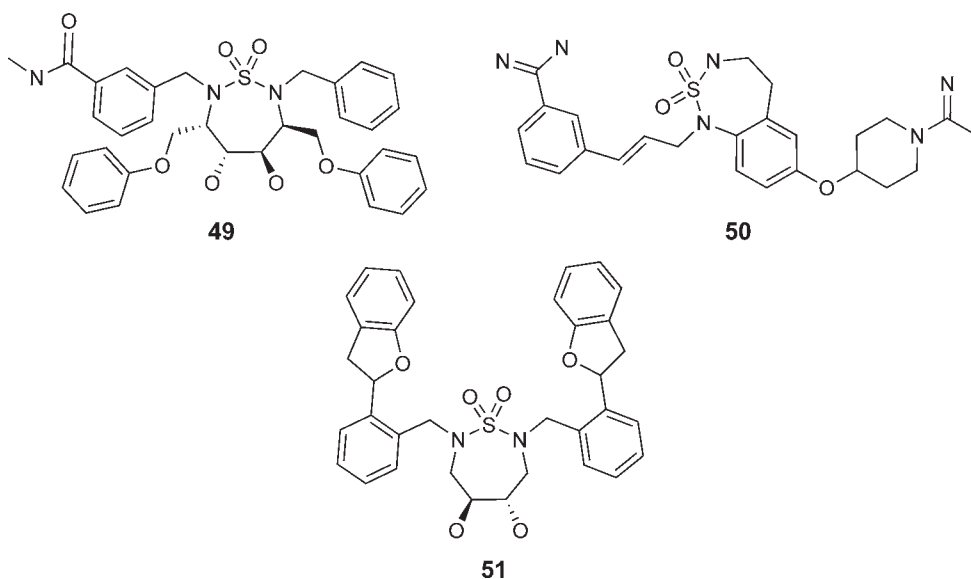
Scheme 5

Nicolaou *et al.* <2002AGE3866, 2004CEJ5581> introduced the Burgess-type reagent for the conversion of aromatic aminoalcohols **47** into cyclic sufamides **48** (Equation 8).



13.13.4.6 Important Compounds and Applications

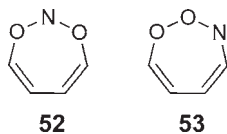
Derivatives of the 1,2,7-thiazepines **49–51** displayed promising inhibitory activity against HIV-1 and other proteases. Medicinal chemistry and binding data for these molecules have been summarized <1998JPP98012970, 2001JME155, 2005BMC755>.



13.13.5 Dioxazepines

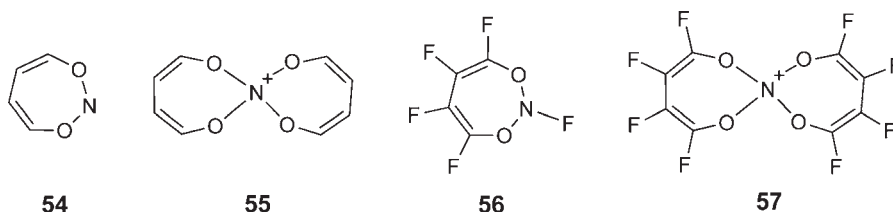
13.13.5.1 Introduction

Of the two possible structures for 1,2,3-heterotriepines with two oxygen and one nitrogen atoms, **52** and **53**, only the derivatives of 1,3,2-dioxazepine template **52** have been described. Several new synthetic protocols to access **52** have been introduced since the publication of CHEC(1996).



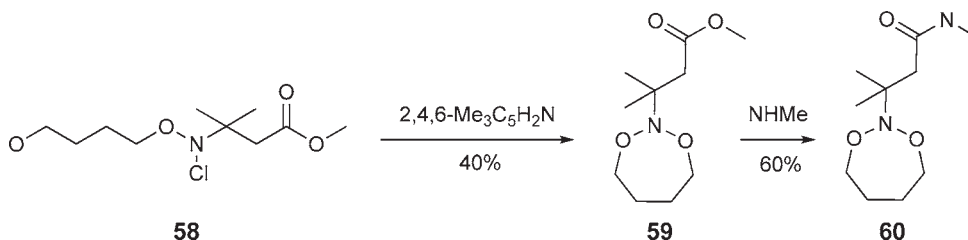
13.13.5.2 Theoretical Methods

Hückel anti-aromaticity versus Möbius aromaticity effects for the seven-membered systems **54** and **55** have been studied computationally using Gaussian98 at the closed shell B3LYP/6-31G(d) level <2003OBC182>. It was shown that the Möbius aromaticity was preferred for the respective perfluorinated derivatives **56** and **57**.



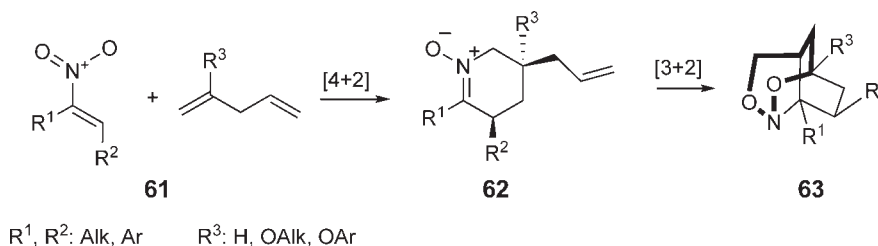
13.13.5.3 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

Perhydro-1,3,2-dioxazepines **59** and **60** <1996ZOR793> were obtained in moderate yields by a base-promoted cyclization of *N*-chloro-*O*-hydroxyalkylhydroxylamines **58** (Scheme 6).



Scheme 6

Several bridged templates that formally contain the 1,3,2-dioxazepine ring, for example, **63**, have been synthesized using inter[4+2]/intra [3+2] molecular cycloadditions of nitroalkenes <1995JA2100, 1997JOC4610, 2001CJC1606> (Scheme 7).

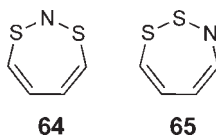


Scheme 7

13.13.6 Dithiazepines

13.13.6.1 Introduction

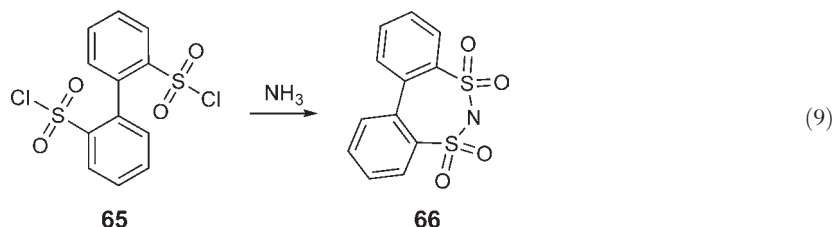
The 1,2,3-heterotriepines with two sulfur and one nitrogen atoms were not discussed in CHEC(1996). In this section, we describe synthetic information that became accessible during the last several years on dithiazepines **64** and **65**.



13.13.6.2 Ring Syntheses from Alicyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

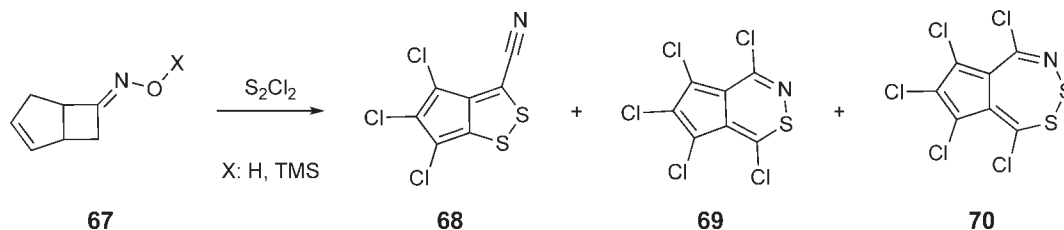
13.13.6.2.1 1,3,2-Dithiazepines

1,3,2-Dithiazepines were obtained in a good yield (75%) by treatment of bis-sulfochlorides with ammonia <1960JCS3063> (Equation 9).



13.13.6.2.2 1,2,3-Dithiazepines

The first derivative of the 1,2,3-dithiazepine template **70** was obtained as a minor product (<5% yield) of reaction between bicyclic oxime **67** and S_2Cl_2 in the presence of Hünig's base (Scheme 8) <1996JOC9178>. The structure of isolated dark-blue compound was confirmed by MS and NMR data. The compound **70** proved to be unstable and readily eliminated sulfur to yield **69**.



Scheme 8

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Biographical Sketch



Alexander Khvat, Senior Director of Chemistry at ChemDiv, Inc., has extensive experience in the area of the heterocycles and natural products chemistry. Dr. Khvat has completed his MS and Ph.D. studies in organic chemistry at Kharkov State University, Ukraine under supervision of Prof. V.D.Orlov and Dr. F.G.Yaremenko. After completion of his Ph.D. work he joined Hormone Synthesis Laboratory at Ukrainian Institute for Endocrinological Diseases Pharmacotherapy. In 1996 Dr. Khvat received Young Scientist Award from Royal Society of Great Britain and scholarship for postdoctoral research at Nottingham University, UK. In 1999 Dr. Khvat joined ChemDiv, Inc. in San Diego, CA.

The main interest of Dr Khvat research lays in chemistry of azaheterocycles and natural products. Dr. Khvat has over 7 years of industrial experience in medicinal and organic chemistry and has authored more than 20 publications in the areas of synthetic and medicinal chemistry. His work has resulted in 12 patents and patent applications.



Alex Kiselyov's, Executive VP of R&D at ChemDiv, Inc., main interest is in the area of lead discovery, with a focus on medicinal chemistry, chemoinformatics, and HTS. Alex received his B.Sc. from Moscow State University and M.Sc. from Zelinsky Institute of Organic Chemistry. Following doctoral studies at Georgia State University with Prof. Strekowski, he completed two postdoctoral appointments at University of Chicago and Columbia University. Alex's main interests include development of specific and dual small molecule modulators for kinase targets, chemokine receptors, and Hh/Wnt signaling cascades. Before joining ChemDiv, Inc., Alex was assistant vice president of Chemistry for ImClone Systems, Inc. Prior to ImClone, Dr. Kiselyov directed an oncology team and combinatorial chemistry efforts at Amgen, Inc.

Dr. Kiselyov has over 13 years of industrial experience in medicinal and organic chemistry and has authored more than 120 publications in the areas of synthetic and medicinal chemistry including oncology. His work has resulted in 26 patents and patent applications.

13.14

Seven-membered Rings with Three Heteroatoms 1,2,4

G. I. Yranzo and E. L. Moyano

Universidad Nacional de Córdoba, Córdoba, Argentina

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13.14.1 Introduction

The chemistry of seven-membered rings with three heteroatoms 1,2,4 has improved since CHEC(1984) was published. In the first volume, these compounds were included in Chapter 6.08 devoted to seven-membered rings with two or more heteroatoms and only few references on synthesis were reported. In CHEC-II(1996), a single chapter for these compounds mainly covered new synthetic methods, spectroscopy, and reactivity, but still there was a lack of activity reports.

In this chapter on seven-membered rings with three heteroatoms 1,2,4, new synthetic methods, theoretical calculations, and spectroscopy are described as well as some pharmacological activities recently reported.

13.14.2 Theoretical Methods

13.14.2.1 Triazepines

13.14.2.1.1 Monocyclic triazepines

13.14.2.1.1(i) Analysis of tautomerism

The relative stability of the different tautomers of the 3-thio-5-oxo- **1**, 5-thio-3-oxo- **2**, 3,5-dioxo- **3**, and 3,5-dithio- **4** derivatives of 2,7-dimethyl-1,2,4-triazepine (**Figure 1**) has been studied through the use of density functional theory (DFT) methods. The structure and vibrational frequencies of all stable tautomers and all the transition states connecting them have been calculated at the B3LYP/6-31G* level of theory. Final energies have been obtained in single-point B3LYP/6-31 + G(3df,2p) calculations <2002NJC711>.

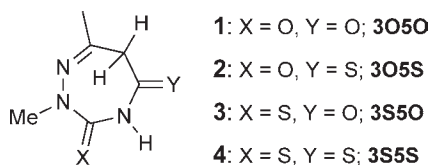


Figure 1

The results of the optimized geometrical parameters showed that substituent effects in triazepines strongly depend on their position in the ring. Thus, the structural characteristics of the ring are quite sensitive to substituents attached to positions C-3 and C-5 but almost independent of the nature of other substituents. For example, the N-2–C-3 and C-3–N-4 bond distances are longer for the 3-oxo than 3-thio derivatives. It is also worth mentioning that the intrinsic characteristics of the carbonyl and thiocarbonyl groups change slightly depending on their relative position in the ring. The corresponding C=O (C=S) bond is weaker (longer bond length) when these groups are attached at C-3. This can be explained by considering the resonance structures, as there are two resonance structures with delocalization of a negative charge in the heteroatom in position 3 and only one in position 5. This fact should be reflected in their reactivity and *a priori* it should be expected that the carbonyl or thiocarbonyl group attached to C-3 to be more basic than when attached to C-5.

The harmonic vibrational frequencies were also calculated; the C=O stretching frequency is characteristic of the relative position of the carbonyl group in the ring. This band appears at 1784 cm⁻¹ for C-3=O linkages but it is blue shifted by 40 cm⁻¹ when the substituent is at C-5. Something similar happens with C-3=S, but in this case the stretching mode appears coupled with other vibrational displacements. It is also interesting to note that the N–H and N-1–N-2 stretching frequencies show a certain dependence on the nature of the substituents (dioxo, oxo-thio, or dithio).

The structure and bonding of the radical cations were also studied in order to compare with the unimolecular fragmentation of these triazepines. It was found that the ionization of these compounds perturbs the bonding characteristics of the ring and that these perturbations are strongly dependent on the substituents attached to C-3 and C-5. When $X = Y = O$ (Figure 1), the weaker bonds are N-2-C-3, N-4-C-5, C-5-C-6, and, to a lesser extent, C-7-N-1. These results agree with the loss of $-NHCO$ and $-CH_2CO$ observed experimentally in previous work <1978OMS353>. When the heteroatom at C-3 is changed from O to S, the weaker bonds are N-4-C-5 and C-6-C-7, which is consistent with the loss of $-CH_2CO$; while in the mass spectrometric study, the same fragmentations as for the dioxo compound were reported <1978OMS353>. When the heteroatom at C-5 is S, the calculated weaker bonds are N-2-C-3 and N-4-C-5.

These authors also studied the prototropic tautomerism of the triazines depicted in Figure 1, which were shown to be the most stable tautomer in the gas phase. The enolization mechanism involving the atom attached to C-5 may come from a 1,3-H shift from the N-H group or a 1,3-H shift from the CH_2 group. Their results indicated that the first mechanism is thermodynamically favored when the heteroatom is sulfur while the second is favored when the heteroatom is oxygen. This difference was attributed to the relative strength of the bonds involved in the tautomerism. Besides, in 2 and 3 (with both heteroatoms), calculations showed that the mercapto group is thermodynamically more stable than the hydroxyl group. The relative stability of the corresponding enethiol tautomers was independent of the nature of the second substituent. In the cases of 1 and 4 where only mercapto or hydroxyl groups can be formed, tautomers at C-5 were slightly favored although the tautomerization barriers were higher than that corresponding to C-3. The double tautomeric structures (hydroxyl, mercapto, dihydroxy, or dimercapto) are the least stable structures.

The tautomerism of 4 (Figure 1) was also studied by UV-Vis (ultraviolet-visible) spectroscopy in polar aprotic solvents; the effect of added water, darkness, and indirect sunlight were also evaluated. The experimental spectroscopic results are discussed in Section 13.14.3.1.1(i). Theoretical calculations using ZINDO/S were performed to state the allowed absorption transitions <2005SAA875>. The five tautomeric structures of 4 as well as the calculated energies for each are depicted in Figure 2.

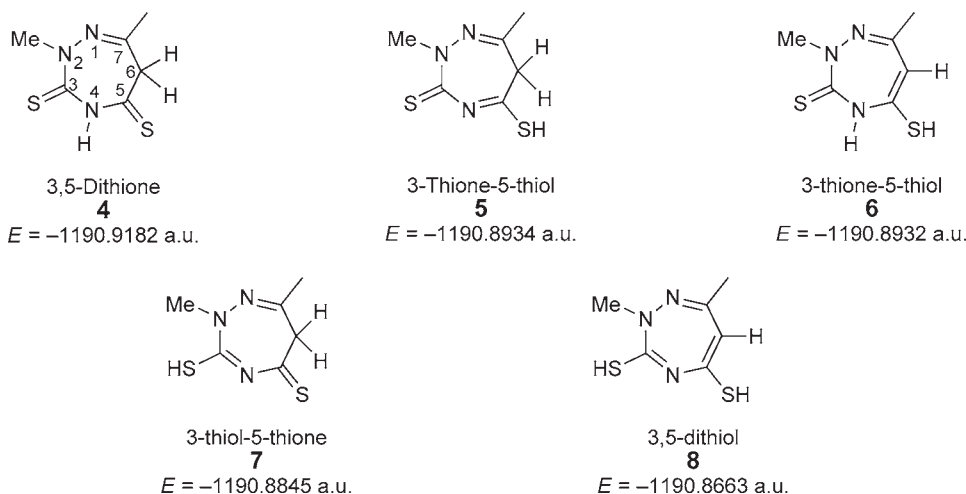


Figure 2

The superposition of the calculated transitions corresponding to all the tautomers (Figure 2) reproduces satisfactorily the entire experimental spectrum. The low-intensity transition observed experimentally in the range 350–450 nm is predicted as forbidden in ZINDO/S calculations. The comparison between these calculations allowed transitions and the experimental absorption spectrum (see Section 13.14.3.1.1(i)) leads to the assumption that the $\pi\pi^*$ band located between 250 and 330 nm belongs principally to tautomers 4 and 7 (thione form).

The effect of added water was also calculated for the five tautomeric forms. The results showed that the spectrum corresponded principally to the dithiol 8 (Figure 1) and monothiols 5–7, which overlap the best of the features enhanced on the spectrum measured at high water content solution. These results suggest that a specific solute–solvent interaction is present favoring the dithiols and monothiols isomers indicating that the hydrogen bond in solute–water is a 1 : n complex.

13.14.2.1.1(ii) Gas-phase basicity

The gas-phase basicity (GB) of 3-thio-5-oxo **1**, 5-thio-3-oxo **2**, and 3,5-dithio **4** derivatives of 2,7-dimethyl-[1,2,4]-triazepine (**Figure 1**) has been measured by means of Fourier transform ion cyclotron resonance (FTICR) mass spectrometry and complemented with theoretical calculations. The experimental FTICR results are discussed in [Section 13.14.4.1.1\(i\)](#). The structures and vibrational frequencies of all stable protonated tautomers and all transition states connecting them have been obtained by means of the B3LPY density functional method, together with 6-31G* basis set expansion. The final energies were obtained at the B3LYP/6-311 + G(3df,-2p) level (2002JPC7383).

The different tautomers of the compounds studied are depicted in **Figure 3**.

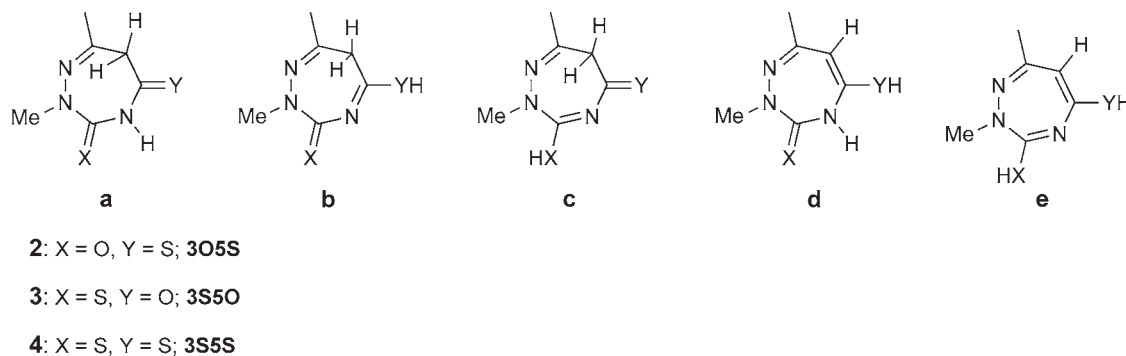


Figure 3

As was discussed in [Section 13.14.2.1.1\(i\)](#), the most stable tautomers are the oxo-thione and dithione compounds, and the barriers between the different tautomers are high enough to predict that these are the stable isomers in the gas phase [<2002NJC711>](#). The order of stability of the different triazepine thio derivatives (**3S5O** and **3O5S**) is **a > d > b > c > e** (**Figure 3**); whereas for **3S5S**, the stability order is **a > c > b > d > e**. As mentioned earlier, the energy gaps connecting the tautomers are very high, which reduces the protonation to two sites – the carbonyl and thiocarbonyl groups in two sites – the carbonyl and thiocarbonyl groups in **3S5O** and **3O5S** and the two thicarbonyl groups in **3S5S**. Theoretical calculations showed that when the heteroatom at position 3 is a sulfur atom, its protonation is systematically favored over the protonation at the heteroatom in position 5. In contrast, **3O5S** protonates preferentially at the heteroatom in position 5. This means that these triazepines behave as sulfur bases in the gas phase, although the active center depends on the nature of the heteroatom at position 3. These facts were confirmed by natural bond orbital (NBO) analysis of **3S5S**, which showed that the net charge in the sulfur in position 3 (−0.325) is much more negative than the net charge on the sulfur at position 5 (−0.153). Besides, the C=S bond length of the thiocarbonyl group at position 3 (1.674 Å) is longer than the thiocarbonyl group attached to position 5 (1.653 Å). The estimated proton affinities are: **3S5O** (215.2 kcal mol^{−1}), **3O5S** (206.8–213.5 kcal mol^{−1}), and **3S5S** (214.3–217.4 kcal mol^{−1}). The calculated proton affinity (PA) for **3S5O** is in agreement with the experimental result (see [Section 13.14.4.1.1\(i\)](#)), whereas, those of **3S5O** and **3S5S** underestimate the corresponding experimental value. As B3LYP/6-311 + G(3d,2p) proton affinities usually overestimate the experimental values, the aforementioned results seem to indicate that for the latter two compounds a different (more stable) protonated species is being observed in the FTICR experiments. This more stable tautomer was explained by the formation of hydrogen-bonded complexes between the neutral and protonated forms.

13.14.2.1.2 Fused triazepines

13.14.2.1.2(i) Conformational study

With the idea that biological activity of benzotriazepines depends not only on the pharmacophoric group but on the conformation of the seven-membered ring as well, some theoretical calculations of the conformational changes of some 1,3,4-benzotriazepin-5-ones **9–12** were performed. The thermodynamic parameters obtained from nuclear magnetic resonance (NMR) experiments with the results of theoretical (molecular mechanics MMX, semiempirical AM, PM3, and MNDO MO) calculations and X-ray measurements were compared [<1997JOC5089>](#) (MNDO = modified neglect of diatomic overlap). The compounds under study are shown in **Figure 4**.

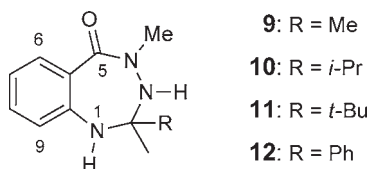


Figure 4

In the solid state, **9** adopts a cycloheptadiene-like boat (**B**) conformation where six atoms are almost coplanar. The calculated values using AM1, PM3, and MNDO MO agree with the X-ray results. The interconversion of conformation **B** to a different **B'** form was calculated to ascertain the lowest-energy pathway. From the different methods, AM1 best reproduced the energy barrier interconversion when compared with the experimental NMR measurements <1997JOC5080>. The calculated heats of formation (ΔH_f°) of the **B** and **B'** forms of **9–12** (Figure 4) were best reproduced by the PM3 rather than by the AM1 and MNDO calculations for **10** and **11**. The experimental results indicated that the **B'** conformation is favored. In the case of **9** and **12**, both PM3 and MNDO gave good results in agreement with the experimental results.

As a conclusion, only the combined experimental (1-D and 2-D NMR techniques and X-ray spectroscopy) and computational (AM1, PM3, and MNDO MO calculations and MMX molecular mechanics) techniques can give good insight into the ground state structures and dynamic interconversion processes involved. Besides, both MMX molecular mechanics and semiempirical PM3, AM1, and MNDO calculations showed a close, qualitative picture of the energy profiles of the possible interconversion pathways for these compounds, but only the PM3 calculations gave a reasonable agreement with the experimental estimates for the ΔG° values in **9–12**. Finally, PM3, AM1, and MNDO calculations satisfactorily reproduced both energy barriers and conformational energy differences for the studied compounds.

13.14.3 Experimental Structural Methods

13.14.3.1 Triazepines

13.14.3.1.1 Monocyclic triazepines

13.14.3.1.1(i) Analysis of tautomerism; spectroscopic study

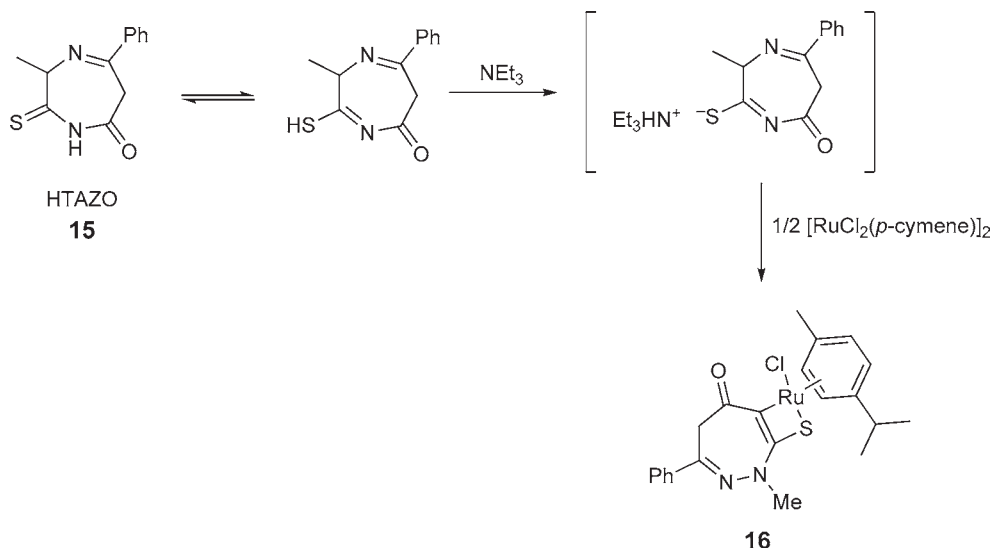
Theoretical calculations depicted in Section 13.14.2.1.1(i) were complemented with experimental measurements of UV–Vis spectroscopy to determine which of the different tautomers of 3,5-dithio-2,7-dimethyl-[1,2,4]-triazepine **4** (Figure 1) are present in different solvents and ambient conditions <2005SAA875>. The results showed that in nonpolar solvents (MeCN), the most stable tautomeric forms seem to be the dithione form **4** followed by the isomers **6** and **7**. The experimental spectrum showed three parts: the first was located between 350 and 450 nm, $\log \epsilon$ 2.72 at 400 nm and $\log \epsilon$ 3.37 at 360 nm, and appears to be composed of one or two $n\pi^*$ bands. The second part of the spectrum located between 250 and 350 nm was a $\pi\pi^*$ band, $\log \epsilon$ 4.46 at 290 nm. The third region below 250 nm was composed of two $\pi\pi^*$ bands located ca. 230 and 210 nm, $\log \epsilon$ 3.92 at 230 nm and $\log \epsilon$ 4.17 at 210 nm, respectively.

When the solvent cage contained more than 15% water, hydrogen bonding interactions shifted the tautomeric equilibrium to the thiol tautomers. The supermolecule solute–water seemed to be of 1:*n* type. Standing at ambient laboratory conditions in the dark favored the dithione tautomeric form, while indirect sunlight favored the monothiol and dithiol.

13.14.3.1.1(ii) Crystal structure

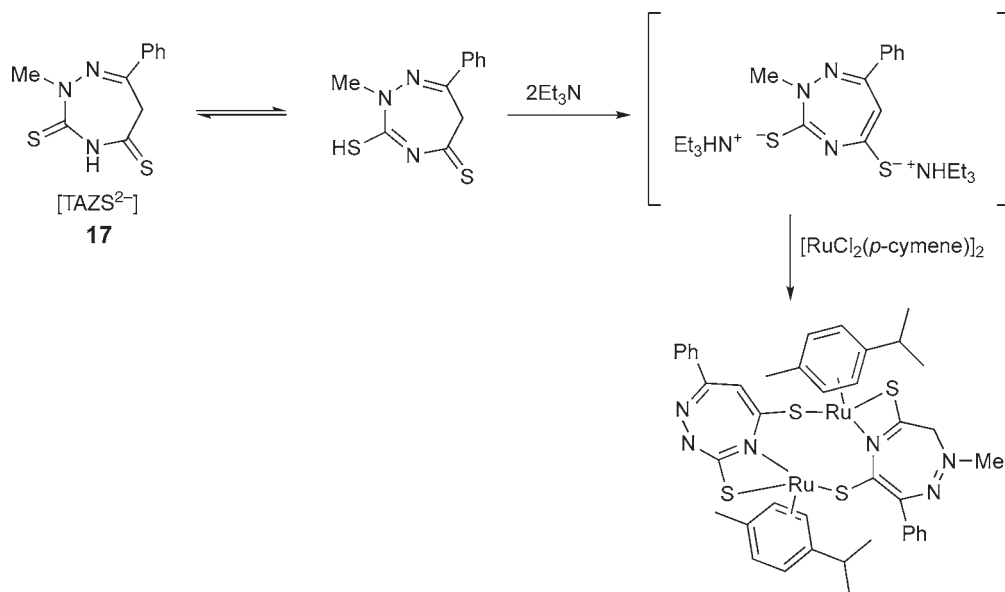
The crystal structure of 2-methyl-7-phenyl-3,5-dithio-3,4,5,6-tetrahydro-2*H*-1,2,4-triazepine **13** has been described <1995AXC2066>. This study was performed to solve a spectroscopic problem in its synthesis via the reaction of 2-methylthiosemicarbazide and ethyl benzoylacetate. This reaction could afford two compounds, **13** and/or 2-methyl-5-phenyl-3,7-dithio-2,3,6,7-tetrahydro-2*H*-1,2,4-triazepine **14**. The NMR spectrum could not resolve this question, so crystal structure analysis was conducted. The crystallographic analysis showed that the condensation of ethyl benzoylacetate with 2-methylsemicarbazide took place through the attack of the hydrazine group to the ketonic carbonyl group, thus affording **13**. The crystal structure also showed that the molecules formed a dimer with two hydrogen bonds.

The first structural example of a transition metal complex containing a 1,2,4-triazepine ligand has appeared [<2000CSC315>](#). Thus, [chloro(η^6 -*p*-cymene)(2-methyl-5-oxo-7-phenyl-5,6-dihydro-2*H*-1,2,4-triazepine-3-thiolato- $\kappa^2 N^4, S$)ruthenium(II)] complex was synthesized from the reaction of (*E*)-2-methyl-7-phenyl-3-thioxo-3,4-dihydro-2*H*-1,4-triazepin-5(6*H*)-one **15** with [Ru(*p*-cymene)Cl₂]₂ in 2-propanol in the presence of triethylamine. The 1,2,4-triazepine ligand is coordinated to the metal center through the N-4 and S atoms, forming an unusual four-membered chelate ring **16**. The mechanism of formation of this complex [<2001JOM265>](#) is described in [Scheme 1](#).



Scheme 1

The crystal structure has two similar molecules in its asymmetric unit pseudo-centrosymmetrically arranged, but no additional crystallographic symmetry was found. Both molecules have the same arrangement and have very close geometries. When O is changed with S, [(*E*)-2-methyl-7-phenyl-2*H*-1,2,4-triazepine-3,5(4*H*,6*H*)-dithione] **17**, the two chlorine atoms are displaced from the complex precursor to afford a good yield of binuclear [Ru(*p*-cymene)TAZS]₂ (TAZS is TAZSH₂ without 2H, in the Ru complex) [<2001JOM265>](#). The mechanism of formation of this complex is depicted in [Scheme 2](#).



Scheme 2

The ^1H NMR spectra as well as X-ray structural analysis confirmed the structures of the different complexes described in **Schemes 1 and 2**. In the case of the Ru-TAZS complex, the asymmetric unit is built up from two halves of the molecule and a CHCl_3 solvent molecule. Each half is linked through the S-5 atom to its related centrosymmetry counterpart, thus resulting in the occurrence of two dinuclear complexes per cell.

13.14.3.2 Thiadiazepines

13.14.3.2.1 Fused thiadiazepines

13.14.3.2.1(i) Crystal structure

Among fused thiadiazepines, 6-methyl-3,8-diphenyl-5*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[4,3-*b*][1,3,4]thiadiazepine **18** (**Figure 5**) belongs to the class of MRE (the most representative adenosine receptor antagonists) analogs, which have shown the best results to date in terms of $\text{A}_{2\text{A}}$ and A_3 antagonistic affinity and selectivity. For this reason, its crystal structure was investigated (2005AXE1466).

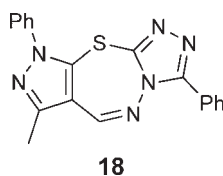


Figure 5

The experimental crystal structure determination showed that this molecule has bond distances with unexpected values, which were not consistent with classically localized bond-valence forms; in particular, the $\text{C-9}=\text{N-4}$ and $\text{C-12}=\text{N-6}$ bonds, which are both formally double bonds, and not of equal length. In addition, the N-1-N-2 , N-3-N-4 , and N-5-N-6 bonds were expected to be shorter than the C-N single bonds, C-1-N-3 , C-2-N-3 , and C-11-N-5 . In fact, none of the former three is shorter than any other of the latter three. They are shorter than the C-12-C-10 bond in the ring system. The bond distances in C-11-S-1-C-1 fragment are normal for their types. These two C-S bonds have effectively ideal lengths and are in the normal range.

The pyrazole and triazole rings are not coplanar, but make an angle of $50.1(2)^\circ$ with each other, while the seven-membered ring adopts a half-chair conformation in which the atoms S and N-4 are out of the plane of the C atoms. In order to reduce steric hindrance with the central ring systems, the phenyl ring C-3-C-8 makes a dihedral angle of $24.8(2)^\circ$ with the triazole ring and the phenyl ring C-14-C-19 makes an angle of $42.4(2)^\circ$ with the pyrazole ring; thus, they are not conjugated with these heterocyclic rings.

In the crystal structure of **18**, the molecules are interconnected by $\text{C-H}\cdots\text{N}$ hydrogen bonds.

13.14.4 Thermodynamic Aspects

13.14.4.1 Triazepines

13.14.4.1.1 Monocyclic triazepines

13.14.4.1.1(i) Gas-phase basicity

The experimental GBs of **2–4** were determined from equilibrium proton-transfer reactions conducted in a modified Fourier transform ion cyclotron resonance (ICR) mass spectrometer using two standard reference bases (2002JPC7383). The experimental PAs are: **3S5O** ($213.8 \text{ kcal mol}^{-1}$), **3O5S** ($211.3 \text{ kcal mol}^{-1}$), and **3S5S** ($215.2 \text{ kcal mol}^{-1}$). As stated when the theoretical calculations were described (**Section 13.14.2.1.2**), the calculated PA of **3S5O** ($215.2 \text{ kcal mol}^{-1}$) is in good agreement with experimental value, but those of **3O5S** ($206.8\text{--}213.5 \text{ kcal mol}^{-1}$) and **3S5S** ($214.3\text{--}217.4 \text{ kcal mol}^{-1}$) are less than experimental results. These facts were explained by formation of more stable different protonated species, observed in the FTICR experiments. Calculations showed that these structures (**Figure 6**) could only be formed by hydrogen-bonded clusters between the corresponding neutral and protonated tautomer.

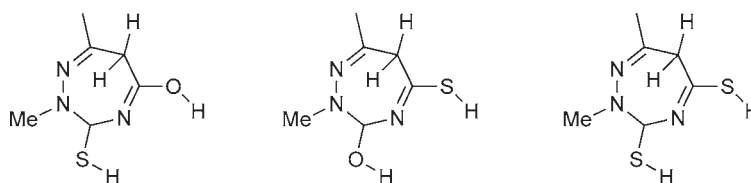
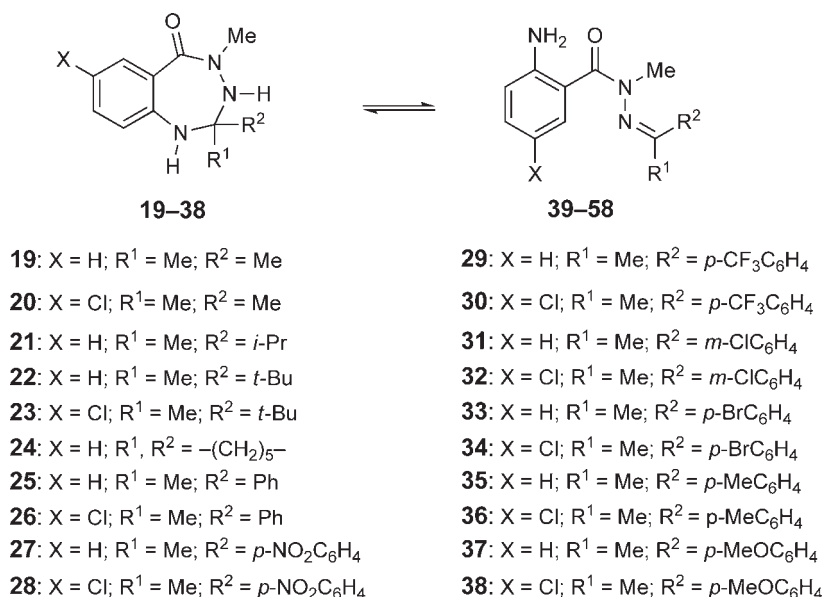


Figure 6

13.14.4.1.2 Fused triazepines

13.14.4.1.2(i) Conformational study

The stereochemistry and conformational behavior of a series of 20 2-methyl-2-alkyl(aryl)-4-*N*-methyl-1,2,3,4-tetrahydro-5*H*-1,3,4-benzotriazepin-5-ones **19–38** and their open-chain hydrazone isomers **39–58** (Scheme 3) in various solvents were studied by 1-D and 2-D NMR techniques in the temperature range from 193 to 410 K <1997JOC5080>. The authors wanted to establish the species present in solution and to study the effect of the different substituents in the ring/open-chain equilibrium.



Scheme 3

The ¹H and ¹³C NMR spectra of **19–22** showed peaks corresponding to three different compounds, one ring (R) and two open-chain (O1 and O2) forms. Within the temperature range examined, three dynamic processes were observed for **19**: (1) a rapid ring interconversion affecting mainly N-3 and C-2 and the respective methyl groups with an energy barrier of ca. 13.0 kcal mol⁻¹ at *T*_c = 273 K and freezing out at 233 K; (2) ring/open-chain rearrangement with an energy barrier higher than 13.0 kcal mol⁻¹ and with Δ*G*^o of 2.3 kcal mol⁻¹ in favor of the ring form; and (3) a rapid (on the NMR timescale) N-3 nitrogen inversion process with an energy barrier lower than 13.0 kcal mol⁻¹.

The ring/open and open/open rearrangements of **20** appeared to be much slower than those of **19**, since the proportion of open form was still increasing after a week. The ¹H and ¹³C NMR spectra of **21** and **22** were rather complex. They were interpreted in terms of a superposition of the three subspectra corresponding to one ring and two open forms, the latter being favored for **22**. Besides, it was concluded that the favored ring form of **21** and **22** in solution was the inverted boat in which the (C-2)-methyl group orientated between the (N-4)-methyl and bulky alkyl groups. On increasing the temperature from 293 to 323 K, the population of the ring form in **21** decreased from

ca. 70% to 62%, mainly at the expense of the major open form. Heating a sample of **22** in DMSO- d_6 caused a more drastic change in population ratios, and only one set of signals for the open forms was detected at 433 K (DMSO = dimethyl sulfoxide).

The time-dependent ^1H NMR spectrum of **22** provided an insight into the thermodynamic features of the ring/open-chain ratio of ca. 1:4 after a week. The energy barriers of the ring/open-chain and the ring inversion processes of **22** were estimated to be higher than those for **19–21**.

A small change in the ring/open-chain ratio was observed for **23**, which was attributed to the electronic effect of the (C-7)-chlorine, as in **20**. The NMR spectra of **24** were similar to those of **19**.

Compound **25** belongs in the series **25–38** with a phenyl or aryl group at C2. At room temperature, all of these molecules seem to be even more flexible than **19–24** and undergo the same complex rearrangement discussed for **19–24**. At room temperature, fast rearrangements take place including pseudorotation of a boat form to an inverted boat form, with exclusive predominance of the former. The time-dependent changes observed mainly in the ^1H NMR spectra of **25** within a period of more than a month clearly showed much slower rearrangements. Below room temperature, **19** was found only in the ring form, whereas **25** underwent a *trans*-(*E*)/*cis*-(*E*) transformation with $\Delta G^\ddagger$ of ca. 12.8 kcal mol $^{-1}$ at $T_c = 253$ K, lower than in the case of **19–24**. The thermodynamic behavior of the open forms of **25** was explained in terms of changes in their electronic properties relative to **19–24** and the conformational behavior of the ring form(s) was explained in terms of the steric effect caused by the phenyl substituent.

Compounds **26–38** were studied to see the influence of electron-withdrawing and -donating groups on the aryl ring(s) upon the rearrangement processes. As for **7**, the initial state of the complex equilibrium favors the ring boat (R1 and R2) form(s) in rapid exchange and the *trans*-(*E*) open-chain isomer. The relative amounts of these forms vary essentially with the substituents. Compounds **27–34** bearing electron-withdrawing groups (EWGs) displayed an easier amide bond and more difficult C=N rotation than in **25** and **35–38**. As to the ring forms, an initial preference of R1 over O1 (ratio ca. 2:1) and the absence of the R3 conformer were noted for **27–34**. Only for **27** and **28** were two different ring forms observed just after dissolution and were assigned to the boat and inverted boat forms. In general, a reduction in the electron-withdrawing influence and an increase in the electron-releasing power of the substituents when going from **27** to **38** favored the (N-3)-inverted boat (R3) form.

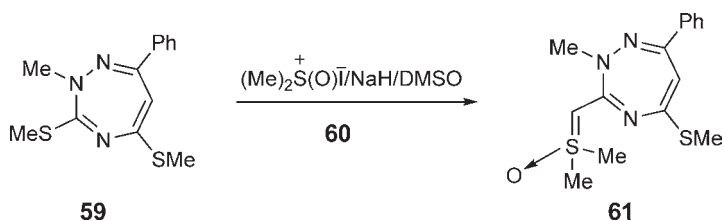
13.14.5 Reactivity of Substituents Attached to Ring Carbon Atoms

13.14.5.1 Triazepines

13.14.5.1.1 Monocyclic triazepines

13.14.5.1.1(i) Reaction with trimethyloxosulfonium iodide

The reaction of (1*E*,3*E*,5*E*)-2-methyl-3,5-bis(methylthio)-7-phenyl-2*H*-1,2,4 triazepine **59** with trimethyloxosulfonium iodide **60** was described <2000MOL186>. This reaction is depicted in **Scheme 4** and was performed under inert atmosphere using standard vacuum line techniques. Trimethyloxosulfonium iodide was suspended in anhydrous DMSO and sodium hydride was added at room temperature. The mixture was stirred and cooled to 10°C before adding rapidly a solution of **59** in anhydrous DMSO. After stirring for 48 h at room temperature the reaction mixture was poured in cold water and extracted with chloroform. The product was identified as 2-methyl-5-methylmercapto-3-dimethylsulfoxymethine-7-phenyl-1,2,4-triazepine **61**, which was obtained, in 85% yield, as an orange solid after recrystallization from carbon tetrachloride.

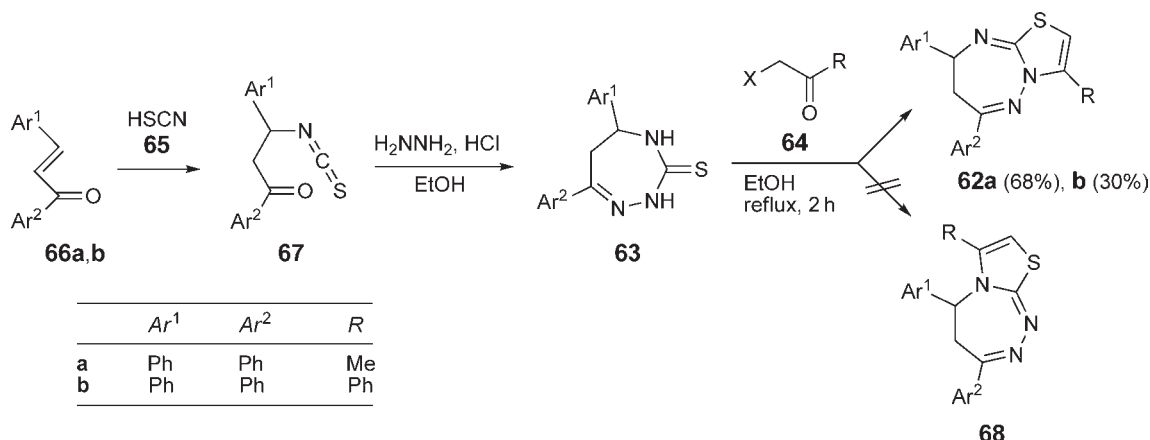


Scheme 4

13.14.5.1.2 Fused triazepines

13.14.5.1.2(i) Reaction of 1,2,4-triazepine-3-thiones with 2-haloketones

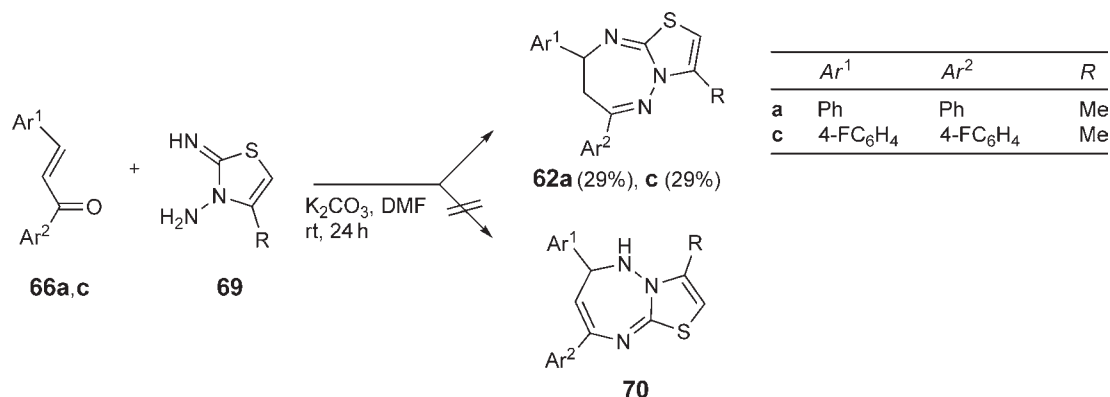
The synthesis of diaryl-thiazolotriazepines **62** from the reaction of 1,2,4-triazepine-3-thiones **63** (1.8 mmol) with 2-haloketones **64** (6.25 mmol) in ethanol under reflux for 2 h was described [<1999T5909>](#) with the goal of creating new immunomodulating agents (**Scheme 5**). The starting triazepines were prepared by the addition of thiocyanic acid **65** to the chalcones **66** according to an already known method, followed by reaction of the intermediate **67** with hydrazine.



Scheme 5

Notably, two isomeric products can be generated. The usual infrared (IR) and mass spectra as well as ^1H and ^{13}C NMR chemical shifts could not define which isomer was formed. The authors used different NMR techniques, such as 2-D heteronuclear multiple bond correlation (HMBC) experiments and phase-sensitive nuclear overhauser enhancement spectroscopy (NOESY) measurements to elucidate the product's structure.

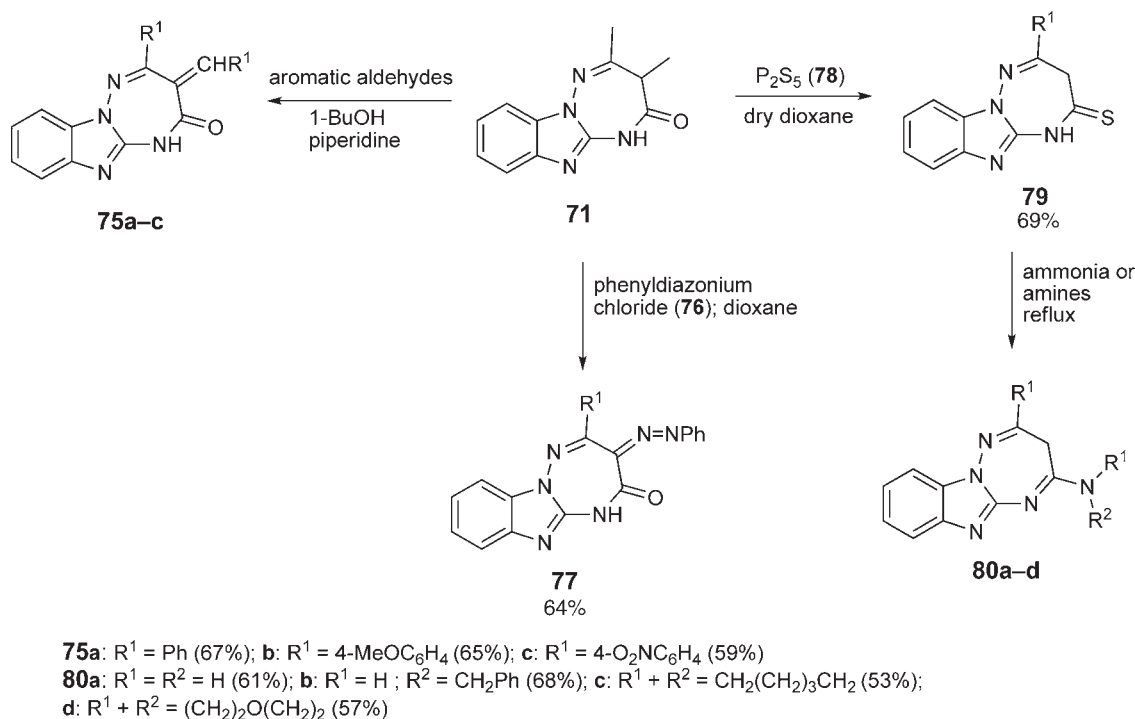
With the idea of obtaining **62** and **68** (**Scheme 5**) by a different methodology, different reactions were conducted. First, **62**, described in **Scheme 6**, was obtained by addition and condensation of the same chalcones **66** with 3-amino-2-imino-4*R*-thiazolines **69**. Under basic conditions, a single product was isolated and shown to be identical with the compound obtained in reaction described in **Scheme 5**. The alternative structure **70** was ruled out by the NMR spectra.



Scheme 6

13.14.5.1.2(ii) Reactions with electrophilic and nucleophilic reagents

Reactions of 5*H*-2-methyl-1,2,4-triazepino[2,3-*a*]benzimidazol-4-one **71**, prepared by reaction of 1,2-diaminobenzimidazole **72** with acetoacetic ester **73**, with different reagents was described, in the search of new heterocycles with biological activity <2002CHE598>. When lactam **71** was treated with aromatic aldehydes in boiling 1-BuOH with addition of piperidine **74**, 5*H*-3-arylidene-2-methyl-1,2,4-triazepino[2,3-*a*]benzimidazol-4-ones **75a-c** were obtained (Scheme 7). Coupling lactam **71** with phenyldiazonium chloride **76** in dioxane afforded the 3-phenylazo-substituted tricycle **77**. When **71** was treated with phosphorus pentasulfide **78** in boiling dioxane or pyridine, its thio analog **79** was obtained. The reaction proceeded most efficiently when lactam **71** was refluxed with twofold excess of **78** in dry dioxane. These thiones **79** react with ammonia and amines by nucleophilic substitution. When **79** was refluxed with ammonia, benzylamine, piperidine, or morpholine, the 4-amino-substituted tricycles **80a-d** were obtained. All the described compounds were identified by NMR, mass spectrometry, and IR spectroscopy.



Scheme 7

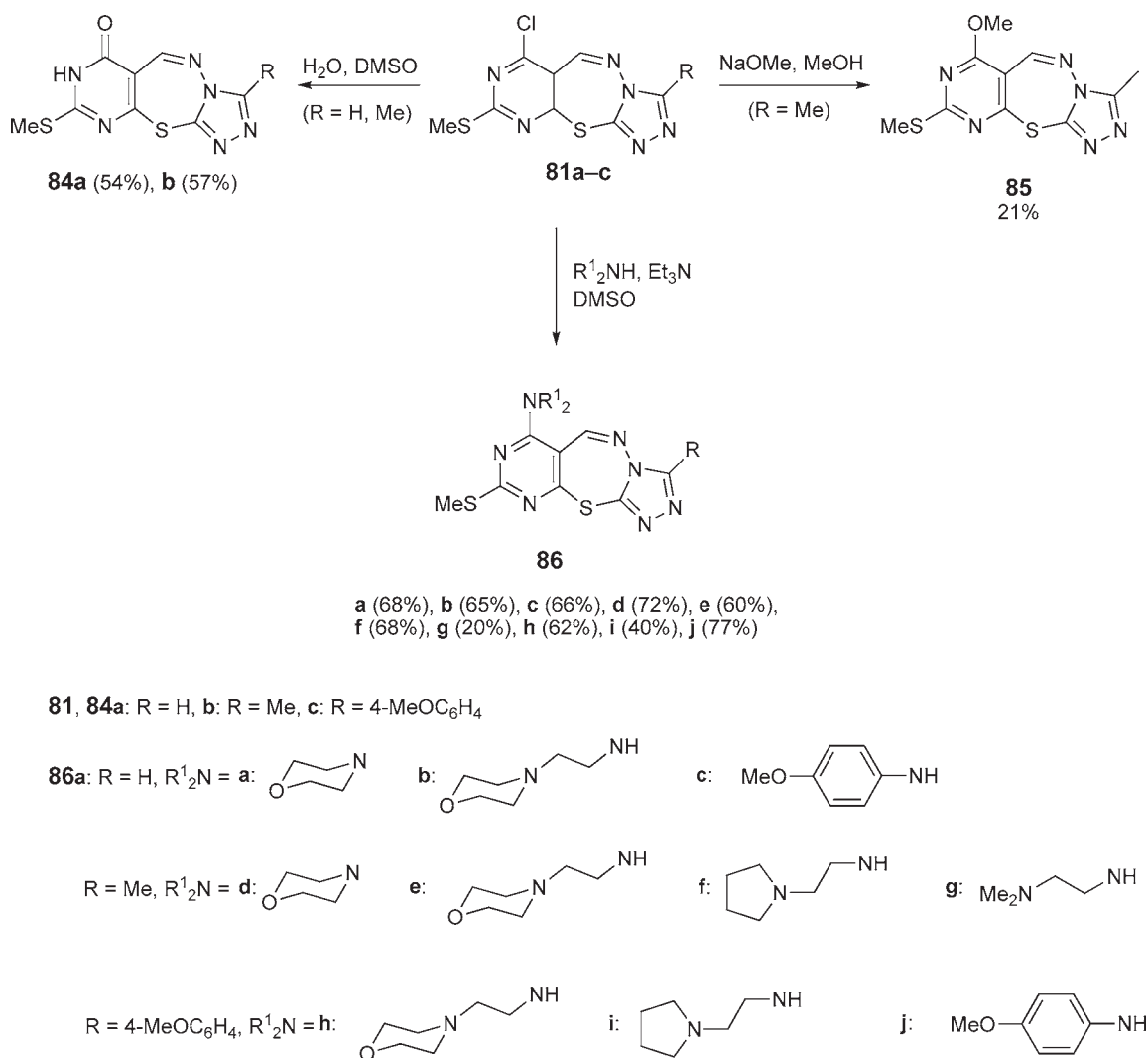
13.14.5.2 Thiadiazepines

13.14.5.2.1 Fused thiadiazepines

13.14.5.2.1(i) Reactions with nucleophiles

The reactions of 7-chloro-pyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazepines **81a-c** with different nucleophiles were described in order to obtain new derivatives with possible antitumor activity <2003MI46>. The substituted **81a-c** were prepared by cyclocondensation of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde **82** with the corresponding 3-substituted 4-amino-1,2,4-triazole-5-thiones **83**. The different reactions as well as the corresponding yields are described in Scheme 8. Interestingly, hydrolysis occurred even during ^1H NMR experiments in DMSO at 80 °C.

Other reactions of 7-chloro-9-methylthio-3-phenylpyrimido-[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine **87** with nucleophiles <2003CHE1079> have been described. The starting material was synthesized by cyclocondensation

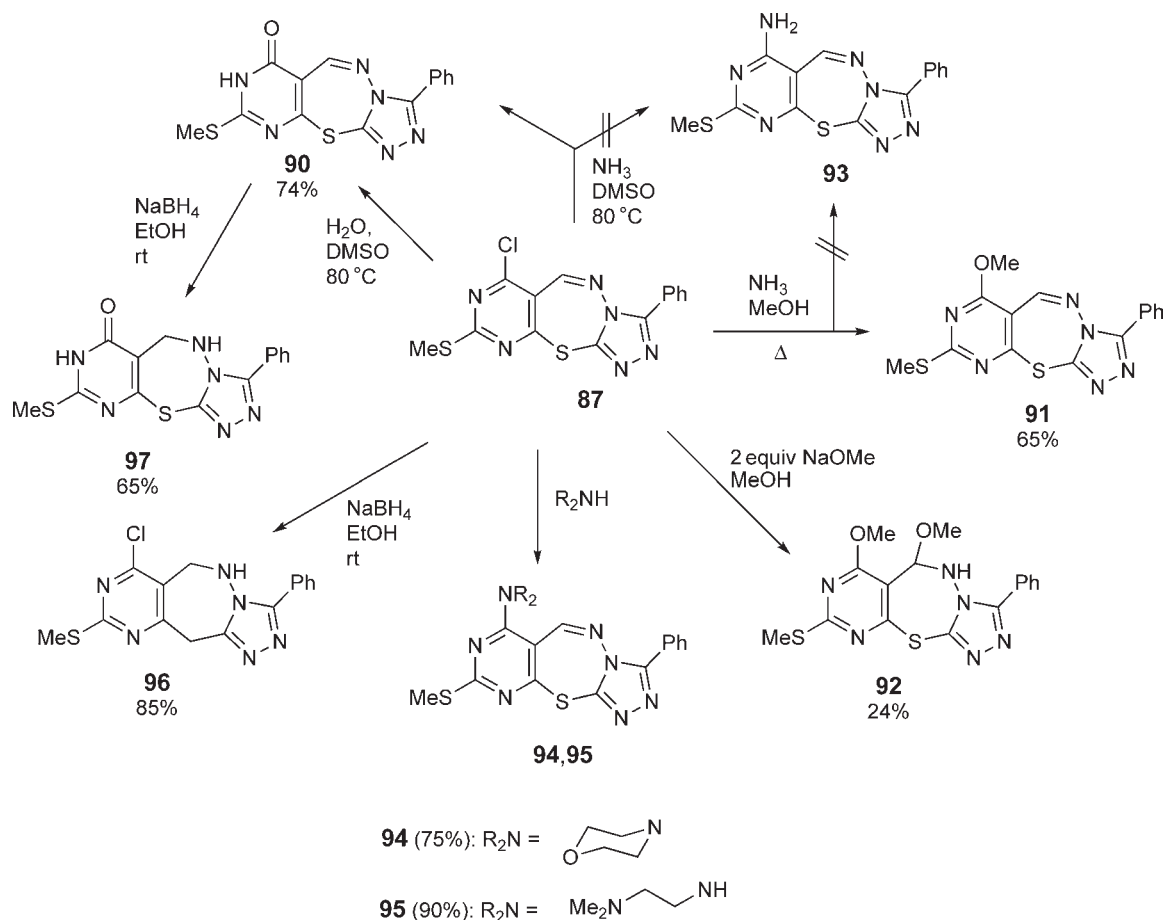


Scheme 8

between 4-amino-3-phenyl-1,2,4-triazol-5-thione **88** and 4,6-dichloropyrimidin-5-carbaldehyde **89**. Some of the nucleophiles studied were similarly described in [Scheme 8](#) and reactions with other ones were conducted, which are described in [Scheme 9](#), as well as the corresponding yields.

Reaction with water was found during ¹H NMR in DMSO at 80 °C. Reactions of **87** with an equivalent amount of sodium methoxide at room temperature gave the 7-methoxy derivative **91**. With 2 equiv of sodium methoxide in boiling MeOH, nucleophilic substitution at the chlorine atom was accompanied by addition of MeOH to the azomethine fragment of the thiadiazepine ring to give the 6,7-dimethoxy derivative **92**. When **87** was heated with ammonia in DMSO or MeOH, the 7-oxo and 7-methoxy derivatives **90** and **91** were obtained instead of the expected product **93**. This was explained by ammonia playing the role of base only, while water, present in DMSO and MeOH, reacts as nucleophiles. Reactions of **87** with morpholine or 2-(dimethylamino)ethylamine in DMSO at 60 °C led to the formation of the corresponding 7-substituted amino derivatives **94** or **95**. Reduction of **87** and **90** with sodium borohydride occurred at room temperature only at the azomethine moiety of the thiadiazepine ring to give the 5,6-dihydro derivatives **96** and **97**, which was confirmed by ¹H NMR and IR.

The synthesis of a new series of polyfused 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepines by reactions of 3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione **98** has appeared [<2002PS2871>](#). The starting material was obtained in good yield via the reaction of 4-amino-5-phenyl-1,2,4-triazole-3-thione **99** with malonyl



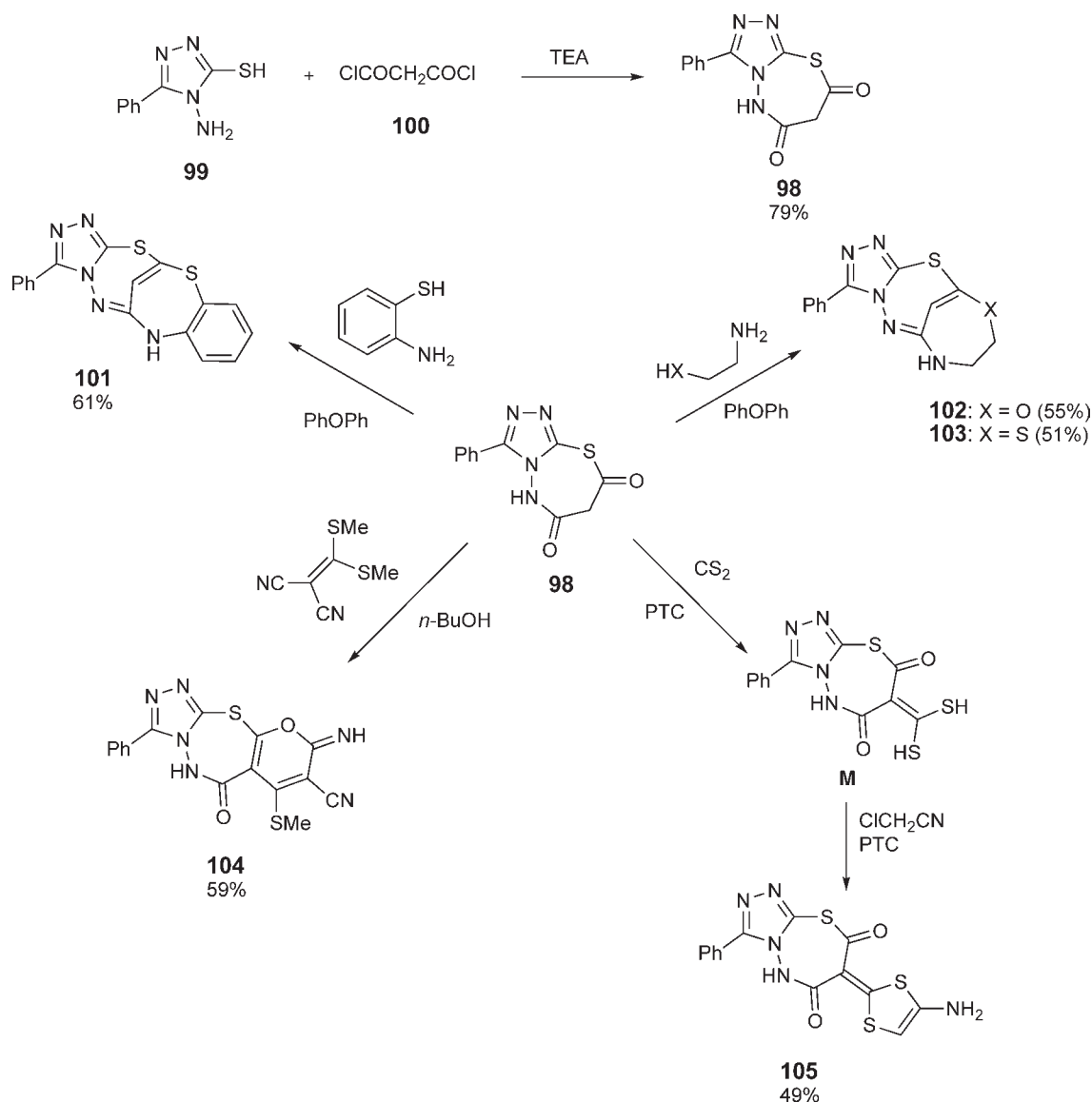
Scheme 9

dichloride **100** and TEA in 1 : 1 : 2 molar ratio at room temperature. The structural assignment of this compound was established by elemental and spectral analyses (Scheme 10).

Compound **98** was condensed with *o*-aminothiophenol, 2-aminoethanol, or cystamine in refluxing diphenyl ether through an intermolecular cyclization with the elimination of two molecules of water to give the polyfused derivatives **101–103**, respectively. Also, the reactions of **98** with dimethylthiomethylenemalononitrile in boiling dimethylformamide (DMF) were studied. The dimethylthiomethylenemalononitrile was prepared via the reaction of malononitrile with CS_2 with 2 equiv of methyl iodide in a one-pot reaction using liquid–liquid phase-transfer catalysis (PTC) technique (NaOH/dioxane/tetrabutylammonium bromide (TBAB)). The product of this reaction was identified as 8-cyano-9-imino-7-methylthio-6-oxo-3-phenyl-5,6,8,9-tetrahydro-7*H*-pyrano[3,4-*f*][1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazepine **104** (Scheme 10).

The 7-(5-amino-1,3-dithiolan-2-ylidene)-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepin-6,8-dione **105** was obtained through the intermediate **M** by treating **98** with CS_2 and chloroacetonitrile in a one-pot reaction under PTC (DMF/ K_2CO_3 /TBAB) (Scheme 10).

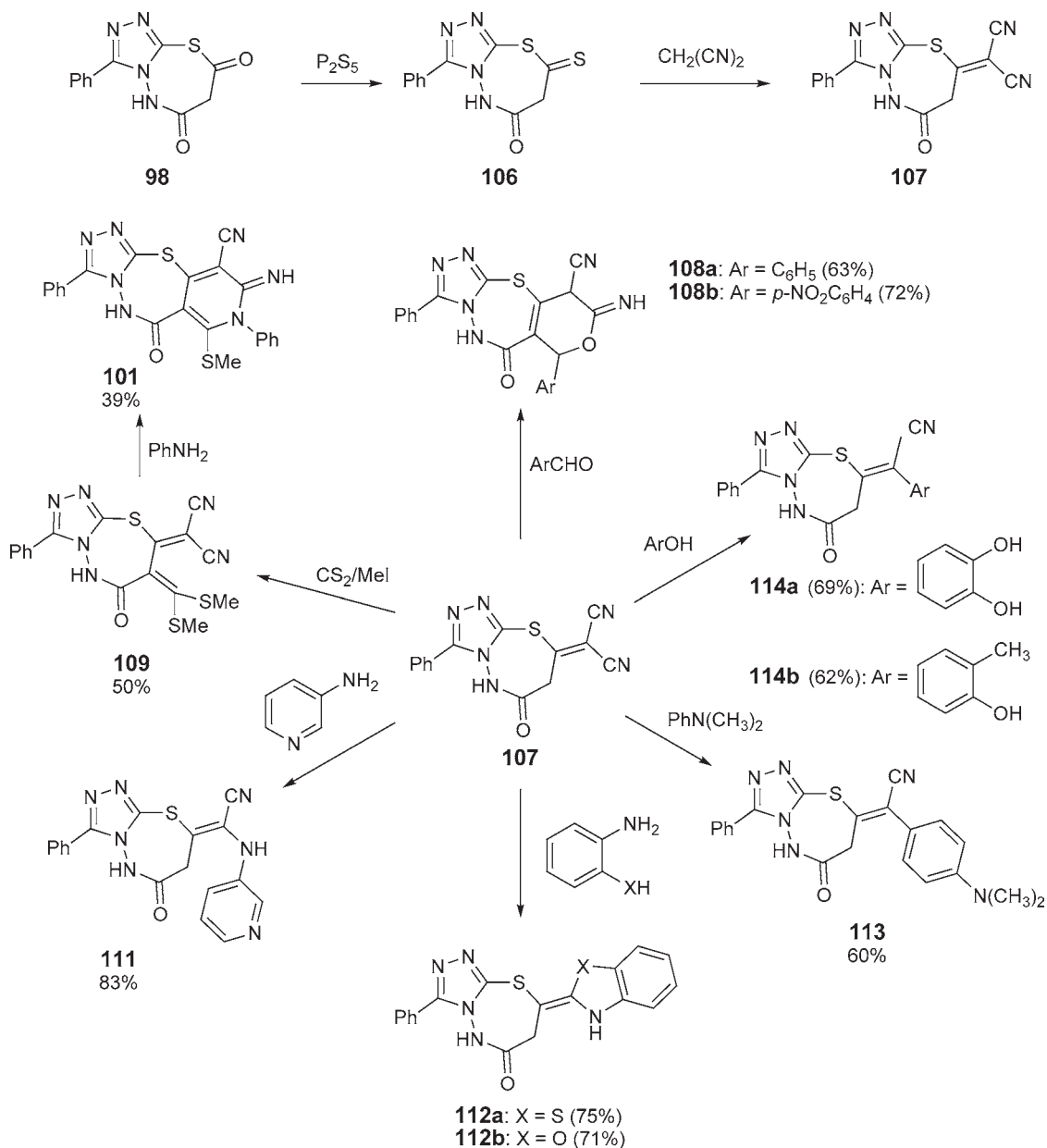
When **98** was treated with P_2S_5 in boiling pyridine, the corresponding thia analog, 3-phenyl-5,6,7,8-tetrahydro[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazepine-6-oxo-8-thione **106**, was obtained in 73% yield (Scheme 11). Condensation of **106** with malononitrile in boiling DMF gave the dicyanomethylene derivative **107** in 68% yield. The reaction of **107** with benzaldehyde or *p*-nitrobenzaldehyde afforded the corresponding 10-cyano-9-imino-6-oxo-3-phenyl-7-phenyl(*p*-nitrophenyl)-5,6,9,10-tetrahydro-7*H*-pyrano[3,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine **108a** (63%) and **108b** (72%), respectively. The reaction mechanism was proposed to proceed through the nucleophilic attack of the active CH_2 group of **107** at the carbonyl group of the aromatic aldehyde producing the corresponding aldol adduct, followed by intramolecular cyclization via a nucleophilic addition of the OH group at the CN group.



Scheme 10

Compound **107** was also treated with an equimolecular ratio of CS₂ and double molarity of methyl iodide to yield the corresponding *S*-methyl derivative **109** (50%); the latter, in turn, underwent cyclization when treated with aniline in 1 : 1 or 1 : 2 molar ratio, affording 3,8-diphenyl-5,6,7,8,9,10-hexahydropyrido-9-imino-7-methylthio-6-oxo[3,4-*f*][1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazepine **110** in 39% yield (Scheme 11).

The behavior of **107** toward amines and phenols was also investigated. The products resulted from initial attack of the nucleophile at the C_α of the dicyanomethylene moiety. Thus, condensation of **107** with 3-aminopyridine in a 1 : 3 molar ratio through elimination of HCN afforded **111** in 83% yield. Also, treatment of **107** with *o*-aminophenol or *o*-phenylenediamine in refluxing DMF yielded the cyclized products **112a** (75%) and **112b** (71%), respectively, via elimination of two molecules of HCN. Moreover, **107** reacted with *N,N*-dimethylaniline or activated phenols, namely resorcinol or *o*-cresol, to furnish compounds **113** (60%), **114a** (69%), and **114b** (62%), respectively. The structures of all compounds were established by using elemental and spectral analyses.



Scheme 11

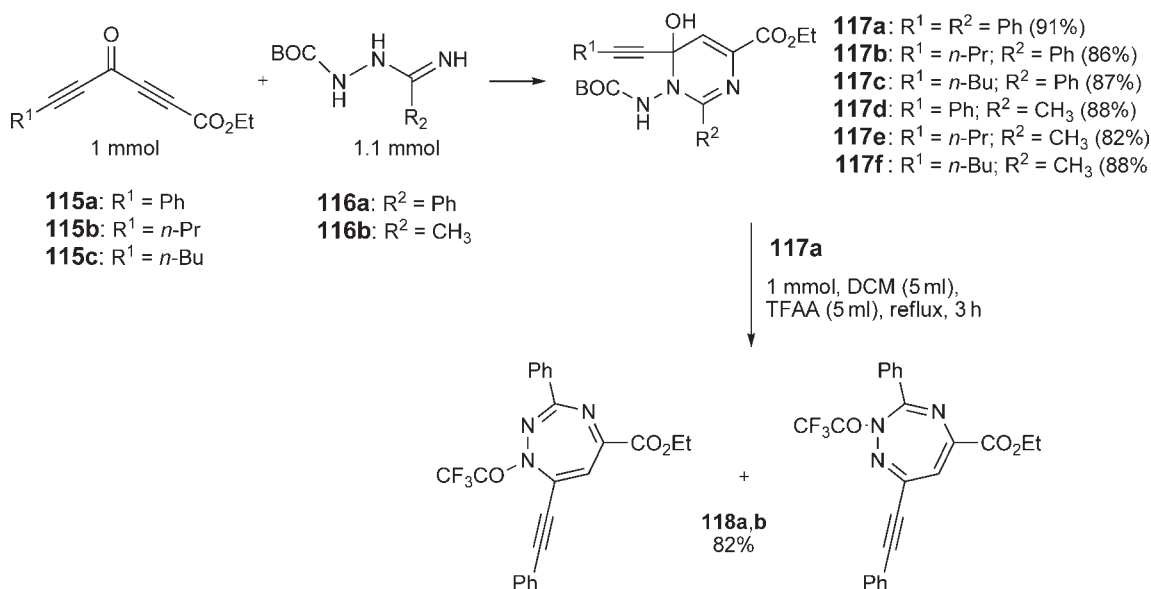
13.14.6 Ring Synthesis from Acyclic Compounds

13.14.6.1 Triazepines

13.14.6.1.1 Monocyclic triazepines

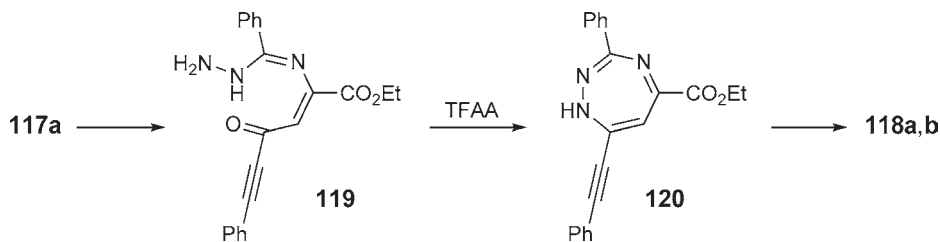
13.14.6.1.1(i) Synthesis from bis-acetylenic ketones

A new synthetic methodology from bis-acetylenic ketones has been described. This is an example of a multi-component reaction in which two carbonyl groups and two alkynyl moieties are present, that could be independently reacted. Thus, **115a–c** were reacted with BOC-amidrazones **116a** and **116b** containing three nitrogen nucleophiles (1.1 equiv) affording **117a–f** (Scheme 12) <2005JOC3307>. The reaction could be run under a wide variety of experimental conditions; it proceeded equally well at low (−78 °C) and room (25 °C) temperatures as well as in a



Scheme 12

variety of solvents, such as tetrahydrofuran (THF), dichloromethane (DCM), hexane, EtOH, and MeOH. The reaction times were surprisingly short, and, typically, no starting materials could be detected just after 5–20 min. Compound **117a** when reacted with refluxing trifluoroacetic anhydride (TFAA) afforded *N*-trifluoroacetyltriazepine **118a** and **118b** in high yield. The synthesis of **118a** and **118b** could be conducted in a one-pot procedure by addition of TFAA after coupling of **115a** and **116a**. Trifluoroacetyltriazepine **118** was isolated in 82% yield as a 4:1 mixture of regioisomers **a** and **b**. The proposed mechanism is depicted in Scheme 13 involving a ring-opened ketone **119**, which undergoes ring closure to triazepine **120** before acylation to **118a** and **118b** in TFAA.



Scheme 13

13.14.6.2 Thiadiazepines

13.14.6.2.1 Monocyclic thiadiazepines

13.14.6.2.1(i) Synthesis from thiosemicarbazides

The results of reaction of 4-substituted thiosemicarbazides **121a–c** with tetracyanoethene **122** were reported <2003ARK118>. Upon addition of double molar amounts of **122** to a solution of **121a–c** in ethyl acetate, with the presence of air, the green color of a transient charge-transfer complex was observed, which quickly changed to a brown color and finally to a characteristic reddish orange color. The concentrate residue from the filtrate was subjected to vacuum sublimation to remove any unreacted **122**. Chromatographic separation of the sublimation residue gave products **123–126** (Figure 7).

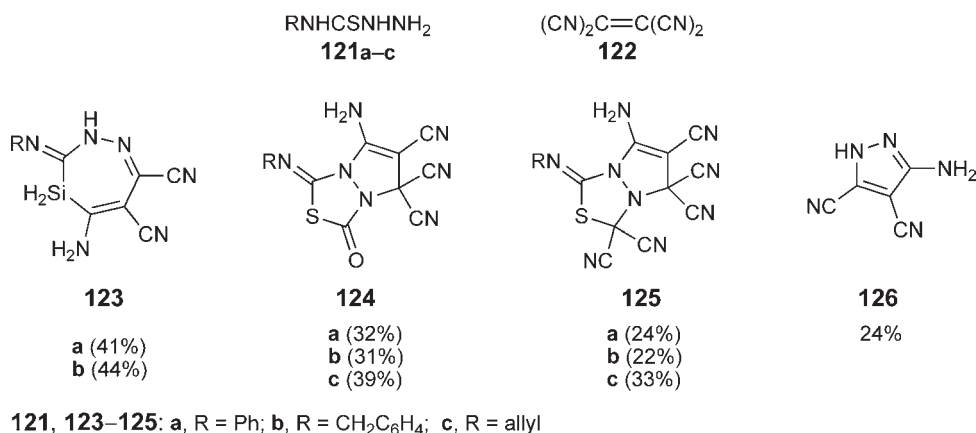


Figure 7

The structures of **123–126** were based on spectroscopic data, on combustion analyses, and chemical evidence. Compounds **124a–c** showed a characteristic orange color attributed to the local push–pull system of conjugated double bonds and lone pairs. Compounds **125a–c** showed a characteristic red color. The results of combustion analysis and spectroscopic data suggested the presence of 3-amino-1*H*-pyrazole-4,5-dicarbonitrile **126** as a precipitate from the reaction between **121c** and **122**. The structure of **126** was confirmed by comparison with authentic sample.

The formation of these unusual products was explained by the following two complex mechanisms, formation of **123–125** as depicted in Scheme 14 while formation of **126** as depicted in Scheme 15.

Formation of **123–125** are explained by formation of the neutral adduct **127**, a tetracyanoethane derivative, from the starting 4-substituted thiosemicarbazides **121a–c** and **122**. Elimination of one molecule of HCN afforded the intermediate **128**, which cyclized to the thiadiazepine derivatives **123a** and **123b**.

Both products **123** and **124** required the intermediate formation of **128**. Cyclization of the latter and elimination of a molecule of HCN formed intermediate **129**, which, in turn, reacted with another molecule of **122** affording **124a–c** via oxidation of **130**. The formation of **125a–c** can be rationalized by elimination of a molecule of malononitrile from **127**, followed by further reaction with another molecule of **122**, and cyclization.

Formation of **126** was explained by an NH_2 to the double bond of **122**, forming the substituted pyrazole via steps **136c** $\rightarrow$ **137** $\rightarrow$ **138**.

13.14.7 Ring Synthesis by Transformation of Another Ring

13.14.7.1 Triazepines

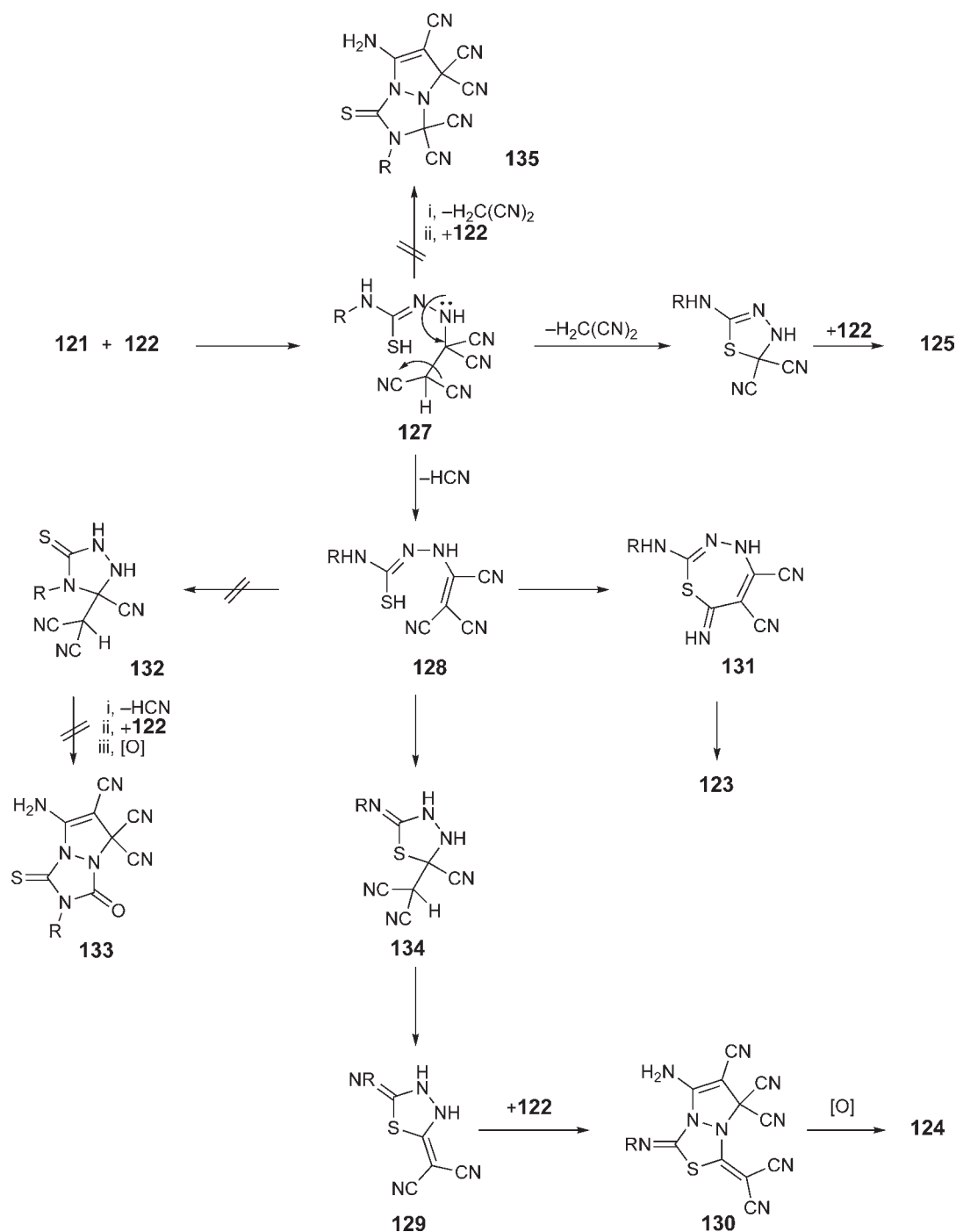
13.14.7.1.1 Fused triazepines

13.14.7.1.1(i) Synthesis by transformation of another triazepine

A one-step synthesis of a new series of biheterocyclic triazepines by condensation of dihaloalkanes **140** with 2-methyl-7-phenyl-3,5-dithioxo-3,4,5,6-tetrahydro-2*H*-1,2,4-triazepine **141** and the oxo analog **142**, via PTC conditions, has been reported in the search of fused heterocyclic systems of potential pharmacological activity <1997TL2087>. At room temperature, 1,2,4-triazepines **141** and **142** were treated with equimolecular quantities of dibromoalkanes **140a–e** using the liquid–liquid PTC technique (benzyltriethylammonium chloride, benzene, and 50% aqueous NaOH). Although two ring closures were expected, the reaction proved to be quite selective; only **143a–e** were obtained, also showing that the dithioxo compound is more reactive (Scheme 16). Only the oxo **142** reacted with two dibromides affording pyrazoles **144a,b**.

The same reactions were also conducted with alkyl bromides **145** and **146**, to check if these reactions were also as selective as the ones with dihaloalkanes (Scheme 17).

As it can be seen, the oxo group in **142** was inactive while the thioxo group at C-3 was very reactive. Formation of pyrazoles in the oxo compound was explained by the reactivity of C-6. When triazepine **141** was treated with 1 or 2 equiv of alkyl bromide, only **152** was obtained; but when a large extent of the alkylating agent was used, a small amount of the dialkylated **150** was formed. The different reactivity of **141** and **142** was explained by a softer basic character of the thioxo group in comparison with the oxo group.

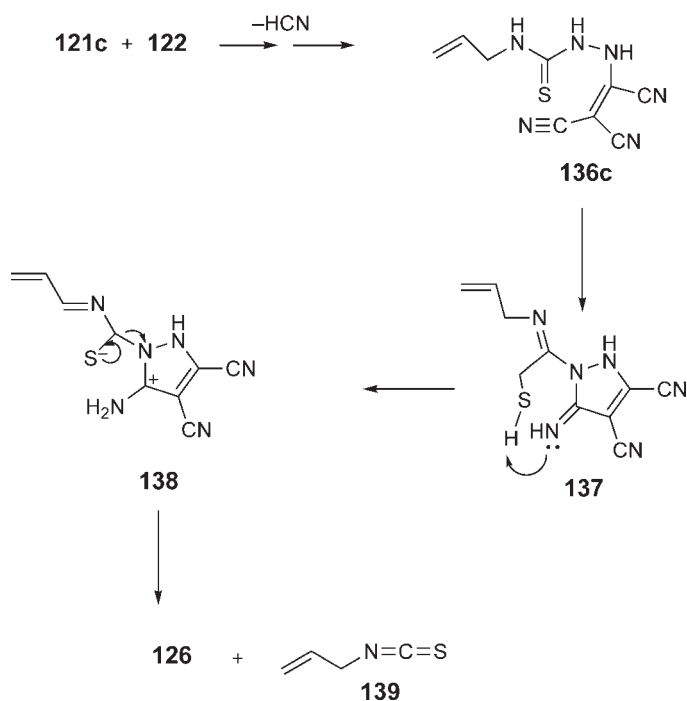


Scheme 14

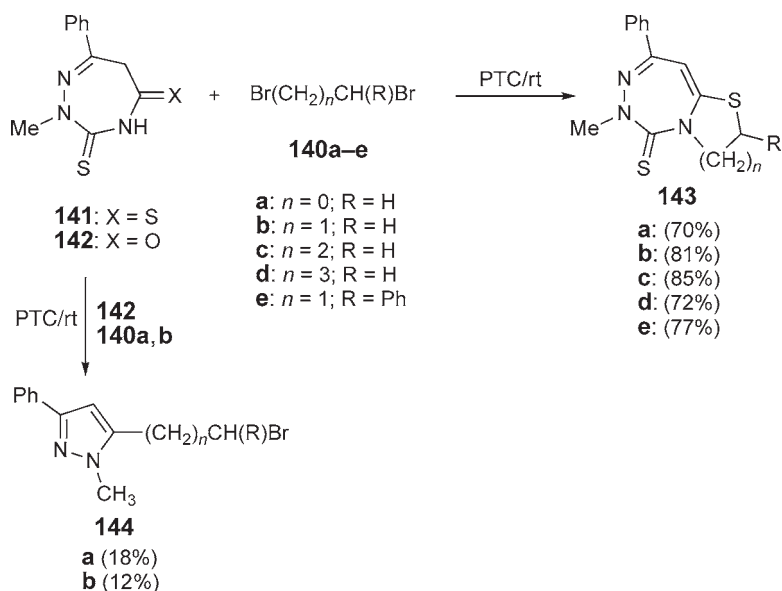
13.14.7.1.1(ii) Synthesis from diaminobenzimidazoles

Reactions of 1,2-diaminobenzimidazole **72** with 1,3-diketones, acetocetic acid, and its derivatives to obtain fused triazepines were studied <2002CHE598>. The obtained products are depicted in Scheme 18.

Different reaction conditions for condensation of **72** with pentane-2,4-dione were evaluated and the best solvent was 1-hexanol with the addition of mineral acids to yield 69% of **154a**. Condensation of **72** with 4-phenylbutane-2,4-dione or dibenzoylmethane required more rigorous conditions, and triazepinobenzimidazoles **154b,c** could only be

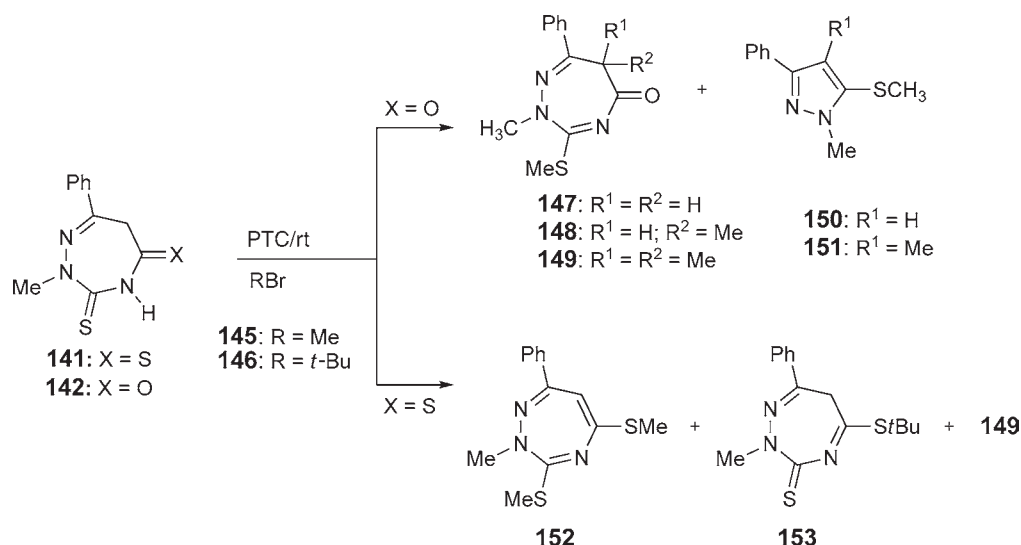


Scheme 15

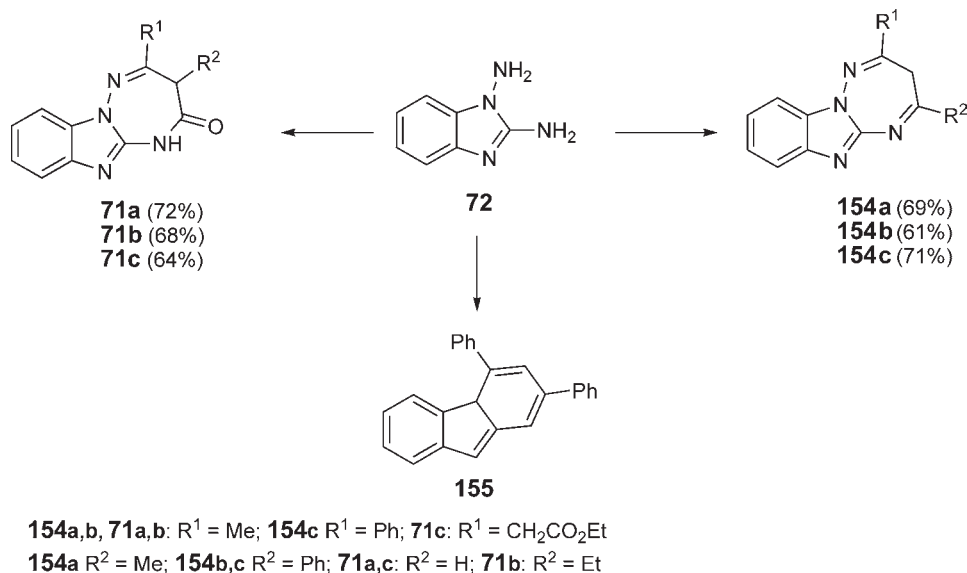


Scheme 16

obtained on heating the starting materials in PPA at 110–115 °C. When reaction of **72** with β -diketones, for example, dibenzoylmethane, was performed in nitrobenzene or without solvent (240–250 °C) in the presence of ZnCl₂, **155** was isolated. A detailed description of mass spectrometry fragmentations, IR, UV, and NMR spectra are described to confirm the proposed structures of the different products.



Scheme 17



Scheme 18

13.14.7.1.1(iii) Synthesis from diaminopyrazoles

The first example of the pyrazolo[1,5-*b*]-1,2,4-triazepine system **156** was obtained by reaction of 1,5-diamino-3-*t*-butylpyrazole **157** with acetylacetone **158** in refluxing acetic acid [<2003OBC4268>](#) (Figure 8). The product was obtained as an oil (39%) after chromatography on alumina.

Compound **156** adopted the 3*H* tautomer exclusively, even in hydrogen bond acceptor solvents, such as acetone-*d*₆. It was proposed by analogy with the 1,5-benzodiazepine system which adopts an analogous tautomer, the seven-membered ring of **156** is likely to be nonplanar and, regarding NMR spectra, interconversion between two equivalent forms may be present.

Diaminopyrazoles **158** and **159** also react with β-ketoesters in refluxing acetic acid (1–1.5 h) to give pyrazolo[1,5-*b*]-1,2,4-triazepin-2-ones **160–163**. Compounds **160–162** were prepared in 42–45% yield using the appropriate ketoesters, though ethyl benzoylacetate and ethyl pivaloylacetate failed to react, presumably by electronic and steric

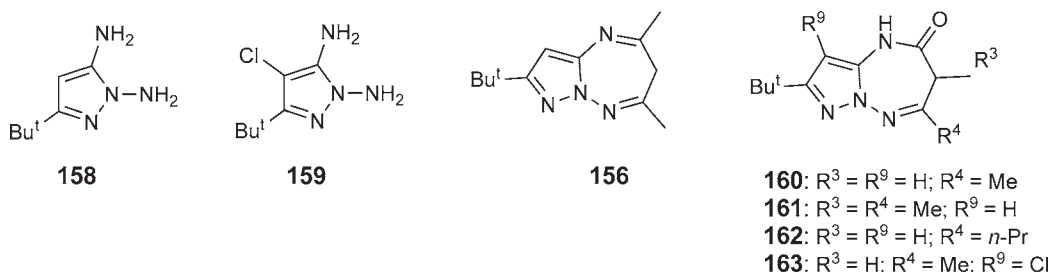
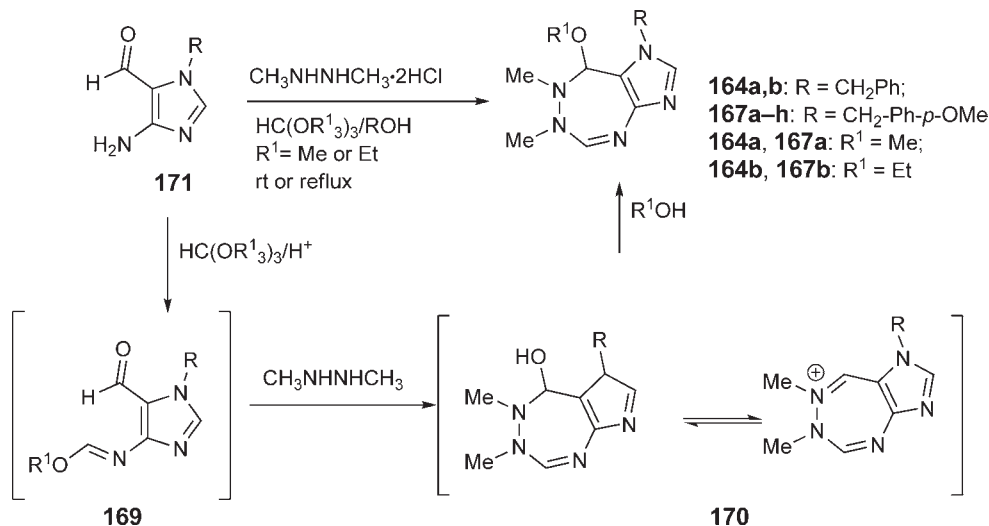


Figure 8

reasons, respectively. When the chloropyrazole **159** was employed, the yield of **163** almost doubled relative to its unsubstituted analogs. The products were characterized by their spectra and the regiochemistry of the reaction and tautomeric form of the products were established by an X-ray crystal structure of the 4-methyl derivative **160**. The observed regiochemistry suggested that the cyclization mode is determined by reaction of the more reactive *N*-amino function of the diaminopyrazole with the ketonic group of the ketoester. The crystal structure of **160** also showed the planarity of the five-membered ring and the boat shape adopted by the seven-membered ring.

13.14.7.1.1(iv) Synthesis from 4-amino-1-benzylimidazole-5-carbaldehyde

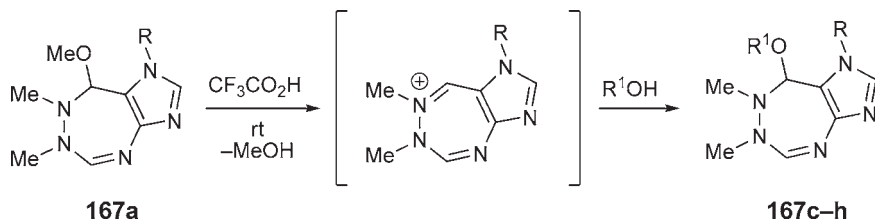
The synthesis of some imidazo[4,5-*e*]triazepines has been recently reported. These compounds were prepared to study their adenosine deaminase (ADA) inhibitory activity as they are analogs of coformycin <2004NNNA263, 2004JME1044>. Compounds **164a** and **164b** (Scheme 19) were both synthesized in 26–32% yield in a single-pot reaction of 4-amino-1-benzylimidazole-5-carbaldehyde **165** with 1,2-dimethylhydrazine dihydrochloride **166** and trimethyl or triethyl orthoformate in the corresponding alcohol, as the solvent. Compounds **167a–h** were prepared by a similar reaction starting from 4-amino-1-*p*-methoxybenzimidazole-5-carbaldehyde **168**. The targets **167a** and **167b** were prepared in 62% and 30% yields, respectively, by reaction with 1,2-dimethylhydrazine, as **164a** and **164b**. The reaction pathway was proposed to involve the initial formation of the imidate **169**, which upon ring closure would form an equilibrium mixture containing the aminol-iminium species **170**.



Scheme 19

The latter upon reaction with the alcohol would form the target imidazotriazepinols **167a** and **167b**. This mechanism is supported by the isolation of **169** in a separate reaction of **171** with triethyl orthoformate at reflux, with or without an acid catalyst. If the intermediates **170** are really present, compounds **167c–h** could be prepared

by exchange reactions of **167a** or **167b** with the appropriate alcohol. This was proven to be correct as compounds **167c–h** were obtained by reactions of **167a** with *n*-propanol, *n*-butanol, 2-propanol, 2-methoxyethanol, 4-methoxybenzyl alcohol, and 3-methylbenzyl alcohol, respectively, under catalysis by trifluoroacetic acid at room temperature in yields of 32–77% (Scheme 20). These experiments support the mechanism proposed in Scheme 19.



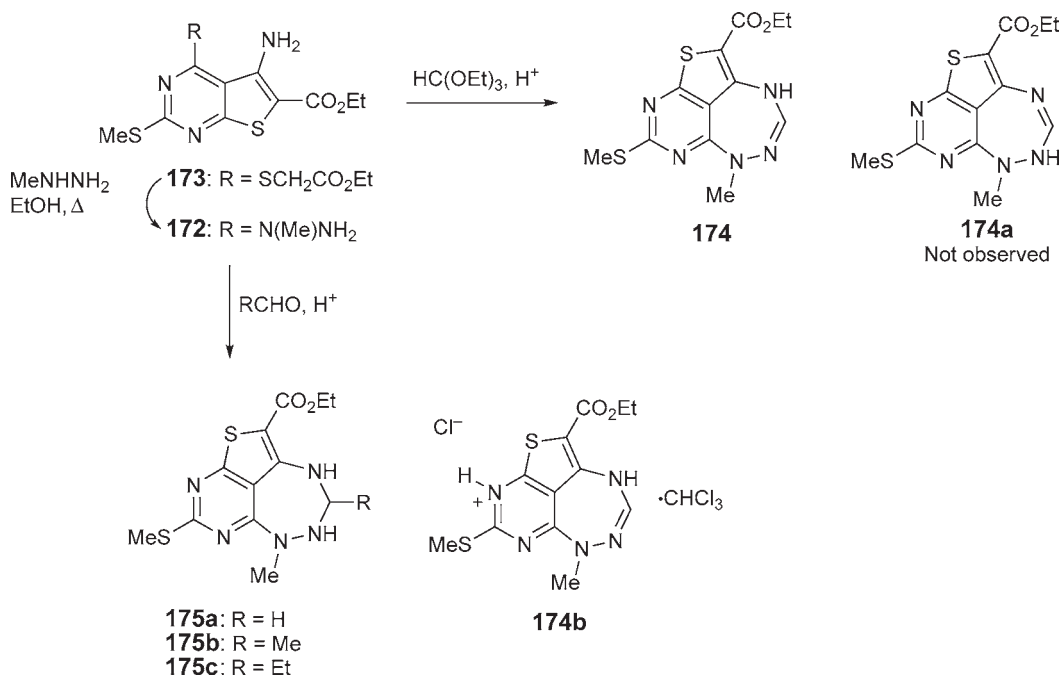
Scheme 20

Compounds **167** are described to be somewhat unstable, especially when they are dry; however, they are reasonably stable in DMSO and/or EtOH solutions or when allowed to retain residual amounts of these solvents during purification process.

13.14.7.1.1(v) Synthesis from 5-amino-4-(1-methylhydrazino)-thienopyrimidine and triethyl orthoformate and aldehydes

The synthesis of 2-thia-3,5,6,7,9-pentaazabenz[*cd*]azulenes, in which thienopyrimidine is *peri*-annulated (SP) with the 1,2,4-triazepine moiety, has been described <2002TL695>.

The 5-amino-4-(1-methylhydrazino)thienopyrimidine **172** bearing suitable substituents for the formation of the triazepine ring in cyclization reactions with one carbon reagents was obtained by heating **1** with excess of methylhydrazine (Scheme 21). When **172** was refluxed with triethyl orthoformate in presence of sulfuric acid, a cyclocondensation occurred to give 6,9-dihydro-2-thia-3,5,6,7,9-pentaazabenz-[*cd*]azulene **174** in 92% yield, as the sole product. The formation of the isomeric triazepine **174a** was not observed. The products were identified by spectroscopy, mass spectrometry, and by single crystal X-ray crystallography.



Scheme 21

As formation of **174** was unexpected because the isomeric **174a** has a double bond conjugated with the aromatic ring, some calculations on the heats of formation of **174** and **174a** were conducted. The results of these calculations were ΔH_f 19.8 and 32.1 kcal mol⁻¹ for **174** and **174a**, respectively.

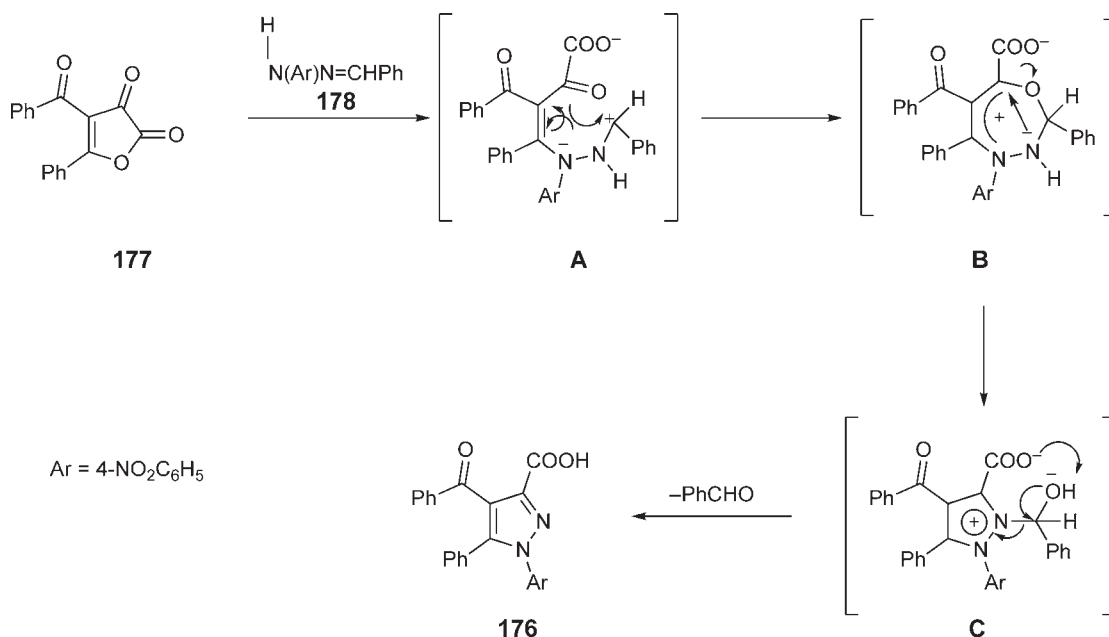
Furthermore, the authors used the same synthetic methodology but with aldehydes as the one carbon reagents. Heating **172** with a slight excess of the corresponding aliphatic aldehyde in the presence of catalytic amount of hydrochloric acid afforded the 8-substituted 6,7,8,9-tetrahydro-2-thia-3,5,6,7,9-pentaazabenz[*a*]azulenes **175a–c** in 85–91% yield. Some broad signals in the ¹H NMR spectra of **175** were assigned to inversion of the triazepine ring and to equilibrium with the open-chain hydrazone in solution.

13.14.7.2 Oxadiazepines

13.14.7.2.1 Monocyclic oxadiazepines

13.14.7.2.1(i) Synthesis from 4-benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid

An oxadiazepine intermediate has been proposed in the synthesis of 4-benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid **176**, prepared by heating furandione **177** and benzaldehyde 4-nitrophenylhydrazone **178** (1/1 mol) for 75 min without any solvent in ca. 45% yield <2004CHE1039> (Scheme 22).



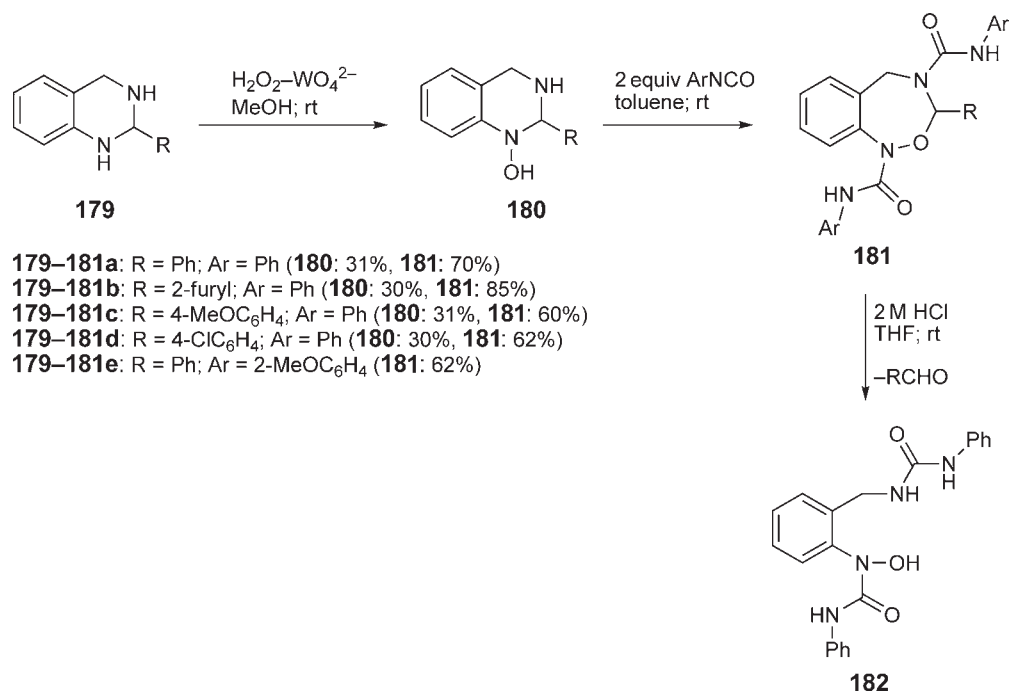
Scheme 22

The proposed mechanism involved ring opening for the formation of the first intermediate **A** that should be initiated by a nucleophilic attack of the NH group adjacent to the phenyl ring of hydrazone at C5 of the furandione ring. Ring closure of the intermediate **A** to oxadiazepine intermediate **B** via the addition of the N=CH-Ph group to the C=O moiety takes place by the catalytic effect of the carboxylic acid proton. Rearrangement of the intermediate **B** generated the pyrazole carboxylate intermediate **C**, and finally loss of a benzaldehyde molecule gave **176**.

13.14.7.2.2 Fused oxadiazepines

13.14.7.2.2(i) Synthesis by oxidation of tetrahydroquinazolines

Quinazolyli-1-ols prepared by oxidation of tetrahydroquinazolines with H₂O₂-tungstate afforded a ring expansion reaction when treated with arylisocyanates in toluene at room temperature <2004TL8973> (Scheme 23).



Scheme 23

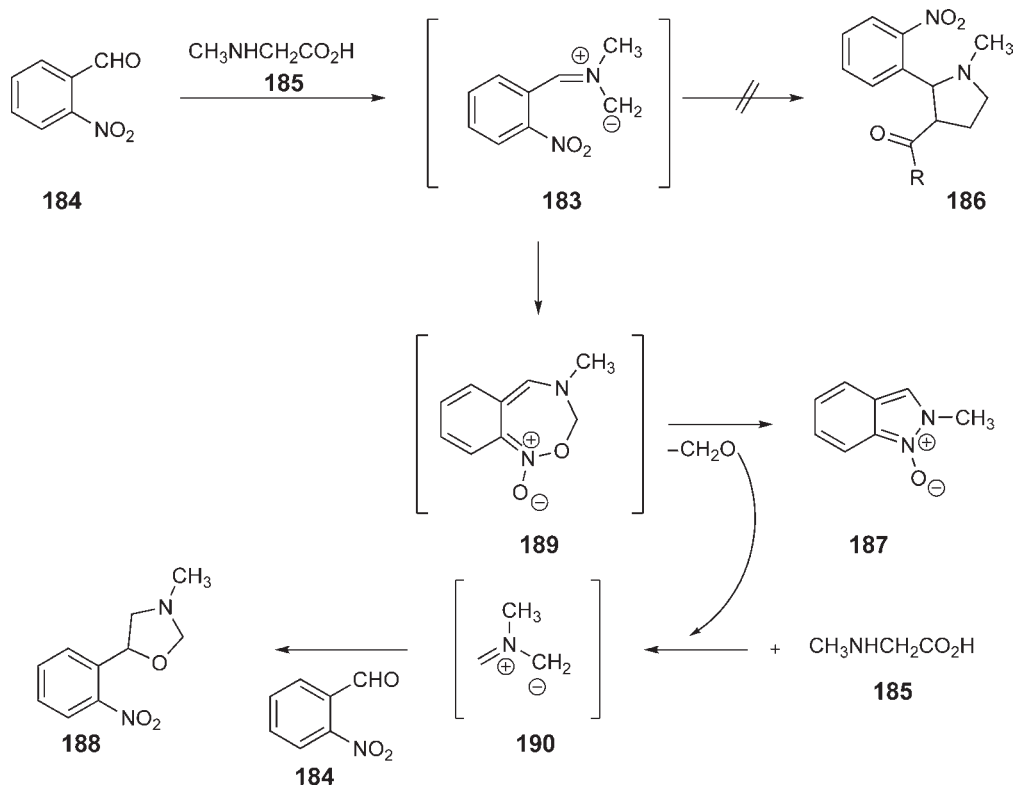
The starting tetrahydroquinazolines were prepared by stirring an equimolecular amount of an aldehyde in MeOH at room temperature. These quinazolines could be isolated and characterized or used without isolation in the following step. The treatment of the isolated or *in situ* formed **179a–d** with H₂O₂ in the presence of catalytic amounts of Na₂WO₄ in MeOH at room temperature led to the formation of MeOH insoluble compounds. The elemental analysis and spectral data proved the structures to be quinazolyl-1-ols **180**, which were treated with 2 equiv of an aryl isocyanate to give the corresponding 6-oxa-5,8-diazabenzocycloheptenes **181** (Scheme 23), whose structures were deduced from their elemental analyses, IR, and NMR data.

To prove the location of the hydroxylation in **180** and hence the position of the oxygen in **181**, compounds **181** were hydrolyzed with 2 M HCl in THF and the diphenylcarbamoylated *N*-(2-aminomethylphenyl)hydroxylamine **182** was obtained. The structure of **182** was confirmed by ¹H NMR spectroscopy, and this unequivocally confirmed the structure of **181**. The energy-minimized model of **180a** was calculated, and the nitrogen atom was shown to be not engaged in hydrogen bonding and thus the atom one that attacks the isocyanate.

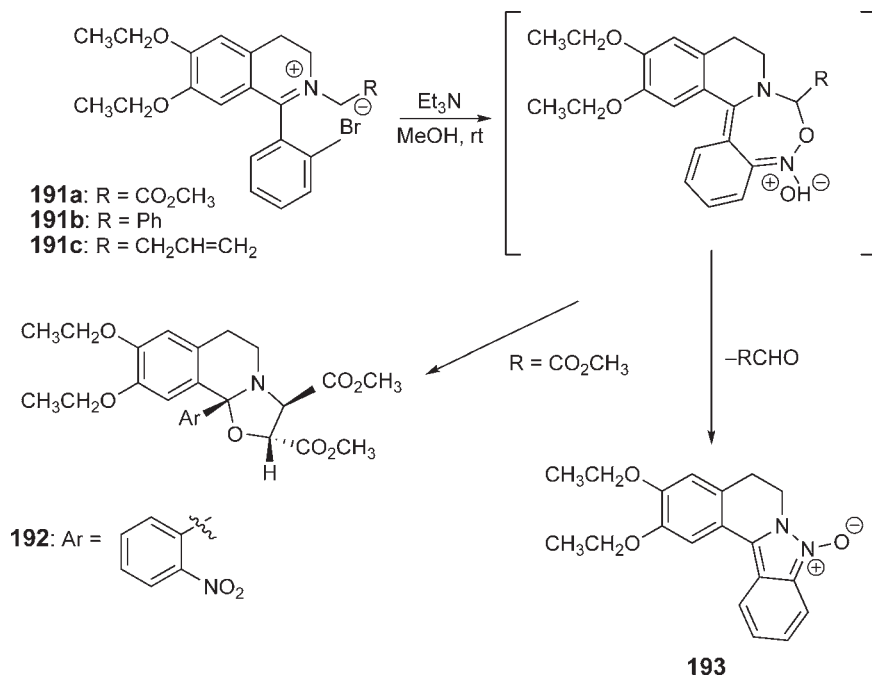
13.14.7.2.2(ii) Intermediate in the reaction of *o*-nitrobenzaldehyde with sarcosine

The formation and reactions of the nonstabilized azomethine ylide **183** in the reaction of *o*-nitrobenzaldehyde **184** with sarcosine **185** in refluxing benzene were conducted in search of new syntheses of the [3,2-*c*]quinoline ring system of the bradykinin receptor antagonist martinelline alkaloids <2001TL5081>. In spite of the presence of a large excess of active dipolarophiles, such as ethyl acrylate or methyl vinyl ketone, no traces of the expected **186** were found in the ¹H NMR spectrum of the reaction mixture. In fact, two other products, an indazole *N*-oxide **187** (40%) and an oxazolidine **188** (43%), were isolated after chromatographic separation. The formation of these products was proposed by fragmentation of the unstable intermediate **189** (Scheme 24), in which the decarboxylative condensation of *o*-nitrobenzaldehyde **184** and sarcosine **185** was followed by a 1,7-electrocyclization of the nonstabilized azomethine ylide **183**.

Another set of experiments with 6,7-diethoxy-3,4-dihydro-1-(2-nitrophenyl)-*N*-substituted-isoquinolinium bromides **191** (Scheme 25) were carried out to confirm the hypothesis depicted in Scheme 24. In all the cases, the isoquinoline-fused indazole-*N*-oxide was formed. In one case (**191a**: R = CO₂Me), the competitive formation of the 1,3-dipolar cycloadduct **192** as a single isomer was observed (ratio **193**:**192** was ca. 3:1) due to the high reactivity of the electron-deficient C=O bond of the by-product aldehyde.



Scheme 24

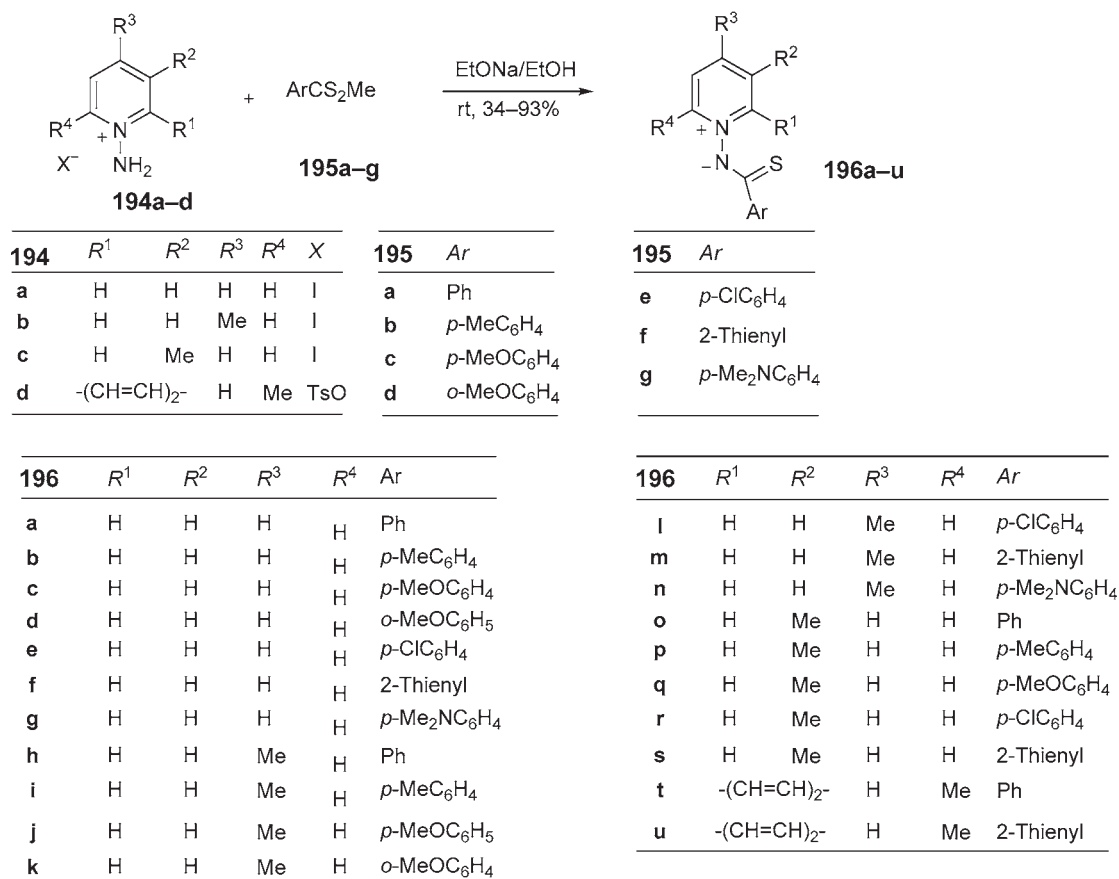


Scheme 25

13.14.7.3 Thiadiazepines

13.14.7.3.1 Fused thiadiazepines

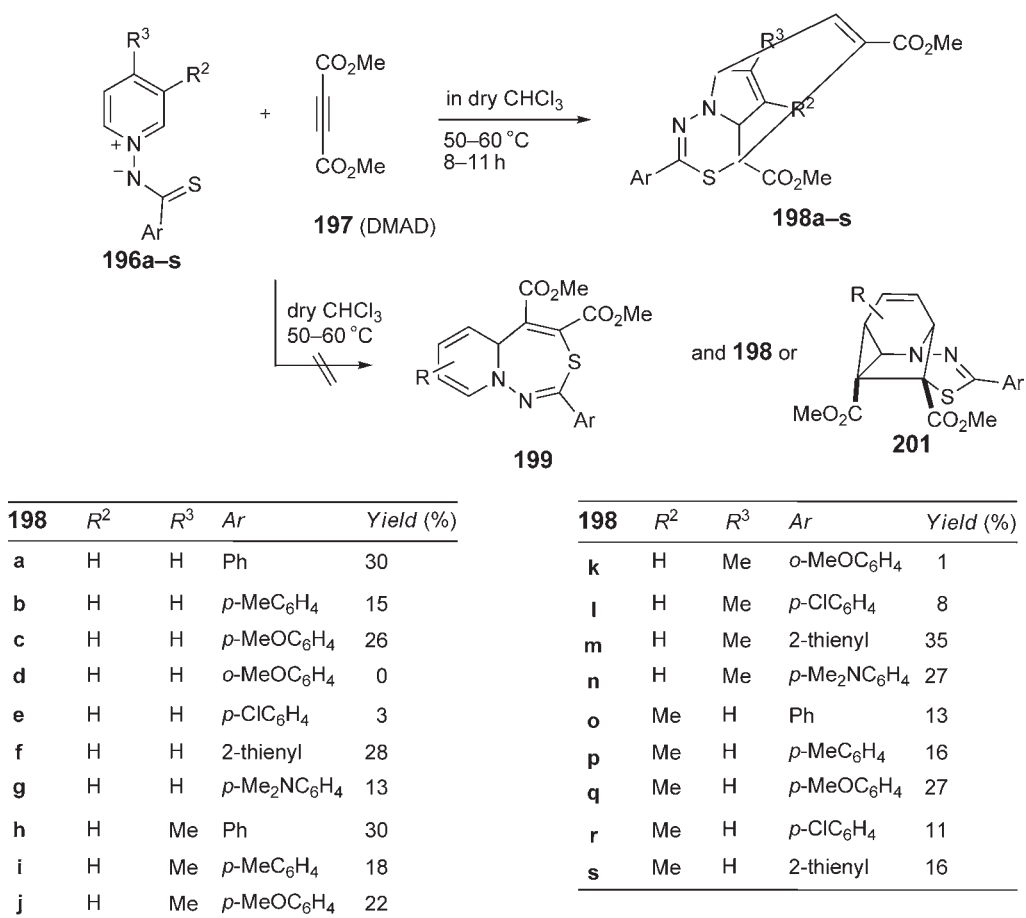
13.14.7.3.1(i) Synthesis from 1-pyridinio(arenethiocarbonyl)amidates and dimethyl acetylenedicarboxylate
 With the aim of preparing fused thiadiazepines, reactions of different 1-pyridinio(arenethiocarbonyl)amidates **196** with dimethyl acetylenedicarboxylate **197** (DMAD) were conducted <1997JOC7788>. When an HCCl₃ solution of the amidates, prepared as described in **Scheme 26**, and DMAD was heated at 50–60 °C in a water bath for 8–11 h, products **198** were obtained and not the desired thiadiazepine (**Scheme 27**).



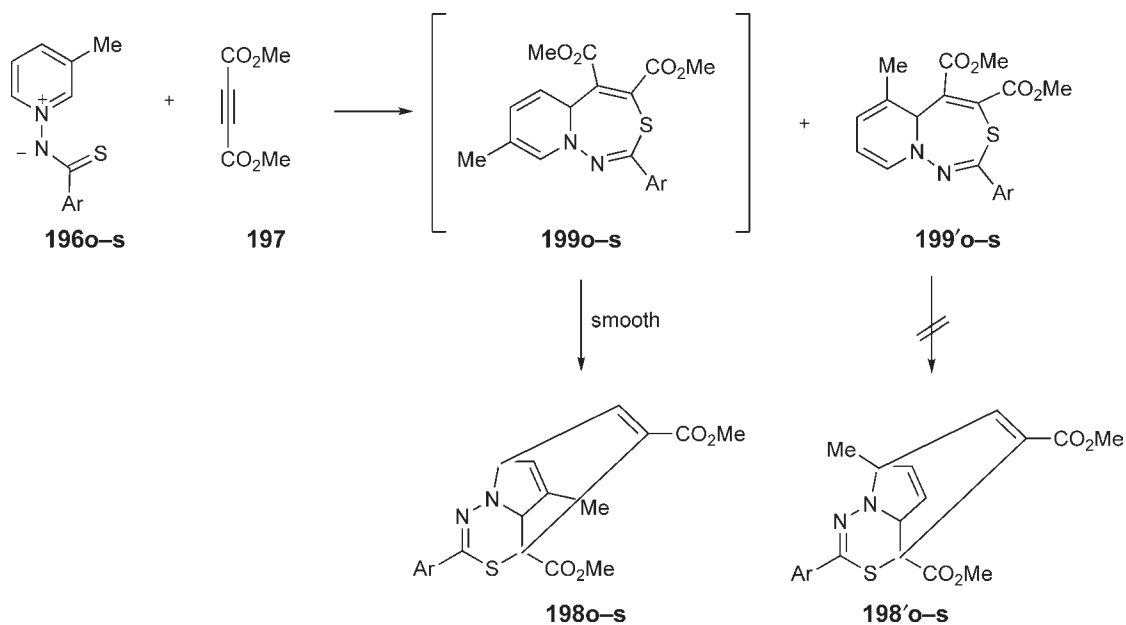
Scheme 26

The formation of **198o-s** should be accompanied by the formation of the 1-methyl isomers **198'o-s** in reactions of unsymmetrically substituted 1-pyridinoamidates with DMAD. Mechanistically, the rearranged products **198o-s** and **198'o-s** are derived from 8-methyl-5*aH*-pyrido[1,2-*d*][1,3,4]thiadiazepines **199o-s** and their 6-methyl isomers (**199'o-s**), respectively, as shown in **Scheme 28**. These results encouraged the authors to make some mechanistic studies in order to obtain the corresponding thiadiazepines with the hypothesis that **199o-s** rearranged to the corresponding **198o-s**, but the **199'o-s** isomers would have steric impediments to give the corresponding **198'o-s**, so there would be some experimental conditions, where **199'o-s** should be found.

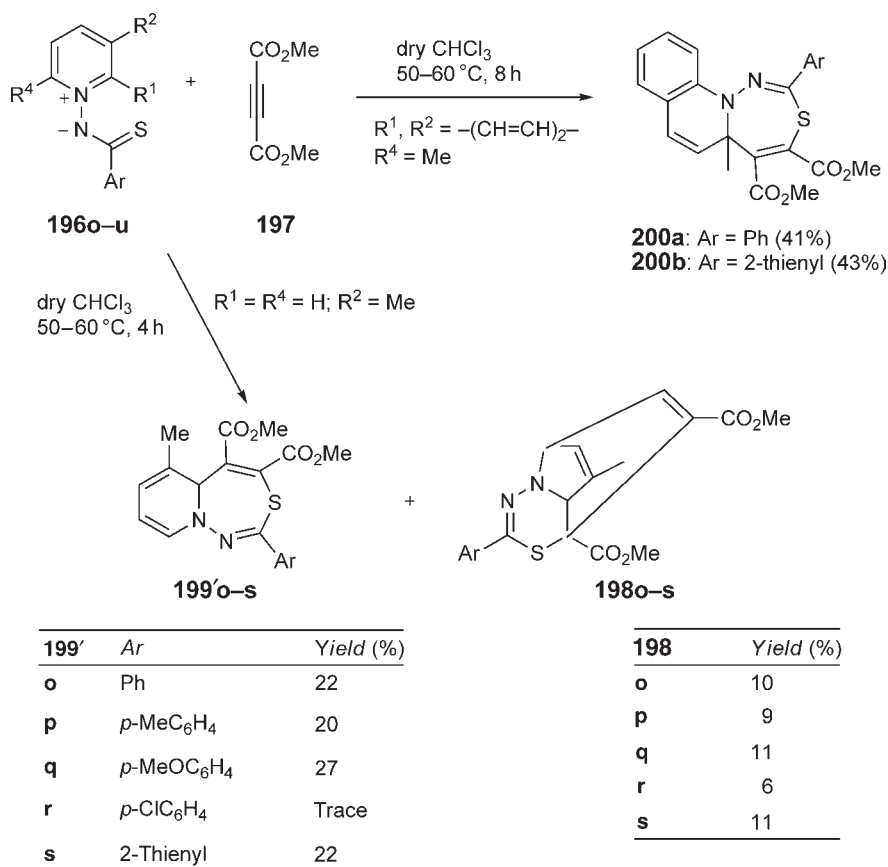
This occurred when reactions of **194o-s** and DMAD were carried out at 50–60 °C for 4 h. In these reactions, the corresponding 2-aryl-6-methyl-5*aH*-pyrido[1,2-*d*][1,3,4]thiadiazepine-4,5-dicarboxylates (**199'o-s**) were obtained in trace to 27% yields as red prisms or needles, together with the rearranged products **198o-s** (6–11%). The reactions of 1-(2-methylquinolinio)amidates **196t** and **196u** with **197** were also conducted and only the expected dimethyl 2-aryl-5*a*-methyl-5*aH*-1,3,4-thiadiazepino[4,5-*a*]quinoline-4,5-dicarboxylates **200a** and **200b** were formed in 41% and 43% yields, respectively, as shown in **Scheme 29**. The successful isolation of the tricyclic **200a** and **200b** was attributed to



Scheme 27



Scheme 28



Scheme 29

the stabilization by the fused benzene ring and to the resistance of the benzene ring to lose aromaticity during the rearrangement.

All of the products were identified by spectroscopic, X-ray, and elemental analysis. The proposed reaction mechanism involved the formation of thiadiazepines **199** and further isomerization to **198**.

13.14.8 Important Compounds and Applications

13.14.8.1 Triazepines

13.14.8.1.1 Fused triazepines

The imidazo[4,5-*e*][1,2,4]triazepines described in Section 13.14.1.1.4 were designed because they have a similar structure to some ADA inhibitors, such as coformycin and 2'-deoxycorformycin. These two natural products have immunosuppressant activity to control cancer associated with the hyperimmune system, such as leukaemia and lymphoma. Unfortunately, these compounds have been shown to be very toxic to liver, kidney, and central nervous system with a strong and almost irreversible binding to ADA. The authors who prepared the imidazo[4,5-*e*][1,2,4]triazepines <2004NNA263, 2004JME1044> proposed that the lack of a sugar moiety may have a benefit if these compounds have a somewhat less tight binding to ADA. With this premise, these compounds were screened for inhibition of ADA from bovine and calf spleen by spectrophotometrically monitoring the rate of hydrolysis of the substrate adenosine into product inosine at 265 nm. All of the target compounds were determined to be competitive inhibitors of ADA with K'_1 in the range of ~ 10 – $100 \mu\text{M}$. These results indicate that the studied compounds bind about 6–9 orders of magnitude less tightly to ADA than do coformycin and deoxycorformycin. This fact was considered consistent with the loss of sugar hydroxyl–protein hydrogen bonds. To date, *n*-propyl and *n*-butyl compounds were found to be the most potent among the group.

13.14.9 Further Developments

This section describes some new literature information concerning the heterocycles described in this chapter.

13.14.9.1 Triazepines

Some new theoretical calculation on triazines **1–4** (Figure 1) were performed in order to get more information on their interaction with cationic species, Cu^+ in this case <2007JPC2213>. The main objective of this study was to compare these results with the ones of thiouracils. These calculations using the 6-31G(d) basis set using the Gaussian-03 series of programs, showed that the triazepine thio derivatives remain as sulfur bases, as in the protonation process <2002JPC7383>. It has been shown that in the case of dioxotriazepine (**1**, Figure 1) the basicity of nitrogen atom at position 1 towards copper becomes important due to the electronic inductive effects issued from the neighboring methyl groups, which may change the concept that only the carbonyl and thiocarbonyl groups are the competitive basic centers of this compound. The copper association is preferred at the thiocarbonyl group regardless of its position (3 or 5, Figure 1). When results for compounds **1** (3O5O) and **4** (3S5S) were compared, it was found that the heteroatom at position 3 is the most basic one.

The initial adduct in which Cu^+ interacts with the heteroatom at position 3 affording **3O5O–Cu⁺** and **3S5S–Cu⁺** complexes, is expected to evolve towards a more stable four-membered ring structure in which the metal ion bridges between the heteroatom at position 3 and the amino group at position 4 of the corresponding enolic tautomer. In the case of the dioxotriazepine, this complex is proposed to be formed by a stepwise mechanism that involve a first attack of Cu^+ to the oxygen atom at position 5. The required tautomerization process involves activation barriers that make the overall process exothermic (Figure 9).

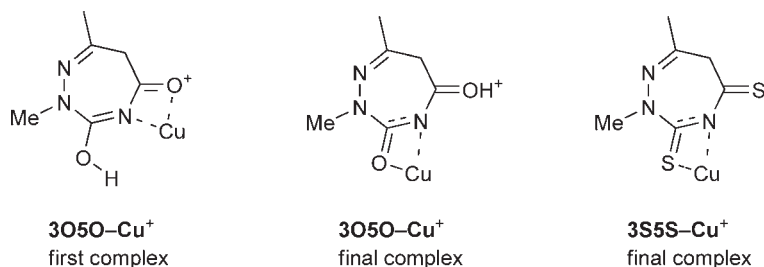


Figure 9

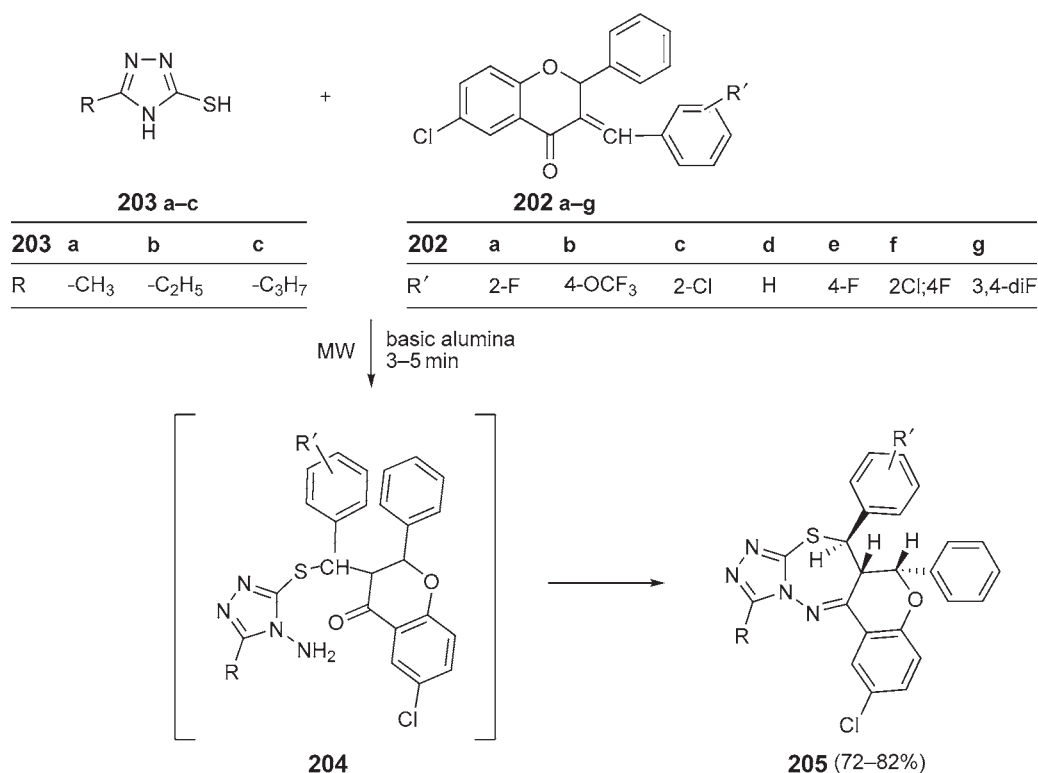
13.14.9.2 Thiadiazepines

A novel synthesis of benzopyrano-triazolo-thiadiazepines involving microwave enhanced solid support synthesis has recently been reported. The authors tried the following experimental conditions to fuse a triazole and a benzopyran ring in a single molecular framework under microwave irradiation: (a) using inorganic solid supports such as aluminas (acidic and basic), montmorillonite KSF and silica gel; (b) using neat reaction; and (c) using a few drops of DMF as homogeneizer and energy transfer media <2006BMC1303>. The best results were obtained with basic alumina as a comparative high yield was obtained in a shorter time. The proposed mechanism of the reaction of 3-arylidene flavanones **202** with 4-amino-5-alkyl-3-mercaptoptriazole **203** first involves the formation of the intermediate Michael adduct **204**, followed by condensation of the carbonyl group with the aromatic primary amine to give a seven-membered ring system, leading to a new class of tetracyclic ring system **205** (Scheme 30).

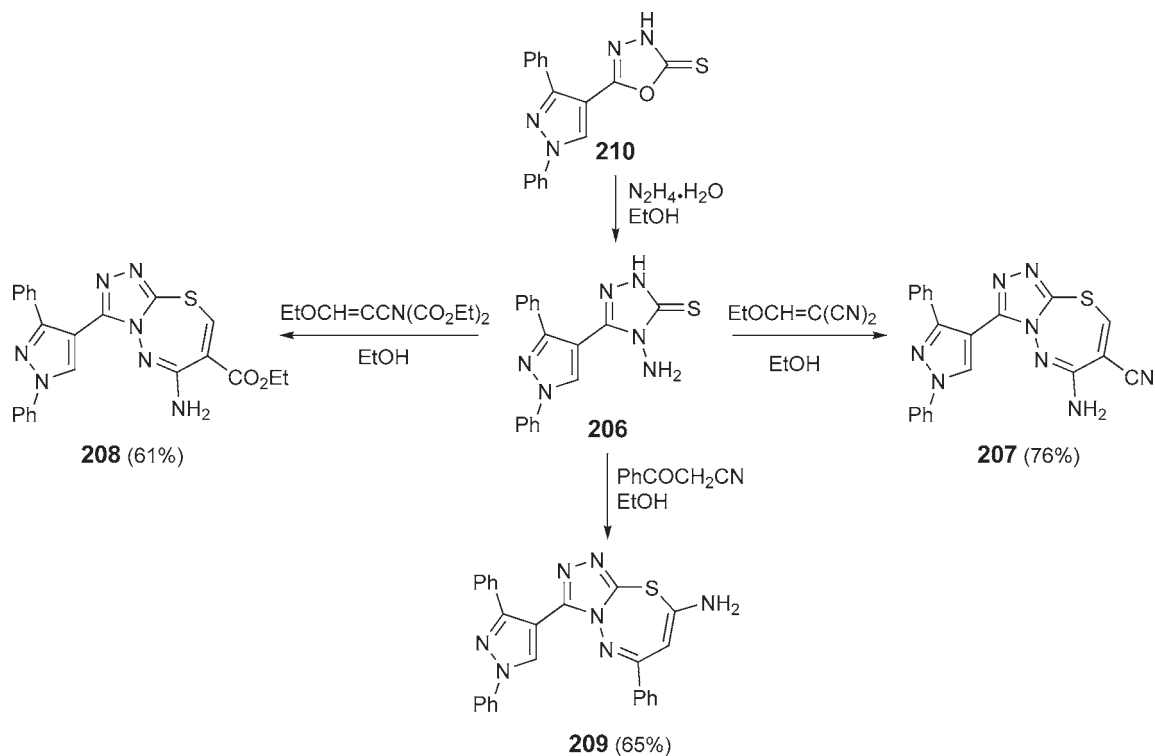
In a study on reactions of 4-amino-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-4,5-dihydro-[1,2,4]triazole-5(1*H*)-thione **206** with different reagents, some novel [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines **207–209** were obtained. The starting material **206** was prepared in good yield by the reaction of the oxadiazole thione **210** with hydrazine hydrate <2006ARK(X)137>. Results and reagents are shown in Scheme 31.

13.14.9.3 Oxadiazepines

Some new oxadiazepines have been reported to be obtained by a one-pot multicomponent reaction. Reaction of (*N*-isocyanimino)triphenylphosphorane (CNNPPH_3) **211** with dialkylacetylenedicarboxylates **212** and

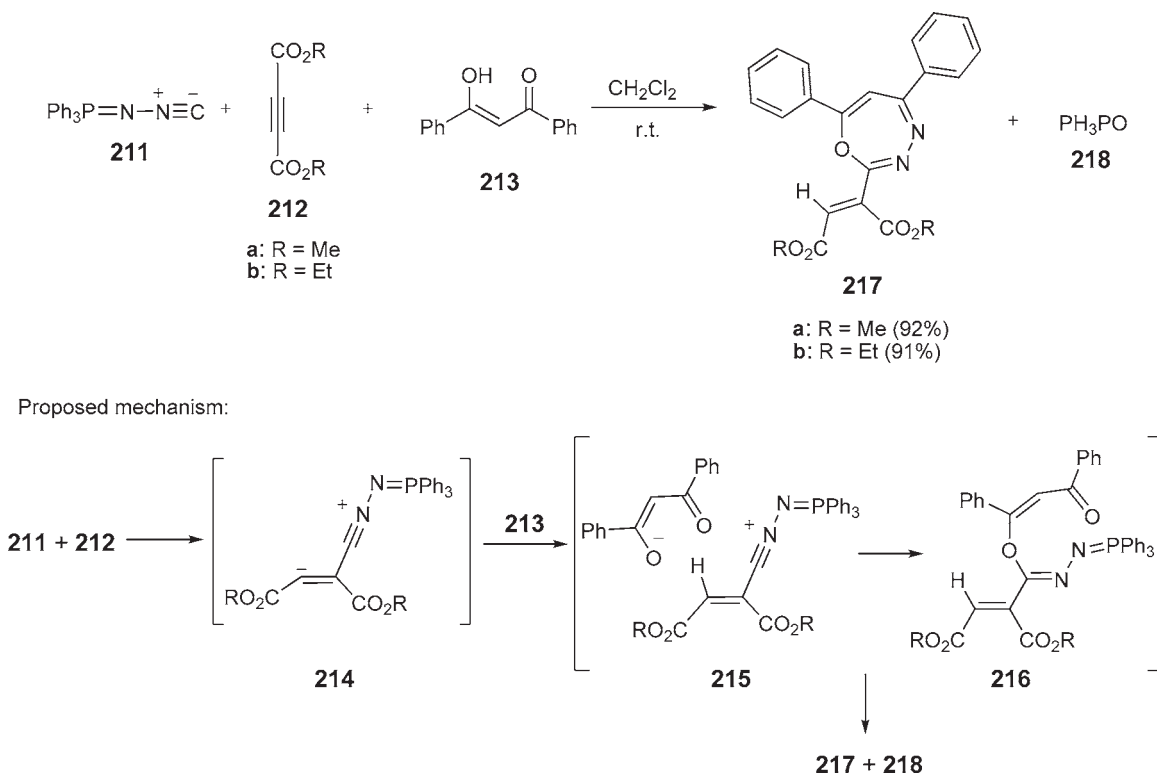


Scheme 30



Scheme 31

1,3-diphenyl-1,3-propanedione **213** in a 1:1:1 ratio in dichloromethane at room temperature gave dialkyl (Z)-2(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)butenedioates **217** and triphenylphosphine oxide **218** (Scheme 32). The reaction was described to take place smoothly and cleanly under mild conditions and although the mechanism of this three component reaction has not been established experimentally, the authors propose formation of intermediates **214–216** from the well established chemistry of isocyanides <2007TL2617>.



Scheme 32

References

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Biographical Sketch



Gloria Inés Yranzo was born in Rosario (Argentina) in 1957. She was educated in Córdoba (Argentina) and received her Ph.D. in organic chemistry at the National University of Córdoba (Argentina) in 1983. During 1989, she joined Prof. Elguero's group in Madrid as a postdoctoral fellow and now she is full professor at the Organic Chemistry Department of the Faculty of Chemical Sciences of the National University of Córdoba (Argentina). She is also a researcher of the National Research Council of Argentina (CONICET). She leads a research group which is studying flash vacuum pyrolysis of heterocycles, mainly nitrogen heterocycles, including the use of heterogeneous catalysis in flash vacuum pyrolysis reactions. The group is also working on nitrogen heterocyclic synthesis with possible biological activity.



E. Laura Moyano was born in Córdoba (Argentina) in 1971. She was educated in Córdoba and received her Ph.D. in chemistry at the Faculty of Chemical Sciences, National University of Córdoba (Argentina), in 2000. In 2001, she joined Dr. Katritzky's group at Florida University (USA), working in thiadiazole synthesis and Nippon Soda's research laboratories (Florida, USA) working in pesticide synthesis. In 2004, she went to Szeged (Hungary) and worked with Prof. Fülop in enzymatic resolution of pharmaceutically compounds. Her work at the University of Córdoba involves synthesis and flash vacuum pyrolysis of nitrogen heterocycles in homogeneous and heterogeneous systems.

13.15

Seven-membered Rings with Three Heteroatoms 1,2,5

R. Ranjith Kumar and S. Perumal
Madurai Kamaraj University, Madurai, India

M. Balasubramanian
Pfizer, Inc., Groton, CT, USA
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13.15.1 Introduction

This subject was covered previously in CHEC(1984) <1984CHEC(7)593> and CHEC-II(1996) <1996CHEC-II(9)333>, both of which are available online. This chapter, comprising a review of literature from 1996 to 2007, is intended to update the previous work concentrating on major new preparations, reactions, and concepts. In the previous reviews in CHEC(1984) and CHEC-II(1996), the reactivity section was not discussed separately but was included in the synthesis section. In this chapter, Sections 13.15.6, 13.15.7, and 13.15.8 cover, respectively, the reactivity of (1) nonconjugated rings, (2) substituents attached to ring carbon atoms, and (3) substituents attached to the ring heteroatoms. The syntheses of 1,2,5-triazepine, oxadiazepine, dioxazepine, trioxepine, thiadiazepine,

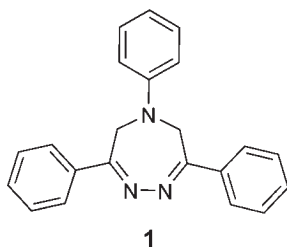
oxathiazepine, dithiazepine, oxadithiepine, and trithiepine are discussed in Sections 13.15.7 and 13.15.8 on the basis of the ring synthesis from acyclic compounds classified by a number of ring atoms contributed by each component and the ring synthesis by transformation of another ring, respectively.

13.15.2 Theoretical Methods

This section, which did not appear in either CHEC(1984) or CHEC-II(1996), discusses the applications of molecular mechanics, semi-empirical (AM1 and PM3) methods, and *ab initio* molecular orbital (MO) calculations to 1,2,5-triheteropine rings.

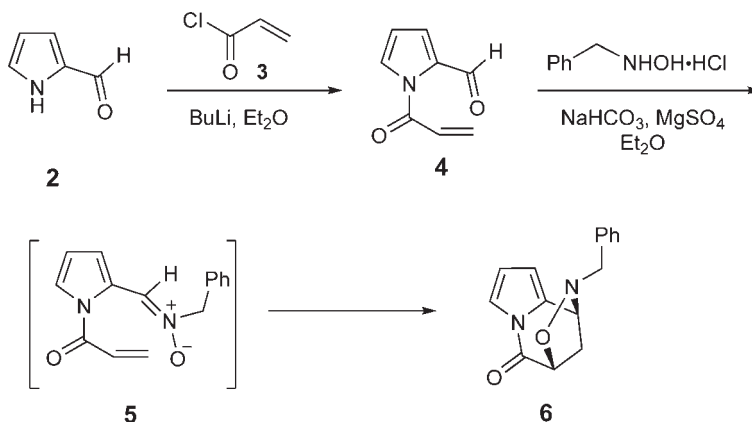
13.15.2.1 1,2,5-Triazepine

The total energy, E , of **1** was calculated to be $-4948.64 \text{ kcal mol}^{-1}$ from semi-empirical PM3 calculations <2007JHC133>.



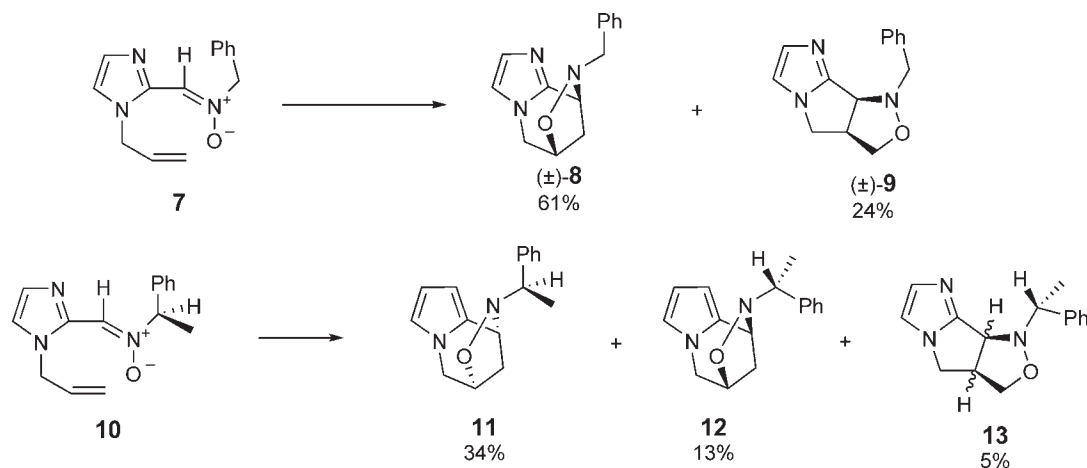
13.15.2.2 1,2,5-Oxadiazepine

Molecular modeling calculations performed on the regio- and stereoselective intramolecular cycloaddition of **5** to give the bridged-ring cycloadduct **6** show that the *transoid*-conformation of acryloyl pendant in **5** is more suitable for the cycloaddition than the *cisoid* one (Scheme 1) <2001H(55)1987>.



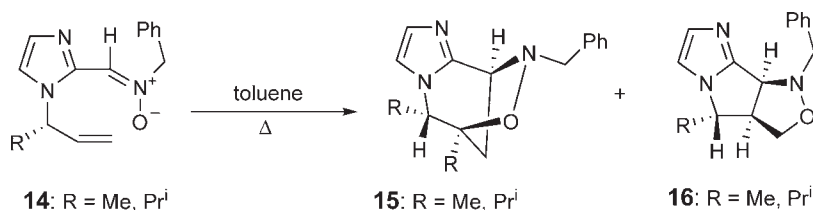
Scheme 1

The predominant formation of bridged-ring cycloadducts **8**, **11**, and **12** from the intramolecular cycloaddition of **7** and **10** is supported by MM+ calculations (Scheme 2). The energy data calculated by imposing various distances between the reaction centers disclose that (1) a concerted mechanism, with the C–O bond formation more advanced than the C–C bond, is favored for all orientations and distances, and (2) the competition between the two paths, one leading to the formation of bridged rings **8**, **11**, and **12**, and the other to fused rings **9** and **13**, is dependent on the distances considered, but the first approach is facilitated by the shorter distance between the reactant atoms <2002T4445>.



Scheme 2

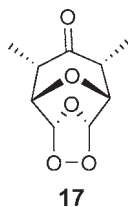
Theoretical calculations for the intramolecular cycloaddition of nitrone functionality over alkenes using *ab initio* at the RHF/6-31G** level (Scheme 3) have been performed on **14**. The results of these calculations are in good agreement with the observed regio-, product, and stereoselectivities, besides affording a lower free energy of activation for the formation of the optically active bridged 1,2,5-oxadiazepine system **15** than the fused system **16** <2004TA3181>.



Scheme 3

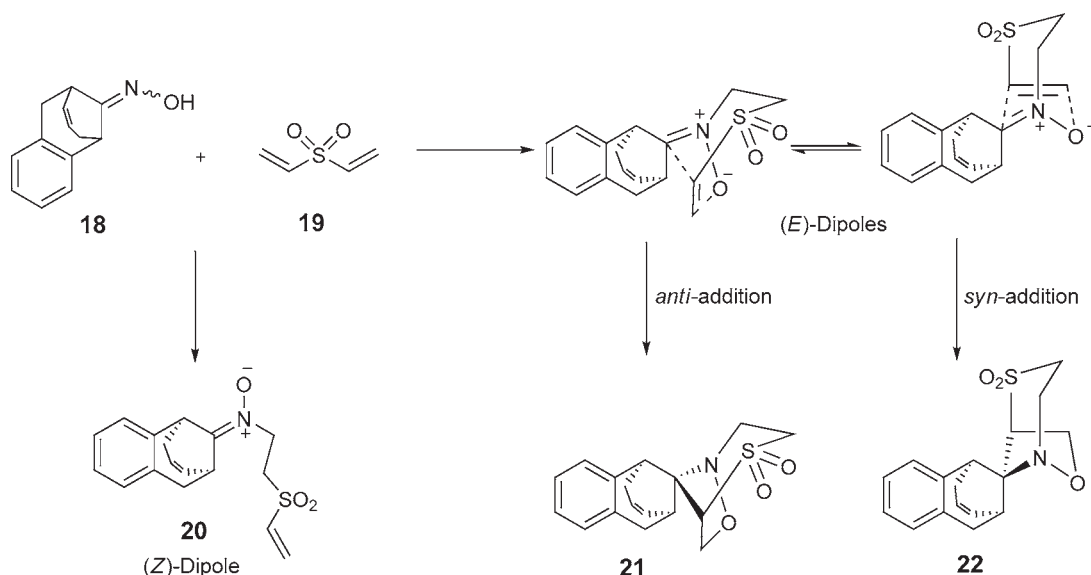
13.15.2.3 1,2,5-Trioxepine

Molecular modeling and energy minimization studies were performed on the 1,2,5-trioxepine **17** including consideration of charge, van der Waals forces, bond angles, and torsion energies. The energy minimum was found to be of the order of 400 kJ mol⁻¹ <1996J(P1)1101>.



13.15.2.4 1,5,2-Oxathiazepine

Although the cycloaddition between **18** and **19** may take place through dipoles possessing either (*E*)- or (*Z*)-geometry, the cycloadducts **21** and **22** result exclusively from only the (*E*)-dipole (Scheme 4). The semi-empirical calculations have been used to probe these regio- and stereochemical preferences <2003T9997>.



Scheme 4

13.15.2.5 1,5,2-Dithiazepine

A comparison of the calculated energies of the lactam **23** and lactim **24** associated with their tautomerism through *ab initio* MO calculations at the Hartree–Fock level with 6-31G** basis set reveals that in vapor phase **23** is more stable by $8.36 \text{ kcal mol}^{-1}$ than **24** and, therefore, the equilibrium lies well to the lactam side <2001H(55)753>.



13.15.3 Experimental Structural Methods

This section did not appear in either CHEC(1984) or CHEC-II(1996). The X-ray crystallographic, nuclear magnetic resonance (NMR), and infrared (IR) spectroscopic studies of some of the 1,2,5-triheteropine rings are discussed.

13.15.3.1 X-Ray Crystallography

The structural and stereochemical features of the compounds listed in Table 1 have been exclusively derived from their single crystal X-ray diffraction studies.

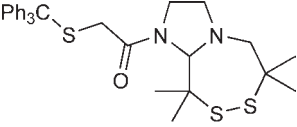
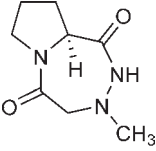
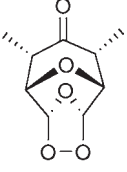
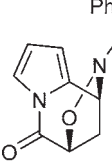
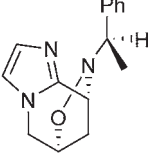
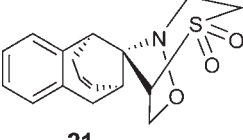
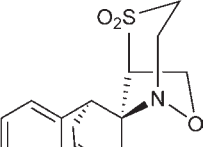
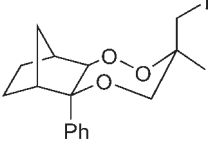
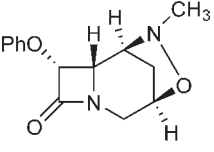
13.15.3.2 NMR Spectroscopy

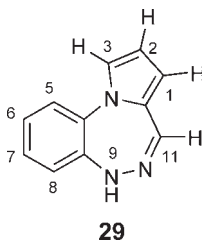
Proton and ^{13}C NMR spectroscopic studies have been extensively used for the structural elucidation, as discussed below.

13.15.3.2.1 1,2,5-Triazepines

The ^1H NMR spectrum of triazepine **29** has a broad singlet at δ 6.67 ppm assignable to the NH-proton. The H-11 appears downfield at δ 7.45 ppm as a singlet. The triplet at δ 6.32 ($J_{2,3} = 3.0 \text{ Hz}$) and the doublet of doublets at 6.45 ($J_{1,2} = 3.6 \text{ Hz}$) are due to H-2 and H-1, respectively, whereas the H-3 signal overlaps with that of H-5 at δ 7.10–7.12 ppm <1996T10751>.

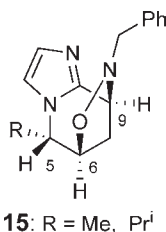
Table 1 X-Ray crystallographic studies of compounds

<i>Compound</i>	<i>Reference</i>
 25	1996CJC574
 26	1996CC85
 17	1996J(P1)1101
 6  11	2002T4445
 21  22	2003T9997
 27	2003JME1957
 (-)-28	1999TL5391

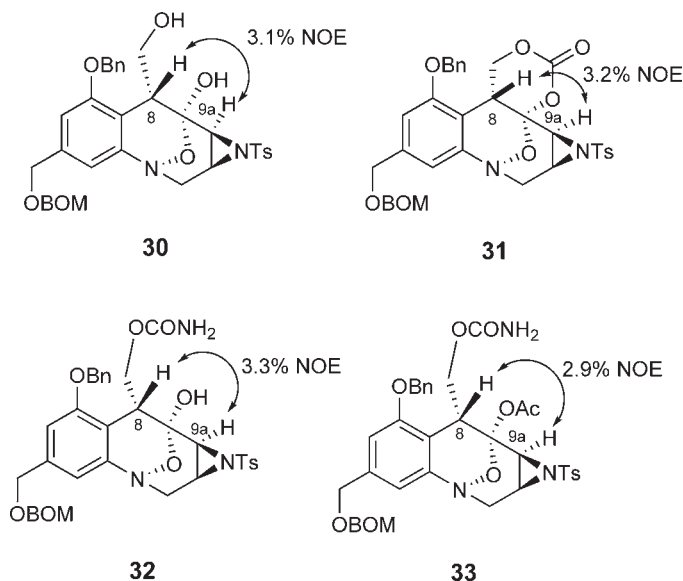


13.15.3.2.2 1,2,5-Oxadiazepine

The bridged **15** exists as a 3:1 mixture of invertomers at 25 °C and the relative configuration of the stereocenters (C-5, C-6, and C-9) has been determined by one-dimensional nuclear Overhauser enhancement spectroscopy (1-D NOESY) experiments [\[2004TA3181\]](#).

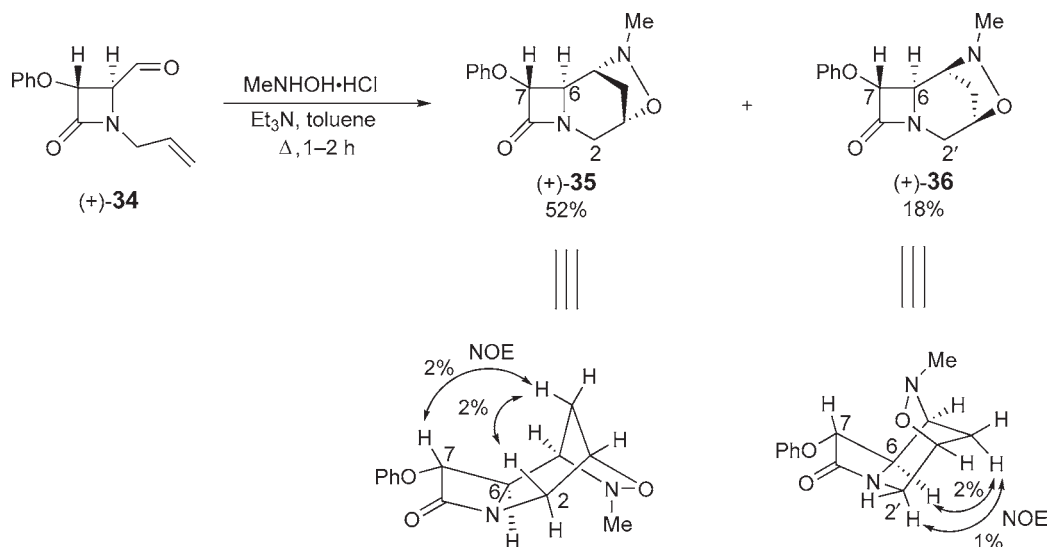


The stereochemical assignment of H-9a of the bridged **30–33** was accomplished from the nuclear Overhauser effect (NOE) data between H-8 and H-9a of **30–33** which were determined to be 3.1%, 3.2%, 3.3%, and 2.9%, respectively [\[1997T10253\]](#).

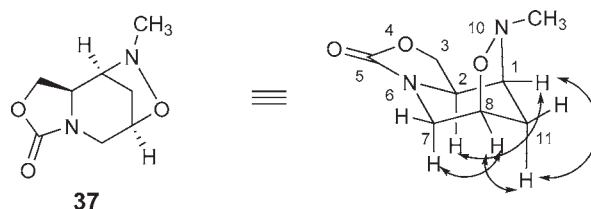


The intramolecular nitronc–alkene cycloaddition of *trans*-alkenylaldehyde (+)-**34** results in a 75:25 mixture of bridged diastereomers (+)-**35** and (+)-**36** in 52% and 18% yield, respectively ([Scheme 5](#)). The stereochemistry of these isomers has been assigned using NOE data [\[2005EJO1680\]](#).

The structural features of **37** have been determined from the 1-D and 2-D NMR spectroscopic data. The ¹H NMR spectrum of **37** shows that H-1 couples equally with both H-2ax and H-11ax ($J_{HH} = 4.8$ Hz). The H-8 couples with H-11ax and H-7ax with J values 6.0 and 4.8 Hz, respectively. These data reveal that both H-1 and H-8 possess an equatorial orientation and are therefore in *cis*-relationship. This has also been confirmed from the 2-D NOESY correlations of **37** [\[2001JP1452\]](#).

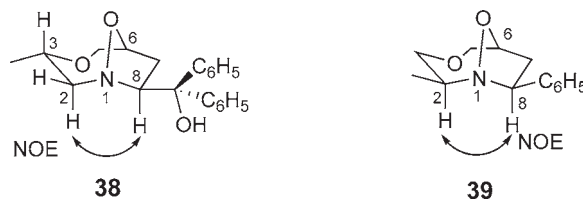


Scheme 5



13.15.3.2.3 1,5,2-Dioxazepines

The stereochemistry of **38** and **39** has been confirmed by ^1H , ^{13}C , and NOESY spectra. The NOE correlation between H-2 and H-8 of **38** and **39** reveals that both these protons are in quasi-axial positions. For **38**, the *trans*-relationship between H-2 (*endo*) and H-3 has been inferred from the coupling constant $J_{23} = 10.3 \text{ Hz}$ <1997SL1004>.



13.15.3.2.4 Thiadiazepines

13.15.3.2.4(i) 1,2,5-Thiadiazepine

The structural elucidation of the 1,2,5-thiadiazepine **40** has been done from the ^1H and ^{13}C NMR spectroscopic data given in Table 2 <1996BMC667>.

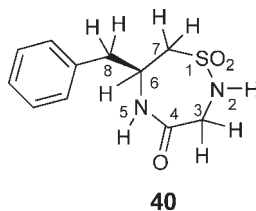
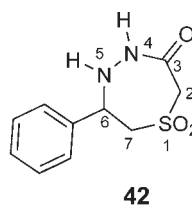
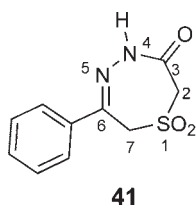


Table 2 ^1H and ^{13}C NMR data for **40**

H	δ (ppm)	J (Hz)			
H-2	5.21, d	10.3			
H-3	3.68, dd	$J_{\text{gem}} = 16.5, J_{\text{vic}} = 0.7$			
	4.11, dd	$J_{\text{gem}} = 16.5, J_{\text{vic}} = 12.1$			
H-5	6.10, br s				
H-6	4.22, m				
H-7	3.03, dd	$J_{\text{gem}} = 13.9, J_{\text{vic}} = 10.3$			
	3.38, d	$J_{\text{gem}} = 13.9$			
H-8	2.91, dd	$J_{\text{gem}} = 14.2, J_{\text{vic}} = 7.2$			
	2.96, dd	$J_{\text{gem}} = 14.2, J_{\text{vic}} = 6.4$			
C	C -3	C -4	C -6	C -7	C -8
δ (ppm)	46.9	173.0	49.9	58.5	40.7

13.15.3.2.4(ii) 1,4,5-Thiadiazepine

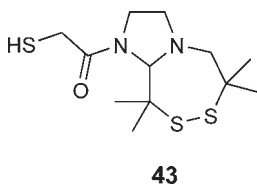
The ^1H NMR spectrum of the tetrahydro[1,4,5]thiadiazepine **41** has signals at 4.25 and 4.89 ppm due to H-2 and H-7, respectively, and a broad singlet at 10.65 ppm for NH, which disappears upon treatment with D_2O . Similarly, the singlet and two multiplets of **42** at 4.35, 4.17–4.22, and 3.84–3.89 ppm have been assigned to H-2, H-6, and H-7, respectively. The NH proton of **42** appears as a broad singlet at 10.58 ppm, which disappears upon treatment with D_2O . The ^{13}C NMR signals of **41** and **42** are given in Table 3 <2004JCM556>.

**Table 3** ^{13}C NMR data for **41** and **42**

<i>Compound</i>	δ (ppm)			
	<i>C-2</i>	<i>C-3</i>	<i>C-6</i>	<i>C-7</i>
41	67.2	166.3	154.8	61.2
42	60.6	165.7	58.9	66.8

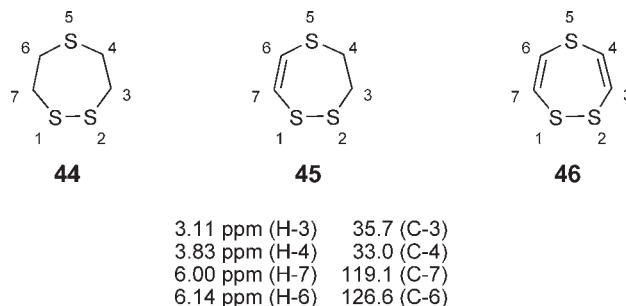
13.15.3.2.5 1,2,5-Dithiazepine

The 1,2,5-dithiazepine **43** has been characterized by NMR spectroscopy. The presence of the thiol group in **43** was confirmed by the addition of D_2O , which causes (1) the disappearance of a triplet at 2.07 ppm in the ^1H NMR spectrum, and (2) the removal of the splitting in the signal at 3.31 ppm due to the CH_2 protons adjacent to SH group <1996CJC574>.



13.15.3.2.6 1,2,5-Trithiepinines

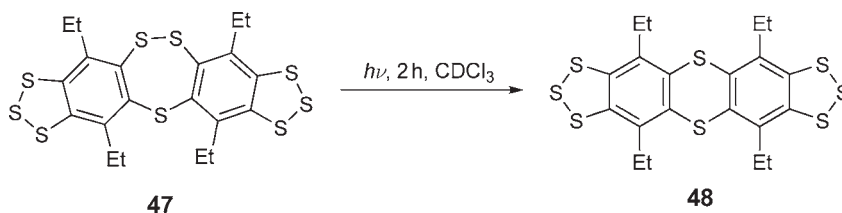
The structural assignment of the trithiepinines **44–46** has been performed using ^1H , ^{13}C , heteronuclear multiple bond correlation (HMOC), heteronuclear multiple quantum correlation (HMBC), and variable-temperature NMR spectroscopic data. The 60 MHz ^1H NMR spectrum of trithiepine **44** exhibits a broad singlet at 3.05 ppm in CDCl_3 , whereas a narrow ABCD multiplet was observed for all of the protons in a 300 MHz spectrum. The two ^{13}C NMR signals at 37.6 and 31.2 ppm have been assigned to C-3/C-7 and C-4/C-5, respectively <1997JOC2432>.



The dihydrotrithiepine **45** has been found to be a dynamic system, since the two CH_2 groups, expected to appear as two triplets, were observed as a triplet at 3.11 ppm ($J = 6.0$ Hz) and as a broad multiplet at 3.83 ppm. To confirm that **45** is dynamic, ^1H dynamic NMR (DNMR) study was performed at various temperatures in a 400 MHz instrument. It was observed that, at -95°C , the signals for both CH_2 groups change into two separate, well-resolved AB systems with further coupling <1997JOC2432>.

The ^1H NMR spectrum of the trithiepine **46** exhibits an AA'XX' system with $H_A = 7.24$ ppm ($J_{AX} = 9.0$ Hz) and $H_X = 6.57$ ppm ($J_{AX} = 9.0$ Hz), while its ^{13}C NMR spectrum gives two signals at 128.6 and 131.5 ppm <1997JOC2432>.

Trithiepine **47** was dissolved in DCCl_3 and the photolysis was monitored by ^1H NMR spectroscopy to determine the kinetic parameter of the reaction. In the spectra, the decrease of the intensity of signals of **47** and the appearance and increase of the intensity of new signals of **48** were observed. The plot of $\ln(\text{trithiepine})$ versus the reaction time reveals that the desulfurization of **47** to **48** follows a first-order kinetics with respect to the substrate concentration. The rate constant and the half-life period of this photoreaction were calculated to be $k = (2.82 \pm 1.11) \times 10^{-4}$ and $t_{1/2} = 41.0$ min <2000TL1801>.



The structure of trithiepine **49** has been elucidated using ^1H and ^{13}C NMR spectroscopy and the data are given in Table 4 <2003T2855>.

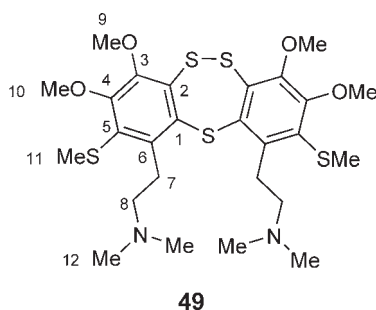


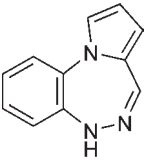
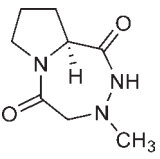
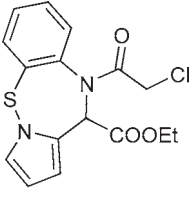
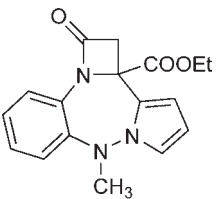
Table 4 NMR spectroscopic data for **49**

Position	δ (ppm)	
	^1H	^{13}C
1		136.6
2		133.4
3		157.2
4		154.2
5		132.8
6		136.4
7	3.59, m	28.7
8	3.17, m	57.7
9	3.95, s	61.5
10	3.94, s	61.3
11	2.46, s	19.2
12	3.01, s	43.5

13.15.3.3 IR Spectroscopy

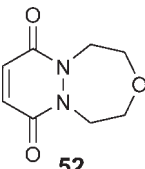
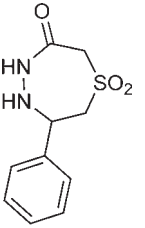
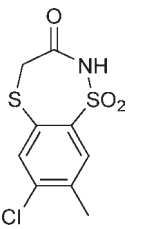
The IR spectra of most of the 1,2,5-triheteropines have been reported, but no systematic study has appeared. The IR spectral data of selected 1,2,5-triheteropine rings are given in [Table 5](#).

Table 5 IR absorption of 1,2,5-triheteropines

Compound	IR absorption (cm^{-1})	Reference
 29	3370 1620 (NH) (C=N)	1996T10751
 26	3101 1699 1597 (NH) (CON) (CONH)	1997J(P1)2297
 50	1670, 1740 (CO)	1996BMC837
 51	1720, 1760 (CO)	1996FES425

(Continued)

Table 5 (Continued)

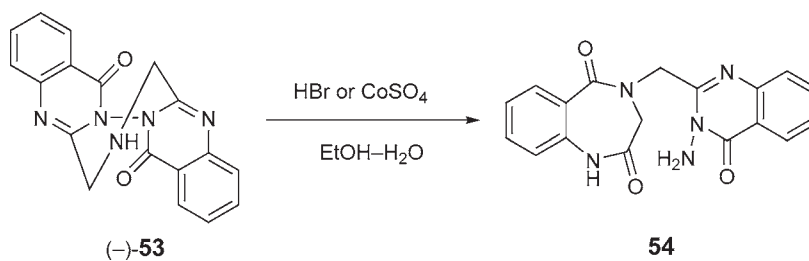
Compound	IR absorption (cm^{-1})	Reference
 52	1680 1600 1140 (CO) (C=C) (COC)	1997CHE1466
 42	3304, 1638, 1322, 1129 (NH) (CO) (SO ₂)	2004JCM556
 23	3125, 3025 1700 1350, 1170 (NH) (CO) (SO ₂)	2001H(55)753

13.15.4 Reactivity of Nonconjugated Rings

This section covers the reactivity of nonconjugated fused, bridged, and bicyclic 1,2,5-triheteropine rings.

13.15.4.1 1,2,5-Triazepines

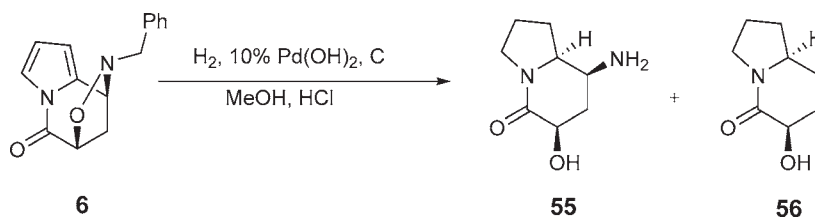
The 1,2,5-triazepinodiquinazoline **53** upon reaction with either HBr or aqueous CoSO₄ affords the rearranged product **54** (Scheme 6) <1999CC1991>.

**Scheme 6**

13.15.4.2 Oxadiazepines

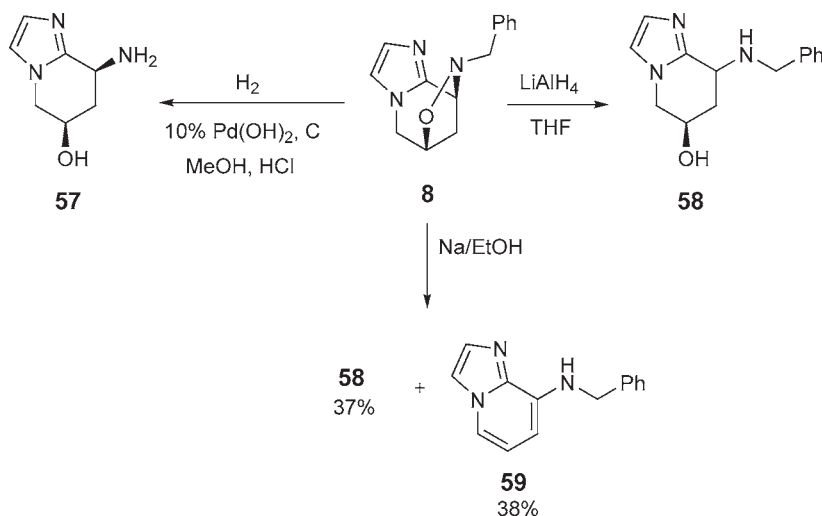
13.15.4.2.1 1,2,5-Oxadiazepine

The catalytic hydrogenation of the bridged fused pyrrole **6** with palladium and charcoal in MeOH results in the cleavage of the N–O bond of **6** giving an amino alcohol **55** and alcohol **56** in 28% and 24% yields, respectively (Scheme 7) <2001H(55)1987>.



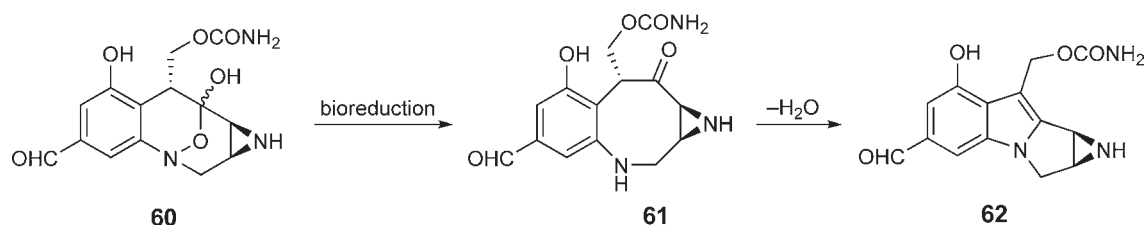
Scheme 7

Similarly, the hydrogenation of **8** with $\text{Pd}(\text{OH})_2/\text{C}$ in the presence of HCl affords the amino alcohol **57** in excellent yields, while lithium aluminium hydride (LAH) reduced **8** to furnish the N-benzylated amino alcohol **58** in moderate yield (Scheme 8). The reaction of **8** with sodium metal in EtOH results in a mixture of **58** and **59** in 37% and 38% yield, respectively <2002T4445>.



Scheme 8

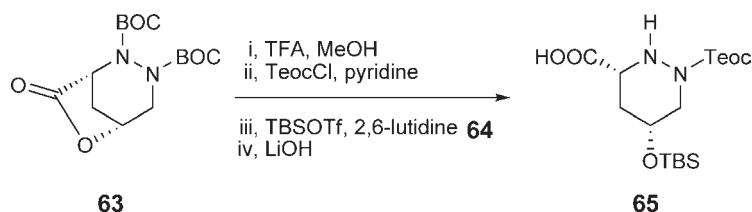
The mode of antitumor action of **60** is activated *in vivo* by bioreduction of the hydroxylamine moiety (Scheme 9) leading to the ring-expanded product, azocinone **61**, which upon cyclization furnishes the mitosene-like **62** <1997T10229>.



Scheme 9

13.15.4.2.2 1,4,5-Oxadiazepine

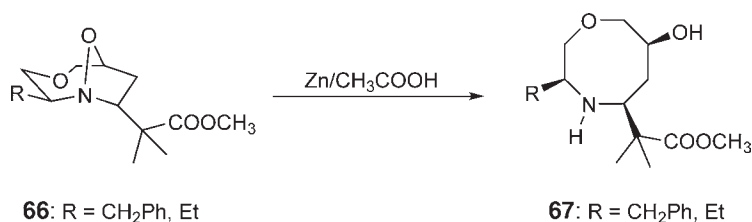
The 1,4,5-oxadiazepine **63** was transformed into **65** by a four-step reaction sequence: (1) cleavage of both *t*-butoxycarbonyl (BOC) and the lactone, (2) acylation of the remote amino group with 2-(trimethylsilyl)ethyloxycarbonyl chloride (TeocCl), (3) protection of the alcohol functionality with a silyl group, and (4) ester hydrolysis (**Scheme 10**) <1998AGE2995, 2001CEJ41>.



Scheme 10

13.15.4.3 1,5,2-Dioxazepine

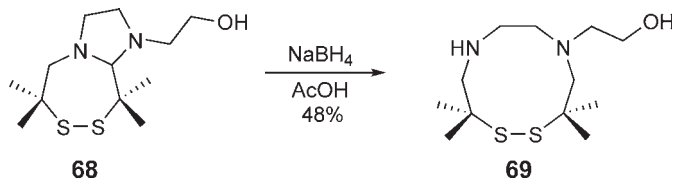
The reaction of 1,5,2-dioxazepine **66** with zinc and AcOH results in the reductive cleavage of the N–O bond, furnishing either methyl 2-(3-benzyl-7-hydroxy-1,4-oxazocan-5-yl)-2-methylpropanoate or methyl 2-(3-ethyl-7-hydroxy-1,4-oxazocan-5-yl)-2-methylpropanoate **67** (**Scheme 11**) <1999ZNB519>.



Scheme 11

13.15.4.4 1,2,5-Dithiazepine

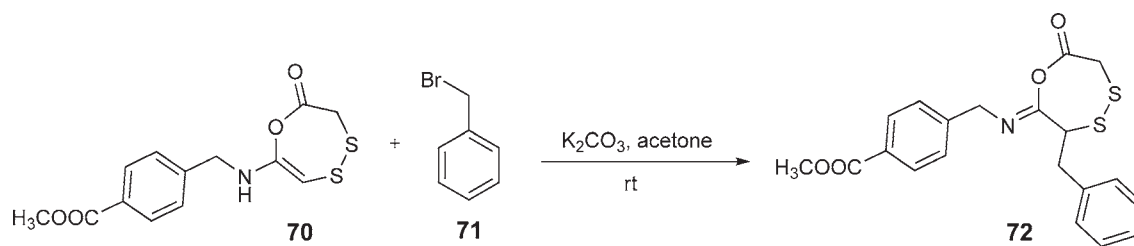
The 6,6,9,9-tetramethyl-2,3,5,6,9,10-hexahydro-1*H*-imidazo[2,1-*d*][1,2,5]dithiazepin-1-ylethanol **68** upon reduction with sodium borohydride undergoes reductive cleavage of the C–N bond of the seven-membered ring to afford 3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodecan-5-yl-ethanol **69** (**Scheme 12**) <1998OPP485>.



Scheme 12

13.15.4.5 1,4,5-Oxadithiepine

The enamino-1,4,5-oxadithiepine **70** reacts with benzyl bromide **71** in the presence of potassium carbonate in acetone to afford **72** in moderate yield (**Scheme 13**) <2002TL4861>.



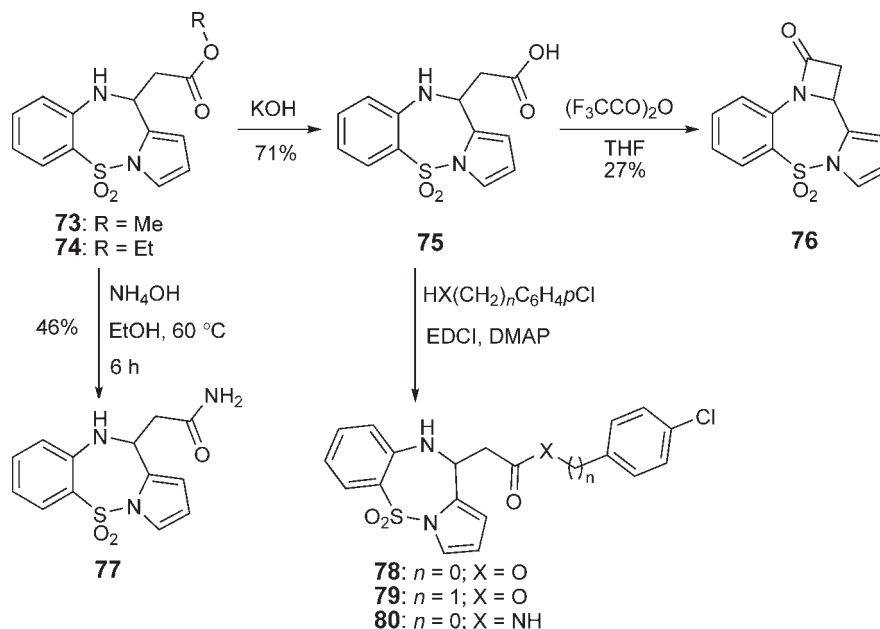
Scheme 13

13.15.5 Reactivity of Substituents Attached to Ring Carbon Atoms

This section describes the reactivity of the substituents attached to the ring carbons of 1,2,5-triheteropines.

13.15.5.1 1,2,5-Thiadiazepine

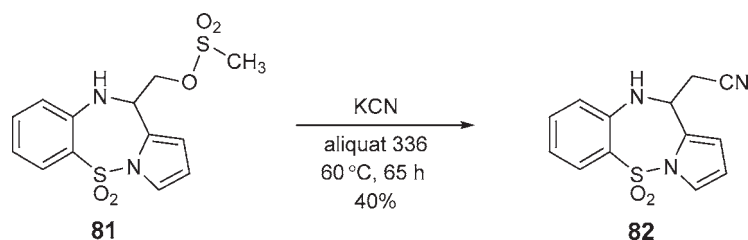
The reaction of methyl 10,11-dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-11-acetate 5,5-dioxide **73** or the corresponding ethyl ester **74** with potassium hydroxide in EtOH at 25 °C gave the acid **75** (Scheme 14), which upon treatment with trifluoroacetic anhydride in tetrahydrofuran (THF) underwent intramolecular cyclization to afford **76**. The 1,2,5-thiadiazepines **73** and **74** were then heated with an excess of concentrated ammonium hydroxide to give the carboxamide **77**. The acid **75** upon reaction with 4-chlorophenol, 4-chlorobenzyl alcohol, or 4-chloroaniline in the presence of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP) afforded the respective esters and amide **78–80** <1996FES425>.



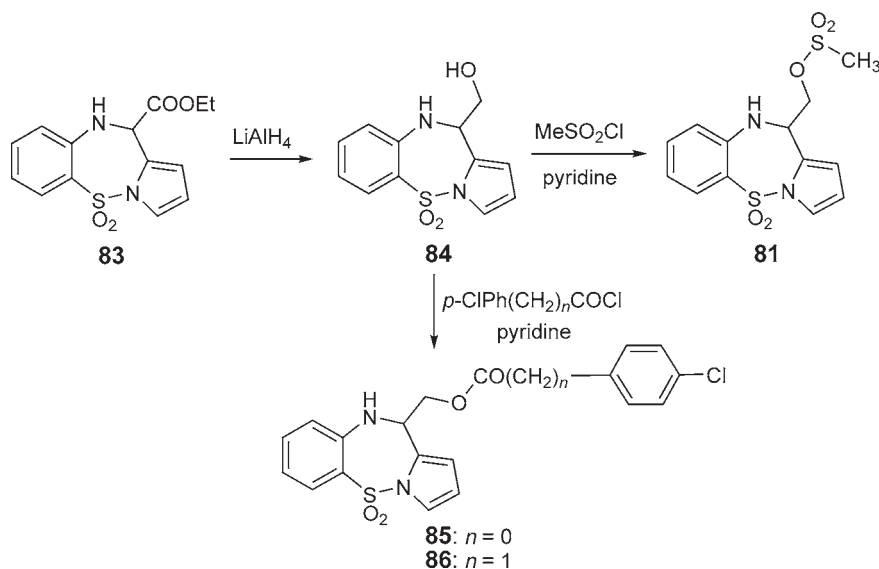
Scheme 14

The reaction of **81** with KCN in the presence of tricaprylmethylammonium chloride (aliquat 336) in 1:1 benzene–water gives the nitrile **82** (Scheme 15) <1996FES425>.

The reduction of 1,2,5-thiadiazepine **83** with LAH affords the alcohol **84**, which upon reaction with methanesulfonyl chloride gives the mesylate **81** (Scheme 16). The reaction of **84** with 4-chlorobenzoyl chloride and 4-chlorophenylacetyl chloride in the presence of pyridine furnishes the respective esters **85** and **86** <1996BMC837>.



Scheme 15



Scheme 16

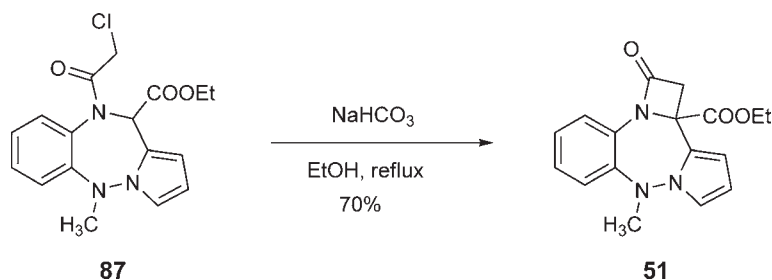
13.15.6 Reactivity of Substituents Attached to Ring Heteroatoms

This section discusses the reactions of substituents attached to the ring heteroatoms of the 1,2,5-triheteropine rings.

13.15.6.1 Reactivity of Substituents Attached to Ring Nitrogen

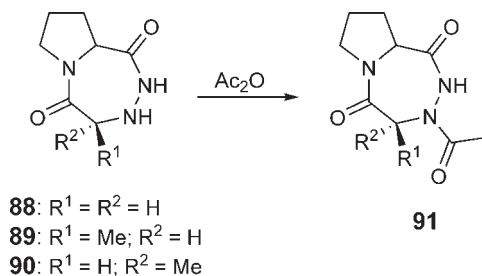
13.15.6.1.1 1,2,5-Triazepines

The intramolecular cyclization of 10-chloroacetyl-10,11-dihydro-11-ethoxycarbonyl-5-ethyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzotriazepine **87** in the presence of sodium hydrogen carbonate results in the formation of ethyl 1,2-dihydro-2-oxo-8-methyl-12*b*-azeto[2,1-*d'*]pyrrole[1,2-*b'*][1,2,5]benzotriazepine-12*b*-carboxylate **51** (Scheme 17) <1996FES425>.



Scheme 17

The triazepines **88–90** react with acetic anhydride affording *N*¹-acetyl-1,2,5-triazepine-3,6-diones **91** (Scheme 18) <1996CC85, 1997J(P1)2297>.

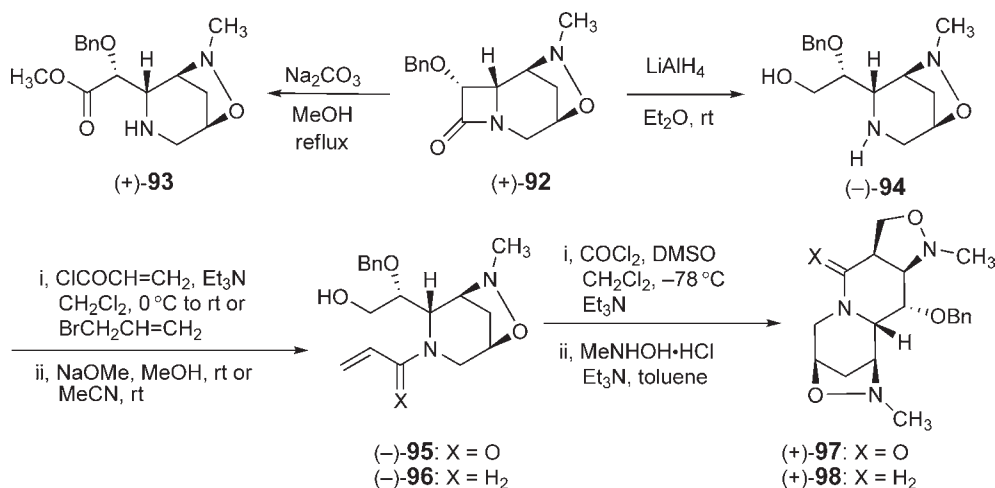


Scheme 18

13.15.6.1.2 Oxadiazepines

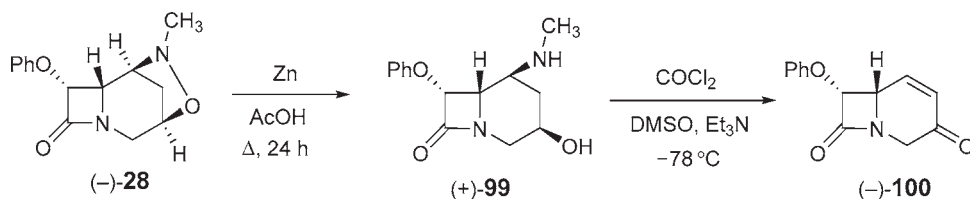
13.15.6.1.2(i) 1,2,5-Oxadiazepine

The reaction of **92** with sodium carbonate in MeOH affords the ester **93**, while the reduction of **92** with LAH leads to ring cleavage, affording the bridged ring system **94** (Scheme 19). Then **94** was converted to the quinolizidines **97** and **98** via **95** and **96**, respectively, in a two-step reaction in 62% and 58% yields <2002SL85>.



Scheme 19

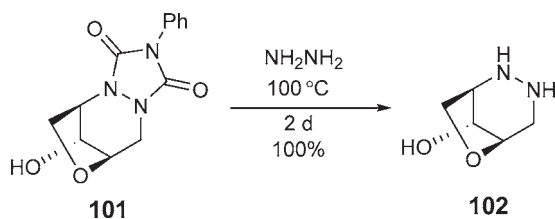
The reductive cleavage of N–O bond in **28** with zinc and AcOH gave the 1-amino-3-hydroxycarbacepham **99**, which upon treatment with Swern's reagent affords 3-oxocarbacepham **100** in quantitative yield (Scheme 20) <1999TL5391>.



Scheme 20

13.15.6.1.2(ii) 1,4,5-Oxadiazepine

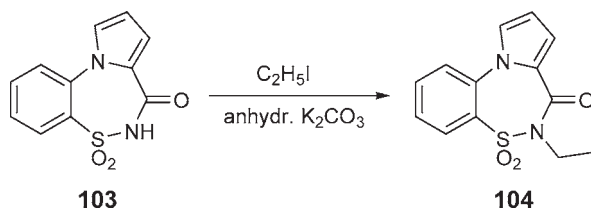
The reaction of **101** with hydrazine furnishes a quantitative yield of 3,4-*trans*-4,5-*trans*-4-hydroxy-5,3-oxymethyl-*trans*-hexahydropyridazine **102** (Scheme 21) <1997T9357>.



Scheme 21

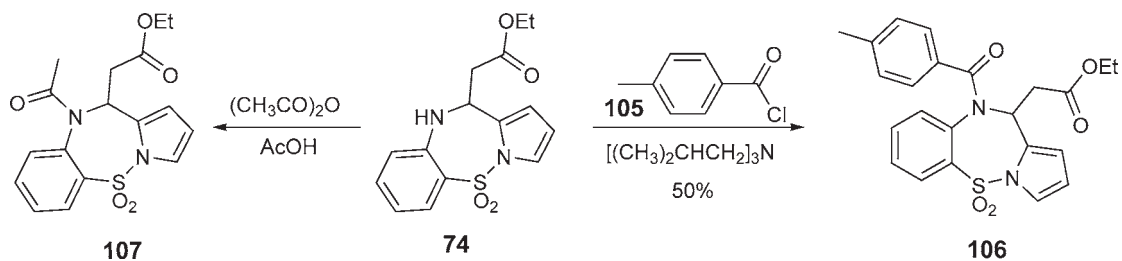
13.15.6.1.3 1,2,5-Thiadiazepine

The pyrrole[2,1-*d*][1,2,5]benzothiadiazepin-7(6*H*)-one 5,5-dioxide **103** upon reaction with ethyl iodide in the presence of anhydrous potassium carbonate gives the *N*-ethyl derivative **104** (Scheme 22) <1997FES375>.



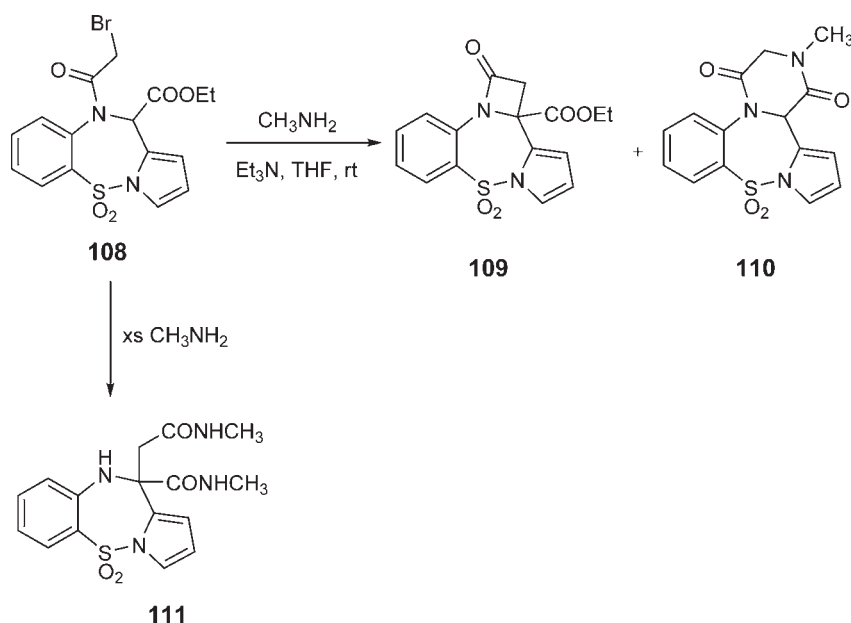
Scheme 22

The reaction of **74** with 4-methylbenzenecarbonyl chloride **105** in the presence of triisobutylamine affords ethyl 10,11-dihydro-10-(4-toluoyl)pyrrole[1,2-*b*][1,2,5]benzothiadiazepine-11-acetate 5,5-dioxide **106** (Scheme 23) <1996FES425>. Acetylation of **74** was performed by reaction with acetic anhydride to give **107** <1996BMC837>.



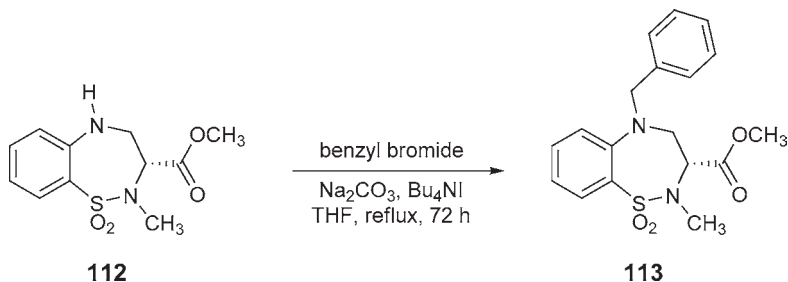
Scheme 23

The benzo[1,2,5]thiadiazepine **108** upon reaction with an equimolar amount of aqueous methylamine and Et_3N furnishes a mixture of **109** and **110** in 15% and 19% yields, respectively, whereas an excess of methylamine afforded exclusively **111** (Scheme 24) <1996FES425>.



Scheme 24

The alkylation of 1,2,5-thiadiazepine **112** with benzyl bromide in the presence of sodium carbonate and tetrabutylammonium iodide affords (±)-5-*N*-benzyl-3-methoxycarbonyl-2-*N*-methyl[1,2,5]benzothiadiazepine 1,1-dioxide **113** in 92% yield (Scheme 25) <2001T7021>.



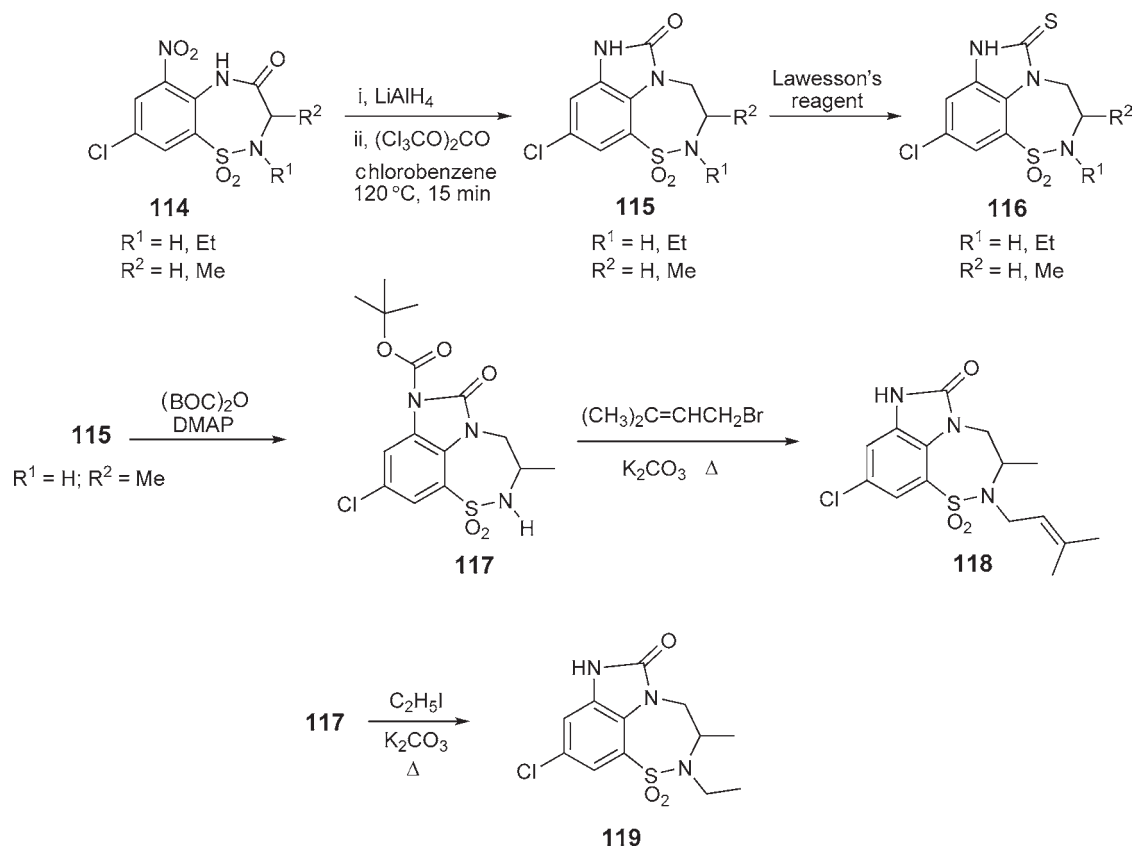
Scheme 25

The reduction of **114** with LAH, followed by reaction with triphosgene, led to benzo[1,2,5]thiadiazepin-6(4*H*)-one 1,1-dioxide **115**, which upon treatment with Lawesson's reagent gave the corresponding thiocarbonyl derivative **116** (Scheme 26). The 1,2,5-thiadiazepine **115** was acylated by treatment with di-*t*-butyldicarbonate in the presence of *N,N*-dimethylaminopyridine to afford **117**, which is alkylated with 3-methyl-2-butenyl bromide or ethyl iodide to give **118** and **119**, respectively <2002JHC81>.

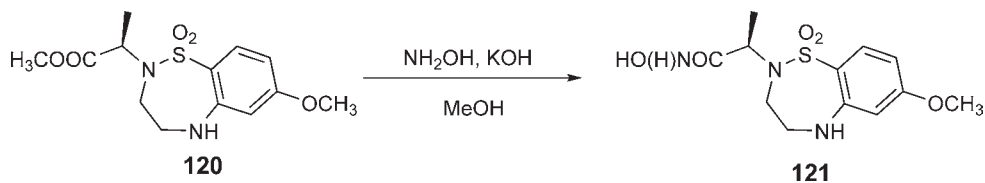
The methyl 1,2,5-thiadiazepinecarboxylate **120** was converted into the hydroxamate **121** by treatment with hydroxylamine in the presence of potassium hydroxide in MeOH (Scheme 27) <2003JME1811>.

13.15.6.1.4 1,2,5-Dithiazepine

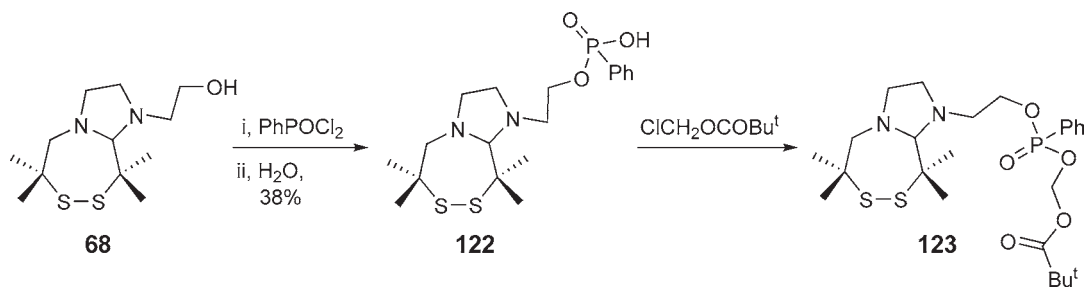
The esterification of 1,2,5-dithiazepine **68** with phenylphosphonic dichloride in benzene and subsequent hydrolysis gave **122**, which upon further esterification with chloromethyl pivalate in MeOH afforded *O*-(1,1,4,4-tetramethyl-2,3,5,6,9,10-hexahydroimidazo[2,1-*d*][1,2,5]dithiazepin-9-yl)ethyl *O*-pivaloyloxymethyl phenylphosphonate **123** (Scheme 28) <1998OPP485>.



Scheme 26



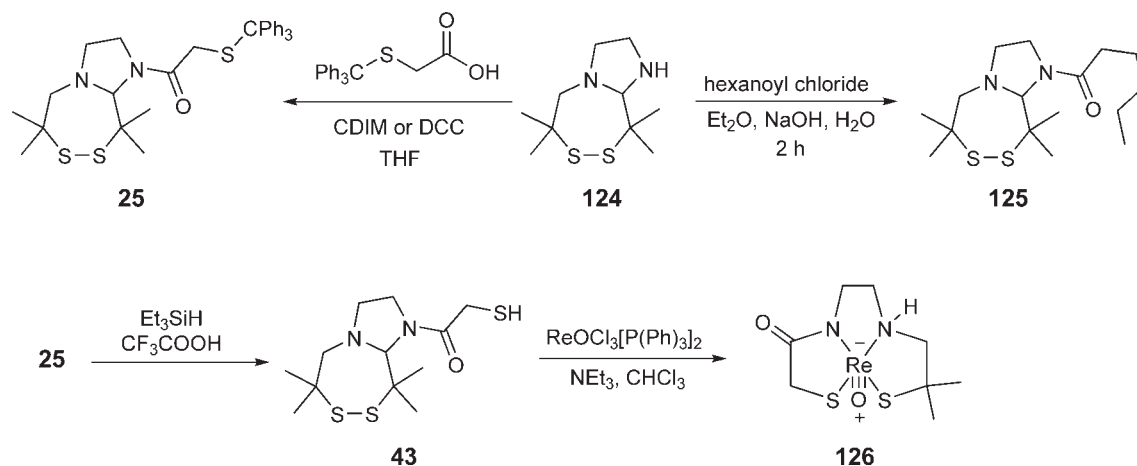
Scheme 27



Scheme 28

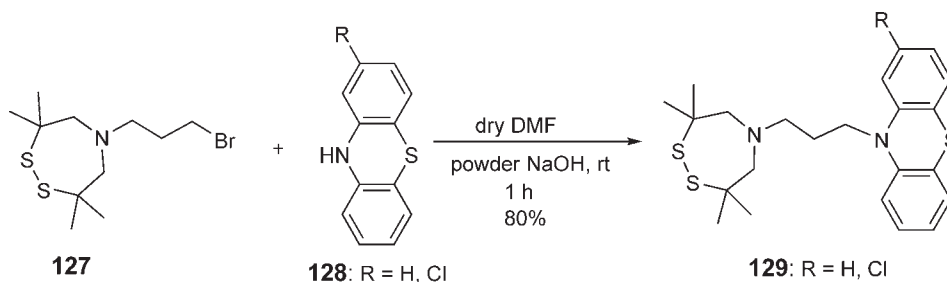
The reaction of 1,2,5-dithiazepine **124** with hexanoyl chloride in the presence of sodium hydroxide led to the formation of 1-hexanoyl-6,6,9,9-tetramethylhexahydroimidazo[2,1-*d*][1,2,5]dithiazepine **125** in 70% yield (Scheme 29) <1996AJC239>. The subsequent reaction of **124** with 2-(triphenylmethylthio)ethanoic acid in the presence of

N,N'-carbonyldiimidazole (CDIM) or 1,3-dicyclohexylcarbodiimide (DCC) in THF gave **25** as a colorless solid. Dithiazepine **43** was obtained from **25** by the reaction of the latter with trifluoroacetic acid (TFA) in triethylsilane, which was then treated with $\text{ReOCl}_3[\text{P}(\text{Ph})_3]_2$ to furnish complex **126** <1996CJC574>.



Scheme 29

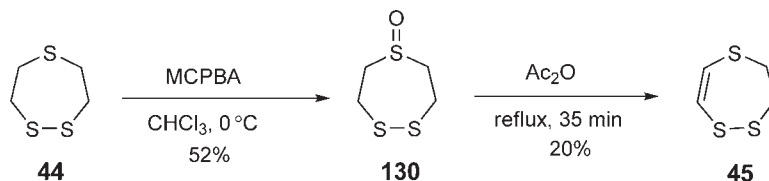
Dithiazepine **127** upon reaction with phenothiazine or chlorophenothiazine **128** in dimethylformamide (DMF) in the presence of sodium hydroxide gave the 1,2,5-dithiazepine **129** (Scheme 30) <2001BML1859>.



Scheme 30

13.15.6.2 Reactivity of Substituents Attached to Ring Sulfur

Oxidation of 1,2,5-trithiepine **44** with *m*-chloroperoxybenzoic acid in CHCl_3 resulted in the formation of crystalline monosulfoxide **130**, which underwent Pummerer rearrangement upon reaction with acetic anhydride to furnish 6,7-dihydro[1,2,5]trithiepin **45** (Scheme 31) <1997JOC2432>.

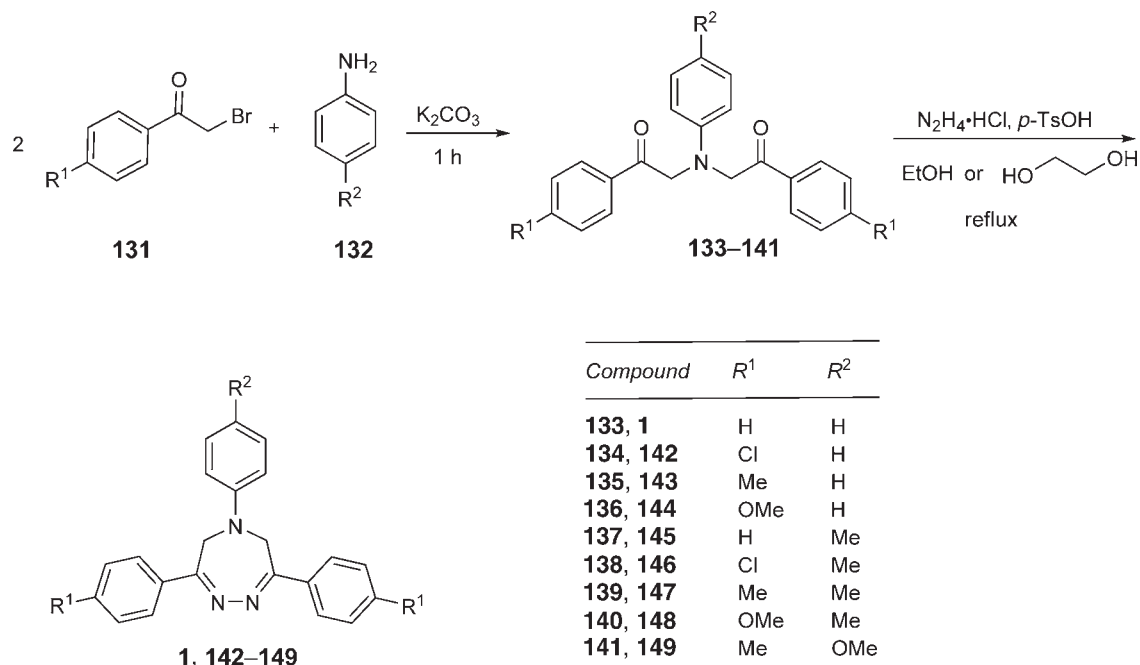


Scheme 31

13.15.7 Ring Synthesis from Acyclic Compounds

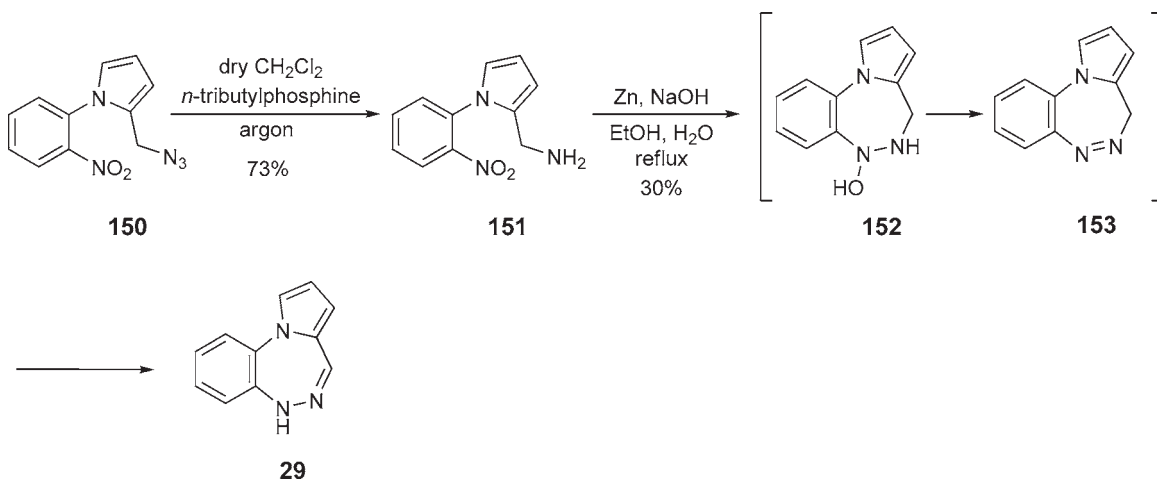
13.15.7.1 1,2,5-Triazepines

The reaction of *N,N*-bis(phenacyl)anilines **133–141** with hydrazine hydrochloride in EtOH or ethylene glycol under reflux led to the formation of novel 1,2,5-triazepines (**1**, **142–149**) (Scheme 32). The precursors **133–141** were, in turn, prepared from the solventless reaction of various phenacyl bromides **131** and anilines **132** in the presence of potassium carbonate <2007JHC133>.



Scheme 32

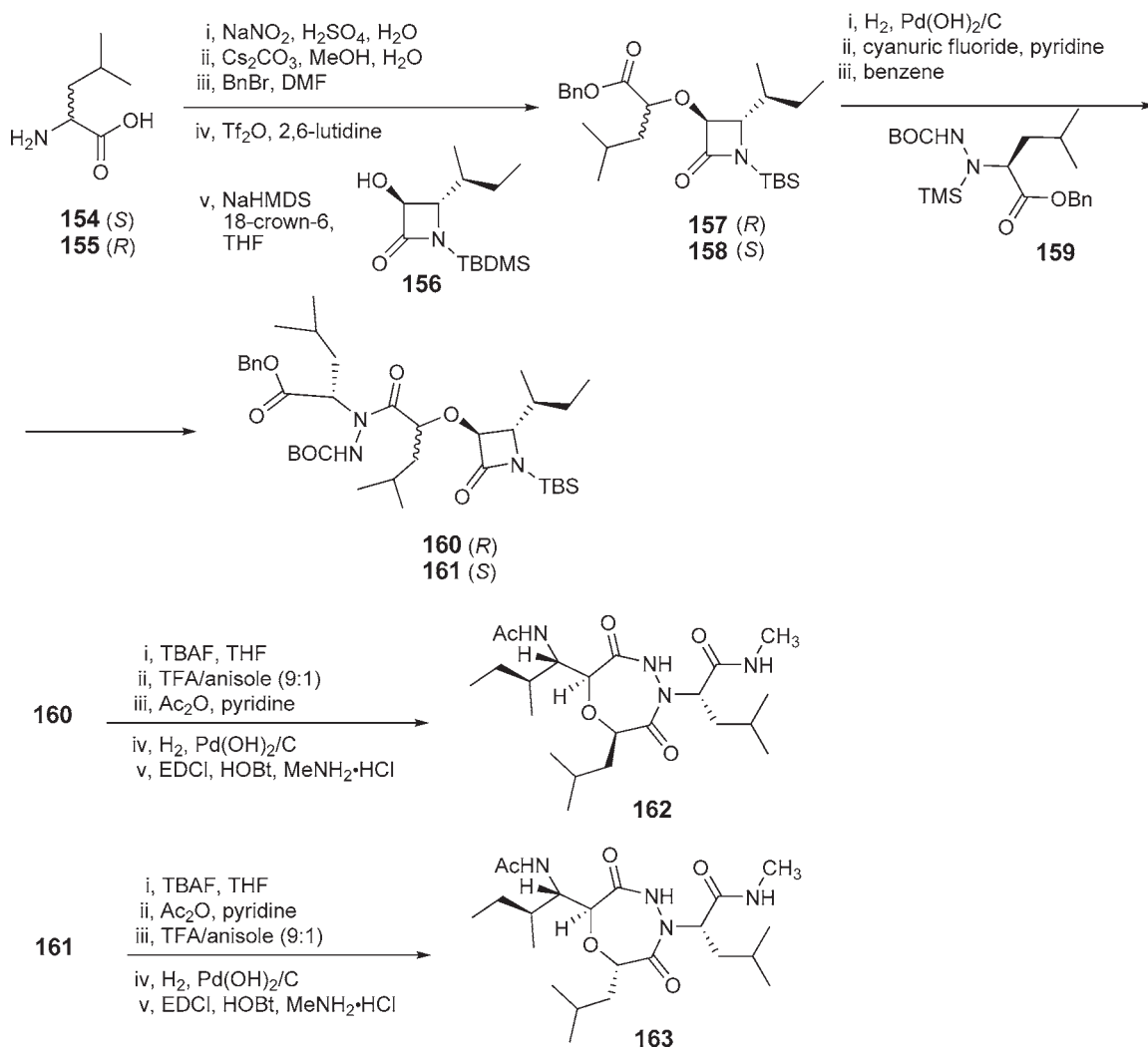
The selective reduction of the azide of pyrrole **150** via Staudinger reaction followed by hydrolysis led to the formation of **151**, which underwent reductive cyclization with zinc under basic conditions to afford pyrrole[1,2,5]-benzotriazepine **29** (Scheme 33) <1996T10751>.



Scheme 33

13.15.7.2 1,4,5-Oxadiazepine

The two epimeric γ -turn mimetics **162** and **163** were synthesized from the respective isomer of leucine **154** and **155** (Scheme 34). The two chiral reagents **156** and **159** were synthesized from (*S*)-BOC isoleucine and (*R*)-leucine, respectively <1997TL6961>.



Scheme 34

13.15.7.3 Dioxazepines

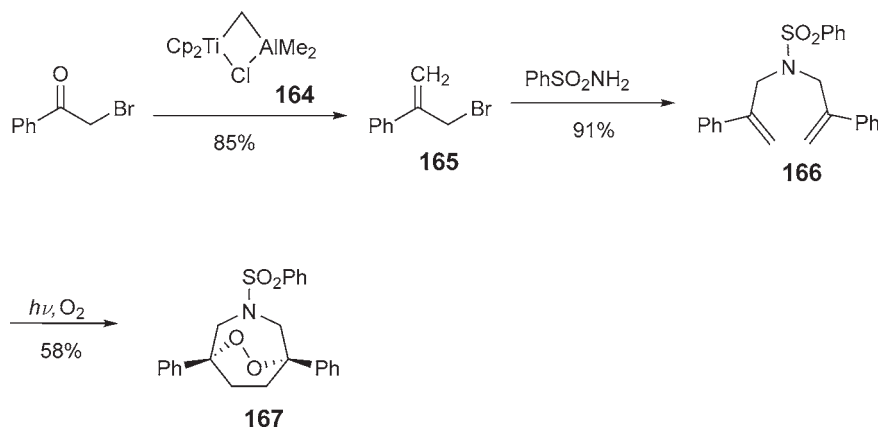
13.15.7.3.1 1,2,5-Dioxazepine

Tebbe methylation <1978JA3611> of α -bromoacetophenone resulted in the formation of allylic bromide **165**, which upon reaction with benzenesulfonamide gave the 1,6-diene **166** (Scheme 35). The acyclic diene **166** underwent photooxidative cyclization to form 1,2,5-dioxazepine **167** <1996TL815>.

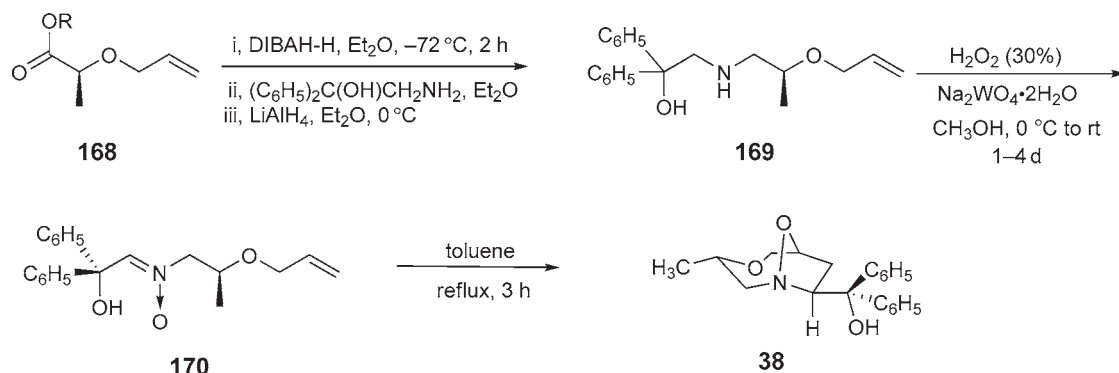
13.15.7.3.2 1,5,2-Dioxazepine

The ester **168** on reduction with diisobutylaluminium hydride (DIBAL-H) followed by the treatment with amino alcohol, $(\text{C}_6\text{H}_5)_2\text{C}(\text{OH})\text{CH}_2\text{NH}_2$, followed by reduction led to the formation of intermediate **169**, which was

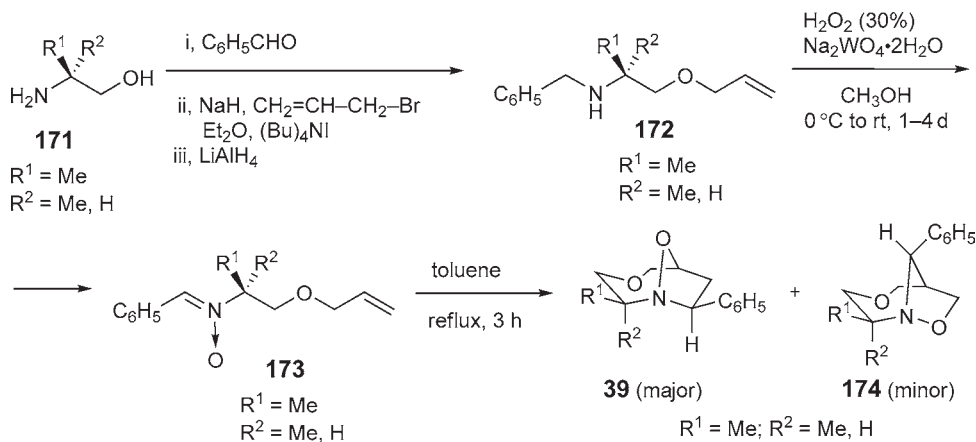
converted to the nitron **170**. On heating in toluene, the nitron underwent intramolecular cycloaddition, regio- and stereoselectively, affording the bridged bicyclic 1,5,2-dioxazepine **38** (Scheme 36). Further, the intramolecular cycloaddition of **173**, which has been derived from the secondary amine **172**, resulted in the formation of two isomers **39** and **174** (Scheme 37) <1997SL1004>.



Scheme 35

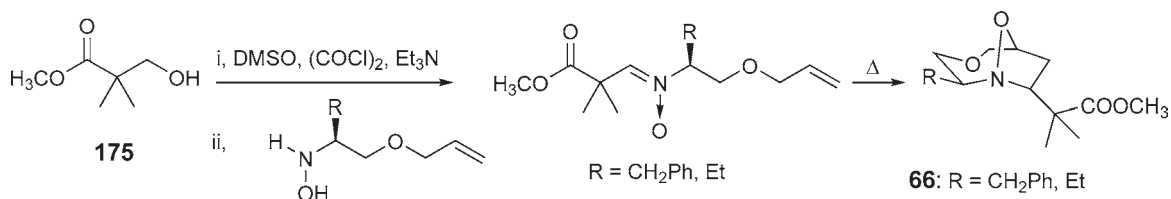


Scheme 36



Scheme 37

Using a similar protocol, the synthesis of the bridged 1,5,2-dioxazepine **66** has been effected from **175** (Scheme 38) <1999ZNB519>.

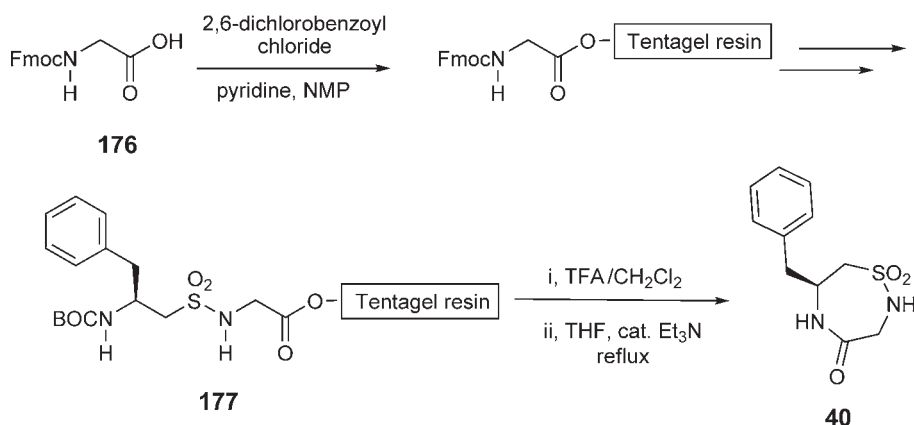


Scheme 38

13.15.7.4 Thiadiazepines

13.15.7.4.1 1,2,5-Thiadiazepine

The 1,2,5-thiadiazepine **40** was synthesized from the sulfonamide **177** by removing the BOC upon treatment with TFA, followed by heating the mixture in the presence of Et₃N (Scheme 39). The sulfonamide **177** was, in turn, synthesized from **176** <1996BMC667> in a multistep protocol.



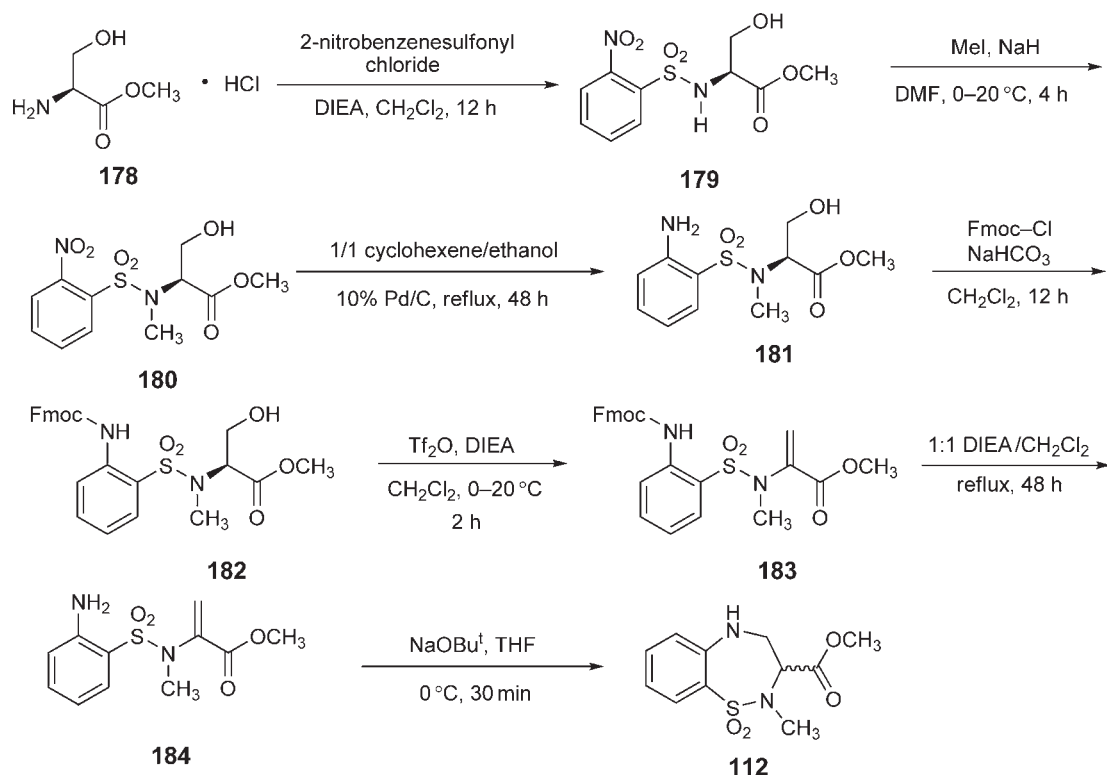
Scheme 39

The sulfonamide **179** was obtained from L-serine methyl ester hydrochloride **178** by the reaction of the latter with 2-nitrobenzenesulfonyl chloride (Scheme 40). The resultant secondary sulfonamide **179** was chemoselectively alkylated with methyl iodide to give **180**, which underwent reduction to give amine **181**, which with 9-fluorenylmethyl chloroformate led to the protection of amine with Fmoc group to afford **182**. Treatment of **182** with triflic anhydride gave the dehydroalanine derivative **183**, which on heating with DIEPA resulted in deprotection leading to the formation of the aniline derivative **184**. Finally, **184** underwent Michael addition on treatment with sodium *t*-butoxide in THF to give the 1,2,5-benzothiadiazepine dioxide, as the sole product **112** <2001T7021>.

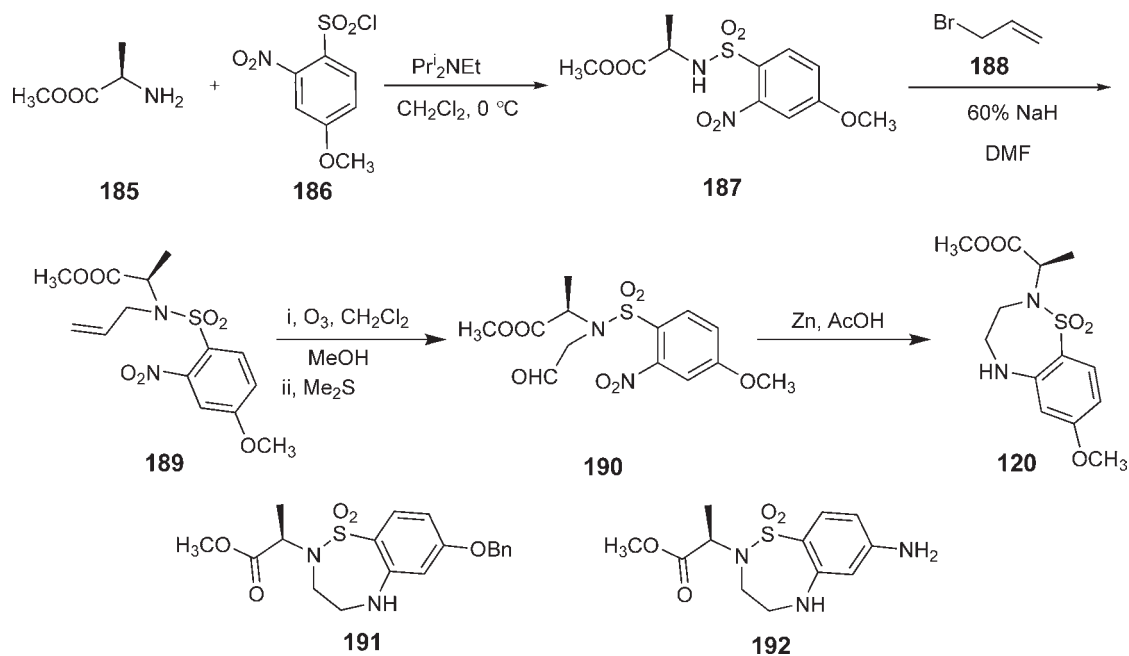
The reaction of methyl ester of D-alanine **185** with 4-methoxy-2-nitrobenzenesulfonyl chloride **186** in presence of ethyl diisopropylamine gave the sulfonamide **187**, which was alkylated with allyl bromide **188** to afford **189** (Scheme 41). Ozonolysis of **189** resulted in the formation of aldehyde **190**, and the subsequent reductive cyclization with zinc and AcOH led to the benzothiadiazepine **120** through intramolecular reductive alkylation. Using similar reaction sequence, the 1,2,5-thiadiazepines **191** and **192** were also synthesized <2003JME1811>.

13.15.7.5 1,5,2-Oxathiazepine

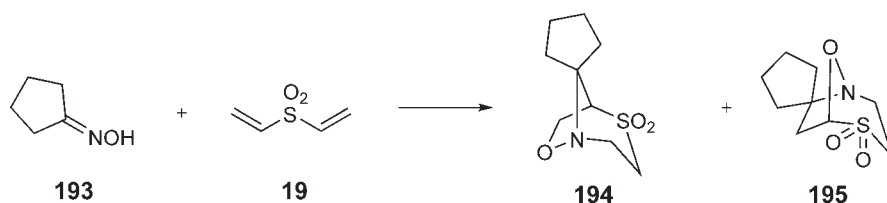
The tandem intermolecular 1,3-azaprotio cyclotransfer–intramolecular cycloaddition of divinyl sulfones **19** with oxime **193** resulted in the formation of bridged cycloadducts **194** and **195** (Scheme 42). In this reaction, the divinyl sulfone behaves either as a bifunctional dipole-generating component or as a bis-dipolarophile <1996TL4597, 1991T8297>.



Scheme 40



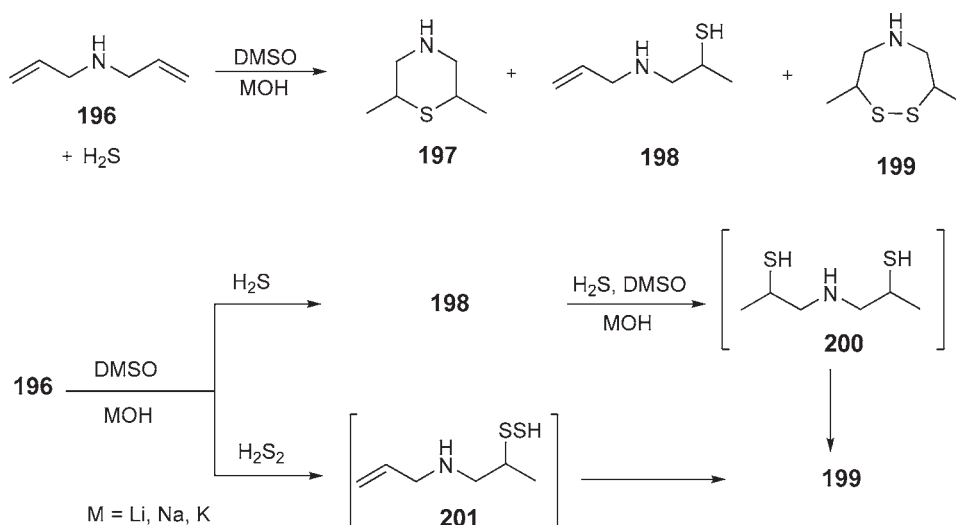
Scheme 41



Scheme 42

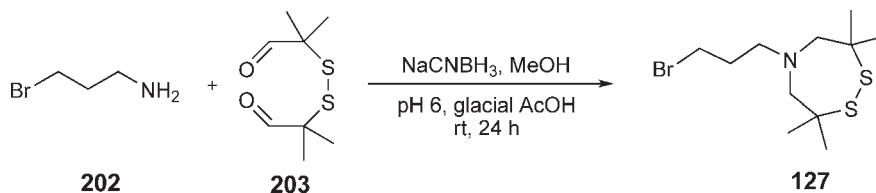
13.15.7.6 1,2,5-Dithiazepine

The amine **196** upon reaction with hydrogen sulfide in dimethylsulfoxide (DMSO) in the presence of base at 25–50 °C afforded the thiazine **197**, allyl(2-mercaptopropyl)amine **198**, and 3,7-dimethylperhydro[1,2,5]dithiazepine **199** in 10–17%, 2–31%, and 1–50% yields, respectively (Scheme 43) <2000RJC1243>. The formation of **199** is assumed via thiol **198**, which reacted with a second hydrogen sulfide molecule to give dithiol **200**. Subsequent oxidation of **200** resulted in **199**. In an alternative mechanistic pathway, the amine **196** can form the intermediate **201**, which could cyclize to give **199**.



Scheme 43

The fully saturated 5-(3-bromopropyl)-3,3,7,7-tetramethyl[1,2,5]perhydrodithiazepine **127** has been prepared from the reductive amination of 2-[(1,1-dimethyl-2-oxoethyl)disulfanyl]-2-methylpropanal **203** with 3-bromopropylamine **202** in the presence of NaCNBH₃ (Scheme 44) <2001BML1859>.



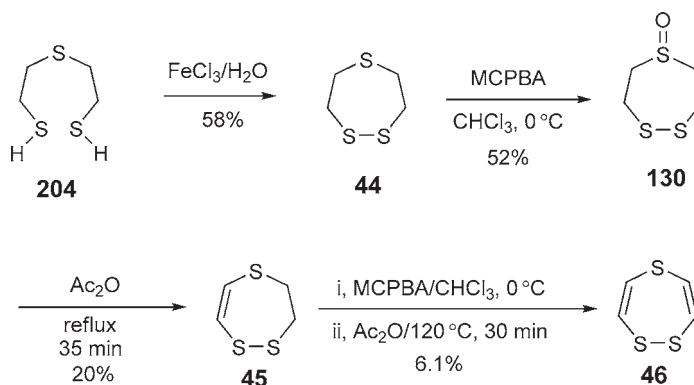
Scheme 44

13.15.7.7 Trithiepinines

All of the three monocyclic trithiepinines, the fully unsaturated, the dihydro, and tetrahydro derivatives, are known.

The ferric chloride oxidation of bis(2-mercaptoethyl) sulfide **204** afforded the 1,2,5-trithiepine **44**, which upon oxidation with one mole of *m*-chloroperoxybenzoic acid afforded 1,2,5-trithiepine-1-sulfoxide **130** chemoselectively (Scheme 45).

Pummerer rearrangement of this sulfoxide in acetic anhydride under reflux furnished 3,4-dihydrothiepine **45**. The trithiepine **46** was obtained upon oxidation and Pummerer rearrangement of 3,4-dihydrothiepine. Alternatively, 3,4-dihydrothiepine was also obtained by the reaction of 1,2,5-trithiepine with *N*-chlorosuccinimide, followed by treatment with Et₃N <1997JOC2432>.

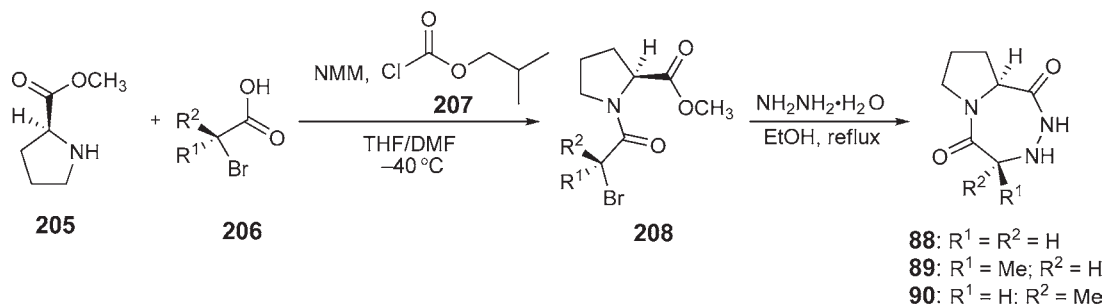


Scheme 45

13.15.8 Ring Synthesis by Transformation of Another Ring

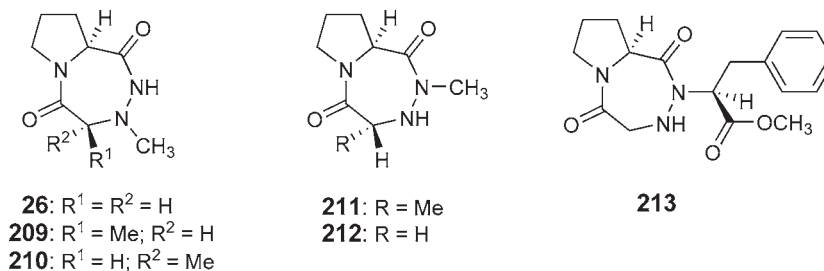
13.15.8.1 1,2,5-Triazepines

4,5-Fused 1,2,5-triazepine-3,6-diones **88–90** were synthesized from (2*S*)-proline methyl ester **205** by treating the latter with bromoacetic acid **206** in the presence of *iso*-butyl chloroformate **207** (Scheme 46). The resultant bromoacetamide **208** on further treatment with hydrazine hydrate in EtOH gave **88–90** via cyclization through displacement of bromine <1996CC85>.

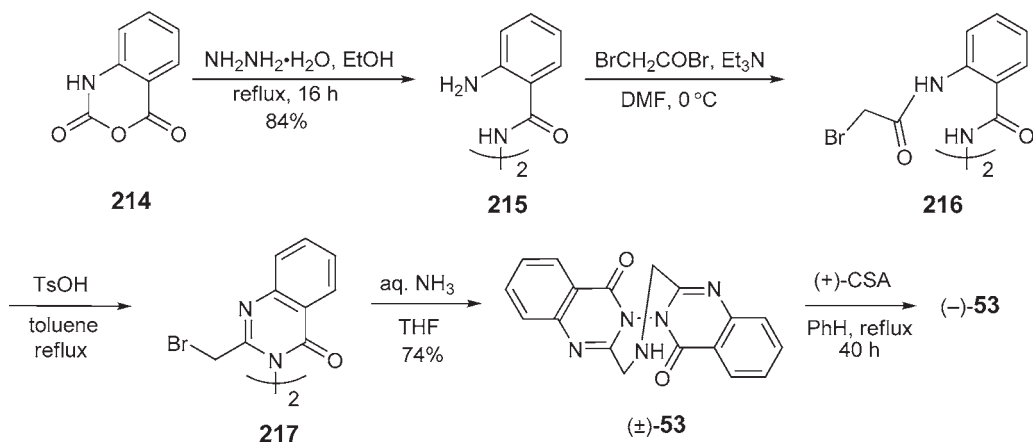


Scheme 46

The reaction of **208** with methylhydrazine gave the *N*¹-methyl[1,2,5]triazepine diones **26**, **209**, and **210**. The *N*²-methyl[1,2,5]triazepine-2,6-diones **211** and **212** were synthesized from the reaction of chloroacetyl (2*S*)-proline with *N*²-*tert*-butoxycarbonyl-*N*¹-methylhydrazine. The 1,2,5-triazepine dione **213** was also synthesized similarly.

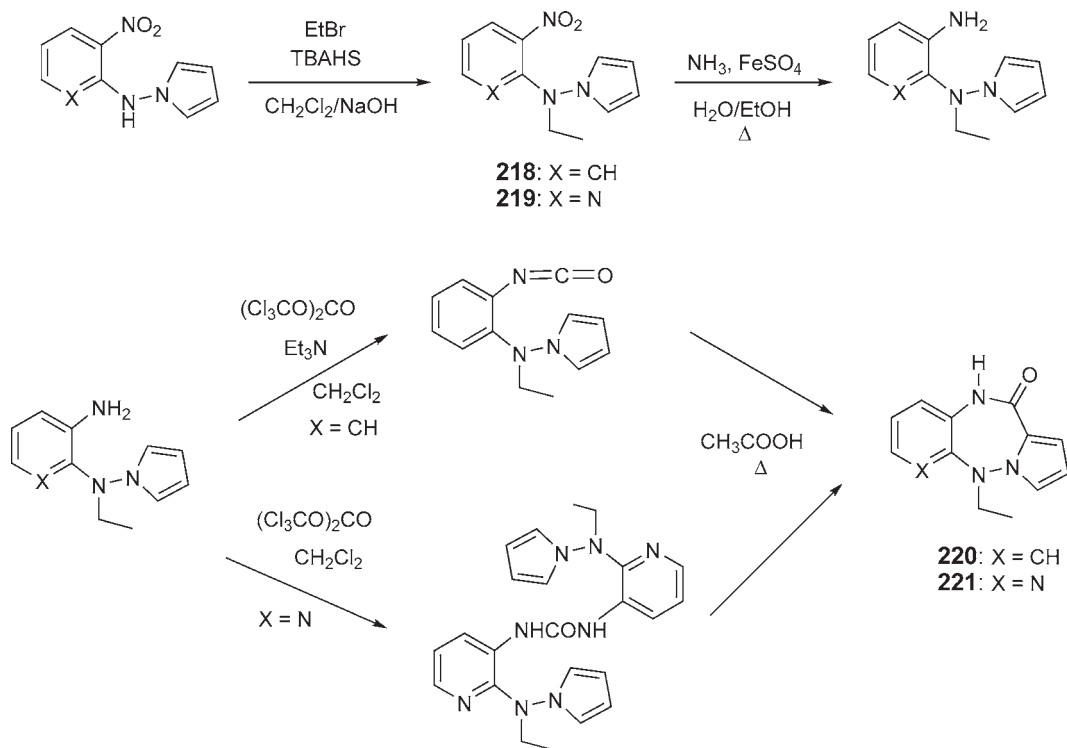


The dione **214** upon treatment with hydrazine afforded **215**, which was converted into 2,2'-bis(bromomethyl)-3,3'-biquinazoline-4,4'-dione **217** (Scheme 47) via **216**. The racemic 1,2,5-triazepine ($\pm$)-**53** was obtained from **217** by reaction with aqueous ammonia in THF. The enantiomerically pure (–)-**53** was formed by refluxing ($\pm$)-**53** with (+)-CSA (camphorsulfonic acid) <1999CC1991>. It is interesting that this work is the first nonracemic example of a C_2 -symmetric bis-heterocycle, which is atropisomeric by virtue of retarded rotation around an N–N bond.



Scheme 47

Fused 1,2,5-triazepinones **220** and **221** were obtained by cyclization of the corresponding isocyanate and bis-substituted urea, which, in turn, were prepared from the nitro compounds **218** and **219** (Scheme 48) <2000JHC1539>.

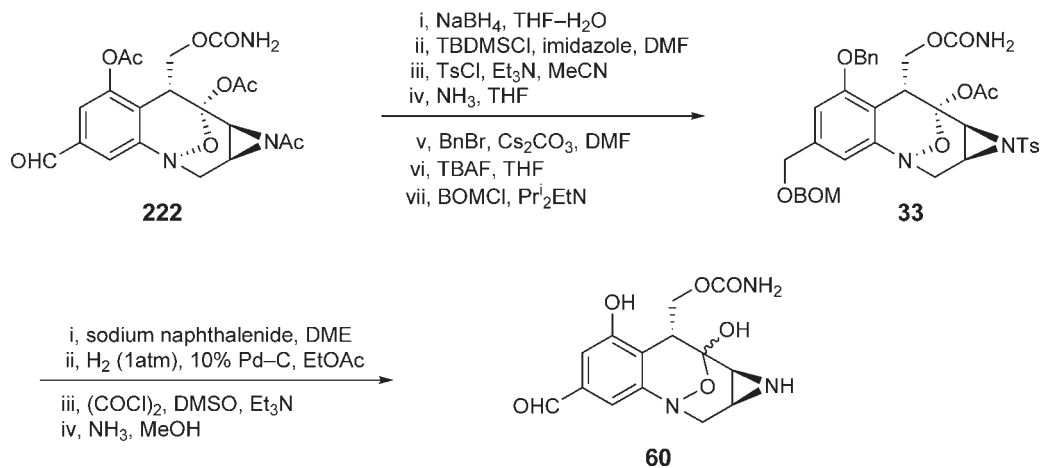


Scheme 48

13.15.8.2 Oxadiazepines

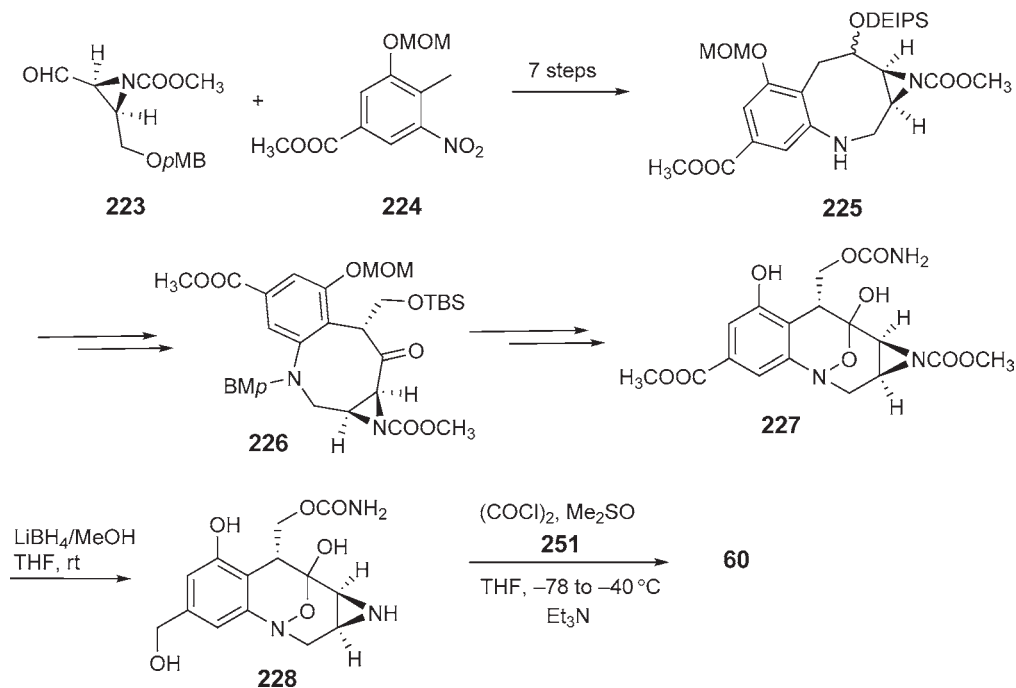
13.15.8.2.1 1,2,5-Oxadiazepine

The total synthesis of the fused 1,2,5-oxadiazepine **60** was carried out commencing from 5-hydroxyisophthalic acid and L-diethyl tartrate (**Scheme 49**). The key intermediate **33** for the synthesis of **60** was obtained from **222**, the triacetyl derivative of **60** <1996TL3471, 1996TL3479, 1997T10229, 1997T10253>.



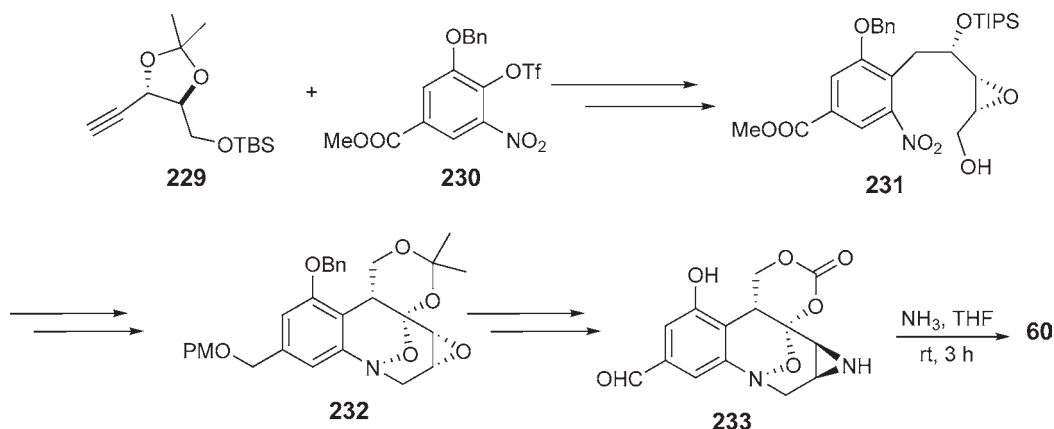
Scheme 49

In another approach for the synthesis of **60**, the intermediate **225** was synthesized by a seven-step reaction starting from **223** and **224** <1997TL4033>. The aziridine **225** was then converted to **60** via the intermediates **226–228** (**Scheme 50**) <2002AGE4683>.



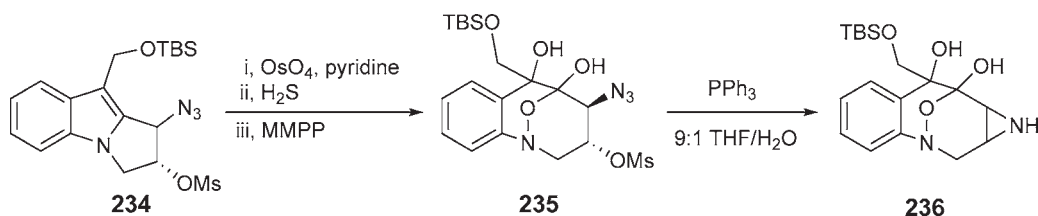
Scheme 50

A stereocontrolled, enantioselective total synthesis of **60** was performed starting from the terminal acetylene **229** and the aryl triflate **230** (Scheme 51) <2002AGE4686>. The reaction led to the formation of the intermediate **231**, which was then converted to **232**. Finally, the target **60** was obtained from **232** through **233**.



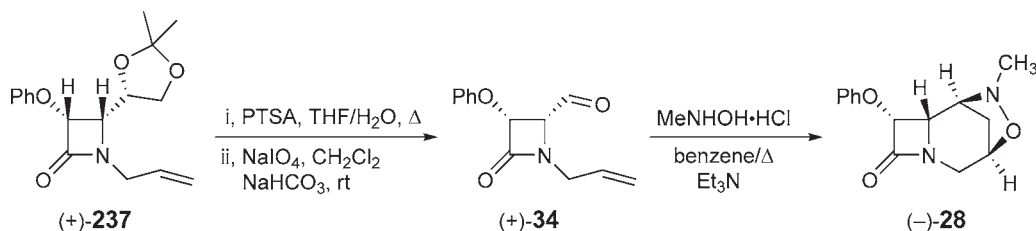
Scheme 51

The synthesis of **60** from 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]indole derivative **234** led to the formation of **236** as a mixture of two diastereomers via **235** (Scheme 52) <2000SC351>.



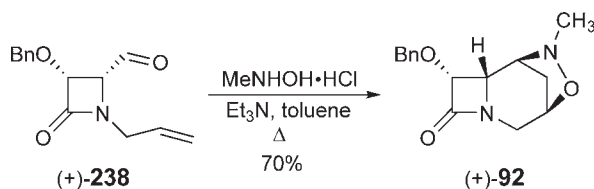
Scheme 52

The bridged 1,2,5-oxadiazepine with a carbacepham structure (–)-**28** <1999TL5391> was synthesized from 1-allyl-4-formyl-2-azetidinone (+)-**34**, which, in turn, was prepared from *cis*-2-azetidinones (+)-**237** (Scheme 53). These azetidinones were easily prepared as single *cis*-enantiomers from imines of (*R*)-2,3-*O*-isopropylidenepropanal through Staudinger reaction with the corresponding acid chlorides in presence of Et_3N <1988JOC4227>.



Scheme 53

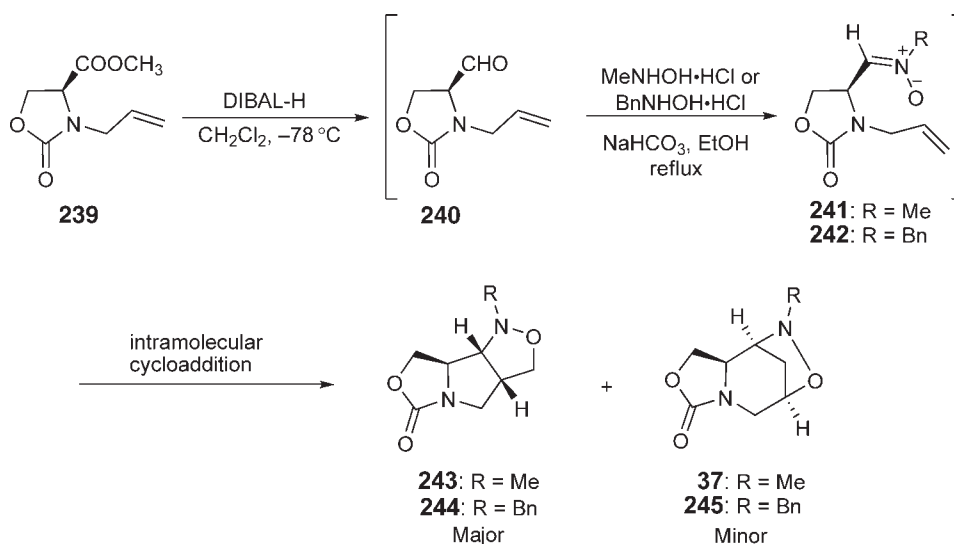
The cycloadduct **92** has been synthesized from **238** through a regio- and stereocontrolled intramolecular nitron–alkene cycloaddition (Scheme 54) <2002SL85>.



Scheme 54

Similarly, regio- and stereoselective syntheses of optically pure fused or bridged 1,2,5-oxadiazepines have been reported via intramolecular nitron–alkene cycloaddition <2005EJO1680>.

The fused tricycles **243** and **244**, as the major products, and bridged 1,2,5-oxadiazepines **37** and **245**, as the minor product, were obtained from the intramolecular cycloaddition of **241** and **242**. The intermediates **243** and **244** were synthesized commencing from **239**, which was reduced with an excess of DIBAL-H to afford the intermediate **240**, which on reaction with *N*-methylhydroxylamine generated the nitrones **241** and **242** (Scheme 55) <2001J(P1)452>.



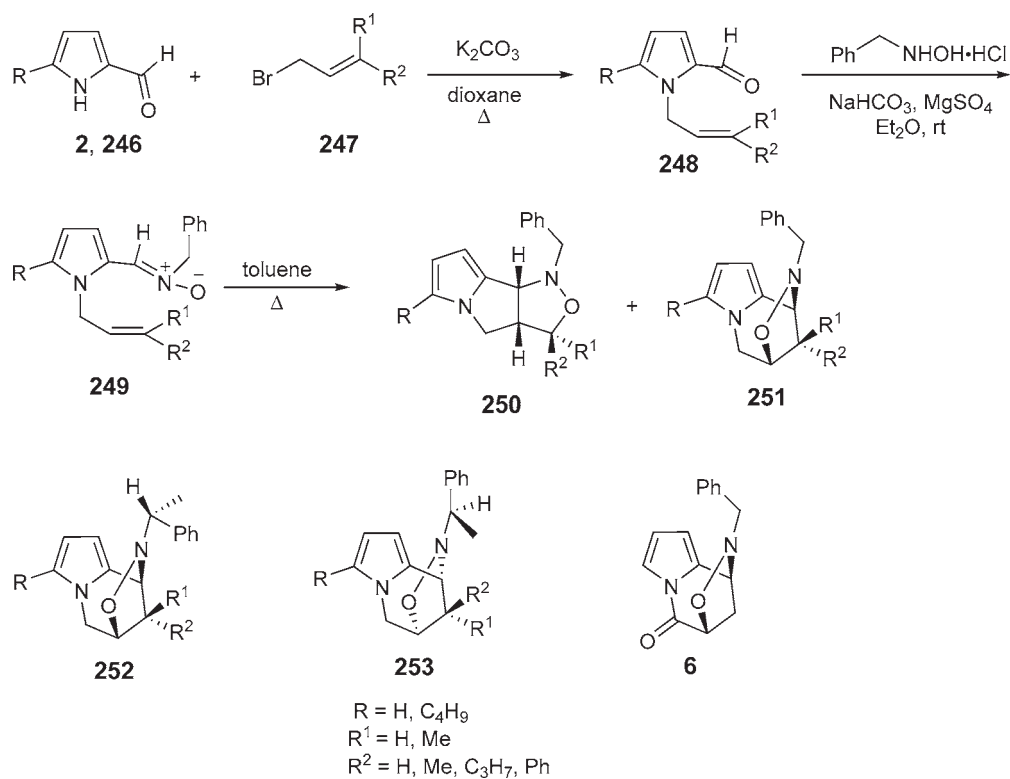
Scheme 55

5-Butyl-2-pyrrolocarbaldehydes (**2**, **246**), upon reaction with **247**, afforded substituted 2-pyrrolocarbaldehydes **248**, which was reacted with benzylhydroxylamine to give the intermediate **249**. This nitron then underwent intramolecular cycloaddition in toluene to give fused **250** and bridged 1,2,5-oxadiazepine **251** cycloadducts. Similar methodology was employed for the synthesis of **252** and **253** using (*R*)- α -methylbenzylhydroxylamine <2001T8323>. The 1,2,5-oxadiazepine **6** was also obtained regio- and stereoselectively (Scheme 56) <2001H(55)1987>.

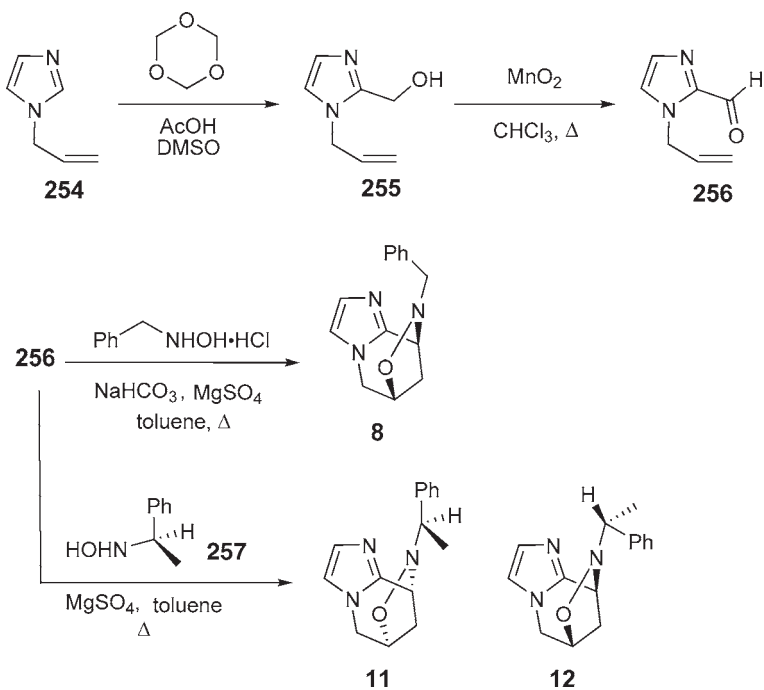
The aldehyde **256** was prepared from 1-allylimidazole **254** through hydroxymethylation, followed by oxidation. The aldehyde **256** upon reaction with benzylhydroxylamine and (*R*)- α -methylbenzylhydroxylamine **257** afforded the bridged 1,2,5-oxadiazepines **8**, **11**, and **12** (Scheme 57) <2002T4445>.

13.15.8.2.2 1,4,5-Oxadiazepine

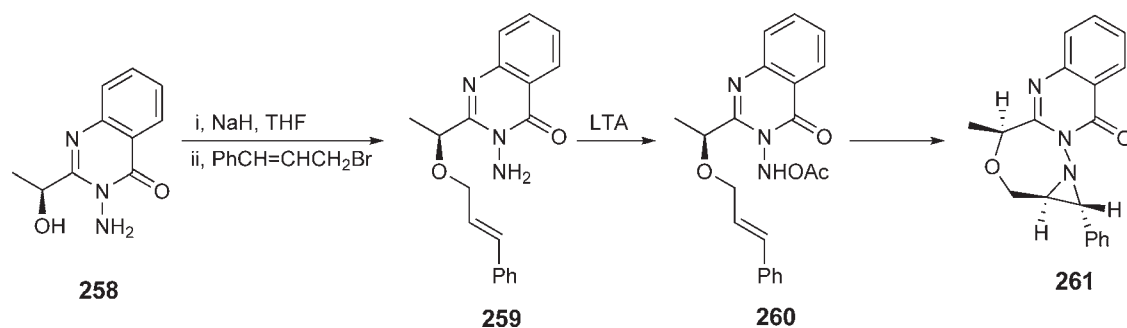
The enantiopure 3-amino-2-(1-hydroxyethyl)quinazolinone **258** upon alkylation with cinnamyl bromide afforded O-alkylated product **259** as minor and N,O-dialkylated product as major (Scheme 58). Further *N*-acetoxylation of **259** led to the formation of **260**, which underwent intramolecular aziridination to give the 1,4,5-oxadiazepine **261** as a single diastereomer <1995J(P2)205>.



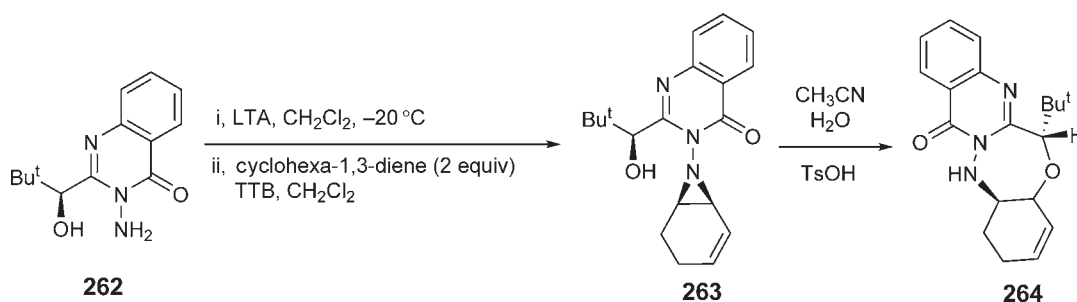
Scheme 56



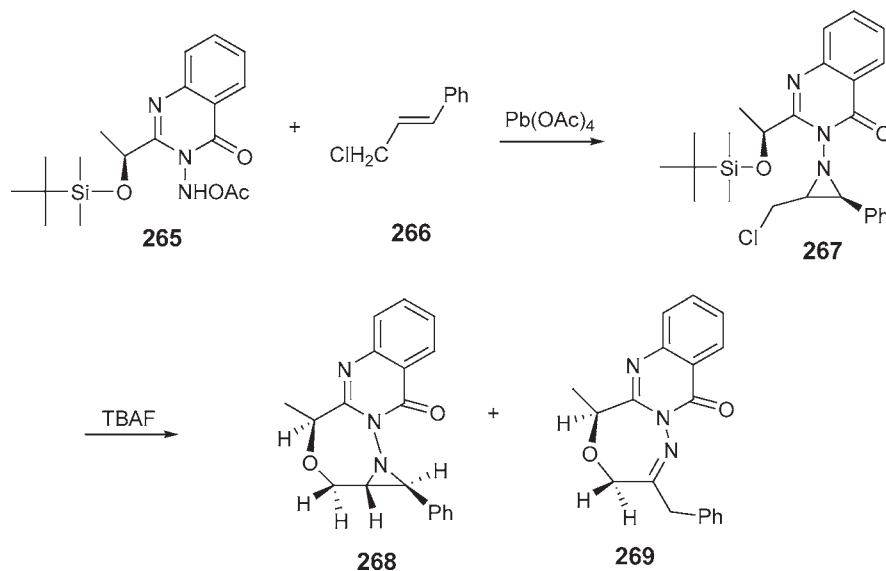
Scheme 57

**Scheme 58**

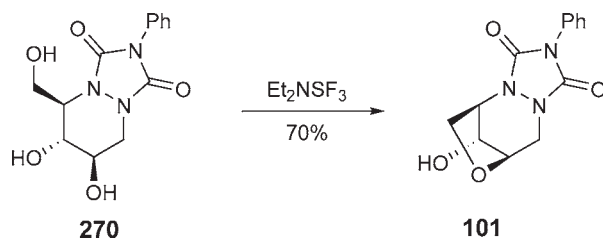
The fused 1,4,5-oxadiazepine **264** was obtained by ring-opening the aziridine ring of **263** with concomitant formation of the seven-membered ring (Scheme 59) <2001J(P1)1518>.

**Scheme 59**

The fused 1,4,5-oxadiazepines **268** and **269** were obtained by tandem desilylation–cyclization via displacement sequence of **267** (Scheme 60). The precursor **267** was obtained by the diastereoselective aziridination of (*E*)- β -chloromethylstyrene **266** with **265** upon treatment with lead tetraacetate <2002J(P2)819>.

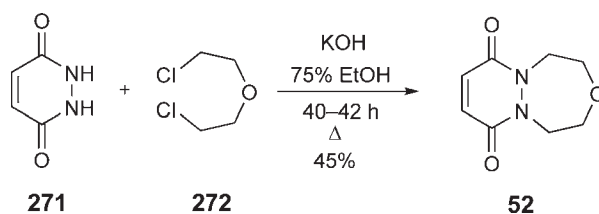
**Scheme 60**

The displacement of 3'-hydroxyl group of **270** with fluorine was attempted with diethylaminosulfur trifluoride (DAST) but the reaction resulted in the formation of a nonfluorinated product **101** (Scheme 61) <1997T9357>.



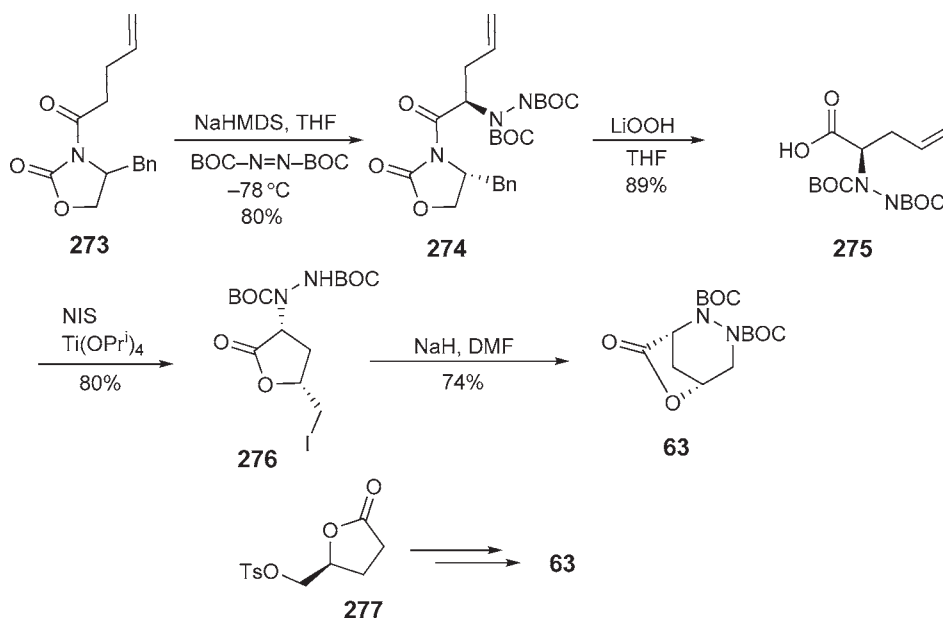
Scheme 61

In connection with the synthesis of new crown ethers of the pyridazine series, fused 1,4,5-oxadiazepine **52** was prepared from 1,2-dihydro-3,6-dioxypyridazine **271** and 3-oxa-1,5-dichloropentane **272** under basic conditions (Scheme 62) <1997CHE1466>.



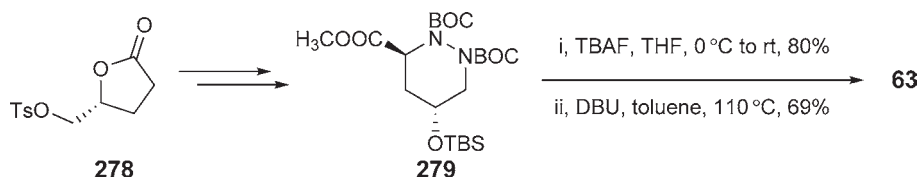
Scheme 62

Bridged 1,4,5-oxadiazepine **63** has been prepared stereoselectively commencing from the pentenoic acid derivative **273**. The anion of the latter, generated by treatment with sodium hexamethyldisilazide (NaHMDS), upon treatment with bis(*t*-butyl)azodicarboxylate afforded **274**. The lithium hydroperoxide-mediated hydrolysis of **274** gave **275** (Scheme 63). Iodolactonization of **275** was conducted in the presence of titanium isopropoxide to give 2,4-*cis*-product **276** along with its *trans*-isomer in a ratio of 6:1. An intramolecular N-alkylation of **276** led to the formation of bicyclic **63** <1998AGE2995>, which has also been synthesized starting from D-glutamic acid initially by conversion of the latter to (*R*)-dihydro-5-(*p*-tolylsulfonyloxymethyl)-2(3*H*)-furanone **277** <2000TL289>.



Scheme 63

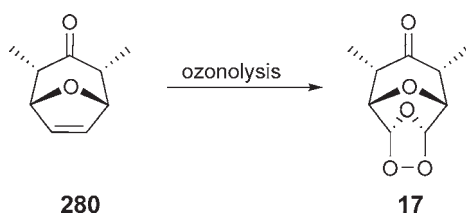
Similarly, the tosylate **278** was converted to a piperazic acid ester **279**, which has been used as a precursor for the synthesis of **63** (Scheme 64) <2001CEJ41>.



Scheme 64

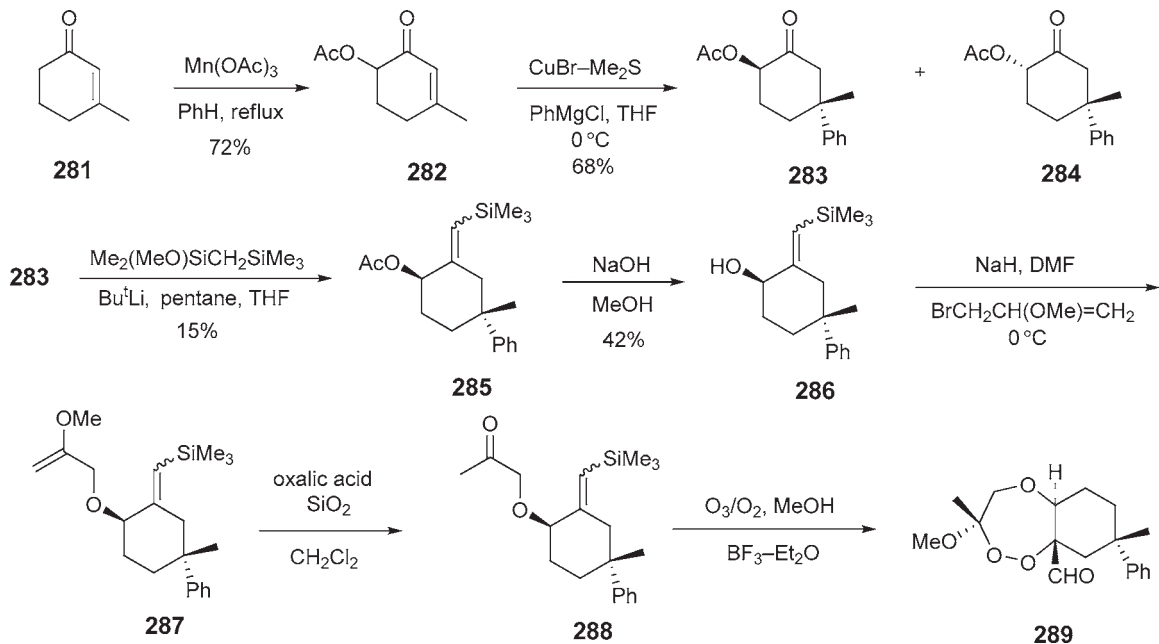
13.15.8.3 1,2,5-Trioxepines

8-Oxabicyclo[3.2.1]oct-6-en-3-one **280** upon ozonolysis at -70°C afforded the bicyclic product **17** (Scheme 65) <1996J(P1)1101>. The substrate **280** for ozonolysis has been synthesized according to previous reports <1986T4611>.



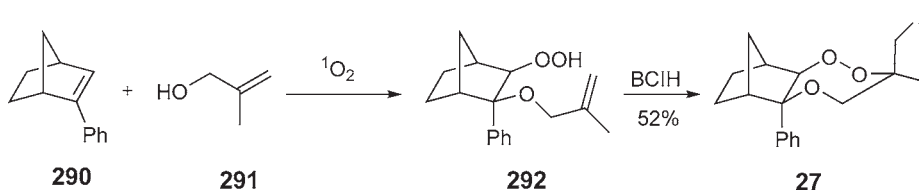
Scheme 65

3-Methylcyclohexenone **281** upon oxidation with $\text{Mn}(\text{OAc})_3$ in benzene under reflux gave **282**, which reacted with phenylmagnesium chloride and $\text{CuBr}\cdot\text{Me}_2\text{S}$ to form two isomeric ketones **283** and **284**. Further, **283** has been transformed to vinylsilane **285** followed by its hydrolysis to form the free alcohol **286**, which in turn was alkylated with methoxyallyl bromide to give **287**. Oxalic acid-mediated deprotection of **287** led to the formation of the ketone **288**. Ozonolysis of **288** in methanol afforded the fused 1,2,5-trioxepine **289** in low yields (Scheme 66) <1997BML2357>.



Scheme 66

Photooxidation of 2-phenylnorbornene **290** in the presence of 3-methylbut-3-en-1-ol **291** afforded the corresponding labile unsaturated hydroperoxide **292**, which upon treatment with bis(collidine)iodine hexafluorophosphate (BCIH) afforded the norbornane-fused 1,2,5-trioxepine **27** (Scheme 67) <2003JME1957>.

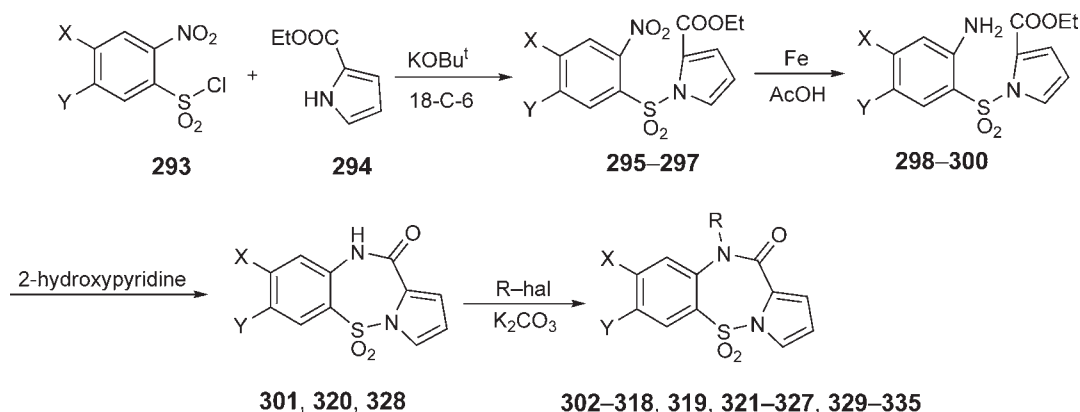


Scheme 67

13.15.8.4 Thiadiazepines

13.15.8.4.1 1,2,5-Thiadiazepine

The thiadiazepine **301** has been already reported <1992SC1433> and thiadiazepine **302–318** and **319** were obtained by the alkylation of **301** with alkyl halides. The chloro derivatives **321–327** and **329–335** were obtained from **320** and **328**, respectively, which in turn were synthesized by the intramolecular cyclization of the corresponding aminosulfones **298–300** (Scheme 68). These aminosulfones were obtained by the reduction of nitrosulfones **295–297** <1996BMC837>.

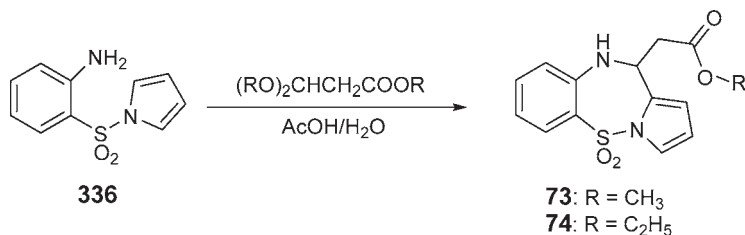


301–319, **295**, **298**: X = Y = H; **320–327**, **296**, **299**: X = Cl, Y = H; **328–335**, **297**, **300**: X = H, Y = Cl

R = Me, Et, Prⁿ, Prⁱ, Buⁿ, Buⁱ, 2-propenyl, 2-butenyl, 3-Me-2-butenyl, CH₂COOMe, CH₂COOEt, CH₂COOBz, CH₂OMe, CH₂CH₂OMe, CH₂cyclopropyl, CH₂Ph, CH₂CH₂N(Me)₂

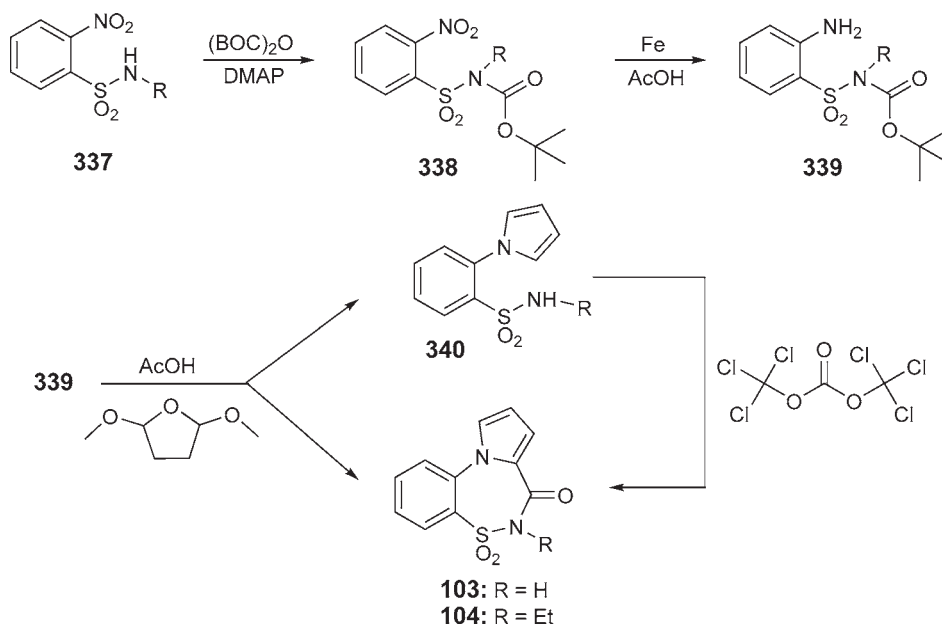
Scheme 68

The reaction of 1-(2-aminobenzenesulfonyl)-1*H*-pyrrole **336** with methyl 3,3-dimethoxypropionate in AcOH afforded the tricyclic 1,2,5-thiadiazepines **73** and **74**, which were converted into several other heterocycles (Scheme 69) <1996FES425>. The starting **336** was synthesized according to previous reports <1994JHC867, 1994JHC1033>.



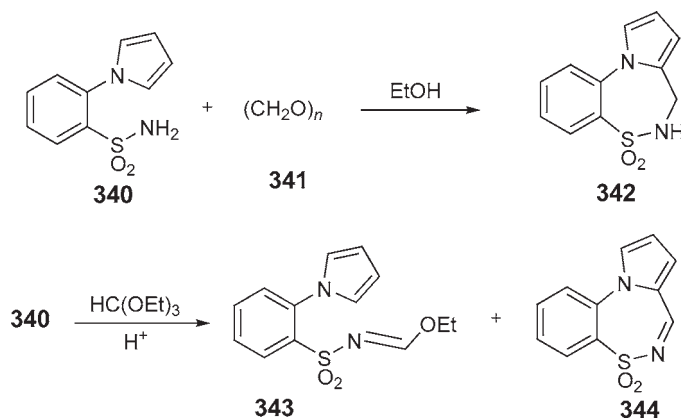
Scheme 69

The reaction of nitro compound **337** with *t*-butyloxycarbonyl anhydride in the presence of DMAP resulted in 2-nitrobenzenesulfonamide **338**, which upon reduction with iron in AcOH gave **339** (Scheme 70). The latter when refluxed with 2,5-dimethoxytetrahydrofuran in AcOH afforded pyrrole sulfonamide **340** in good yield along with the fused 1,2,5-thiadiazepines **103** and **104**, as a side product. Subsequently, **340** upon reaction with triphosgene afforded **103** and **104**.



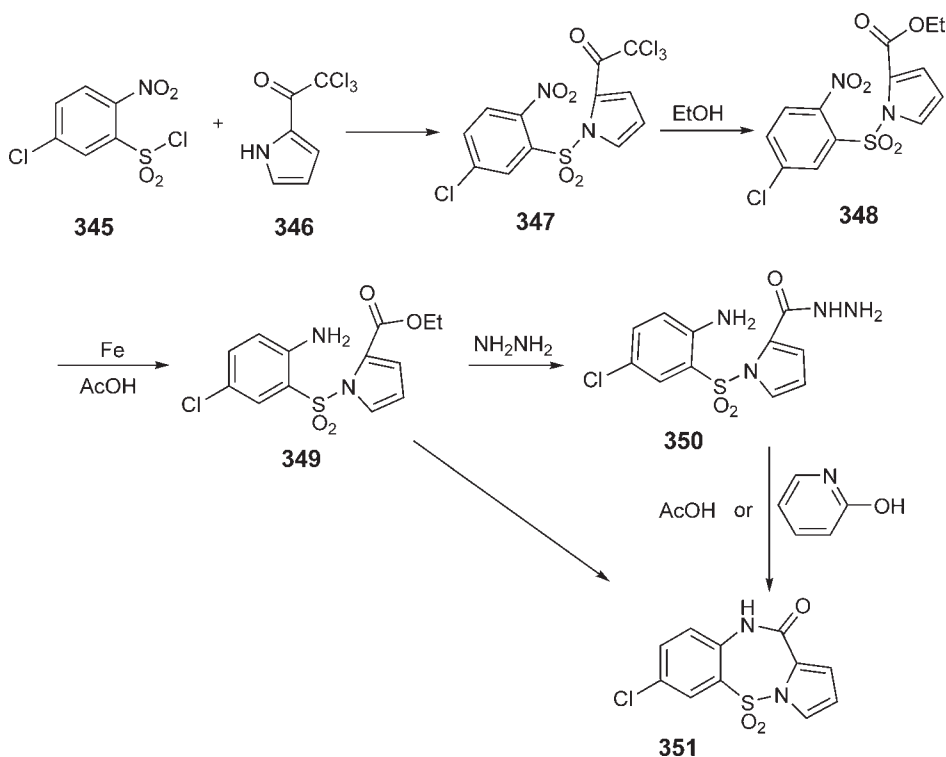
Scheme 70

Treatment of **340** with paraformaldehyde **341** in EtOH gave **342** through an intramolecular cyclization, whereas the reaction with triethyl orthoformate resulted in the formation of **343** and the thiadiazepine **344** (Scheme 71). The pyrrole **343** was converted into **344** under acidic conditions <1997FES375>.



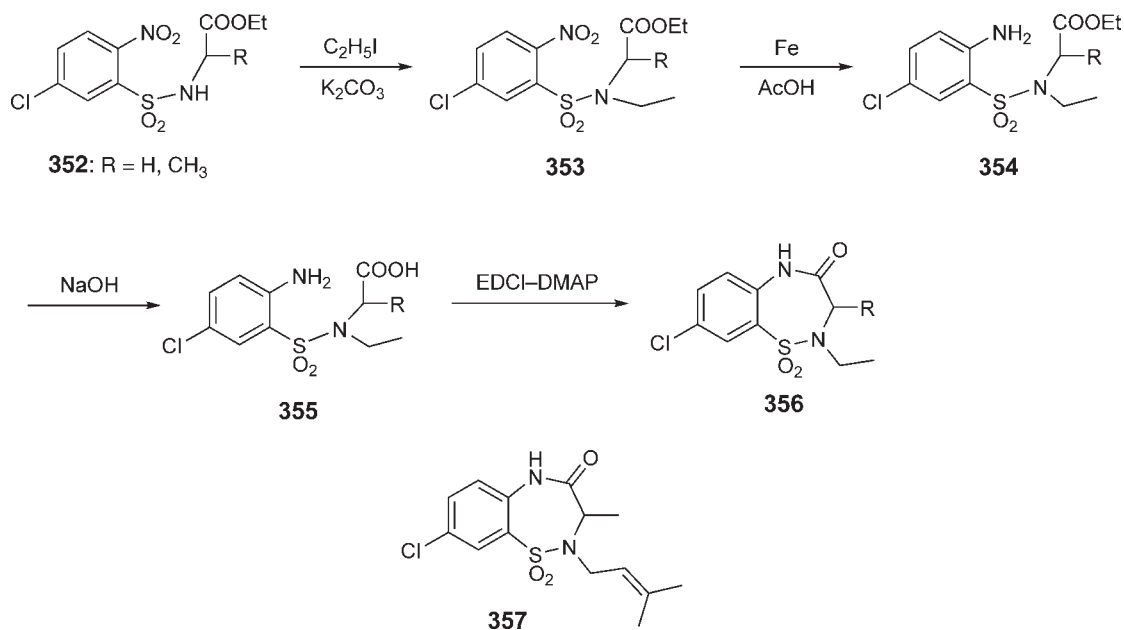
Scheme 71

Intramolecular cyclization of the sulfonamide **349** gave the fused 1,2,5-thiadiazepine **351**, whereas reaction of **349** with hydrazine afforded **350** (Scheme 72). The reaction of **350** with either 2-hydroxypyridine or acetic acid led to the formation of **351** <2000H(53)2163>.



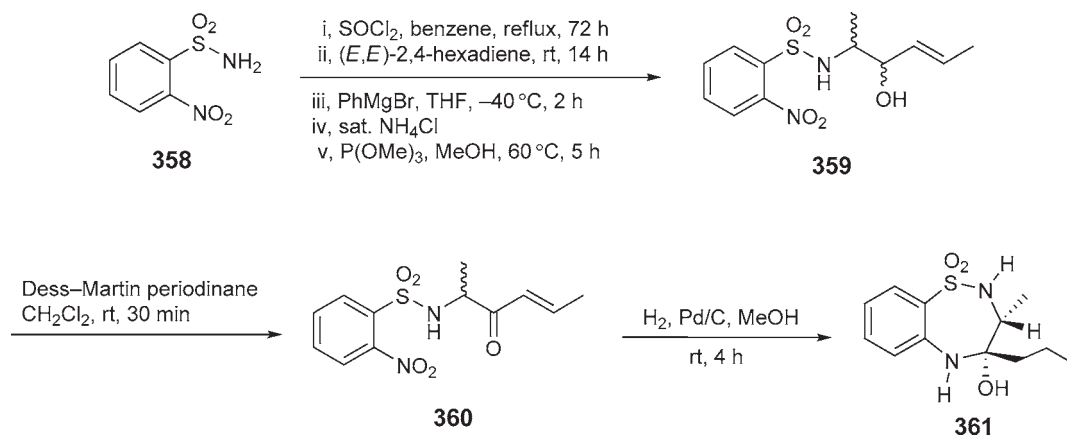
Scheme 72

Ethylation of **352** followed by reduction with iron and subsequent hydrolysis afforded the amino acid **355**, which underwent intramolecular cyclization catalyzed by *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride–*N,N*-dimethylaminopyridine complex to give 1,2,5-thiadiazepine **356** (Scheme 73). Similar methodology was employed to obtain the thiadiazepine **357** using (CH₃)₂C=CCHCH₂Br for alkylation <2002JHC81>.



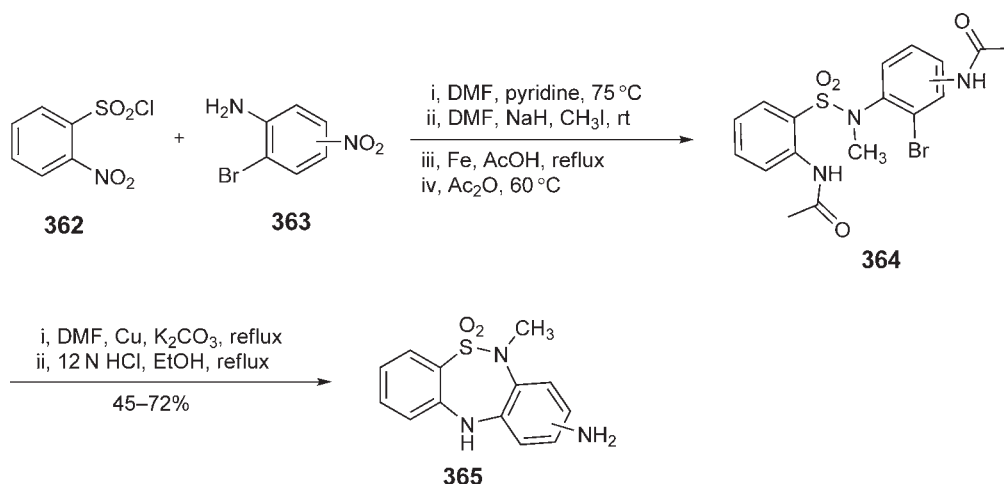
Scheme 73

The 2-(*o*-nitrobenzenesulfonamido)alcohol **359** was obtained from **358** through a sequence of reactions, which was then subjected to oxidation with Dess–Martin periodinane to give the 2-(*o*-nitrobenzenesulfonamido)ketone **360** in 84% yield (Scheme 74). Upon reductive cyclization with hydrogen and palladium over activated carbon, **360** gave the 1,2,5-benzothiazepine **361** <2004T3349>.



Scheme 74

The sulfonamide **364** was obtained from the reaction of 2-nitrobenzenesulfonyl chloride **362** and the substituted anilines **363**, which were then converted to the 1,2,5-thiadiazepines **365** by refluxing **364** with copper, followed by hydrolysis of the amide (Scheme 75) <2004H(63)2457>.

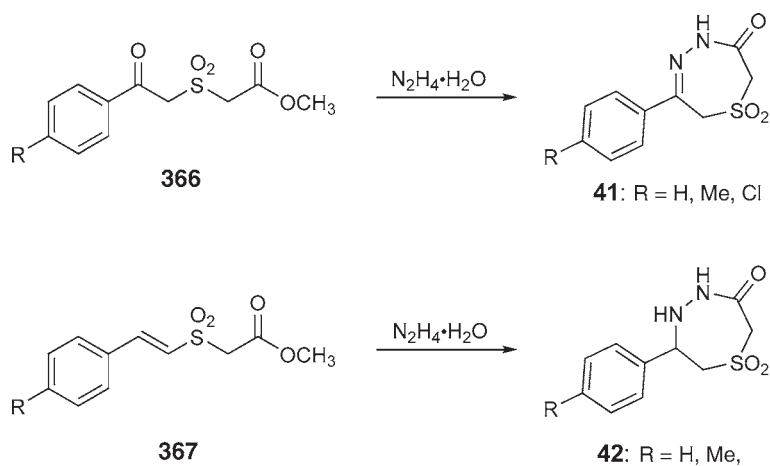


Scheme 75

The condensation of 2-nitrobenzenesulfonyl chlorides with 3-amino-2-chloropyridine in the presence of pyridine at 60°C gave the corresponding sulfonamides, which were reacted with sodium hydride and iodomethane to give the N-methylated products. Catalytic hydrogenation of the N-methylated compounds followed by acetylation, treatment with sodium hydride in DMF, and reaction with arylalkyl chlorides or methanesulfonates resulted in the formation of novel benzo[*f*]pyrido[3,2-*c'*][1,2,5]thiadiazepines <2005JME7363>.

13.15.8.4.2 1,4,5-Thiadiazepine

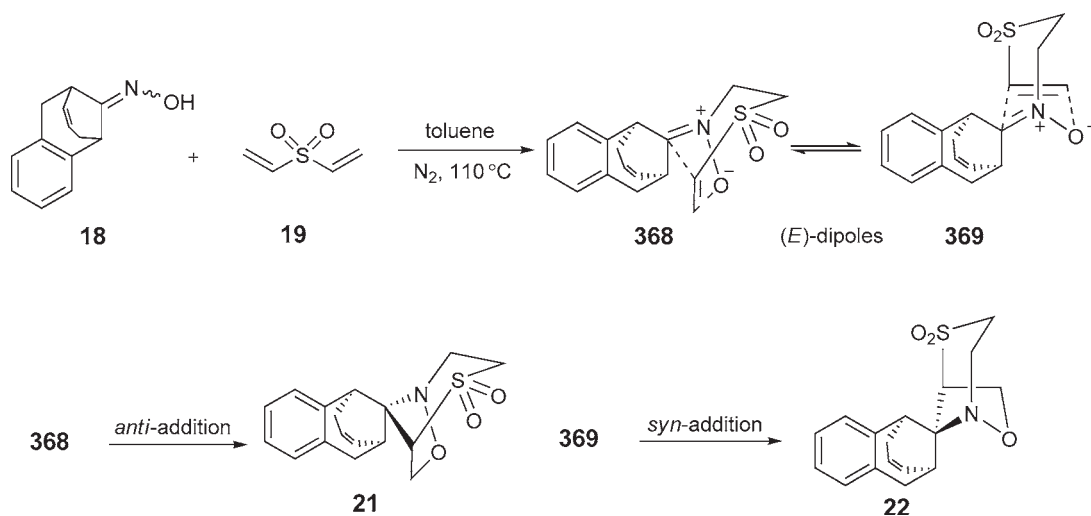
The methyl esters of phenacylsulfonylacetic acid **366** and styrylsulfonylacetic acid **367** upon treatment with hydrazine hydrate furnished the 1,4,5-thiadiazepines **41** and **42**, respectively (Scheme 76) <2004JCM556>.



Scheme 76

13.15.8.5 1,5,2-Oxathiazepine

The 1,3-azaprotio cyclotransfer reaction of benzobicyclononenone oxime **18** with divinyl sulfone **19** in toluene under nitrogen atmosphere gave a mixture of cycloadducts **21** and **22** in a ratio of 1:3 in 87% combined yield through the *syn*- and *anti*-addition of the (*E*)-dipoles **368** and **369** (Scheme 77) <2003T9997>.

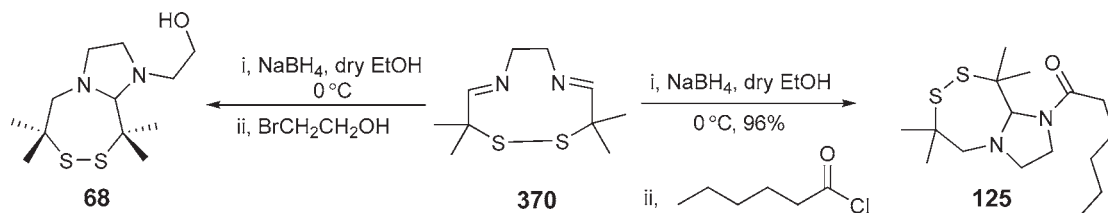


Scheme 77

13.15.8.6 Dithiazepines

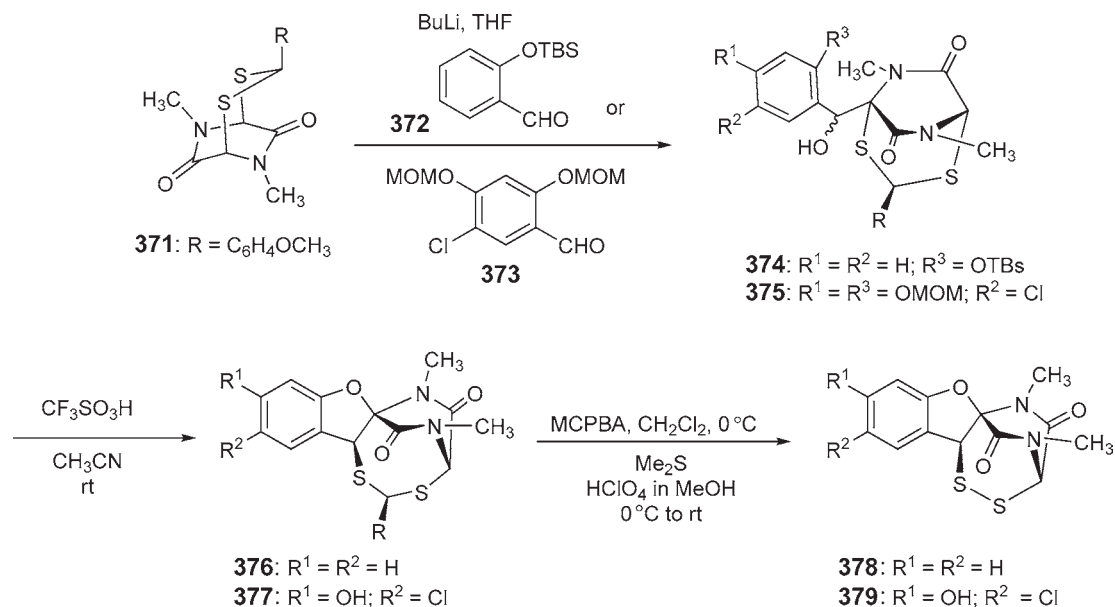
13.15.8.6.1 1,2,5-Dithiazepine

6,6,9,9-Tetramethylhexahydroimidazo[2,1-*d*][1,2,5]dithiazepine **68** was prepared from the NaBH₄ reduction of 3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene **370** in dry EtOH (Scheme 78) <1996AJC239>. Similarly, the 1,2,5-dithiazepine **125** has been synthesized from **370** through the reduction of latter and subsequent acylation <1998OPP485>.



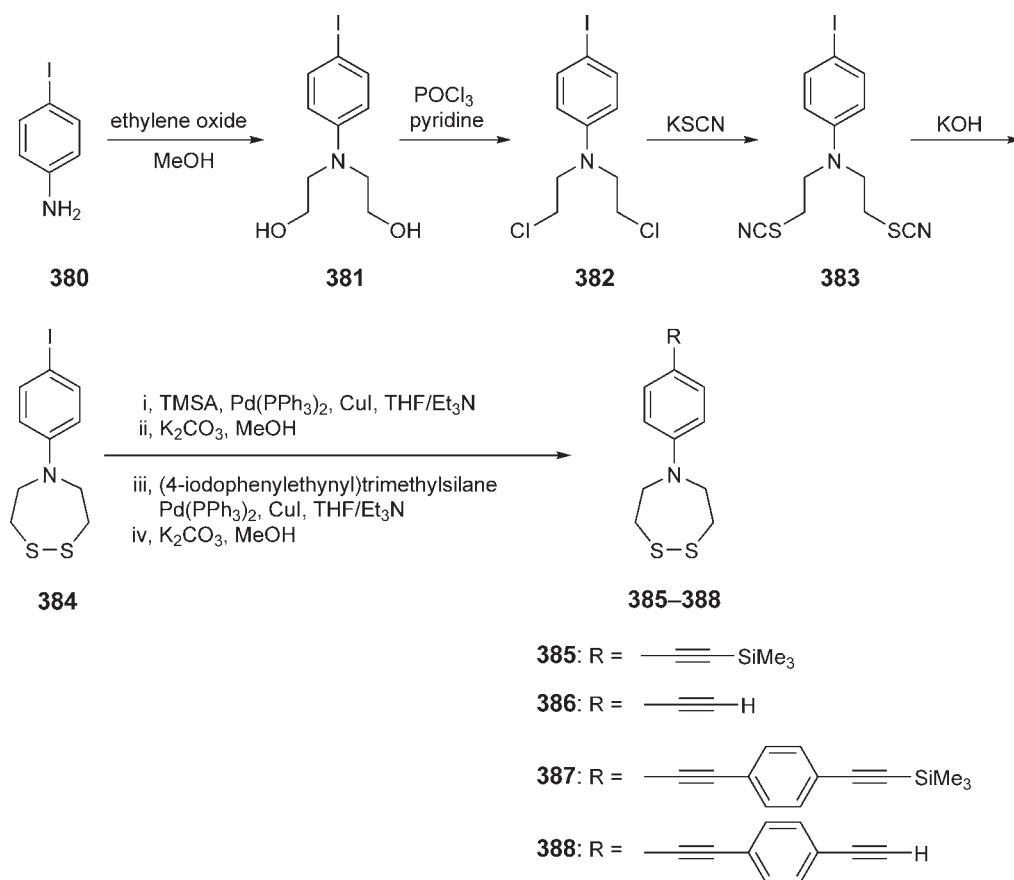
Scheme 78

The condensation of the diamide **371** with the corresponding aldehydes **372** and **373** afforded **374** and **375**, respectively, which upon treatment with anhydrous trifluoromethanesulfonic acid in MeCN gave the cyclized products **376** and **377**, as a single diastereoisomer (Scheme 79). The action of *m*-chloroperoxybenzoic acid, followed by the treatment of the monosulfoxide with perchloric acid, resulted in the 1,2,5-dithiazepines **378** and **379** <2000AGE3866>.



Scheme 79

The tetrahedral-shaped nanoscale molecules with 1,2,5-dithiazepine ring **391**–**393** (Scheme 81) were synthesized from the corresponding tetraiodide by a series of Sonogashira coupling reactions <2002OL3631>. Initially, the 1,2,5-dithiazepines **384**–**388** have been synthesized starting from 4-iodoaniline **380**, which upon treatment with ethylene oxide gave the diol **381**, followed by conversion into the dichloride **382** (Scheme 80). Reaction of **382** with KSCN gave the dithiocyanate **383**, which was converted to 1,2,5-dithiazepine **384** by treatment with KOH. The reaction of **384** with trimethylsilylacetylene gave **385** and the treatment of **385** with a base gave alkyne **386**. The Sonogashira coupling of **386** was achieved with (4-iodophenylethynyl)trimethylsilane to afford **387**, which, in turn, gave the terminal alkyne **388**.



Scheme 80

The 1,2,5-dithiazepine **386**, upon reaction with the adamantane **389**, gave the symmetrically tetrasubstituted adamantane **391**, whereas **386** and **388** upon treatment with **390** afforded the tetraphenylmethane **392** and its larger analogue **393** (Scheme 81). Similar procedures were adopted in synthesizing other tetrahedral-shaped nanoscale molecules <2003JOC4862>.

13.15.8.6.2 1,5,2-Dithiazepine

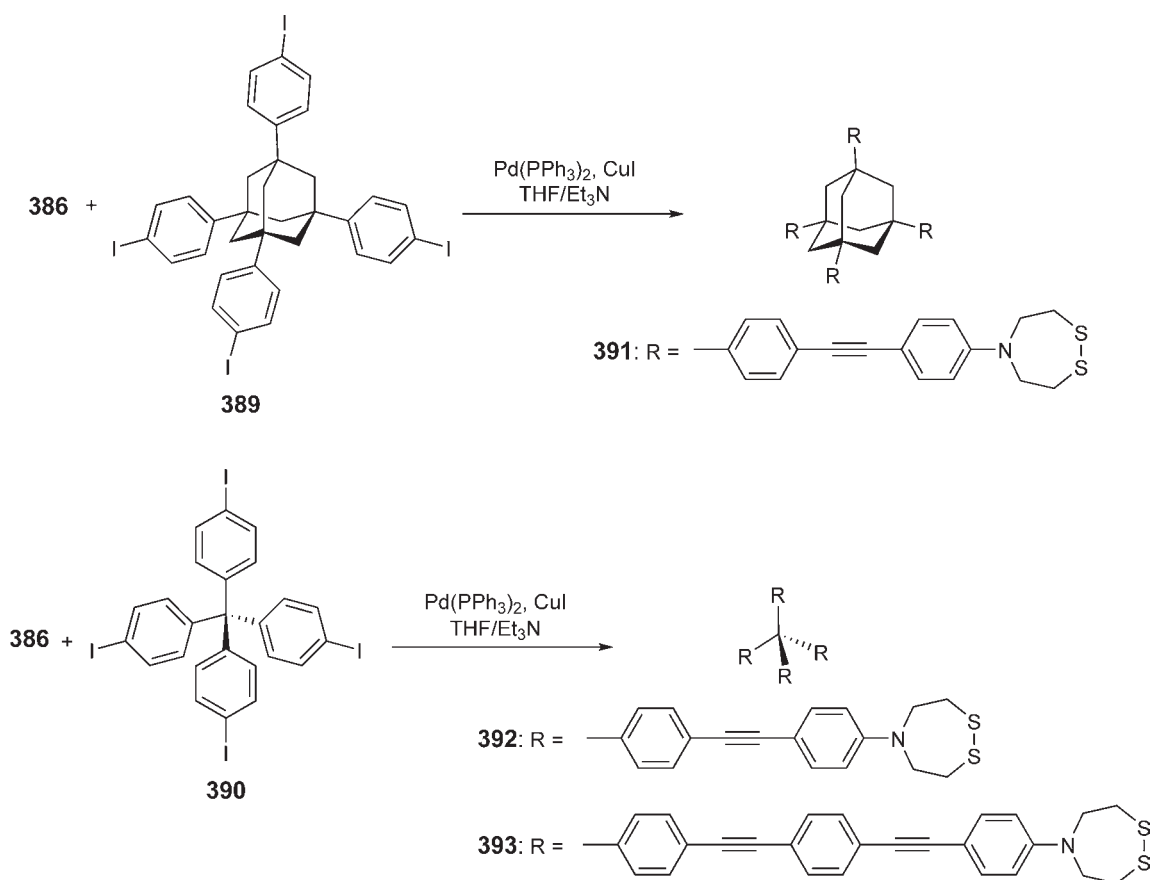
The synthesis of benzo[*f*][1,5,2]dithiazepin-3-ones **23**, **396**, and **397** have been achieved starting from appropriate 2-sulfamoylphenyl(thio or sulfonyl)alkanoates **394** (Scheme 82) <2001H(55)753>.

13.15.8.7 1,4,5-Oxadithiepine

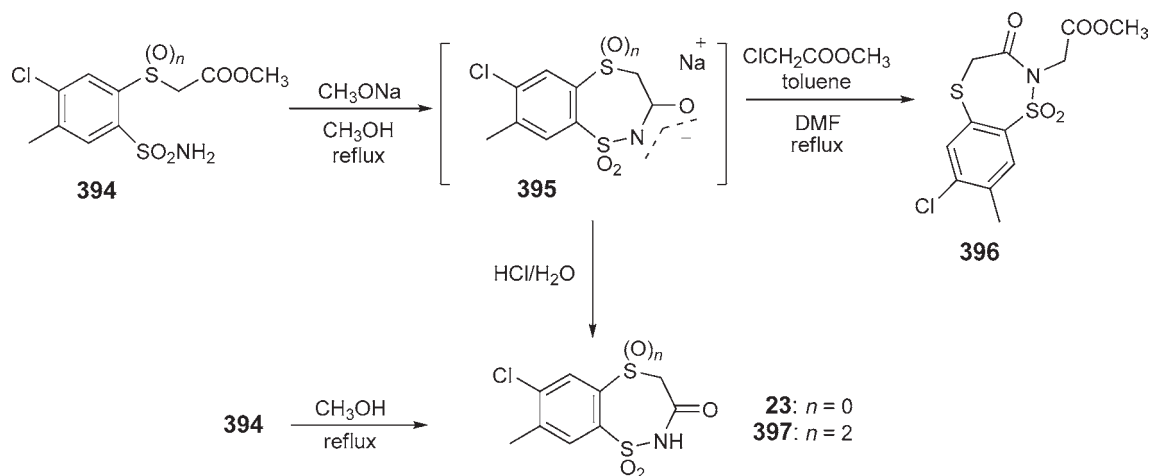
The coupling reaction of dithiodiglycolic acid **398** and *N*-hydroxysuccinimide **399**, followed by the addition of methyl (4-aminomethyl)benzoate hydrochloride in the presence of Et₃N, afforded an unexpected seven-membered 1,4,5-oxadithiepine **70** (Scheme 83) <2002TL4861>.

13.15.8.8 Trithiepinines

Both *trans*- and *cis*-[1,2,5]trithiepan-4,6-dicarboxylates **402** and **403** were obtained by the reductive ring opening and rearrangement of 1,2,3-thiadiazole-4-carboxylates **401** upon reaction with samarium and iodine (Scheme 84). The expected thiadiazoline **404** was not obtained in this reaction <2004OBC2870>.

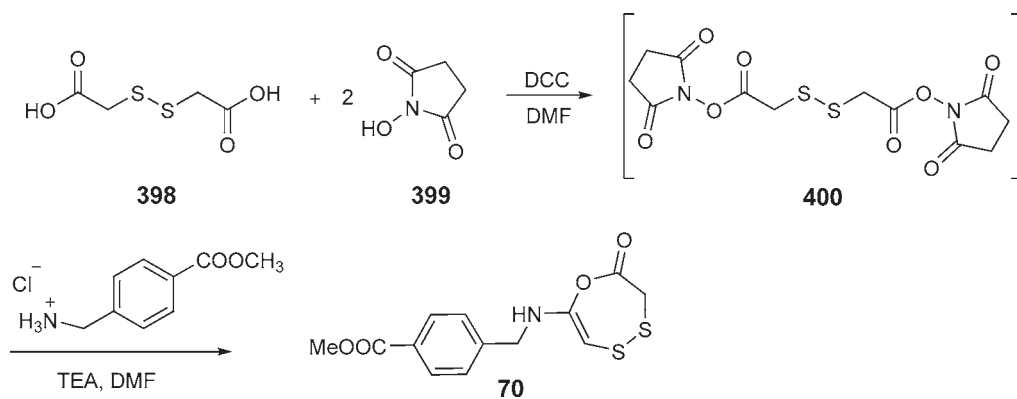


Scheme 81

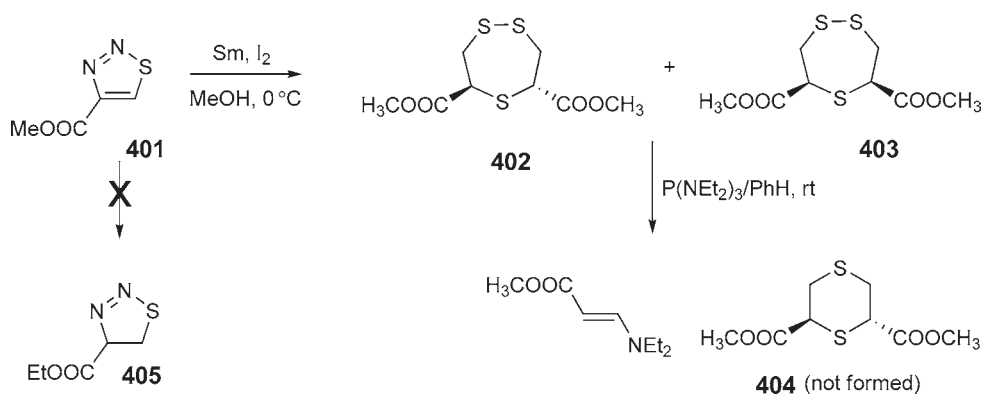


Scheme 82

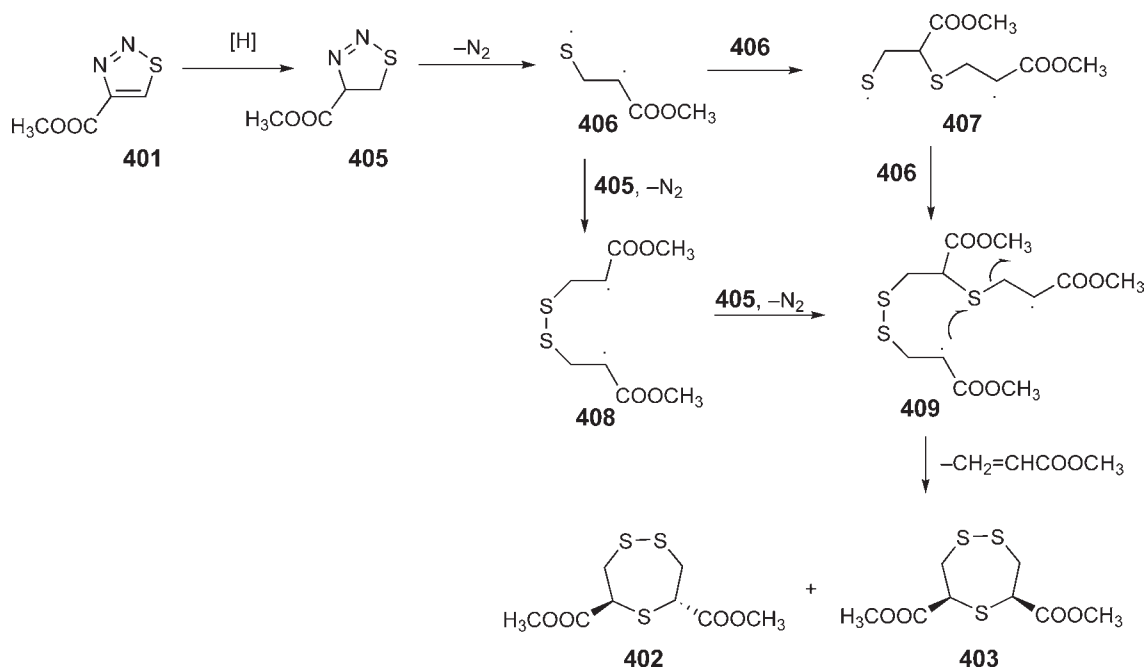
The formation of 1,2,5-trithiepan-4,6-dicarboxylates was explained by the mechanism depicted in [Scheme 85](#) <2004OBC2870>. This reaction presumably involves an initial reduction of **401** to Δ^2 -[1,2,3]thiazoline **405**, which forms the S,C-biradical **406** by ring opening and release of nitrogen. Dimerization of **406** gives the S,C-biradical **407**, which forms a C,C-biradical **409**. A tandem intramolecular cyclization–expulsion of acrylic ester from **409** affords the trithiepine- dicarboxylates **402** and **403**. An alternative pathway for the reaction would involve the formation of **408** from **406**, which would be converted to **409** and then to the products.



Scheme 83

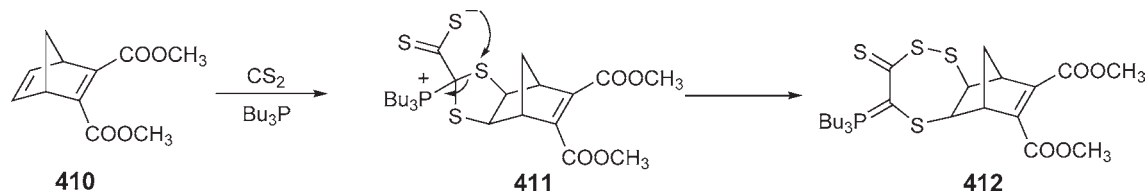


Scheme 84



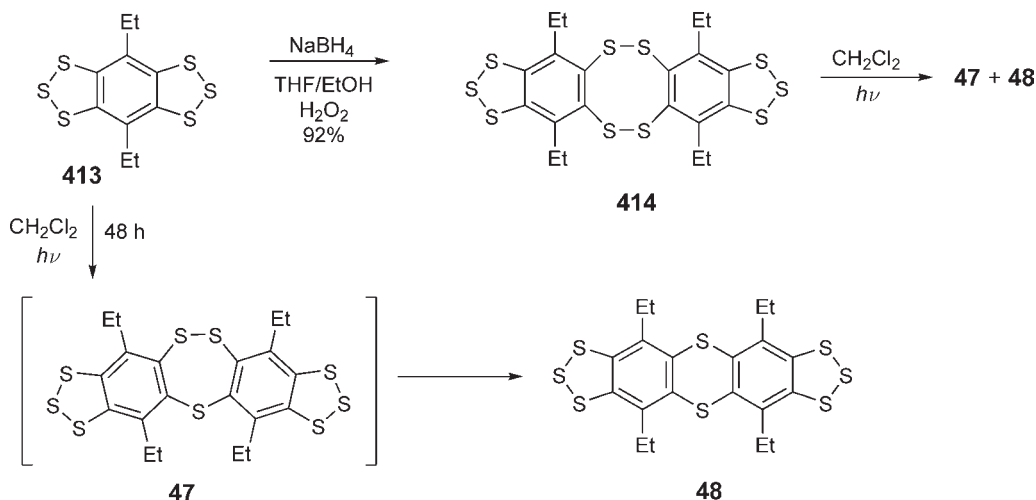
Scheme 85

The reaction of dimethyl 1,2-norbornadienedicarboxylates **410** with carbon disulfide afforded a zwitterionic **411**, which underwent ring expansion to give the norbornene-fused 1,2,5-trithiepine ring system **412** (Scheme 86) <1999TL1061>.



Scheme 86

Photolysis of **413** afforded a trace of dibenzotrithiepin **47** along with 13% yield of **48** (Scheme 87). The sodium borohydride reduction of **413** afforded **414**. Photolysis of **414** in CH_2Cl_2 for different time durations afforded different amounts of **47** and **48**, the amount of **47** decreasing with increasing irradiation time; for example, when the irradiation was done for 12, 24, and 72 h, the ratio of **47** and **48** was found to be 34:32%, 10:63%, and 8:22%, respectively <2000TL1801>.



Scheme 87

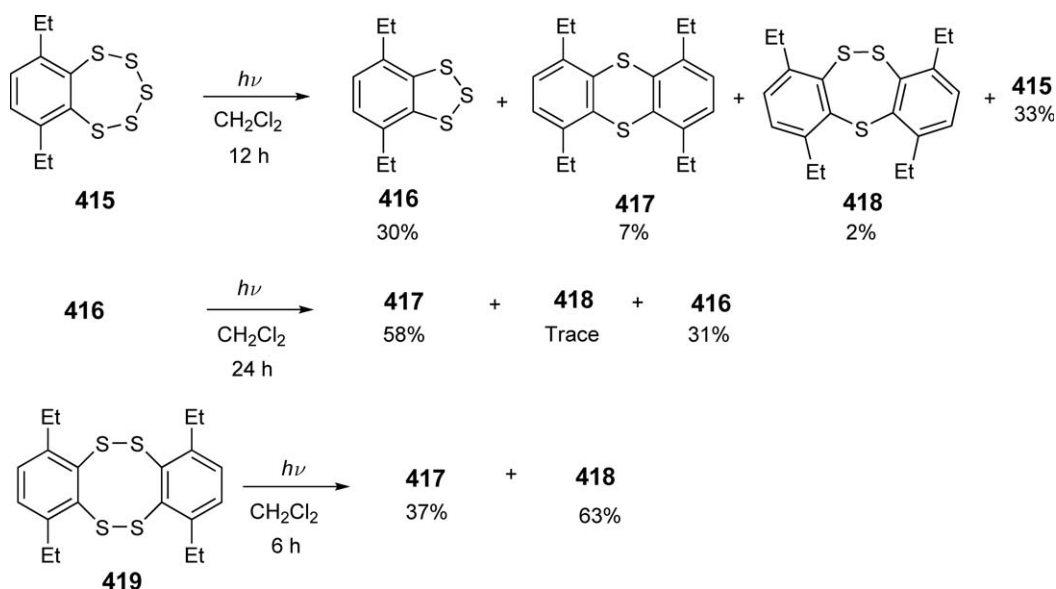
Photolysis of **415**, **416**, and **419** led to the formation of the fused 1,2,5-trithiepin **418** along with other products (Scheme 88) <2002BCJ2647>.

13.15.9 Important Compounds and Applications

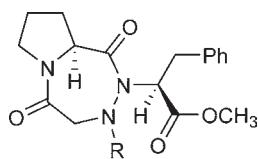
This section, which has not been dealt with in CHEC(1984) and CHEC-II(1996), discusses the applications of important 1,2,5-triheteropine ring systems.

13.15.9.1 Triazepines

In the synthesis of 1,2,5-triazepine-1,5-diones, which are expected to mimic the structural features of *cis*-peptidyl prolinamides, the preparation of N^2, N^3 -disubstituted derivatives **213a** from the reaction of (*Z*)-alanine with the N^2 -substituted triazepines **213** resulted in lower yields. It has been reported that these fused triazepinediones could be elaborated to give constrained *cis*-peptidyl proline peptide mimetics of defined stereochemistry and sequence <1997J(P1)2297>.

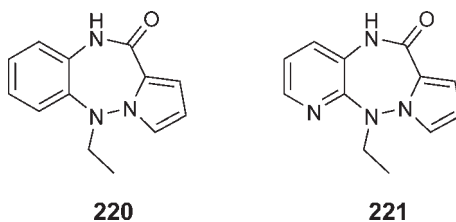


Scheme 88



213: R = H
213a: R = ZAla

The activity of triazepines **220** and **221** against the human immunodeficiency virus 1 (HIV-1) multiplication in acutely infected cells has been studied on the basis of inhibition of virus-induced cytopathogenicity in MT-4 cells. The triazepines **221** having a pyridine ring were found to be less potent than **220**. The results of activity studies are given in Table 6. Nevirapine has been used as the reference [\[2000JHC1539\]](#).

Table 6 Activities of triazepines **220** and **221**

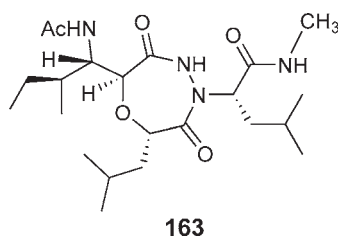
Compound	CC ₅₀ (μM cm ⁻³)	EC ₅₀ (μM cm ⁻³)	SI ^a (μM cm ⁻³)
220	159	48	3.3
221	>200	>200	
Nevirapine	>200	0.1	>2000

^aSelectivity index = ratio CC₅₀/EC₅₀.

13.15.9.2 Oxadiazepines

13.15.9.2.1 1,4,5-Oxadiazepine

A preliminary biological evaluation of the 1,4,5-oxadiazepine **163** revealed 10% inhibition at 10 μM for neuropeptide Y [\[1997TL6961\]](#).



13.15.9.2.2 1,2,5-Oxadiazepine

The *in vitro* cytotoxicity assay of the enantiomeric pairs of **60**, **420**, and **421** against P388 murine leukemia has been conducted. From the IC_{50} values listed in Table 7, the cytotoxicity of the C₉-O-acetyl derivatives **420** and **421** was found to be ca. 10–100 times more potent than **60**. Also it has been shown that **60**, **420**, and **421** with natural absolute configuration were ca. 100 times more cytotoxic than the corresponding enantiomers possessing unnatural absolute configuration <1997T10253>.

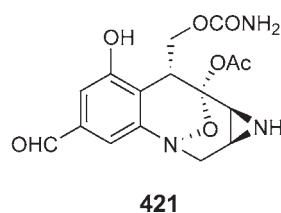
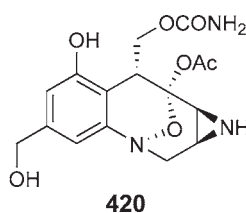
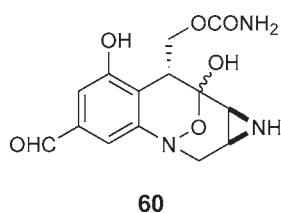
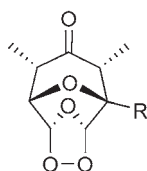


Table 7 *In vitro* cytotoxicity of enantiomeric pairs of **60**, **420**, and **421**

Compound	IC_{50} ($\mu M cm^{-3}$)	Compound	IC_{50} ($\mu M cm^{-3}$)
60	3.3×10^{-2}	<i>ent</i> -4	3.1
420	4.7×10^{-3}	<i>ent</i> -5	3.0×10^{-1}
421	3.6×10^{-4}	<i>ent</i> -6	4.0×10^{-2}

13.15.9.3 Trioxepines

The *in vitro* antimalarial activity of **17** and **422–430** against a multiresistant strain of *Plasmodium falciparum* from Thailand has been studied and the results are given in Table 8 <1996J(P1)1101>.



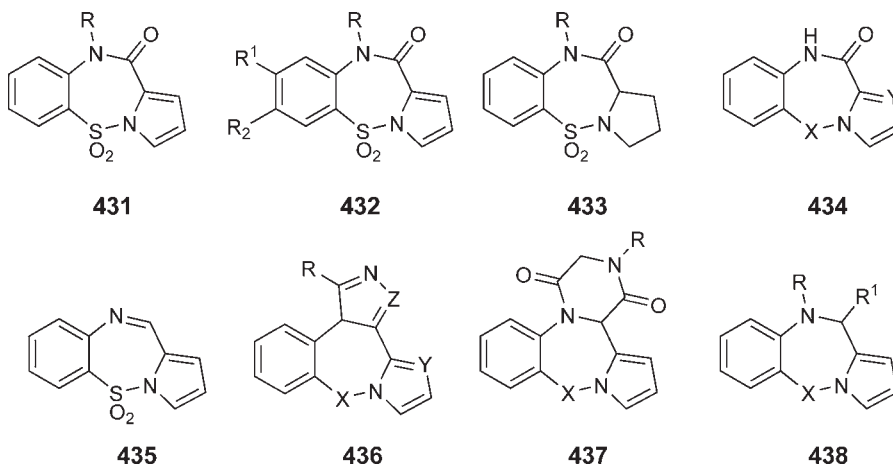
Compound	R
17	H
422	Et
423	CH ₂ OAc
424	Heptyl
425	CH ₂ CH ₂ CH ₂ OAc
426	CH ₂ CH ₂ CH ₂ OH
427	CH ₂ CH ₂ CH ₂ OC(O)Ph
428	CH ₂ CH ₂ CH ₂ OCH ₂ Ph
429	CH ₂ CH ₂ CH ₂ OMe
430	CH ₂ CH ₂ CH ₂ Cl

Table 8 *In vitro* antimalarial activities of **17** and **422–430**

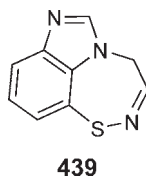
Compound	IC ₅₀ (μg cm ⁻³)
17	18
422	12
423	>500
424	26
425	3
427	11
428	6
429	2
430	7

13.15.9.4 1,2,5-Thiadiazepine

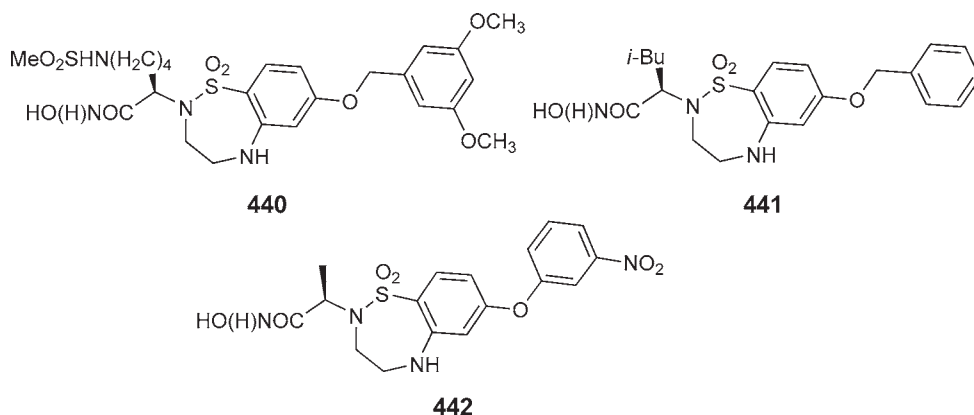
The antiviral activity of **431–438** has been investigated to study their cytotoxicity and capability to inhibit HIV-1-induced cytopathicity in MT-4 cells. AZT and nevirapine have been used as the references. A majority of these compounds were found to be noncytotoxic for MT-4 cells at doses higher than 300 μM. Maximum activity was obtained with the compounds of series **431** and other related chloro derivatives **432**, some of which displayed highest potency with EC₅₀ = 1.0 and 0.5 μM, respectively. Compounds belonging to other series were found to be considerably less potent and selective or totally inactive <1996BMC837>.



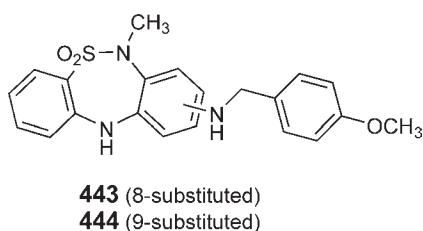
Derivatives of **439**, a novel tricyclic ring system useful as lead structure for the design of novel non-nucleoside reverse transcriptase (NNRT) agents of therapeutic interest, has been synthesized <2002JHC81>.



Several benzothiadiazepines, as potent and selective TACE inhibitors, have been synthesized with variation in P1 and P1' and evaluated versus porcine TACE, and the initial selectivity was assessed with counterscreens of MMP-1, MMP-2, and MMP-9. Several potent and selective inhibitors were discovered, **440** being the most active against porcine TACE. Most compounds were assessed in the human peripheral blood mononuclear cell (PBMC) assay and the human whole blood assay (WBA) to determine their ability to suppress tumor necrosis factor alpha (TNF-α). Compound **441** was found to be the most potent in the PBMC assay (IC₅₀ = 0.35 μM), while **442** was the most active in the WBA (IC₅₀ = 1.4 μM) <2003JME1811>.



The dibenzo[1,2,5]thiadiazepines **443** and **444** have been tested for their antiproliferative activity against the L1210 leukemia cell line. Both compounds display low cytotoxicity with IC_{50} values of 12.7 and 29.9 μM , respectively <2004H(63)2457>.

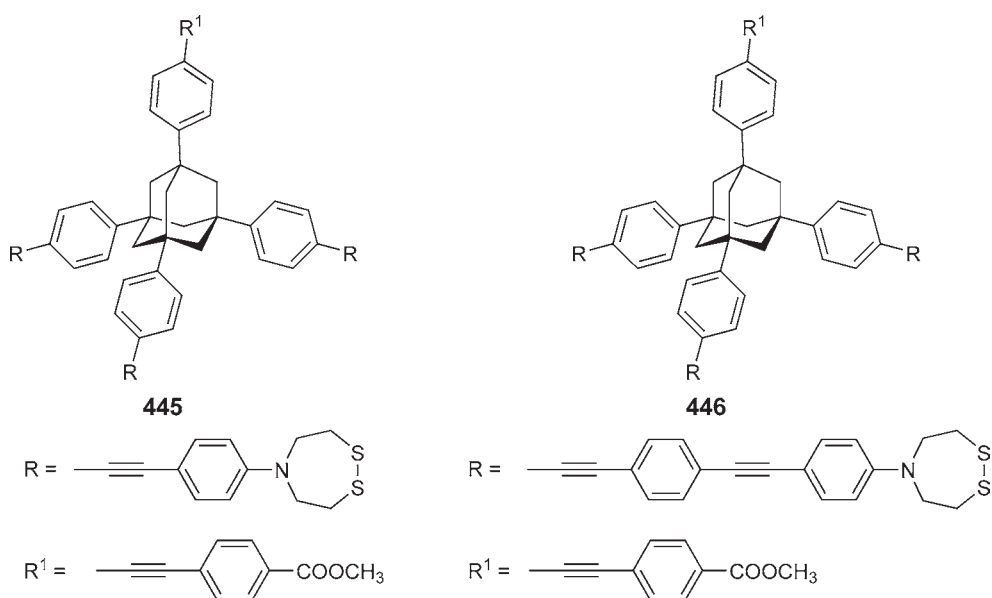


1-(4-Methoxyphenylethyl)-6-methylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-dioxide inhibited L1210 leukemia cell proliferation in the submicromolar range and tubulin polymerization in the micromolar range <2005JME7363>.

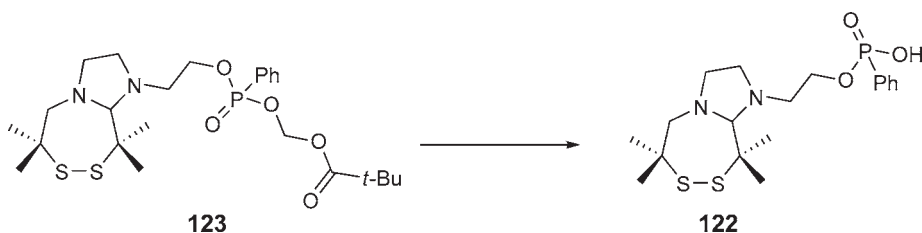
13.15.9.5 Dithiazepines

13.15.9.5.1 1,2,5-Dithiazepine

Synthesis of **445** and **446** that may find applications as chemically well-defined nanoscale objects for calibration of atomic force microscopy has been reported <2002OL3631, 2003JOC4862>.

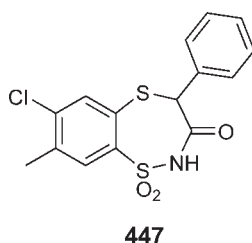


Preliminary pharmacological evaluation of **123** showed that it has the ability to penetrate through the blood–brain barrier and then was hydrolyzed to the very polar **122** in the central nervous system (CNS) <1998OPP485>.



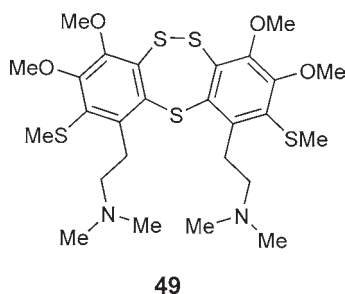
13.15.9.5.2 1,5,2-Dithiazepine

The *in vitro* anticancer activity of **447** has been studied using a total of 60 human cell lines derived from nine different cancer types (lung, colon, melanoma, prostate, breast, renal, ovarian, CNS, and leukemia). This compound has been tested in a broad concentration range (10^{-4} – 10^{-8} M), and it was found that the 1,5,2-dithiazepine **447** is the only compound among its analogues which showed a moderate activity in some tumor cell lines <2001H(55)753>.



13.15.9.6 Trithiepine

The trithiepine **49** has been tested for cytotoxicity against the MDA-MB-468 human breast carcinoma cell lines. On the basis of the IC_{50} value of **49** ($1.5 \mu\text{g ml}^{-1}$), further biological evaluations were performed. In an attempt to determine whether **49** selectively inhibits the PI3K/AKT/mTOR cellular signaling pathway, it has been tested in the MDA-MB-435S (PTEN^{+/+}) human breast carcinoma cell line. The trithiepine **49** displayed cytotoxicity against the MDA-MB-435S human breast carcinoma cell line with IC_{50} value of $4.2 \mu\text{g ml}^{-1}$ showing greater potency against the PTEN-deficient cell line and making it an important compound for further screening <2003T2855>.



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Biographical Sketch



Raju Ranjith Kumar obtained his M.Sc. degree in chemistry from Government Arts College, Ooty, India. He joined as a research scholar under the guidance of Prof. S. Perumal at the School of Chemistry, Madurai Kamaraj University, Madurai, India, in 2003. His research interests include synthesis and characterization of novel heterocyclic compounds employing 1,3-dipolar cycloadditions, atom-economic transformations, and one-pot multistep tandem reactions. In particular, the synthesis, NMR spectroscopic, and X-ray crystallographic studies of novel spiro-isoxazolidines, isoxazolines, dioxazoles, pyrazoles, pyrrolidines, and fused ring systems such as pyridopyrans and benzopyridooxadiazoles have been performed.



Subbu Perumal obtained his Ph.D. degree in physical organic chemistry from Madurai Kamaraj University, Madurai, India. He became professor of organic chemistry at the School of Chemistry, Madurai Kamaraj University, in 1994. During 1989–90, he was a postdoctoral fellow and carried out research work in evolving newer synthetic methodologies and investigating equilibrium processes using NMR spectroscopy with Professor Alan R. Katritzky, FRS, at the Department of Organic Chemistry, University of Florida, for a period of 18 months. He was again with Professor Alan R. Katritzky, FRS, at the Department of Organic Chemistry, University of Florida, for a shorter duration. During 2003–04, he was a visiting scientist with Professor Jose Carlos Menendez for a period of 12 months at Universidad Complutense, Madrid, Spain. His research interests include study of reaction mechanisms, NMR spectroscopic studies of organo-sulfur compounds, synthesis of novel heterocyclic compounds employing one-pot multistep and multicomponent tandem reactions, green synthetic protocols, asymmetric synthesis, and cycloadditions. He was instrumental for getting funds for the purchase and installation of a 300 MHz Bruker (Avance) NMR spectrometer under IRHPA programme of the Department of Science and Technology (DST), New Delhi. He is a life member of the National Magnetic Resonance Society, India. He was the convener of the DST-sponsored National Workshop on Green Chemistry held in 2006. He is also the convener of the DST-sponsored National Workshop on One- and Two-Dimensional NMR Spectroscopy – Theory and Applications, which is to be conducted on an yearly basis for five consecutive years commencing from 2007.



Marudai Balasubramanian 'BALU' obtained his Ph.D. degree in Organic Chemistry from the Indian Institute of Technology, Chennai, India in 1987. He carried out postdoctoral work with Dr. Alan R. Katritzky at the Department of Chemistry, University of Florida, Gainesville, Florida (1988–1992). He subsequently moved to Reilly Industries Inc., Indianapolis, Indiana, where he was a research chemist until 2002. His research interests include synthesis of heterocyclic compounds, particularly pyridine derivatives, and synthesis of intermediates for pharmaceuticals, agrochemicals, performance products, and heterocyclic polymers. In 2002, he joined Research Informatics, Pfizer at Ann Arbor, Michigan, as information professional. Currently he works at Pfizer, Groton and manages content and vendor relationship for the chemical related commercial databases. He is author/co-author of more than fifty scientific papers and has written several reviews, chapters for monographs and comprehensive heterocyclic chemistry series. He currently serves as an international editorial board member of *Heterocyclic Communications* an international journal of heterocyclic chemistry.

13.16

Seven-membered Rings with Three Heteroatoms

1,3,5

O. V. Denisko

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13.16.1 Introduction

In contrast to previous surveys of seven-membered ring heterocycles with 1,3,5 heteroatoms organized according to the type of the triheteropine ring system, the material of this chapter is arranged by investigation methods, properties, reactivity, and ring synthesis. To ensure the comprehensive coverage of these sections, several publications that appeared before 1994 but were not reviewed in the corresponding CHEC(1984) <1984CHEC(7)I593> and CHEC-II(1996) <1996CHEC-II(9)353> chapters are included. Also, in contrast to the corresponding chapters in CHEC(1984) and CHEC-II(1996), bridged polycyclic compounds containing the required heterocyclic ring are discussed along with monocyclic and fused derivatives.

13.16.2 Theoretical Methods

Semi-empirical geometry optimization of 5-(*p*-tolyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*][1,3,5]benzotriazepine **1** (Figure 1) using the AM1 method indicated that the tautomer **A** is favored over **B** by 3.9 kcal mol⁻¹ <2005FA127>. An exhaustive conformational analysis using the molecular dynamics technique and SAM1 method was conducted for oxadiazepane **2** and tetrahydrotriazepinone **3** to study their ability to mimic the geometric and electronic properties of a peptide γ -turn <1996MI16>. Tautomeric studies of oxathiazepane **4** using modified neglect of diatomic overlap (MNDO) calculations indicated the higher stability of the thiol form by more than 6 kcal mol⁻¹ in contradiction to the experimental findings <1992RJO1769>.

All possible polymorphs of formyl and acetyl derivatives **5** (R = R¹ = NO₂, R² = CHO, MeCO) of highly energetic hexanitrohexaazaisowurtzitane (HNIW) **5** (R = R¹ = R² = NO₂) were studied by AM1 and PM3 semi-empirical methods <2003JEM261, 2003MI281>. Molecular modeling of the bridged acetal **6** using combined molecular mechanics–Monte Carlo method revealed that while most of the molecule is rigid and essentially planar, the 1,3,5-trioxepane ring is flexible and able to adopt several distorted chair conformations with shallow minima. The lowest-energy structure is similar to the one determined by X-ray crystallography <1998J(P1)2353>.

13.16.3 Experimental Structural Methods

13.16.3.1 X-Ray, Neutron and Electron Diffraction, and Microwave Spectroscopy

X-Ray studies of **1** determined that the seven-membered heterocyclic ring exists in the twist-sofa form with the atoms N(4), C(7), C(12), N(13), and C(14) forming a flattened fragment and atoms C(5) and N(6) located above the mean plane <2005FA127>. The similar sofa-like conformation was observed for ethylene-bridged

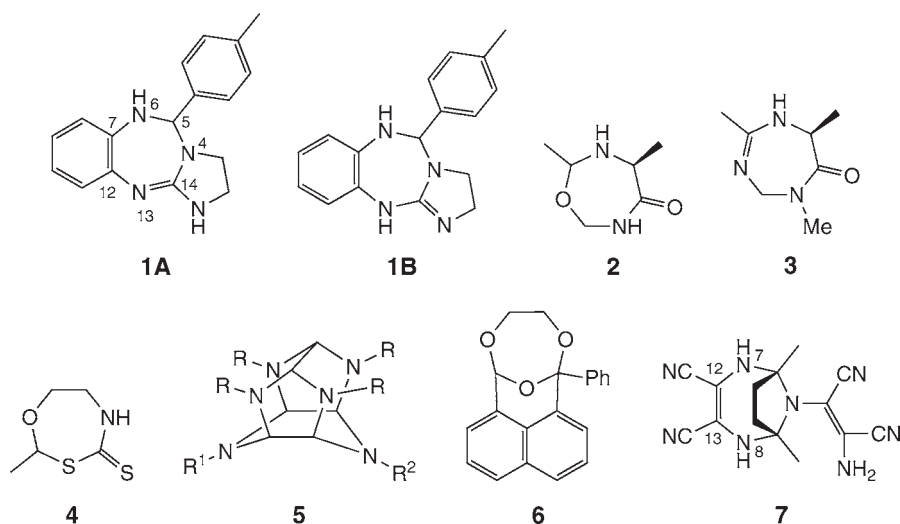


Figure 1

tetrahydrotriazepine **7**, where the additional rigidity is provided by significant π -delocalization over the N(7)–C(12)–C(13)–N(8) fragment [\[2000MI311\]](#). The seven-membered ring of pyrrolo[3,4-*f*][1,3,5]triazepine **8** ([Figure 2](#)), which exists in the solid state as a dimer with strong hydrogen bonds between amino group of one molecule and pyrrole nitrogen of another, is almost planar but puckered at C(4) [\[1993CC834\]](#).

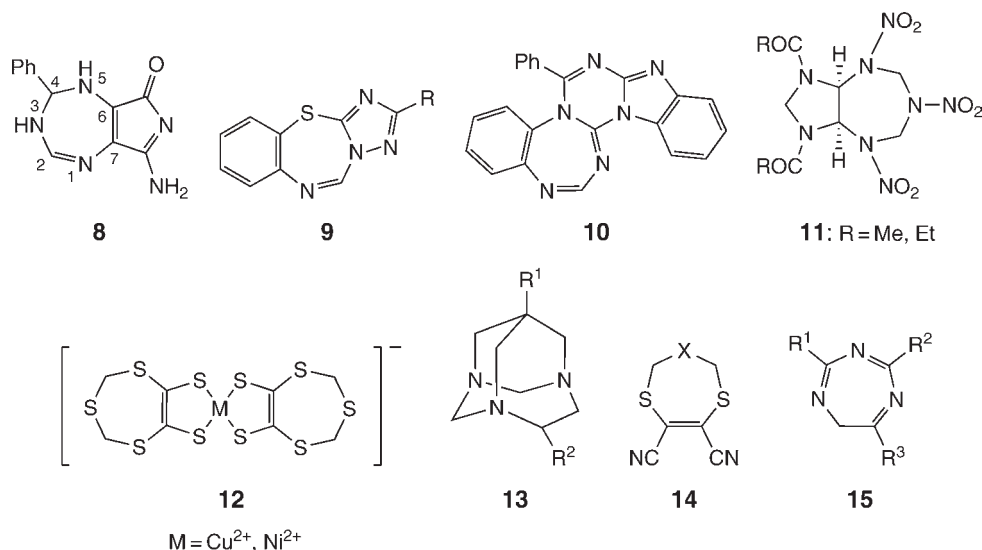


Figure 2

Similarly, the puckered conformation was observed for triazole- and benzimidazole-fused benzothiadiazepines, for example, **9** ($R = 4\text{-ClC}_6\text{H}_4$) [\[1996AXC3131, 1999H\(51\)161\]](#). In contrast, the triazepine ring of benzotriazepine **10** adopts a pronounced boat conformation with N(1) being quasi-pyramidal [\[1980AGE566\]](#). As expected, the seven-membered ring of fully hydrogenated triazepanes **11** [\[1992AXC1530, 1992AXC1872\]](#) and of fused trithiepins **12** [\[1986BCJ627, 1998JMC319\]](#) is more flexible and accepts the chair-like conformation. The chair conformation was also established for both seven-membered heterorings of homoazaadamantane **13** ($R^1 = \text{NO}_2$; $R^2 = \text{COPh}$) [\[1991CHE534\]](#) and hexaazaisowurtzitane **5** ($R = R^1 = R^2 = \text{ArCH}_2$) [\[1993J\(P2\)923, 2003CEJ687\]](#). Interestingly, the heteroring in trithiepin **14** ($X = \text{S}$) exhibits a twisted ring conformation, whereas that in oxadithiepin **14** ($X = \text{O}$) adopts chair-like conformation [\[1999EJI269\]](#).

13.16.3.2 NMR Spectroscopy

Insufficient data are available on the ^1H nuclear magnetic resonance (NMR) shifts of the parent saturated heterocycles except for 1,3,5-trithiepane <1981PS89>, 1,3,5-triazepanes with electron-withdrawing N-substituents <1998RCB2201>, and N-substituted 1,5,3-dithiazepanes <1979CPB1691, 1998JHC1531>, which indicate the following proton resonance ranges: 3.2–3.8 ppm for $\text{NCH}_2\text{CH}_2\text{N}$, 4.7–5.0 ppm for NCH_2N , 2.9–3.0 ppm for $\text{SCH}_2\text{CH}_2\text{S}$, and 4.3–4.4 ppm for NCH_2S fragments. The introduction of a double bond into the heterocyclic ring, as in **14**, or fusion with a benzene ring deshields the chemical resonances of the neighboring fragments by 0.5–0.6 ppm <1998RCB2201, 1999EJI269>. An effect of a bridgehead substituent on the ^1H NMR chemical shifts of monosubstituted homoazaadamantanes **13** ($\text{R}^1 = \text{H}, \text{Br}, \text{NH}_2, \text{NO}_2$; $\text{R}^2 = \text{H}$) has been studied <1990CHE578>.

The $4n$ π -electron system of unsaturated heterocycles is antiaromatic and its spectra are not indicative of a ring current existence. Furthermore, triazepines **15** ($\text{R}^1 = \text{H}, \text{NEt}_2$; $\text{R}^2, \text{R}^3 = \text{OMe}, \text{NEt}_2$), formed on ring expansion of pyrimidines and pyrazines (see Section 13.16.10), do not aromatize and exist as tris(imine) structure shown with CH_2 protons resonating at 4.1–4.3 ppm <1990CC723>. Similarly, no tautomerization to the fully conjugated form was observed for 4,5-dicyano-1,3,5-triazepine-2,4-dione <2004ARK71>.

The signals of methylene and methine ring protons of 3-methyl-1,3,5-trioxazepanium cation in SO_2 appear at 4.3 and 5.7 ppm in ^1H NMR and at 64.9 and 111.9 ppm in ^{13}C NMR spectrum, respectively <1982MMC1587>.

Low-temperature photolysis of single crystals of hexaazaisowurtzitane **5** ($\text{R} = \text{R}^1 = \text{R}^2 = \text{NO}_2$) was investigated by electronic paramagnetic resonance spectroscopy <1996JPC163>.

13.16.3.3 Mass Spectroscopy

Mass spectrometric methods were used for analysis of hexaazaisowurtzitane **5** ($\text{R} = \text{R}^1 = \text{R}^2 = \text{NO}_2$) and its oxo-analog, 4,10-dinitro-2,6,8,12-tetraoxa-4,10-diazaisowurtzitane, in the presence of various complex-forming anions <2005ANC7796>.

13.16.3.4 UV, IR, and Photoelectron Spectroscopy

Prototropic tautomerism of pyrimidinedione-fused 1,3,5-triazepine **16** (Figure 3) and analogs was studied by measuring ultraviolet (UV) spectra in various solvents. Solution in MeOH showed a strong negative Cotton effect

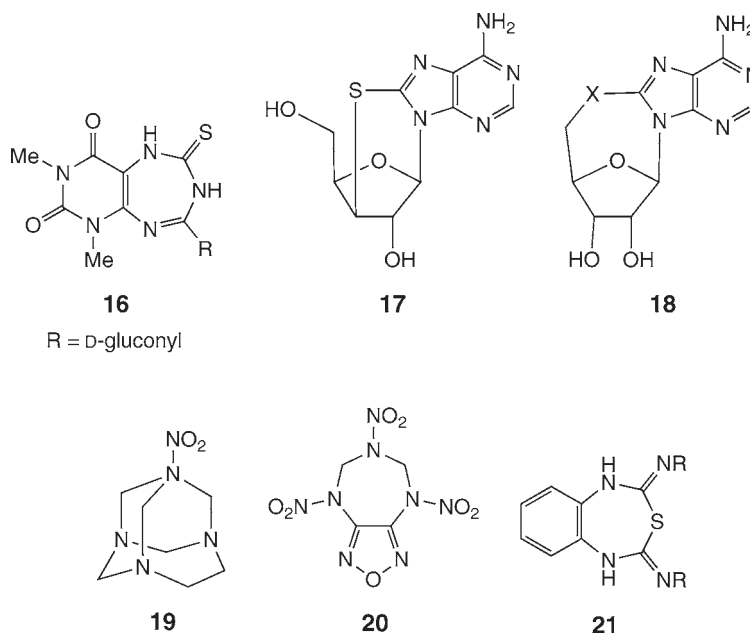


Figure 3

at 283 nm explained by the presence of the thiol form and a weak negative effect at 330 nm, which indicated the presence of the thione form. On changing the solvent from polar to nonpolar, the intensities of the bands reversed suggesting the predominance of the thione form in nonpolar solvents <1981CPB1832>. The tautomeric behavior of adenosine derivatives **17** and **18** (X = NH, O, S) in solution was studied using both experimental and calculated UV <1989MB1311> and circular dichroism <1995MB824> spectra. The UV spectra indicated the charge transfer across the σ -bond in the triazepane ring-containing homotetraazaadamantane **19** <1988DOK322>.

13.16.4 Thermodynamic Aspects

The thermochemical characteristics of 1,3,5-trinitro-1,3,5-triazepane, such as energies of dissociation of N–NO₂ bonds, enthalpies of formation, vaporization, and combustion, as well as enthalpy of formation of amine radicals, have been determined <2004MI92>. The rate constants of initial monomolecular stages of thermal decomposition in the solid phase were measured for its furazano-fused analog **20** <1999RCB1250> and the ratio of the rate constants of decomposition in the melt and solid states, characterizing the reaction retardation in the crystal lattice, was determined. The kinetics of the thermal decomposition of **20** has also been studied <1995MI885>.

Viscosities and densities were measured for benzodithiazepines **21** (R = *tert*-Bu, Ph, 2-MeC₆H₄, 4-ClC₆H₄, etc.) in aqueous acetone, aqueous ethanol, and aqueous dioxane of different percentages <2003MI41435>. The relative viscosities were calculated and used to study the molecular interactions in the solutions and estimate the substituent effect on the viscosity. The refractive indexes of benzodithiazepines **21** were also determined in acetone/water and dioxane/water mixtures and used to calculate the molar refraction and polarizability constants aiming to estimate the substituent and solvent effects <2003MI715>.

13.16.5 Reactivity of Fully Conjugated Rings

Due to the antiaromaticity of the fully unsaturated system, no full conjugation occurs. Therefore, the reactions of unsaturated heterocycles with three double bonds and their fused analogs are discussed together with those of saturated and partially unsaturated heterocyclic rings.

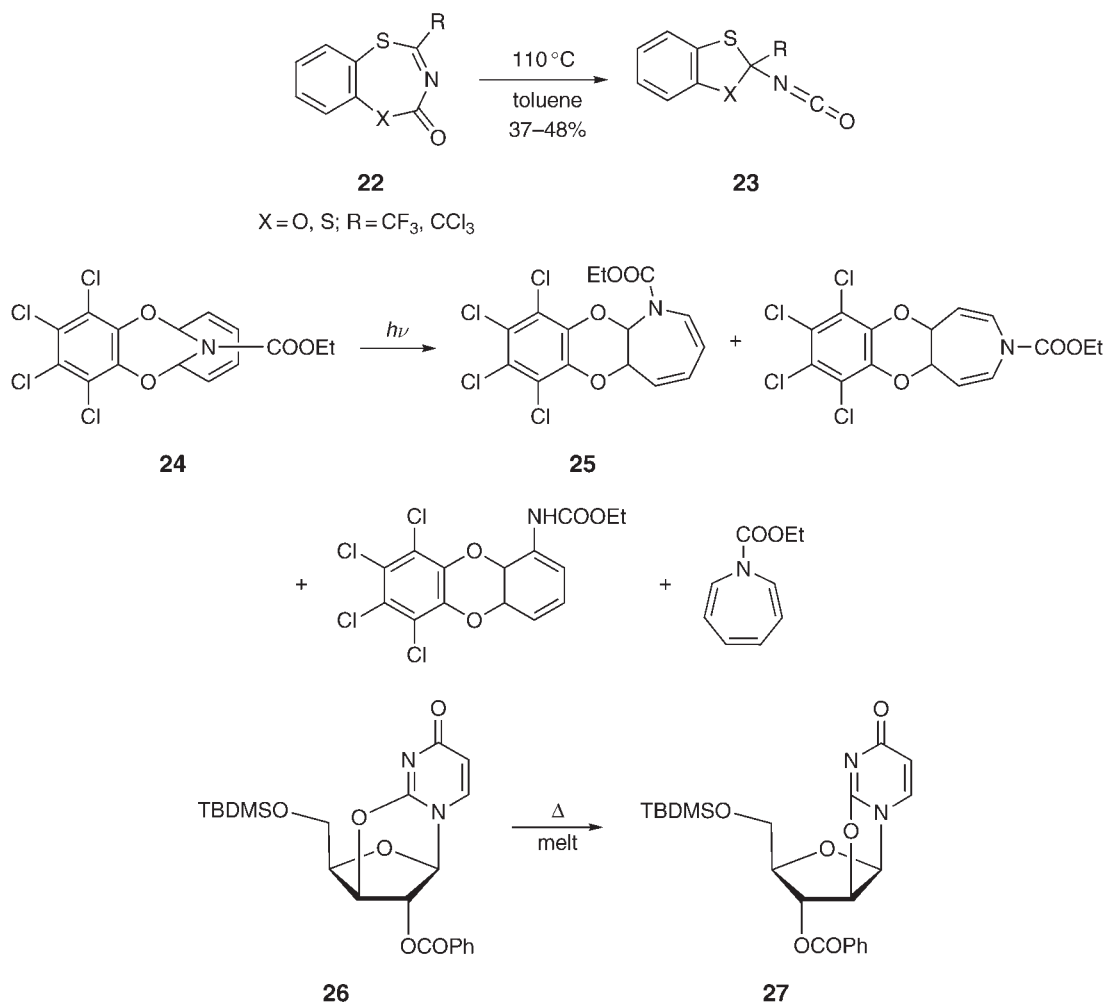
13.16.6 Reactivity of Nonconjugated and Partially Conjugated Rings

13.16.6.1 Unimolecular Thermal and Photochemical Reactions

Benzo-fused oxathiazepinones and dithiazepinones **22** (Scheme 1) undergo thermal rearrangement accompanied by ring contraction to afford heterocyclic isocyanates **23** in moderate yields <1993CHE1265>. Photoirradiation of bridged dioxazepine **24** (for the preparation, see Section 13.16.9.4.2) at 254 nm produced a range of products in ratios depending on the solvent used with azepine **25** being the major product in most of the solvents <2001H(54)567, 2003H(59)265>. Thermal decomposition of **24** at 180 °C gave azepine **25** as the only product in 84% yield <1982H(19)1197>. Thermal rearrangement of anhydrouridine **26** and its ¹⁷O and ¹⁸O labeled analogs resulted in the seven-membered ring opening–recyclization accompanied by benzoyl group transfer to give **27** in 54–65% yields <2002JOC1816>.

13.16.6.2 Electrophilic Attack at Nitrogen Ring Heteroatoms

Hydrogen-bearing nitrogen ring heteroatoms undergo all the common substitution reactions of secondary amines. Thus, acetylation of thiadiazepines **21** (Figure 3) <2004MI139, 2004MI773> and hexaazaisowurtzitane **5** (R = R¹ = NO₂; R² = H) (Figure 1) <2004WO076383> has been readily achieved in high yields with acetic anhydride in acetic acid or acetyl chloride, respectively. Interestingly, exclusive monoacetylation was observed on treatment of **5** (R = Ac; R¹ = R² = H) with acetic anhydride in acetic acid at 60 °C <2000JHC1647>. The product can be further formylated with formic acid to afford the unsymmetrical hexaazaisowurtzitane **5** (R = R¹ = Ac; R² = CHO). Trifluoroacetylation of **5** (R = Ac; R¹ = R² = H) allowed the introduction of an excellent protecting group, which is stable under harsh acidic conditions, such as HNO₃/oleum medium, but could be readily removed on treatment with AcONa in ethanol <2004MI133, 2004WO076384>. Nitrosation of **21** using NaNO₂/HCl <2004MI139, 2004MI773> and of **5** (R = R¹ = NO₂; R² = H) using NOBF₄ <2004RCB566> and addition of



Scheme 1

hexaazaisowurtzitane **5** ($\text{R}^1 = \text{H}$) to isocyanates <2004WO076383> were also reported. Methylation of oxathiadiazepane **4** (Figure 1) with MeI in KOH/DMSO occurred chemoselectively at the nitrogen atom <1992RJO1769>.

Deprotonation of the imide nitrogen atom in triazepinediones **28** ($\text{R}^1 = \text{cycloalkyl}$; $\text{R}^2 = \text{acylmethyl}$; $\text{R}^3 = \text{H}$) (Figure 4) followed by treatment with bromoacetates afforded the corresponding N-alkylated derivatives **28** ($\text{R}^3 = \text{CH}_2\text{COOR}^4$; $\text{R}^4 = \text{Et}$, *tert*-Bu, PhCH_2) <2004WO098610>. The similar deprotonation/alkylation reactions of triazepinedione **29** produced either mono- or dialkylated products depending on the reactant ratio, solvent, and the nature of the electrophile and the base <2001WO096318>. However, due to the higher reactivity of the sterically constrained heterocyclic ring, benzoylation of 2,5'-iminouridine **30** in pyridine under mild conditions resulted in seven-membered heteroring opening <1992J(P1)1065>. Similarly, acetylation or tosylation of homotriazaadamantane **13** (Figure 2) ($\text{R}^1 = \text{NO}_2$; $\text{R}^2 = \text{H}$) led to the opening of the triazepine ring <1994CHE349>.

Heating diaminopyridazine-fused triazepinedione **31** (Scheme 2) with triethyl orthoformate in acetic anhydride gave tetracyclic cyclocondensation product **32** <2004ARK71>. Hydrolysis of azetidinone-fused oxathiazepane *S,S*-dioxides **33** ($\text{X} = \text{SO}_2$; $\text{R} = \text{H}$, Me; $\text{R}^1 = 4\text{-O}_2\text{NC}_6\text{H}_4$) by reflux in aqueous AcOH led to the seven-membered ring opening with formation of the corresponding (2-hydroxyethyl)sulfonyl azetidinones <1980JA2039, 1992S1179>.

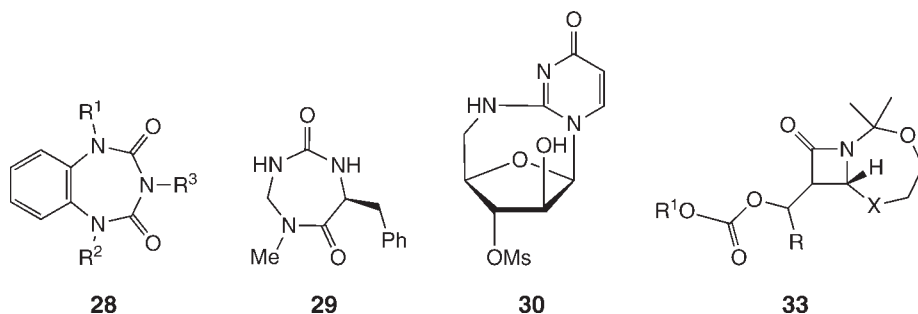
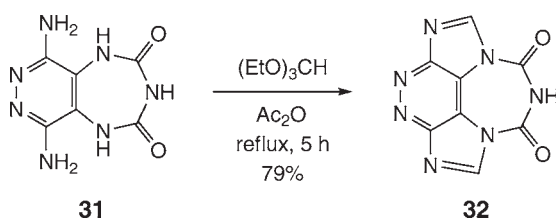


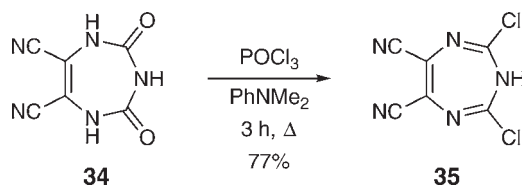
Figure 4



Scheme 2

13.16.6.3 Electrophilic Attack at Ring Carbon Atom

Chlorination of triazepinedione **34** (Scheme 3) with POCl_3 in *N,N*-dimethylaniline gave triazepine **35** in 77% yield <2004ARK71>.



Scheme 3

13.16.6.4 Electrophilic or Nucleophilic Attack at Sulfur or Oxygen Ring Heteroatoms

Azetidinone-fused oxathiazepane *S,S*-dioxides **33** ($\text{X} = \text{SO}_2$; $\text{R} = \text{H}, \text{Me}$; $\text{R}^1 = 4\text{-O}_2\text{NC}_6\text{H}_4$) (Figure 4) were readily synthesized by *m*-chloroperbenzoic acid (MCPBA) oxidation of the corresponding sulfides **33** ($\text{X} = \text{S}$) under mild conditions <1980JA2039, 1992S1179>. Similarly, indolocarbazole-fused thiadiazepines **36** ($\text{X} = \text{S}$; $\text{Y}, \text{Z} = \text{H}_2, \text{O}$; $\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^3 = \text{H}, \text{SiPr}_3$) (Figure 5) were easily oxidized to sulfones **36** ($\text{X} = \text{SO}_2$) on treatment with MCPBA in CH_2Cl_2 or dimethyl formamide (DMF) <1994BML1333, 1994WO07895>. Sulfur oxidation of tetracyclic thiadiazepine **37** ($\text{X} = \text{S}$) with H_2O_2 in AcOH at reflux afforded an equimolar mixture of sulfoxide **37** ($\text{X} = \text{SO}$) and sulfone **37** ($\text{X} = \text{SO}_2$) <2002MC131>.

The cationic ring-opening polymerization of L-arabinofuranose 1,2,5-orthopivalate **38** <2000MM1148> and D-glucopyranose 1,2,4-orthoesters **39** ($\text{R}^1 = \text{Me}, \text{Et}, \text{tert-Bu}, \text{Ph}$; $\text{R}^2 = \text{Me}, \text{PhCH}_2$; $\text{R}^3 = \text{H}, \text{Me}, \text{CH}_2\text{OMe}, \text{CH}_2\text{OCH}_2\text{Ph}$, etc.) <1996JA1677, 1997MM2891, 2001CAR405, 2001MM2476, 2002PSA4167, 2002MI538> has been studied extensively. Acid-assisted polymerization of **38** and **39** ($\text{R}^1 = \text{tert-Bu}$) occurred in a stereo- and regioregular fashion to produce poly(1→5)- α -L-arabinofuran and poly(1→4)- β -D-glucopyrans, respectively. Orthoesters **39** with R^1 other than *tert*-Bu gave stereoregular, but not regioregular, polysaccharides.

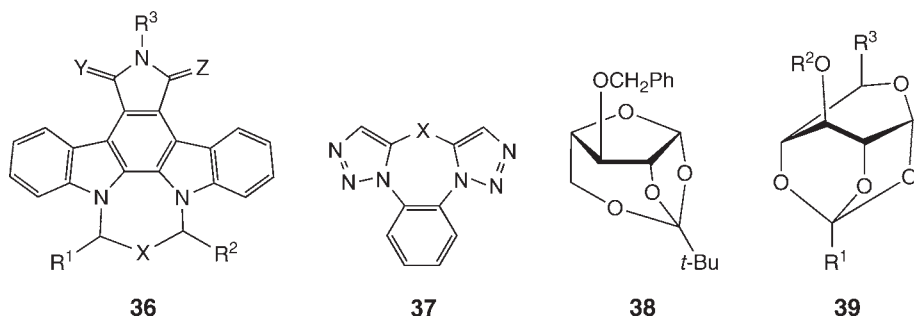
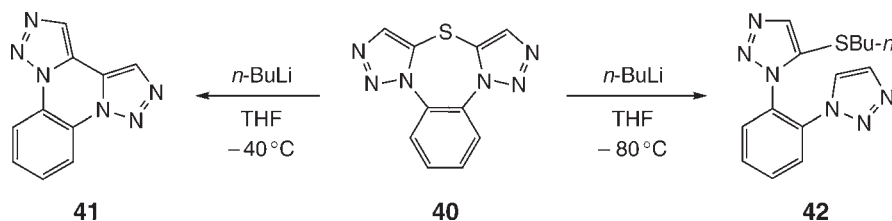


Figure 5

The transformations of bis(triazole)-fused benzothiadiazepine **40** (Scheme 4) on treatment with *n*-BuLi depended on the reaction temperature: at -40°C , the sulfur extrusion occurred to afford fully aromatized bis(triazolo)quinoxaline **41**, whereas at -80°C , a seven-membered ring opening took place with formation of bis(triazolyl)benzene **42** <2002MC131>.

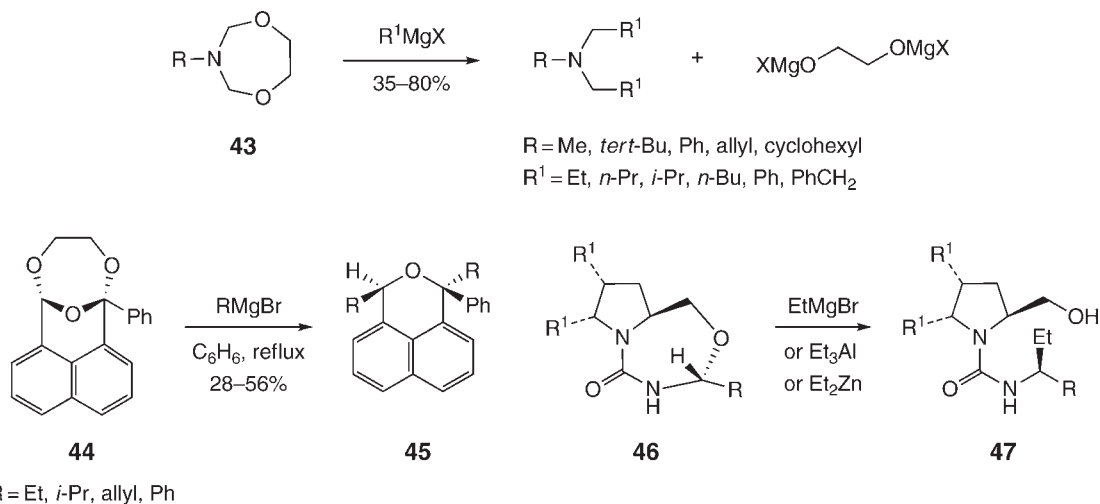


Scheme 4

13.16.6.5 Nucleophilic Attack at Ring Carbon Atom

13.16.6.5.1 Monocyclic and fused seven-membered rings

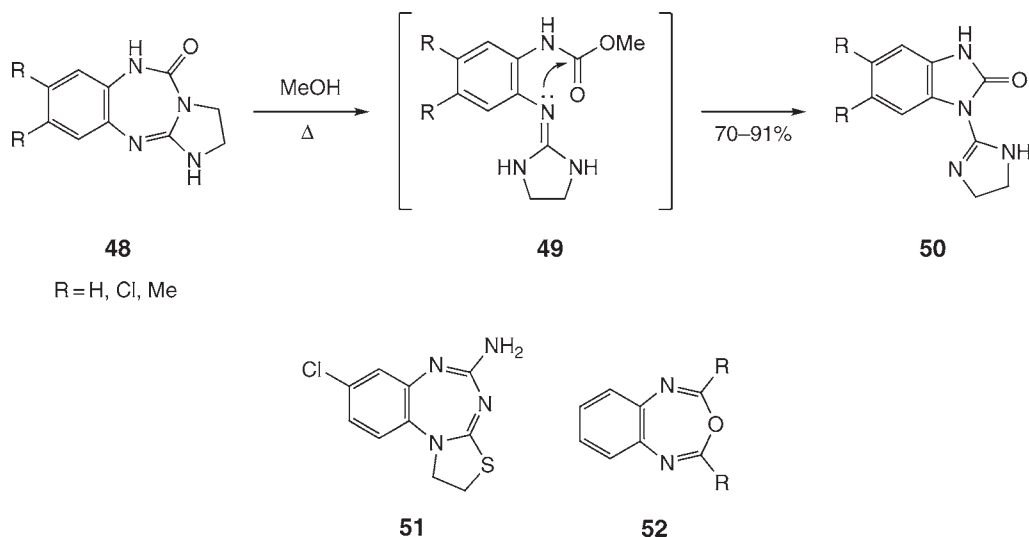
The heterocyclic ring of *N*-substituted 1,5,3-dioxazepines **43** was readily cleaved by various alkyl, aryl, or benzyl Grignard reagents with the formation of symmetrical tertiary amines (Scheme 5) <1983TL1597>. Similarly, Grignard reagents readily attack the acetal ring carbon atom of 1,3,5-trioxepane **44** or its phenanthrene-bridged analog resulting in cleavage of dioxethylene fragment and formation of cyclic ethers, such as **45**, with high stereoselectivity in some cases



Scheme 5

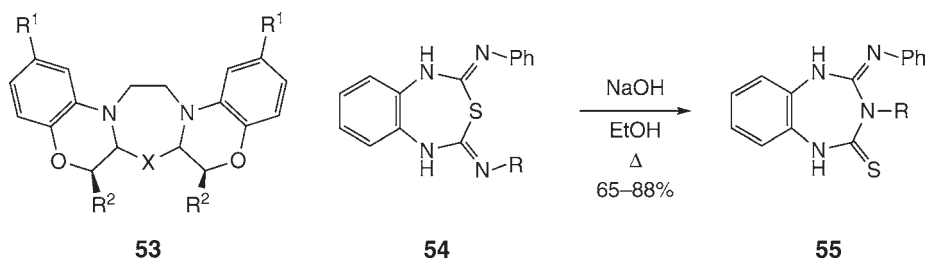
<1998J(P1)2353>. The reaction of enantiopure proline-derived oxadiazepanones **46** ($R = i\text{-Pr}$, cyclohexyl, Ph, 1-naphthyl, etc.; $R^1 = \text{H}$ or $R^1_2 = (\text{CH}_2)_3$) with EtMgBr , Et_3Al , or Et_2Zn occurred at the aminal carbon and led to the stereoselective formation of ring-opened products **47** in high yields <1990CPB2627, 1990H(30)287, 1996LA927>. The stereoselectivity depended on the organometallic reagent used with Et_2Zn showing the best results.

On heating in boiling methanol, imidazolidine-fused benzotriazepinones **48** underwent nucleophilic ring opening followed by intramolecular recyclization to afford the ring-contraction products **50** via the formation of the intermediate carbamates **49** (Scheme 6) <2005FA127>. Thiazolidine-fused benzotriazepine **51** underwent similar ring contraction in hot aqueous HCl to give 2-amino-5-chloro-1-(mercaptoethyl)benzimidazole in 67% yield <1990T2009>, whereas benzooxadiazepine **52** ($R = \text{Me}$) on treatment with HBr in 1,2-dichloroethane was transformed into 1-acetyl-2-methylbenzimidazole in 59% yield <1988M1279>.



Scheme 6

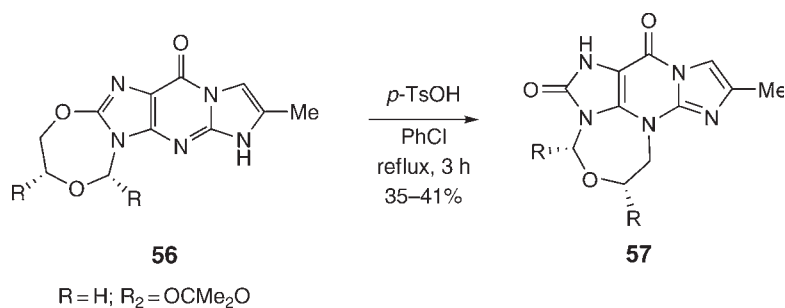
Reductive cleavage of polycyclic oxadiazepanes **53** ($X = \text{O}$; $R^1 = \text{H}$, Me ; $R^2 = \text{OH}$) (Scheme 7) with $\text{BH}_3 \cdot \text{THF}$ ($\text{THF} = \text{tetrahydrofuran}$) gave the corresponding symmetrical diamines **53** ($X = \text{nothing}$; $R^2 = \text{OH}$) <2001T55>. Nucleophilic ring opening–ring closure was observed on refluxing the ethanolic solution of bis(imino)benzothiadiazepines **54** ($R = t\text{-Bu}$, aryl) with NaOH affording the (imino)benzotriazepinethiones **55** in moderate to high yields <2004MI139, 2004MI773>.



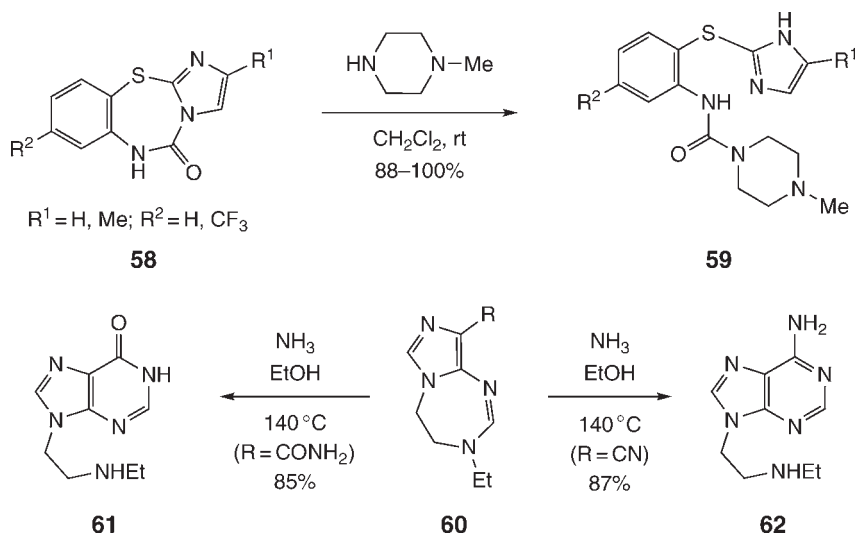
Scheme 7

On treatment with $p\text{-TsOH}$ in refluxing chlorobenzene, fused dioxazepanes **56** (Scheme 8) underwent ring opening at the imidazole aminal center followed by recyclization to provide the oxadiazepanes **57** in moderate yields <2004NN117>.

The 7-membered heteroring of imidazole-fused benzothiadiazepinones **58** (Scheme 9) was cleaved on treatment with secondary amines, such as $N\text{-methyl}$ piperazine, producing the corresponding $N\text{-}[o\text{-(imidazolylthio)aryl}]$ ureas **59** <1983JHC1287>. Reaction of imidazotriazepines **60** with ammonia in ethanol at 140°C resulted in triazepine ring opening–recyclization with formation of the corresponding purines **61** and **62** <1991S822>.



Scheme 8

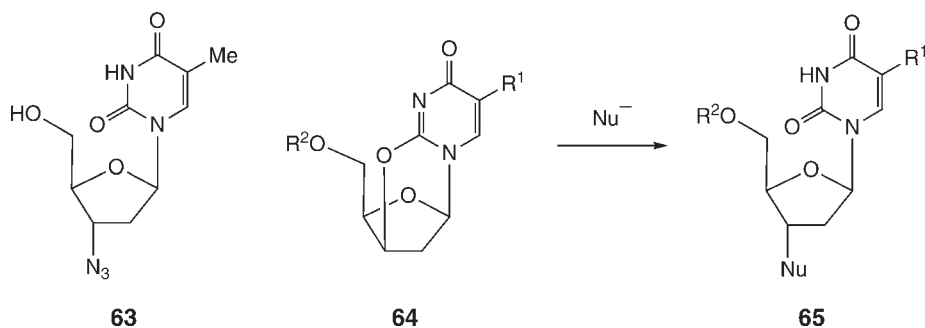


Scheme 9

13.16.6.5.2 Nucleoside derivatives

13.16.6.5.2(i) Nitrogen nucleophiles

Antiviral drug azidothymidine **63**, known also as AZT and zidovudine, is useful in treatment of AIDS as an agent impeding the human immunodeficiency virus replication process. One of the most common approaches to the synthesis of AZT is the nucleophilic ring opening of anhydrothymidine **64** ($\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{H}$) or its O-protected derivatives (Scheme 10) with azide anion. Generally, sodium azide [<1995SUA2034848, 1996NN899>](#) or lithium azide (with or without benzoic acid as catalyst) [<1990NN587, 1991JME1426>](#) in DMF at 100–130 °C are used. The



Scheme 10

reaction with trimethylsilyl azide as a nucleophile in MeCN under catalysis with boron trifluoride etherate took place already at 50 °C <1993JCM326>. Preliminary alkylation of *O*-trityl anhydrothymidine with methyl or benzyl triflates allowed for even milder conditions (10 °C) for the ring opening with LiN₃ giving access to N(3)-alkylated AZT derivatives <1993TL8411>. The effect of the alkyl group of alkyl triflate on the extent of O(4) versus N(3) alkylation was studied in detail <1993JOC3030>.

The kinetic studies of the *O*-benzoyl anhydrothymidine ring opening with dimethylammonium azide in DMF–dioxane indicated the first-order kinetics for each reactant and the involvement of a six-center transition state <2000RJO1369>. This approach using NaN₃ or LiN₃ was also successfully applied to the synthesis of labeled AZT derivatives <2003MI669>, thia-analogs <1991JME2782>, and azido-substituted uridines <1990JME845, 2001JOC4079> and 5'-aminothymidines <1993T4365>. When mesyl group was used as a protecting R² group, its substitution with the azide anion may also occur resulting in the formation of the corresponding bis(azides) <2003NN1939, 2004BML4233>.

Other nitrogen nucleophiles, such as bis[2-(5-tetrazolyl)ethyl] ether <2002TL1901> and potassium phthalimide <2003JOC331>, have also been utilized for ring opening of *O*-protected anhydrothymidines with formation of nucleosides **65** (Nu = 2-tetrazolyl, phthalimido). The kinetic studies of the similar transformation of *O*-benzoyl anhydrothymidine to **65** (Nu = 2-tetrazolyl) on treatment with triethylammonium tetrazolide indicated the second order kinetics and established the reaction mechanism as a classical S_N2 process <2001RJO1767>. In contrast, the anion generated from tosylamide on treatment with NaH in DMF or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in MeCN attacks the C(2) atom of the pyrimidine ring of **64** leading to the retention of the stereochemistry at the C(3') center (see structure **66**, Figure 6) <2003NN1623, 2003T4047>. The ring openings of (β-L-lyxofuranosyl)benzimidazole **67** with isopropylamine <1999JOC4169> and anhydronucleosides **68** (X = OH, N₃; R = H, Me; Y = H) with ammonia <1989JME1891, 2003JOC367> in MeOH, respectively, were similarly initiated by the nucleophilic attack at the azole/azine moiety.

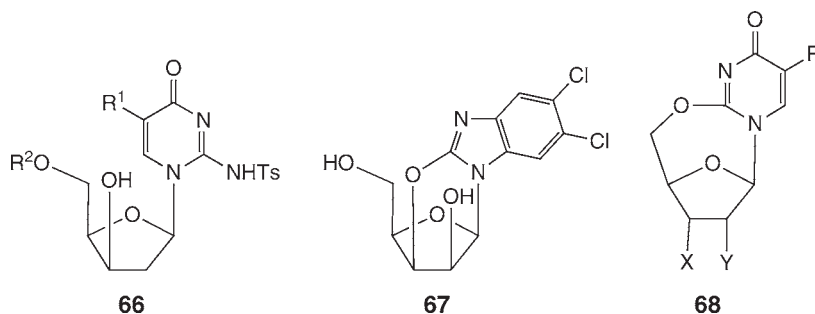
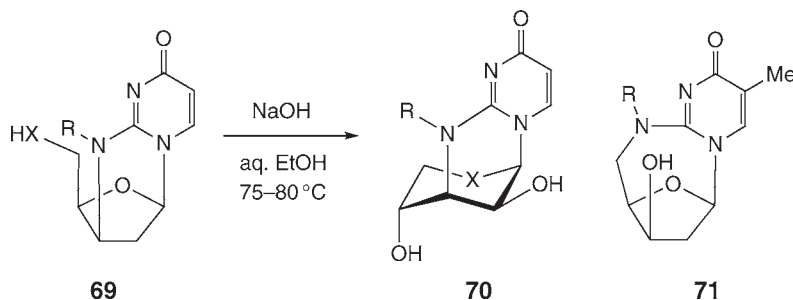


Figure 6

Deprotonation of the secondary amino group of 2,5'-iminonucleosides **69** (X = NR¹; R¹ = Me, Ph, PhCH₂; R = Me, Ph) (Scheme 11) created the nucleophilic center which attacked intramolecularly the aminal carbon atom of **69** producing the uracil derivatives **70** in moderate yields <1990J(P1)3027>.

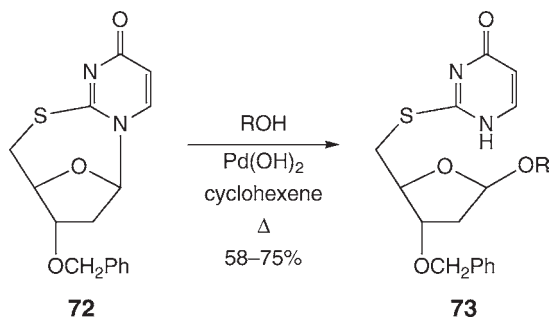


Scheme 11

13.16.6.5.2(ii) Oxygen Nucleophiles

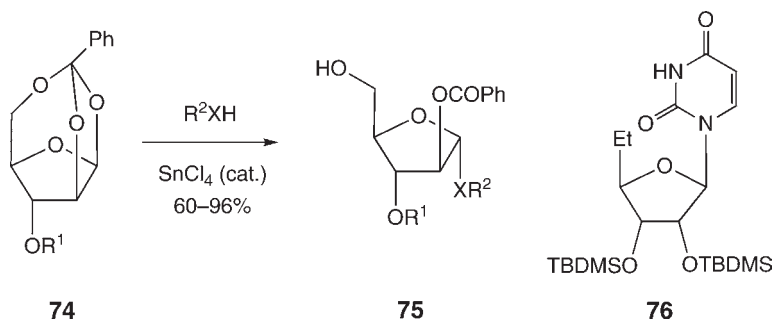
Reaction of anhydronucleosides **64** (Scheme 10) or their thia analogs with NaOH in aq. EtOH occurred at the pyrimidine C(2) atom giving the ring-opened products of type **65** (Nu = OH) but with the retention of configuration at C(3') <1989NN327, 1994TL7569, 1995NN279, 2004OL2169>. The same products were obtained when acetic acid was used instead of NaOH <1987CPB4498>. The ring opening of **71** (R = H, Me) (Scheme 11) with aq. NaOH occurred similarly <1987JOC2892>.

On the other hand, preliminary alkylation of **64** with methyl triflate followed by treatment with water resulted in the formation of N(3)-methylated products **65** (Nu = OH) with inverted configuration at C(3') under mild conditions <1993TL8411>. The attack of nitrate anion also took place at C(3') affording **65** (Nu = ONO₂) <2003JME995>. Palladium-catalyzed ring opening of cyclic nucleosides **72** (Scheme 12) with alcohols (MeOH, EtOH) occurred at the aminor moiety to form **73** in moderate yields <1992NN603>.



Scheme 12

Deprotonation of the hydroxy group of cyclonucleoside **69** (Scheme 11) (X = O, R = Me, Et, MeNH) created a nucleophilic center which reacted intramolecularly with the aminor carbon atom to give uracil-containing tetrahydropyrans **70** in 28–32% yields <1986JOC4417, 1989JOC4543>. Acid-catalyzed alcoholysis of 1,2,5-benzylidene-D-arabinofuranoses **74** (R¹ = H, CH₂Ph) (Scheme 13) resulted in the orthoester cleavage to form furanoses **75** (X = O; R² = Me, *n*-pentyl, *n*-octyl, etc.) <2000CC659, 2000TL7447>. The similar reaction was observed for mannopyranoside orthoester <1999TL6423>.



Scheme 13

13.16.6.5.2(iii) Sulfur and selenium nucleophiles

Treatment of anhydrobases **64** (Scheme 10) with various aliphatic <1989NN1463, 1992TL2371, 2000S149, 2003JOC331>, benzylic <1996J(P1)2237, 2003JOC331>, acyl <2003NN1343, 2004NAR495>, and phosphinoyl <2004TL2473> thiols or with phenylselenenol <1995NN1227> under basic conditions afforded the corresponding sulfides and selenides **65** (Nu = RS, PhSe) in moderate to high yields. Only one mercapto group of aliphatic dithiols participated in the reaction <1987NAR5305>. The effect of reducing agents and reaction conditions on selenynylation of **64** with diphenyl diselenide was investigated <1991JOC2161, 1992TL2371>. Methylation of **64** (R¹ = Me; R² = trityl) with methyl triflate followed by treatment with NaSCN gave the corresponding N(3)-methylated

thiocyanate **65** (Nu = SCN) in 60% yield <1993TL8411>. SnCl₄-catalyzed ring opening of 1,2,5-benzylidene-D-arabinofuranoses **74** (R¹ = H, CH₂Ph) (Scheme 13) with ethylthiol or phenylselenenol produced substituted furanoses **75** (X = S, R² = Et; X = Se, R² = Ph) <2000CC659, 2000TL7447>.

13.16.6.5.2(iv) Halogen Nucleophiles

The anhydronucleosides and anhydrothymidine ring opening with fluoride anion is generally carried out by treatment of anhydronucleosides with anhydrous HF in the presence of a metal catalyst. Although the organoaluminium compounds <1991TL2091, 1992EPP470355, 1992EPP495225> are most commonly used as catalysts, organoiron <1994WO26762> and lanthanide or transition metal compounds <1993USP5231175> are also effective. The effect of the catalyst structure on the yield of the products **65** (Nu = F) has been extensively studied. The modified procedure using Kryptofix 2.2.2 as the catalyst was applied to the synthesis of labeled **65** (Nu = ¹⁸F) <2002MI55>.

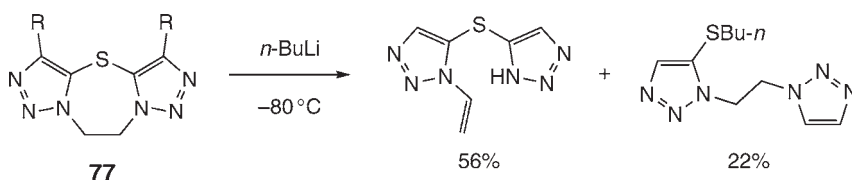
Treatment of *O*-benzoyl anhydrothymidine **64** (R¹ = Me; R² = C(=O)Ph) with MgX₂ (X = Br, I) in toluene at 100 °C afforded halo-substituted thymidines **65** (Nu = Br, I) in 70–75% yields <1995NN307, 1995TL873>. Alkylation of *O*-trityl anhydrothymidine with methyl triflate followed by reaction with NaBr or NaI gave the corresponding N(3)-methylated thymidines **65** (Nu = Br, I) in 70–90% yields <1993TL8411>.

13.16.6.5.2(v) Carbon and hydrogen nucleophiles

Methylation of anhydrothymidine **64** (R¹ = Me; R² = trityl) with methyl triflate followed by reaction with CuCN or sodium dimethylmalonate afforded the N(3)-methylated derivatives of **65** (Nu = COOH, CH(COOMe)₂) in 50–65% yields under mild conditions <1993TL8411>. Reaction of anhydronucleoside **68** (R = H; X = Y = OTBDMS) (Figure 6) with Me₂CuLi took place at the C(5') atom giving uridine **76** (Scheme 13) <1990CPB355>. Treatment of 5'-*O*,8-anhydroadenosines with NaBH₃CN in acetic acid resulted in reductive cleavage of the O–C(8) bond with formation of the corresponding adenosines <1987CC1298>.

13.16.6.6 Nucleophilic Attack at Hydrogen Attached to Ring Carbon Atom

In contrast to benzothiadiazepines **40** (see Scheme 4), the nucleophilic attack of *n*-BuLi on bis(triazolo)thiadiazepine **77** (R = H) (Scheme 14) occurred both at the sulfur atom and at the proton of the seven-membered ring resulting in formation of two ring-opened products <2002MC131>. Carbanion formation at the bridgehead of **78** (R¹ = R² = H) (Scheme 15) is easily achieved by treatment with *n*-BuLi or lithium diisopropylamide (LDA); subsequent alkylation with MeI afforded the monomethylated product **78** (R¹ = Me; R² = H) in 54% yield <1981T2045>.

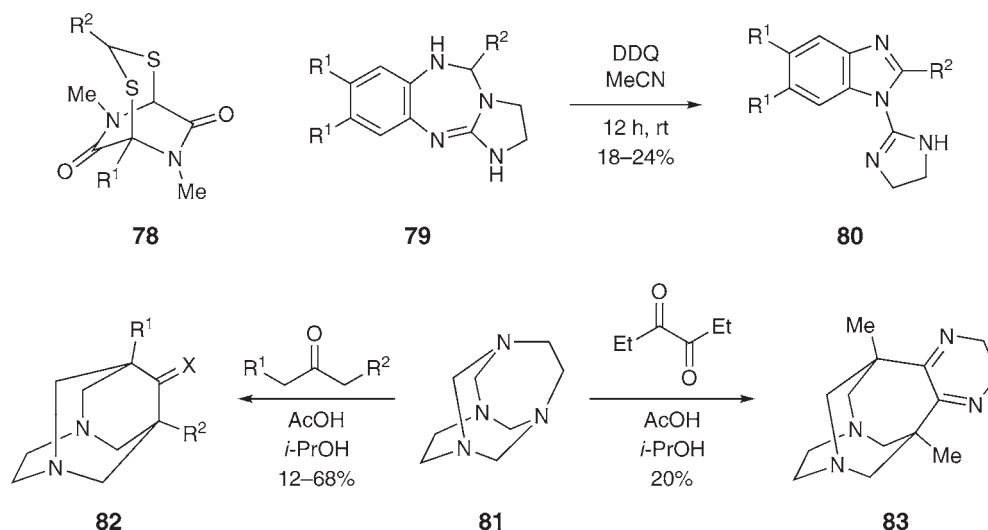


Scheme 14

13.16.6.7 Other Transformations Affecting Seven-Membered Heterocyclic Ring

Treatment of imidazo[2,1-*b*][1,3,5]benzotriazepines **79** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in acetonitrile at ambient temperature resulted in oxidative ring contraction with formation of stable (dihydroimidazoly)benzimidazoles **80** (Scheme 15). The reaction was suggested to occur via the initial hydride abstraction from N(6) followed by triazepine ring scission and formation of nitrenium ion <2005FA127>.

The common C–C bond of two triazepine rings in hexaazaisowurtzitane **5** (R = R¹ = R² = CH₂Ph) (Figure 1) can be oxidatively cleaved by reaction with *n*-BuONO in aqueous NH₄Cl or with CAN in aqueous acetonitrile <1999MOL69>. Condensation of 1,4,6,9-tetraazatricyclo[4.4.1.1^{4,9}]dodecane **81** with α -hydrogen-bearing ketones <1988CHE1409, 1990CHE572> or diketones <2004RJO140> led to the seven-membered ring opening–recyclization to afford polycyclic compounds **82** (X = O; R¹ = H, alkyl; R² = H, alkyl, Ph) and **83**, respectively. The reaction of **81** with nitromethane



Scheme 15

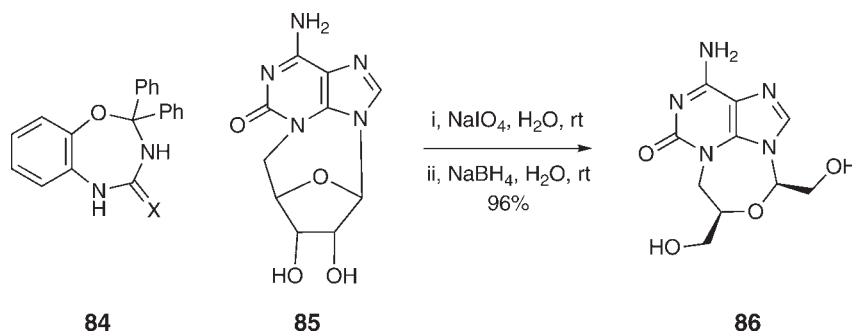
under similar conditions produced **82** ($X = H_2$; $R^1 = NO_2$; $R^2 = H$) in 44% yield [\[1990CHE578\]](#). On treatment with ammonium fluoride in water, **81** underwent seven- to six-membered ring contraction [\[2004TL7563\]](#).

13.16.7 Reactivity of Substituents Attached to Ring Carbon Atoms

In contrast to oxathiazepane **4** (Figure 1), which was selectively methylated at the nitrogen atom (Section 13.16.6.2), various monocyclic and fused triazepinethiones (including oxo-substituted derivatives) underwent methylation exclusively at the sulfur atom [\[1991JHC1597, 1995JME5066, 2002JHC1293\]](#). The methylthio group of the so-formed thioimide can be further readily substituted by reaction with a primary or a secondary amine [\[1983JHC1287, 2002JHC1293\]](#).

Deprotonation of indolocarbazole-fused thiadiazepine *S,S*-dioxides **36** ($X = SO_2$; $R^1 = R^2 = H$) (Figure 5) and their analogs followed by methylation gave mono- or disubstituted products **36** depending on the quantity of the electrophile. In contrast, alkylation with ethyl chloroformate gave only monosubstituted product **36** ($R^1 = COOEt$; $R^2 = H$), whereas treatment of the deprotonated **36** with gaseous formaldehyde formed *cis*-fused **36** ($R^1R^2 = CH_2OCH_2$) [\[1994BML1333, 1994WO07895\]](#).

Thiation of the benzoaxadiazepinone **84** ($X = O$) (Scheme 16) with Lawesson's reagent gave the corresponding thione **84** ($X = S$) in 74% yield [\[1989RJO2158\]](#). Oxidative cleavage of nucleoside **85** or its oxo-analog under mild conditions followed by reduction occurred with preservation of the seven-membered ring to afford the corresponding diols, such as **86** [\[2004NN347\]](#). For analogs without the oxo group at the 2-position of the pyrimidine ring, the ring opening of the latter was observed.



Scheme 16

Various transformations of the methoxycarbonyl substituents of 6,7-bis(methoxycarbonyl)-1,3,5-trioxepane were reported <1992HCA2171, 1995USP5466797>. Dipotassium salt of 1,3,5-trithiepin-6,7-dithiol readily reacted with various metal salts, such as KAuCl_4 , K_2PtCl_4 , CuCl_2 , NiCl_2 , or ZnCl_2 , to give the anionic complexes of type **12** (Figure 2) <1996IC3856, 1997SM1457, 1998JMC319, 1999POL1545>. Condensation of oxadithiepins and trithiepins **14** ($\text{X} = \text{O}, \text{S}$) (Figure 2) with Mg in isopropanol afforded the corresponding heterocycle-fused phthalocyanines in 19–27% yields <1999EJI269>.

13.16.8 Reactivity of Substituents Attached to Ring Heteroatoms

Reactivity of substituents attached to ring heteroatoms is studied almost exclusively for N-substituents of hexaazaisowurtzitane **5** (Figure 1). Due to their different reactivity, the selective modification of the N-substituents is possible. Thus, reductive debenzoylation of **5** ($\text{R} = \text{R}^1 = \text{R}^2 = \text{CH}_2\text{Ph}$) was successfully conducted by palladium-catalyzed hydrogenation in acetic anhydride to give tetraacetylated **5** ($\text{R} = \text{MeCO}$; $\text{R}^1 = \text{R}^2 = \text{CH}_2\text{Ph}$) <1995T4711, 1998T11793, 2004CCL1153>. Further debenzoylation can be achieved only at the expense of the reduction of the introduced acetyl groups. The Pd-catalyzed hydrogenation of **5** ($\text{R} = \text{R}^1 = \text{R}^2 = \text{NO}_2$) in ethyl acetate resulted in the cleavage of only one R group <2005SC2709>, whereas the reduction with SnCl_2 gave a mixture of the pentanitrohexaazaisowurtzitane with cleaved R or R^1 nitro group with regioisomeric ratio depending on the reaction conditions <2004RCB566>. Both benzyl groups of **5** ($\text{R} = \text{MeCO}$; $\text{R}^1 = \text{R}^2 = \text{CH}_2\text{Ph}$) were readily substituted by nitroso groups on treatment with N_2O_4 in aqueous AcOH. Subsequent nitration with $\text{HNO}_3/\text{H}_2\text{SO}_4$ mixture involved all the N-substituents to give hexanitrohexaazaisowurtzitane (HNIW) **5** ($\text{R} = \text{R}^1 = \text{R}^2 = \text{NO}_2$) with high purity <2000OPD156>. HNIW was also readily prepared by nitration of **5** ($\text{R} = \text{MeCO}$; $\text{R}^1 = \text{R}^2 = \text{H}$) in the presence of NH_4NO_3 <2003SUA2199540>. Multistep syntheses of **5** ($\text{R} = \text{NO}_2$; $\text{R}^1 = \text{R}^2 = \text{H}$) and **5** ($\text{R} = \text{R}^1 = \text{NO}_2$; $\text{R}^2 = \text{H}$) from **5** ($\text{R} = \text{MeCO}$; $\text{R}^1 = \text{R}^2 = \text{H}$) were reported <2004MI133, 2004WO076384>.

13.16.9 Ring Synthesis Classified by Number of Ring Atoms in Each Component

13.16.9.1 One-Component Reactions

13.16.9.1.1 Intramolecular substitution reactions

2-Amino- and 2-thio-substituted 1-(3-pyrazolyl)benzimidazoles **87** (Scheme 17) undergo intramolecular cyclization on heating in DMF in the presence of 18-crown-6 to give triazepines and thiadiazepines **88** in moderate yields <1994BSB57>. Heating chlorocarbonyl-substituted arylaminopyrazoles **89** ($\text{R} = \text{Me}, \text{Et}$; $\text{R}^1 = \text{H}, \text{Me}$) in xylene afforded pyrazole-fused benzotriazepinones **90** <1988BSB387>. The direction of the intramolecular alkylation of (alkylthio)pyrimidinone **91** depends on the reaction conditions: carrying out the reaction at ambient temperature afforded the thermodynamic control product **92**, whereas low temperature favored the formation of the kinetic product **93** <1999M1499>.

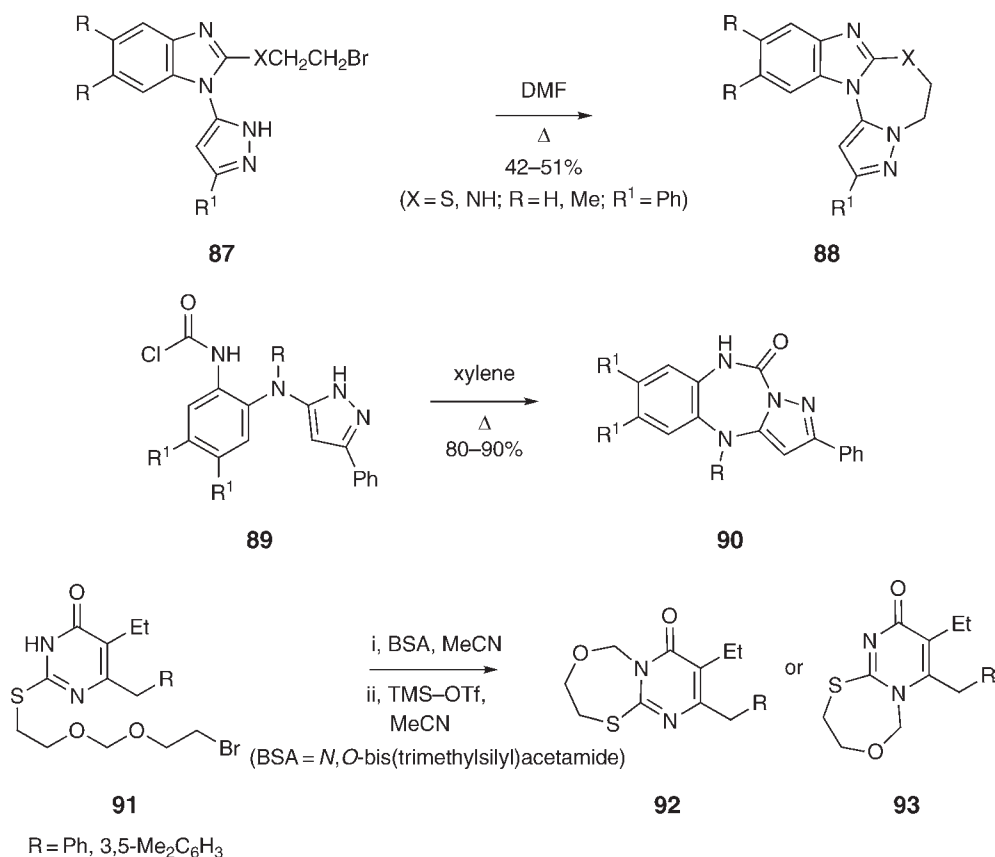
Reaction of 8-(alkylthio)xanthine **94** with PCl_5 generated chloroimidate, which readily cyclized to tricyclic thiadiazepine **95** (Scheme 18). The regioisomeric thiadiazepine was obtained similarly from 7-amidoalkyl-8-mercaptopurine <1994M1273>. Treatment of trifluoroacetate of peptidic amino carbamate **96** with a base in acetonitrile led to intramolecular cyclization with formation of triazepinedione **29** (Figure 4) <2001WO096318>. Various chiral pyrrolidine-fused triazepinediones were prepared similarly. Nucleophilic *ipso*-substitution of the nitro group in carbamate **97** gave the imidazole-fused oxadiazepinone **98** <1997WO01562>.

Intramolecular cyclocondensation of amino-substituted diacetal **99** ($\text{R} = 4\text{-morpholinyl}$) (Scheme 19) under acidic conditions took place both at the primary amino group and at the thiourea sulfur atom affording triazepinethione **100** along with the corresponding 1-(2-thiazolyl)-1,2,4-triazole <1991JHC1597>. Acid-assisted ring opening of ketal **101** ($\text{R}^1 = \text{Me}_2\text{C}=\text{CHCH}_2\text{CH}_2$) was accompanied by the *in situ* attack at the ketone carbonyl group, followed by stereoselective trioxepane ring closure <1991J(P1)693>.

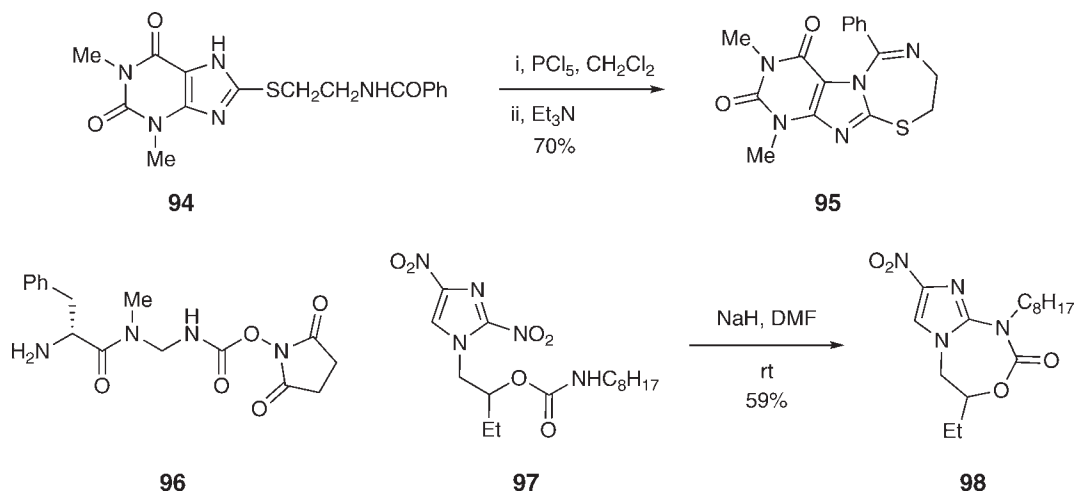
In the presence of NaH in DMF, β -lactams **104** underwent intramolecular cycloaddition to afford bicyclic oxathiazepines **105** <1981TL3695>.

13.16.9.1.2 Cycloaddition reactions

Intramolecular cyclization of bis(amides) **106** ($\text{X} = \text{O}$; $\text{R}^1, \text{R}^2 = \text{Me}, \text{Ph}, 4\text{-BrC}_6\text{H}_4$) (Scheme 20) on treatment with Ph_3PBr_2 in the presence of triethylamine gave the corresponding benzoxadiazepines **107** in 52–74% yields <1988M1279>. Similarly, reaction of bis(thioureas) **106** ($\text{X} = \text{S}$; $\text{R}^1 = \text{R}^2 = \text{NHBU-}t$, arylamino) with $\text{I}_2/\text{KI}/\text{KOH}$ system in ethanol afforded in 68–79% yields the benzothiadiazepines **107**, existing as exocyclic bis(imino) tautomers



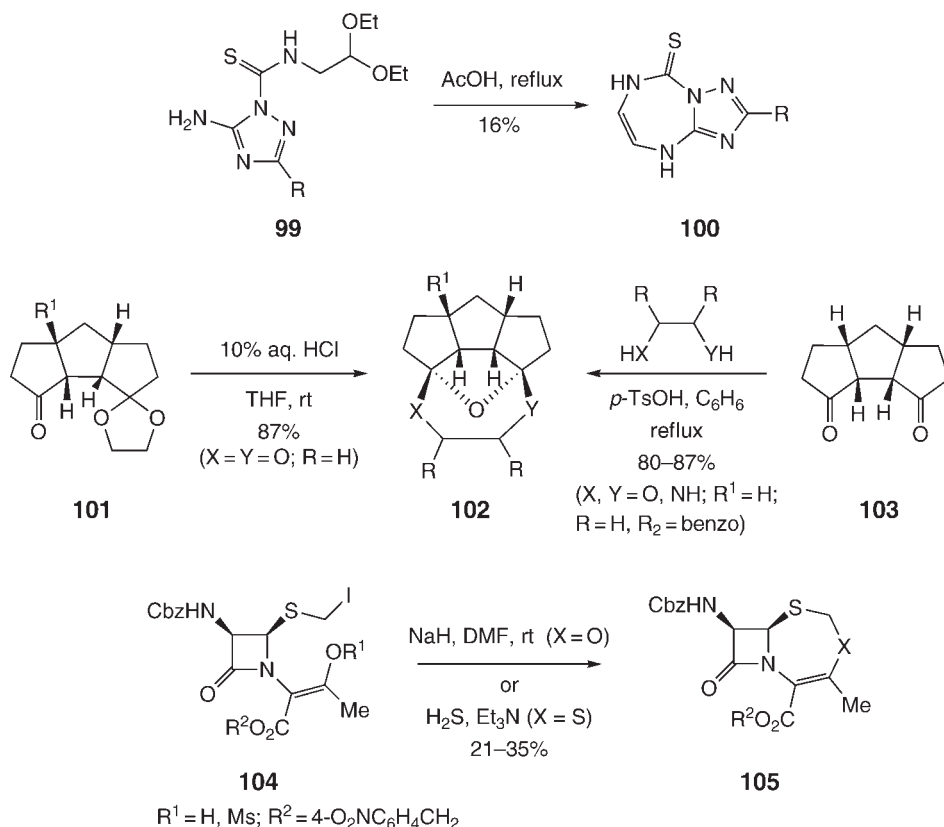
Scheme 17



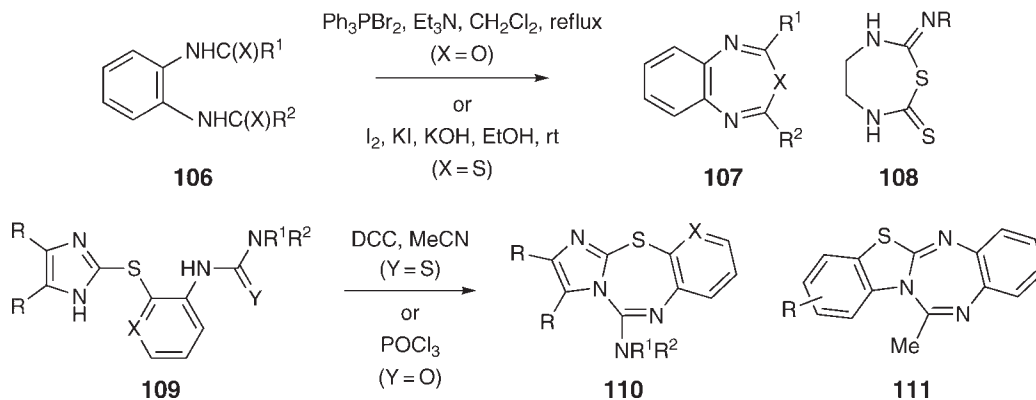
Scheme 18

<2004MI139, 2004MI773>. Bis(thioureas) [CH₂NHC(S)NHR]₂ (R = allyl, Ph, benzyl) with ethylene instead of 1,2-phenylene linker cyclized to thiadiazepines **108** in the presence of tetracyanoethylene in THF at ambient temperature <2004ZNB910> or neat on conventional heating or under microwave irradiation <2003HAC535>.

Various heterocycle-fused thiadiazepines were synthesized by intramolecular cyclization of (*o*-aminoaryl)thioazaheterocycles. The un(substituted) benzimidazoles **109** (R₂ = benzo) with thiourea-functionalized (Y = S;



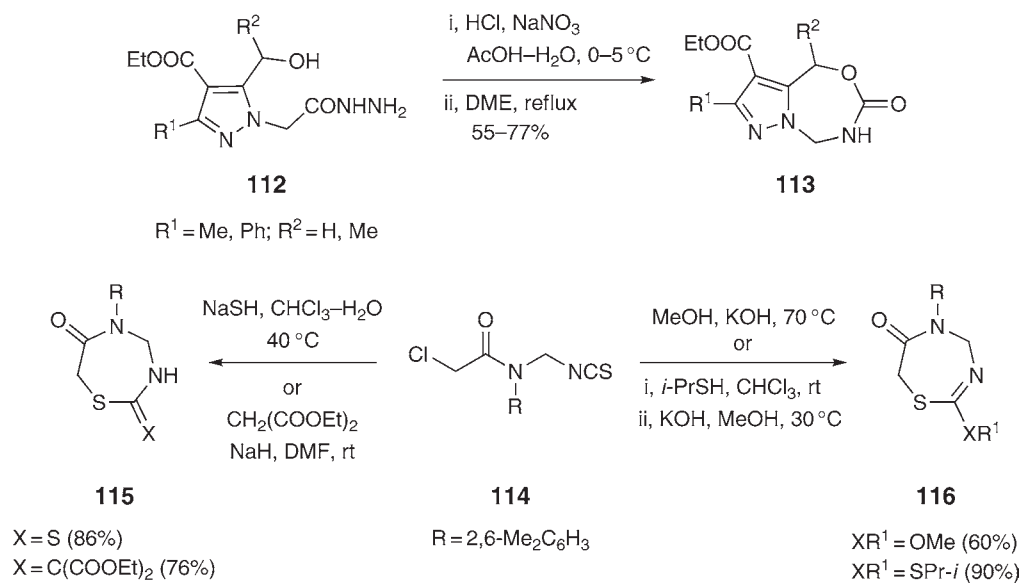
Scheme 19



Scheme 20

R¹=R²=H; R¹=H, R²=PhCO) aryl groups (X=CH, N) are most commonly used [<1994H\(38\)1213, 1996AXC3131>](#), although the reactions of the analogous 1,2,4-triazoles are also reported [<1999H\(51\)161>](#). The similar transformation was observed for arylthio-substituted imidazoles **109** (R=H; X=O; R¹R²N=4-methyl-1-piperazinyl) [<1983JHC1287>](#). (Arylthio)benzimidazoles bearing isothiuronium fragments instead of thioureas can also be used [<1994H\(38\)1213, 1994MI382>](#). Cyclization of 2-[(2-acylamino)phenyl]amino]benzothiazoles in the presence of POCl₃ occurred similarly to give benzothiazole-fused benzotriazepines **111** [<1993OPP105>](#).

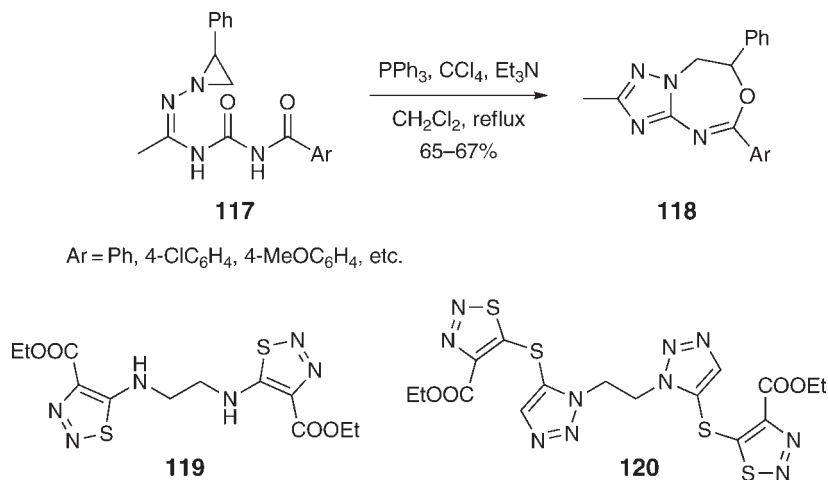
Allyloxy-substituted dithiocarbamic acid $\text{CH}_2=\text{CHOCH}_2\text{CH}_2\text{NHC(S)SH}$, generated *in situ* from its potassium salt, immediately cyclized to give 2-methyl-3,1,5-oxathiazepane-4-thione **4** (Figure 1) in 98% yield <1992RJO1769>. 6,7-Dicyano-1,3,5-triazepine-2,4-dione was prepared in 89% yield by base-assisted intramolecular amine–isocyanate addition of acyl isocyanate $\text{H}_2\text{NC(CN)=C(CN)NHCONCO}$ <2004ARK71>. Isocyanates, generated from hydrazides **112** (Scheme 21) via Curtius rearrangement, readily underwent the alcohol addition with formation of pyrazole-fused oxadiazepinones **113** <1982JCM20>. Cyclization of isothiocyanates **114** in the presence of oxygen, sulfur, or carbon nucleophiles afforded thiadiazepinones **115** or **116** in moderate to high yields <1986S817>.



Scheme 21

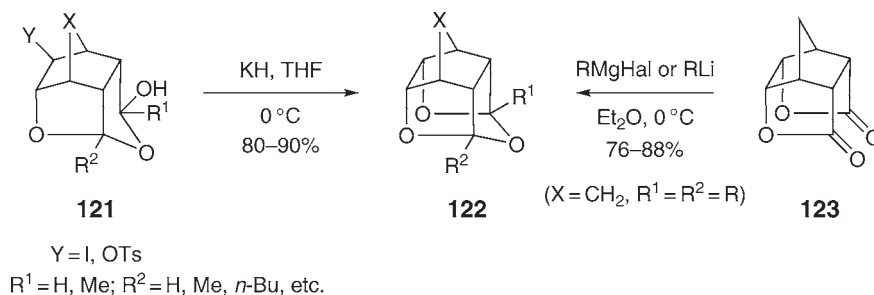
13.16.9.1.3 Other cyclization reactions

Under mild conditions, *N*-acyl ureas **117** (Scheme 22) underwent aziridine ring opening–electrocyclization with formation of both heterocyclic rings of triazolooxadiazepines **118** <1995TL2815>. Heating bis(thiadiazolyl)ethylenediamine **119** or bis[(thiadiazolylthio)triazolyl]ethane **120** in ethanol in the presence of a base afforded bis(triazolo)thiadiazepine **77** ($\text{R} = \text{COOEt}$) (Scheme 14) <1999CC2273, 2003OBC4030>.

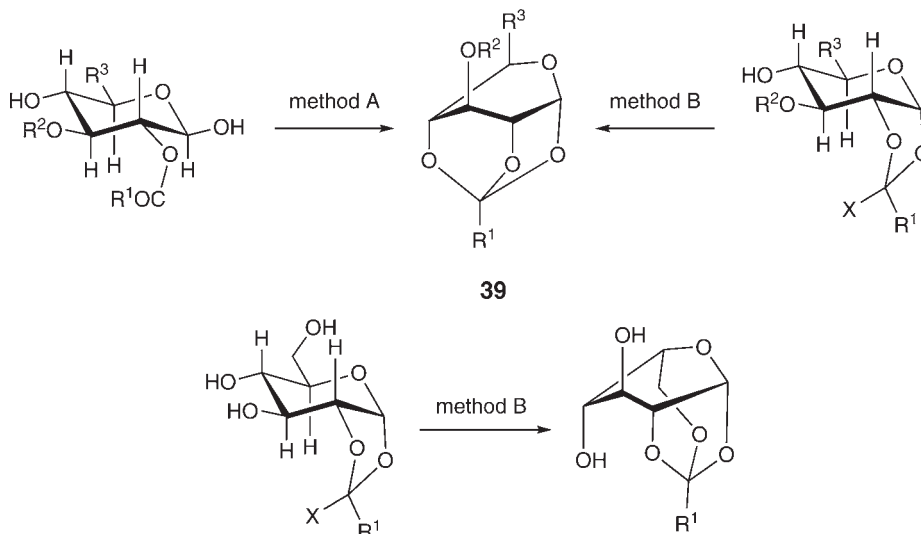


Scheme 22

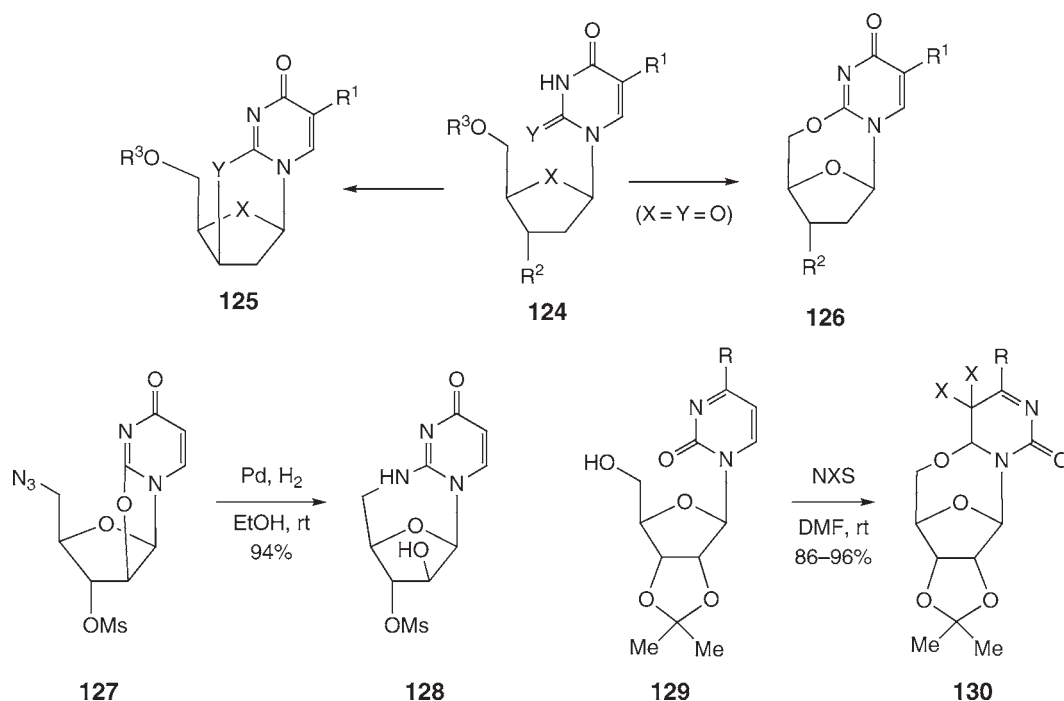
Treatment of iodo- or tosyl-substituted polycyclic ketals **121** (X=CH₂, CH₂CH₂) (**Scheme 23**) with KH in THF afford bridged trioxepanes **122** in 80–90% yields <1996TL8209, 1997JOC6367, 2000T341>. Compounds **122** can also be prepared by addition of Grignard reagents or alkylolithiums to diester **123** <1995SC3723, 1996SC2363>. Prolonged treatment with Grignard reagents, however, led to cleavage of the both ketal fragments. Reduction of **123** with LiAlH₄ in THF afforded **122** (X=CH₂; R¹=R²=H) <1994MRC452>.



There are two common approaches to the synthesis of carbohydrate orthoesters of type **39** (Figure 5), namely, from dihydroxy esters (Scheme 24, method A) via formation of two carbon–oxygen bonds or from hydroxy ketals via formation of one carbon–oxygen bond (method B). The cyclizing agents used for the method A are 1,1'-carbonyldiimidazole <1996JA1677, 1996MM6126, 1997MM2891, 2001MM2476> or phenylsulfonyl chloride/triethylamine <2002CAR951>. Cyclization by the method B (X=OMe, OEt) occurs in the presence of trialkylsilyl chlorides/imidazole <1999TL6423, 2005ARK189>, a sulfonic acid <2001CAR405>, or pyridinium halides <1986JOC189, 1999TL6423> and was applied also to synthesis of furanose orthoesters of type **38** <2002EJO3864>. The latter compounds, however, are more commonly prepared from the acetal-protected derivatives bearing the CCl₃ substituent at the acetal carbon, which produce the corresponding CHCl₂-bridgehead-substituted orthoesters on treatment with *tert*-BuOK <1994TL9233, 2002EJO3864, 2004CAR1739>.



Anhydronucleosides **125** (X=Y=O) and **126** (Scheme 25) are generally prepared by cyclocondensation of 3-O-protected and unprotected nucleosides **124**, with the reaction pathway being dependent on the C(3')-substitution.

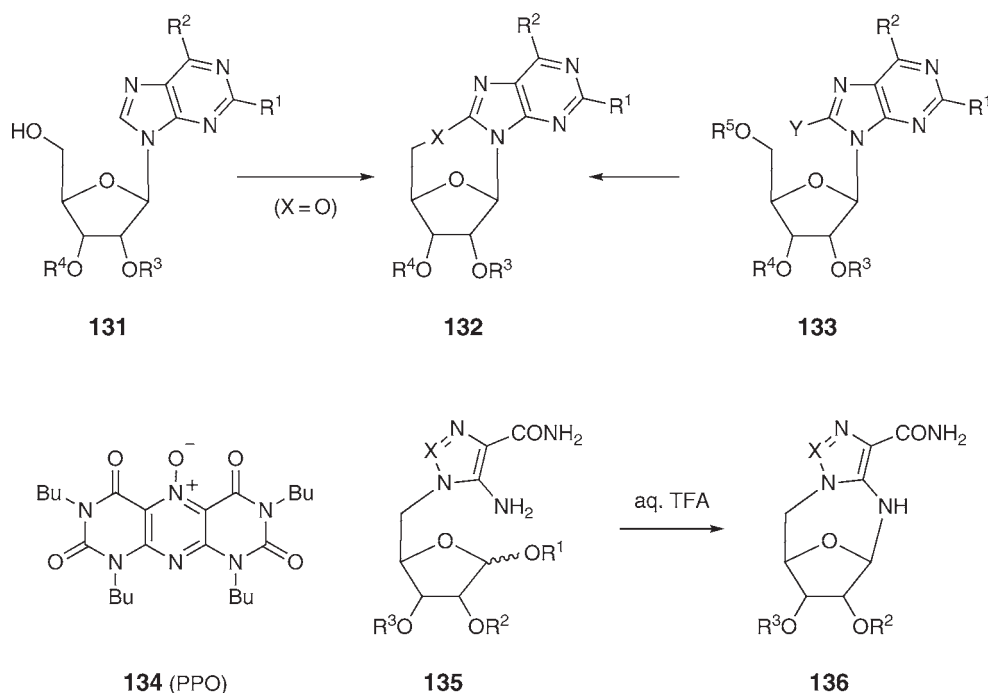


Scheme 25

Cyclization to **125** took place on treatment of **124** (R^2 = mesyloxy) with secondary <1993T4365> or tertiary amines (usually, DBU or triethylamine) <1993JCM326, 1995NN279, 1996J(P1)2237, 2001JOC4079, 2002MI55, 2003JOC331, 2003JOC367, 2003NN1343, 2003NN1939>. Under similar conditions, **124** (R^2 = H, N₃) <1989JME1891> or **124** (R^2 = OH; R^3 = tosyl) <1989CPB2287> afford anhydronucleosides **126**. Another widely used method for the synthesis of **125** is based on Mitsunobu reaction of **124** (R^2 = OH) with diethyl or diisopropyl azodicarboxylate and triphenylphosphine with or without arylcarboxylic acid <1990CC801, 1990JME845, 1991JME1426, 1994WO26762, 1995NN1227, 1996NN899, 2003JME995, 2004NAR495>. This procedure has also been applied to the 2-thiouridine analogs **124** (X = O; Y = S) <1989NN1179>. Other cyclocondensation agents successfully used for the transformation of **124** to **125** include NaOH in aqueous ethanol <2004OL2169>, potassium phthalimide <1987NAR5305, 2004BML4233>, 1,1'-sulfonyldiimidazole <2000SC3873>, perfluorobutylsulfonyl fluoride <1996NN739, 2002NN849>, diethylaminosulfur trifluoride (DAST) <1988RJO2375, 1989NN327>, morpholinosulfur trifluoride <1988RJO2375, 1992NN273>, 1-methylimidazole diphenyl sulfite <1989CC997>, and tetrabutylammonium fluoride or Amberlyst A-26 (F⁻ form) (for **124**: R^2 = tosyloxy; R^3 = silyl) <1995S1121>. The 4'-thiouridines **124** (X = S; Y = O) were cyclized to **125** using DAST <1994TL7569> or Yarovenko reagent <1991JME2782>. Anhydronucleosides **126** (R^1 = H, Me; R^2 = N₃) were synthesized by treatment of iodo-substituted nucleosides **124** (X = Y = O, iodine instead of OR³) with silver acetate <1989JME1891>.

Reduction of azido-substituted 2,2'-anhydrouridine **127** resulted in ring opening–recyclization to form the 2,5'-iminonucleoside **128** <1992J(P1)1065>. Halogenation of protected uridines **129** (R = OH, NH₂, NHCOPh) with *N*-chloro- or *N*-bromosuccinimide afforded *gem*-dihalogenated cyclized products **130** (X = Cl, Br) in high yields <1987S829>. The similar reaction of nonprotected **129** gave nonprotected **130** as a minor product.

Cyclocondensation of N(3)-unsubstituted purine nucleosides to the corresponding anhydrobases containing oxadiazepine heterocyclic ring is achieved by Mitsunobu reaction similarly to uridine-type nucleosides <2004NN347, 2004WO013300>. For the synthesis of more extensively studied anhydronucleosides **132** (X = O) (Scheme 26), a range of oxidative cyclization procedures has been developed. Thus, appropriately protected purine nucleosides **131** can be converted to **132** by irradiation with UV light <1986CC1704> or by oxidation with lead tetraacetate <1984CC1658, 1992NN365>, copper(II) chloride <1991CPB1902>, *N*-bromo- or *N*-iodosuccinimide <1988H(27)347>, or pyrimido[5,4-*g*]pteridine *N*-oxide **134** <1992J(P1)1801>. Photoinduced cyclization of the 5'-amino analog, 5'-amino-2',5'-dideoxyguanosine, however, occurred with the cleavage of the imidazole



Scheme 26

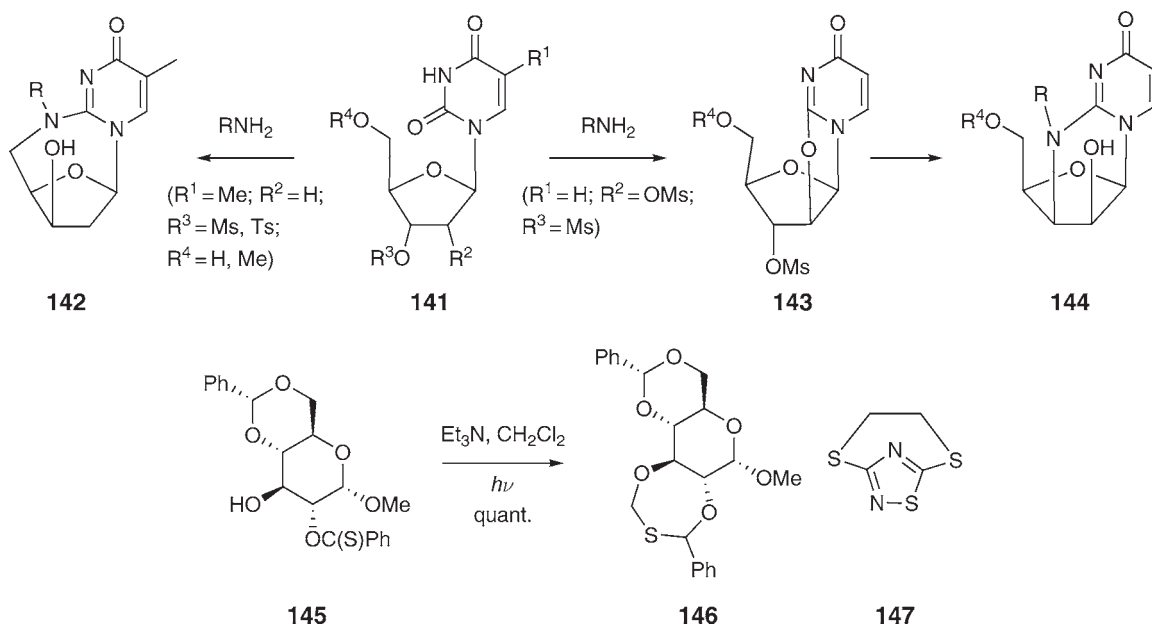
fragment <1995MI792>. Treatment of **131** ($R^2 = \text{NH}_2$) with acyl chlorides, anhydrides <1984JOC5076>, or with phenyl chloroformate <1986LA1309> gave the N(7)-acylated analogs of **132** along with noncyclized acylated products.

Another approach to compounds **132** is based on cyclization of the C(8)-substituted purine nucleosides **133**. Thus, **133** ($Y = \text{OH}$; $R^5 = \text{tosyl}$) <2003NN735> and **133** ($Y = \text{Cl}$; $R^5 = \text{SiEt}_3$) <2000HCA1331> readily cyclized in the presence of DBU or triethylamine with formation of **132** ($X = \text{O}$) in 66–77% yields. The similar cyclization was observed for **133** ($Y = \text{Br}$; $R^5 = \text{H}$) on treatment with NaH <1985NN477>. Mitsunobu reaction of **133** ($Y = \text{SH}$, NHR ; $R^5 = \text{H}$) or treatment of **133** ($Y = \text{NHR}$; $R^5 = \text{H}$) with 1,1'-carbonyldiimidazole or diphenyl carbonate afforded **132** ($X = \text{S}$, NR) <1985J(P1)2337, 1993NN941>.

Under acidic conditions, amino-substituted imidazoles and triazoles **135** ($X = \text{CH}$, N) underwent intramolecular nucleophilic substitution reaction to give **136** in yields depending on the C(2') substituent orientation <1999CAR190, 1999MI441>. Thiouridine derivative **73** ($R = \text{Me}$) (Scheme 12) cyclized similarly to **72** on treatment with hexamethyldisilazane(HMDS)–ammonium sulfate <1992NN603>.

13.16.9.2 [1+6] Cycloaddition

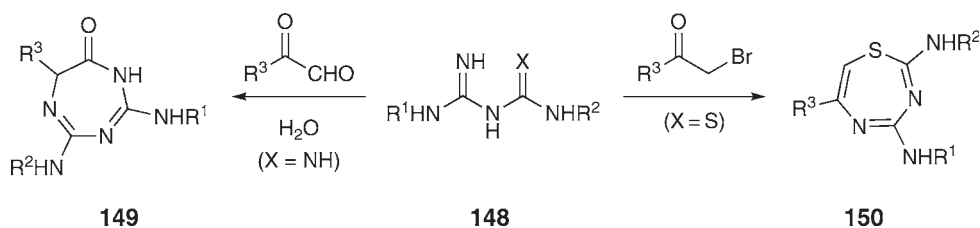
This approach to the synthesis of monocyclic and fused seven-membered rings is based on the connection of two remote functional groups of a complex molecule with one-carbon synthon. The most common procedure is cyclocondensation of various diamines with carbonyl or thiocarbonyl compounds (Scheme 27) generally used in the preparation of triazepines and thiadiazepines. Thus, DBU-assisted heterocyclization of conjugated linear diamine $\text{H}_2\text{NCH}=\text{NC}(\text{CN})=\text{C}(\text{CN})\text{NH}_2$ with aldehydes and ketones gave pyrrole-fused triazepines of type **8** (Figure 2) <1993CC834, 1994J(P1)3571>. As diamine component, *o*-aminophenyl thioureas <2001SC375>, 5-amino-1-(2-aminoaryl)-substituted pyrazoles <1982MI221>, imidazoles <1983JHC511>, 1,2,3-triazoles <2002JHC1293>, 1,2,4-triazoles <1987JHC927, 1988JHC1751>, 5-amino-1-(2-ethylaminoethyl)imidazoles <1991S822>, 2-(2-aminoarylthio)imidazoles <1983JHC1287>, 3-(2-aminoaryl)pyrazoles <1988BSB387>, 2-imino-1-(2-aminoaryl)-substituted thiazolidines <1990T2009>, imidazolidines <1982MI211> and (2-aminoaryl)imino-imidazolidines <2003FA1171, 2005FA127>, and quinazolines <1993M733> were successfully used. As carbonyl (thiocarbonyl) component, various aldehydes and ketones <1987JHC927, 1990T2009, 2001SC375, 2003FA1171, 2005FA127>,



Scheme 29

sulfide [146](#), thiadiazolodithiazepine [147](#) (Scheme 29) from 3,5-dimercapto-1,2,4-thiadiazole [145](#), of fused triazepines and thiadiazepines [88](#) (X=S, NH) (Scheme 17) from the corresponding 1-pyrazolyl-2-aminobenzimidazoles via *in situ* formation of intermediates [87](#) [148](#), and of homotriazaadamantane [13](#) (R¹=NO₂; R²=H) (Figure 2) from the relevant (nitro)triazadamantane [149](#).

Cyclocondensation of biguanidines [148](#) (X=NH) (Scheme 30) with α -oxoaldehydes gave triazepinones [149](#) in moderate yields [150](#), whereas reaction of [148](#) (X=S) with α -bromo ketones resulted in formation of thiadiazepines [150](#) [151](#).



Scheme 30

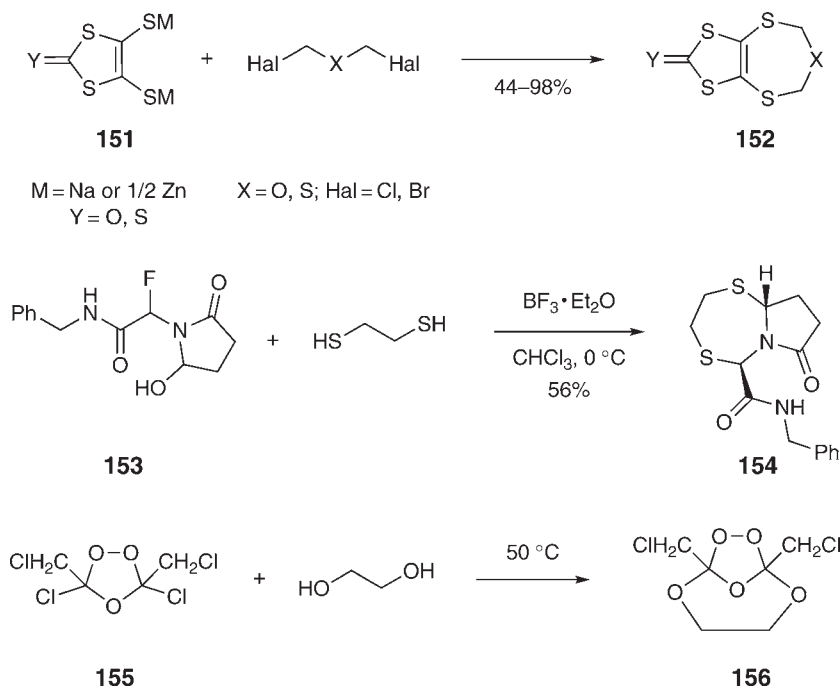
3-Methyl-1,3,5-trioxazepanium cation was generated on treatment of 1,3-dioxolane with methoxymethyl cation in SO₂ [152](#).

13.16.9.4 [3+4] Cycloaddition

Heterocyclization of two-carbon one-heteroatom synthon with two-carbon two-heteroatom synthon is the most common approach to the synthesis of monocyclic and fused seven-membered heterocycles with 1,3,5-heteroatoms. These reactions can be further subdivided to substitution and addition reactions.

13.16.9.4.1 Substitution reactions

These reactions are generally based on the cyclocondensation of vicinal diols, dithiols, or diamines with 1,3-dihalo compounds or their equivalents. The representative of this type is the synthesis of the parent 1,3,5-trithiepane by condensation of ethylene dithiol with di(chloromethyl) sulfide [<1992T8065>](#). Analogous cyclizations of sodium or zinc salts of dithiolane derivatives **151** gave bicyclic oxadithiepanes and trithiepanes **152** (Scheme 31) [<1987CHE1183, 1993BCJ1773, 1994JCF763, 1995JMC1731, 1995SM1181, 1997SM1457>](#). Monocyclic 6,7-dicyano-substituted oxadithiepins and trithiepins **14** (Figure 2) were similarly prepared from zinc salt of 1,2-dicyano-1,2-dimercaptoethene [<1999EJ1269>](#).



Scheme 31

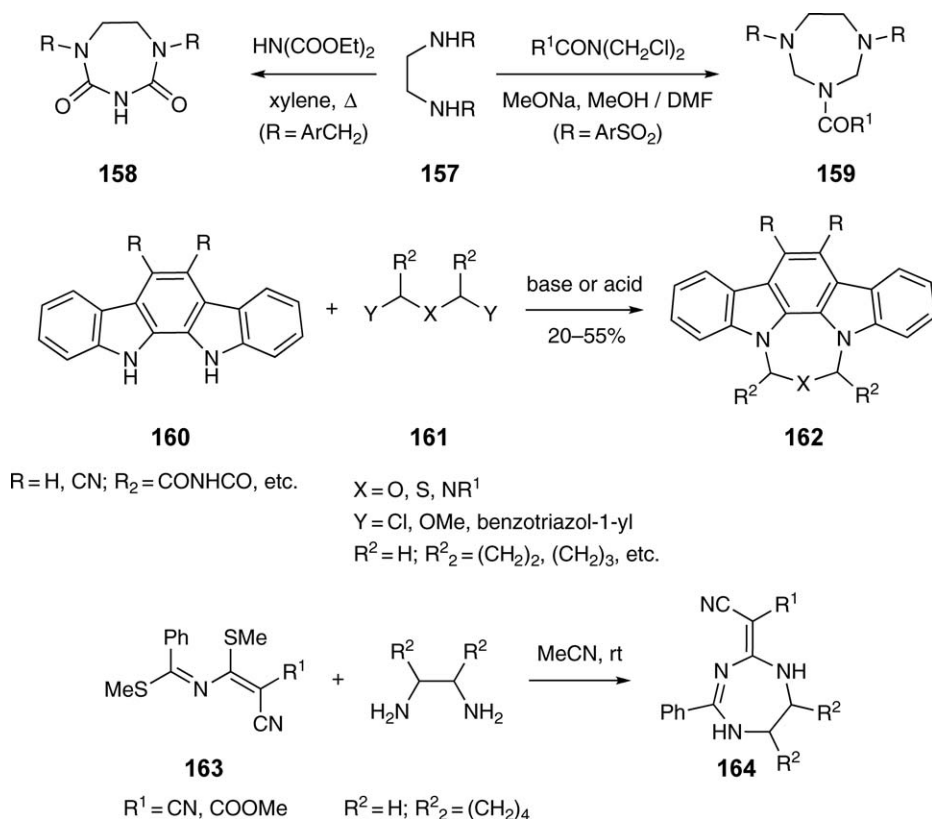
Acid-catalyzed cyclocondensation of ethylene dithiol with amide **153** occurred stereoselectively to give bicyclic dithiazepane **154** [<1998TL7755>](#). Heating endoperoxide **155** with ethylene glycol produced peroxide-bridged trioxepane **156** in yields depending on the stereochemistry of **155** [<1997LA2581>](#).

Cyclocondensation of diamines **157** (Scheme 32) with diethyl iminodicarboxylate gave the corresponding 1,3,5-triazepine-2,4-diones **158** in 48–53% yields [<1995JME5066>](#), whereas the reaction of **157** with *N,N*-bis(chloromethyl) amides afforded triazepanes **159** [<1998RCB2201>](#). The nonsymmetrical and benzo-fused analogs of **159** were prepared similarly. This approach was also applied to the synthesis of polycyclic carbazole-fused triazepines, oxadiazepines, and thiadiazepines **162**, including their bridged analogs (when compounds **161** are THF, pyrrolidine, or piperidine derivatives) from indolocarbazoles **160** [<1992EPP508792, 1994BML495, 1994BML1333, 1994WO07895, 2001OL1689>](#). Adenine-fused oxadiazepinium salts were prepared similarly from adenine and bis(halomethyl) ethers [<1989HCA1495>](#).

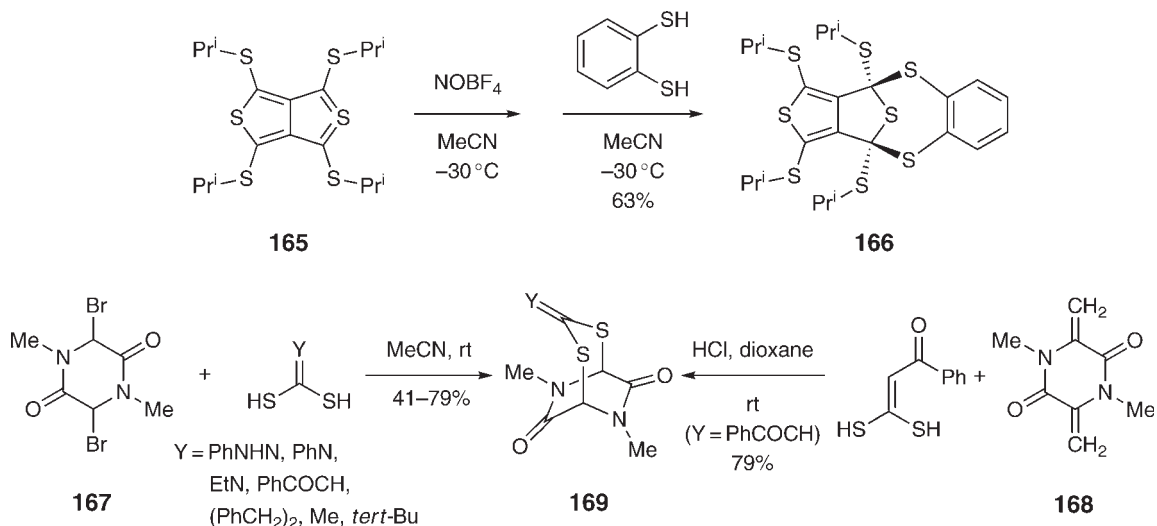
Substitution of both methylthio groups of thioimides **163** with diamines gave tetrahydrotriazepines **164** as major products [<1996H\(43\)1943>](#).

The three-atom component can also be generated *in situ*. Thus, acid-mediated cleavage of 5-(*tert*-butyl)-perhydro-1,3,5-triazin-2-one in the presence of ethylene dithiol afforded 5-(*tert*-butyl)-1,3,5-dithiazepane in 45% yield [<1998JHC1531>](#). Oxidation of thieno[3,4-*c*]thiophene **165** (Scheme 33) with NOBF₄ generated the corresponding dication, which readily reacted with *o*-benzenedithiol to give polycycle **166** containing trithiepane ring [<1991CC520, 1991J\(P\)12935>](#).

Bridged structure **169** containing two dithiazepane rings was readily prepared from diketopiperazines **167** and *gem*-dithiols under mild conditions [<1981JHC1545>](#).



Scheme 32

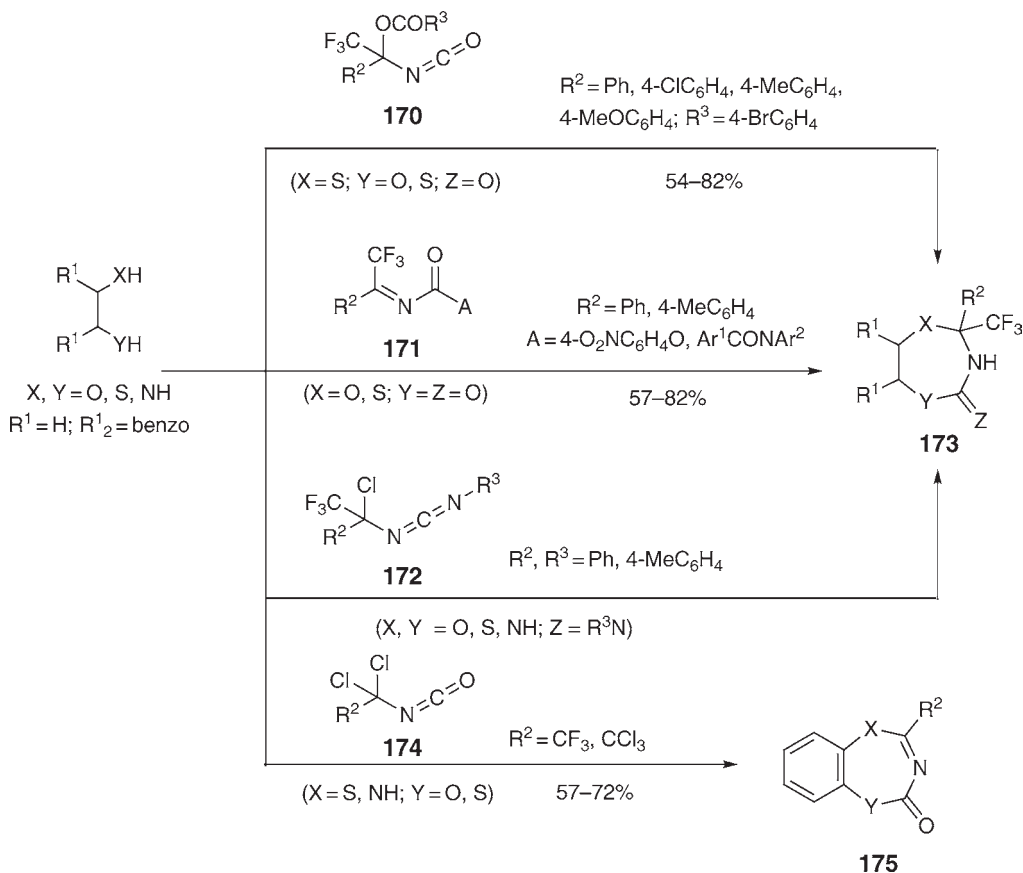


Scheme 33

13.16.9.4.2 Cycloaddition reactions

One of the most common procedures constituting the second subtype, addition reactions, is based on addition of ethylene glycol, pyrocatechol, or their thia or amino analogs to carbon–heteroatom double bonds. The latter compounds include α,α -dichloro- [1993CHE1265](#) or α -aryloxy- α -trifluoromethyl isocyanates **170** [1989RJO2154](#), [1989RJO2158](#), [1993MI82](#), *N*-alkylidene carbamates [1993MI140](#), [2004CHE241](#) and *N*-alkylidene-*N'*-acylureas [1989RJO2213](#)

171, and α -chloroalkyl carbodiimides **172** <1997RJO96> (Scheme 34). The reactions of unsymmetrical dinucleophiles ($X \neq Y$) with carbodiimides occur regioselectively. 1,5-Disubstituted benzotriazepine-2,4-diones were readily synthesized by cyclocondensation of the corresponding phenylenediamines with isocyanofomates <2004WO098610>. Various 1,7-disubstituted 1,3,5-triazepine-2,4-diones were prepared similarly in 65–92% yields from resin-supported ethylenediamines <2001OL2797>.

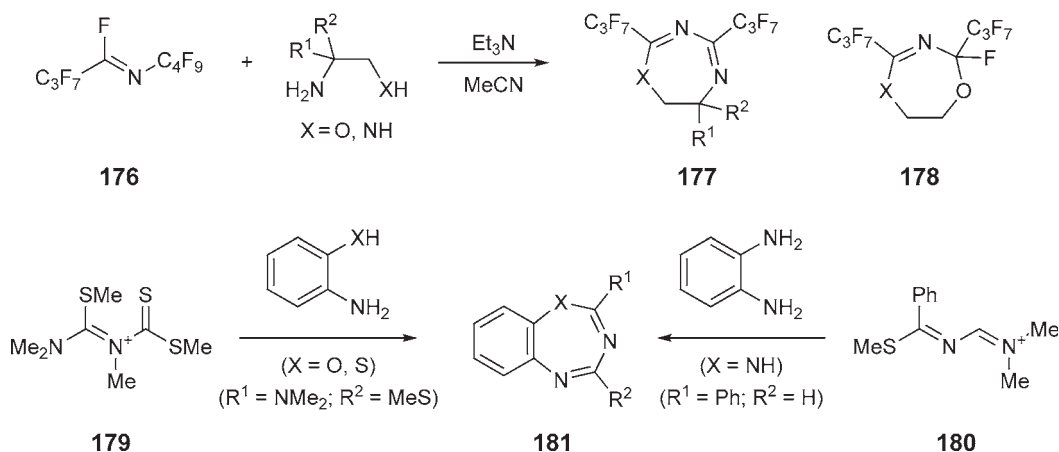


Scheme 34

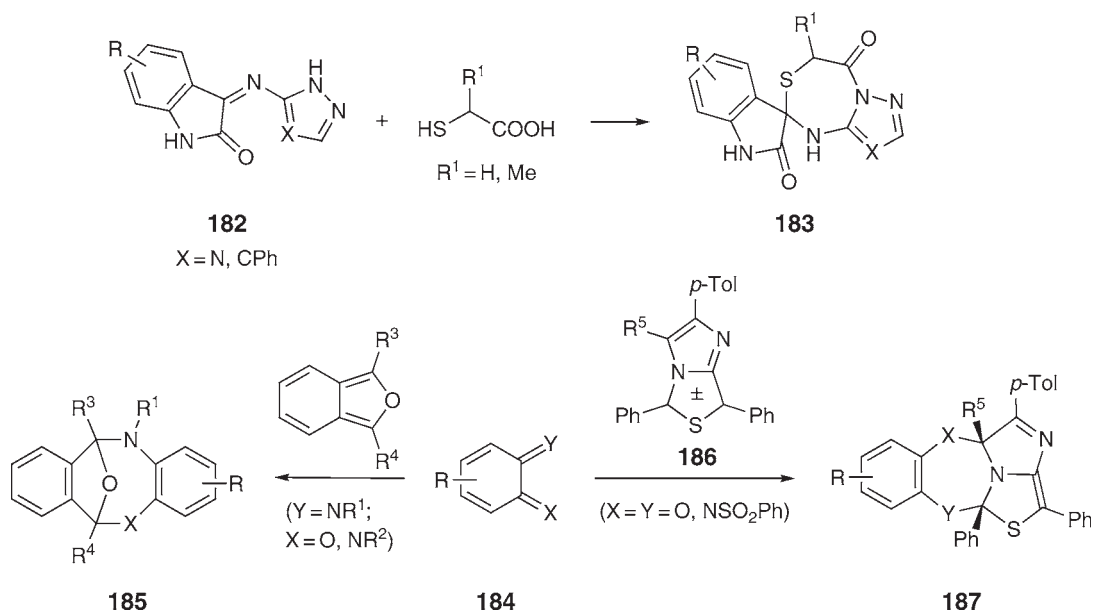
Partially unsaturated analogs **177** (Scheme 35) were synthesized by the addition of ethanolamines or ethylenediamines to perfluorinated imine **176**; whereas reaction of **176** with ethylene glycol gave dioxazepine **178** ($X = \text{O}$) <2001JFC11>. Differently substituted derivatives of **178** ($X = \text{O}, \text{S}$) were obtained by 4-dimethylaminopyridine(DMAP)-catalyzed reaction of *N*-acyl(thioacyl) imines $\text{ArC}(\text{X})\text{N}=\text{C}(\text{CF}_3)_2$ with epichlorohydrin <1988CZ111>. Cyclocondensation of *o*-substituted anilines with iminium iodides **179** or **180** afforded benzotriheteropines **181** as major products in most cases <1982J(P1)1059, 1991MI517>.

Reaction of various aromatic or heteroaromatic diamines with *N*-acyl isothiocyanates gave the corresponding benzo- or heterocycle-fused 1,3,5-triazepine-2-thiones, for example, **16** (Figure 3) from 5,6-diamino-1,3-dimethyluracil and D-gluconyl isothiocyanate <1981CPB1832>. Cycloaddition of *N,N'*-disubstituted ethylenediamines with bis(isocyanato)dimethylsilane or bis(isothiocyanato)dimethylsilane followed by treatment with 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole afforded a series of 1,5-disubstituted 1,3,5-triazepine-2,4-diones, -2,4-dithiones, and 4-oxo-1,3,5-triazepine-2-thiones <1980AGE327>.

Heterocyclization of α -mercapto acids with (azolylimino)indolones **182** (Scheme 36) afforded the spirocyclic thiadiazepinones **183** <1989JJB639, 1994PS27>. *gem*-Dithiol addition to bis(methylene)-substituted diketopiperazine **168** afforded the bridged bicyclic structure **169** featuring two dithiazepane rings (Scheme 33) <1981JHC1545>.



Scheme 35



Scheme 36

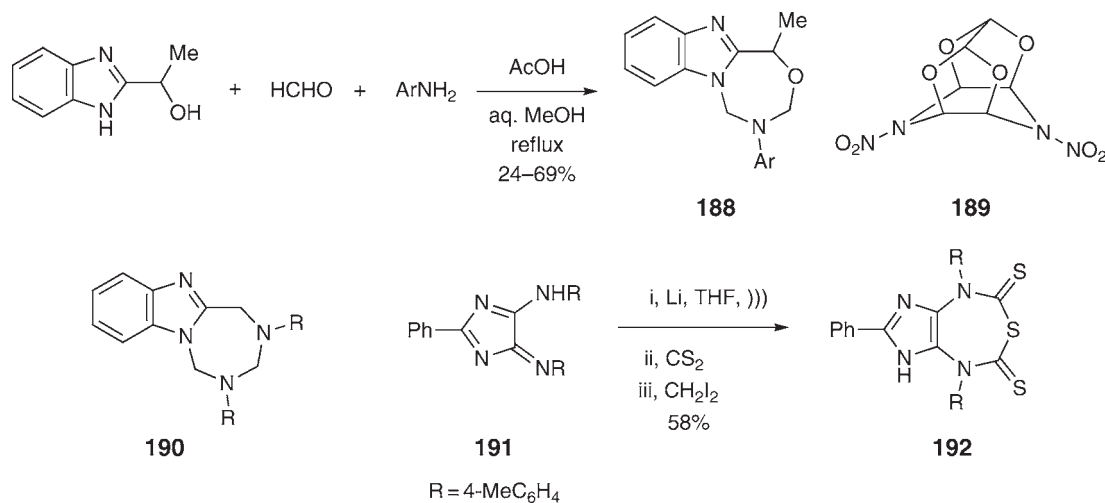
Addition of bifunctional alcohols and amines to aldehydes and ketones was successfully used in the synthesis of fused and bridged heterocycles, especially trioxepanes. Thus, acid-catalyzed reaction of ethylene glycol with phenanthrene-4,5-dicarbaldehyde or 8-benzoyl-1-naphthaldehyde gave the corresponding phenanthrene- or naphthalene-fused trioxepanes, for example, diacetal **6** (Figure 1) <1998J(P1)2353>. Addition of ethylene glycol, pyrocatechol, or ethanolamine to tricyclic all-*cis* diketone **103** (Scheme 19) afforded bridged trioxepanes and dioxazepane **102** in good yields <1989T2743, 1990SC3467>, although similar reaction with *o*-phenylenediamine gave only 6% of **102** ($\text{X} = \text{Y} = \text{N}$). Cycloaddition of vicinal diols or diamines with dialdehydes and diketones was used for the synthesis of ethene-bridged trioxepanes from acyclic γ -oxo- α,β -unsaturated ketones <1986T1345>, oxadiazole-fused triazepines from 3-acyl-1,3,4-oxadiazol-2-ones <1991H(32)237>, bis(benzoxazine)-fused oxadiazepines **53** ($\text{X} = \text{O}$) (Scheme 7) from glyoxal and *N,N'*-diarylethylenediamines <2001T55>, and tetrahydrotriazepine **7** (Figure 1) from diaminomaleonitrile and 2,5-hexanedione <2000MI311>.

[4 π +4 π] Cycloaddition of *o*-quinone mono- or diimides **184** with 1,3-diphenylisobenzofuran produced the phenylene-bridged heterocycles **185** in 54–98% yields <1981ZNB632, 1989JOC5926>. The reaction of *o*-chloranil or 4,5-dimethyl-*N,N'*-bis(phenylsulfonyl)quinonediimine with mesoionic compounds **186** occurred similarly under mild conditions providing polyheterocycles **187** in 83–87% yields <1988ZNB347>.

[6+4]-Type cycloadduct **24** (Scheme 1) was obtained as the major product on cycloaddition of *o*-chloranil with 1-ethoxycarbonyl-1*H*-azepine <1982H(19)1197>. Treatment of 4-ethoxycarbonyl-5-chloro-1,2,3-thiadiazole with ethylenediamine under basic conditions occurs with heterocyclic ring opening/recyclization to form bis(triazole)-fused thiadiazepine **77** (R=COOEt) (Scheme 14). The benzo-fused analog was prepared by the similar reaction with *o*-phenylenediamine <1999CC2273>.

13.16.9.5 Multicomponent Cyclocondensation

The most widely used procedure constituting this type of transformations is based on three-component condensation of a 1,2-bifunctionalized compound (i.e., vicinal diamine, diol, β -amino alcohol) with a primary amine and 2 equiv of formaldehyde (or paraformaldehyde). This procedure was successfully used to prepare a series of 1,5,3-dioxazepanes from vicinal diols and alkyl or cycloalkyl amines <1980TL2949> and of benzimidazole-fused oxadiazepanes **188** (Scheme 37) from arylamines and 2-(α -hydroxyethyl)benzimidazole <1990H(31)1245, 2001IJH89>. Oxadiazole-fused triazepane **20** (Figure 3) was prepared similarly starting from 3,4-diamino-1,2,5-oxadiazole and potassium sulfamate <1994CHE976>. The Mannich reaction of *N,N'*-dinitroethylenediamine with formaldehyde and primary amines or *tert*-butylhydrazine gave the corresponding 3-substituted-1,5-dinitro-1,3,5-triazepanes in 54–99% yields <1992MI313, 1995MI138, 2002MI174>.



Scheme 37

Hexabenzyl-substituted hexaazaisowurtzitanes **5** (R = R¹ = R² = ArCH₂) (Figure 1), the common intermediates in the synthesis of various hexaazaisowurtzitanes, are generally prepared by acid-catalyzed multicomponent condensation of benzylamines with glyoxal <1990JOC1459, 1993J(P2)923, 1998T11793, 2003BML2887, 2003CEJ687>. Mannich reaction of 1-methyladenine or *N*⁶-methyladenine with HCHO and MeNH₂ in aqueous solutions yielded the corresponding triazepinopurines <1987MI1230>, whereas cyclocondensation of optically active dimethyl tartrates with paraformaldehyde afforded enantiopure 6,7-bis(methoxycarbonyl)-1,3,5-trioxepanes <1991C238>. Acid-assisted condensation of urea with *N,N'*-diformylpiperidine-2,3,5,6-tetraol gave the tetraoxa analog **189** of hexaazaisowurtzitanes <1995WO04062>.

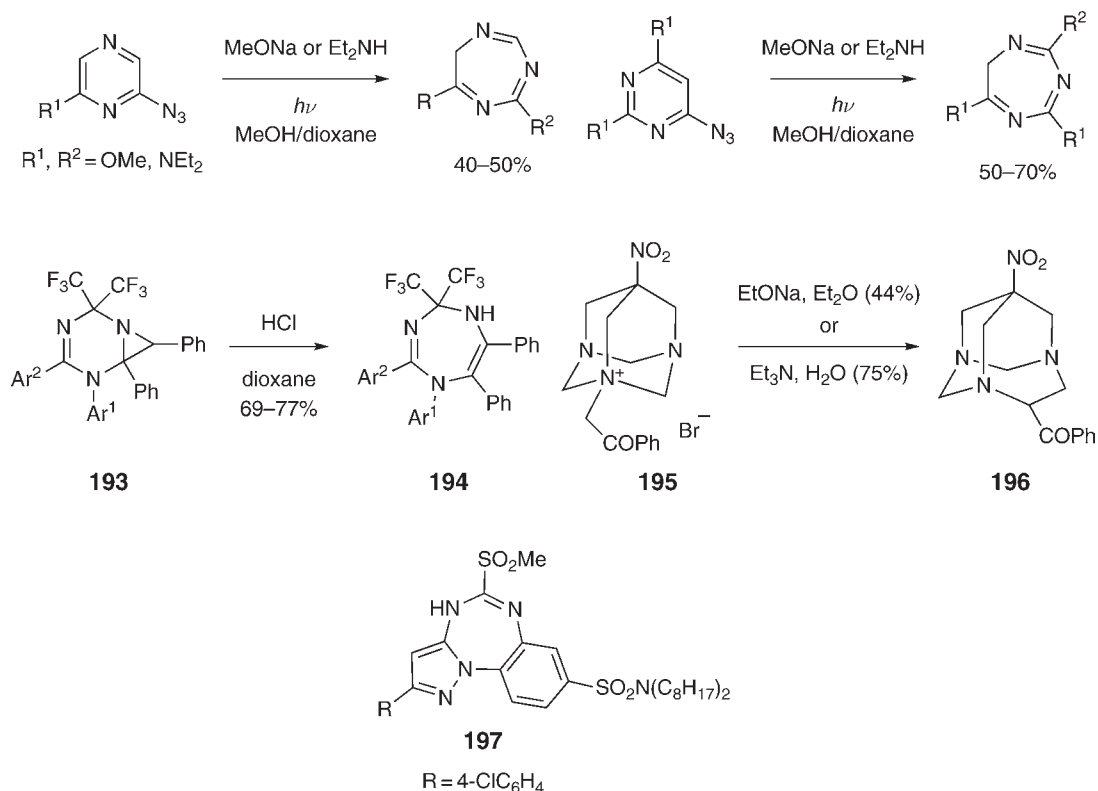
Treatment of 2-(chloromethyl)benzimidazole with primary aliphatic amines RNH₂ (R = Me, Et) in dichloromethane under mild conditions provided benzimidazole-fused triazepanes **190** in moderate yields <1990AGE933>. The similar transformation was observed for 8-(chloromethyl)xanthine. The cyclocondensation

of *o*-phenylenediamine with acyl chlorides RCOCl (R = alkyl, aryl) formed either 2-substituted benzimidazoles or benzoxadiazepines **52** (Scheme 6) in excellent yields depending on the reactant ratio <2004TL4185>. Acid-assisted cyclocondensation of ethylenediamine (or its source) with urotropin and nitromethane under mild conditions produced homotriazaadamantane **13** (R¹ = NO₂; R² = H) in 44–66% yields <1990CHE578, 1994CHE349>.

Reaction of 4-ethoxycarbonyl-5-bromo-1,2,3-thiadiazole with various substituted *o*-phenylenediamines occurred with heterocyclic ring opening/recyclization affording bis(triazole)-fused benzothiadiazepines of type **37** (X = S) (Figure 5) in moderate yields <2002J(P1)1574, 2003OBC4030>. Sonication of (imino)imidazole **191** in the presence of lithium followed by treatment with CS₂ and quenching with diiodomethane gave imidazolo-fused thiadiazepine-dithione **192** <1999H(51)763>.

13.16.10 Ring Synthesis by Transformation of Another Ring

Irradiation of azido-substituted pyrazines and pyrimidines bearing strong electron-donating substituents in the presence of a base, such as MeONa or diethylamine, resulted in ring expansion with formation of 1,3,5-triazepines (Scheme 38) <1990CC723>. A similar transformation was observed on irradiation of a series of 6-azidouracils in the presence of a primary or a secondary amine <1984J(P1)1719>.



Scheme 38

Low-temperature photooxygenation of 7,8-dihydro-8-oxoguanosine gave 3-substituted 1,3,5-triazepane-2,4,6,7-tetraone as the second major product <1995JA474>. Thermolysis of 5-phenyltetrazolo[1,5-*c*]quinazoline provided polycyclic dimer **10** (Figure 2) along with 1-cyano-2-phenylbenzimidazole in yields depending on the solvent used <1980AGE566>. On heating in the presence of an acid, aziridine-fused triazines **193** rearranged to 4,5-dihydro-1,3,5-triazepines **194** <1989JFC51>. Under basic conditions, triazaadamantane salt **195** underwent Stevens rearrangement to give homotriazaadamantane **196** <1991CHE534>. The similar reaction of bis(triazaadamantane) analog with 2-oxo-1,3-propanediyl linker occurred with ring expansion of both triazaadamantyl moieties.

Deoxygenation of pyrazine endoperoxides with triphenylphosphine resulted in ring contraction to imidazoles, the process involving the heterocyclic analogs of arene oxides, these being in equilibrium with the corresponding fully unsaturated 3,1,5-oxadiazepines. Some of the latter compounds were isolated and characterized [<1983CC399>](#). Acid-catalyzed ring opening–recyclization of dioxazepines [56 \(Scheme 8\)](#), having dioxazepine heterocyclic ring, led to the formation of oxadiazepines [57 <2004NN117>](#).

13.16.11 Synthesis of Particular Classes of Compounds and Critical Comparison of Various Routes Available

13.16.11.1 1,3,5-Triazepines

All the approaches discussed in [Sections 13.16.9 and 13.16.10](#) were widely applied to the synthesis of 1,3,5-triazepine heterocyclic ring. For the monocyclic and fused compounds, the [1+6] and [3+4] cyclization reaction and the azine ring expansion are the most popular routes (for additional information on the early reports, see CHEC-II(1996)). The bridged derivatives, such as hexaazaisowurtzitane [5 \(Figure 1\)](#), are available by multicomponent condensation.

13.16.11.2 Oxadiazepines

Monocyclic and fused 1,3,5- and 1,3,6-oxadiazepines are accessible either by one-component cyclization (see [Scheme 22](#)), [1+6] cyclocondensation, [3+4] condensation (substitution) reaction, heterocyclic ring rearrangement (see also CHEC(1984) and CHEC-II(1996)), or multicomponent reactions ([Scheme 37](#)). The 1,3,5-oxadiazepine heterocyclic ring is also present in iminonucleosides, such as compounds [142 \(Scheme 29\)](#), which are available via one-component cyclization and [1+6] cyclocondensation reactions.

13.16.11.3 Thiadiazepines

The most common approaches to monocyclic and fused thiadiazepines are based on one-component ([Schemes 17 and 21](#)), [1+6] and [3+4] cyclization reactions. For the detailed information on two latter types of transformations published before 1994, see CHEC-II(1996).

13.16.11.4 Dioxazepines

A limited range of monocyclic or fused dioxazepines is available either by [3+4] cyclization or multicomponent reactions. The more important representatives of this class of compounds are various anhydrobases, for example, [125](#) ($X=Y=O$) ([Scheme 25](#)), containing 1,3,5-dioxazepine heterocyclic ring. These compounds are generally prepared by intramolecular dehydrative cyclocondensation of the corresponding nucleosides (see [Section 13.16.9.1.5](#)).

13.16.11.5 Dithiazepines

Two examples for the preparation of heterocycle-fused dithiazepines by multicomponent reactions were discussed in CHEC-II(1996). The more common, however, is [3+4]-approach, which was successfully used for the synthesis of both monocyclic and bridged dithiazepines. [1+6] Cyclization has been applied for the synthesis of β -lactam-fused derivatives ([Scheme 19](#)).

13.16.11.6 Oxathiazepines

Two examples of synthesis of monocyclic oxathiazepines (via the intramolecular cycloaddition reaction and [3+4] cyclization) were discussed in CHEC-II(1996). No additional information on the synthesis of this class of compounds has appeared since.

13.16.11.7 Trioxepins

No information on 1,3,5-trioxepins and 1,3,5-trithiepins as well as on oxadithiepins and dioxathiepins appeared in CHEC(1984) or CHEC-II(1996). The monocyclic disubstituted 1,3,5-trioxepane was synthesized by multicomponent cyclocondensation ([Section 13.16.9.5](#)). The most common approach to various fused and bridged trioxepanes,

including carbohydrate orthoester, are intramolecular cyclization (see Section 13.16.9.1.4) and [3+4] substitution and cycloaddition reactions.

13.16.11.8 Oxadithiepins

Dithiolane-fused oxadithiepins, widely used in the synthesis of charge-transfer complexes, are available by [3+4] substitution reactions of dithiolane dithiolates with di(chloromethyl) ether (see Section 13.16.9.4.1).

13.16.11.9 Dioxathiepins

Glycoside-fused dioxathiepins were synthesized by photochemical [1+6] cyclization reaction (Scheme 29).

13.16.11.10 Trithiepins

Parent 1,3,5-trithiepane as well as substituted and dithiolane-fused derivatives, useful in synthesis of charge-transfer complexes, were synthesized by cyclocondensation of the corresponding 1,2-dithiols or their salts with di(chloromethyl) sulfide (see Section 13.16.9.4.1).

13.16.12 Important Compounds and Applications

(*R,R*)-6,7-Bis(hydroxydiphenylmethyl)-1,3,5-trioxepane was used as dopant inducing (M)-helix in Merck liquid-crystal material ZLI-1695 <1997HCA2507>. *N*-Dodecyl-1,5,3-dithiazepane was applied as additive to prevent fading and light discoloration of organic dyes <1988JAK63208837>, whereas pyrazolotriazepine **197** as an additive to red- and green-sensitive silver halide emulsion provides storage-stable and heat- and humidity-resistant images <1989JAK01003658>. Various dithiolane-fused oxadithiepanes and trithiepanes were applied as ligands in the synthesis of charge-transfer complexes <1993BCJ1773, 1995SM1181, 1996IC3856>. Polynitrated triazepanes, especially hexaazaisowurtzitane **5** ($R = R^1 = R^2 = \text{NO}_2$) (Figure 1), also known as CL-20, are highly energetic materials and extensively studied as potential explosives and propellants.

3-Alkyl-1,5-bis(arylsulfonyl)-1,3,5-triazepanes have shown significant activity in the increase of the drug sensitivity of P388/ADR multidrug-resistant cells exceeding that of the noncyclic analogs <1998MI2961>. Imidazocarbazole-fused oxadiazepines of the general formula **36** ($X = \text{O}$) (Figure 5), where $R^1\text{CHXCHR}^2$ fragment forms an additional THF or tetrahydropyran heterocyclic ring, were found to be strong inhibitors of cell proliferation of human leukemia cells <2001MI165>, antiangiogenic agents <2000JAN426>, and potent inhibitors of nerve growth factor (NGF)-induced neurite outgrowth and neuronal differentiation in rat pheochromocytoma PC12 cells <1999JAN921, 2002JAN355, 2004JAN627>.

13.16.13 Further Developments

A review on methods of synthesis and properties of HNIW **5** ($R = R^1 = R^2 = \text{NO}_2$) (Figure 1), including physico-chemical properties, polymorphism, cage construction, and nitrolysis, has recently been published <2005RCR757>.

13.16.13.1 Theoretical and Experimental Structural Methods

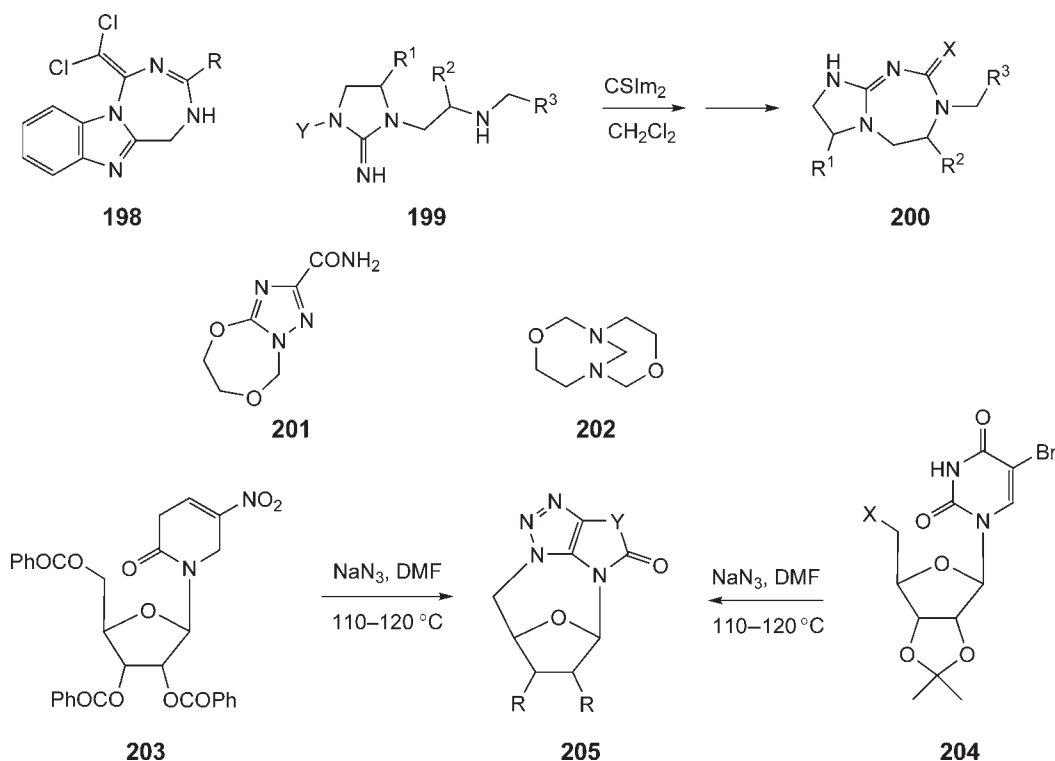
The applicability of several semi-empirical MO methods and DFT methods with various basis sets to prediction of the molecular volumes and densities of energetic nitramines, such as 1,3,5-trinitro-1,3,5-triazepane, HNIW and its tetraoxa-analog **189** (Scheme 37) has been evaluated <2007JPC2090, 2007JPC2787, 2007MI280>. The analysis of the heteroatom effect on the crystal and molecular structure of hexaazaisowurtzitanes **5** (Figure 1) and their analogs indicated that replacement of two or four nitrogen atoms of the five-membered rings by oxygen leads to decreased planarity of all the remaining nitrogen atoms <2005MI566>.

13.16.13.2 Reactivity of Heterocyclic Ring and Substituents

The further investigations of *N*-alkylation reactions of cyclic peptidomimetics, such as triazepinedione **29** (Figure 4), allowed for selective preparation of either dialkylated (using excess of NaH/alkyl bromide) or monoalkylated (in the presence of KF/Al₂O₃) derivatives. The collidine-assisted *N*-acylation of **29** provided N(1)-acylated products regioselectively in 70–85% yields <2006CEJ8498>. The regioselectivity of nucleophilic substitution reactions of anhydronucleoside **64** (R¹ = Me, R² = trityl) (Scheme 10) was shown to be nucleophile-dependent: whereas treatment with AcSH at reflux gave the heterocyclic ring opening product of type **65** (Nu = MeCOS), the reaction with NaN₃ in DMF at 60 °C afforded exclusively the trityloxy-substitution product with the polycyclic structure left intact <2005CL432>.

13.16.13.3 Ring Synthesis (Monocyclic and Fused Compounds)

Already reported (see Section 13.16.9.1) intramolecular cyclization of activated dipeptides, such as **96** (Scheme 18), to cyclic triazepinediones, e.g., **29** (Figure 4), has been applied to a large number of dipeptides and developed either as a solution-phase synthesis (using small-molecule or polymer-supported base) or as a solid-phase synthesis <2006CEJ8498, 2006JME6768>. Treatment of oxalic acid with CS₂ in water at 175 °C for 72 h produced 1,3,5-trithiepan in 39% yield as the major product <2005MI749>. Base-assisted [3+4] cyclocondensation of 2-(amino-methyl)benzimidazole with (tetrachloro)azabutadienes RC(Cl)=N-CCl=CCl₂ (R = Ph, 4-MeC₆H₄, 4-ClC₆H₄) afforded benzimidazolotriazepines **198** (Scheme 39) in 69–79% yields <2006S2323>. A series of imidazole-fused triazepines **200** (X = S, NH; R¹, R² = Me, PhCH₂, 4-ClC₆H₄CH₂; R³ = Ph, 2,4-F₂C₆H₃, 3-NCC₆H₄, etc.) has been synthesized via [1+6] cyclization of resin-supported (imino)imidazolidines **199** (Y = resin) with 1,1'-thiocarbonyl-diimidazole <2006JCO127>.



Scheme 39

Triazolo-fused dioxazepine **201** was obtained as a by-product in Suzuki coupling reactions of 5-bromo-1-(2-hydroxyethoxymethyl)-1,2,4-triazole-3-carboxamide; the reaction, however, can be shifted towards **201** by using a strong base <2007TL2389>.

13.16.13.4 Ring Synthesis (Bridged Compounds)

Condensation of primary 1,2-amino alcohols with formaldehyde in water under acidic pH gave a mixture of three products: the corresponding oxazolidines, *N,N'*-bis(oxazolidinyl)methanes and bicyclic compounds of the general structure **202** containing two oxadiazepane rings in ratios depending on the amino alcohol structure <2004H(64)277>. Various substituted hexaazaisowurtzitanes **5** ($R = R^1 = R^2 =$ allyl, propargyl, cinnamyl, 2-furylmethyl, etc.) (Figure 1) were successfully prepared by formic acid-catalyzed multicomponent condensation of the corresponding primary amines with glyoxal in aq. MeCN <2006CEJ3339>. Heating *N,N'*-diformylpiperazine-2,3,5,6-tetraol, readily available from glyoxal and formamide, in nitric/sulfuric acid mixture gave the tetraoxa-analog **189** (Scheme 37) in 31% yield <2005EPP1598359>. Azidation of (β -D-ribofuranosyl)-substituted nitropyridinone **203** <2005NN957> or bromopyrimidinediones **204** ($X = N_3$, OCOPh, OCOC₆H₄F-4) <2005NN1531> with NaN₃ at 110–120 °C afforded the relevant triazoloazine anhydronucleosides **205** ($Y = CH=CH$, $R = OCOPh$; $Y = CONH$, $R_2 = CMe_2$).

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Biographical Sketch



Olga V. Denisko was born in Krasnoyarsk (Russia) and studied at the Moscow State University (Russia), where she obtained her Ph.D. in 1993 under the direction of Professor N. S. Zefirov. During 1994–96, she worked as a postdoctoral research fellow at the Center for Heterocyclic Compounds under the supervision of Professor A. R. Katritzky at the University of Florida; then she returned to Russia and was employed as a chemist in the Central Laboratory of ‘Krasfarma’ Pharmaceuticals (Krasnoyarsk, Russia). In 1998, she returned to the University of Florida as a postdoctoral research fellow/group leader. After working at the University of Florida for another two years, she was employed as a senior research chemist by Alchem Laboratories (Alachua, Florida). In June 2002, she took up her present position as associate scientific information analyst at Chemical Abstracts Service, Columbus, Ohio. Her scientific research interests include various aspects of heterocyclic organic chemistry and chemistry of organosulfur compounds.

13.17

Seven-membered Rings with Four or More Heteroatoms

G. N. Nikonov

Alchem Laboratories Co., Alachua, FL, USA

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13.17.1 Introduction

In this chapter, similar to CHEC(1984) and CHEC-II(1996), tetrazepines, diazatrithiepine, tetrathiepanes, tetrathiepins, pentathiepanes, pentathiepins, hexathiepins, etc., with different disposition of heteroatoms (oxygen, nitrogen, sulfur), excluding heterocycles with phosphorus, arsenic, and other heteroatoms, are considered. The standard nomenclature of heterocycles is used. The present review covers the period from 1994 to the beginning of 2006.

During the period of 1994–2006, several reviews of the synthesis and properties of heterocycles with seven-membered rings were published. A special review was devoted to pentathiepins <2004CRV2617>. Synthesis, methodology, reactivity, physical properties (nuclear magnetic resonance (NMR), ultraviolet (UV), infrared (IR), Raman spectroscopy, mass spectrometry (MS), X-ray diffraction, electrochemistry, conformation, chirality), theoretical properties (density functional theory (DFT) calculations of structures and reactions), and biological activity (cytotoxicity toward cancer cells) of pentathiepin and its derivatives are discussed up to late 2003 and *Chemical Abstracts*, vol. 136; see also two reviews <2004MI57, 2004MI253> concerning 1,4-dithiins and 1,2,3-thiadiazoles.

A synthesis of varacin, a cytotoxic naturally occurring benzopentathiepin isolated from a marine ascidian and the total synthesis of the novel benzopentathiepin varacinium trifluoroacetate: the viability of varacin free base was reviewed <1994MI242>.

The synthesis of many benzopolychalcogenides, for example, benzotrithioles, benzotetrathiins, and benzopentathiepins, from corresponding 1,2-benzenedichalcogenols, as starting compounds, was discussed <2002HAC419>. The following types of seven-membered S-heterocycles were mentioned in the review as well as other heterocycles (Figure 1).

The stability of the pentathiepin ring toward functional groups was confirmed by the use of amino and sulfide groups as substituents on benzopentathiepin. Based on the reactivity of benzopentathiepin, many reactions resulting in many kinds of heterocyclic compounds that include sulfur atoms on the benzene ring were discussed <2002HAC419>. A review on the preparation of cyclic and acyclic ureas has appeared <2005MI665>.

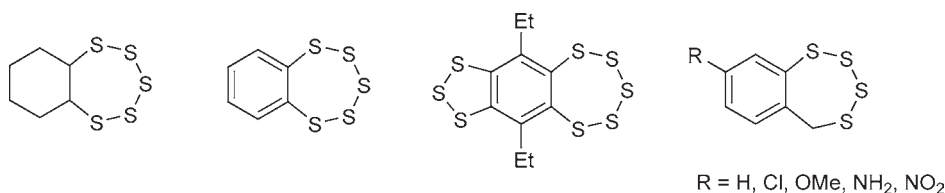


Figure 1

13.17.2 Theoretical Methods

13.17.2.1 Tetrazepines

Molecular mechanics (MM+), semi-empirical (modified neglect of diatomic overlap ((MNDO), AM1, PM3), and *ab initio* (RHF/3-21G, RHF/6-311G) methods have been used to generate optimized theoretical 1,2,3,5-benzotetrazepinone geometries (Figure 2) <1997JMT27>. The optimized structures were compared to X-ray data. The PM3 and *ab initio* methods most successfully reproduced X-ray benzotetrazepinone geometries. Important structural features of the nonplanar benzotetrazepinone conformation were discussed and a procedure to generate optimized benzotetrazepinone geometries in the absence of X-ray data was presented. Semi-empirical and *ab initio*-optimized geometries of the hypothetical non-benzo-fused (lone) tetrazepinone ring were compared with optimized geometries of the benzo-fused counterpart. Both the lone and benzofused tetrazepinone rings have similar nonplanar conformations. Racemization of chiral benzotetrazepinone was studied with semi-empirical methods, and shown to occur through a concerted mechanism with a chiral transition state. The energy barrier to benzotetrazepinone racemization depends upon the size of the alkyl substituents on the N-3 and N-5 tetrazepinone ring atoms <1997JMT27>.

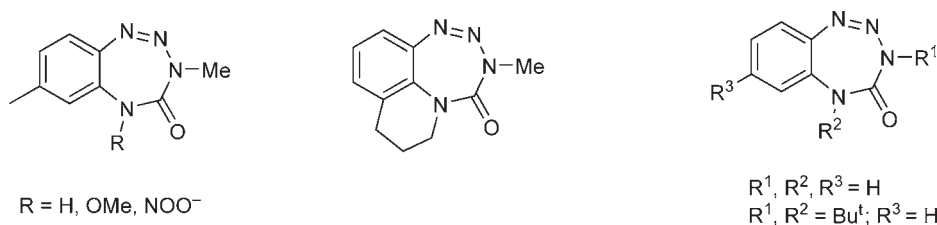


Figure 2 Synthesized and hypothetical benzotetrazepinones predicted in the study.

A mechanism for benzo-1,2,3,5-tetrazepinone ring opening in acid media was proposed and investigated by a semi-empirical PM3 method. The results indicated that benzotetrazepinone most likely protonates at O as opposed to N-3 and that ring opening could occur from either an O- or N-3-protonated species <1997JOC7006>. Representative tetrazepinones are shown in Figure 3. Synthesis of benzotetrazepinones was described earlier (see references in <1997JOC7006>).

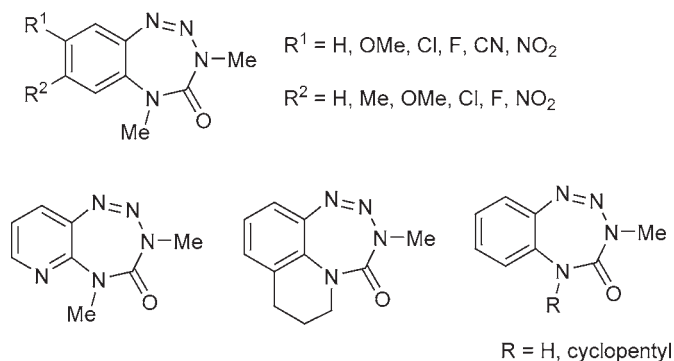


Figure 3

13.17.2.2 N,S-Heterocycles

Electronic structures of 1,2,3,5-thiatriazepine-1,1-dioxide **1** and 1,2,3,5-benzothiatriazepine-1,1-dioxide **2** were studied <1995NJC325>. The dioxide **1** (Figure 4) is formally a homoaromatic analog of 1,2,4-triazine, which is known to be aromatic; however, electronic structure calculations, conducted at the HF/6-31G** and MP2/6-31G** levels, indicated that 1,2,3,5-thiatriazepine-1,1-dioxide is neither planar nor aromatic. The lack of aromaticity in 1,2,3,5-thiatriazepine-1,1-dioxide is reflected in bond lengths and covalent bond orders that exhibit a large degree of alternation. Similar conclusions were reached for the 1,2,3,5-benzothiatriazepine-1,1-dioxide **2**, in which only the benzene ring is found to be aromatic.

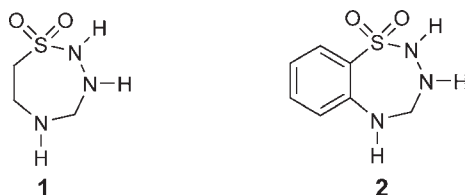


Figure 4

The properties of 2*H*-1,5,2,4-benzodithiadiazepinyl radical and 2*H*-1,5,2,4-dithiadiazepinyl radical were studied <1994PS445, 1997IC4772> (Section 13.17.5.5). Properties of this novel family of 9 π -electron systems are discussed on the basis of DFT calculations. Compared to 1,2,3,5-dithiadiazolyls, this novel family of 9 π -electron radicals is predicted to have low disproportionation and dimerization energies, properties that are advantageous for the preparation of molecular conductors. The singly occupied molecular orbital for radicals is depicted in Figure 5. This orbital resembles the SOMO of the radical **20**; it is N–S and C–C antibonding but bonding with respect to S–C. A nodal plane passes through the unique C atom.

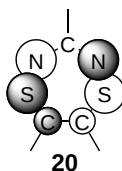


Figure 5

13.17.2.3 Pentathiepanes

Ab initio calculations at HF/6-31+G* level of theory for geometry optimization and MP2/6-31+G**/HF/6-31+G* level for single-point total energy calculations were reported for lenthionine (1,2,3,5,6-pentathiepane). The unsymmetrical twist-chair conformation is the most stable conformation of lenthionine. The unsymmetrical twist-boat form is 33.0 kJ mol^{−1} less stable. Conformational racemization of twist-chair conformation can take place via plane symmetrical chair geometry as transition state and requires 50.7 kJ mol^{−1} <2003JMT225>.

13.17.2.4 Pentathiepinines

Computational and experimental studies of the role of amine in the mechanism of pentathiepin (polysulfur) antitumor agents (Figure 6) were presented <2001JA10379, 2003JA396>, in which it became evident that the amine has an opportunity to engage in bonding with pentathiepin to promote its decomposition. The study provided mechanistic insight into the process that gives rise to pentathiepin biological activity. Primary or secondary amine will

allow for an intramolecular addition to the pentathiepin ring at the nearest sulfur S-1. In contrast, the tertiary amine adds reversibly to S-1, because nitrogen cannot lose its positive charge by deprotonation; this precludes the amine promotion step. An energetically low-lying process was characterized, corresponding to S-3 loss- triggered by nucleophilic activation with a primary or secondary amine. Pentathiepin desulfurization via S₃-unit transfer was supported by a trapping study with norbornene. The fact that the amine may confer an enhanced reactivity in the natural products varacin and lissoclinotoxin A adds further to the understanding of the pathway for pentathiepine activation.

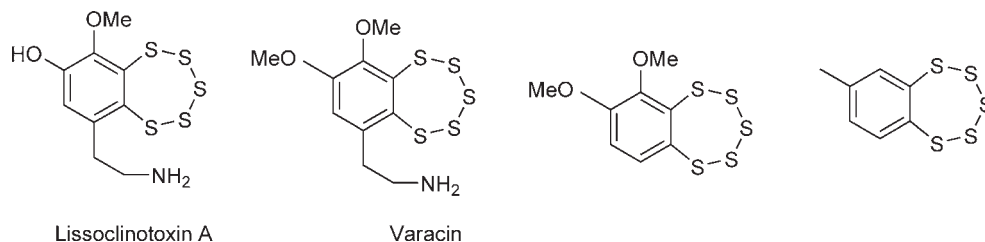


Figure 6

B3LYP/6-31G(d) calculations were used to predict the stability of possible *ortho*-fused heterocycles, *o*-C₆H₄S_x (where *x* = 1–8). With *o*-C₆H₄S_x (*x* = 3, 5, 7) an even number of out-of-phase overlaps was achieved, whereas with *o*-C₆H₄S_x (*x* = 2, 4, 6, 8) an odd number of out-of-phase overlaps was achieved (e.g., compare structures **A** and **B**) (Figure 7) <2004JOC5483>.

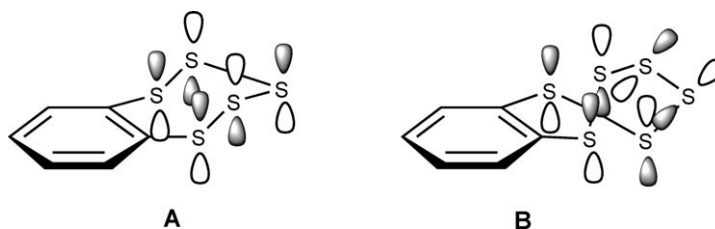


Figure 7

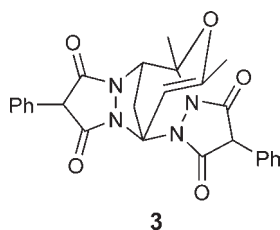
13.17.3 Experimental Structural Methods

13.17.3.1 X-Ray Diffraction

Nowadays, X-ray diffraction together with NMR spectroscopy is a routine method and has been used for the identification of most crystalline organic structures. Not all data but only the typical or special cases in which X-ray investigation was conducted will be presented in this review.

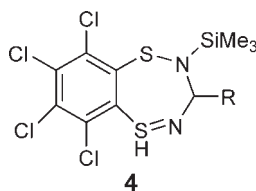
13.17.3.1.1 Tetrazepanes and tetrazepines

The molecular structure of polycycle **3** with tetrazepane fragment (Figure 8) was characterized by X-ray diffraction <2002CC1956>. X-Ray diffraction of nitrobenzotetrazepinone derivatives <1998H(48)1347> showed that despite the electron-withdrawing effect of a nitro group *para* to the triazene chain, N-3 exhibited significant pyramidal character. The 1,2,3,5-tetrazepinone cycles have an almost perfect seven-membered ring boat shape.

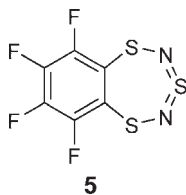
**Figure 8**

13.17.3.1.2 Dithia- and trithiadiazepines

The tetrachlorobenzodithiadiazepine **4** (Figure 9) was structurally characterized by X-ray diffraction. The puckered seven-membered ring displays localized single and double bonds. The structural data indicated that there is no steric strain on the amidine moiety <1997IC4772>. This compound is also a precursor to obtain the radical (Section 13.17.7.4).

**Figure 9**

The structure of trithiadiazepin **5**, a 14 π -electron compound (Figure 10), was detected by X-ray diffraction to be planar within ± 0.018 Å <1997CBR247>.

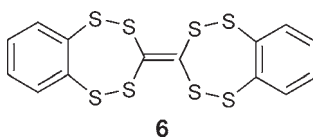
**Figure 10**

13.17.3.1.3 Tetrathiepanes

The crystal structure of diethyl 1,2,3,4-tetrathiepane-6,6-dicarboxylate was detected from low-temperature (110 K) X-ray diffraction data. Two intramolecular contacts 3.124 and 3.188 Å, between the two carbonyl oxygen atoms and two terminal sulfur atoms, are somewhat shorter than the sum of their van der Waals radii (3.25 Å). These interactions appear to be important for the stabilization of the molecule. The geometry of C–S–S–S–C fragments observed in 6–16-membered ring systems revealed that the torsion angles C–S–S–S and S–S–S–S vary with the size of the ring system and with a distinctly preferred conformation for each size of the ring <1994ACS652>.

13.17.3.1.4 Tetrathiepinines

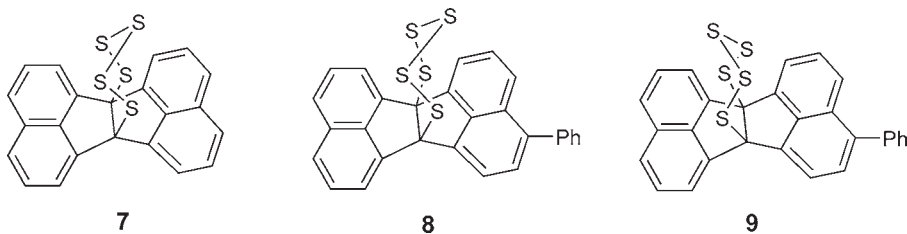
The unstable bright yellow crystals of 5*H*-benzo[*f*]-1,2,3,4-tetrathiepine-1-oxide **26** (Section 13.17.5.3) were characterized by an X-ray diffraction study <1996ZN1511>. The X-ray crystal structural analysis of bis-tetrathiepinyliden **6** (Figure 11) showed that it possesses *C_i* symmetry with a central exocyclic CC double bond similar to tetrathiafulvalences <1995CB561>.

**Figure 11**

13.17.3.1.5 Pentathiepanes

Single crystal X-ray structural analysis was carried out for 4,7-bis(1,3-dithian-2-ylidene)-1,2,3,5,6-pentathiepane (see Section 13.17.7.13) <1995MI1>.

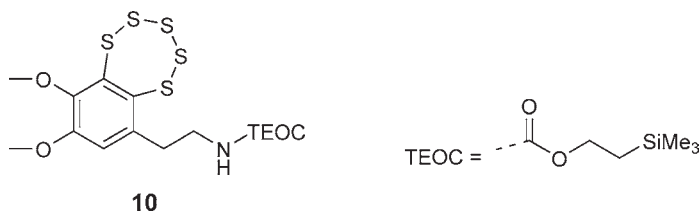
To confirm the nonequivalence of two naphthalene rings, the conformations of pentathiepanes fragment of **7–9** (Figure 12) (Section 13.17.7.12) were determined by X-ray single crystallographic analysis <1998TL2605, 1999EJO597>. In agreement with the prediction by NMR, the pentathiepane ring of **7** adopted a typical chair conformation in which it is fixed over one of the naphthalene rings. The single intramolecular C(1)–C(2) bond length, 1.633(3) Å, is much longer than bond lengths of common C(sp³)–C(sp³) bonds, probably because the pentathiepane ring constitutes a part of the rigid [5.3.3]propellane structure. These results reveal that the pentathiepane ring of **7** is more strained than those of typical pentathiepinines, which adopt chair conformations. These observations mean that, when introducing a proper substituent into one of the naphthalene rings of **7** a pair of separable conformers will be formed; this hypothesis was successfully confirmed. A pair of individual conformers of 5-phenylacenaphtho[1,2-*a*]acenaphthylenepentathiepanes **8** and **9** were isolable and their stereochemistry was determined by X-ray diffraction analysis <1998TL2605, 1999EJO597>.

**Figure 12**

13.17.3.1.6 Pentathiepinines

The crystal structure of the simple 1,2,3,4,5-benzopentathiepin was determined by single crystal X-ray diffraction <2000EJI921>. The crystals were found to be orthorhombic with four molecules in the unit cell. The molecules have *C_s* symmetry. The crystallographic mirror plane passes through the center of the C(3)–C(39) bond and contains S-4. The conformations of sulfur homocycles and sulfur-rich heterocycles can best be characterized by the motif, which describes the order of the signs of the torsion angles around the ring. The motif for the C₂S₇ heterocycle is + – + – 0 + – + – with a value of zero at the carbon–carbon bond. Such a motif has not previously been observed for any nine-membered heterocycle of the type C_{*x*}S_{*y*}. The absolute values of the torsion angles at the SS bonds lie between 85° and 110°.

The structure of varacin was accomplished by complete spectral characterization of two derivatives (Section 13.17.7.14.2), including an X-ray diffraction analysis of (trimethylsilyl)ethoxycarbonyl (TEOC)-protected varacin **10** (Figure 13) <1994JOC5955>. The pentathiepin ring exists in the expected chair conformation.

**Figure 13**

In the crystal structure of the varacinium chloride, the seven-membered ring also adopted a chair conformation. The crystal structure is stabilized by N–H···Cl–H bonds <2002AXEo465>.

The crystal structure of pentathiepin[6,7-*b*]indole has been determined <1994TL5279>. X-Ray crystal structure analysis revealed that 4,5-ethylenedithio-4,5-pentathiotetrathiofulvalene <1999AM758> moiety has a bent structure resembling the molecular structure of neutral bis(ethylenedithio)tetrathiafulvalene and that the pentathio group adopts a chair-formed conformation. The intradimer interplane distance is 3.35 Å, which is much shorter than the interdimer one (4.45 Å). In a molecule, there are many intermolecular S–S contacts shorter than the sum of the van der Waals radii (3.7 Å), and a two-dimensional network of sulfur atoms was developed between the pentathio groups and tetrathiafulvalene moieties. Furthermore, chlorobenzene molecules are beside the anion and occupy the void space as the interstitial solvent. They are also located on the mirror plane and are disordered at two positions with inversion symmetry because of the cavity structure of the void space.

The molecular structure of pentathiepin **11** (Figure 14) was absolutely verified by a representative X-ray crystallographic analysis. The PLUTO representation clearly showed the presence of a pentathiepin ring, which exists in the expected chair conformation. The distinctive feature of **11** is the large dihedral angle (62 Å) of two diarylmethylene moieties and each one of the aryl group stacked against each other <1997MI2399>.

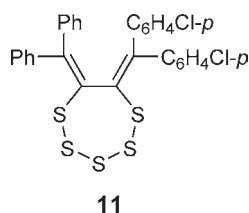


Figure 14

It is impossible to establish the precise position of the oxidized sulfur atom, the exact configuration of the sulfinyl group, and the conformation of the pentathiepin ring of compounds **12–15** (Figure 15) by spectral data (Section 13.17.5.4) <1997TL1607, 1999CL1305, 2002BCJ817>. So the structure of the four monoxides was determined by X-ray crystallographic analysis revealing that they have the oxygen atom on the trithiole ring, not on the pentathiepin ring; **12** and **13** are benzotrithiole 2-oxides, while **14** and **15** are benzotrithiole 1-oxides. In these molecules, the oxygen atoms coordinated to the sulfur atoms of **12** and **13** orient to the ‘end’ of the trithiole ring, and the oxygen atoms of **14** and **15** are located to the *exo*-side of the trithiole ring. Meanwhile, the oxygen atoms of **12** and **14** exist on the *syn*-side to the pentathiepin ring (*syn*-isomers), and the oxygen atoms of **13** and **15** orient to the *anti*-side to the pentathiepin ring (*anti*-isomers).

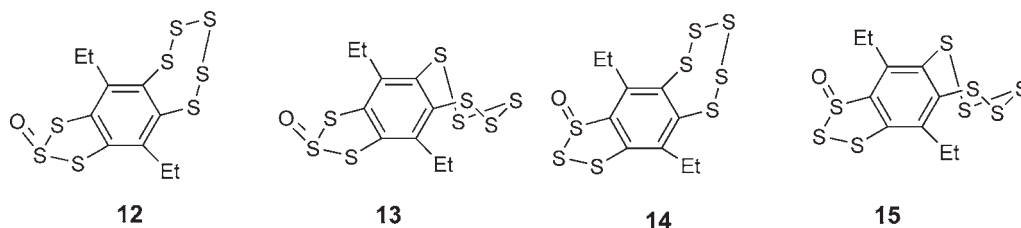


Figure 15

Compounds **12** and **13**, and **14** and **15**, are isomers with respect to the conformation of the 1,2,3,4,5-pentathiepin rings.

Two polymorphic forms were found for pentathiepin[6,7-*b*]benzo[*d*]thiophene, displaying similar conformations but different packing schemes <2002JOC6220>. Form I crystallized from a 4:1 mixture of hexane–CH₂Cl₂ in the space group *P*21/*c* with the unit-cell parameters *a*: 4.467(1), *b*: 13.514(1), *c*: 18.049(1) Å and β: 94.59(1)°, *V*: 1086.1(3) Å³; form II was obtained from hexane adopting the space group *P*21/*n* with the unit cell dimensions

a : 8.997(1), b : 10.115(1), c : 12.116(1) Å and β : 93.89(1)°, V : 1100.1(2) Å³. The molecular conformations of the two forms are quite similar; however, the largest difference in the torsion angles is less than 5°.

X-Ray crystal structures are provided for several of the pentathiepins, for example, 6,8-dichloro-7-methyl-7*H*-[1,2,3,4,5]pentathiepine[6,7-*c*]pyrrole, 6,8-dichloro-7-*t*-butyl-7*H*-[1,2,3,4,5]pentathiepine[6,7-*c*]pyrrole <2005OBC3496>, and bispiperidinothienopentathiepine <2003OL1939>. In general, the geometry of this pentathiepin is quite close to other pentathiepins.

The molecular structure of ferrocene-pentathiepins **16** (Figure 16) (see Section 13.17.7.14) has been sufficiently characterized by X-ray crystallographic analysis <2002TL5825, 2005BCJ2026>. In the solid state, two sulfur atoms bound to carbon atoms of ferrocene are almost coplanar with the cyclopentadienyl ring, while two sulfur atoms at 2- and 4-position deviated from this plane (the S–S–C–C torsion angles are 88.1(3)° and –88.6(4)°, respectively) to avoid the ferrocene moiety. The S–S–S torsion angles of 76.6(3)° and –76.0(2)°, which are in good agreement with those of reported pentathiepins, fused to five-membered heteroaromatic rings.

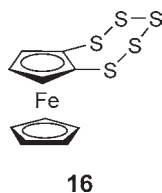


Figure 16

13.17.3.2 NMR Spectroscopy

Lately, NMR has become a widely used routine method. Each paper contains NMR data to confirm the structure of compounds. In this chapter, only the references in which NMR spectroscopy was used in special cases are mentioned.

The ¹³C NMR spectrum of lissoclinotoxin A was reported for the first time in 1994 <1994JOC6600>.

A dynamic NMR spectrum analysis revealed that naphthalene rings of pentathiepine derivatives of acenaphtho[1,2-*a*]acenaphthylene **7** are chemically nonequivalent up to 100 °C. The pentathiepane ring of **7** adopts a chair conformation both in solution and crystals. The ¹H NMR spectrum of **7** showed a pair of doublets of doublets and a pair of four doublets in the aromatic region, and the ¹³C NMR spectrum showed 12 peaks in the range δ 120–144 ppm due to the aromatic carbons and one peak at δ 97 ppm due to the bridgehead carbons, revealing the nonequivalency of the two naphthalene rings. Dynamic ¹H NMR in toluene-*d*₈, monitored up to 100 °C, did not show the coalescence of signals. In accordance with NMR, the sulfuration of 5-phenylacenaphtho[1,2-*a*]acenaphthylene gave a pair of conformers **8** and **9**, which were isolated in pure form <1998TL2605, 1999EJO597> (Section 13.17.7.12).

For the pentathiepane **17** (Figure 17), 12 coalescence phenomena in the ¹H and ¹³C NMR point to $\Delta G_{\text{thermod.}} = 13.4 \text{ kcal mol}^{-1}$. The process was interpreted as a stereomutation on the pseudorotation circuit for twist-chair and chair <1997LA1517>.

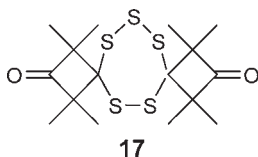


Figure 17

The molecular structure of the ferrocenopentathiepins **16** was studied by NMR <2002TL5825, 2005BCJ2026>. The ¹H NMR spectrum of pentathiepin **16** in CDCl₃ showed a pair of doublets and triplets at 4.53 and 4.42 ppm, respectively, assigned to the α and β cyclopentadienyl protons, and a singlet at 4.32 ppm of unsubstituted cyclopentadienyl protons. The ¹³C NMR spectrum showed the resonance at 70.0, 71.1, and 75.4 ppm assigned to the Cp-H carbons, and at 93.3 ppm assigned to the Cp-S *ipso*-carbon. The remarkable large downfield shift observed for the *ipso*-carbon reflects the deshielding effect of the sulfur substituent.

The ^{15}N NMR spectra of the several seven-membered 1,2,3,5-tetrazepinone ring systems **18** were studied <1998MI59, 1998MRC87>. The chemical shift of N-2 was found to be significantly responsive to substituent changes at the Ph ring. As the electron-withdrawing character of the substituents increased, N-2 became more deshielded. Solid-state NMR data indicated that N-3 was significantly more delocalized in the 1,2,3-triazene moiety of the tetrazinone **19** than in the electron-deficient tetrazepinone **18** (Figure 18).

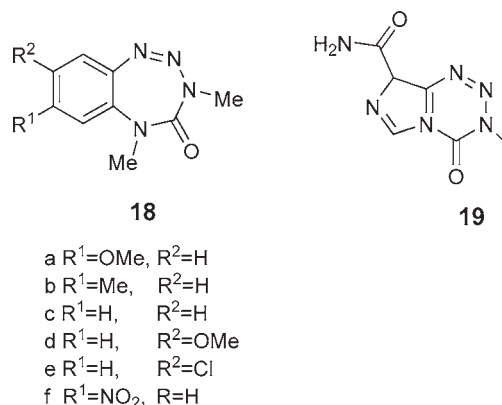


Figure 18

13.17.3.3 Mass Spectrometry

The molecular structure of the ferrocenopentathiepin **16** was detected by spectra <2005BCJ2026>. The structure of isoindolo[1,2-*d*][1,2,3,5]benzotetraazepine (Section 13.17.7.7) was based only on mass and NMR spectrometric evidence as well as its acidity <1999AJC775>.

MS was widely used for identification of volatile compounds, for example, from oil of garlic <2005MI548>, leaf oil from *Adenocalymna alliaceum* <2004MI323>, sediment of the eastern Gulf of Finland <2004MI731>, volatile compounds generated from thermal interaction of 2,4-decadienal and the flavor precursors of garlic <1994MI61>, volatile compounds generated from thermal interaction of glucose and alliin or deoxyalliin in propylene glycol <1994MI281>, volatile compounds in garlic slices <1994MI1342>, etc.

13.17.3.4 Photoelectron Spectroscopy

The He(I) photoelectron spectrum of trithiadiazepin **5** was assigned by Koopmans' correlation with PM3 eigenvalues based on the structural data, and by the π -perfluoro effect observed. The π -system can be rationalized by heteroatom first-order perturbation, which reduces the cyclic π -delocalization. Replacement of the four F substituents by H affected neither the long-wavelength absorption band in the UV/Vis (Vis = visible) spectrum nor the $\delta^{15}\text{N}$ shift in the ^{15}N NMR <1997CBR247>.

13.17.3.5 ESR Spectroscopy

The ESR spectrum of dithiadiazepinyl radical **20** (Figure 19) consists of a slightly asymmetric quintet ($g=2.0070$ and $A_{\text{N}}(\text{iso})=4.9\text{ G}$) <1997IC4772> (Section 13.17.7.4).

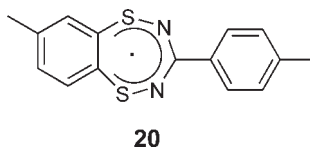


Figure 19

13.17.3.6 Optical Activity and Chirality

13.17.3.6.1 Pentathiepinines

Chirality in unsymmetrically substituted benzopentathiepinins is a result of a high barrier to ring inversion. It was established by ^1H NMR spectrum of varacin **21** (Figure 20), the first naturally occurring compound detected to possess a 1,2,3,4,5-benzopentathiepin ring, which showed unexpectedly complex signals for the side-chain methylene protons. Evidence was presented which indicates that unsymmetrically substituted benzopentathiepinins are asymmetrical molecules as a result of a high energy barrier to inversion of the low-energy chair conformations of the polysulfide ring. Derivatization of varacin **21** with a chiral auxiliary provided diastereomeric products, which can be separated by fractional recrystallization <1994TL7185>.

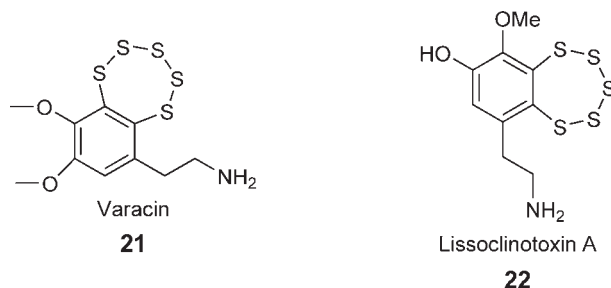


Figure 20

Lissoclinotoxin A **22** is chiral <1994JOC6600>. The ^1H NMR spectrum of **22** showed diastereotopic signals for the side-chain methylene groups, similar to that observed for varacin **21**. The observation of diastereotopism led to the conclusion that **22** is chiral, at least on the NMR timescale. The origin of the chirality in **22** and its derivatives is best explained by slow inversion of the benzopentathiepin ring due to an exceptionally high barrier (ca. 29 kcal mol $^{-1}$) to ring inversion, as has been noted for simple benzopentathiepinins. The reason for the high barrier to inversion in **22** and its analogs lies, presumably, in unfavorable eclipsing between the sulfur 3sp ^{3} lone pair orbitals when passing through the half-chair transition state during ring inversion.

13.17.4 Thermodynamic Aspects

13.17.4.1 Physical Constants, Thermal Stability, and Solubility

Physical constants and thermal stability of seven-membered cyclic compounds are strongly dependent on the nature of structure and substituents. Most of trithiadiazepines, trithiatriazepines, and cyclic polysulfides are as a rule relatively low-melting solids; for example, 5*H*-benzo[*f*]-1,2,3,4-tetrathiepine-1-oxide **26** is an unstable bright yellow crystal <1996ZN1511>. Tetrazepines and thiatriazepines are more high-melting solids, for example, benzotetrazepine, (see **68**) remarkably stable at 600 °C <1999AJC775>. As a rule, cyclic polysulfides are very volatile compounds. In spite of the large number of ring heteroatoms, the seven-membered heterocycles are readily soluble in organic solvents; the cyclic polysulfides are easily soluble in both nonpolar and polar organic solvents. In rare cases, the benzotetrazepinone derivative (see **69**) <2000BML2325>, for example, is water soluble.

13.17.4.2 Thermal Stability and Aromaticity

Members of a series of carbon-poor sulfur–nitrogen heterocycles and polycycles are shown by direct *ab initio ipso*-centric calculation to support diatropic ring currents and hence to be aromatic on the basis of magnetic criteria. They include several seven-membered cycles (Figure 21), all with 10 π -electrons <2002JA11202>. All molecular structures were optimized at the restricted Hartree–Fock (RHF) and DFT (B3LYP) levels in the 6-31G** basis set, known to be sufficient for semiquantitative calculation of current density maps. The unknown trithiatetrazepine S $_3$ N $_4$ is predicted to be at least as aromatic as its known diaza and triaza homologs.

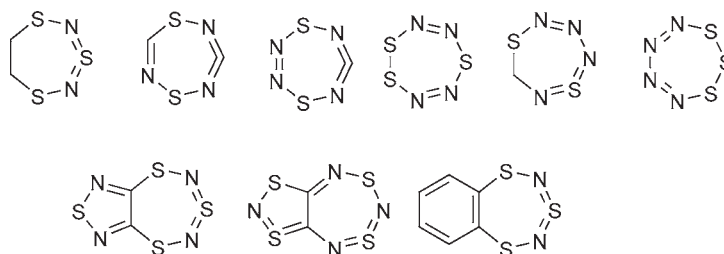


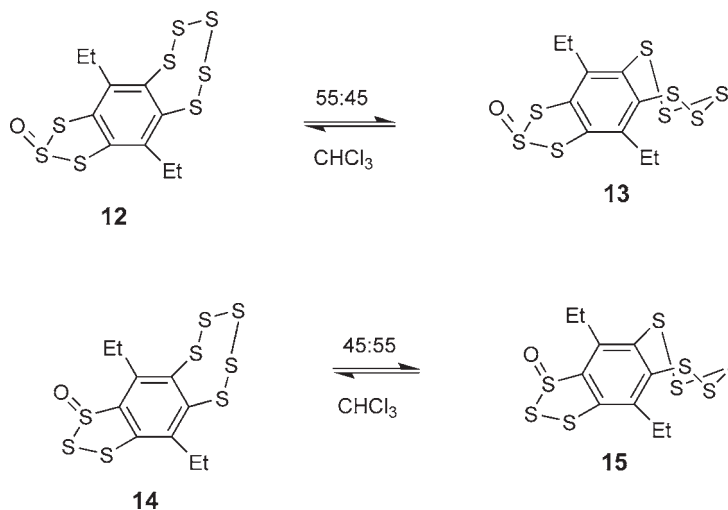
Figure 21

Angular momentum arguments show that the π -electron-rich nature of $(4n+2)$ SN heterocycles is the key to their diatropic current. Formal expansion of $(4n+2)$ - π -carbocyclic systems by insertion of NSN motifs in every CC bond is predicted to lead to structures that support diatropic ring currents: explicit *ab initio* calculation of magnetic response predicts the 24-center, 30π -electron heterocycle $S_6N_{12}(CH)_6$, formally derived from benzene, to be aromatic on the basis of this criterion <2002JA11202>.

13.17.4.3 Conformations

Conformations of heterocyclic fragments of 1,3,5,2,4-trithiadiazepines and 1,3,5,2,4,6-trithiatriazepines are planar. Cyclic polysulfides possess as a rule in the chair conformation both in crystal (Section 13.17.5.4) and in solution because these conformers have lowest torsion strain.

The conformational behavior of heterocycles with pentathiepin ring was described in <2002BCJ817> (Scheme 1). Compounds **12** and **13** are isomers with respect to the conformation of the 1,2,3,4,5-pentathiepin ring, and **14** and **15** are also the conformational isomers. These compounds pair members, **12** and **13**, and **14** and **15**, were found to isomerize into each other by inversion of the pentathiepin ring, not by the pyramidal inversion of the sulfinyl group and the S-S bond cleavage of the trithiole ring. Because of the slow inversion of the pentathiepin ring, isolation of unsymmetrical substituted benzopentathiepin as a chiral molecule is possible <2002BCJ817>.



Scheme 1

A dynamic NMR analysis revealed that the naphthalene rings of pentathiepinacene[1,2-*a*]acenaphthylene **7** (see Section 13.17.7.12) are chemically nonequivalent up to 100 °C due to freezing of the inversion of the pentathiepane ring. Thus, sulfuration of 5-phenylacenaphtho[1,2-*a*]acenaphthylene gave a pair of conformers **8** and **9** which were isolable and whose stereochemistry was determined by X-ray diffraction analysis. These conformers isomerized

slowly into each other in solution at room temperature. The activation parameters for this process were determined. Based on the experimental observations, a probable mechanism for the inversion process was proposed <1998TL2605, 1999EJO597>.

13.17.5 Reactivity of Fully Conjugated Rings

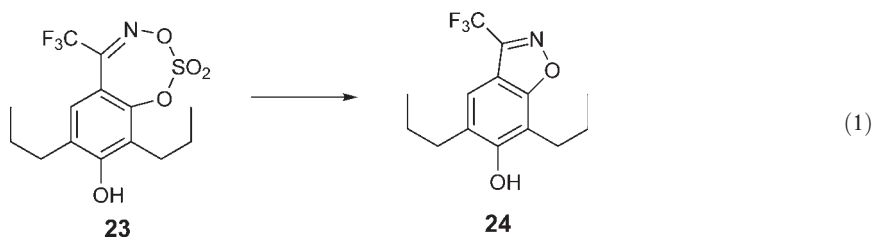
The reactivity of seven-membered heterocycles was presented more fully in CHEC-II(1996) (Section 9.17.5) and other reviews <2004CRV2617>.

13.17.5.1 1,2,4,6-Tetrazepines

meso-Ionic [1,2,4]triazolo[5,1-*c*]thiadiazoles were synthesized by oxidation of *N*-methyl-*N'*-(substituted benzal)-5-amino-3-substituted-1,2,4-triazol-1-ylthiohydrazide bases or their [1,2,4]triazolo[5,1-*d*][1,2,3,6]tetrazepin-5-thione tautomers (Section 13.17.7.9) <2000JHC261>. Oxidation of *N*-methyl-*N'*-(substituted benzal)-5-amino-3-substituted-1,2,4-triazol-1-ylthiohydrazide bases or their [1,2,4]triazolo[5,1-*d*][1,2,4,6]tetrazepin-5-thione tautomers led to formation of *meso*-ionic [1,2,4]triazolo[5,1-*c*]thiadiazoles.

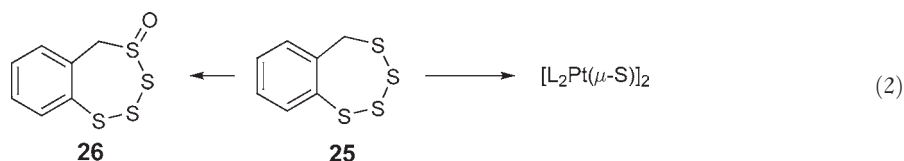
13.17.5.2 1,3,2,4-Dioxathiazepines

Cyclic sulfite **23** formed benzisoxazole **24** with 94% yield in the presence of diisopropylethylamine <2005JOC8560>. Although the mechanism of the cyclic sulfite **23** rearrangement has not been fully delineated, simple kinetic experiments showed that the rate of formation of benzisoxazole **24** was second order in the concentration of **23** and first order in the concentration of diisopropylethylamine (Equation 1).



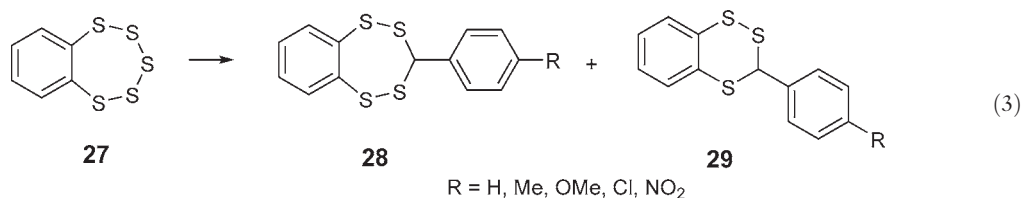
13.17.5.3 Tetrathiepinines

The 5*H*-benzo[*f*]-1,2,3,4-tetrathiepine-1-oxide **26** was prepared by oxidation of the corresponding benzotetrathiepine **25** <1996ZN1511>. Moreover, the Pt(0) complexes reacted with benzotetrathiepine to give products of an oxidative addition of S, the corresponding sulfido-bridged diplatinum complexes [L₂Pt(μ-S)]₂ (Equation 2).



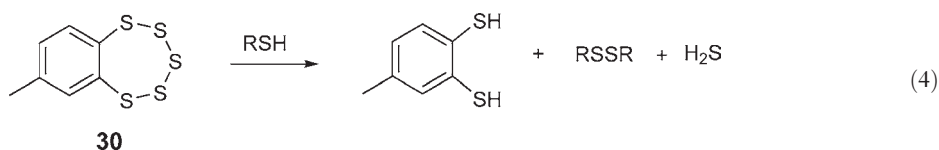
13.17.5.4 Pentathiepinines

Benzopentathiepin **27** reacts with phosphorus ylides 4-RC₆H₄CH₂PPh₃Cl (R = MeO, Me, H, Cl, NO₂) to form a mixture of benzotetrathiepins **28** and benzotrithiins **29** (Equation 3). The carbanion fragment of the phosphorus ylides replaced the one or two sulfur atoms in the multi-sulfur linkages of benzopentathiepin. Systematic desulfurization to form a new cyclic system was accomplished by the use of a combination of phosphorus ylide and triphenylphosphine in the reactions of benzopentathiepin, benzotetrathiepins, and benzotrithiins <1997H(44)187>.

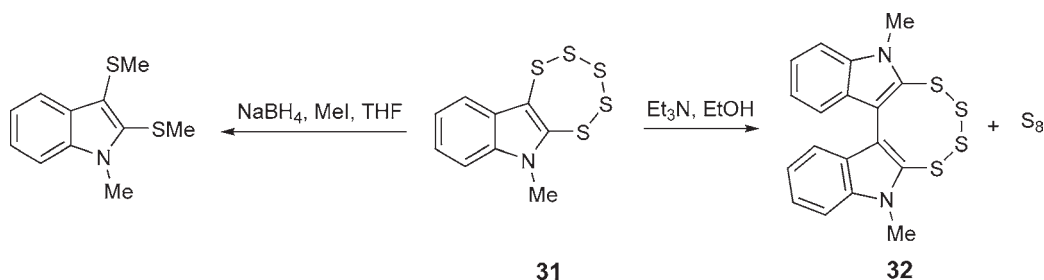


6,9-Diethyl-1,2,3,4,5-benzopentathiepin was photolyzed by a 100 W high-pressure mercury lamp in CH_2Cl_2 under an argon atmosphere to produce 1,4,6,9-tetraethylthianthrene by way of desulfurization, dimerization, and ring contraction reactions <2002BCJ2647>.

The reaction of thiols with the 7-methylbenzopentathiepin ring system <2003BML1349> initially produced a complex mixture of polysulfides that further decomposed in the presence of excess thiol to yield the corresponding 1,2-benzenedithiol with concomitant producing of H_2S and dimerized thiol (Equation 4). In this reaction, a single molecule of the pentathiepin **30** consumed approximately 6 equiv of thiol. The reaction of thiols with the pentathiepin ring system was faster than the analogous reaction involving typical di- and trisulfides.

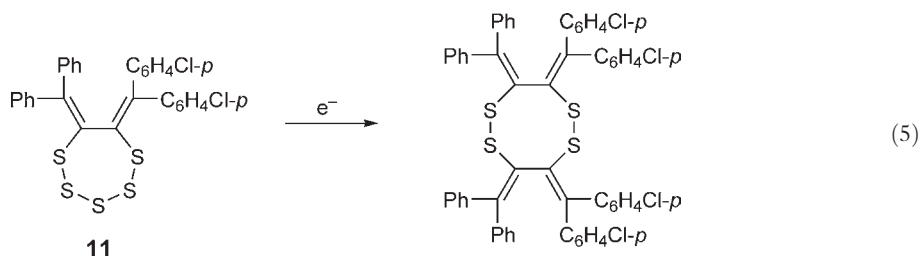


N-Methylindolopentathiepin **31** underwent reduction with sodium borohydride in the presence of MeI to give a 1-methyl-2,3-bis(methylthio)indole (Scheme 2). After a pure sample was heated at reflux in EtOH containing NEt_3 , a relatively rapid reaction was observed, and apart from elemental sulfur, compound **32** was only major product observed <2001T7185>.



Scheme 2

The controlled potential macroelectrolysis of pentathiepin **11** using a glassy carbon cathode was conducted at -0.85 V in dimethylformamide (DMF) containing 0.1 mol dm^{-3} Et_4NOTs and produced tetrathiocin in a high yield (Equation 5) <1997MI2399>.



The first preparation and structure determination of optically pure cyclic polysulfides, 6,10-diethyltrithio[*h*]benzopentathiepin monoxides, were described in 1997 <1997TL1607>. Then the oxidation reaction and properties of

compounds of this type were studied in detail <1997TL1607, 1999CL1305, 2002BCJ817>. Syntheses of starting benzopentathiepin **33–35** and **37** were published earlier (see CHEC-II(1996) (chapter 9.17), references in <1997TL1607, 1999CL1305, 2002BCJ817>, and Section 13.17.3.1.6).

6,10-Diethyl[1,2,3]trithiolo[4,5-*h*]benzopentathiepin **33** (Figure 22) was oxidized by *m*-chloroperbenzoic acid (MCPBA) or by Sharpless reagent which consisted of $\text{Ti}(\text{O-}i\text{-Pr})_4/R,R\text{-DET}/t\text{-BuOOH}$ in CH_2Cl_2 at -20°C under an argon atmosphere for 24 h. The reactants, **33**/ $\text{Ti}(\text{O-}i\text{-Pr})_4/R,R\text{-DET}/t\text{-BuOOH}$ were in the ratio of 1:2:4:4, which gave the best result in the asymmetric oxidation. In spite of a large amount of an oxidizing reagent, the corresponding bis-sulfoxide and sulfone were not detected at all; the oxidation of **33** proceeded very slowly under the reaction conditions. By this reaction, four monoxides **12–15** were obtained, similar to the case of the MCPBA oxidation. In these monoxides, **12** and **13** are not chiral, while **14** and **15** are optically active molecules with respect to the conformation of the pentathiepin ring and the configuration of the sulfinyl sulfur atom. Compounds **14** and **15** could be separated easily by column chromatography in 18% and 23% yields, respectively <2002BCJ817>. At the same time, when 6,9-diethylbenzopentathiepin **34** was oxidized by MCPBA, a ring construction of the pentathiepin ring proceeded under the reaction conditions to produce not 6,9-diethylbenzopentathiepin monoxide but rather 4,7-diethylbenzotrithiole monoxides <2002BCJ817> (Scheme 3).

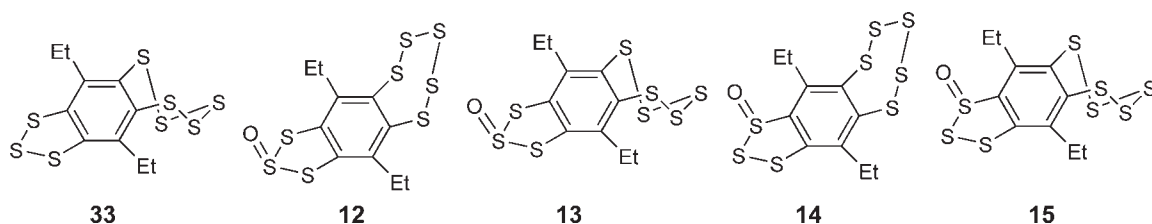
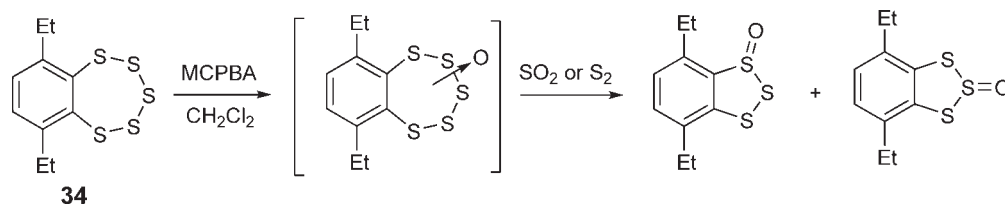
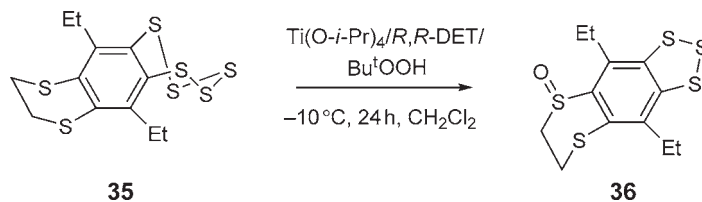


Figure 22



Scheme 3

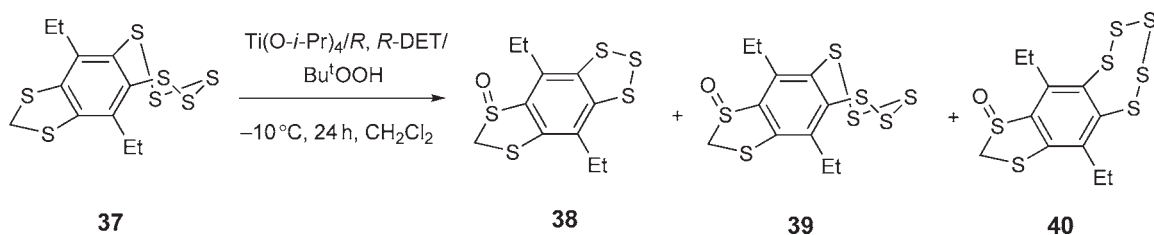
Oxidation of 6,11-diethyl[1,4]dithiino[5,6-*h*]benzopentathiepin **35** by a Sharpless reagent [$\text{Ti}(\text{O-}i\text{-Pr})_4/R,R\text{-DET}/t\text{-BuOOH}$] produced optically active 4,9-diethyl[1,4]-dithiino[5,6-*f*]benzo[1,2,3]trithiole-5-oxide **36** (Scheme 4). The reaction was accompanied by desulfurization and ring contraction of the pentathiepin ring <2003HAC88>.



Scheme 4

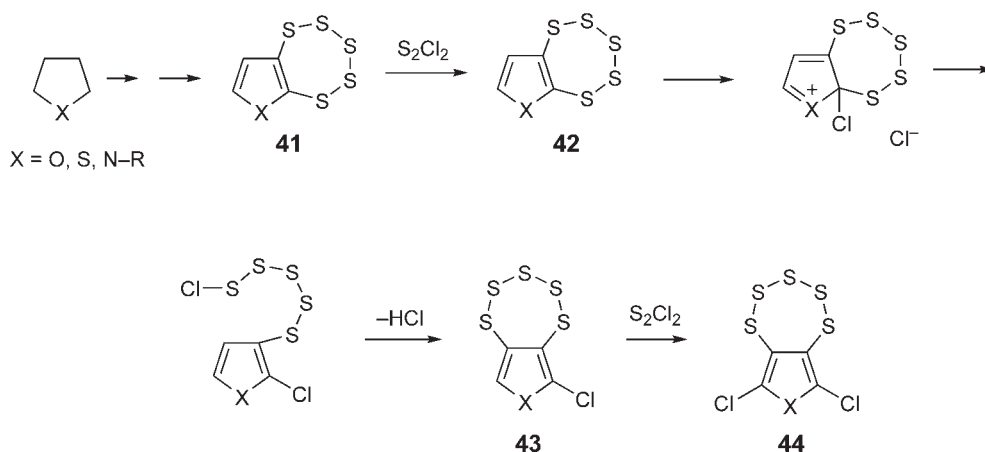
The analogous asymmetric oxidation of 6,10-diethyl[1,3]dithiolo[4,5-*f*]benzo[1,2,3,4,5]pentathiepin **37** gives optically active 4,8-diethyl[1,3]dithiolo[4,5-*f*]benzo[1,2,3]trithiole 5-oxide **38** together with a 26% yield of a mixture of

6,10-diethyl[1,3]dithiolo[4,5-*b*]benzopentathiepin 7-oxides **39** and **40**. The recrystallization failed to produce optically pure crystals of **39** and **40** (Scheme 5).



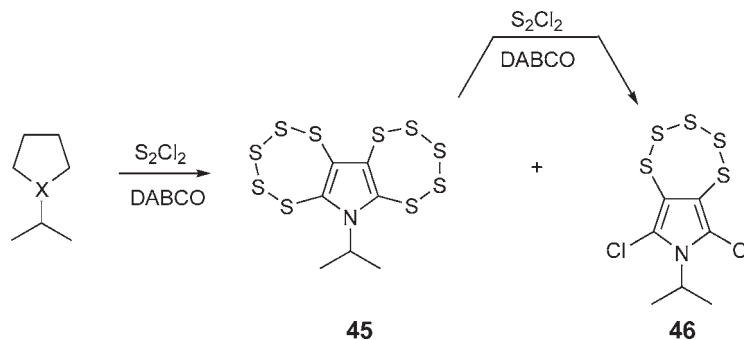
Scheme 5

A special experiment showed that the unsymmetrical pentathiepin **41** can be converted into the symmetrical pentathiepin **44** by S_2Cl_2 -DABCO in good yield (52%, DABCO = 1,4-diazabicyclo [2.2.2]octane); this is a new and unexpected rearrangement of a 2,3- to a 3,4-fused pentathiepin accompanied by ring chlorination (Scheme 6) <2005OBC3496>.



Scheme 6

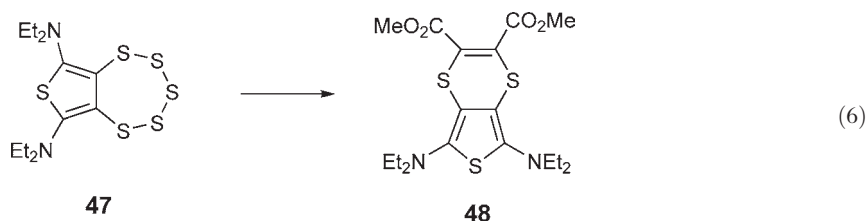
Moreover, separate experiments showed that bis(pentathiepin)pyrrole **45** can be converted into **46** by S_2Cl_2 -DABCO in high yield (78%) and **46** was unchanged by further treatment (Scheme 7). This conversion of **45** into **46** is presumably mechanistically related to the rearrangement of the monopentathiepin **41** to **44** above <2005OBC3496>.



Scheme 7

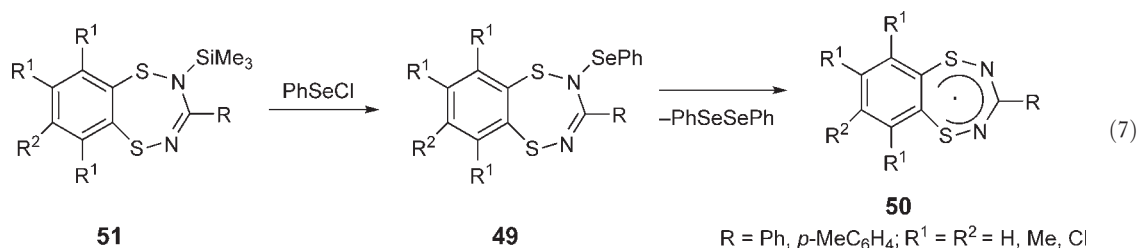
All these cascade reactions show how readily and uniquely thermodynamically stable 1,2,3,4,5-pentathiepin rings can be fused onto certain heterocyclic rings in one-pot reactions and suggest many possible extensions of this simple procedure.

The mild reaction of thienopentathiepin **47** with dimethyl acetylenedicarboxylate (DMAD) and triphenylphosphine in CH_2Cl_2 at room temperature gave the 1,4-dithiin **48** (Equation 6) <2003OL1939>.



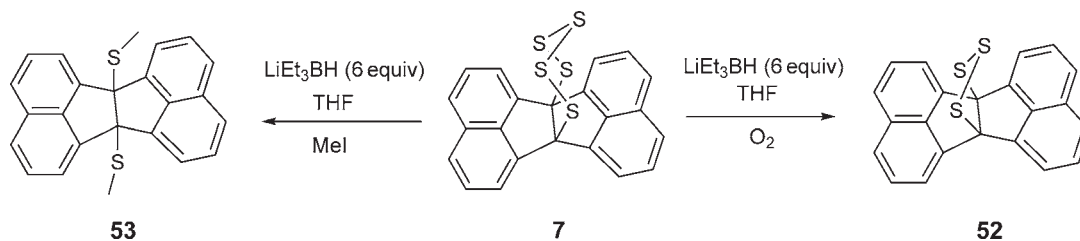
13.17.5.5 1,5,2,4-Dithiadiazepines

The seven-membered ring precursor **51** (Section 13.17.7.4) has an N-bonded trimethylsilyl group, which may be replaced by PhSe upon reaction with PhSeCl. Using the tendency of the Se–N bond to undergo homolysis, the PhSe-substituted derivative was decomposing to the radicals **50** (Equation 7) <1997IC4772>.



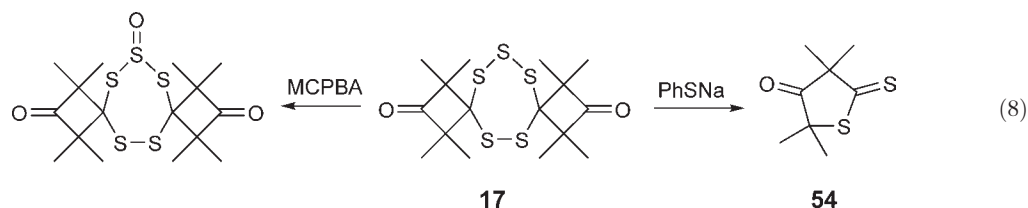
13.17.6 Reactivity of Nonconjugated Rings

The reduction of 6*b*,12*b*-epipentathioacenaphth[1,2-*a*]acenaphthylene **7**, prepared by sulfuration of acenaphth[1,2-*a*]acenaphthylene, with LiEt₃BH, followed by air oxidation, resulted in desulfuration leading to 6*b*,12*b*-epitrithioacenaphth[1,2-*a*]acenaphthylene **52** in 87% yield (Scheme 8) <1999HAC638>. Reduction of **7** with LiEt₃BH, followed by treatment with MeI, gave a 66% yield of the bis-sulfide **53**, whose two naphthalene rings are equivalent in ¹H and ¹³C NMR. These observations are in harmony with the given chair structure **7** with a C_s symmetry where two naphthalene rings are placed in a different environment <1998TL2605, 1999EJO597>.



Scheme 8

The octamethylpentathiadispiro[3.3.3.2]tridecane-2,9-dione **17** is converted into a γ -butyrodithiolactone **54** by prolonged treatment with the thiophenolate catalyst in a Baeyer–Villiger-type reaction <1997LA1517>. The oxidation of pentathiepane with MCPBA at 0 °C gave the corresponding 12-oxide <2001ZFA1518> (Equation 8).



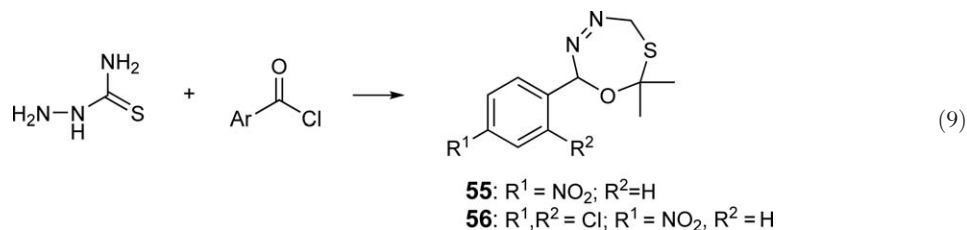
The *exo*-4,5,6,7,8-pentathiatetracyclo[9.3.0^{2,10}.0^{3,9}]pentadec-12-ene (Section 13.17.7.13) was decomposed on silica gel to the trithiolane and elemental sulfur <1995JOC8056>.

13.17.7 Synthesis of Seven-Membered Rings with Four and More Heteroatoms

13.17.7.1 Oxathiadiazepine

N-Hydroxyiminoyl chlorides reacted with *N*-alkyl ethynesulfonamides in the presence of triethylamine in CH₂Cl₂ to afford the 4-alkyl-3-aryl-4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-diones as the major products together with *N*-alkyl-3-aryl-5-isoxazolesulfonamides <1999HAC461>.

In fact, when 4-nitrobenzoyl chloride was used to achieve 4-nitrobenzoylthiosemicarbazide, a cyclic product was obtained with high yields. Based on analytical and spectral data, the obtained product was 1,3,4,5-oxathiadiazepine **55** and not the expected carbazide. A similar behavior was observed when 2,4-dichlorobenzoyl chloride was reacted, though with some difference. In this case, a mixture of two products was obtained, which after purification were identified as 1,3,4,5-oxathiadiazepine **56** and the desired 2,4-dichlorobenzoylthiosemicarbazide (Equation 9) <2004FA945>.



Burgess reagent, (methoxycarbonylsulfamoyl)triethylammonium hydroxide, usually used for the dehydration of secondary or tertiary alcohols, was successfully employed in the formation of cyclic sulfamidates from the corresponding epoxides. It was further shown that the same reaction with aromatic epoxides resulted in the formation of seven-membered ring systems, for example, **57** (Figure 23) <2003SL1247>.

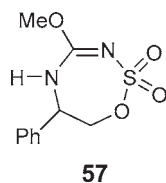


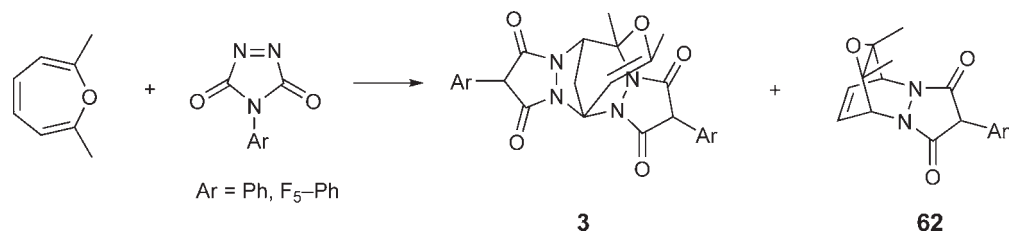
Figure 23

The reactions of thiadiazolopyrimidines **58** (R = Me, allyl) with ethoxycarbonyl isothiocyanate and CS₂ gave heterocycle **59** via thermal decomposition of 1:1 cycloadducts, which have a hypervalent sulfur (Equation 10). The mechanistic and reactivity features of these reactions were described <2004JHC99>.



4-Phenyl-1,2,4-triazoline-3,5-dione, 'Cookson's dienophile', and its 4-pentafluorophenyl analog are highly efficient reagents for trapping benzene oxide–oxepines that can give crystalline adducts readily analyzed by high-performance liquid chromatography (HPLC) and MS techniques. Thus, reaction of 2,7-dimethyloxepin with dienophiles gave two

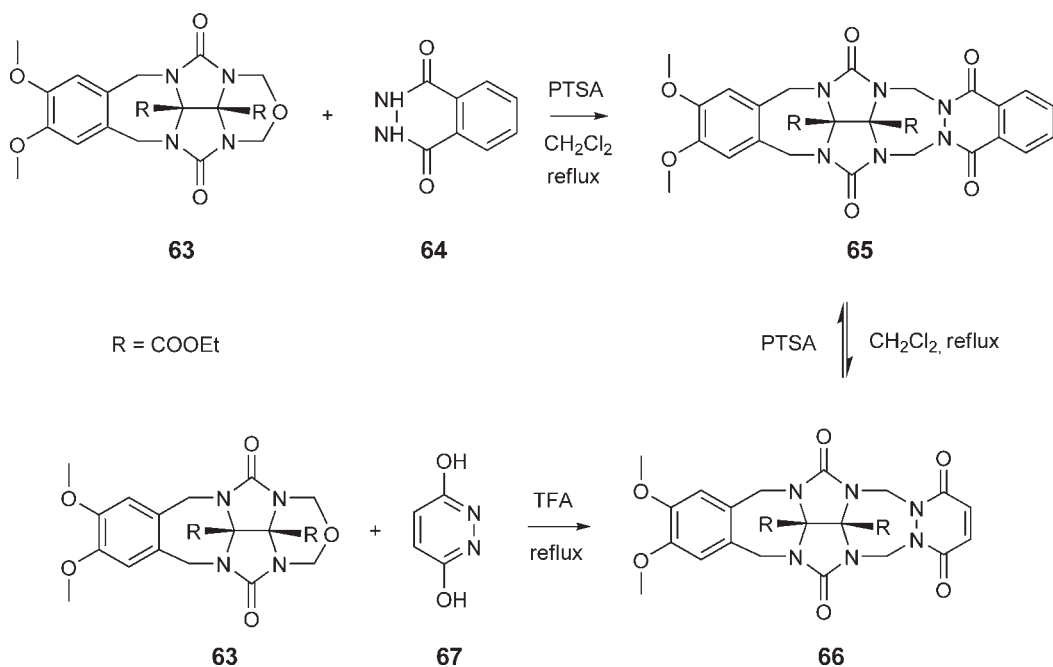
adducts, one of which was the expected 1+1 adduct **62**; the second adduct **3** arises from two molecules of dienophile and one molecule of oxepin and contains the 1,2,4,5-tetrazepane fragment (**Scheme 10**) <2002CC1956>.



Scheme 10

13.17.7.6 1,2,4,6-Tetrazepanes

Condensation of hydrazine derivatives **63** with the bis(cyclic ether) building blocks **64** gave highly selective heterodimerization polycyclic compounds **65** containing 1,2,4,6-tetrazepine fragment – glycoluril units (**Scheme 11**) <2005JOC10381>. The same result was observed for condensation of **63** and **67** in trifluoroacetic acid (TFA). Interestingly, if **66** is submitted to PTSA/(ClCH₂)₂ at reflux with 1 equiv of **64**, a replacement reaction is observed to afford **65** in 81% yield (PTSA = *p*-toluenesulfonic acid). This result indicated that **64** is a superior partner in these reactions, presumably because it sacrifices less resonance energy upon condensation and suggests that CH₂ bridges between glycoluril and phthalhydrazide rings form reversibly.



Scheme 11

The polycyclic compounds of type **65** (glycoluril units), containing 1,2,4,6-tetrazepine fragment, are included into the macrocyclic system – cucurbit[6]uril analogs (CB[6] analogs) <2003OL3745, 2005JOC10381>. CB[6] is a macrocycle comprising 12 methylene bridges connecting six glycoluril units, which define a hydrophobic cavity guarded by two carbonyl fringed portals. The relative rigidity of the CB[6] framework resulted in highly selective recognition

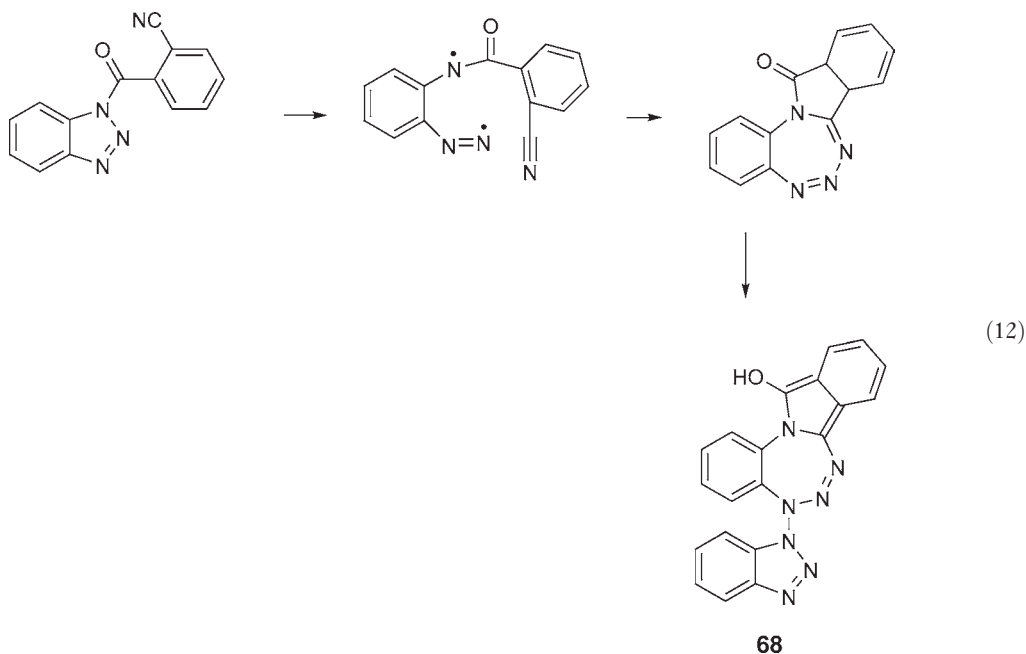
properties toward cationic and hydrophobic species (e.g., alkane diamines) through noncovalent interactions including ion-dipole, hydrogen-bonding, and the hydrophobic effect <2005JOC10381, 2005USP2005080068, 2005PCB7686, 2006JOC1181>.

13.17.7.7 1,2,3,5-Tetrazepines

Reaction of 5-azido-4-cyanoimidazole with active methylene compounds $R^1COCH_2R^2$ ($R^1=Me$, $R^2=COMe$; $R^1=Me$, $R^2=COPh$; $R^1=Me$, $R^2=CO_2Et$) or malononitrile in the presence of base led to either imidazo[5,1-*d*]-[1,2,3,5]tetrazepines or imidazolyltriazoles, depending on the reaction conditions <1995JHC457>.

In order to determine the effect of substituents on the stability of benzo-fused 1,2,3,5-tetrazepin-4-ones, 5-, 7-, and 8-substituted derivatives were synthesized. The stability of the tetrazepinones increased with the electron-withdrawing substituents at the benzene ring. A bulky group at the 5-position destabilizes the tetrazepinone ring. The unstable tetrazepines are decomposed in $CHCl_3$ at room temperature to benzotriazole derivatives <1998H(48)1347>.

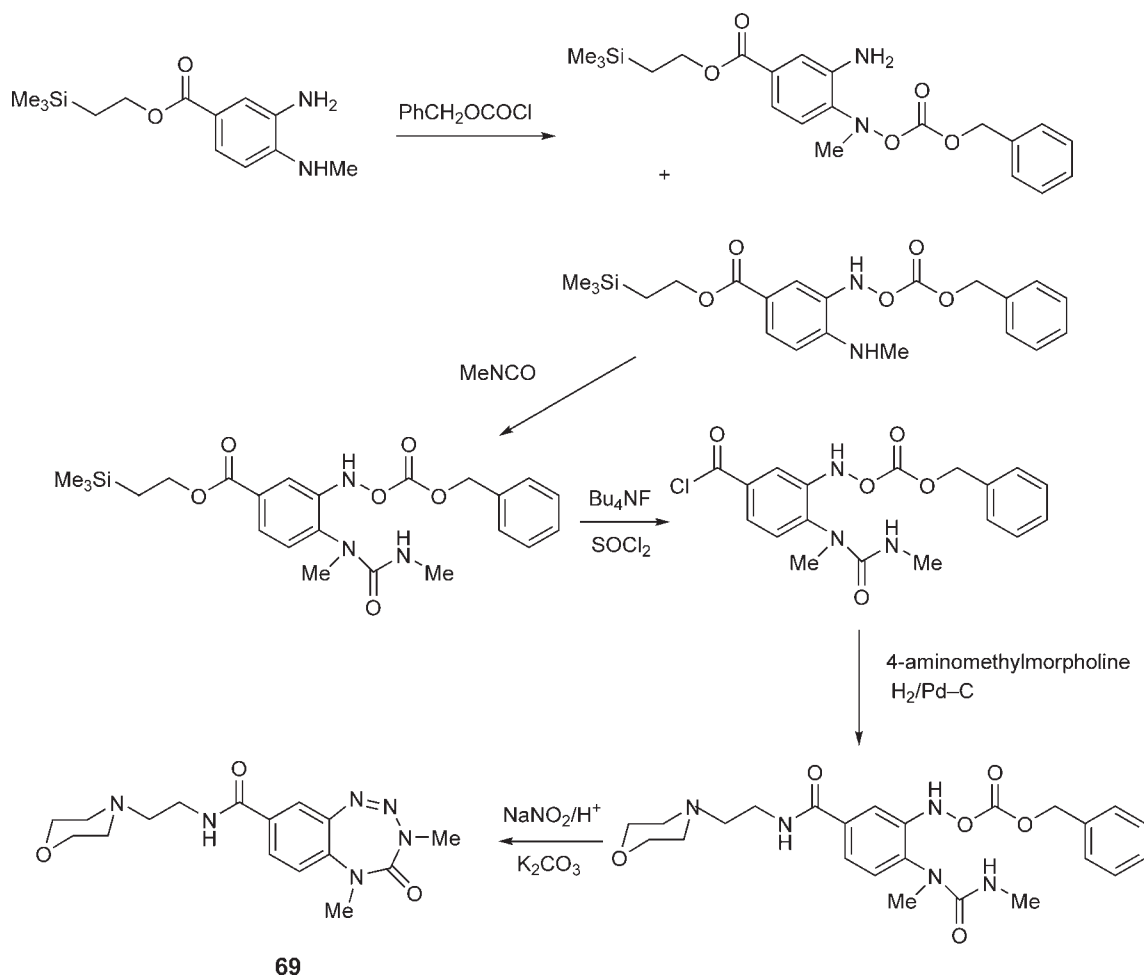
The flash vacuum pyrolysis of 1-acyltriazoles at $520^\circ C$ gave a mixture of oxazole (16%) and **68** in 33% yield to which was tentatively assigned the isoindolo[1,2-*d*][1,2,3,5]benzotetraazepine structure, based only on mass and NMR spectrometric evidence and its acidity. Benzotetrazepine **68** is believed to be formed by radical recombination of the first formed diradical from 1-acyltriazoles, and followed by addition of benzotriazole, itself formed by fragmentation of 1-acyltriazole (Equation 12) <1999AJC775>.



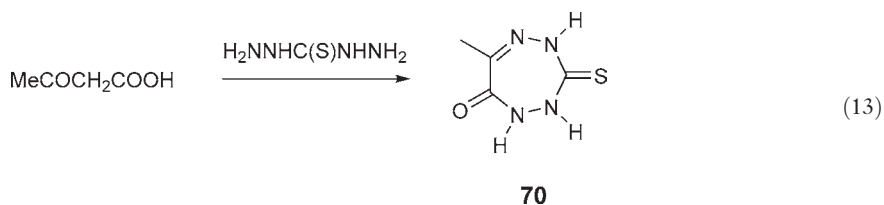
To confer water solubility to the benzotetrazepinone ring system, the synthesis of tetrazepinone **69** was undertaken (Scheme 12) <2000BML2325>. The design and synthesis of **69** were based upon previously established structural requirements for the stability of the 1,2,3,5-tetrazepin-4-one ring system. It was shown that tetrazepinone **69** was extremely water soluble.

13.17.7.8 1,2,4,5-Tetrazepines

Reaction of pyruvic acid with $H_2NNHC(S)NHNH_2$ gave the cyclic Schiff bases possessing the 1,2,4,5-tetrazepine fragment (Equation 13) <1996MI67>.



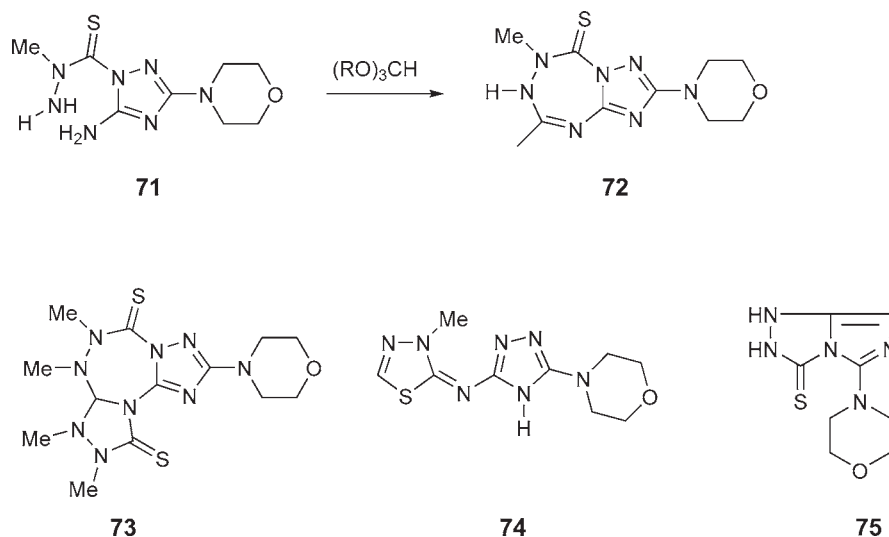
Scheme 12



13.17.7.9 1,2,4,6-Tetrazepines

Reaction of isomeric 5-amino-3-morpholino-1*H*-1,2,4-triazolylcarbothiohydrazides **71** with orthoesters yielded the expected [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione **72** in the case of triethyl orthoacetate, but in other cases rearranged products such as **73–75** were obtained (Scheme 13). Possible explanations were given for the formation of the rearranged products <1997JHC1575, 2000JHC261>.

The tetracyclic systems, triazolothienopyrimidines, tetrazolothienopyrimidines, and related tetrazepino derivatives, were obtained from 2,3,5,6,7,8-hexahydro-3-amino-2-hydrazino-1-benzothieno[2,3-*d*]pyrimidine-4(3*H*)-one <1995PS85>.

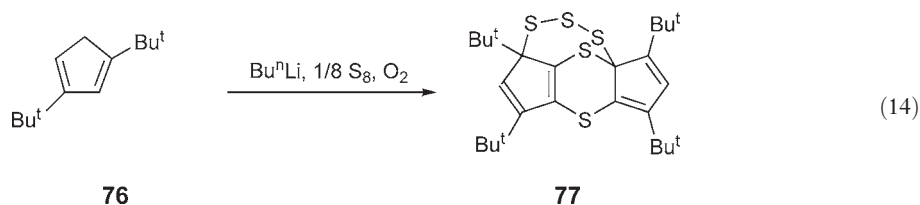


Scheme 13

13.17.7.10 Tetrathiepins

Tetrathiepanes and tetrathiepinines as well as other cyclic polysulfides were identified as volatile compounds of many natural products and extractions: volatile oil of garlic <2005MI548>, leaf oil from *Adenocalymna alliaceum* <2004MI323>, sediment of the eastern Gulf of Finland <2004MI731>, volatile compounds generated from thermal interaction of 2,4-decadienal and the flavor precursors of garlic <1994MI61>, volatile compounds generated from thermal interaction of glucose and alliin or deoxyalliin in propylene glycol <1994MI281>, volatile compounds in garlic slices <1994MI1342>, etc. (Section 13.17.10).

Reaction of di-*tert*-butylcyclopentadiene **76** with excess $\text{KO}^\text{t}\text{Bu}$ in the presence of elemental sulfur leads to hitherto unknown cyclopentadienes **77** bridged by S-atoms via one or two dithioketal functionalities. Thus, polycyclic compounds with tetrathiepin fragment as well as eight- and more membered heterocyclic rings, containing sulfur and carbon atoms, were formed (Equation 14) <2000ICA184>.



The tetrathiooxalate complex, $\text{Cp}_2\text{Ti}_2\text{C}_2\text{S}_4$, was treated with equimolar amounts of the bifunctional sulfonyl chloride, 1,2- $\text{C}_6\text{H}_4(\text{SOCl}_2)_2$, and the bicyclic tetrakisdisulfane **78** (Figure 24) was obtained <1995CB561>.

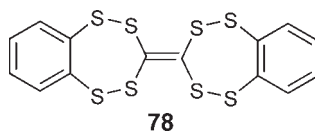
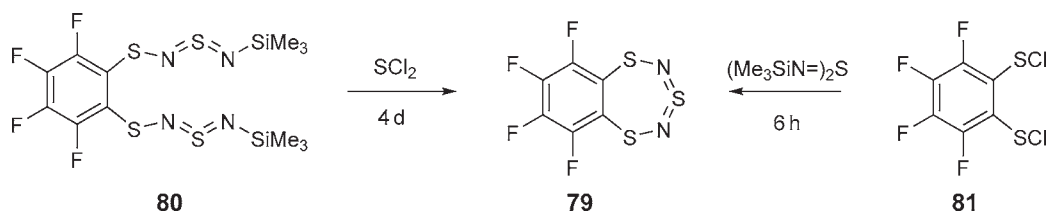


Figure 24

13.17.7.11 1,3,5,2,4- Trithiadiazepines

The synthesis of 1,3,5,2,4-trithiadiazepine **79** was realized in <1997CBR247> by two methods – from bis(trimethylsilazane) derivatives **80** and disulfonyl chloride **81** (Scheme 14).

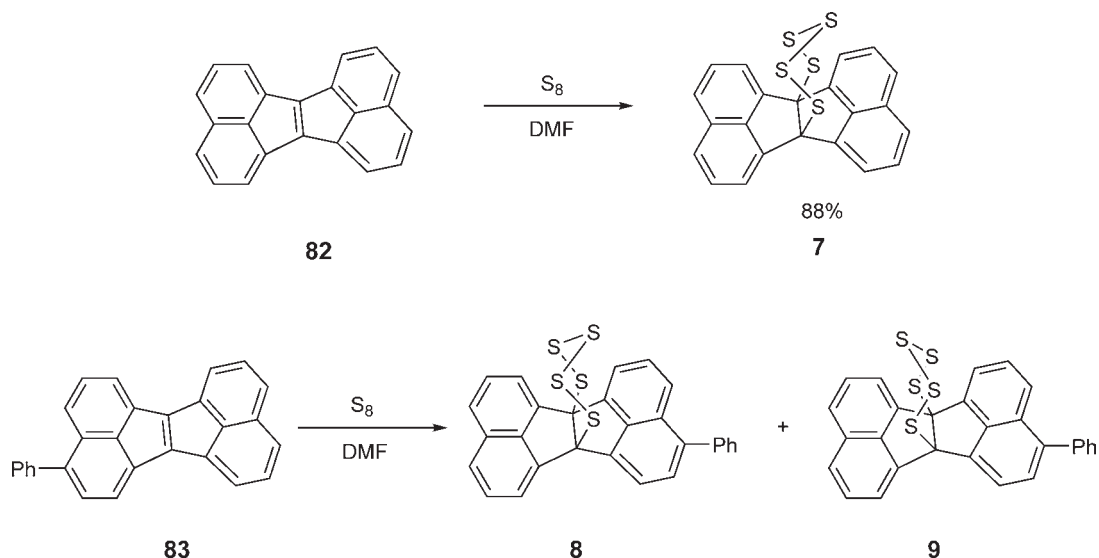


Scheme 14

13.17.7.12 1,2,3,4,5-Pentathiepanes

A process for the preparation of lenthionine (1,2,3,4,5-pentathiepane) and its analogs, which comprises cyclizing CH_2Cl_2 with polysulfides under homogeneous conditions using ethanol as solvent, has been described [\[2003CNP1413994\]](#). The polysulfides were generated by reaction of S with NaOH. For instance, treatment of NaOH with sulfur in refluxing ethanol for 30 min under nitrogen followed by reaction with CH_2Cl_2 at 20–35 °C for about 7 h gives lenthionine in >8.5% yield and 93% purity. The synthetic process of lenthionine was improved by using CH_2Br_2 instead of CH_2I_2 to reduce the cost and procedures; thus, the reaction time was shortened to 12 h and the yield was increased from 35% to 38% [\[2005MI21\]](#).

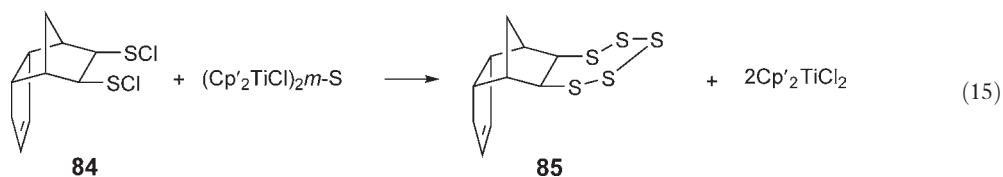
Sulfuration of acenaphtho[1,2-*a*]acenaphthylene **80** with elemental sulfur (1 molar amount as S_8) in DMF at 130 °C gave the pentathiepane **7**, with a [5.3.3]propellane structure, as the sole product, in 88% yield ([Scheme 15](#)) [\[1998TL2605, 1999EJO597\]](#). In the case of 3-phenylacenaphtho[1,2-*a*]acenaphthylenes **83**, pentathiepanes were separated as a mixture of two conformers **8** and **9** in the equilibrium ratio of 55:45. Both isomers **8** and **9** slowly isomerized into each other in solution at room temperature.



Scheme 15

Thiobenzophenone and adamantanethione react with sulfur (1:1) under catalysis by sodium thiophenoxide in acetone at room temperature furnishing 1,2,4,5-tetrathianes in high yields. With more sulfur, adamantanethione produces 1,2,3,5,6-pentathiepanebis(spiroadamantane), which interconverted with the tetrathiane, but not with the 1,2,4-trithiolane [\[1997H\(45\)507\]](#).

The generation of *exo*-4,5,6,7,8-pentathiatetracyclo[9.3.0^{2,10}.0^{3,9}]pentadec-12-ene **85** was succeeded without any $\text{C}_{10}\text{H}_{12}\text{S}_3$ as by-product using $(\text{Cp}'_2\text{TiCl})_2\text{S}_3$ as a sulfur-transfer reagent and tricyclo[5.2.1.0^{2,6}]dec-3-ene-8,9-disulfenyl chloride **84** as the organosulfenyl chloride [\[1995JOC8056\]](#) (Equation 15). Preparative thin-layer chromatography (TLC) on reversed-phase material using methanol, as an eluent, separated the reaction mixture nearly quantitatively.



13.17.7.13 1,2,3,5,6-Pentathiepanes

In the course of exploring new synthetic routes to extended tetrathiafulvalene (TTF) derivatives, lithiation of *S,S*-acetals, followed by reaction with CS_2 and PhCOCl , gave α -dithiomethylenes, which are possible versatile intermediates to extended TTFs. 1,2,3,5,6-Pentathiepanes **86** (Figure 25) were prepared from these intermediates <1995MI1>.

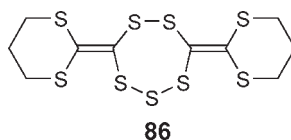


Figure 25

1,2,3,5,6-Pentathiepanebis(spiroadamantane) **87** (Figure 26) was produced with excess of sulfur in the reaction of thiobenzophenone and adamantanethione under catalysis by sodium thiophenoxide, which interconverted with the tetrathiane, but not with the 1,2,4-trithiolane <1997H(45)507>.

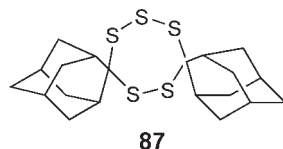
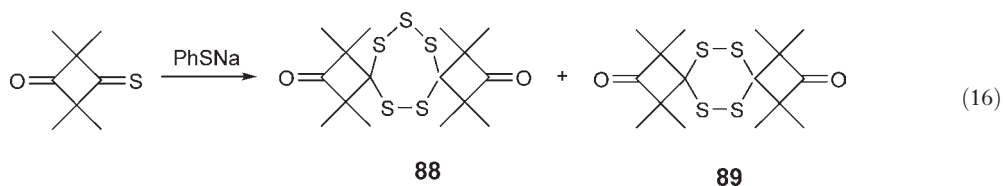


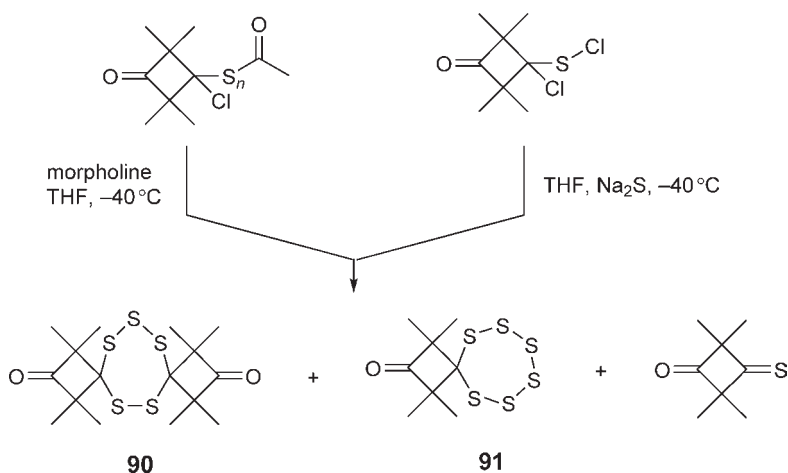
Figure 26

The same type of compounds was obtained by treatment of 2,2,4,4-tetramethyl-3-thioxocyclobutanone with elemental S and a catalytic amount of PhSNa in acetone at room temperature. The bis-spiropentathiepane **88** and bis-spirotetrathiane **89** were separated (Equation 16). The initial attack by the Ph oligosulfide anion takes place at the C-atom of the thiocarbonyl group <1997LA1517>.



'Unzipping' reactions of 2,2,4,4-tetramethyl-3-thioxocyclobutanones with morpholine in tetrahydrofuran (THF) at -40°C led to the formation of mixture of two sulfur-rich heterocycles identified as the pentathiepane **90** and the hexathiepane **91**. A mixture of analogous products was obtained when 2,2,4,4-tetramethyl-3-sulfonylchloride-cyclobutanone

was treated with sodium sulfide in anhydrous THF at -40°C (Scheme 16). The formation of pentathiepane and hexathiepane was believed to occur via an intermediate dithiirane and/or the isomeric thiosulfine <1997LA1517, 1998SR1, 2002JOC5690>.



Scheme 16

The simple 1,2,3,5,6-pentathiepane **92** (Figure 27) was obtained by refluxing CH_2I_2 and sodium tetrathiocarbonate for 10 h. After optimization, the results showed that the optimum solvent was CCl_4 , and the method was simple. The reaction time could be reduced from 48 to 12 h <2004MI117>.

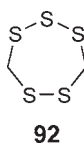


Figure 27

13.17.7.14 1,2,3,4,5-Pentathiepines

Pentathiepines have attracted considerable attention because of their remarkable stability and their potent biological activity. Pentasulfides occur in nature in a variety of plants and animals. Since it was first isolated from marine organisms in 1991, the cyclic pentasulfide varacin **95** has been the focus of great synthetic and structural interest. As well as possessing a highly unusual pentathiepin ring, varacin exhibits potent antifungal and antitumor activity and cytotoxic properties. Pentasulfides are also used as antifouling agents and as components of lithium batteries, etc. (Section 13.17.10). Pentasulfides can be synthesized from the reaction of mercaptans or mercaptide salts with sulfur halides, by nucleophilic displacement on sulfur, or the reaction of methoxycarbonyl trisulfanes with hydrogen sulfide (see reviews, Section 13.17.1).

13.17.7.14.1 Isolation from natural objects

Lissoclinotoxin B **94**, a pentathiepin derivative, was isolated from the tunicate *Lissoclinum perforatum*. Structure elucidation of this compound is described based on spectroscopic data, together with a revised structure for lissoclinotoxin A **93** (Figure 28) <1994T5323, 1994PAC2223>, which was isolated along with other alkaloids from *Lissoclinum* sp. collected from the Great Barrier Reef, Australia <1994JOC6600>.

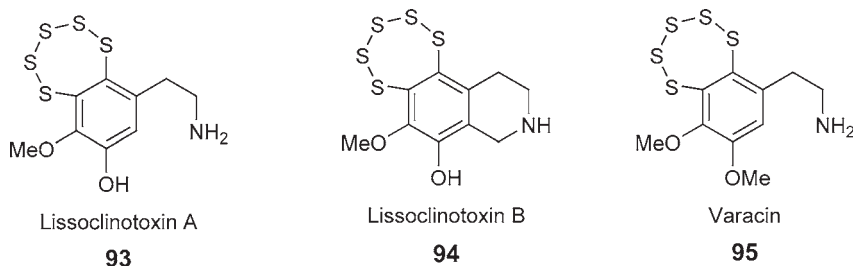
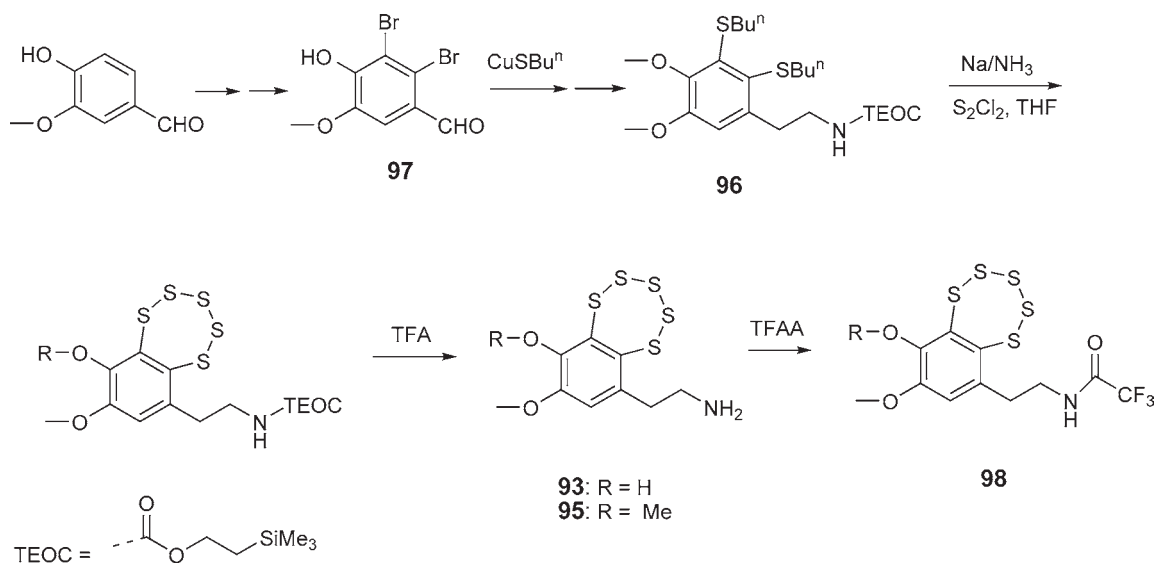


Figure 28

The ascidian *Lissoclinum japonicum* from Palau contained the antimicrobial and antifungal metabolites *N,N*-dimethyl-5-(methylthio)varacin and 3,4-dimethoxy-6-(2'-*N,N*-dimethylaminoethyl)-5-(methylthio)benzotrithiane, both of which were isolated as the trifluoroacetate salts [\[1994T12785\]](#). They selectively inhibit protein kinase. Also, varacin and three new antimicrobial marine polysulfides, varacins A–C, were isolated from the Far Eastern ascidian *Polycitor* sp. [\[1995JNP254\]](#), extracted from the New Zealand ascidian *Lissoclinum notti* [\[2002T9779\]](#).

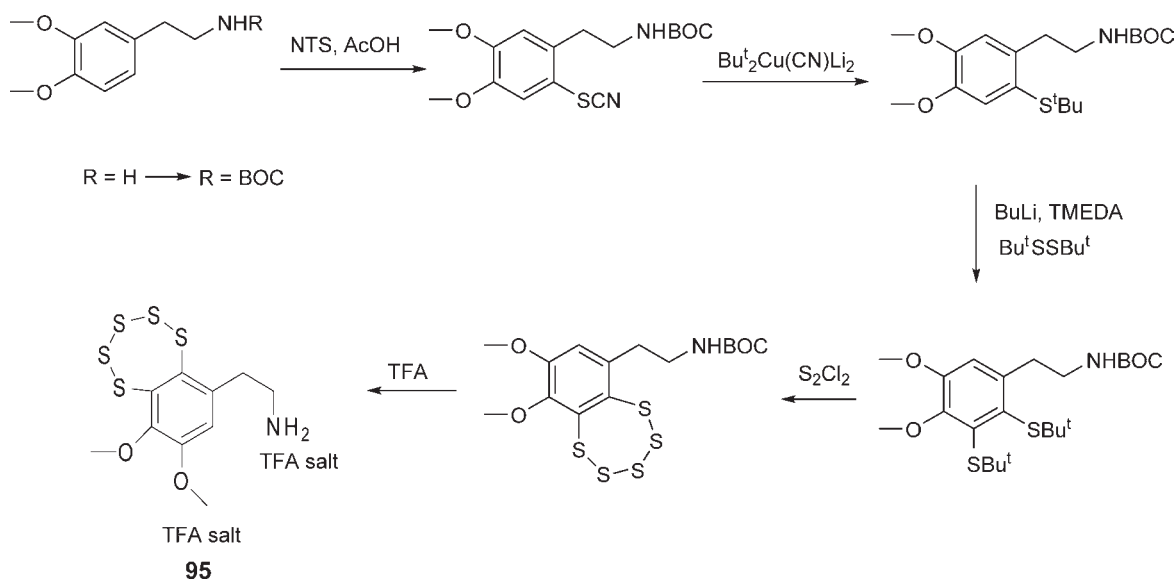
13.17.7.14.2 Synthesis of 1,2,3,4,5-pentathiepin

A few methods were proposed for synthesizing benzopentathiepin varacin **95** and isolissoclinotoxin A **93** [\[1994JOC5955, 1994MI101, 1994MI242\]](#). In 1994, the unique pentathiepin-containing isolissoclinotoxin A **93** and varacin **95** have each been synthesized in eight steps from vanillin (**Scheme 17**). Formation of the pentathiepin ring was accomplished by treatment of the dithiolate anion, generated from the Na/NH₃ reduction of bisbutyl sulfide intermediate **96** with 2 equiv of S₂Cl₂. Placement of the sulfur atoms on the aromatic ring was accomplished by treatment of 5,6-dibromovanillin **97** with cuprous *n*-butylmercaptide in pyridine/quinoline at 160 °C. The structure of the penultimate intermediate, TEOC-protected varacin **98**, was confirmed by X-ray diffraction analysis.



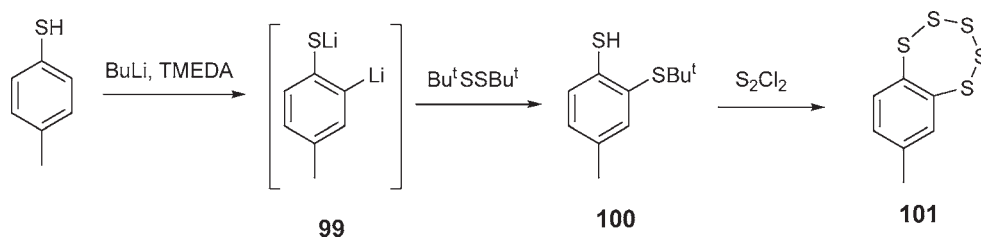
Scheme 17

A new route to the synthesis of the benzopentathiepin varacin **95** in six steps from 3,4-dimethoxyphenethylamine with an overall yield of 18% was described in 1995 (**Scheme 18**). The synthetic sequence includes novel thiocyanation and ligand-exchange steps, as well as an important modification in the pentathiepin construction step [\[1995JA7261\]](#).



Scheme 18

In the same work [<1995JA7261>](#), an approach which relied upon the introduction of only a single sulfur substituent (**Scheme 19**) and a final step using S_2Cl_2 for the construction of the pentathiepin ring was realized. Regioselective double lithiation of *p*-toluenethiol afforded intermediate **99**, which was treated with di-*tert*-butyl disulfide to form **100**. Subsequent thiation of **100** with S_2Cl_2 gave the pentathiepin **101** in 86% yield after chromatography [<1995JA7261>](#).



Scheme 19

Efficient synthesis of 6,7-dimethoxybenzopentathiepin **102** and 6-(2-aminoethyl)benzopentathiepin **103** (**Figure 29**), which are sectional structures of varacin, were proposed from 1,2-dimethoxybenzene and 1,2-benzenedithiol, respectively [<1995H\(41\)893>](#).

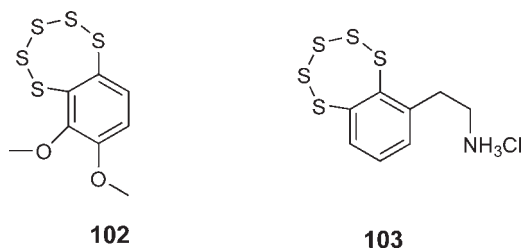
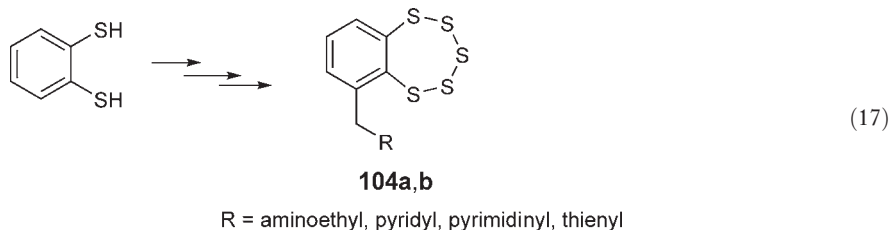
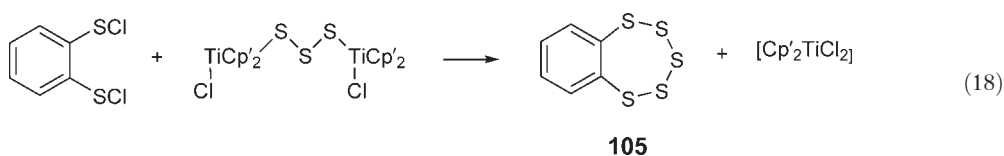


Figure 29

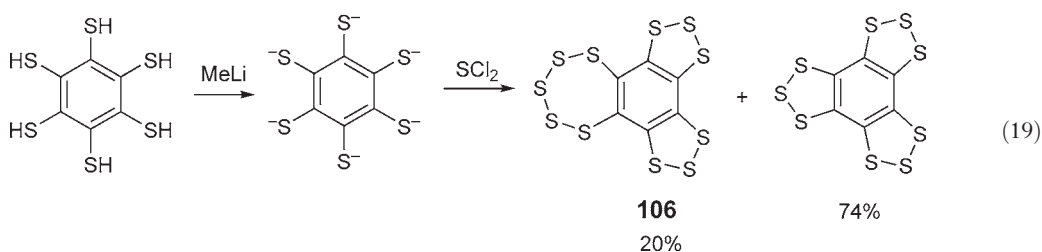
Four benzopentathiepin **104a** and **104b** having a functional group, such as aminoethyl, pyridyl, pyrimidinyl, and thienyl groups, on the benzene ring were synthesized from 3-substituted 1,2-benzenedithiol by sulfurization with elemental sulfur in the presence of ammonia (Equation 17) <2001H(55)145>. These benzopentathiepin were characterized in the light of interaction of the pentathiepin ring with the functional group.



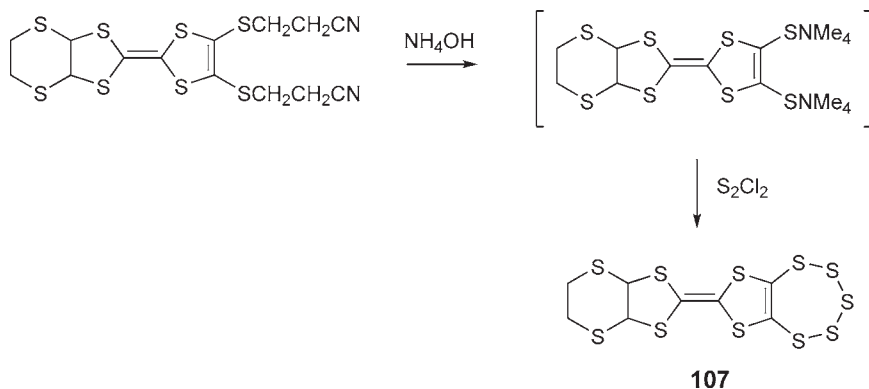
Benzenedisulphenyl chloride, prepared by chlorination of benzenedithiol, reacted with the titanocene complex $(\text{Cp}'_2\text{TiCl})_2\text{S}_3$ at low temperature in carbon disulfide to give the known 1,2,3,4,5-benzopentathiepin **105** in 73% (Equation 18) <2000EJI921>.



Benzobis(trithiolo)pentathiepin **106** was isolated as a by-product from reaction of the thiolates with sulfur dichloride by extraction with carbon disulfide and removal of the solvent (Equation 19) <1995T2533>.

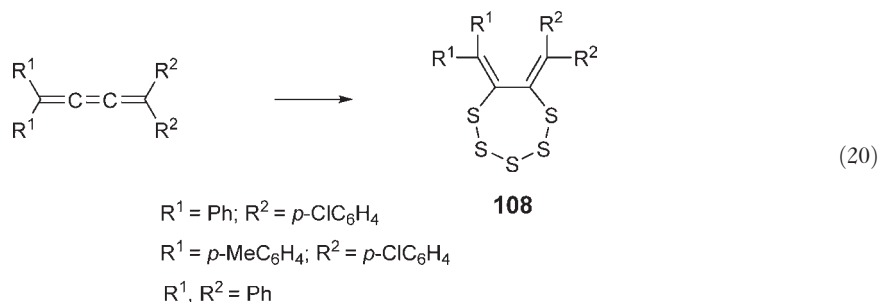


The synthesis, structure, and electrochemical properties of 4,5-ethylenedithio-4,5-pentathiotetrathiofulvalene **107** as a donor were reported <1999AM758>. The pentathio-substituted unsymmetrical donor **107** was synthesized as shown in Scheme 20. 4,5-Bis(2'-cyanoethylthio)-4,5-ethylenedithiotetrathiafulvalene was hydrolyzed with a 25 wt.% MeOH solution of tetramethylammonium hydroxide in THF to generate the corresponding dithiolate, which was treated with sulfur monochloride in dry DMF at -50°C . After purification of the resultant precipitates, black plate-like crystals of **107** were obtained in 27% yield.

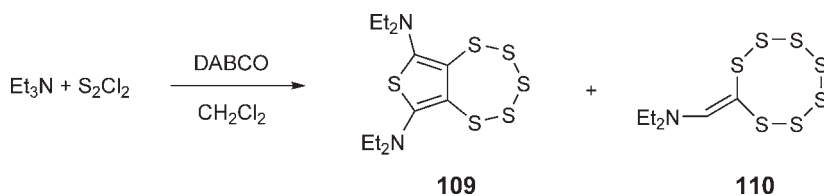


Scheme 20

Electrosynthesis of organic polysulfides from cumulenes was studied using a sacrificial sulfur–graphite electrode <1997MI2399, 1999MI2899>. 1,1-Di-*p*-chlorophenyl-4,4-diphenylbuta-1,2,3-triene, 1,1-di-*p*-chlorophenyl-4,4-di-*p*-methylphenylbuta-1,2,3-triene, 1,1,4,4-tetraphenylbuta-1,2,3-triene, and 1,1-di-*p*-methoxyphenyl-4,4-diphenylbuta-1,2,3-triene were used as cumulenes. Seven-membered ring compounds with five S atoms, such as pentathiepin **108**, were produced as major products <1997MI2399> (Equation 20). In the case of trifluoromethyl-substituted cumulene, these reactions led to dimeric compounds with a 1,2,5,6-tetrathiocin skeleton as the major product, accompanied by seven- and eight-membered ring compounds with five and six sulfur atoms such as pentathiepin and hexathiocins in minor amounts <1999MI2899>.



Pentathiepin **109** as well as heptathiocane **110** were obtained by a remarkable cascade reaction of a pre-equilibrated solution of S_2Cl_2 and DABCO in chloroform with triethylamine (Scheme 21) <2003OL1939>. Thus, equimolar amounts of S_2Cl_2 and DABCO were stirred in chloroform at 0°C for 48 h, since this reaction is much slower than that of S_2Cl_2 with triethylamine. The S_2Cl_2 –DABCO solution thus formed retained its activity for a few days at 0°C . Addition of triethylamine after 48 h at 0°C , followed by refluxing for 2 h, gave two entirely new and unexpected products, **109** and **110**, different from all those produced when the reagents were not premixed. The two products were not interconverted under the reaction conditions and were presumably formed in simultaneous, competing reactions. The conversions of Et_3N into pentathiepin **109** and heptathiocane **110** both involved an oxidative reaction of one ethyl group together with several other transformations. Thus, two triethylamines had combined with all the hydrogens of two ethyl groups being replaced with six sulfur atoms, leaving four identical ethyl groups. The same reactions were observed with other tertiary *N*-ethylamines but in lower yields. Diethyl *n*-propylamine, ethyldiisopropylamine, benzyldiethylamine, dibenzylethylamine, and *N*-ethylpiperidine all gave corresponding thienopentathiepin (1–28%) analogous to **109**.



Scheme 21

Direct synthesis of fused 1,2,3,4,5-pentathiepin by treatment of nucleophilic heterocycles like pyrroles, thiophenes, pyrrolidines, indoles, and their tetrahydro derivatives, with S_2Cl_2 and DABCO in CHCl_3 at room temperature, provides a simple one-pot synthesis of fused mono- and bispentathiepin (Figure 30) <2002CC1204, 2004MC91>. *N*-Methylpyrrole and its 2-chloro and 2,5-dichloro derivatives and *N*-methylpyrrolidine all give the same dichloropentathiepin **111**. *N*-Et, *iso*-Pr, and *tert*-butylpyrrolidine behave similarly **114** and **115**; the isopropylpyrrolidine also gives the bispentathiepin **112**, which undergoes an intriguing rearrangement to the symmetrical monopentathiepin. *N*-methyl- and *N*-ethylindole gave either 2,3-dichloro derivatives or the pentathiepinindoles, depending upon the reaction conditions. Thiophene and tetrahydrothiophene give the pentathiepin **113**. The extensive cascade reaction profile was changed and the regioselectivity enhanced when the S_2Cl_2 and DABCO were premixed and equilibrated before the heterocycle was added.

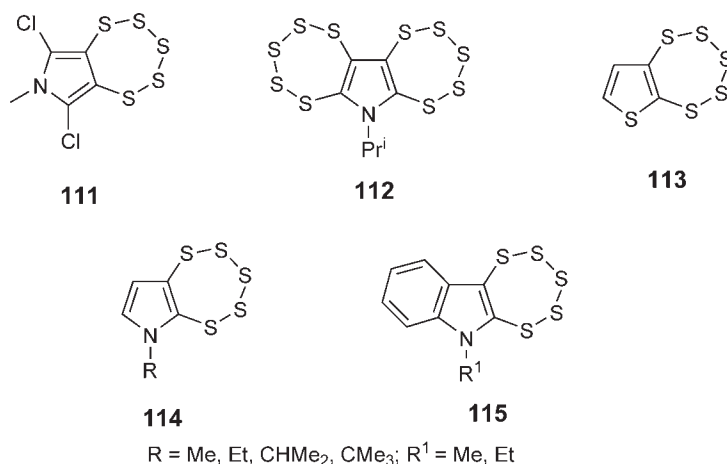
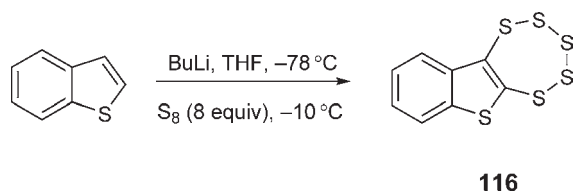


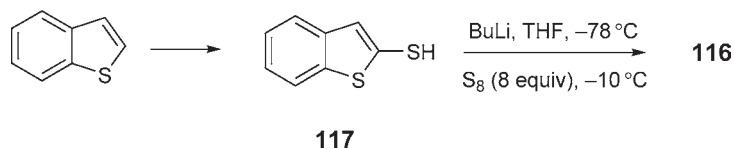
Figure 30

The reaction of 2-lithiated benzo[*b*]thiophene with 8 equiv of elemental sulfur gave pentathiepinino[6,7-*b*]-benzo[*d*]thiophene **116** (Scheme 22) <2002JOC6220>.



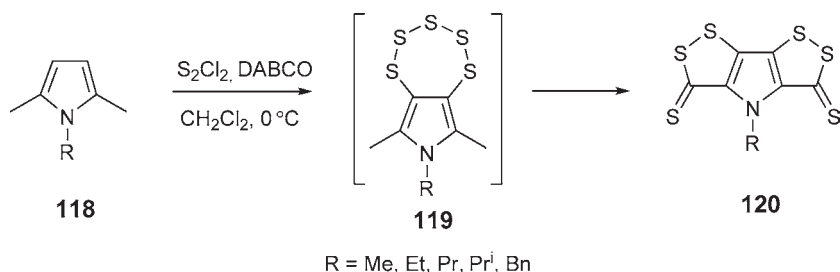
Scheme 22

It was speculated that the process leading to the formation of the pentathiepin ring involved initial formation of benzo[*b*]thiophene-2-thiol **117**, which then reacted further in its thiolate anion form with the sulfur present in excess, and the growing sulfur chain so obtained finally attacked the neighboring 3-position of the thiophene ring, thus producing the pentathiepin **116** (Scheme 23) <2002JOC6220>.



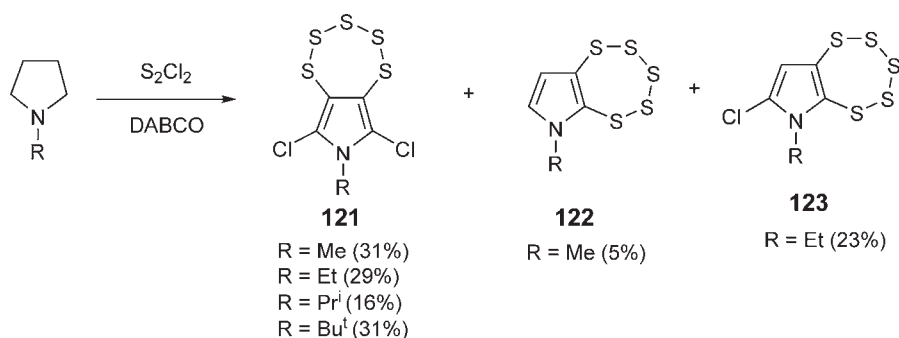
Scheme 23

Treatment of N-substituted 2,5-dimethylpyrroles **118** (R = Me, Et, Pr, Prⁱ, Bn) with an equilibrated mixture of S₂Cl₂ and DABCO in CHCl₃ at 0 °C gave pentathiepinopyrroles **119** in moderate yields; further reaction of **119** with the same mixture at room temperature led, in an extensive reaction cascade, to bis(dithiolo)pyrroles **120** in high yield; **118** can be converted into **120** in a one-pot operation under unusually mild conditions (Scheme 24) <2005OL5725>.



Scheme 24

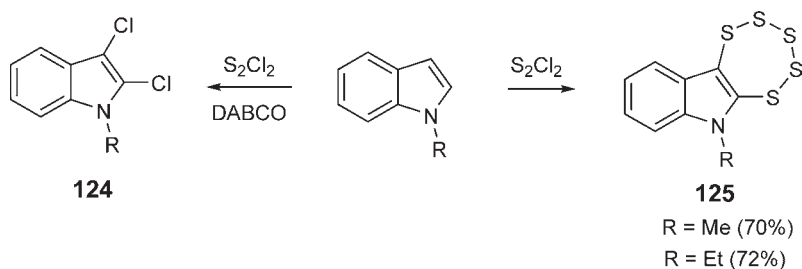
Pentathiepinopyrroles were also described in <2005OBC3496>. *N*-Methyl-, *N*-ethyl-, *N*-isopropyl- and *N*-*t*-butylpyrrolidines all gave the corresponding *N*-alkyl dichloropentathiepinopyrrole **121** as the main product in low to moderate yields (16–31%) (Scheme 25). Additionally, *N*-methylpyrrolidine gave a small amount (5%) of unchlorinated **122** with the pentathiepin ring fused across the 2,3-pyrrole bond and *N*-ethylpyrrolidine gave rather more (23%) of a similarly fused product **123** but now chlorinated in the free α -position of pyrrole (Scheme 25).



Scheme 25

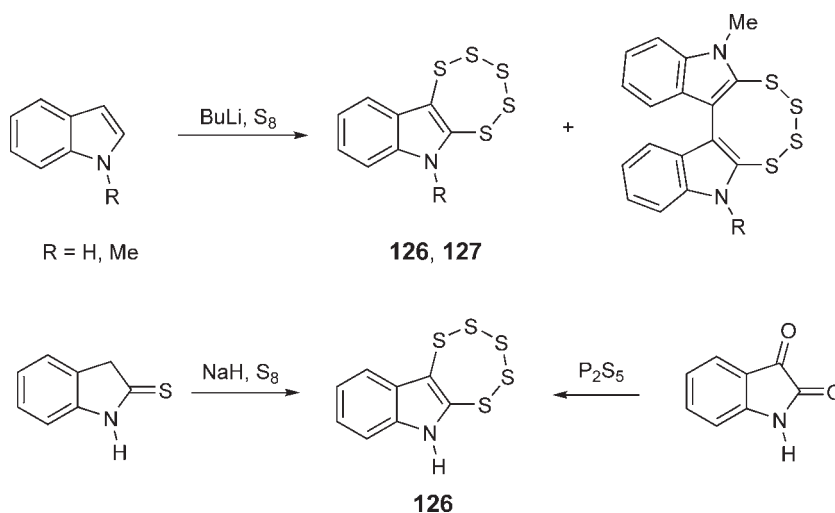
Only a minor quantity of 6,8-diphenyl-1,2,3,4,5-pentathiepin[6,7-*c*]pyrrole was detected in the reaction of acetophenone oximes with S₂Cl₂ in the presence of 2-aminophenol <1997BSB605>.

Structurally similar *N*-alkylindoles, with only the 2,3-indole bond available for pentathiepin fusion, were also treated with S₂Cl₂–DABCO in the same way. However the major products from the *N*-methyl and *N*-ethyl compounds were the 2,3-dichloroindoles **124** (75% and 78%; Scheme 26); some unchlorinated pentathiepin **125** was formed in the case of *N*-ethylindole but in very low yield (8%). But with a deficiency of S₂Cl₂ (0.8 equiv) and in the absence of a base the only products were unchlorinated pentathiepin **125** in 70% and 72% yields. The reactions of Scheme 26 underline the influential role of the base DABCO, possibly resulting from complexes formed between it and S₂Cl₂. No characterizable products were obtained when *N*-unsubstituted indole, as well as *N*-unsubstituted pyrrole and pyrrolidine, were treated similarly with S₂Cl₂–DABCO <2005OBC3496>).



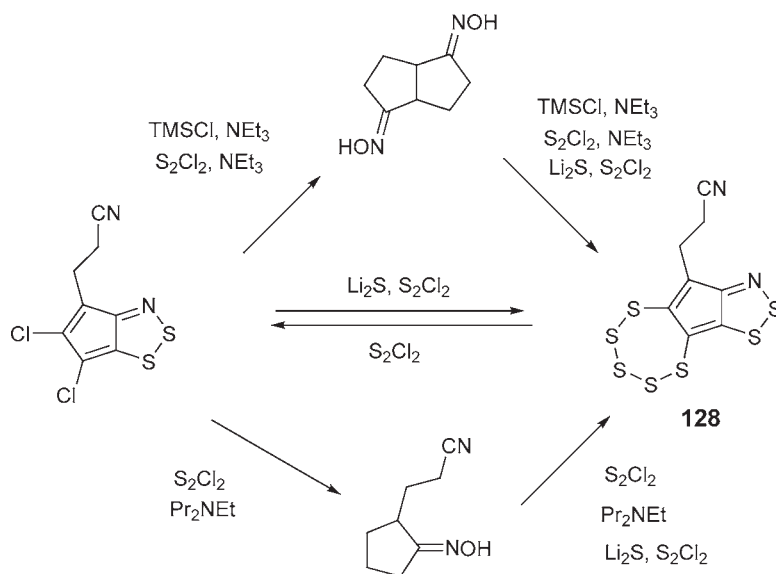
Scheme 26

Another way was used to synthesize pentathiepineindoles [<2001T7185>](#). Thus, the reactions of 2-lithiated indole and 1-methylindole with elemental sulfur were studied, leading, for example, to a rational approach to the corresponding pentathiepine[6,7-*b*]indoles **126** and **127**. Treatment of the anions of the corresponding indoline-2-thiones with sulfur also gave both pentathiepineindoles (**Scheme 27**). Pentathiepine[6,7-*b*]indole **126** can be isolated from reaction of P_4S_{10} with isatin in pyridine (**Scheme 27**) [<1994TL5279>](#).



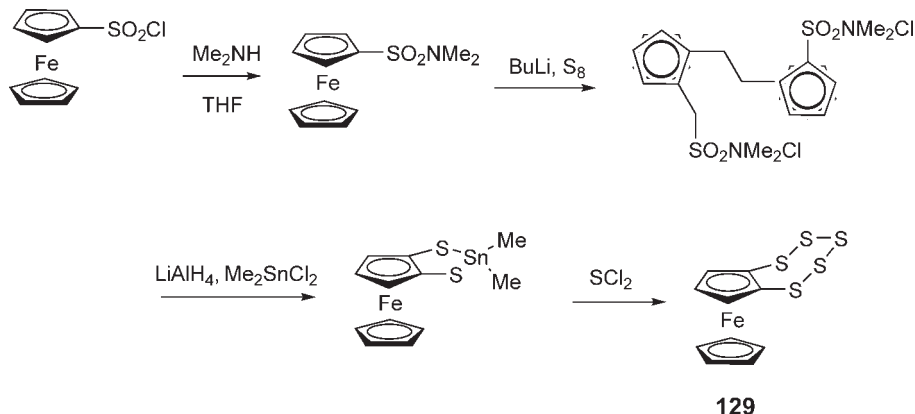
Scheme 27

The first example of pentathiepine rings fused with cyclopentadienyl ring and having a functionalized aliphatic chain was obtained by reaction of oxime [<2005JOC9314>](#) or dioxime [<2001CC403>](#) with S_2Cl_2 in the presence of Hünig's base (**Scheme 28**). An extensive domino sequence, including a vinylogous sulfur-assisted Beckmann fragmentation, is involved in the one-pot conversion of an oxime or dioxime by S_2Cl_2 into a cyanoethyl-1,2,3-dithiazole and a tricyclic pentathiepine; the yield of pentathiepine **128** was increased by added lithium sulfide, and both cyanoethyl-1,2,3-dithiazole and pentathiepine are formed in higher yields from 2-(cyanoethyl)cyclopentanone oxime; reaction mechanisms are proposed for these cascade reactions [<2001CC403>](#).



Scheme 28

In 2002, the first synthesis and structure of a stable pentathiepin fused to a single cyclopentadienyl ring of ferrocene was performed by the treatment of the corresponding dithiastannole, as a synthetic equivalent of unstable ferrocene-1,2-dithiol with sulfur dichloride [<2002TL5825>](#). Pentathiepin **129** was synthesized as follows ([Scheme 29](#)).



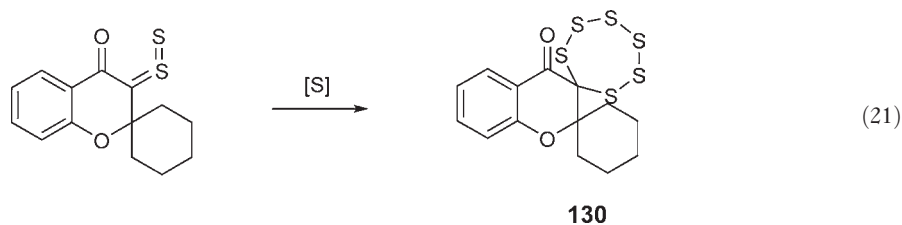
Scheme 29

Later, the ferrocenodithiastannole, which has inherent low stability in organic solvents at ambient temperature, was replaced by ferrocenodithiatitanole and transformations into ferroceno[1,2-*f*][1,2,3,4,5]pentathiepin were successfully conducted with some electrophiles containing sulfur atom [<2005BCJ2026>](#).

13.17.7.15 Hexathiepanes

More often, hexathiepanes are obtained together with other cyclic polysulfones. Thus, hexathiepane was obtained together with lenthionine by the cyclization of CH_2Cl_2 with polysulfides under homogeneous conditions in EtOH [<2003CNP1413994, 2005MI21>](#) (Section 13.17.7.12). 2,2,4,4-Tetramethylcyclobutanone–hexathiepane was obtained together with pentathiepane under reaction of 2,2,4,4-tetramethylcyclobutanone with morpholine in THF at -40°C (Section 13.17.7.13) [<2002JOC5690>](#). The halogenation of bis(disulfides) led to a mixture of hexathioananes, hexathiepanes, and tetrathiolanes, which was, however, not obtained in pure form [<2000EJO2583>](#).

In the case of chroman-4-one-derived thiosulfines, extensive sulfur scrambling takes place with formation of the dispiro[cyclopentane-1,2'-chroman-3',7''-[1,2,3,4,5,6]hexathiepan]-4'-one **130** (Equation 21) [<1998JOC9840>](#).



The treatment of hydrazones derived from 1-adamantyl(phenyl)ketone, pivalophenone, and benzophenone with S_2Cl_2 gave hexathiepanes **131** ([Figure 31](#)) along with other products as tetra- and pentathianes ([1997H255](#)).

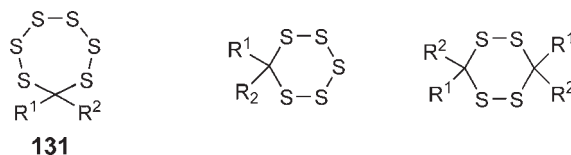
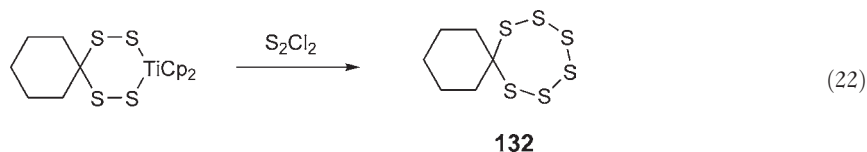


Figure 31

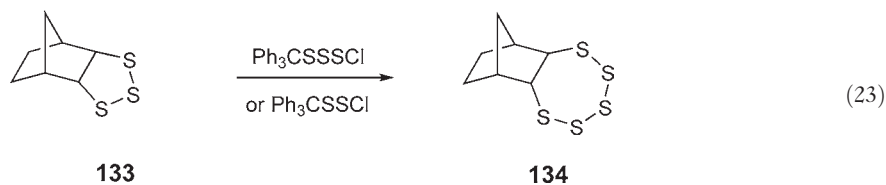
The insertion of the titanocene fragment Cp_2Ti , generated *in situ* from $\text{Cp}_2\text{Ti}(\text{CO})_2$, into S–S bonds of heterocycles provided a route to larger, more S-rich heterocycles under mild conditions. Initially formed titanocene thiolato complexes may be relatively unstable in solution and therefore sometimes difficult to obtain in high purity. Their rapid reaction with sulfonyl chlorides and certain C–Cl compounds, such as COCl_2 and CSCl_2 , provided cyclic di- and polysulfanes inaccessible by other routes. Thus, by reaction of $(\text{Cp})_2\text{Ti}(\mu\text{-S}_2)_2\text{C}_6\text{H}_{10}$ with S_2Cl_2 , 7,8,9,10,11,12-hexathiaspiro[5.6]dodecane **132** is prepared (yield 51%) and characterized by UV, IR, Raman, mass, and NMR spectra (Equation 22). The seven-membered CS_6 ring undergoes pseudorotation in solution <1996ZFA1594, 1997CBR757>.



13.17.8 Ring Synthesis by Transformation of Another Ring

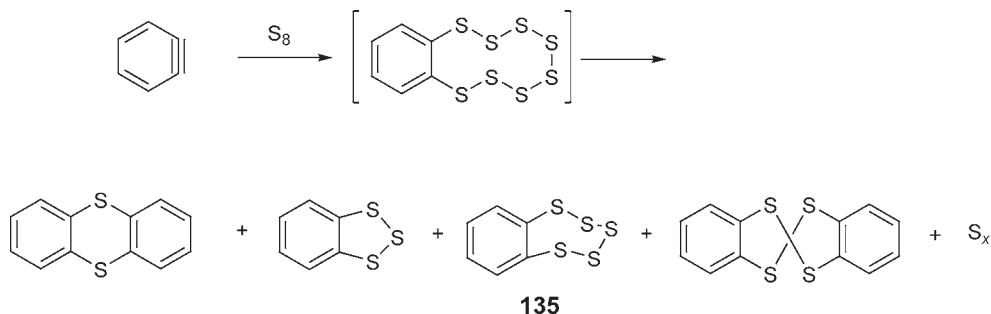
13.17.8.1 1,2,3,4,5-Pentathiepanes

In the reaction of cyclic trisulfide **133** with chloro(triphenylmethyl)trisulfide or triphenylthiosulfenyl chloride, only two of the three sulfur atoms were ultimately delivered resulting in the pentasulfide **134** in 30% yield. This apparently reflected the overall stability of pentasulfide versus the hexasulfide (Equation 23) <2000TL7809, 2000TL7169>.



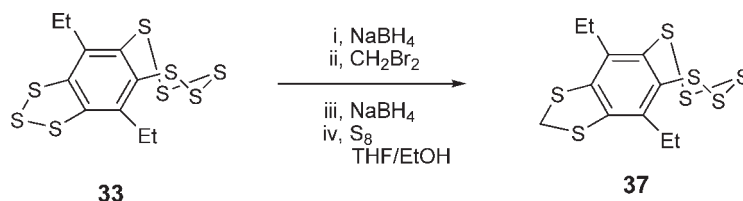
13.17.8.2 1,2,3,4,5-Pentathiepinines

Benzyne was shown to add elemental sulfur and gave rise to a series of polysulfane compounds including benzo-pentathiepine. Odd-membered $o\text{-C}_6\text{H}_4\text{S}_x$ rings ($x = 1\text{--}8$, except $x = 1$), which suffer from ring strain, have enhanced stability compared to even-membered rings. The formation of benzothiepine **135** is a result of decomposition of an initial $o\text{-C}_6\text{H}_4\text{S}_x$ intermediate (Scheme 30) <2004JOC5483>.



Scheme 30

Preparation of 6,11-diethyl[1,4]dithiino[5,6-*b*]benzopentathiepin **37** by reduction of 6,10-diethyl[1,2,3]-trithiolo[4,5-*b*]benzopentathiepin **33** with NaBH_4 in THF and EtOH was described <2002BCJ817, 2003HAC88>. This benzopentathiepin was used for asymmetric oxidation (see Section 13.17.3.1.6) (Scheme 31).



Scheme 31

13.17.9 Synthesis of Particular Classes of Compounds and Critical Comparison of Various Routes Available

During this period the traditional approach to construct seven-membered rings was developed. Most of the publications were dedicated to pentathiepines. But several new types of compounds were described, for example, diazepinyl radical **20** and stable pentathiepines fused to a single cyclopentadienyl ring of ferrocene **129**. Synthesis and establishing the right structure of important biological compounds such as lenthionine, varacine, lissoclinotoxin A, lissoclinotoxin B, etc. Moreover, during this period, numerous publications were presented and dedicated to the application of these compounds with seven-membered rings, especially for pentathiepin derivatives.

13.17.10 Important Compounds and Applications

Seven-membered rings with four and more heteroatoms attract attention because of their biological activity. An important class of compounds is that of the seven-membered cyclic polysulfides with five sulfur atoms, which are well known as lenthionine and varacin.

13.17.10.1 Dioxadithiepines

Dioxadithiepines are used for electrolyte solution in secondary batteries. <2004JPP2004281325>.

13.17.10.2 Tetrazepines and Trithiadiazepines

The mechanism of action of 3,5-dimethylpyrido-1,2,3,5-tetrazepin-4-one (PYRZ) and tetrazepinone 8-nitro-3-methylbenzo-1,2,3,5-tetrazepin-4(3*H*)-one (NIME), structurally related to temozolomide, were studied in the human ovarian tumor cell line OVCAR-3 <1997MI467, 1999BP753>. Protein *O*-6-methylguanine-DNA Me-transferase (MGMT) inactivation by tetrazepinones was studied <1999MI484>. Cytotoxicity, reduction of macromolecular synthesis, and cell cycle perturbations by the 3-(2-chloroethyl)-tetrazepinones PYRCL and QUINCL (TETs) were compared with those produced by the 3-(2-chloroethyl)tetrazinone mitozolomide (MIT) in the human ovarian tumor cell line OVCAR-3 <1988MI59>. Tetrazepinone **69** is extremely water soluble and was 10-fold more potent than an imidazo-1,2,3,5-tetrazin-4-one counterpart, against the human MCF-7 breast cancer cell line <2000BML2325>. Tetrazepinones are equally cytotoxic to Mer+ and Mer- human tumor cell lines <1999MI484>.

The trithiadiazepines **136** (Figure 32) are microbicides useful against *Aspergillus niger*, *Pseudomonas aeruginosa*, *Escherichia coli*, etc. <1994GBP2278278>.

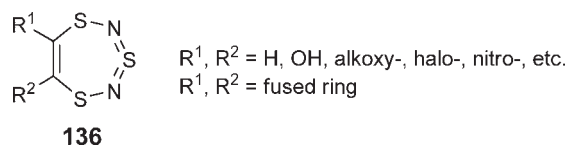


Figure 32

13.17.10.3 Pentathiepanes and pentathiepinines

Lenthionine (1,2,3,5,6-pentathiepane) was extracted from the Shiitake mushroom with an organic solvent or a mixture of an organic solvent with water <2005WO2005034974>. The tetrathiepanes were identified as volatile compounds in Shiitake mushrooms using modern analytical techniques including gas chromatography (GC) olfactometry <B-2004MI284>; they were extracted by solid-phase microextraction (SPME) and then analyzed by GC and GC-MS <2000MI166>. Sulfuric-flavored compounds lenthionine and its analogs were extracted from Shiitake (*Lentinus edodes*) and their inhibitory activity against platelet aggregation was investigated <2004MI177>. In <1997MI154> the authors demonstrated that lenthionine was produced during the thawing of frozen Shiitake. Based on NBS library data, lenthionine, trithiolan, and other aroma compounds were successfully identified in the biomass and in the fruiting body as well <1997MI271>. The sulfur compounds, such as 1,2,3,5,6-pentathiepane as well as other compounds of heavy metals, sulfur, hydrogen sulfide, and thiosulfuric acid *S*-(2-amino ethyl ester), were detected by AAS in sediment of Lake Van <2005MI125>.

The 1,2,3,5,6-pentathiepane was used for synthesis of metal complexes with platinum(0). The reaction of the 1,2,3,5,6-pentathiepane with a fourfold excess of $(\text{Ph}_3\text{P})_2\text{Pt}(\mu^2\text{-C}_2\text{H}_4)$ affords a 1:1:1 mixture of $[\text{Pt}_2(\text{PPh}_3)_4(\mu\text{-S})_2]$, the Pt(0) complex $(\text{Ph}_3\text{P})_2\text{Pt}(\mu^2\text{-thioadamantanone})$, and the bis-thiolato Pt(II) complex $[\text{cyclic}](\text{Ph}_3\text{P})_2\text{Pt}(\text{SCPh}_2\text{S})$ <2000ZNB453>. 1,2,3,5,6-Pentathiepane (lenthionine) and other sulfur compounds have been reported as key compounds that have been studied sufficiently in connection with smell <2004JWS358>. The 4,7-diethyl-1,2,3,5,6-pentathiepane was used as a flavoring agent or aromatizer <2006WO2006027352>.

Antimicrobial activity of lissoclinotoxin A **93** and lissoclinotoxin B **94** (pentathiepine derivatives) was reported <1994T5323>. The 7-methylbenzopentathiepin **101**, a simple analog of the benzopentathiepin antitumor antibiotic varacin, was shown to be a potent thiol-dependent DNA-cleaving agent <1998BML535>. Biological experiments previously suggested that DNA cleavage might play a role in the cytotoxicity of varacin; however, this is the first direct evidence that benzopentathiepins can cause DNA strand breaks under physiological relevant conditions <1998BML535>.

Bioassay-guided isolation from the ascidian *Lissoclinum* sp. (cf. *L. badium* Monniot and Monniot, 1996) collected at Manado, Indonesia, yielded a novel trimeric alkaloid, lissoclibadin, mistakenly named tribenzotetrathiepin, together with two known monomeric polysulfides, *N,N*-dimethyl-5-(methylthio)- and 3,4-dimethoxy-6-(2'-*N,N*-dimethylaminoethyl)-5-(methylthio)benzopentathiepine (varacin). Compounds showed antimicrobial activity against *M. hiemalis* and *R. atlantica* <2004TL7015>. Benzopentathiepin varacin as well as new alkaloids were isolated from the bioactive crude extract of the New Zealand ascidian *L. notti* <2002T9779>. 6,7-Dimethoxybenzopentathiepin **102** and 6-(2-aminoethyl)benzopentathiepin **103**, which are partly structures of varacin, exhibited cytotoxicity in the range 6.12–0.26 $\mu\text{g ml}^{-1}$ toward HeLa S3 cells. Protection of the amino group and changing substituents on the benzene ring of **103** lowered the cytotoxicity <1995H(41)893>. It was demonstrated that the DNA-cleaving activity by varacin is apparently promoted by its acidic environments. Varacin showed cytotoxic activity against human tumor cell lines <2002CCC2112>.

Polycyclic sulfur compounds were used for silver halide emulsion and silver halide photographic material <1994JPP06118537, 1995JPP06102610, 1997JPP09061956, 1999JPP11119368, 2000JPP2000047344, 1997EPP809136, 1997JPP09211801>, for silver halide photographic material for printing plate <1995JPP07072570A2>. Lithium secondary batteries with high energy density are key devices for portable electronic equipments. The specific capacity of metal oxide-based positive active materials was considerably lower than that of lithium metal. Organosulfur compounds, such as disulfides including pentathiepinines, are useful as a possible active material for lithium secondary cells <2005MI345>.

Polysulfur heterocycles are included in spice flavor compositions <2005JPP2005013138>, manufacture of vegetable flavor compositions <2005JPP2005015684>, and as an inhibitory activity of Shiitake flavor against platelet aggregation <2004MI177>. Powdery encapsulation of shiitake flavors, extracted from dried Shiitake, and containing lenthionine, was investigated by spray drying <2004MI166>.

Sulfur heterocycles, including those with more than two sulfur atoms, are used for optical materials <2000JPP2002040201>. The molecular third-order optical nonlinearity γ_R (Second hyperpolarizability or nonlinear refractive index) was measured for pentathiepinethiafulvalene <1999PCA6930>.

Pentathiepinines based on a new fulvalene- C_6S_{12} were proposed as 'organic metals' <2005MCL575>.

13.17.11 Further Developments

Since the previous account on the seven-membered rings with four or more heteroatoms in CHEC-II, considerable progress has been made in synthesis, structural, and reactivity studies. In a current review, careful structural analyses,

supported by quantum chemical calculations, provided us with information on the bonding situation of these classes of compounds. The seven-membered heterocyclic compounds with several heteroatoms are often the promising precursors in the constructions of the new heterocycles. We should also mention the development of the efficient synthetic approaches to the synthesis of these heterocycles as well as wide areas of application of this class of compounds. The number of references in this field is increasing every year as well as a number of publications in special journals and patents.

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Biographical Sketch



George N. Nikonov (born 1954, Kazan, Russia) received a degree of Master of Science in Chemistry (Chemical Technology of Rubber and Plastics) in 1976 at Kazan Institute of Chemical Technology (now Kazan State Technological University), then entered A. E. Arbuzov Institute of Organic and Physical Chemistry of Russian Academy of Sciences (Kazan, Russia) as a postgraduate student. For more than 15 years, he worked under the supervision of the leader of phosphorus chemistry in Russia, world famous academician Boris A. Arbuzov. In 1980, he received a Ph.D. degree in the field of organic heteroatom chemistry and in 1987 received the Degree of Doctor of Science (Dr.Sc.) in the field of organic heteroatom chemistry at Kazan State University. From 1986 to 1989, George Nikonov was a senior researcher at Arbuzov Institute, and later, from 1989 to 1994, became a principal researcher/team leader. He was the head of a laboratory of organophosphorus compounds during the period from 1994 to 1999. Along with that, in 1996, he was elected into administration of the institute as a scientific secretary and served in that position until 1999. From 1999 to 2002, he worked in the Center for Heterocyclic Compounds of the University of Florida, under the supervision of Kenan Professor, Dr. A. R. Katritzky. From 2002 to the present time, George Nikonov has been working in Alchem Laboratories Corp. (Alachua, Florida). He is a co-author of about 200 scientific publications including 134 scientific papers, 10 reviews, 24 patents, and 1 book.