Edited by

J.H. BATESON

and

M.B. MITCHELL

ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS

ACADEMIC PRESS

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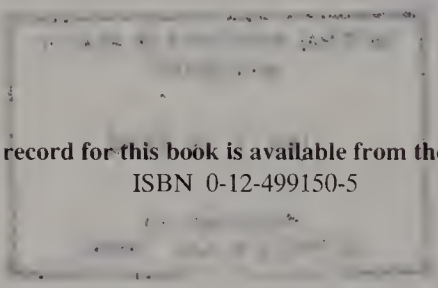

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Foreword

It was my pleasure to welcome the participants and to open this conference on Organometallic Reagents in Organic Synthesis. This was the sixth in a series of conferences sponsored by SmithKline Beecham. Previous conferences have focused on important areas of biological and chemical research, including ion transport, chirality in drug design and enzyme catalysis in chemical synthesis.

This symposium was dedicated to organometallic chemistry. Organometallic chemistry has always been an important part of organic chemistry and the earliest references on organometallic compounds date to the middle of the 18th century in a Paris military pharmacy. There, Cadet working on inks made 'Cadet's fuming liquid' which was an organometallic compound containing arsenic. The 19th century saw the first metal carbonyl complexes made, but the number of major advances increased dramatically in the following century. Reactions like the hydroformylation, which O'Roelen discovered in 1938, and the discoveries of Ziegler and Natta in 1955, made an enormous economic impact. The pace of discovery has continued to quicken in more recent years with the pioneering work of Wilkinson, Brown and Sharpless, to name just a few, finding important applications in organic synthesis.

But never in the past have organometallic reagents played such a crucial role as they do now. There are at least two reasons why these reagents are so important today. First, they provide a means of activating small molecules like oxygen, carbon monoxide, HCN and hydrogen for incorporation into larger structures; and secondly, they are an extraordinarily valuable tool because of their ability to confer diastereo and enantioselectivity. How many total syntheses do you see today in the literature that have not employed at least one organometallic reaction—the answer is probably none, and there is a good chance that all the key steps in a given synthesis will be organometallic reactions.

Despite the fact that organometallic reagents and catalysts have been prominent in organic chemistry for so long, their application in synthesis is today still a frontier in chemical science. It is an area of chemistry where historically we have possessed less of a mechanistic understanding of the chemistry than is the case with more conventional organic reactions. Now the delicate and intricate mechanisms which govern these reactions are being uncovered and they are leading to even more exciting discoveries.

I think you will agree that this is an extremely important area of chemistry. You can see from the presentations that some very exciting research discoveries were discussed in this conference. It was more than a pleasure for SmithKline Beecham to be able to host a symposium in this area; it was a great honour because we had such a distinguished list of speakers. The session chairmen are also a very outstanding group of scientists, and I would like to take this opportunity to thank them all for their participation.

George Wellman
Vice President, Chemical Development
SmithKline Beecham Pharmaceuticals Research and Development

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To Bea and Sam

Introduction

The chapters of this volume comprise the lectures delivered by an invited group of highly distinguished chemists at the 6th SmithKline Beecham Research Symposium. The Symposium was entitled 'Organometallic Reagents in Organic Chemistry' and was held at Robinson College, Cambridge, in March 1993. SmithKline Beecham Pharmaceuticals instigated and sponsored this series of symposia with the intention of promoting the understanding and growth of some core scientific areas in both the molecular and biological disciplines. To achieve this the symposia have drawn on an international body of leading exponents in the particular fields to present the results of their latest research. The themes and topics chosen have been perceived as crucial in enabling future advances within the pharmaceutical sciences and ultimately the processes of drug discovery and development. The OROS Symposium fulfilled our expectations in all these respects.

The organizers would like to thank all the contributors for the quality of their endeavours and for their commitment. This resulted in an educative process consisting of a perfect combination of scholarly review and the disclosure of new results. We were particularly pleased to provide a forum for the exchange of information between delegates both from the pharmaceutical industry and from academe. The benefits to all are self-evident and many of the participants, both presenters and delegates, have since commented to us on the valuable opportunities for informal discussion provided by the unique atmosphere of the meeting.

The content of the presentation and posters (see Appendix) was wide-ranging and subsumed all topics relating to the assembly of molecules involving organometallic reagents and metallo-intermediates. These included the synthesis of natural products and biomolecules, synthetic methodology, enantioselectivity and stereocontrol, together with aspects of molecular recognition.

Whilst organometallic reagents have been known for hundreds of years, the expansion of synthetic methodology employing organometallic reagents and metallo-species in the last twenty years has been phenomenal. This includes the stereocontrol and aldol and similar reactions using metal enolates of defined geometry; an extensive array of transition metal-catalysed cross-coupling reactions employing a wide range of organometallic donors; organometallic derivatives of reactive species such as carbenes and radicals, and powerful

processes for asymmetric induction using catalytic quantities of chiral organometallic reagents. The application of this methodology to organic synthesis has been demonstrated by some remarkably direct and efficient syntheses of novel molecules and of natural products of formidable complexity. Our speakers clarified and developed these themes superbly and suggested that still greater advances will be made in organometallic chemistry in the future.

Rigorous control of the stereochemistry of chemical processes and reactions is crucial to the pharmaceutical industry for the design and construction of molecular 'probes' of its target biological macromolecules, i.e. the synthesis of drug candidates. This stereochemical control is of fundamental importance in obtaining a molecular understanding of complex biological systems. Indeed, many believe that a chemical and biochemical renaissance is already upon us and that whole frontier areas—hitherto a 'no-man's land' between the molecular and biological sciences—are now available as the realm of the organic chemist. Furthermore, developments in organometallic chemistry continue to provide valuable synthetic methodology for the design of efficient large-scale chemical processes to complex targets previously considered unattainable or uneconomic.

Looking to the future from Cambridge 1993 reveals an ever-broadening horizon for organic chemistry and the molecular sciences. One certainty is that organometallic reagents and metallo-intermediates, the subjects of this symposium, are sure to play an important part in the adventure.

John Bateson and Mike Mitchell

1

The Use of $\eta^2Co_2(CO)_6$–Acetylene Complexes for the Synthesis of Enediyne Antitumor Antibiotics

PHILIP MAGNUS

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, TX 78712, USA

1 Introduction

In 1987 the Lederle (Lee *et al.*, 1987a,b) and Bristol-Myers (Konishi *et al.*, 1985; Golik *et al.*, 1987a,b) groups reported the unprecedented structures of calicheamicin γ_1 **1**, esperamicin A_1 **2**, A_{1b} **3**, A_2 **4** and the metabolite esperamicin X **5** (Scheme 1). They were isolated from fermentations of *Micromonospora echinospora* sp. *calichensis*, and cultures of *Actinomadura verrucosospora* BBM 1675, ATCC 39334, respectively. Presently, these compounds are the most potent antitumor antibiotics known, being approximately 10^3 times more active than adriamycin against murine tumors, and represent a new class of natural products based upon the *Z*-enediyne functionality. Dynemicin **6** is the latest antitumor antibiotic to be added to the growing list of enediyne natural products (Konishi *et al.*, 1989, 1990; Langley *et al.*, 1991; for recent synthetic studies see Porco *et al.*, 1990; Nicolaou *et al.*, 1990, 1991; Wender *et al.*, 1991; for the $\eta^2Co_2(CO)_6$-mediated approach see Magnus and Fortt, 1991; for calculations concerning the rate of diyl formation see Snyder and Tipsword, 1990; Semmelhack *et al.*, 1990). It exhibits extraordinarily potent antimicrobial and antitumor activity, and moreover it shows little *in vivo* toxicity.

While the esperamicins–calicheamicins contain a number of unusual structural features, such as the allylic trisulfide, a hydroxylamino sugar and C_1–C_2 bridgehead double bond, it is the *Z*-enediyne that embues these molecules with a unique mechanism for cleaving DNA. It was proposed (Konishi *et al.*, 1985; Golik *et al.*, 1987a,b; Lee *et al.*, 1987a,b) that the trisulfide is cleaved by nucleophilic attack at the central sulfur atom to give the thiol (or thiolate; **7**), which can conjugatively add to C_1 to give the dihydrothiophene derivative **8**.

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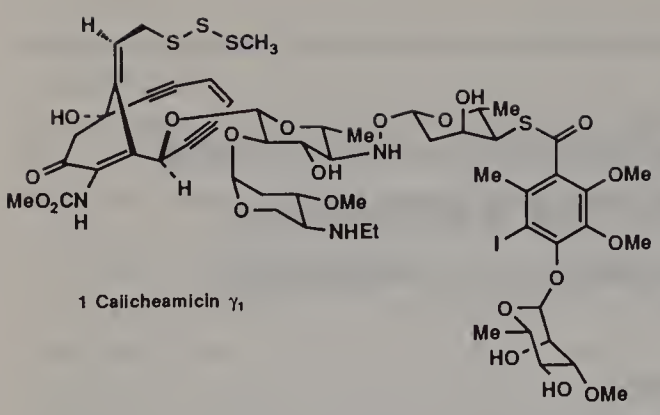
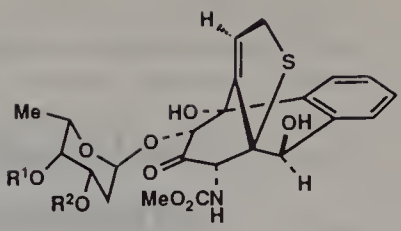
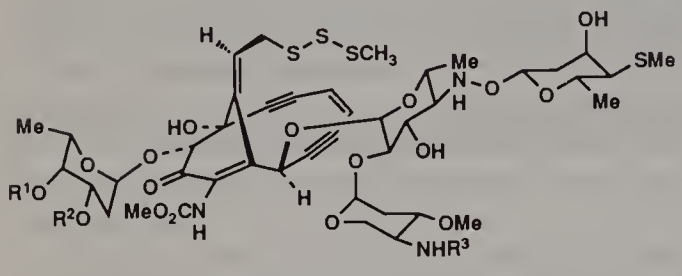


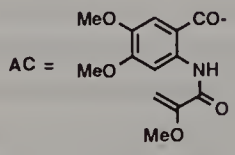
1 Calicheamicin γ_1

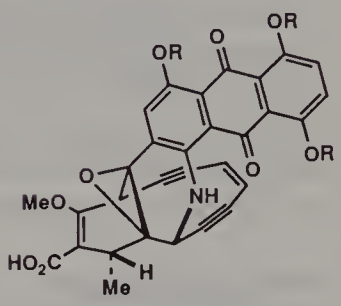


5 Esperamicin X



2 Esperamicin A_1, R^1= H, R^2 = AC, R^3 = *i*-Pr.
3 Esperamicin A_{1b}, R^1= AC, R^2 = H, R^3 = *i*-Pr.
4 Esperamicin A_2, R^1 = H, R^2 = AC, R^3 = Et.





6 Dynemicin, R = H and R = Ac.

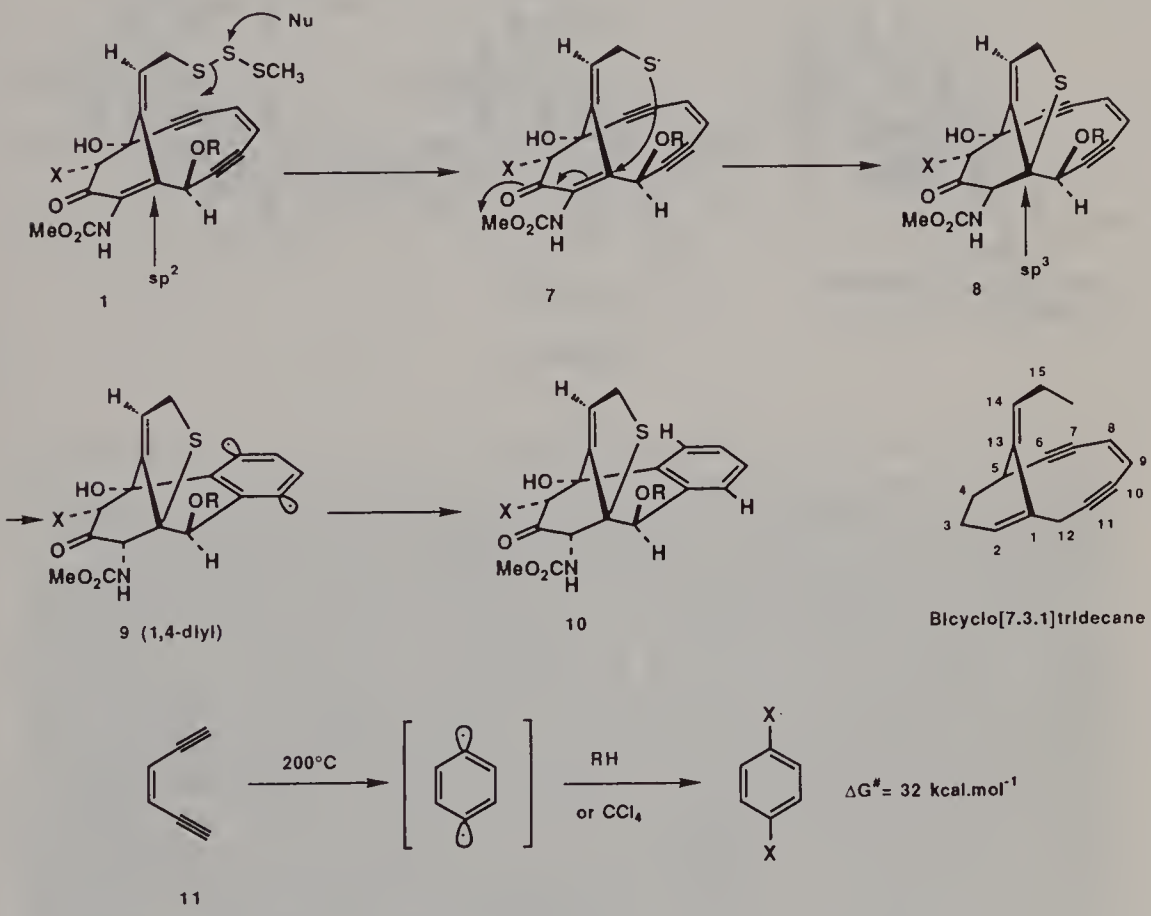
Scheme 1

Once the hybridization at C_1 is changed from trigonal (sp^2) to tetrahedral (sp^3), the transition state for the formation of the 1,4-diyl **9** is energetically feasible. The transition state in going from **8** to **9** must be substantially bicyclo-[3.3.1]nonane-like in geometrical character, and would be greatly elevated in energy if the C_1–C_2 double bond were still present (anti-Bredt). We will return to this point and the factors that permit access to the 1,4-diyl later.

The 1,4-diyl **9** can abstract a hydrogen atom in a highly exothermic process to give the cycloaromatized adduct **10**. It is interesting and historically instructive to note that Bergman's classical physical organic study of the thermal chemistry of the *Z*-enediyne prototype **11**, preceded the reports of the structures of natural products containing this functionality by 25 years (Jones and Bergman, 1972; Bergman, 1973; for more recent studies of the 1,4-diyl see Lockhart and Bergman, 1981; Lockhart *et al.*, 1981; the conversion of enediynes into antisymmetric benzene-1,4-diyl is a symmetry allowed process: Hoffmann *et al.*, 1968; Dewar and Li, 1974; for biradical activity see Darby *et al.*, 1971; Chapman *et al.*, 1976; Wong and Sondheimer, 1980). It is more than likely that

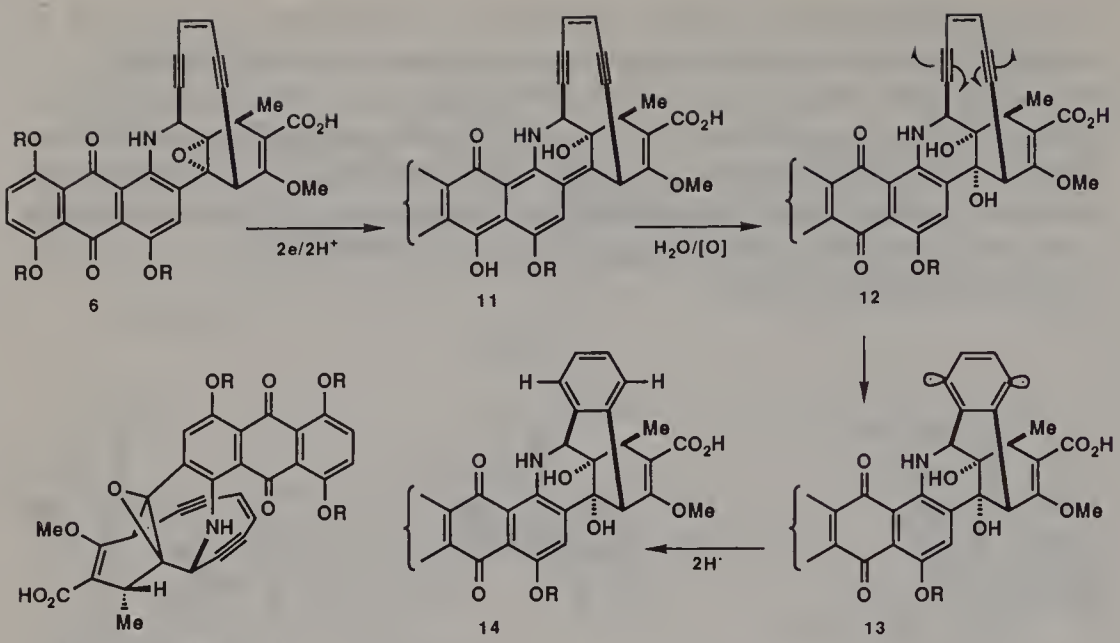
the 1,4-diyl hypothesis described in Scheme 2 would not have been at all obvious in the absence of the basic physical organic chemical research.

Studies on the interaction of **1** with DNA suggest that it binds into the minor groove, and in the presence of thiols causes double and single strand scissions (Zein *et al.*, 1988; Long *et al.*, 1989; Kishikawa *et al.*, 1991). Molecular modelling indicates that the carbohydrate components are responsible for the molecular recognition and subsequent site specificity at TCCT sites (Zein *et al.*, 1989; Hawley *et al.*, 1989).



Scheme 2

It has been speculated that dynemicin **6** undergoes bioreductive activation with concomitant epoxide ring opening to give the extended quinone methide **11**. Hydration of **11** to give **12**, followed by Bergman cycloaromatization of the diol leads to the diyl **13**, which can hydrogen abstract to provide the adduct **14** (Konishi *et al.*, 1985, 1989, 1990; Golik *et al.*, 1987a,b; Porco *et al.*, 1990; Snyder and Tipsword, 1990; Semmelhack *et al.*, 1990; Nicolaou *et al.*, 1990, 1991; Langley *et al.*, 1991; Wender *et al.*, 1991; Magnus and Fortt, 1991;



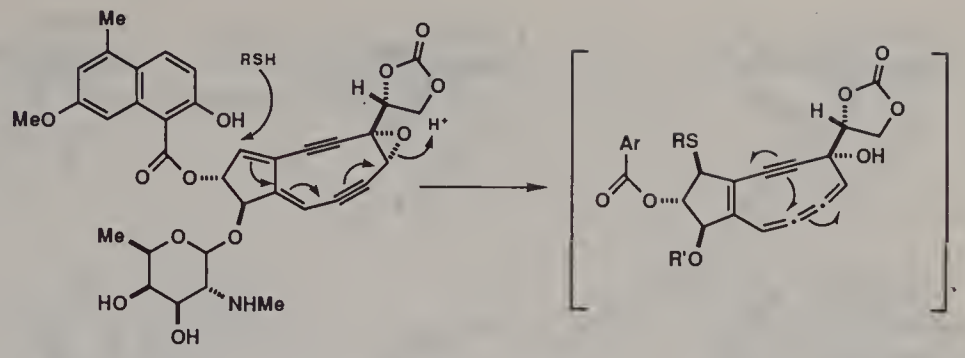
6,drawn to show its relationship to esperamicin.

Scheme 3

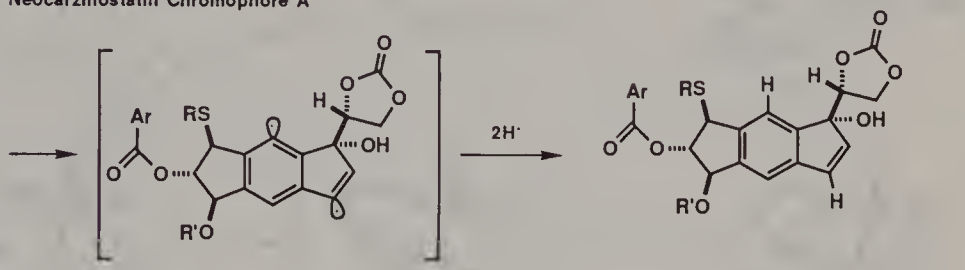
Scheme 3). Consequently, if dynemicin, or one of the subsequent adducts **11**, **12** and **13** is bound to DNA, the diyl is fully capable of back-bone scission.

Related to the esperamicin–calicheamicin enediynes is the compound called neocarzinostatin chromaphore A **15**, which also cleaves DNA via the speculated sequence shown in Scheme 4 (Napier *et al.*, 1979; Koide *et al.*, 1980; Myers, 1987; for synthetic studies on the bicyclo[7.3.0]dodecaenediyne core see Wender *et al.*, 1988, 1990; Hirama *et al.*, 1989; Fujiwara *et al.*, 1990; Myers *et al.*, 1991; for the $\eta^2Co_2(CO)_6$-mediated approach see Magnus and Pitterna, 1991). Because of the unique structures and beautifully designed mechanism of DNA cleavage the esperamicins and calicheamicins have immediately attracted a great deal of synthetic interest (for an interesting and thought-provoking account of 'Why are secondary metabolites (natural products) biosynthesized', see Williams *et al.*, 1989).

The overall strategy we have adopted is based on the following premise (Danishefsky *et al.*, 1988b; Cabal *et al.*, 1990; Haseltine *et al.*, 1991; for other papers from this group see Danishefsky *et al.*, 1988a; Mantlo *et al.*, 1989; Haseltine *et al.*, 1989; Kende *et al.* have reported a conceptually identical strategy to the Danishefsky work, except at a lower oxidation level: Kende and Smith, 1988; Schreiber and Kiessling, 1988, 1989; Nicolaou *et al.*, 1988a,b; Schoenen *et al.*, 1989; for review articles see Nicolaou and Dai, 1991; Nicolaou *et al.*, 1992). The enediyne-containing natural products represent a new class of

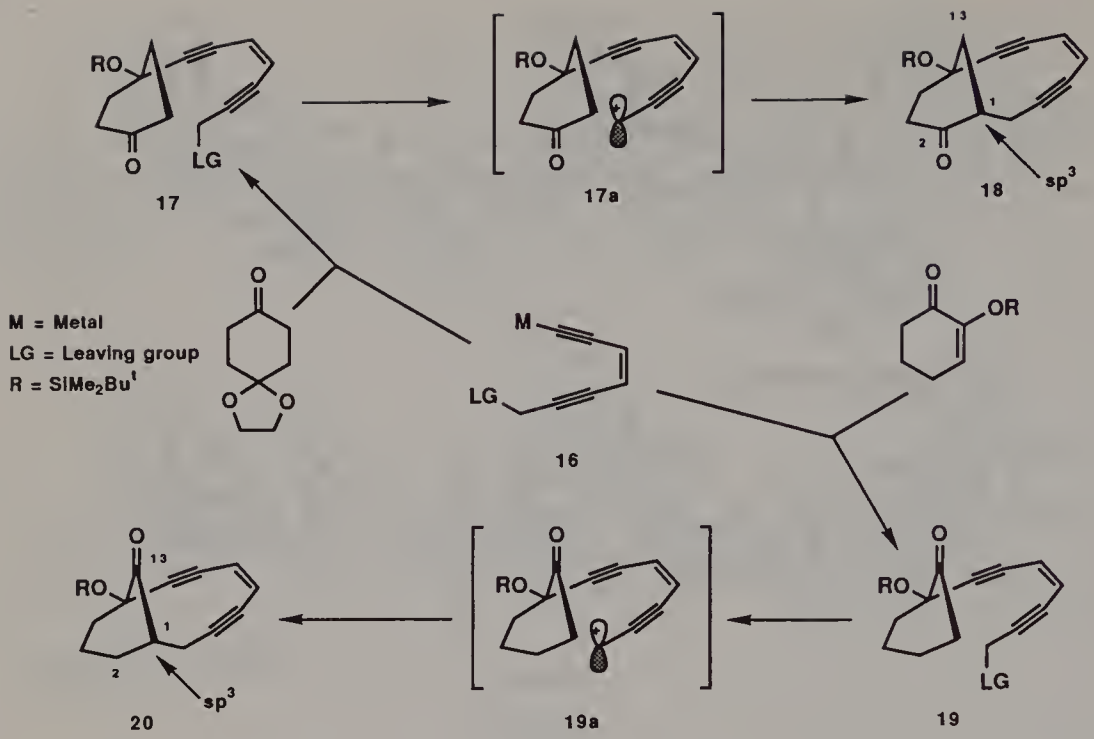


15, Neocarzinostatin Chromophore A



Scheme 4

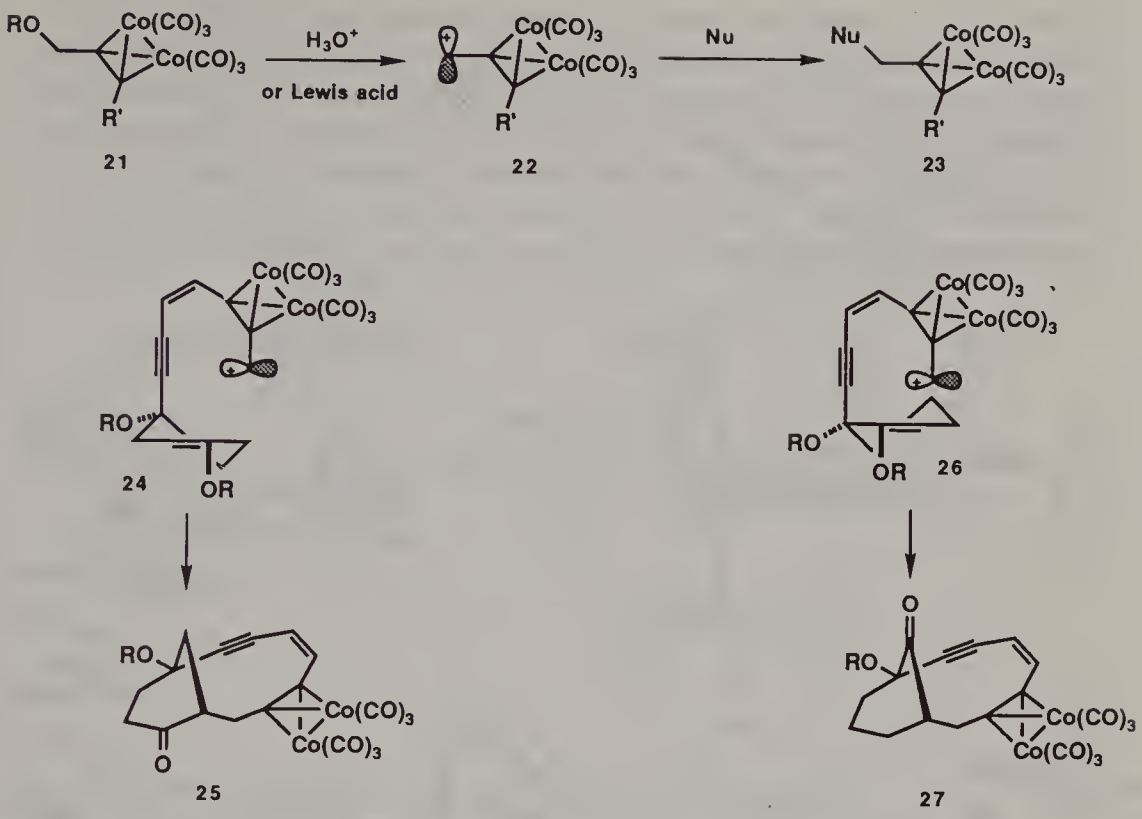
compounds, whose chemistry had not yet been explored. A synthetic strategy that probes the reactivity of enediynes and the factors that control the rate of cycloaromatization was warranted. We have, at least initially, deliberately pursued a non-convergent strategy in order to accrue a corpus of knowledge about the chemistry of the core bicyclo[7.3.1]enediyne system (synthesis of 2-ketobicyclo[7.3.1]tridecaenediyne: Magnus and Carter, 1988; synthesis of 13-ketobicyclo[7.3.1]tridecaenediyne: Magnus *et al.*, 1988; synthesis of the trisulfide functionality: Magnus *et al.*, 1989; conjugation addition of thiol to initiate 1,4-diyl formation: Magnus and Lewis, 1989; selenium dioxide oxidation of bridgehead trialkylsilyl enol ethers: Magnus and Bennett, 1989; molecular strain rather than π-bond proximity determines the cycloaromatization rates of bicyclo[7.3.1]tridecaenediynes: Magnus *et al.*, 1990; for a recent extension of the $\eta^2Co_2(CO)_6$-acetylene methodology see Maier and Brandstetter, 1991; synthetic and mechanistic studies on the antitumor antibiotics esperamicin A_1 and calicheamicin γ_1, synthesis of 2-ketobicyclo[7.3.1]enediyne and 13-ketocyclo[7.3.1]enediyne cores mediated by η^2-dicobalthexacarbonyl alkyne complexes, cycloaromatization rate studies: Magnus *et al.*, 1992a; synthetic and mechanistic studies on the antitumor antibiotics esperamicin A_1 and calicheamicin γ_1, oxidative functionalization of the 13-ketobicyclo-[7.3.1]tridecaenediyne core structure, construction of the allylic trisulfide trigger: Magnus *et al.*, 1992b). The overall strategy is outlined in general terms in Scheme 5.



Scheme 5

Addition of an acetylide **16** to the mono-protected 1,4-diketone should lead to **17**, which upon ionization to the propargylic cation **17a** results in the 2-ketobicyclo[7.3.1]tridecaenediyne **18**. Similarly, addition of **16** to the 1,2-diketone derivative should provide **19**, which leads to the 13-ketobicyclo-[7.3.1]tridecaenediyne **20**, via **19a**. Some of the many questions to be addressed were, are the isomeric bicyclo[7.3.1]enediynes **18** and **20** stable, isolable compounds with respect to their potential for cycloaromatization, and if so, what chemistry can be carried out on them?

A very convenient way to generate the propargylic cation-type intermediates **17a**, **19a** is to make use of the η^2-dicobalthexacarbonyl alkyne complexes **21** which have been shown by Nicholas and others to ionize to the cation **22** when treated with Brönsted or Lewis acids (Sly, 1959; Nicholas *et al.*, 1978; Howard, 1983; the propargyl cation chemistry has recently been reviewed: Nicholas *et al.*, 1980; Schreiber *et al.*, 1986, 1987; Nicholas, 1987; Montana *et al.*, 1988). Trapping by a carbon nucleophile gives **23**. A further benefit of the η^2-$Co_2(CO)_6$-alkyne complexes is that they bend the normally linear digonally hybridized acetylene triple bond to approximately 145°. The propargylic cation is situated with near to axial alignment to the enol derivative **24/26** π-system (Scheme 6).



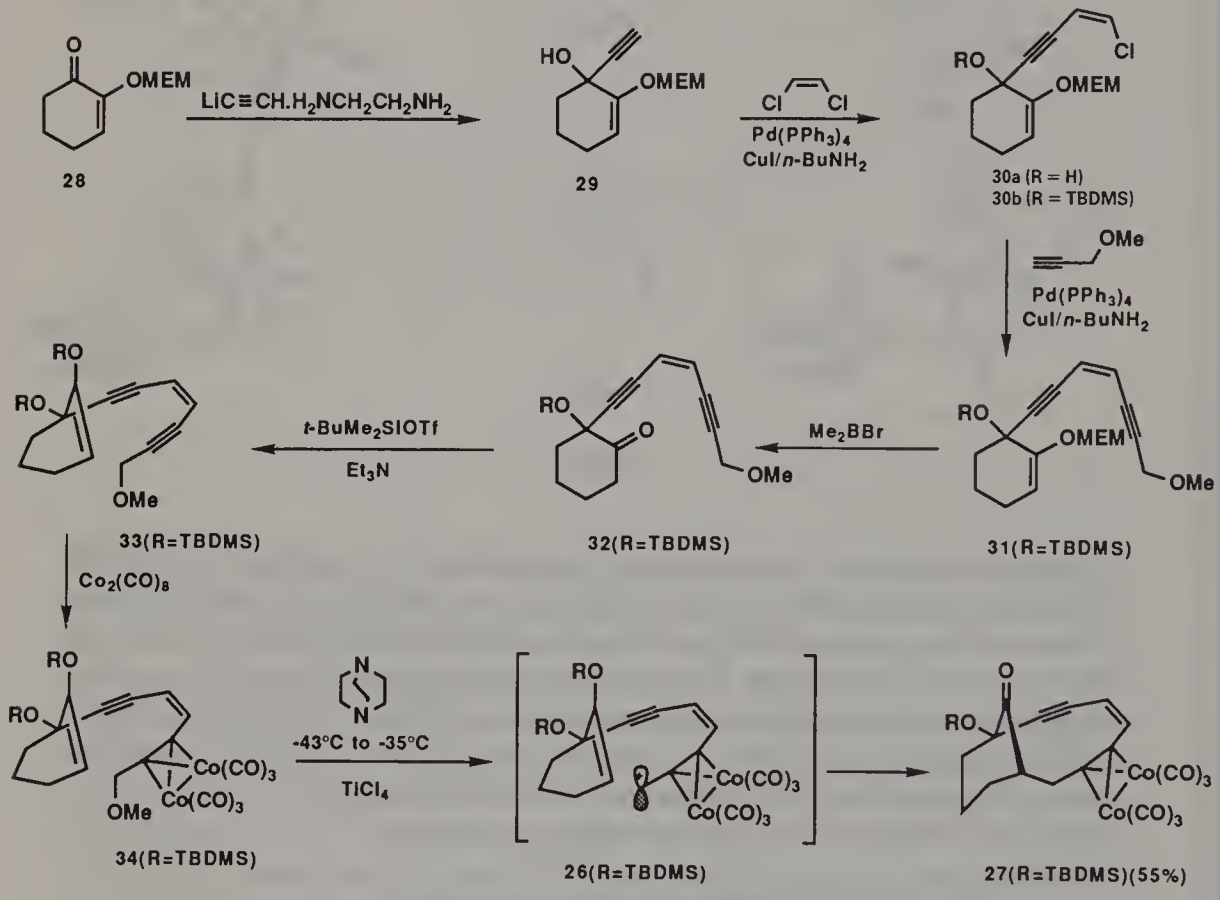
Scheme 6

Finally, if successful, the corresponding bicyclo[7.3.1]tridecaenediynes **25**/**27** will be formed as their mono-$Co_2(CO)_6$ complexes and therefore prevent cycloaromatization until the $Co_2(CO)_6$ cap is removed (Scheme 6). This device should allow us to examine the release of the enediyne by oxidation and its subsequent cycloaromatization as separate steps. While we initially studied the 2-ketobicyclo[7.3.1]enediyne system **18**, the 13-ketobicyclo[7.3.1]enediyne system **20** proved to be more useful, although the former isomer will be mentioned later in the cycloaromatization rate studies.

2 13-Ketobicyclo[7.3.1]tridecaenediyne system

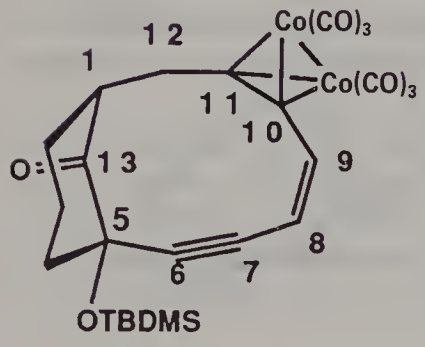
Treatment of cyclohexane-1,2-dione with NaH/MEMCl/THF at −10°C gave **28** (82%), which was exposed to lithium acetylide ethylenediamine complex in dioxane to give **29** (74%). Coupling of **29** to Z-dichloroethylene to give **30a** (77%) was accomplished with $Pd(PPh_3)_4$/CuI/*n*-$BuNH_2$ (Stephans and Castro, 1963; Ratovelomanana and Linstrumelle, 1984; Guillem and Linstrumelle, 1985, 1986). Protection of **30a** (*t*-$BuMe_2SiOTf/NEt_3/CH_2Cl_2$) gave **30b** (72%) which was coupled, as before, to methyl propargyl ether to give **31** (88%). Selective removal of the MEM-enol ether in **31** using Me_2BBr at −35°C gave **32**

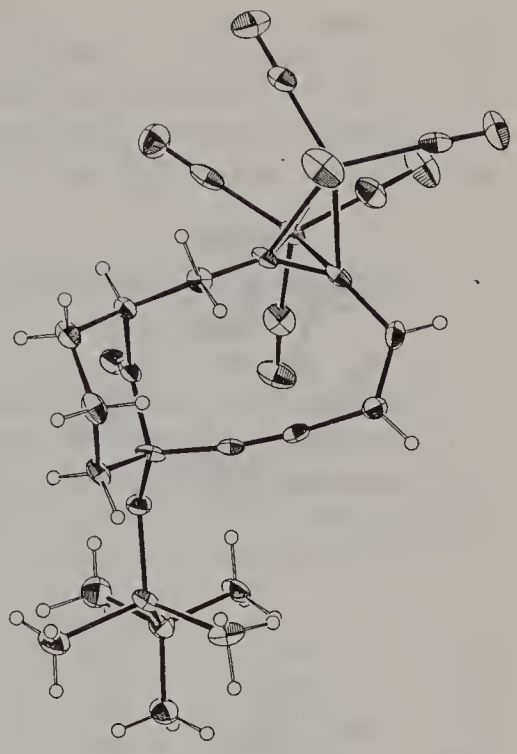
(>95%), from which the derived *t*-BuMe$_2$Si-enol ether **33** (85%) was prepared. Treatment of **33** with $Co_2(CO)_8$/heptane at room temperature resulted in complexation predominately at the sterically less hindered acetylenic bond to give **34** (90%). Small amounts of the $Co_2(CO)_6$-acetylene regioisomer and its *bis*-$Co_4(CO)_{12}$ complex are also formed. Treatment of **34** with $TiCl_4$/DABCO at −43°C gave the required bicyclo[7.3.1]enediyne-10,11-η^2-dicobalthexacarbonyl adduct **27** (55%) as a crimson crystalline solid (Scheme 7).



Scheme 7

The structure of **27** was secured by single crystal X-ray crystallography. Figure 1 shows an ORTEP representation. The newly formed carbon–carbon bond (C_1–C_{12}) is axial (with respect to the cyclohexanone ring) and consequently the hydrogen atom at C_1 is in an equatorial configuration. The C_1–H bond is orthogonal to the C_{13} carbonyl π-system and as a consequence should exhibit reduced kinetic acidity. In other words, there is a kinetic barrier to bridgehead enolization in **27** because of poor overlap in the developing enolate



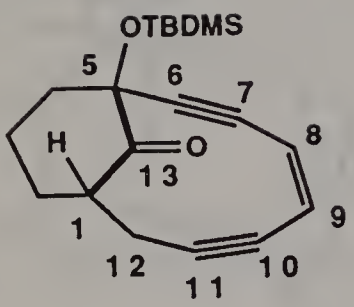


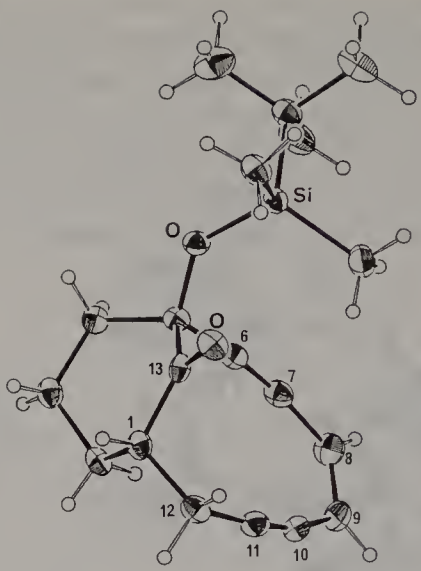
$C_{12/11/10}$	139.6°	$C_{8/9}$	1.34 Å
$C_{9/8/7}$	121.9°	$C_{8/7}$	1.42 Å
$C_{8/7/6}$	173.7°	$C_{6/7}$	1.19 Å
$C_{7/6/5}$	170.7°	$C_{6/5}$	1.47 Å

Fig. 1 ORTEP representation of **27**.

π-system. The axial C_1–C_{12} bond can only be accommodated in this configuration if the cyclohexanone ring is in a chair conformation, which is clearly shown in Figure 1 (Loev and Kormendy, 1963).

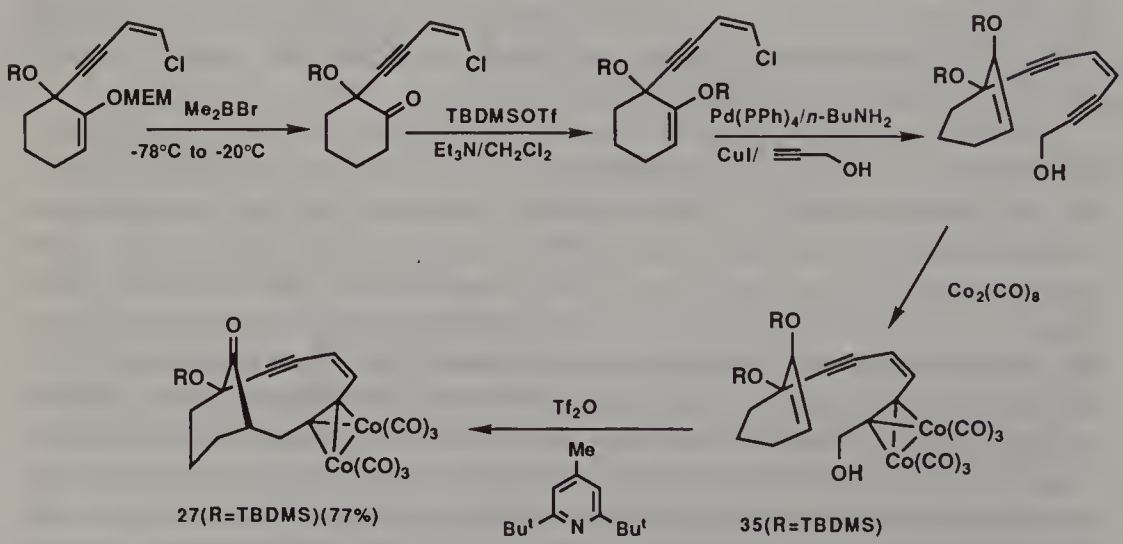
Oxidative decomplexation of **27** using iodine/THF at room temperature gave the 13-ketobicyclo[7.3.1]enediyne **20** (82%) as a stable crystalline solid. Figure 2 shows an ORTEP representation. When the 10,11-η^2-dicobalthexacarbonyl group is removed, the $C_{9,10,11}$ and $C_{10,11,12}$ bond angles change from approximately 139° to 165.7° and 169.8°, respectively. This causes the previously axial $C_{1,12}$ bond to assume an equatorial configuration and thus forces the six-membered ring into a boat conformation. The bond angles and bond lengths of the $C_{8,9}$ double bond are normal, indicating that the strain in **20** is accommodated by the weak bending modes of the triple bonds. The bridgehead C_1-H bond is axial and in the same plane as the C_{13} carbonyl π-system. Consequently **20** should be capable of forming a bridgehead enol derivative because the developing π-character at C_1 can directly participate in enolate resonance stabilization.





		$C_{6/11}(r)$	3.39 Å
$C_{5/6/7}$	171.5°	$C_{5/6}$	1.48 Å
$C_{6/7/8}$	168.7°	$C_{6/7}$	1.20 Å
$C_{7/8/9}$	118.8°	$C_{7/8}$	1.43 Å
$C_{8/9/10}$	119.1°	$C_{8/9}$	1.34 Å
$C_{9/10/11}$	165.7°	$C_{9/10}$	1.43 Å
$C_{10/11/12}$	169.8°	$C_{10/11}$	1.20 Å
$C_{11/12/1}$	111.1°	$C_{11/12}$	1.46 Å
$C_{5/13/1}$	118.3°	$C_{12/1}$	1.54 Å

Fig. 2 ORTEP representation of **20**.

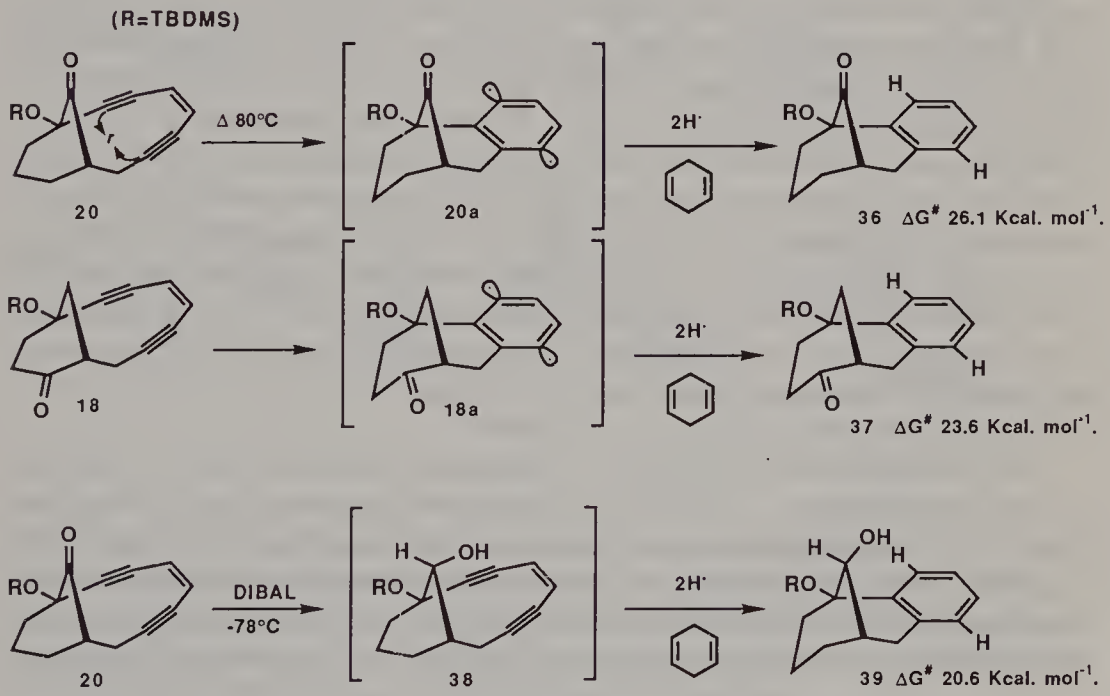


Scheme 8

When **35** was exposed to triflic anhydride in dichloromethane at −10°C in the presence of 2,6-di-*t*-butyl-4-methylpyridine, the 13-ketobicyclo[7.3.1]-enediyne-η^2-dicobalthexacarbonyl adduct **27** was isolated in 77% yield. Consequently, the route shown in Scheme 8 provides the best overall yield of the 13-ketobicyclo[7.3.1]enediyne-η^2-dicobalthexacarbonyl adduct **27** (10% from cyclohexane-1,2-dione).

3 Rate of cycloaromatization of the 13-ketobicyclo[7.3.1]trideca-enediyne system and related studies

Initial qualitative experiments readily showed that the 13-bicyclo[7.3.1]-enediyne **20** is considerably more resistant to cycloaromatization than the 2-ketoisomer **18** (made by similar chemistry). While we could not isolate **18, 20** is a stable crystalline compound below 80°C. At 80°C, in 1,4-cyclohexadiene, **20** is converted into the aromatic adduct **36** (72%) via the 1,4-diyl **20a** (Scheme 9).



Scheme 9

The Bergman prototype enediyne **11** (Scheme 2) requires heating at 195°C in the presence of a hydrogen atom donor in order to convert it into benzene. The $\Delta G^{\#}$ for this conversion is approximately 32 kcal/mol. It is clear that the esperamicins and calicheamicins **1–4** embody structural features that enable diyl formation to take place under physiological conditions (37°C).

Recently De Voss *et al.* (1990) have reported that treatment of calicheamicin (**1**) with *n*-Bu_3P at −67°C in methanol-d_4 gave the dihydrothiophene **8**

(X = H). At −11°C **8** (X = H) was transformed into the calicheamicin equivalent of esperamicin X (**10**) (X = H) at a convenient rate (VT ^{1}H NMR) that allowed useful first-order rate data to be measured: $k = 5 \pm 2 \times 10^{-4}$ sec^{-1} and $\Delta G^{\#}$ 19.3 ± 0.2 kcal/mol. Thus the half-life of the dihydrothiophene intermediate **8** (X = H) is 4.5 ± 1.5 sec at 37°C.

Nicolaou *et al.*, 1988a,b, 1990, 1991, 1992; for a review see Nicolaou and Dai, 1991) has examined a number of monocyclic enediynes, and concluded from their relative stability, and several other similar previously reported enediynes, that the ease of cycloaromatization can be correlated to the distance between the bonding acetylenic carbon atoms $r(C_{sp}–C_{sp})$. It should be noted as a reference point that the distance *r* between the two bonding acetylenes in **11** is 4.17 Å (Adiwidjaja and Groun-witte, 1980). In the ground state a distance *r* of 3.16 Å is sufficient to cause spontaneous ambient cycloaromatization to the 1,4-diyl **9**. Snyder and Tipsword (1990) has calculated (MM2, parameterized to reproduce the PRDDO-GVB-C1 transition state) for **20** $\Delta G^{\#}$ 26.1 kcal/mol, for **18** $\Delta G^{\#}$ 23.6 kcal/mol, and for **38** $\Delta G^{\#}$ 20.6 kcal/mol. The first value is in excellent agreement with the experimental value (see below), and the latter two values qualitatively parallel our observations. For the 2-ketobicyclo-[7.3.1]enediyne **18** the distance *r* is calculated to be 3.34 Å, for the isomeric 13-ketobicyclo[7.3.1]enediyne **20**, *r* is 3.41 Å, and for the alcohol **38**, *r* is 3.32 Å. Therefore, if the distance *r* between the bonding acetylenes in the ground state were the only factor governing the rate of cycloaromatization, the isomeric ketones **18** and **20** should be of comparable stability. Nevertheless there is a substantial rate difference in their respective first-order cycloaromatization. This points to factors other than simply the magnitude of *r* in the ground state controlling the rate of diyl formation. It is reasonable to assume that the rate of diyl hydrogen atom quenching is very fast compared with diyl formation, since it is a highly exothermic process.

The crystalline 13-ketobicyclo[7.3.1]enediyne **20** has been characterized by X-ray crystallography, *r* = 3.39 Å, in excellent agreement with calculation (3.41 Å). The cyclohexanone ring is in a boat conformation in the crystal and in solution. Heating a solution of **20** in 1,4-cyclohexadiene at temperatures ranging from 71°C to 104°C and monitoring both the rate of disappearance of **20** and the rate of formation of **36** (>70%) gave the *first-order* rate constants

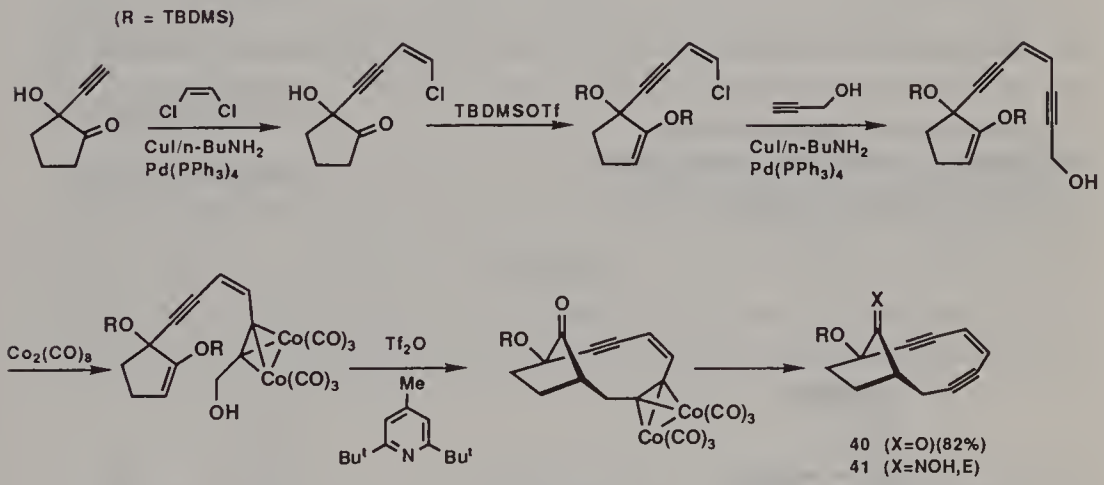
Table 1 Kinetic parameters for the thermal cyclization of enediyne **20**

T (°C)	k (sec^{-1})	$t_{1/2}$ (τ)
71	1.07×10^{-4}	2.10 h
79	2.56×10^{-4}	45 min
87	5.00×10^{-4}	23 min
95	1.16×10^{-3}	10 min
104	2.58×10^{-3}	4.30 min

shown in Table 1. Extrapolated to 37°C, the thermodynamic parameters are $\Delta G^{\#} = 26.3$ kcal/mol (calculated 26.1 kcal/mol), $\Delta H^{\#} = 24.0$ kcal/mol, $\Delta S^{\#} = -7.33$ eu, E_a 24.6 kcal/mol and $k = 1.85 \times 10^{-6}$ sec^{-1} (error ±2%).

The transition state for the conversion of **20** into **36** should be substantially bicyclo[3.3.1]nonane-like in geometrical character. If we replace the six-membered ring with a five-membered ring, the transition state for cycloaromatization will now be bicyclo[3.2.1]octane-like in geometrical character (more strained), but with little or no change in the distance *r* between the bonding acetylenes.

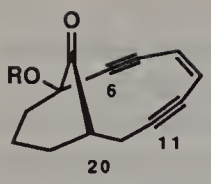
The five-membered ring analog of **20**, namely 12-ketobicyclo[7.2.1]enediyne **40**, was readily made in the same way (Scheme 10) except the starting material was cyclopentane-1,2-dione.



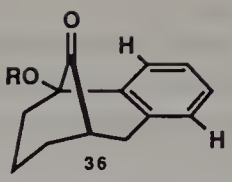
Scheme 10

The *E*-oxime **41** gave suitable crystals for X-ray analysis (Fig. 3). The bond angles and bond lengths in the enediyne portions of **20** and **41** are very similar. The only significant differences in **41** are the increased bending of the C5–C6 acetylene (167.4°/166.8° *vs* 171.5°/168.7° for **20**), and the carbonyl bond angle (110.5° *vs* 118.3° in **20**) [ν_{max} 1764/cm **40** and 1734/cm **20**].

The C_5/C_{10} separation is $r = 3.37$ Å (*vs* 3.39 Å for **20**). Although the distance between the two acetylenic carbons is almost within the range postulated for ambient cycloaromatization (<3.35 Å) and slightly below *r* in **20**, compound **40** is remarkably resistant to ring closure. At 124°C (averaged over five runs) $k = 2.08 \times 10^{-5}$ sec^{-1} for conversion of **40** into the bicyclo[3.2.1] system **42** (73%). This corresponds to a $\Delta G^{\#}$(124°C) of 32.0 kcal/mol and gives $\Delta\Delta G^{\#}$(**40-20**) = 5.1 ± 0.2 kcal/mol at the same temperature. In other words even though *r* is less in **40** than in **20**, **40** *cycloaromatizes 650 times more slowly* at 124°C (Scheme 11)!

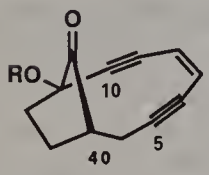


[3.3.1]-like transition State

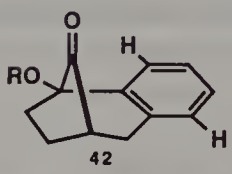


Distance between C-6 and C-11 is 3.39 Å

$t_{1/2}$ = 51 sec at 80 °C



[3.2.1]-like transition State



Distance between C-5 and C-10 is 3.37 Å

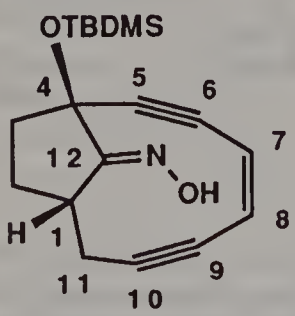
$t_{1/2}$ = 9 hr 15 sec at 80 °C

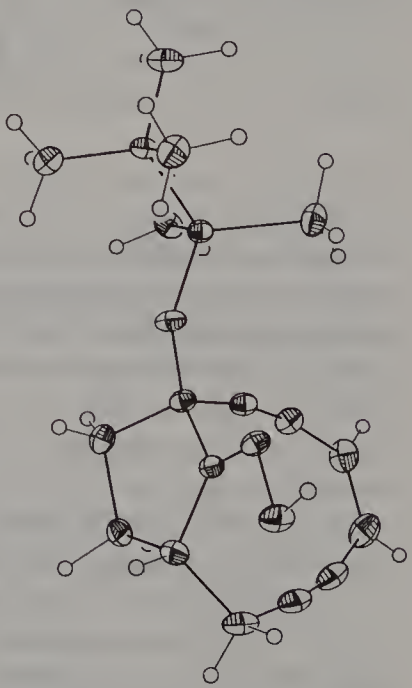
$\Delta\Delta G^{\dagger}$ = 5.0 kcal. mol-1

Rate difference of 650!

The factor that determines the rate of aromatization is the change in strain energy in the transition state, and not the distance between the bonding acetylenes.

Scheme 11





		$C_{5/10}$ (*r*)	3.37 Å
$C_{4/5/6}$	167.4°	$C_{4/5}$	1.49 Å
$C_{5/6/7}$	166.8°	$C_{5/6}$	1.19 Å
$C_{6/7/8}$	118.4°	$C_{6/7}$	1.43 Å
$C_{7/8/9}$	119.7°	$C_{7/8}$	1.33 Å
$C_{8/9/10}$	162.2°	$C_{8/9}$	1.42 Å
$C_{9/10/11}$	173.7°	$C_{9/10}$	1.19 Å
$C_{10/11/1}$	111.5°	$C_{10/11}$	1.46 Å
$C_{4/12/1}$	110.5°	$C_{11/1}$	1.54 Å

Fig. 3 ORTEP representation of **41**.

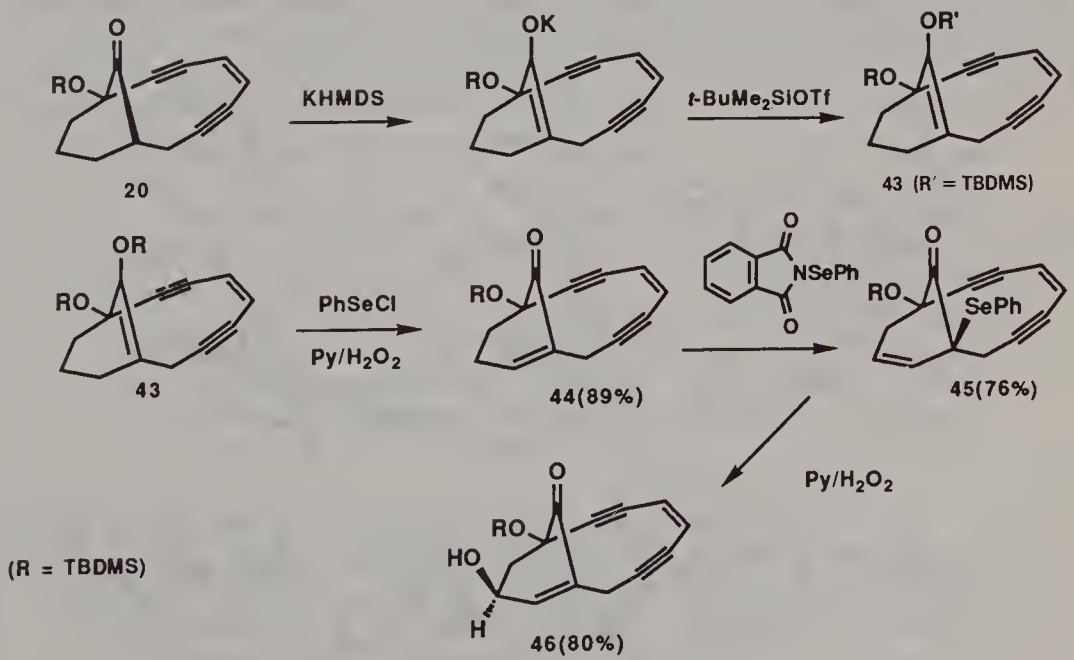
A significant conformational difference between the five- and six-membered ring analogs is that the boat cyclohexanone in **20** becomes a chair in **36**, and provides approximately 6 kcal strain release in the transition state, whereas the five-membered ring system **40** has no comparable driving force. The simple notion that the distance between the bonding acetylenic carbon atoms in the ground state determines the rate of diyl formation does not provide an adequate prediction of the ease of cycloaromatization for the bicyclic enediynes described above. The transition state model developed by Snyder (1989, 1990) is in good accord with the experimental results.

4 C_1–C_{13} bridgehead enolate chemistry

The cyclohexanone ring in **20** adopts a boat conformation (the C_1–C_{12} bond is equatorial to accommodate the enediyne in the ten-membered ring), and consequently the axial C_1 hydrogen atom is in the plane of the carbonyl π-system. This results in increased kinetic acidity since the developing carbanion at C_{13} enjoys direct resonance delocalization without the necessity for geometric changes.

Treatment of **20** with Et_3N/*t*-$BuMe_2SiOTf/CH_2Cl_2$ at 20°C for 5 days gave the bridgehead *t*-butyldimethylsilyl enol ether **43** (54%) as a stable crystalline compound. More conveniently **43** can be made from **20** by treatment with KHMDS/THF/*t*-$BuMe_2SiOTf$ at −78°C for 0.5 h in 100% yield (Scheme 12).

Treatment of the bridgehead *t*-butyldimethylsilyl enol ether **43** with phenylselenenyl chloride followed by pyridine/H_2O_2 gave the α,β-unsaturated ketone

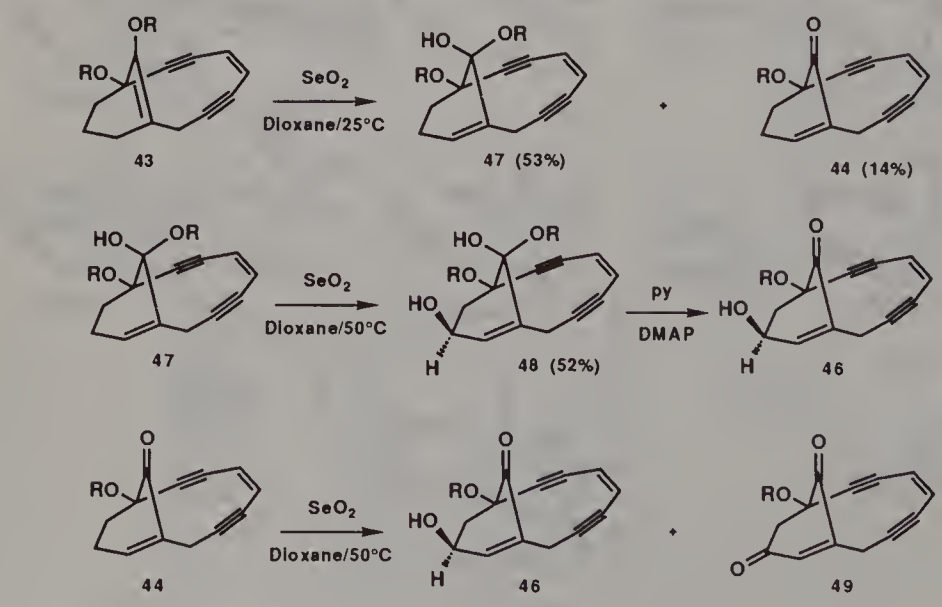


Scheme 12

44 (66%) (for numerous references to the α-selenenylation of ketones see Back, 1987). It should be borne in mind that highly unsaturated molecules such as **44** have very simple ^{1}H NMR and ^{13}C NMR spectra and as a consequence do not contain so much information (connectivity); consequently it is important to be cautious when assigning structures. The enone **44** has unexceptional IR and UV spectral properties, and undergoes reactions typically associated with an α,β-unsaturated ketone.

It was found that the enone **44** could be converted into the C_1 phenylselenenyl adduct **45** (76%) by treatment with the Nicolaou reagent *N*-(phenylseleno)phthalimide (Nicolaou *et al.*, 1979, 1985). Oxidation of **45** with H_2O_2/pyridine gave the 3β-hydroxy-1,2-enone **46** (76%) via [2,3]-sigmatropic rearrangement of the resulting selenoxide (Scheme 12; for review of [2,3]-sigmatropic rearrangements see Reich, 1987).

The 3β-hydroxybicyclo[7.3.1]enediyne system **46** is available in two oxidative steps, both involving selenium chemistry. At this stage in the development of this research we did not have a method to introduce the 12β-hydroxy substituent (Magnus *et al.*, 1990a). In a completely empirical manner we decided to treat the enol ether **43** with a variety of oxidizing agents with the expectation of observing either C_{12} functionalization (propargylic) or C_3 functionalization (allylic). Without belaboring the fact, after treating the enol either **43** with a range of oxidants that only led to complex mixtures or complete destruction of **43**, it was found that treatment of **43** with SeO_2 (1.1 eq)/dioxane at 25°C for 3 h gave the hemiketal **47** (53%) as a stable crystalline material, m.p. 114–116°C, along with the enone **44** (14%) (Sharpless and Laver, 1972; Arigoni *et al.*, 1973; Jensen and Sharpless, 1975; Sharpless and Gordon, 1976; Magnus and Bennett, 1989; stable hydrates of bridged ketones have been isolated, the most recent described in Bonjoch *et al.*, 1989).



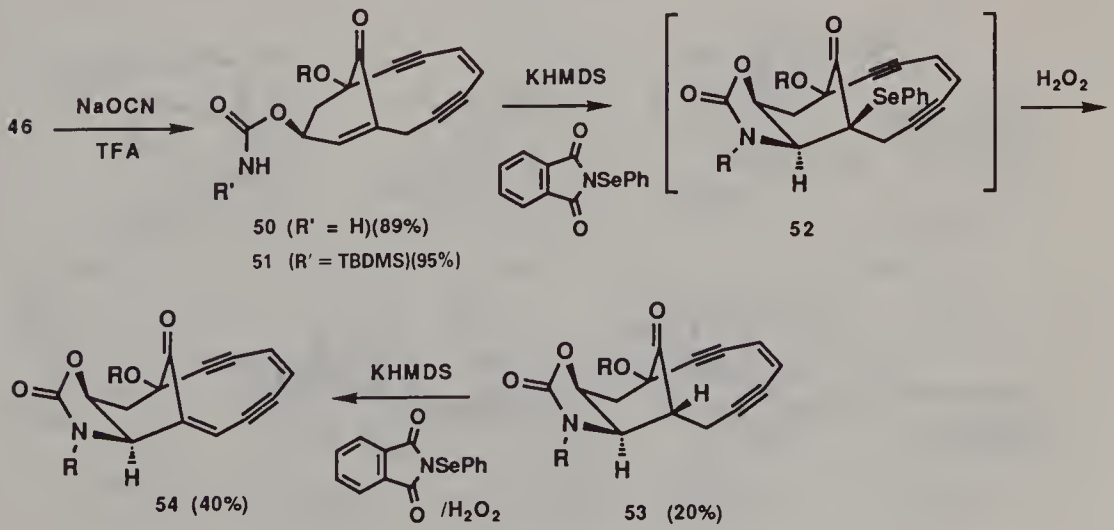
Scheme 13

The structure and relative stereochemistry of **47** was determined by single crystal X-ray crystallography. Further exposure of **47** to SeO_2 (1.1 eq)/dioxane at 50°C for 16 h gave the 3β-hydroxy compound **48** (45%) along with starting material. Treatment of the hemihydrate **48** in pyridine with *N,N*-dimethylaminopyridine cleanly converted it into the 3β-hydroxyenone **46** (89%). The structure and relative stereochemistry of **48** was verified by single crystal X-ray crystallography.

It was further found that SeO_2 (73°C for 21 h) cleanly converted the enone **44** into the 3β-hydroxyenone **46** (75%) along with smaller amounts of the dienone **49** and the starting enone **44** (Scheme 13).

5 Introduction of the C_2 nitrogen substituent

Treatment of the alcohol **46** with sodium cyanate in the presence of trifluoroacetic acid gave the carbamate **50** (89%). Interestingly, if potassium cyanate is used the alcohol **46** is recovered unchanged (Loev and Kormendy, 1963). The carbamate **50** was readily *N*-silylated by treatment with *t*-butyldimethylsilyl triflate/NEt_3/CH_2Cl_2 to give **51** (95%). Treatment of the *N*-silylated derivative **51** with potassium *bis*(trimethylsilyl)amide at −78°C followed by *N*-phenylselenenylphthalimide gave a mixture of the bridgehead selenide **52** and the protonated compound **53** (2:1). Oxidation of the mixture with hydrogen peroxide/pyridine resulted in elimination of the intermediate selenoxide into the ten-membered ring to give the torsionally strained enone **54** (40% from **51**). The IR spectrum of **54** exhibits two carbonyl stretching frequencies at 1759/cm (carbamate) and 1744/cm (C_{13} enone carbonyl). The ^1H NMR spectrum shows the C_{12} enone proton at δ 5.67 with a small coupling of 1.5 Hz to the C_9 olefinic proton. The bridgehead protonated compound **53** can be converted into the enone **54** (44%) by the same procedure used to convert **51** into **54**. Ring opening of the cyclic carbamate **54** could not be achieved without complete destruction of the molecule (Scheme 14).

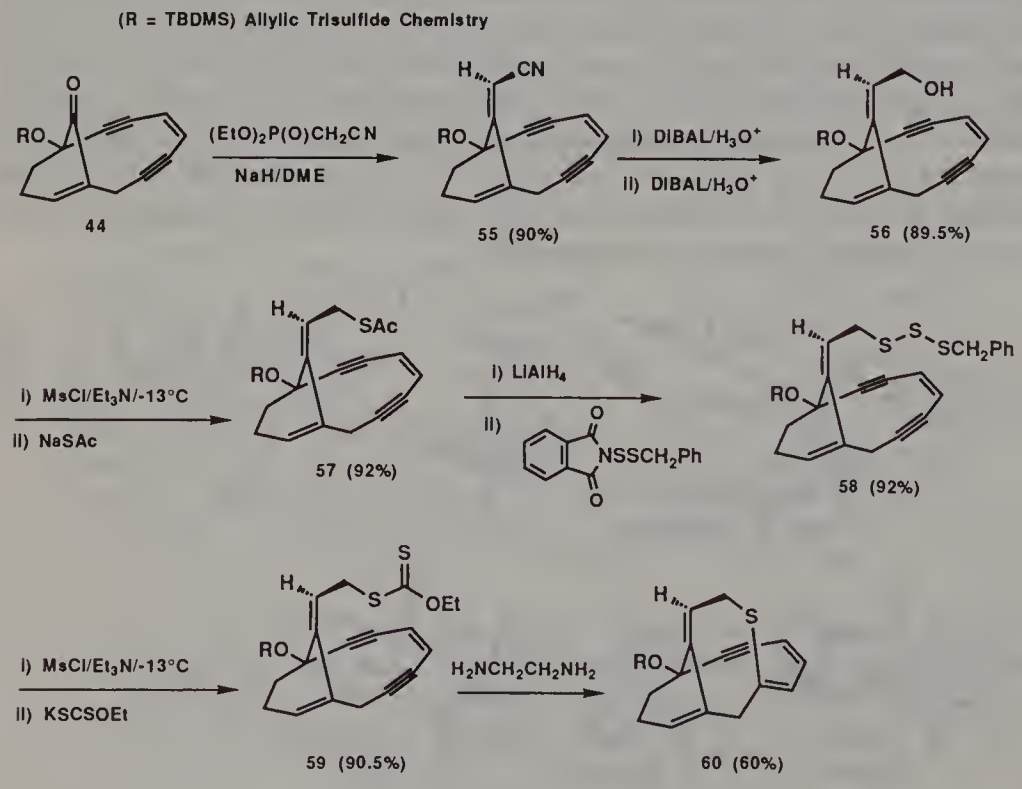


Scheme 14

6 Construction of the allylic trisulfide trigger

While the allylic trisulfide (general reviews on polysulfides: Kuthey and Turnbull, 1982; Harpp, 1987; diallyl trisulfide and methyl allyl trisulfide are natural products: Augusti and Mathew, 1974; Ariga *et al.*, 1981) might appear to be a formidable challenge, there is in fact a reasonable body of literature, particularly the work of Harpp, that shows the construction of allylic trisulfides to be a relatively straightforward task (Sullivan and Boustany, 1971; Harpp and Ash, 1971; Harpp *et al.*, 1978; Mott and Barany, 1984). Treatment of the enone **44** with diethyl cyanomethyl phosphonate/NaH/DME gave the α,β-unsaturated nitrile **55** (90%), as a single stereoisomer. At this stage we did not know the relative stereochemistry of **55** but, as will be seen later, the configuration of the double bond was shown to be that depicted. The nitrile was reduced using diisobutylaluminum hydride, first to give the aldehyde (after hydrolysis of the intermediate imine), and repetition of the same reduction gave the allylic alcohol **56** (89.5% overall yield from **55**). The derived mesylate was converted into the thioacetate **57** (92%) by treatment with freshly prepared sodium thioacetate in methanol.

Subsequent reduction of the thioacetate **57** with lithium aluminum hydride in ether followed by quenching the intermediate thiolate with *N*-(benzylthiosulfenyl)phthalimide gave the *S*-benzyl trisulfide **58** (92%). The *S*-benzyl



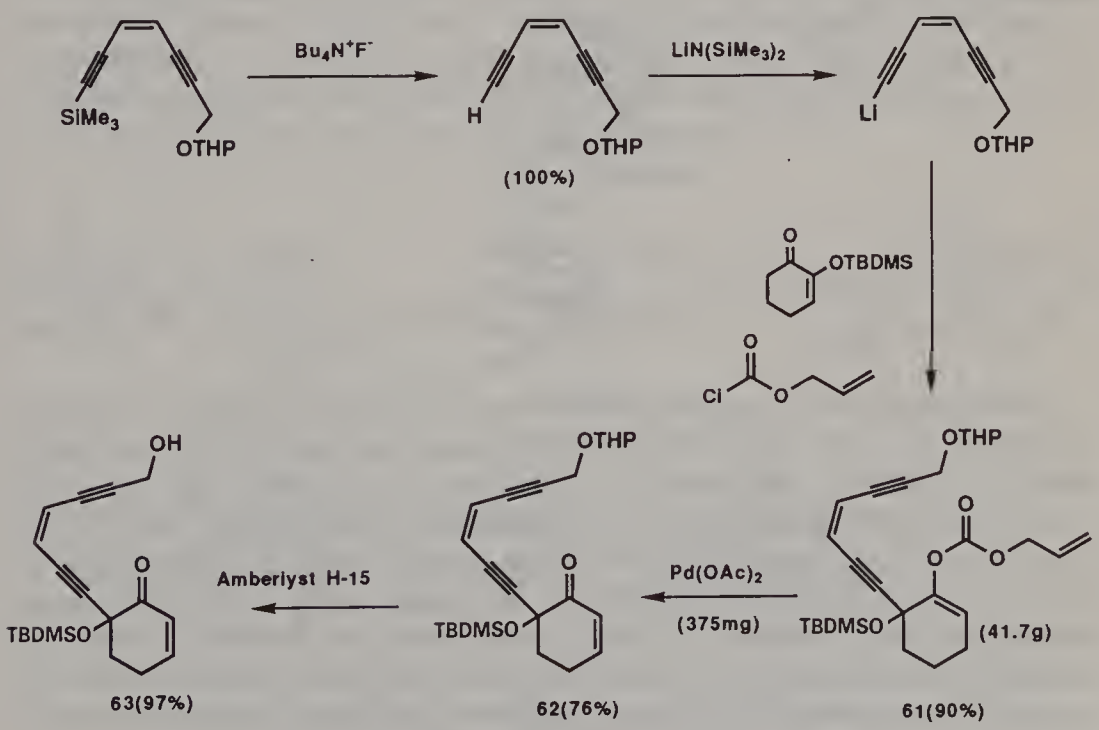
Scheme 15

derivative was chosen [(-SCH_2Ph) large enough to detect, for example, the corresponding disulfide (-$SCH_2Ph)_2$] in order to examine the thermal stability of **58** with respect to potential [2,3]sigmatropic rearrangement processes, and potential disproportionation processes (Trivette and Coran, 1966; Pickering *et al.*, 1967; Barnard *et al.*, 1969; Hofle *et al.*, 1971; Baechler *et al.*, 1973). In the event thermolysis of **58** in toluene at reflux for several days only resulted in complete recovery of **58**, and no evidence for any decomposition. The -SMe analog can be made in the same way. The sequence of transformations from the allylic alcohol to the trisulfide was used by Danishefsky (Haseltine *et al.*, 1991) in his synthesis of calicheamicinone, and more recently Nicolaou *et al.* (1992) demonstrated that it is completely compatible with the more highly functionalized bicyclo[7.3.1]enediyne system (Scheme 15).

We also examined more nucleophilic sources of thiolate and it was in the course of this study, by chance, that unequivocal chemical evidence for the assigned stereochemistry of the 13,14 double bond was found. When the xanthate **59** was hydrolyzed using ethylenediamine we isolated the cyclic sulfide **60** (60%), thus confirming the stereochemical assignments.

7 Convergent route and 12β-hydroxyl functionality

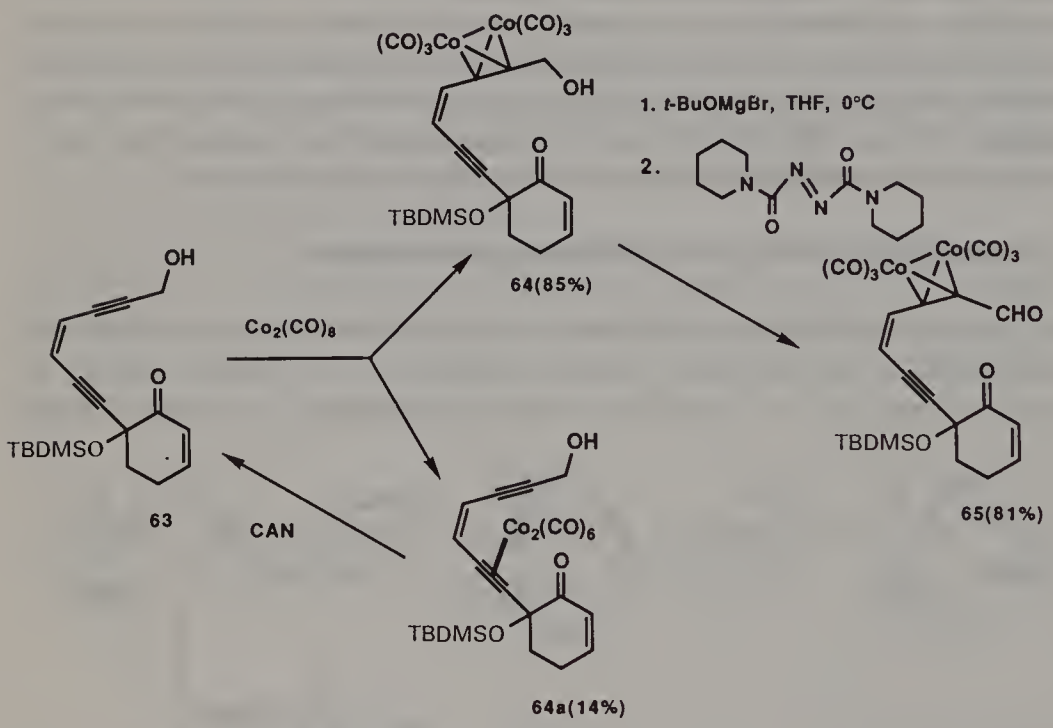
At this stage we needed to introduce the 12β-hydroxyl group, and make the introduction of the enediyne portion convergent. The sequence shown in Scheme 16 represents an optimized route of the enone **63**. In a single step the



Scheme 16

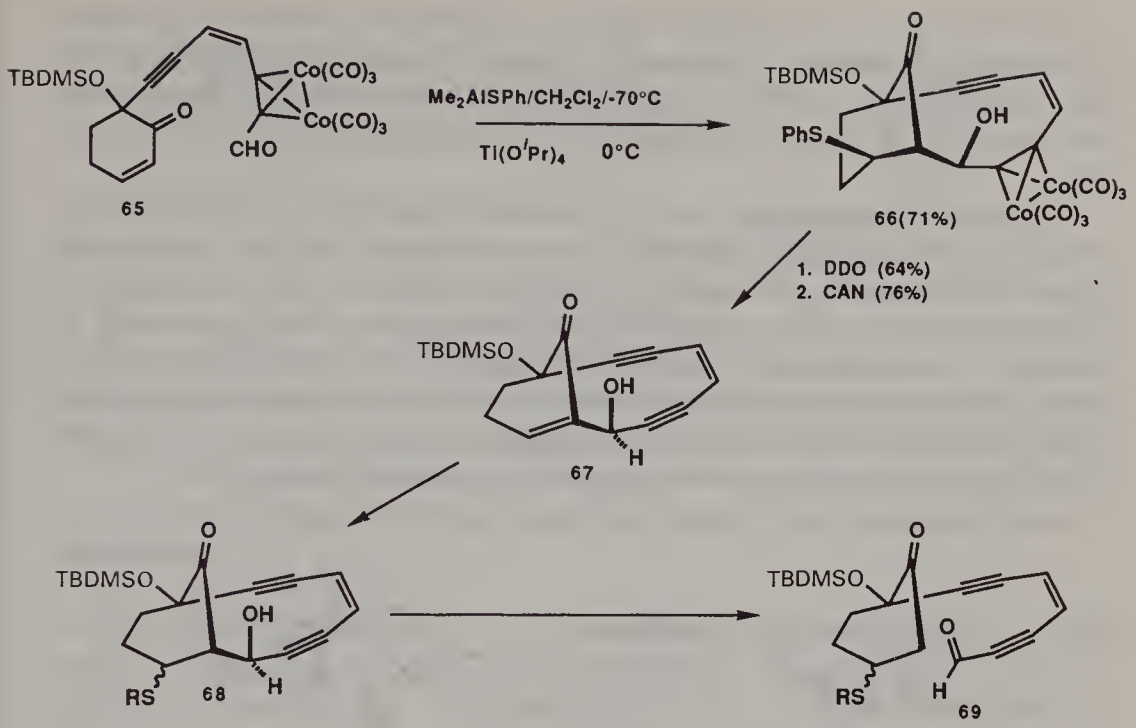
lithio-enediyne is added to the 1,2-diketone and the enolate (after TBDMS migration) is trapped with allyl chloroformate to give the allyl carbonate **61** in 90% yield on a large scale. Palladium diacetate-catalyzed oxidation of **61** gave the enone **62**, which was deprotected to the alcohol **63**.

Treatment of the enediyne **63** with dicobaltoctacarbonyl gave **64** (85%) and the regioisomer **64a** (14%). The incorrect regioisomer can be recycled by oxidation using ceric ammonium nitrate to give **63**. Oxidation of the $\eta^2Co_2(CO)_6$-acetylene complex gave the aldehyde **65**. It should be noted that the aldehyde is more stable as the $\eta^2Co_2(CO)_6$-acetylene complex than the free aldehyde. The complexes are air stable and can be chromatographed without decomposition (Scheme 17).



Scheme 17

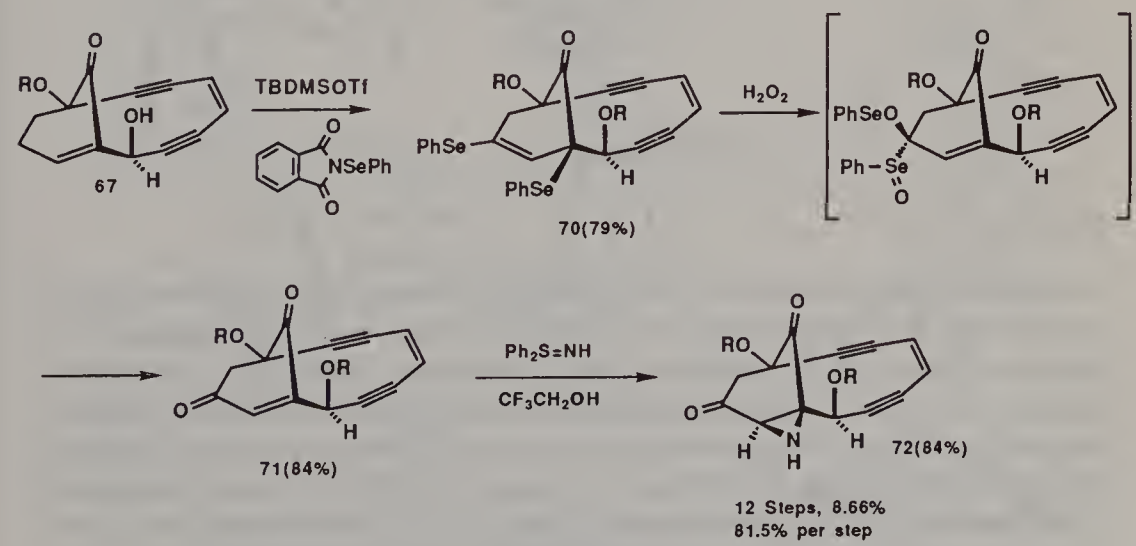
After considerable experimentation it was found that treatment of **65** with Me_2AlSPh at −70°C followed by $Ti(O^iPr)_4$ and quenching the mixture with silica gel resulted in the bicyclo[7.3.1]enediyne cobalt adduct **66** as a single stereoisomer (J. F. Kadow, private communication; Kadow *et al.*, 1989, 1992). This is the only ring closure that gives exclusively the correct stereochemistry at the C_{12} hydroxyl group. Oxidation of the sulfide using dimethyldioxirane followed by decomplexation (CAN) gave the enone **67**. The derived diol is a potent antitumor agent (*in vivo*). Treatment of **67** with a thiol resulted in extensive degradation via conjugate addition to give **68** and subsequent retro-aldol reaction to the ring cleaved aldehyde **69** (Scheme 18).



Scheme 18

8 Introduction of the C_2 nitrogen functionality

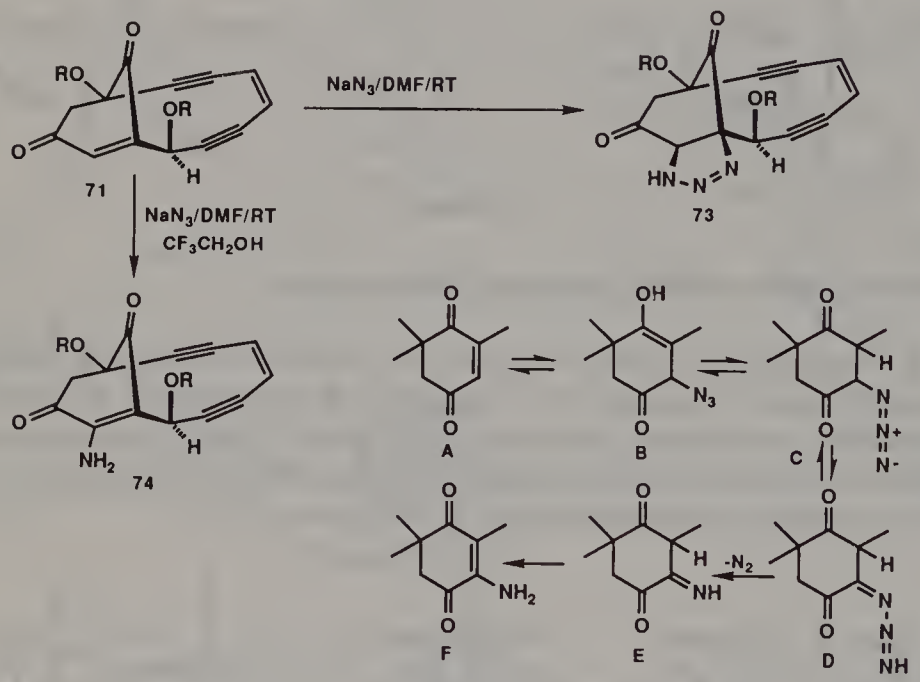
The α,β-unsaturated ketone **67** readily formed the allylic–vinylic bisphenylselenide **70** upon treatment with *N*-phenylselenenylphthimide. It is essential that this transformation be conducted with freshly crystallized reagent, and the reaction mixture protected from light. Oxidation of **70** with hydrogen peroxide or dimethyldioxirane gave the enedione **71** (Scheme 19).



Scheme 19

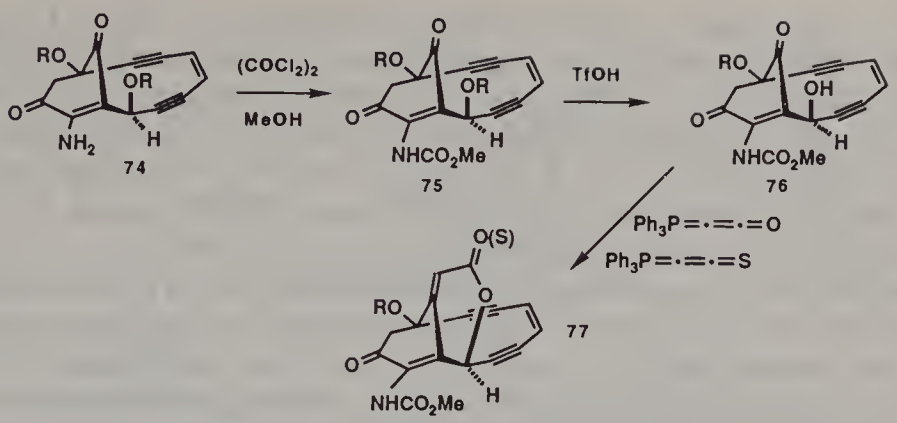
Initial efforts to introduce the required nitrogen functionality at C_2 resulted in the discovery that the enedione **71** reacted with diphenyliminosulfurane to give the aziridine **72** (84%). The aziridine **72** is an isomer of the required vinylamine and we intend to convert it into the aziridine analog of calicheamicinone.

In principle, if azide anion could be conjugatively added to the enedione **71** it is in the correct oxidation level to give the vinylamine **74**. The tautomerism shown in Scheme 20 can convert an α-azido ketone **C** into **D**, and loss of dinitrogen results in the imine **E** which can tautomerize to the vinylamine **F**. In practice, it was eventually found that treatment of **71** with sodium azide in dimethylformamide and trifluoroethanol (1:1) gave the required vinylamine **74** (55%). If this reaction is carried out in dimethylformamide alone, the triazole **73** is formed, and does not convert into the vinylamine (Scheme 20).



Scheme 20

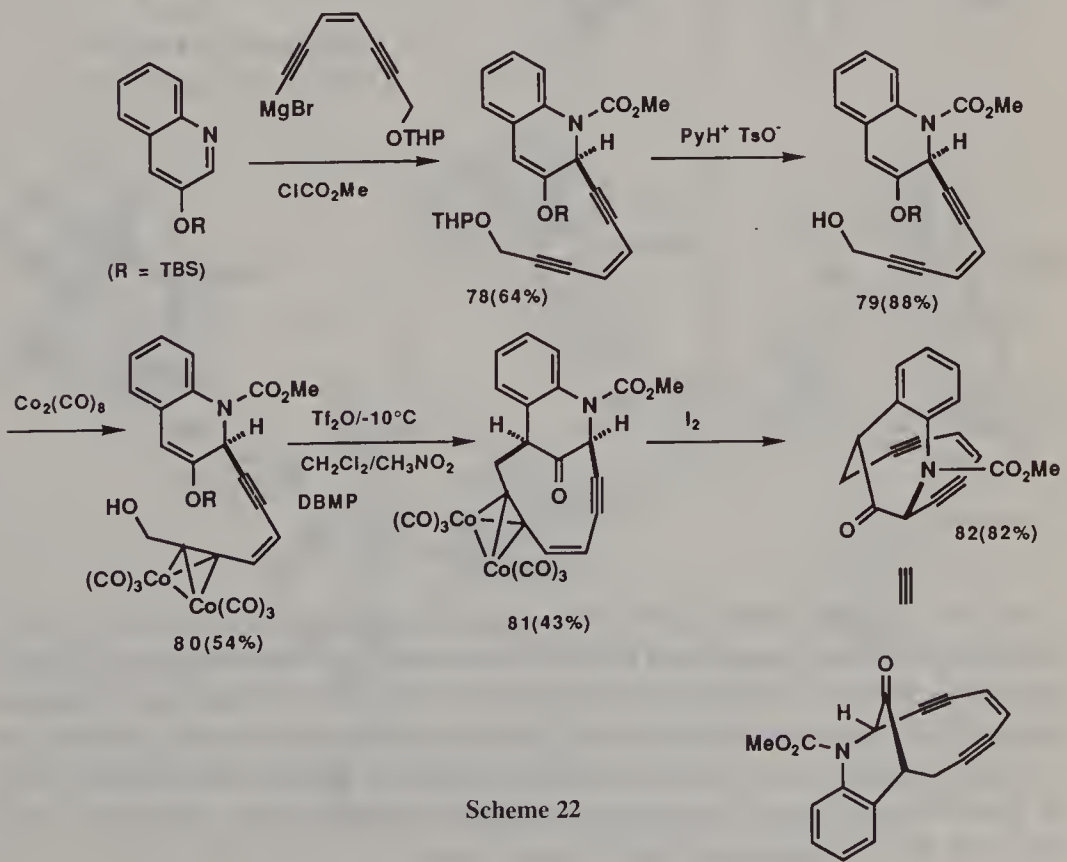
The two reactions from the α,β-unsaturated ketone **67** add all of the required functionality for calicheamicinone. The vinylamine was converted into the methylcarbamate **75** by treatment with diphosgene followed by methanol. Hydrolysis of the secondary *t*-butyldimethylsilyl ether was achieved by treatment with triflic acid in dichloromethane to give **76**. We are currently exploring the reaction of **76** with the Bestmann reagent (Ph_3PCCO) to give the lactone **77**. We are also exploring the thioanalog (Ph_3PCCS), and the conversion of **77**, using the sequence in Scheme 15, to calicheamicinone (Scheme 21).



Scheme 21

9 The $\eta^2Co_2(CO)_6$-acetylene complex route to the dynemicin core structure

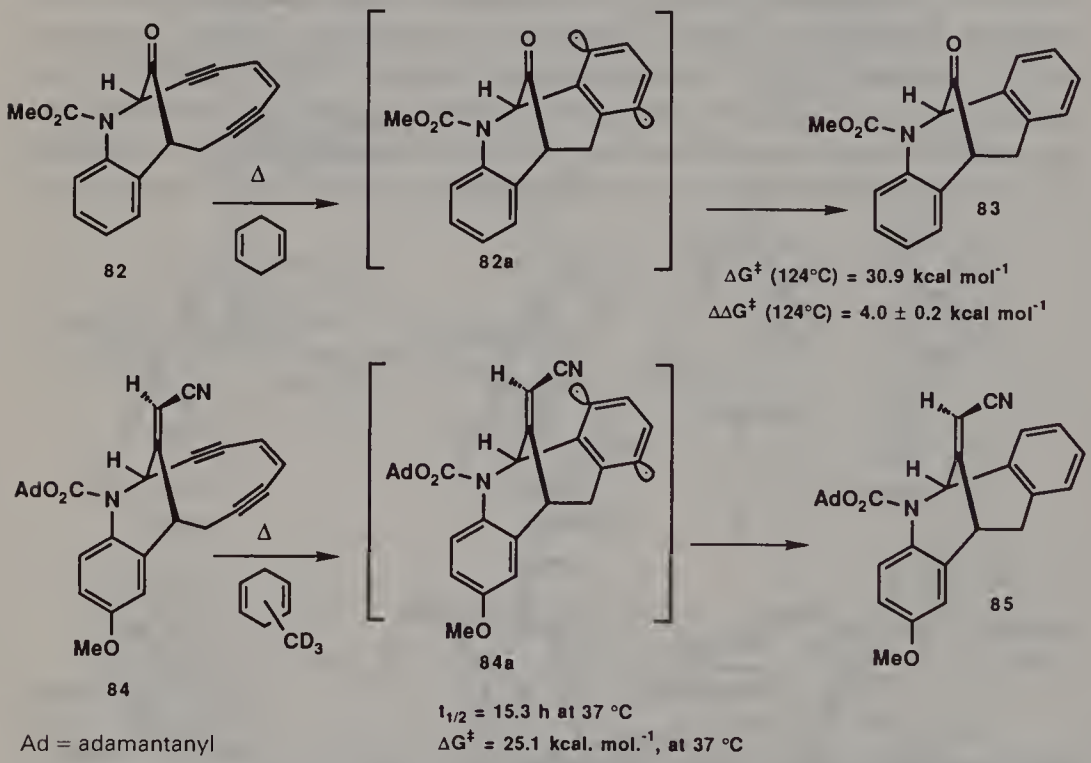
We have extended the chemistry developed for the esperamicins and calicheamicins to the synthesis of the dynemicin core structure (Magnus and Fort, 1991). Treatment of the *t*-butyldimethylsilyl ether of 3-hydroxyquinoline with the magnesio enediyne acetylide in the presence of methylchloroformate gave, in a completely regiospecific reaction, the dihydroquinoline **78** (64%) (Scheme 22). Selective deprotection of the THP ether to give **79** (88%) was accomp-



Scheme 22

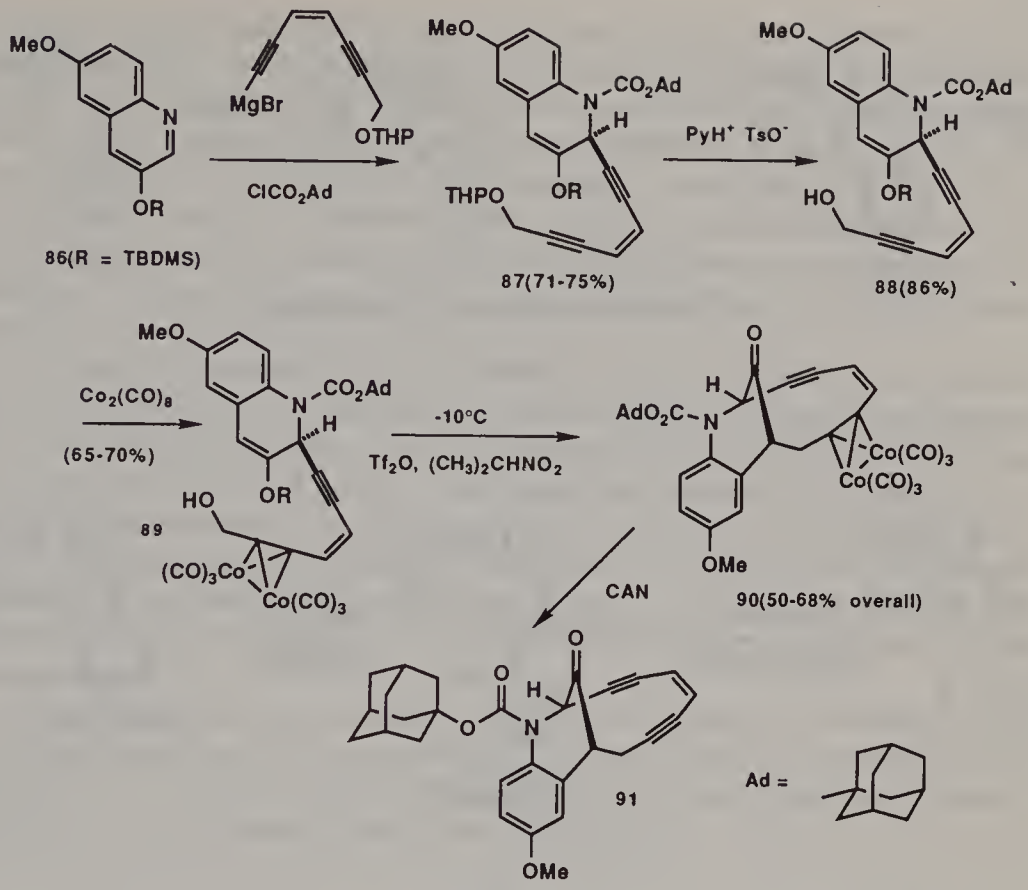
lished using pyridinium tosylate/EtOH. Complexation of **79** with $Co_2(CO)_8$ gave **80** (54%) along with some complexation at the other acetylene (*ca* 15%) and *bis*-complexation. The incorrect regioisomer can be recycled. Treatment of **80** with triflic anhydride/DBMP in CH_3NO_2/CH_2Cl_2 (1:2) at −10°C gave the cyclized product **81** (43%). It is essential to use a nitroalkane solvent; dichloromethane alone gave a symmetrical ether derived from **80**. Oxidative decomplexation using iodine gave the core structure **82** (82%).

The dynemicin core azobicyclo[7.3.1]enediyne **82** proved to be remarkably resistant to cycloaromatization. It required heating in 1,4-cyclohexadiene at 124°C for hours to convert it into **83** (84%), giving an approximate $\Delta G^{\#}$30.9 kcal/mol (Scheme 23). This should be compared to the conversion of **18** and **20** into **37** and **36**, respectively (Scheme 9). The presence of three additional trigonal atoms in **82** makes the transition state leading to the diyl **82a** more strained. The α,β-unsaturated nitrile **84** is considerably more susceptible to cycloaromatization. It clearly shows that the factors that influence the rate ($\Delta G^{\#}$) are subtle. This increase in rate was predicted by MM2 calculations.



Scheme 23

The route to the simple dynemicin core structure **82** can be extended to the 6-methoxyquinoline system, and the carbamate changed to an adamantyl group to assist its removal. Using the same sequence of transformations the quinoline derivative **86** was converted into the cyclization precursor **89** via **87** and **88**. The crucial $\eta^2Co_2(CO)_6$-acetylene-mediated cyclization of **89** to give **90** proceeded in 50–68% yield, and oxidative decomplexation gave the crystalline core structure **91** (Scheme 24 and Fig. 4).



Scheme 24

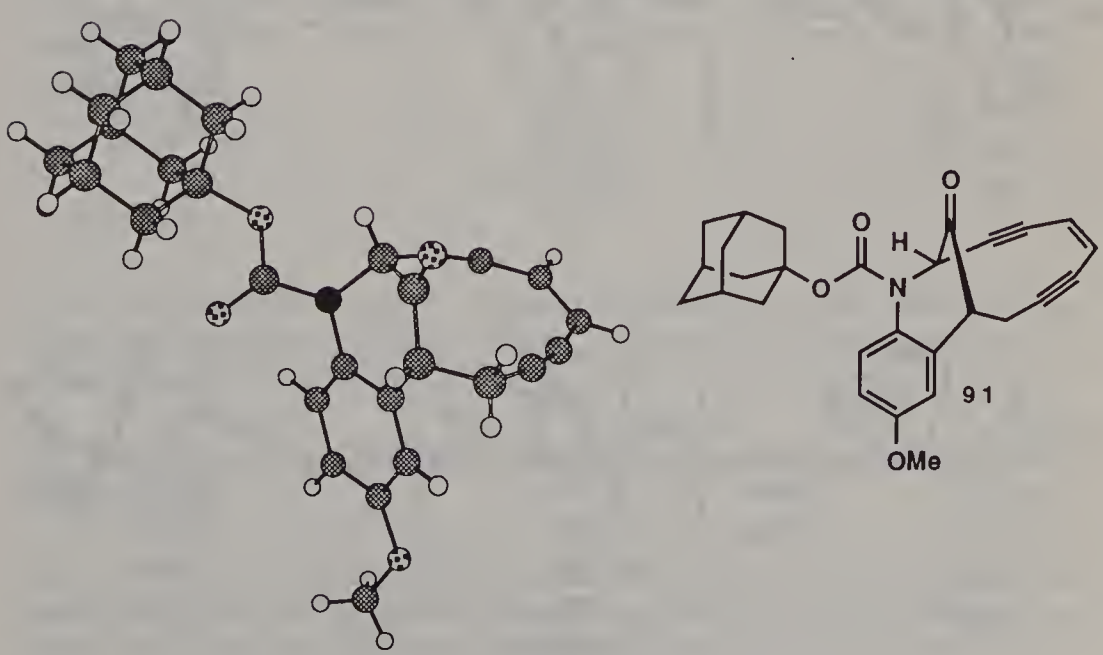
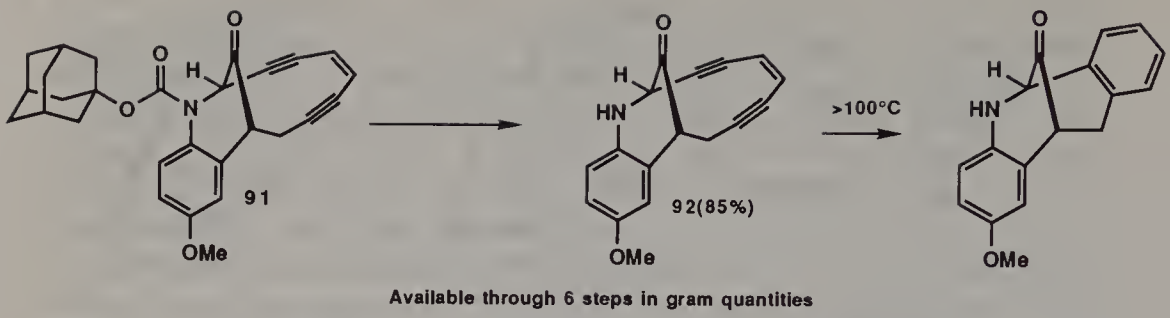
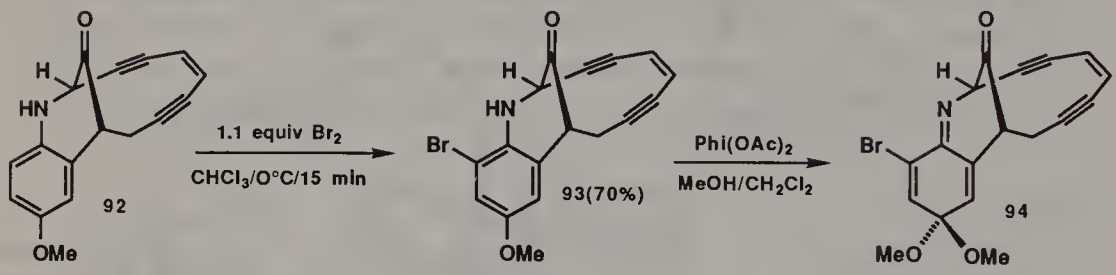


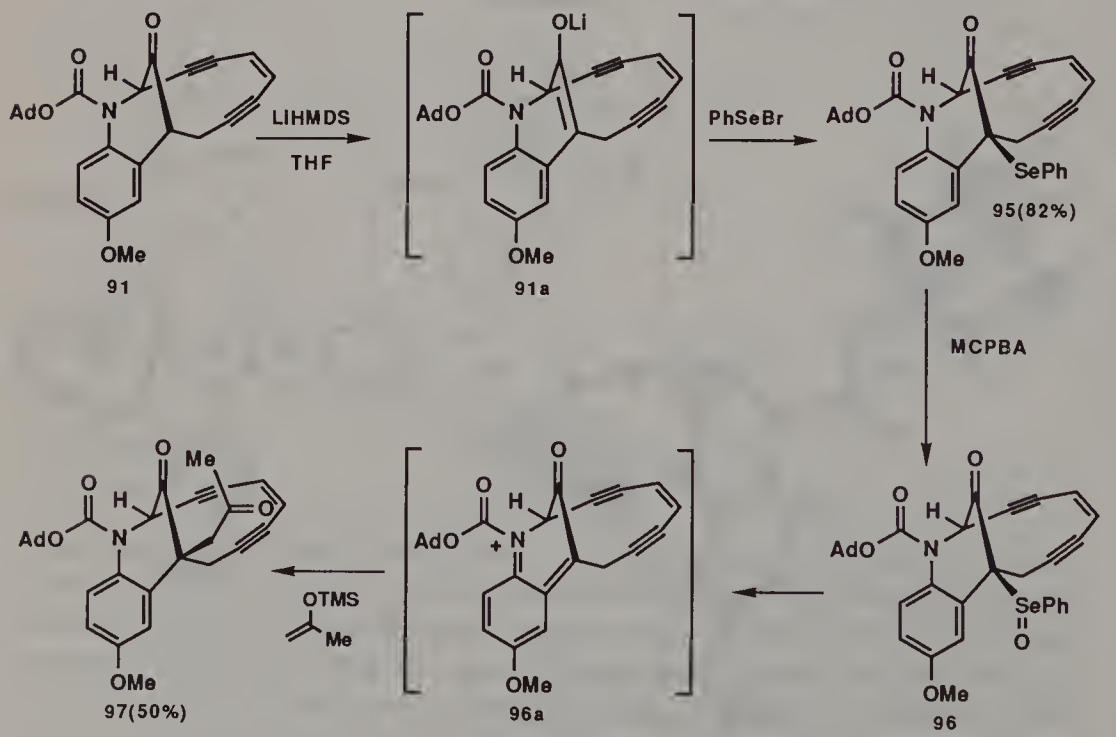
Fig. 4 Computer-generated representation of **91** from X-ray coordinates.



Scheme 25



Scheme 26

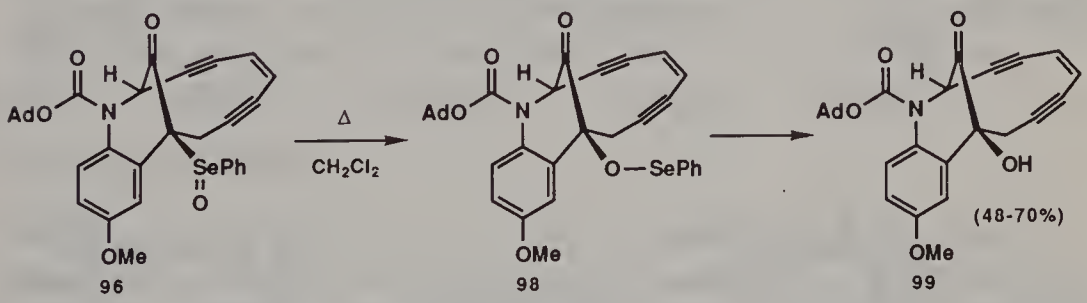


Scheme 27

The adamantyl carbamate protecting group survives the above reaction conditions intact, and is readily removed by treatment of **91** with trifluoroacetic acid in dichloromethane to give the stable amine **92**. The amine **92** shows promising antitumor activity (*in vivo*), and is available in gram quantities in six steps (Scheme 25). Surprisingly, the secondary amine **92** could be cleanly brominated to give **93**. Excess bromine did not add to the enediyne system. The bromide **93** was cleanly oxidized to the imine **94**. We are currently exploring the chemistry of this compound with a view to assembling the anthraquinone portion of dynemicin (Scheme 26).

The bridged ketone **91** is particularly prone towards enolization. The lithium enolate **91a** was treated with phenylselenenyl bromide to give the bridgehead derivative **95**. Oxidation gave the relatively stable selenoxide **96**. When **96** was warmed to 40°C in the presence of the trimethylsilyl enol ether of acetone, the only product that could be isolated was the adduct **97**. This compound has presumably arisen from addition to the iminium ion **96a**. We had hoped that the iminium ion **96a** would lose a proton to give a torsionally strained enone. The chemistry of this system is dominated by the readily formed iminium ion **96a** (Scheme 27).

As a further illustration for the propensity for iminium ion formation, the selenoxide was heated alone in dichloromethane. There was observed slow conversion to an intermediate (probably **98**) which was subsequently transformed into the bridgehead alcohol **99** (Scheme 28).

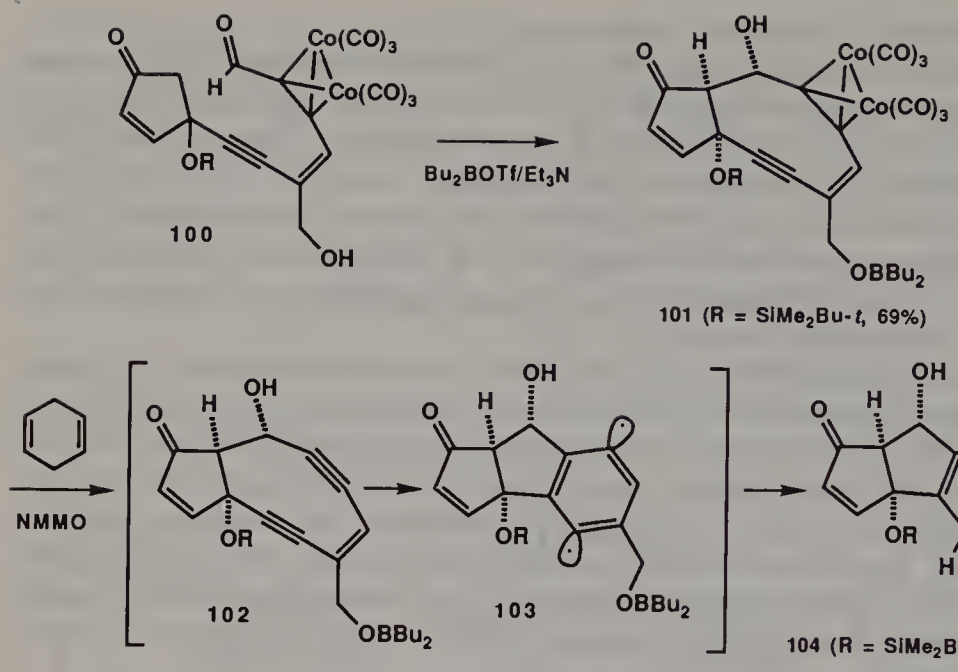


Scheme 28

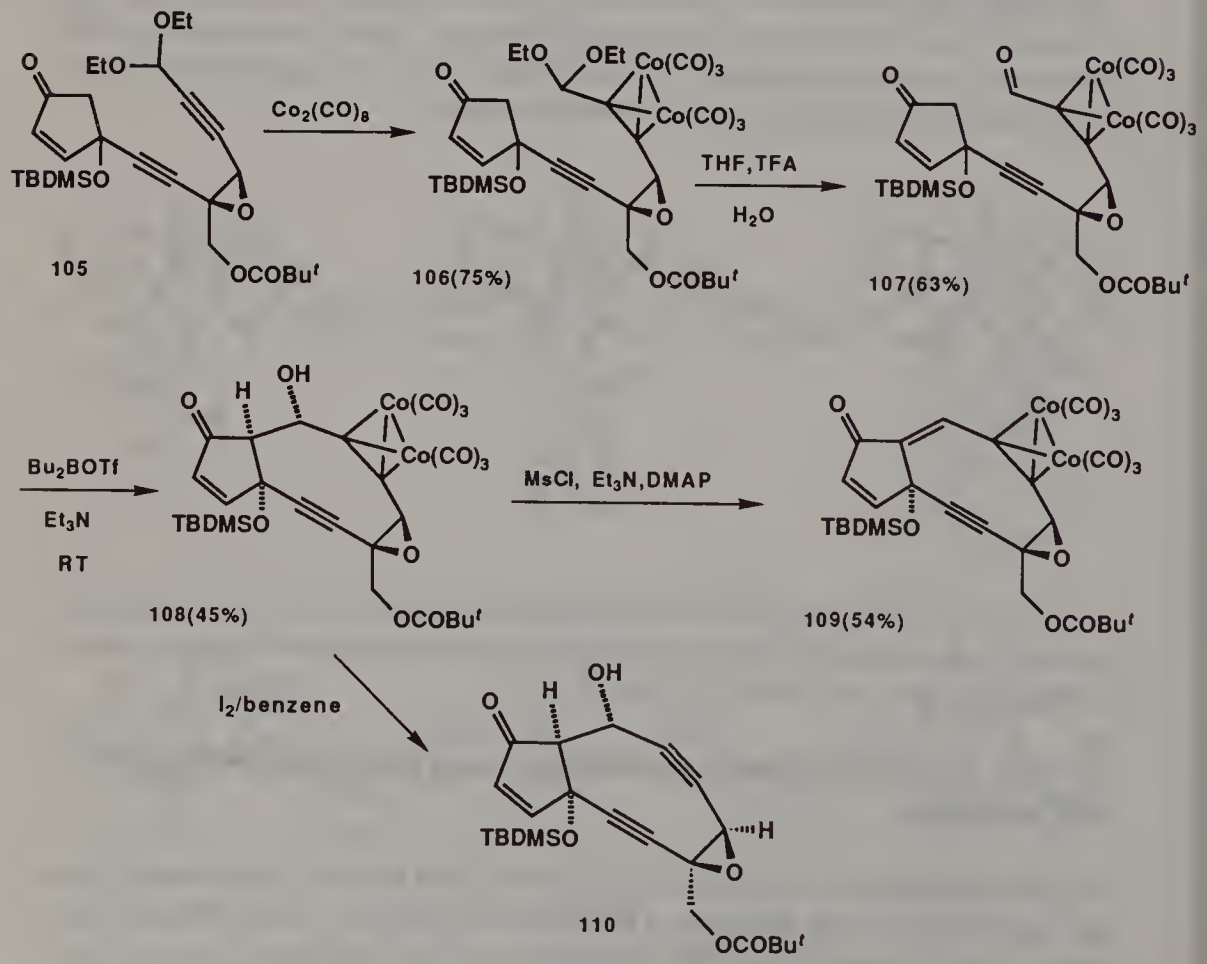
We have recently started to develop a short route to the anthraquinone portion of dynemicin, but since it does not involve organometallic chemistry it is not included in this report.

10 The $\eta^2Co_2(CO)_6$-acetylene complex route to the neocarzinostatin core structure

The cobalt-mediated aldol cyclization can be used for the construction of the neocarzinostatin core structure (Magnus and Pitterna, 1991; Magnus and Davis, 1991). The aldehyde **100** was made by a short sequence similar to those



Scheme 29



Scheme 30

described in Schemes 16 and 17. Treatment of the aldehyde **100** with di-*n*-butylboron triflate/Et_3N gave the cyclized aldol product **101** (69%). As expected, when the cobalt metallocycle was oxidatively removed the enediyne **102** was too unstable to be isolated and immediately cycloaromatized to give the compound **104** (Scheme 29).

We were interested to see if an epoxide would be stable enough to be carried through the reaction sequence shown in Scheme 30. At the outset, it was decided not to conduct any model work to see if simpler compounds that contain an epoxide adjacent to the cobalt metallocycle would be stable. This proved to be a wise (in retrospect) decision, because the transformations shown in Scheme 30 work for the real system, but so-called simple epoxyacetylenes do not form isolable $\eta^2Co_2(CO)_6$-acetylene adducts such as **106**. The key aldol reaction involves treatment of **107** with di-*n*-butylboron triflate/Et_3N to give **108** in moderate yield. The aldol adduct can be dehydrated to give **109**, or oxidatively decomplexed to give **110**.

11 Summary

In all of the $\eta^2Co_2(CO)_6$-acetylene-mediated cyclizations the blank reaction without the cobalt metallocycle was unsuccessful. Either the substrate was completely destroyed or there was no reaction. The routes to the core enediynes are all quite short, and make available sufficient material for the more meaningful *in vivo* biological evaluations. The rate studies clearly show that ring strain and conformational factors control the ease of cycloaromatization. This information should assist the design of non-natural enediynes with potential antitumor activity.

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2

Metals in Organic Chemistry. Is it Worth taking the Risk?

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1 Metal-catalysed epoxidation of electron-deficient olefins

With the collaboration of M. Bailey, P. F. Richardson and N. Hindley

Oxidations (and reductions) are among the most important functional group interconversions in organic chemistry. It is extremely rare to find a total synthesis of some importance that does not involve, at one stage or another, an oxidative (or reductive) step. It is therefore not too surprising that a lot of effort has been invested in chemoselective and stereoselective oxidation processes. Perhaps the best known, and most useful, oxidative transformation is the Sharpless titanium-catalysed epoxidation of allylic alcohols (Fig. 1) that produces epoxy-alcohols of high optical purity (Gao *et al.*, 1987).

For synthetic reasons presented later in this chapter, we became interested in the diastereoselective epoxidation of electron-deficient olefins possessing a stereogenic centre at either the β- or γ-position. More specifically, we wondered if it would be possible to control the stereochemistry of epoxidation of β-hydroxyenones to produce either the *syn* or the *anti* epoxide. These β-hydroxyenones, readily available via a Baylis–Hillman reaction (Drewes and Roos, 1988), are interesting starting materials since they are hybrids of allylic alcohols and α,β-unsaturated ketones and should normally not be epoxidized by metal catalysts such as Ti, V and Mo reagents. That they are indeed electron-deficient alkenes is clearly revealed by their complete lack of reactivity towards peracids (Fig. 2, Entry 4). As expected, Weitz–Scheffer-type nucleophilic epoxidation proved successful. However, although we varied considerably the experimental conditions, a 2:3 ratio of *syn* to *anti* epoxyalcohols was consistently produced. At this stage, and nearly resigned to such a poor ratio, we attempted, almost in desperation, the Sharpless-type epoxida-

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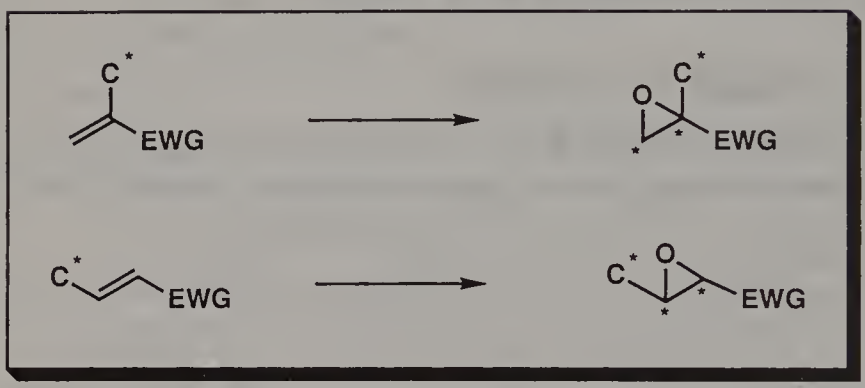
Sharpless and Katsuki (1980)



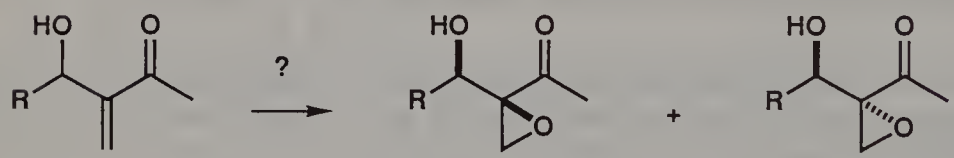
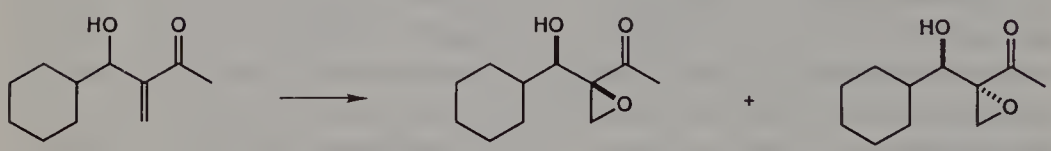


Fig. 1 The Sharpless titanium-catalyzed epoxidation of allylic alcohols.



H_2O_2 / NaOH / MeOH / 0°C	40	60
TBHP / NaOH / MeOH / -40°C	33	67
BQBr / CHP / Tol / NaOH / -20°C	40	60
mCPBA / CH_2Cl_2 / 20°C / 3 days	no reaction	

Fig. 2 Diastereoselective epoxidation of the model system. BQBr, benzyl quinimium bromide; CHP, cumene hydroperoxide.

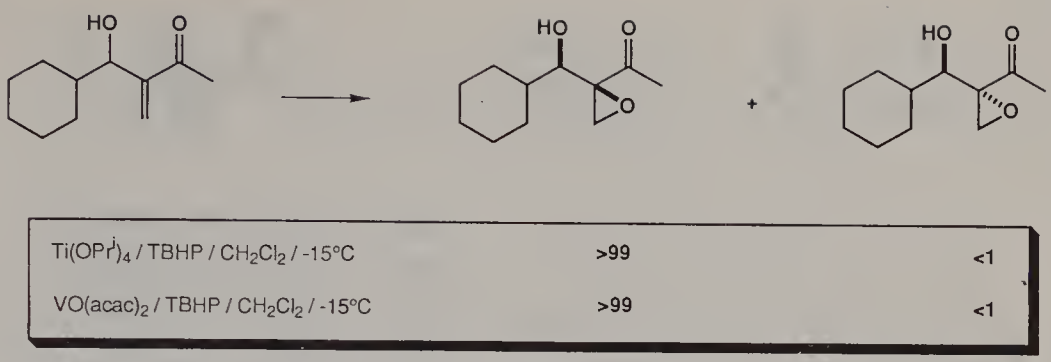


Fig. 3 *A stroke of luck* (from Bailey *et al.*, 1990).

tion of these β-hydroxyenones. Gratifyingly, and much to our surprise, the *syn*-epoxyalcohol was obtained as a sole isomer in good yield. Vanadium-catalysed epoxidation proceeded likewise (Fig. 3). This is, we believe, the first example of titanium and vanadium-catalysed epoxidation of electron-deficient olefins. Other examples, including β-hydroxyacrylates, are shown in Fig. 4. In every instance, regardless of the size or electronics of the substituent present on the stereogenic centre, only the *syn*-epoxyalcohol was produced. In the case of a methyl ester, transesterification accompanies the epoxidation. If the free hydroxyl group is protected (for example as TMS ether) no epoxidation takes place. This observation suggests that coordination of the β-hydroxyenone (acrylate) to the metal catalyst somehow overrides the negative effect of transferring an 'electron-deficient oxygen atom onto an electron-deficient alkene', an otherwise unlikely process (Bailey *et al.*, 1991b).

Oxidation of cyclic substrates proved equally successful using Ti or V reagents. Again, essentially complete *syn*-epoxidation was observed. However, and in sharp contrast to acyclic systems, base-catalysed epoxidation also provided predominantly the *syn*-epoxyalcohol. Although the example shown in Fig. 5 involves a cyclohexene derivative, similar selectivity, the extent of which varies with the size of the epoxidizing agent, was observed for cyclopentene and cycloheptene homologues.

In order to understand and rationalize this inverse selectivity, differently protected β-hydroxyenones were prepared and epoxidized. As can be seen from Fig. 6, replacing the free hydroxyl group by a TBS ether did not alter the sense of the epoxidation and barely affected the ratio itself (Entry 2), thus suggesting that hydrogen bonding does not play an important part in this facial selectivity. Remarkably, no selectivity was observed if an acetoxy or pivaloxy protecting group was employed (Entries 3 and 4).

Based on MM calculations of the preferred ground state conformations of β-hydroxyenones, performed in collaboration with Prof. J. S. Svendsen and Ms M. Skar, at the University of Tromsø (Norway), we tentatively propose that coordination of the hydroxyl or TBS ether *oxygen lone pairs* onto the incoming nucleophile (either to the sodium counterion or to the proton of the non-

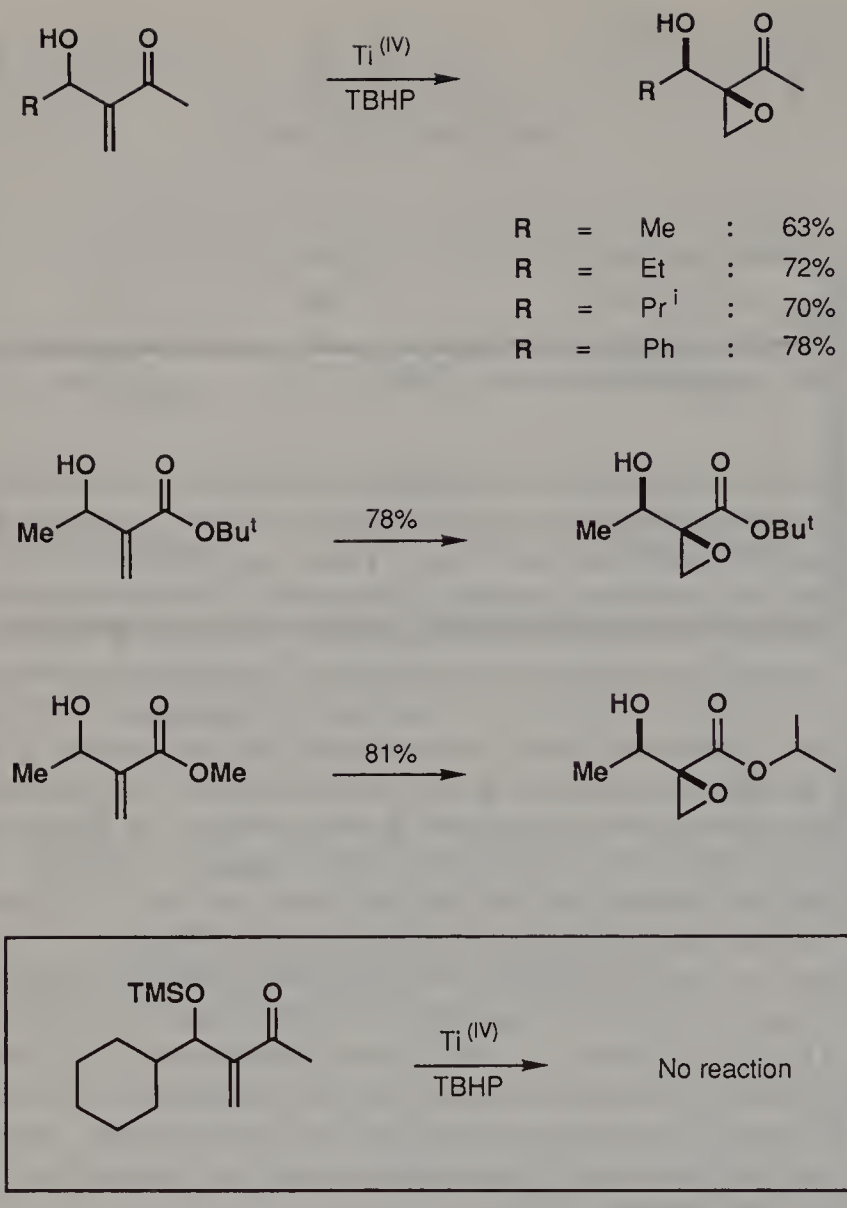


Fig. 4 Titanium(IV)-catalysed *syn*-epoxidation.

ionized peroxide) is responsible for the observed facial recognition (Fig. 7). In this coordinated state, the conformation leading to the *syn*-epoxide is favoured because of minimum eclipsing interactions (Bailey *et al.*, 1991a; similar conclusions were also reached by R. J. K. Jackson). The conformation leading to the *anti*-epoxide suffers from more serious steric hindrance. This rationalization also provides an explanation for the lack of selectivity displayed by the acetate and pivalate derivatives. Indeed, these substrates can no longer coordinate the epoxidizing agent, their oxygen lone pairs being tied up by virtue of the conjugation with the carbonyl function. Attack of the peroxide then occurs on the conformation in which the olefin is equally accessible from both sides, resulting in the observed 1:1 ratio.

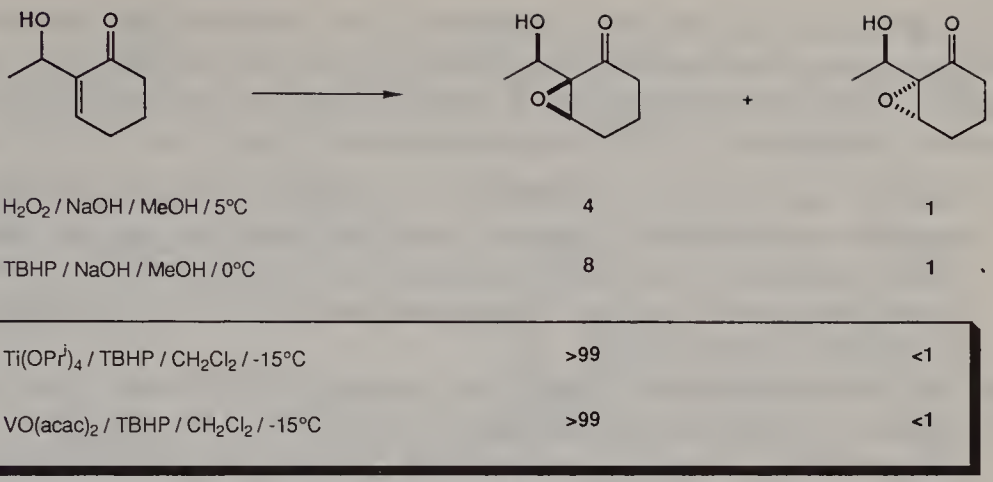


Fig. 5 Epoxidation of cyclic systems.

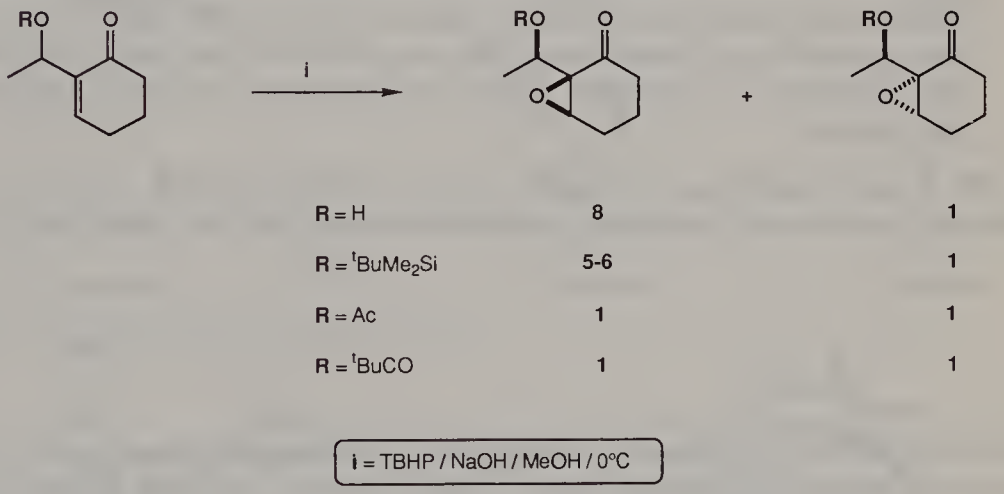


Fig. 6 Epoxidation of protected cyclic systems (from Bailey *et al.*, 1991b).

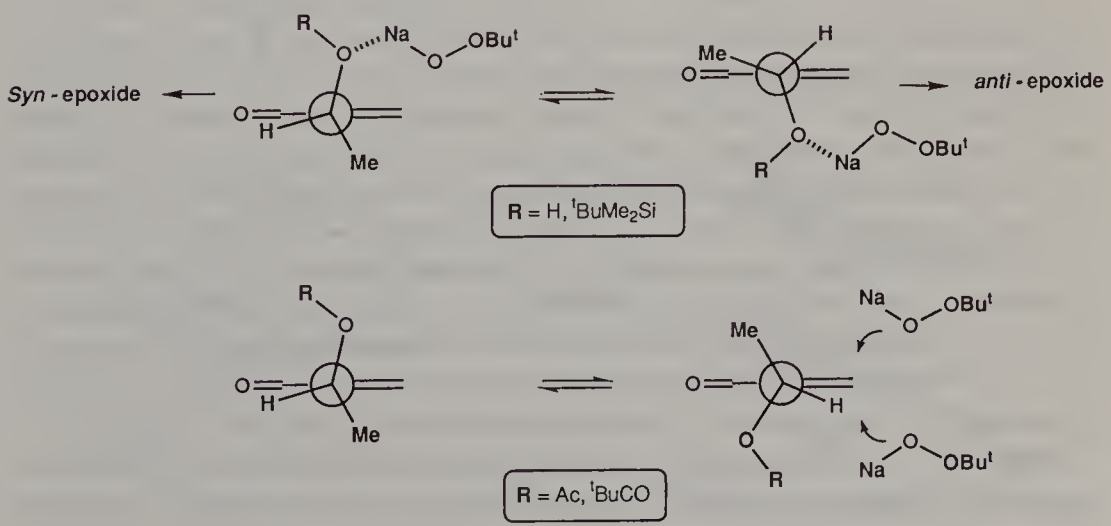


Fig. 7 Facial selectivity in the nucleophilic epoxidation.

The persistent *syn*-selectivity displayed by the titanium (and vanadium) catalyst can also be tentatively rationalized (Fig. 8). We believe that a non-reactive half-chair titanium chelate is initially formed as the major species in solution. Transfer of the TBHP oxygen can occur by one of two mechanisms:

(i) The first one involves an intramolecular pathway proceeding through a boat-like transition state. However, if such was to be the case, one would expect variations of the *syn:anti* epoxide ratio as the allylic strain interactions change with the size of the substituent present at the stereogenic centre of the starting enone.

(ii) The second mechanism requires the opening of the chelate. Two conformers, in which the correct trajectory for delivery of the oxygen atom of the peroxide is respected, are possible. The first one has the titanium moiety located below the plane of the alkene. However, in this conformer, the ligands on the metal clash with the substituent present on the hydroxyl-bearing centre and it is thus disfavoured. In the second conformer, the titanium unit is positioned above the plane of the alkene and the ligands only encounter a hydrogen atom. This conformer leads to the *syn*-epoxyalcohol.

The kinetic resolution of β-hydroxyenones was also briefly investigated using the Sharpless asymmetric epoxidation protocol (Fig. 9). Although DET

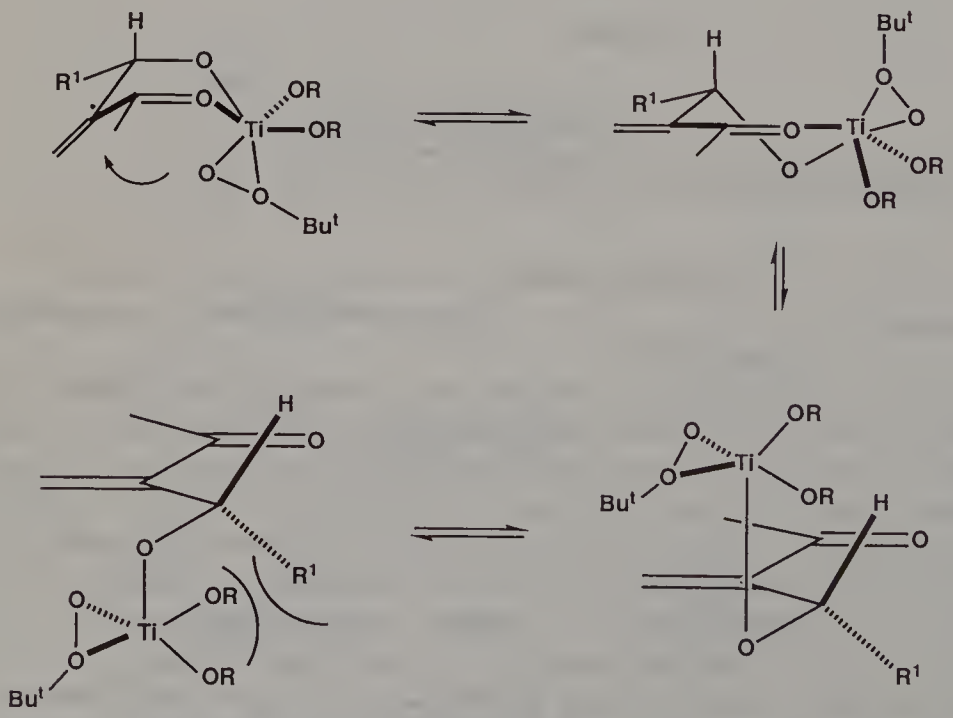


Fig. 8 Metal-catalysed epoxidation.

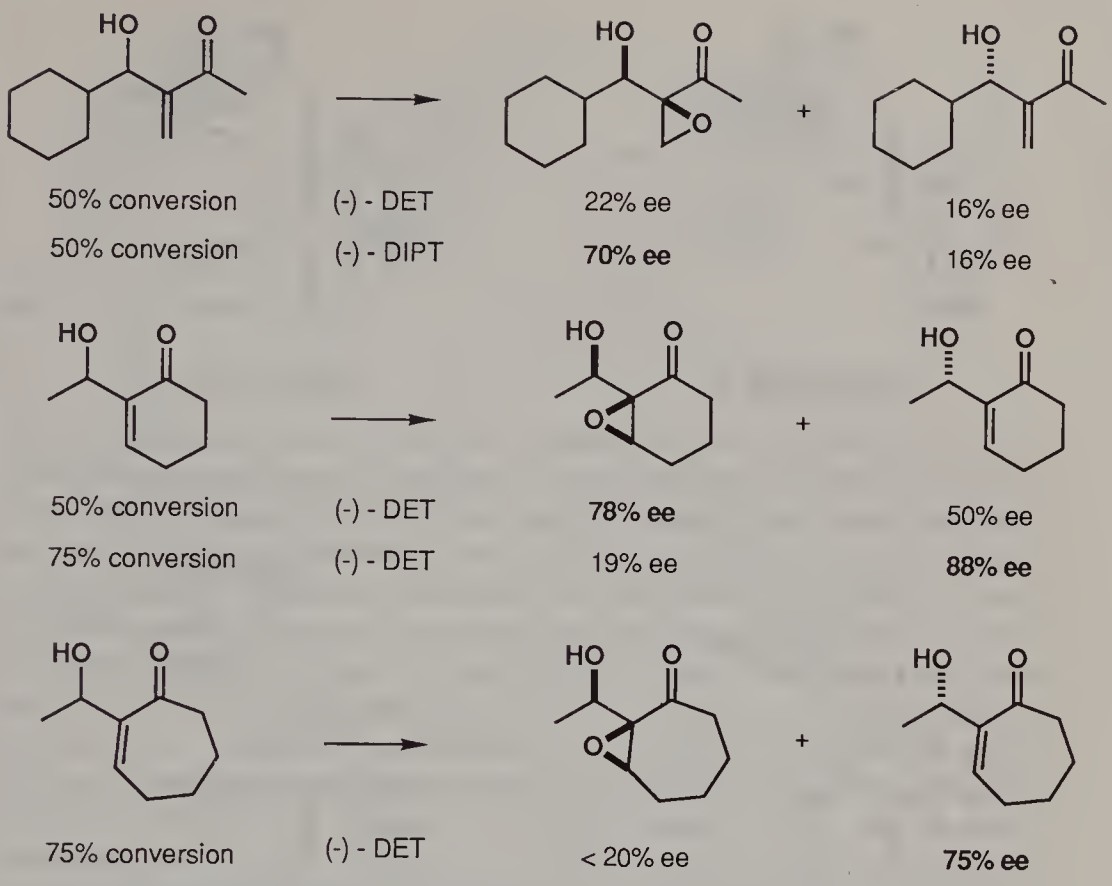
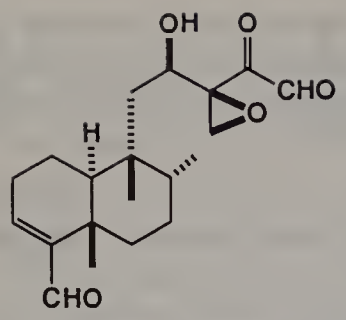


Fig. 9 Kinetic resolution of β-hydroxyenones.

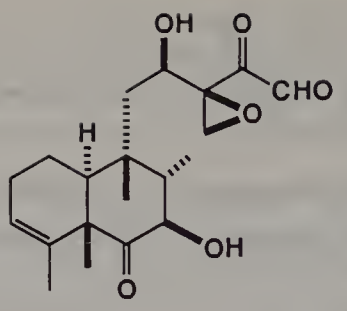
proved inefficient in the case of alicyclic β-hydroxyenones, its use allowed, for the first time, the preparation of cyclic β-hydroxyenones and related epoxides of high optical purity. Recourse to DIPT was necessary to obtain decent ees in the kinetic resolution of alicyclic systems.

Recently, the dihydroxylation of β-hydroxyenones has also been investigated (Jacobsen *et al.*, 1988). Much to our surprise (and delight), it was found that high levels of diastereocontrol could be exercised in this reaction, with diasteroisomeric ratios usually higher than 10:1. Even more intriguing is the unusually high rapidity of these osmylations (they are typically complete within 30 min at 0°C). *In complete contrast to the epoxidation reaction, β-acetoxyenones are osmylated with higher diastereocontrol than the free alcohol or the TBS ether.* Although the *syn/anti* relationship between the acetoxy substituent and the diol function has not yet been established beyond doubt, we believe that the scope of this reaction deserves to be fully studied.

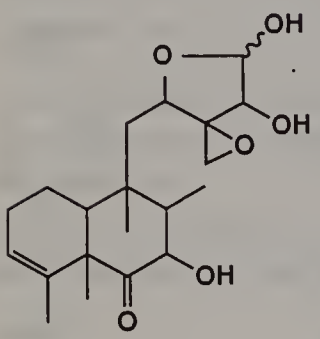
Meanwhile, the utility of functionalized *syn*-epoxyalcohols as key precursors in the total synthesis of some natural products, was investigated. Clerocidin **1**, terpenticin **2**, spirocardin A **3** and spirocardin B **4** (Fig. 10) are novel clerodane



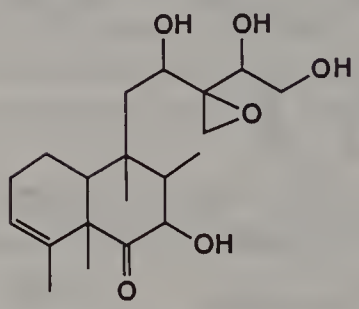
CLEROCIDIN **1**



TERPENTICIN **2**



SPIROCARDIN A **3**



SPIROCARDIN B **4**

Fig. 10 The targets.

diterpenoids possessing interesting pharmacological activities (Andersen *et al.*, 1984). Although the absolute and relative stereochemistries of all the chiral centres present in clerocidin and terpenticin have been fully determined, no such information is available for compounds **3** and **4**. As part of a programme aimed at the preparation of various anticancer and antiviral natural products, we became interested in the total synthesis of clerocidin and its congeners. Besides their biological properties, these diterpenoids also possess intriguing structures, the most unusual part being the highly oxidized side chain in which five carbon atoms, each connected to an oxygen atom, are formally at a different oxidation state. Interestingly, a *syn*-epoxyalcohol function is present in this side chain amongst other unusual features such as an α-ketoaldehyde function.

Our retrosynthetic analysis of clerocidin **1**, based upon the observations described above in this chapter, is shown in Fig. 11. We reasoned that the β-

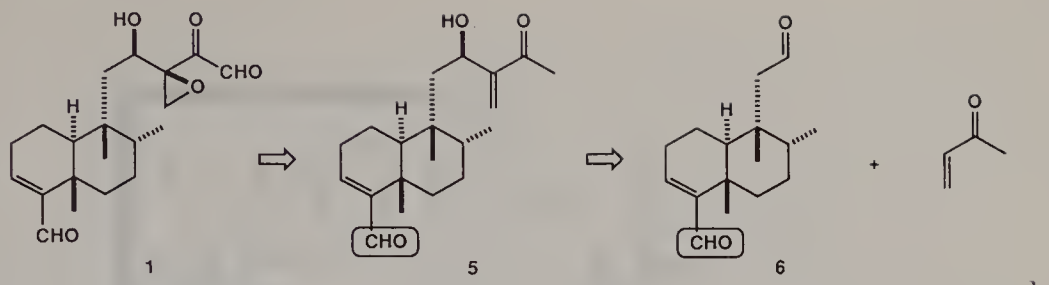


Fig. 11 Retrosynthetic analysis.

hydroxyenone derivative **5** could be a suitable precursor to clerocidin. Indeed, *syn*-epoxidation followed by oxidation of the methyl ketone function into an α-ketoaldehyde should give the desired target **1**. A Baylis–Hillman condensation between protected aldehyde **6** and methyl vinyl ketone could be used to prepare **5**. However, before embarking into the synthesis of **6**, one must be able to build the side chain with the correct functionalities. Therefore, we initiated some model studies, using the condensation product of cyclohexanecarboxaldehyde and MVK, as shown in Figs 12 and 13. Access to the clerocidin chain proved to be straightforward (Bailey *et al.*, 1990). Protection of the free hydroxyl function of the *syn*-epoxyalcohol model gave the acetate which was reacted with selenium dioxide in boiling dioxane giving the desired α-ketoaldehyde in good yield. For characterization purposes, the *ortho*-phenylenediamine adduct was prepared as a nicely crystalline white solid. A modification of this strategy produced a simple route towards the side chain of spirocardin B. For tactical reasons, a TBS protecting group was selected instead of the acetate employed earlier. Silyl enol ether formation proceeded smoothly and was followed by a Rubottom oxidation, giving the α-hydroxyketone derivative in moderate yield. Oxidation of the primary alcohol to the aldehyde provides a second route to the clerocidin side chain. Non-selective reduction of the ketone function gave a mixture of diols. Deprotection of the TBS group afforded the desired triols which were separated by careful chromatography. Both of these compounds were, of course, required since the relative stereochemistry of spirocardin B is unknown. The synthesis of protected aldehyde **6** has already been achieved in our group and the total synthesis of clerocidin is reaching completion.

Another challenging natural product is the tumour-promoting agent ingenol which possesses an all-*syn*-triol function. It was thought that ready access to such a triad could be reached employing our *syn*-epoxyalcohols (Fig. 14). Thus, addition of allyltrimethylsilane to epoxyalcohol **7**, prepared in two steps from cyclopentenone, proceeded regio- and stereo-selectively, affording the desired 1,2-*syn*-diol. Reduction of the ketone function leads to a model for the A-ring of ingenol in which all four chiral centres have been correctly established.

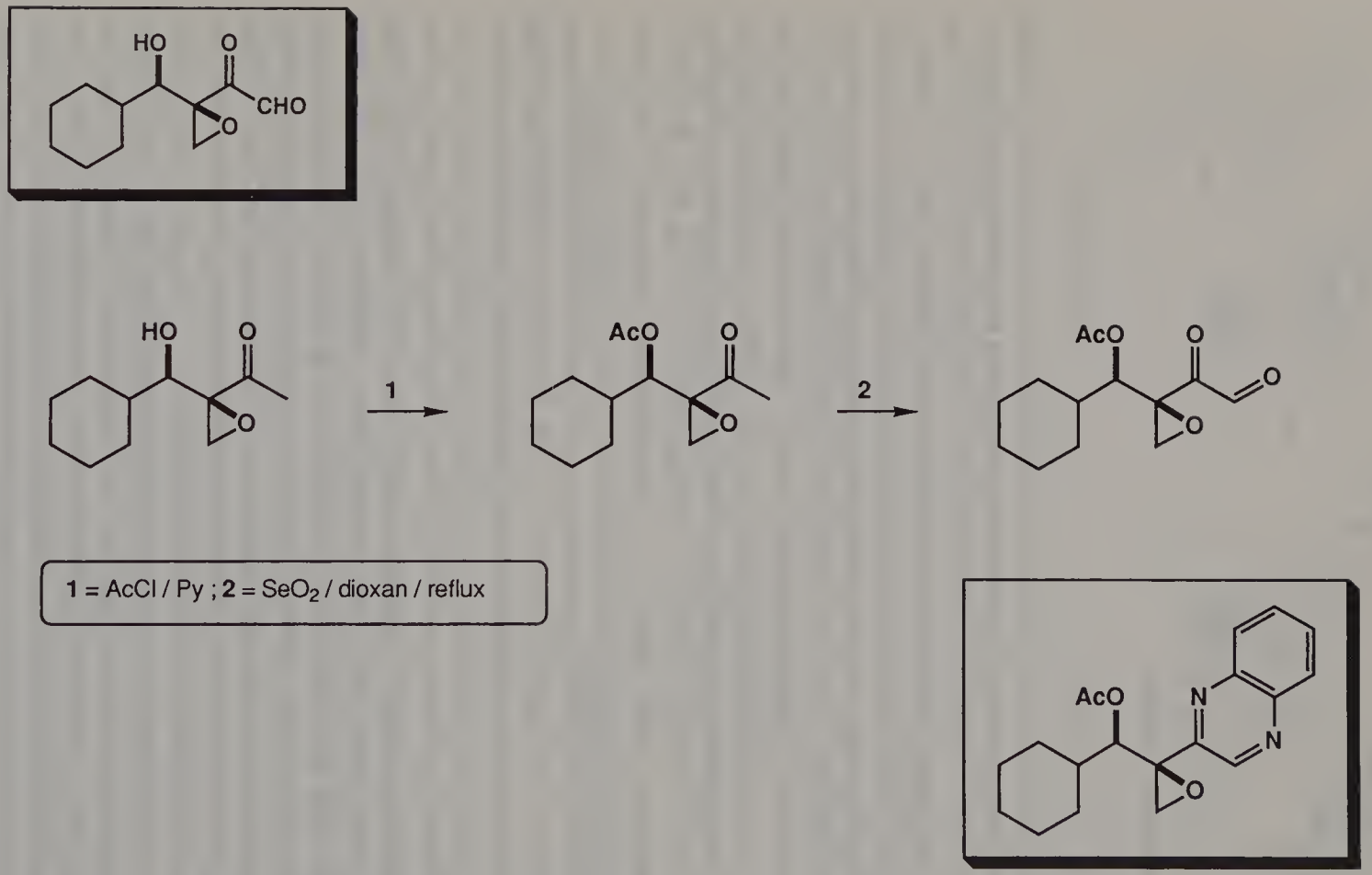


Fig. 12 Model studies: the clerocidin/terpenticin side chain.

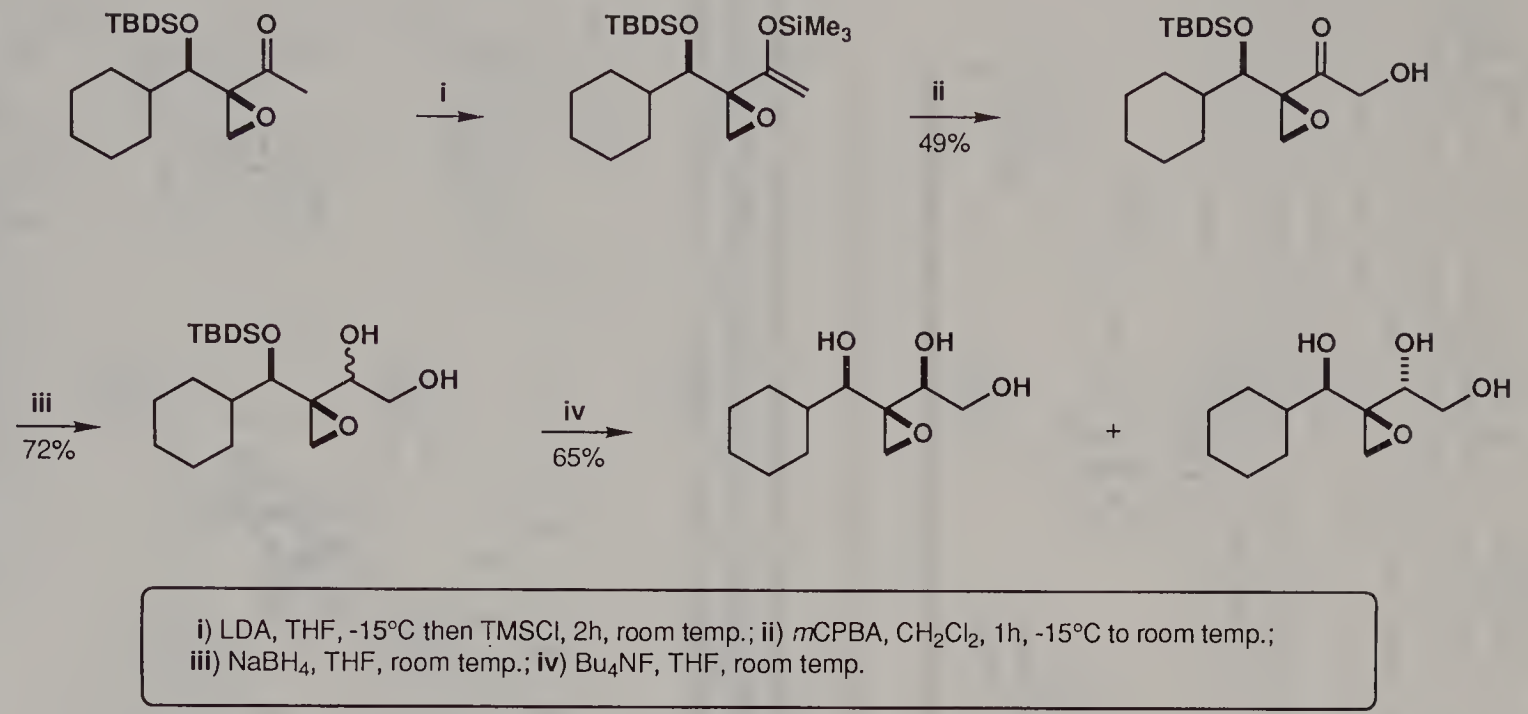


Fig. 13 Model studies: the spirocardins side chain.

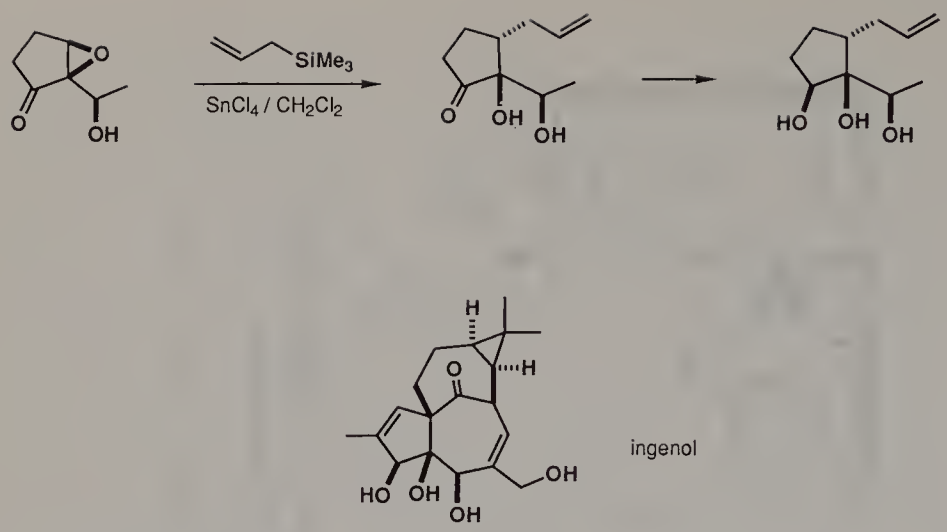


Fig. 14 Synthetic applications.

2 Tandem pericyclic reactions of 2-pyrone and derivatives

With the collaboration of L. Kennard, P. Seres and G. R. Evans

The Diels–Alder reaction of 2-pyrone with various alkenes is a known though not very efficient preparation of cyclohexadiene systems (Posner *et al.*, 1992). This process, involving two steps, begins with the initial formation of an

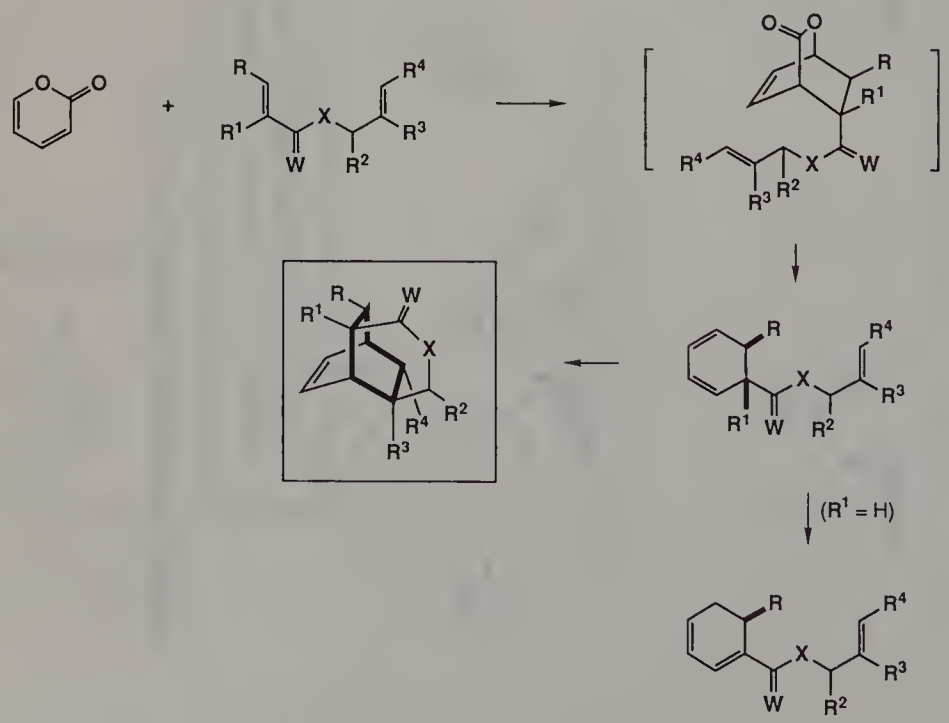


Fig. 15 Tandem pericyclic reactions: the concept.

unstable CO_2 adduct which rapidly loses CO_2. Cyclohexadienes possessing a suitably positioned alkene unit are known to undergo intramolecular Diels–Alder reactions, affording interesting polycyclic structures containing a plethora of stereochemical information. We wondered if, starting with 2-pyrone and using an α,ω-diene, the whole process could be performed *in a single step* (Fig. 15). At the onset of our work, only one article, by Krantz and Lin (1973), suggested that the idea might be viable.

The Diels–Alder reaction of 2-pyrone with some simple olefins was initially investigated (Figs 16, 17) and it soon became apparent that high pressure was required to promote these cycloadditions. *We were very surprised to find that*

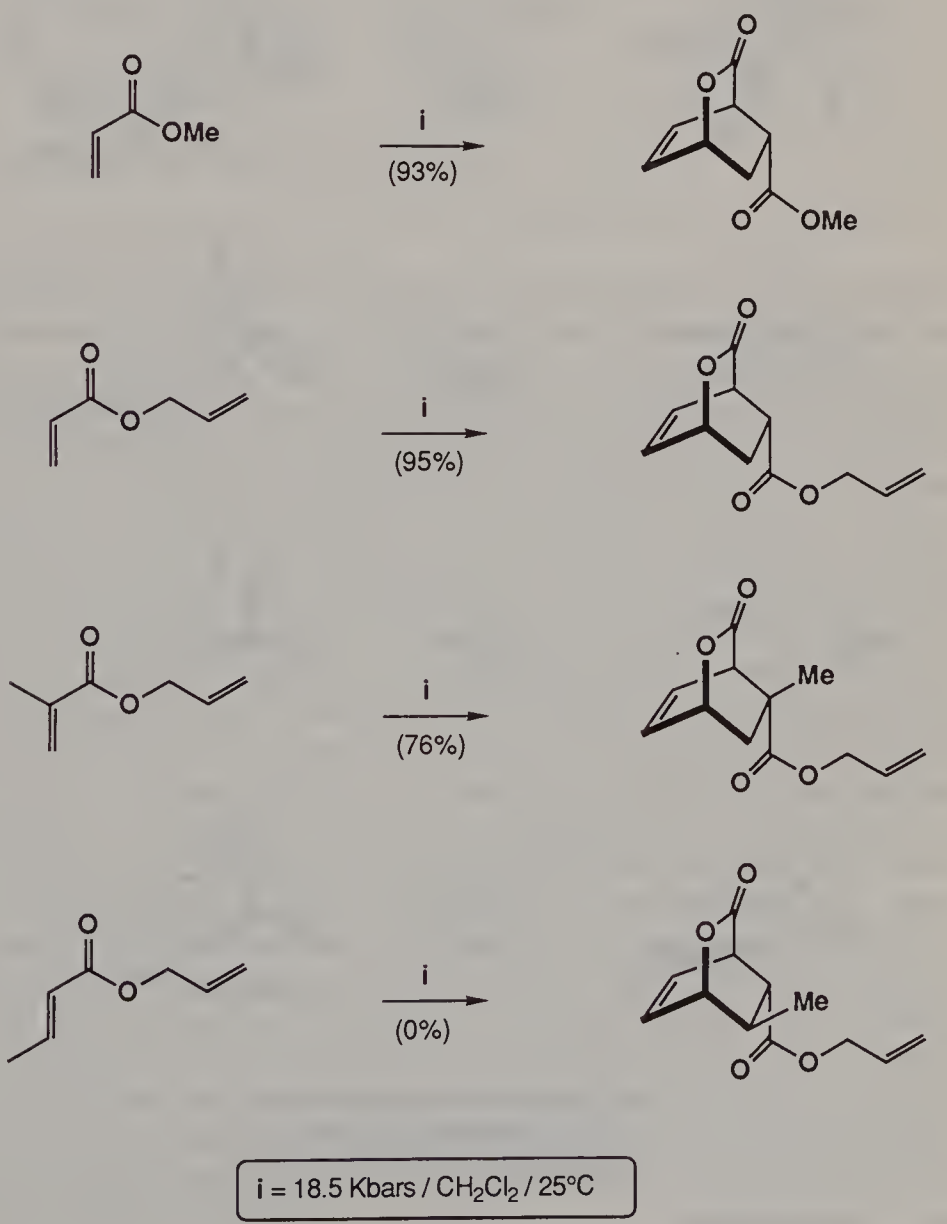


Fig. 16 Initial CO_2 adducts.

the initial CO_2 adducts, reputed to be unstable with respect to ready extrusion of CO_2, could be isolated in good yield from these high-pressure reactions. Even unfunctionalized olefins could be forced to react by selecting the correct conditions: in these cases a lower pressure but a higher temperature was required. Remarkably, the primary cycloadducts proved to be particularly robust, surviving under extreme conditions such as boiling nitrobenzene (150°C). These bicyclic lactones also possess rich stereochemical features embedded in their structures which can be revealed by simple manipulations.

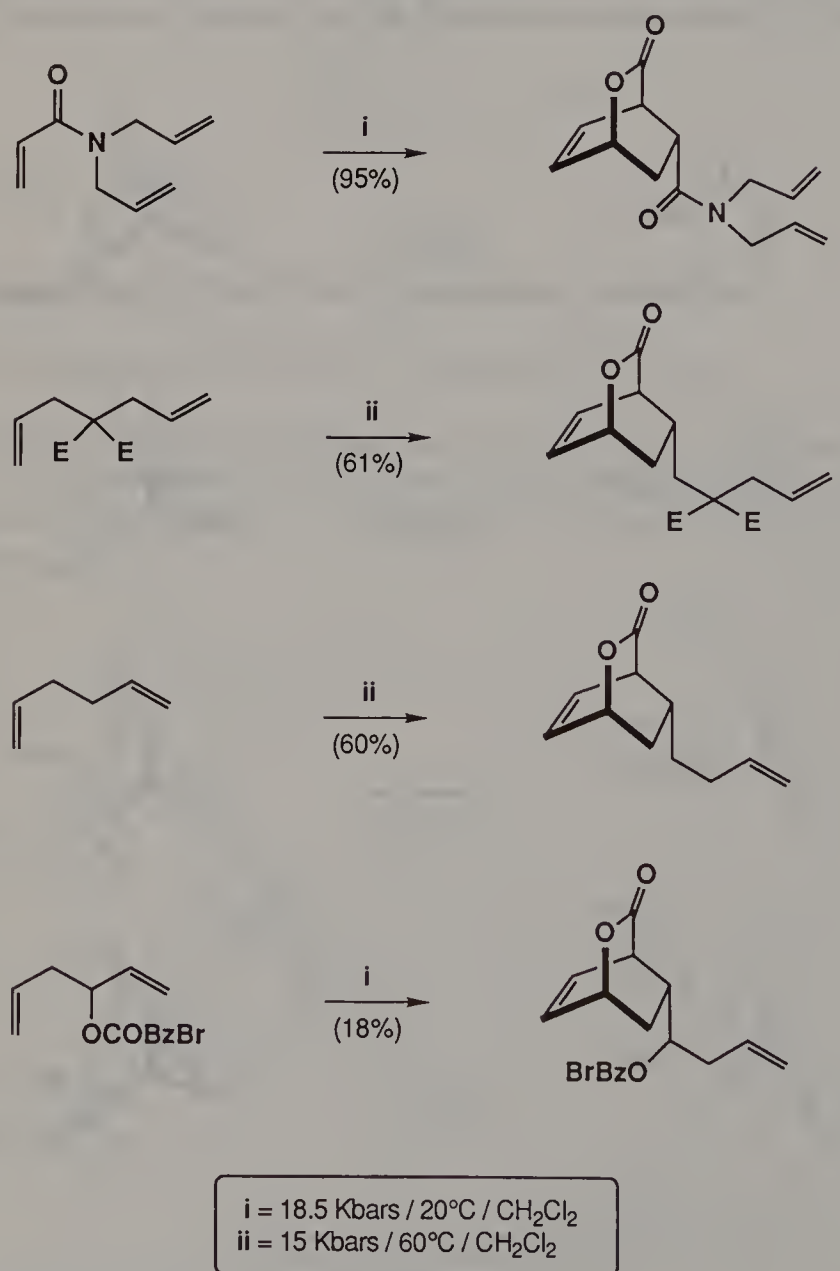


Fig. 17 Initial CO_2 adducts.

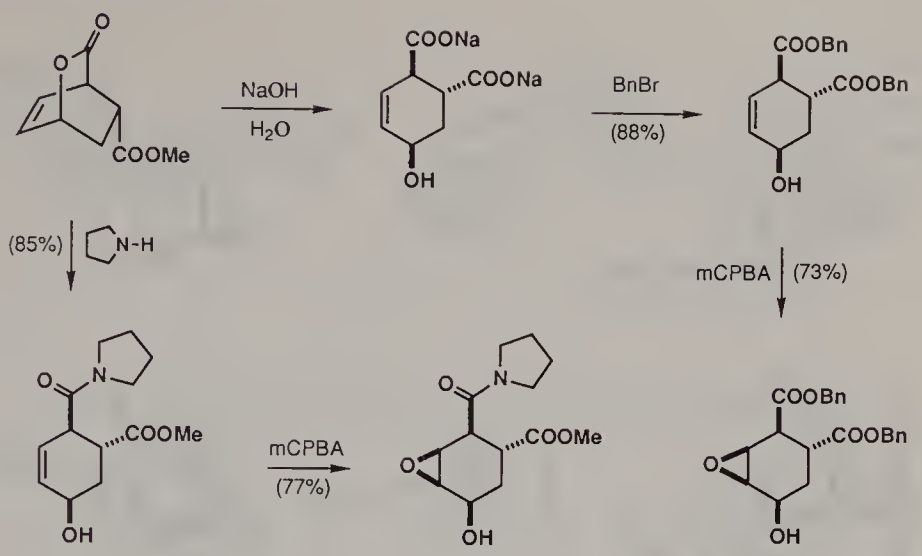


Fig. 18 Some useful transformations of CO_2 adducts.

For example, treatment of the bicyclic lactone derived from methyl acrylate and 2-pyrone with aqueous sodium hydroxide not only opened the lactone ring but also saponified the ester function (Fig. 18). Alkylation of the *bis*-carboxylate with benzyl bromide provided a di-ester. Hydroxyl-directed epoxidization then afforded the *syn*-epoxyalcohol. It is noteworthy that *five chiral centres on a cyclohexane ring system have been established with full stereochemical control, in a very short sequence of steps*. In order to discriminate between the two ester functions, the lactone ring was chemoselectively opened with pyrrolidine. Peracid treatment provided the *syn*-epoxyalcohol. These highly oxygenated cyclohexane derivatives are useful precursors for the synthesis of inositols, shikimic acid and their analogues (Markó *et al.*, 1992). The transformation of the bicyclic lactones into the final TPR adducts requires loss of CO_2 followed by an intramolecular Diels–Alder reaction. This conversion could be easily achieved (Fig. 19) by heating the lactones at temperatures around 220°C. In only one case was a temperature of 275°C necessary. The highly functionalized tetracyclic derivatives thus obtained are superb precursors for the synthesis of a variety of natural products (Swarbrick *et al.*, 1991). For example, oxidative cleavage of the C–C double bond of the TPR adducts produces [3,*n*,1] bicyclic aldehydes (Fig. 20). It is interesting to ignore the two aldehydic functions and look at the [3,*n*,1] bicyclic system in a retrosynthetic manner, highlighting the carbon atoms that originate from 2-pyrone. As can be seen (Fig. 20), *only two carbon atoms in the final [3,n,1] bicycle belong to the pyrone. All the others derive from the starting α,ω-diene*. This observation leads to a very simple retrosynthetic analysis of bicyclo[3,*n*,1] derivatives. A few examples are shown in Fig. 21.

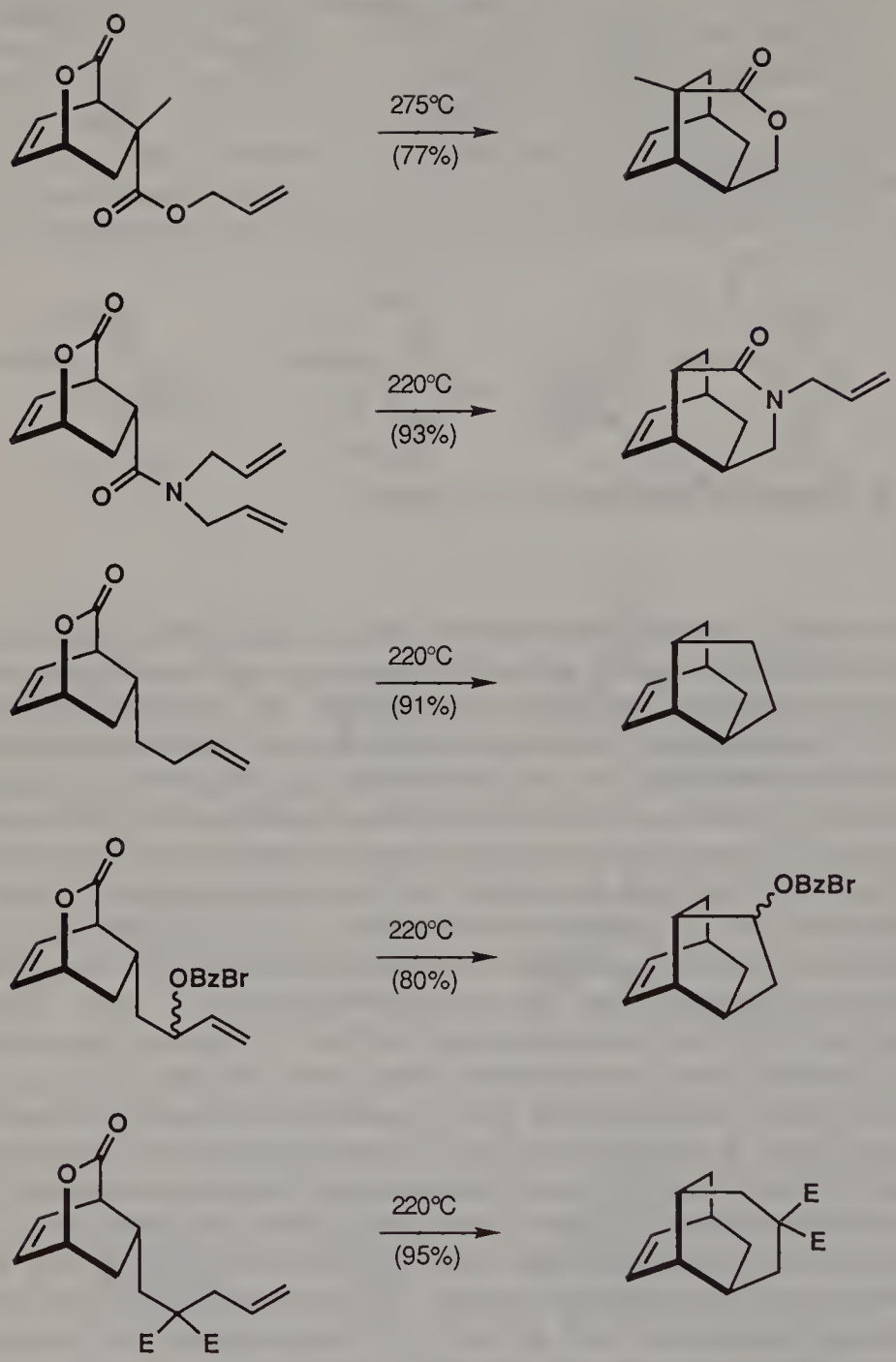


Fig. 19 Tandem pericyclic reactions.

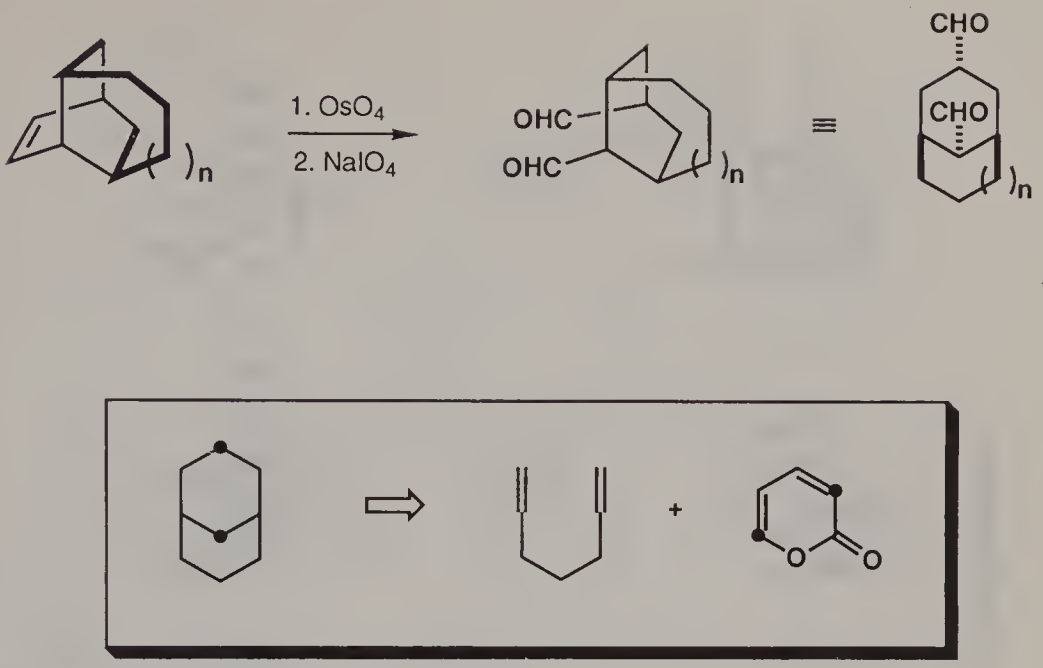


Fig. 20 General route to [3,*n*,1] bicycles.

Based on this analysis, a simple disconnection of the bicyclo[3.2.1]octane core of gibberellic acid and zizaene can be devised (Fig. 22) for which 2-pyrone and 1-butenylcyclopentene appear as attractive starting materials. For strategic reasons, we decided to utilize 2-butenylcyclopentenone as the α,ω-diene. A high-pressure Diels–Alder reaction provided a moderate yield of the CO_2 adduct. However, it is important to remember that this reaction was performed under the 'old' (high pressure, room temperature) rather than the 'optimized' conditions requiring lower pressure but higher temperatures. Attempts to promote the CO_2 extrusion/intramolecular Diels–Alder cycloaddition using a variety of thermal conditions totally failed. *Gratifyingly, treatment of the primary adduct with a mixture of* $TiCl_4/Ti(OPr^i)_4$ *at room temperature led smoothly to the desired pentacyclic adduct in a remarkable 69% yield.* Oxidative cleavage gave (Fig. 24) the highly functionalized model of the tricyclic core of zizaene and gibberellic acid in *only four steps from 2-pyrone.*

Three operations are required to convert our model into the desired gibberellic acid tricyclic core (Fig. 25): (1) the incorporation of the tertiary alcohol function; (2) the appendage of the *exo*-methylene unit (this problem has already been partially solved since we have been able to incorporate a hydroxyl function at that position); and (3) the decarbonylation of the two aldehydic functions. Since an enol ether is required in the starting diene in order to generate the desired bridgehead hydroxyl group, we wondered if the use of electron-deficient pyrones could not overcome the serious limitation

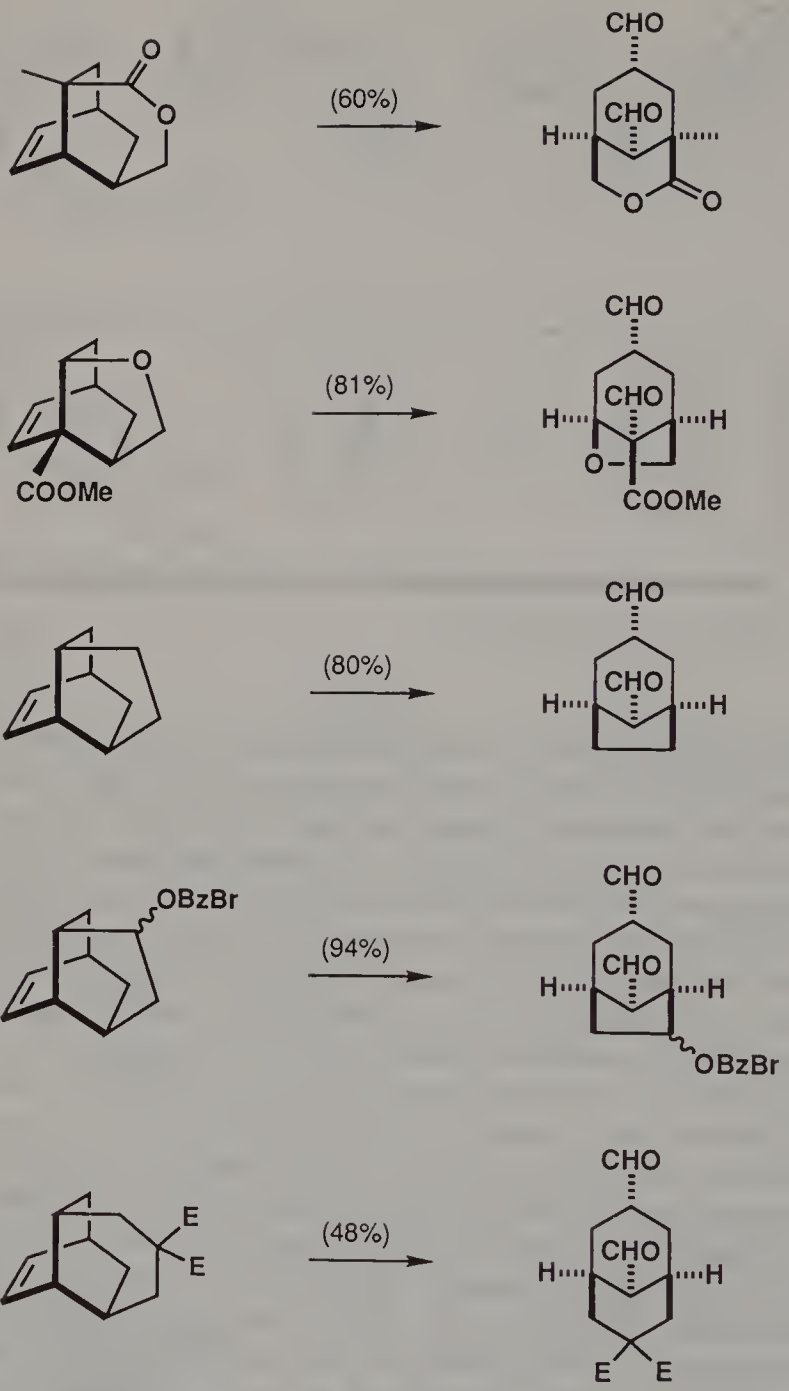
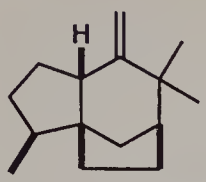
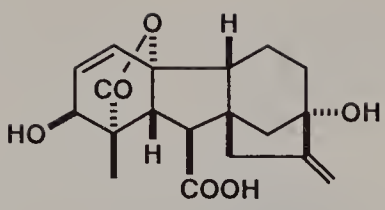


Fig. 21 Bicyclo[3.*n*.1] systems.



zizaene



gibberellic acid

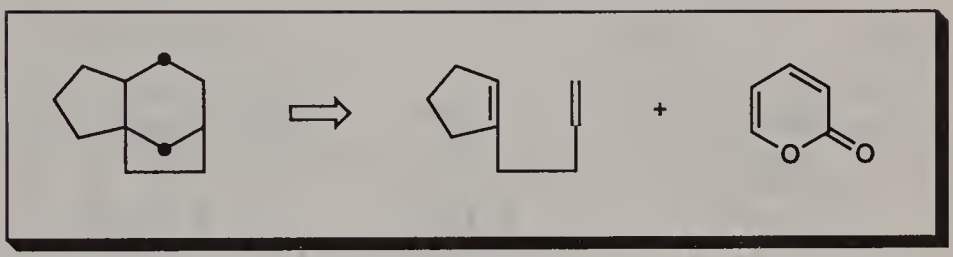
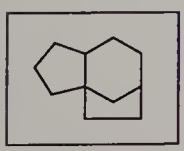
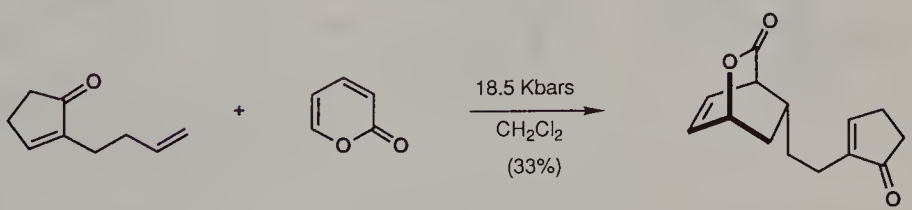


Fig. 22 Bicyclo[3.*n*.1] derivatives.





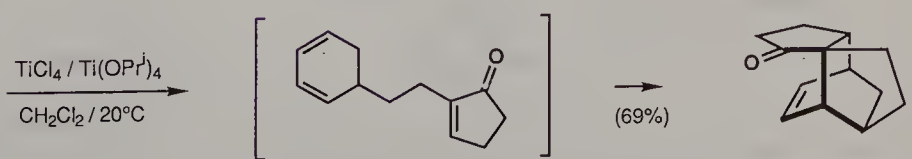


Fig. 23 En route towards zizaene and the gibberellins.

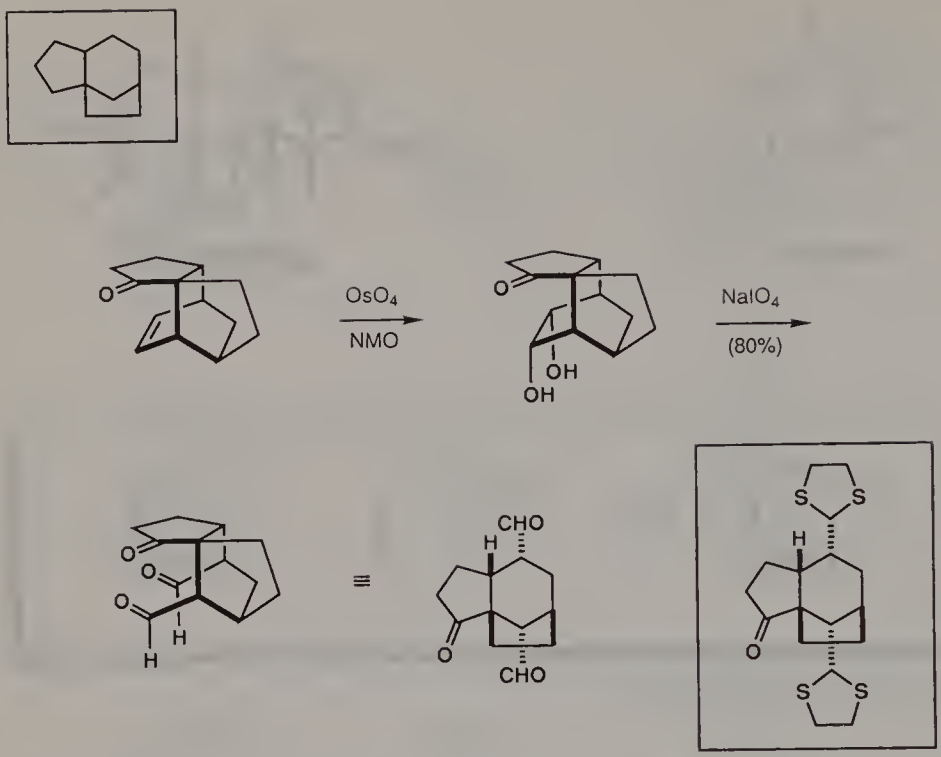


Fig. 24 En route towards zizaene and the gibberellins.

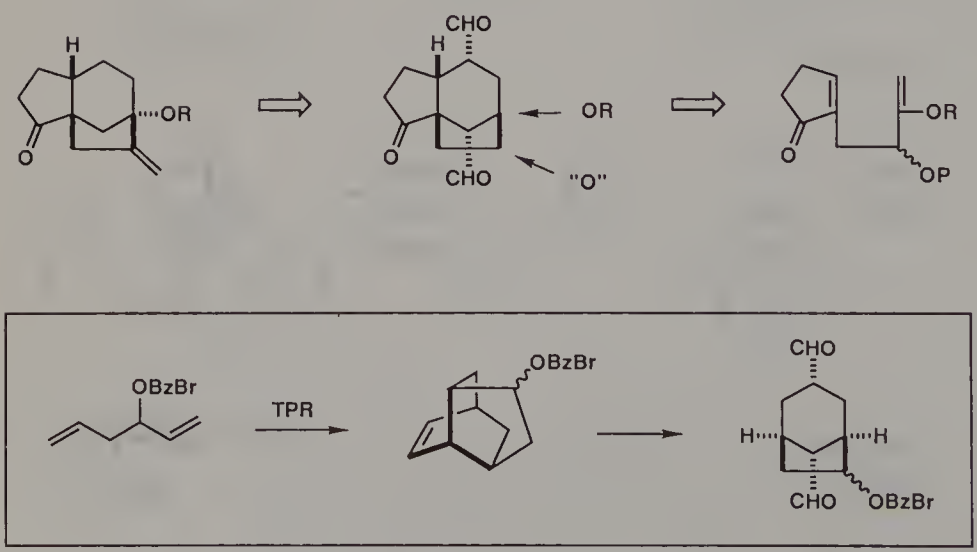


Fig. 25 Conversion to the gibberellic acid tricyclic core.

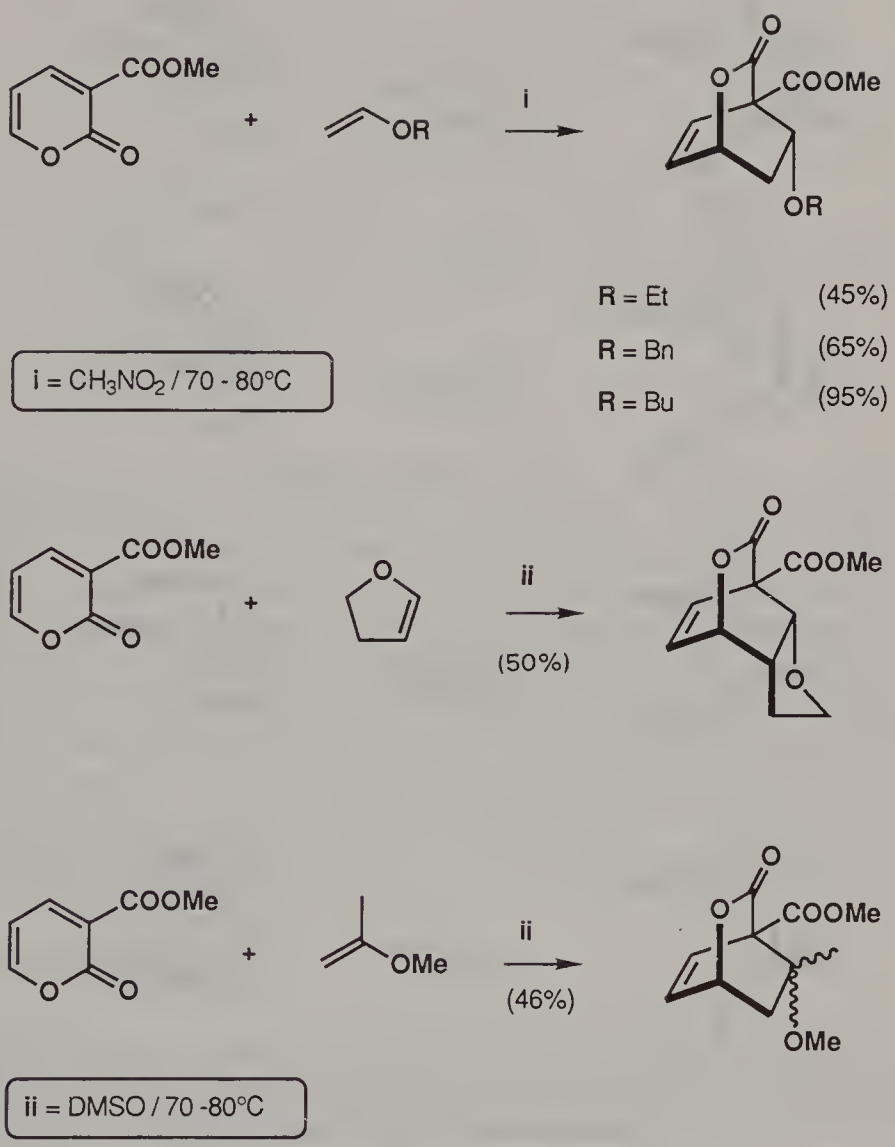


Fig. 26 Away from pressure.

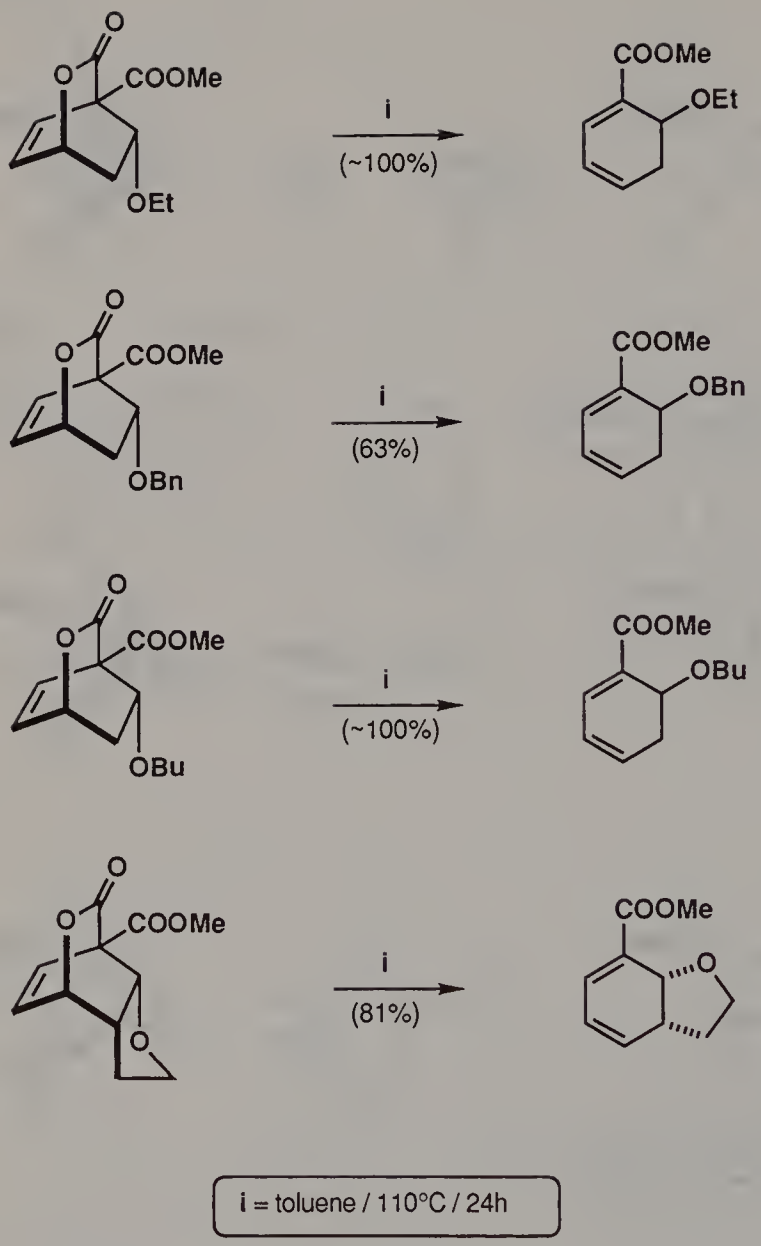


Fig. 27 Diene preparation.

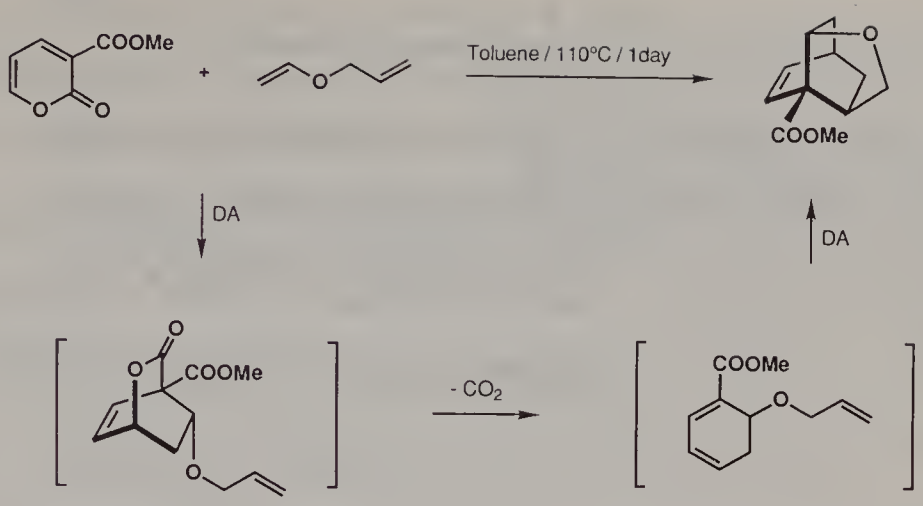


Fig. 28 A dream come true.

imposed by the use of high pressures. Under the correct conditions 3-carbomethoxy-2-pyrone (3-CMP) proved to be a suitable candidate and formation of stable bicyclic lactones ensued *at atmospheric pressure* when 3-CMP was reacted with enol ethers (Fig. 26). Most remarkably, heating these primary adducts in toluene at 110°C, led to the smooth production of the corresponding dienes (Fig. 27). *These compounds are stable in boiling toluene for several hours but rapidly aromatize under the slightest acidic provocation*. At this stage, and for the very first time, we were able to perform (Fig. 28) the complete tandem pericyclic reaction *in a single step* by heating 3-CMP with allylvinyl ether in toluene at reflux. The TPR adduct was formed by an intermolecular Diels–Alder reaction, a CO_2 extrusion and an intramolecular Diels–Alder cycloaddition.

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3

Recent Studies on the Development of Some New Organometallic Reactions for Organic Synthesis

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1 Introduction

It has frequently been stated that 'a little knowledge is a dangerous thing'. In terms of scientific research however, and particularly in synthetic organic chemistry, a powerful argument can be constructed for a different point of view. All too often, the assembled weight of the chemical literature can be used in a negative way to construct carefully reasoned arguments for discounting a particular approach to a problem. In reality however, our knowledge of the exact nature of a solvated or aggregated species in solution is often so poor that a simple change in experimental protocol can have a profound influence on the outcome of a reaction. Irrespective of the degree of conception (or misconception!) which goes into the design of a new reaction, luck and the observations of the skilled experimentalist still play a major role (Barton and Motherwell, 1981).

The purpose of the present chapter is to illustrate, using two current themes of organometallic interest in our group, how our ideas in these areas have originated and developed as we continued to learn.

2 A new route to enolate anion chemistry

The introduction of modern methods for the regio- and stereospecific formation of enolate anions from carbonyl compounds of various types has undoubtedly served as one of the major cornerstones for controlled carbon–carbon bond formation in organic synthesis over the last twenty years (Waring, 1978 and references therein; Buncel and Durst, 1984). Some four years ago, however, we embarked on a programme based on the simple concept that

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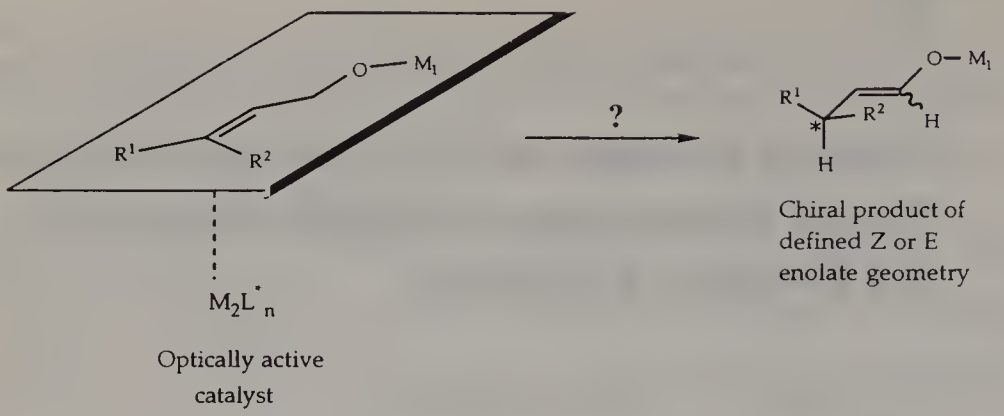


Fig. 1

controlled isomerization of a preformed allylic metal alkoxide using a transition metal complex could form enolate anions of defined geometry (Fig. 1). In this way, an allylic alcohol is chosen as the direct precursor instead of a carbonyl compound; and the essence of the idea may be encapsulated in the almost naïve viewpoint that the uniquely useful properties of an enolate stem from its behaviour both as an OLATE and as an ENE, without any necessity for consideration of the acidity of protons adjacent to a carbonyl group. Our intention was therefore to sever the historical but unnecessary link which inextricably binds the carbonyl group and enolate anion chemistry.

Furthermore, as implied in Fig. 1, and certainly inspired by the elegant studies of Noyori *et al.* (1984) on allylic tertiary amines, potential exists for the use of a chiral transition metal complex to act as a catalyst, in conjunction with a prochiral trisubstituted allylic alcohol, for the production of a chiral enolate anion of defined geometry.

Before describing our studies in this area, it is perhaps of interest to show how this idea evolved (El-Karim *et al.*, 1988) as a consequence of achieving the

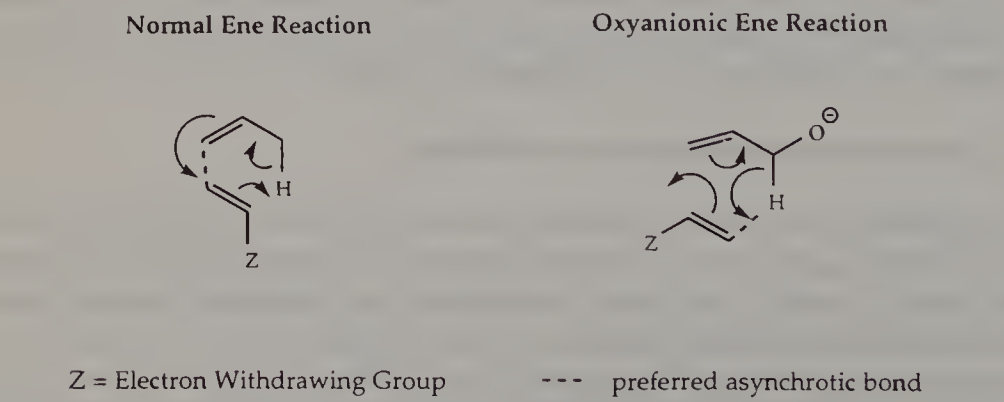


Fig. 2

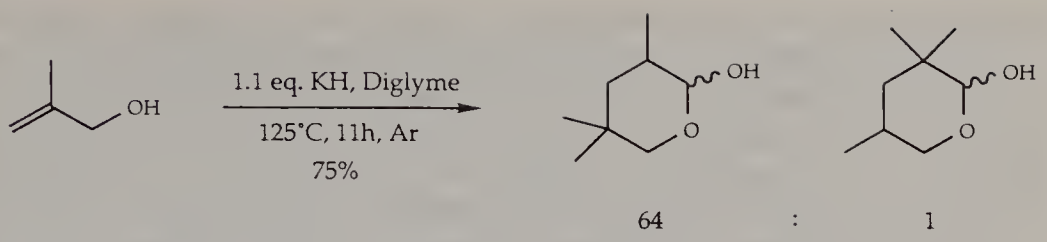


Fig. 3

entirely different objective of reversing the normal regiochemistry and asynchronicity of the Ene reaction, through use of the remarkable rate accelerating oxyanion effect in allylic alkoxides, as suggested in Fig. 2. The reaction which we investigated (El-Karim *et al.*, 1988) in this context was the thermal dimerization of the potassium alkoxide of methallyl alcohol (Fig. 3) and the mechanism which we uncovered (Fig. 4) shows that the overall sequence is a (non-radical!) chain reaction featuring, either in a stepwise or highly

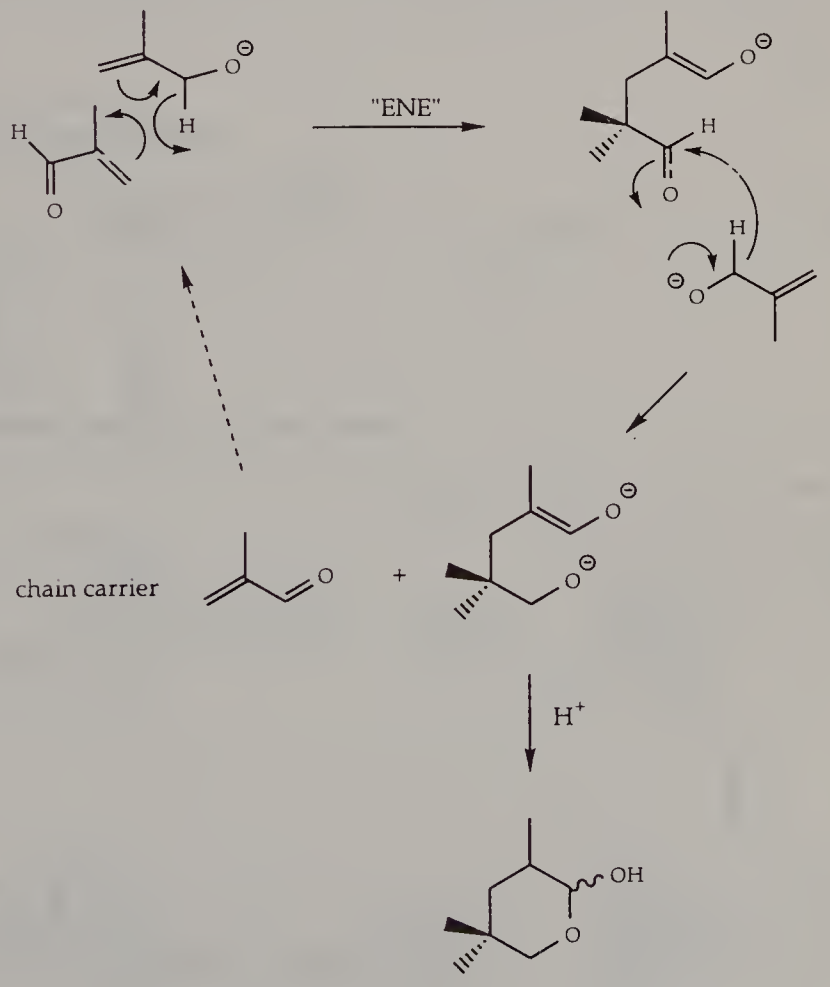


Fig. 4

asynchronous manner, the formation of isobutyraldehyde enolate from the corresponding alkoxide via hydride transfer to methacrolein. In this way, the concentration of readily polymerizable methacrolein is kept low at all times, and, by way of comparison, reaction of equimolar amounts of the potassium alkoxide and α,β-unsaturated aldehyde led to the isolation of a beautiful bicyclic product via a delightful tandem sequence involving methylpropenoxide addition to methacrolein followed by three consecutive Michael reactions: intramolecular aldolization, a Cannizzaro reaction, and finally a translactonization (Fig. 5).

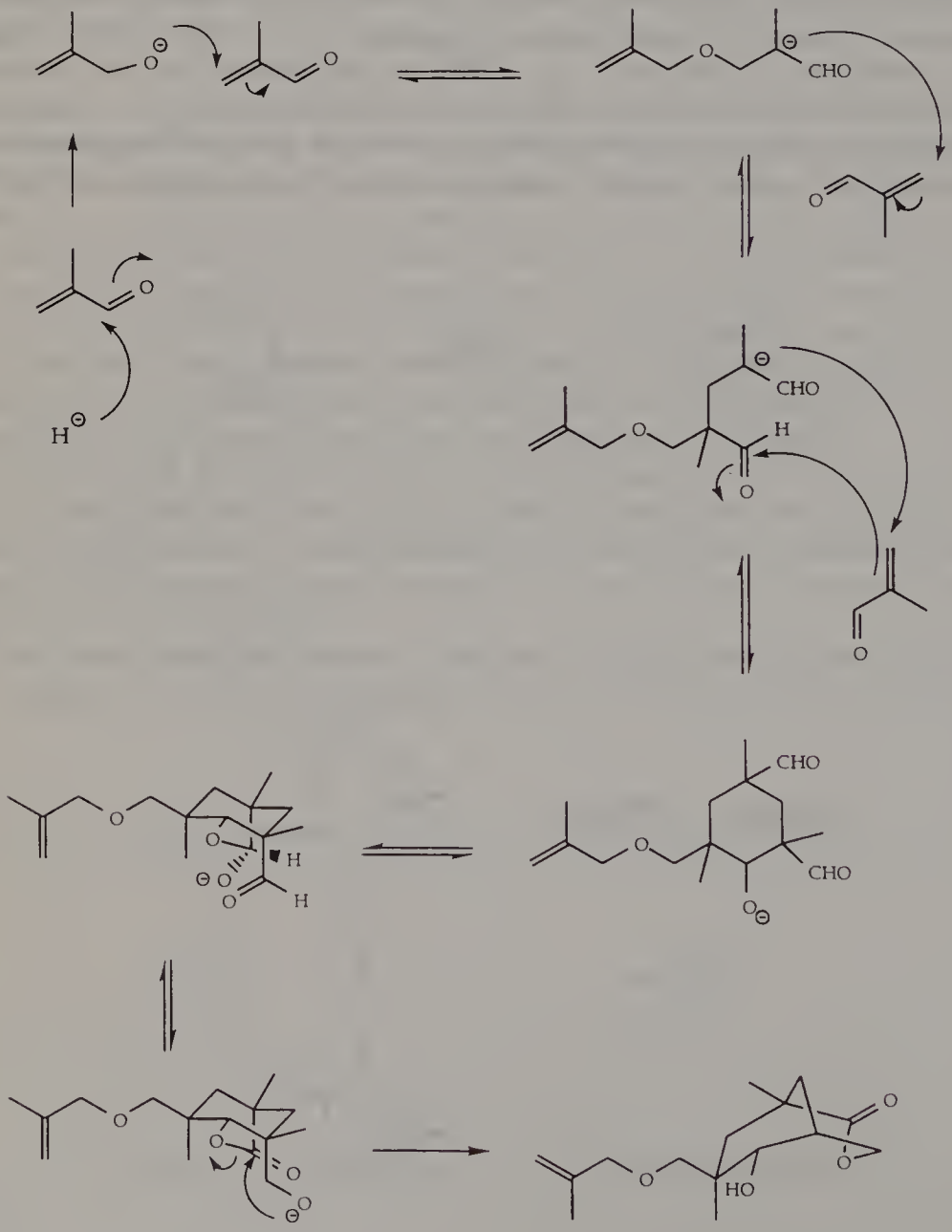


Fig. 5

When confronted by the simple sequence involving hydride transfer-initiated isomerization of the allylic alkoxide, it was then an obvious step to realize that a transition metal catalyst should be capable of achieving a similar result. The isomerization of a wide range of allyl ethers and allylic alcohols themselves of course finds ample precedent in the literature, but the application to alkoxide anions and hence to enolates seems to have passed unnoticed. Our preliminary studies (Edwards *et al.*, 1991) focussed on the formation of well-documented lithium enolates and covalent potassium triethylboronate complexes. Of the two major mechanisms for transition metal-catalysed isomerization (Fig. 6), we elected in the first instance to use the cationic rhodium diphos complex $[dppeRh]^+[ClO_4^-]$, which is readily prepared from the air-stable precursor shown by hydrogenation. This choice was made in the belief that operation of the π-allyl hydride mechanism would offer the best opportunities for a controlled pathway (*vide infra*). Unbeknown to us at the time, Bergens and Bosnich (1991) were using the same catalyst to isomerize allylic alcohols and demonstrate that the resultant enols were remarkably persistent species, although they did eventually lose their identity and inevita-

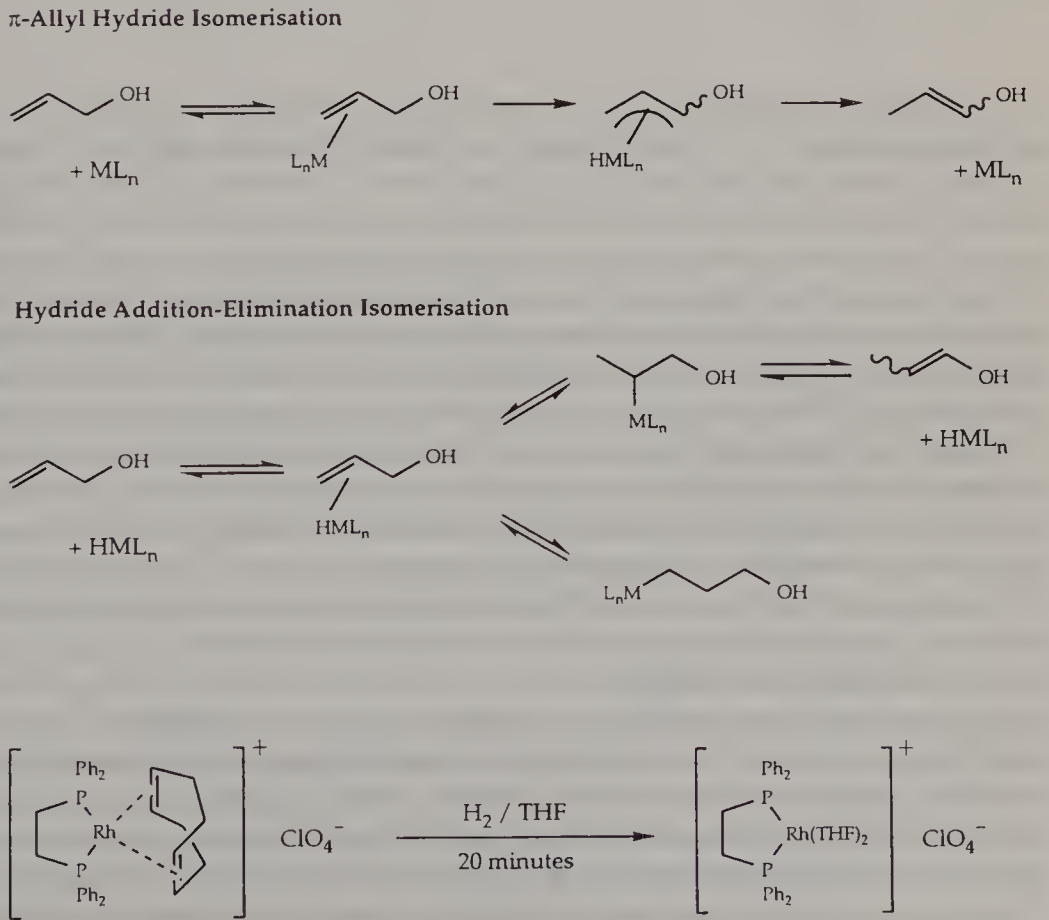
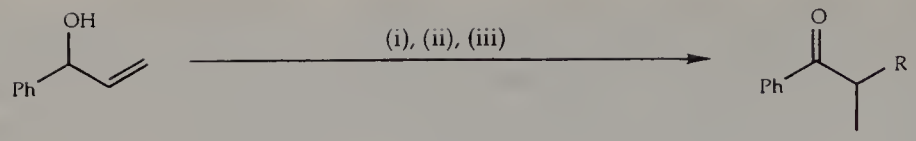


Fig. 6



Reagents: (i) *n*-BuLi, THF, 0°C; $[Rh(dppe)]^+$, THF, 60°C; (iii) RX, 0°C

RX	Yield
	82%
	75%
MeI	62%
	60%

Fig. 7

bly succumb to tautomerization. A series of simple alkylation reactions (Fig. 7) convinced us that the overall principle was valid. Moreover, the use of butyl iodide as the electrophile was encouraging in that it implied that the rhodium catalyst did not substantially interfere in a potentially destructive way at this stage. Our attention then turned to the inherent possibilities of controlling the enolate geometry in such a process, and indeed the selection of the rhodium catalyst was made, in the first instance, in the belief that operation of the π-allyl hydride-type mechanism could contribute to controlling the outcome, as shown in Fig. 8. The supervisor's prediction was, of course, that the highly solvated and aggregated nature of the lithium alkoxide would favour conformer B, and hence lead to a stereoselective method for the production of generally less accessible *E*-enolates. As is often the case however, the outcome of a series of simple aldol reactions performed under kinetic control and proceeding via the Zimmerman–Traxler transition state served to establish that the opposite was true, and a distinct preference for the *Z*-enolates was noted, as summarized in Fig. 9.

In extending the range of this approach however, we examined the case of 1-phenylpent-4-en-3-ol **1**, and discovered that an attempted isomerization of this substrate with the rhodium catalyst system led to the disastrous result that we were not even able to maintain the regioselectivity of the first-formed enolate! (Fig. 10). At this time in the lab, the days were long and dark and our list of failures with rhodium was accumulating at an unacceptable rate. Substrates

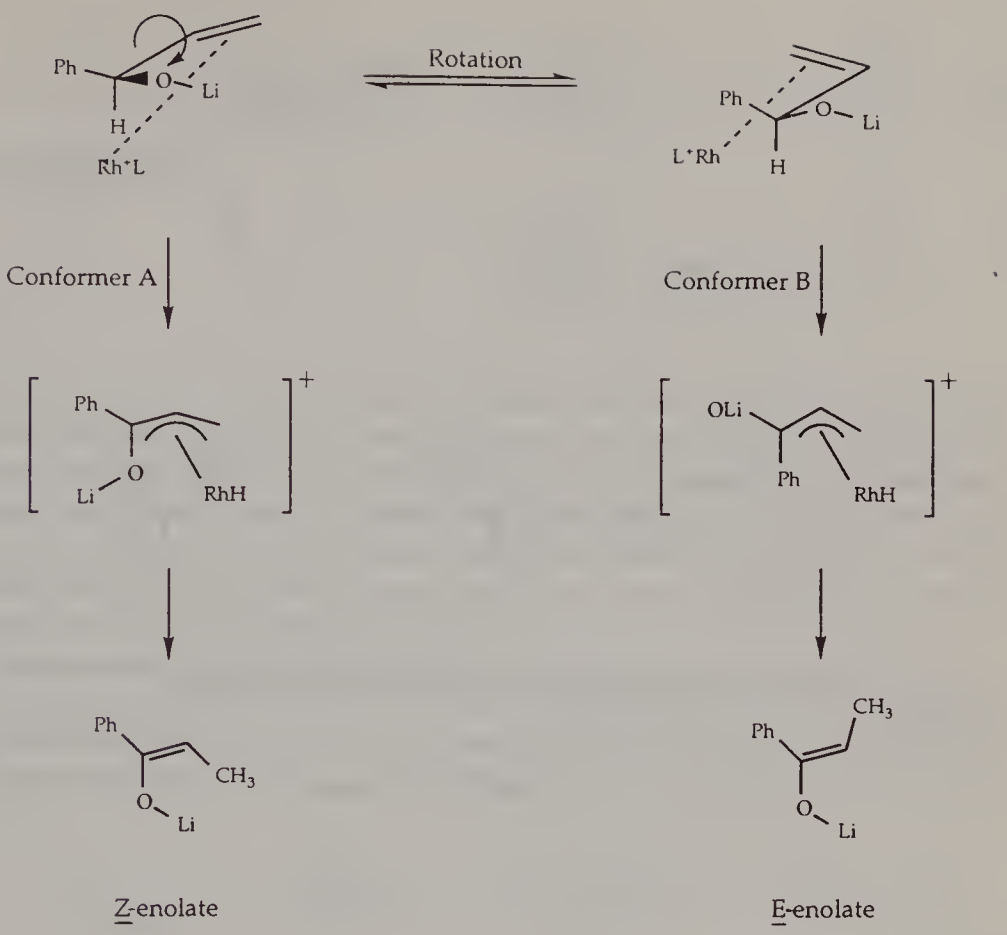
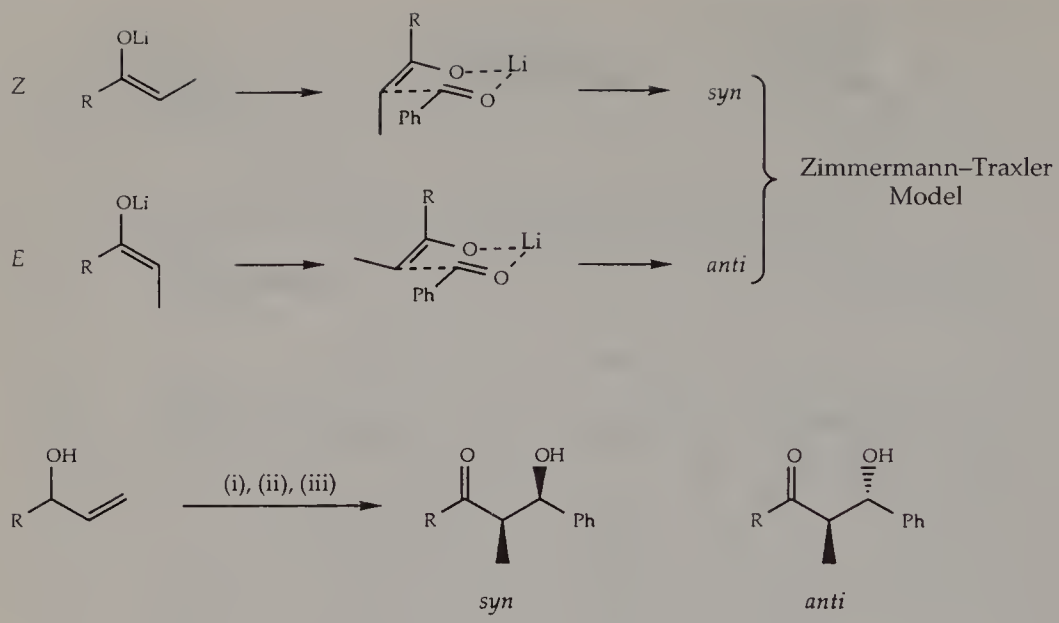


Fig. 8

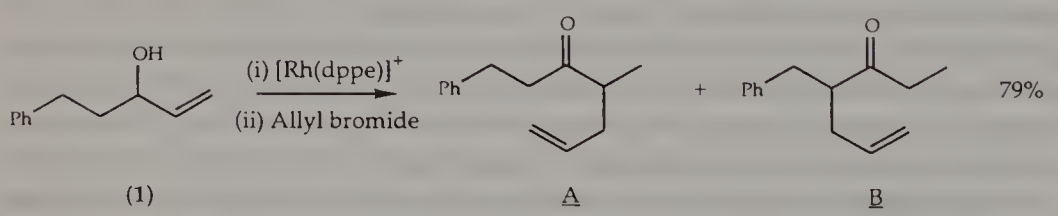
such as the cyclic allylic alcohol, cyclohexenol and allylic alkoxides with more substituted double bonds were proving to be extremely stubborn. Fortunately, however, perusal of the organometallic literature (Kalies *et al.*, 1980) revealed that hydride transfer from lithium isopropoxide (Fig. 11) to *bis*(tricyclohexylphosphine)nickel dichloride had led to isolation of a hydridochloride complex **2**. We therefore reasoned that *in situ* generation of this species should be possible from an allylic alkoxide and that this could function either *per se* as an isomerization catalyst, operating by the M–H addition–elimination mechanism, or via a subsequent 'conjugate addition' to the enone which was also produced. In the event (Motherwell and Sandham, 1992), addition of the divalent nickel dichloride catalyst to preformed lithium alkoxide did lead to a somewhat sluggish isomerization catalyst system. Fortunately, however, at this stage, serendipity entered the scene, and a second experiment was performed in which an additional portion of *n*-butyl lithium corresponding in molar equivalents to the proportion of catalyst used was also added, to 'ensure' reduction of the complex **3**. This resulted not only in the generation of a much more active species, but also one which effectively solved the regiochemical



Reagents: (i) *n*-BuLi, THF, 0°C; (ii) $[Rh(dppe)]^+$, THF, 60°C; (iii) PhCHO, -78°C

R	*syn* : *anti*	Yield
Ph	8.6 : 1	84%
Et	3.9 : 1	79%

Fig. 9



A : B = 1 : 1.2

Fig. 10

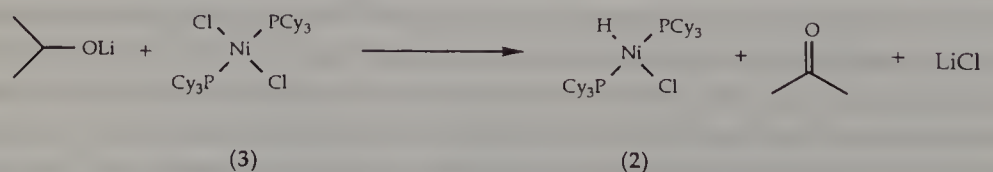


Fig. 11

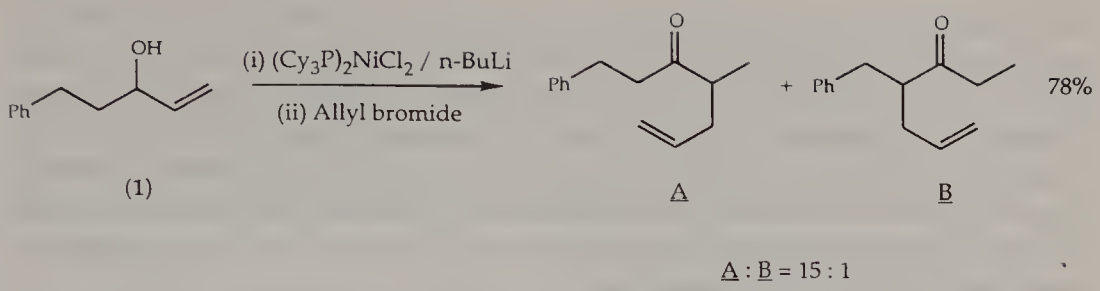
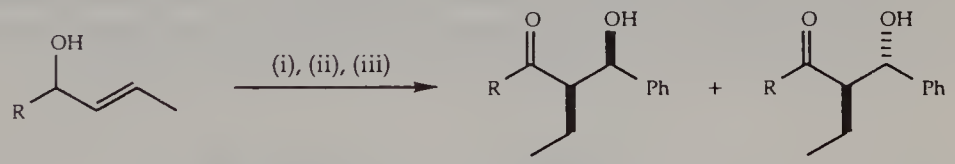


Fig. 12

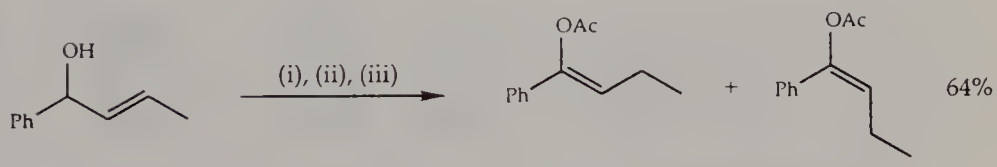
problem found in the case of 1-phenylpent-4-en-3-ol (Fig. 12). In our initial studies, we had deliberately selected monosubstituted allylic alkoxides since these exomethylene-like substrates would be most accessible to the metal complex. With both the rhodium and nickel systems in hand, however, it became possible to tackle the more challenging problems posed by increasing substitution, which is generally accepted to be a more demanding process for transition metal mediated isomerization.

The results for some simple disubstituted alkoxides are shown in Fig. 13, and reveal that, once again, in these cases, an inherent preference for *Z*-selectivity is maintained throughout. These reactions also indicated, however, the importance of the nature of the substituents around the alkoxide, as reflected in



Reagents: (i) n-BuLi; (ii) catalyst; (iii) PhCHO, −78°C

R	Catalyst	*syn* : *anti*	Yield
Ph	Rh	3 :1	71%
Ph	Ni	3 :1	86%
t-Bu	Ni	20 : 1	80%



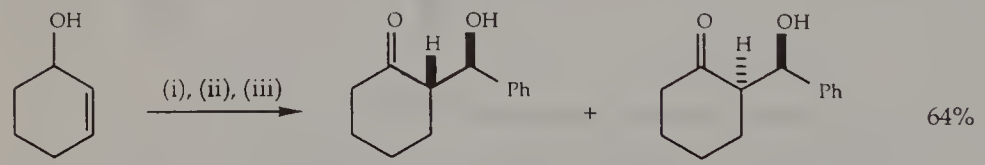
Reagents: (i) n-BuLi; (ii) $[Rh(dppe)]^+$; (iii) acetyl chloride, −78°C

Fig. 13

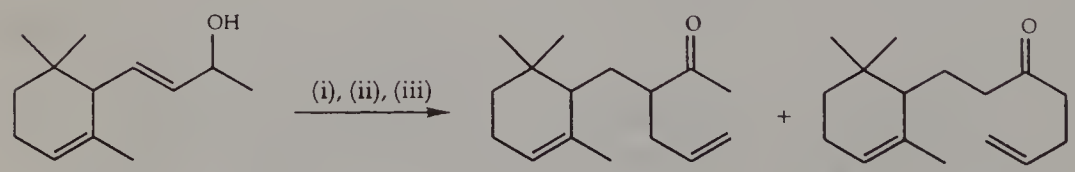
the comparison of the phenyl and *t*-butyl congeners with the nickel catalyst. Most importantly of all however, as emphasized by comparison of the results from both the kinetic aldol and enol acetate trapping of butyrophenone enolates, extrapolation of the *Z:E* ratios of enolate geometry on the assumption that a Zimmerman–Traxler transition state will always operate is a suspect process. While our earlier aldol reactions were based on documented enolate geometry, it is apparent that butyrophenone differs markedly from propiophenone enolate under these conditions.

Two other examples of disubstituted systems are shown in Fig. 14. Thus, the nickel system was successfully used for the isomerization of the lithium alkoxide of 2-cyclohexen-1-ol, in which formation of an *E*-enolate is of course mandatory, and where the use of the $[Rh(dppe)]^+[ClO_4]^-$ catalyst led to recovery of starting material. It was also of interest to note that the relatively hindered disubstituted double bond of the ionol derivative **4** proved to be accessible for the nickel catalyst and that the isolated trisubstituted alkene of the cyclohexenyl ring which was also present remained substantially intact.

As expected, within the more demanding series of trisubstituted allylic alkoxides (Fig. 15), including those derived from both primary (*vide infra*) and secondary alcohols, success is dependent on the exact pattern of substitution, and nickel catalysts are in general found to be more effective than rhodium, as shown for example by the alkylation of the tetrasubstituted enolate derived from **5**. It is significant to note, however, as implied by the altered isomeric ratio of the recovered starting material in this reaction, that additional isomerization processes may well occur prior to enolate formation.

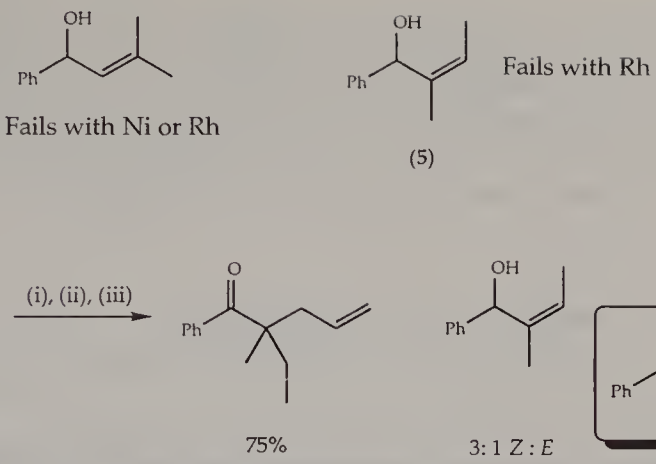


Reagents: (i) n-BuLi; (ii) $(Cy_3P)_2NiCl_2$ / n-BuLi; (iii) PhCHO, -78°C



Reagents: (i) n-BuLi; (ii) $(Cy_3P)_2NiCl_2$ / n-BuLi; (iii) allyl bromide

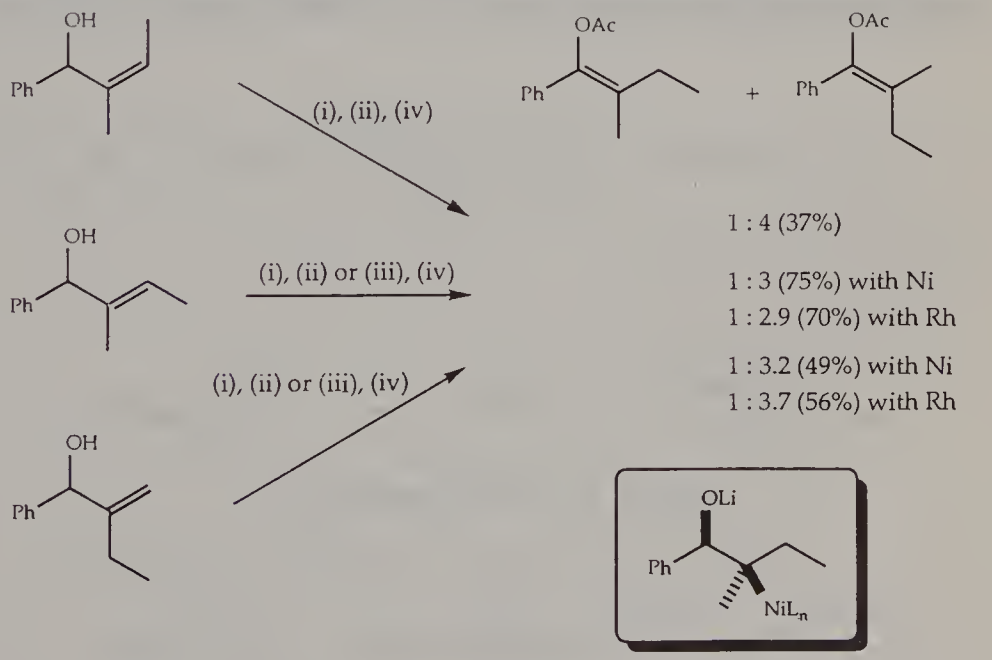
Fig. 14



Reagents: (i) n-BuLi; (ii) $(Cy_3P)_2NiCl_2$ / n-BuLi (20 mol%); (iii) allyl bromide

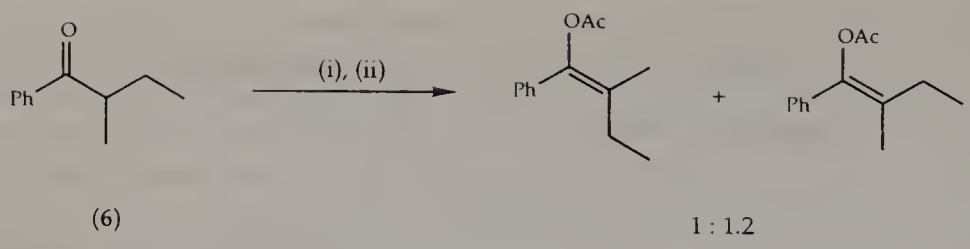
Fig. 15

The use of the allylic alkoxide approach to enolate anion generation has also allowed us to begin to tackle some problems which are not directly soluble using the chemistry of the carbonyl group, as, for example, in the stereoselective formation of tetrasubstituted enolates (Fig. 16). In the ideal world, our hope was that a given enolate geometry could be effectively preordained



Reagents: (i) n-BuLi; (ii) $(Cy_3P)_2NiCl_2$ / n-BuLi; (iii) $[Rh(dppe)]^+$; (iv) acetyl chloride, -78°C

Fig. 16



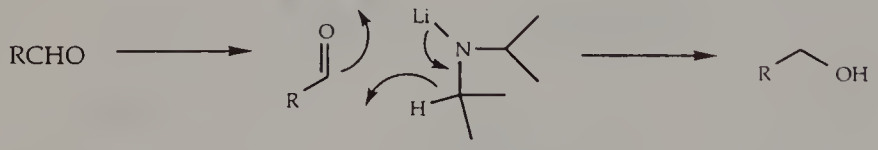
(6) 1 : 1.2

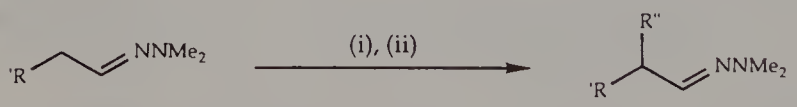
Reagents: (i) LDA, -78°C; (ii) AcCl, -78°C

Fig. 17

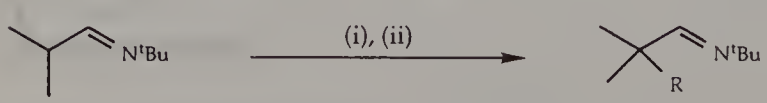
through selection of the appropriate substitution pattern in the allylic alcohol, and use of the '*Z*-selectivity factor' in allylic alkoxide isomerization. In the real world, as shown in Fig. 16, it would appear at the present time that some degree of 'scrambling' of the allylic alkoxides occurs prior to enolate anion formation. Nevertheless, the results indicate that some degree of stereoselection is possible, and certainly represent an improvement over simple deprotonation of the corresponding carbonyl compound. Thus, by way of comparison, treatment of **6** with LDA followed by enol acetylation gave an almost equimolar mixture of the two possible isomers (Fig. 17).

A second problem which we have addressed is the formation of simple lithium enolates of aldehydes, where the use of the classical bases such as lithium diisopropylamide leads to reduction (Majewski, 1988), and elegant but





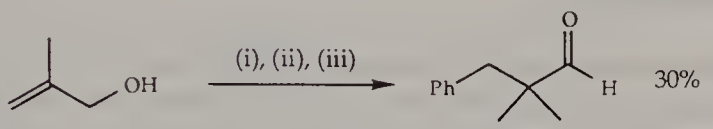
Reagents: (i) Li / Et_2NH, HMPA; (ii) R"X



Reagents: (i) EtMgBr; (ii) RX

Fig. 18

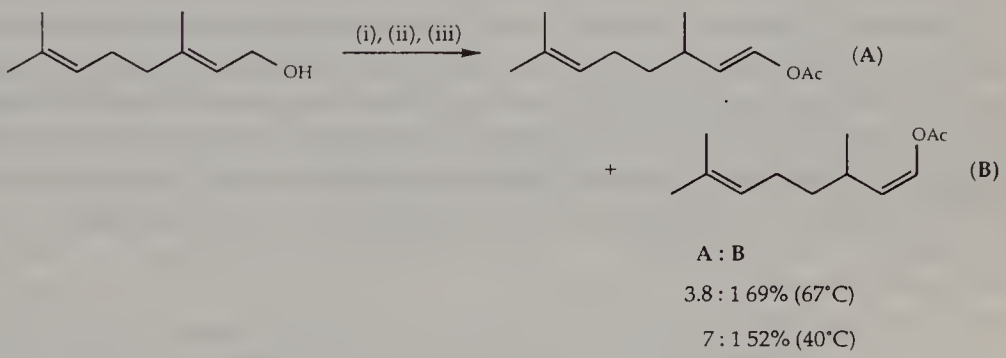
multistep solutions, such as the use of *t*-butyl imines or *N,N*-dimethylhydrazones (Stork and Dowd, 1963; Stork and Benaim, 1971; Normant *et al.*, 1976) have had to be devised (Fig. 18). Thus, as shown, methallyl alcohol can serve as a convenient replacement for isobutyraldehyde. The purification and handling of simple aldehydes is, of course, often problematical because of their tendency to form cyclic acetal trimers and their susceptibility to oxidation.

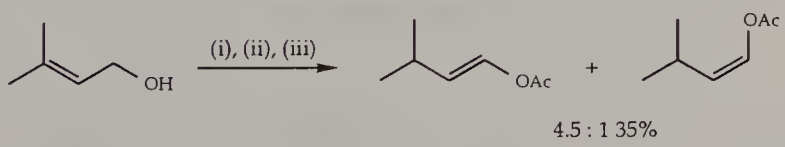


Reagents: (i) $K^+[Et_3BH]^-$, Et_3B (catalyst); (ii) $[Rh(dppe)(thf)_2]^+ClO_4^-$

(iii) $PhCH_2Br$

Even more interestingly, and in contrast to our work on secondary allylic alcohols, we have successively isomerized the trisubstituted primary lithium alcoholates in geraniol and prenyl alcohol (Fig. 19), and found that a useful stereoselective preference exists for the formation of *E*-enolates, as judged on the basis of enol acetylation. At this stage of our work, the preliminary studies have been almost completed, and the stage is now set for fine tuning and further exploration of such exciting prospects as the preparation of new metalloenolates and developing efficient chiral catalysts for use with appropriately





Reagents: (i) n-BuLi; (ii) $(Cy_3P)_2NiCl_2$ / n-BuLi; (iii) Ac_2O, -78°C

Fig. 19

trisubstituted prochiral allylic alcohols. For the bench chemist, however, our initial studies have hopefully indicated that an allylic alcohol can be considered as a direct synthon for entry into enolate anion chemistry without recourse to the chemistry of the carbonyl group and the necessity of using strong non-nucleophilic amide bases.

3 The direct generation and chemistry of organozinc carbenoids from carbonyl compounds

It is almost twenty years since we showed that the reaction of a variety of cyclic ketones with chlorotrimethylsilane and zinc provided the simplest 'one-pot' route for direct deoxygenation of this functional group to an alkene without any necessity for prior derivatization (Motherwell, 1973). The reaction proceeds under mild conditions, and in chemoselective terms tolerates acetate and, perhaps even more surprisingly, bromide functionality (Fig. 20). For unsymmetrical ketones (Fig. 21), there is a regioselective preference for the formation of the more substituted alkene, and as shown by the conversions of 5α-cholestan-3-one (Hodge and Khan, 1975) and coprostanone, reactions probably proceed via a late transition state, with formation of the less strained alkene. It was simple to demonstrate that silyl enol ethers were recovered intact and hence not intermediates in this reaction; and our first mechanistic clue came from a reaction with cyclooctanone (Fig. 22) which furnished not only *cis*-cyclooctene, but also bicyclo[3,3,0]octane, the latter being a classical indication of transannular carbenoid insertion.

It was at this stage that we began to appreciate that the essential mechanistic features of this reaction correspond closely to those of the much more familiar Clemmenson reduction (Vedejs, 1975), the sole difference being that the proton has been replaced by a silicon electrophile (Fig. 23). When viewed in this way, the sequence can be seen as a series of electron transfer steps which lead to the formation of some organozinc carbenoid as a key intermediate. By analogy with the equally famous Simmons-Smith reaction (Simmons *et al.*, 1973), this can be represented as the tetrahedral chloro congener 7. An

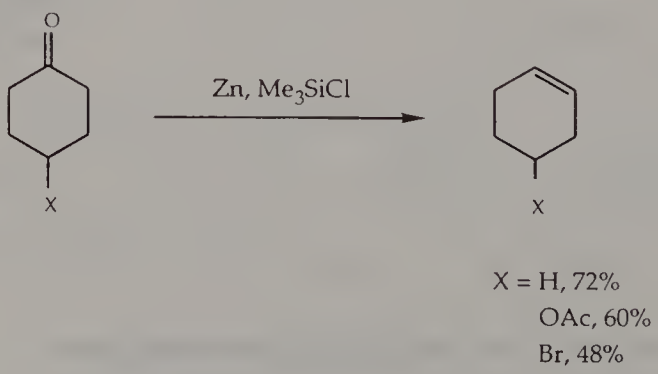


Fig. 20

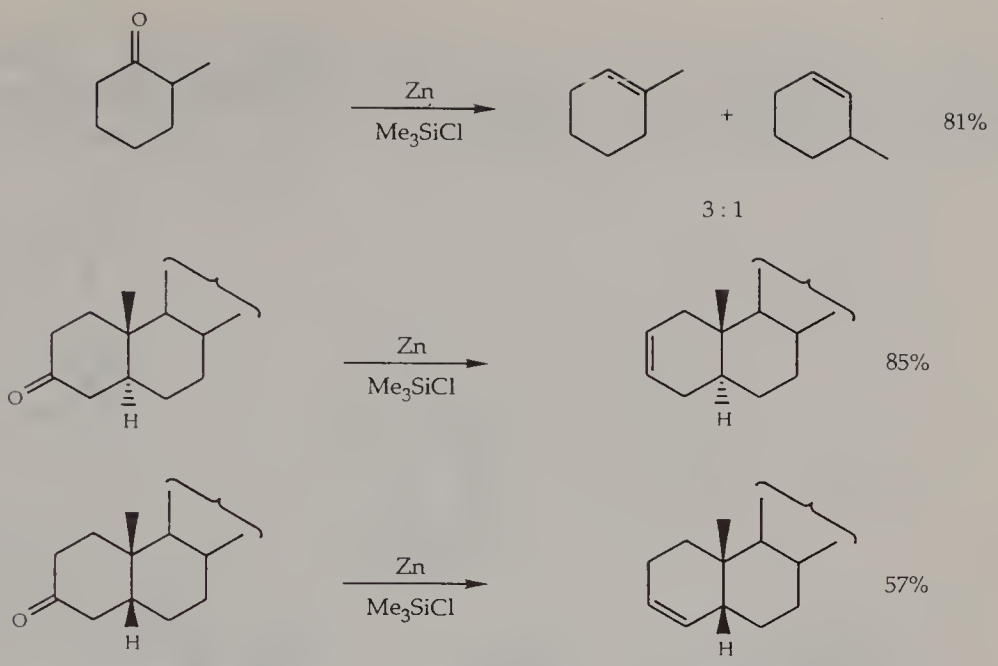


Fig. 21

electrochemist, however, might prefer to envisage the growth of a metallocarbenoid on a zinc surface with a concomitant erosion producing zinc chloride. In the final analysis, of course, the vital difference from the Clemmenson pathway lies in the observation that the carbenoid does not evolve to a geminal disilane.

However, when our investigations turned to the behaviour of intermolecular reactions using α,β-unsaturated carbonyl compounds as substrates, we were plagued in the first instance by problems of competitive pinacolic coupling or dimerization at the softer β-carbon atom of the enone, as a consequence of single electron transfer. Since examination of the overall stoichiometry of the reaction reveals that two silicon electrophiles are required for production of hexamethyldisiloxane as a leaving group, we reasoned very simply that the longevity of 'radical' intermediates could be reduced and the efficiency of carbenoid generation improved by the selection of 1,2-*bis*(chlorodimethylsilyl)ethane as the electrophile. As shown in Fig. 24, this can then allow delivery of the second silicon atom in an intramolecular fashion.

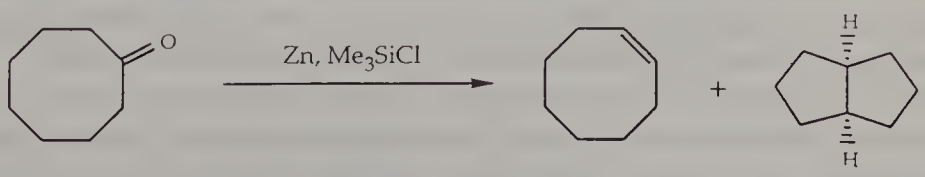
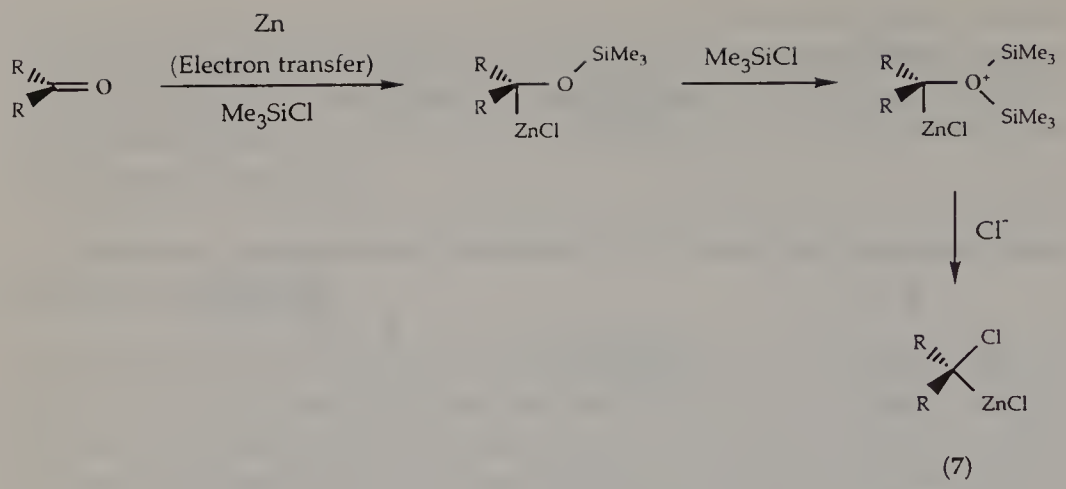


Fig. 22



(7)

Or,

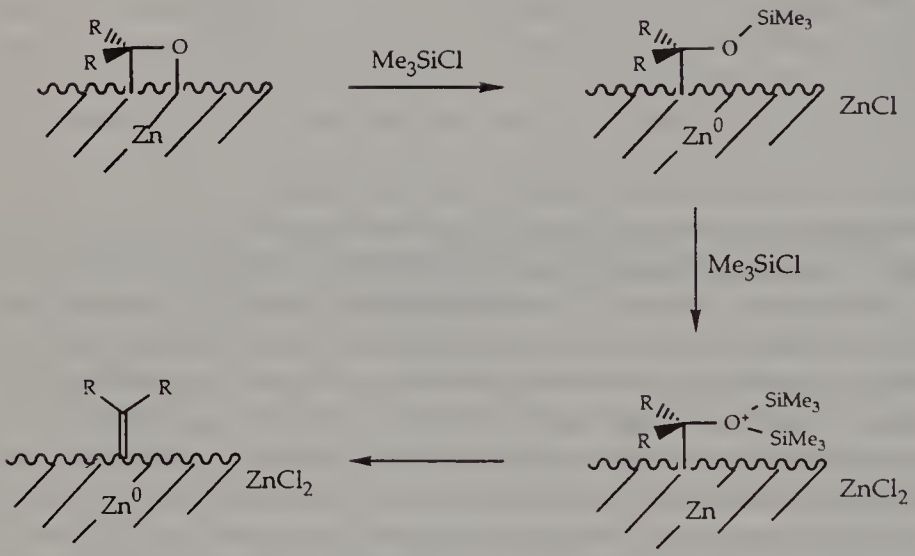


Fig. 23

The use of this reagent allowed us to streamline the efficiency of a symmetrical dicarbonyl coupling reaction for aryl and α,β-unsaturated carbonyl compounds which we had uncovered some years earlier during efforts to prepare 1,3-cyclohexadienes from cyclohexenones. Some examples are shown in Fig. 25, and reveal potential for the construction of some highly hindered trienes and stilbene derivatives (Bannerjee *et al.*, 1986; Afonso *et al.*, 1992a).

It was of interest to note within the series of stilbene derivatives that the best yields were obtained with electron-rich aromatic aldehydes. This may well be a consequence of increased efficiency in carbenoid generation as a result of assisted expulsion of the siloxane, as implied in Fig. 26.

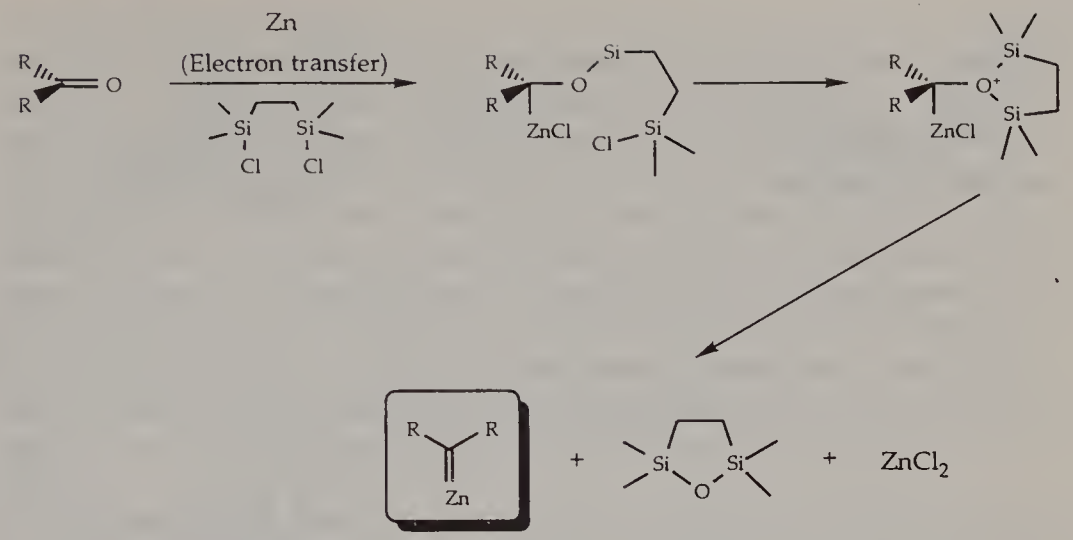
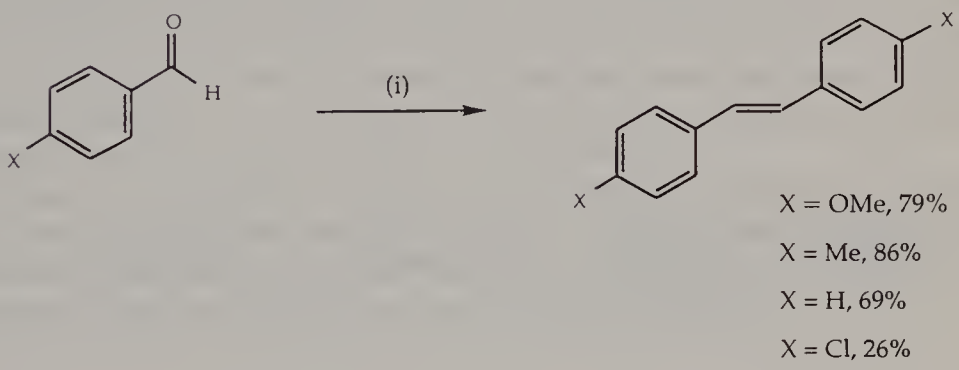
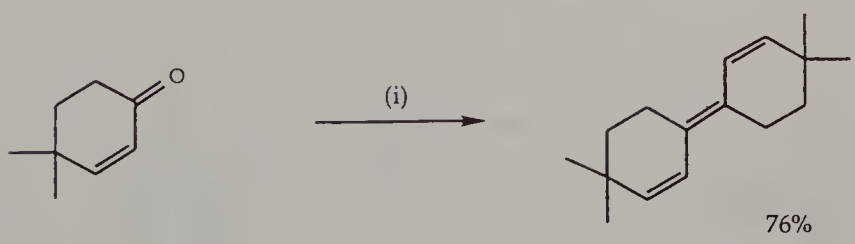
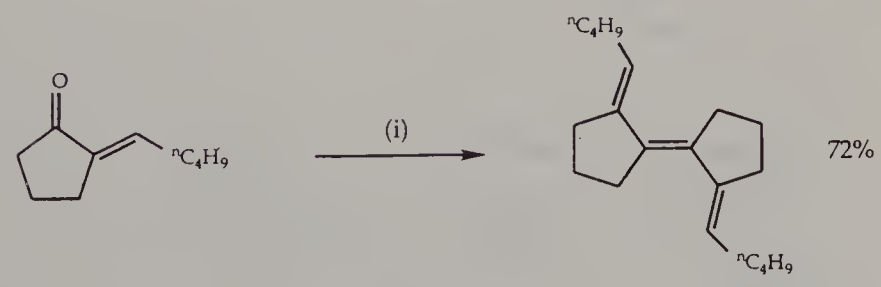


Fig. 24







Reagents: (i) Zn, $ClMe_2Si$ ⌒ $SiMe_2Cl$

Fig. 25

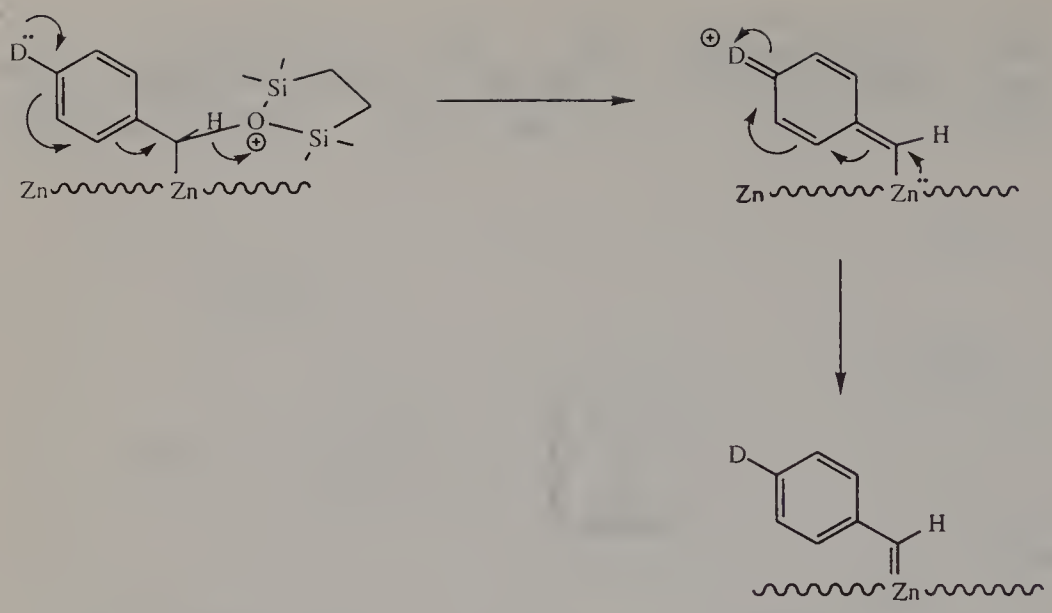
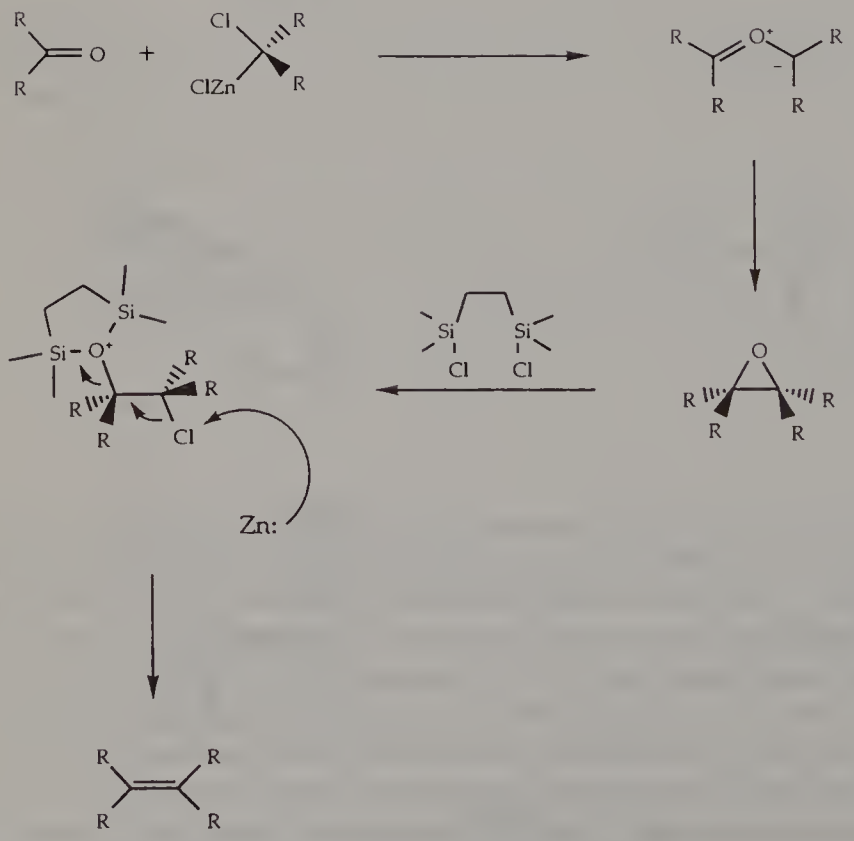

D
Si
H
O
Si
Zn
Zn
D
H
Zn
Zn
D
H
Zn

Fig. 26


R
R
O
+
Cl
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ClZn
R
R
O+
R
R
R
Si
Si
Cl
Cl
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R
R
R
Si
O+
R
R
R
Cl
Zn:
R
R
R
R

Fig. 27

We had learned at an early stage that the mechanism of this reaction (Figs 23 and 27) was quite unlike one of the pathways for the McMurry reaction (McMurry, 1989) inasmuch as vicinal diols or their derived silyl ethers were inert; and a separate study established that suitably substituted epoxides were much more likely candidates for deoxygenation via siloxychlorohydrin ethers (Afonso *et al.*, 1992b). In the first instance, we considered that the oxiranes could be formed via a Darzens-like pathway in which the organozinc carbenoid functioned as a 'Reformatsky-like' nucleophile for the carbonyl group. Such nucleophilic behaviour of these inherently electron-deficient intermediates, however, ran contrary to all of our expectations, and we now consider that a much more probable mechanism involves trapping of the carbenoid by the oxygen lone pair of a second molecule of carbonyl substrate to give a carbonyl ylide.

Support for this pathway comes from an attempted intramolecular coupling of the dione **8** which totally failed to produce any evidence for a cyclopentenoid product (Fig. 28). The isolation of the 2,6-diphenyldihydropyran **9** is most readily explicable in terms of a carbonyl ylide in which both steric and electronic factors combine to frustrate epoxide formation and hence divert the reaction pathway. This observation now paves the way for the potential generation and trapping of a variety of ylide species.

We have also pursued the analogy with the Simmons-Smith reagent, which offers the opportunity of developing a useful cyclopropanation reaction without the necessity for preparing and handling the diazo precursors or gem dihalo compounds which are required for other metallocarbenoids.

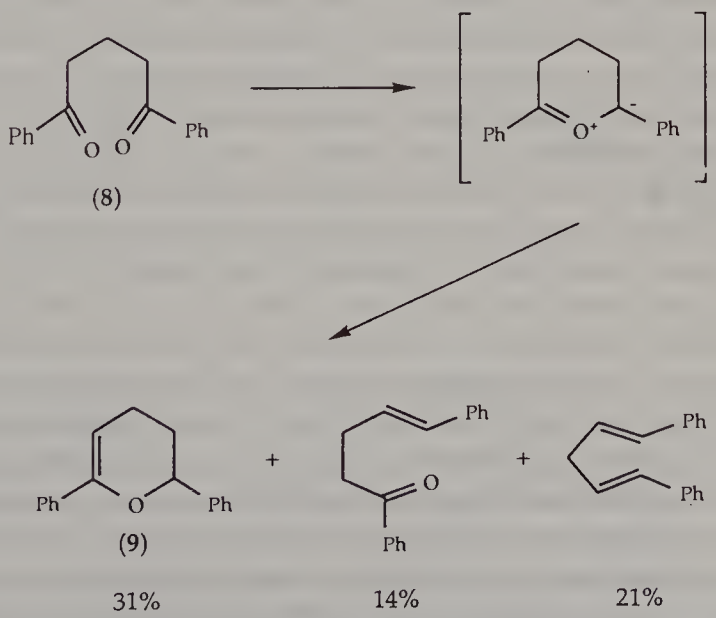
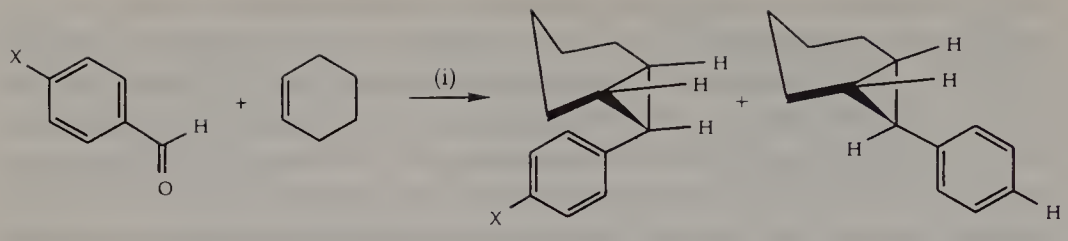


Fig. 28



X	Yield %	Ratio (endo : exo)
Cl	46	3 : 1
H	68	4 : 1
Me	75	8 : 1
OMe	96	15 : 1

Reagents: (i) Zn, $ClMe_2Si$⌒$SiMe_2Cl$

Fig. 29

The results for the trapping of a series of aromatic aldehydes with only two molar equivalents of cyclohexene are shown in Fig. 29, and reveal some features of interest (Motherwell and Roberts, 1992). Once again, as in the dicarbonyl coupling, the isolated yields are best for electron-rich substrates, thereby confirming the suggestion that the latter actively participate in carbenoid generation. We were initially very puzzled, however, by the fact that the highly stereoselective preference for the formation of the more hindered endo isomer was most marked in the case of para-anisaldehyde, and that stereoselectivity decreased smoothly, and apparently in concert with isolated yields, as a function of the decreasing electron release from the aromatic ring. Similar observations in the chemistry of stoichiometric tungsten alkylidenes by Casey *et al.* (1979) have been elegantly rationalized as shown in Fig. 30, and would also seem to apply to the present situation. Thus, approach of the alkene to the metal carbenoid always occurs in such a way as to place any substituents on the alkene '*trans*' to, or away from, the metal. As the bulk of the substituent increases, this tendency increases and path B, resulting in the formation of a *trans*-isomer, is favoured. However, in sterically less demanding cases, opportunities exist for additional electronic stabilization of the developing positive charge on the alkene through electron donation via the *ipso* carbon of the aromatic ring, and path A, leading to the more hindered *cis*-substituted cyclopropane is then followed. This model also rationalizes our observation that yields in the cyclopropanation of *trans*-disubstituted alkenes will always

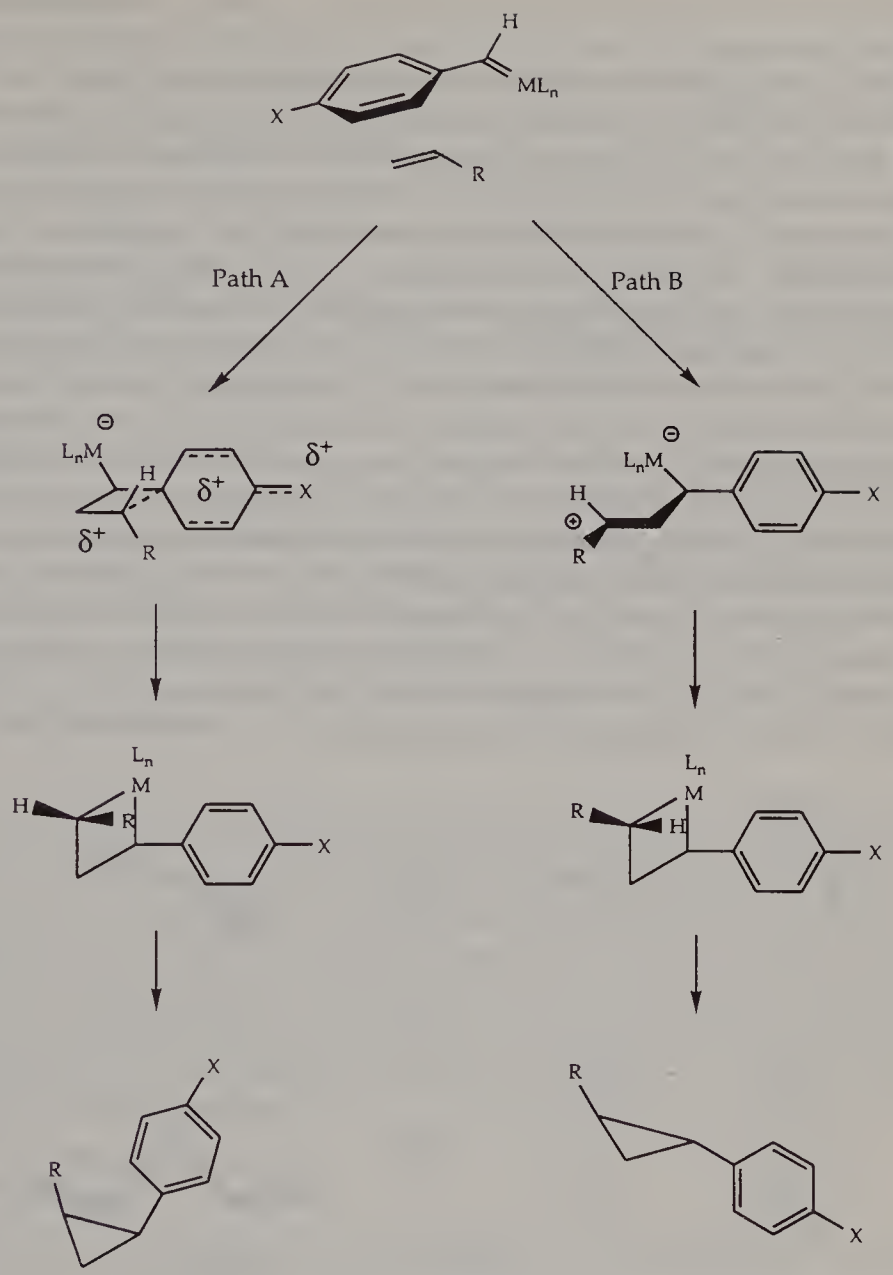


Fig. 30

tend to be lower than in the case of their *cis*-congeners, as a consequence of steric approach control.

We were also interested, of course, to examine the behaviour of non-aromatic organozinc carbenoids in cyclopropanation reactions. In the first instance, we elected to study those derived from certain acyclic and alicyclic α,β-unsaturated aldehydes and ketones, since we reasoned that the propensity for rearrangement of the carbenoids to cyclopropenes or allenes would be more energetically demanding, and would thus provide opportunities for

intermolecular trapping (Motherwell and Roberts, 1992). The outcome of this study has proven to be considerably more complex than the simple analysis above would suggest. The vinylidene carbenoids generated from such substrates are most simply classified into two categories, those which work, and those which do not. Among the latter may be numbered cyclohexenone, cyclopentenone, and cyclopentene-1-carboxaldehyde, while the results of some successful cyclopropanations are shown in Fig. 31, and include 3-methylcyclohexenone, 4,4-dimethylcyclohexenone, and 3-methylcyclopentenone. Comparison of these two classes would suggest the empirical guideline that some degree of steric crowding around the β-olefinic terminus of the enone or enal unit has a profound beneficial effect. It is interesting to note that in the above reactions we have now diverged considerably from the Clemmenson analogy, since many cyclohexenone derivatives lead to double bond reduction and ring contraction products via a bicyclo[3,1,0]hexanol intermediate. The *cis*-selective preference noted for aromatic aldehydes also seems to operate in the cases of the isoprenoid enal and cyclohexenone substrates, but is absent in the more planar and rigid cyclopentenones, thereby reinforcing the idea that the stereochemical outcome is governed to some extent by the three-dimensional shape and environment around the β-terminus. Nevertheless, a simple and useful cyclopropanation method has been developed.

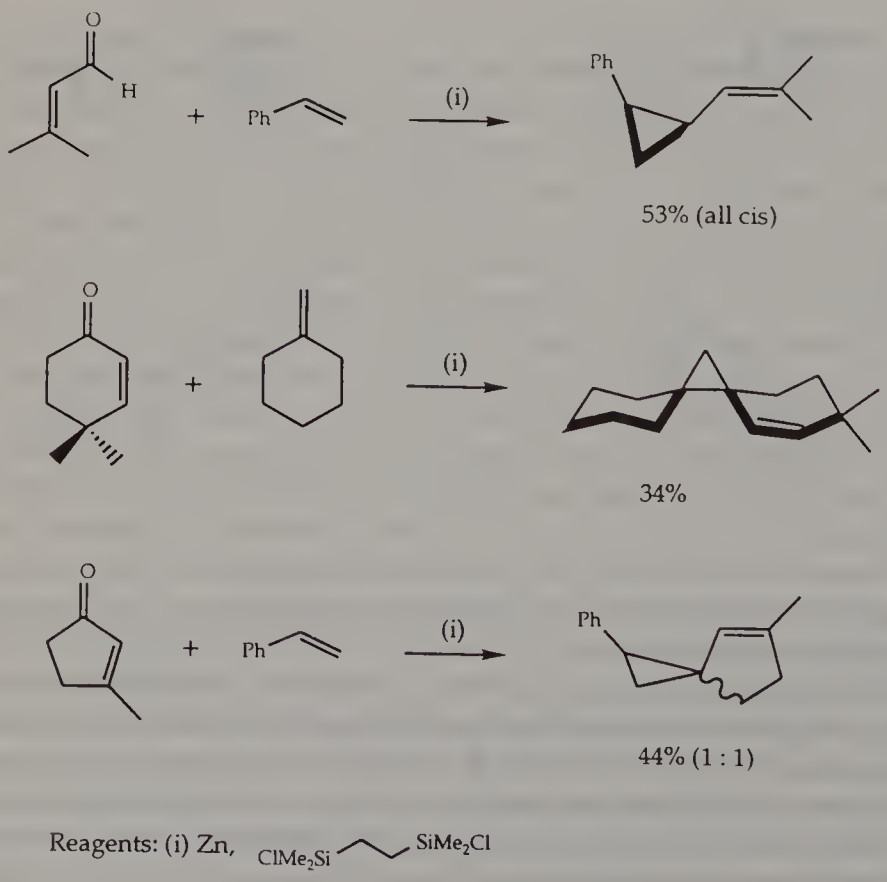


Fig. 31

4 Conclusions

Both of the themes which have been discussed stem from our belief that new reactions for organic synthesis should, if at all possible, be simple in concept, and of practical use. In the isomerization of allylic alkoxides, our hope is that the synthetic chemist will recognize that an allylic alcohol is a direct synthon for entry into enolate anion chemistry without the necessity for the use of hindered non-nucleophilic amide bases. In the chemistry of carbonyl compounds with zinc and 1,2-*bis*-(chlorodimethylsilyl)ethane the recognition feature is that this reaction provides a useful entry into the rich manifold of metallocarbenoid chemistry, with possibilities for C-H insertion, ylide formation and cyclopropanation.

As in all investigations, however, several of our discoveries have been based on misconception and luck, in addition to the naïve equations on a two-dimensional piece of paper which initiated our studies. The fact, however, that we are continually driven to ask further questions and to provide *a posteriori* rationale only convinces us that while a little knowledge is a most dangerous thing, it is also a most useful starting point.

Acknowledgements

First and foremost, it has been my privilege and pleasure to be associated with those postgraduate students and postdoctoral fellows who have worked in our group on these themes, and whose names may be found in the references. The vast bulk of the work which I have described today has been produced by two postgraduate students, Mr David Sandham (enolate anion chemistry) and Dr Lee Roberts, and to them, in particular, I owe an enormous debt of gratitude for their insight and dedication. Finally, I wish to acknowledge the SERC and colleagues in ICI and Zeneca and Quest International who have provided invaluable financial assistance.

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4

Stereocontrol in Palladium-catalyzed Reactions

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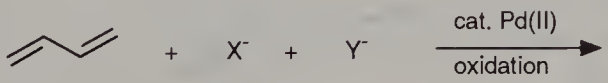
1 Introduction

Nucleophilic additions to unsaturated hydrocarbons coordinated to a transition metal are important reactions in organic synthesis (Bäckvall, 1986, 1989; Faller and Linebarrier, 1988; Pearson *et al.*, 1989). A number of transition metals can be used for such transformation and in many cases the reactions are part of a catalytic process (Collman *et al.*, 1987). The regio- and stereochemistry of these nucleophilic additions are of central importance for applications in selective organic synthesis. As far as stereochemistry is concerned the nucleophile may attack the hydrocarbon ligand either from the same face as the metal or the opposite face. It is of particular importance if one can alter the stereochemistry of the nucleophilic addition for a given nucleophile.

A few years ago we developed several palladium-catalyzed 1,4-oxidations of conjugated dienes which allow the regio- and stereoselective addition of nucleophiles to the 1- and 4-positions of the conjugated diene (equation 1,



(1)

X = OAc, OOCR, OR
Y = Cl, OAc, OOCR, OR

Scheme 1) (Bäckvall *et al.*, 1984, 1985a; Bäckvall, 1989). These reactions proceed via nucleophilic attack on (π-diene)- and (π-allyl)palladium complexes. Coordination of the diene to Pd(II) gives a π-diene complex, which is attacked by the first nucleophile (X^-) at the 1-position of the diene. This produces a π-allyl complex. Coordination of benzoquinone to palladium in this (π-allyl)palladium intermediate induces nucleophilic attack by the second

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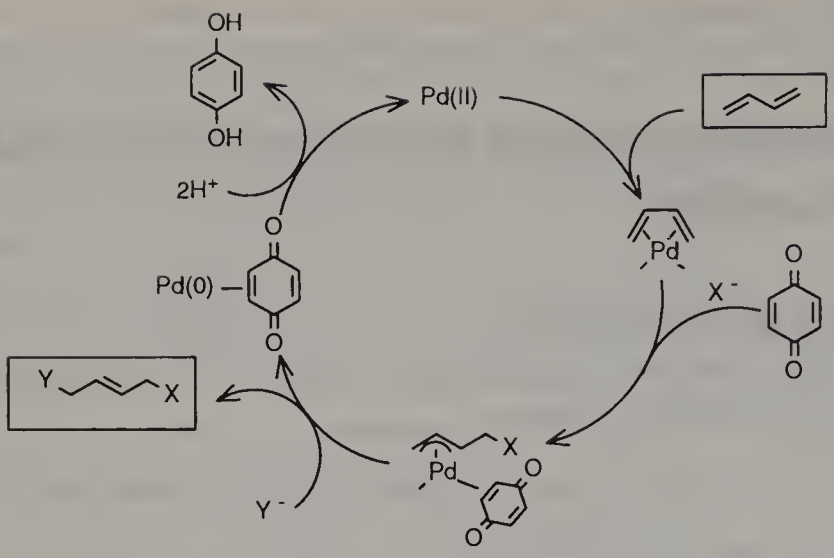
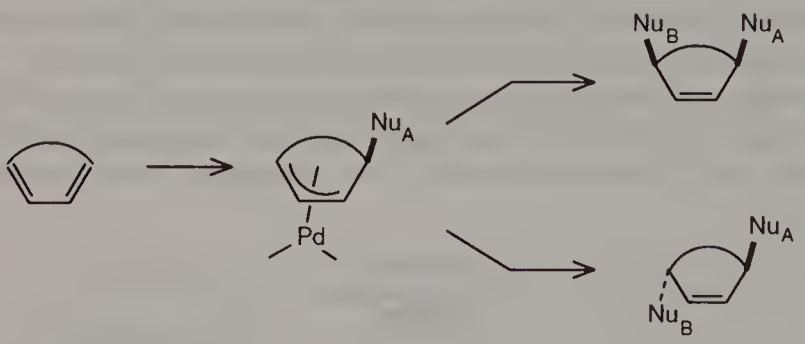


Scheme 1

nucleophile (Y^-) and product formation. In this latter process a Pd(0)-benzoquinone complex is formed which undergoes an intramolecular redox reaction (Grennberg *et al.*, 1993) to give hydroquinone and Pd(II). The reactions are highly 1,4-regioselective which is an effect of the electronegativity of the first nucleophile introduced (X^-). In a number of cases it is possible to obtain a dual stereocontrol in the overall 1,4-addition (Scheme 2). This dual stereocontrol originates from the nucleophilic attack on the π-allyl intermediate, which may occur either *cis* or *trans* to the metal.



Scheme 2

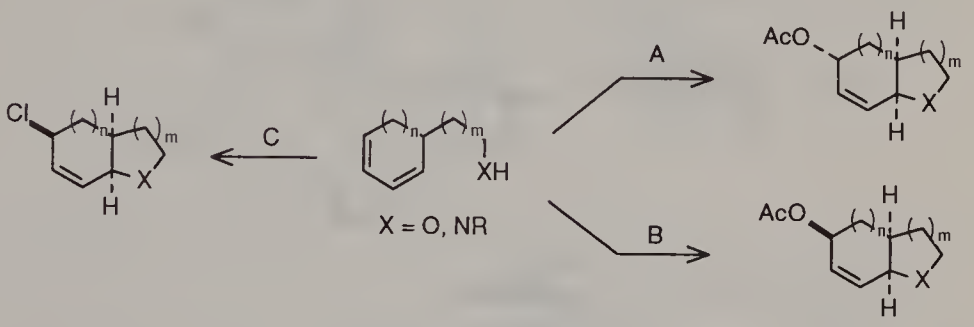
The stereodefined 1,4-functionalized products are useful building blocks and key intermediates in organic synthesis. They have been employed in natural product syntheses in both cyclic and acyclic systems (Bäckvall *et al.*, 1985b, 1990; Nyström and Bäckvall, 1983; Schink *et al.*, 1991; Tanner *et al.*, 1989).

Recently, the palladium-catalyzed 1,4-oxidations were extended to intramolecular variants (Andersson and Bäckvall, 1992; Bäckvall *et al.*, 1989, 1993a; Bäckvall and Andersson, 1990, 1991, 1992). In this way three princi-

pally different 1,4-oxidations have been developed: annulation (Sections 2 and 3), spirocyclization (Section 4), and tandem cyclization (Section 5).

2 Heteroannulation

Cyclic conjugated dienes with a side chain in the 5-position, containing a heteronucleophile, underwent smooth annulation reactions (Scheme 3). By

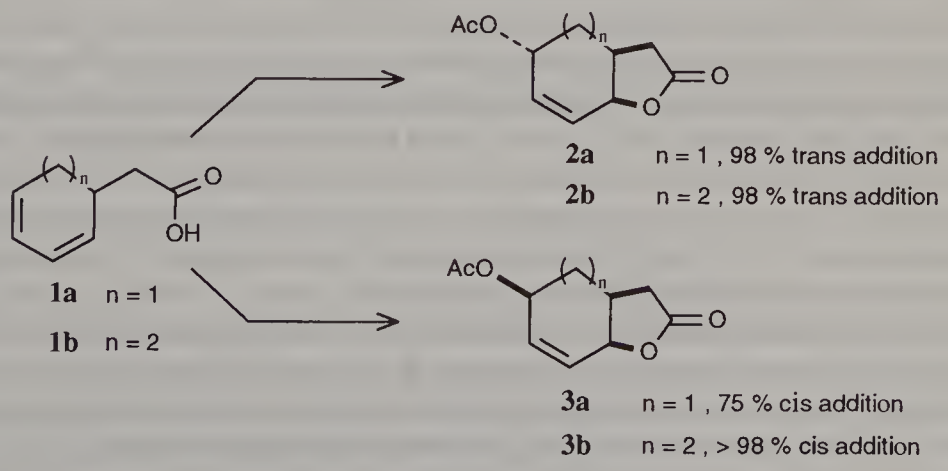


Scheme 3 Heteroannulation.

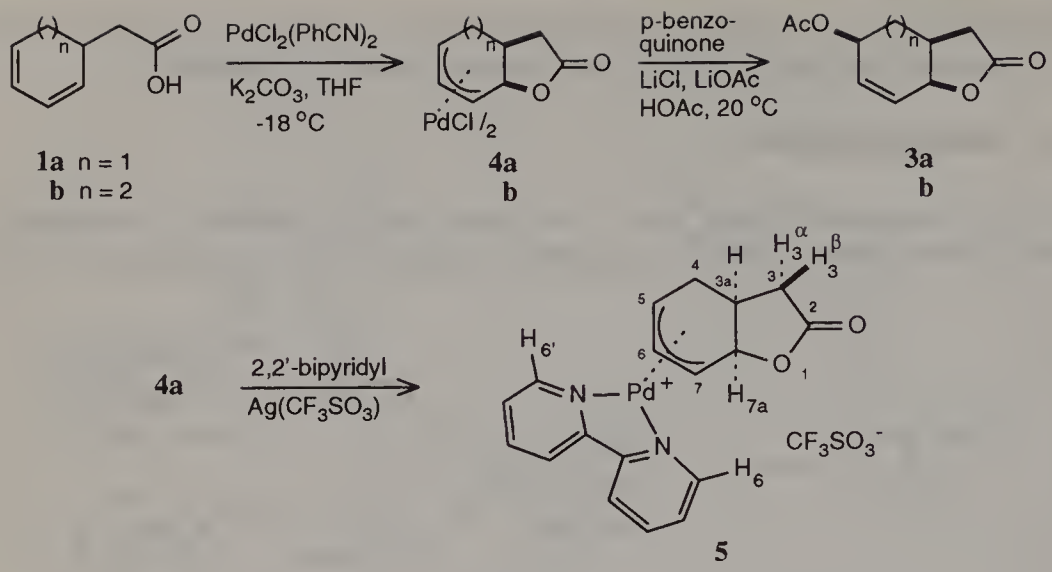
slight variation of the LiCl concentration (A: no LiCl, B: catalytic amounts of LiCl, C: stoichiometric amounts of LiCl) the reaction can be directed to the products shown in the stereocontrolled manner.

2.1 Stereocontrolled lactonization reactions

Reaction of diene acids **1** in acetone-HOAc 4:1 afforded lactones **2** and **3** in a stereocontrolled manner (Scheme 4). If the reaction was performed in the absence of LiCl, a highly stereoselective *trans*-acetoxylactonization to give **2** was obtained. In the presence of chloride the stereochemistry was reversed



Scheme 4



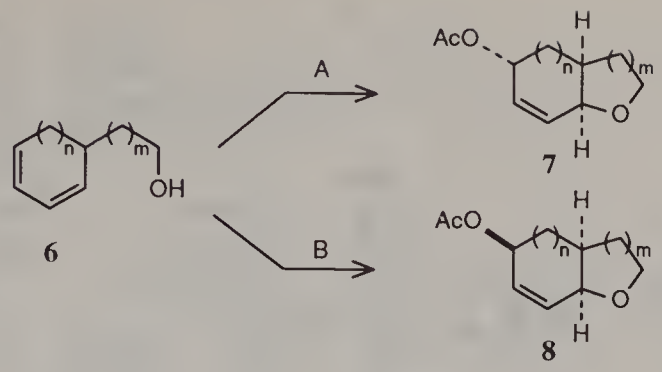
Scheme 5

resulting in an overall *cis*-acetoxylactonization. The intermediate π-(allyl)palladium complexes in these reactions were in each case isolated and characterized (Scheme 5). In order to independently establish the configuration of the π-allyl complex **4**, it was transformed into the bipyridyl derivative **5**. The bipyridyl ligand in this case serves as a reporter ligand (Albinati *et al.*, 1990, 1991) and the configuration of **5** was established by ^{1}H NOE difference and 2D NOE (NOESY) experiments. The reporter protons (H-6 and H-6′ of bipyridyl) show strong cross peaks to the outer π-allyl protons and to H-7a in the NOESY experiment. Also, the NOE difference experiment gave a significant NOE between the reporter protons and H-7a. There was no observable NOE between the reporter protons and H-3$^\alpha$ or H-3$^\beta$. These results establish the *trans* relationship between palladium and oxygen (Bäckvall *et al.*, 1993a).

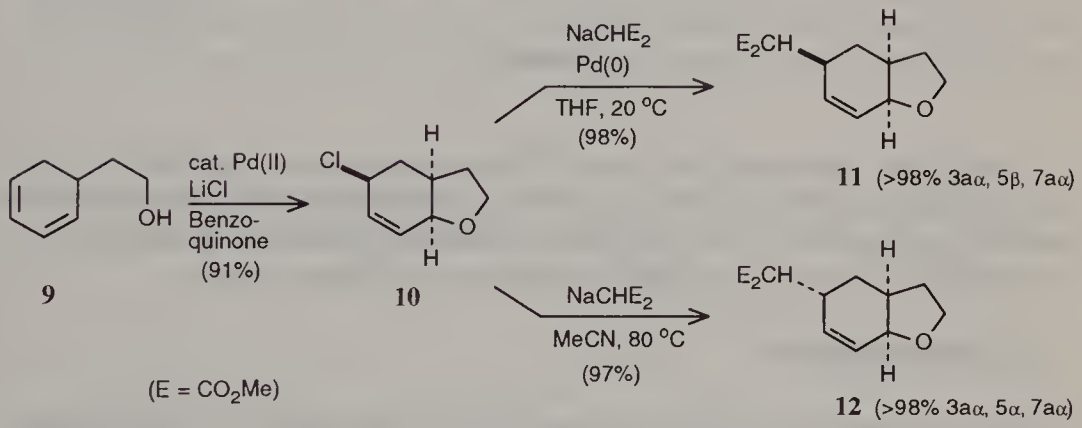
2.2 *Fused tetrahydrofurans and tetrahydropyrans*

Palladium-catalyzed reaction of diene alcohols **6** in acetone–acetic acid (4:1) with benzoquinone as oxidant afforded (Scheme 6) stereodefined tetrahydrofurans and tetrahydropyrans of type **7** and **8** (Bäckvall and Andersson, 1992). Again the stereochemical outcome of the reaction was determined by the LiCl concentration. As for the lactonization, an overall *trans* addition was obtained in the absence of LiCl. A *cis*-1,4-oxyacetoxylation was obtained in the presence of catalytic amounts of chloride.

At an increased chloride concentration a highly stereoselective *cis*-oxychlorination takes place. In this way a number of stereodefined fused tetrahydrofurans and tetrahydropyrans were obtained. The synthetic utility of these allylic chloride-containing heterocycles is enhanced by the fact that the allylic chloride can be replaced with either retention or inversion. Thus,



Scheme 6

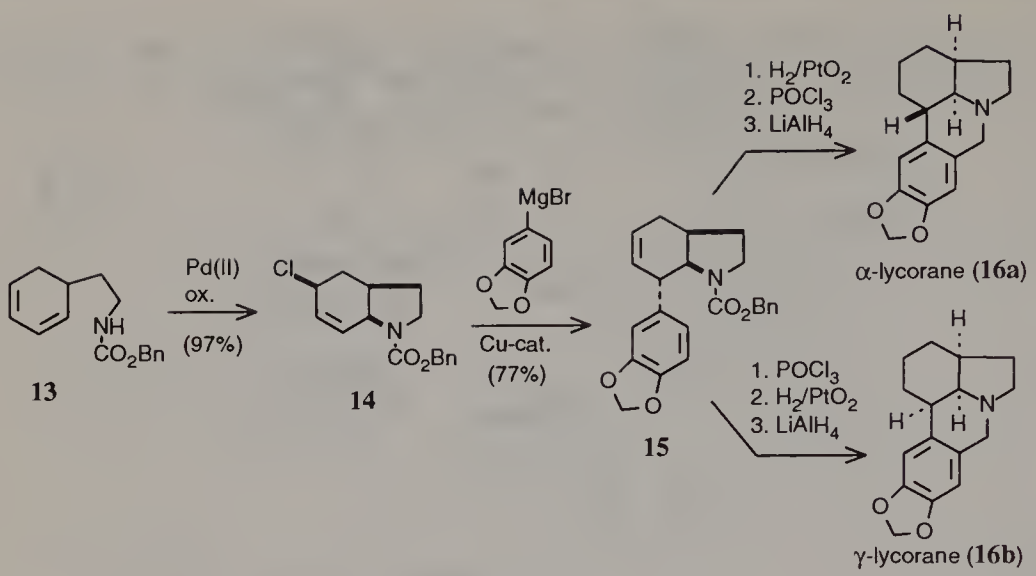


Scheme 7

compound **10** obtained from diene alcohol **9** in the intramolecular Pd-catalyzed reaction was transformed to **11** and **12** (Scheme 7) (Bäckvall and Andersson, 1992). Palladium-catalyzed reaction of **10** with dimethyl sodiomalonate at room temperature proceeded with complete retention of configuration at the 5-position of the hexahydrobenzofuran. The corresponding uncatalyzed reaction between **10** and dimethylsodiomalonate at 80°C afforded the product resulting from Walden inversion.

2.3 Fused pyrrolidines

The intramolecular version of the palladium-catalyzed reaction also allows the use of nitrogen nucleophiles (Bäckvall *et al.*, 1991; Bäckvall and Andersson, 1990). Thus, fused [7,5] and [6,5] pyrrolidines were obtained in regio- and stereoselective reactions (Scheme 3, XH = NHCOR, n = 1,2, m = 1). The formation of hexahydroindole **14** from **13** with defined stereochemistry was recently applied to the synthesis of lycorane alkaloids (Scheme 8) (Bäckvall *et*



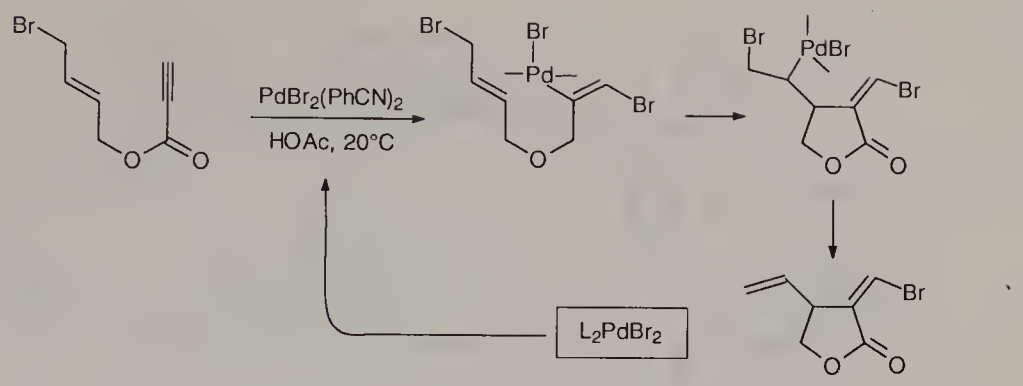
Scheme 8

al., 1991). By switching the order of hydrogenation and cyclization in the transformation of **15** to **16**, it was possible to obtain the α- and γ-lycoranes (**16a** and **16b**) with complete stereoselectivity. Bischler–Napieralsky cyclization of **15** with $POCl_3$ resulted in a highly stereoselective epimerization.

3 Carboannulation

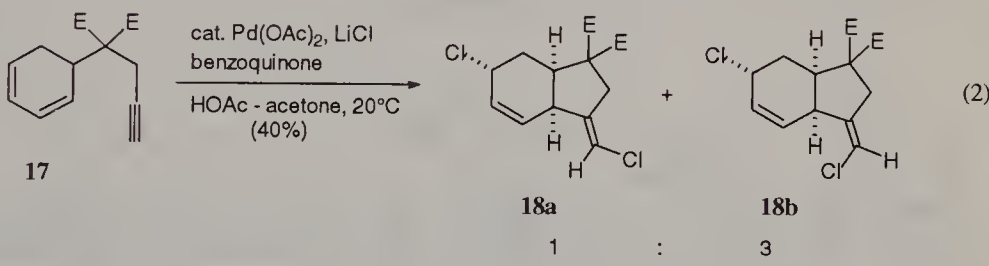
With the objective to extend the intramolecular palladium-catalyzed reactions to include carbon nucleophiles, we studied a number of dienes from Scheme 3 where the nucleophile in the side chain is a stabilized carbon nucleophile. However, all attempts to obtain a carboannulation by this approach have so far been unsuccessful. We therefore turned our attention to vinyl and aryl nucleophiles, which are known to add to double bonds in palladium-catalyzed reactions (Heck, 1982). In these reactions the nucleophile is coordinated to palladium. A vinylpalladium species may be obtained from an acetylene via an addition such as a hydropalladation or chloropalladation. The latter reaction would be particularly useful since it involves a Pd(II) chloride salt. A recent example of the generation of a vinylpalladium intermediate from halopalladation of an acetylene in a catalytic reaction is given in Scheme 9 (Ma and Lu, 1991). A *trans*-bromopalladation of the acetylene generates a vinylpalladium species, which subsequently adds to the olefin to give a σ-alkylpalladium intermediate. Debromopalladation gives the product and regenerates the palladium(II) catalyst.

With the objective to obtain a carbopalladation, by generating a vinylpalladium species, the diene acetylene **17** was allowed to react under the standard conditions for intramolecular 1,4-oxidation of dienes. Indeed, an addition of



Scheme 9

the vinyl and chloride across the diene had occurred (J. E. Bäckvall *et al.*, unpublished results, 1993). Analysis of the product revealed that there were two isomers in a ratio of 1:3 (equation 2). From NOE experiments the



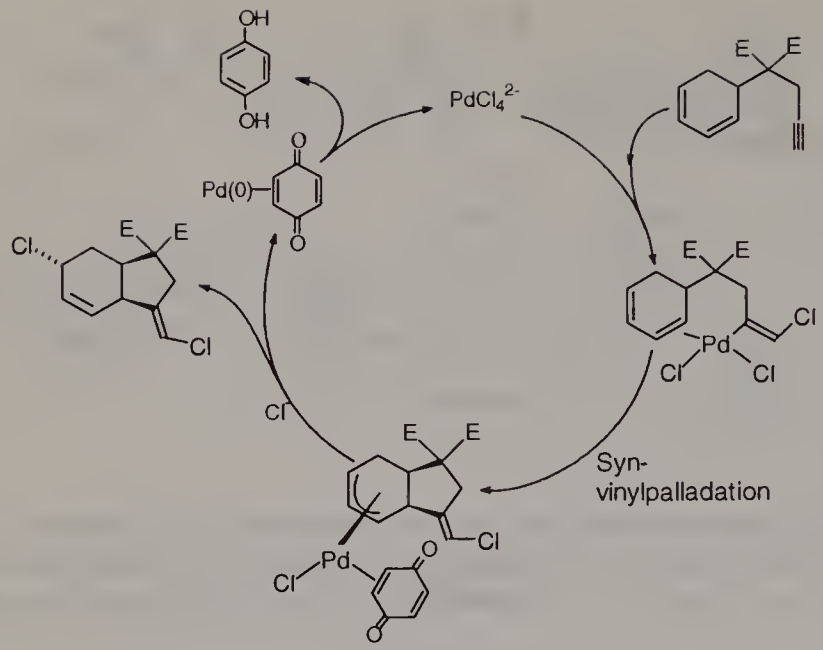
18a : **18b**

1 : 3

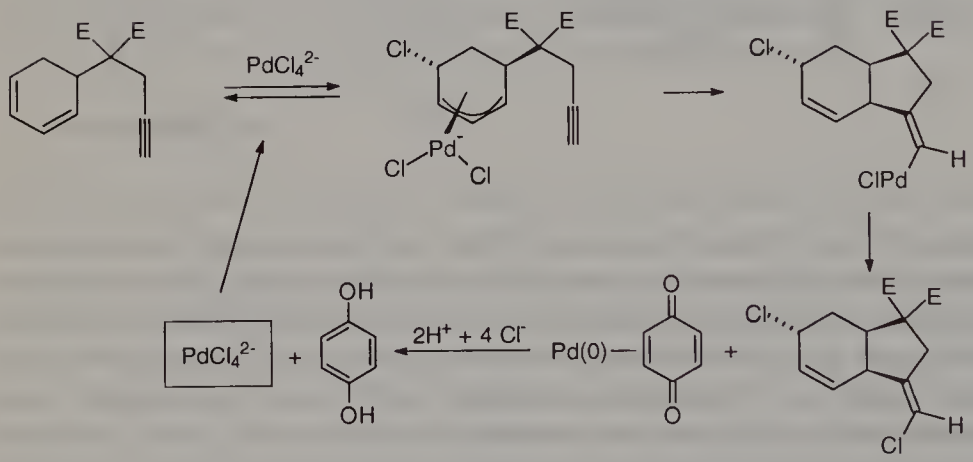
(2)

structures **18a** and **18b** were assigned. There are two possible mechanisms to account for the products. An initial chloropalladation may lead either to a vinylpalladium(II) complex (Scheme 10) or to a (π-allyl)palladium(II) complex (Scheme 11). The former mechanism (Scheme 10) follows the usual catalytic cycle for 1,4-oxidation. Addition of the vinyl nucleophile to the conjugated diene and subsequent nucleophilic attack on the (π-allyl)palladium complex formed gives the product. This mechanism has support from the mechanism in Scheme 9 suggested by Ma and Lu (1991). In this mechanism a *cis*-chloropalladation would account for product **18b**.

The alternative mechanism for the formation of the carbopalladation product, involving a chloropalladation of the diene, is shown in Scheme 11. The (π-allyl)palladium species thus formed would add to the acetylene. In this addition the allyl carbon and palladium add *syn*. Reductive elimination with retention of configuration at carbon would give the vinyl chloride observed. Again, the Pd(0)-quinone complex formed would rearrange to Pd(II) and hydroquinone. The latter mechanism has precedence in previous work where a (π-allyl)palladium(II) complex, generated *in situ*, adds to an olefin (Oppolzer *et al.*, 1988; Oppolzer, 1990) or to an acetylene (Ihle and Heathcock, 1993).



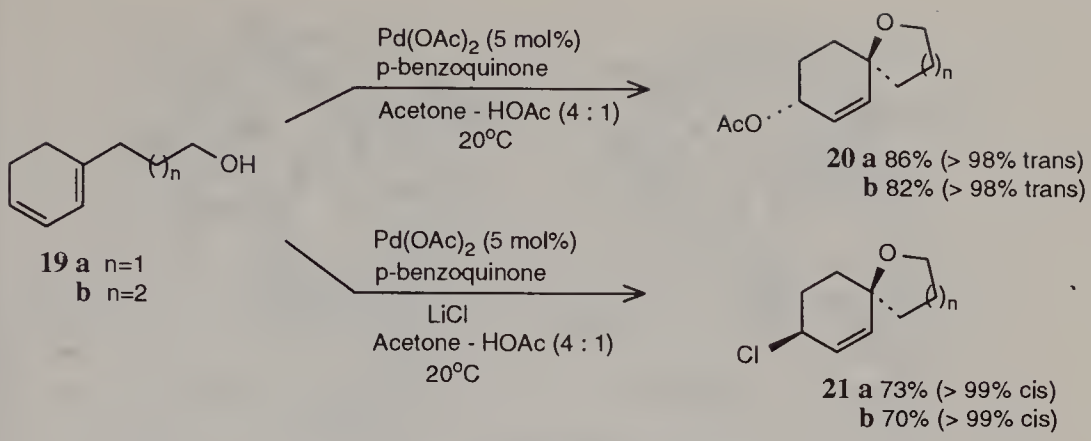
Scheme 10



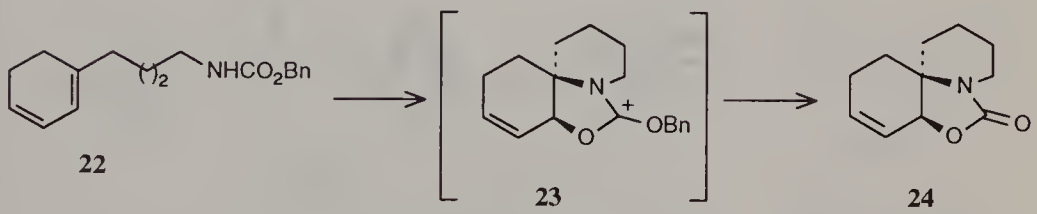
Scheme 11

4 Spirocyclization

If the side chain containing the nucleophile is sitting in the 1-position of a cyclic diene, a spirocyclization takes place under the usual reaction conditions for Pd-catalyzed 1,4-oxidation (Bäckvall and Andersson, 1991). The Pd(II)-catalyzed oxidation of diene alcohol **19** in the absence of chloride afforded an acetoxy spiroether **20** where *trans* addition across the double bond has occurred (Scheme 12). The reaction in the presence of chloride, in this case stoichiometric amounts, produced the oxaspirocycle **21** via a *cis*-oxychlorination. The

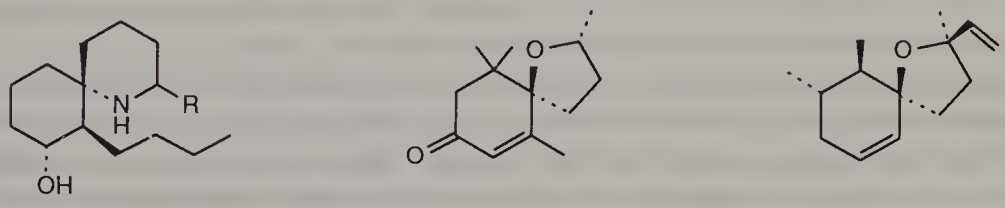


Scheme 12



Scheme 13

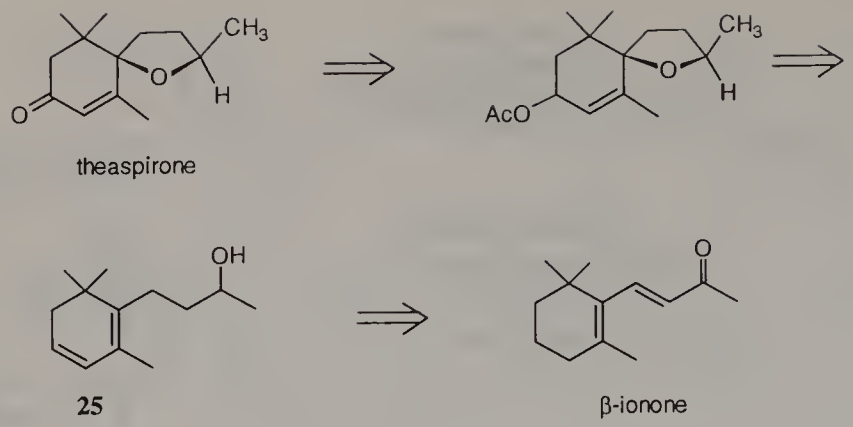
corresponding azaspirocyclization of **22** afforded **24** most likely via intermediate **23** (Scheme 13). Several natural products with heterospirocyclic structures are known such as histrionicotoxins (Daly, 1982), theaspirone (Ina *et al.*, 1988) and dactyloxene-B (Schnitz and McDonald, 1974). Theaspirone is a compound with a strong smell and taste. It is a flavor component of tea (hence its name)



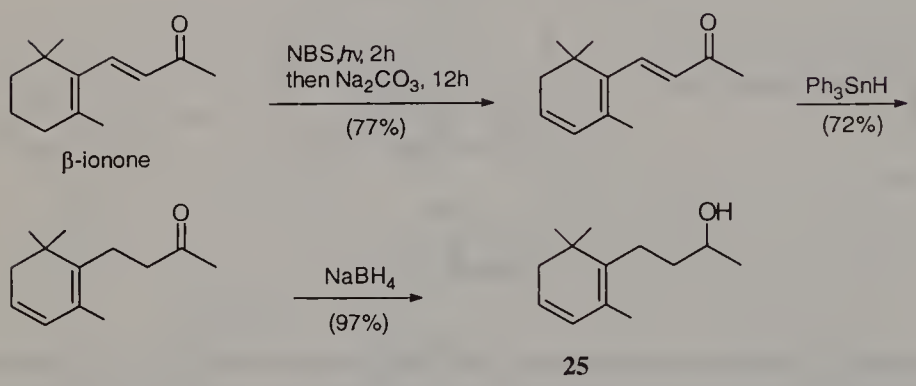
histrionicotoxins theaspirone dactyloxene-B

but it also occurs in raspberry and passion fruit. Our strategy of creating oxaspirocycles would be particularly suited for the synthesis of this compound. A retrosynthetic analysis is given in Scheme 14.

Theaspirone would be readily available from the acetoxyspirocyclization product derived from diene **25**. The latter diene would be obtained from β-ionone.



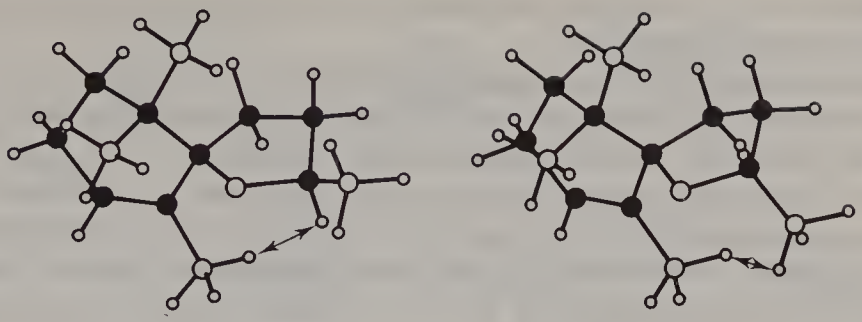
Scheme 14 Retrosynthetic analysis.



Scheme 15

The transformation of β-ionone to the requisite diene for palladium-catalyzed spirocyclization was accomplished by a one-pot procedure involving an allylic bromination–elimination sequence (Scheme 15). The α,β-double bond was selectively reduced by triphenyltin hydride and the ketone was transformed to alcohol by $NaBH_4$ reduction.

Initial attempts to cyclize diene **25** under the standard conditions for intramolecular 1,4-oxidation in acetone-acetic acid (4:1) failed. There are two possible explanations as to why the reaction did not work: (i) the π-allyl intermediate is not formed or (ii) the π-allyl complex is formed but is unreactive. At this stage we decided to study the spirocycle by molecular mechanics (MM2) calculations. In the spirocyclization two different diastereoisomers can be formed, either with the methyl on the tetrahydrofuran pointing away from or pointing towards the methyl group on the double bond (A and B, respectively). MM2 calculations provided information about the relative stabilities of these diastereoisomers (Fig. 1). The calculated energy for diastereoisomer A is 2.23 kcal lower than that of diastereoisomer B. To simplify the calculation the acetate of the six-membered ring is replaced by a hydrogen. This should add very little to the energy differences. Furthermore, we argue that the steric interactions developed during the oxygen addition to



A
Free energy = 21.55 kcal/mol

B
Free energy = 23.78 kcal/mol

$\Delta G° = -2.23$ kcal/mol

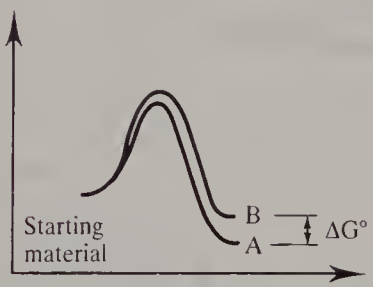
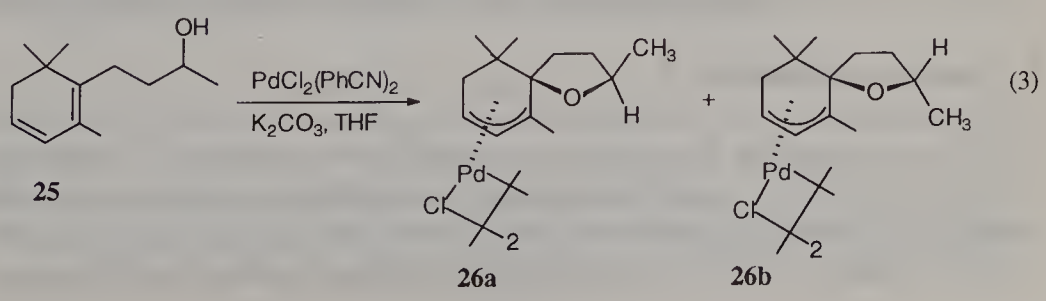


Fig. 1

the double bond in the transition state are very similar to the steric interaction in the product. One would therefore expect an energy difference between the transition states to be of the same order of magnitude as between the products. A likely situation is depicted in the energy diagram. The calculated energy difference between the transition states for formation of A and B should be smaller than that of the product. The energy difference of the products (2.23 kcal/mol) corresponds to a 97:3 ratio.

Because of the failure to run the catalytic reaction of diene **25** we decided to try to prepare the intermediate (π-allyl)palladium complex. Reaction of diene **25** with $PdCl_2(PhCN)_2$, in THF in the presence of K_2CO_3 gave a quantitative yield of the spirocyclic π-allyl complex **26** in a diastereomeric ratio of 10:1 (equation 3). The major isomer had the configuration predicted by the



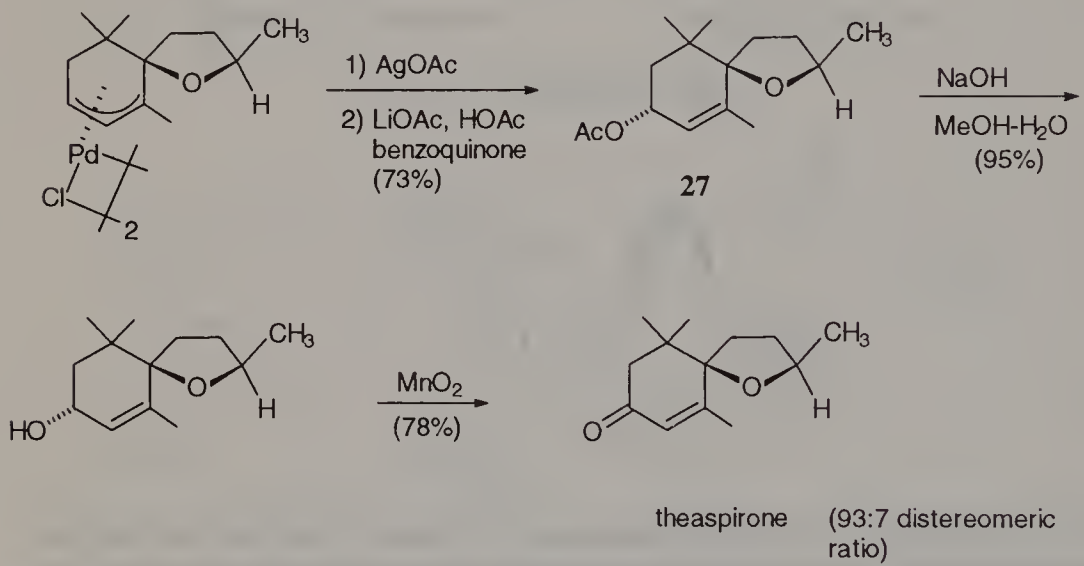
25 **26a** : **26b**

10 : 1 (3)

calculations and, interestingly, the diastereoselectivity obtained was in good agreement with that predicted.

The results show that the (π-allyl)palladium complex can be prepared and is stable and importantly, good asymmetric induction is observed in the cyclization. It is interesting to note that the diene alcohol **25** is obtained from reduction of the corresponding ketone and by employing an enantioselective reduction, optically active alcohol would be accessible for the cyclization.

We next studied the reactivity of the (π-allyl)palladium complex (Scheme 16). Replacement of the chloride by acetate using AgOAc and subsequent

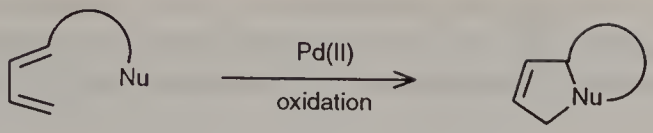


Scheme 16

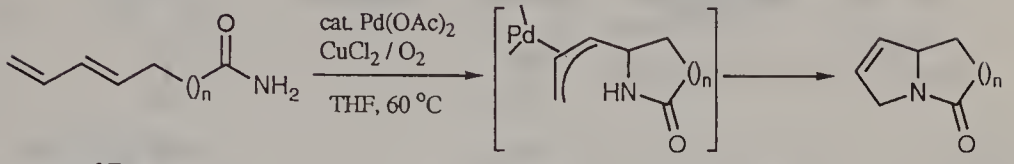
reaction with LiOAc–benzoquinone in *acetic acid* afforded acetate **27**. The difference from the attempted catalytic reaction was that acetic acid was used as solvent in place of acetone–acetic acid (4:1). The acetate **27** was hydrolyzed and oxidized to theaspirone which, on analysis by ^{1}H NMR, revealed a 93:7 diastereomeric ratio (Y. Nilsson, A. Aranyos and J. E. Bäckvall, unpublished results, 1993). Spectral data of the product were identical to those of the theaspirone reported in the literature (Ina *et al.*, 1968; Heckman and Roberts, 1969). In preliminary experiments we have been able to obtain a catalytic reaction by using acetic acid as the solvent. However, at present this reaction suffers from a β-hydride elimination in the (π-allyl)palladium intermediate to give diene and at full conversion only 25–30% of the desired acetate is formed.

5 Tandem cyclization

A further extension of the palladium-catalyzed intramolecular 1,4-oxidation would be to utilize a nucleophile with the ability of making a two-fold nucleophilic attack. This would constitute a synthetically useful [4+1] cycloaddition (Scheme 17). If the nucleophile employed is nitrogen, this leads to



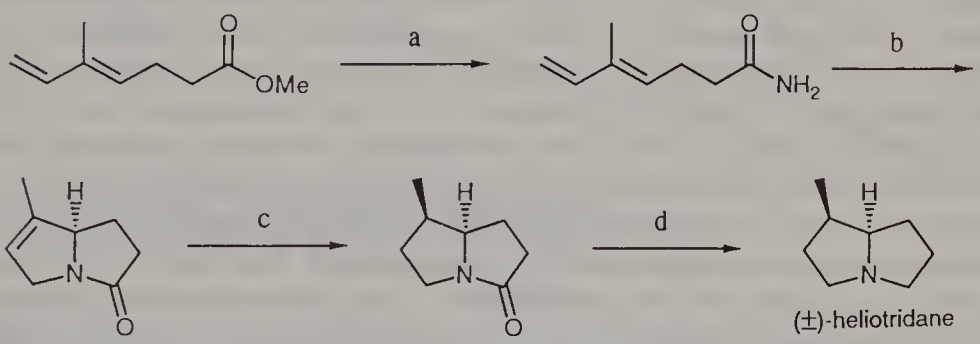
Scheme 17 Formal [4+1] cycloaddition.



27, n = 1
28, n = 2

29, n = 1: 90%
30, n = 2: 85%

Scheme 18



Scheme 19

pyrrolizidine and indolizidine derivatives. A number of alkaloids contain this structural unit. Palladium-catalyzed reaction of dieneamides **27** and **28** in THF employing $CuCl_2/O_2$ as the oxidant afforded the azabicyclic products **29** and **30** (Scheme 18) (Andersson and Bäckvall, 1992). The mechanism of this cyclization involves a (π-allyl)palladium intermediate formed by amide attack on coordinated diene. Subsequent nucleophilic attack by the amide nitrogen on the π-allyl provides the bicyclic product.

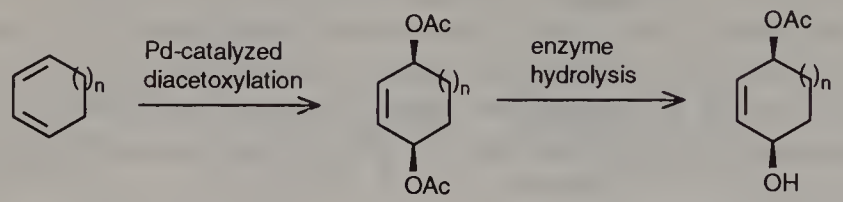
The tandem cyclization was applied to the synthesis of the pyrrolizidine alkaloid (±)-heliotridane (Scheme 19) (Andersson and Bäckvall, 1992).

6 Enantiodivergent synthesis of annulation products

Because of the stereocontrol in the annulation reaction, it would be of great importance to have the starting material of Scheme 3 in an enantiomerically pure form. In this way a number of stereodefined enantiomerically pure heterocyclic compounds with three chiral centres would be available.

Our approach to these chiral 5-substituted-1,3-cycloalkadienes in enantiomerically pure form utilizes the enantiomerically pure monoacetate of *cis*-2-

cycloalken-1,4-diol as the key intermediate. These monoacetates **32** were prepared from the corresponding 1,3-cycloalkadiene via a palladium-catalyzed *cis*-1,4-diacetoxylation and subsequent enzyme hydrolysis (equation 4) (Bäckvall *et al.*, 1993b). Chiral monoacetates **32** are versatile synthons which can be substituted by nucleophiles at either allylic position employing palladium catalysis. This gives access to either enantiomer and was applied to the synthesis of both enantiomers of (cyclohexa-2,4-dienyl)- and (cyclohepta-2,4-dienyl)acetic acid, respectively (Scheme 20). The reactivity of the allylic leaving groups is altered so that either enantiomer of acetoxy malonate **35** is available by choice. The enantiomeric allylic acetates (−)-**35** and (+)-**35** were transformed to the corresponding enantiomers of the dienecarboxylic acids.



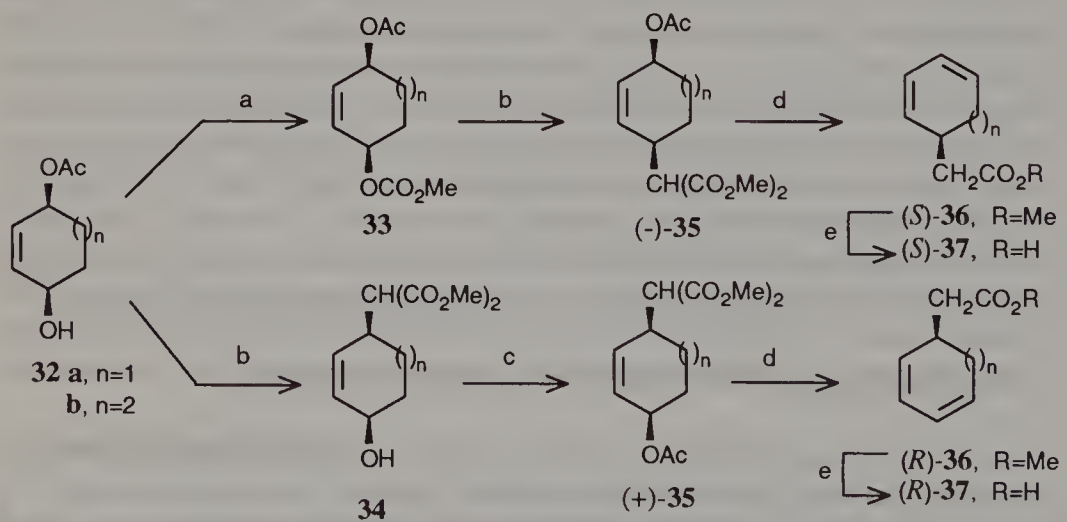
(4)

a, n = 1
b, n = 2

31a
b

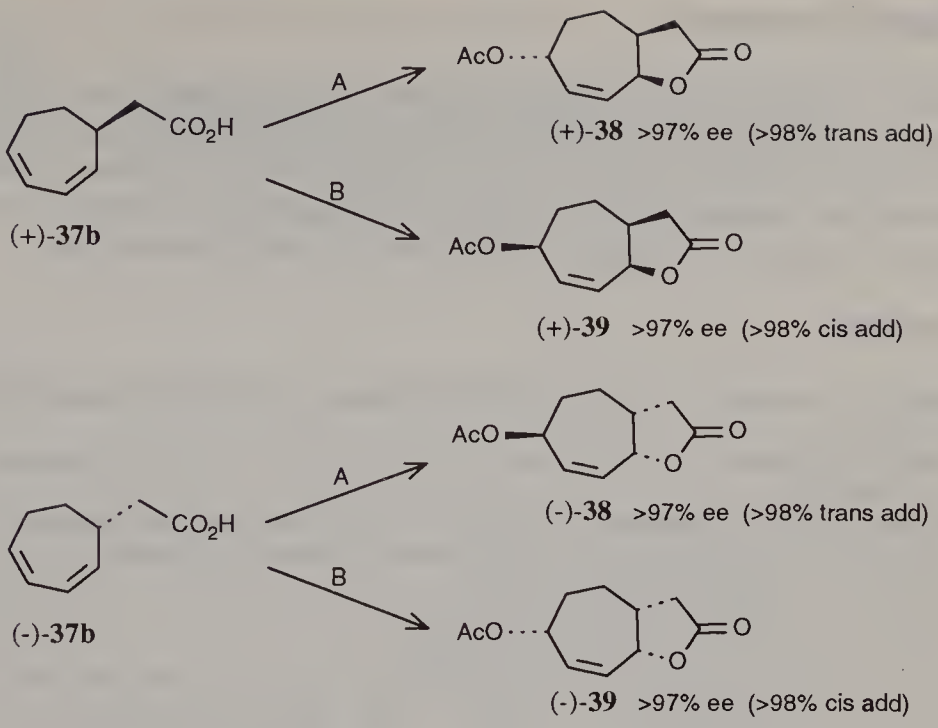
32a (>98% ee)
b (>98% ee)

To demonstrate the synthetic utility of this approach diene acid (+)-**37b** and (−)-**37b** were subjected to the stereoselective lactonization reactions (Scheme 21). In this way four enantiomers in >97% ee were prepared by employing the two different reaction conditions leading to *cis*- or *trans*-acetoxylactonization, respectively.



Reagents: (a) MeO_2CCl, pyridine, CH_2Cl_2; (b) $NaCH(CO_2Me)_2$, $Pd(OAc)_2$, PPh_3, THF; (c) AcCl, pyridine, CH_2Cl_2; (d) i. Pd(0), ii. $NaCN$-H_2O, DMSO. (e) KOH, $MeOH$-H_2O.

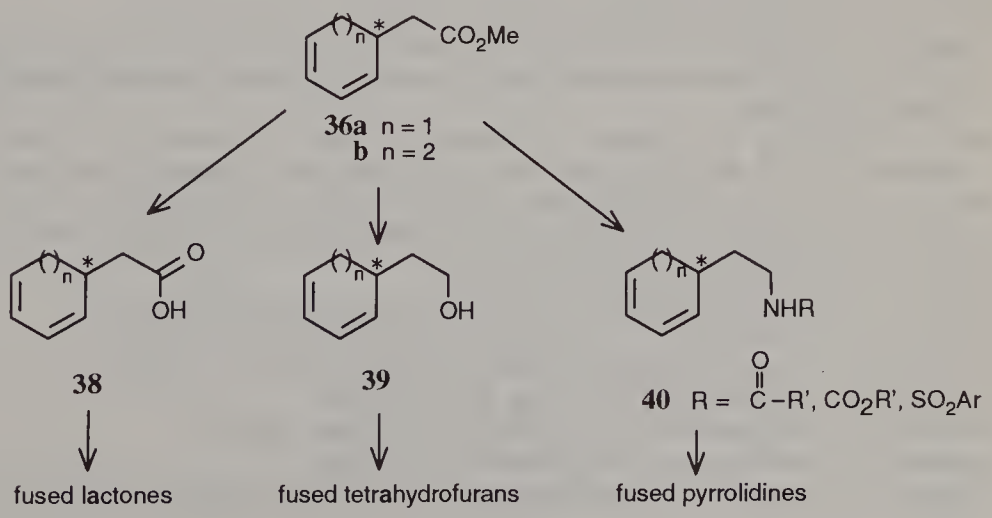
Scheme 20



A: cat. $Pd(OAc)_2$, *p*-benzoquinone, HOAc - acetone
B: cat. $Pd(OAc)_2$, *p*-benzoquinone, LiOAc, LiCl, HOAc - acetone

Scheme 21

The methodology developed gives access to both enantiomers of diene esters **36** via an enantiodivergent transformation of 1,3-cycloalkadienes. The esters are important key synthons for further enantioselective transformations. The ester can be hydrolyzed to acid, reduced to alcohol, or be transformed into a number of amides (Scheme 22). In this way enantiomerically pure lactones, fused tetrahydrofurans, and fused pyrrolidines are at hand.



Scheme 22

Acknowledgements

I wish to express my sincere appreciation to my collaborators, whose names appear in the references, for their efforts in exploring the chemistry outlined in this review. Financial support from the Swedish Natural Science Research Council, the Swedish Board of Technical Development and the Swedish Research Council for Engineering Science is gratefully acknowledged.

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5

Highly Diastereoselective Additions of Organometallics to Chiral 1,3-Oxazolidines

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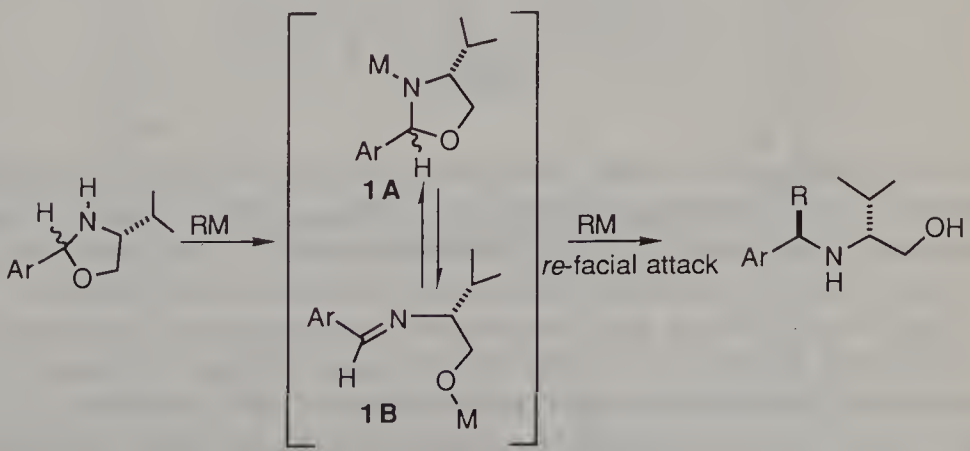
1 Introduction

Diastereoselective addition of organometallic reagents to imines and their derivatives offers an attractive approach for asymmetric synthesis of amines (Coppola and Schuster, 1987). Recent studies have shown that the diastereoselective addition of various organometallic reagents to non-racemic imines and 1,3-oxazolidines derived from non-racemic amino alcohols proceeds in a highly efficient manner, ultimately providing a route for generating chiral amines in high chemical and optical yields (Scheme 1; Takahashi *et al.*, 1990).

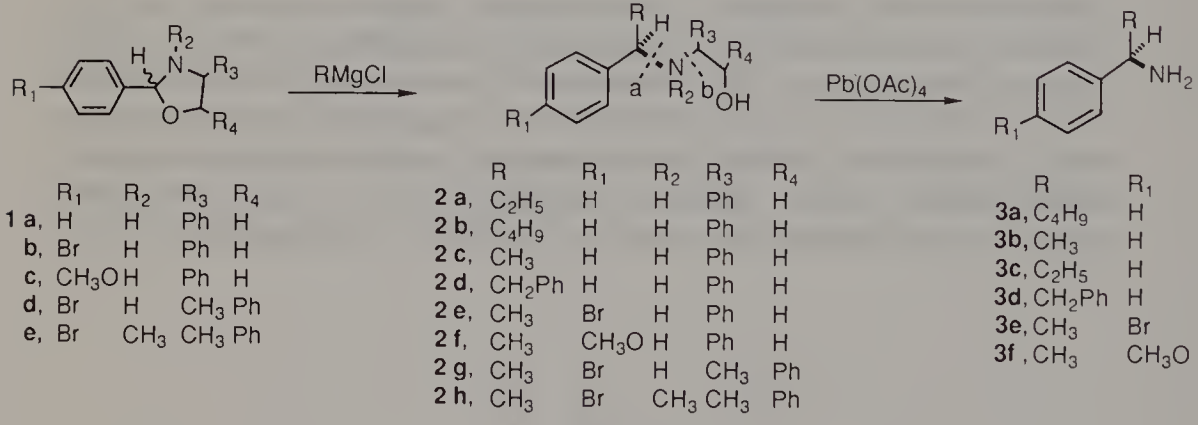


Scheme 1

ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS
ISBN 0-12-499150-5

2 α-Alkyl phenylmethylamines

This laboratory had a requirement to fulfil a request for substantial quantities of (*R*)-α-methyl-*p*-bromophenylmethylamine to be used as a resolving agent on a continual basis. Normally, this class of amines is readily available for small-scale use, but the commercial availability of large quantities is severely limited. We therefore sought a synthesis that would permit facile access to these amines in high optical purity in a manner that would be amenable to pilot plant-scale development. Many of the published routes to α-alkyl phenylmethylamines require a tedious resolution of the corresponding racemate (Ingersoll, 1943). The few reported asymmetric approaches are unacceptable for a number of reasons, such as high cost, multiple steps, low chemical yields, or low diastereoselectivity (Kunz, 1987). Based on Takahashi's asymmetric synthesis of *optically pure* *N*-alkyl-1-cyclohexyl-2-phenylethylamines by stereoselective addition of benzylmagnesium chloride to (4*R*)-2-cyclohexyl-4-phenyl-1,3-oxazolidine (Takahashi *et al.*, 1986) and on the fact that Grignard addition to chiral oxazolidines has enjoyed widespread success in asymmetric synthesis, we decided to explore the use of the analogous 2-aryl-4-phenyl-1,3-oxazolidine **1** as a general substrate for organometallic additions (Scheme 2).



	R_1	R_2	R_3	R_4
1 a	H	H	Ph	H
b	Br	H	Ph	H
c	CH_3O	H	Ph	H
d	Br	H	CH_3	Ph
e	Br	CH_3	CH_3	Ph

	R	R_1	R_2	R_3	R_4
2 a	C_2H_5	H	H	Ph	H
2 b	C_4H_9	H	H	Ph	H
2 c	CH_3	H	H	Ph	H
2 d	CH_2Ph	H	H	Ph	H
2 e	CH_3	Br	H	Ph	H
2 f	CH_3	CH_3O	H	Ph	H
2 g	CH_3	Br	H	CH_3	Ph
2 h	CH_3	Br	CH_3	CH_3	Ph

	R	R_1
3a	C_4H_9	H
3b	CH_3	H
3c	C_2H_5	H
3d	CH_2Ph	H
3e	CH_3	Br
3f	CH_3	CH_3O

Scheme 2

At the initiation of this work, Takahashi had reported only benzylic Grignard addition to 2,4-disubstituted oxazolidines. Consequently, we sought to extend the scope of this reaction with the ultimate intention of employing the amino alcohol adduct as a source of chiral α-substituted phenylmethylamines.

Table 1 outlines our initial results in the stereoselective organometallic nucleophilic addition to **1** with its subsequent oxidative cleavage to α-substituted phenylmethylamines (Wu and Pridgen, 1991). All substrate oxazolidines were readily synthesized by condensation of the appropriate aldehyde with the prerequisite chiral amino alcohol (Fülöp *et al.*, 1989). Most of our

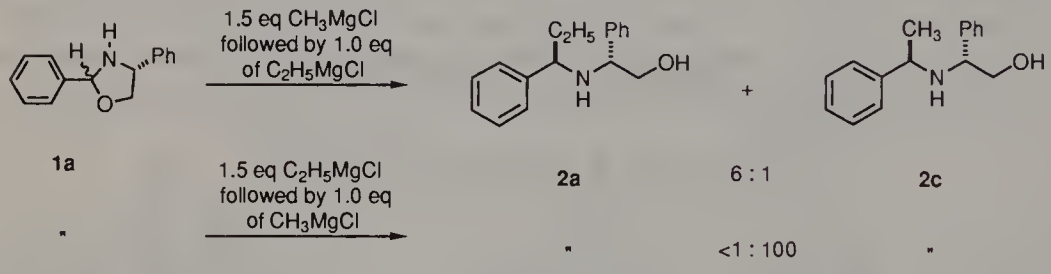
Table 1 Yields and selectivities for Grignard additions to oxazolidines **1** and cleavage yields of **3**

Entry	Substrate	RMgCl	Yield (%)	Diastereo-selectivity[c]		Cleavage yield (%)		$[\alpha]_D^{25}$ (c, $CHCl_3$) **3**	%ee
1	**1a**	Et	62	98:2	**2a**	—		—	—
2	**1a**	Bu	47	98:2	**2b**	52	**3a**	+11.7(1.0)	92
3	**1a**	Me	56	95:5	**2c**	50	**3b**	+28.8(1.0)	94
4	**1a**	Et (3 eq, $CeCl_3$)	85	>99:1	**2a**	46	**3c**	+35.2(1.2)	95
5	**1a**	Me [$MgBr_2 \cdot O(Et)_2$]	31	96:4	**2c**	—		—	—
6	**1a**	Benzyl	87	94:6	**2d**	—		—	—
7	**1a**	Benzyl (3 eq, $CeCl_3$)	78	98:2	**2d**	59	**3d**	−10.9(1.6)	>99
8	**1b**	Me	60	95:5	**2e**	65	**3e**	+24.1(1.6)	98
9	**1c**	Me	45	97:3	**2f**	46	**3f**	+24.6(1.0)	96
10	**1d**	Me	51	94:6	**2g**	—			—
11	**1e**	Me	77	60:40	**2h**	—			—
12	**1a**	MeLi (−78°C)	48	95:5	**2c**	—			—
13	**1a**	MeLi (25°C)	49	77:23	**2c**	—			—
14	[a]	Me	50	87:13	[b]	—			—

[a] The imine in this case was the methyl ether of the imine **1B** of Scheme 4.
[b] This product is the methyl ether analog of **2e** [−9.7 (c 1.0, $CHCl_3$)].
[c] Diastereomeric isomer ratios were determined by using 400 MHz ^{1}H NMR.

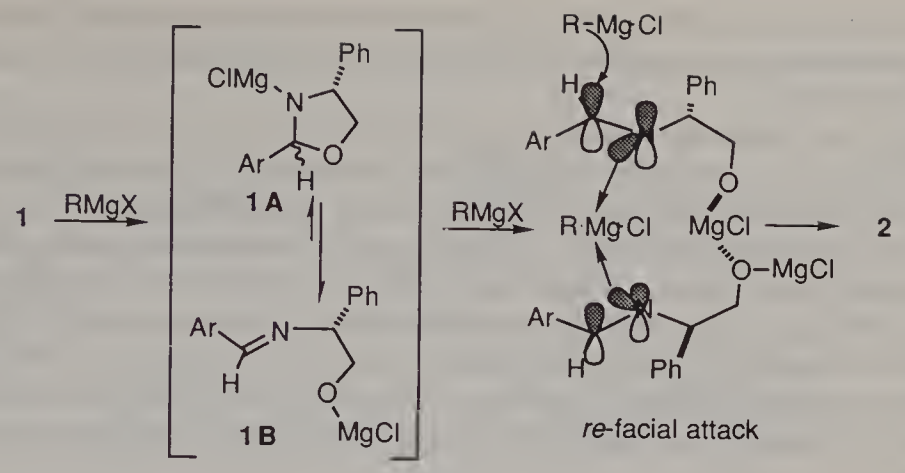
reactions were done utilizing the readily available (*R*) or (*S*) phenylglycinol, prepared in bulk via our recently reported BH_3/DME amino acid reduction procedure (Pridgen *et al.*, 1989). Grignard addition to oxazolidine **1** occurred quite readily under THF reflux (4–24 h) with usually very high diastereoselection for **2** (averaging ~96% de) as determined by 400 MHz ^{1}H NMR spectroscopy. Typically, 2.5–3.0 eq of Grignard reagent was required to force the reaction to completion *and* achieve high diastereoselectivity. In fact Grignard addition would not occur cleanly until at least ~1.5 equivalents of the organometallic had been added.

In an interesting experiment, we added 1.5 eq of methyl Grignard to **1** in THF at room temperature followed shortly by 1.0 eq of ethyl Grignard and then warmed the reaction mixture to THF reflux temperature. The resulting product was that predominately from addition of the ethyl group rather than methyl (6:1 ratio). Reversing the order of addition led to a reversal of product selectivity (Scheme 3), but with an even greater disparity in the ratio of



Scheme 3

products (>100:1). This unprecedented high level of asymmetric induction for Grignard addition to the normally tautomeric oxazolidine/imino functionality may be attributed to a highly ordered transition state resulting from significant chelation of the alkoxy substituent and imino nitrogen to at least one/half magnesium cation. The Grignard reagent then attacks the *re* face of C-2 of either **1A** and **1B** (Takahashi *et al.*, 1986) from the less hindered side, distal to the (*R*)-substituent of the amino alcohol moiety (Scheme 4). Our data to date do not allow us to discern whether or not Grignard addition is preceded by ring opening since the stereochemical result would be equivalent. However, the ^{1}H NMR ($CDCl_3$) solution spectrum of **1a** indicates that the oxazolinyl/imino tautomeric equilibrium lies predominately toward the imine (Takahashi *et al.*, 1986, 1990; Fülöp *et al.*, 1989). This observation is in agreement with the postulate of Hauser (Stewart and Hauser, 1955) who suggested that amino ethers form a 2:1 strongly coordinated nitrogen/oxygen to magnesium complex, which in our case forms after deprotonation with the first equivalent of Grignard. Consequently, 1.5 eq of Grignard is unavailable for addition to carbon. This mode of addition is not very dissimilar to the one invoked by Takahashi (Takahashi and Suzuki, 1983) and Koga (Coppola and Schuster,



Scheme 4

1987) in their reported chelation-controlled nucleophilic addition to chiral valinol derived hydrazones and *t*-leucine derived α,β-unsaturated aldimines, respectively.

In attempts to further exploit this 'chelation handle' and also possibly decrease the quantity of Grignard reagent required, we explored the use of Lewis acid chelators. For example, when we used either $ZnCl_2$, $TiCl_4$, $BF_3 \cdot O(Et)_2$, CuI, or $CuBr_2 \cdot S(CH_3)_2$ with methyl Grignard, we obtained at best a 77:23 ratio of isomeric products. However, with a 1:1 ratio of cerium chloride to Grignard reagent (3 eq) under our standard reaction conditions, essentially one stereoisomer was obtained. Thus, the strong oxophilicity of cerium has enhanced the selectivity of the organometallic addition to the extent that a single diastereomer may be produced (Imamoto and Sugiura, 1985). Unlike other organometallic reagents that we investigated, the cerium organometallic is highly regioselective for C-2 of **1** and is the reagent of choice in a nucleophilic addition to **1**. The methoxy analog of imine **1B** gave a diminished ratio of isomers (~87:13) as did the *p*-bromophenyloxazolidine analog of ephedrine (Table 1, entries 10, 11 and 14). Takahashi *et al.* (1988) and Davidsen and Chu-Moyer (1989) obtained comparable or worse results with chiral N-substituted valinol-derived oxazolidines. Thus, at least one of the nitrogen or oxygen–magnesium bonds in Scheme 4 should be covalent in order to produce the higher selectivity.

Takahashi *et al.* and Davidsen and Chu-Moyer also demonstrated the applicability of aliphatic oxazolidines as substrates. We similarly employed (4*R*)-2-*n*-butyl-4-phenyloxazolidine as a substrate in a reaction with phenyl Grignard and obtained a 9:91 ratio of **2b**. As expected, the minor isomer in Table 1 (entry 2) is now major. Thus, with the exception of the unstable 2-methyl-4-phenyloxazolidine, both aliphatic and aryl-2-oxazolidines may be employed in this reaction. Therefore, in addition to being able to employ either enantiomer of the chiral auxiliary, one has an alternative entry to the different

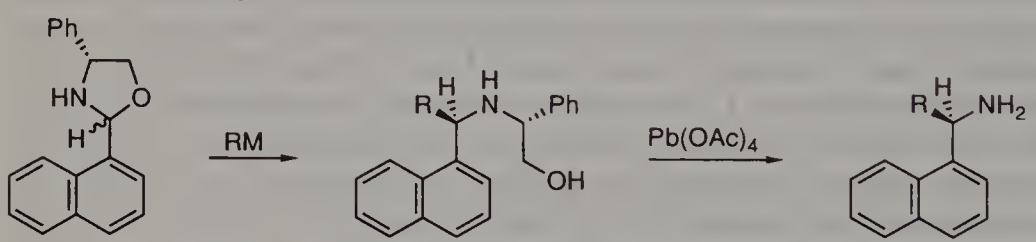
diastereoisomers. In related work, diastereoselective organometallic addition to nitrones bearing stereogenic N-substituents have been reported (Chang and Coates, 1990a,b).

Unlike the Takahashi examples, which contain only one benzylic amine bond susceptible to reductive cleavage, we anticipated the need to devise a hydrogenolysis procedure to selectively cleave the ethanolamine carbon–nitrogen bond (b) of **2** (Scheme 2). All of our attempts to hydrogenolyze **2** to **3** were without much success, at least up to hydrogen pressures of 80 psi. We also attempted to exploit the hydrogenolysis conditions of Bringmann and Geisler (1989) but obtained the undesired bond cleavage at (a) (Scheme 2). Only the carefully controlled oxidative conditions of Gawley *et al.* (1989) proved to be effective in obtaining the desired chiral phenylmethylamines, albeit in moderate yields.

3 1,2- vs 1,4-addition

On expanding our study of organometallic additions to 1,3-oxazolidines to include naphthalenes, we observed that 2-(1-naphthyl) derivatives of **1** underwent *exclusively 1,4-addition with Grignard reagents and 1,2-addition with lithium, cerium, and copper organometallic reagents* (Tables 2 and 3) (Pridgen *et al.*, 1992). Such a result, particularly for the latter metal, was highly surprising in light of its propensity for predominantly conjugate-type addition. Two of the aminoalcohol products resulting from the 1,2-addition were

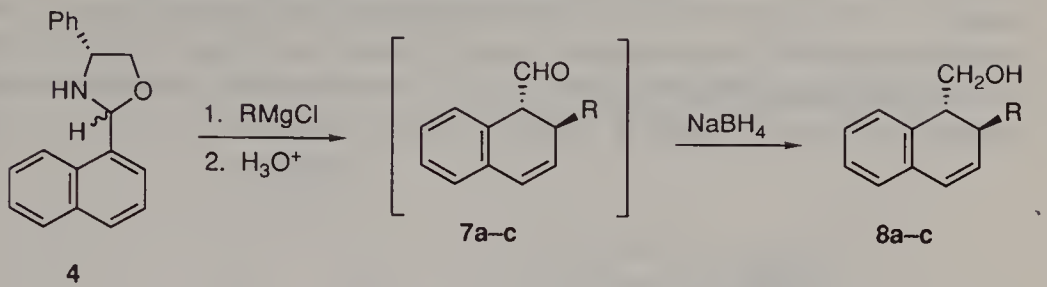
Table 2 1,2-Addition of organometallic reagents to (*R*)-2-(1-naphthyl)-4-phenyl-1,3-oxazolidine **4** and oxidative cleavage results



4 **5a–d** **6a–d**

Entry	cpd	RM	Yield (% **5**)	de (%)	Yield (% **6**)	cc (%)
1	**a**	CH_3Li (−78°C)	46	95		
2	**a**	CH_3CeCl_2 (−45°C)	75	96	61	>99
3	**a**	$CH_3Cu \cdot BF_3$ (−78°C)	71	52	80	54
4	**b**	$C_2H_5CeCl_2$ (−45°C)	75	>99	57	>99
5	**c**	BuLi (−78°C)	81	26		
6	**d**	PhLi (−78°C)	48	>99		

Table 3 1,4-Addition of Grignard reagents to (*R*)-2-(1-naphthyl)-4-phenyl-1,3-oxazolidine **4**



4 **7a–c** **8a–c**

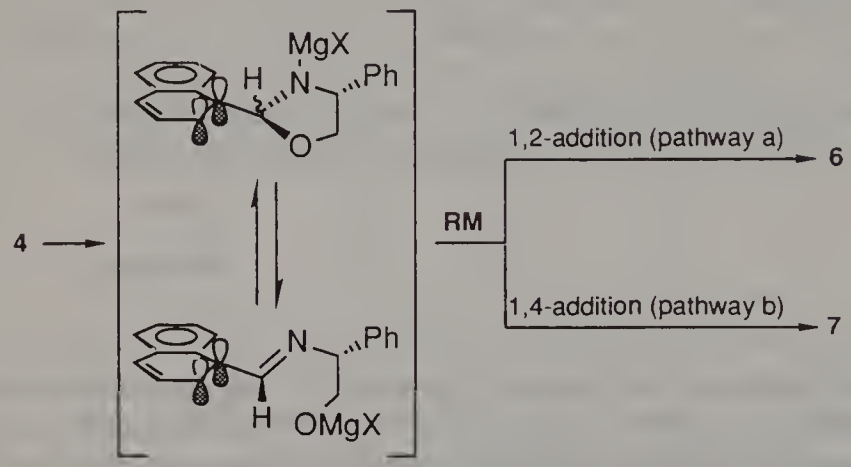
Entry	cpd	R	Yield (% **8**)	ee (%)
1	**a**	Ph	50	93 (94)
2	**b**	Bu	83	93
3	**c**	Et	65	96

ultimately converted via oxidative cleavage to enantiomerically enriched α-(1-naphthyl)alkylamines analogous to the aryl examples reported above. The 1,4-conjugate addition products, which are enantiomerically enriched *trans* disubstituted 1,2-dihydronaphthalenes, have been previously reported by Meyers and demonstrated by him to be valuable intermediates in syntheses of the natural products (+)-phyltetralin (Meyers *et al.*, 1988), (−)-podophyllotoxin (Andrews *et al.*, 1988) and the AB-ring of aklavinone (Meyers and Higashiyama, 1987). Tomioka has also formed these same dihydronaphthalenes by organolithium addition to the cyclohexylimine of 1-naphthalenecarboxaldehyde in the presence of an enantiomerically enriched diether co-catalyst (Tomioka *et al.*, 1989a). The majority of this previous work on organometallic addition to optically active α,β-unsaturated imines and/or oxazolines originated from the laboratories of Tomioka (Tomioka and Koga, 1983) and Meyers (Meyers *et al.*, 1987a,b).

Organometallic addition to the naphthalene nucleus has been limited so far to lithium reagents. In Tomioka's report of organolithium addition to naphthalene carboxylates, predominantly *cis* addition products were obtained, although epimerization to *trans* derivatives was easily accomplished with sodium methylate in THF. We herein report that organomagnesium reagents also add to the naphthalene ring in THF yielding *trans* disubstituted 1,2-dihydronaphthalenes. To the best of our knowledge, this is the first report of organomagnesium reagents adding to the naphthalene nucleus.

Oxazolines (Lutomski and Meyers, 1984), imines (Tomioka *et al.*, 1989a,b), carboxylates (Tomioka and Koga, 1983) and now apparently oxazolidines, activate through induction the *ortho* position of naphthyl ring toward nucleophilic attack. Thus, the proposed mode of addition accounting for the subsequently obtained absolute stereochemistry of the resulting product is

analogous to that depicted previously in Scheme 4. The strong Lewis base character of both the imino nitrogen and amino alcohol oxygen results in very strong complexation to at least one-half equivalent of Grignard reagent, thus limiting the flexibility of the transition state. Consequently, nucleophilic attack occurs predominantly from the less sterically demanding face, that opposite the 4-phenyl (Scheme 5). Attack by lithium, cerium, and copper reagents occurs at

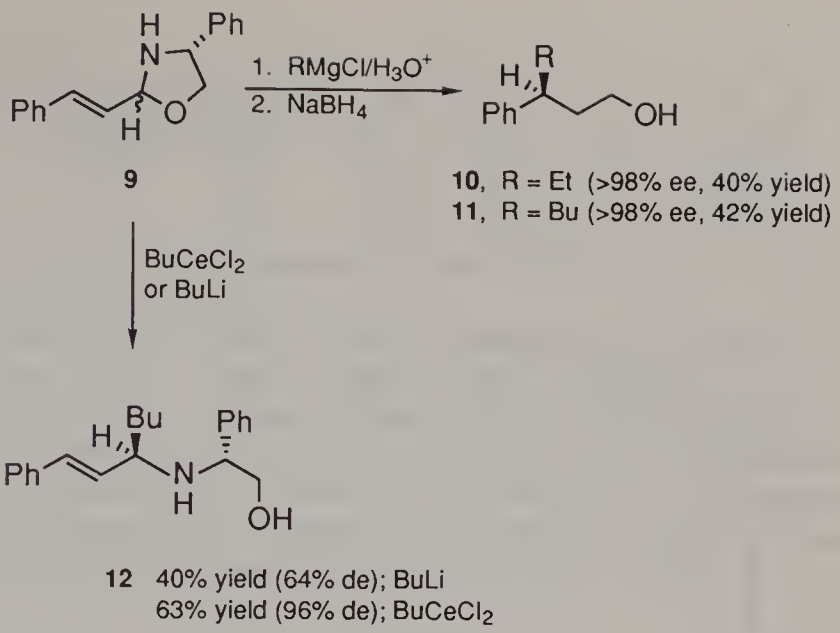


Scheme 5

the hard aminal/imino carbon (pathway a) leading to 1,2-addition products (Table 2). Note that all the organolithiums gave exclusively 1,2-addition products, with butyllithium being almost non-selective. The resulting disubstituted amino alcohols were oxidatively cleaved to enantiomerically enriched α-(1-naphthyl)alkylamines. Pathway b requires attack at the softer electrophilic γ-carbon and is the exclusive pathway for Grignard addition in this ring system (Table 2).

Lithium, cerium, and magnesium organometallic reagents exhibited similar addition behaviors when reacted with oxazolidine **9**, the cinnamyl derivative of **4**. Scheme 6 shows our results where the former two reagents added in a 1,2-fashion while Grignard reagents afforded the 1,4-addition products. Reaction of **9** with ethyl and butyl organomagnesium reagents yielded **10** (40% yield, 96% ee) and **11** (42% yield, 98% ee), respectively. Conversely, reaction of **9** with butyllithium or butylcerium chloride gave **12** in 40% yield (64% de) and 63% yield (96% de), respectively.

Thus, the choice of metal becomes important in adding organometallics to 2-(1-naphthyl)-1,3-oxazolidines or to 2-cinnamyl-1,3-oxazolidines. Either conjugate addition products or products resulting from addition at the aminal/imino carbon are obtained in high stereoselectivity. The stereoselectivities reported herein for the Grignard 1,4-additions are comparable to those reported by Lutomski and Meyers (1984) and Tomioka and Koga (1983). Moreover, this



9

10, R = Et (>98% ee, 40% yield)
11, R = Bu (>98% ee, 42% yield)

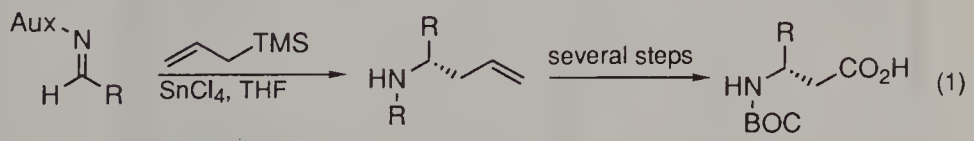
12 40% yield (64% de); BuLi
63% yield (96% de); $BuCeCl_2$

Scheme 6

work, as well as the previously reported study from this laboratory, have established organoceriums as the organometallics of choice for nucleophilic 1,2-addition to 2-substituted 1,3-oxazolidines.

4 β-Amino esters

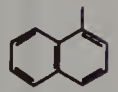
Chiral β-amino acids are highly important intermediates in certain very attractive syntheses of β-lactam derivatives (Salzmann *et al.*, 1980). As a consequence, several varied approaches have been reported for their synthesis (d'Angelo and Maddaluno, 1986; Estermann and Seebach, 1988; Gmeiner, 1990). One of these approaches, employed principally by Kunz (Laschat and Kunz, 1991), is based on a diastereoselective addition of allylsilane to carbohydrate derived Schiff bases followed by oxidative cleavage of the *protected* amino olefin (equation 1).

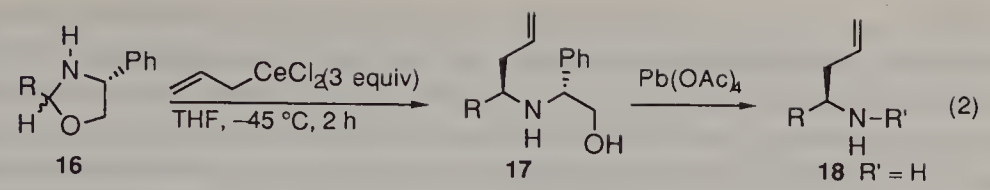


13 **14** R = Aux **15** (1)

Our entry into this area relied on the more efficiently prepared chiral 2-aryl-1,3-oxazolidine **16** as a substrate in an allyl organocerium stereoselective addition reaction (~88% de) (Wu and Pridgen, 1990). The resulting amino alcohol product **17** was subsequently oxidized upon treatment with lead

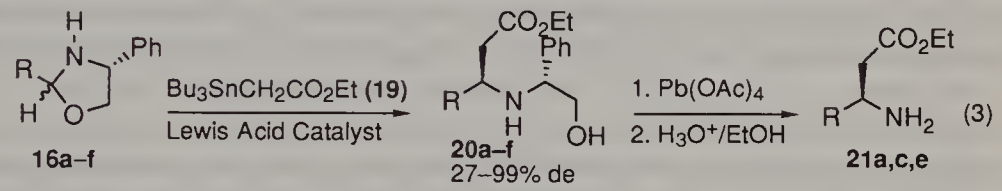
Table 4 Allyl organocerium addition to 2-aryl-1,3-(*R*)-phenyloxazolidine **16**

Ar	Crude yield (R,R) **17** (%)	Diastereoselectivity (isomeric ratio)	Yield (R) **18** (%)	Enantioselectivity (%)	$[\alpha]_D^{25}$	M.p.(°C) (HCl)
	94	(93:7)	87	86	+36.2(1.4)	233–235
	52	(90:10)	69	92	+48.7(1.5)	212–214
	98	(94:6)	82	88	+29.8(1.3)	255–259
	99	(94:6)	75	89	+82.3(1.3)	226–230
	94	(95:5)	78	78	+25.9(0.9)	217–219



tetraacetate to yield homoallylamine **18** (Table 4 and equation 2). This material can thus be transformed to **15**.

Since that initial report, we have investigated other means to further increase the efficiency of this approach, *without using protecting groups*. We have subsequently reported our results employing the highly stable ethyl tributylstannylacetate **19** as a nucleophile in addition reactions to oxazolidine **16**. Under Lewis acid-catalyzed conditions, the addition occurs with remarkable stereocontrol, despite the prolonged reaction conditions (Table 5 and equation 3) (Mokhallalati and Pridgen, 1993; Mokhallalati *et al.*, 1993).



a, R = Ph **d**, R = 1-naphthyl
b, R = *p*-$CH_3C_6H_4$ **e**, R = cyclohexyl
c, R = *p*-BrC_6H_4 **f**, R = *i*-propyl

Table 5 Lewis acid-catalyzed addition of ethyl tributylstannylacetate (**19**) to 2-substituted-4-phenyl-1,3-oxazolidines (**16a–f**) and conversion of **20a,c,e** to **21a,c,e**

Substrate[a]	Lewis acid	Reaction time (h)	Yield **20** (%)	de (%)	Yield **21** (%)	ee (%)
16a	$ZnCl_2$	100	39	96		
16a	$Et_2O \cdot BF_3$	6	82	28		
16a	$Ti(OPr^i)_3Cl$	48	43	—		
16a	$TiCl_4$	15	43	40		
16a	$Sn(OTf)_2$	72	53	70		
16c	$ZnCl_2$	72	21	96		
16c	$Et_2O \cdot BF_3$	72	68	27		
16a	$ZnCl_2/Et_2O \cdot BF_3$	66	71	92	86	91
16b	$ZnCl_2/Et_2O \cdot BF_3$	192	58	92		
16c	$ZnCl_2/Et_2O \cdot BF_3$	96	67	91	87	95
16d	$ZnCl_2/Et_2O \cdot BF_3$	144	60	99		
16e	$ZnCl_2/Et_2O \cdot BF_3$	72	33	94	73	94
16f	$ZnCl_2/Et_2O \cdot BF_3$	264	43	96		

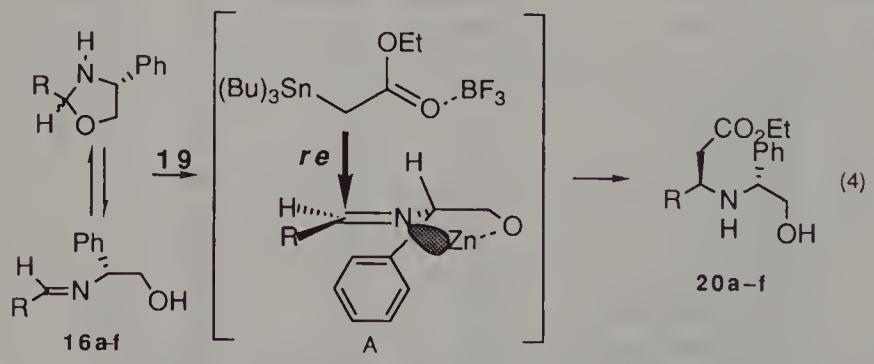
[a] Substrates **16a–f** are defined in equation 3.

After several unsuccessful attempts at trying the zinc derivative of ethyl bromoacetate (Reformatsky reagent) and ethyl trimethylsilylacetate as nucleophilic acetates, we found ethyl tributylstannylacetate **19** to be most effective in this capacity. Table 5 presents the results of the addition of **19** to oxazolidines **16a–f** yielding amino alcohols **20a–f**. Reaction of **16a** with **19** in the presence of $ZnCl_2$ in refluxing THF resulted in only a 39% crude yield of **20a** after a 100 h reflux, but at the same time providing a 98:2 ratio of diastereomeric amino alcohols (entry 1). Using boron trifluoride etherate as a catalyst on the same substrate accelerated the rate of addition, albeit at the expense of stereoselectivity (entry 2).

We also employed a variety of other Lewis acid catalysts (Table 5) but none were as effective as either $ZnCl_2$ or $Et_2O{\cdot}BF_3$. Further reasoning that $ZnCl_2$ was acting primarily as a chelator that would restrict flexibility in a transition state similar to (A) *and* $Et_2O{\cdot}BF_3$ was most probably activating **19** by complexation with the ester carbonyl, we used combinations of these two catalysts. One half eq of each of the Lewis acids, $ZnCl_2$ and $Et_2O{\cdot}BF_3$, represents our best found combination to obtain both good chemical yields and high diastereofacial selectivity (Table 5). The activation of **19** through the use of a fluoride source (e.g. KF + 18-Crown-6) was ineffective.

Equation 4 with its transition state (A) appears to best depict our experimental observations which are similar to our earlier reports. Namely, the nucleophilic acetate adds across the *re* face of the imino/oxazolidine moiety, opposite to (*R*)-phenyl of the auxiliary. This highly selective and efficient synthesis of *β*-amino esters is applicable for synthesizing both antipodal isomers of *aliphatic and aromatic* derivatives.

A Possible Transition State



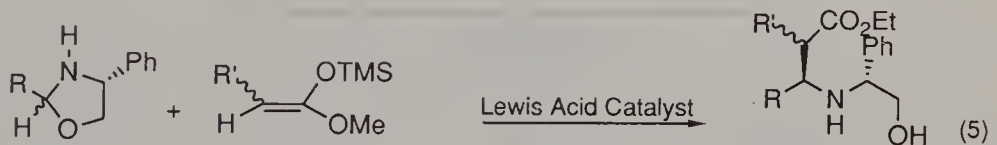
A recent report by Andrés *et al.* (1992a) describes the addition of the moisture sensitive Reformatsky reagent to an *N*-benzylated analog of **16**. This

approach is limited to aliphatic amino esters because of the use of Pd/C to remove the auxiliary. In addition, their lower observed diastereoselectivity of addition serves to reinforce our earlier observation that the secondary amino function is necessary for greater selectivity. Addition of diethylaluminum cyanide (Andrés *et al.*, 1992b) and trimethylsilylcyanide (Chakraborty *et al.*, 1991) to **16** has also been shown to occur with good to moderate selectivity (~80:20 isomer ratio), thereby providing another asymmetric synthesis of α-amino esters.

5 Silyl enol ether addition

O-Alkyl-*O*-(trimethylsilyl)ketone acetals are known to react with either imines or iminium ions generated *in situ* (Hart and Ha, 1989; Harding *et al.*, 1991; Martin and Corbett 1992). The resulting β-amino esters can be converted to β-lactams using standard methodology. Examples of Lewis acid-mediated reactions between ketene acetals and other azomethines are also well documented (Hart and Ha, 1989).

In seeking to expand the range of the nucleophilic additions to 2-substituted 1,3-oxazolidines, we explored the addition of *O*-methyl-*O*-(trimethylsilyl)ketene acetal **22a** to **16**. Poor results were obtained (equation 5) employing a variety of catalysts. The best results were obtained with $TiCl_4$ and $Et_2O \cdot BF_3$ as catalysts. For the $TiCl_4$-catalyzed examples, a 41% yield with



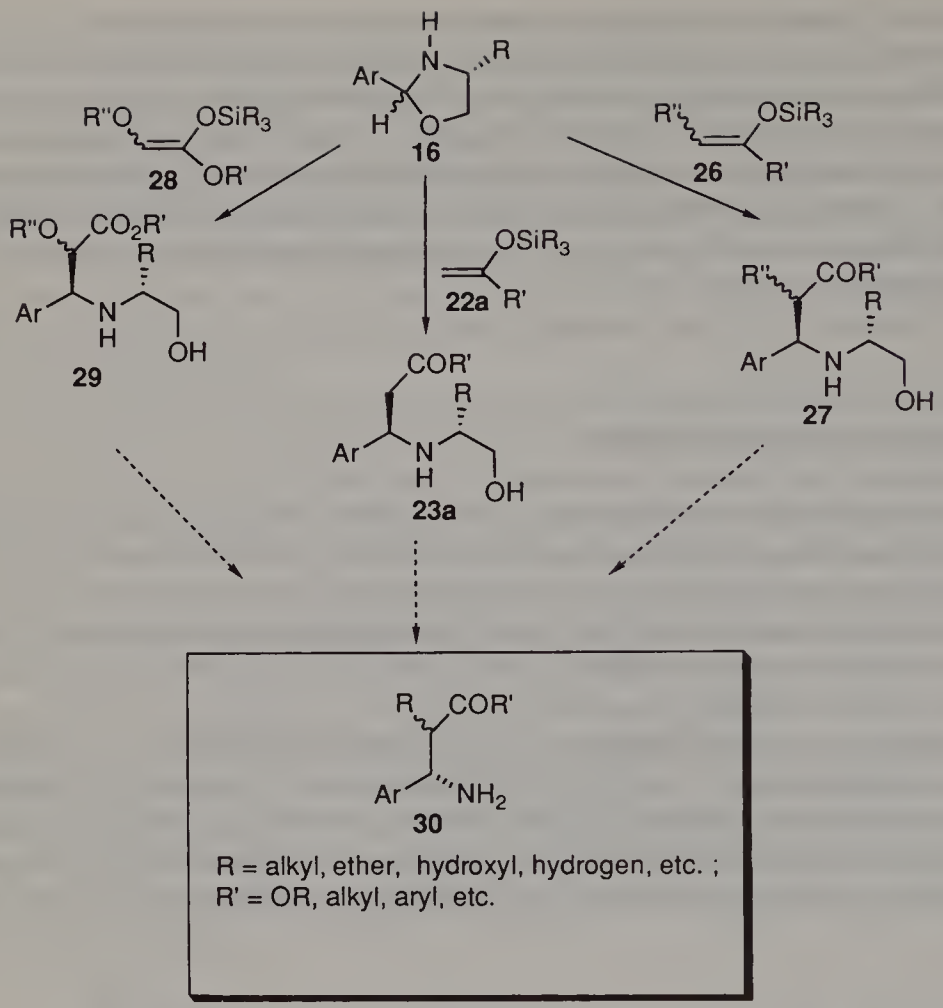
16a

22a, R′ = H
22b, R′ = Ethyl

23a, R′ = H
23b, R′ = Ethyl

53% de was obtained, while with $Et_2O \cdot BF_3$, an 88% yield with 22% de was obtained. A similar reaction with *O*-ethyl-*O*-trimethylsilyl ethylketene acetal **22b** gave results similar to that of $Et_2O \cdot BF_3$.

Exploitation of the addition of enol silyl ethers to 1,3-oxazolidines offers the possibility of synthesizing a variety of chiral β-amines (Scheme 7), e.g. α-hydroxy-β-aminoethers **29** from α-siloxylketene acetal **28** and α-substituted-β-aminoketones **27** from silyl enol ether **26**. In most cases of enol ether addition, the reaction was stereospecific. Thus, in addition to studying the parameters that will allow us to control the reaction pathways of addition, we will also have to be able to stereoselectively form the desired silyl (or siloxy) enol ether.



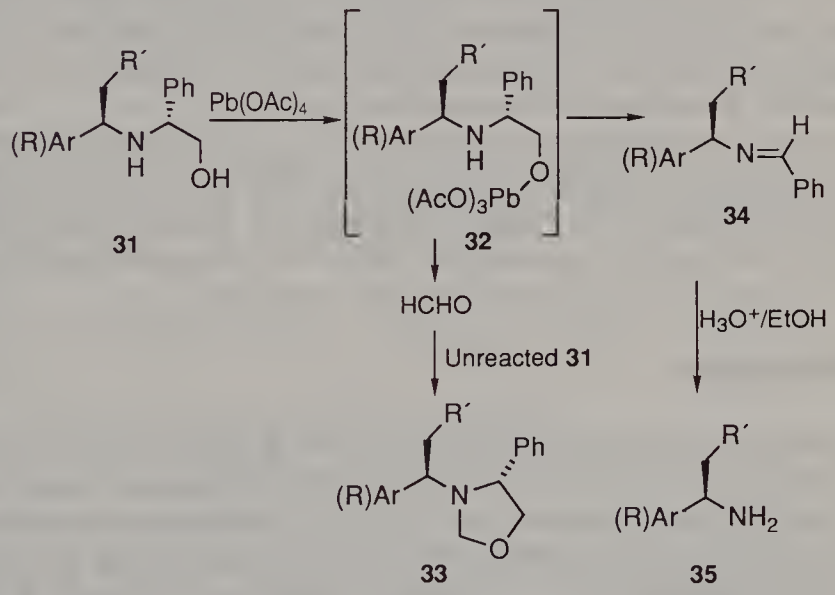
Scheme 7

6 Oxidative chiral auxiliary cleavage

Described above is an asymmetric synthesis of secondary *N*-(2′-hydroxy-1′-phenylethyl)-α-substituted aryl- and alkylmethylamines **31** by 1,2- addition of nucleophilic agents to chiral 2-substituted-1,3-oxazolidines. The amino alcohols **31** were oxidatively cleaved via the intermediacy of imines **34** to primary amines **35**. Although we were able to report excellent diastereoselectivity in the organometallic addition step to the oxazolidines, until just recently we obtained only moderate yields of the primary amines **35** via the reported lead tetraacetate (LTA) oxidative cleavage procedure (Mokhallalati and Pridgen, 1993).

Several excellent reductive conditions are available for carrying out transformations similar to that for converting **31** to **35** (Quirion *et al.*, 1988 and references therein; Ram and Ehrenkaufer, 1988). However, they mostly

employ palladium-based reducing conditions which non-selectively cleave benzylic amino or ether bonds. The lithio di-*tert*-butylbiphenyl (LiDBB) procedure utilized by Meyers and Burgess (1991) may be considered as an alternative when two benzylic amino groups are present but its overall efficiency is less than the $Pb(OAc)_4$ procedure. As a consequence, such conditions are inappropriate for substrates containing two differing benzylic amino carbons. The alternative use of lead tetraacetate or periodic acid (Chang and Coates, 1990a,b; Narukawa *et al.*, 1992) for cleavages of amino alcohols is well documented. However, as mentioned above, our initial results using the reported conditions for both reagents were capricious, providing only moderate yields. Because the hydroxymethyl functionality offers a manipulative handle, a considerable amount of time was invested in seeking to improve the oxidative cleavage, thereby exploiting the possible advantage of being able to selectively cleave the desired benzylic amino bond of **31**.



Scheme 8

Coates (Chang and Coates, 1990b) was the first to observe that formaldehyde, which was formed as an expected periodic acid oxidative cleavage product, will survive the reaction conditions long enough to react with an unreacted substrate similar to **31** and furnish an oxazolidine impurity similar to **33** (Scheme 8). We observed (^{1}H NMR) a similar result employing lead tetraacetate as oxidant. An oxazolidine of the type **33** was isolated and identified as our major contaminant initiating a major effort to minimize its formation. After trying several reagents and reaction conditions, we discovered that by inversely adding the amino alcohol in methylene chloride or methanol to lead tetraacetate in methanol at 0°C we obtained optimum results.

Table 6 Lead tetraacetate conversion of amino alcohols **31** to amines **35**

Ar (R)	R′	Substrate	% de	Product	Yield (%)	% ee
C_6H_5	CO_2Et	**31a**	92	**35a**	86	91
p-BrC_6H_4	CO_2Et	**31b**	94	**35b**	87	95
C_6H_{11}	CO_2Et	**31c**	94	**35c**	73	94
C_6H_5	H	**31d**	>99	**35d**	83	>99
$C_{10}H_7$	C_3H_7	**31e**	23	**35e**	87	24
$C_{10}H_7$	C_6H_5	**31f**	>99	**35f**	88	>99

Using this protocol, apparently the formaldehyde was trapped as formaldehyde dimethylacetal (methylal) as it was formed, thereby preventing its reaction with **31**. The resulting phenylimine intermediates **34** were isolated quantitatively and subsequently hydrolyzed under aqueous ethanolic acidic conditions to aryl(alkyl)methylamines **35** in high yields. In examples where R was aliphatic and R′ contained an ester functionality, some decomposition on chromatography was noted. In no instance was racemization of the chiral center detected. Table 6 outlines our results.

This procedure is applicable to both aryl and alkyl amines and appears to be appropriate for other amino acid-derived auxiliaries. The ability to isolate **34** quantitatively and so cleanly by this procedure also offers the possibility of employing it as substrate for nucleophilic additions to form other chiral amino analogs.

Acknowledgements

The author wishes to acknowledge the initial contributions to this work by Drs Conrad Kowalski and Vance Novack; the very helpful suggestions of Drs Ivan Lantos, Larry Overman, and the late Dr Paul Gassman; and postdoctoral associates Drs Mohamed K. Mokhallalati and Ming-Jung Wu for their intellectual and synthetic contributions; and finally M. Mentzer, L. Killmer, E. Reich, D. Staiger, D. Eggleston, G. Zuber, and W. Johnson, all of the Analytical and Physical Chemistry Departments.

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6

First Total Synthesis of Scopadulcic Acid B. An Illustration of the Utility of Palladium-catalyzed Polyene Cyclizations

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1 Introduction

1.1 Isolation, structure and biological activity of the scopadulcic acids

The plant *Scoparia dulcis* has a long use in traditional medicine. In Paraguay it is used to protect the stomach and improve digestion (Gonzales Torres, 1986); in India the same plant is used to treat toothaches, stomach disorders and blennorhagia (Satyanarayana, 1969), while in Taiwan it is employed to cure hypertension (Chow *et al.*, 1974). In their search for biologically active substances from the Paraguayan crude drug 'Typychá kuratû', Hayashi and co-workers reported in 1987 the isolation, from whole plants of *Scoparia dulcis* L. (Scrophulariaceae), of two structurally novel tetracyclic diterpene acids, the scopadulcic acids B **1** and A **2** (Hayashi *et al.*, 1987). The structures of **1** and **2** were initially assigned on the basis of spectroscopic data; the structure of scopadulcic acid A was subsequently confirmed by single crystal X-ray analysis (K. Hayashi *et al.*, 1988) (Fig. 1). In 1990 Ahmed and Jakupovic reported the isolation of **3** (originally termed dulcinol) from a Bangladeshi collection of *Scoparia dulcis* L. (Ahmed and Jakupovic, 1990). This alcohol was later described also from the Paraguayan extract, and termed scopadulciol, a name that would appear preferred since scopadulcic acid B and **3** differ only in the oxidation state of C(19) (Hayashi *et al.*, 1991). The scopadulan ring system

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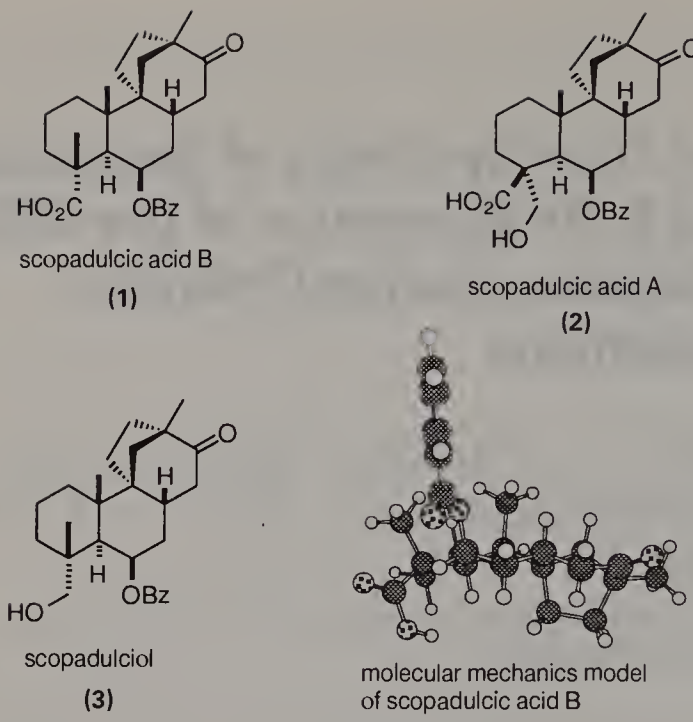

Fig. 1 Scopadulan diterpenes.

exemplified in **1–3** is unique in nature. Only stemarin (Fig. 2) and one other diterpene have the same core ring system, although a different stereochemistry and pattern of methyl substitution, as the scopadulcic acids (Manchand and Blount, 1975; Bohlmann *et al.*, 1984). The scopadulan diterpenes are more distantly related in structure to tetracyclic diterpenes of the aphidicolin class (Brundret *et al.*, 1972).

Preliminary biological investigations reveal a variety of promising pharmacological activities for the scopadulan diterpenes. Antiviral activity against herpes simplex virus type 1 (HSV-1) of five diterpenoids from *Scoparia dulcis* L. and 20 semi-synthetic derivatives of scopadulcic acid B has been disclosed (T. Hayashi *et al.*, 1988, 1990a). Of these **1** is the most active and inhibits viral replication *in vitro* with a therapeutic index of 16.7. *In vivo* in a hamster test

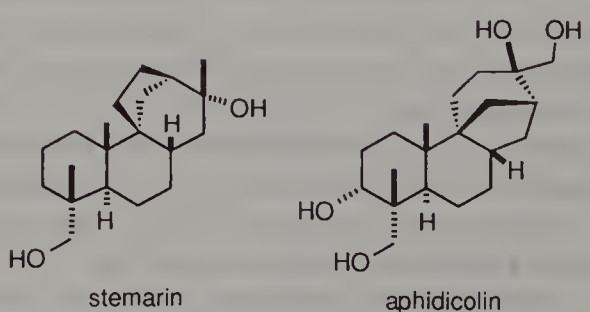

Fig. 2 Representative tetracyclic diterpenes with a bicyclo[3.2.1]octane substructure.

model, oral or intraperitoneal treatment with **1** immediately after virus inoculation prolonged both the appearance of herpectic lesions and the survival time at doses of 100 and 200 mg/kg per day (T. Hayashi *et al.*, 1988). An initial investigation of the antitumor activity of scopadulcic acid B recently appeared also (Hayashi *et al.*, 1992). Studies *in vitro* with six human cancer cell lines showed **1** to be more cytotoxic against larynx and cervical cancer tissue than against cell lines from normal tissues. Antitumor activity *in vivo* was documented with mice inoculated with Ehrlich ascites tumor cells, where intraperitoneal administration of **1** at doses of 25, 50, or 100 mg/kg per day increased survival rates by 12.5%, 12.5%, and 25%, respectively.

Of perhaps greater significance, scopadulcic acid B and several congeners have been shown to be powerful inhibitors of H^+, K^+-adenosine triphosphatase, the proton pump for gastric acid secretion (Hayashi *et al.*, 1990b, 1991). Inhibition of this enzyme is an important new approach for the clinical treatment of peptic ulcer disease. The most active of the scopadulan diterpenes and analogs screened to date, scopadulcic acid B methyl ester and the C(18) acetate of scopadulciol, showed IC_{50} values of 3–5 μM against the hog gastric enzyme, which are similar to that of omeprazole. Omeprazole is the first of this new class of antisecretory drugs to be introduced worldwide. Inhibition of H^+, K^+-adenosine triphosphatase by **1** (and an analog lacking the benzoyl group) has been shown to involve irreversible inhibition of the K^+-dependent dephosphorylation step (Asano *et al.*, 1990). Since this mechanism of inactivation is distinct from that of omeprazole and most other clinical candidates in this area, scopadulcic acid B represents an exciting new lead in the development of new antisecretory agents.

1.2 Evolution of a synthesis plan

During the past 40 years, the laboratory synthesis of polycarbocyclic molecules by biomimetic cyclizations of polyene cations, and more recently cyclizations of polyene radicals, has been developed to a high degree of practical utility. However, it is only within the last five years that a complimentary polyene cyclization chemistry catalyzed by transition metals, particularly palladium, has emerged as an important stratagem for the preparation of polycyclic skeleta (Overman *et al.*, 1992). In contrast to polycyclizations of electron-deficient carbenium ions and radicals, a polycyclization event resulting from sequential intramolecular insertions of transition metal alkyls is expected to be most efficient when the transition metal propagates at the least substituted termini of the participating alkene units, e.g. **4** → **5** → **6** (Fig. 3). As a result, intramolecular insertions of organopalladium intermediates (intramolecular Heck reactions) are particularly useful for forming quaternary carbon centers (Grigg *et al.*, 1986; Abelman *et al.*, 1987; Overman *et al.*, 1992).

Our plan for assembling the scopadulcic acids from a 5-methylenecycloheptene precursor by a palladium-catalyzed *bis*-cyclization is shown in Fig. 4.

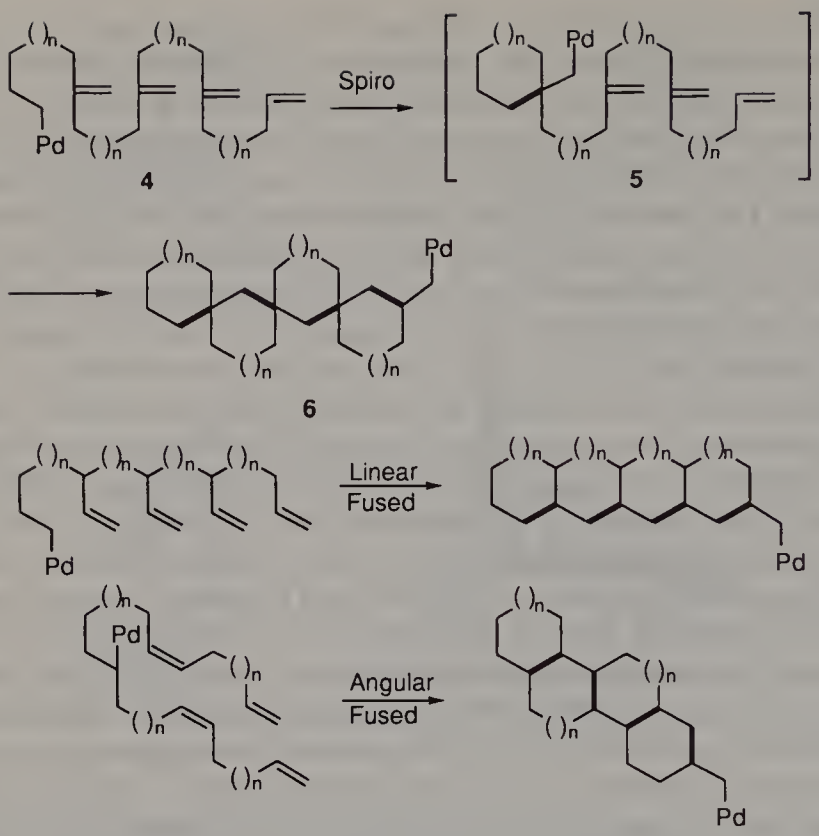

Fig. 3 Three topographies of palladium-catalyzed polyene cyclization.

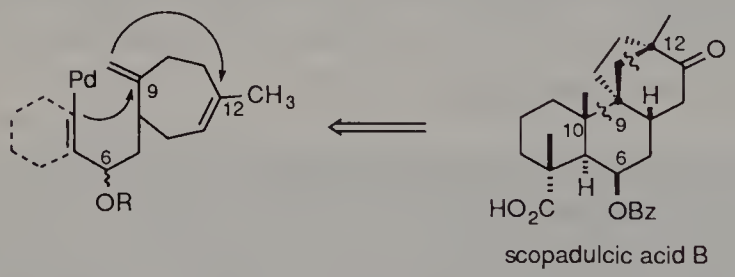

Fig. 4 Synthesis plan.

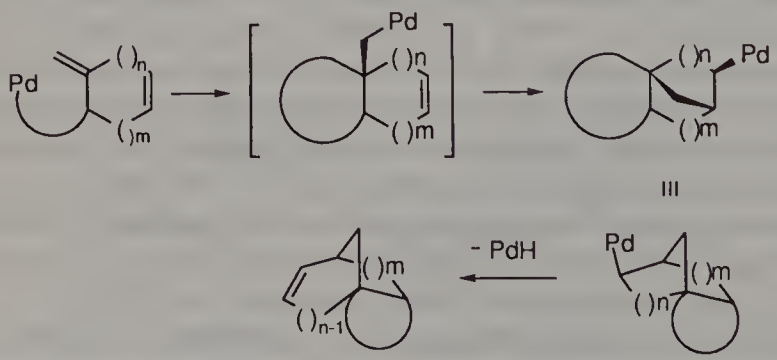

Fig. 5 A general approach to bridged polycyclic molecules.

This unusual synthesis strategy projects construction of the BCD ring system of the scopadulcic acids, and the critical quaternary centers at C(9) and C(12) of the bicyclo[3.2.1]octane substructure, in a single step. This sequence represents one example of a general approach for preparing bridged polycyclic frameworks (Fig. 5).

Our earliest studies examined the cyclization of dienyl aryl iodide **7**, an intermediate that lacks the methyl substituent at C(12) of the cycloheptene ring (Abelman and Overman, 1988). We chose this model system for initial investigation, since diene **7** could be readily assembled from 2-carbomethoxy-4-cyclohepten-1-one and the second step in the projected *bis*-cyclization would involve a favorable insertion of a disubstituted (rather than a trisubstituted) double bond. The pivotal cyclization of **7** proceeded cleanly, under fairly standard Heck reaction conditions, to form two major tetracyclic hydrocarbons, **8** and **9** (Fig. 6). Extensive 2D NMR and ^{1}H NOE studies established that the major product **8** had the desired core tetracyclic skeleton of the scopadulcic acids, while the minor product **9** had the stemodane skeleton found in tetracyclic diterpenes such as stemodin. In principle, four tetracyclic hydrocarbons could have been formed from *bis*-cyclization of **7**. The fact that **8** and **9** strongly predominate demonstrates that the tricyclic intermediates **10** and **11**, which result from insertion into the two faces of the exomethylene group, both insert with high regioselectivity into the disubstituted double bond of the cycloheptene ring. Since regioselection in the insertion of **10** (as shown in Fig. 6) should only be enhanced by the presence of a methyl substituent at C(12), we

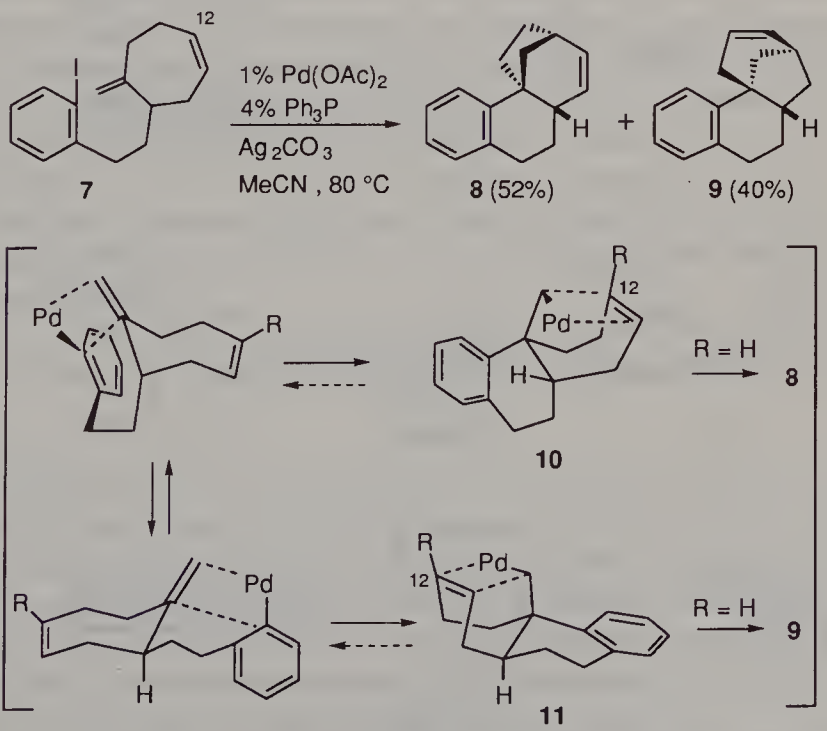

Fig. 6 First model study towards the scopadulcic acids.

were encouraged to develop this strategy for the synthesis of the scopadulcic acids themselves.

2 First generation approach. The first total synthesis of (±)-scopadulcic acid B

2.1 Efficient construction of the tetracyclic skeleton

In our first generation approach, we chose to examine the key cyclization depicted in Fig. 4 with an aromatic substrate that contained carbonyl functionality at C(6) (Overman *et al.*, 1993). An optimized sequence for preparing the requisite dienone aryl iodide **16** is summarized in Fig. 7. This sequence is patterned on regioselective syntheses of 4-cycloheptenones that had been developed much earlier (Piers and Nagakura, 1976; Marino and Browne, 1976; Wender and Filosa, 1976). The preparation of **16** begins with 2-iodobenzaldehyde, which in a conventional sequence is converted to the 4-arylbutanal **12**. Reaction of this intermediate with (*Z*)-2-ethenyl-2-methylcyclopropylmagnesium bromide **13** (Skattebol, 1964) followed by oxidation and enol silylation gives the siloxy *cis*-divinylcyclopropane **14**. Thermal [3,3]-sigmatropic rearrangement of this intermediate, which takes place in nearly quantitative yield, is the key step in assembling **16**.

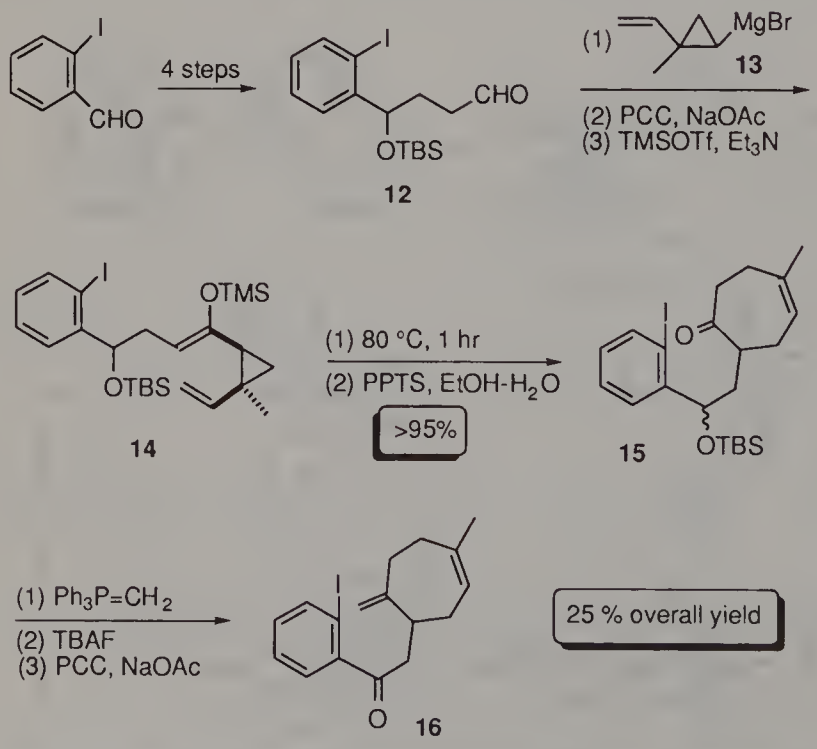

Fig. 7 Synthesis of cyclization precursor **16**.

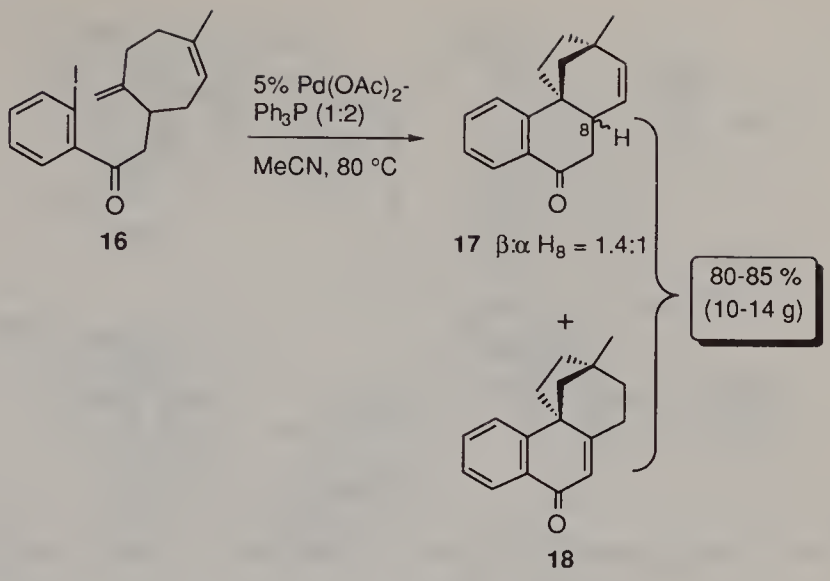

Fig. 8 Cyclization to form the scopadulan ring system.

The salient *bis*-cyclization of the dienyl aryl iodide **16** could be accomplished with a wide variety of palladium(0) catalysts (Fig. 8). Preparative-scale cyclizations were best carried out in refluxing acetonitrile in the presence of 5–10% of a coordinatively unsaturated catalyst prepared from $Pd(OAc)_2$ and Ph_3P. Cyclizations conducted on scales as large as 14 g provided the enones **17** and **18** in a combined yield of 80–85%. Contamination by the rearranged enone **18** was somewhat reduced in cyclizations conducted in the presence of silver salts (Abelman and Overman, 1987), however no conditions completely suppressed double bond isomerization. Stereoselection in the initial insertion step was not high, since the $\Delta^{13,14}$ enone **17** was formed as 1.2–1.5:1 mixture of stereoisomers. None the less, the sequence summarized in Figs 7 and 8 provides a notably direct entry to this tetracyclic ring system, providing **17** and **18** on multigram scales and ~20% overall yield from commercially available 2-iodobenzaldehyde.

*2.2 Elaboration of the tetracyclic enones **17** and **18** to (±)-scopadulcic acid B*

The stereochemical logic from this point on was to exploit the facial bias provided by the bicyclo[3.2.1]octane fragment to control elaboration of both the aromatic A ring and the C/D bicyclooctane unit. We initially fashioned the C ring functionality by converging the three tetracyclic enone isomers to form dienone **19** (Fig. 9). The required oxidation at C(13) was readily developed by an epoxidation–reduction sequence, which provided **20** in 67% yield from dienone **19**. Our first serious difficulties were encountered in attempts to saturate the 7,8 double bond of this intermediate. Conventional catalytic

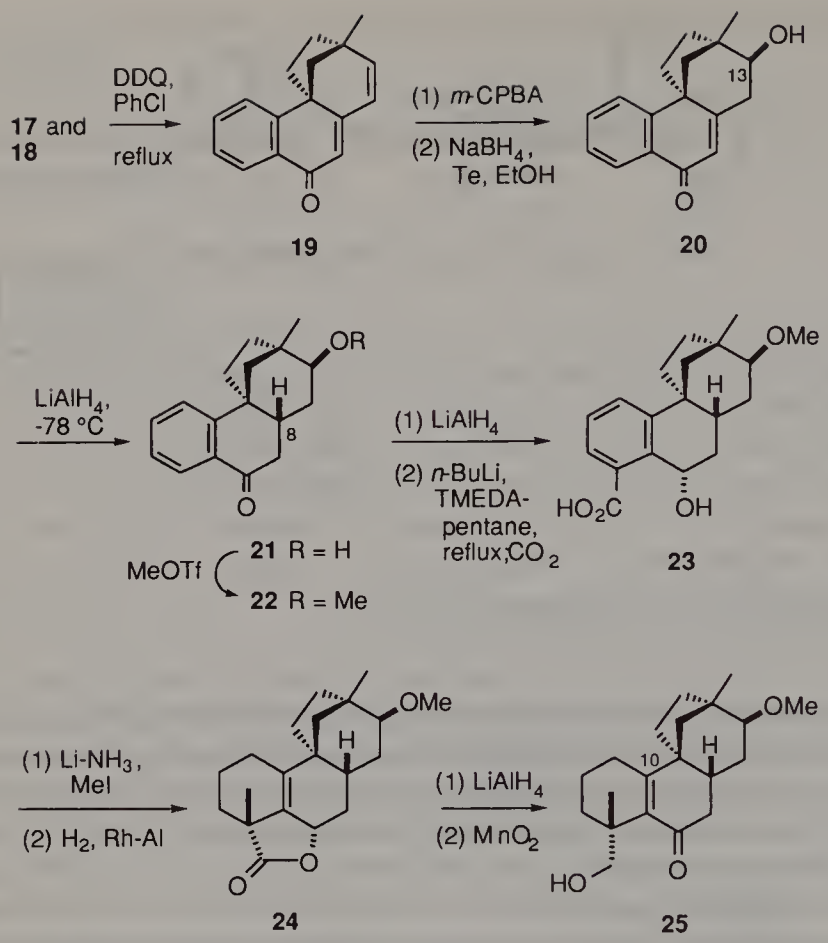

Fig. 9 Functionalization of the C and aromatic A rings.

hydrogenation of **20** over Pd/C or PtO_2 resulted in extensive deoxygenation at the benzylic C(6) position. Hydrogenolysis at C(6) could be prevented by reduction under transfer hydrogenation conditions (e.g. Pd/C, NH_4HCO_2, DMF), however, this reduction surprisingly occurred preferentially from the ostensibly more hindered α-face to give the C(8) α-epimer of **21** predominantly (ds = 8:1). Fortunately, this keto alcohol was highly crystalline and the unexpected outcome of this catalytic hydrogenation was readily revealed by single crystal X-ray analysis. The β-oriented methine hydrogen at C(8) was finally introduced by delivery of hydride intramolecularly from the C(13) alcohol (Solomon *et al.*, 1988). Final protection of this latter functionality as a methyl ether provided **22** in 37% overall yield from dienone **19**, and set the stage for the critical functionalization of the aromatic ring.

In preparation for developing the A-ring functionality, the aromatic ring of **22** was activated for Birch reduction by introducing a carboxylic acid group at

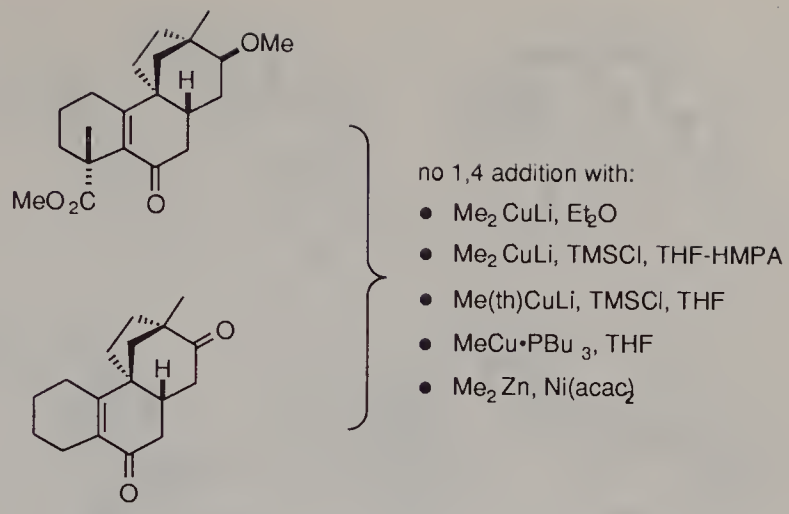

Fig. 10 Reluctance of tetrasubstituted enones to undergo 1,4-addition of methyl organometallics.

C(4). This selective conversion could be accomplished by *ortho*-lithiation–carboxylation of the α-tetralol derived from **22**. Finally, Birch reduction–methylation (Taber, 1976; Hook *et al.*, 1982) of **23** proceeded to deliver, after selective saturation of the 2,3-double bond, the lactone **24** in 65% overall yield from **22**. Much to our satisfaction, methylation at C(4) occurred exclusively from the β-face to introduce the requisite C(4) methyl group of scopadulcic acid B.

Completion of the synthesis of scopadulcic acid B required development of the remaining quaternary center at C(10). This elaboration proved to be remarkably difficult. All attempts to directly introduce the C(10) angular methyl group by conjugate addition of methyl organometallics to a variety of intermediates having C(6) enone functionality were unsuccessful. Examples of the substrates and the nucleophiles we examined are depicted in Fig. 10. In the cases shown, either the starting enone was recovered or methyl addition occurred in a 1,2 fashion to afford the corresponding C(6) tertiary alcohol.

This final obstacle was finally surmounted in an efficient, albeit classical fashion (Fig. 11). Treatment of **25** with Et_2AlCN (Nagata, 1977) provided the cyano ketone **26** in 47% overall yield from acid **23**. Conversion of **26** to diol **28** was simplified when we discovered that reduction of **26** at 75°C in THF with an excess of $LiAlH_4$ proceeded stereoselectively to give the pentacyclic aminal **27** in essentially quantitative yield. Wolff–Kishner reduction of this remarkably stable cyclic aminal could be accomplished, under forcing conditions, to provide the tetracyclic diol **28** in 74% yield. Standard functional group modification, culminating in the double oxidation of the C(13) methyl ether and C(4) primary alcohol with RuO_4 (Carlsen *et al.*, 1981), provided (±)-scopadulcic acid B (**1**) in 55% overall yield from **28**.

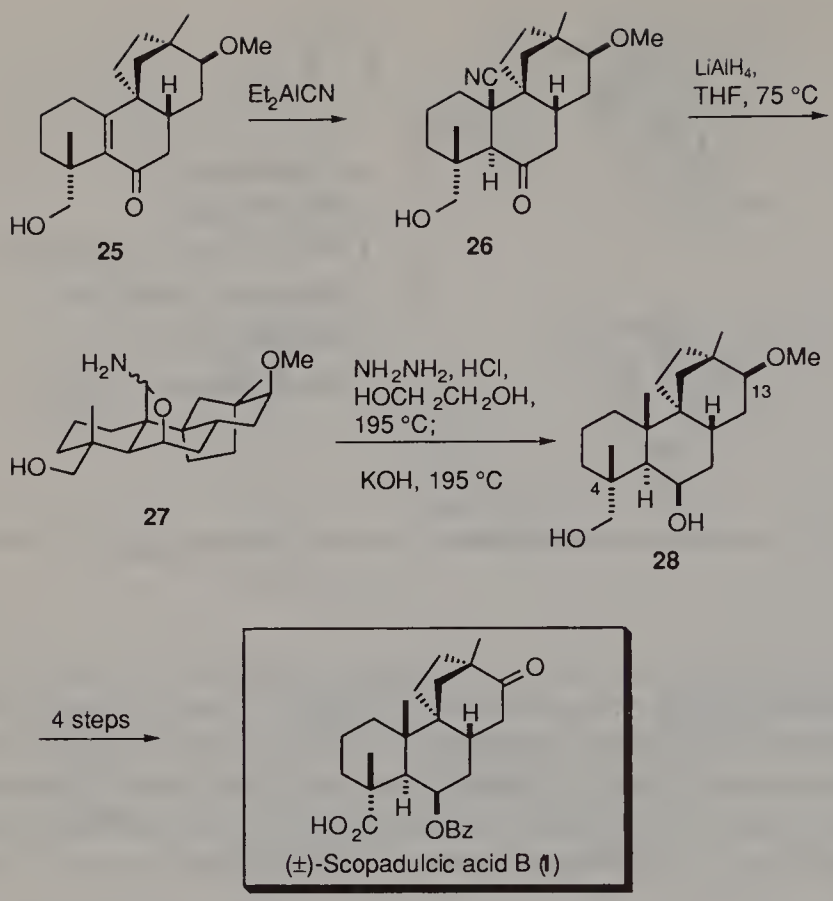

Fig. 11 Completion of the total synthesis of (±)-scopadulcic acid B.

3 Conclusion

This first total synthesis of scopadulcic acid B **1** is capable of providing 10–100 mg amounts of **1** and congeners for pharmacological investigation. Besides being the first successful entry to the scopadulan class of biologically active terpenoids, the efficient conversion of **16** to tetracycles **17** and **18** provides an excellent illustration of the power of intramolecular Heck cyclizations to solve formidable problems in complex molecule synthesis.

Two aspects of our first generation entry to the scopadulan terpenes require improvement if a truly efficient synthesis of these pharmacologically significant materials is to be realized. First, an aromatic ring obviously is not an ideal structural template for evolving the two quaternary centers of the scopadulan A ring. Secondly, considerable synthetic efficiency would result if the initial step of the *bis*-Heck cyclization occurred stereoselectively to form the required *cis* arrangement of the angular C(8) hydrogen and the one carbon bridge of the bicyclo[3.2.1]octane unit. These objectives have been realized in a second generation strategy, which is illustrated in a retrosynthetic format in Fig. 12.

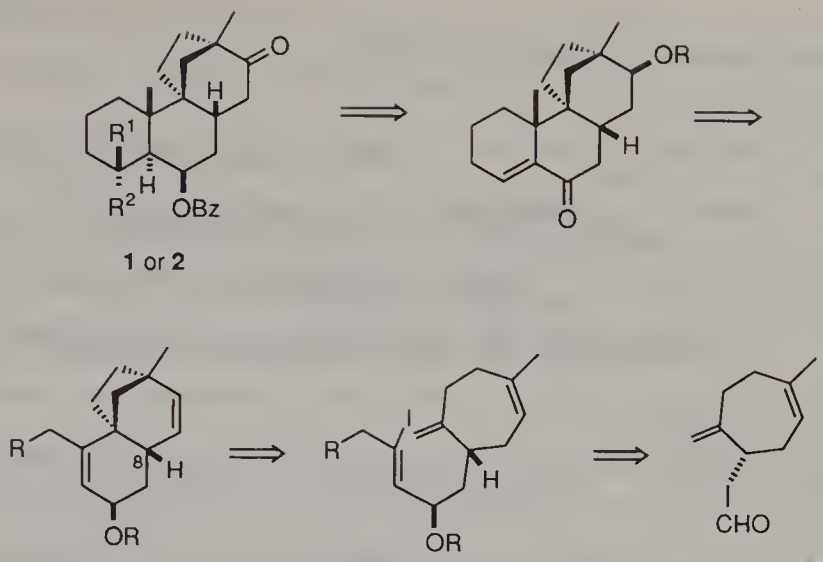

Fig. 12 Second generation *seco* A-ring strategy for the total synthesis of the scopadulcic acids A and B.

The initial development of this improved strategy has been described (Kucera, 1991), while the successful use of this *seco* A-ring approach to prepare the scopadulcic acids A and B will be disclosed shortly.

Acknowledgements

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7

The Synthesis of α-Heteroalkenylmetals via Hydrometallation and Metallometallation of Alkynes

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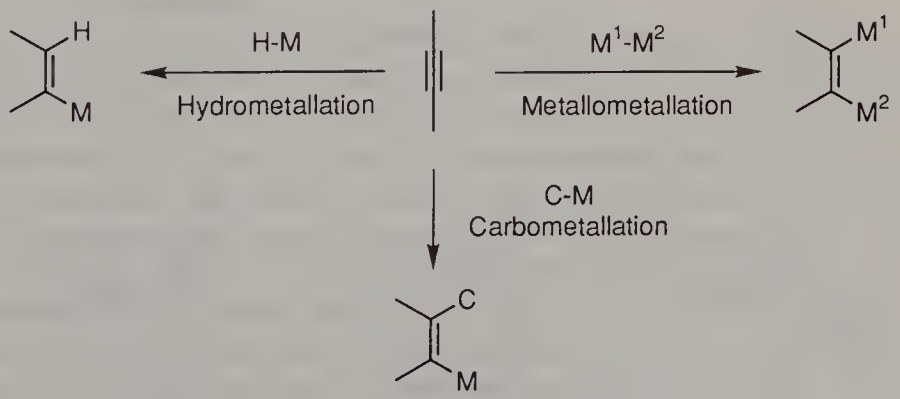
1 Introduction

Trisubstituted alkenes are ubiquitous in natural products and many biological compounds. Consequently their regio- and stereoselective synthesis is a perpetual challenge to synthetic chemists. Alkenylmetal species are versatile precursors to substituted alkenes and have been intensively studied, initially using Mg and Li, progressing latterly to softer metals such as Cu, Zn, Al etc. The hydrometallation and carbometallation of terminal and internal alkynes (Scheme 1) has proved to be a popular method of generating alkenylmetals. The former proceeds well for Al, Zr, B, Sn and Ge, while Cu and Al have proved useful for the latter (Sharma and Oehlschlager, 1989c). More recently,



Scheme 1

ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS
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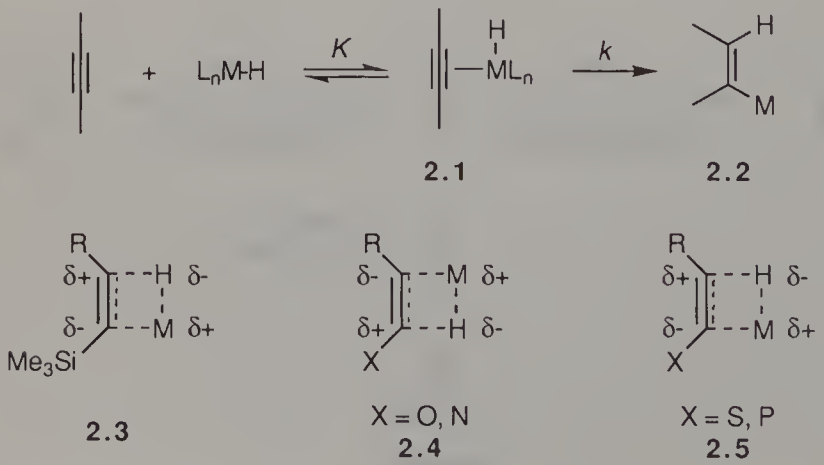
metallometallation has emerged as a means of simultaneously generating two adjacent regio- and stereodefined alkenylmetal bonds of differential reactivity. To date metallometallation has been used mainly to introduce Si or Sn in conjunction with Li, Mg, Al, Cu, B or Zn.

Unfortunately, poor regiocontrol detracts from many hydrometallations and metallometallations and in some cases stereocontrol is a problem too. In this review we highlight the valuable influence of heteroatoms on the crucial issue of regio- and stereocontrol of hydrometallations and metallometallations of alkynes.

2 Hydrometallation

The hydrometallation of alkynes offers the simplest and most direct route to alkenylmetals. There are over 50 potentially useful metals (including the lanthanides and actinides) which will participate in the reaction. In practice there are only a handful of metal hydrides which have found general favour and these include **B** (Bubnov *et al.*, 1970; Brown, 1975; Uchida *et al.*, 1976, 1977; Zweifel and Backlund, 1977; Hassner and Soderquist, 1977; Miyaura *et al.*, 1982; Smith and Pelter, 1991; Evans *et al.*, 1992a, 1992b), **Al** (Eisch and Foxton, 1971; Eisch and Rhee, 1975; Eisch *et al.*, 1975) **Zr** (Vincent *et al.*, 1982; Negishi *et al.*, 1987; Hegedus *et al.*, 1987; Lipshutz and Ellsworth, 1990; Labinger, 1991) and **Sn** (Leusink *et al.*, 1967; Ichinose *et al.*, 1987; Kikukawa *et al.*, 1988; Zhang *et al.*, 1990; Magriotis *et al.*, 1991). In the case of **Sn** and **Si** (Tamao *et al.*, 1975; Hudrlik *et al.*, 1979; Ojima *et al.*, 1990; Wada *et al.*, 1991; Doyle *et al.*, 1991; Tanaka *et al.*, 1991; Adams *et al.*, 1992), **Ge** (Wada *et al.*, 1991), and **Mg** (Sato *et al.*, 1982, 1983; Sato, 1985). The reaction is best achieved under transition metal catalysis. The hydrometallation of unactivated terminal or internal alkynes generally proceeds with clean *cis*-stereoselectivity initially though isomerization can subsequently take place.

On a simplistic level, the *uncatalysed* hydrometallation of an alkyne involves two principal steps (Scheme 2): (i) reversible coordination of the alkyne to a



Scheme 2

vacant orbital on the metal atom and (ii) insertion of the coordinated metal–hydride bond into the alkyne π-bond. The overall rate of formation of **2.2** will be related to the product of the equilibrium and rate constants K and k. The concentration of intermediate **2.1** should decrease as the size of substituents attached to the unsaturated bond increases but the effect can be comparatively small since coordination takes place at the centre of the alkyne bond where steric effects are minimized. On the other hand the concentration of **2.1** should increase as the electron density in the π-system increases; hence the presence of electron donating substituents should favour formation of the intermediate **2.1** and promote reaction. However, if intermediate **2.1** is too stable, the second step (insertion) may be slow or precluded altogether (Thorn and Hoffman, 1978).

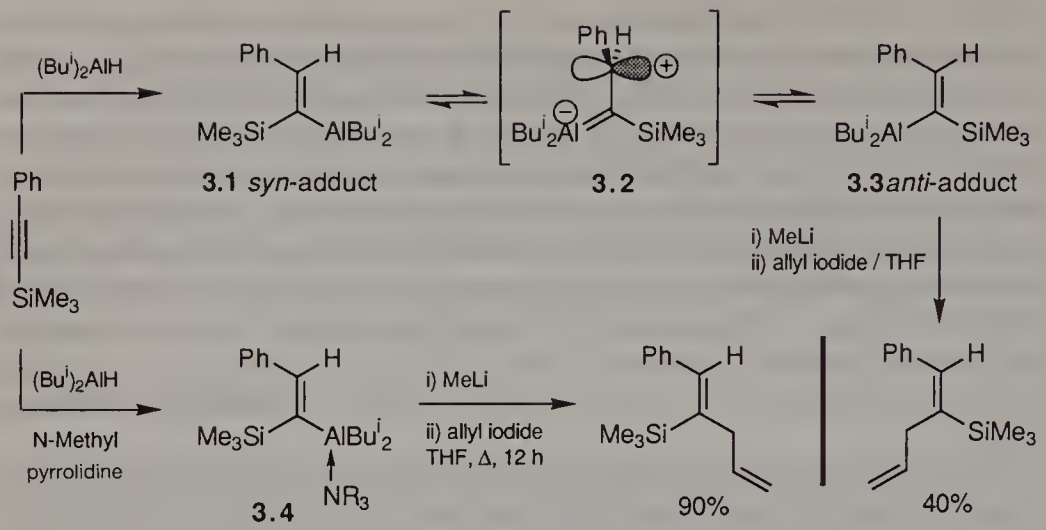
The heteroatoms under consideration determine the regiochemistry of the hydrometallation by polarizing the alkyne bond. In the case of trialkylsilyl and other electron releasing metal groups, the polarization is governed by a σ-bond hyperconjugation (Hanstein *et al.*, 1970) resulting in stabilization of electron deficiency β to the M–C bond as in **2.3**; hence the metal is attracted to the carbon bearing the silyl group. In the case of mesomeric donors such as N or O, the metal is attracted to the electron-rich β-carbon as in **2.4**. Mesomeric donors with non-bonded electrons in the third shell, show inverted regiochemistry relative to their second shell siblings. Thus, thio- and phospha-alkynes react as if they were polarized in the sense depicted in **2.5**. In the following sections we will consider in more detail the consequences of heteroatom substitution on alkyne hydrometallation.

2.1 1-Trialkylsilyl-1-alkynes

Silicon has been the most commonly exploited heteroatom in activating alkynes towards hydrometallation and metallometallation. The hydrometallation of silylalkynes can occur with *syn* or *anti* stereochemistry depending on the conditions.

2.1.1 Hydroalumination

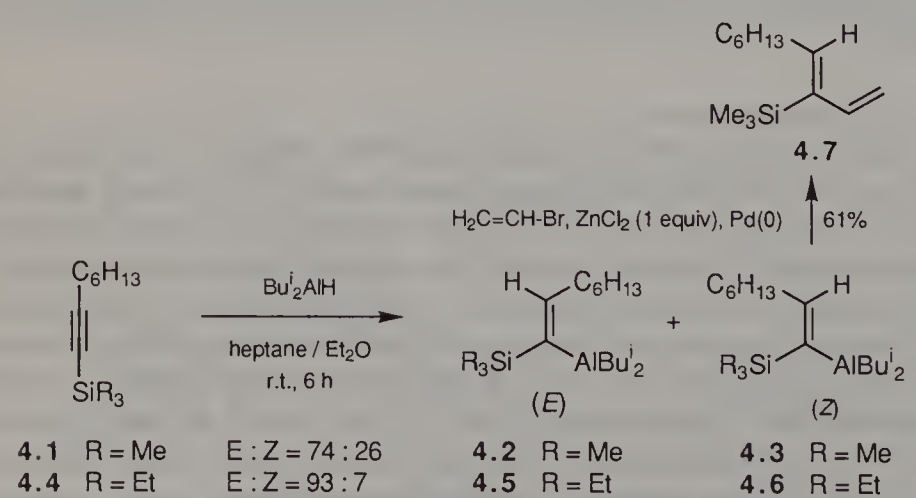
The hydroalumination of alkynes (Eisch, 1991) can be accomplished with alanes such as DiBALH in hydrocarbon solvents at r.t. or with aluminium hydrides in ethereal solvents at 0°C. The trimethylsilyl moiety facilitates the hydroalumination of trimethylsilylalkynes and controls the regiochemistry of addition leading to clean formation of 1,1-dimetalloalkenes. Eisch and Rhee (1975) provided a quantitative measure of substituent effects on hydroalumination of various alkynes and they showed that Ph–C≡C–$SiMe_3$ underwent hydroalumination 431 times faster than Ph–C≡C–Ph and 40 times faster than Ph–C≡C–H. The observed stereochemistry of the reaction depends on conditions. The kinetic product of the hydroalumination is the *syn*-adduct (Scheme 3) but rapid isomerization to the more thermodynamically stable *anti*-adduct occurs readily—perhaps because the barrier to rotation is lowered by



Scheme 3

σ-bond hyperconjugation in the transition state leading to **3.2**. However, the isomerization can be greatly retarded by adding a suitable donor such as *N*-methylpyrrolidine resulting in formation of the *syn*-adduct **3.4** (Eisch and Foxton, 1971; Eisch and Damasevitz, 1976). Both metals in the 1,1-dimetalloalkenes can be replaced leading to a stereoselective synthesis of tri-substituted alkenes. The first step in the sequence requires enhancement of the nucleophilicity of the C–Al bond by conversion of the alane to an alanate using MeLi. Subsequent alkylation with reactive electrophiles proceeds with retention of configuration.

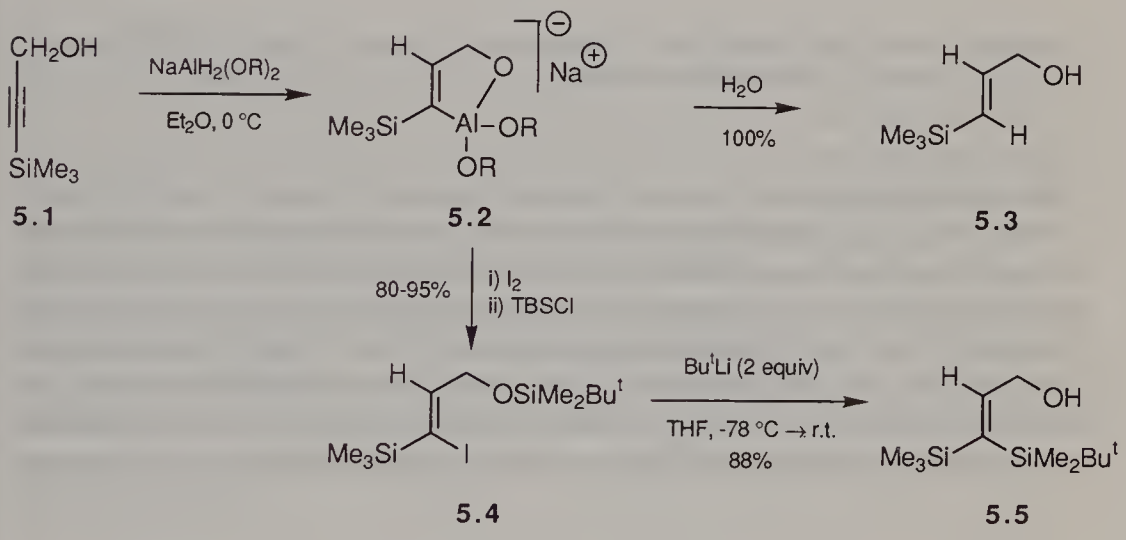
A small increase in the steric bulk of the trialkylsilyl group can significantly alter the observed stereochemical course of hydroalumination (Scheme 4). Thus, reaction of 1-trimethylsilyl-1-octyne **4.1** with DiBALH, in heptane/ether afforded a mixture of (*Z*-di-*iso*butyl-[1-(trimethylsilyl)-1-octenyl]alane **4.3** and



Scheme 4

the (*E*)-isomer **4.2** (*E*:*Z* = 74:26) with the isomeric ratio depending on the reaction conditions (Uchida *et al.*, 1976). However, with the corresponding triethylsilyl alkyne **4.4**, the *E*:*Z* ratio was improved (93:7). The alane **4.3** undergoes Pd(0)-catalysed coupling with bromoalkenes in the presence of $ZnCl_2$ to afford a route to 2-(trimethylsilyl)-1,3-butadienes (Negishi and Luo, 1983).

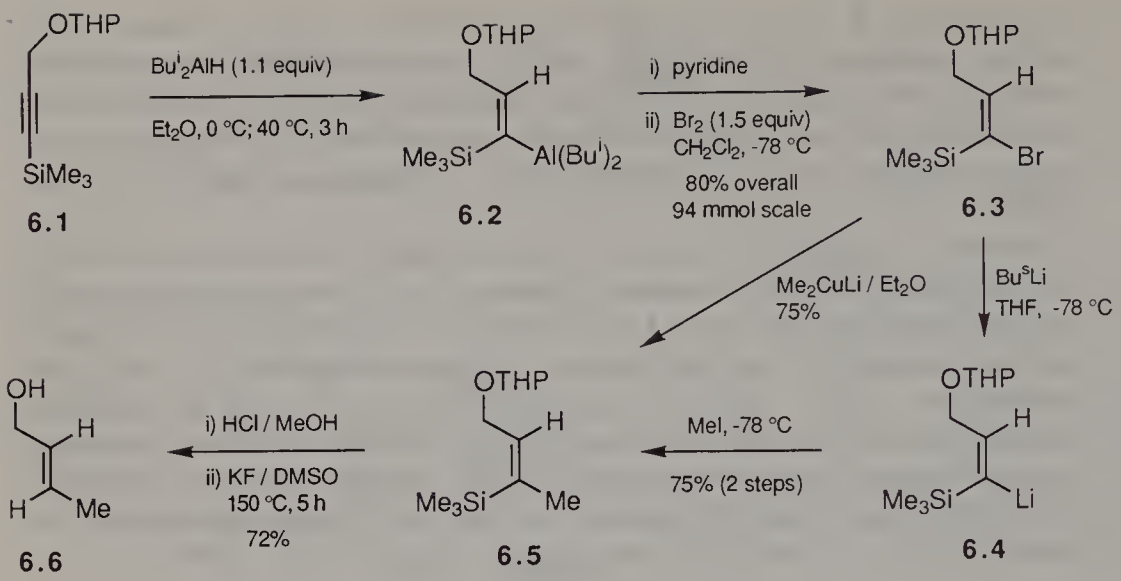
Proximate heteroatoms can markedly influence the stereochemistry of hydroalumination. For example (Scheme 5), hydroalumination of 3-(trimethylsilyl)-2-propyn-1-ol **5.1** with sodium *bis*(2-methoxyethoxy)aluminium hydride proceeded in an *anti* fashion to give intermediate **5.2** which was protonolysed to give (*E*)-3-(trimethylsilyl)-2-propen-1-ol **5.3** in essentially quantitative yield (Denmark and Jones, 1982). On the other hand, quenching alanate intermediate **5.2** with iodine gave the (*Z*)-iodoalkene **5.4** in 83–96% yield which then served as a precursor to the 3,3-*bis*(trialkylsilyl)propen-1-ol **5.5** via a 1,4 O → C silyl migration reaction (Magriotis *et al.*, 1990).



5.1 **5.2** **5.3** **5.4** **5.5**

Scheme 5

Hydroalumination of the tetrahydropyranyl ether of 3-(trimethylsilyl)-2-propyn-1-ol **6.1** with DiBALH occurred with *syn*-stereochemistry (Scheme 6). Selective brominolysis of the C–Al bond in alane intermediate **6.2** proceeded with retention of configuration to give bromoalkene **6.3** in 80% yield [>99% (*E*)]. Replacement of the bromine atom in **6.3** with a methyl group was accomplished by two complementary procedures (Miller and Al-Hassan, 1983). Halogen–metal exchange achieved conversion to the lithium reagent **6.4** which was then alkylated with methyl iodide to give **6.5** in 75% yield. Alternatively, coupling of the bromoalkene with lithium dimethylcuprate gave **6.5** in identical yield. It is noteworthy that the trimethylsilyl group can be

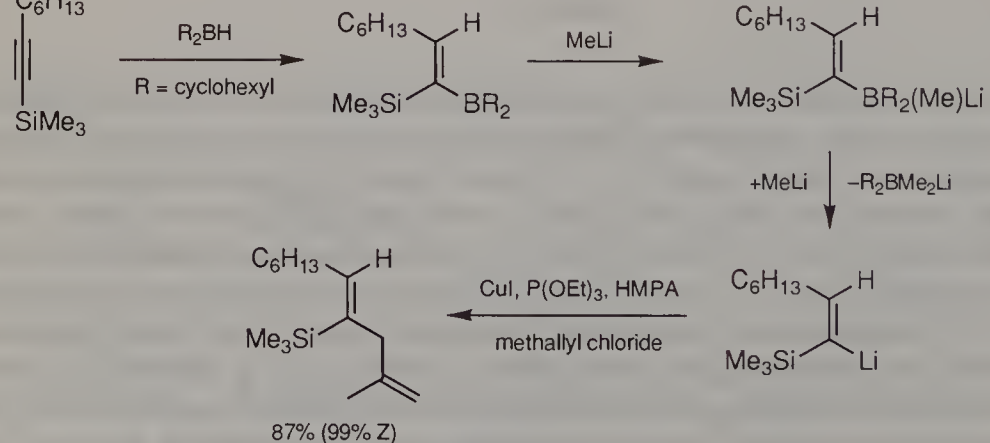


Scheme 6

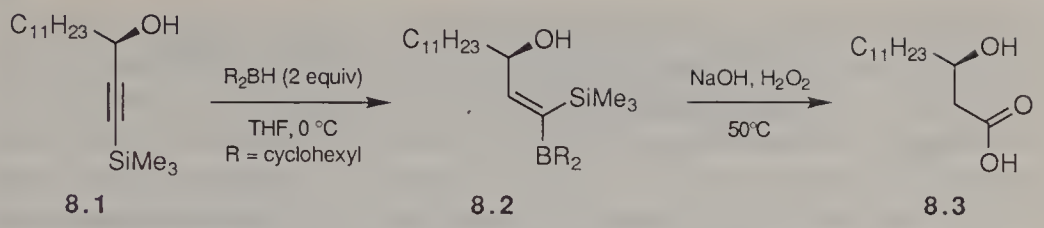
replaced with clean retention of configuration by treating the allylic alcohol with anhydrous KF in DMSO at 150°C.

2.1.2 *Hydroboration*

The hydroboration of 1-(trimethylsilyl)-1-alkynes (Zweifel and Backlund, 1977) parallels the regio- and stereochemistry observed in the related hydroalumination reactions. However there are two advantages to the hydroboration procedure: (i) dialkylboranes of variegated structure are more readily available than the corresponding alanes and (ii) the *syn*-adducts appear to isomerize less readily (Smith and Pelter, 1991). Two synthetic sequences will serve to illustrate the utility of 1-boryl-1-silyl-1-alkenes. The first sequence (Scheme 7) depicts a method for preparing trisubstituted alkenyl silanes from



Scheme 7



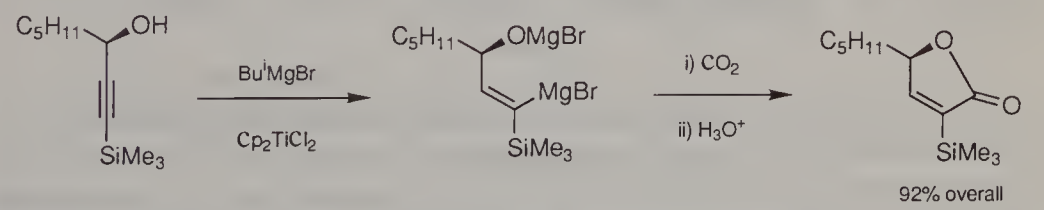
8.1 8.2 8.3

Scheme 8

1-(trimethylsilyl)-1-alkynes by hydroboration, transmetallation, and carbodemetallation (Uchida *et al.*, 1977). The second example, taken from a synthesis of the pancreatic lipase inhibitor (−)-tetrahydrolipstatin (Pons and Kocienski, 1989), illustrates the conversion of readily available (Noyori *et al.*, 1984; Midland and Graham, 1985; Yadav *et al.*, 1990) homochiral 1-alkyn-3-ols to β-hydroxy acids (Scheme 8). The key step in the sequence, oxidation of the 1-boryl-1-(trimethylsilyl)-1-alken-3-ol **8.2**, accomplished the conversion of 1-(trimethylsilyl)-1-alkyn-3-ol **8.1** to the carboxylic acid **8.3** in 75% yield.

2.1.3 Hydromagnesiation

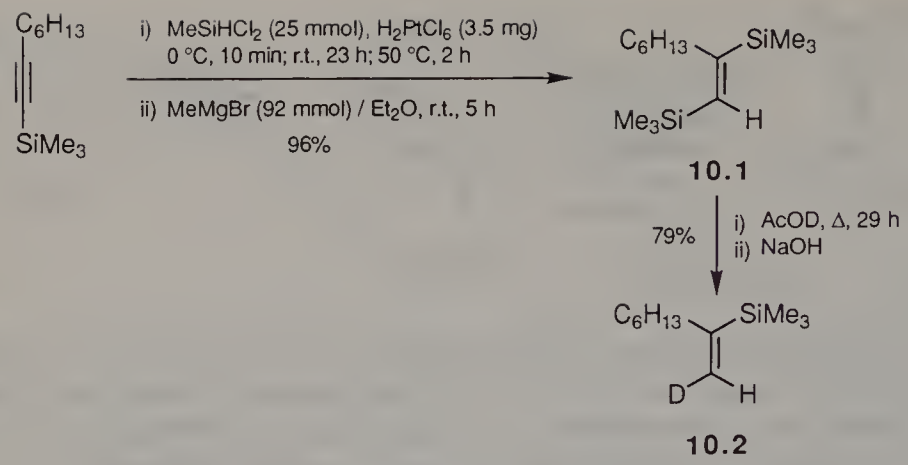
Sato and co-workers developed a novel route to alkenylmagnesium chlorides by the hydromagnesiation of alkynes (Sato, 1985). The reaction simply involves treatment of the alkyne with *i*-BuMgCl in ether at r.t. in the presence of 10–15 mol% of titanocene dichloride. Like the preceding hydrometallations, the *syn*-adduct is the kinetic product but isomerization to the more stable *anti*-adduct takes place on standing. Scheme 9 illustrates the formation of a Grignard reagent directly from a propargylic alcohol—a reaction which would not be feasible using the traditional Grignard methods (Ito *et al.*, 1990; Lautens and Huboux, 1990). The products of the hydromagnesiation reaction may be protonolysed to produce (*E*)-(trimethylsilyl)alkenes (Sato *et al.*, 1982), or coupled with various electrophiles such as alkyl halides, allyl halides, aldehydes or ketones.



Scheme 9

2.1.4 Hydrosilylation

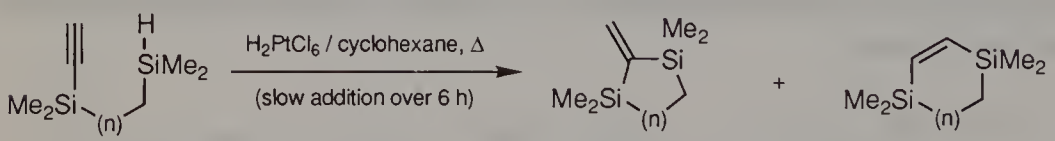
The hydrosilylation of alkenes and alkynes is a commercially crucial process for the synthesis of a wide range of silane intermediates (Ojima, 1989). Compared with the hydrometallations discussed so far, the reaction is sluggish and appreciable rates are only achieved at elevated temperature in the presence of



Scheme 10

a transition metal catalyst such as chloroplatinic acid or $[Ph_3P]_3RhCl$ (Hiyama and Kusumoto, 1991). Mixtures of stereo- and regioisomers are typical. In contrast, the chloroplatinic acid-catalysed hydrosilylation of 1-(trimethylsilyl)-1-octyne (Scheme 10) occurs in a highly regioselective manner to give, after treatment with MeMgBr, (*E*)-1,2-*bis*(trimethylsilyl)-1-octene **10.1** in 96% yield (Hudrlik *et al.*, 1979). The regioselectivity observed here—the nascent C–Si bond distal to the terminal silane—is noteworthy since the hydrometallations of 1-(trimethylsilyl)-1-alkynes usually proceed with the opposite regiochemistry, placing the metal on the carbon adjacent to the silane.

Steric constraints consequent to intramolecular hydrosilylations can reverse the normal regioselectivity observed in the acylic reactions. Thus Steinmetz and Udayakumar (1989) observed high *exo*-selectivity in the intramolecular hydrosilylation of 1-(trimethylsilyl)-1-alkynes **11.1** bearing pendant alkylsilane chains (Scheme 11). With the exception of the case where $n = 0$, in which ring



Scheme 11

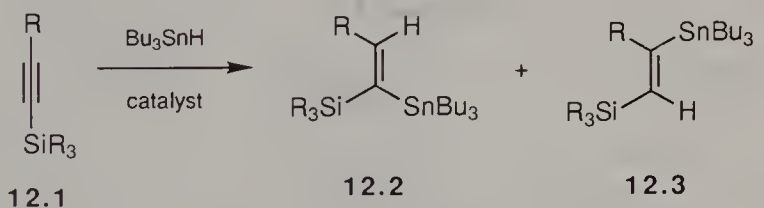
strain prevents cyclization altogether, the regioselectivities observed for $n = 1$–3 are consistent with preferential formation of the less strained intermediate σ-complex of the alkene with platinum.

2.1.5 Hydrostannylation

Hydrostannylation and hydrogermylation of alkynes takes place considerably more readily than hydrosilylation. The addition of stannanes occurs without the aid of transition metal catalysts by a radical mechanism whose stereo-

chemistry and regiochemistry has been elucidated by Leusink and coworkers (1967). For the purposes of this review we will focus on the transition metal-catalysed variant which has received comparatively little attention (Kikukawa *et al.*, 1988). Palladium, molybdenum and rhodium catalysts have been used in the hydrostannylation of terminal alkynes to give exclusively (*E*)-alkenyl-stannanes but mixtures of regioisomers are typical. Molybdenum catalysts are reported to be superior to Pd(0) for some sterically hindered or deactivated alkynes (Zhang *et al.*, 1990).

The influence of trimethylsilyl substitution on the rate and regiochemistry of alkyne hydrostannylation contrasts sharply with the hydrometallations discussed above (Zhang *et al.*, 1990). In the case of 1-(trimethylsilyl)-1-hexyne **12.1b**, not only is the reaction *retarded* but also the Sn atom becomes attached preferentially to the distal carbon giving **12.3b** as the major product (Scheme 12). Interestingly, hydrostannylation of (trimethylsilyl)ethyne with the same molybdenum catalyst proceeds with the opposite regioselectivity to give the 1,1-dimetallo-alkene **12.2a** as the main product. The deactivating influence of the trimethylsilyl substituent can be ameliorated by the presence of another activating group. Thus, ethyl 3-(trimethylsilyl)-propynoate **12.1c** was regio- and stereoselectively hydrostannylated using Pd(0) as the catalyst to give (*E*)-2-(tributylstannyl)-3-(trimethylsilyl)-propenoate **12.3c** in 70% yield. 1,2-*Bis*(trimethylstannyl)-ethyne was inert regardless of the catalyst used.

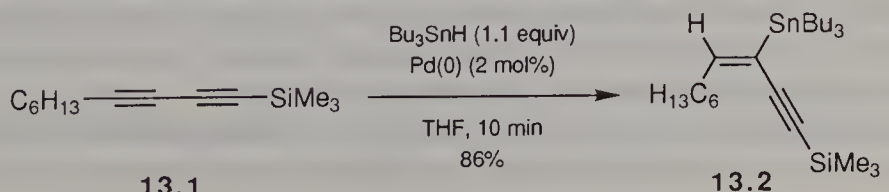


12.1 12.2 12.3

	R	Catalyst	Yield	12.2 : 12.3
a	H	Mo	80%	85 : 15
b	Bu	Mo	83%	27 : 73
c	COOEt	Pd	70%	0 : 100

Scheme 12

As a final measure of the deactivating influence of the trimethylsilyl group, 1-(trimethylsilyl)-1,3-decadiyne **13.1** hydrostannylates under Pd(0) catalysis preferentially at the internal triple bond to afford (*E*)-1-(trimethylsilyl)-3-(tributylstannyl)-3-decen-1-yne **13.2** selectively (Scheme 13).

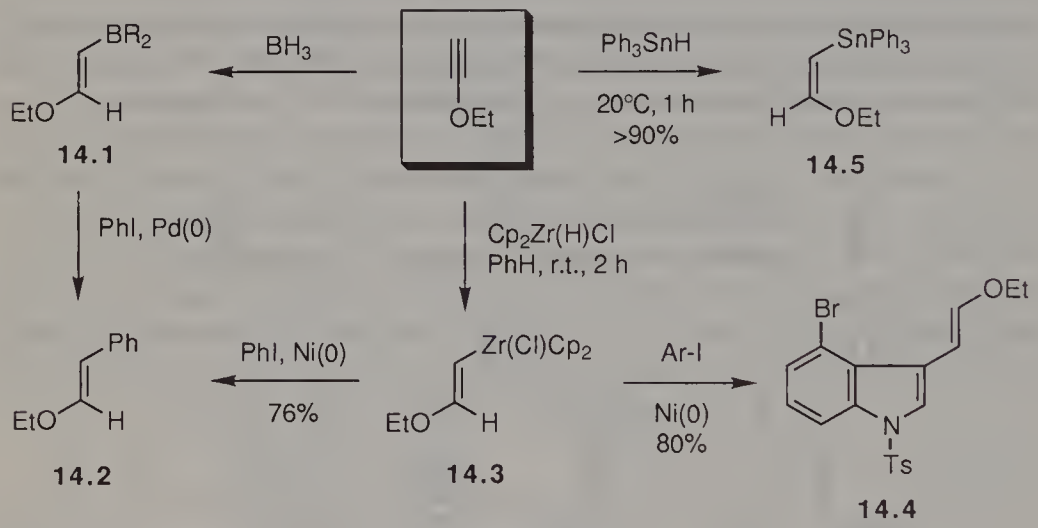


13.1 13.2

Scheme 13

2.2 1-Alkoxyalkynes

The benefits of increased functional diversity and improved rate and regiocontrol offered by dialkylamino and alkoxy substituents has hardly impinged on hydrometallation chemistry. No doubt one reason for the paucity of data is the comparative instability of ynamines and alkoxyalkynes, making them awkward compounds to handle and prepare. What little information we have, has mostly been gleaned from reactions with the only alkoxyalkyne which is commercially available: ethoxyethyne. Hydroboration (Bubnov *et al.*, 1970; Miyaura *et al.*, 1982), hydrozirconation (Vincent *et al.*, 1982; Hegedus *et al.*, 1987; Negishi *et al.*, 1987), and uncatalysed hydrostannylation (Leusink *et al.*, 1967) of ethoxyethyne have all been accomplished and in every case the metal became attached to the distal carbon in accord with the electronic effects discussed above. Hydroalumination of somewhat more interesting alkoxyalkynes was investigated by Eisch and co-workers with the same regiochemical consequence (Eisch *et al.*, 1975). An example which illustrates the improved opportunities for exploiting the heteroatom is shown in Scheme 14. Hydro-



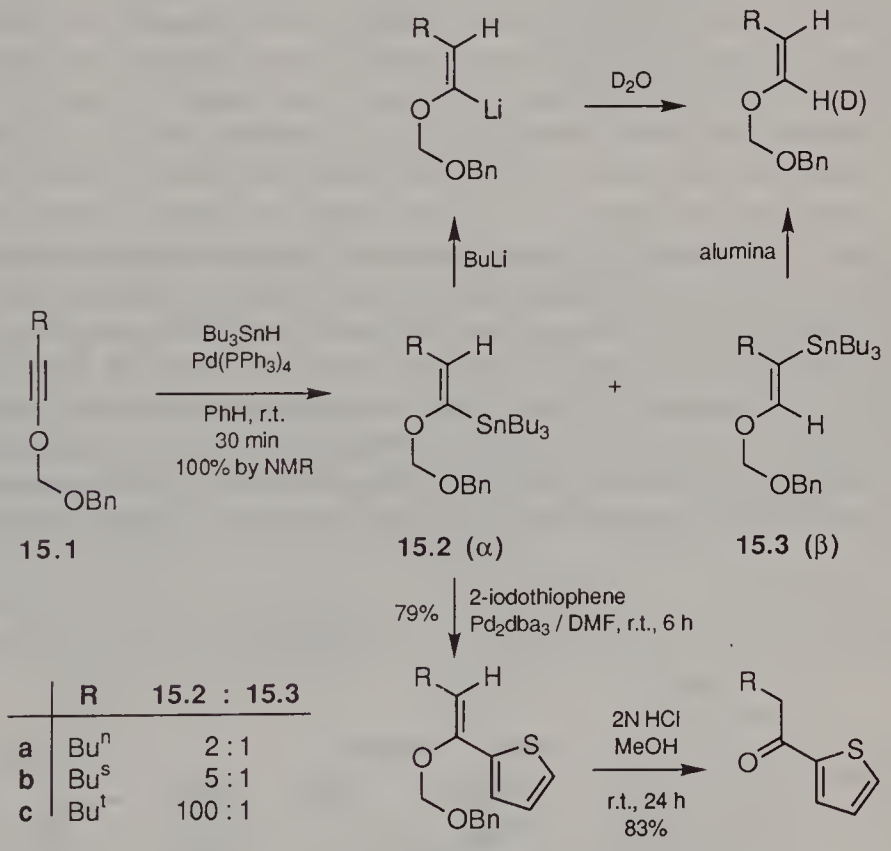
Scheme 14

boration of ethoxyethyne (Miyaura *et al.*, 1982) with diborane gave trialkenylborane **14.1** which underwent Pd(0)-catalysed coupling under basic conditions with iodobenzene. The significance of this transformation lies in the effective appendage of acetaldehyde to an sp^2 centre—a reaction normally beyond the pale of traditional enolate chemistry. A similar transformation was accomplished using hydrozirconation followed by Ni(0)-catalysed coupling (Negishi *et al.*, 1987). A synthesis of the aurantioclavine precursor **14.4** attests to the synthetic utility of the sequence (Hegedus *et al.*, 1987).

In keeping with the vast store of precedent, hydrometallations of alkoxyalkynes adhere to the preference for *syn*-addition. An apparent exception is

the uncatalysed hydrostannylation of ethoxyethyne (Scheme 14) (Leusink *et al.*, 1967) which gave the *anti*-adduct **14.5** in excellent yield contaminated with minor amounts of the *syn*-adduct. However, once again this was no exception: the *syn*-adduct forms as the kinetic product which then is easily isomerized by addition–elimination of stannane.

Under the stimulus of securing a new and general route to α-alkoxyalkenyl stannanes, Casson and Kocienski investigated the Pd(0)-catalysed hydrostannylation of 10 1-alkoxy-1-alkynes and found that the regiochemical bias for placing the Sn at the distal β-carbon presaged in the studies with ethoxyethyne was subverted. Simple alkyl substitution was sufficient to cause a shift in regiochemical bias to the desired α-alkoxyalkene as illustrated in Scheme 15.



	R	15.2 : 15.3
a	Bu^n	2 : 1
b	Bu^s	5 : 1
c	Bu^t	100 : 1

Scheme 15

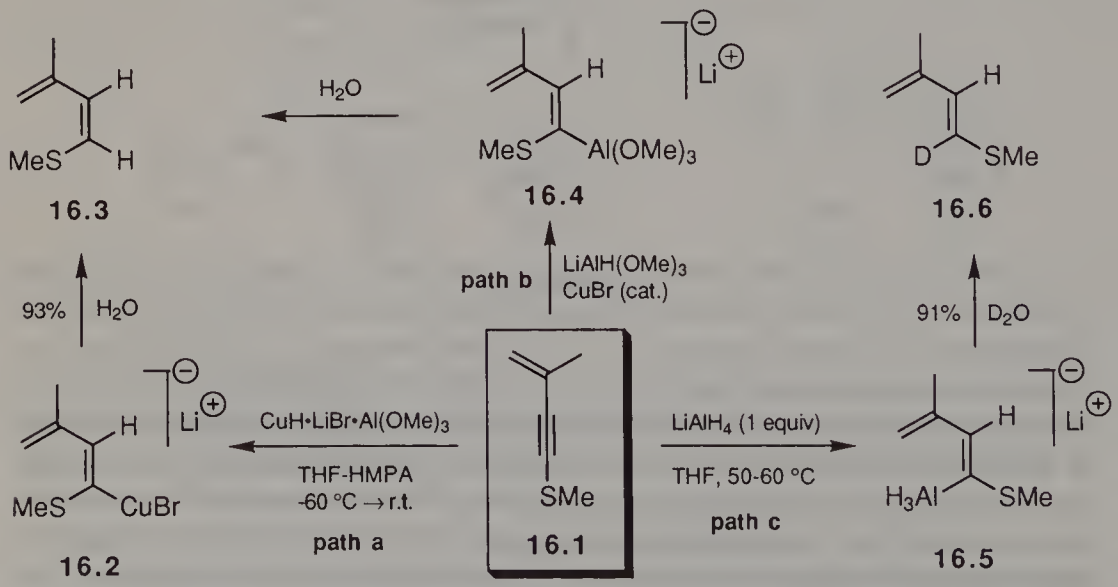
When the substituent at the β-position was bulky (*t*-Bu), the preference for α-stannylated regioisomer **15.2** was virtually total but decreasing steric bulk led to increasing contribution from the β-stannylated product **15.3**. From the practical point of view, the annoying presence of the β-stannylated compounds was not a problem because they were so unstable: a single rapid pass down a short column of basic alumina selectively destroyed them by protonolysis. The significance of the unexpected shift in regiochemical bias is that for the first

time, α-alkoxyalkenyllithiums are generally available by transmetallation; equally important are the new opportunities for accomplishing Pd(0)-catalysed acylation of arenes.

The high stereoselectivity (*syn*-addition) observed in the Pd(0)-catalysed hydrostannylations illustrated in Scheme 15 required experimental vigilance. In the presence of excess stannane, ordinary daylight was sufficient to cause isomerization but careful exclusion of light and the addition of trace amounts of a radical inhibitor (galvinoxyl) to the reaction mixture were sufficient to ensure the stereo- and regiochemical integrity of the *syn*-adducts.

2.3 1-Phenylthio-1-alkynes

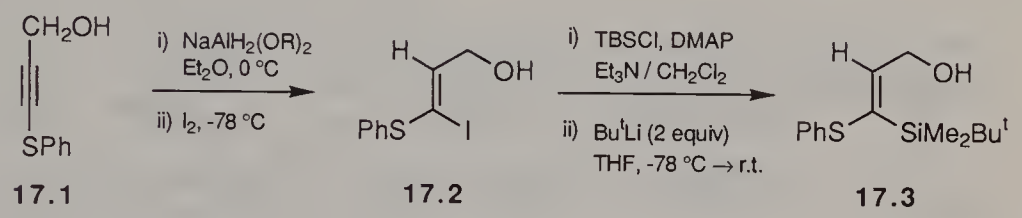
Thioalkynes are more stable than their oxygen counterparts in accord with diminished electronic communication between the non-bonded 3p electron pairs on the sulphur atom and the π-system of the alkyne at level 2. The improved stability and ease of preparation makes thioalkynes more practical substrates for hydrometallation studies. The phenylthio group is an electron sink and polarizes the alkyne in a sense opposite to that observed with alkoxyalkynes (see Scheme 2). The net reversal of polarization determines the regiochemistry of hydrometallation as shown in Scheme 16: there is a strong preference for attachment of the metal to the α-position. With a putative CuH reagent prepared by reaction of stoichiometric amounts of CuBr and $LiAlH(OMe)_3$, thioalkyne **16.1** undergoes *syn*-hydrocupration (path a) affording the diene **16.2** (Vermeer *et al.*, 1976; Masure *et al.*, 1982). Furthermore, the same combination of reagents—but with CuBr present in catalytic amounts—accomplished the hydroalumination of alkyne **16.1** (path b) giving the diene



Scheme 16

product **16.3**. The regiochemistry of both reactions was determined by deuterolysis experiments. Complementary *anti*-stereochemistry can be obtained by hydroalumination of **16.1** with LAH (path c).

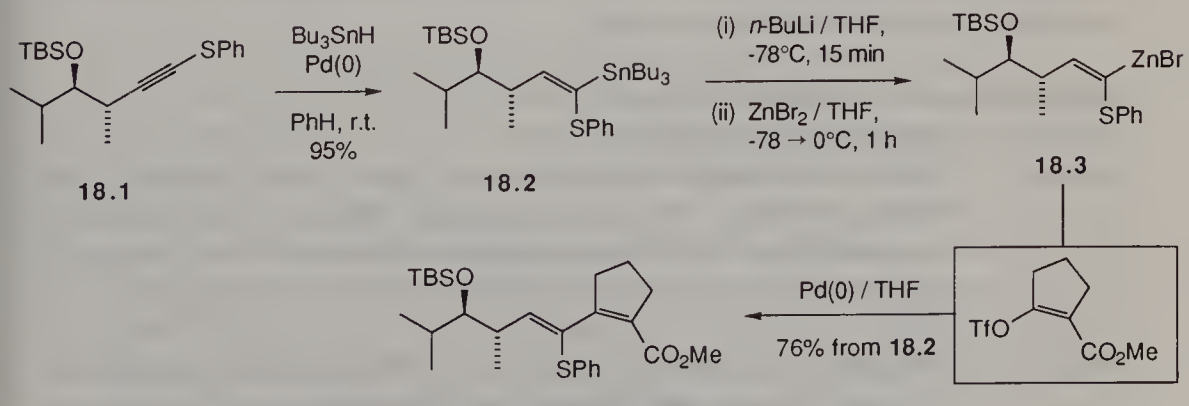
Kim and Magriotis (1990) prepared (*Z*)-iodoalkene **17.2** in excellent yield by the hydroalumination of 1-phenylthio-1-propyn-3-ol **17.1**. In the example shown in Scheme 17, *anti*-hydroalumination was predominant (10:1). The (*Z*)-iodoalkenes **17.2** served as a precursor to α-phenylthioalkenyl silane **17.3** via 1,4 O → C silyl migration of an alkenyl–lithium intermediate.



17.1 **17.2** **17.3**

Scheme 17

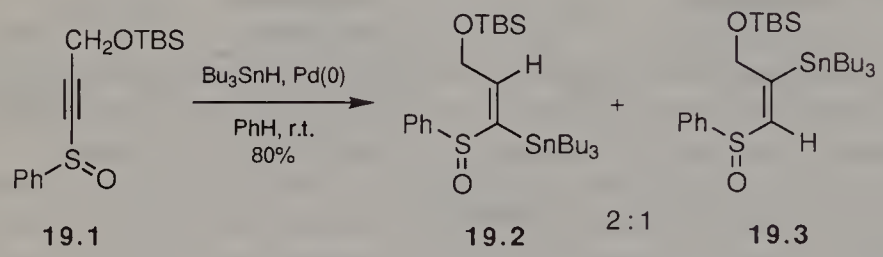
Two groups have recently shown that 1-phenylthio-1-alkynes undergo easy and efficient Pd(0)-catalysed hydrostannylation (Magriotis *et al.*, 1991: Pimm *et al.*, 1992). Scheme 18 illustrates the procedure and shows that the reaction is both regioselective and stereoselective. Stannane **18.2** does not participate readily in Pd(0)-catalysed cross-coupling reactions but the corresponding α-(phenylthio)alkenyl zinc reagent **18.3** reacts with a wide variety of substrates under mild conditions providing a significant enhancement to the cross-coupling chemistry of α-heteroalkenyl metals. Since α-(phenylthio)alkenes can be hydrolysed to ketones or cross-coupled with Grignard reagents in the presence of Ni(0) catalysts, reagent **18.3** serves as an exceptionally mild substrate for the nucleophilic acylation and alkylation of arenes and hetarenes.



18.1 **18.2** **18.3** **18.4**

Scheme 18

Alkynes with sulphur substituents in higher oxidation states are also known to undergo hydrometallation. The enhanced polarization of the π-system should, if anything, reinforce the regiochemical preference for α-attachment of the metal. Hydroalumination of alkynyl sulphones behaves as expected in a regiochemical sense but they give *anti*-adducts (Eisch *et al.*, 1985). However, Pd(0)-catalysed hydrostannylation of alkynyl sulphoxides has been reported (Magriotis *et al.*, 1991) to give mixtures of regioisomers as exemplified in Scheme 19.



Scheme 19

3 Metallometallation

Metallometallation of alkynes has emerged as a versatile tool for the construction of 1,2-dimetallo-1-alkenes which, in theory, may be sequentially reacted with suitable electrophiles to form di- and trisubstituted alkenes with excellent regio- and stereocontrol. Metallometallations usually involve bimetallic reagents of the type $R_3Si\text{-}MR_n$ or $R_3Sn\text{-}MR_n$ in which M = B, Al, Mg, Mn, Cu, Zn, Si, or Sn. A noteworthy feature of these reagents is their low basicity. In many cases metallometallations can be performed on substrates which contain functional groups such as hydroxyl, ester, amine, and halide.

Metallometallation reactions can be divided into three categories depending on the nature of the bimetallic reagent:

(i) Stoichiometric metallo-cuprations:

GeCu (Ichinose *et al.*, 1987).

SnCu (Piers and Chong, 1983; Cox and Wudl, 1983; Fleming and Taddei, 1985a,b; Zweifel and Leong, 1987; Piers *et al.*, 1987; Lipshutz *et al.*, 1989; Sharma and Oehlschlager, 1991; Marek *et al.*, 1991; Beaudet *et al.*, 1991; Marino *et al.*, 1992; Barbero *et al.*, 1992).

SiCu (Fleming *et al.*, 1981; Fleming and Taddei, 1985a,b; Lipshutz *et al.*, 1989; Millar, 1989; Sharma and Oehlschlager, 1991; Ricci *et al.*, 1992; De Marigorta and Fleming, 1993).

(ii) Metallometallations with Cu(I) catalysis:

Sn–Zn (Hibino *et al.*, 1984; Matsubara *et al.*, 1985; Nonaka *et al.*, 1986).
Sn–Al (Hibino *et al.*, 1984; Matsubara *et al.*, 1985; Wakamatsu *et al.*, 1986; Sharma and Oehlschlager, 1986; Beaudet *et al.*, 1991; Aksela and Oehlschlager, 1991).
Sn–Mg (Hibino *et al.*, 1984; Matsubara *et al.*, 1985; Beaudet *et al.*, 1991; Aksela and Oehlschlager, 1991).
Sn–B (Sharma and Oehlschlager, 1989a; Nozaki *et al.*, 1986; Aksela and Oehlschlager, 1991).
Si–B (Nozaki *et al.*, 1986).
Si–Al (Sato *et al.*, 1983; Hibino *et al.*, 1984; Wakamatsu *et al.*, 1986).
Si–Zn (Sato *et al.*, 1983; Hibino *et al.*, 1984; Wakamatsu *et al.*, 1986).
Si–Mg (Sato *et al.*, 1983; Okuda *et al.*, 1984)

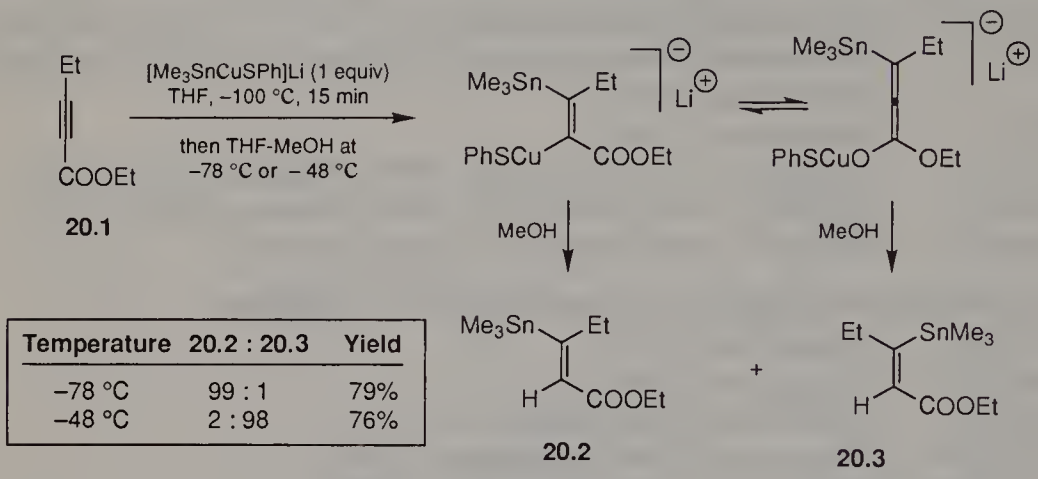
(iii) Metallometallations with other transition metal catalysts:

Si–B/Co (Nozaki *et al.*, 1986).
Sn–B/Co (Nozaki *et al.*, 1986).
Sn–B/Pd (Sharma and Oehlschlager, 1988).
Si–Si/Mn (Hibino *et al.*, 1985; Fugami *et al.*, 1988).
Sn–Sn/Mn (Hibino *et al.*, 1985; Fugami *et al.*, 1988).
Sn–Mg/Pd (Matsubara *et al.*, 1985).
Sn–Al/Pd (Matsubara *et al.*, 1985; Sharma and Oehlschlager, 1989b).
Sn–Zn/Pd (Hibino *et al.*, 1984; Matsubara *et al.*, 1985).
Sn–Sn/Pd (Piers and Skerlj, 1986; Mitchell *et al.*, 1983, 1986; Piers and Tilyer, 1989; Beaudet *et al.*, 1991).
Si–Mg/Pd (Hayama *et al.*, 1983; Wakamatsu *et al.*, 1986).
Si–Al/Pd (Hayama *et al.*, 1983; Wakamatsu *et al.*, 1986).
Sn–Si/Pd (Mitchell *et al.*, 1986; Chenard *et al.*, 1985; Chenard and Van Zyl, 1986; Beaudet *et al.*, 1991).
Si–Si/Pd (Tamao *et al.*, 1975, 1976; Watanabe *et al.*, 1981; Yamashita *et al.*, 1991).
Ge–Ge/Pd (Hayashi *et al.*, 1991).

Although terminal alkynes may be metallometallated with a high degree of regio- and stereocontrol, internal alkynes usually require the presence of some activating group such as CO_2R, to achieve useful control (Piers and Chong, 1983; Piers and Tilyer, 1989). In addition to the inherent bias in the bimetallic reagent, the regio- and stereochemical outcome of the reaction may be influenced by the catalyst employed, reaction conditions, solvents, Lewis acids, and the presence of suitable functional groups on the substrate (Sharma and Oehlschlager, 1988, 1989b; Piers and Tilyer, 1989). In the following brief review, we will summarize research on the scope, regiochemistry, stereochemistry, and synthetic utility of terminal alkyne metallometallation. We will then turn to metallometallation of heteroalkynes.

3.1 Metallocuprations using stoichiometric Cu(I)

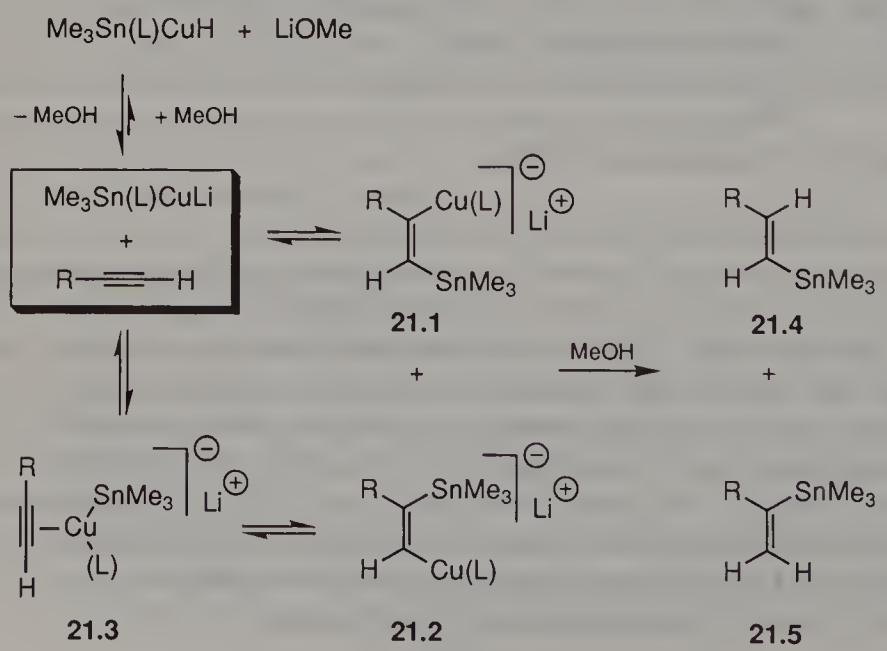
Piers and Chong (1983) were the first to show that (trimethylstannyl)copper(I) reagents can be effectively employed for the conversion of α,β-alkynoate esters into β-(trimethylstannyl)-α,β-alkenoates such as **20.2** and **20.3** (Scheme 20).



Scheme 20

Both the (*E*)- and (*Z*)-3-(trimethylstannyl)-2-alkenoates could be produced with high selectivity corresponding to the kinetic and thermodynamic products, respectively, by judicious choice of reagent and reaction conditions.

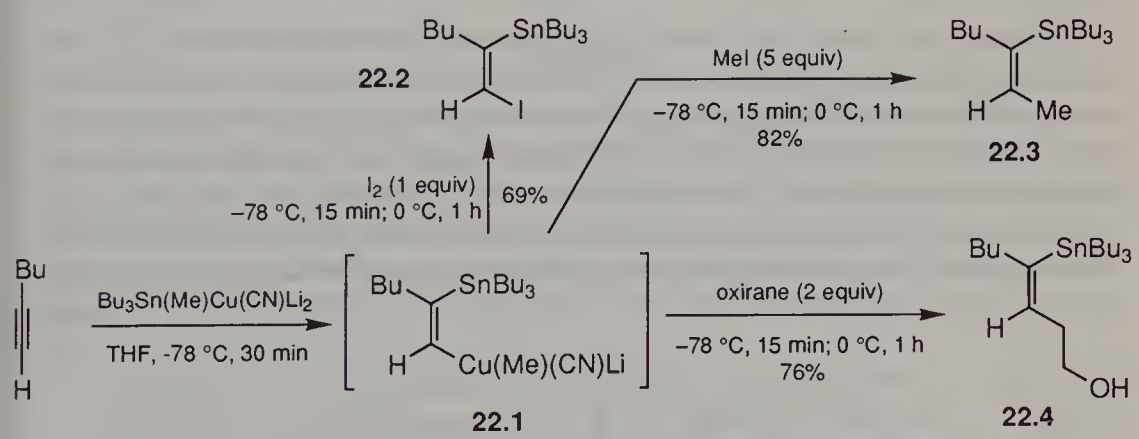
Scheme 21 outlines the course of stannylcupration of a terminal alkyne and draws attention to one of its major limitations: reversibility. In principle, the



Scheme 21

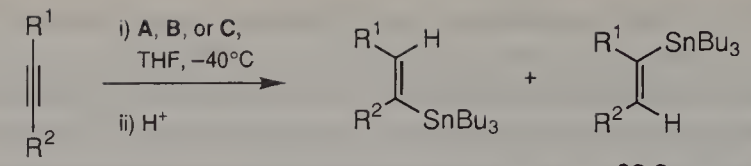
adducts **21.1** and **21.2** could be trapped *in situ* by a suitable electrophile giving trisubstituted alkenyl stannanes as products. However, in practice, most electrophiles react preferentially with the bimetallic reagent rather than the adduct. The problem of reversibility can be circumvented in part by conducting the stannylcupration in the presence of MeOH as a proton source. Selective protonation of the alkenylcopper intermediates **21.1** and **21.2** occurs because they are more basic than $Me_3Sn(L)CuLi$ thereby forcing the equilibrium to the right. Cox and Wudl (1983) estimate the CuH conjugate acid of a stannylcuprate has a pK_a of about 5. Low temperature ^{13}C and ^{2}H NMR spectroscopy and crossover experiments have unequivocally established the existence of the intermediates **21.1** and **21.2**, although π-complexation between the cuprate and the alkyne in the initial step giving **21.3** cannot be ruled out (Hutzinger *et al.*, 1990; Singer *et al.*, 1991). The alkenylcopper intermediates were only formed at temperatures above −35°C (Sharma and Oehlschlager, 1989a).

The stannylcupration of terminal alkynes generally places the copper atom at the terminus. Recently Pulido and co-workers (Barbero *et al.*, 1992) showed (Scheme 22) that a mixed higher order stannylcuprate $Bu_3Sn(Me)Cu(CN)Li_2$ gave *syn*-adducts which could be trapped with electrophiles other than the quotidian proton. These results suggest that the position of equilibrium can be influenced by the nature of the stannylcupration reagent. Stannylcopper reagents appear to favour the alkyne whereas the stannylcuprates favour the adduct. In fact, the issue of reversibility in all the various Cu(I)-catalysed metallometallations discussed below is difficult to assess. However, in the absence of pertinent experimental evidence, we presume that all the Cu(I)-catalysed metallometallations presented below are reversible processes in principle and that the position of equilibrium is amenable to tuning by deft manipulation of reagents and conditions.



Scheme 22

Enynes harbouring a terminal alkyne react with stannylcuprates to place the tin atom at the terminus—contrary to the regioselectivity observed with simple terminal alkynes (Scheme 23). Aksela and Oehlschlager (1991) investigated



23.1 23.2 23.3

	R^1	R^2
a	$H_2C{=}C(Me)$	H
b	$HOCH_2CH{=}CH$	H
c	$H_2C{=}C(Me)$	Et

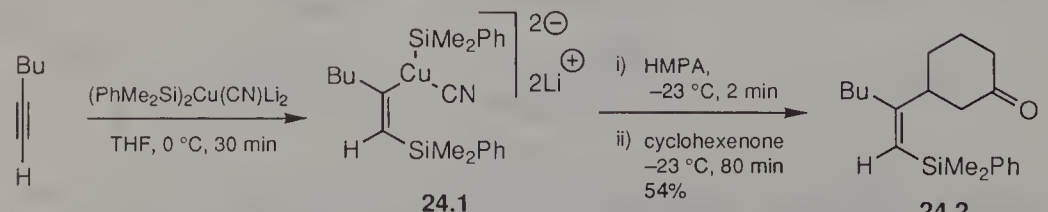
A = $Bu_3SnCu(CN)Li$
B = $(Bu_3Sn)_2Cu(CN)Li_2$
C = $(Bu_3Sn)(Bu)Cu(CN)Li_2$

Enyne 22.1	Reagent	H^+ / °C	23.2 : 23.3	Yield (%)
a	A	NH_4Cl / –40	19 : 81	56
a	B	MeOH / –40	3 : 97	72
a	C	NH_4Cl / –40	3 : 97	95
b	A	NH_4Cl / –60	38 : 62	58
b	B	MeOH / –40	39 : 61	77
b	C	NH_4Cl / –50	18 : 82	91
c	A	MeOH / –60	20 : 80	45
c	B	MeOH / r.t.	0 : 100	82

Scheme 23

the influence of steric factors on enyne stannylcupration using lower order [$R_3SnCu(CN)Li$], higher order [$(R_3Sn)_2Cu(CN)Li_2$] and mixed stannylcuprates [$R^1_3Sn(R^2)Cu(CN)Li_2$]. They found that lower order cuprates were only moderately selective but the homostannylcuprate $(R_3Sn)_2Cu(CN)Li_2$ provided a synthetically useful bias (97:3) towards the 1-stannylated isomer in some terminal alkynes, while the mixed stannylcuprate gave the 1-stannylated isomer in good yields and a regiocontrol >97:3 for both terminal and internal alkynes.

In contrast to stannylcuprations, the corresponding silylcuprations proceed with *opposite regiochemistry*, i.e. the silicon atom is placed at the terminus, and the equilibrium is well to the right. The reaction and some of its consequences are shown in Scheme 24. Thus, $(PhMe_2Si)_2CuLi$ reacted with hex-1-yne, propyne, phenylethyne and hex-3-yne via *syn*-addition to give 2,2-disubstituted alkenylsilanes (Fleming *et al.*, 1981) after trapping with suitable electrophiles. In the example shown, the alkenylcuprate **24.1** reacted with cyclohexenone to give the conjugate addition product **24.2** in 54% overall



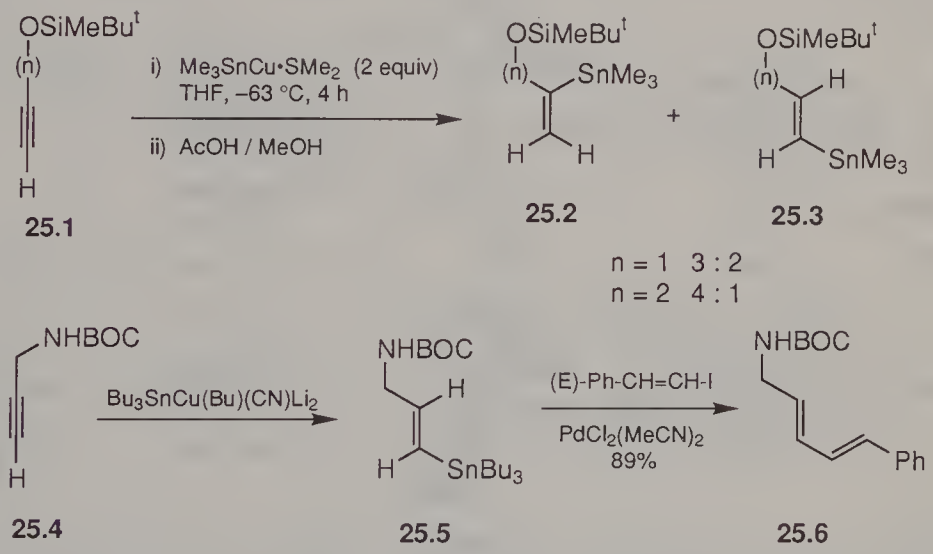
24.1 24.2

Scheme 24

yield. Other electrophiles used include iodine, acyl and alkyl halides, and epoxides.

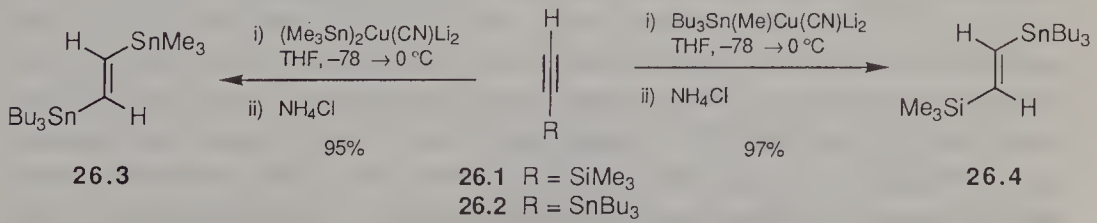
3.1.1 Heteroatom effects in metallocuprations

Depending on their distance from the alkyne unit, proximate heteroatoms can influence the regiochemistry of metallometallation by perturbation of electron density or coordination. An example of electronic perturbation (Scheme 25) is apparent in the stannylcupration of the silyl ethers **25.1**. The propargyl ether gave regioisomers **25.2** and **25.3** in a ratio of 3:2 whereas the homopropargyl ether gave the corresponding adducts in 4:1 ratio (Piers and Chong, 1983). Similarly, the BOC derivative of propargylamine (**25.4**) underwent atypical stannylcupration because of the coordination of the copper by the BOC group (Ricci *et al.*, 1992).



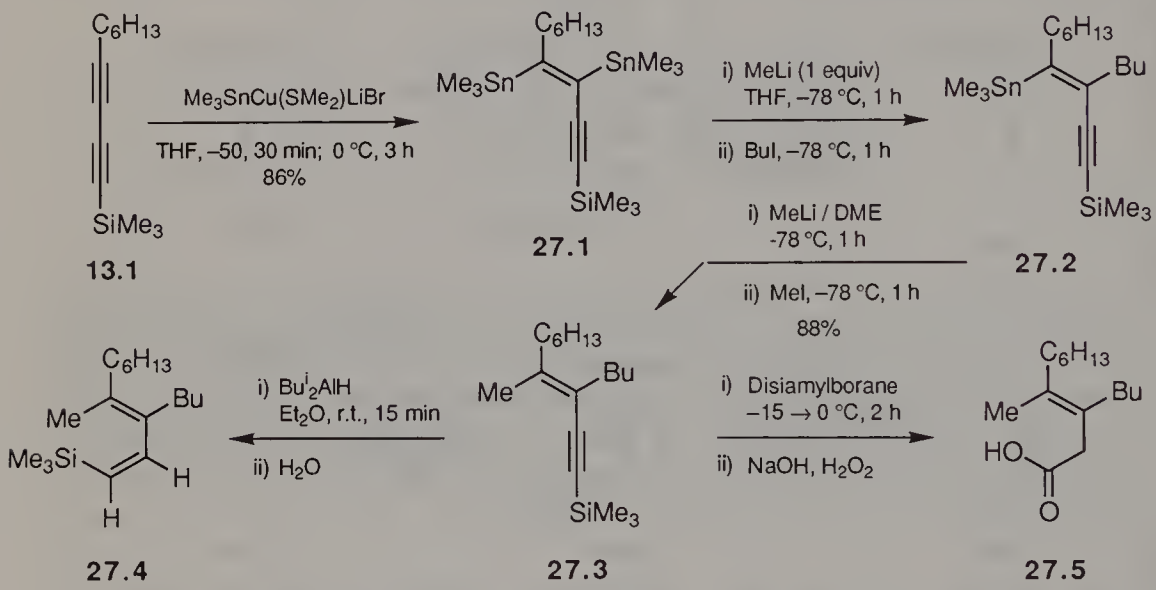
Scheme 25

Heteroatoms bound directly to the alkyne can exert a powerful electronic effect as witnessed by the transformations depicted in Scheme 26. Higher order cuprates $(Me_3Sn)_2Cu(CN)Li_2$ and $Bu_3SnCu(Me)(CN)Li_2$ reacted with 1-(trimethylsilyl)ethyne and 1-(tributylstannyl)ethyne to form alkenes **26.3** and **26.4** in high yield and with excellent regio- and stereocontrol (Barbero *et al.*, 1992).



Scheme 26

The differential reactivity imparted by the trimethylsilyl moiety to the triple bonds of 1-trimethylsilyl-1,3-diynes has been used to synthesize a variety of stereodefined tri- and tetrasubstituted enynes (Zweifel and Leong, 1987). For example (Scheme 27), (*E*)-*bis*(trimethylstannyl)enyne **27.1** was obtained in high yield when the silyl diyne **13.1** was treated with $Me_3SnCu(SMe_2)\cdot LiBr$. The formation of **27.1** can be rationalized by initial stereoselective addition of the stannylcopper reagent to the more nucleophilic alkyl-substituted triple bond followed by exchange of copper by tin. The two C–Sn bonds in **27.1** are amenable to stepwise conversion into the corresponding vinyllithium reagents as shown by the formation of **27.3**. Subsequent hydroalumination–protonation of the triple bond in **27.3** gave the diene **27.4** and hydroboration–oxidation led to the corresponding carboxylic acid **27.5**.



Scheme 27

3.2 Cu(I)-catalysed metallometallations

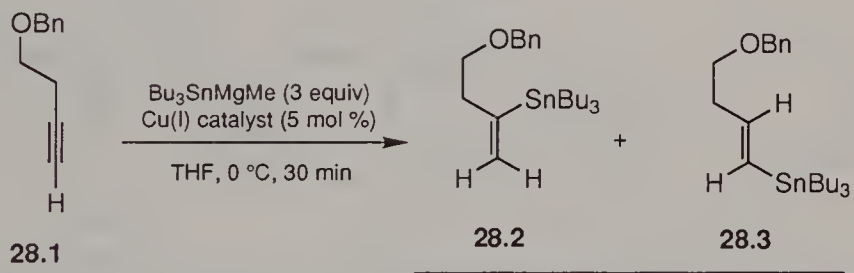
In the absence of added transition metal catalysts, metallometallations are slow (Sharma and Oehlschlager, 1988, 1989a,b). Cu(I) and Pd(0) are the most commonly used catalysts although Co and Mn have been effective in specific examples. Several problems have been encountered in the Sn- and Si-based metallometallations. Reactions wherein the second metal is **Al** (Hibino *et al.*, 1984; Matasubara *et al.*, 1985; Sharma and Oehlschlager, 1986; Nonaka *et al.*, 1986), **Mg** (Hibino *et al.*, 1984; Matsubara *et al.*, 1985; Sharma and Oehlschlager, 1986; Nonaka *et al.*, 1986) and **Zn** (Hibino *et al.*, 1984; Matsubara *et al.*, 1985; Sharma and Oehlschlager, 1986; Nonaka *et al.*, 1986; Okuda *et al.*, 1985) require a 3-fold excess of reagent to achieve high alkyne consumption. The use of excess reagents leads to the formation of byproducts that are not readily

separable from the organometallic species unless the substrate contains a polar functionality (Sharma and Oehlschlager, 1989a).

The regioselectivity of transition metal-mediated metallometallations is a function of a number of interdependent variables which include solvent, the presence of Lewis acids and bases, catalyst, temperature, and steric bulk of the alkyl groups on the bimetallic reagent. Each of these factors will be discussed in turn below.

3.2.1 Effect of catalyst on regiochemistry

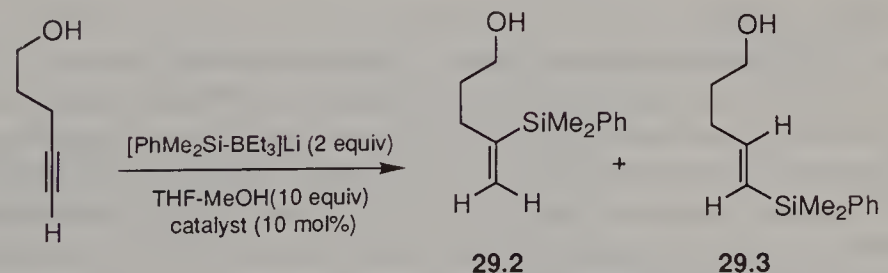
The stannylmagnesiation of 4-benzyloxy-1-butyne **28.1** with $Bu_3SnMgMe$ in the presence of a catalytic amount of CuCN (Scheme 28) provided (*E*)-4-benzyloxy-1-(tributylstannyl)-1-butene **28.3** as a single product in 88% yield whereas the Cu(I)-catalysed reaction reversed the selectivity and gave a mixture of regioisomers **28.2** and **28.3** (66:34) in 23% yield (Matsubara *et al.*,



Catalyst	28.2 : 28.3	Yield
CuCN	0 : 100	88%
$CuBr{\bullet}SMe_2$	66 : 34	23%

Scheme 28

1985). Similarly, the stannylboration of 5-hydroxypent-1-yne **29.1** with $PhMe_2SiBEt_3Li$ in the presence of catalytic CuCN (Scheme 29) provided a regioisomeric mixture (66:24) in favour of the 1-silyl-1-alkene **29.3** but $CoCl_2(PPh_3)_2$ provided a single diastereoisomer (Nozaki *et al.*, 1986).



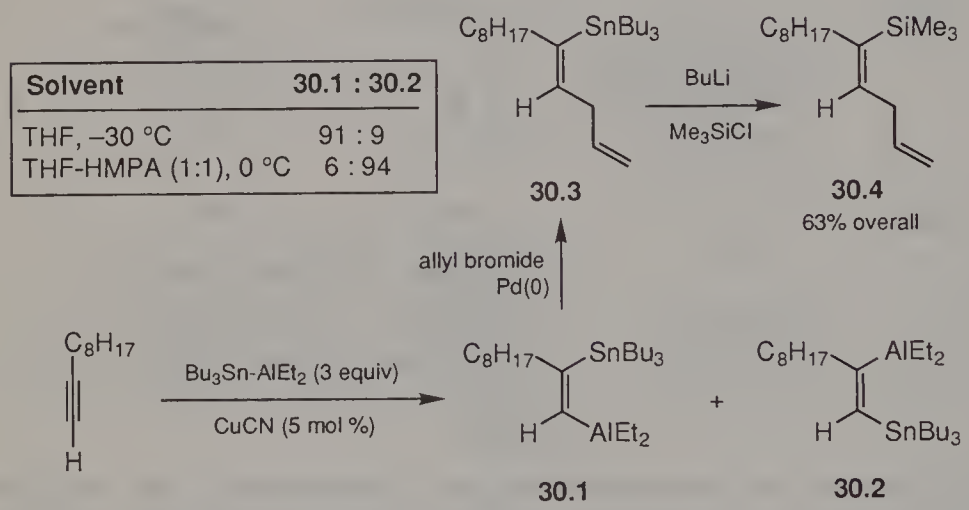
Catalyst	29.2 : 29.3	Yield
CuCN	34 : 66	96%
$CoCl_2(PPh_3)_2$	0 : 100	81%

Scheme 29

3.2.2 *Effect of Lewis acids and bases on regiochemistry*

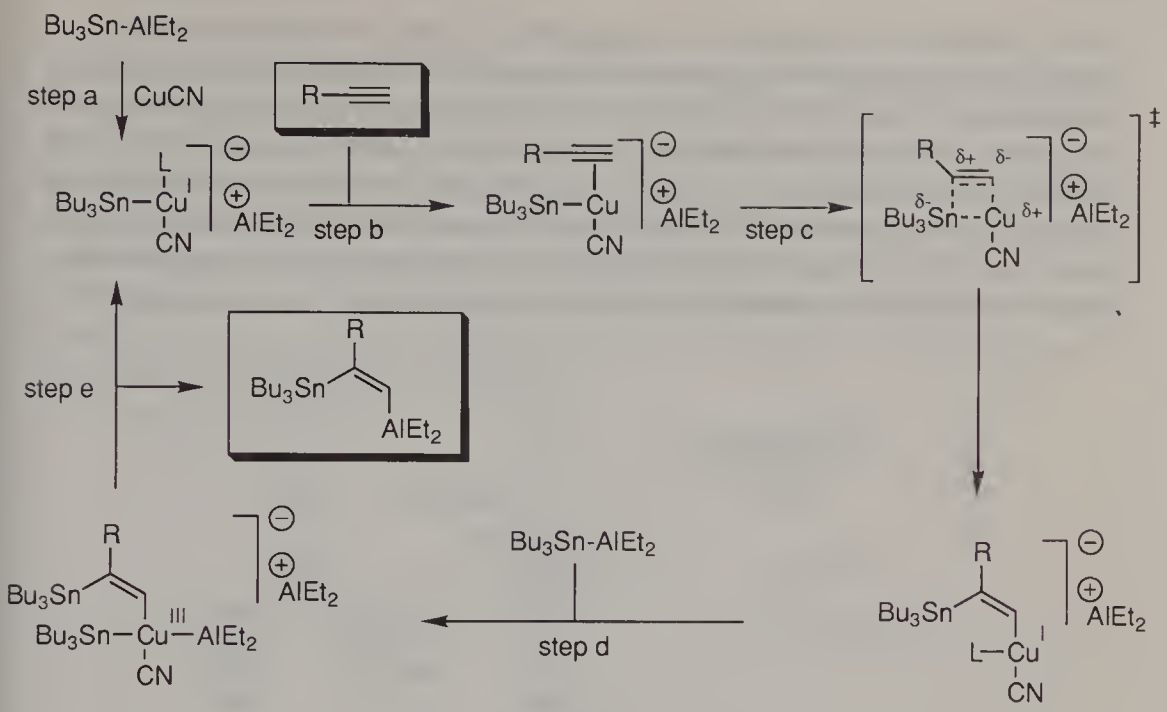
Sharma and Oehlschlager (1989b) conducted an extensive series of experiments on the metallometallation of 1-decyne in order to assess the role of a wide range of variables on the course of the reaction. Their results clearly show that the regiochemistry can be manipulated. As can be seen from Scheme 30, reaction of 1-decyne with 3 equivalents of Bu_3Sn-$AlEt_2$ in THF at −30°C in the presence of catalytic CuCN gave a mixture of regioisomers (81:19) in which the major regioisomer **30.1** has the tin atom placed on the internal carbon. However, by running the reaction at 0°C in THF–HMPA (1:1), the regioselectivity was reversed (6:94): the major isomer **30.2** has the tin atom placed on the terminal carbon. Owing to a favourable equilibrium, the Cu(I)-catalysed stannylalumination of terminal alkynes affords opportunities for trapping the adducts with suitable electrophiles (Scheme 30).

Solvent	30.1 : 30.2
THF, –30 °C	91 : 9
THF-HMPA (1:1), 0 °C	6 : 94



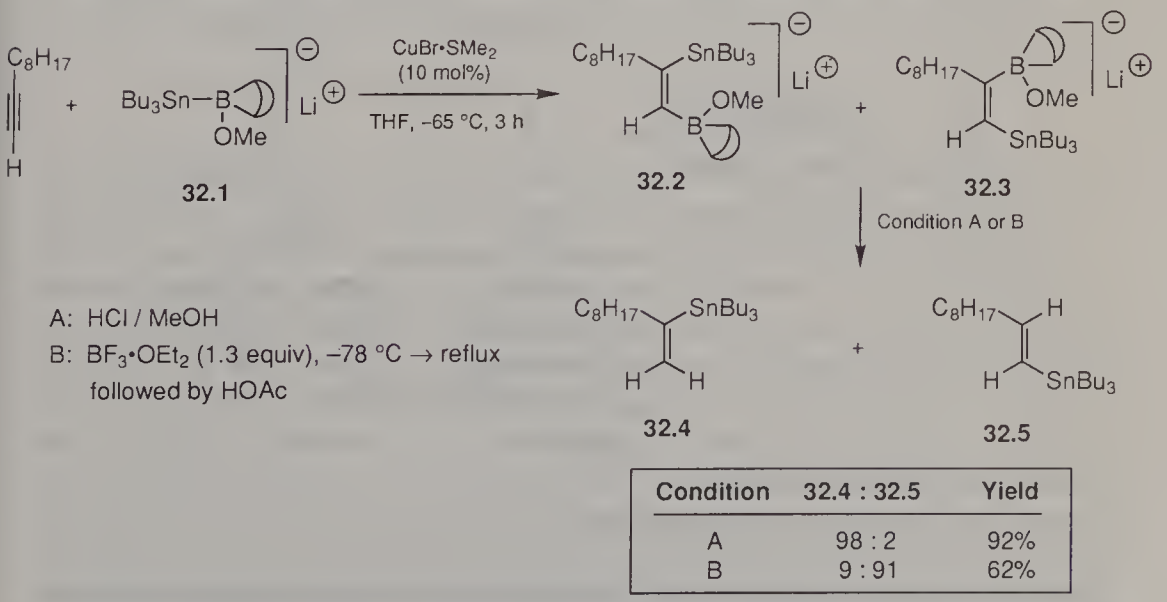
Scheme 30

The effect of HMPA on the regioselectivity of Cu(I)-catalysed stannylmetallations of 1-alkynes has been ascribed to a change in the regioselectivity of step c in the catalytic cycle shown in Scheme 31 (Sharma and Oehlschlager, 1989b). Under normal circumstances (THF, −50°C) the trialkylstannyl group migrates to the electropositive internal carbon of the alkyne because the trialkylstannyl group is negatively charged relative to Cu. However, HMPA coordination to the Cu could reverse the polarity of the weakly polarized Cu–Sn bond thereby tipping the balance of negative charge in favour of Cu with a consequent change in regioselectivity. An alternative argument in accord with NMR experiments ascribes the change in regiochemistry to a lower steric requirement for the copper centre resulting from a lower aggregation state in the presence of the HMPA.



Scheme 31

In an earlier study it was shown that the regioselectivity of Cu(I)-catalysed stannylborations could be reversed by the addition of $BF_3 \cdot Et_2O$ (Sharma and Oehlschlager, 1986) (Scheme 32).

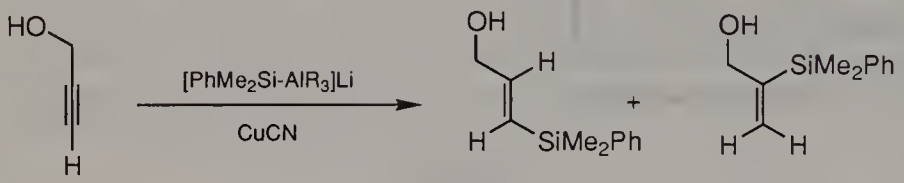


Condition	32.4 : 32.5	Yield
A	98 : 2	92%
B	9 : 91	62%

Scheme 32

3.2.3 Effect of the structure of the bimetallic reagent on regiochemistry

In this section we indicate two ways in which the structure of the bimetallic reagent can influence the regiochemistry of metallometallation. First, the steric bulk of the carbon ligands on the metal play a significant role. Scheme 33 illustrates the effect in the CuCN-catalysed silylalumination of propargyl alcohol (Wakamatsu *et al.*, 1986). Bulky *t*-Bu groups on the aluminium caused it to favour the terminal carbon leading to **33.2** preferentially whereas smaller Et groups behaved 'normally' placing the aluminium on the internal carbon.

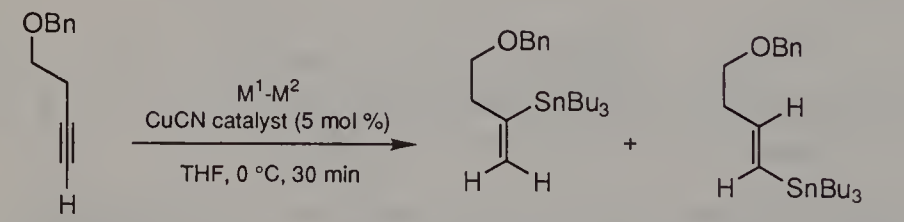


33.1 **33.2**

R	33.1 : 33.2	Yield
Et	100 : 0	89%
t-Bu	14 : 86	90%

Scheme 33

Secondly, the CuCN-catalysed stannylmetallation of terminal alkyne **34.1** (Scheme 34) displayed a regiochemistry that depended on the nature of the metal partner (Matsubara *et al.*, 1985). When Mg was the partner, the tin occupied the terminal carbon exclusively, but with Zn, the opposite regioisomer **34.2** predominated.



34.1 **34.2** **34.3**

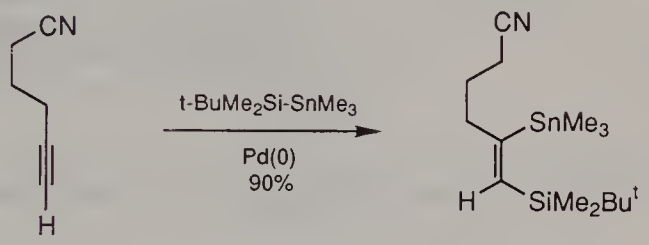
M^1-M^2	Yield	34.2 : 34.3
Bu_3Sn-MgMe	88%	0 : 100
Bu_3Sn-$AlEt_2$	86%	18 : 81
Bu_3Sn-Zn-$SnBu_3$	63%	74 : 26

Scheme 34

3.3 Pd(0)-catalysed metallometallation

The vast majority of alkyne metallometallations reported to date have been mediated by Cu(I) though other catalysts have been employed (e.g. Rh, Co,

Ti), albeit to no great apparent advantage yet. However, there is a small class of metallometallations involving bimetallic reagents containing Sn–Sn (Mitchell *et al.*, 1986), Si–Si (Watanabe *et al.*, 1981), and Sn–Si (Chenard *et al.*, 1985; Mitchell *et al.*, 1985; Chenard and Van Zyl, 1986) bonds which are not promoted by Cu(I) but are effectively catalysed by Pd(0) (Scheme 35). In every case examined so far unactivated terminal alkynes add the bismetallic reagent with clean *syn*-stereochemistry. In the case of Si–Sn addition, the Si becomes attached to the terminal carbon. Pd(0) also catalyses the addition of Si–Al (Wakamatsu *et al.*, 1986), Sn–Zn (Nonaka *et al.*, 1986), and Sn–Al reagents (Sharma and Oehlschlager, 1989b).



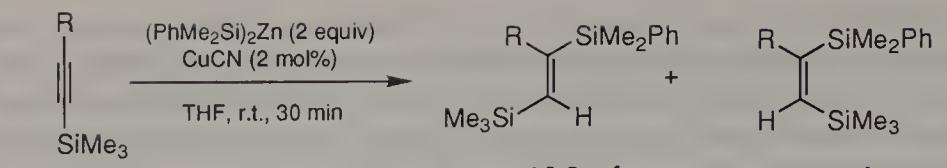
Scheme 35

4 Metallometallation of heteroalkynes

The metallometallation of internal alkynes rarely provides synthetically useful regiocontrol unless one of the substituents on the triple bond is sufficiently activating (Piers *et al.*, 1985). In the following sections we examine the relatively small amount of data which describes the influence of Si, O, S, and N substituents on the regiochemistry of various metallometallation reactions.

4.1 1-Trialkylsilyl-1-alkynes

The Oshima group has examined the Cu(I)-catalysed reaction of 1-trimethylsilyl-1-alkynes with the silylzinc reagent $(PhMe_2Si)_2Zn$ (Wakamatsu *et al.*, 1986). The reaction was highly regioselective and invariably gave 1,2-disilyl-1-alkenes regardless of the alkyne substituent. However, the stereochemistry depended on the presence of proximate hydroxyl groups. 1-(Trimethylsilyl)-1-octyne **36.1b** and 4-(2-tetrahydropyranyloxy)-1-(trimethylsilyl)-1-butyne **36.1e** gave *syn*-adducts which afforded the (*E*)-1,2-disilyl-1-alkenes **36.2b,d** on workup. However, 3-(trimethylsilyl)-2-propyn-1-ol **36.1c** and 4-(trimethylsilyl)-3-butyn-1-ol **36.1d** provided the *anti*-adducts which protonated to give the (*Z*)-isomers **36.3c,d**. The authors postulated that the initial addition proceeded with *syn*-stereochemistry but that isomerization later occurred driven by intramolecular coordination of the hydroxyl group to the zinc atom. The chelation effect disappeared when the hydroxy group was separated from



36.1 a-f **36.2 a-f** (E) **36.3 a-f** (Z)

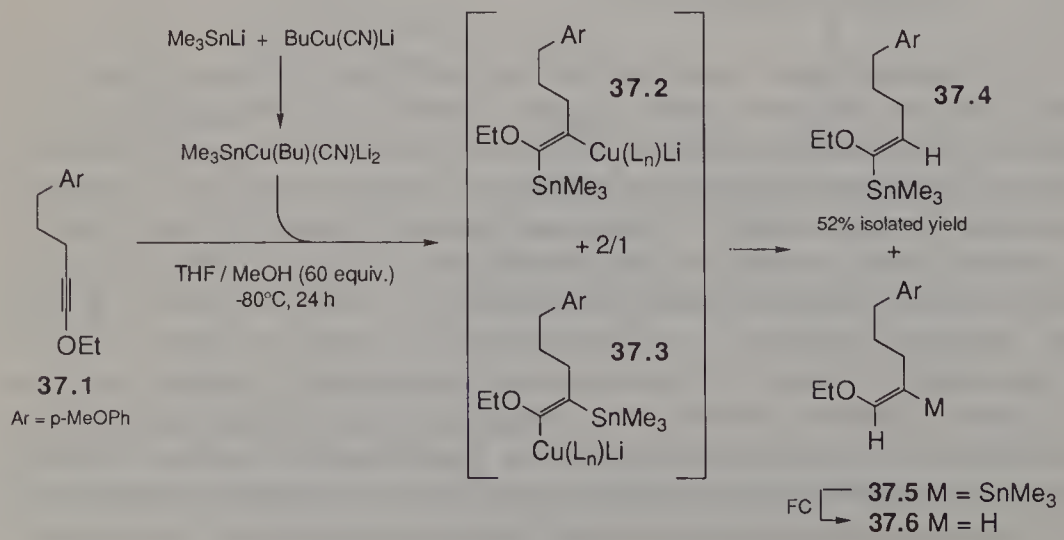
	R	E : Z	Yield
a	H	100 : 0	78%
b	n-C_6H_{13}	100 : 0	58%
c	CH_2OH	0 : 100	75%
d	CH_2CH_2OH	0 : 100	44%
e	CH_2CH_2OTHP	100 : 0	72%
f	$CH_2CH_2CH_2OH$	100 : 0	74%

Scheme 36

the alkyne by three carbons (**36.1f**) leading to the expected *syn*-adduct exclusively.

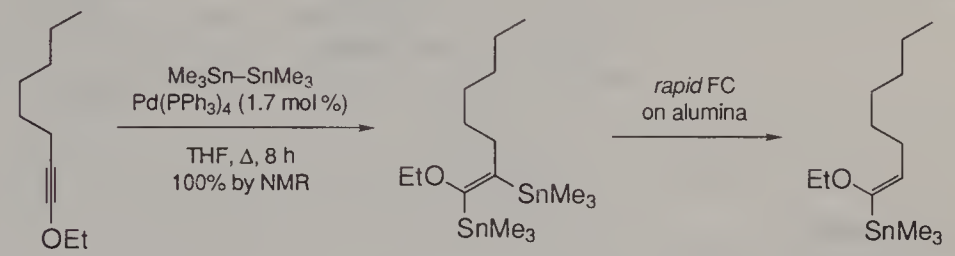
4.2 1-Alkoxyalkynes

To our knowledge Christopher Barber, working at the University of Southampton, was the first to investigate the metallometallation of 1-alkoxy-1-alkynes in an attempt to find a general route to α-alkoxyalkenyl stannanes (Scheme 37). Stannylcupration of ethoxyalkyne **37.1** gave the desired α-alkoxyalkenyl stannane **37.4** in 52% yield after aqueous workup. Unfortunately, the reaction was only modestly regioselective with the *syn*-adducts **37.2** and **37.3** being formed in a ratio of 2:1. The high lability of the β-trialkylstannyl group in the minor product **37.3** ensured its protonolysis during flash chromatography.



Scheme 37

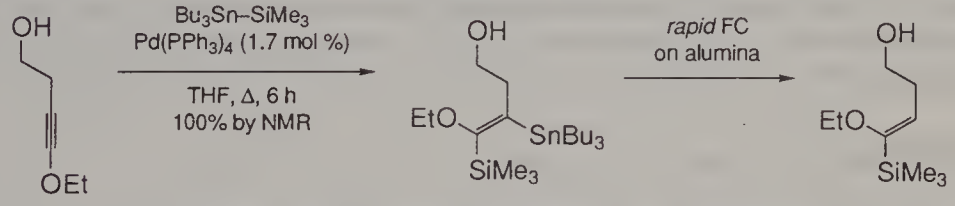
Sharon Casson, also at the University of Southampton, has recently investigated the Pd(0)-catalysed stannylstannylation of alkoxyalkynes. The reaction is much slower than the corresponding hydrostannylation but the yield is virtually quantitative according to NMR analysis of the crude reaction mixture (Scheme 38). Although the adduct **38.2** could be isolated pure in 26% yield by very rapid chromatography on alumina, the major product was **38.3** resulting from protodestannylation of the labile β-stannyl group.



38.1 **38.2** **38.3**

Scheme 38

In a related study Barber showed that Pd(0)-catalysed silylstannylation of alkoxyalkyne **39.1** was highly regioselective (Scheme 39) and was comparable in ease and efficiency to the stannylstannylation reaction described above. The tin atom was placed exclusively at the β-position. The regioselectivity was not governed by the proximate hydroxyl function since similar silylstannylations on alkyl substituted alkoxyalkynes displayed identical regioselectivity.



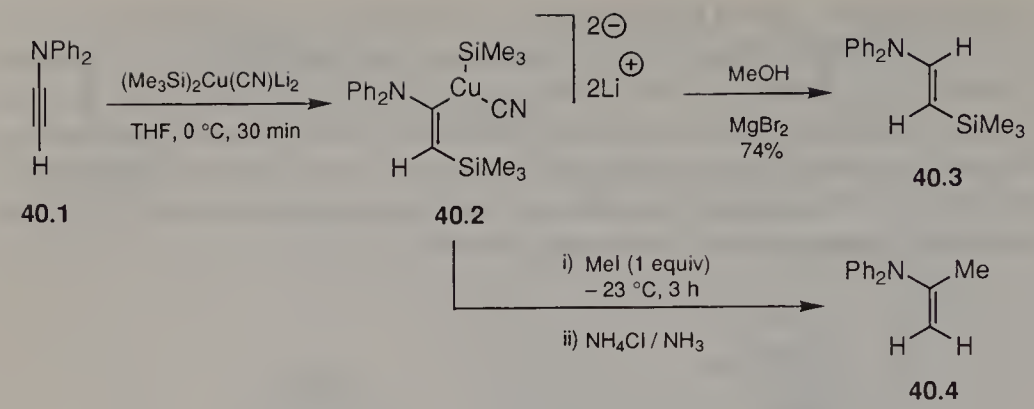
39.1 **39.2** **39.3**

only regioisomer
63% isolated yield

Scheme 39

4.3 1-Aminoalkynes (ynamines)

Ricci and co-workers (1992) recently described a highly regioselective silylcupration of *N,N*-diphenylaminoethyne **40.1** (Scheme 40) in which the copper atom was placed at the α-position next to the heteroatom—a result which appears to be opposite to the trend set by alkoxyalkynes. However, in this case it is likely that the regiochemisty is governed by internal coordination of the copper by the amino group in adduct **40.2**.



Scheme 40

5 Conclusion

The hydrometallation and metallometallation of the alkynes provides an exceptionally mild and expeditious route to alkenylmetals which are pivotal intermediates for the stereocontrolled synthesis of alkenes. A salient feature of the reactions is their compatibility with a wide range of functional groups. Whilst hydrometallation has long been a staple of the synthetic repertoire, metallometallation has received comparatively little attention despite the fact that bimetallic reagents are essentially non-basic. Synthetic chemists to date have been largely preoccupied with the stereochemistry and regiochemistry of metallometallation; little attention has been paid to the crucial issue of selective reaction of the two carbon–metal bonds. The hydrometallation and metallometallation of heteroalkynes amplifies the opportunities for synthetic manipulation and, at the same time, offers a means for influencing regio- and stereoselectivity.

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8

Stereocontrolled, Catalytic Transition Metal–Ene Type Cyclizations in Organic Synthesis

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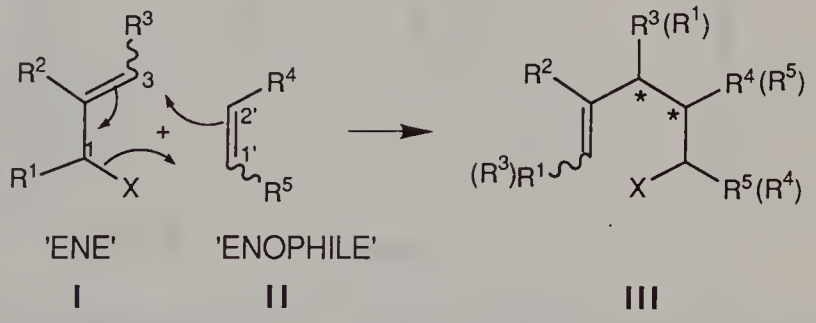
1 Introduction

The classical ene reaction usually involves the thermal addition of an alkene carrying an allylic hydrogen atom (ene) to an unsaturated compound (enophile, e.g. **I** + **II** → **III**, X = H; Scheme 1).



Scheme 1

Additions of allylmetal compounds to alkenes and alkynes resemble this ene process but involve the transfer of a metal instead of a hydrogen. This analogy prompted us to clarify transformations like **I** + **II** → **III** (X = metal), as metallo-ene reactions. Low yields, as well as poor regio- and stereoselectivities rendered allylmetal/alkene additions initially unattractive. However, the situation improved dramatically when metallo-ene reactions were carried out in an intramolecular manner. These versions, particularly with transfer of magnesium, turned out to be powerful and highly selective tools in organic

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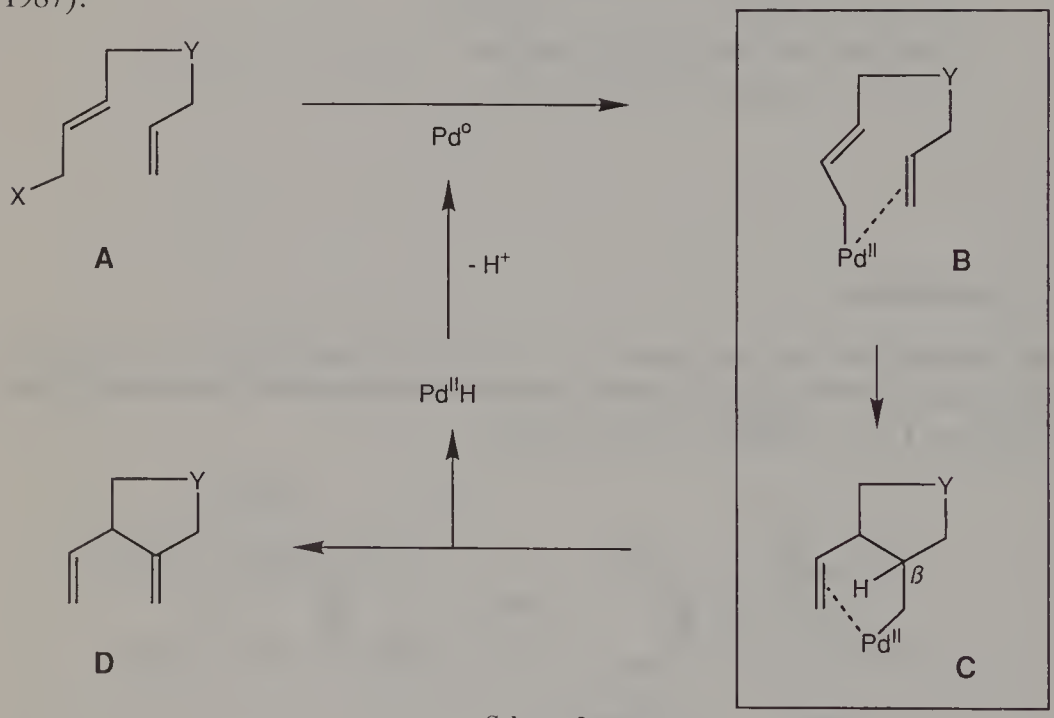
synthesis. Numerous strategic applications in natural product synthesis attest to their utility (Oppolzer, 1989, 1991). We then became interested in extending the scope of metallo-ene reactions to the transfer of transition metals which hold greater potential in terms of functional group compatibility and stereochemical control. At the outset of our studies it was known that stoichiometric amounts of allylpalladium complexes can be added to norbornenes and 1,3-dienes but not to simple olefins. Hence, at first sight, this did not look like a synthetically useful reaction. None the less, in 1987 we introduced a *catalytic* and *more general* process which centers on an entropically favored intramolecular palladium-ene step **B** → **C** (Scheme 2) (Oppolzer and Gaudin, 1987).



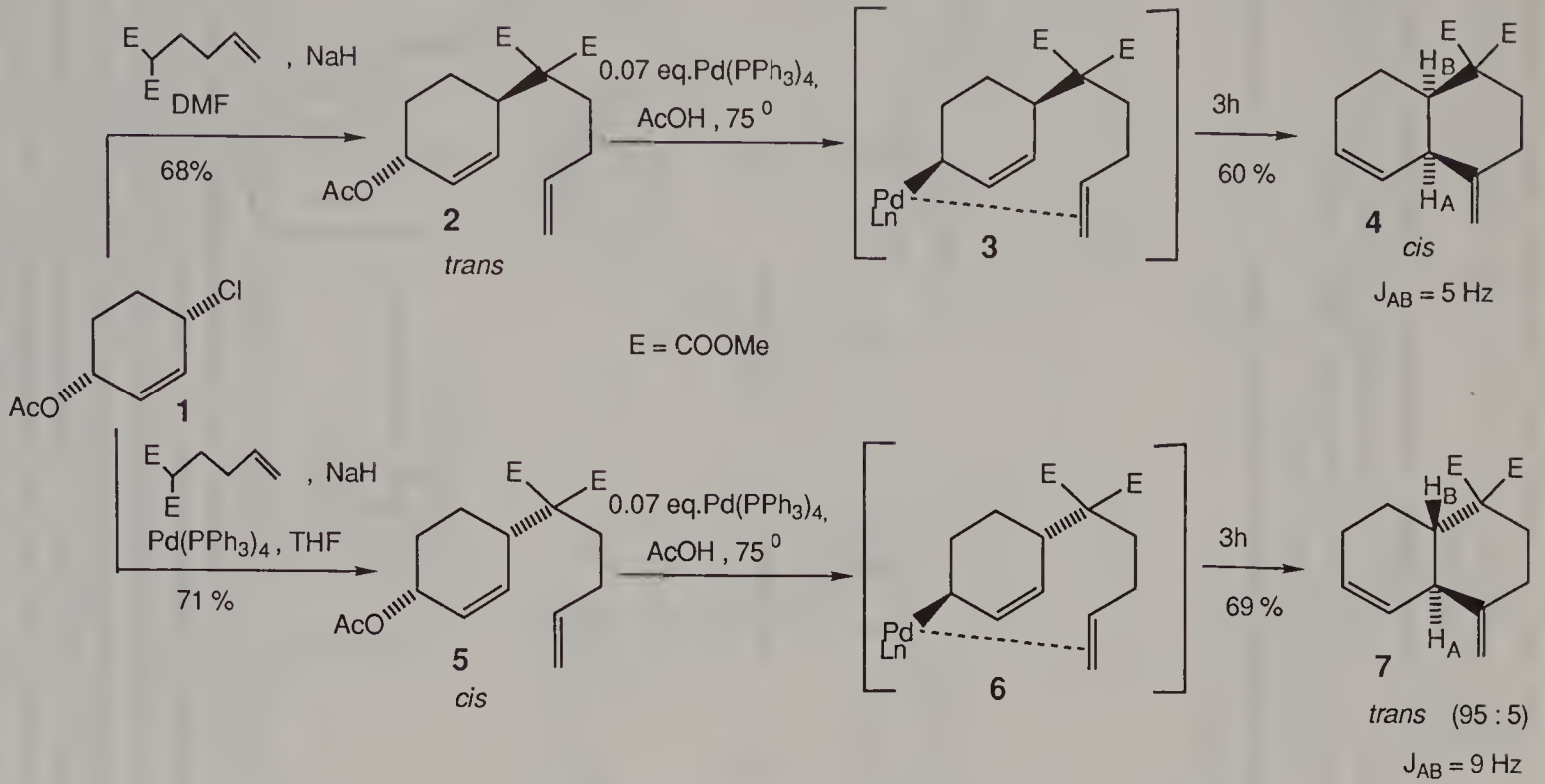
Scheme 2

A subsequent β-hydride elimination (**C** → **D**) regenerates a Pd(0) species which continues the catalytic cycle by oxidative addition to allyl derivates **A** (e.g. X = OR), thus providing *in situ* the alkenic allylpalladium intermediates **B**. This account will focus on several synthetically important features of the transition metallo-ene process in combination with β-elimination or other catalyst regenerating termination steps. Stereochemical aspects will serve as a 'Leitmotiv' which accompanies us throughout this review.

2 Allylmetal–alkene cyclization/β-eliminations

2.1 Allyl faciality

The first stereochemical issue we dealt with was the question of whether the carbon–metal bond cleavage and carbon–carbon bond formation occur in a



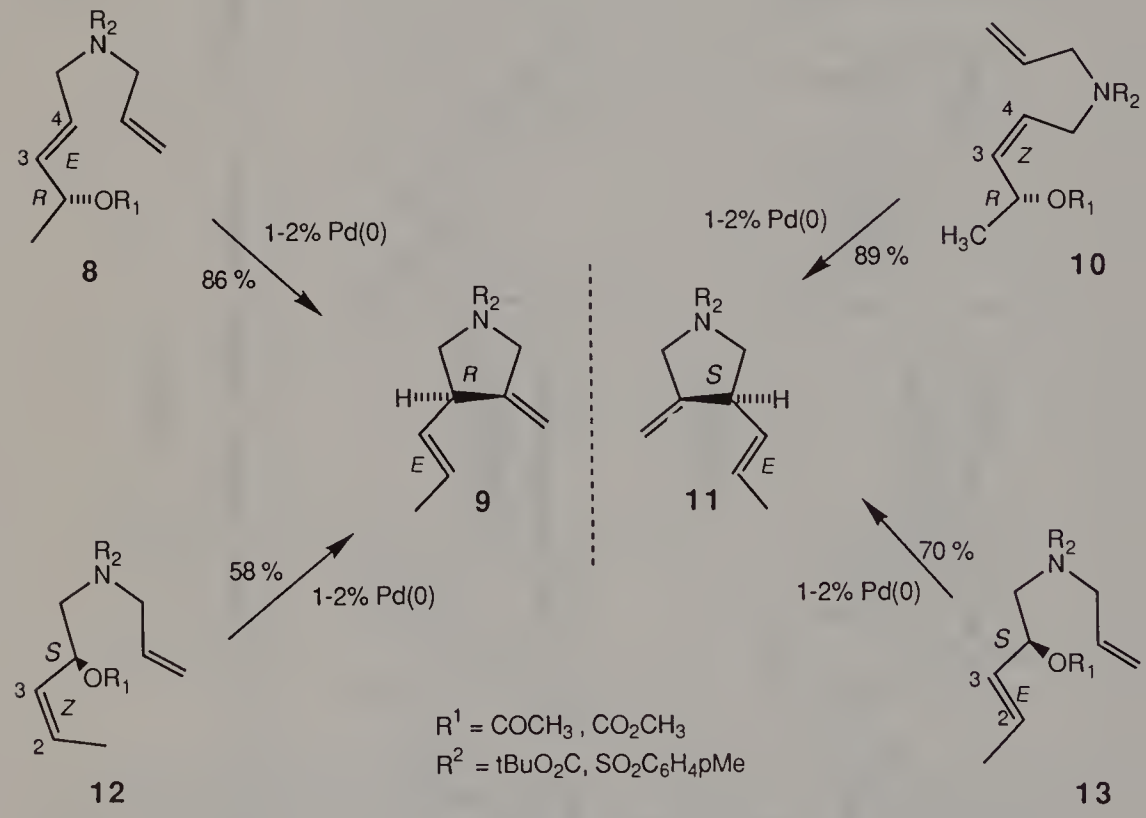
Efficient C-O → C-Pd → C-C Chirality Transfer: Enophile - Insertion *cis* to Palladium

Scheme 3

supra- or *antarafacial* manner relative to the allyl unit. Treatment of the *trans*- or *cis*-acetoxy-2-cyclohexenes **2** or **5** with Pd(0) furnished *cis*-fused octahydronaphthalene **4** (~100% specificity) from **2** or the *trans*-annulated product **7** (95% specificity) from **5** (Scheme 3).

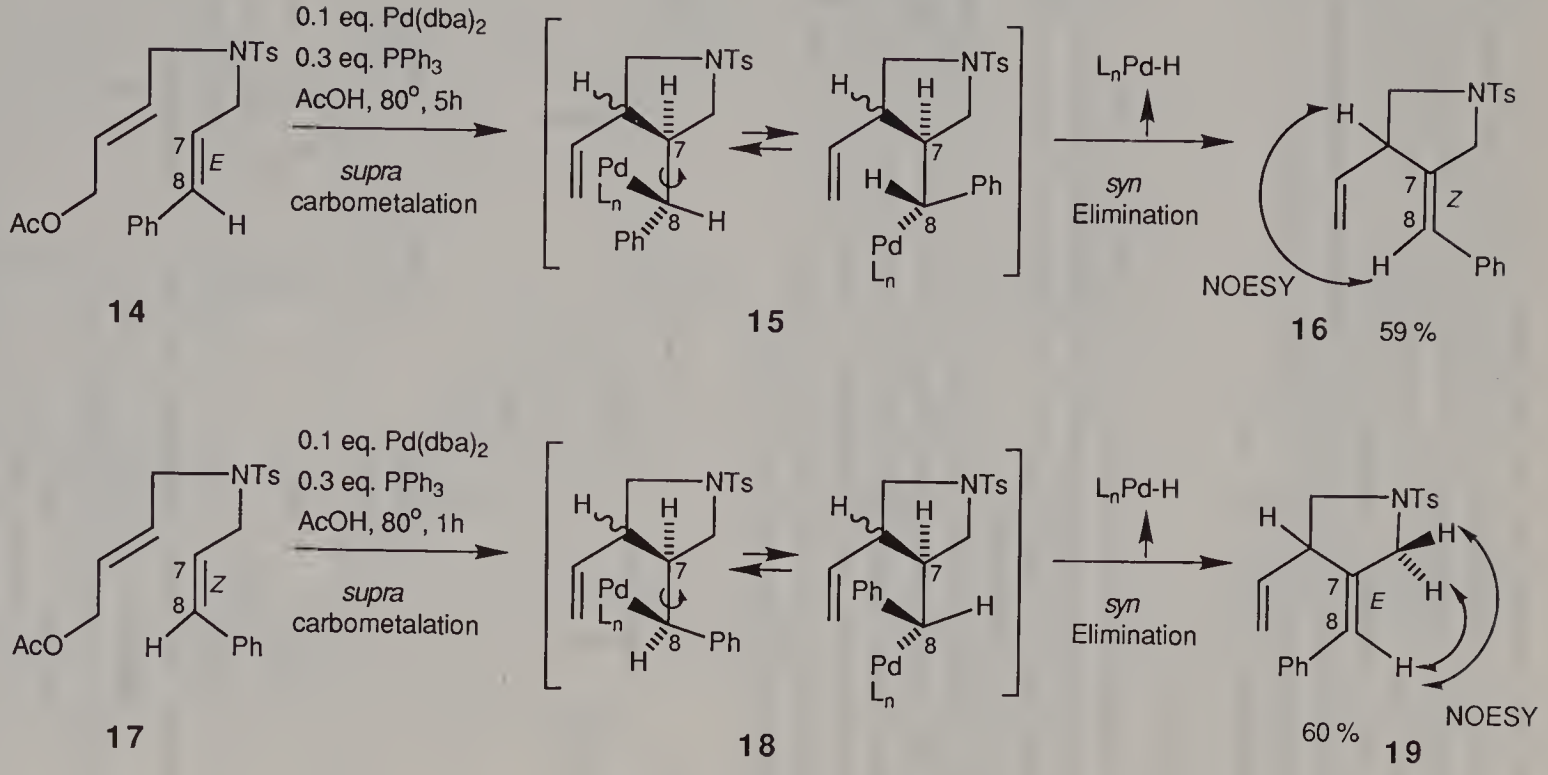
This topicity implies conventional displacement of the acetate group by Pd(0) with inversion (**2** → **3** or **5** → **6**); more notably, the alkene moiety attacks the allylpalladium unit *cis* relative to the metal (suprafacially) in the second step **3** → **4** or **6** → **7** (Oppolzer *et al.*, 1988).

This stereospecific tandem oxidative addition/allylation was also extended to *acyclic* substrates (Scheme 4).



Scheme 4

Indeed, palladium-catalyzed cyclization of (*E*)-dienyl acetates or carbonates gave (*E*)-propenylpyrrolidines with net inversion at the allylic center and with retention of the olefinic (*E*)-configuration (**8** → **9** and **13** → **11**). On the other hand, net retention at the allylic center coupled with *Z* → *E* isomerization was observed on analogous cyclization of the corresponding (*Z*)-dienes (**12** → **9** and **10** → **11**). This specific C–O/C–Pd/C–C chirality transfer (96–97%) reflects the conformational mobility of the acyclic π-allylpalladium intermediates which undergo complete π-σ-π *anti* → *syn* isomerization prior to a suprafacial allylpalladium/alkene insertion (Oppolzer *et al.*, 1990a). Hence diastereo- and enantiomerically pure ring systems can be readily synthesized in a predictable manner from chiral allyl alcohols.


0.1 eq. Pd(dba)2
0.3 eq. PPh3
AcOH, 80°, 5h
supra
carbometalation
LnPd-H
syn
Elimination
NOESY
14
15
16
59 %
0.1 eq. Pd(dba)2
0.3 eq. PPh3
AcOH, 80°, 1h
supra
carbometalation
LnPd-H
syn
Elimination
NOESY
17
18
19
60 %

Scheme 5

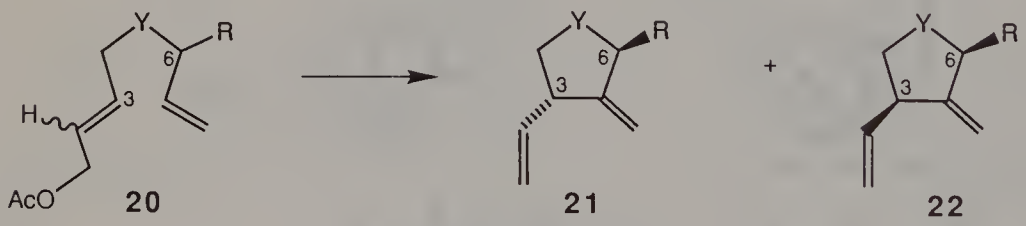
2.2 Alkene faciality

We then studied the faciality of the palladium allylation of the olefinic 'enophile' (Scheme 5). Pd(0)-catalyzed cyclization of (*E*)-styrene **14** furnished stereospecifically the (*Z*)-benzylidenepyrrolidine **16**. The corresponding (*E*)-isomeric product **19** was obtained exclusively from the (*Z*)-styrene **17**. These cyclizations involving efficiently controlled generation of a trisubstituted olefinic bond are consistent with a suprafacial formation of the carbon–carbon and carbon–palladium bonds (**14** → **15** and **17** → **18**) followed by a *syn*-elimination of palladium hydride.

2.3 Resident stereocenters

Another stereochemical issue concerns the topological influence of pre-existing over developing stereogenic centers in the carbometallation step **B** → **C**. Scheme 6 shows the stereodirecting effect of a C(6)-substituent on cyclization of 1-acetoxy-2,7-octadienes **20**.

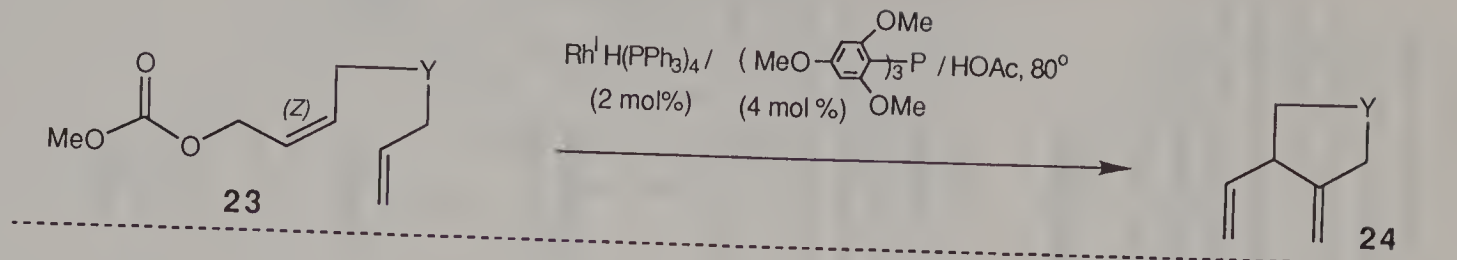
It is interesting to note that the nickel-ene cyclization is significantly more selective than the palladium-catalyzed ring closure. Thus, Ni(0) catalysis provided almost exclusively *trans*-disubstituted five-membered rings **21**. *Trans*-substituted tetrahydrofuran and cyclopentane products were also obtained with over 97% selectivity on nickel-catalyzed cyclization of C(4)-substituted 1-acetoxy-2,7-octadienes (Oppolzer *et al.*, 1990a,b).

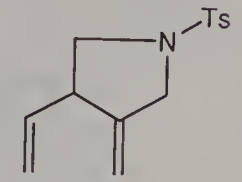


Y	R	Catalyst [a] (mol %)	Yield 21 + 22	Ratio 21 / 22
O	*n*-C_6H_{13}	Pd (5)	62	52 : 48
O	*n*-C_6H_{13}	Ni (10)	79	> 99 : < 1
CH_2	CH_2OBn	Pd (10)	67	72 : 28
CH_2	CH_2OBn	Ni (10)	88	97.3 : 2.7

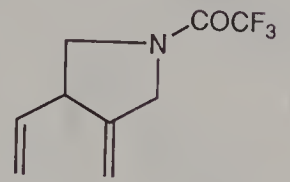
a) Pd = $Pd(dba)_2$ / PPh_3 (1:3), AcOH, 80°C; Ni = $Ni(COD)_2$, dppb (1:1), THF, 20 - 51°C

Scheme 6

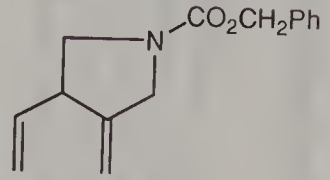




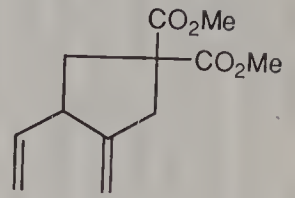
24a 80 %



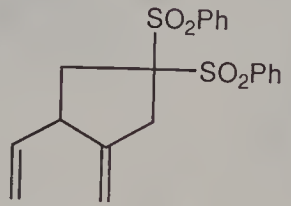
24b 83%



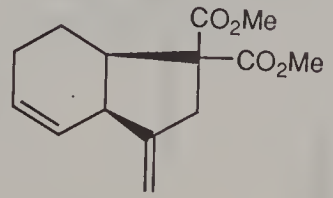
24c 60 %



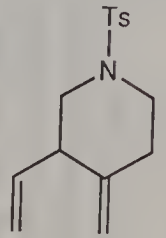
24d 75 %



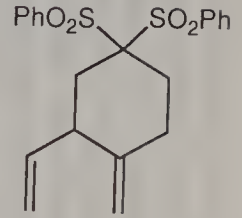
24e 88 %



(5 % Rh)
24f 60 %



(8 % Rh)
24g 65 %



(8 % Rh)
24h 55 %

Scheme 7

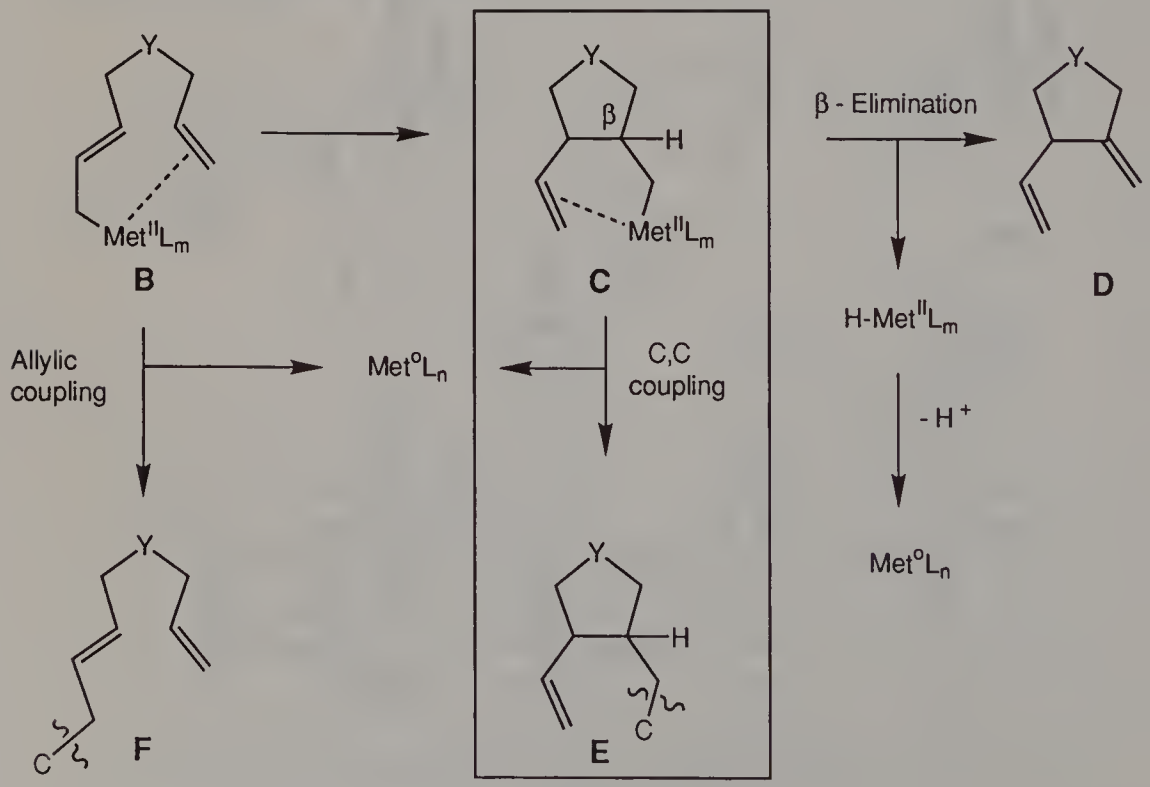
2.4 Rhodium(I) catalysis

Very recently, we accomplished smooth cyclizations **23** → **24**, catalyzed by 2 mol% of $RhH(PPh_3)_4$ (Scheme 7). We conclude that this reaction resembles closely its Pd(0)- and Ni(0)-catalyzed versions, i.e. that oxidative addition of Rh(I) to allylcarbonate **23** forms an Rh(III)-allyl intermediate which undergoes an intramolecular alkene *cis*-insertion, followed by elimination of rhodium(III) hydride. Subsequent deprotonation of the metal hydride regenerates the Rh(I) catalyst. The rhodium-ene cyclization may offer new stereochemical perspectives owing to the octahedral-hexacoordination of Rh(III) complexes. Pd(II) and Ni(II) complexes are planar tetracoordinated.

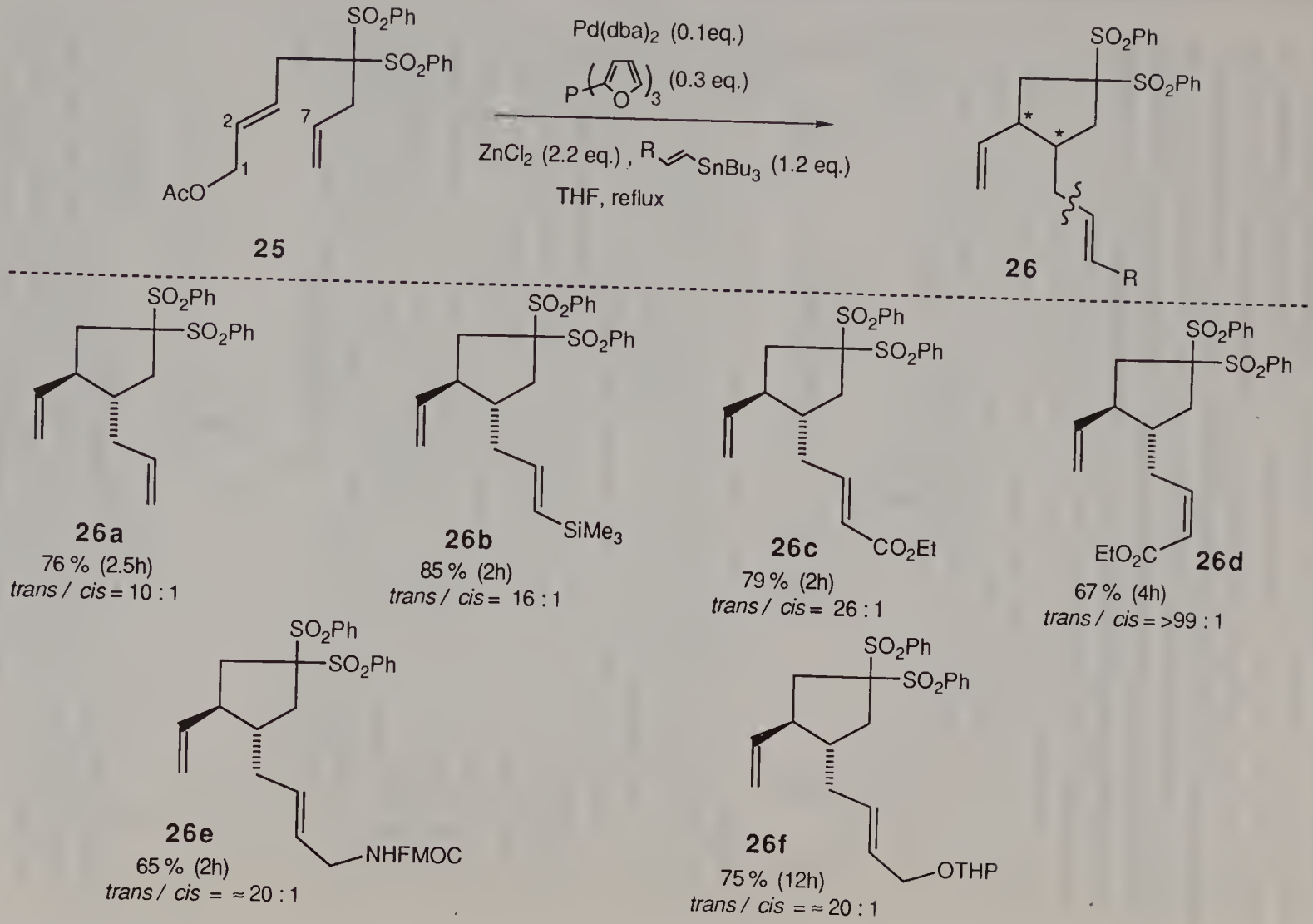
3 Allylpalladium–alkene (alkyne) cyclization/alkenylstannane coupling

It is particularly attractive to replace the β-hydride elimination step **C** → **D** by trapping the transient σ-alkylmetal species by means of C,C coupling reactions with simultaneous regeneration of the catalyst (**C** → **E**) (Scheme 8). This requires not only that the trapping process **C** → **E** is faster than the β-hydride elimination **C** → **D**, but also that the allylation step **B** → **C** prevails over allylic coupling **B** → **F**.

Scheme 9 shows how it is possible to intercept σ-palladium complexes **C** with vinylmetal reagents.



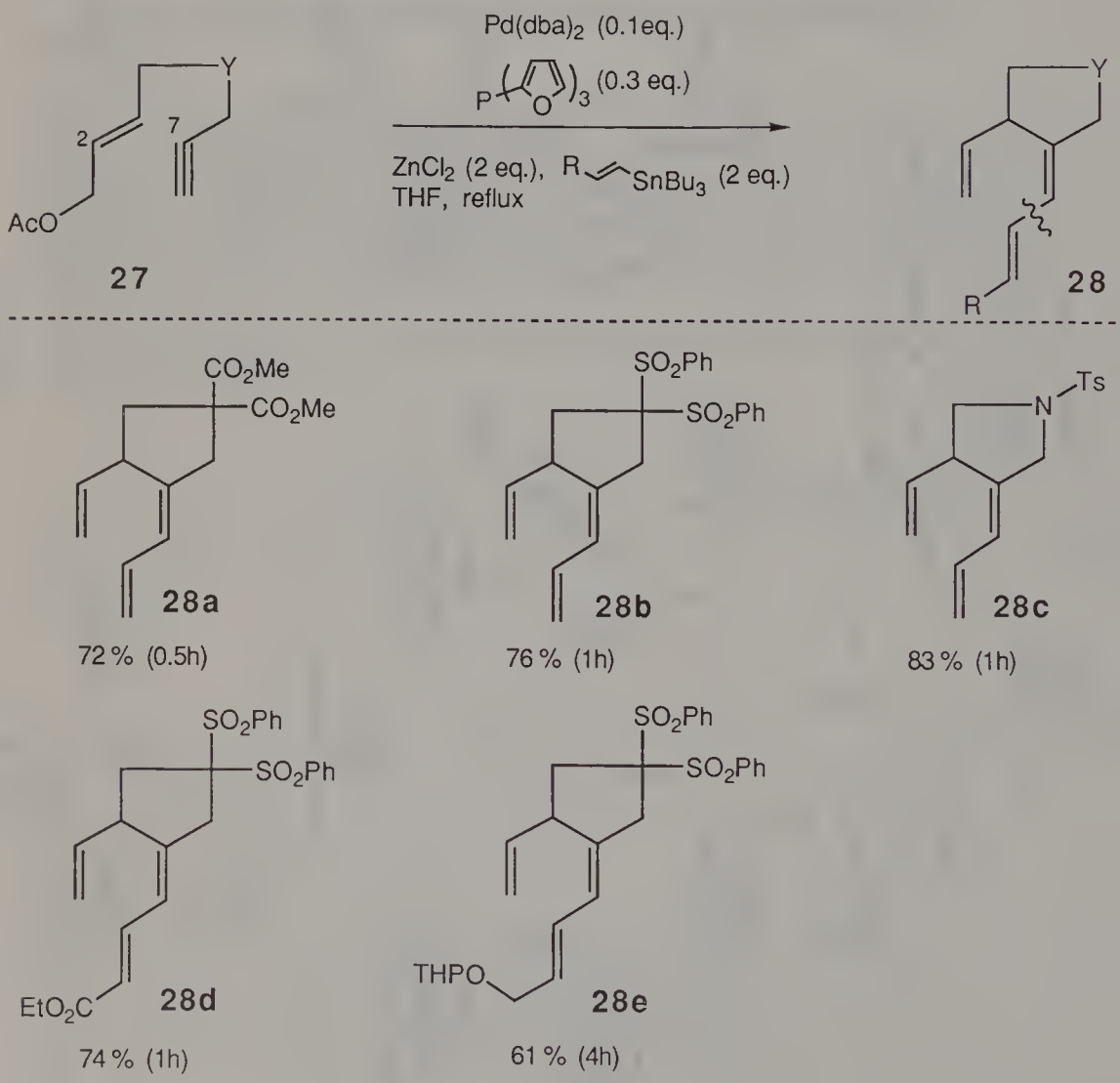
Scheme 8


SO2Ph
SO2Ph
2
7
1
AcO
25
Pd(dba)2 (0.1eq.)
P(O)3 (0.3 eq.)
ZnCl2 (2.2 eq.), R SnBu3 (1.2 eq.)
THF, reflux
SO2Ph
SO2Ph
26
R
26a
76 % (2.5h)
trans / cis = 10 : 1
26b
SiMe3
85 % (2h)
trans / cis = 16 : 1
26c
CO2Et
79 % (2h)
trans / cis = 26 : 1
EtO2C
26d
67 % (4h)
trans / cis = >99 : 1
26e
NHFMOC
65 % (2h)
trans / cis = ≈ 20 : 1
26f
OTHP
75 % (12h)
trans / cis = ≈ 20 : 1

Scheme 9

Palladium*bis*(dibenzylideneacetone)/tri(2-furyl)phosphine-catalyzed cyclizations of acetoxydiene **25** in the presence of 1-alkenyltributylstannane and zinc dichloride provided *trans*-substituted 3-alkenyl-4-vinylcyclopentanes **26** in good yields. Analogous intramolecular carbometallation/C,C-coupling of acetoxyenynes **27** furnished, stereospecifically, cyclic trienes **28** (Scheme 10) (Oppolzer and Ruiz-Montes, 1993).

The configuration of the exocyclic trisubstituted (conjugated) olefinic bond corresponds to allylpalladium/alkyne *syn*-insertion followed by C,C coupling with retention.



Scheme 10

4 Allylmetal–alkene (alkyne) cyclization/carbonylation

4.1 Ligand dependence

The combination of palladium- and nickel-ene cyclizations with carbonylation reactions is synthetically most appealing. The reaction course can critically depend on the nature of the metal ligands. For example, $Ni(CO)_3PPh_3$ (25 mol%) in THF/MeOH under CO (1 atm, r.t.) readily catalyzed the conversion of iodoenyne **29** to a 3:5 mixture of monocyclized (*Z*)-ester **31** and bicyclo[3.3.0]octanone **32** (Scheme 11). However, more advantageously, complete bicyclization **29** → **32**, involving insertion of two CO molecules, could be achieved when using the bidentate ligand DPPB (Oppolzer *et al.*, 1989). Scheme 12 highlights the substituent-controlled stereoselective formation of four carbon–carbon bonds in a single process catalyzed by DPPB-coordinated nickel(0).

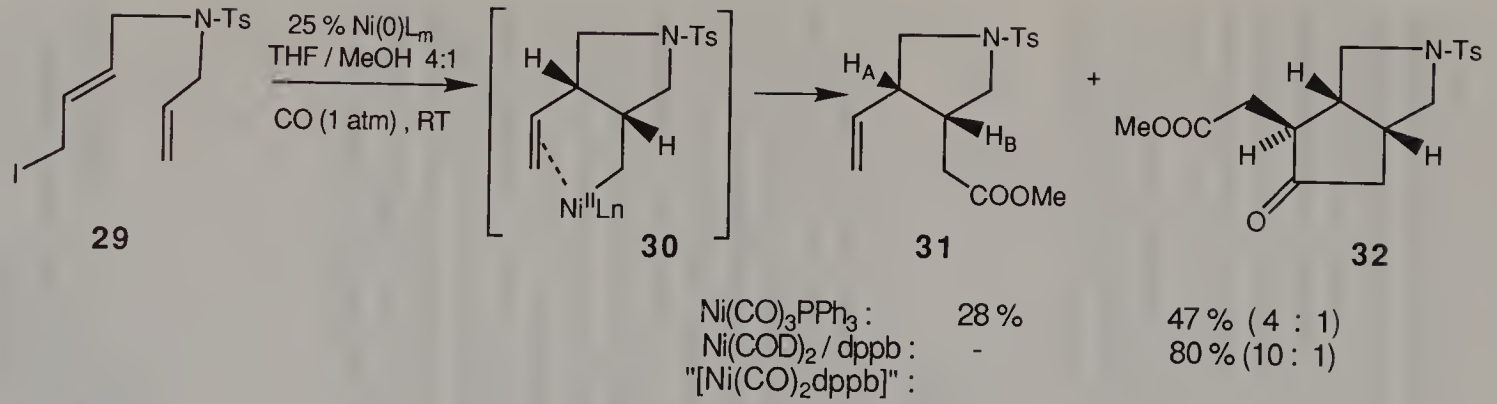
4.2 Relative 'ene/enophile' faciality

Schemes 11 and 12 show a clear predominance of products derived from a cyclized intermediate (e.g. from **30**) with *cis*-disposed nickel donor and acceptor sites. The opposite relative faciality was found on palladium(0)-catalyzed allylation/carbonylation of acetoxydiene **36** which provided (after esterification) only the *trans*-methyl ester **38** (Scheme 13) (Oppolzer *et al.*, 1989). This result parallels the formation of *trans*-substituted cyclopentanes **26** when subjecting acetoxydiene **25** to the palladium(0)-catalyzed cyclization/alkenylstannane trapping protocol (cf. Scheme 8). However, examination of models allowed us to predict that a (*Z*)-palladiumallyl unit is unlikely to yield a *trans*-substituted five-membered ring system. Consequently, if the allylpalladium unit is part of a conventional ring (e.g. in **40**) only *cis*-substituted products should be expected. Indeed, treatment of cyclohexenylacetate **39** with $Pd(DBA)_2/PPh_3$ under CO in AcOH, addition of water and esterification afforded exclusively all *cis*-hexahydroindole **41** (Scheme 14) (Oppolzer *et al.*, 1989).

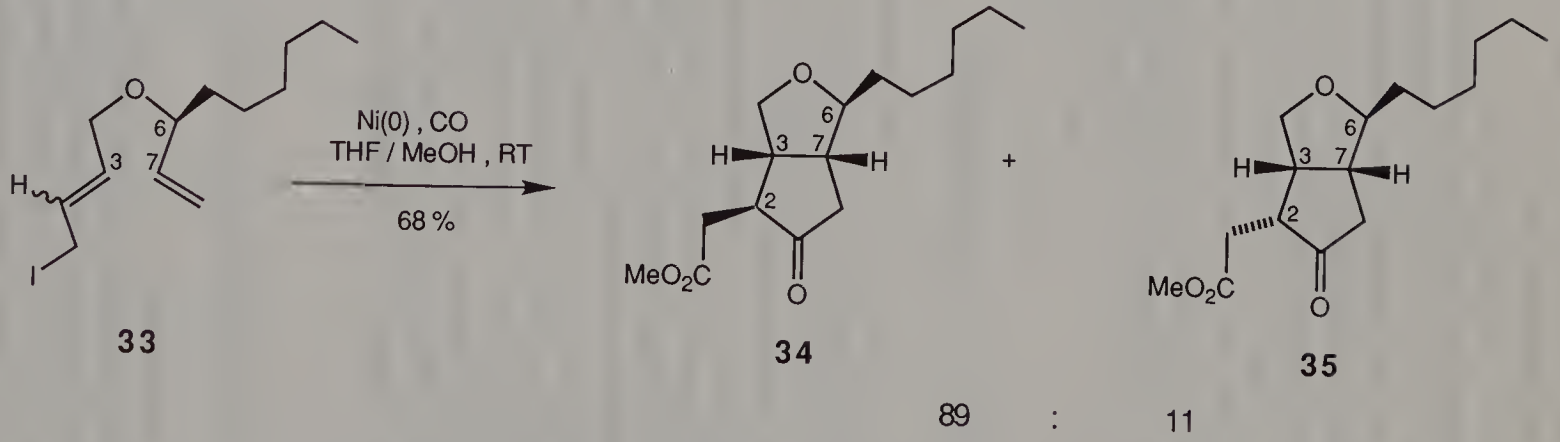
4.3 Strategic applications in synthesis

4.3.1 Fenestranes

A striking example is the efficient synthesis of the [5.5.5.5.]fenestrane **43** by palladium-catalyzed cyclization/carbonylation of bicyclic acetoxydiene **42** (Scheme 15) (Keese *et al.*, 1992). Thus, four carbon–carbon bonds and four stereocenters were formed selectively in a single operation.

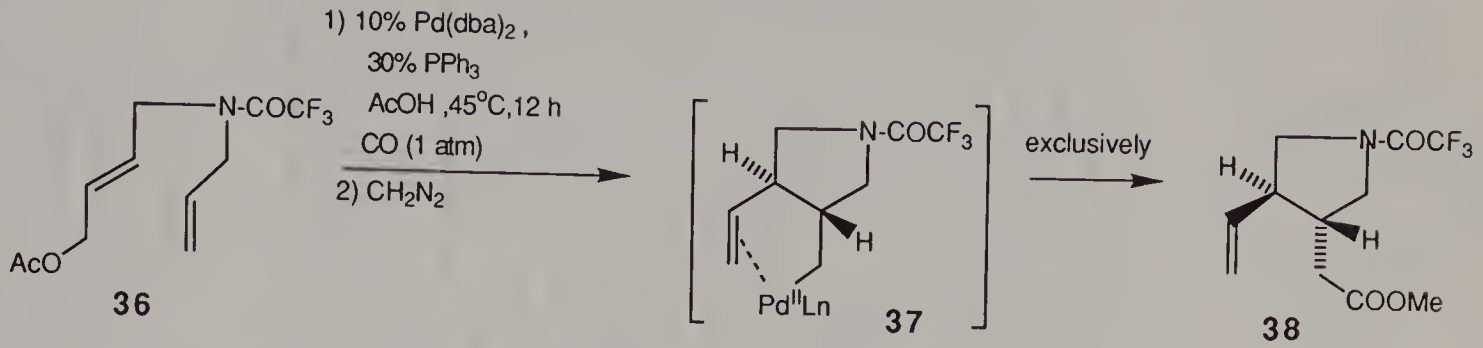


Scheme 11



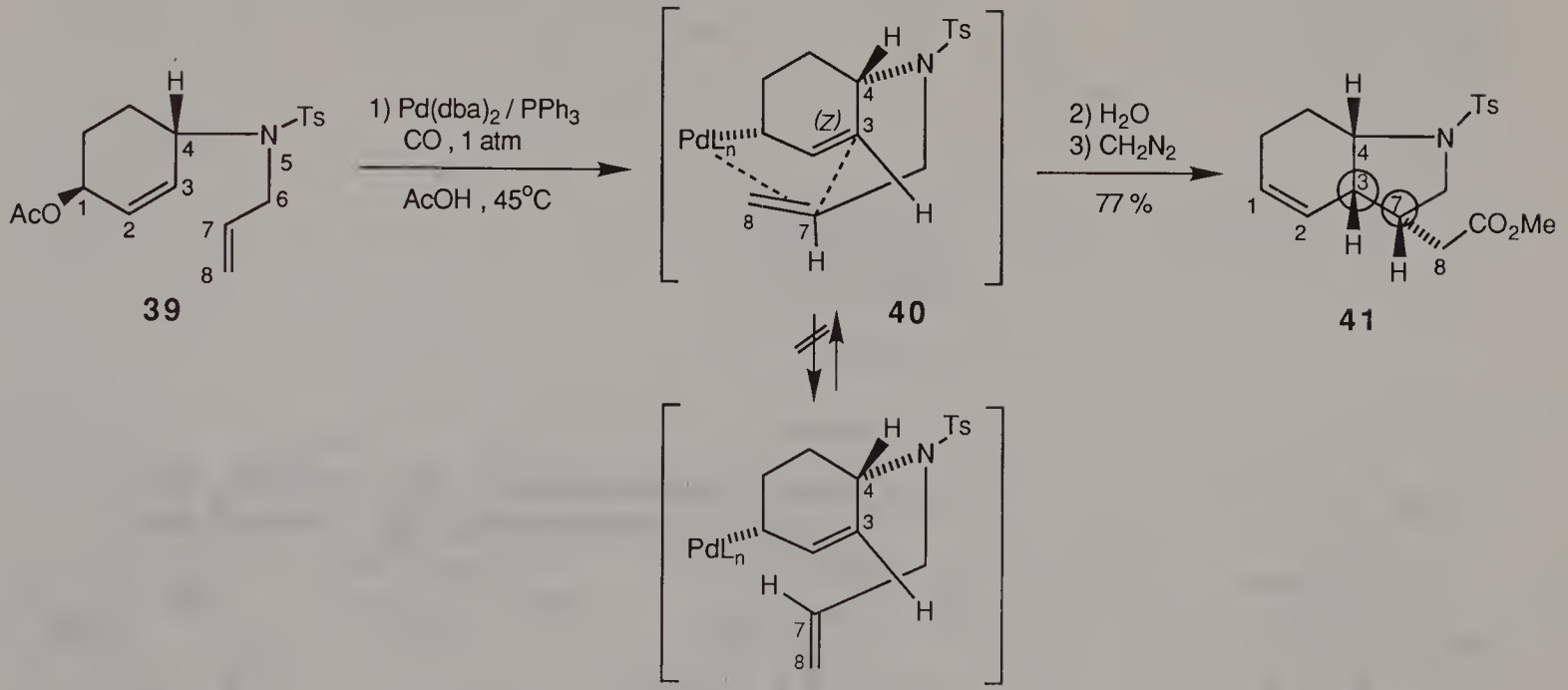
∴ Nickel - Ene Step ~ 100 % Stereocontrolled

Scheme 12

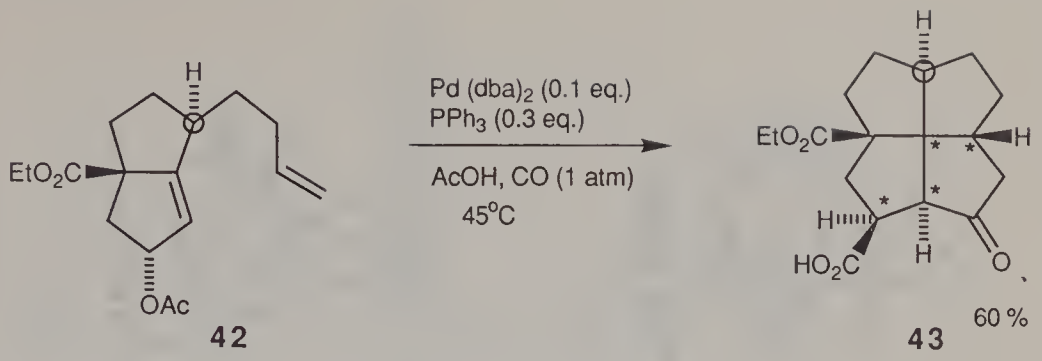


∴ Ni(0) - catalysis : *Exo* - Diastereoselectivity (→ *cis*)
Pd(0) - catalysis : *Endo* - Diastereoselectivity (→ *trans*)

Scheme 13



Scheme 14



Scheme 15

4.3.2 Triquinane sesquiterpenoids

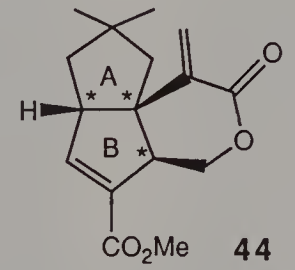
The potential of Pd- and Ni-catalyzed 'ene-type cyclization'/carbonylation protocols for the synthesis of fused five-membered ring systems is amply demonstrated by their employment in the synthesis of pentalenolactone E methyl ester **44**, coriolin **45** and hirsutene **46**. All three approaches feature a stereocontrolled bicyclization **G** → **H** (Scheme 16). Thus, Pd-catalyzed allylation/carbonylation of alkyne **48**, followed by esterification, provided pure bicyclooctenone **49** in 57% yield (Scheme 17) (Oppolzer *et al.*, 1991b). Catalytic hydrogenation of the olefinic bond, acetalization and *Barton* degradation of methyl ester **50** furnished nor-alcohol **51** which had been previously converted into (±)-pentalenolactone E methyl ester **44**.

A formal synthesis of coriolin **45** was designed around the Ni(0)-catalyzed tandem alkene allylation/carbonylation reaction of iododiene **53** giving a mixture of bicyclic ketoester **54** and isomeric lactone **55** (Scheme 18) (Oppolzer and Ando, 1992). In this step, the developing centers C(9), C(2) and C(3) were completely controlled by the pre-existing stereocenter C(1). The non-separated mixture **54** + **55** was then readily transformed into the advanced intermediate **57**, previously employed for the synthesis of (±)-coriolin **45**.

A total synthesis of (±)-hirsutene **46** features the 'palladium-ene'/carbonylation reaction of enynyl carbonate **59** which afforded bicyclooctenone **60** with 85% diastereoselective control of angular and quaternary centers. The third ring was subsequently closed by a radical/alkene addition **61** → **62** (Scheme 19).

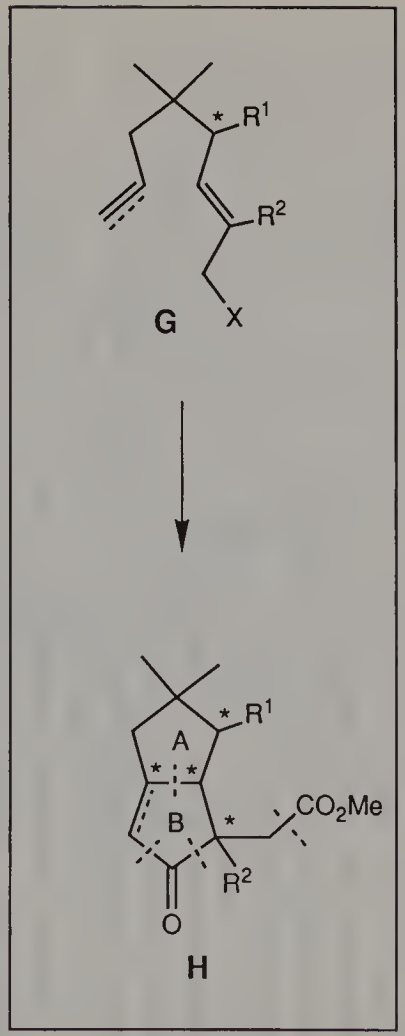
4.3.3 (+)-3-Isorauniticine

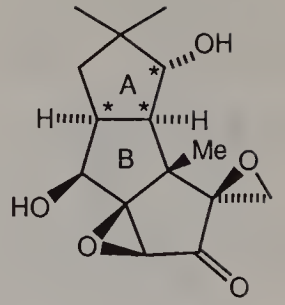
An enantioselective construction of 3-isorauniticine (**63**) (Oppolzer *et al.*, 1991a) starts with the generation of the resident stereocenter C(3) by asymmetric C-alkylation of chiral glycinate equivalent **67**. This center induces the new centers C(15) and C(20) in the strategic Pd-catalyzed allylation/carbonylation/β-elimination cascade **65** → **64** (Schemes 20 and 21). After chromatographic removal of the minor C(20)-epimer, bicyclic product **64** was obtained in 52% yield. The remaining steps involved catalytic hydrogenation of **64** and Baeyer–Villiger oxidation which yielded lactone **69** (Scheme 22).



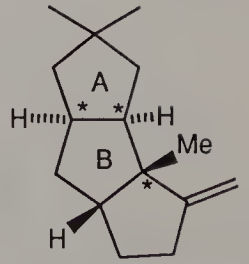
44

Pentalenolactone E
Methyl Ester



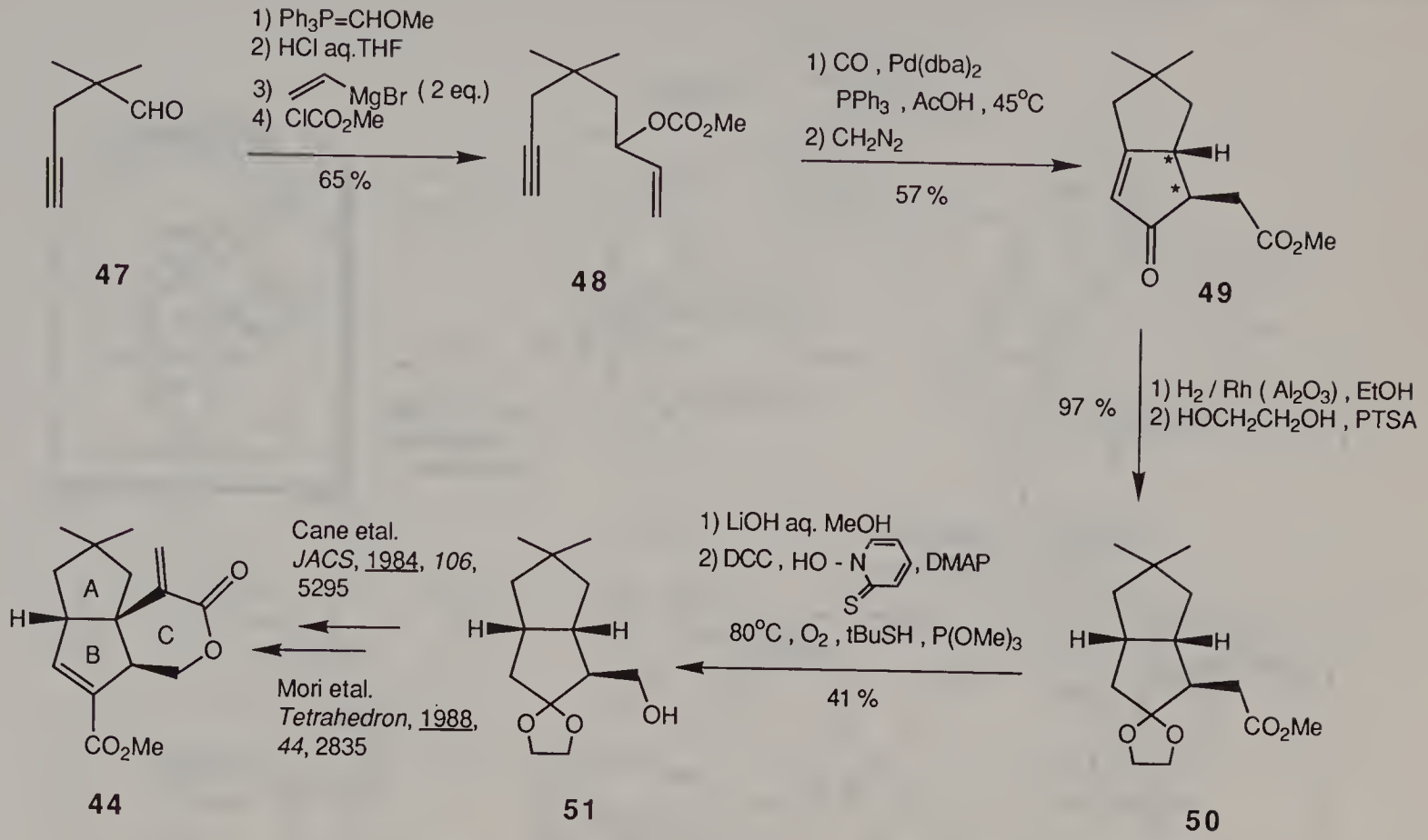


45 Coriolin

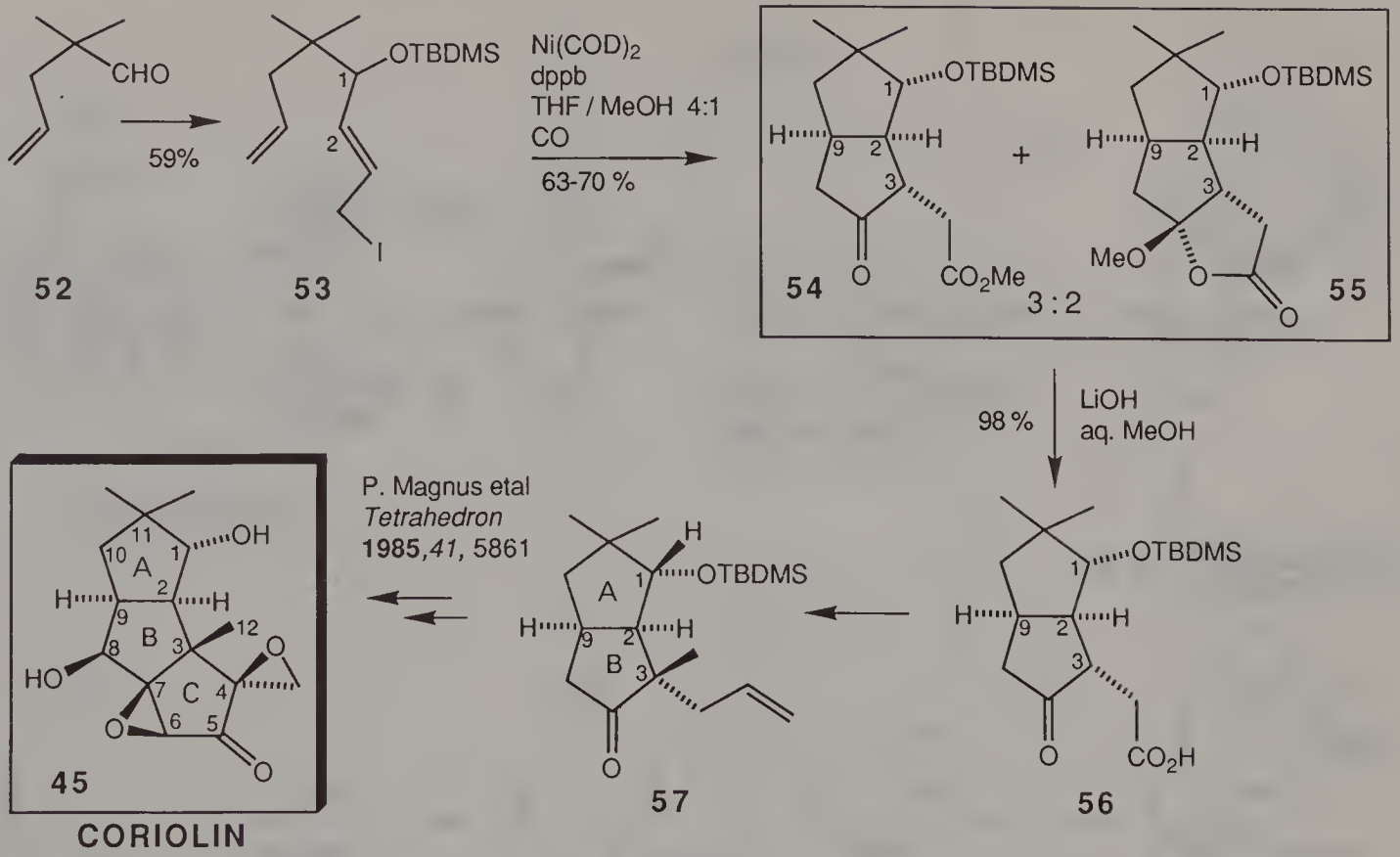


46 Hirsutene

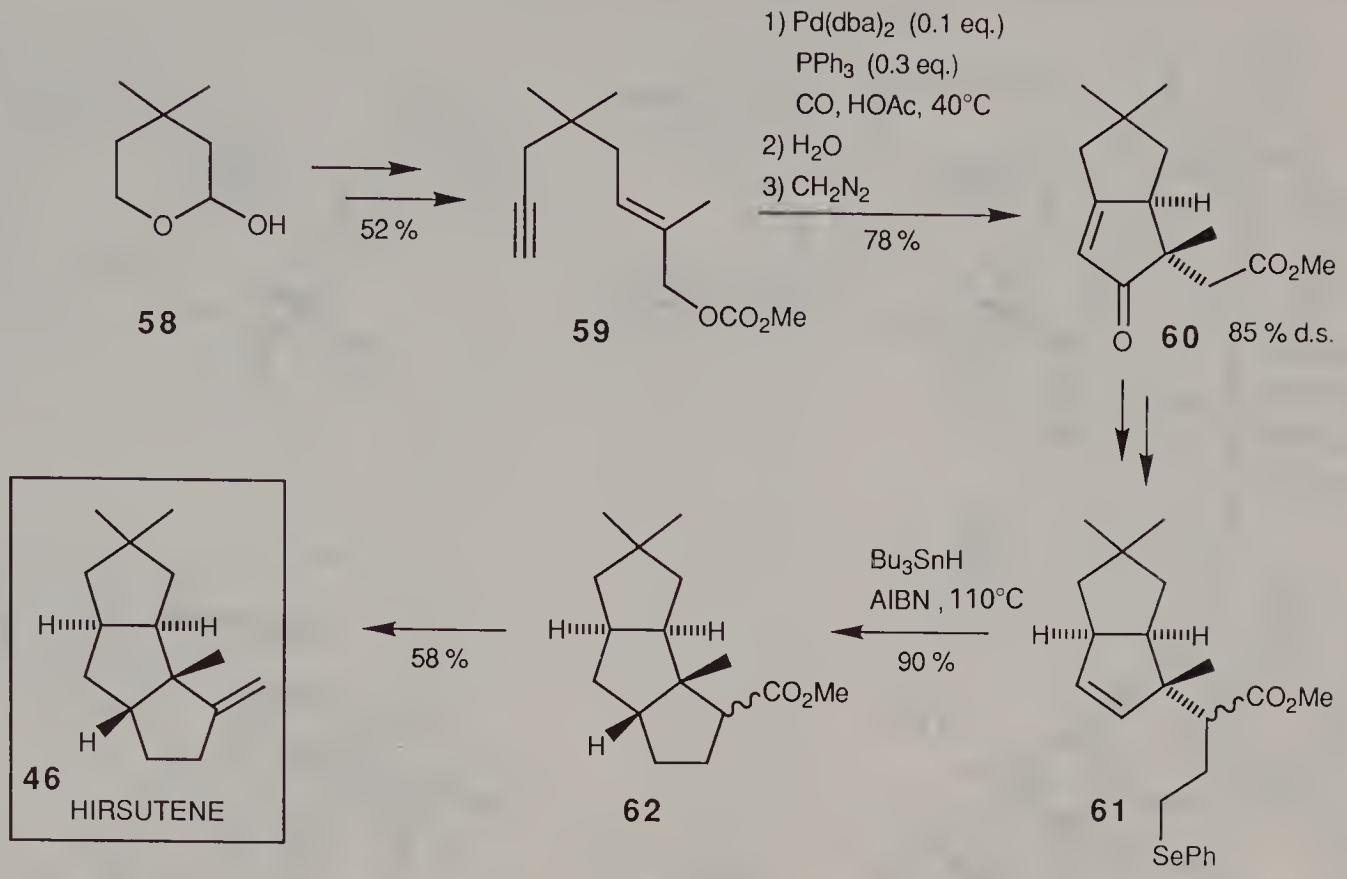
Scheme 16


1) Ph3P=CHOMe
2) HCl aq.THF
3) MgBr (2 eq.)
4) ClCO2Me
65 %
1) CO , Pd(dba)2
PPh3 , AcOH , 45°C
2) CH2N2
57 %
97 %
1) H2 / Rh (Al2O3) , EtOH
2) HOCH2CH2OH , PTSA
1) LiOH aq. MeOH
2) DCC , HO - N , DMAP
80°C , O2 , tBuSH , P(OMe)3
41 %
Cane etal.
JACS, 1984, 106, 5295
Mori etal.
Tetrahedron, 1988, 44, 2835
47
48
49
50
51
44

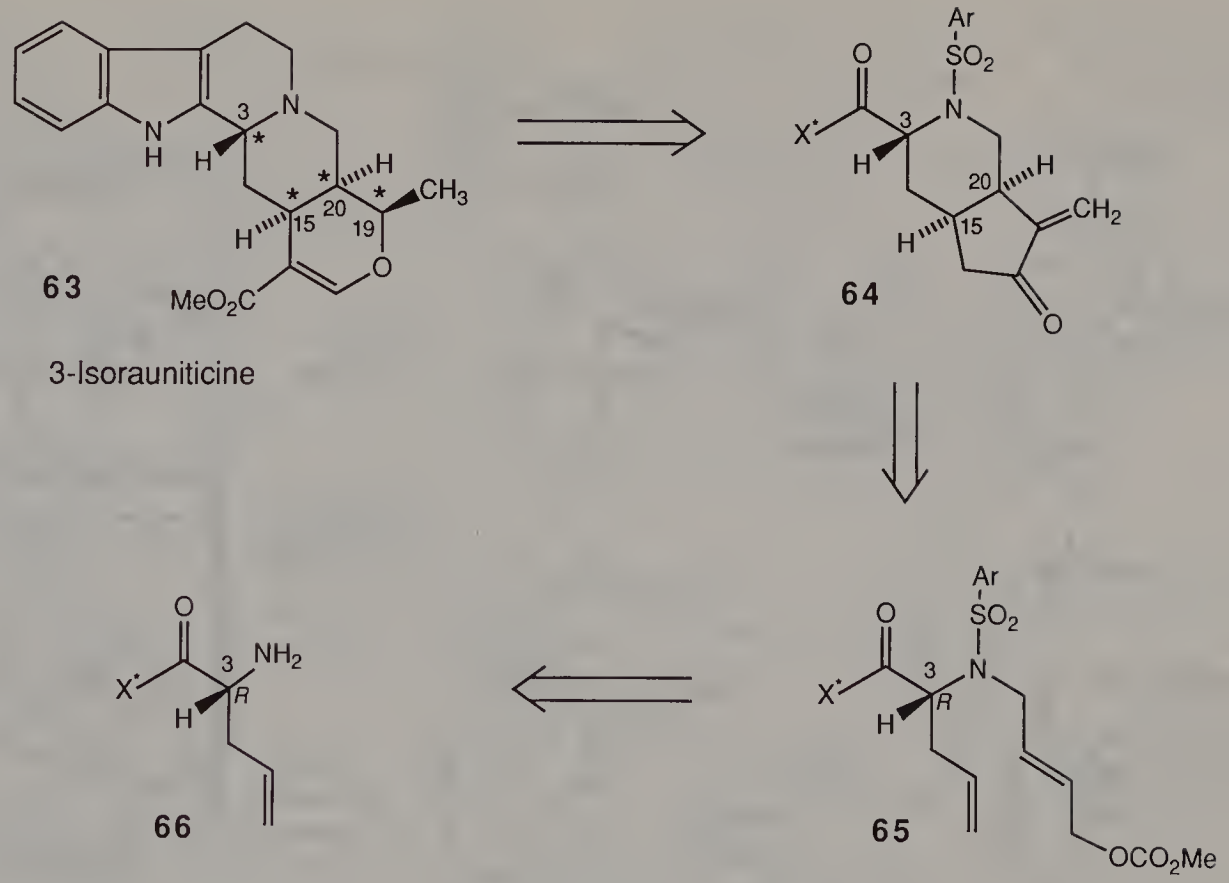
Scheme 17


CHO
59%
OTBDMS
I
52
53
Ni(COD)2
dppb
THF / MeOH 4:1
CO
63-70 %
OTBDMS
CO2Me
54
3 : 2
MeO
55
98 %
LiOH
aq. MeOH
OTBDMS
56
CO2H
P. Magnus etal
Tetrahedron
1985,41, 5861
OTBDMS
57
OH
HO
45
CORIOLIN

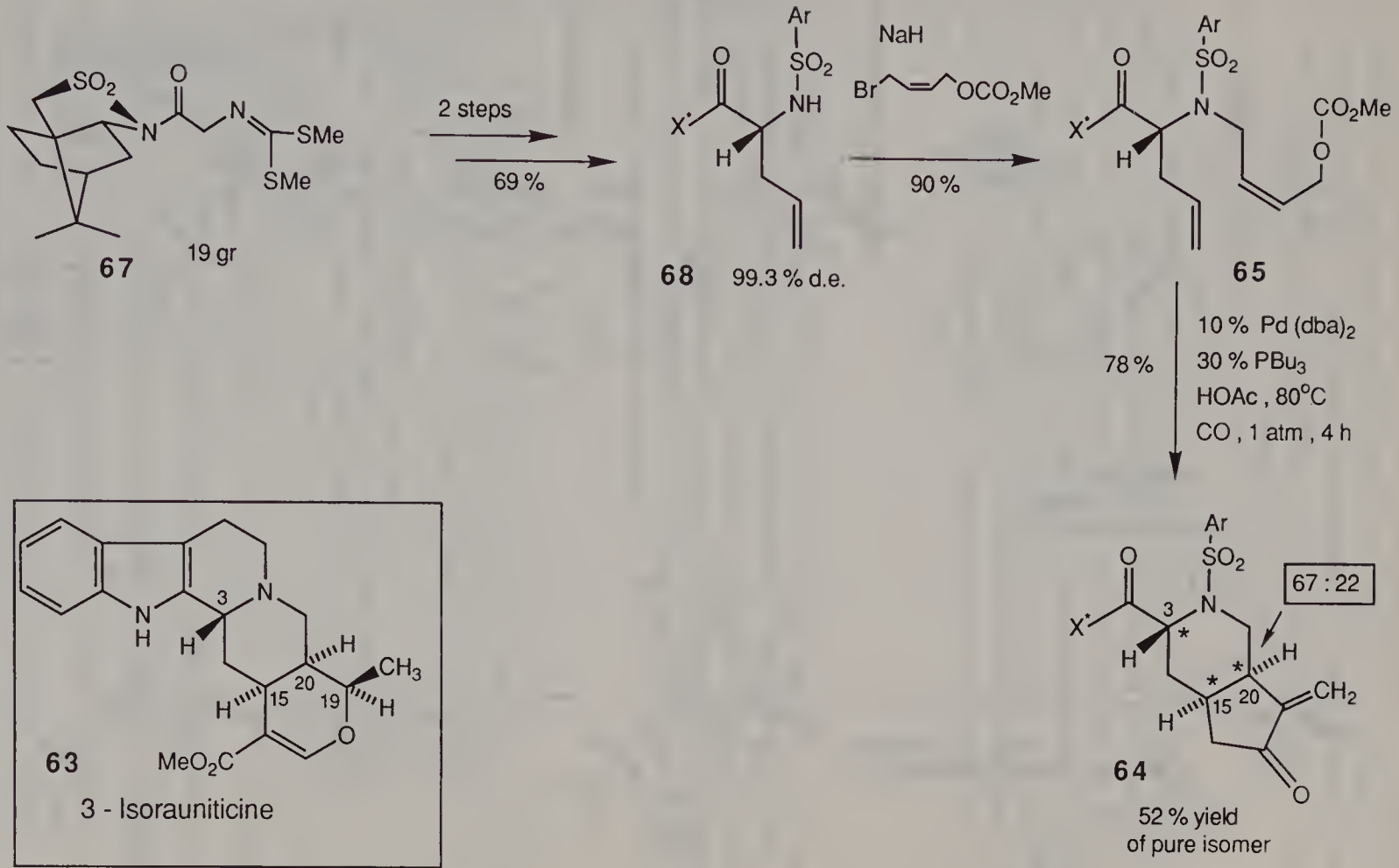
Scheme 18


1) Pd(dba)2 (0.1 eq.)
PPh3 (0.3 eq.)
CO, HOAc, 40°C
2) H2O
3) CH2N2
78 %
52 %
58
59
60
85 % d.s.
61
SePh
Bu3SnH
AIBN , 110°C
90 %
58 %
62
46
HIRSUTENE

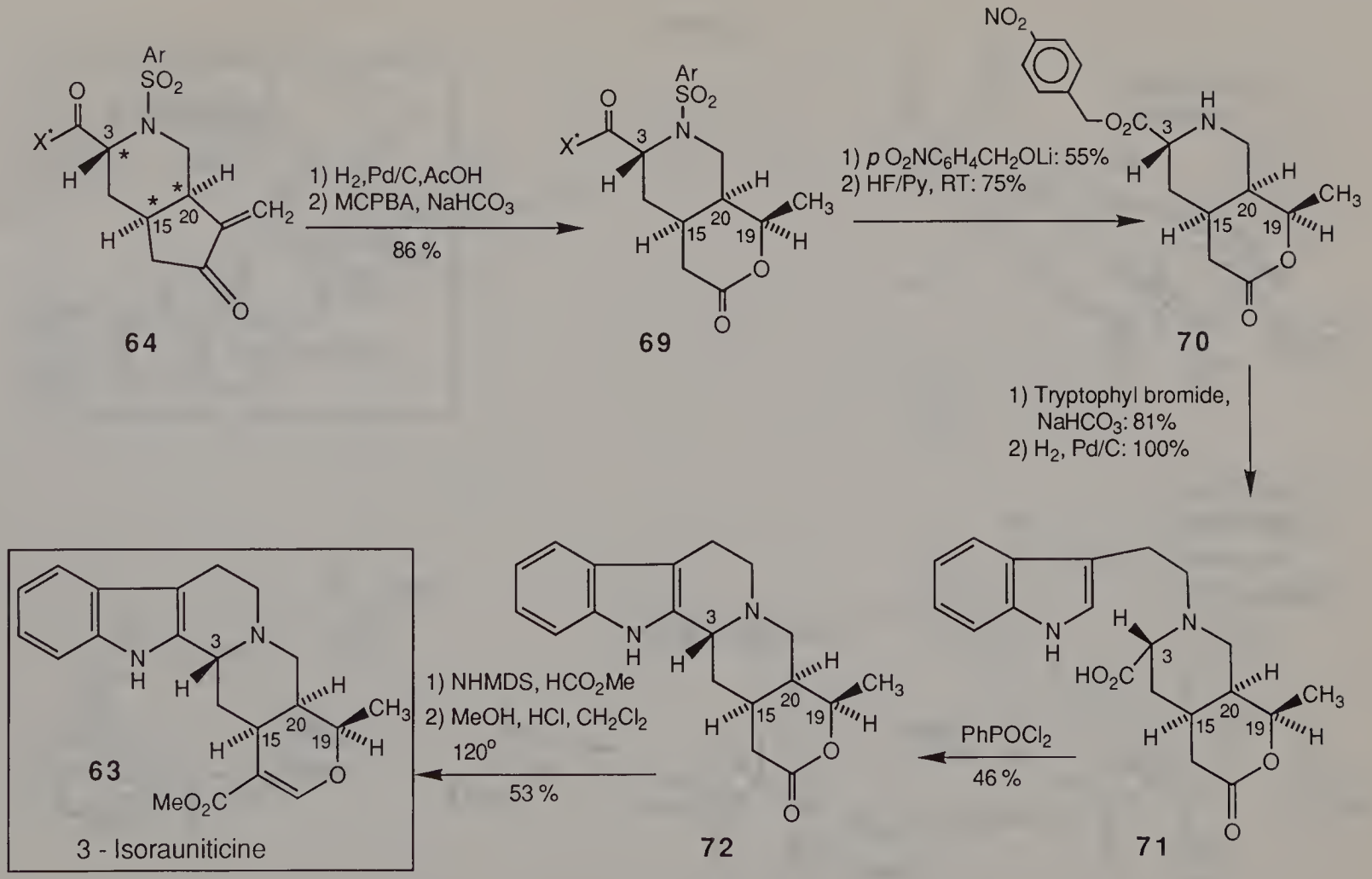
Scheme 19



Scheme 20


SO2
O
N
N
SMe
SMe
67
19 gr
2 steps
69 %
Ar
SO2
NH
O
X•
H
68
99.3 % d.e.
NaH
Br
OCO2Me
90 %
Ar
SO2
N
O
X•
H
CO2Me
O
65
78 %
10 % Pd (dba)2
30 % PBu3
HOAc , 80°C
CO , 1 atm , 4 h
67 : 22
Ar
SO2
O
X•
3
N
H
*
*
*
H
H
15
20
CH2
O
64
52 % yield
of pure isomer
N
H
3
N
H
H
CH3
H
15
20
19
H
O
MeO2C
63
3 - Isorauniticine

Scheme 21


Ar
SO2
X
O
3
N
H
15
20
CH2
64
1) H2,Pd/C,AcOH
2) MCPBA, NaHCO3
86 %
69
CH3
19
1) p O2NC6H4CH2OLi: 55%
2) HF/Py, RT: 75%
NO2
O2C
70
1) Tryptophyl bromide,
NaHCO3: 81%
2) H2, Pd/C: 100%
71
HO2C
PhPOCl2
46 %
72
1) NHMDS, HCO2Me
2) MeOH, HCl, CH2Cl2
120°
53 %
63
MeO2C
3 - Isorauniticine

Scheme 22

Removal of the chiral auxiliary, cleavage of the sulfonamide, *N*-alkylation with tryptophyl bromide and $PhPOCl_2$-mediated *Rapoport* cyclization of *N*-tryptophylamino acid **71** gave pentacyclic lactone **72**. Finally, formylation and acid-promoted *Korte* 'rearrangement' provided pure (+)3-isorauniticine **63**.

5 Conclusion

Palladium- and nickel-catalyzed intramolecular alkene (alkyne) allylations, combined with β-elimination, vinylstannane coupling or CO insertion reactions offer an attractive stereocontrolled route to five- and six-membered carbo- and heterocyclic systems. Analogous rhodium-catalyzed cyclizations hint at the possibility to extend this concept to further transition metal catalysts. Strategic applications to the syntheses of non-conventional or of naturally occurring structures testify to the battle-proven status of this reaction type.

Acknowledgements

It is a privilege to acknowledge the essential collaboration of J. Ruiz-Montes, A. Fürstner, A. J. M. Janssen, B. Stammen and C. Robyr whose work is not yet published. Those who have contributed, not less crucially, to published work are cited in the appropriate references. We thank the Swiss National Science Foundation, Sandoz Pharma Ltd., Basel and Givaudan-Roure AG, Dübendorf, for generous financial support.

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9

Perspectives in Supramolecular Chemistry: From Molecular Recognition towards Self-organization

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1 Introduction

Supramolecular chemistry has relied on more or less preorganized molecular receptors for effecting molecular recognition, catalysis and transport processes. A step further consists in the design of systems undergoing *molecular self-organization*, i.e. systems capable of spontaneously generating a well-defined supramolecular architecture by *self-assembling* from their components in a given set of conditions.

The *molecular information* necessary for the process to take place and the *algorithm* that it follows must be stored in the components and operate through selective molecular interactions. Thus, these systems may be termed *programmed supramolecular systems*, that generate organized entities following a defined plan based on molecular recognition events (Lehn, 1990). Several approaches to self-assembling systems have been pursued. *Mesophases and liquid crystalline polymers* of supramolecular nature have been generated from complementary components, amounting to macroscopic expression of molecular recognition (Fig. 1) (Fouquey *et al.*, 1990). *Ordered solid state structures* are formed through molecular recognition directed self-assembly of complementary hydrogen bonding components (Lehn *et al.*, 1990, 1992). A *bis-porphyrin supramolecular cage* is obtained by self-assembly of two porphyrin components bearing uracil-type units that interact through hydrogen bonding with two complementary triaminopyrimidine units (Fig. 2) (Drain *et al.*, 1993).

2 Self-assembly of inorganic structures

The self-assembly of inorganic structures of several types has been achieved, based on ligand design and on the use of suitable coordination geometries that act as the assembling algorithm.

ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS
ISBN 0-12-499150-5

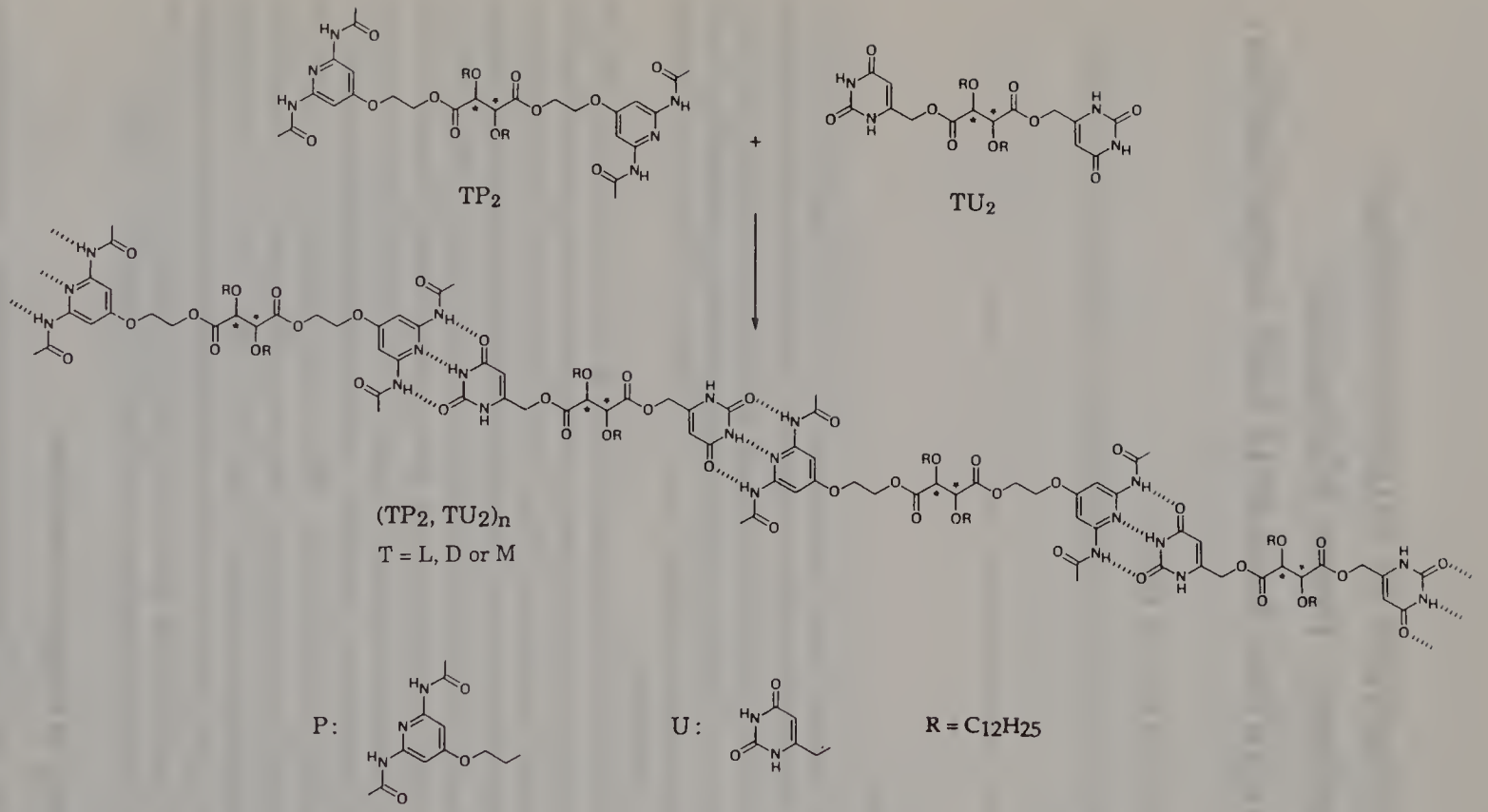

Fig. 1

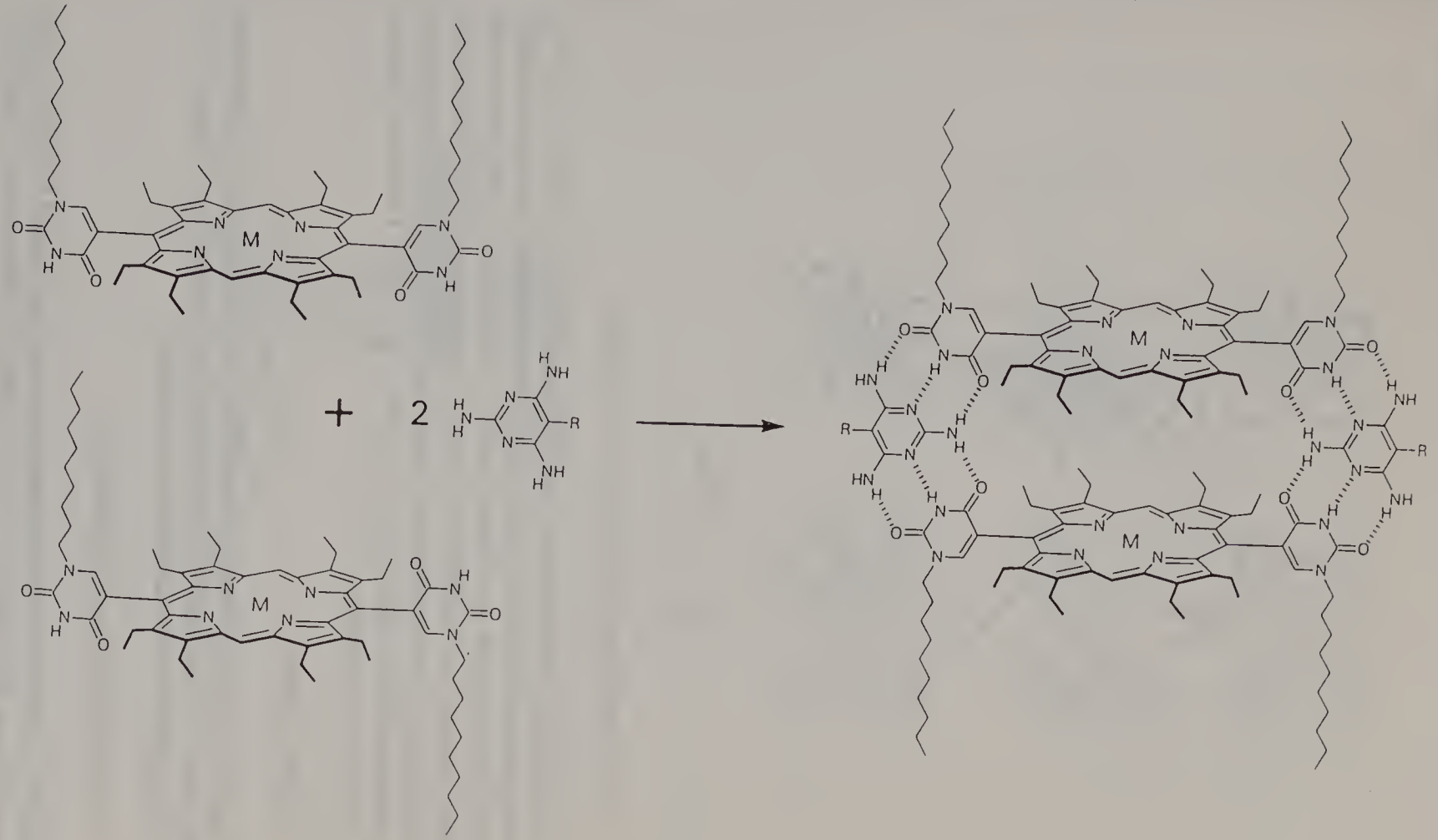

Fig. 2

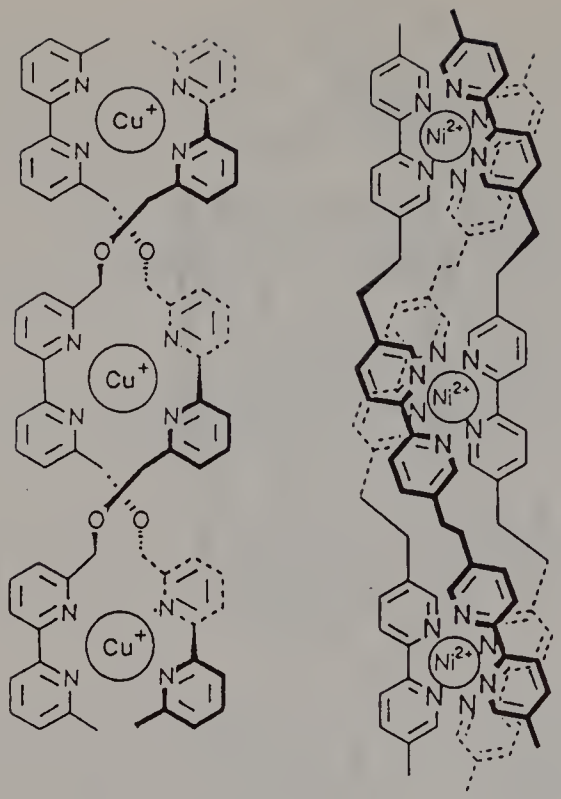

Fig. 3

2.1 *Double-stranded and triple-stranded helicates*

Double helical and triple helical metal complexes are formed by the spontaneous organization of two or three linear polybipyridine ligands of suitable structure into a double or a triple helix by binding of specific metal ions displaying respectively tetrahedral [Cu(I)] and octahedral [Ni(II)] coordination geometry. These species are illustrated by the trinuclear double and triple helicates shown above (Fig. 3) (Lehn *et al.*, 1987; Lehn and Rigault, 1988; Krämer *et al.*, 1993).

2.2 *Circular complex*

A complex of circular shape is formed from the assembly of a trinucleating ligand, three 2,2′-bipyridine units and three Cu(I) ions (Fig. 4) (Baxter *et al.*, 1993). A *capped structure* has also been obtained.

2.3 *Multiple component self-assembly*

A cylindrical cage-like structure is spontaneously generated from five ligands of two different types and six Cu(I) ions (Fig. 5) (Baxter *et al.*, 1993). This

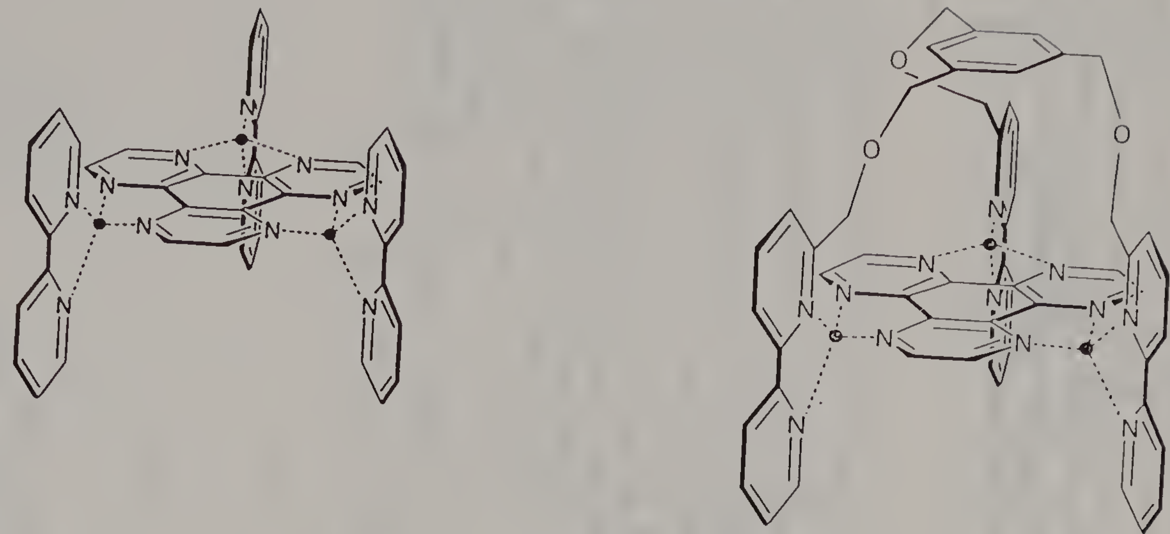

Fig. 4

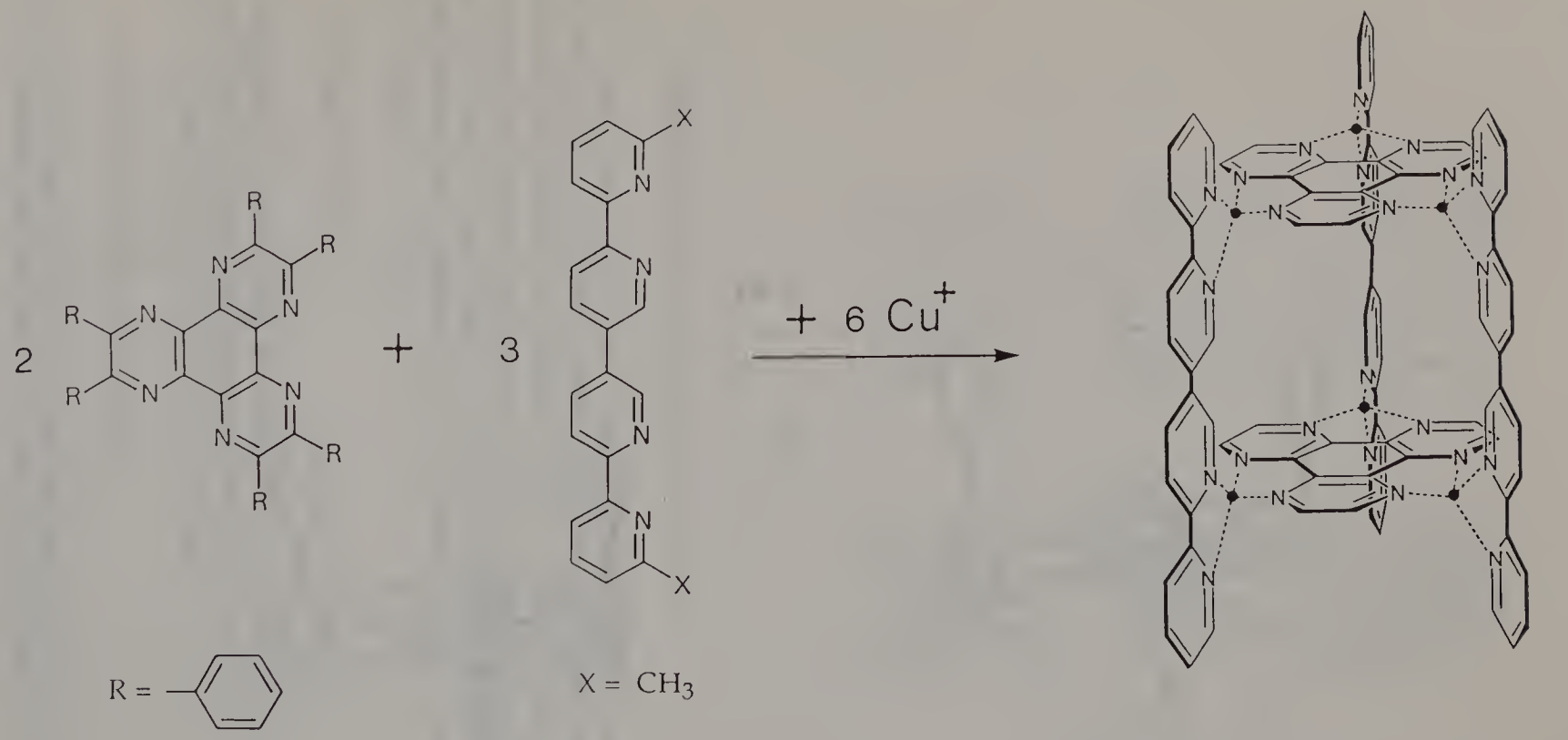
2
R
R
R
R
R
R
N
+
3
X
X
+ 6 Cu+
R =
X = CH3
Ni
C6H5 and CH3 substituents omitted

Fig. 5

process represents the remarkable self-organization of a closed inorganic architecture from multiple components, by the spontaneous and correct assembly in one stroke of altogether 11 particles belonging to two types of ligands and one type of metal ion. The operation of this instructed supramolecular system fulfils the three levels of molecular programming and of information input: *recognition*, *orientation* and *termination*, that determine the generation of a discrete supramolecular architecture. The steric and binding information contained in the ligand is read out by the metal ions following a tetrahedral coordination algorithm. This process represents a further step in the control of the self-organization of large and complex supramolecular architectures through molecular programming.

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10

Cram's Rule in Radical Chemistry

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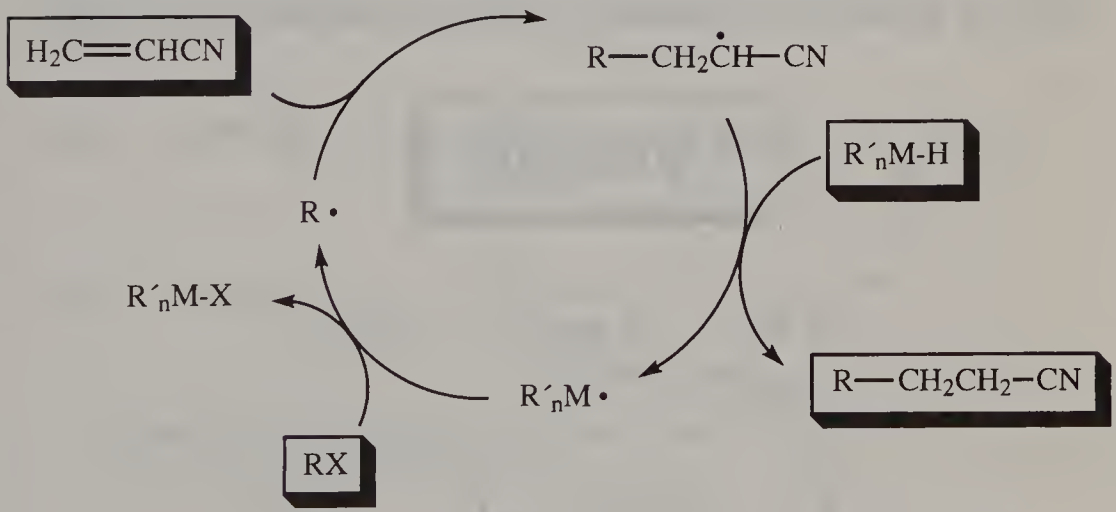
1 Introduction

Recently we have developed synthetic methods of C,C bond formation via intermolecular radical addition to π-bonds using organomercury (Giese and Meister, 1977) and organotin (Giese and Dupuis, 1983) compounds as mediators (Giese, 1985). In these reactions Hg-organic and Sn-organic radicals are involved as intermediates. Other metal-centered radicals that can be used in synthesis contain Fe, Mn (Giese and Thoma, 1991) and Co (Giese *et al.*, 1989) (Scheme 2).



Mediators : RHg-H (1977, Freiburg) — Bu_3Sn-H (1983, Darmstadt) — $(Me_3Si)_3Si$-H (1989, Basel)

Scheme 1

ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS
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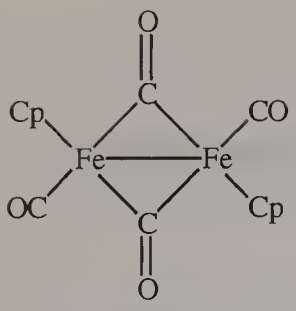
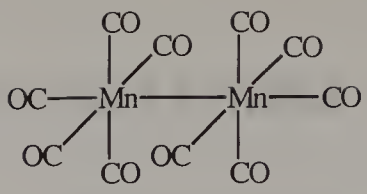
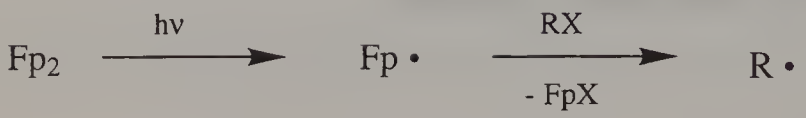
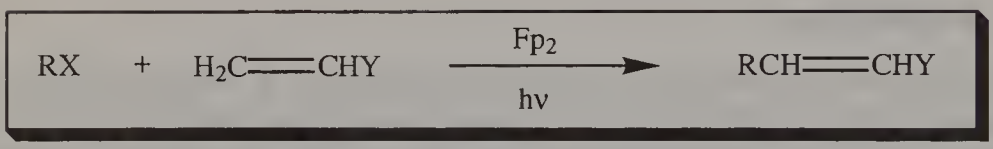






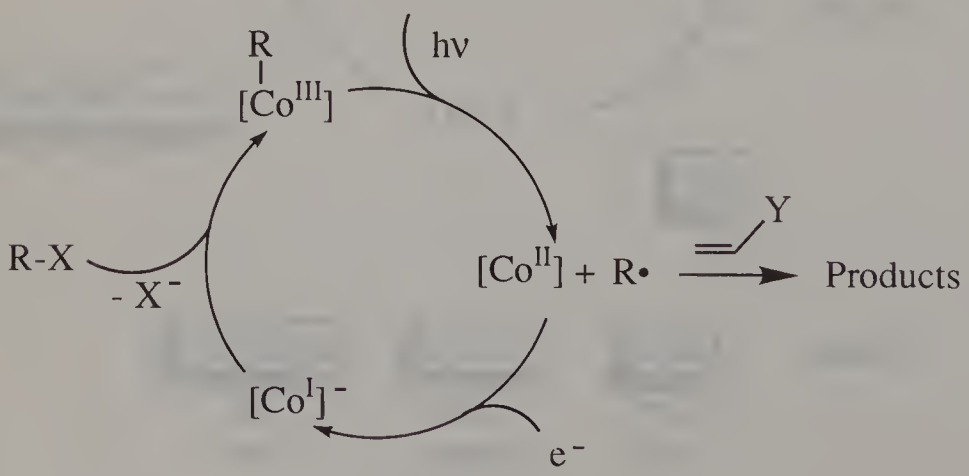


Scheme 2

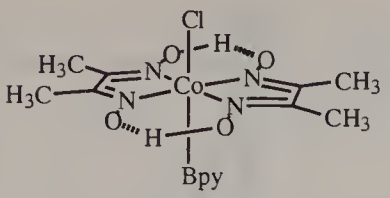
A catalytic use is possible with Co complexes (Giese *et al.*, 1992b) if the ligands facilitate reduction to Co(I) (Scheme 3).

According to the redox potentials I-Co(Costa) and I-Co(tim) complexes should be as useful as vitamin B_{12} (Scheme 4). Addition and cyclization

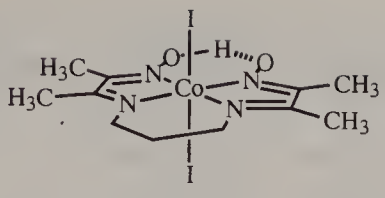
Catalysis



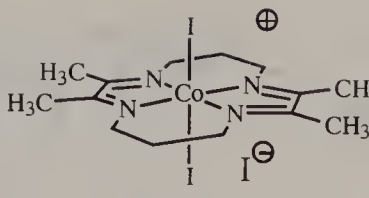
Scheme 3



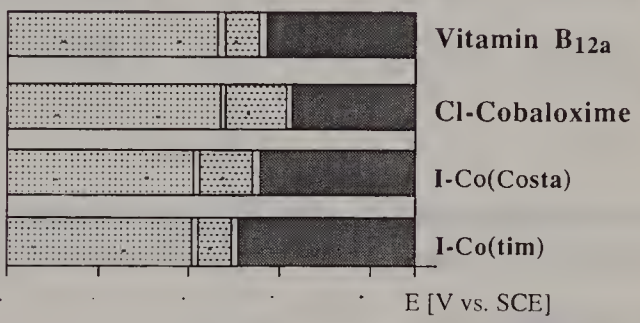
$ClCo(dmgH)_2Bpy$
= Cl-Cobaloxime



$I_2Co[(DO)(DOH)pn]$
= I-Co(Costa)



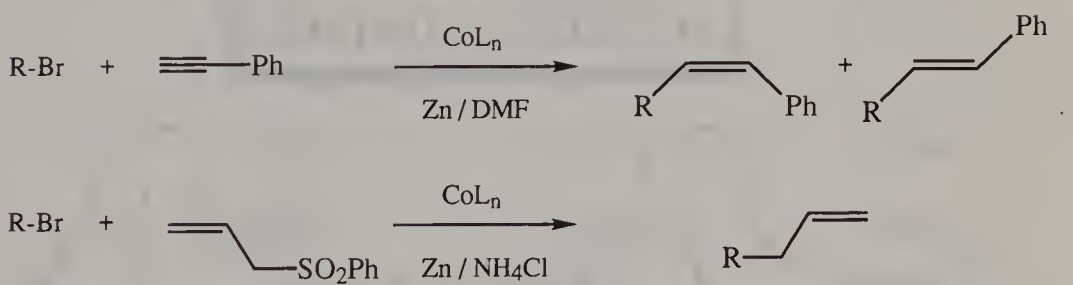
I-Co(tim)

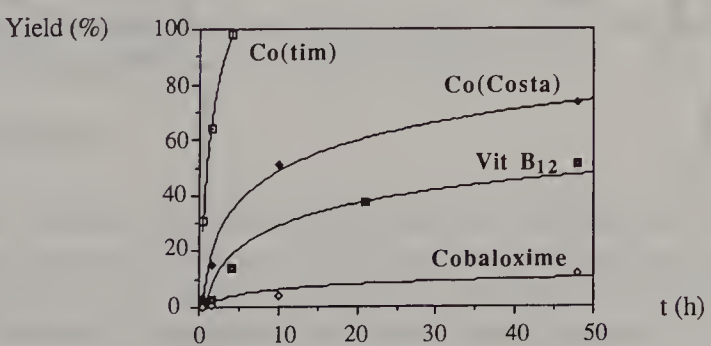


Scheme 4

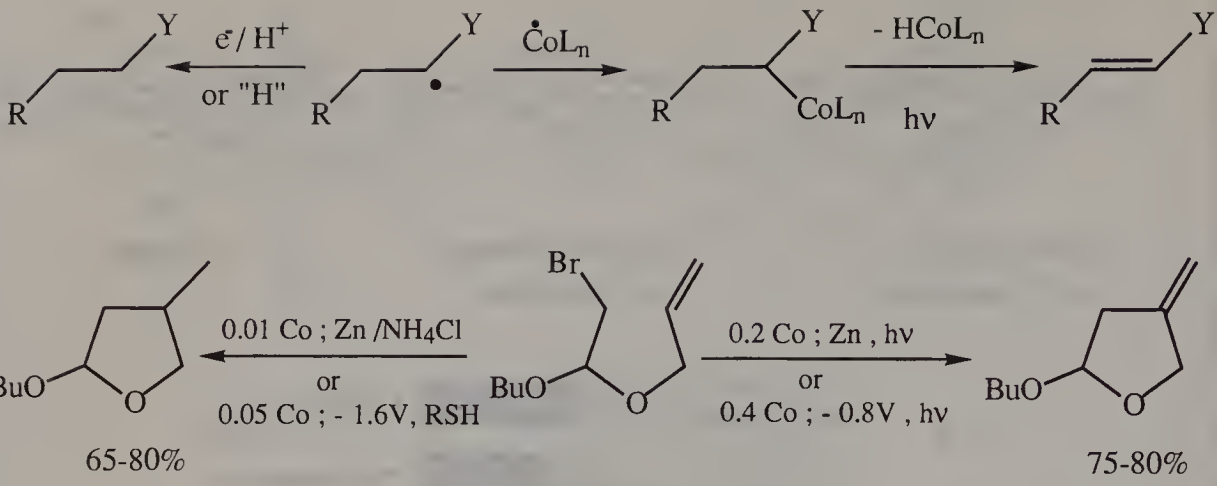
experiments prove this (Scheme 5). Depending on the conditions either addition or substitution products are formed (Scheme 6).

Thus, organometallic compounds are useful mediators for synthesis via radicals and these methods became very popular. But, at the end of the last





Scheme 5

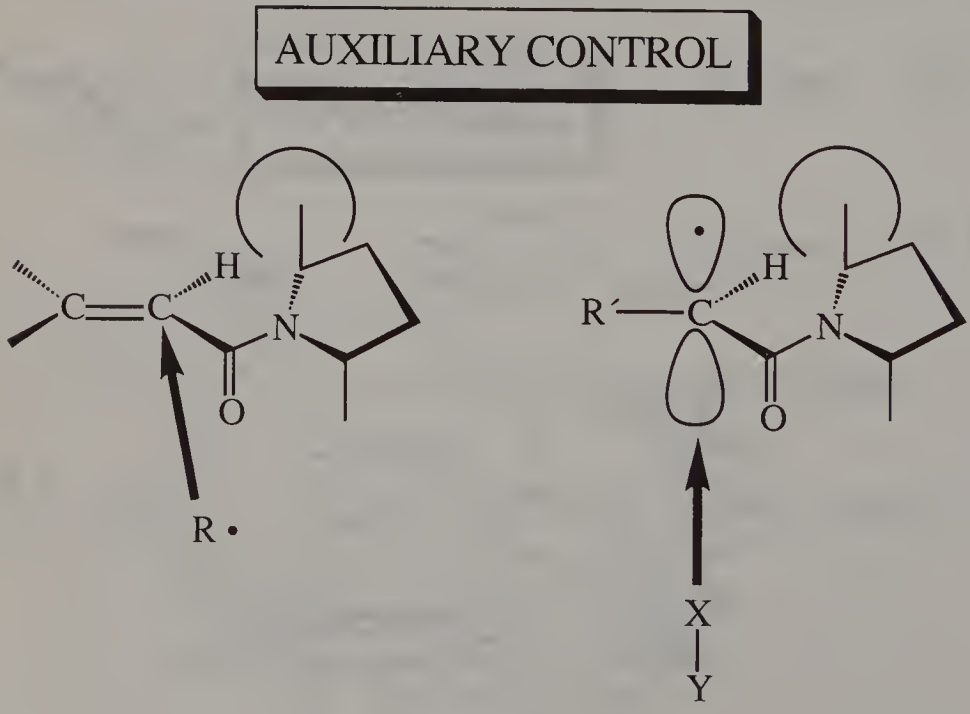


Scheme 6

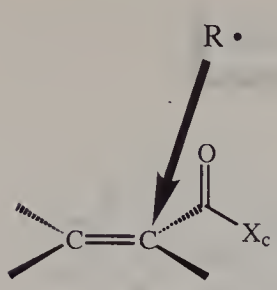
decade, it was not possible to carry out stereoselective radical reactions with acyclic systems. This situation has changed completely in the last three years.

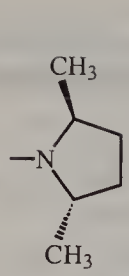
2 Chiral auxiliaries

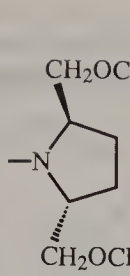
Recent studies have shown that chiral auxiliaries with C_2 symmetry induce high stereoselectivity also in radical reactions (Scheme 7) (Porter *et al.*, 1991). With suitably substituted amines these reactions are completely stereoselective (Giese *et al.*, 1993b) (Scheme 8). The increase in selectivity is a result of the

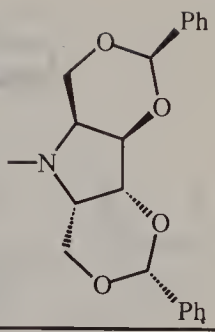


Scheme 7 (Porter *et al.*, 1991)



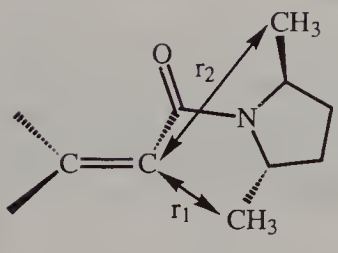


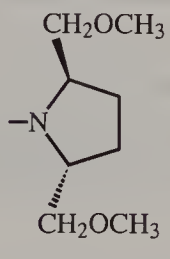


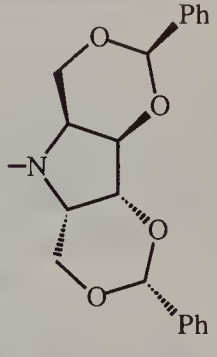


R •			
t-C_4H_9 •	82 : 1	112 : 1	> 200 : 1
c-C_6H_{11} •	48 : 1	67 : 1	> 200 : 1
n-C_6H_{13} •	16 : 1	35 : 1	> 200 : 1

Scheme 8







r_1 :	334 pm	327 pm	310 pm
r_2 :	435 pm	440 pm	430 pm

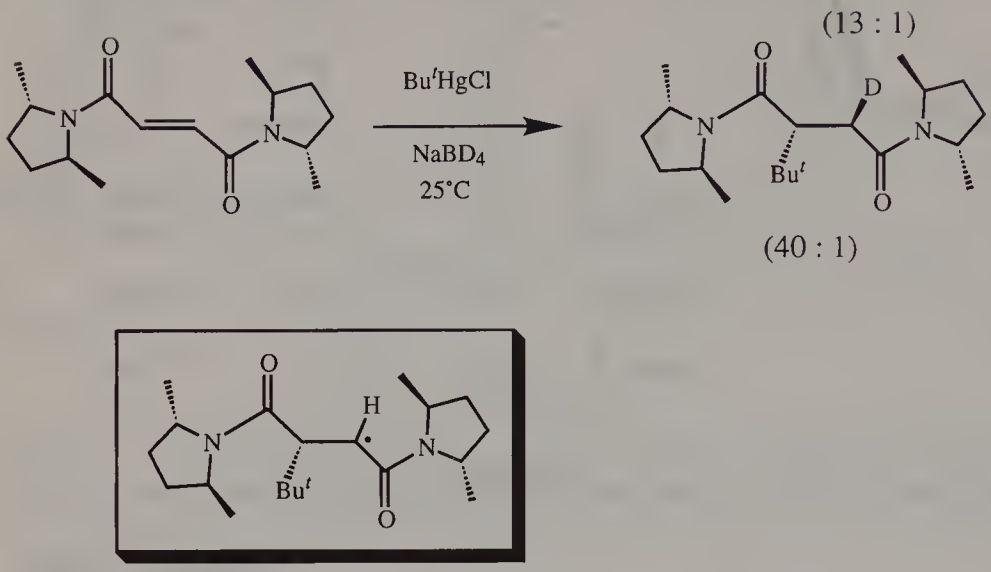
Scheme 9

decreasing distance between the substituents at the chiral center and the center of attack (Scheme 9).

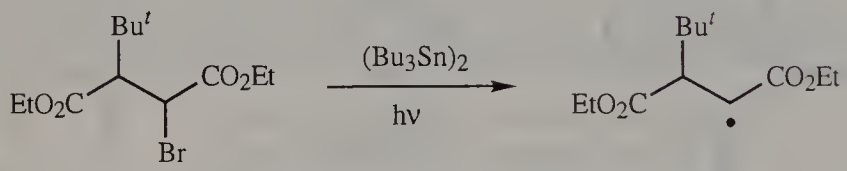
3 Allylic strain

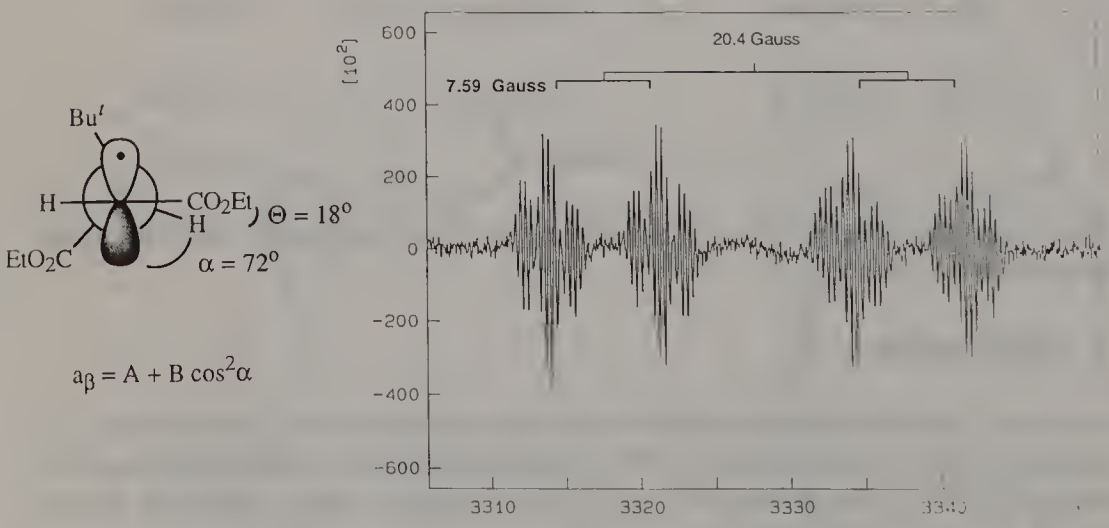
An early experiment showed that substrate control can be as important as auxiliary control (Giese *et al.*, 1990). In the intermediate radical (Scheme 10), the hydrogen atom abstraction occurs from the face that is shielded by the chiral auxiliary. Obviously, the chiral center adjacent to the radical center overcompensates this shielding.

AUXILIARY versus SUBSTRATE CONTROL

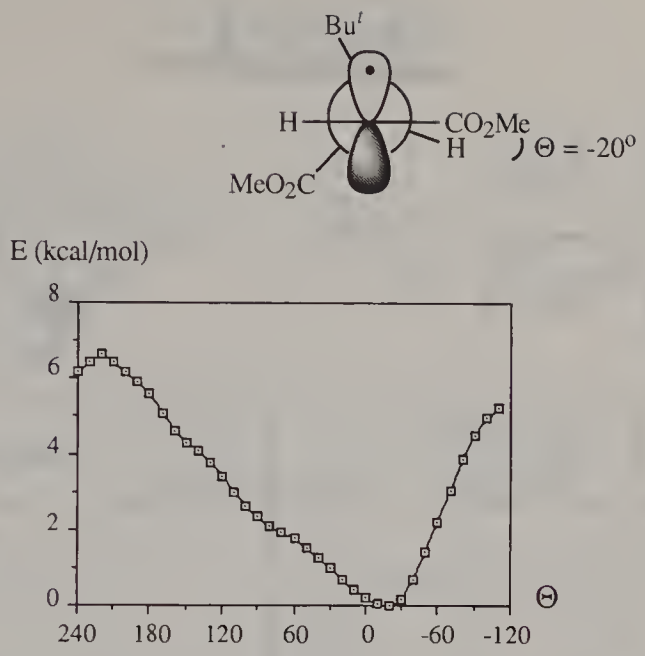


Scheme 10 (Giese *et al.*, 1990)





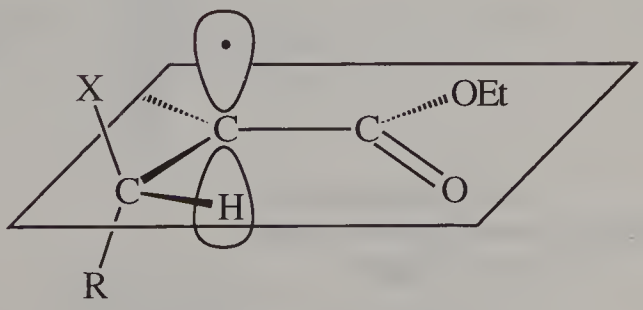
Scheme 11



Scheme 12

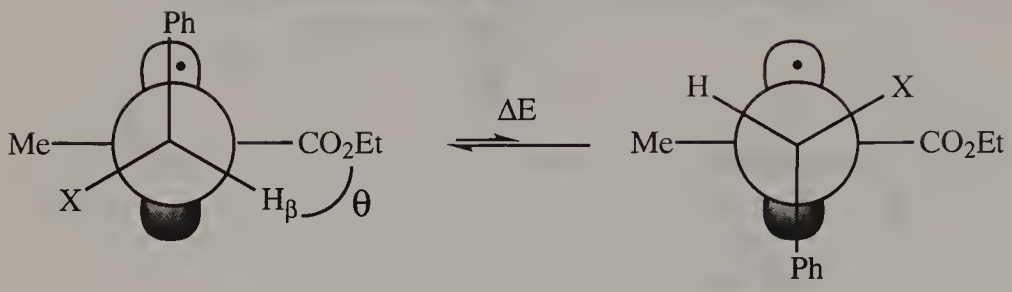
ESR measurements and calculations show that radicals with an ester substituent (Scheme 11) adopt preferred conformations (Scheme 12) (Giese *et al.*, 1992c). These preferred conformations are explained by allylic strain effects (Scheme 13) (Hart and Krishnamurthy, 1991; Giese *et al.*, 1991a). However, dipole–dipole interactions can influence the conformation slightly (Scheme 14).

In cyclic systems the stereoselectivity can be reversed, because now the stereogenic center cannot adopt the 'allylic strain' conformation (Scheme 15). In general, substituents that are in conjugation with the radical center and that



Scheme 13

Polar Effects

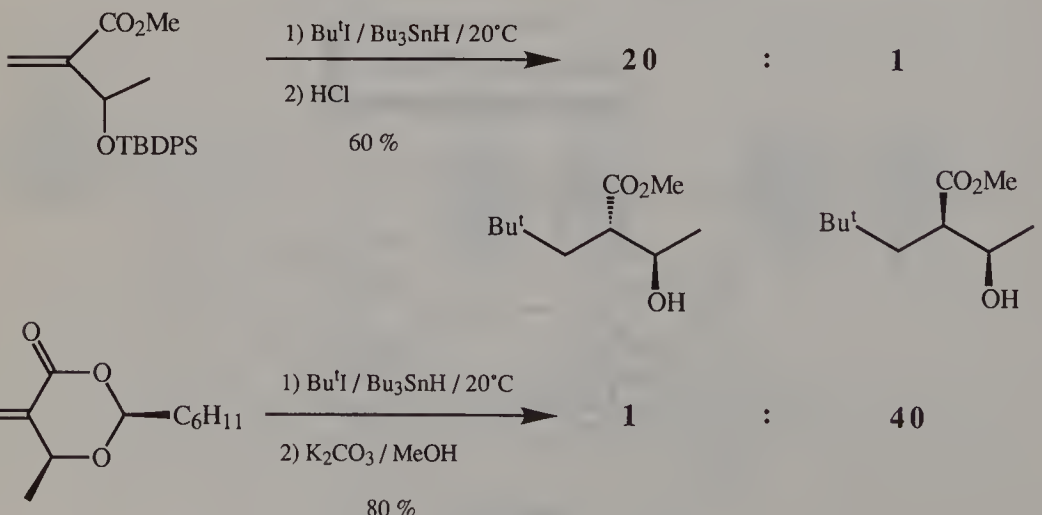


X	AM1 θ	AM1 ΔE	AM1 a(H_β)	ESR a(H_β)	Selectivity
Me	4°	0.5	7.0	6.0	66 : 34
F	31°	2.3	11.0	9.0	95 : 5
OMe	34°	2.4	9.0	8.0	97 : 3

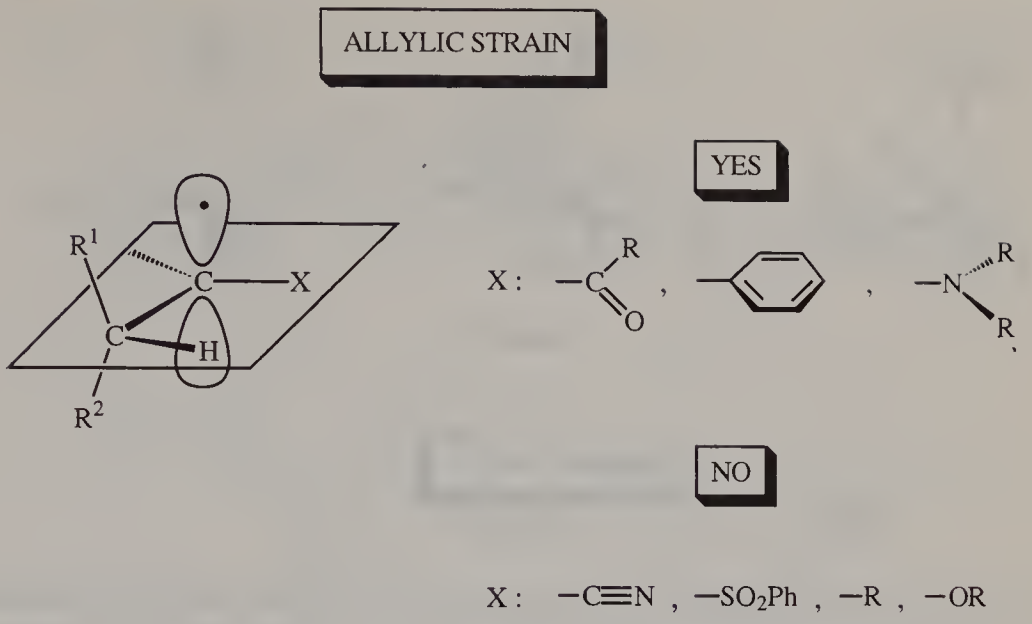
Scheme 14

are branched at the α-atom should adopt preferred conformations according to the allylic strain model. Thus, carbonyl, phenyl, and amine substituted radicals should react stereoselectively (Scheme 16). On the other hand, the conformation of a radical with an alkoxy substituent should not be governed by allylic strain effects.

ACYCLIC versus CYCLIC RADICALS



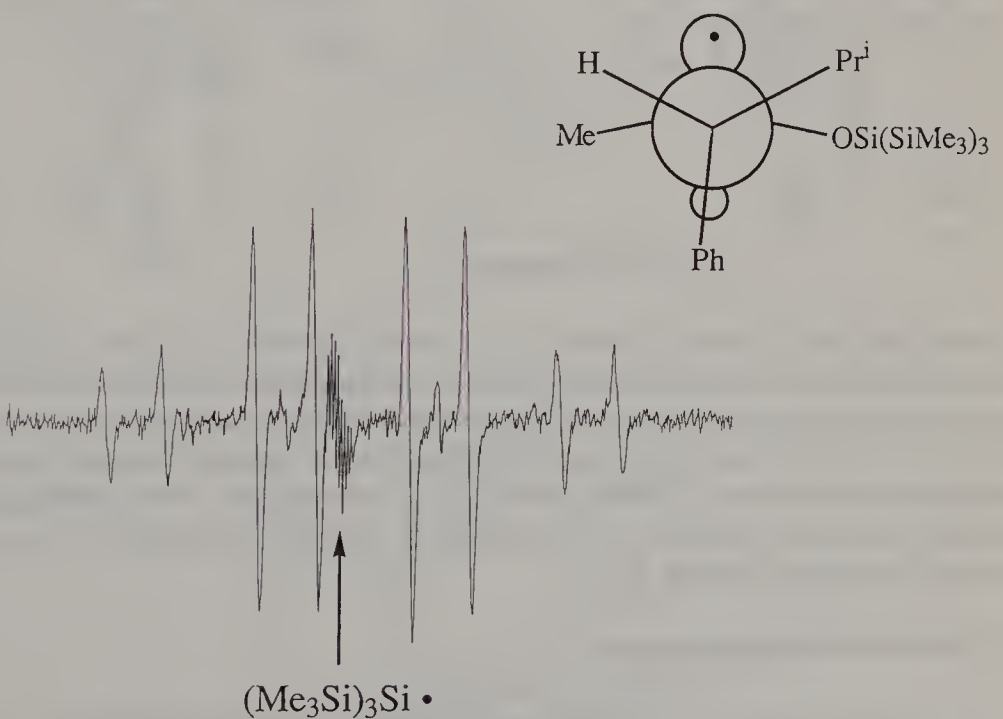
Scheme 15 (Bulliard *et al.*, 1991)



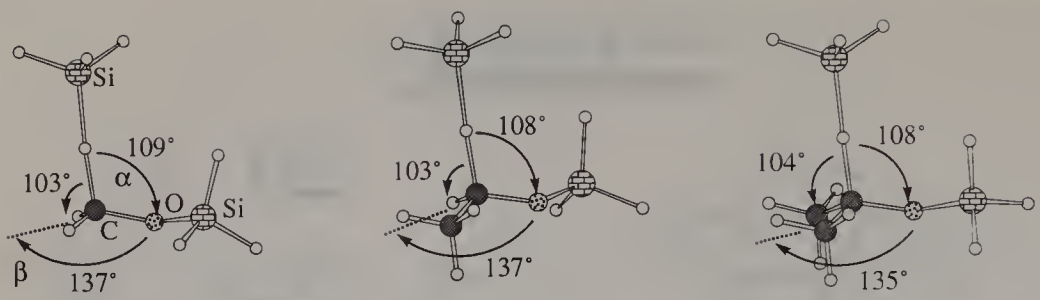
Scheme 16

4 Cram's rule

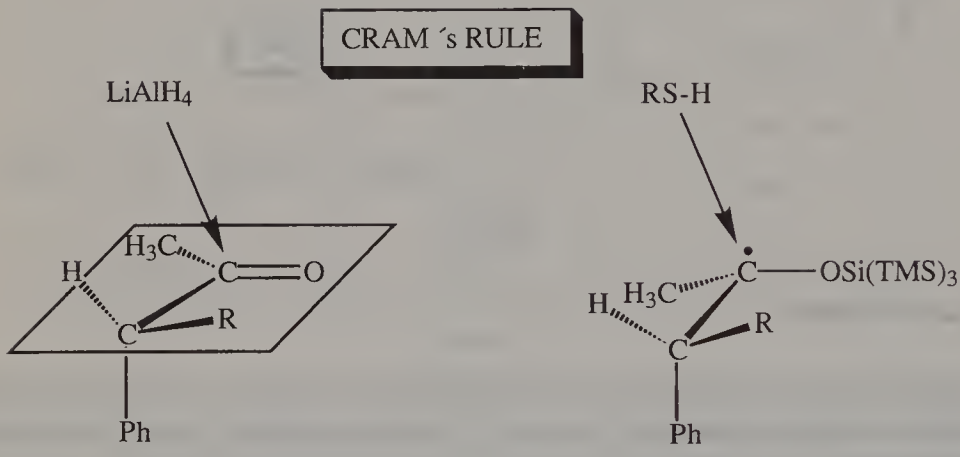
A simple way to synthesize radicals bearing an oxygen substituent is the reaction of silyl radicals with ketones. ESR experiments prove that *tris*(trimethylsilyl)silyl radicals add cleanly to the oxygen of chiral ketones and lead to



Scheme 17



Scheme 18



R (30°C)	Cram : anti-Cram
Me	2.9 : 1
i-Pr	13 : 1
t-Bu	8.2 : 1

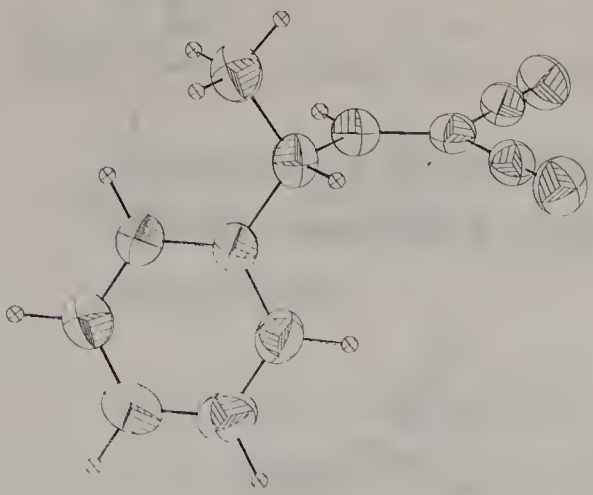
R (30°C)	Cram : anti-Cram
Me	2.9 : 1
i-Pr	13 : 1
t-Bu	5.3 : 1

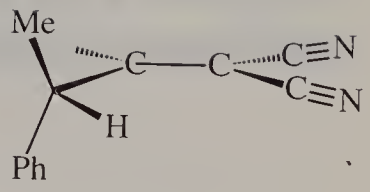
Scheme 19

a preferred conformation (Giese *et al.*, 1991b) (Scheme 17). The measurements demonstrate that oxygen-substituted radicals adopt the Felkin–Anh and not the allylic strain conformation. Calculations have shown that the transition states of radical hydrogen atom abstractions are very similar to ionic hydride abstractions (Giese *et al.*, 1993a) (Scheme 18). It is therefore not surprising that both reactions have similar stereoselectivities. Thus, Cram's rule holds also in radical chemistry (Scheme 19).

5 Curtin–Hammett principle

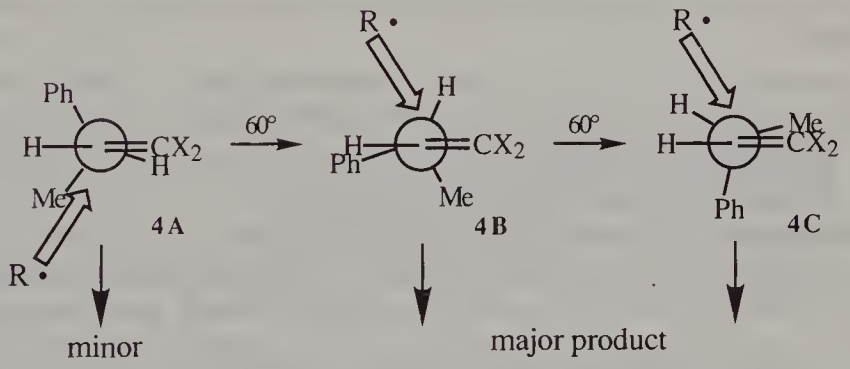
With oxygen-substituted radicals the conformations of the radical and of the transition state are very similar. This is, of course, not always the case:

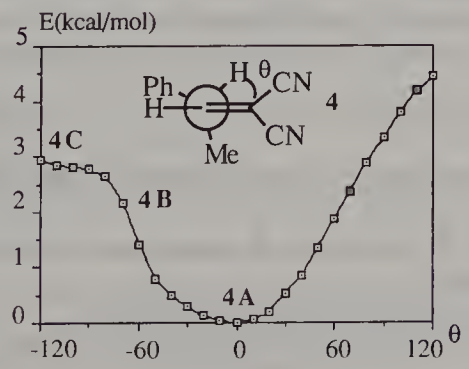




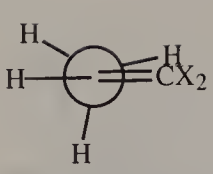
Scheme 20

although *Z*-alkenes with allyl substituents adopt the allylic strain conformation (Scheme 20), the reactions do not occur from this conformation (Giese *et al.*, 1992a). A rotation of 60° or 120° leads to such reactive conformers that the energy loss caused by rotation is overcompensated by the gain in reactivity (Scheme 21). Therefore the Felkin–Anh transition state (Scheme 22) can be more important than allylic ground state effects.

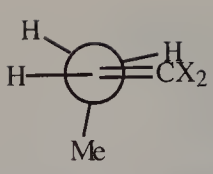




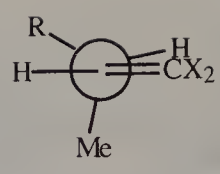
Scheme 21



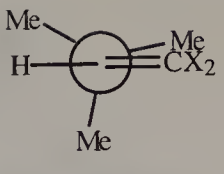
k = 1.0



0.9

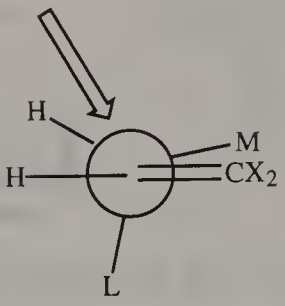


R = Me : 1/150
R = Ph : 1/200



< 1/1000

Felkin-Anh



Scheme 22

Acknowledgement

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11

Polycycle Constructions by Transition Metal-catalysed and Radical-mediated Processes

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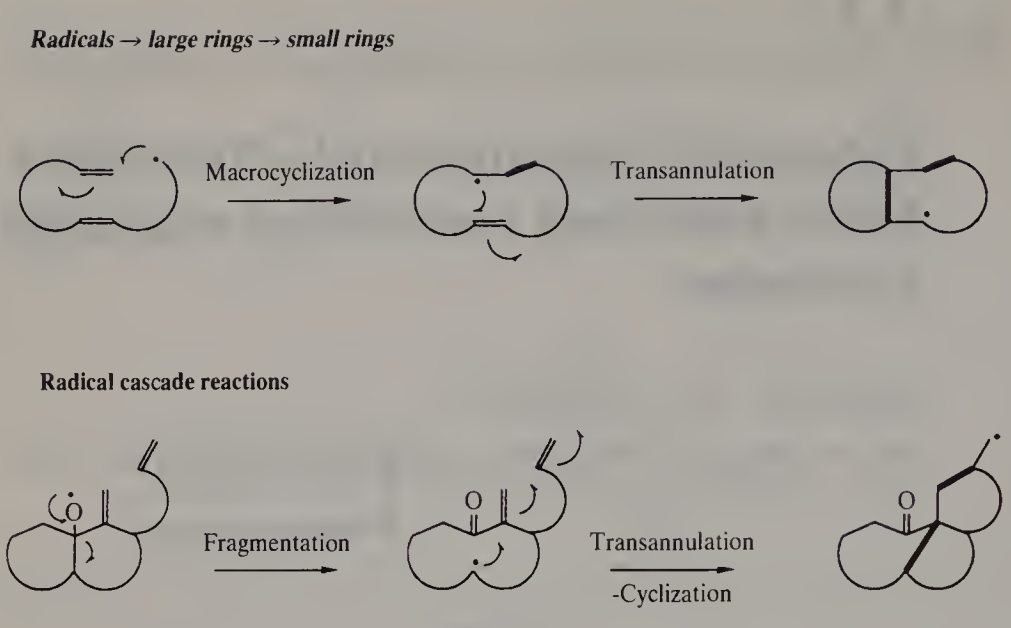
1 Introduction

The synthesis of ring systems—whether they are small, medium or large in size, fused or not fused to others, carbo- or heterocyclic, naturally occurring or otherwise, or a combination of all these features—has been a fascination for synthetic organic chemists since almost the early beginnings of modern organic chemistry. Much of this fascination comes from the often bewildering and alluring molecular architecture of the ring systems, and the sheer excitement and challenge they offer for developing new synthesis methodology, strategy and design. Another reason for the fascination however, has been the incidence of polycyclic natural products with profound biological activities—together with their biosynthesis, their biogenetic interrelationships and their *modus operandum*. Indeed, biologically active natural ring systems, whether they are singular or polycyclic, have not only provided much of the focus for synthetic organic chemists, but a huge array of pharmaceuticals and agrochemicals in commerce today also show structures which are based very much on the presence of one or more combinations of carbo- or heterocyclic rings.

In the past decade and more, electrophilic polyolefin cyclizations (Cheng *et al.*, 1987; Sutherland, 1991), together with a number of tandem transition metal-catalysed reactions (Carpenter *et al.*, 1989; Dorrity *et al.*, 1990; de Meijere *et al.*, 1991; Shi and Trost, 1992) and pericyclic cycloadditions (see for example Deslonghcamps, 1991), have proved to be exceptionally valuable in the elaboration of polycyclic compounds. We have now considered the feasibility of developing new and powerful synthetic strategies for polycycle construction based on combinations of cascade radical and macrocyclization–transannular processes and radical fragmentation–transannular-cyclization

ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS
ISBN 0-12-499150-5



Scheme 1

reactions (Scheme 1). In this chapter we highlight the scope for some of these processes in approaches towards ring systems in target natural products, e.g. lophotoxin **3**, taxol **5**, and laurenene **36**.

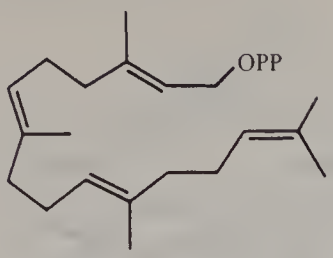
2 Diterpene ring systems

The isomeric 14-ring diterpene hydrocarbons neocembrene **1** and casbene **2** are related biogenetically, and they are also likely precursors to the novel polycyclic natural products lophotoxin **3**, ingenol **4**, bertyadionol **6**, phorbol **7** and taxol **5** by way of sequential electrophilic transannular cyclizations accompanied by a range of biological oxidation reactions (Adolf *et al.*, 1970; Crombie *et al.*, 1980). Part of the reason for researching the cascade radical reactions summarized in Scheme 1 was to: (a) develop the scope for radical macrocyclization reactions in the synthesis of neocembrene and related 14-ring diterpenes; (b) explore the use of radical transannulation reactions within terpenoid macrocycles as a stratagem for the synthesis of a range of polycycle natural products (similar to those shown above); and (c) demonstrate the potential for radical fragmentation reactions in tandem with transannulation reactions, in constructing polycycles.

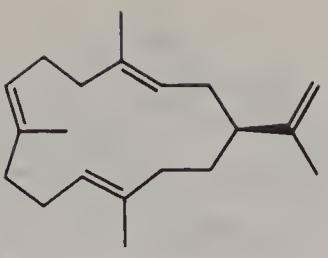
3 Radical macrocyclizations: towards lophotoxin

3.1 Cembranoids

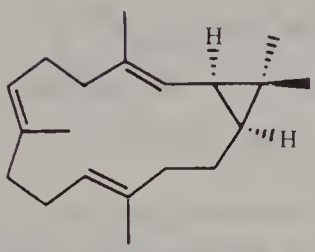
Cembranoids, e.g. asperdiol **8** (Matson *et al.*, 1977) and lobolide **9** (Groweiss and Kashman, 1977), occur widely in nature, and several members show



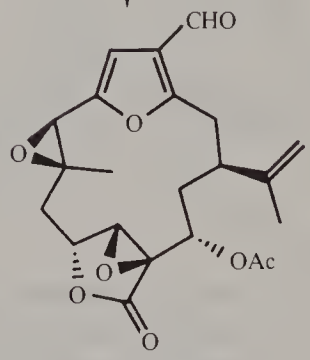
Geranylgeranyl PP



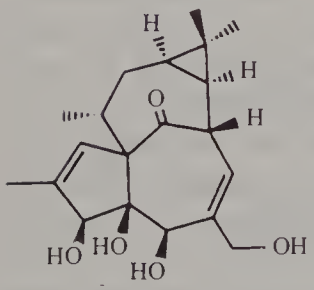
1, neocembrene



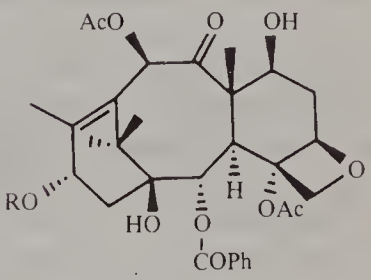
2, casbene



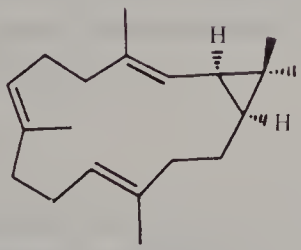
3, lophotoxin



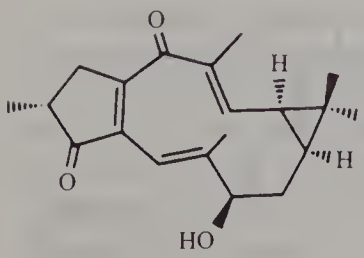
4, ingenol



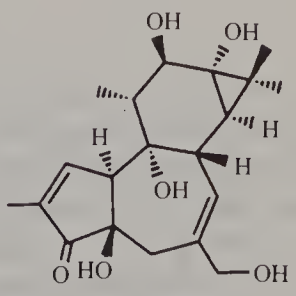
5, taxol
R=COCH(OH)CH(Ph)NHCOPh



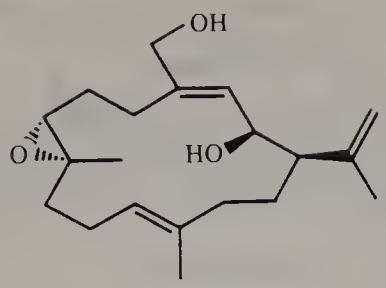
Casbene



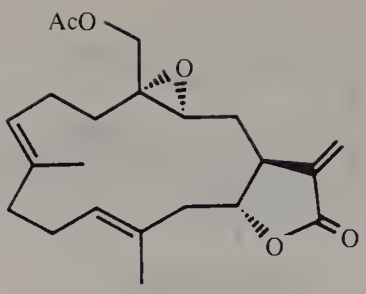
6, bertyadionol



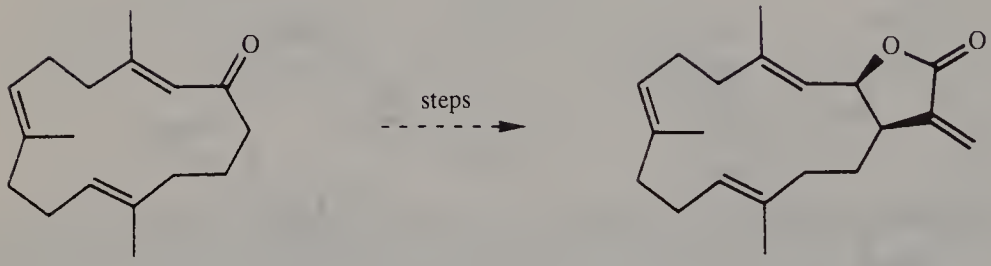
7, phorbol



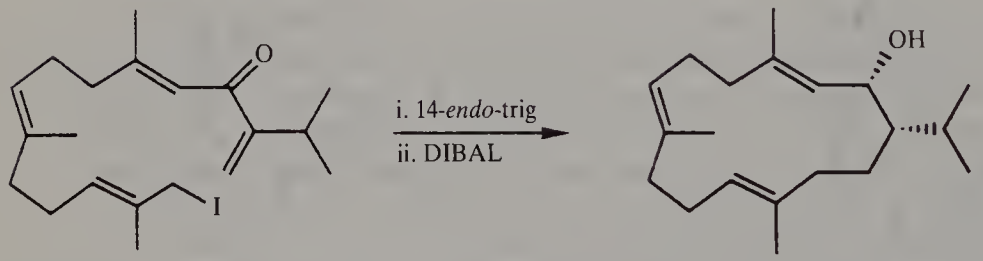
8, asperdiol



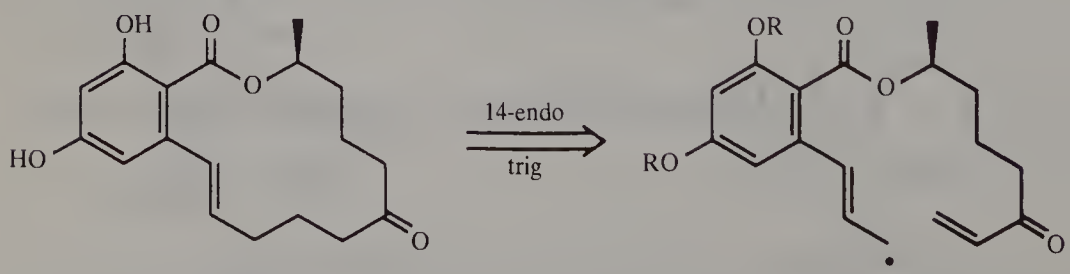
9, Lobolide



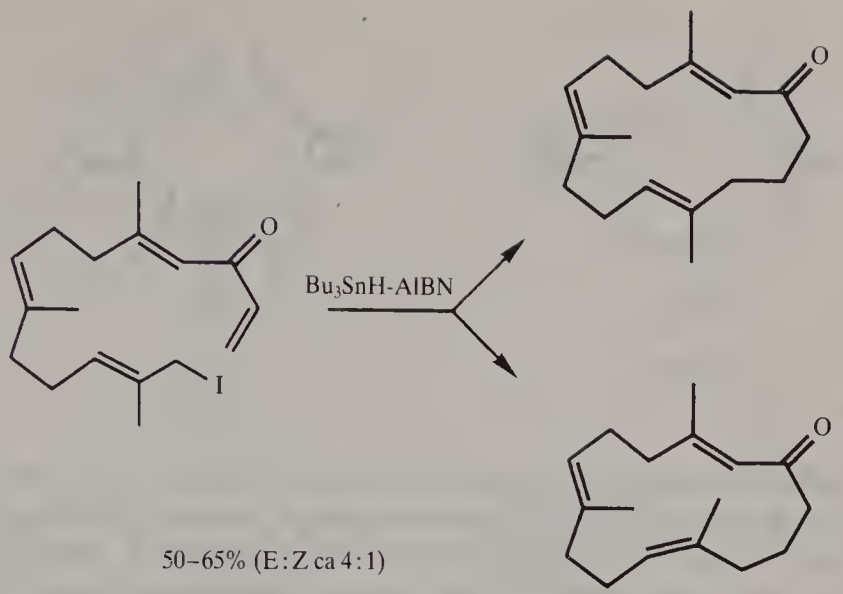
10, cembranolide



11, mukulol



12, zearalenone

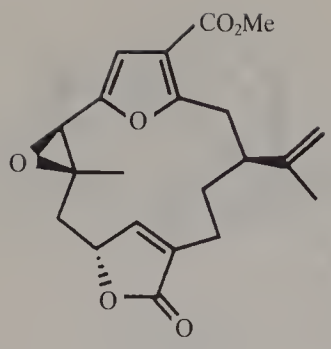


Scheme 2

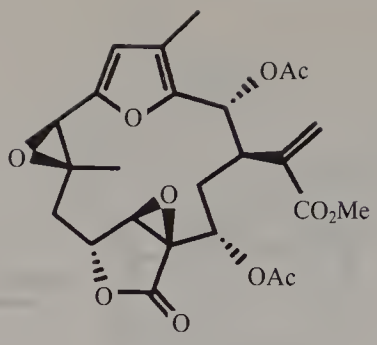
useful biological properties. A wide range of methods has been developed for the construction of the 14-ring carbocyclic portions of these structures. In published work, we have described the total synthesis of mukulol **11** found in *Comiphora mukul* and the cembranolide lactone **10** isolated from the soft coral *Sinularia maji* (Cox *et al.*, 1992). Both of these syntheses are based on facile, regioselective 14-*endo* trigonal cyclizations involving allylic radical intermediates, e.g. Scheme 2. In neither of the cyclizations shown, were we able to detect the co-formation of smaller ring products resulting from competing *exo*/*endo* trig cyclizations, or products resulting from allylic radical transposition or H-abstraction processes in the starting materials. A closely similar 14-*endo* trig radical macrocyclization strategy was also used in a new approach to the oestrogenic mycotoxin zearalenone **12** (Hitchcock and Pattenden, 1992), and these early investigations laid the foundation for our contemporaneous studies with the furanoterpene lophotoxin **3**.

3.2 Furanocembranes

In efforts designed to expand the scope for radical macrocyclizations to more ambitious and more densely functionalized molecules we have examined a strategy towards the synthesis of the furanocembrane unit **15** which makes up the bicyclic ring system in the potent neurotoxin lophotoxin **3** (Bandurraga *et al.*, 1981) and the related pukalide **13** (Burreson *et al.*, 1975) and bipinnatin **14** (Burres *et al.*, 1989). This synthesis, which is shown in retrosynthetic terms in Scheme 3, is based on the idea that a 14-*endo* trig cyclization from the unsaturated acyl radical intermediate **16** would first lead to the macrocycle **17**,

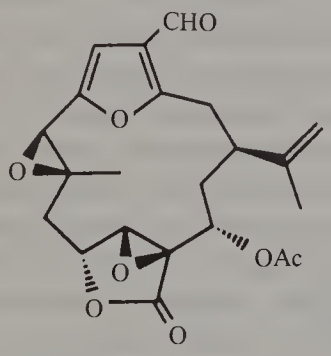


13, pukalide

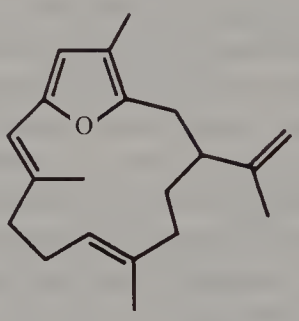


14, bipinnatin

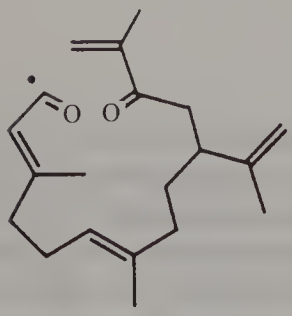
and that following acid treatment of the intermediate dione **17**, the furanocembrane **15** would be produced in a tandem fashion. Indeed, this sequence was realized in the laboratory (Scheme 4) (Astley and Pattenden, 1992), and new research is now at an advanced stage in the elaboration of the key chiral intermediates **18** and **19** en route to the functionalized furanocembrane precursor **20** towards the novel target natural product lophotoxin.



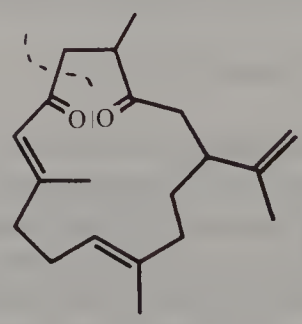
3, lophotoxin



15, furanocembrane

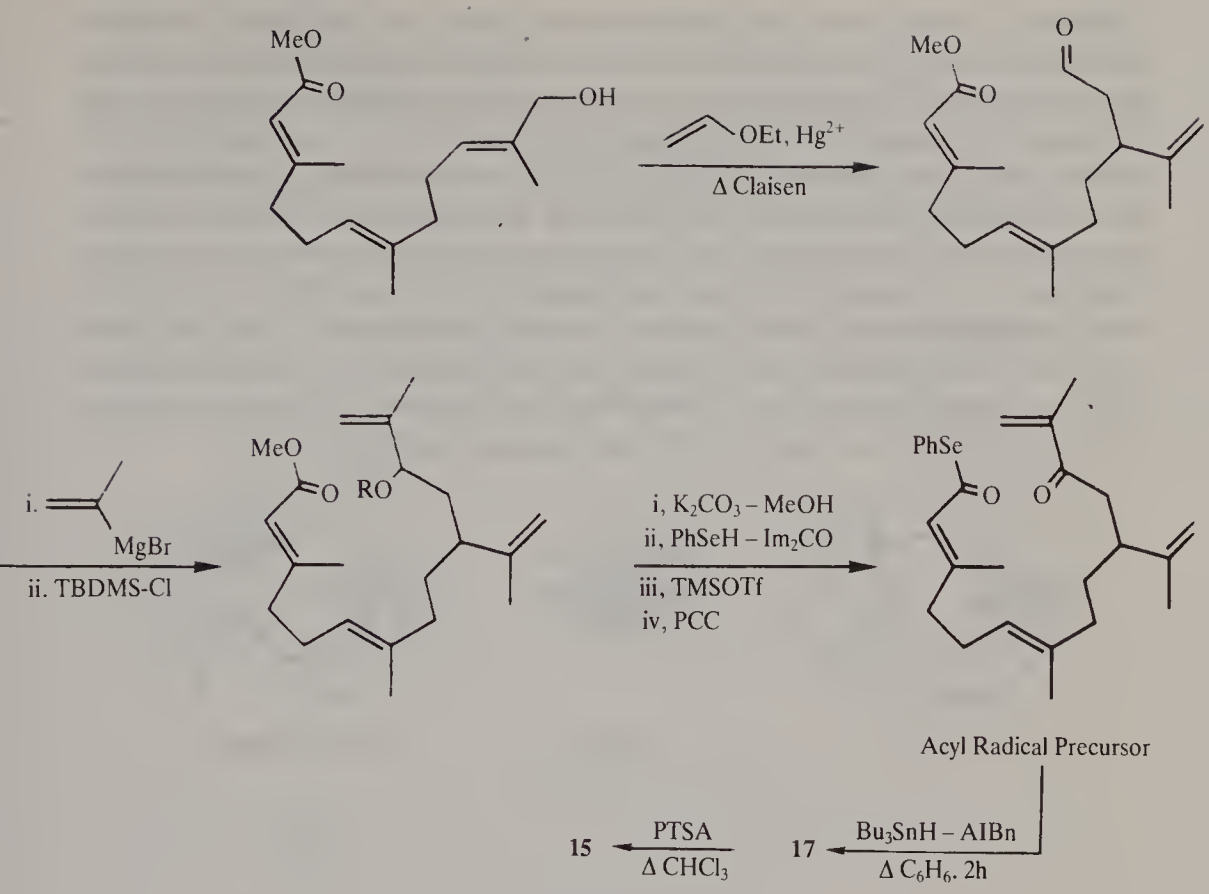


16

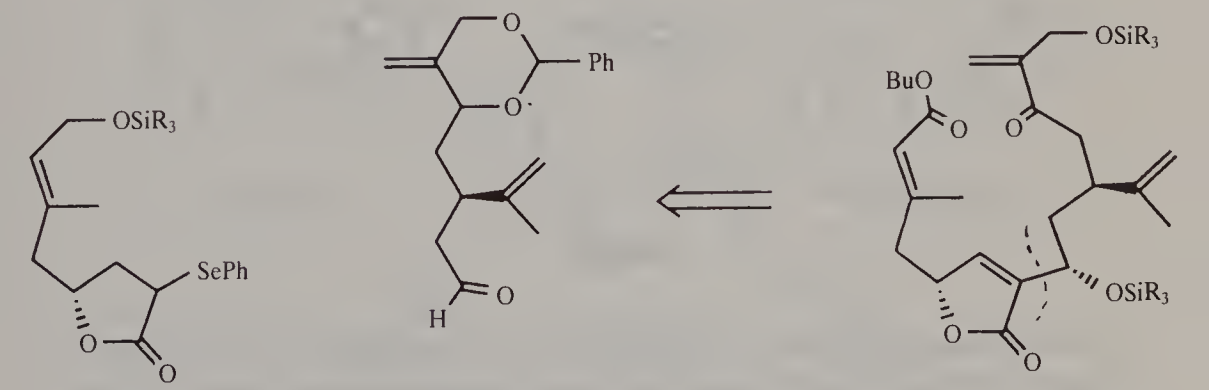


17

Scheme 3



Scheme 4



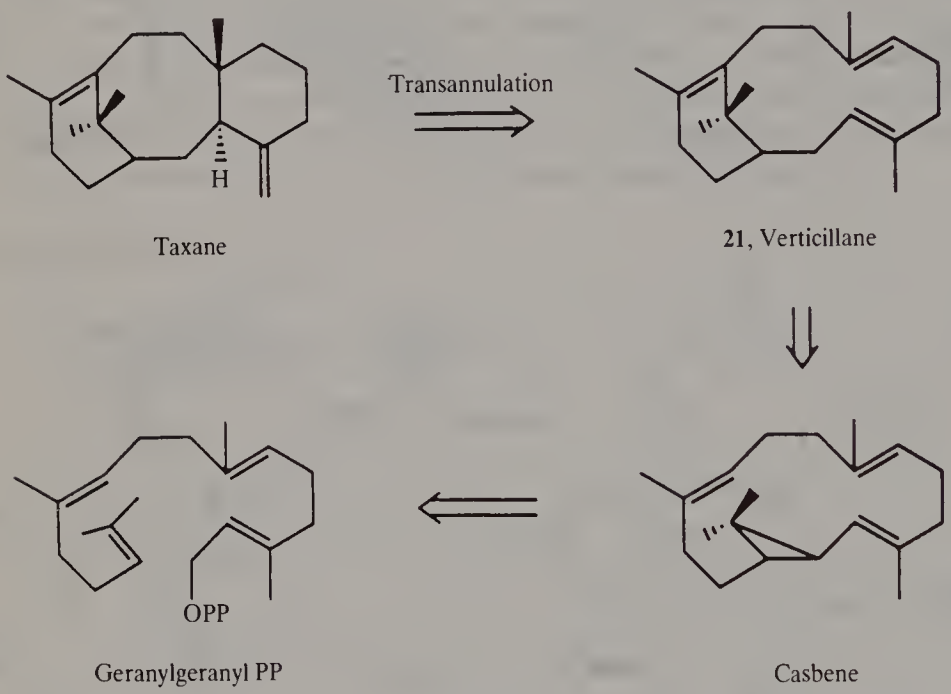
18 **19** **20**

4 Cascade macrocyclization–transannulation reactions

4.1 Taxane ring system

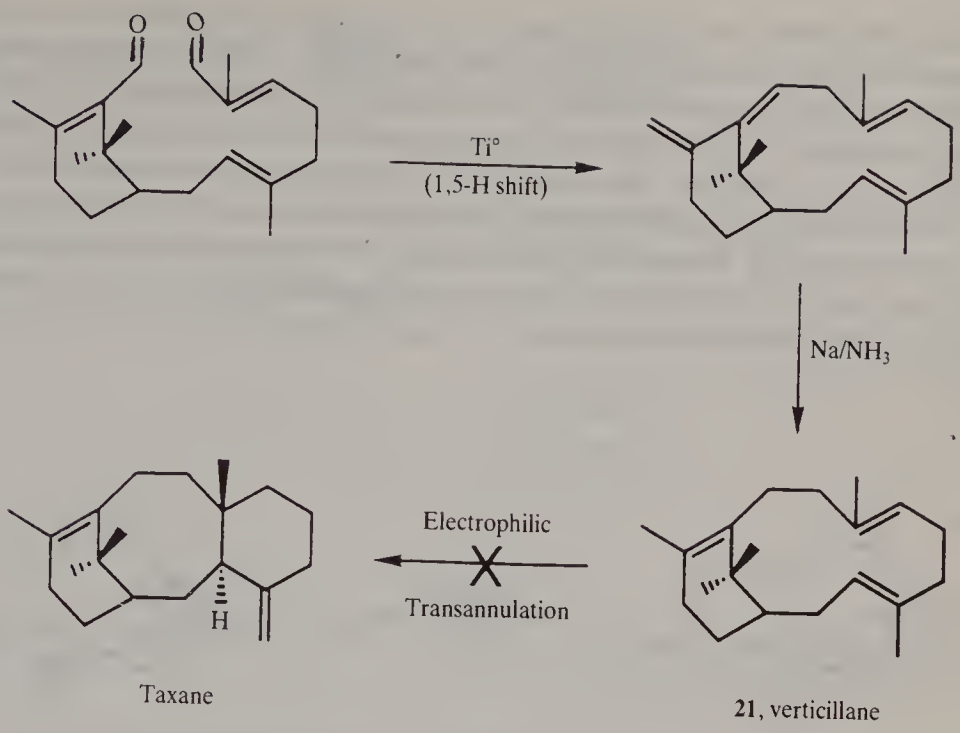
Taxol **5** (Coggon *et al.*, 1971) and related alkaloids have rapidly established themselves as one of the most sought-after families of natural products for the

treatment of leukaemia and cancers of the ovary and the breast (Borman, 1991). Probably no other molecule has received more attention in the literature and in the press than taxol in recent years. Synthetic studies towards taxol, and the unique tricyclo[9.3.1.0]pentadecane ring system in the taxanes, have been intense, and a plethora of ingenious synthetic designs have been described in the contemporary literature (see Hitchcock and Pattenden, 1992b and references therein). Nevertheless, only one report of a total synthesis of a taxane diterpene, i.e. taxusin, has been published at this time (for a review see Blechert and Guenard, 1990; see also Jackson and Pattenden, 1985; Begley *et al.*, 1985, 1990; Bonnert and Jenkins, 1989; Blechert *et al.*, 1989; Lupia and Zuycker, 1990; Maynard *et al.*, 1990; Patel and Swindell, 1990 and references therein; Allentoff and Snider, 1991; Ravishankar and Yadav, 1991).

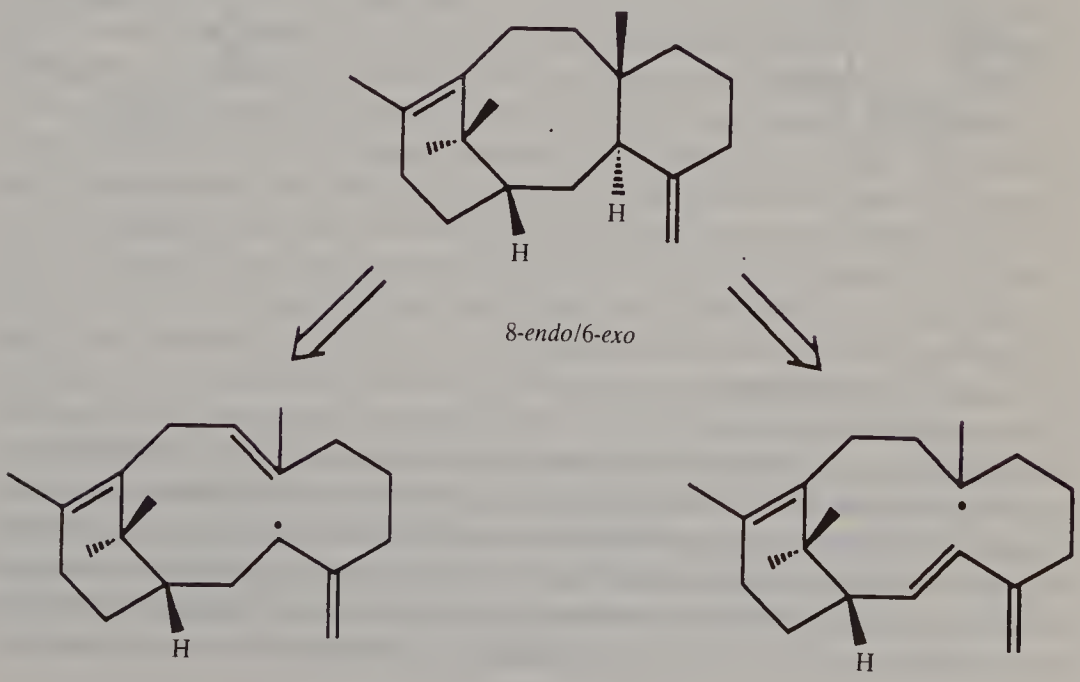


Scheme 5

Several years ago, and as a consequence of our interest in the biosynthesis of taxanes (Scheme 5) and related polycyclic diterpenes (see Section 2), we examined a biomimetic approach to the taxane ring system based on transannular *electrophilic* cyclization of the putative verticillane precursor **21** (Begley *et al.*, 1990). In spite of much effort however, we were not able to achieve the aforementioned transannulation (see Scheme 6). Time has now moved on, and as a result of our interest in developing cascade radical ring-forming reactions in synthesis, we have now examined a corresponding *radical* transannulation approach to the taxane ring system based on intermediates similar to those shown in Scheme 7.

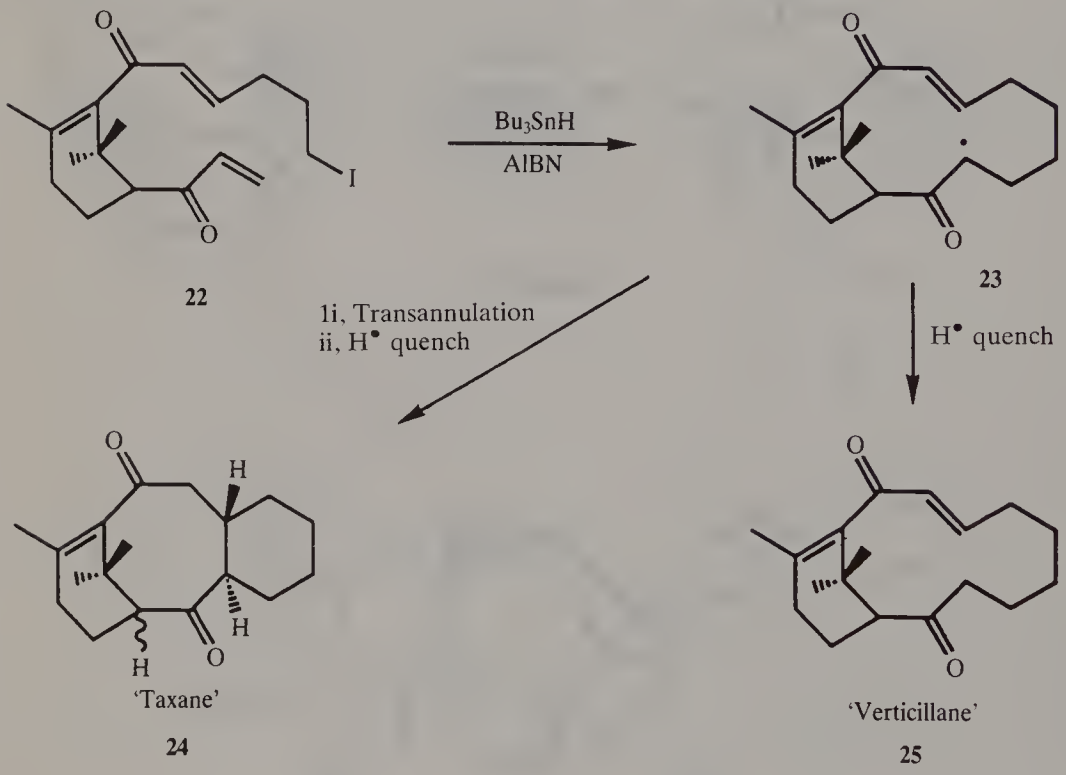


Scheme 6



Scheme 7

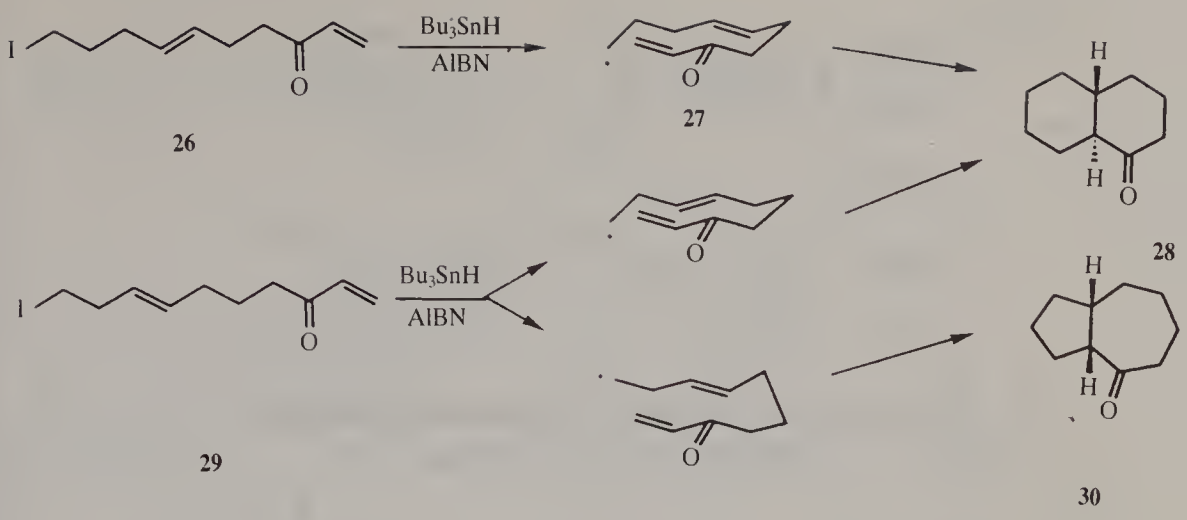
Thus, in tandem with initial 12-*endo*-trig radical macrocyclization from the iodo-trienone **22**, in the presence of Bu_3SnH-AIBN, radical transannulation cyclization from the intermediate radical **23** produced the tricyclo[9.3.1.0]pentadecane ring system **24** in the taxanes in approximately 25% yield (Hitchcock and Pattenden, 1992b). The formation of **24** was also accompanied by the analogous verticillane intermediate **25** and also the product of straightforward C-I reduction of **22**. Work is now continuing to develop and expand this novel strategy towards the taxanes, using alternative designs and more heavily functionalized precursor molecules.



22 23 24 25

4.2 Decalone synthesis

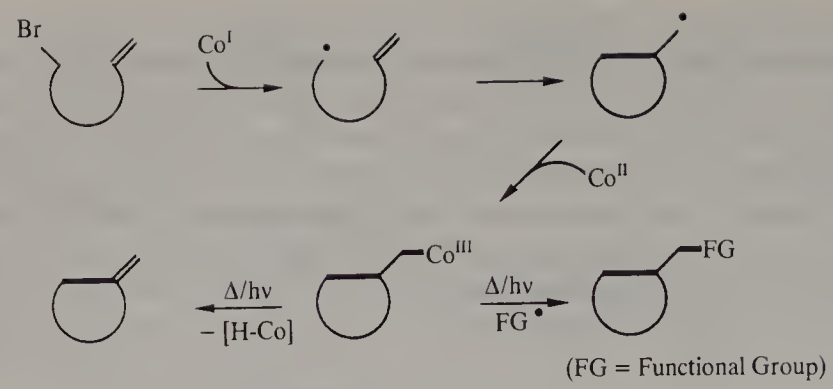
In investigations related to those described with taxanes, we have also demonstrated the scope for tandem radical macrocyclization–transannulation reactions in the synthesis of linear fused 6,6- and 7,5-fused bicycles (G. Pattenden and A. J. Smithies, unpublished results). Thus treatment of the iododienone **26** with Bu_3SnH-AIBN leads exclusively to the decalone **28**, presumably via the transition state **27**, whereas cyclization of the isomeric iododienone **29**



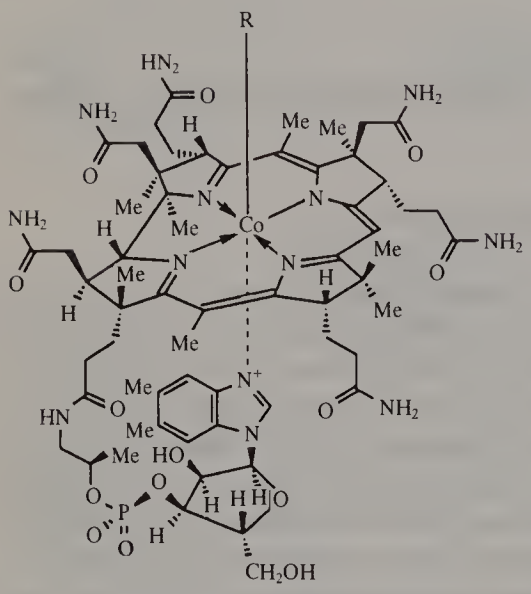
under the same condition leads to a 1:1 mixture of **28** and the 7,5-fused bicyclic ketone **30**.

4.3 Cobalt-mediated tandem radical cyclizations

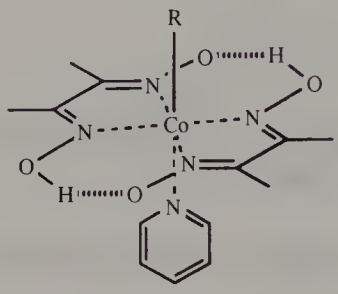
An alternative and attractive way to produce carbon-centred radicals and hence cyclic molecules, is by homolysis of carbon–cobalt bonds in organocobalt compounds (cf. vitamin B_{12}) (see Ali *et al.*, 1992). One of the special features that distinguishes these cobalt-mediated radical carbon–carbon bond forming reactions from most other methods, e.g. Bu_3SnH, R_3SiH, is that they proceed with transfer of the cobalt group from the precursor molecule to the product molecule or intermediate leading to new cobalt-functionalized compounds. These new molecules are then available for further synthesis, e.g. by dehydrocobaltation leading to an alkene product or by interception with an external radical trapping agent (Scheme 8). In recent publications we have described the development and use of a wide range of alkyl, acyl, vinyl and carbamoyl cobalt reagents in radical carbon–carbon and carbon–heteroatom bond forming reactions, including ring synthesis (Ali *et al.*, 1992). We have also developed this chemistry to effect cobalt-mediated tandem radical cyclization reactions, in a controlled manner, allowing trapping and interception of intermediate organocobalt intermediates, leading to functionalized linear and spiro-fused bicyclic systems. Some examples are collected in Schemes 9 and 10 (Ali *et al.*, 1992). These cobalt-mediated cyclization reactions complement similar transition metal-mediated polycycle constructions, particularly those involving palladium (Carpenter *et al.*, 1989; Dorrity *et al.*, 1990; de Meijere *et al.*, 1991; Shi and Trost, 1992), and emphasize the importance of these powerful methods in contemporary synthesis.



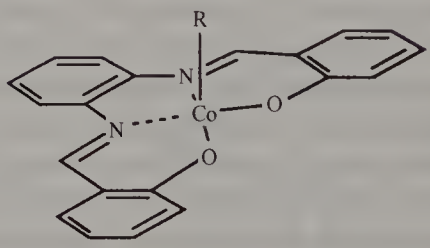
e.g Cobaloxime, $Co(dmgH)_2py$. Cobalt salophen (*cf.* vitamin B_{12})



Vitamin B_{12}



Cobaloxime
$Co(dmg)_2H$



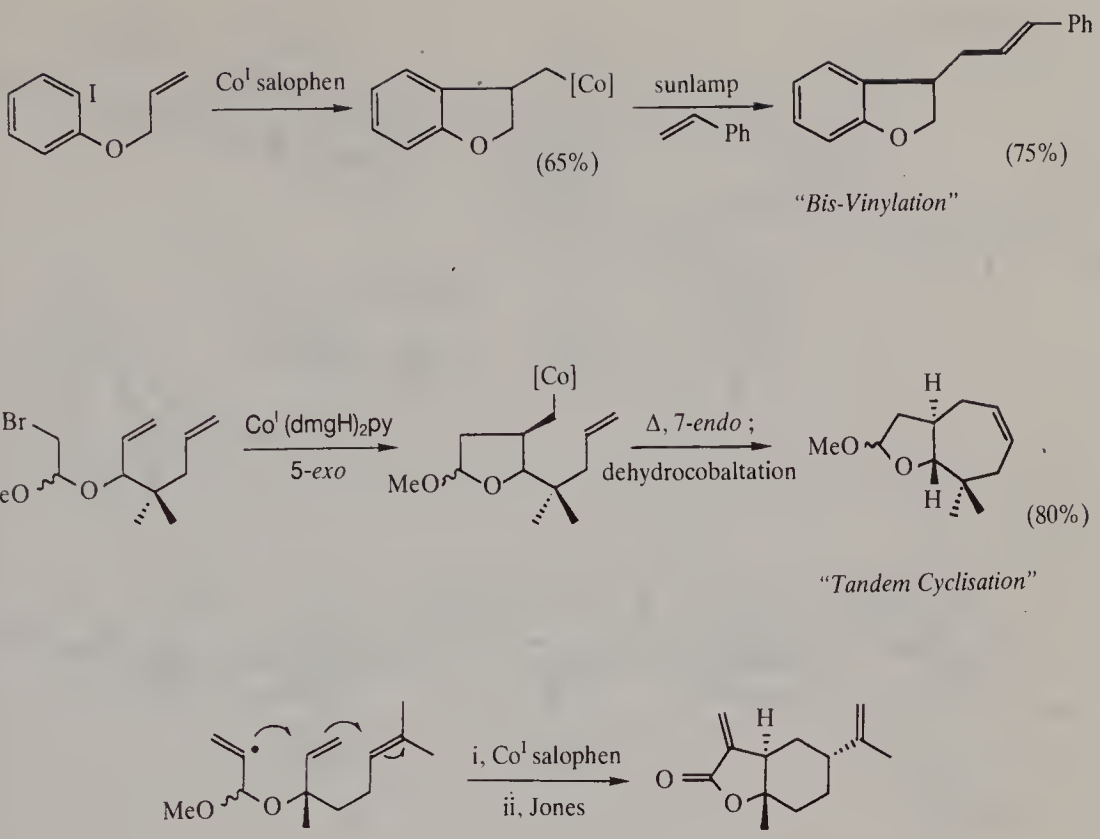
Cobalt salophen complex

Scheme 8

5 Cascade radical fragmentation–transannular-cyclization reactions

5.1 Towards laurenene

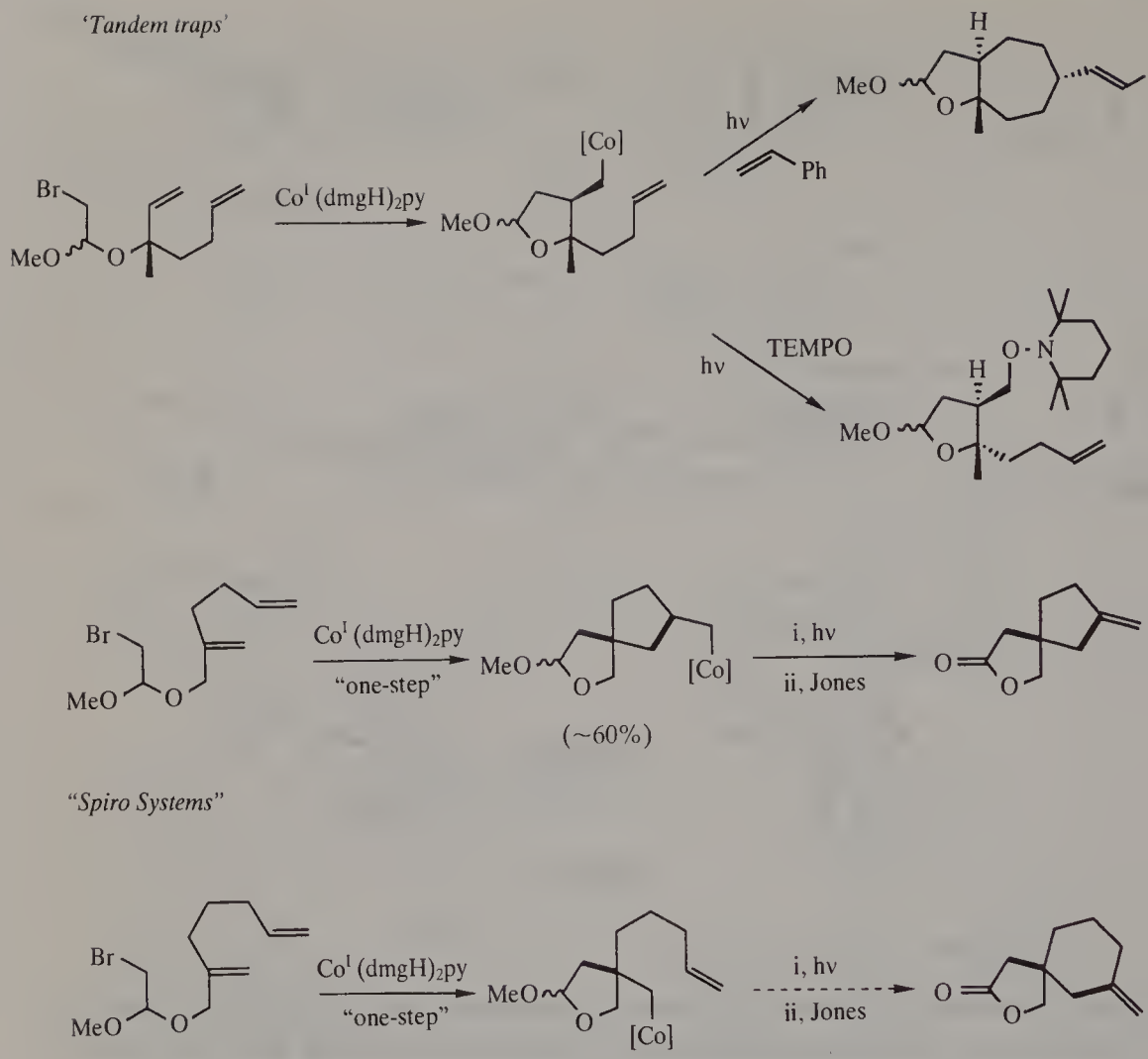
The aforementioned preliminary studies with the synthesis of the taxane and decalin ring systems, by way of a cascade radical-mediated macrocyclization–transannulation strategy, served to highlight the scope for this design in the rapid construction of novel polycycles. Although 10-membered rings are often



Scheme 9

one of the more difficult ring systems to construct directly, the ease with which the decalone **28** could be accessed from **26** by this strategy was particularly interesting. An alternative approach to 10-membered carbon-centred radical intermediates we have considered, however, is one based on the oxy-radical fragmentation sequence from an angular substituted cyclodecanol, highlighted in Scheme 1. We chose an allyloxy rather than an alkyloxy radical as precursor for this sequence of reactions, (i) to control the directionality of the fragmentation step, and (ii) to set up the necessary stereoelectronics for the following tandem radical cyclizations.

Preliminary studies of this design using the readily available unsaturated bicyclodecanols **31** as precursor molecules were most encouraging. Thus, when these molecules were treated with iodosylbenzene diacetate–iodine they underwent smooth fragmentation–transannulation producing the bicyclo-[5.3.0]decanones **32** in good to excellent yields (Ellwood and Pattenden, 1991). When this general protocol was extended to the allyl substituted bicyclodecanol **33** a beautiful sequence of cascade radical fragmentation–transannulation–cyclization reactions ensued, leading to the novel 7,5,5-angular fused tricycles

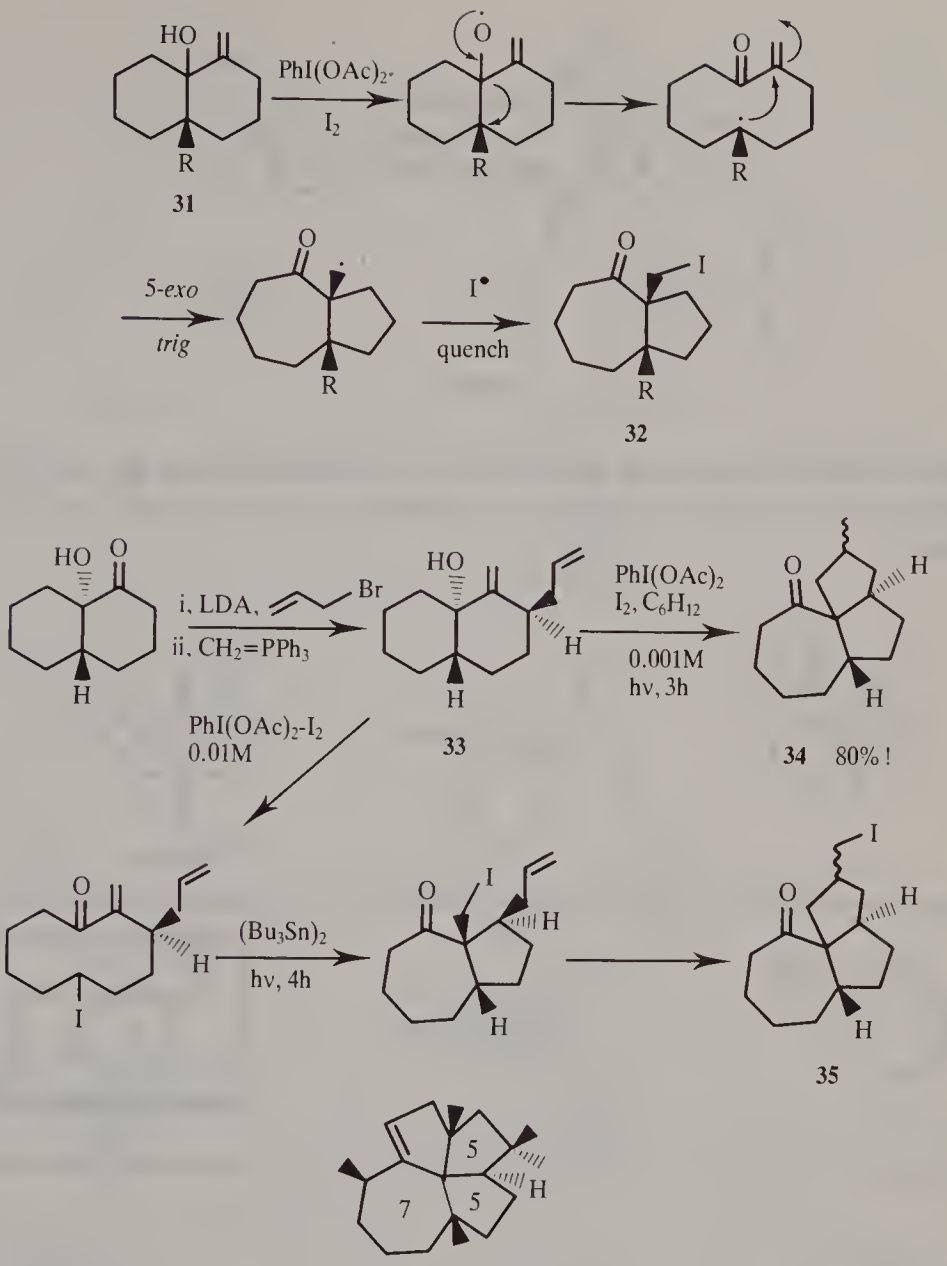


Scheme 10

34 and **35** in 60–80% yields, depending on reaction conditions (Mowbray and Pattenden, 1993). Further studies are now in progress to develop this particular chemistry in the direction of a synthesis of the unusual tetracyclic natural product laurenene **36** which shows a similar topology to structures **34** and **35**.

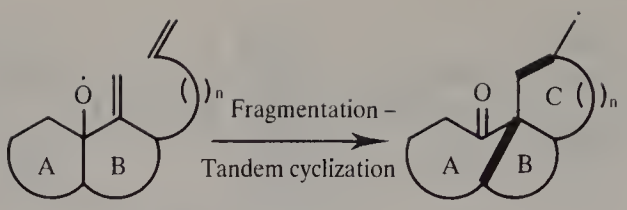
5.2 A cyclobutane double ring expansion

In principle the angular hydroxy-substituted bicyclic precursor in the sequence shown in Scheme 11 could assume any ring size (but not less than four for ring A, or six for ring B) and the alkenyl side chain can accommodate one or more methylene units. This flexibility, together with the possibility of incorporating heteroatoms within the framework, could provide a powerful strategy to a wide variety of polycarbo- and heterocycles.



36, laurenene
(ex. *Daerydium cupressinium*)

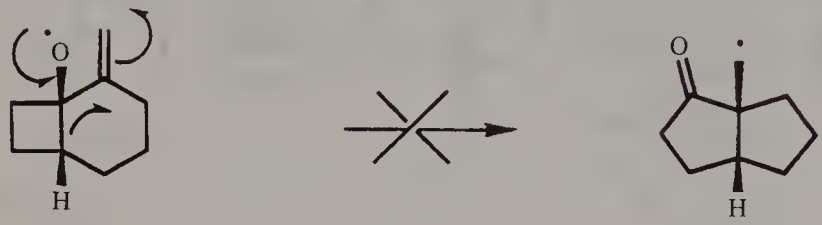
A particularly intriguing ring system we have examined in some detail is the substituted bicyclo[4.2.0]octane **37** with a view to developing a one-pot route to angular fused triquinanes. In the event, this approach was not successful. Nevertheless during the course of these studies we discovered perhaps an even more interesting sequence of radical reactions, i.e. the 'one-pot' conversion of the acetylene substituted cyclobutanone oxime **38** to the 6,5-bicyclic oxime **39** in 60% yield (G. Pattenden and D. Schulz, unpublished work). This conversion, which presumably occurs by fragmentation from the initially produced



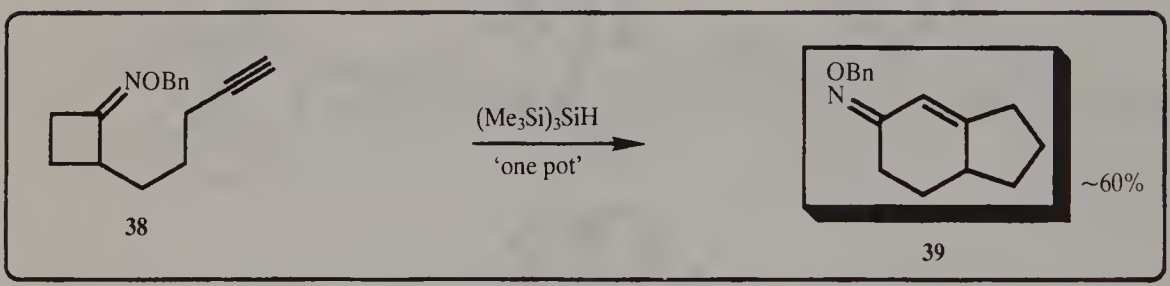
A	4 → 7	*A*	5 → 8
B	6 → 9	*B*	5 → 8
n	1 → 4	*n*	5 → 8

Scheme 11

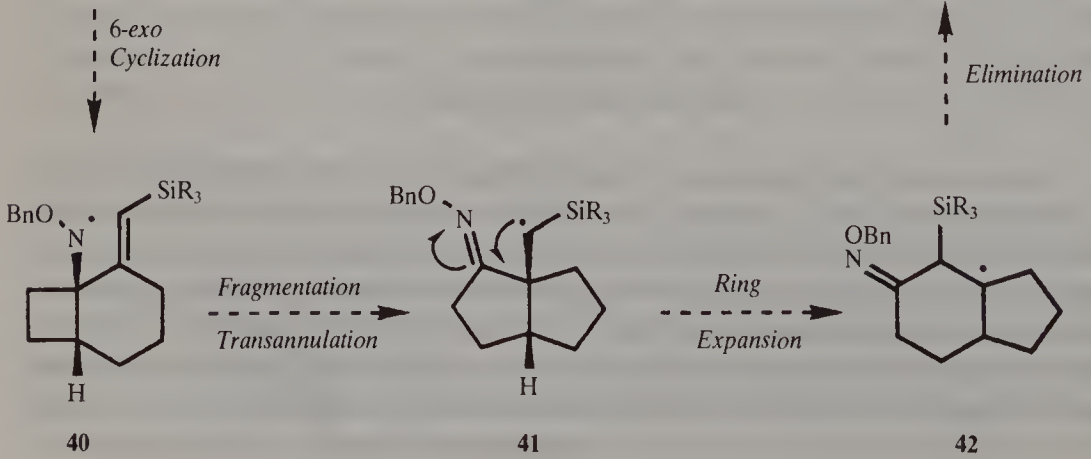
aminyl radical intermediate **40**, followed by transannulation (to **41**) and the ring expansion step **41** → **42**, could be developed into a useful ploy in synthesis design.



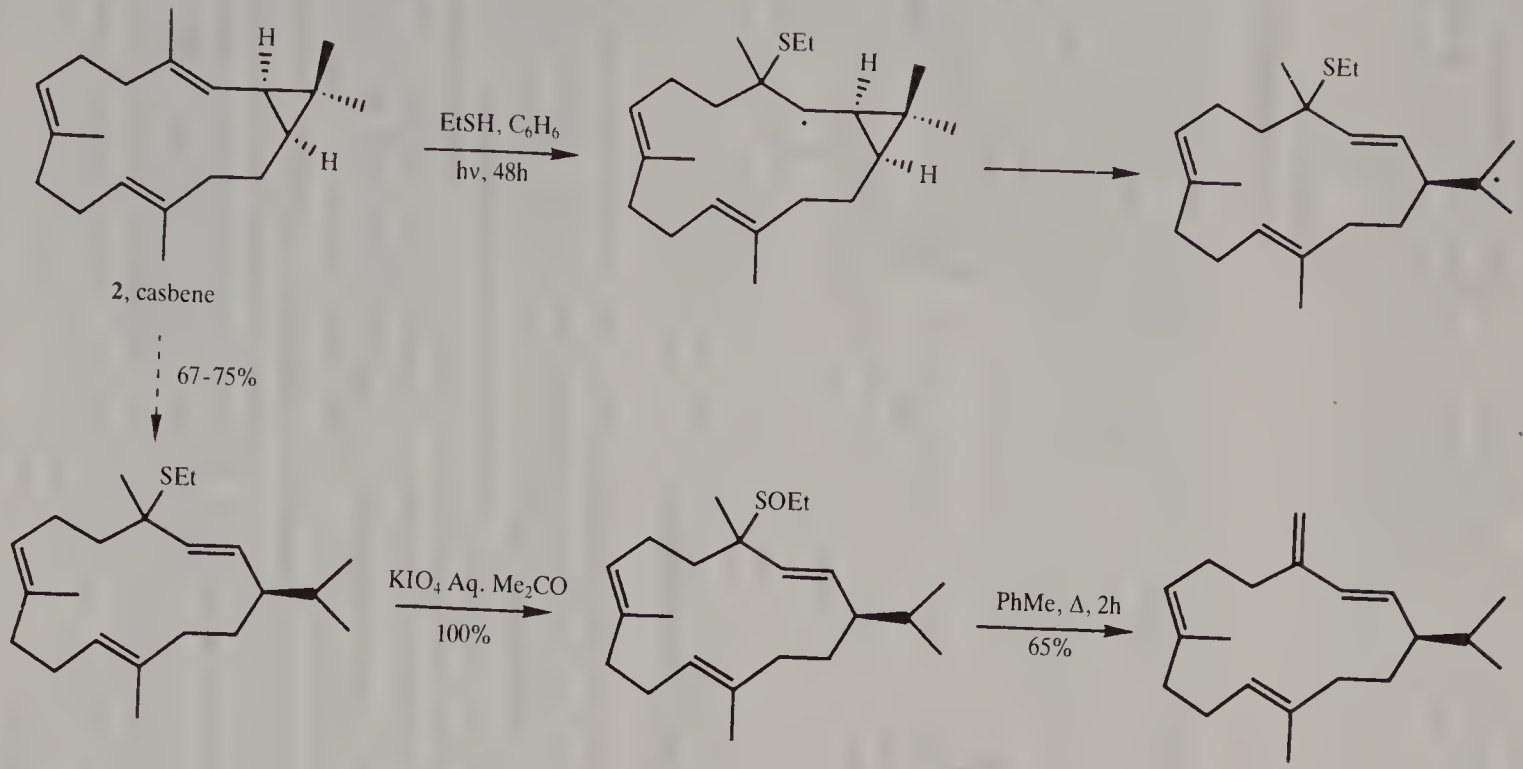
37 Diquinane



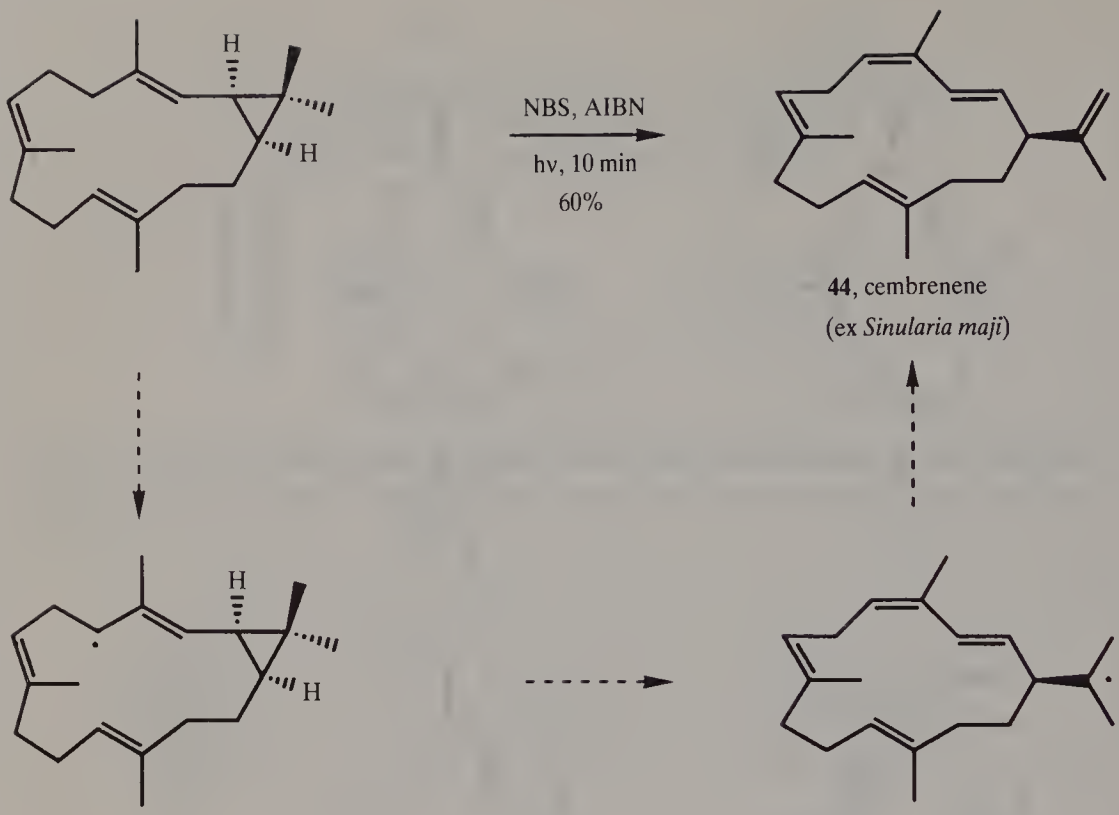
38 **39**



40 **41** **42**



43, isocembrene
(ex. *Pinus sibirica*)



6 Radical reactions from casbene

The foundation, and some of the driving force, for the investigations highlighted in this review, was our complementary interest in the possible role of casbene **2** in the biosynthesis of other polycyclic diterpenes by transannulation processes *in vivo*. It was logical therefore that we should carry out an examination of possible radical cyclization reactions from this unusual hydrocarbon. Surprisingly however, and to our disappointment we have not been able to demonstrate radical-mediated transannular cyclization reactions in casbene. We have nevertheless observed that when a solution of casbene **2** in benzene is irradiated in the presence of ethanethiol, it produces a sulphide intermediate in 67–75% yield, which can be readily converted into the natural cembranoid isocembrene **43** found in *Pinus sibirica*. Furthermore, in a 'one-pot' procedure casbene can be converted into natural cembrenene **44** in 60% yield, following brief treatment with *N*-bromosuccinimide and AIBN (Pattenden and Smithies, 1992).

Acknowledgements

It is a great pleasure to have this opportunity to express my sincere thanks to my young colleagues Nick Cox, Martin Astley, Steve Hitchcock, Allison Smithies,

Amjad Ali, Charles Ellwood, Charlie Mowbray and Darren Schulz who have contributed greatly to developing the area of polycycle constructions by radical-mediated processes in Nottingham. We are grateful for the financial support these studies have received from ICI Strategic Fund, Glaxo Group Research, Fisons Pharmaceuticals, Boots Ltd, Pfizer Central Research, Rhône-Poulenc Rorer and the Science and Engineering Research Council.

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Appendix: Abstracts of Posters

Contents

Synthesis of Natural Products and Biomolecules

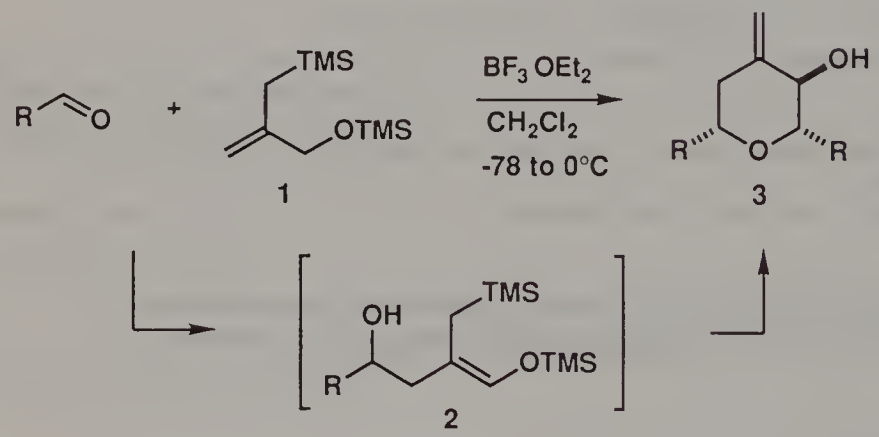
Synthetic Methodology

Enantioselectivity and Stereocontrol

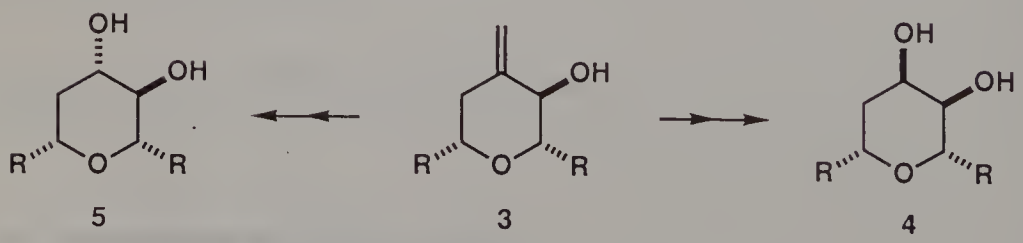
Synthesis of Natural Products and Biomolecules

The Intramolecular Silyl Modified Sakurai Reaction. An Easy Access into the Core of Pseudomonic Acid and Ambruticine. Daniel J. Bayston and István E. Markó. *Université Catholique de Louvain, Département de Chimie, Laboratoire de Chimie Organique, Bâtiment Lavoisier, Place Louis Pasteur 1, B-1348 Louvain-La-Neuve, Belgium*

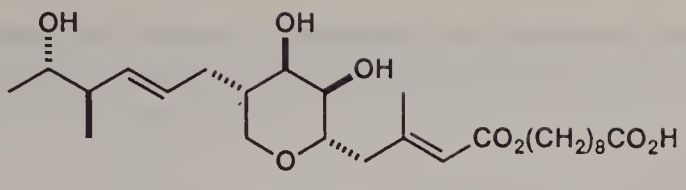
Whilst attempting to broaden the scope of our recently reported ISMS reaction [1–4], we have discovered that the condensation of aldehydes with the *bis*-silyl reagent **1**, under Lewis acid catalysis, provides tetrahydropyrans **3** as a single diastereomer [5]. Isolation of the silyl enol ether **2**, an intermediate in this reaction, has led to the observation of a remarkably fast proton elimination, in preference to the elimination of a trimethylsilyl group.



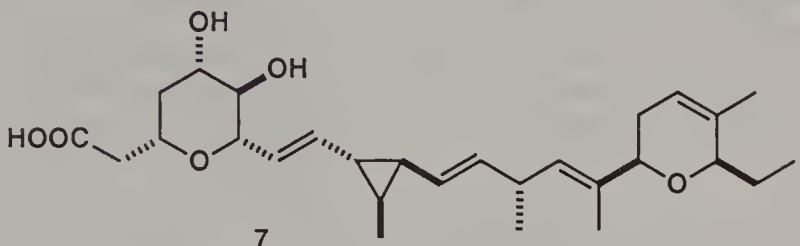
Scheme 1



Scheme 2



6



7

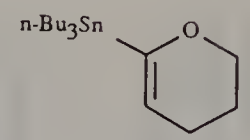
Scheme 3

The transformation of **3** into diols **4** and **5** has been achieved with full stereocontrol and thus provides a good model for the tetrahydropyran units found in the natural products pseudomonic acid **6** and ambruticine **7**.

[1] Mekhalfia, A. and Markó, I. E. (1991). *Tetrahedron Lett.* **32**, 4779.
[2] Mekhalfia, A. and Markó, I. E. (1991). *Tetrahedron Lett.* **32**, 4783.
[3] Markó, I. E., Mekhalfia, A., Bayston, D. J. and Adams, H. (1992). *J. Org. Chem.* **57**, 2211.
[4] Markó, I. E. and Mekhalfia, A. (1992). *Tetrahedron Lett.* **33**, 1799.
[5] Bayston, D. J. and Markó, I. E., manuscript in preparation.

Synthesis of Some Cephem Spiroacetal-Lactones. John H. Bateson, George Burton, Susan A. Elsmere and Richard L. Elliott. *SmithKline Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ, UK*

Reaction of the cephem-3-triflate **2** and of the 3-chloromethyl cephem **4** with tri-*n*-butyl (5,6-dihydropyran-2-yl)stannane **1** in the presence of catalytic quantities of *bis*(dibenzylideneacetonyl)-palladium(0) [$Pd(dba)_2$] and tri(2-furyl)phosphine gave enol ethers **3** and **5**, respectively. Exposure of **3** to trifluoroacetic acid produced the spiroacetal-γ-lactones **6** and **7** in similar proportion, whereas deprotection of **5** afforded an isomer of the spiroacetal-δ-lactone **8** as the major product.



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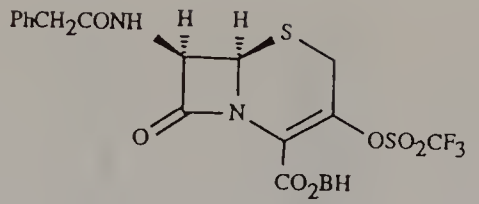

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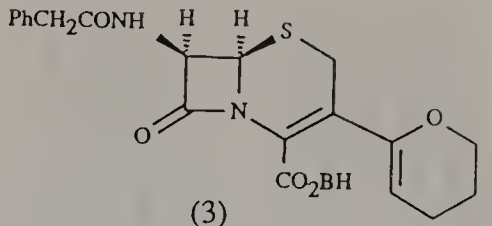

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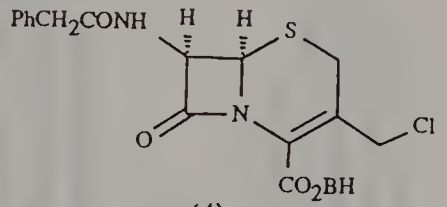
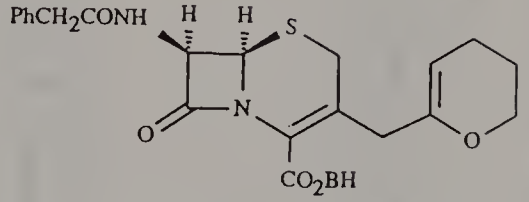


(4)



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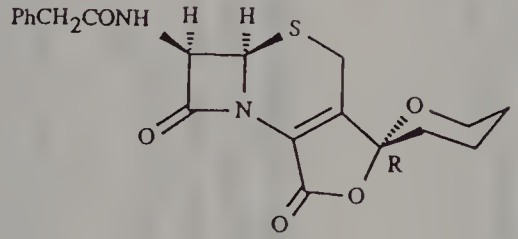
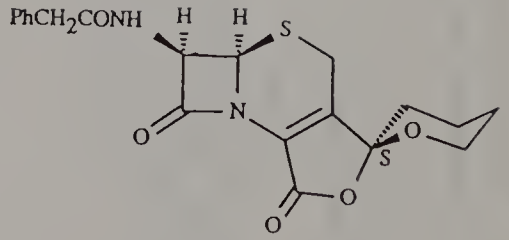
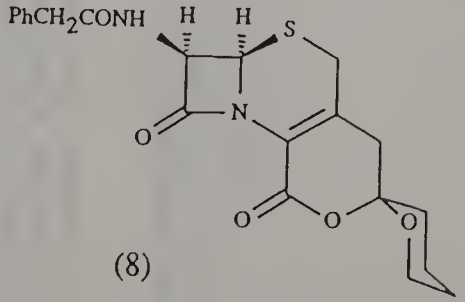


(6)



(7)



(8)

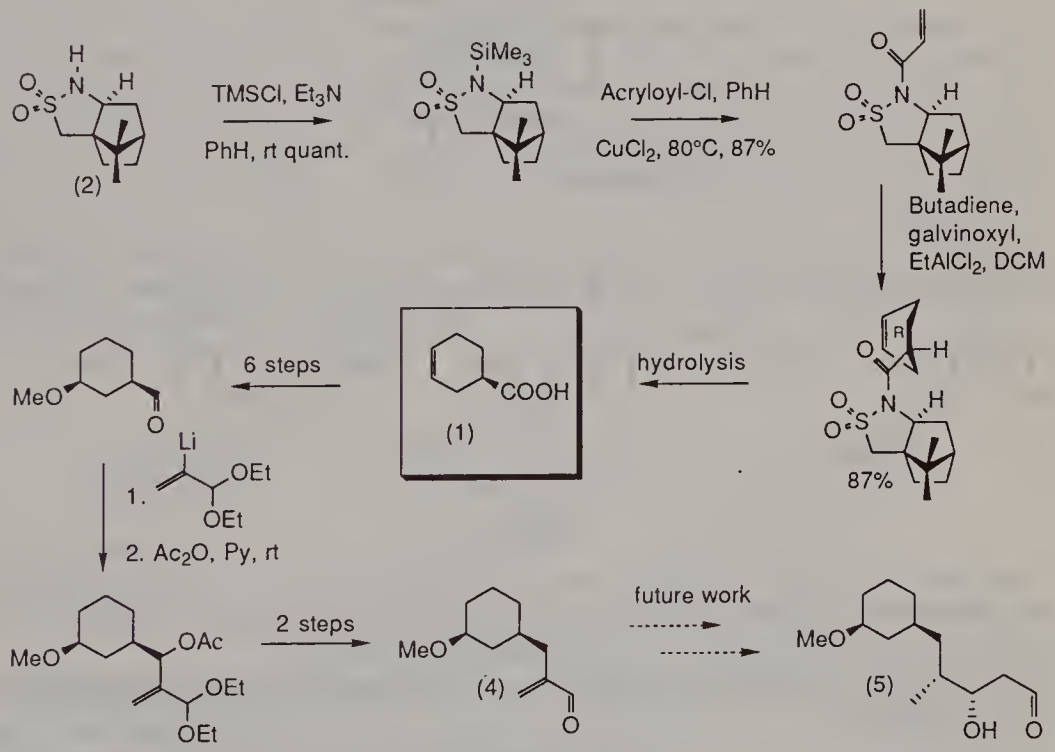
Scheme 4

Synthetic Methods Directed Towards the Synthesis of Rapamycin.

Catriona Thom. *Department of Chemistry, University of Southampton, Southampton SO9 5NH, UK*

Rapamycin, a 31-membered macrocyclic lactone, displays immunosuppressive activity and is a challenging synthetic target. This poster describes the efficient and practical asymmetric synthesis of (*R*)-cyclohex-3-enecarboxylic acid **1**, a key starting material being used currently in the construction of fragment **5**. Acid **1** was to be prepared via an asymmetric Diels–Alder reaction employing Oppolzer's chiral sultam **2** [1]. Problems encountered during the synthesis were overcome by (a) the development of a new method for *N*-acylation [2] and (b) the efficient inhibition of unwanted polymerization [3]. The acid is incorporated into a fragment of rapamycin via the addition of lithiated acrolein diethylacetal to aldehyde **3** [4] followed by palladium-catalysed removal of the allylic acetate and hydrolysis of the acetal to give aldehyde **4**.

A large-scale, efficient and practical synthesis of (*R*)-cyclohex-3-enecarboxylic acid **1** has been achieved and the incorporation of **1** into the Northern fragment of rapamycin is proceeding well.



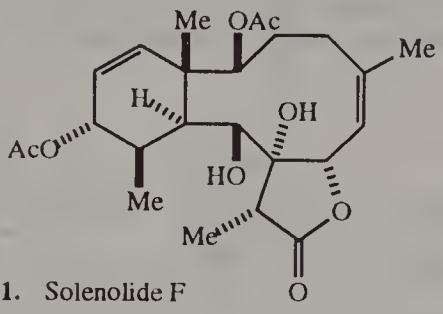
Scheme 5

[1] Oppolzer, W., Chapuis, C. and Bernardinelli, G. (1984). *Helv. Chim. Acta* **67**, 1397.
[2] Thom, C. and Kocienski, P. J. (1992). *Synthesis* 582.
[3] Thom, C., Kocienski, P. J. and Jarowicki, K. *Synthesis*, in press.
[4] Ficini, J. and Depezay, J-C. (1969). *Tetrahedron Lett.* 4797.

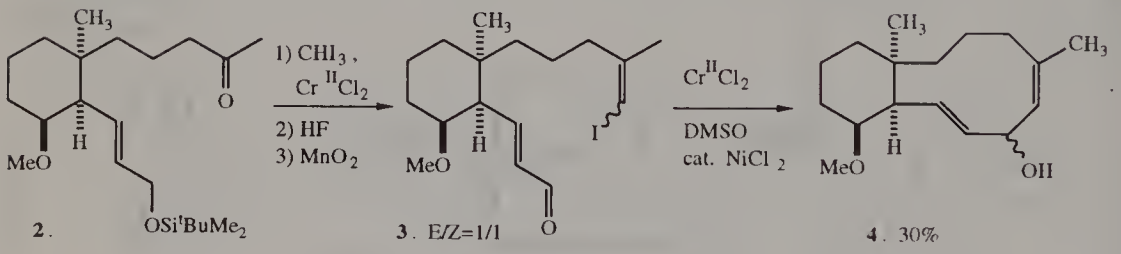
Synthetic Studies Towards Solenolides. Michael B. Roe and Garry Procter. *Department of Chemistry, University of Salford, Salford M5 4WT, UK*

Solenolides are a class of marine diterpenoids typified by solenolide F, **1**, that are found to be potent anti-inflammatory agents [1]. This poster describes how an intramolecular chromium-mediated Grignard-type reaction, as developed by Nozaki [2], might be used to effect the key 10-membered ring closure.

One carbon homologation of the ketone **2** using Takai's chromium chemistry [3] followed by desilylation and oxidation provided the iodide **3**. When subjected to the chromium-mediated coupling conditions we observed cyclization to give the model cyclic compound **4**.



1. Solenolide F

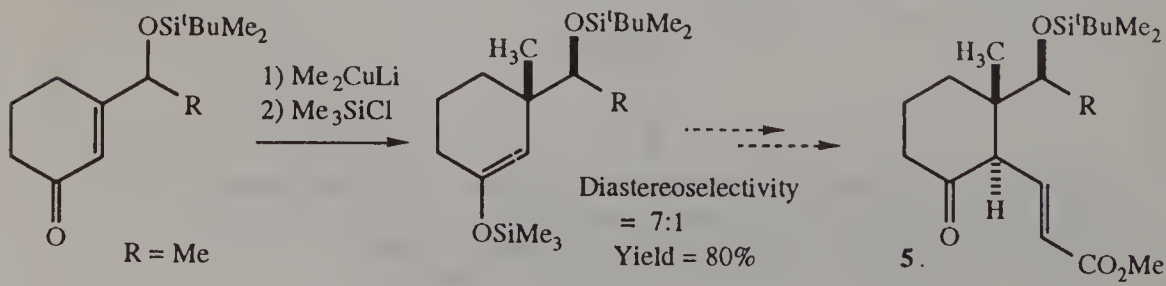


2. **3.** E/Z=1/1 **4.** 30%

Scheme 6

This poster also details the synthesis of the model compound **5** (R = Me). This employs a stereoselective conjugate addition–trapping procedure that generates the adjacent oxygenated and quaternary centres and sets up the *trans* fused ring junction relationship.

We are hopeful that a combination of these strategies will allow the synthesis of solenolide F and related compounds.



Scheme 7

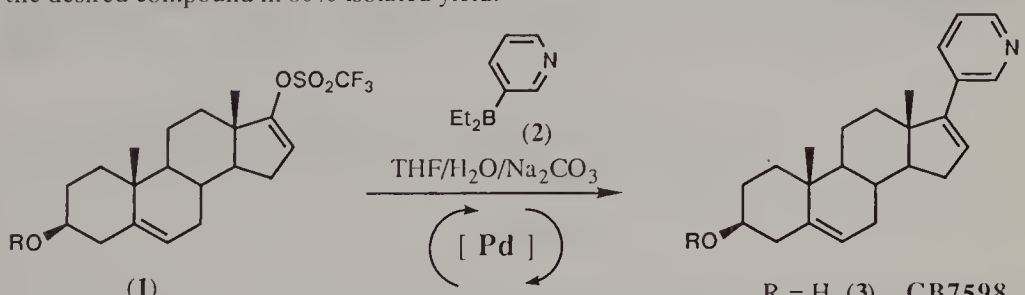
[1] Groweiss, A., Look, S. A. and Fenical W. (1988). *J. Org. Chem.* **53**, 2401.
[2] For a review see Cintas, P. (1992). *Synthesis* 248.
[3] Takai, K., Nitta, K., Fujimura, O. and Utimoto, K. (1986). *J. Am. Chem. Soc.* **108**, 7408.

Discovery of Highly Potent and Selective Enzyme Inhibitors with Potential for the Treatment of Prostate Cancer; The Important Dual Role of Transition Metal Chemistry in Both Drug Design and Synthesis.

G. A. Potter and S. E. Barrie. *Drug Development Section, Institute of Cancer Research, Sutton, Surrey SM2 5NG, UK*

The effective inhibition of androgen biosynthesis or antagonism of androgen receptor action represent major objectives in prostatic cancer therapy. We have demonstrated the utility of organotransition metal chemistry in the discovery [1] and development [2] of hormone receptor antagonists and present here the important role of transition metal chemistry in both the design and synthesis of novel inhibitors of hormone biosynthesis.

The 17α-hydroxylase/C_{17-20}lyase iron-containing cytochrome P-450 is the key enzyme responsible for androgenic hormone biosynthesis. By using a *de novo* mechanism-based approach a complete catalytic cycle for this enzyme was postulated. By considering the juxtaposition of the steroid D-ring to the haeme co-factor iron atom in the putative hydroxylase and lyase transition states the novel 17-(3-pyridyl)Δ^{16-17} steroid CB7598 **3** was designed. Synthesis of this molecule was envisaged via a possible palladium-catalysed cross-coupling [2] of a steroidal enol triflate **1** with a suitable 3-pyridyl nucleophilic coupling partner. This was achieved by using diethyl(3-pyridyl)borane in aqueous THF, with sodium carbonate as nucleophilic activator. The reaction proceeded remarkably efficiently, without possible triflate hydrolysis or ethyl coupling, providing the desired compound in 80% isolated yield.



Scheme 8

When assayed against the human hydroxylase/lyase enzyme [3] *in vitro* CB7598 displayed highly potent inhibitory activity and gave an IC_{50} value of 1 nM ($Ki_{app} \sim 0.5$ nM). Furthermore it was inactive against a related P-450 enzyme, indicating excellent target enzyme selectivity. When assayed *in vivo* it reduced plasma testosterone to undetectable levels and produced a pronounced decrease in the size of the prostate.

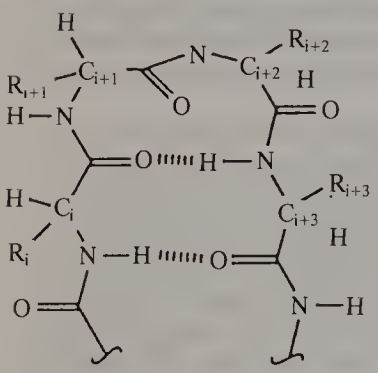
The development of these compounds illustrates the synergistic benefits of understanding transition metal mediated processes in synthesis and biosynthesis.

[1] Potter, G. A. and McCague, R. (1992). *J. Chem. Soc., Chem. Commun.* 635–637.
[2] Potter, G. A. and McCague, R. (1990). *J. Org. Chem.* **55**, 6184–6187.
[3] Barrie, S. E., Jarman, M., McCague, R., Potter, G. A. and Rowlands, M. G. (1992). UK Patent GB 2,253,851A.

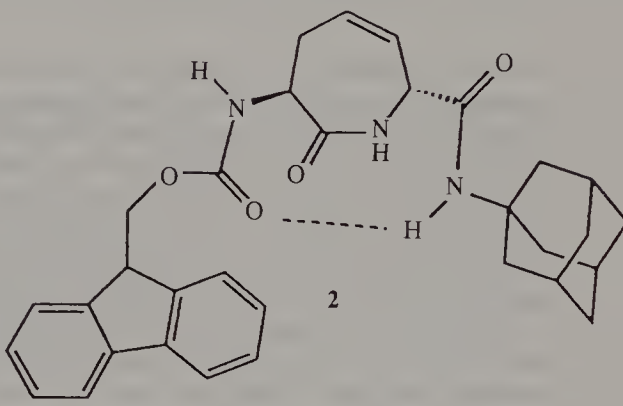
Design and Synthesis of a β-turn Mimic. Alan Nadin and Andrew B. Holmes. *University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK*

β-Turns are a very common element of protein structure, comprising an average 25% of the amino acid residues. The β-turn is a four amino acid residue unit (**1**) (residues i to i+3) where the peptide chain reverses its overall direction.

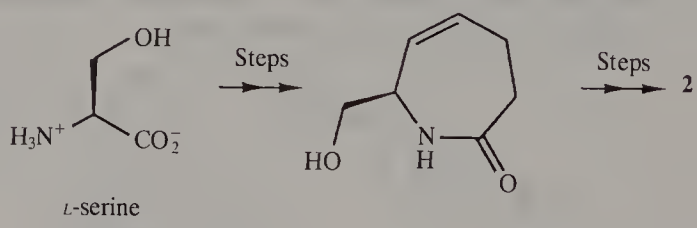
The design and synthesis of **2**, a putative type II β-turn mimic, from L-serine is described. Some evidence for the conformation of **1** is also presented.



1, idealized type II β-turn



2



L-serine

Scheme 9

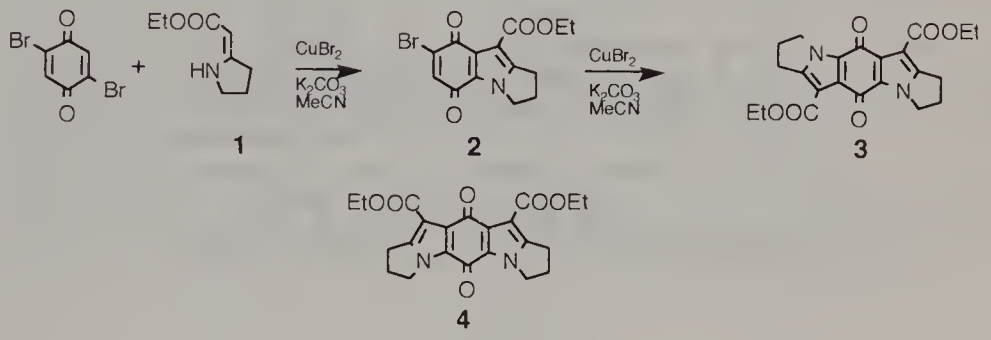
[1] Kabasch, W. and Sander, C. (1968). *Biopolymers* **6**, 1425.
[2] Wilmott, C. M. and Thornton, J. M. (1988). *J. Mol. Biol.* **203**, 221.

Cu(II)-catalysed Annulation of Bromoquinones with Enamines. Synthesis of Novel Mitomycin and Kinamycin Analogues. W. S. Murphy and P. J. O'Sullivan. *University College, Cork, Ireland*

We have recently shown that annulation of bromoquinones with enamines presents a particularly simple regiospecific route to the anticancer mitomycins [1]. The methodology was extended to a

first synthesis of the kinamycin framework [2]. We now report the successful extension of this approach to novel *bis*-annulated analogues. These substrates have the capability of inducing *bis*-crosslinkage of DNA with enhanced potential for inhibiting DNA replication and of leading thereby, to repression of tumour growth. This synthetic approach to novel anticancer drugs has the inherent capability of incorporating in an intimate way the characteristic electrophilic functionalities of two known electrophilic anticancer reagents within the same substrate.

Employing 2,6-dibromobenzoquinone, annulation was undertaken with pyrrolidine enaminoester, **1**, as a model. Reaction was successful with the formation of the *bis*-indoloquinone **3**, albeit in low yield. A closer examination of the reaction revealed that a two-step sequence was more effective. Thus the overall yield of *bis*-indoloquinone **3** was increased to 40% when the reaction was stopped after the formation of the *mono*-annulated product **2**, which was then isolated with subsequent treatment with the same reagents.



Scheme 10

Extension to the symmetrical *bis*-indoloquinone **4** from the corresponding dibromide was equally successful. Synthesis of the annulated *bis*-products and mixed *bis*-products derived from substituted electrophilic and homochiral enaminoesters, is under investigation.

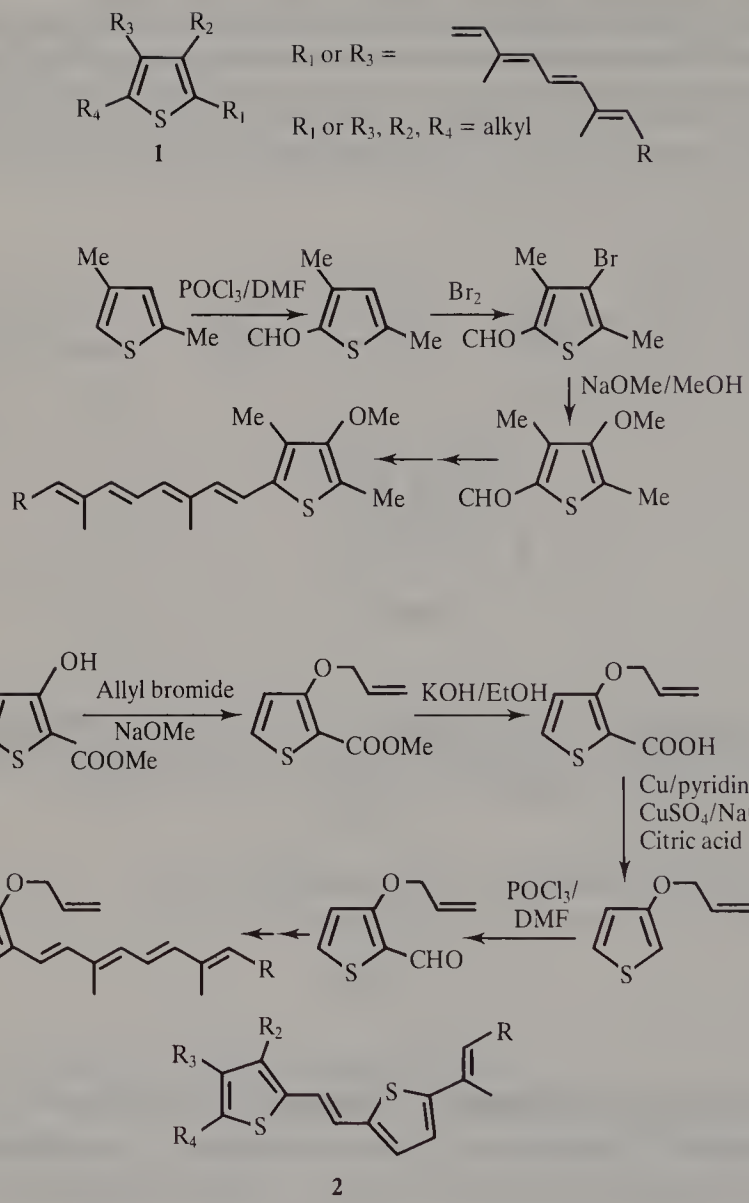
[1] Murphy, W. S. and O'Sullivan, P. J. (1992). *Tetrahedron Lett.* 531.
[2] O'Sullivan, P. J. and Murphy, W. S. (1992). *Tetrahedron Lett.* 535.

Routes to Thiophene Analogues of Vitamin A.

C. Nallaiah[1], R. Keane[1] and L. S. Fuller[2]. [1]*University of Wolverhampton, West Midlands, UK*; [2]*Synthetic Chemicals Ltd, Four Ashes, Nr. Wolverhampton, UK*

Thiophene analogues of vitamin A of the type **1** have been reported in the literature [1]. We have attempted to synthesize thiophene analogues of vitamin A and related molecules of the type **2**, with allyloxy and methoxy substituents in the 3-position. The synthetic routes we have tried are represented in Schemes 1a and b.

[1] Klaus, M. J. and Pawson, B. A. (1981). US Patent 4,256,878.


R3
R2
R4
S
R1
1
R1 or R3 =
R1 or R3, R2, R4 = alkyl
R
Me
POCl3/DMF
CHO
Br2
Br
NaOMe/MeOH
OMe
OH
Allyl bromide
NaOMe
COOMe
KOH/EtOH
COOH
Cu/pyridine or
CuSO4/NaOH
Citric acid
POCl3/
DMF
2

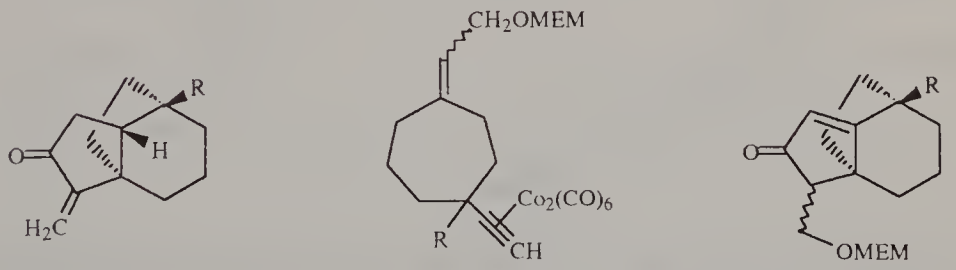
Scheme 11

An Organocobalt-mediated Route to the Quadrone Skeleton. Synthesis of the Antitumour Agent, Bisdemethyldescarboxyquadrone. G. S. Forsyth[1], W. J. Kerr[1] and T. Ladduwahetty[2]. [1]*Department of Pure and Applied Chemistry, University of Strathclyde, Thomas Graham Building, Cathedral Street, Glasgow G1 1XL, UK;* [2]*Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*

In recent years a number of α-methylene cyclopentanones have been shown to have potential as antitumour agents. Among these are the quadrone family of fungal metabolites and their analogues, with *bis*demethyldescarboxyquadrone (**1a**) having been shown to be one of the most active compounds in this class.

The descarboxyquadrone skeleton **4** is formed by efficient and novel intramolecular Pauson–Khand cyclization of the hexacarbonyldicobalt alkyne complexes **2** and **3** to furnish cyclopentenones **4a** (82%) and **4b** (98%), respectively. Complexes **2** and **3** are synthesized in 11 and 10 steps (overall yield 29% and 32%), respectively, from readily available 2-cyclohepten-1-one. The route to the complexes incorporates a newly developed allylic oxidation procedure.

From cyclopentenones **4a** and **4b** the α-methylene cyclopentanones **1a** and **1b** are subsequently formed in a further two synthetic steps (83% and 79% yield). The overall yield of *bis*demethyldescarboxyquadrone **1a** from 2-cyclohepten-1-one is an outstanding 20% over some 14 steps.



(**1a**) R= -H
(**1b**) R= -OH

(**2**) R= -H
(**3**) R= -OH

(**4a**) R= -H
(**4b**) R= -OH

MEM- = $CH_3OCH_2CH_2OCH_2$-

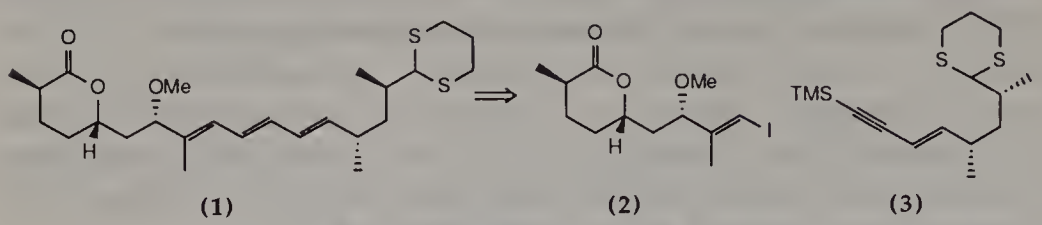
Scheme 12

Modified Nicholas carbocation chemistry has also been developed to efficiently dehydroxylate propargyl alcohol complexes of type **3**. Compound **2**, required for the synthesis of *bis*demethyldescarboxyquadrone **1a**, has been reached in 92% yield from **3** by the use of catalytic amounts of trifluoroacetic acid and triethylsilane at 0°C. The generality of this technique is currently being explored in our laboratory.

Rapamycin: A Convergent Approach to the Southern Fragment. Richard Bellingham. *Department of Chemistry, University of Southampton, Southampton SO9 5NH, UK*

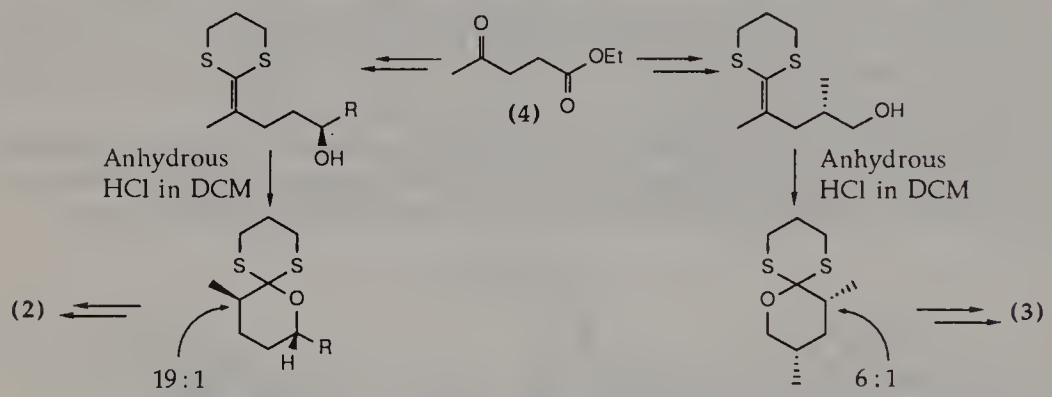
Rapamycin is a powerful immunosuppressant which exerts its biological activity when bound to FK binding protein. A total synthesis will give access to more simple fragments which may exhibit immunosuppressant activity. A convergent approach to the Southern fragment has been designed, and is well underway.

A retrosynthetic analysis of the Southern fragment **1** is shown.



Scheme 13

The syntheses of fragments **2** and **3** both start from cheap, readily available, starting material ethyl levulinate **4** (£45.60/500 g). The syntheses of both **2** and **3** involve the same key, acid-catalysed, diastereoselective cyclization reaction reported by Suzuki [1].



Scheme 14

The diastereoselection of this reaction seems dependent on the position of the directing chiral centre relative to the dithiaketene acetal moiety.

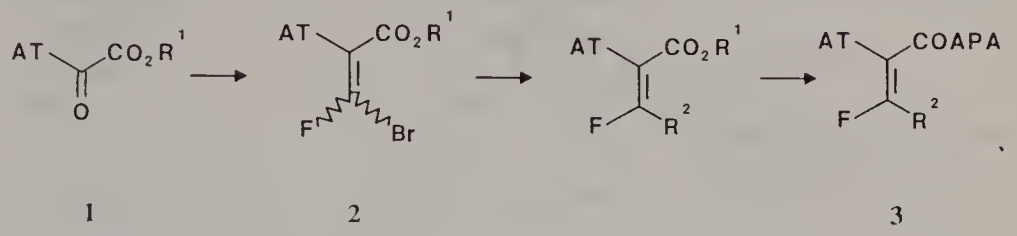
To sum up, the syntheses of both **2** and **3** are almost complete. With these sub-fragments in hand, we will attempt deprotection and then hydroboration of the acetylene **3** followed by a palladium-catalysed coupling reaction with **2**.

[1] Suzuki, K., Tomooka, K., Katayama, E., Matsumoto, T. and Tsuchihashi, G. (1986). *J. Am. Chem. Soc.* **108**, 5221–5229.

Synthesis of Fluorinated Olefins via 1-Bromo-1-fluoroalkenes; Applications in β-lactam Derivatives. Richard L. Elliott. *SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ, UK*

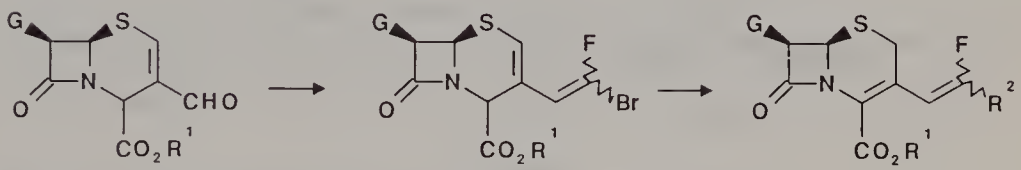
This poster describes the synthesis of fluoroacrylamido penicillins **3** and cephalosporins from the glyoxylate **1** via transition metal-catalysed alkylation of the fluorobromoacrylate **2**. A similar

procedure is employed to synthesize 3-(2-fluorovinyl)ceph-3-ems **5** from the ceph-2-em aldehyde **4**. The antibacterial activity of the fluorine-containing derivatives is slightly inferior to the corresponding hydrogen analogues.



1 2 3

AT = (protected) 2-aminothiazol-4-yl
R^1 = $CHPh_2$
R^2 = alkyl



4 5

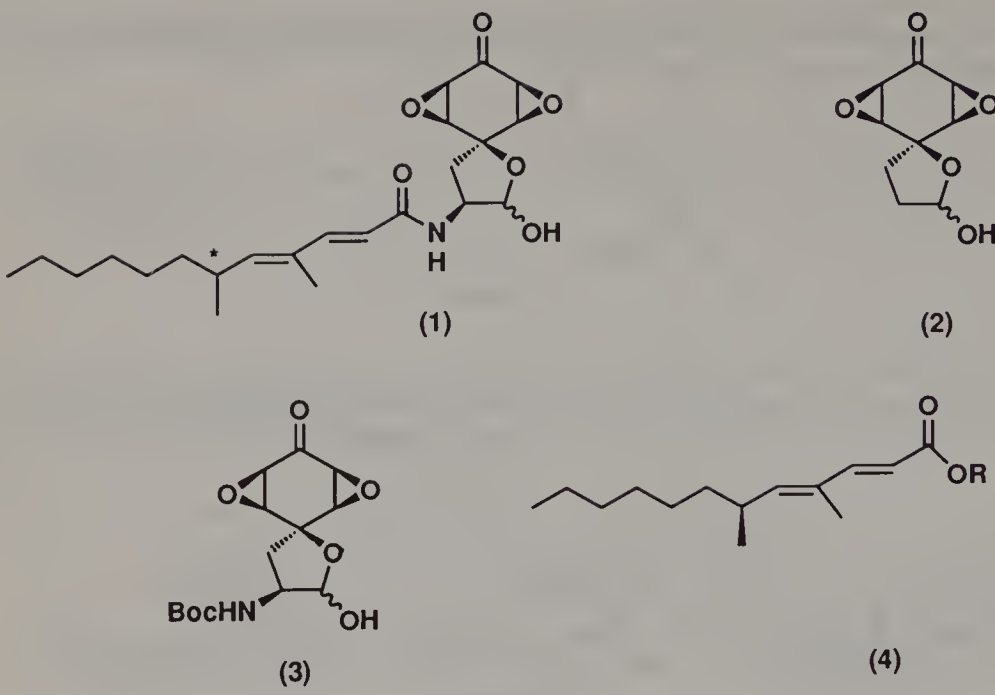
G = $PhCH_2CONH$
R^1 = $CHPh_2$
R^2 = H or alkyl

Scheme 15

Synthetic Approaches to the Novel Antibiotic, Aranorosin. A. McKillop[1], L. McLaren[1], R. J. K. Taylor[1], R. J. Watson[1] and N. Lewis[2]. [1]*University of East Anglia, Norwich NR4 7TJ, UK;* [2]*SmithKline Beecham Pharmaceuticals, Old Powder Mills, Tonbridge TN11 9AN, UK*

Aranorosin **1** was isolated from the fungal strain, *Pseudoarachniotus roseus* and found to have potent antibacterial, antifungal and antineoplastic activity [1]. Our poster describes a variety of synthetic approaches to the natural product and successful synthesis of the model hemiacetal **2** and the tetracyclic nucleus **3** in highly concise routes. The side chain **4** has been prepared following Evans' methodology [2]. Future work aimed at the completion of the natural product synthesis will also be outlined. (See Scheme 16, overpage.)

[1] Fehlhaber, H. W., Kogler, H., Mukopadhyay, T., Vijayakumar, E. K. S., Roy, K., Rupp, R. H. and Ganguli, B. N. (1988). *J. Am. Chem. Soc.* **110**, 8242.
[2] Evans, D. A., Ennis, M. D. and Mathre, D. J. (1982). *J. Am. Chem. Soc.* **104**, 1737.



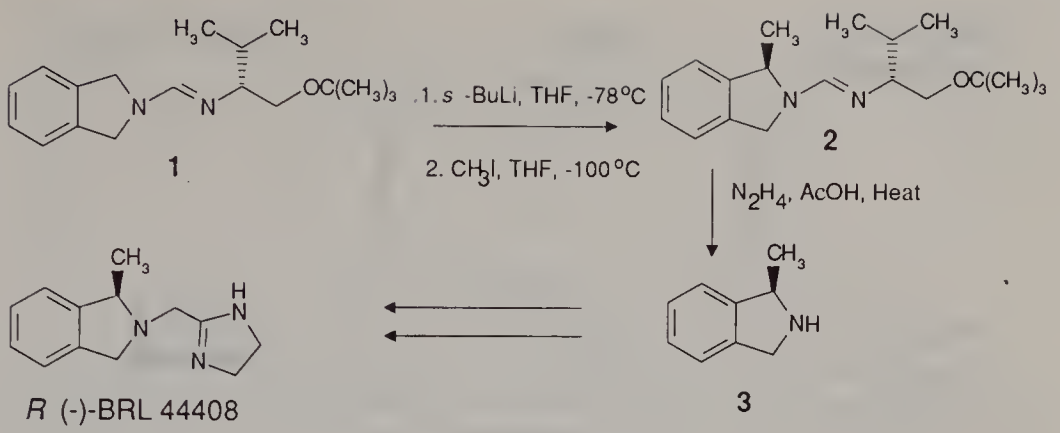
Scheme 16

Synthesis and Adrenergic Activity of the Enantiomers of BRL 44408, a Selective α_{2A}-Antagonist. L. J. Beeley, J. M. Berge, B. C. C. Cantello, C. J. M. Rockell and P. W. Young. *SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ, UK*

The subclassification of the α_2-adrenoceptor into α_{2A}- and α_{2B}-subtypes [1] has been given support by the discovery of an α_{2A}-selective antagonist, (±)-BRL 44408 [2]. This α_2-antagonist selects against α_{2B}-receptors and shows only weak α_1-agonist properties. Alpha-2 receptors control physiological responses that are potentially involved in many disease states including diabetes, obesity, depression, glaucoma and hypertension. A greater understanding of the significance of α_2-adrenoceptor subtypes will assist the progress of drug discovery in these areas.

The individual enantiomers of BRL 44408 were prepared from isoindoline using the Meyers' chiral auxiliaries [3], derived from valinol. The synthesis of (−)-BRL 44408 is shown in which the key step is the stereoselective alkylation of the chelated α-lithioanion of the isoindolinyl formamidine **1**, derived from (*R*)-valinol. Subsequent cleavage of the formamidine gave the isoindoline **3**. This isoindoline was then converted via an *N*-cyanomethyl derivative into (−)-BRL 44408. The (+)-enantiomer of BRL 44408 was prepared using the formamidine of opposite stereochemistry. The (−)- and (+)-enantiomers were obtained in 97% and 98% enantiomeric excesses, respectively, as determined by chiral HPLC.

The absolute configuration of the enantiomers was determined from the X-ray crystallographic data on the (1*S*)-camphorsulphonic acid salt of the (+)-enantiomer of BRL 44408. The X-ray data show the presence of two independent conformations.



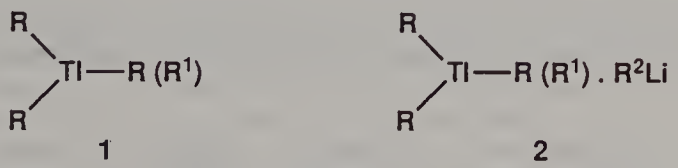
Scheme 17

[1] Bylund, D. (1985). *Pharmacol. Biochem. Behav.* **22**, 835.
[2] Young, P., Berge, J., Chapman, H. and Cawthorne, M. (1989). *Euro. J. Pharmacol.* **168**, 381.
[3] Meyers, A., Boes, M. and Dickman, D. (1984). *Angew. Chem., Int. Ed. Engl.* **23**, 458.

Synthetic Methodology

Synthesis and Properties of Organothallium(III) Complexes. Chiu W. Leung and István E. Markó. *Université Catholique de Louvain, Département de Chimie, Laboratoire de Chimie Organique, Bâtiment Lavoisier, Place Louis Pasteur 1, B-1348 Louvain-la-Neuve, Belgium*

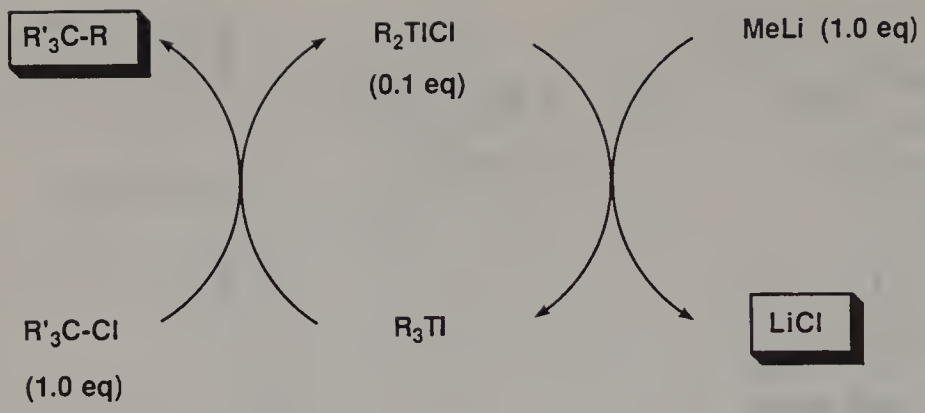
Triorganothallium (TOT) compounds **1** and triorganothallium 'ate complex' derivatives **2** are useful reagents in organic synthesis. This poster will emphasize the preparation of simple and mixed triorganothallium derivatives [1–4] and their utility in the smooth formation of alkyl, aryl and alkynyl ketones from the corresponding acid chlorides.



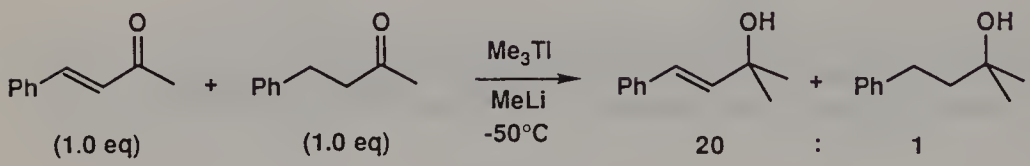
Scheme 18

The catalytic reactions of these triorganothallium reagents with tertiary halides have also been shown to give high yields of quaternary carbon centres. This is the first example of a catalytic system employing thallium as the catalyst (Scheme 19).

Finally, the unusual behaviour of the triorganothallium 'ate complex' will also be discussed [5]. An example is shown in Scheme 20.



Scheme 19



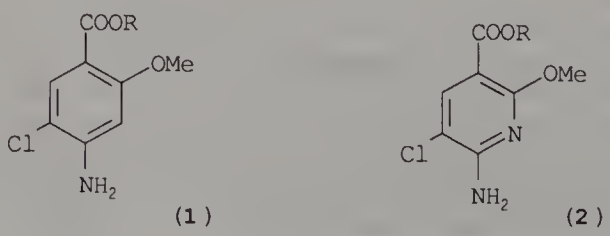
Scheme 20

[1] Markó, I. E. and Southern, J. M. (1990). *J. Org. Chem.* **55**, 3368.
[2] Markó, I. E., Southern, J. M. and Kantam, M. L. (1991). *Synlett.* 235.
[3] Markó, I. E. and Kantam, M. L. (1991). *Tetrahedron Lett.* **32**, 2255.
[4] Markó, I. E. and Rebière, F. (1992). *Tetrahedron Lett.* **33**, 1763.
[5] Leung, C. W. and Markó, I. E., manuscript in preparation.

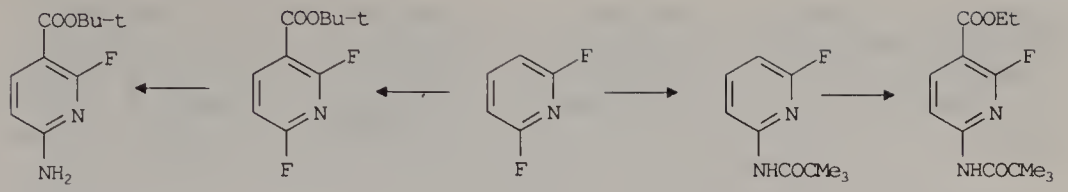
The Synthesis of 2,6-Disubstituted Nicotinic Acids by Directed Lithiation of Fluoropyridines.

Frank D. King and David J. Nash. *SmithKline Beecham Pharmaceuticals, Harlow, Essex CM19 5AD, UK*

The 4-amino-5-chloro-2-methoxybenzoate nucleus **1** is common to a large number of serotonergic 5-HT_2, 5-HT_3 and 5-HT_4 receptor antagonists, 5-HT_4 receptor agonists and dopamine D_2 receptor antagonists.



Scheme 21



Scheme 22

Two syntheses of the pyridyl isostere **2** are described from the readily available 2,6-difluoropyridine **3** via directed lithiation. In the first method, monofluoro displacement by ammonia, derivatization as the pivalamide **4**, lithiation and reaction with ethyl chloroformate gave a mixture of 2- and 6-fluoro esters which were separated by chromatography. The 2-fluoro isomer **5** was converted to **2** (R = H) by methoxide displacement, chlorination and hydrolysis.

Alternatively lithiation of **3** [1] and reaction with di-*t*-butyl dicarbonate gave the 3-*t*-butyl ester **6**. Reaction with NH_3 again gave a mixture which was readily separable to give the 6-amino-2-fluoronicotinic ester **7**. Displacement with methoxide, chlorination and hydrolysis again gave **2**.

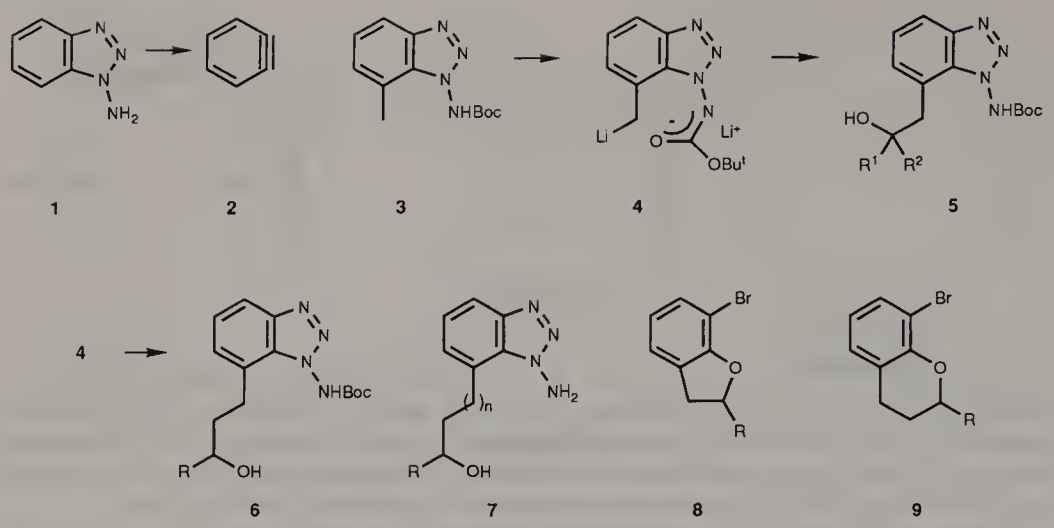
The authors thank D. Saunders for his helpful suggestions.

[1] US Patent No. 939,428; C.A. **109**, P230816u.

Benzyne Trapping by Alcohols: New Approaches to Dihydrobenzofurans and Chromans.

Michael A. Birkett[1], David W. Knight[1] and Michael B. Mitchell[2]. [1]*Chemistry Department, University Park, Nottingham NG7 2RD, UK;* [2]*SmithKline Beecham Pharmaceuticals, Old Powder Mills, Tonbridge TN11 9AN, UK*

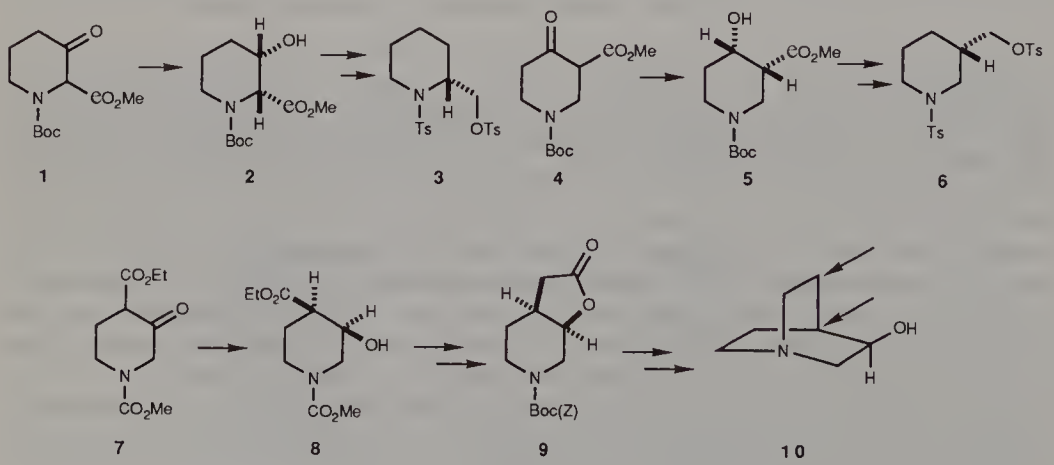
A major limitation of benzyne chemistry in synthesis is the difficulty in the preparation of suitably functionalized precursors. As a contribution to this area, we have been examining methods for the elaboration of substituted 1-aminobenzotriazoles. Although efficient precursors of benzynes **2**, following treatment with either NBS or lead(IV) acetate, only the parent of this series **1** has been used for this purpose on a regular basis, probably both because of the synthetic problems mentioned above and also poor regioselectivity associated with the subsequent reactions of these reactive intermediates. We have found that substituted 1-aminobenzotriazoles **5** can be efficiently obtained by condensations between the novel dianion **4** and aldehydes or ketones. The precursor to this sequence, benzotriazole **3**, is prepared in five steps from commercial 2-methyl-6-nitroaniline. The dianion **4** also condenses efficiently with epoxides to give the homologous alcohols **6**. Both types of condensation product can be smoothly deprotected; subsequent treatment of the free amines **7** with NBS results in formation of the dihydrobenzofurans **8** and the chromans **9**, respectively (Scheme 23, overpage). As the trapping of the benzyne by the hydroxyl function is intramolecular, regioselectivity problems do not arise. Further functionalizations of these initial products and applications to asymmetric synthesis will be outlined.



Scheme 23

New Members of the Chiral Pool: Hydroxypiperidine Carboxylates from Yeast Reductions of Ketopiperidine Carboxylates. Neil Lewis[1], David W. Knight[1] and David Haigh[2]. [1]*Chemistry Department, University Park, Nottingham NG7 2RD, UK;* [2]*SmithKline Beecham Pharmaceuticals, Great Burgh, Epsom, Surrey KT18 5XQ, UK*

Amongst the many applieations of baker's yeast in synthesis, reductions of β-keto-esters to the eorresponding hydroxy-esters are some of the most useful transformations. During the design stage of a number of projected syntheses of piperidine-based natural products, it beeame clear that there is a distinct lack of chiral precursors available in this area. We have therefore examined yeast reduetions of β-keto-piperidine carboxylates; we find that all three possible isomers are effieiently and enantioselectively redueed.



Scheme 24

The 2,3- and 3,4-ketopiperidine carboxylates (**1** and **4**) are thus converted into the corresponding hydroxy-esters **2** and **5**. In both cases, the chemical yields are 70–80% on 5–20 g scales. Each product is obtained diastereospecifically (>99%) as the *cis*-isomer. The absolute configurations shown were determined by degradations to the piperidine methanol derivatives (**3** and **6**) and comparisons with literature data. This also revealed, along with chiral shift reagent experiments, that both initial products (**2** and **5**) had optical purities in excess of 93%.

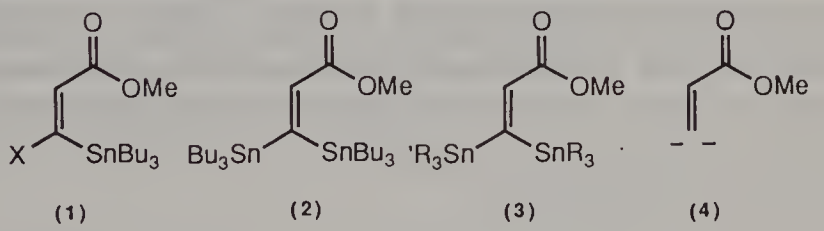
The third keto-ester **7** is also smoothly reduced but to the hydroxy-ester **8** in similar chemical and optical yields. Conversion into the lactone **9** will be described as well as further elaboration into the hydroxyquinuclidine **10**. These rather more constructive transformations represent a new asymmetric approach to the quinuclidine nucleus which should permit further functionalizations to be effected at the positions indicated. Aspects of this chemistry will be outlined on the poster.

Aspects of Organotin Chemistry.

P. Quayle and Y. K. Zhao. *Department of Chemistry, University of Manchester, Manchester M13 9PL, UK*

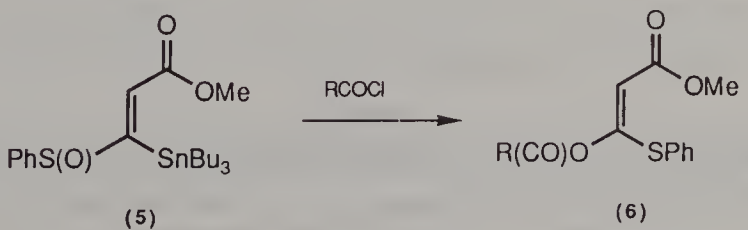
The use of organotin reagents in organic synthesis has experienced an exponential growth in recent years. Our interest in this area has centred upon the stereoselective synthesis and subsequent manipulation of α-heterosubstituted organostannanes.

We have recently shown that the readily available stannanes [1] undergo clean addition–elimination reactions with tin-centred anions to afford the geminal *bis*-stannanes **2**. In addition, we have also developed a stereoselective synthesis of the mixed *bis*-stannanes **3** (Scheme 25). Such intermediates have the synthetic equivalence of the di-anion **4**, and as such, are potentially versatile synthetic intermediates.

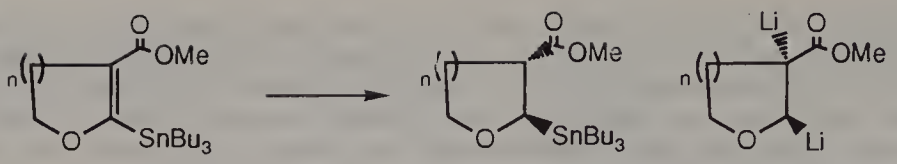


Scheme 25

In connection with the studies outlined above, we have observed [2] a novel, stereoselective *tin-Pummerer rearrangement:* reaction of the sulphoxide **5** with a variety of acyl halides provides ready access to the O,S-ketene acetals **6** (Scheme 26). A mechanistic rationale for this process is presented.



Scheme 26



(7) (8) (9)

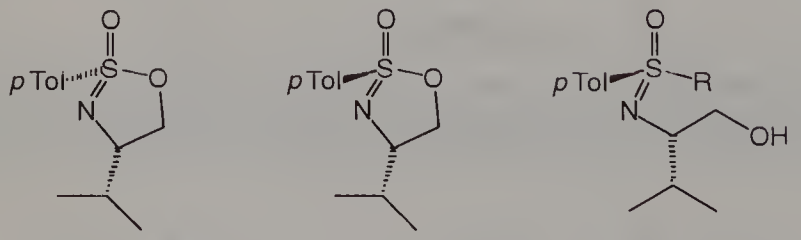
Scheme 27

As a continuation of our studies on the chemistry of vinyl stannanes, we have also shown, for example, that the heterocyclic stannanes **7** undergo clean ionic reduction to the *trans*-substituted organostannanes **8** [3]. Such intermediates may be viewed as having the synthetic equivalence of the di-anions **9**, a theme which is currently under investigation.

[1] Imanich, H., MacLeod, D., Quayle, P. and Zhao, Y. K. (1992). *Tetrahedron Lett.* **33**, 405.
[2] Beddoes, R. L., MacLeod, D., Quayle, P. and Zhao, Y. K. (1992). *Tetrahedron Lett.* **33**, 417.
[3] Quayle, P. and Zhao, Y. K., unpublished results.

Stereoselective Synthesis of Enantiomerically Pure Sulfoximines via New Heterocyclic Sulfonimidates. Heinz Weinberger and Michael Reggelin. *Institut für Organische Chemie, J.W. Goethe-Universität, Niederurseler Hang, W-6000 Frankfurt/Main 50, Germany*

We describe the synthesis of both diastereomers of the new cyclic sulfonimidates (*S*)-4-isopropyl-2-*p*-toluene-4,5-dihydro-[1,2λ^6,3]oxathiazole-2-oxide **1** and **2** [1]. They were prepared from *p*-toluenesulfinyl chloride and (*S*)-O-trimethylsilyl valinol without isolation of intermediates. The key step in the synthesis is the fluoride-induced cyclization of sulfonimidoyl chlorides. After chromatographic purification of the resulting mixture of enantiomerically pure diastereomers, the title compounds were isolated as colorless, stable crystals in 70% overall yield. Their clean reaction with Grignard and organolithium reagents RM offers a versatile entry to optically active sulfoximines **3** in good to excellent yields.



1 2 3

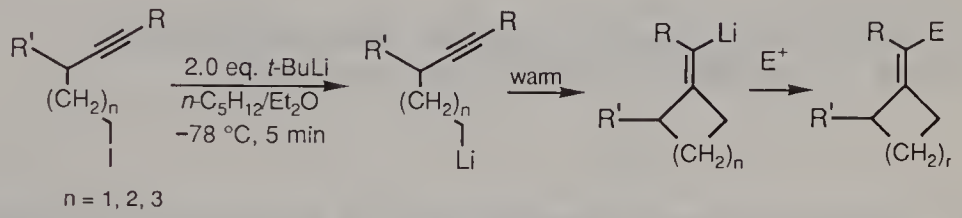
Scheme 28

Further investigations of the synthetic potential of 2-alkenyl sulfoximines as asymmetric d^3-building blocks are in progress.

[1] Reggelin, M. and Weinberger, H. (1992). *Tetrahedron Lett.* **33**, 6959–6962.

Preparation of Functionalized Cycloalkylidenes by Anionic Cyclization of Acetylenic Alkyllithiums. Nanette Wachter-Jurcsak[1], William F. Bailey[1] and Timo V. Ovaska[2]. [1]*Department of Chemistry, University of Connecticut, Storrs, CT 06269, USA;* [2]*Department of Chemistry, Connecticut College, New London, CT 06320, USA*

Acetylenic alkyllithiums, which may be prepared in virtually quantitative yield by low-temperature lithium–iodine exchange between *t*-butyllithium (*t*-BuLi) and an appropriate organoiodide, undergo regiospeeifie and highly stereoselective cyelization upon warming. The vinyllithium produets of the *syn*-selective isomerizations may be trapped to afford isomerieally pure, functionalized produets in high yield.



Scheme 29

The Nicholas Reaction — An Intramolecular Approach to the Synthesis of β-Alkynyl Ketones, a Reaction that is the Equivalent of a Conjugate Addition of a Terminal Alkyne to an Enone. Elizabeth Tyrrell and Parissa Heshmati. *School of Applied Chemistry, Kingston University, Kingston upon Thames KT1 2EE, UK*

Propargyl carbonium ions stabilized by dieobalt hexaearbonyl ean be treated with a variety of carbon nucleophiles to afford alkylated produets, the Nicholas reaction [1]. To date most interest in this ehemistry has been direeted towards the intermoleeular applieations of the Nicholas reaetion with the introduetion of eobalt-eomplexed propargyl earbonium ions into the aldol reaetion with O-silyl enol cthers [2,3] to afford *syn* produets and more reecntly with aldehydie *N,N*-dibenzylcnamine [4] to yield iminium ions. Despite the faet that an intramolecular Nicholas reaetion ean be usefully exploited for the construction of highly functionalized ring systems, few examples have been reported in the literature. Magnus [5] used an intramolecular hexacarbonyl dieobalt-eomplexed propargyl earbonium ion-mediated cyelization reaction in his approach to the antitumour antibiotic dynemiein. Marshall [6] also made use of an α-alkoxyallylstannane dieobalt hexaearbonyl alkynal eomplex in his synthesis of a eyeloundeeadienyne aleohol, a eembranoid preeursor.

This poster deseribes the preliminary results that we have obtained in our investigations into an intramolecular Nieholas reaetion which makes use of a fluorine-indueed fragmentation reaetion in the key cyclization step. Our aim has been to synthesize a range of moleeules eomprised of a propargyl aleohol at one terminus separated by 5, 6 or 7 carbon atoms from an O-silyl enol ether at the other terminus. We envisaged that the dicobalt hexaearbonyl eomplex of these moleeules

should, after dehydroxylation, undergo a fluorine–silicon-induced fragmentation to afford, after decomplexation, a β-substituted cycloalkanone.

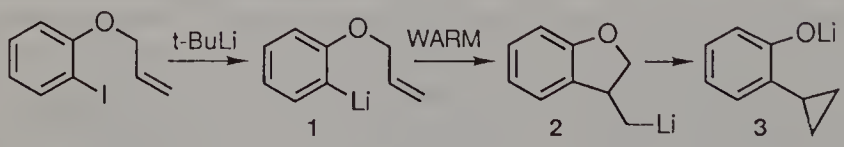
A mixture of the two isomers of O-*tert*-butyldimethylsilyl enol ether of 7-hydroxynon-8-yn-2-one (obtained in three steps from 1-methyl-1-cyclohexene) was complexed with dicobalt octacarbonyl. When the dicobalt hexacarbonyl complex was sequentially treated with tetrafluoroboric acid followed by tetrabutylammonium fluoride and finally decomplexed with iron(III)nitrate, a mixture of two cycloadducts was obtained. Analysis of the products showed a presence of 1-acetyl-2-ethynylcyclopentane and 2-ethynylcycloheptanone in a ratio of 1:2. Application of the methodology to the synthesis of other ring systems is presently under investigation.

[1] Nicholas, K. M. (1987). *Acc. Chem. Res.* **20**, 207, and references cited therein.
[2] Hanaoka, M., Kataoka, O. and Mukai, C. (1991). *Tetrahedron Lett.* **32**, 7553.
[3] Nicholas, K. M., Khan, M., Montana, A. M., Tester R. and Varghese, V. (1990). *J. Org. Chem.* **55**, 186.
[4] Roth, K-D. (1992). *Synlett* 435.
[5] Magnus, P. and Fortt, S. M. (1991). *J. Chem. Soc., Chem. Commun.* 544.
[6] Marshall, J. A. and Gung, W. Y. (1989). *Tetrahedron Lett.* **30**, 309.

3-Oxa- and 4-Oxa-5-Hexenyllithiums.

Eric R. Punzalan and William F. Bailey. *Department of Chemistry, University of Connecticut, Storrs, CT 06269-3060, USA*

Low temperature lithium–iodine exchange between *t*-butyllithium and the appropriate iodide has been used to generate 3-oxa-5-hexenyllithium, 2-allyloxyphenyllithium **1**, and a variety of 4-oxa-5-hexenyllithiums. The parent 3-oxa-5-hexenyllithium fragments at low temperature via facile β-elimination to give the anion of allyl alcohol and ethylene. The 2-allyloxyphenyllithium **1**, in contrast, is stable at low temperature but undergoes 5-exo-trig cyclization at room temperature in the presence of TMEDA to give **2**, which isomerizes slowly to the lithium salt of 2-cyclopropylphenol (**3**). The 4-oxa-5-hexenyllithiums undergo a novel [1,4]-Wittig rearrangement when warmed to room temperature to give 4-alken-1-ols in good yield.



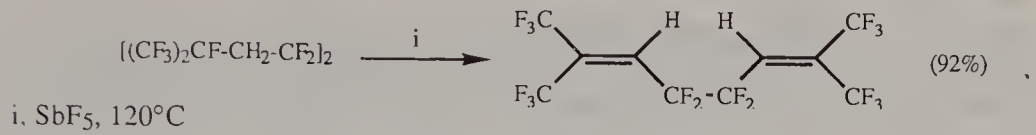
Scheme 30

Synthesis of Fluorinated -Alkenes, -Dienes, and -Polyenes.

R. D. Chambers, P. Odello, G. Apsey and T. Nakamura. *University of Durham Science Laboratories, South Road, Durham DH1 3LE, UK*

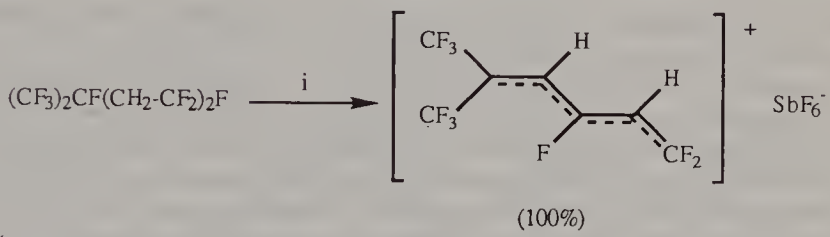
Base-induced elimination to produce a fluorinated alkene is sometimes unsuccessful because the product is reactive towards nucleophilic attack; in such circumstances we find that elimination of

hydrogen halides by antimony pentafluoride can be highly effective (Scheme 31). In some circumstances further removal of fluoride ion occurs, leading to some remarkably stable carbocations (Scheme 32). An alternative approach to a new range of electron-deficient dienes (Scheme 33) involves defluorination by either sodium amalgam or tetrakisdimethyl-aminoethylene (TDAE). In some cases stable conjugated anions are observable (Scheme 34).



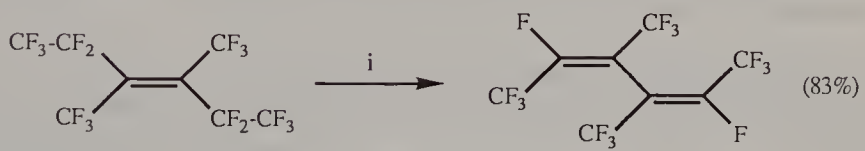
i, SbF_5, 120°C

Scheme 31



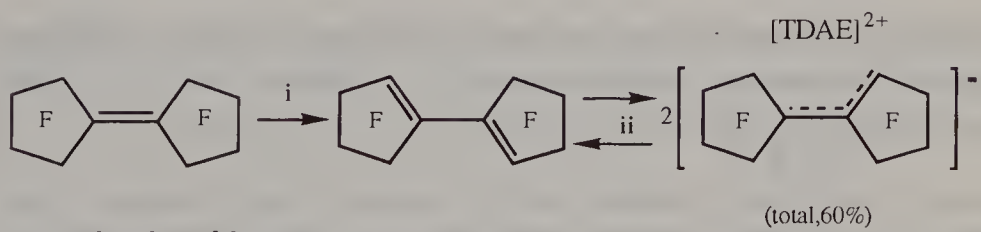
i, SbF_5, r.t..

Scheme 32



i, TDAE, r.t..

Scheme 33

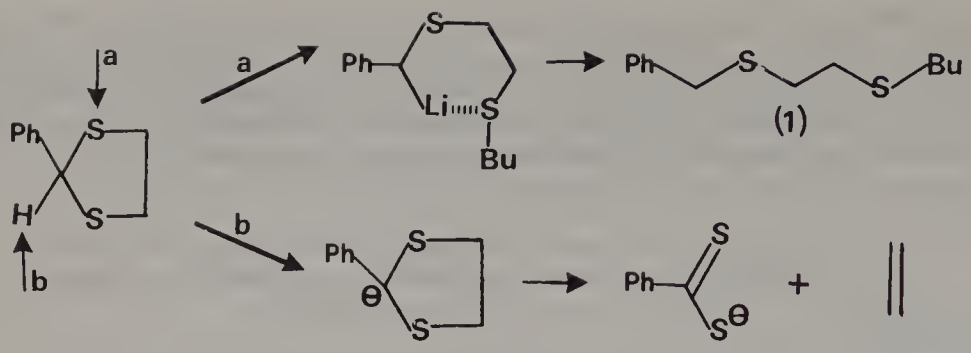


i, TDAE, CH_2Cl_2, 0°C, r.t.; ii, BF_3OEt_2

Scheme 34

Competitive Nucleophilic and Base-induced Ring Opening Reactions of 2-Phenyl-1,3-Dithiolane with BuLi. K. Latham, C. Nallaiah and C. J. Perry. *School of Applied Sciences, University of Wolverhampton, West Midlands, UK*

The usefulness of umpolung in contemporary organic synthesis cannot be overemphasized. However 2-substituted 1,3-dithiolanes are unsuitable as acylanion equivalents, as initial proton



Scheme 35

abstraction leads to various cleavage products [1–3]. Nevertheless reactions of 2-substituted dithiolanes with a large excess of a strong base such as BuLi, LDA etc. have been used successfully to effect regioselective ring opening, depending on the reaction conditions employed [2,3].

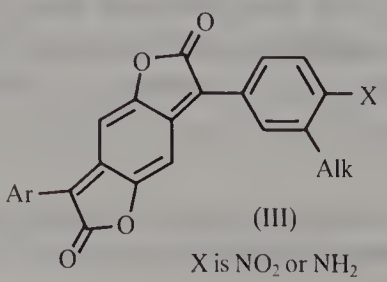
We have studied the reaction of 2-phenyl-1,3-dithiolane with a slight excess of BuLi (1:1.1) in THF at −65°C and have observed a different ring opening pathway, giving mainly the disulphide **1** in good yield (≈75%). At very low temperature (−65°C) there are two possible ring opening routes, as depicted in Scheme 35. Our studies have revealed that path a is favoured at −65°C, indicating that nucleophilic ring opening is favoured, as the acidic hydrogen at C-2 is sterically hindered. However when 2-benzyl, 2(1-alkenyl) and 2(2-alkenyl)dithiolanes are used [2,3], depending on the reaction conditions, ring opening occurs via abstraction of 2-H or 4-H. Although 2-substituted 1,3-dithiolanes are unsatisfactory for use as acylanion equivalents, their reactions with organometallic reagents are quite useful in organic synthesis.

[1] Corey, E. J. and Seebach, D. (1975). *J. Org. Chem.* **40**, 231.
[2] Wilson, S. R., Georgiadis, G. M., Khatri, H. N. and Bartmess, J. E. (1980). *J. Am. Chem. Soc.* **102**, 3578.
[3] Oida, T., Tanimoto, S. H. and Okano, M. (1986). *J. Chem Soc., Perkin Trans.* **1**, 1715.

A Synthesis of Benzodifuranone Dyes Exploiting Conjugate Addition of Grignard Reagents to Nitrobenzenes.

S. J. Bentley and D. J. Milner.
Zeneca Specialties Research Centre, Blackley, Manchester M9 3DA, UK

Treatment of nitrobenzenes, substituted in the 4-position with protected aldehyde, ketone or ketoester functions, with alkyl Grignard reagents followed by DDQ yields the corresponding 2-alkyl compounds. These addition products give ready access to two series of benzodifuranone dyes (**III**) bearing either nitro or amino substituents. The Grignard addition is operable at −15°C and is most suitable for the introduction of primary or secondary alkyl groups.



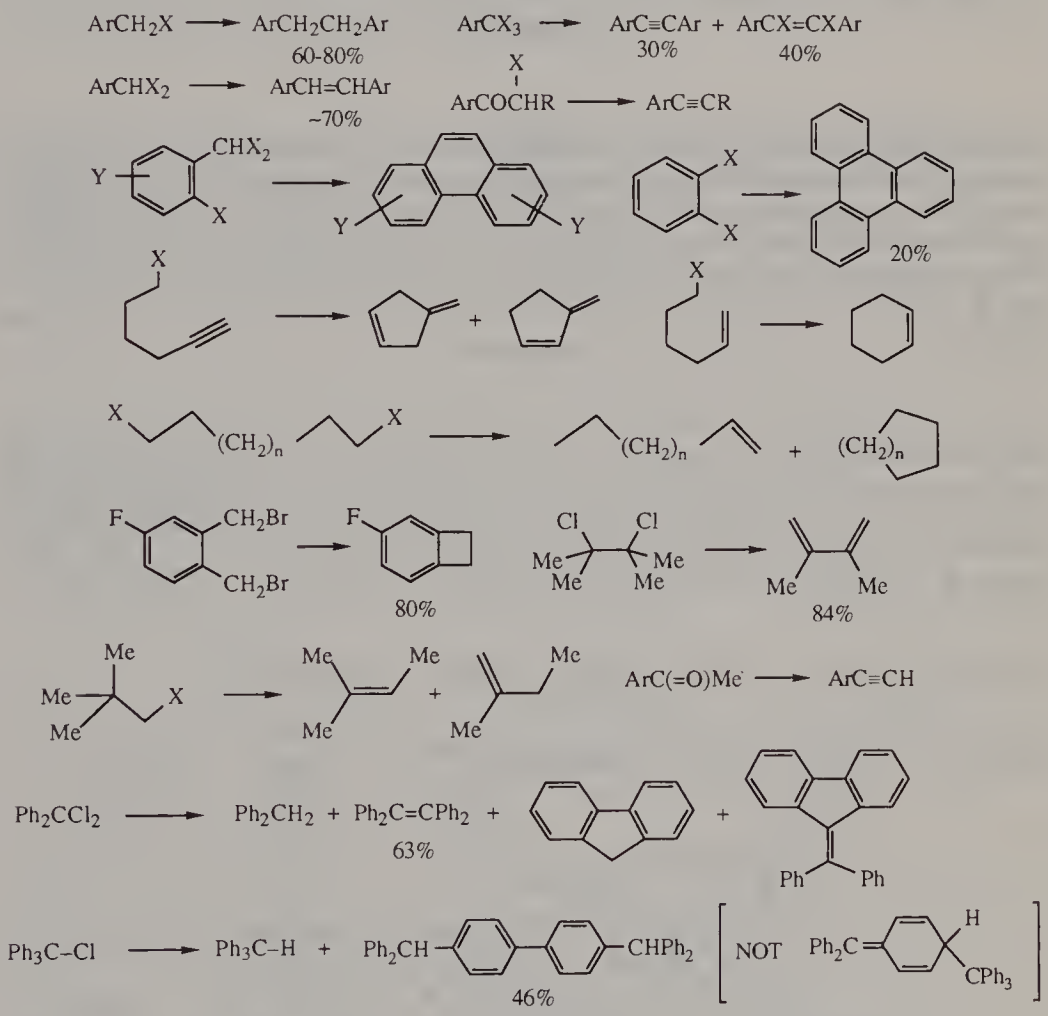
(III)

X is NO_2 or NH_2

Scheme 36

Organometallic Chemistry in the Gas Phase: Flash Vacuum Pyrolysis of Organic Halides over Sublimed Magnesium. R. Alan Aitken, John J. Morrison and Adebayo O. Oyewale. *Department of Chemistry, University of St. Andrews, North Haugh, St. Andrews, Fife KY16 9ST, UK*

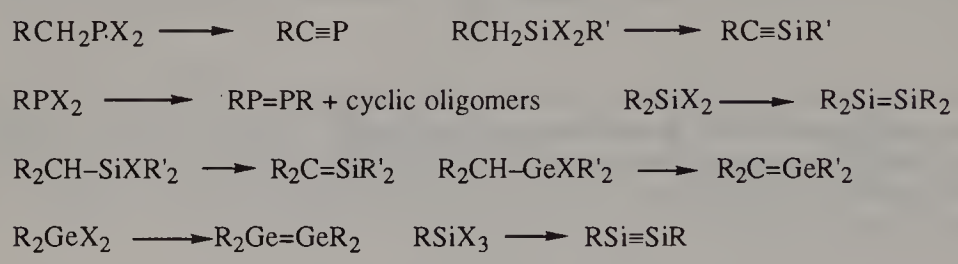
Flash vacuum pyrolysis over freshly resublimed magnesium has been evaluated as a synthetic method starting from a wide variety of halogenated substrates. As shown by the examples below, many useful transformations are possible and the products formed lead to the conclusion that surface-adsorbed organometallic species are often involved rather than, for example, free gas phase radicals or carbenes.



Scheme 37

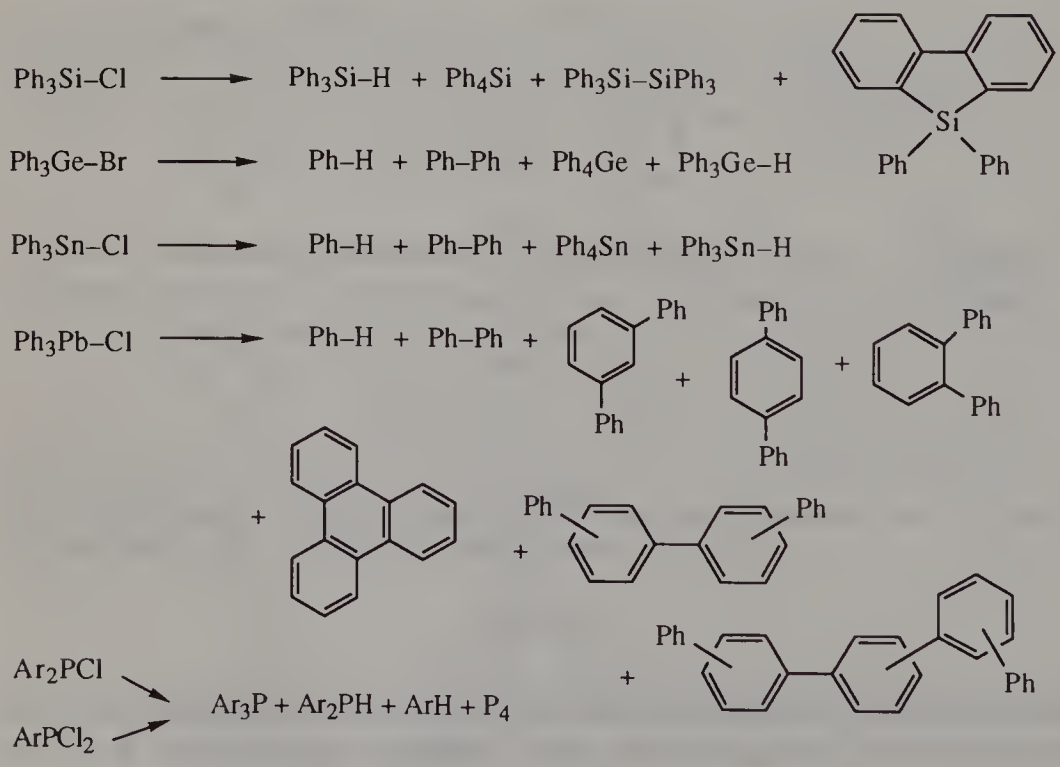
Organometallic Chemistry in the Gas Phase: Flash Vacuum Pyrolysis of Heavier Main Group Halides over Sublimed Magnesium. R. Alan Aitken, Wayiza Masamba and John J. Morrison. *Department of Chemistry, University of St. Andrews, North Haugh, St. Andrews, Fife KY16 9ST, UK*

Building on the success achieved with carbon-based halides, we have evaluated FVP over magnesium as a synthetic method for other main group elements. Possible processes leading to multiple-bonded compounds of great current interest include:



Scheme 38

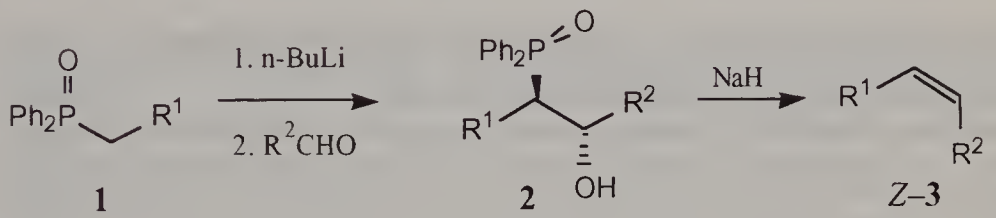
In the examples studied so far, there generally appears to be free exchange of organic groups around the heavier atom leading to some unexpected products. In addition, for the more metallic elements, the element plates out in the furnace to give purely organic products. Although the reactions here are only occasionally of preparative interest, the interaction of the heavy element with the magnesium surface may lead to unexpected catalytic activity as illustrated in the case of lead. Synthetic and mechanistic implications of the reactions shown below are still being considered.



Scheme 39

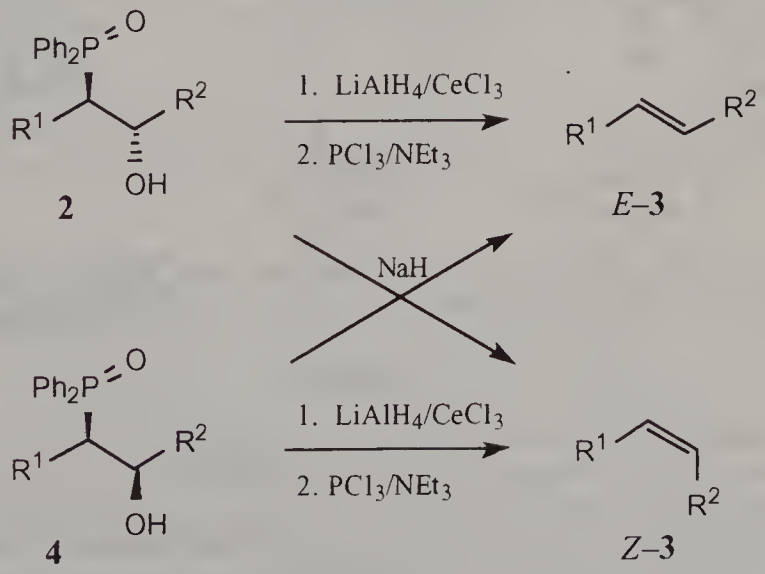
Modified Horner–Wittig Chemistry. Nicholas J. Lawrence and Faiz Muhammad. *Department of Chemistry, UMIST, PO Box 88, Manchester M60 1QD, UK*

The synthesis of carbon–carbon double bonds is both an important and fundamental process of organic chemistry. The most widely used method is the Wittig reaction and its many variants. One such modification is the Horner–Wittig reaction of phosphine oxides. Warren [1] has elegantly illustrated the advantages of this type of reaction. Nevertheless, there are problems associated with the reversible nature of the reaction **1** to **2** which lead to loss of stereocontrol. The process is especially problematic when the anion from **1** is particularly stable and the alkene is hindered. We were interested to see whether these problems could be avoided if the elimination of **2** were to be carried out under acidic conditions. We describe our initial endeavours to make disubstituted alkenes by non-basic elimination of phosphinoyl alcohols **2**.



Scheme 40

Phosphine oxide **2** was reduced, using Imamoto's $CeCl_3/LiAlH_4$ reagent [2], to the corresponding phosphine, which when treated with PCl_3/NEt_3 gave the alkene *E*-**3**, in good yield (by NMR) and stereospecifically. We believe this to be the first example of an *anti* elimination of a 1,2-phosphinyl alcohol. It is interesting to note that when the phosphine oxide **2** is treated under standard Horner–Wittig conditions the *cis* isomer, *Z*-**3**, is obtained. Hence both isomers of the



Scheme 41

alkene can be isolated from a single phosphinoyl alcohol mirroring the case of the Peterson elimination of 1,2-silylacohols.

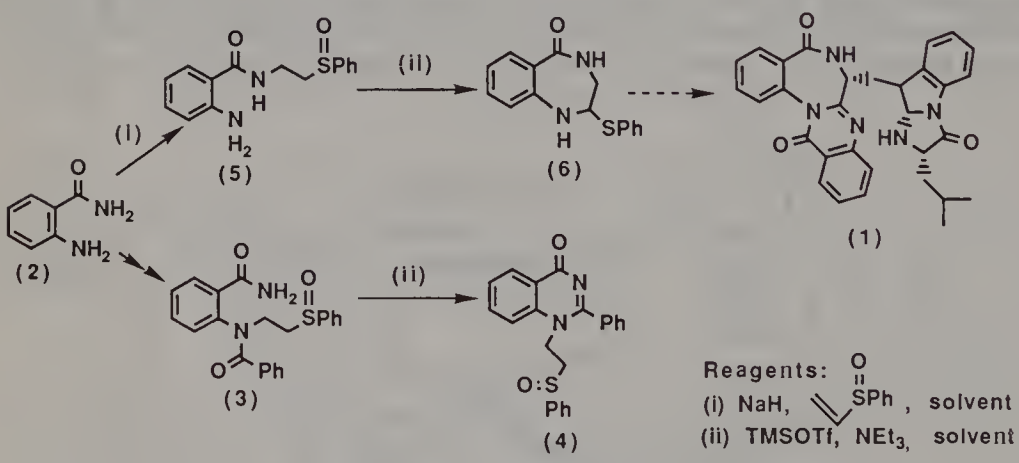
[1] Buss, A. D. and Warren, S. (1983). *Tetrahedron Lett.* **24**, 3931.
[2] Imamoto, T., Takeyama, T. and Kusumoto, T. (1985). *Chem. Lett.* 1491.

Synthetic Studies Towards Asperlicin and the Pyrrolo-[1,4]-Benzodiazepine Antibiotics Using an Interrupted Intramolecular Pummerer Rearrangement (IIMPR).

Rachael C. Hunter and I. A. O'Neil. *The University of Liverpool, Liverpool, UK*

The poster describes the synthesis of a 7-membered benzo-fused heterocycle **6** using an interrupted intramolecular Pummerer rearrangement (IIMPR), and studies towards the tricyclic molecule **9**, the core nucleus of the pyrrolo-[1,4]-benzodiazepine antibiotics.

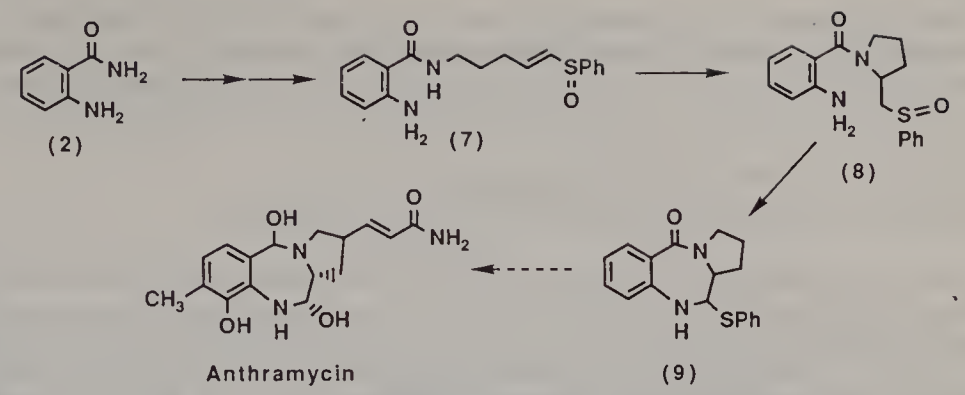
Asperlicin **1** is a potent and selective competitive antagonist to the peptidal hormone cholecystokinin. We envisaged using an IIMPR to form the 7-membered ring of this molecule. Model studies involved the synthesis of intermediate **3** from anthranilamide **2**. However, under Pummerer conditions, only the 6-membered heterocycle **4** was isolated. An alternative approach starting from **2** using a conjugate addition to phenyl vinyl sulphoxide, and subsequent treatment of **5** under Pummerer conditions gave the desired 7-membered heterocycle **6** in good yield. A variety of cyclization conditions have been studied. We anticipate extending this methodology to the synthesis of asperlicin **1**.



Scheme 42

This methodology has also been applied to the synthesis of the core nucleus of the anthramycin class of DNA-minor groove binding antibiotics. Our key intermediate 7 is easily synthesized from anthranilamide **2**. Intramolecular conjugate addition to the vinyl sulphoxide function and subsequent cyclization under Pummerer conditions would be expected to give **9**, a potentially useful intermediate to this class of biologically active compounds.

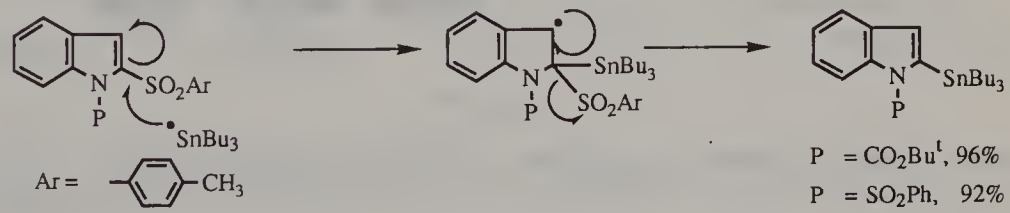
We have shown that the IIMPR methodology has potential in the synthesis of a variety of biologically interesting molecules.



Scheme 43

Novel Free Radical Substitution Reactions of Heteroaromatic Aryl Sulphones. S. Caddick, K. A. Aboutayab and S. Joshi. *Department of Chemistry, Birkbeck College, Gordon House, 29 Gordon Square, London WC1H OPP, UK*

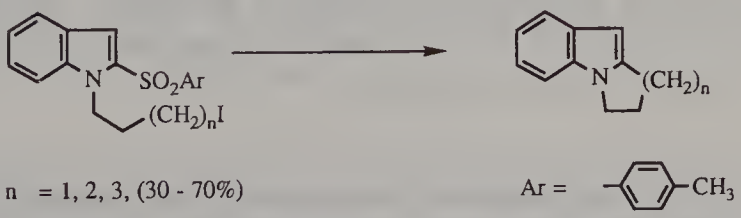
We have been investigating a variety of free radical reactions in which a 4-(methyl)phenylsulphone substituent is displaced by a nucleophilic radical via an addition–elimination mechanism. We have recently found that treatment of *N*-protected 2-[4-(methyl)phenylsulphonyl]indoles with tri-*n*-butyltin hydride under free radical conditions effects an efficient substitution reaction to provide the corresponding *N*-protected 2-[tri-*n*-butylstannyl]indoles in good yields [1].



Reagents and Conditions; Bu3SnH, AIBN, Benzene, Reflux.

Scheme 44

Further studies in the indole series have demonstrated the viability of a related intramolecular substitution process. A novel approach to fused [1,2-a]indoles has been developed and is based on this strategy [2].



Reagents and Conditions; Bu3SnH, AIBN, Toluene, Reflux.

Scheme 45

Further application of this methodology to other heterocyclic systems will be described.

We gratefully acknowledge financial support from the following: SERC, Central Research Fund (University of London), Birkbeck College and the Wellcome Foundation Ltd (Beckenham).

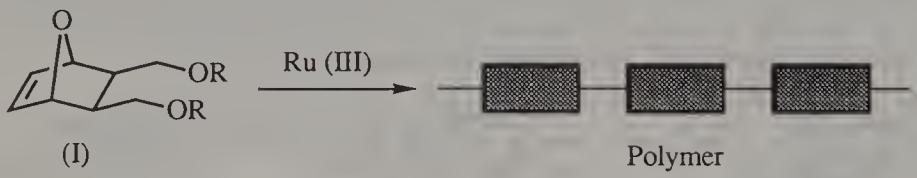
[1] Caddick, S. and Joshi, S. (1992). *Synlett* 805.
[2] Caddick, S., Aboutayab, K. A. and West, R. A. (1993). *Synlett*, 231.

ROMP Polymerization of Strained Olefins.

A. L. J. Byerley and P. Quayle. *Department of Chemistry, University of Manchester, Manchester M13 9PL, UK*

The metathesis of strained olefins presents a potentially novel route for the synthesis of highly functionalized oligomers and polymers. We have recently carried out an in-depth investigation into the ROMP polymerization of a variety of functionalized oxanorbornene derivatives **I** [1,2], affording high molecular weight polymers possessing a polyether backbone. The aqueous ROMP metathesis of such systems is potentially of great interest for the synthesis of a variety of 'catalytic' pockets attached to a polymer backbone.

The scope and limitation of the Ru(III)-promoted ROMP polymerization of a number of substrates will be presented, with an indication of further synthetic developments.



Scheme 46

[1] Lu, S., Quayle, P., Heatley, F. and Booth, C. (1992). *Macromolecules* **25**, 2692.
[2] Lu, S., Quayle, P., Heatley, F., Booth, C., Yeates, S. G. and Padget, J. C. (1993). *Eur. Polym. J.* **29**, 269.

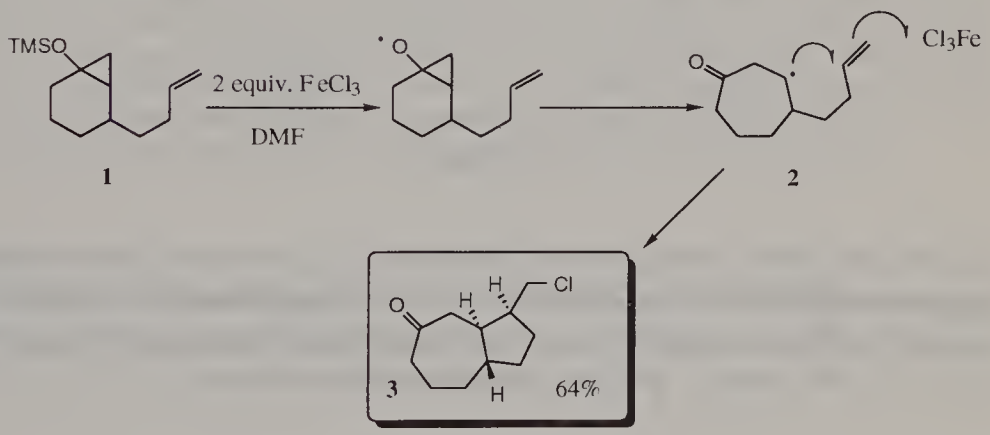
Tandem Ring Expansion–Cyclization Reactions.

Kevin I. Booker-Milburn and David F. Thompson. *Department of Chemistry, The University of Salford, Salford M5 4WT, UK*

A new free radical ring expansion–cyclization sequence has been developed [1] which allows rapid access to fused bicyclic chloro-ketones from cyclopropyl silyl ethers. The key step is based on the ferric chloride mediated cleavage of cyclopropyl silyl ethers [2] which is thought to proceed via an intermediate cyclopropyl alkoxy radical (Scheme 47).

Scheme 47

We have found that treatment of the cyclopropyl silyl ether **1** (prepared in two steps from cyclohexenone) with ferric chloride leads to the bicyclic chloroketone **3** as a single diastereoisomer in 64% yield (Scheme 48). The reaction proceeds via 5-exo cyclization of the intermediate carbocyclic radical **2** followed by chlorine abstraction from the ferric chloride.



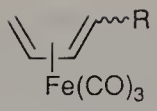
Scheme 48

Application of this methodology for the construction of 6,5- and 8,5-carbocycles is in progress.

[1] Booker-Milburn, K. I. (1992). *Synlett* 809.
[2] Ito, Y., Fujii, S., Nakatsuka, M., Kawamoto, F. and Saegusa, T. (1988). *Org. Synth. Coll Vol.* **6**, 327.

Organoiron Routes to α,β-Dioxygenated Dienes. A. K. Banham and G. R. Stephenson. *School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK*

Acyclic organometallic complexes are important in organic synthesis since they undergo stereocontrolled reactions adjacent to the complexed diene unit. The synthesis of α-oxygenated and α,β-dioxygenated diene iron complexes (**1–4**) by the use of Friedel–Crafts acylation can give access to valuable synthetic intermediates. The chemistry of the 1,2-dioxygenated derivatives will be described in work directed towards the asymmetric synthesis of natural products.



1; R=COR' 3; R=COCOR'
2; R=CH(OH)R' 4; R=COCH(OH)R'

Scheme 49

The regio- and stereoselectivity of substitution reactions leading to **1** and **3** have been defined by the use of nOe NMR experiments. Stercocontrolled reduction forms chiral centres adjacent to the metal complex, for example:

Scheme 50

Organometallics in the Synthesis of 6-Aryl-3-substituted Pyridin-2(1H)-ones.

R. A. Porter and D. A. Pardoe. *SmithKline Beecham Pharmaceuticals Ltd, The Frythe, Welwyn, Herts AL6 9AR, UK*

During the course of a programme of work directed to identifying non-nucleotide mimetics of cyclic adenosine monophosphate, 3-substituted-6-arylpyridin-2(1H)-ones were identified as targets. Versatile methods for introducing a range of either 3- or 6-substituents were therefore required.

6-Aryl-3-cyano-pyridin-2(1H)-ones are readily available from the corresponding acetophenone in two steps. However, due to the harsh conditions required to modify the 3-substituent, flexibility of these compounds as intermediates is limited. Milder more versatile methods were therefore developed for the introduction of both pyridin-2(1H)-one-3- and 6-substituents. These methods include:

(i) palladium-mediated hetero-biaryl coupling;
(ii) ortho-lithiation of methoxypyridines;
(iii) aryl phosphate ester rearrangement to the corresponding aryl phosphonate.

Palladium-mediated coupling to aryl iodides, bromides or trifluoromethanesulphonates with arylboronic acids is a flexible and mild method for preparing biaryls with only limited requirement for protection of other functional groups. Application to the preparation of heterobiaryls and the use of aromatic chlorides is, however, less well documented.

Synthesis of both 6-aryl-2-methoxypyridines and 6-aryl-3-substituted pyridin-2(1H)-ones from the corresponding 6-chloro derivative will be described.

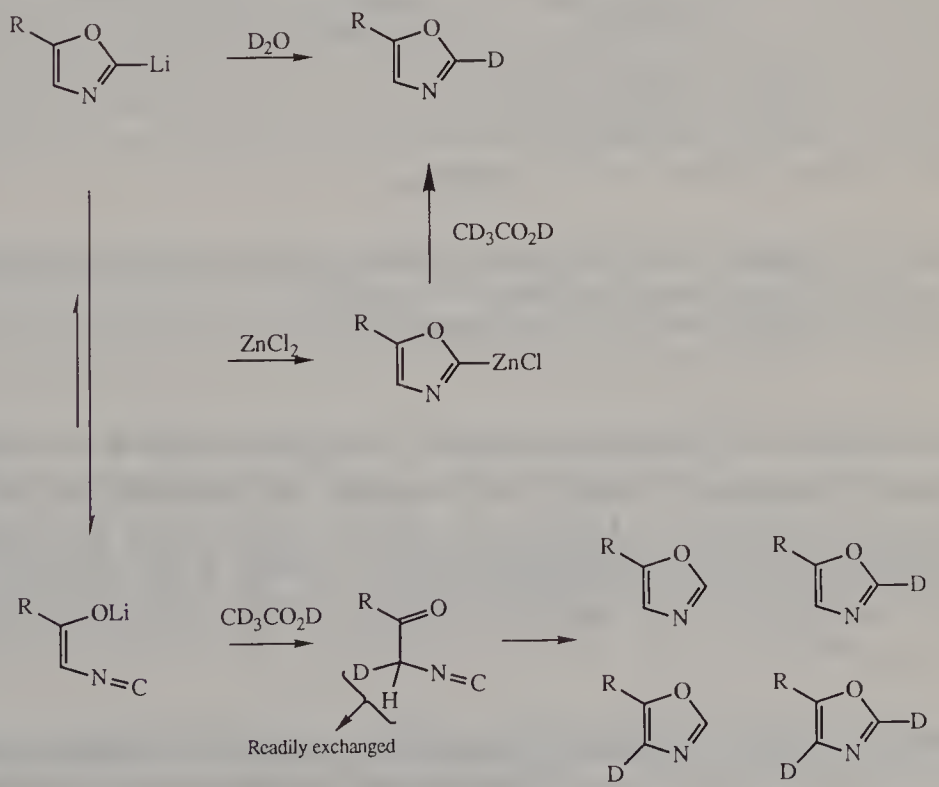
2-Lithiation of methoxybenzenes is well known, however only recently has this strategy been applied to alkoxypyridines. Extension of this methodology to the 3-functionalization of 6-aryl-2-methoxypyridines will be illustrated.

Several reports have described the rearrangement of phenol phosphates to the 2-hydroxyaryl phosphonate. Using a simple one-pot procedure 6-substituted pyridin-2(1H)-ones have been converted to the corresponding 3-phosphonates.

A Novel, Practical Synthesis of 17β-*N*-*t*-Butylcarboxamide-estr-1,3,5(10)-triene-3-carboxylic acid (SK&F 105656) from Estrone, using a Palladium-catalyzed Carbomethoxylation of a 3-Fluorosulphonate Precursor in the Key Step. Michael A. McGuire, Edmund Sorenson, Frank Owings, Theodore Resnick and Neil H. Baine. *SmithKline Beecham Pharmaceuticals, Synthetic Chemistry Department, P.O. Box 1539, King of Prussia, PA 19406, USA*

The title compound was prepared from estrone in nine steps, in 18.7% overall yield. Each step was performed on a 50–150 gal scale and 3.5 kg of the title compound were prepared. Estrone was 3-mesylated and 17-cyanated using TMSCN. Elimination with phosphorus oxychloride/pyridine followed by Pd/C-catalyzed hydrogenation gave the 17β-cyano,3-mesylate stereoselectively. Hydrolysis with NaOH in ethylene glycol gave a 3/1-β/α mixture of 17-carboxylic acid isomers. Reaction with Vilsmeier reagent and quenching into *t*-butylamine, followed by selective crystallization, yielded the desired 17β-amide,3-phenol. Reaction with fluorosulfonic anhydride yielded the 3-fluorosulfonate. Palladium-catalyzed carbonylation in the presence of methanol gave the 3-carboxylic acid methyl ester. Finally, NaOH hydrolysis yielded the desired product.

2-Metallated Oxazoles; pK_a-dependent Deuterations, NMR Studies and Palladium-catalysed Couplings. Frank Hossner and Mark J. Hughes. *Synthetic Chemistry, SmithKline Beecham Pharmaceuticals, Coldharbour Road, Harlow, Essex CM19 5AD, UK*



Scheme 51

Deuteration experiments on 2-lithiated oxazoles show a pK_a-dependent regioselectivity suggesting that the ring-cleaved isomer dominates the equilibrium. Transmetallation to the zinc derivative gives a species which behaves as a ring-closed nucleophile as judged by deuteration and palladium-catalysed coupling experiments. NMR studies on the organometallics support assigning a ring-opened structure to the lithiated oxazole and a ring-closed structure to the zinc derivative for the dominant species in solution.

Selectivity of Hydrogen Isotope Exchange Catalysed by Organoiridium Complexes.

J. Richard Heys, Arthur Y. L. Shu, Niko M. Phillips and Stephen G. Senderoff. *Radiochemistry Section, Synthetic Chemistry Department, SmithKline Beecham Pharmaceuticals Research and Development, King of Prussia, PA 19406, USA*

Of the various preparative approaches to compounds labelled with deuterium or tritium, catalytic hydrogen isotope exchange of the unlabelled compound is attractive for its simplicity, since it avoids the need for synthesis. Many catalytic exchange methods with varying degrees of efficiency and selectivity have been reported. We have become interested in exploring the ability of certain homogeneous organotransition metal complexes, already known to be capable of carbon–hydrogen bond activation, to catalyse the exchange of isotopic hydrogen gas with hydrogens of compounds in solution. In preliminary investigations, the complex $[IrH_2(Me_2CO)_2(PPh_3)_2]BF_4$ was found to efficiently and selectively catalyse the exchange of deuterium gas with hydrogens in several substrate structural types [1,2].

This poster will present some more recent results of continuing investigations, which are aimed at expanding the range of compound types to undergo exchange and learning something about the nature of the exchange process. Investigations to be covered include rate studies and fixed-length exchange reactions on *p*-substituted ethyl benzoates, *p*-substituted *N,N*-dimethylbenzamides, and mono-*p*-substituted benzophenones. Inhibition studies using potentially chelating ligands will be presented, as well as exchange studies on additional compound structural types, and preliminary studies of exchange catalysed by modified catalysts.

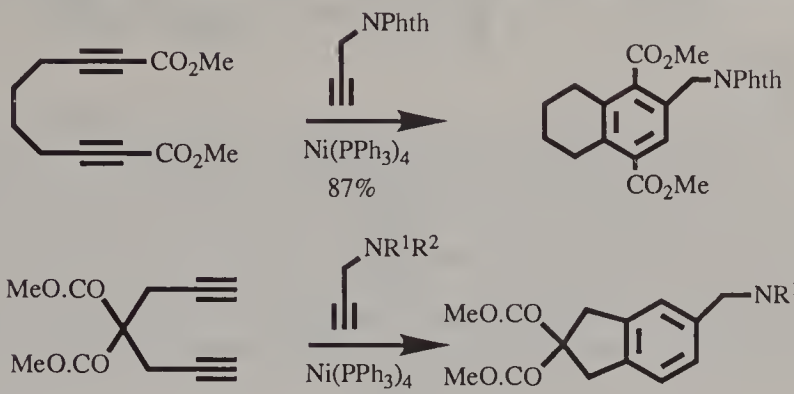
[1] Heys, J. R. (1991). Fourth International Symposium on the Synthesis of Isotopes and Isotopically Labelled Compounds, Toronto, 3–7 September.
[2] Heys, R. (1992). *J. Chem. Soc., Chem. Commun.* 680.

Co-cyclizations of Nitrogen-containing Acetylenes Induced by a Nickel Triphenylphosphine Complex to give Indane and Isoindole Derivatives.

Malcolm Duckworth[1], Edward H. Smith[2] and Simon Lee-Wong[2]. [1]*SmithKline Beecham Pharmaceuticals, Harlow, Essex CM19 5AD, UK;* [2]*Department of Chemistry, Imperial College, South Kensington, London SW7 2AY, UK*

Previous work has shown that the nickel(0)-mediated co-cyclization of 1,6-heptadiynes and 1,7-octadiynes with propargylic alcohols and ethers proceeds in moderate to good yields to give indane

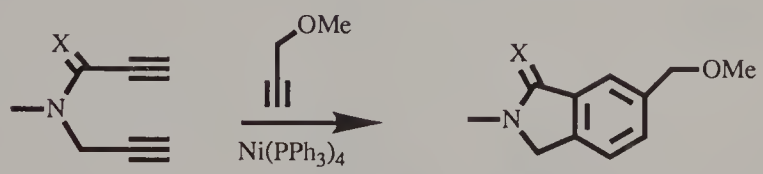
and tetralin derivatives, respectively [1,2]. The same has now been shown to hold for propargylamine derivatives:



R^1	Me	Et	Bn	COMe	COPh
R^2	Me	Et	H	H	H
%	62	60	47	35	21

Scheme 52

Similarly, dipropargylamine derivatives give isoindole products:



X = 2 x H, RT, 46%
X = O, 67°C, 30%

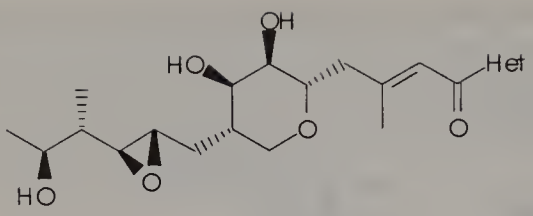
Scheme 53

The application of this methodology in alkaloid synthesis is being investigated.

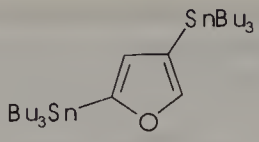
[1] Bhatarah, P. and Smith, E. H. (1990). *J. Chem. Soc., Perkin Trans.* **1**, 2603.
[2] Bhatarah, P. and Smith, E. H. (1992). *J. Chem. Soc., Perkin Trans.* **1**, 2163.

Regiospecific Generation of some Lithioheterocycles. Andrew K. Forrest and Jean E. Pons. *SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ, UK*

A range of heteroaryl ketone derivatives of monic acid were prepared using heteroaryllithium intermediates. For **1a**, specific lithiation at the 5-position of 2-methyl thiazole was achieved by



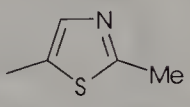
(1)



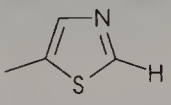
(2)

Het

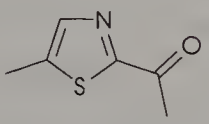
a)



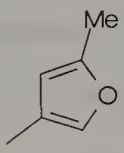
b)



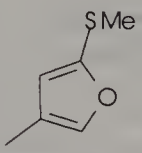
c)



d)



e)



Scheme 54

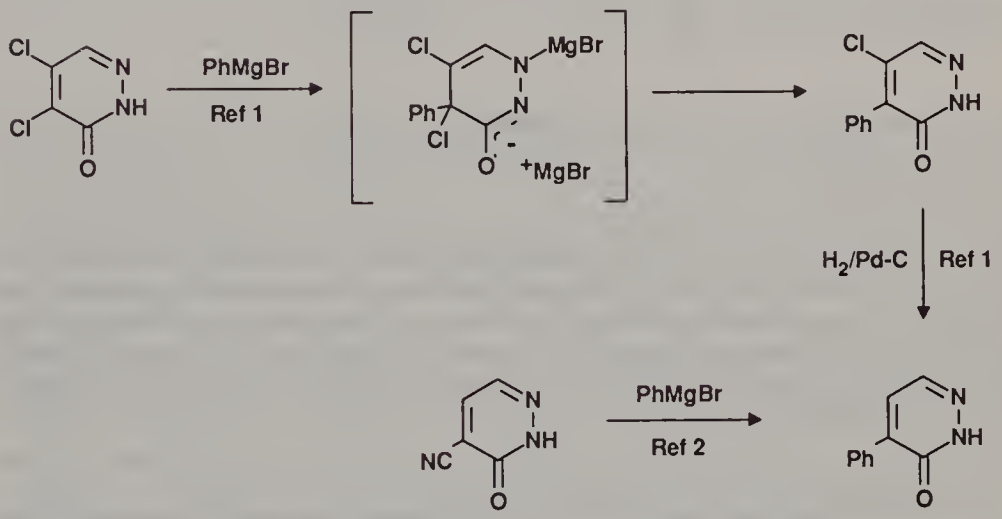
metal–halogen exchange of the 5-bromo derivative. 5-Lithiothiazole rapidly converted to the 2-isomer, so trimethylsilyl protection of the thiazole 2-position was used for the preparation of **1b** [1]. The methyl ketone moiety of 2-acetyl thiazole was masked as the triisopropylsilyl enol ether for the preparation of **1c**. The 3-bromo furan precursor to **1d** was obtained by a variation of a literature procedure [2], while sequential lithiation of the novel *bis*-stannyl furan **2** enabled the methylthiofuryl analogue **1e** to be prepared.

[1] Dondoni, A., Mastellari, A. R., Mediei, A., Negrini, E. and Pedrini, P. (1986). *Synthesis* 1757.
[2] Obrecht, D. (1989). *Helv. Chim. Acta* **72**, 447.

Reactions of 4,5-Dichloro-3(2*H*)-Pyridazinone with Organometallic Reagents. W. J. Coates[1], S. T. Flynn[1] and A. McKillop[2]. [1]*Medicinal*

Chemistry, SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR, UK; [2]School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK

While organolithium and Grignard reagents are known to take part in 1,4-addition to pyridazine derivatives, our early attempts to exploit this for the synthesis of 4- or 5-aryl-3(2*H*)-pyridazinones were complicated by the formation of unstable dihydropyridazinones. To avoid this problem the readily available 4,5-dichloro-3(2*H*)-pyridazinone was selected as a substrate: the initially formed adduct was expected to re-aromatize by loss of metal (or hydrogen) halide. This was confirmed by reaction with phenylmagnesium bromide to give, *selectively*, 5-chloro-4-phenyl-3(2*H*)-pyridazinone in good yield [1]. Subsequent hydrogenolysis gave 4-phenyl-3(2*H*)-pyridazinone [1] which has recently been prepared by reaction of phenylmagnesium bromide with 4-cyano-3(2*H*)-pyridazinone [2]. 6-Aryl-3(2*H*)-pyridazinones are well known and of interest both as intermediates

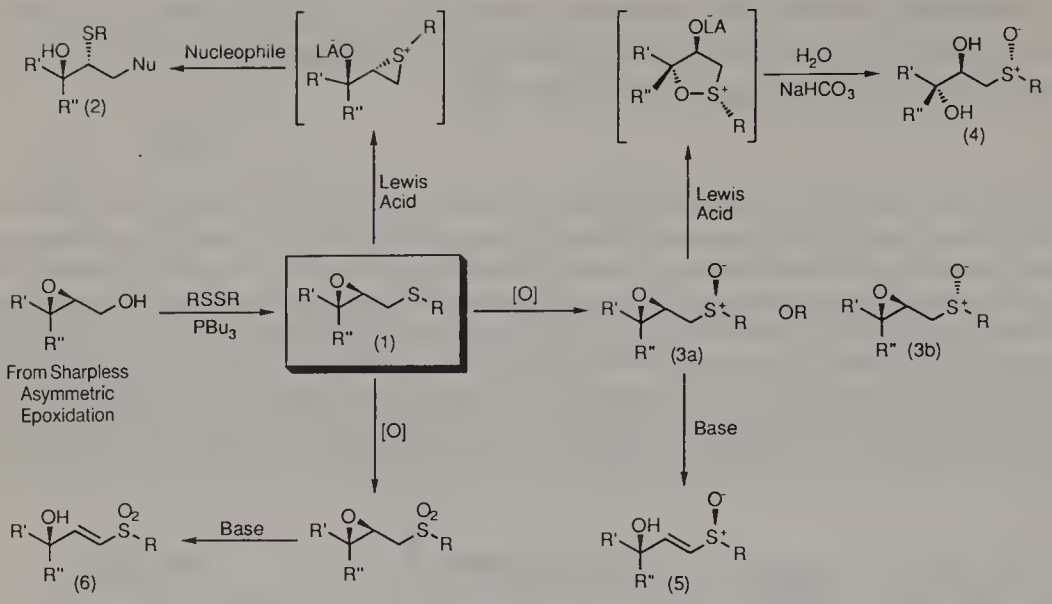


Scheme 55

and because of their biological activity, but there is much less literature regarding the 5-aryl- and particularly 4-aryl-3(2*H*)-pyridazinones. The preliminary results of our investigation into the scope and utility of the title reactions for the preparation of the latter compounds will be presented.

[1] Breukelman, S. P., Coates, W. J., Meakins, G. D., Roe, A. M. and Slater, R. A. (1985). Eur. Patent 138,344.
[2] Haider, N., Heinisch, G. and Moshuber, J. (1991). *Tetrahedron* **47**, 8573.

Investigations into the Chemistry of 2,3-Epoxy Sulphides. Duncan M. Gill, Christopher M. Rayner and Andrew D. Westwell. *School of Chemistry, University of Leeds, Leeds LS2 9JT, UK*



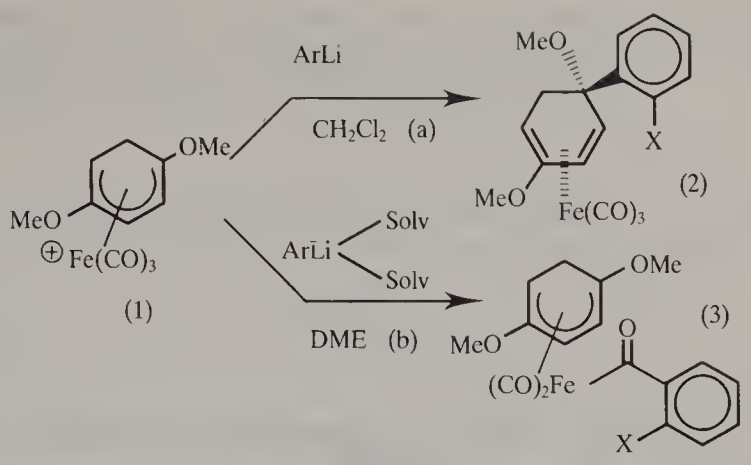
Scheme 56

The ability of the Sharpless asymmetric epoxidation to produce a wide variety of optically active 2,3-epoxy alcohols has lead to their exploitation as valuable synthetic intermediates. The corresponding 2,3-epoxy sulphides **1**, which may be readily prepared from the corresponding epoxy alcohols, have however been little investigated and represent a new, readily available, optically active building block for use in synthesis. These simple molecules have a rich and varied chemistry as summarized in Scheme 56.

Thus treatment of **1** with a Lewis acid generates an episulphonium ion intermediate which may be trapped with suitable nucleophiles [1,2]. Selective oxidation allows preparation of either 2,3-epoxy sulphoxide diastereomer **3a** or **3b** [3], and further oxidation furnishes the sulphone. Under basic conditions the sulphoxide and sulphone derivatives eliminate with full retention of stereochemistry to give the γ-hydroxy vinyl sulphoxides **5** or sulphones **6**, respectively. Treatment of either 2,3-epoxy sulphoxide **3a** or **3b** with a Lewis acid allows regiospecific hydrolysis at C-3 of the epoxide to form the 2,3-dihydroxy sulphoxide **4** via an intermediate sulphoxonium salt with full stereochemical control [4].

[1] Gill, D. M., Pegg, N. A. and Rayner, C. M., submitted to *J. Chem. Soc., Chem. Commun.*
[2] Rayner, C. M. (1992). In *Organosulphur Chemistry Series* (P. C. B. Page, ed). Pergamon Press, Oxford.
[3] Rayner C. M., Sin, M. S. and Westwell, A. D. (1992). *Tetrahedron Lett.* **33**, 7237.
[4] Westwell, A. D. and Rayner, C. M. (1992). *Tetrahedron Lett.* **33**, 2409.

Solvent Effects Control the Selective Functionalization of Organoiron Complexes. Andrey V. Malkov and G. Richard Stephenson. *School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK*



Scheme 57

Electrophilic organoiron π-complexes are important as stoichiometric reagents in organic synthesis due to the activating and control influence of the tricarbonyliron group. Products of type **2** from aryl group addition to the dienyl salt **1** are under investigation as chiral intermediates in the stereocontrolled synthesis of alkaloids [1,2]. Results explaining the factors controlling the addition of *o*-substituted aryllithium reagents to **1** will be presented.

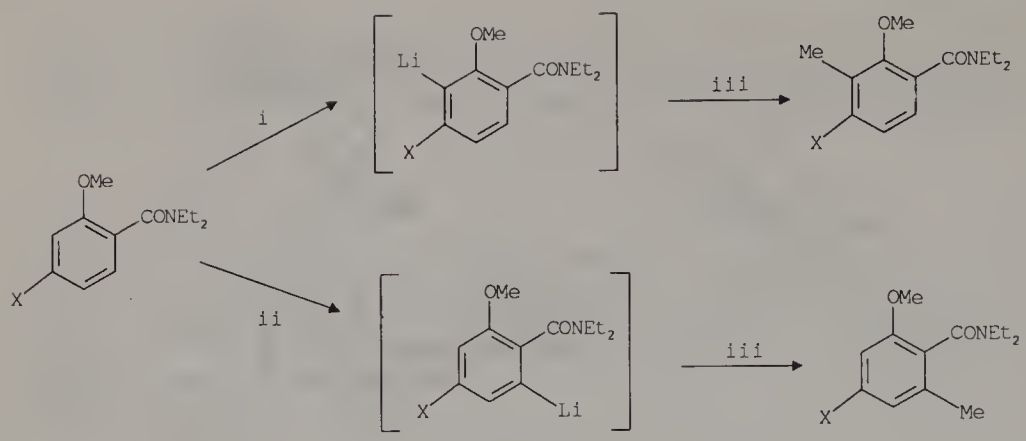
The reactivity properties of the nucleophile can be adjusted by selection of either non-coordinating (a) or coordinating (b) solvents. This allows selective access to either an arylcyclohexadiene building block, or a novel $Fe(CO)_2$(acyl) complex **3**. The properties of complexes of this type are under investigation. The nature of the group X also influences the selectivity between **2** and **3**. Details of control effects in the arylation reaction will be discussed.

[1] Stephenson, G. R., Owen, D. A., Finch, H. and Swanson, S. (1991). *Tetrahedron Lett.* **32**, 1291.
[2] Stephenson, G. R., Owen, D. A., Finch, H. and Swanson, S. (1993). *Tetrahedron* **49**, 5649.

Regioselective Lithiation of 4-Halo-2-Methoxybenzamides. John Berge.

SmithKline Beecham, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ, UK

Regioselective lithiation of the title compounds can be achieved by judicious choice of reaction solvent (tetrahydrofuran or diethyl ether). Quenching of the resultant anion with an electrophile leads to either the 3- or 6-substituted benzamide derivatives in good yield. A possible explanation of regioselectivity observed in this reaction is proposed on the basis of the relative complexing abilities of tetrahydrofuran and diethyl ether to the respective organolithium bases.



Scheme 58

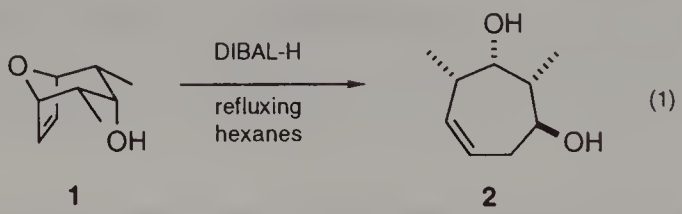
Reagents: (i) *s*-BuLi or *t*-BuLi, THF, −78°C, 2 h; (ii) *t*-BuLi, Et_2O, −78°C, 2 h; (iii) MeI, −78°C to room temperature, 2.5 h.

Enantioselectivity and Stereocontrol

Transition Metal-catalysed Reductive Ring Opening of Oxabicyclic Compounds.

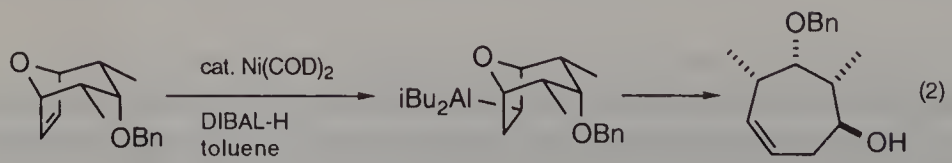
Mark Lautens and Pauline Chiu. *Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1*

Oxabicyclic compounds such as **1** are precursors to stereochemically complex cycloalkenols and acyclic arrays through nucleophilic ring opening by organometallic reagents [1,2]. A reductive ring opening has also been developed which delivers hydride in an S_N2' fashion to generate cycloalkenols **2** bearing up to four contiguous stereocentres (equation 1). This reaction has been exploited in a synthesis of a subunit of ionomycin [3].



Scheme 59

Recently, transition metals such as NiO have been found to catalyse the reductive ring opening reaction, and have afforded improved yields of products. The catalysed ring opening occurs by a two-step process: hydroalumination, followed by elimination (equation 2).



Scheme 60

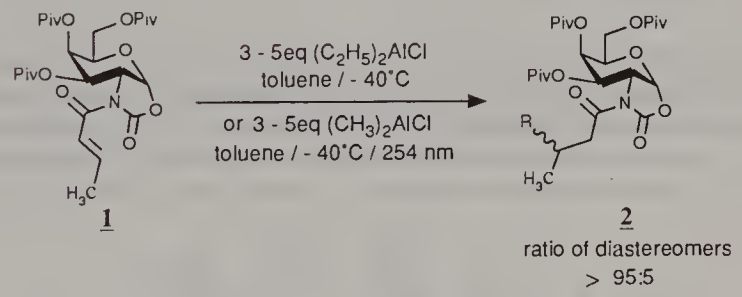
Results from the investigation of the effect of different transition metals, ligands, and Lewis acids on the reductive ring opening will be detailed. Mechanistic studies of the uncatalysed and catalysed versions of the reaction using DIBAL-D will also be presented.

[1] Lautens, M., Abd-El-Aziz, A. S. and Lough, A. (1990). *J. Org. Chem.* **55**, 5305.
[2] Lautens, M. and Belter, R. K. (1992). *Tetrahedron Lett.* **33**, 2617.
[3] Lautens, M., Chiu, P. and Colucci, J. T. (1993). *Angew, Chem. Int. Ed. Engl.* **32**, 281.

Carbohydrate-linked Oxazolidinones as Chiral Auxiliaries in Stereoselective Syntheses.

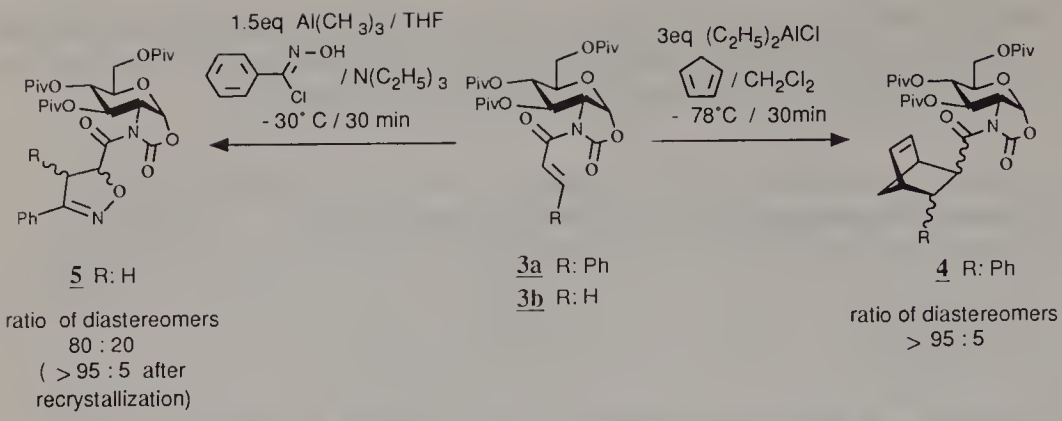
S. Engel, H. Kunz and K. Rück. *Johannes Gutenberg-Universität Mainz, Institut für Organische Chemie, Becher-Weg 18-20, D-6500 Mainz, Germany*

The diastereoselective 1,4-addition of dialkylaluminium halides to α,β-unsaturated *N*-acyl-urethanes proved to be a valuable method for the synthesis of β-branched carboxylic acid derivatives **2** [1]. Due to the difficult stereochemical control of the alkyl transfer the bicyclic *N*-acyl-glycosyl-oxazolidinone **1** has especially been developed as chiral auxiliary for this purpose [2]. Except for dimethylaluminium chloride, the alkyl transfer observed in the reactions of dialkylaluminium chlorides with **1** occurs exclusively via a polar pathway. In contrast dimethylaluminium chloride obviously reacts by a homolytic mechanism (Scheme 61).



Scheme 61

The promising results in these reactions has induced further examinations of the carbohydrate-linked oxazolidinone as the stereodifferentiating auxiliary in several other reactions. In Diels–Alder cycloadditions it proves to be a pronounced electron-deficient dienophile and, thus, the unreactive *N*-cinnamoyl-derivative **3a** reacts with cyclopentadiene to form the cycloadduct **4** (Scheme 62). The reaction proceeds under diethylaluminium chloride catalysis with excellent yields and complete endo- and high diastereoselectivity. In stereochemically even more demanding 1,3-dipolar cycloaddition reactions with nitrile oxides leading to isoxazoline derivatives **5**, the diastereoselectivity observed is only moderate. *N*-Acryl-glycosyl-oxazolidinone **3b** does react at room temperature in reasonable yield and excellent regio- but only low diastereoselectivity. When Lewis acids such as trimethylaluminium or titanium tetrachloride are used as catalysts, the reaction can be carried out at −30°C to give almost quantitative yield of **5** (Scheme 62). Unfortunately, it has not been possible to influence the stereoselectivity of the cycloaddition by chelation control yet.

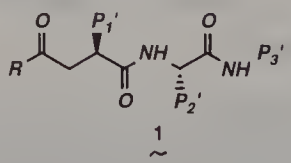


Scheme 62

[1] Kunz, H. and Pees, K. J. (1989). *J. Chem. Soc., Perkin Trans.* **I**, 1169.
[2] Kunz, H. and Rück, K. (1992). *Synlett* 343.

The Asymmetric Synthesis of Gelatinase Inhibitors. J. R. Porter, N. R. A. Beeley, B. A. Boyce, J. Leonard, B. Mason, T. A. Millican and J. R. Morphy. *Division of Chemistry, CELLTECH Ltd, 216 Bath Road, Slough SL1 4EN, UK*

Amongst the members of the matrix metalloproteinase family of zinc-containing endopeptidases are the collagenases, stromelysins and gelatinases. 72 kD a gelatinase has recently been implicated as a causal agent in the process of tumour invasion and metastasis. Using a panel of pure human versions of these enzymes we have identified a series of extremely potent and selective inhibitors of gelatinase having the general structure **1** which may be of therapeutic value in the treatment of cancer.

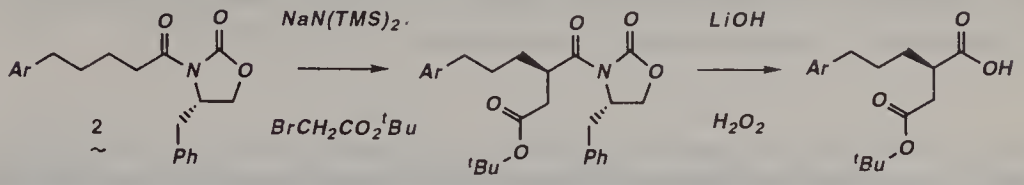


1

Scheme 63

Retrosynthetic cleavage of the amide bonds in **1** gives three fragments, two of which contain a chiral centre. The fragment containing P_2' is usually obtained from an amino acid derivative of known chirality. In our early analogues the succinate moiety containing P_1' was constructed racemically via malonate chemistry. Our first asymmetric method involved the use of chymotrypsin in the enantioselective hydrolysis of a suitably substituted succinate diester. Unfortunately, this method was not satisfactory when P_1' was arylpropyl. Since this substituent gave the most

interesting series in terms of *in vitro* activity and selectivity we developed an alternative route based on Evans chiral oxazolidinone methodology as shown below:



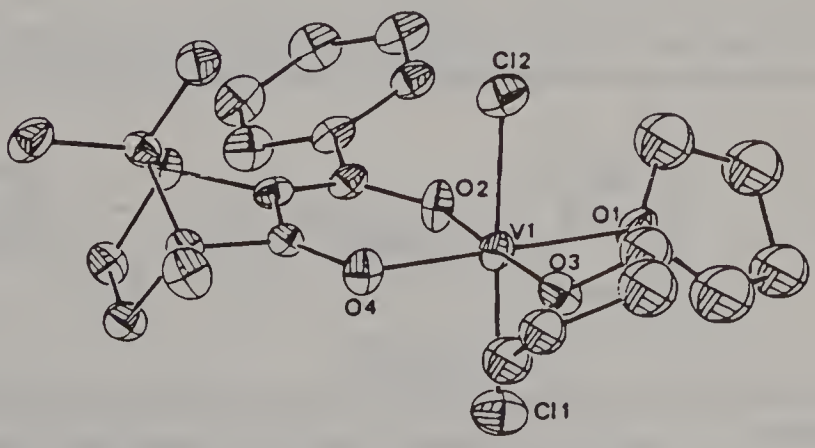
Scheme 64

A number of methods were investigated for the construction of the oxazolidinone **2** (where Ar is aryl, substituted aryl or heteroaryl) which will be summarized. Asymmetric alkylation followed by cleavage of the chiral auxiliary were readily achieved by the Evans protocol. Coupling of the fragments using standard peptide methodology and deprotection gave the desired gelatinase inhibitors.

Chiral Vanadium Complexes for Enantioselective Pinacol Coupling.

Pier Giorgio Cozzi, Romano Dorta and Carlo Floriani. *Institute of Inorganic Chemistry, University of Lausanne, Switzerland*

Pinacol coupling mediated by low valent early transition metals is a useful procedure in organic synthesis. Recently, Petersen described an efficient coupling procedure by using V_2Cl_3-$(THF)_3Zn_2Cl_6$ prepared *in situ*. From a mechanistic point of view the reaction is poorly understood. For a better comprehension of the reaction and with the goal of developing chiral complexes for efficient enantioselective pinacol coupling, we have synthesized some structurally characterized vanadium complexes, e.g. **1**, and have studied their reductions and subsequent reactivities with carbonyl compounds. Preliminary results will be presented.

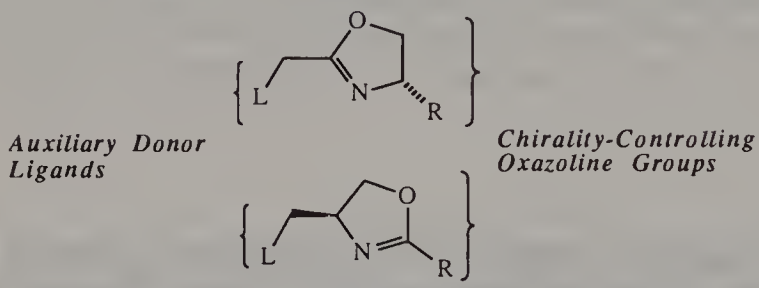


1

Scheme 65

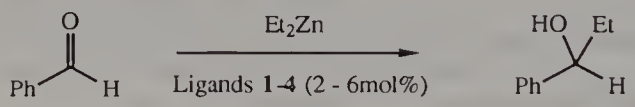
Enantiomerically Pure Hydroxymethyl Oxazolines: Catalysts for the Addition of Dialkylzinc to Aldehydes. Joanne V. Allen and Jonathan M. J. Williams. *Department of Chemistry, Loughborough University of Technology, Loughborough, Leicestershire LE11 3TU, UK*

The use of homochiral oxazolines as ligands in metal-catalysed reactions has recently been receiving a great deal of attention [1]. We are currently investigating the use of ligands which exploit the stereochemistry-directing properties of the homochiral oxazoline moiety and also contain a further donor atom [2]. This approach affords the flexibility to tailor the ligand to the electronic requirements of a particular catalytic reaction, which we have exploited for palladium-catalysed allylic substitution [3].



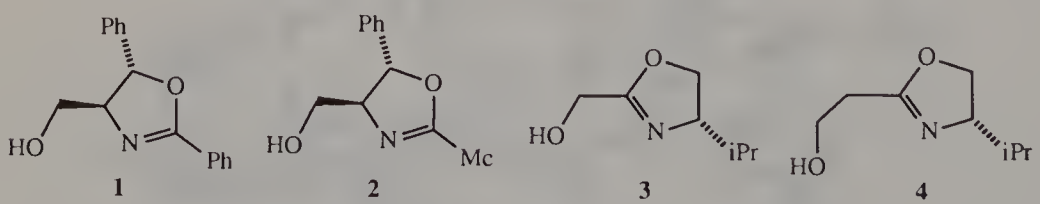
Scheme 66

Where the auxiliary binding group L is a hydroxy functionality, we reasoned that the combination of oxazoline with hydroxy would afford a good asymmetric environment for the addition of dialkylzinc reagents to aldehydes [4]. To this end, we are examining the ligands **1–4** as catalysts for the reaction between diethylzinc and benzaldehyde.



Scheme 67

The levels of enantioselectivity are very encouraging (up to 80% ee with ligand **2**), and we are currently optimizing the reaction conditions and ligand design to increase selectivities still further.



Scheme 68

We thank the SERC for an earmarked quota award (to J.V.A.) and the Nuffield Foundation for financial assistance.

[1] Evans, D. A., Woerpel, K. A. and Scott, M. J. (1992). *Angew, Chem. Int. Ed. Engl.* **31**, 430 and references therein.

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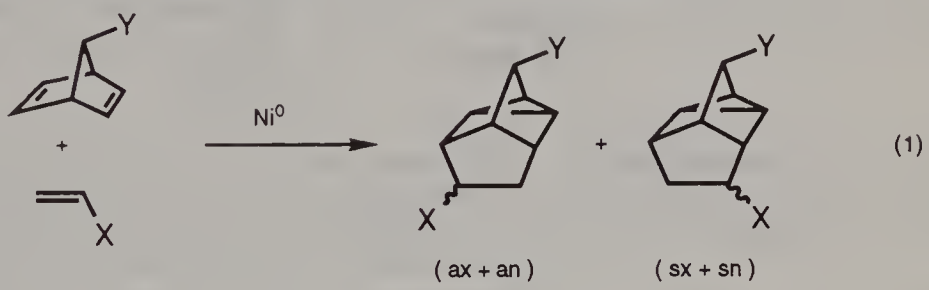
Transition Metal-catalysed Enantioselective and Stereoselective Cycloaddition Reactions.

Mark Lautens and William Tam. *Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1*

Part 1: Nickel-catalysed Homo Diels–Alder Reaction

As part of our continuing efforts to develop novel strategies for constructing polycyclic natural products, studies on the nickel-catalysed homo Diels–Alder reaction between 7-substituted norbornadienes and a variety of dienophiles was recently undertaken (equation 1).

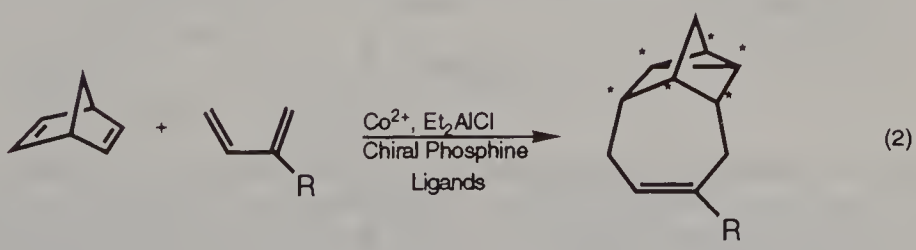


Scheme 69

Four possible homo Diels–Alder adducts may be formed in this reaction, namely *anti-exo* (ax), *anti-endo* (an), *syn-exo* (sx), *syn-endo* (sn). The remote 7-substituent on norbornadiene exerted significant control on the stereoselectivity of the reaction. Details of these studies will be presented.

Part 2: Enantioselective Cobalt-catalysed [4+2+2] Cycloadditions

As part of a synthetic program aimed at the synthesis of terpenoids such as longicyclene and pseudoquianolides, we recently achieved an enantioselective higher order [4+2+2] cycloaddition with enantiomeric excess >70% (equation 2). Syntheses of a variety of diene precursors and the conditions to achieve high enantioselectivity will be presented.



Scheme 70

[1] Lautens, M. and Edwards, L. G. (1989). *Tetrahedron Lett.* **30**, 6813.
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[3] Lautens, M. and Crudden, C. M. (1989). *Organometallics* **8**, 2733.
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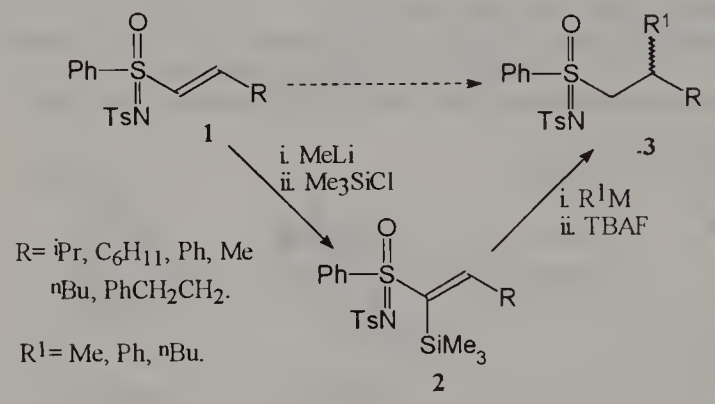
Sulphoximines — New Applications in Asymmetric Synthesis.

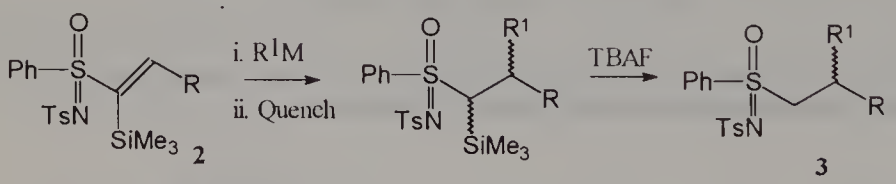
A. D. Briggs and R. F. W. Jackson. *Newcastle University, Newcastle upon Tyne, UK*

In recent years, a variety of chiral electrophilic olefinic substrates that undergo conjugate addition with organometallic reagents with high asymmetric induction have been prepared. These substrates have allowed for the preparation of chiral 3-alkylalkanoic acids and 3-alkylcycloalkanones and their derivatives in high enantiomeric excess. We report here a study of the conjugate addition of organometallic reagents to simple *N*-tosyl vinylsulphoximines **1** leading to adducts **3** and demonstrate the potential of these substrates for enantioselective synthesis.



Scheme 71

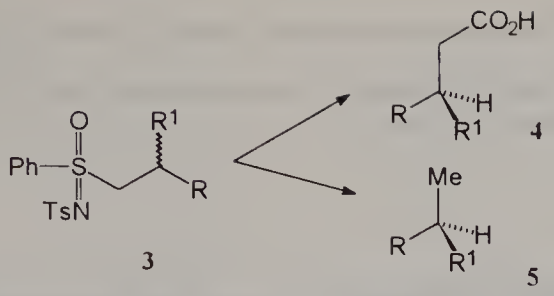
The above methodology was effected by blocking the α-position with a suitable group, e.g. trimethylsilyl. A range of α-silyl vinylsulphoximines **2** were prepared and their subsequent reaction with alkyllithiums, lower order cuprates and alkylmagnesium halides was investigated and the extent of diastereofacial control of the conjugate addition established upon desilylation.



Scheme 72

Alkyllithiums gave the highest diastereofacial control, with the β-cyclohexyl- and β-*iso*-propyl-substrate systems giving the highest selectivity. Hence, branching is required in the β-alkyl substituent in α-silyl vinylsulphoximines **2** to obtain high diastereofacial control in this addition.

The stereochemistry of the newly created chiral carbon (C-2) in adducts **3** was investigated by ^{1}H NMR and was found to possess excellent diastereoselectivity (>90%) in specific cases, for example **3a** where R = *i*-Pr and R^1 = Me. The absolute configuration is currently being established by converting **3a** to the corresponding known 3-alkylalkanoic acids **4**. In some cases (R $\neq$ Me, $R^1 \neq$ Me) the stereochemistry of C-2 can be established by simple reduction with aluminium amalgam to give the corresponding alkane **5**.

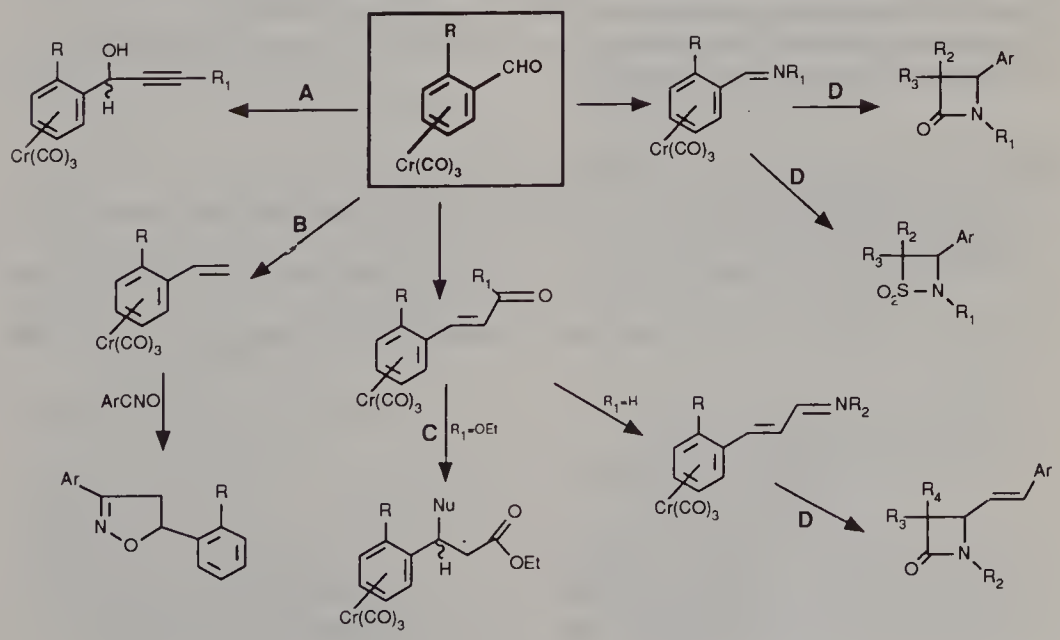


Scheme 73

Chiral Benzaldehyde Chromium Tricarbonyl Complexes: Efficient Synthons in Asymmetric Synthesis. Clara Baldoli, Paola Del Buttero and Stefano Maiorana. *CNR Centro Sintesi e Stereochimica Speciali Sistemi Organici e Dipartimento di Chimica Organica e Industriale dell'Universita', Via C. Golgi, 19. 20133 Milano, Italy*

Chiral chromium arene complexes are valuable because they provide templates for the highly stereoselective elaboration of side chains. We present in a general scheme the results we have recently achieved, using chiral $Cr(CO)_3$ complexed benzaldehydes, in the stereoselective synthesis of optically active organometallic and organic compounds:

(A) Addition of lithium acetylides to chiral complexed benzaldehydes gives alkynyl alcohols in good yields and complete stereoselection.
(B) Cycloaddition of benzonitriloxide to chiral complexed styrenes offers a synthetic route to optically active dihydroisoxazoles.



Scheme 74

(C) Michael addition of nitromethane to complexed 2-methoxy ethyl cinnamate proceeds with full stereoselection.
(D) Optically active β-lactams and β-sultams are obtained in high ee using $Cr(CO)_3$ complexes of benzaldehyde and cinnamaldehyde imines.

Stereospecific Synthesis of Chiral Caprolactam Monomers from Carbohydrates. Guylaine M. Defossemont, Lois B. Olivant, George H. W. Milburn and David J. Mincher. *Department of Applied Chemical and Physical Sciences, Napier University, Edinburgh, UK*

Mainly from the viewpoint of ease of separation and thus recycling, and in response to the growing need for optically pure compounds, synthetic polymeric materials have found some application as supports for chiral chemical reagents and as media for the chromatographic separation of racemates. The majority of so-called chiral polymers central to these applications have their chirality contained in pendent groups [1–3]. This programme attempts to address the current scarcity of synthetic chiral polymers having intrinsic main chain chirality, and in which the stereochemical properties of the polymeric matrix are closely controlled. Depending upon the supramolecular structure and macroscopic properties of the final materials, it is recognized that polymers with intrinsic main chain chirality could improve the enantioselective characteristics of catalytic systems [4], furnish artificial membranes for the separation of enantiomers, have a synergistic effect on the therapeutic action of drugs released from polymeric delivery systems, and act as chiral chromatographic media.

Synthetic routes to optically pure highly functionalized caprolactam monomers from D-glucose and D-xylose are described. Key intermediates required for the construction of the azacycloheptanc ring system are produced by C-branching of monosaccharides using zinc–copper couple-mediated reactions and by organotin-promoted free radical carbon branching.

The support of SERC (Innovative Polymer Synthesis Initiative) and Napier University Research and Consultancy Committee is acknowledged.

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[3] Lecvalier, P., Bald, E., Tiang, Y., Frechet, J. M. J. and Hodge, P. (1985). *React. Polym., Ion Exch., Sorbents* **3**, 315.
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