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Stereocontrolled Synthesis of Spirocyclics

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Introduction

The general approaches that have been used to make spiro compounds in a stereochemically controlled manner involve, as the key step, alkylation, transition-metal based processes, rearrangement, cleavage of bridged systems, ring closure of geminally disubstituted starting materials, cycloaddition, and radical cyclization. Cases are also known in which an achiral spiro compound is elaborated into one that is chiral.

In the following review[1] the synthetic methods have been categorized as far as possible, but inevitably some assignments are arbitrary. Coverage is limited to those substances in which the spirocenter is attached directly to four carbons.

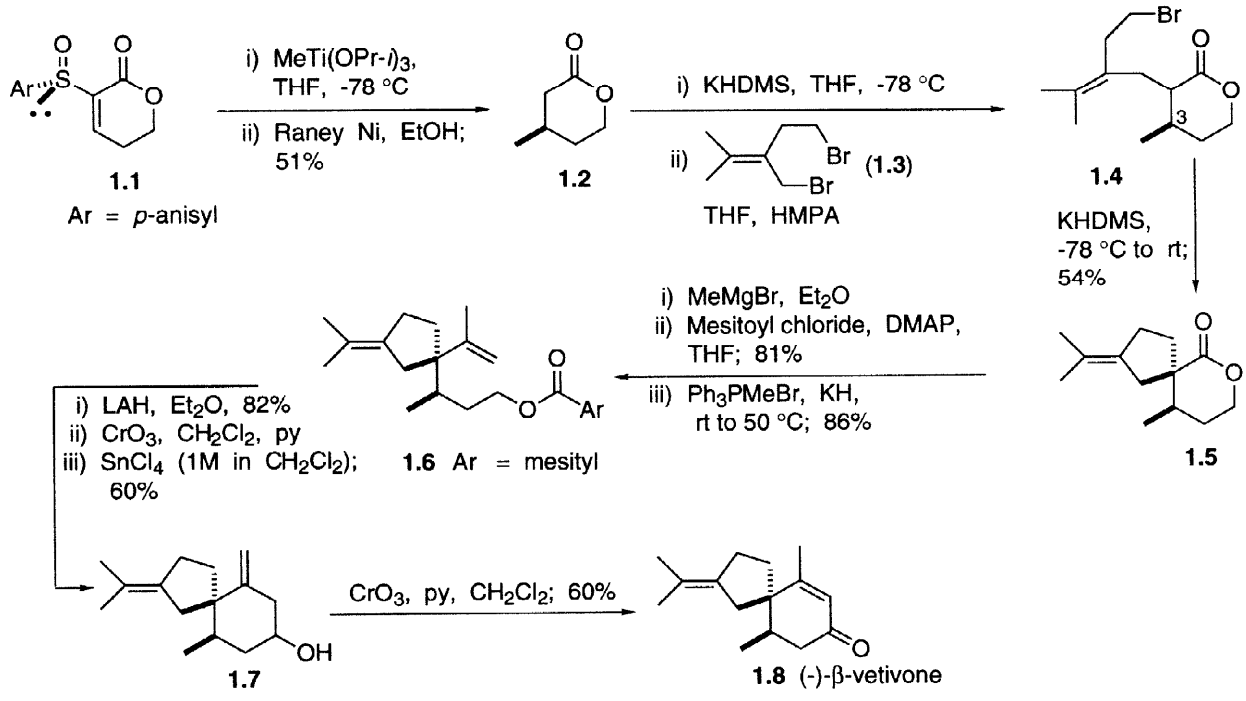
1 Use of Alkylation

A number of examples have been reported in which the committing step, which generates the spirocenter, is a stereoselective alkylation.

1a Intramolecular alkylation

Posner *et al.*[2] have made the fragrant sesquiterpene β-vetivone (**1.8**, Scheme 1) by asymmetric synthesis, using intramolecular alkylation (Scheme 1). The enantiomerically pure vinylic sulfoxide **1.1** under-

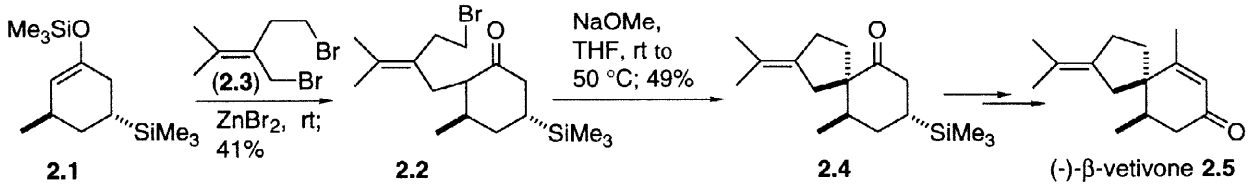
Scheme 1



went highly enantioselective (27:1) conjugate methyl addition (see **1.1** → **1.2**). Reductive cleavage of the sulfinyl group then produced the conformationally biased lactone **1.2**, and when this was alkylated with the allylic-homoallylic dihalide **1.3**, first in an intermolecular process (**1.2** → **1.4**), and then intramolecularly,[3] spirolactone **1.5** was formed. The observed stereochemical outcome of the spiroannulation was expected on the basis that the intramolecular step (**1.4** → **1.5**) should occur on the face *anti* to the methyl group at C(3). Lactone ring opening with methylmagnesium bromide, acylation of the resulting primary alcohol with mesitoyl chloride, and Wittig olefination, then afforded **1.6**. Reduction of the ester, and Collins oxidation, gave the expected aldehyde, which underwent an intramolecular ene reaction in the presence of tin tetrachloride, to give the spirobicyclic alcohol **1.7**. Finally, Collins oxidation, which was accompanied by double bond migration, completed the synthesis of natural (-)-β-vetivone (**1.8**).

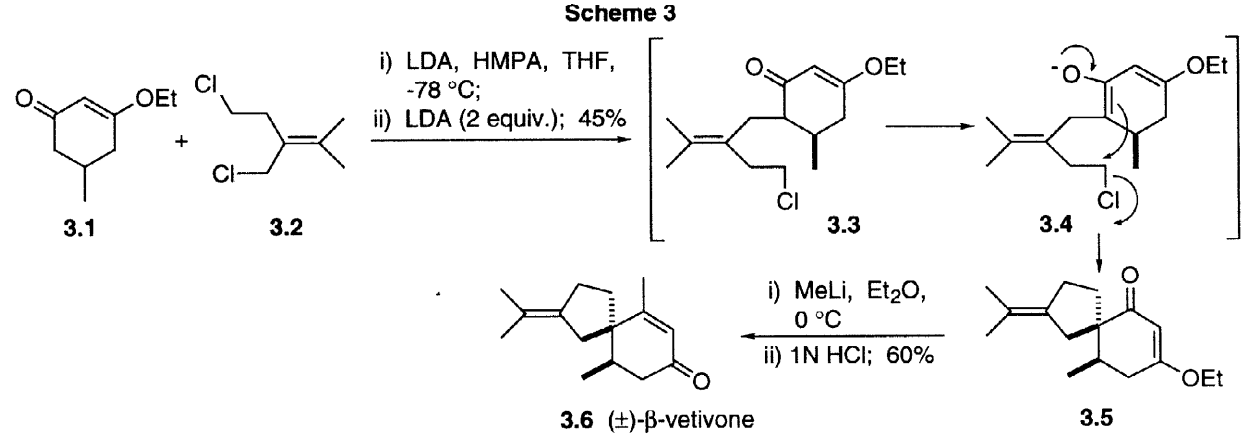
Asaoka *et al.*[4] used the same dihalide (**2.3** ≡**1.3**) to alkylate a different substrate (Scheme 2) in their route to (-)-β-vetivone; again, the same stereochemical directing effect came into play (see **2.1** → **2.2** → **2.4**).

Scheme 2



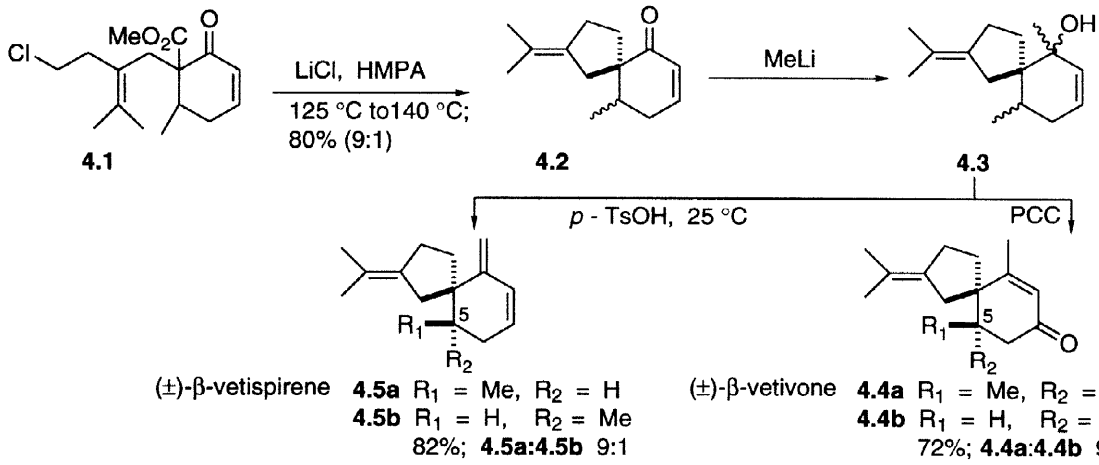
The above use of an allylic-homoallylic dihalide for construction of a spiro system has precedent in an earlier synthesis of (±)-β-vetivone (Scheme 3) by Stork *et al.*[3] When enone **3.1** was alkylated with the allylic-homoallylic dichloride **3.2**, the spiroketone **3.5** was formed via **3.3** and **3.4** . Addition of methyllithium to **3.5**, and treatment with acid, then gave (±)-β-vetivone (**3.6**).

Scheme 3



Eilerman and Willis[5] developed a spiroannulation technique that employs a similar dihalide for double alkylation, but in a manner that avoids the use of strong base. The method, which involves a decarboxylation induced by halide ion, was used in the synthesis of (±)-β-vetivone and (±)-β-vetispirene (Scheme 4). The key substrate (**4.1**), prepared from the corresponding β-ketoester, reacted with anhydrous lithium chloride in HMPA at 125-140 °C to provide ketone **4.2** as a 9:1 mixture of diastereomers, the stereochemical outcome at the spirocenter depending on the same factors that prevail in Stork's method (*cf.* Scheme 3).[3] Addition of methyllithium to **4.2** furnished the allylic alcohols **4.3**, and oxidation by PCC then gave a 9:1 mixture of the

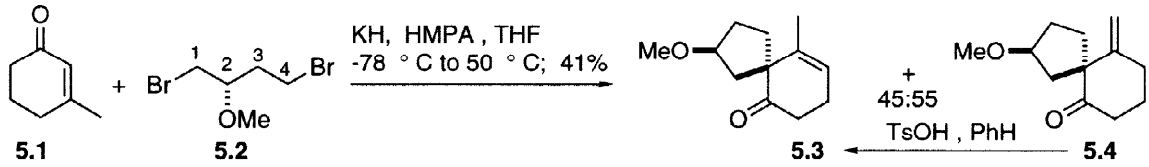
Scheme 4



C(5) epimeric ketones **4.4a,b**, the major component being (±)-β-vetivone (**4.4a**). Dehydration of **4.3** led to a 9:1 mixture of C(5) epimers, in which the major isomer was (±)-β-vetispirene (**4.5a**).

A stereoselective spirocyclization relevant to the synthesis of vetivanes (Scheme 5) was developed by Cannone.[6] The method involves use of the optically pure dibromide **5.2** to alkylate an enone (**5.1**). The alkylation occurs at the more accessible halogenated terminus [C(4)] of the dibromide, and this step is followed by facially selective intramolecular alkylation, to afford **5.3** and **5.4**. The latter can be isomerized to the former.

Scheme 5

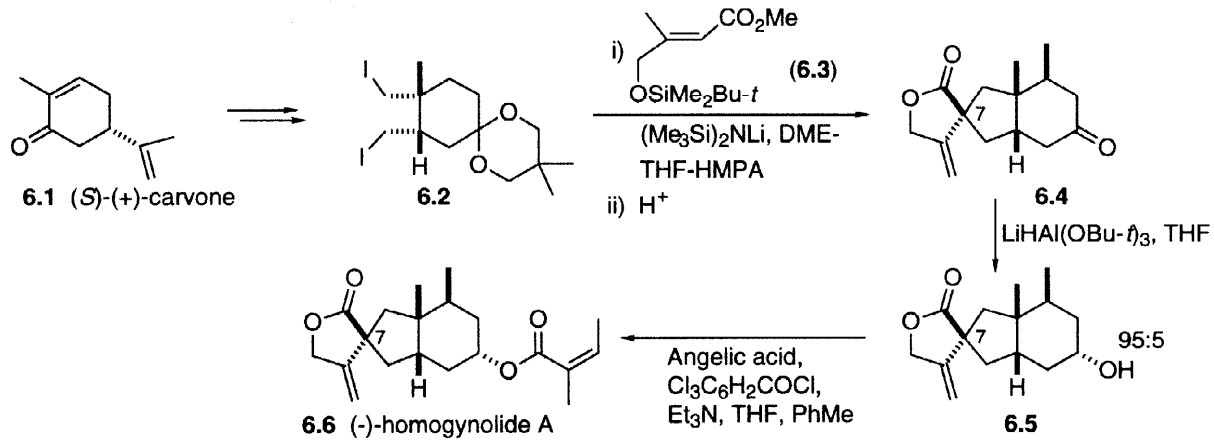


In Cannone's method the diastereoselectivity is controlled by the asymmetric center in the dibromide. In principle, compound **5.3** can serve as a precursor to sesquiterpenes with a spiro [4.5] skeleton.

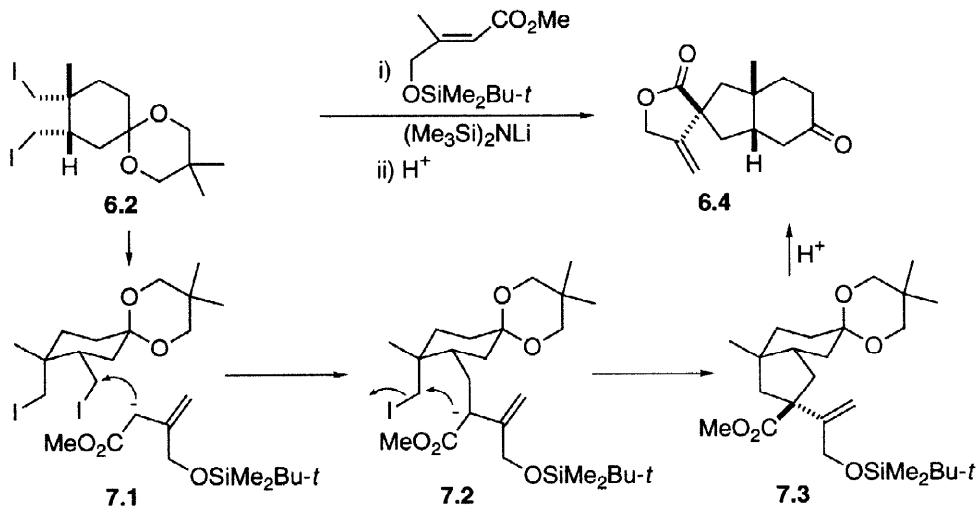
An unusual use of stereoselective cycloalkylation as the key step in generating a spirocenter is provided by the synthesis of the bakkane (-)-homogynolide-A (**6.6**).[7,8] When diiodide **6.2**, prepared from enantiopure (*S*)-(+)-carvone (**6.1**), was used to alkylate the lactone synthon **6.3**, and the initial product then exposed to acid, the spirolactone **6.4**, with the *R*-configuration at C(7), was generated as the major isomer (*ca* 3:1). The mechanism presumably involves the steps shown in Scheme 7, with the more accessible iodide being displaced first, but it is not obvious what controls the stereochemistry of the spirocenter in the step **7.2** → **7.3**. Stereoselective reduction of **6.4** (Scheme 6) furnished **6.5** and, on esterification with angelic acid, this then afforded the target **6.6**.

The bakkane (±)-palmosalide C (**8.6**), was synthesized stereoselectively by Greene *et al.*[9] (Scheme 8), using a conceptually similar alkylation to generate the spirocenter. When the diester **8.2**, prepared from 1,6-dimethylcyclohexene, was reduced to the diol and treated with ethanesulfonyl chloride, the bis-electrophile **8.3** was formed. It was converted stereoselectively (see Scheme 8) into the hydrindane bis-ester **8.4**, from which lactone **8.5** was easily reached. The natural product **8.6** was then obtained by introduction of a methyl group and a double bond, followed by regioselective epoxidation.

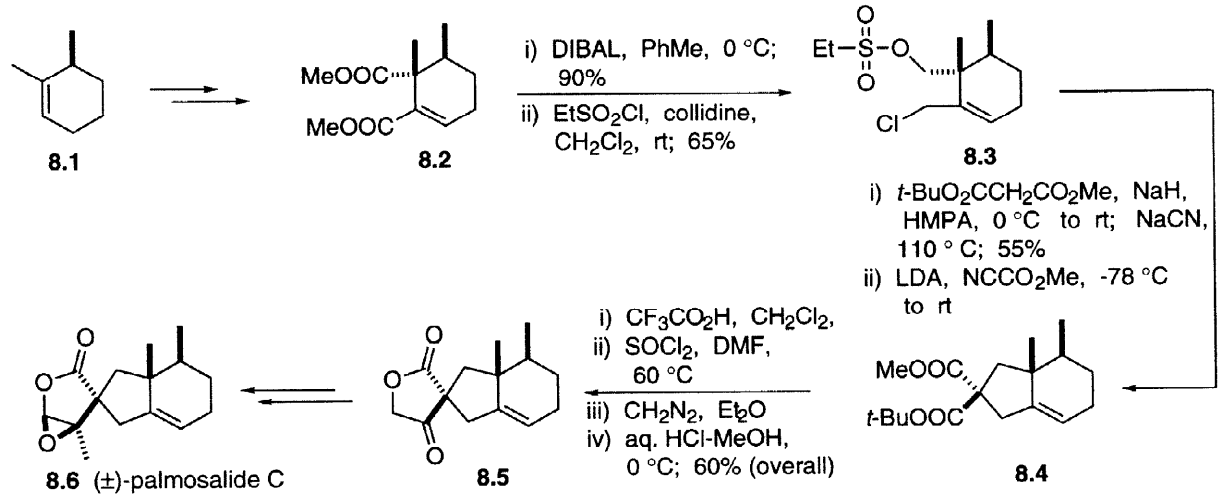
Scheme 6



Scheme 7



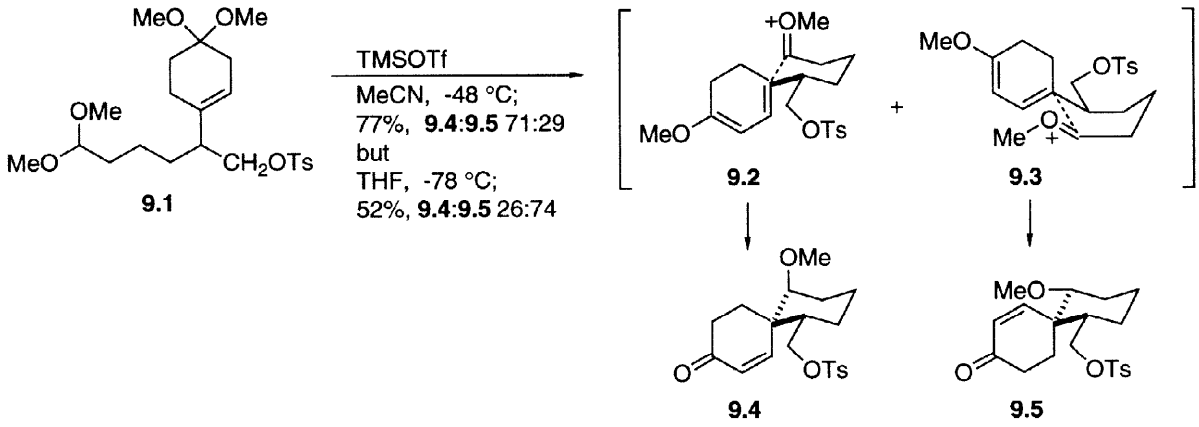
Scheme 8



1b Use of acetals

The use of acetals to generate a spirocenter, by formation of a carbon-carbon bond, is seen in the construction of compounds related to the spiro[5.5]undecane subunit of the aphidicolane and stemodane diterpenes (Scheme 9).[10] When bis-acetal **9.1** was treated with trimethylsilyl triflate in acetonitrile, a 71:29 mixture of **9.4** and **9.5** was formed via transition states **9.2** and **9.3**, respectively. The product ratio was reversed in THF.

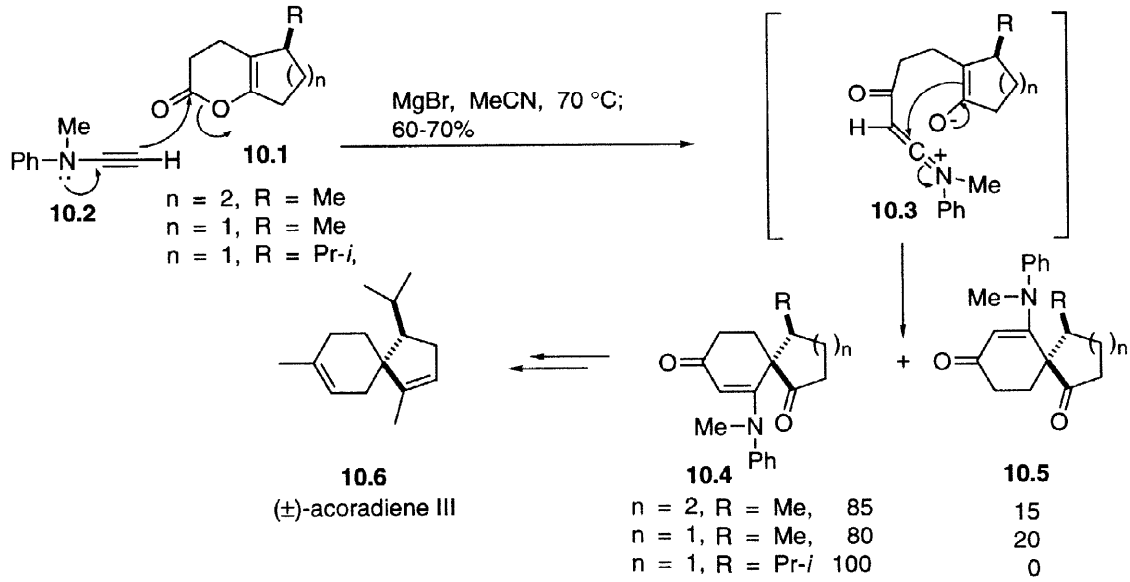
Scheme 9



1c Use of ynamines

Ficini[11] developed a stereoselective spiroannulation which involves acylation of ynamine **10.2** by enol lactones **10.1**, followed by intramolecular alkylation (Scheme 10). The process gave rise to two products, **10.4** and **10.5**, in the ratios indicated. Complete stereoselectivity was observed when R is an isopropyl group, and the selectivity is clearly dependent on the steric congestion created by the substituent R. The methodology of ynamine acylation was applied in the synthesis of (±)-acoradiene III[12a] (**10.6**) by elaboration of **10.4** (n = 1, R = *i*-Pr).[12b]

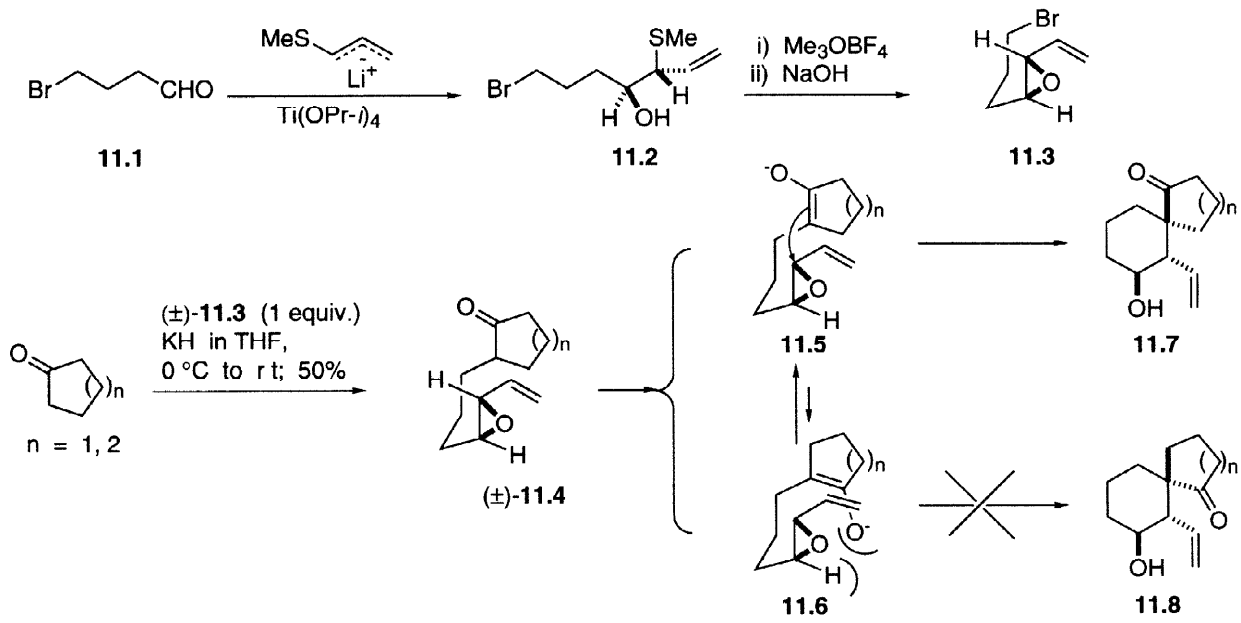
Scheme 10



1d Cyclization of epoxides

Stork's synthesis[13] of (-)-histrionicotoxin and (-)-histrionicotoxin 235A utilized a general method[14] previously developed in his laboratory for the preparation of cyclohexyl spiro systems, and in this case, the key intermediate needed for elaboration into the target alkaloids was the spiroketone **11.7**. The synthetic method is based on cyclization of allylic epoxides, and its application in the present instance involved generating the (*E*)-substituted bromoepoxide (±)-**11.3** by the sequence shown (**11.1** → **11.2** → **11.3**).[15] Epoxide **11.3** can also be made in optically pure form if an asymmetric Sharpless epoxidation is employed in its preparation. When cyclopentanone was treated with potassium hydride and (±)-**11.3**, the spiroketone **11.7** was formed stereoselectively in 50% yield, and a similar result was observed with cyclohexanone. The stereochemical outcome is understandable by comparison of the two possible pathways via **11.5** or **11.6**, of which the former is clearly favored.

Scheme 11

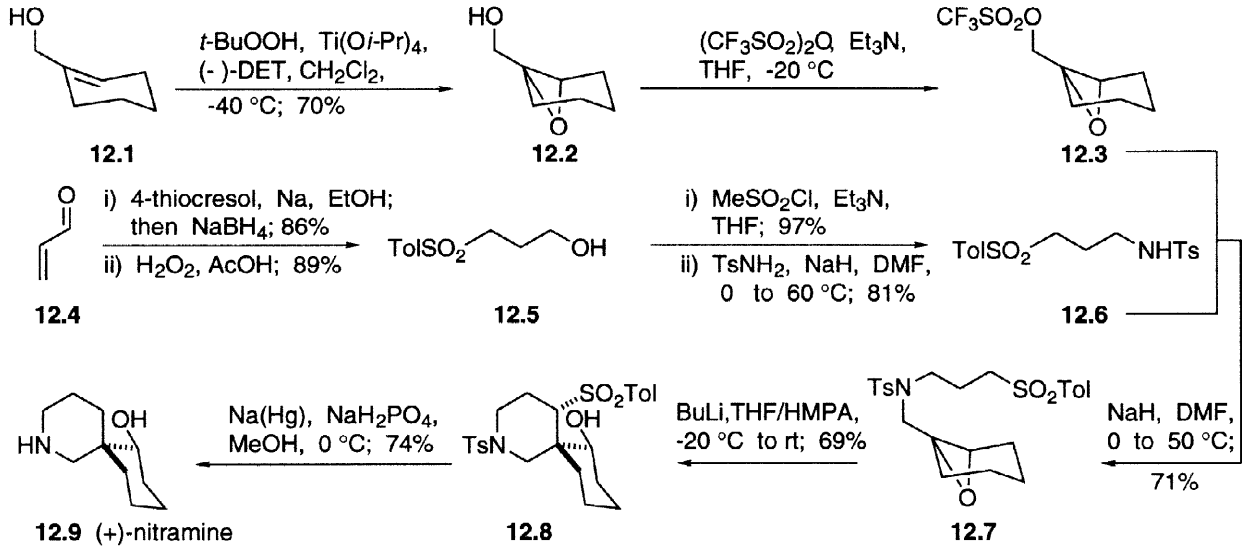


In a convergent synthesis of (+)-nitramine (**12.9**), Tanner and He[16] used Sharpless asymmetric epoxidation to prepare one of the two key synthons enantioselectively. Epoxy alcohol **12.2**, prepared as shown, from the corresponding allylic alcohol **12.1**, was transformed into the triflate **12.3**. The other required unit — that containing the amino group — was generated from acrolein in two steps (**12.4** → **12.5** → **12.6**).[17] Linking of units **12.3** and **12.6** under basic conditions provided **12.7**, which underwent an intramolecular epoxide opening on treatment with butyllithium, to give **12.8**. Finally, desulfonation (sodium amalgam in methanol) furnished (+)-nitramine (**12.9**) with *ca* 93% ee.

1e Intramolecular aldol and related condensations

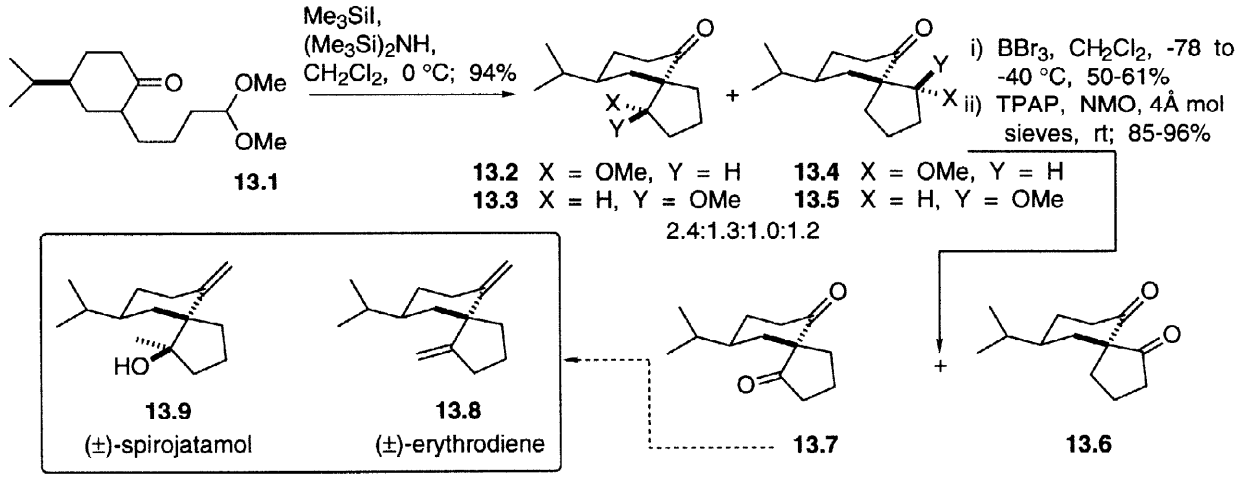
Recently, Ihara's group[18] used an intramolecular Mukaiyama aldol reaction in a formal synthesis (Scheme 13) of the sesquiterpenes (±)-erythrodiene (**13.8**) and (±)-spirojatamol (**13.9**). Acetal **13.1**, obtained by alkylation of the corresponding cyclohexylimine, gave a mixture of **13.2**-**13.5** when treated with $Me_3SiI/(Me_3Si)_2NH$. Although the stereoselectivity of this key step was significantly lower than in the

Scheme 12



method of Huang and Forsyth (see later[19]), which also involves an intramolecular alkylation, the diastereomers were separable, and they were demethylated and oxidized to the corresponding ketones **13.6** and **13.7**. The latter had previously[20] been converted into each of the sesquiterpenes **13.8** and **13.9**.

Scheme 13

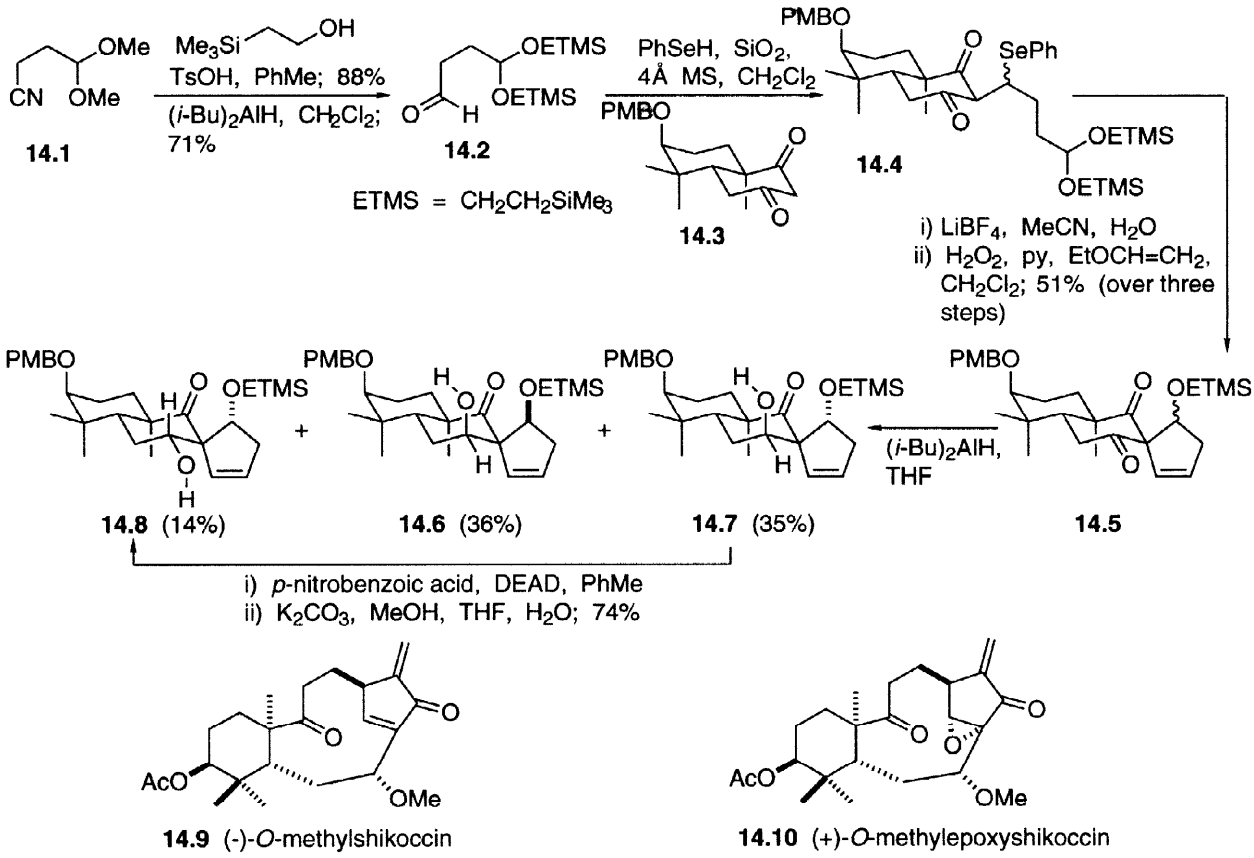


Another use of the Mukaiyama-aldol reaction is seen in the syntheses by Paquette *et al.*[21] of the structurally complex diterpene (-)-*O*-methylshikoccin (**14.9**) and the corresponding naturally occurring epoxide (+)-*O*-methylepoxyshikoccin (**14.10**) (Scheme 14).

Acetal exchange of **14.1** with 2-(trimethylsilyl)ethanol, followed by reduction of the nitrile, gave **14.2**, and condensation of this aldehyde with **14.3** in the presence of benzeneselenol served to link the two subunits in a manner suitable for generation of the required spiro structure (**14.2** → **14.4**). Cyclization of the resulting diastereomeric mixture of selenides (**14.4**) in the presence of lithium tetrafluoroborate, followed by selenoxide elimination, gave **14.5** in 51% yield. The material was a 1:1 mixture of epimers (at the protected hydroxyl site), but the spirocenter had been generated with complete stereocontrol. Reduction of diketones **14.5** to the corresponding alcohols yielded three chromatographically separable compounds (**14.6-14.8**). Compound **14.7**

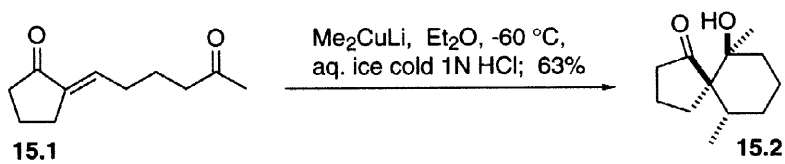
could be converted into **14.8** by Mitsunobu inversion, and both of the spiroketones **14.6** and **14.8** were then elaborated into (-)-*O*-methylshikoccin (**14.9**) and (+)-*O*-methylepoxyshikoccin (**14.10**) by multistep sequences whose eventual stereochemical outcome was determined by the stereochemistry at the spirocenter.

Scheme 14



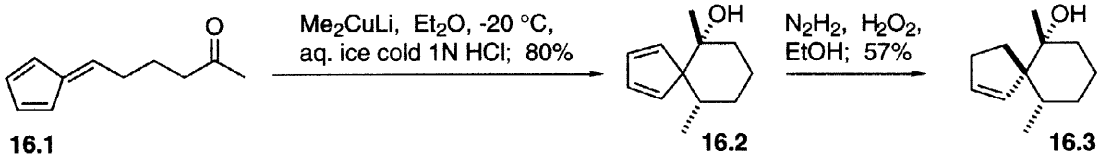
A group at Firmenich has used[22] conjugate addition to an enone (Scheme 15), followed by capture of the resulting enolate by a suitably located ketone carbonyl, as a method for preparing spiro compounds. For example, conjugate addition of lithium dimethylcuprate to **15.1**, and spontaneous intramolecular aldol condensation, gave the spiro hydroxy ketone **15.2** with high diastereoselectivity, although the factors responsible for the stereochemical outcome have not yet been identified.

Scheme 15



In a conceptually related process (Scheme 16), Büchi *et al.*[23] have used sequential organocuprate addition to a fulvene and intramolecular trapping of the resulting cyclopentadienide by a suitably located carbonyl (**16.1** → **16.2**). Interestingly, the reaction afforded a single stereoisomer, and in high yield (80-90%). One of the double bonds in **16.2** was selectively reduced, so as to render the spirocenter asymmetric.

Scheme 16

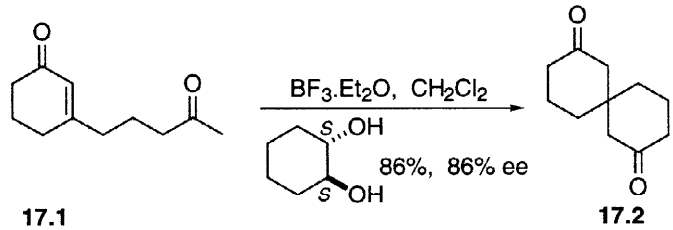


16.1 16.2 16.3

1f Intramolecular Michael addition: use of diketones

When compound **17.1**[24] (Scheme 17) was treated with a Lewis acid, in the presence of optically pure (*S,S*)-cyclohexane-1,2-diol, the diketone **17.2** was formed with good enantioselectivity (85% ee), by way of a Michael addition mechanism.[24]

Scheme 17



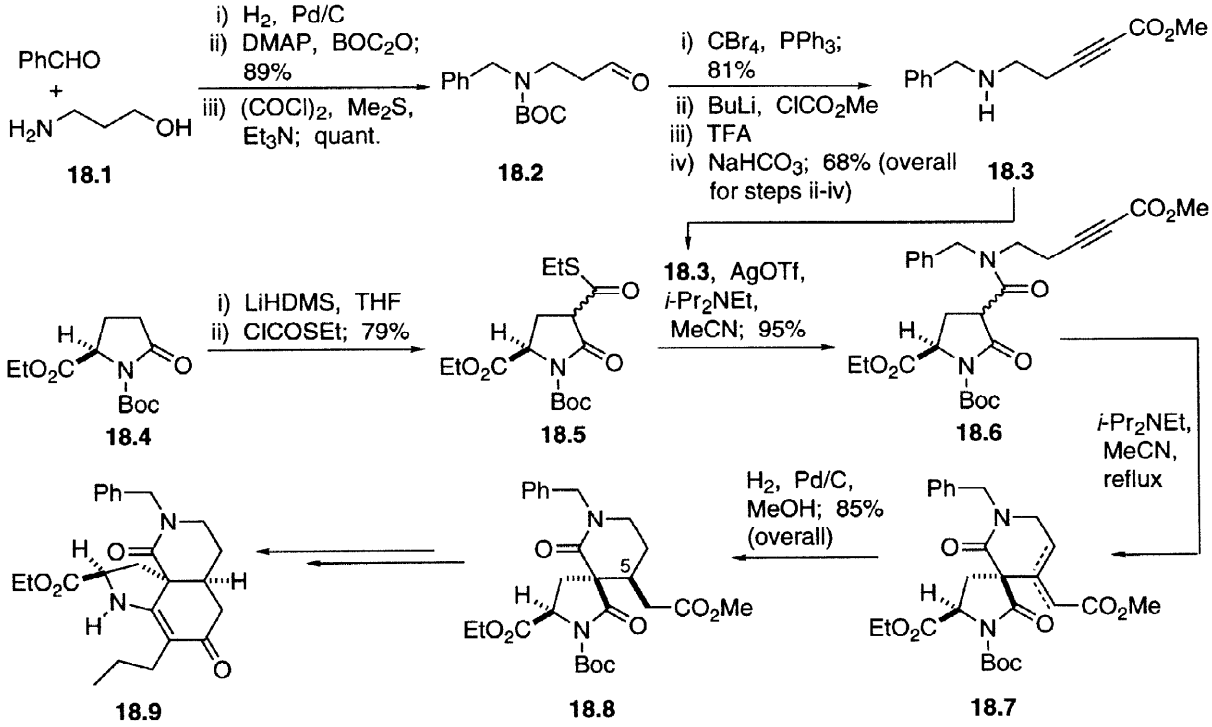
17.1 17.2

1g Intramolecular Michael addition: use of ynoates

In a synthesis of the core structure (**18.9**) of manzamine-A, Brands and DiMichele used[25] an intramolecular Michael reaction to construct the spirocenter with the desired stereochemistry.

One of the required synthons (**18.3**) was prepared from 3-amino-1-propanol (**18.1**), as shown in

Scheme 18



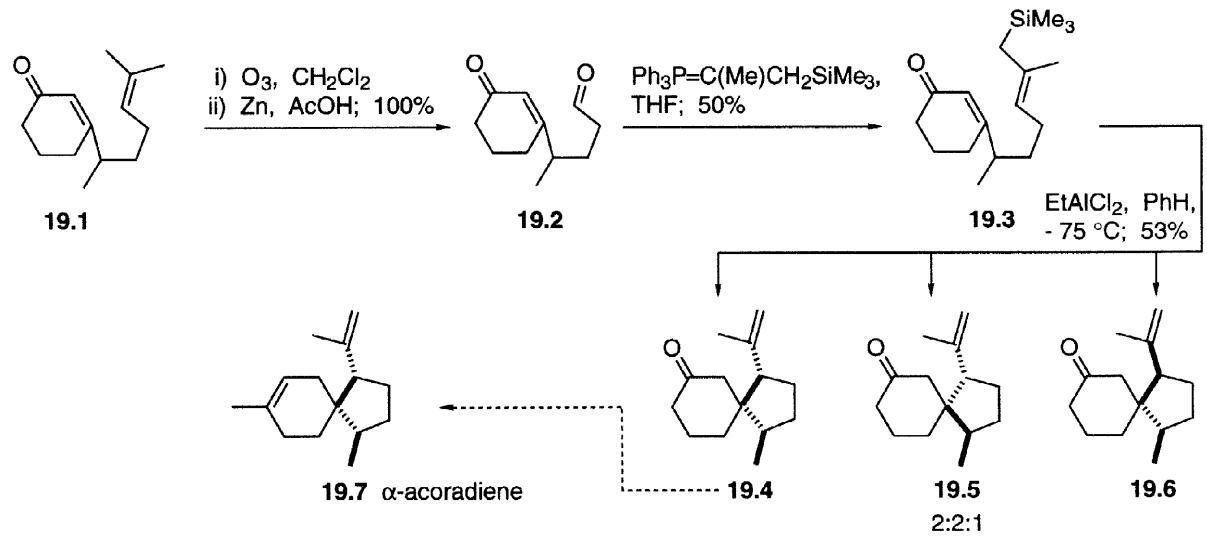
18.1 18.2 18.3 18.4 18.5 18.6 18.7 18.8 18.9

Scheme 18. The other unit (**18.5**) was obtained from a derivative of optically pure pyroglutamic acid. Linking of the two units under basic conditions yielded **18.6** and, on treatment with base, this material underwent intramolecular Michael addition to give **18.7**, as a mixture of double bond isomers. Hydrogenation then yielded a single product (**18.8**), which was elaborated into **18.9** — the desired core structure of manazamine-A. The complete stereocontrol of the spirocyclization step is due to the presence of the asymmetric center in the pyroglutamic moiety, but this center has a subtle effect on the outcome of the reaction, as the olefinic material corresponding to **18.6** (*E* double bond in place of the triple bond) gives a single spirocycle, corresponding to **18.8**, but with the opposite configuration at C(5).

1h Intramolecular Michael addition: use of allyl silanes

Allyl silanes have been used[26] to make spiro compounds by intramolecular Sakurai-Hosomi reaction (Scheme 19), as illustrated in a formal synthesis of α-acoradiene (**19.7**).[26a] The required allyl silane was made by the sequence **19.1** → **19.2** → **19.3**, and the action of ethylaluminum dichloride then brought about cyclization. Unfortunately, the stereoselectivity was poor (2:2:1), and only **19.4** is convertible into **19.7** in order to complete a formal synthesis.

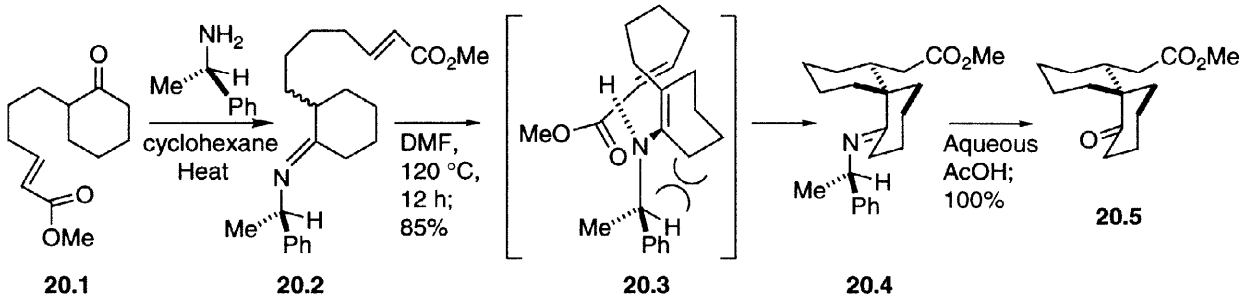
Scheme 19



1i Intramolecular Michael addition: use of imines

d'Angelo[27] has developed a method for constructing spiro [5.5] systems enantioselectively using an intramolecular Michael addition. In this work, compound **20.1** was made from cyclohexanone. The derived imines (**20.2**) were then prepared by reaction with (*R*)-1-phenylethylamine, and obtained as a 1:1 mixture of diastereomers (Scheme 20). Although formally an intramolecular Michael addition, the thermally induced cyclization (**20.2** → **20.4**) may actually proceed by way of an aza-ene process. This involves a cyclic transition state (*cf.* **20.3**) in which attack occurs on the π-face of the enamine opposite to the phenyl ring of the chiral auxiliary, the reacting rotamer being one in which the indicated nonbonded interactions are minimized. The resulting spiro derivative **20.4**, formed with high stereoselection (>90:10), was hydrolyzed with aqueous acetic acid to the spiroketone **20.5**.

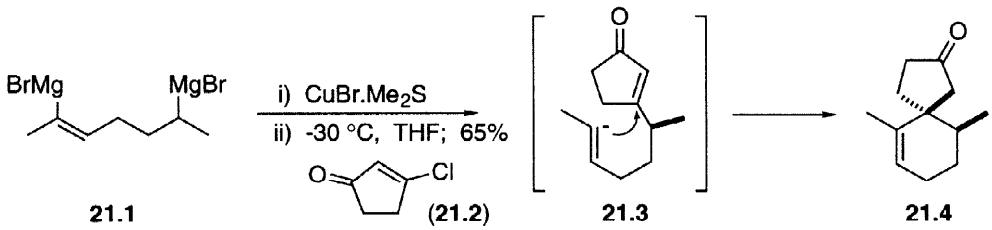
Scheme 20



1j Sequential inter- and intramolecular Michael addition

Cannone *et al.*[28] used the bis-Grignard reagent (**21.1**) to form a spiro [4.5] skeleton (**21.4**) with a double bond α to the quaternary carbon (Scheme 21). When reagent **21.1** was converted into a cuprate and then allowed to react with ketone **21.2**, the spiro compound was formed stereoselectively. This reaction proceeds by displacement of the chlorine by the secondary alkyl organometallic function, followed by closure from the side opposite to the methyl group introduced in the first step (**21.1** → **21.3** → **21.4**).

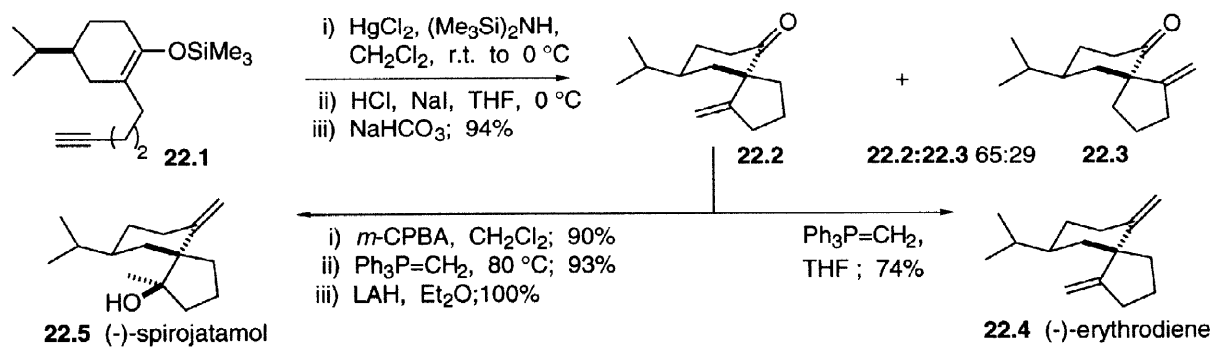
Scheme 21



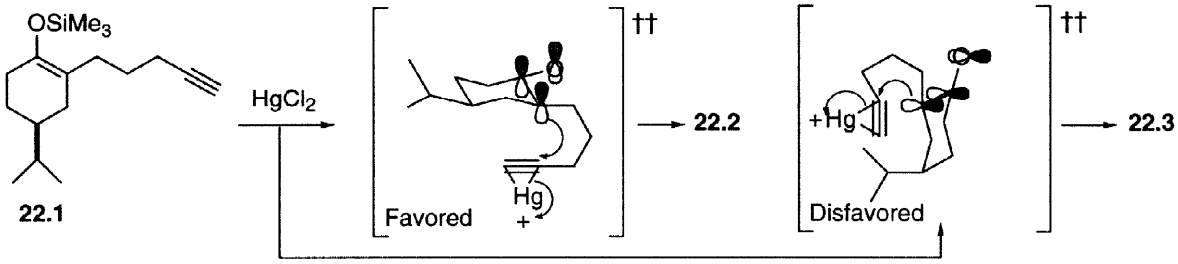
1k Use of mercuronium species

Huang and Forsyth,[19] in their synthesis of the sesquiterpenes (-)-spirojatamol (**22.5**) and (-)-erythrodiene (**22.4**) (Scheme 22), used an intramolecular alkylation that was induced by mercuric chloride. The reaction was stereoselective, and is the key step in the synthesis. Optically active **22.1**, which served as the precursor to the spiro system, was synthesized in a straightforward manner from (*S*)-perillyl alcohol. When allowed to react with a mercuric salt, followed by protodemercuration, it gave a 65:29 mixture of spiroketones **22.2** and **22.3**, and the former was elaborated into (-)-erythrodiene (**22.4**) and (-)-spirojatamol (**22.5**) (the enantiomer of the natural product), using the simple reactions summarized in the Scheme. The course of the spirocyclization is understandable in terms of the process shown in Scheme 23, if it is assumed that axial *C*-vinylation is preferred (because of better overlap with the enolic π-system).

Scheme 22



Scheme 23



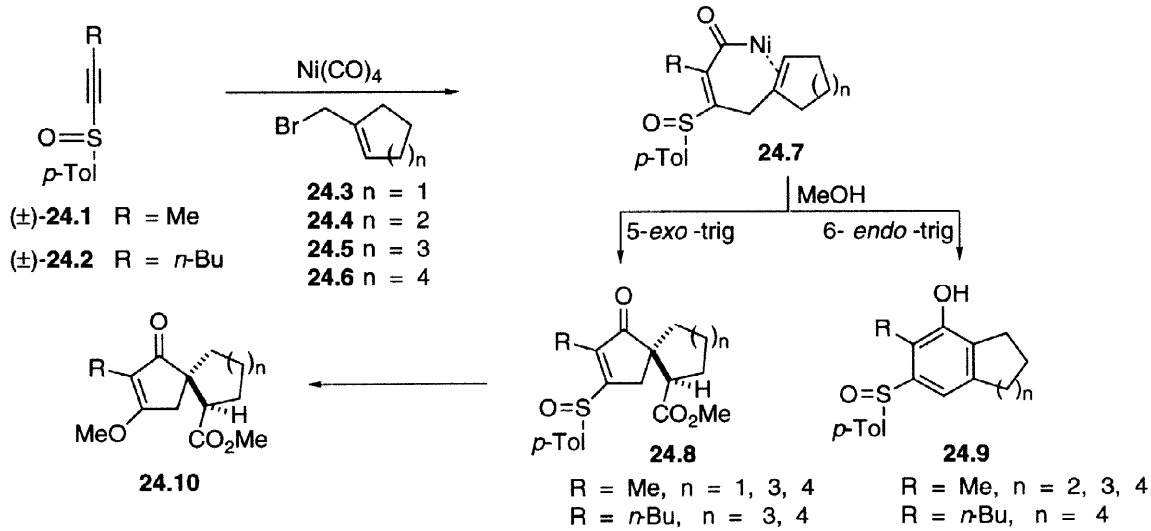
2 Transition metal-based processes

Several cases are known in which spirocenters have been generated by transition metal-mediated processes, but few natural products have, as yet, been made using such reactions.

2a Nickel-promoted alkylation and cyclocarbonylation

An approach to the creation of a spirocenter in an asymmetric fashion, based on organometallic chemistry, was reported by Moretó *et al.*,[29] and is shown in Scheme 24. The method uses an asymmetric acetylenic sulfoxide for stereocontrol, and involves nickel-catalyzed addition of an allylic halide to one end of the triple bond and carbonylation of the other end. The intermediate acylnickel species **24.7**, then undergoes 5-*exo*-trigonal and/or 6-*endo*-trigonal cyclization (**24.7** → **24.8** and/or **24.9**), depending on the steric and conformational restrictions imposed by the cycloalkenyl moiety. The process **24.7** → **24.8** shows good diastereoselectivity, but the yields are modest (9-50%), mainly because the acylnickel intermediate **24.7** can undergo various competing reactions.

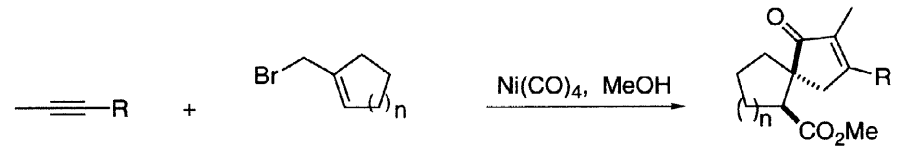
Scheme 24



In a systematic survey, using racemic sulfoxides (±)-**24.1** and (±)-**24.2** with halomethylcycloalkanes **24.3**-**24.6**, a mixture of products was obtained, with the spiro and fused compounds being formed by competing 5-*exo*-trigonal and 6-*endo*-trigonal cyclizations, respectively. The competition between the two pathways is presumably related to conformational properties of the bromocycloalkyl ring systems and/or the derived nickel species, but it is difficult to identify the specific details. Compounds **24.8** were formed in each case as a single diastereomer.

A previous study[30] from the same laboratory, involved an achiral acetylenic system to synthesize spirocyclopentanones by the same type of intramolecular carbonylative cycloaddition (see Scheme 25). In these examples, two new asymmetric centers have again been created in the product, and their relationship is compatible with the pathway shown in Scheme 24.

Scheme 25



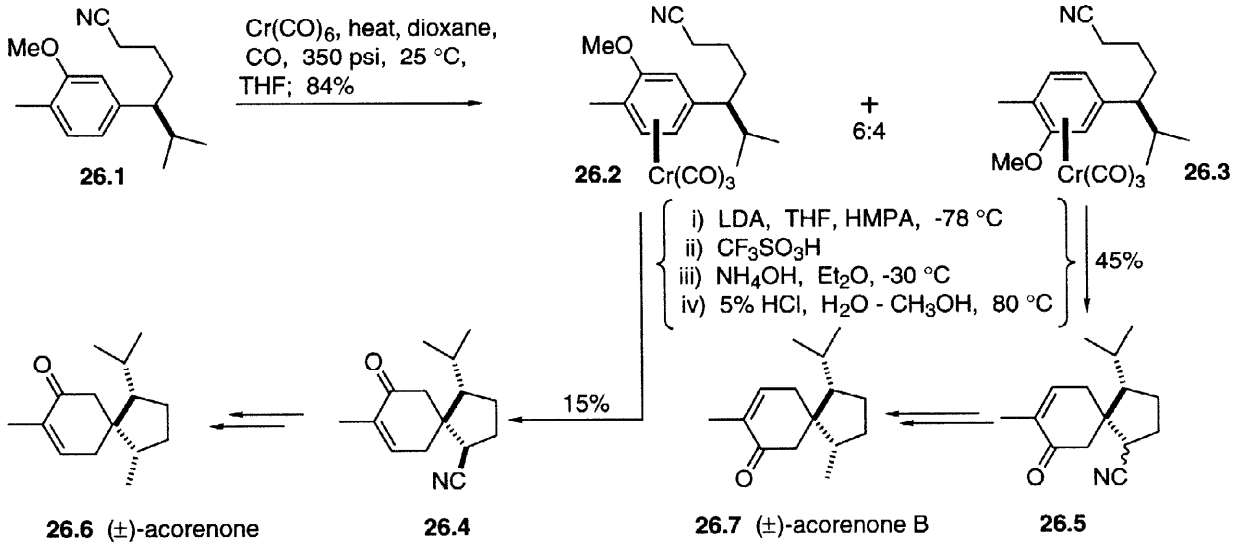
25.1
R = CH_2OH or
R = CO_2Me

		25.6 R = CH_2OH	R = CO_2Me
25.2	n = 1	50%	45%
25.3	n = 2	15%	11%
25.4	n = 3	48%	42%
25.5	n = 4	-	47%

2b Use of chromium aryl complexes

Semmelhack[31] has explored the use of arene-metal complexes in the synthesis of (±)-acorenone and (±)-acorenone B (Scheme 26). When the anisole derivative **26.1** was treated with chromium hexacarbonyl, a 6:4 mixture of the diastereomers **26.2** and **26.3** was obtained. The chromatographically separable complexes were individually processed to give **26.4** and **26.5**, respectively. Compound **26.4**, which was obtained as a single isomer, was converted into (±)-acorenone (**26.6**), and the spiroketone **26.5**, obtained as a mixture of

Scheme 26

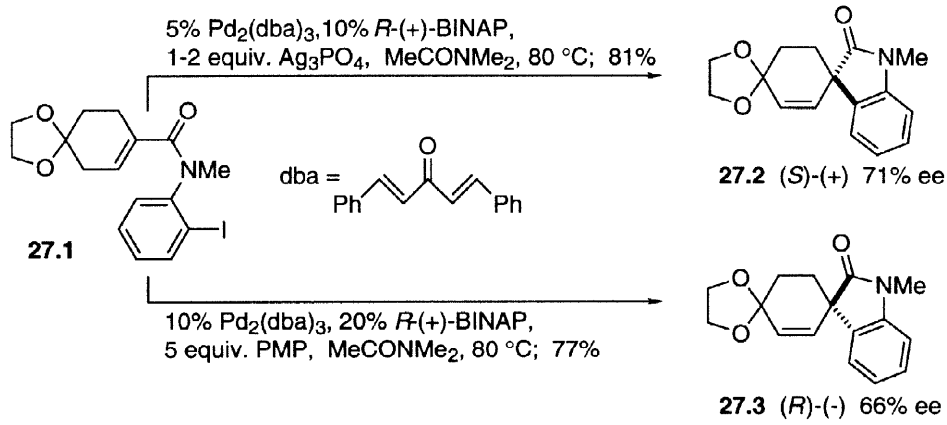


isomers, into (±)-acorenone B (**26.7**), using straightforward transformations. In the key step (**26.2** → **26.4**) and (**26.3** → **26.5**), the influence of chromium complexation is to cause the ring to be alkylated *meta* to the methoxy group; consequently a spirocyclopentane forms. The bulk of the chromium unit confines alkylation to the opposite face, and in this way the relative configuration of the spirocenter is controlled by the facial selectivity of the initial complexation.

2c *Palladium-based methods*

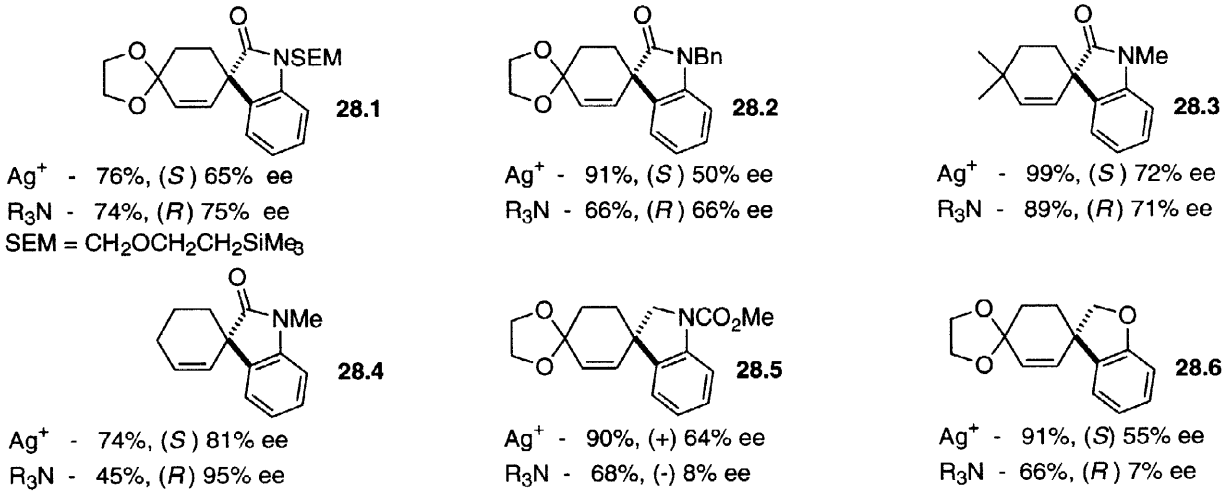
Formation of carbon-carbon bonds by an asymmetric Heck reaction has been used by Overman *et al.*[32] to make spirooxindoles (Scheme 27). In this work, compounds **27.2** and **27.3** (Scheme 27) and the related substances **28.1-28.6** (Scheme 28) were synthesized from the corresponding aryl iodides by palladium-catalyzed cyclizations carried out in the presence of an asymmetric catalyst. Representative procedures are

Scheme 27



shown in Scheme 27. When the acryloyl-2'-iodoanilide **27.1** was treated with tris(dibenzylideneacetone)-palladium(0) in a polar solvent in the presence of both (*R*)-BINAP and a silver salt, then oxindole **27.2** (with *S*-stereochemistry) was formed, the ee being 71%. However, when a tertiary amine (pentamethylpiperidine) is used instead of the silver salt, the reaction takes longer and affords the *R*-enantiomer; the ee is comparable

Scheme 28



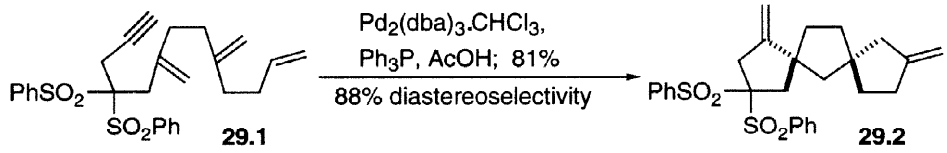
(66%). The enantioselectivity of the base-promoted reactions leading to **28.5** and **28.6** is conspicuously lower (*ca* 8% ee), while the other compounds listed in Scheme 28 are formed with modest enantioselectivity. These results are difficult to understand on the basis of the evidence presently available, but two factors that might contribute to the stereochemical outcome can be identified.[32-34] Mechanistic studies on the Heck reaction favor a tetra-coordinated palladium(II) intermediate. In the base-promoted reaction, this intermediate is neutral, and the phosphine ligand is bound to the palladium center through one coordination site, making the

complex more flexible than in the Ag^+-promoted cationic intermediate, where the phosphine ligand binding is through two coordination sites.[33] In view of the different types of nitrogen or oxygen substituent in the starting materials (amide or ether), another factor that must contribute to the stereochemical outcome is the stronger binding to the metal of electron-poor substrates in the neutral intermediate, and of electron-rich substrates in the cationic intermediate. Exactly how these factors influences the ee is unclear, except for the general expectation that more rigid intermediates should increase transfer of chirality information from ligand to substrate.

Reversal of the stereochemical outcome as a function of the reaction conditions used in the construction of spiro compounds by the Heck reaction is probably a general phenomenon, and has also been observed in work directed towards the synthesis of the alkaloid gelsemine.[35] In an unrelated study, in which the palladium-catalyzed Heck reaction was used for polyene cyclizations of trienyl triflates in the presence of phosphine ligands and base, enantioselectivities up to 45% were observed.[36]

Formation of two spirocenters in tandem was achieved by the Trost group[37] by means of carbopalladation (Scheme 29). The trienyne **29.1**, when subjected to standard carbopalladation conditions, gave a bis-spiro compound, tentatively assigned structure **29.2**, in good yield and with 88% diastereoselectivity.

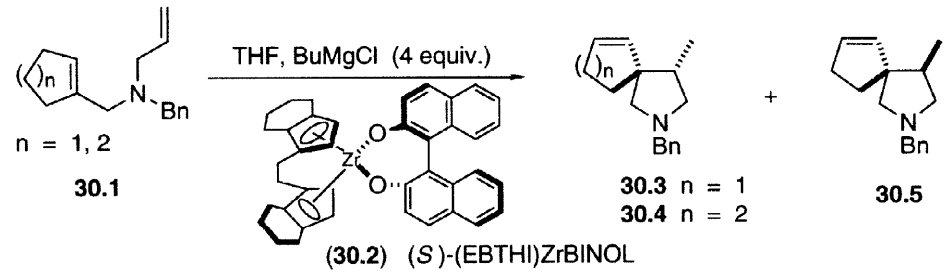
Scheme 29



2d Use of zirconacycles

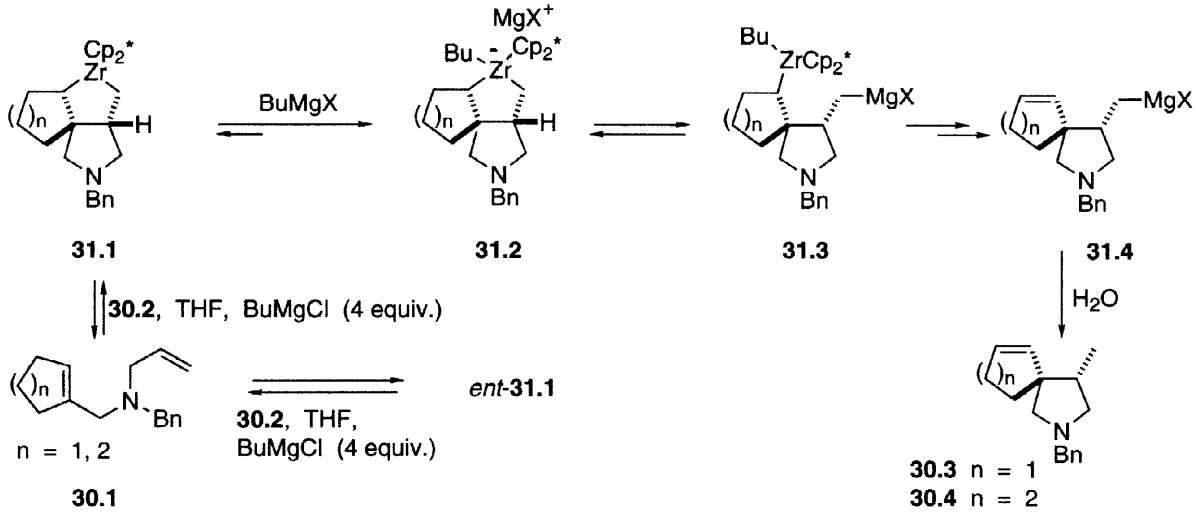
A recent publication by Mori *et al.*[38] reported the use of a chiral zirconium complex **30.2** as an effective catalyst to induce enantioselectivity during the formation of spiro [4.4] compounds **30.3-30.5** (Scheme 30). Treatment of dienes **30.1** with 10 mol% of (*S*)-(EBTHI)$ZrBu_2$ [EBTHI = ethylenebis(tetrahydroindene)], generated *in situ* from butylmagnesium chloride and (*S*)-(EBTHI)ZrBINOL (**30.2**), gave zirconacycles **31.1** and *ent*-**31.1** (Scheme 31). Metallocycles **31.1** then undergo ate-complexation (**31.1** →

Scheme 30



31.2), followed by transmetallation (**31.2** → **31.3**), and formation of the olefinic Grignard reagents **31.4**. On treatment with water, these give the corresponding spiro compounds **30.3** (46%, 86% ee) and **30.4** (47%, 94% ee). Compound **30.5** (see Scheme 30) is also formed in low yield, but with high enantioselectivity (24%, 84% ee). The stage in which the enantioselectivity is established is not yet clear, but the mechanism leading to the major product is suggested to involve a set of equilibria, as shown in Scheme 31.

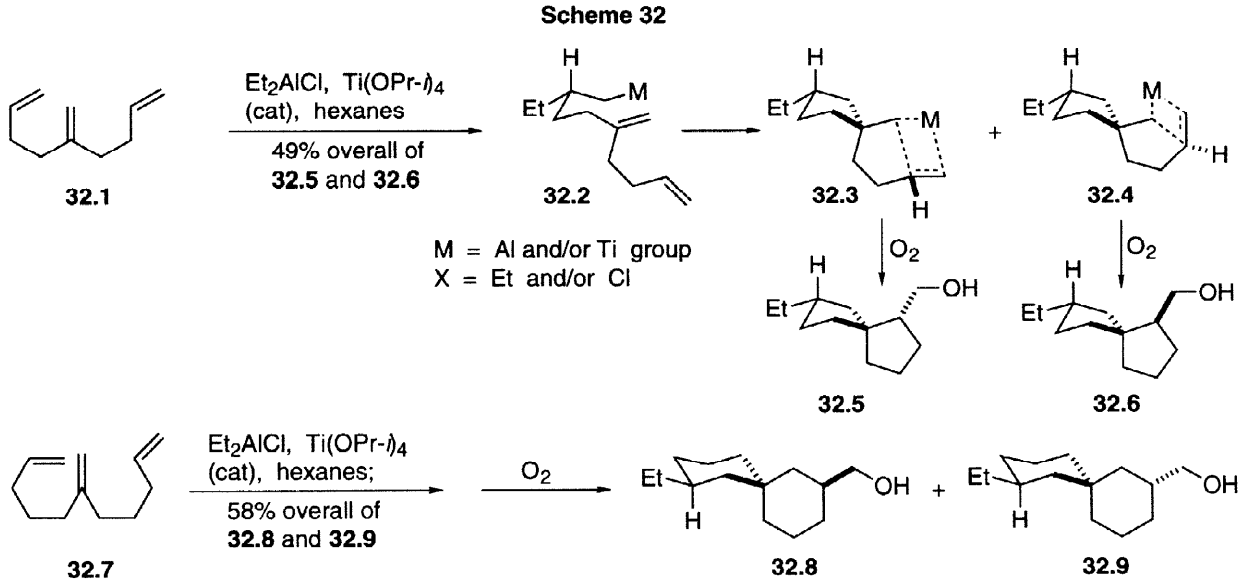
Scheme 31



2e *Titanium-catalyzed carboalumination*

Negishi *et al.*[39] used titanium-catalyzed cascade carboalumination of trienes **32.1** and **32.7** to generate spirobicycles. Treatment of **32.1** or **32.7** with a catalytic amount of titanium(IV) isopropoxide and diethylaluminum chloride generated the quaternary carbon center stereoselectively. Further cyclization gave a 1:1 diastereomeric mixture of **32.5** and **32.6**, and **32.8** and **32.9**, respectively, after treatment with oxygen.

Scheme 32



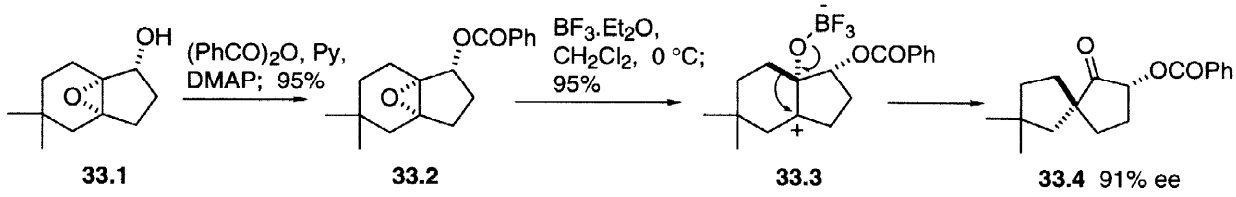
3 Rearrangement methods

A wide variety of rearrangement processes have been used to generate spiro systems.

3a *Epoxide rearrangement*

In an extensive study on optically active spirocyclanes, Kita and his group developed[40] a stereospecific method to make spiro[4.4]nonanes by Lewis acid catalyzed rearrangement of *cis*-α,β-epoxy alcohol derivatives (Scheme 33). *cis*-Epoxy alcohol **33.1** was easily obtained by a combination of asymmetric ketone reduction and Sharpless epoxidation (99% de). The derived benzoate **33.2** underwent Lewis acid promoted

Scheme 33

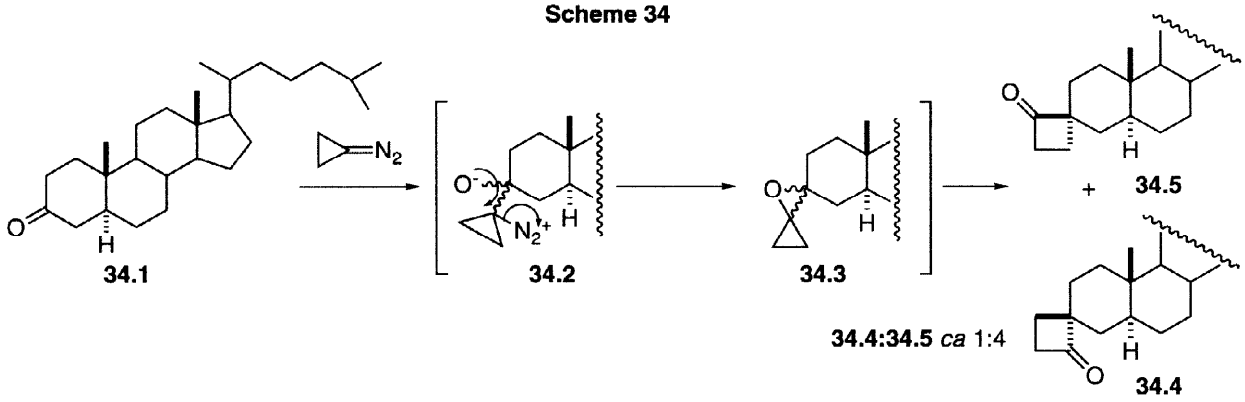


ring opening and rearrangement to the spiro compound **33.4**. This had an optical purity of 91%. Interestingly, model experiments with *trans* α,β-epoxy alcohol derivatives (as opposed to the *cis* isomers) produced spiro compounds only as minor products.[40a] However, later work, aimed at applying the methodology to the synthesis of fredericamycin A,[40b] revealed that the superiority of *cis* over *trans* epoxy alcohol derivatives is not a general phenomenon.

A follow-up study, whose results might be applicable to stereoselective construction of spiro compounds, has been carried out by the same group.[41]

Formation of spiro compounds by rearrangement of epoxy cyclopropanes has been achieved (Scheme 34) by reaction of diazocyclopropane with 5α-cholestan-3-one (**34.1**). For example, the cyclobutanones **34.4** and **34.5** are formed in a ratio of 1:4 as major products by the process shown.[42]

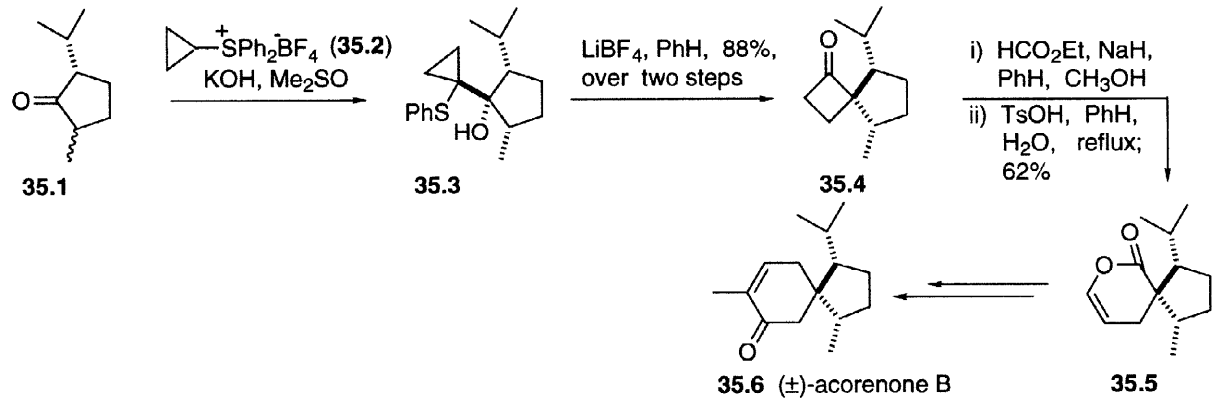
Scheme 34



3b Ring expansion of cyclopropanes

(±)-Acorenone B was synthesized stereoselectively[43] by Trost *et al.* (Scheme 35), by using a spiroannulation procedure based on the rearrangement of an oxaspiropentane.[44,45] An isomeric mixture of

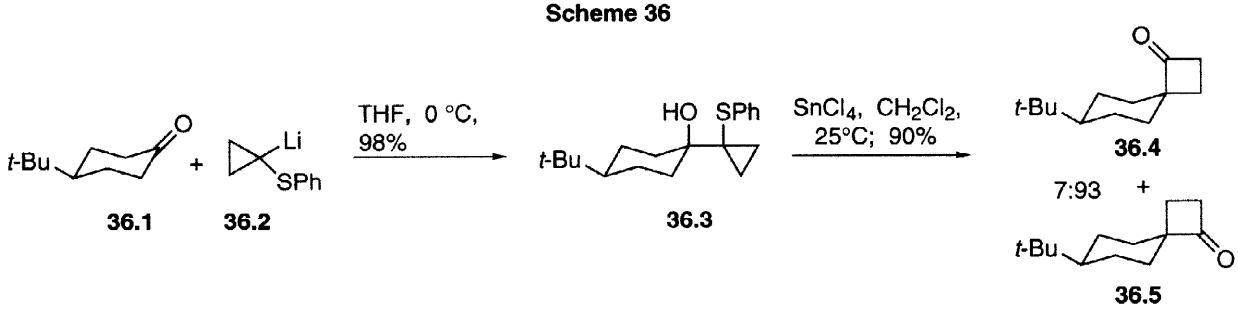
Scheme 35



ketones **35.1** was treated with cyclopropylidenediphenylsulfonium fluoroborate (**35.2**) to give **35.3**, which underwent rearrangement (**35.3** → **35.4**) in the presence of a Lewis acid. This last step set up the relative stereochemistry at the three contiguous asymmetric centers, and its success must be due to epimerization of the starting ketone faster than addition of the reagent to the carbonyl group. The isomer of starting ketone **35.1** having both substituents *cis* presents a sterically unhindered face to the reagent. Cyclobutanone **35.4** was subjected to ring expansion into lactone **35.5**, and the latter was then elaborated into (±)-acorenone B (**35.6**).

The utility of a related method[46] was demonstrated (Scheme 36) by reaction of ketone **36.1** with organolithium **36.2**. The major product (**36.3**) underwent Lewis acid catalyzed rearrangement to afford a mixture of **36.4** and **36.5**, in a ratio of 7:93, respectively.

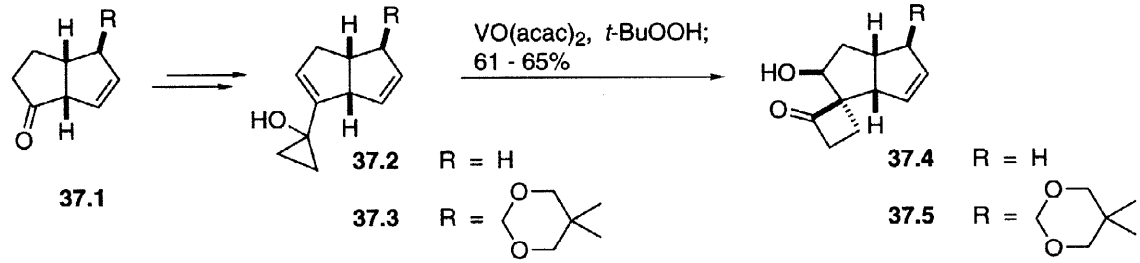
Scheme 36



36.1 **36.2** **36.3** **36.4** **36.5**

In a variant of this methodology (Scheme 37),[47] in which compounds **37.2** and **37.3** were epoxidized in the presence of a vanadium catalyst, very high stereoselectivity was again observed, **37.4** and **37.5** being the only stereoisomers obtained.

Scheme 37

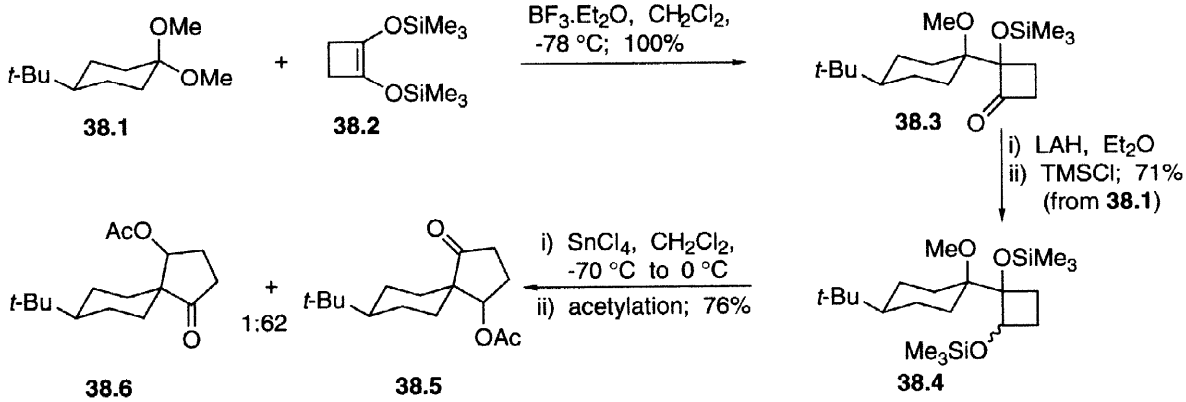


37.1 **37.2** R = H **37.3** R = **37.4** R = H **37.5** R =

3c *Acyloin condensation and ring expansion*

A spiroannulation method[48] based on conversion of an acetal into a spiro[4.5]decane has been

Scheme 38

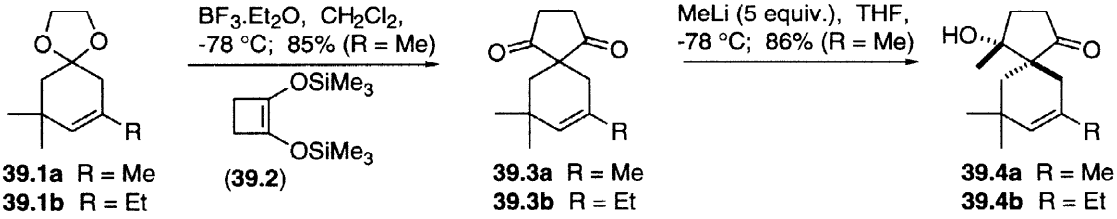


38.1 **38.2** **38.3** **38.4** **38.5** **38.6**

employed as the key step in the synthesis of various natural products.[49,50] The method is illustrated by construction of the simple spiro systems **38.5** and **38.6** (Scheme 38). Acetal **38.1** was treated with the silylated acyloin **38.2** in the presence of an equivalent of boron trifluoride etherate, and the resulting ketone (**38.3**) was reduced and silylated, to produce compounds **38.4**. Lewis acid mediated ring enlargement to **38.5** proceeded in a highly stereoselective manner (62:1). Best yields were observed for acetals with little steric hindrance around the doubly oxygenated carbon of the acetal (*cf.* **38.1**).

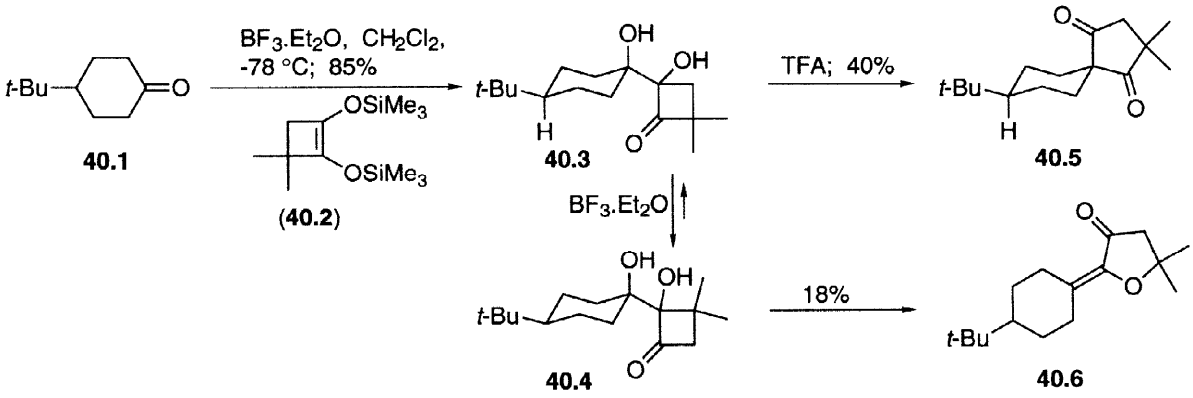
A slight modification of this method has been applied by Burnell[49] to the synthesis of pentalenene. By using an excess of the Lewis acid, instead of 1 equivalent, direct conversion (Scheme 39) to a spiro compound is achieved (**39.1a** → **39.3a**). The initial carbocyclic spiro compound (**39.3a**) is achiral, but was subsequently converted, with very high diastereoselectivity, into a substance (**39.4a**) in which the spirocenter is asymmetric (Scheme 39). This sequence was repeated with **39.1b** and, although the intermediates were obtained as isomer mixtures, the series with the ethyl substituent led more directly to the natural product, which was best reached by elaboration of **39.4b**. Desymmetrization (*cf.* **39.3** → **39.4**) can also be done microbially.[51]

Scheme 39



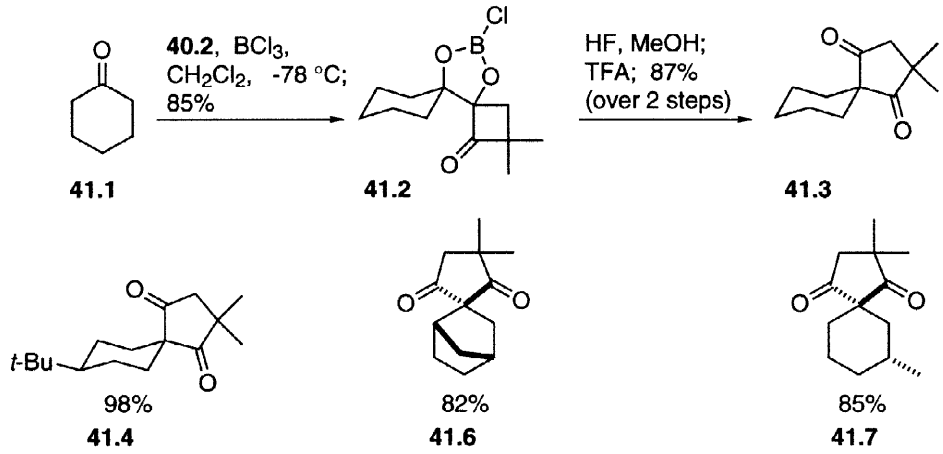
For some substrates[52] (Scheme 40), the use of boron trifluoride etherate gives a significant amount of byproduct (**40.6**) due to equilibration of the initial aldol (**40.3** → **40.4**),[53] but this problem can be avoided[53] by

Scheme 40



using BCl_3, which traps the initial adduct as a cyclic ester (Scheme 41) and inhibits the equilibration. Treatment of the cyclic ester with hydrogen fluoride in methanol, followed by trifluoroacetic acid, gives the spirocycle, and in this way, spiro compounds **41.4-41.6** were prepared in high yield.

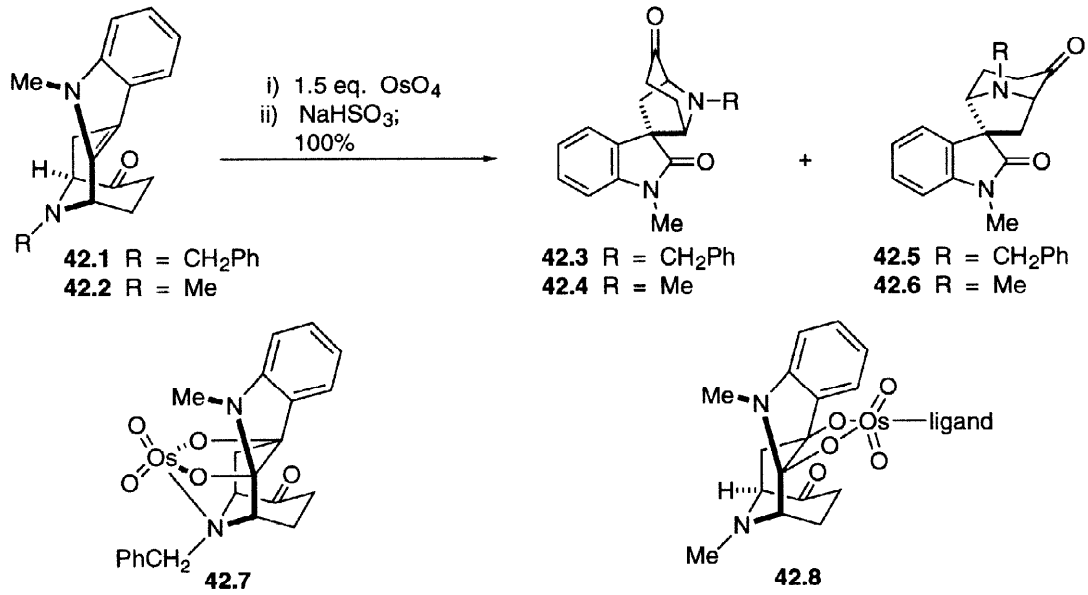
Scheme 41



3d Pinacol and related rearrangements

A study directed towards the enantiospecific synthesis of the oxindole alkaloids of *Gardneria*, *Voacanga* and *Alstonia* species had to deal with the special situation that prevails, namely that the alkaloid alstonisine (from *Alstonia muelleriana*) is diastereomeric at the spirocenter with respect to chitosenine and gardmultine (both from *Gardneria multiflora*), as well as to some other related alkaloids. In response to the need for stereochemically complementary syntheses of the oxindole units, the use of the pinacol rearrangement was developed by Cook *et al.*[54] in the following way (Scheme 42).

Scheme 42



Compound **42.1**, which can be obtained in large quantities,[55] was used as the precursor to the spiro system. When racemic **42.1** was treated successively with osmium tetroxide-pyridine and sodium bisulfite a 1:1 diastereomeric mixture of **42.3** and **42.5** was formed. The lack of selectivity is attributed to the ability of the osmium tetroxide-pyridine complex to attack both the convex and concave faces of the starting material. The product arises by vicinal dihydroxylation, followed by pinacol rearrangement. When phthalazine ligands are used, the osmium tetroxide-ligand complex preferentially attacks the concave face of **42.1** to give a 76:24

mixture in favor of **42.5**.

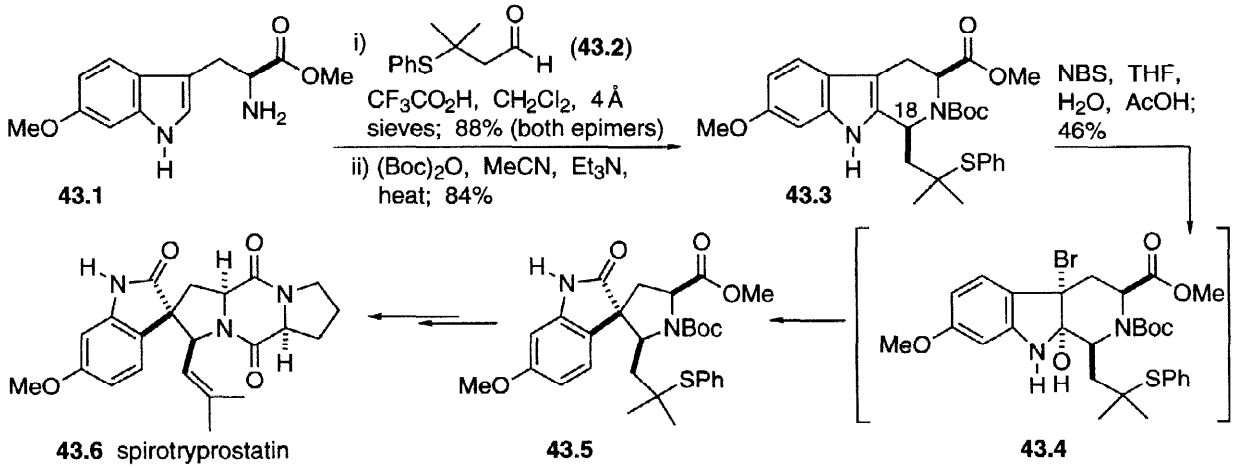
Interestingly, in the absence of any ligand, osmylation of **42.1**, using 1 equivalent of osmium tetraoxide, proceeds mainly intramolecularly because the reagent becomes complexed to the piperidine nitrogen (*cf.* **42.7**). In contrast, **42.2** appears to be osmylated intermolecularly (from the concave face) in the absence or presence of added ligand (*cf.* **42.8**).

When optically pure (-)-**42.1** was treated with osmium tetroxide and a phthalazine ligand, then the diastereoselectivity was significantly higher (e.g., 97:3 vs 76:24) than when the reaction was run using racemic **42.1**. Evidently, one enantiomer of the substrate responds more strongly to the asymmetry in the osmium reagent.

In principle, compound (-)-**42.1** could be used to make the *Gardneria*, *Voacanga* and *Alstonia* oxindoles, by applying the above osmylation and then elaborating the products, but this has not yet been reported.

In a recent synthesis of the alkaloid spirotryprostatin A (**43.6**), Edmunson and Danishefsky,[56] used a pinacol-like rearrangement to construct the spirooxindole unit. Pictet-Spengler reaction of aldehyde **43.2** and the 6-methoxytryptophan derivative **43.1** gave an epimeric mixture [(*cis*:*trans* 2:1 at C(18)] of amines which were separated, and the *cis* isomer was protected as its *t*-butoxycarbonyl derivative **43.3**. When heated with *N*-bromosuccinimide in the presence of acetic acid, **43.3** underwent rearrangement via an intermediate bromohydrin **43.4** to give the spirooxindole **43.5** with the desired relative stereochemistry at the spirocenter. This intermediate was then elaborated into spirotryprostatin A (**43.6**).

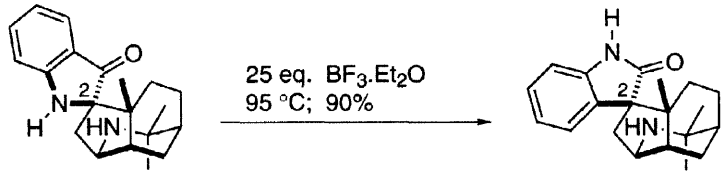
Scheme 43



3e Pseudoindoxyl rearrangement

During a study of the alkaloid aristotelone (**44.1**, Scheme 44) Güller and Borschberg[57] serendipitously found that pseudoindoxyls such as **44.1**, and its C(2)-epimer **44.2**, can be transformed into the corresponding oxindoles by a highly stereoselective rearrangement. When (+)-aristotelone (**44.1**) was treated with boron trifluoride etherate in dichloromethane at 95 °C in a sealed tube, **44.3** was formed quantitatively. Treatment of the C(2)-epimeric compound **44.2** under similar conditions led to the formation of (-)-tasmanine (**44.4**). The generality of this remarkable rearrangement has not been established.

Scheme 44



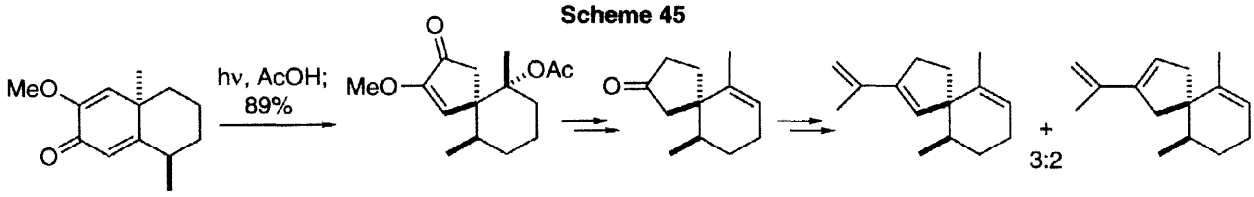
44.1
44.2 (C-2 epimer)

44.3
44.4 (C-2 epimer)

3f Dienone ring contraction

Photolysis of cross conjugated dienones[58-60] has been used for creating spirocenters, and an application to the synthesis of (±)-α-vetispirene is summarized by Scheme 45. In this work,[60] a solution of the cross-conjugated cyclohexadienone **45.1** in glacial acetic acid was irradiated through Pyrex with a high pressure

Scheme 45

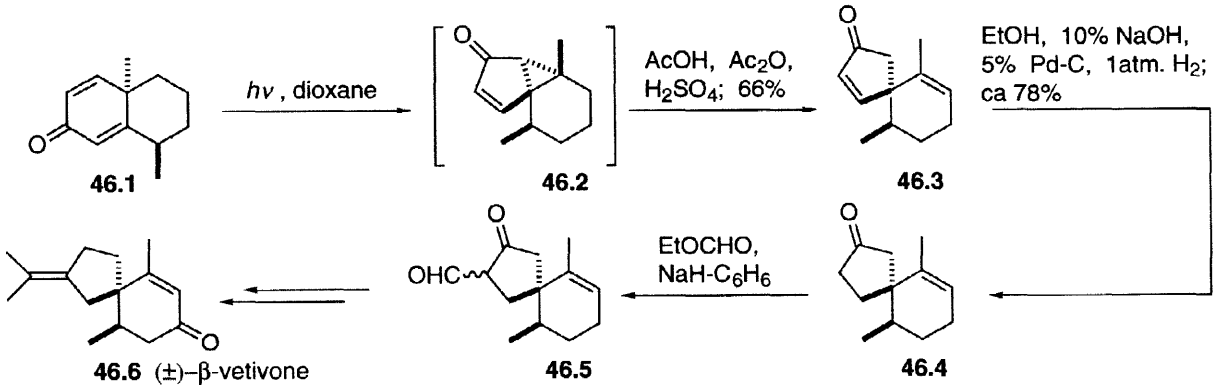


45.1 **45.2** **45.3** **45.4** (±)-α-vetispirene **45.5**

mercury lamp; the spirocycle **45.2** was formed in good yield (89%) with the desired relative stereochemistry at the three asymmetric centers. This compound was converted into (±)-α-vetispirene (**45.4**) via **45.3**. The final product, however, was accompanied by the isomer **45.5**.

Marshall and Johnson[61] also used the above approach in their synthesis of (±)-β-vetivone (Scheme 46). Irradiation of cyclohexadienone **46.1** in acid furnished **46.2**, which solvolyzed in the strongly acidic medium to spiroketone **46.3** with the desired relative configuration at the asymmetric centers. Compound **46.4**, obtained by selective reduction (alkaline conditions) of the enone, underwent condensation with ethyl formate to give **46.5**; this was then converted into (±)-β-vetivone (**46.6**).

Scheme 46



46.1 **46.2** **46.3**

46.6 (±)-β-vetivone **46.5** **46.4**

3g Rearrangement of vinylcyclobutanols and vinylcyclopropanes

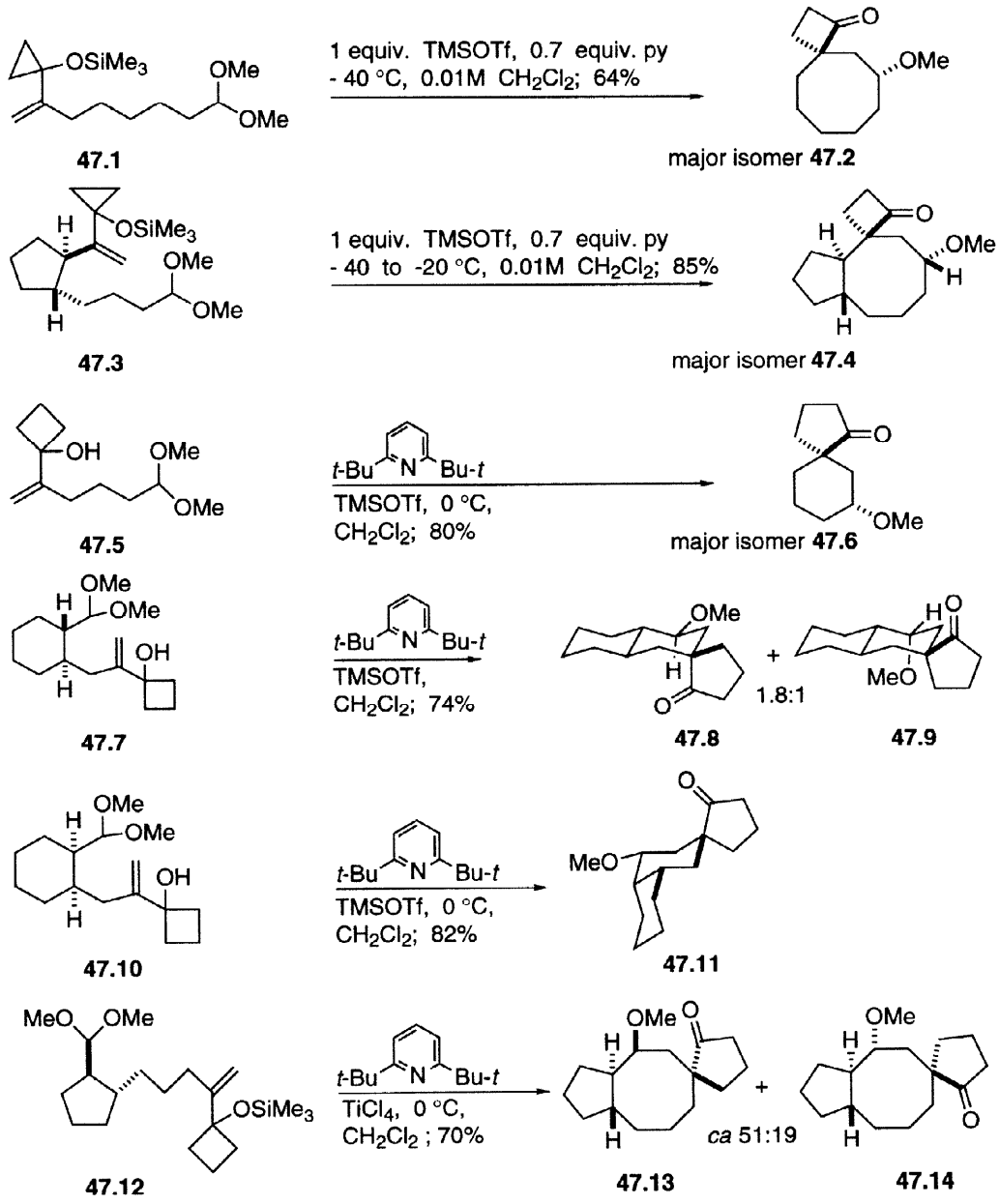
An unusual ring expansion developed by Trost[62,63] has been applied in the synthesis of spiro compounds. The process (Scheme 47) involves a Lewis acid promoted cyclization of a composite functional group comprising either a cyclopropyl[62] or cyclobutyl[63] unit, an alcohol (or the corresponding silyl ether), and

a double bond — all juxtaposed in such a way that the composite unit can act as a nucleophile towards an electrophilic center generated by the acid. Some selected applications of this methodology are shown in Scheme 47.

When compounds **47.1**, **47.3**, **47.5**, **47.7**, and **47.10** were each treated with a Lewis acid in the presence of a base, the corresponding spirocycles **47.2**, **47.4**, **47.6**, **47.8**, **47.9**, and **47.11** were formed. Brönsted acid promoted cyclizations failed for the cyclopropanol systems. Cyclization to [4.5] and [4.6] spiro systems (the latter not shown in Scheme 47) proceeded smoothly in the case of cyclobutanols, but cyclization to [4.7] spirocycles failed. These, however, were easily prepared by attaching the cyclization termini to a preexisting ring system so that tricyclic compounds containing a [4,7] spiro unit are formed (**47.12** → **47.13**, **47.14**).

The diastereoselectivity of the above reactions was generally in favor of the isomer with the carbonyl

Scheme 47

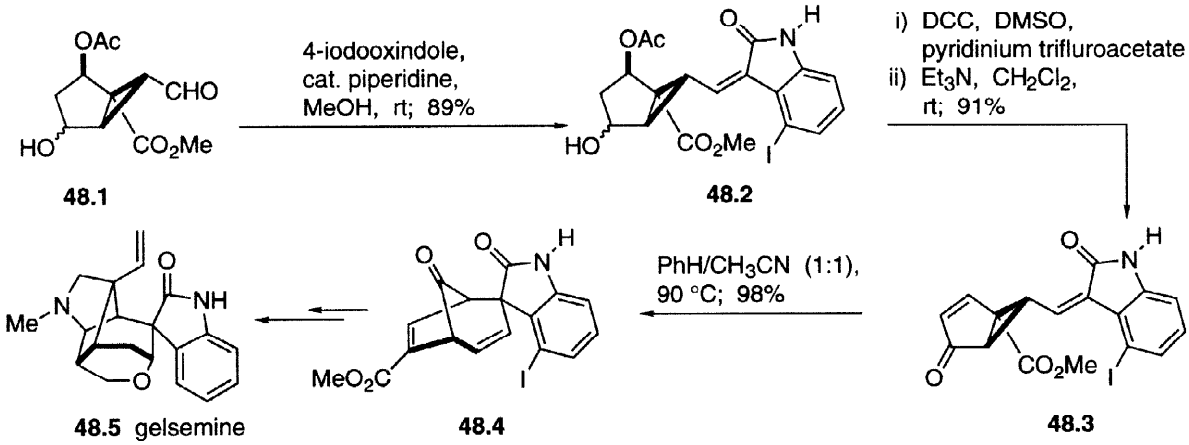


group of the cyclopentanone *trans* to the alkoxy substituent on the larger ring. The two main factors involved in the mechanism are (i) the release of strain that accompanies ring expansion and (ii) the π-like character of the cyclopropyl and cyclobutyl bonds, which allows interaction with a nearby alkenyl group.

3h Rearrangement of divinylcyclopropanes

Recently, Fukuyama and Liu reported[64] the first stereocontrolled synthesis of the spiroindolinone gelsemine. The crucial step involved rearrangement of a stereochemically defined divinylcyclopropane (Scheme 48). Thus, condensation of cyclopropylcarboxaldehydes **48.1** and 4-iodooxindole gave **48.2**, which were converted into enone **48.3** in two steps. Divinylcyclopropane-cycloheptadiene rearrangement of **48.3** then provided the bicyclo [3.2.1] framework stereoselectively (**48.3** → **48.4**). Once the crucial spirocenter was established with the correct relative stereochemistry, the remainder of the target structure was elaborated (**48.4** → gelsemine).

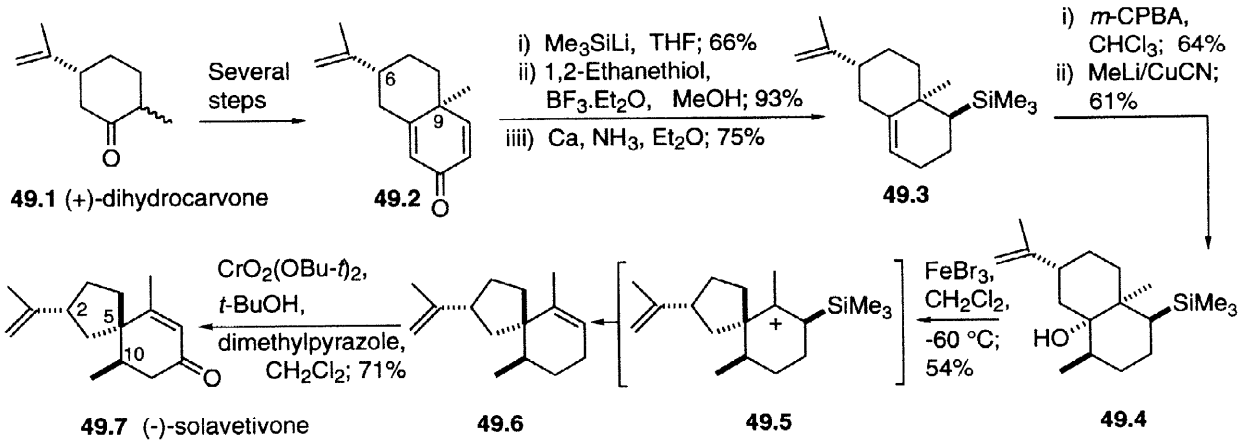
Scheme 48



3i Silicon-facilitated ring contraction

The first stereoselective synthesis of the phytoalexin solavetivone was achieved by Hwu and Wetzel,[65] using a silicon-assisted ring contraction to generate the spirocenter (Scheme 49). The cross-conjugated trienone **49.2** was constructed from dihydrocarvone (**49.1**) by a literature procedure.[66,67] Conjugate addition of trimethylsilyllithium, and removal of the carbonyl group by desulfurization of the derived dithioacetal, gave

Scheme 49

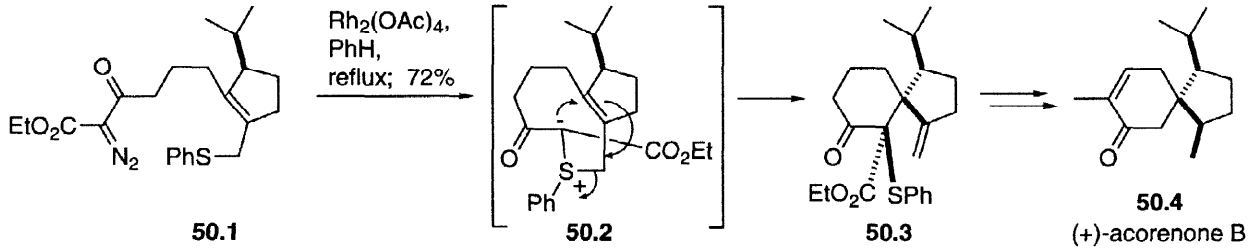


olefin **49.3**. From that point, epoxidation and epoxide ring opening with lithium dimethylcuprate afforded the decalin **49.4**, and when this compound was treated with ferric bromide in dichloromethane at a low temperature, optically active **49.6** was obtained with the desired relative configuration at the asymmetric centers. The silicon group facilitates rearrangement by stabilizing the carbocation intermediate **49.5**. Finally, oxidation of **49.6** with a reagent derived from chromyl chloride yielded optically active (-)-solavetivone (**49.7**).

3j [2,3]-Sigmatropic rearrangement

Kido *et al.*[68] developed a spiroannulation based on [2,3]-sigmatropic rearrangement (Scheme 50) of a cyclic allylsulfonium ylide (**50.2**), and applied it to the synthesis of (+)-acorenone B (**50.4**). The key diazo ketoester **50.1** was prepared by using straightforward reactions, starting from (-)-perillaldehyde. The stereoselectivity of the key step is due to the fact that the carbanion approaches from the side opposite to the bulky isopropyl group (see **50.2**).

Scheme 50

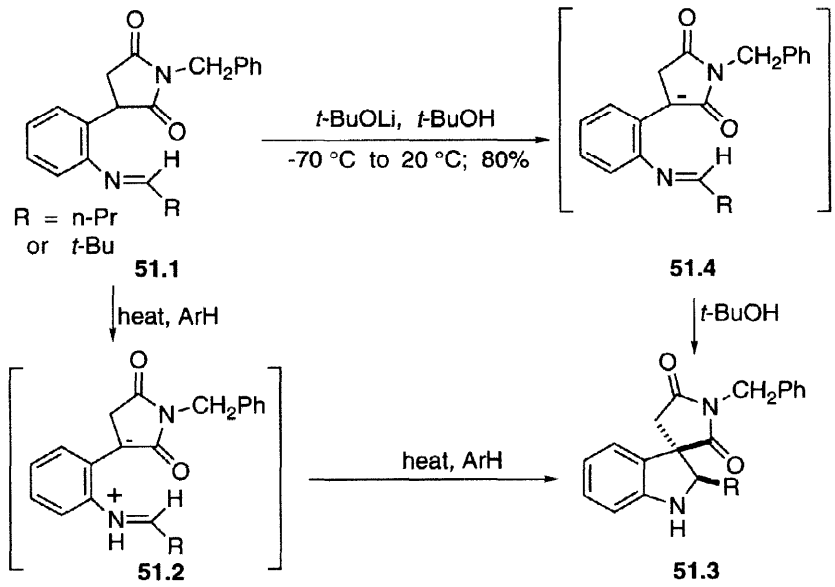


50.1 **50.2** **50.3** **50.4** (+)-acorenone B

3k Electrocyclization

A reaction sequence that can be classified formally as a 1,5-electrocyclization has been used to construct spiro compounds containing the 2,3-dihydroindole unit; such spiro substructures occur in intermediates for the synthesis of *Aspidosperma* alkaloids. In this connection, Speckamp[69] demonstrated that imines derived from appropriate *ortho*-substituted aminobenzenes (Scheme 51) undergo a stereoselective

Scheme 51

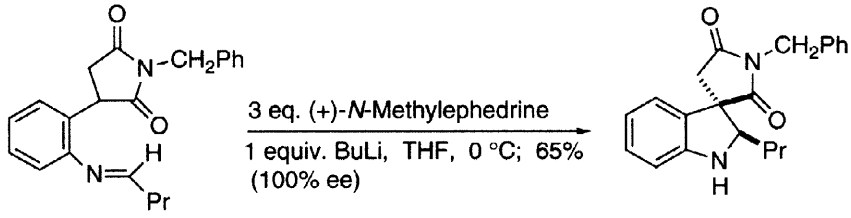


51.1 **51.4** **51.2** **51.3**

1,5-electrocyclization (**51.1** → **51.3**), which can be brought about thermally (**51.1** → **51.2** → **51.3**) or by deprotonation (**51.1** → **51.4** → **51.3**). When the base-induced reaction is performed in the presence of optically pure amino alcohols, the process is enantioselective, and in favorable cases it can proceed with very high ee (Scheme 52). A mechanism has been proposed that serves to predict the absolute configuration of the product.

When the *thermal* reaction is done in the presence of an optically pure alcohol (menthol or borneol) the enantioselectivity is again 100% but the yield is poor (17-31%).

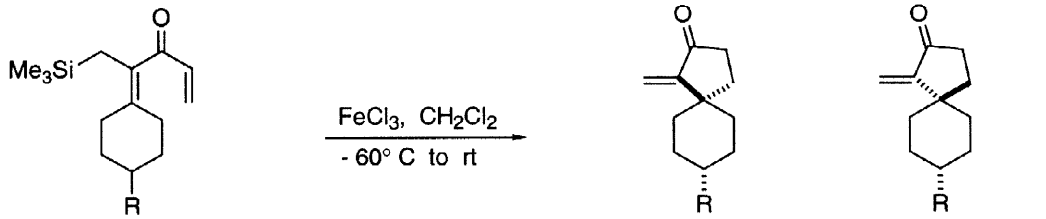
Scheme 52



52.1 **52.2**

Spiro compounds have also been constructed[70] by means of a Nazarov cyclization (Scheme 53), using the cross-conjugated ketones **53.1-53.3**. In these compounds, the function of the silyl group is to stabilize a carbocation intermediate,[71] and thereby facilitate ring closure. The allyl silanes **53.1** and **53.2** each produced a 5:1 mixture of spiroketones **53.4/53.7** and **53.5/53.8**, respectively, in the presence of the mild Lewis acid ferric chloride.

Scheme 53



53.1 R = *t*-Bu
53.2 R = Me
53.3 R = H

53.4:**53.7** = 5:1; 59%
53.5:**53.8** = 5:1; 61%
53.6; 67%

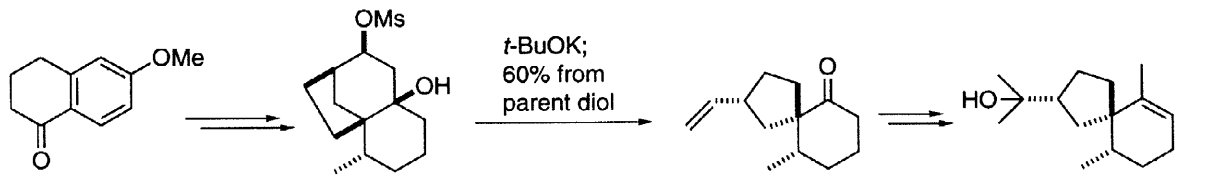
53.4 R = *t*-Bu
53.5 R = Me
53.6 R = H

53.7 R = *t*-Bu
53.8 R = Me

4 Conversion of bridged systems into spirocycles

Appropriately constructed bridged systems afford spiro compounds when one of the bridges is cleaved. The use of Grob fragmentation for this purpose is seen in Marshall and Brady's synthesis[72] of (±)-hinesol (**54.4**), where monomesylate **54.2** (Scheme 54), prepared from **54.1**, serves as the precursor for the key reaction.

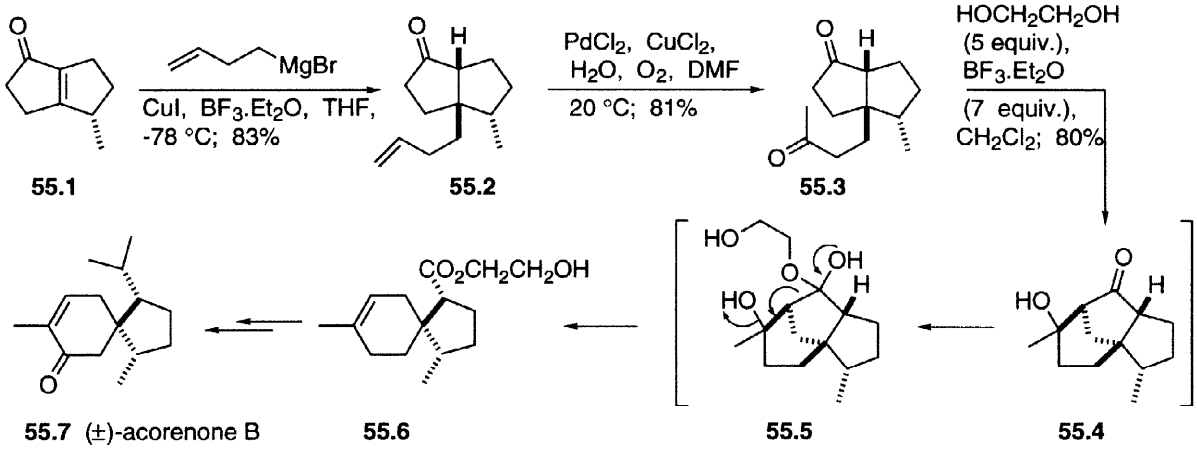
Scheme 54



54.1 **54.2** **54.3** **54.4** (±)-hinesol

A subtle form of Grob fragmentation to convert a bridged into a spiro system was used in a synthesis[73] of (±)-acorenone B (Scheme 55). 1,4-Addition[73] of an organocuprate to **55.1** gave **55.2** which, on Wacker oxidation, afforded the diketone **55.3**. Treatment with boron trifluoride etherate and ethylene glycol then induced sequential intramolecular aldol condensation (**55.3** → **55.4**), hemiacetalization (**55.4** → **55.5**), and

Scheme 55

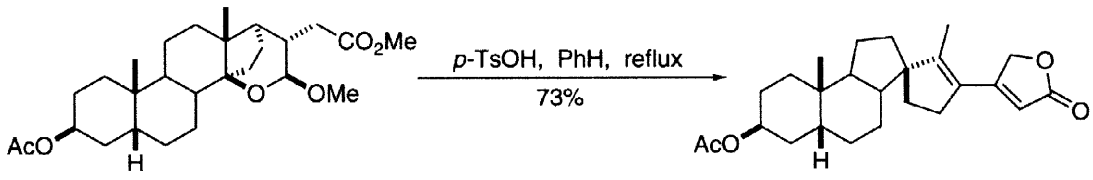


55.1 **55.2** **55.3** **55.7** (±)-acorenone B **55.6** **55.5** **55.4**

Grob fragmentation, giving rise to the spiro compound **55.6** in a highly diastereoselective manner. This product was then converted in several steps into (±)-acorenone B (**55.7**).

Acid catalyzed rearrangement represents another strategy for the synthesis of spirocycles by selective cleavage of bridged systems. In a stereoselective synthesis[74] of bufadienolide analogs (Scheme 56), a spirocyclic intermediate (**56.2**) was formed on treatment of **56.1** with *p*-toluenesulfonic acid in refluxing benzene.

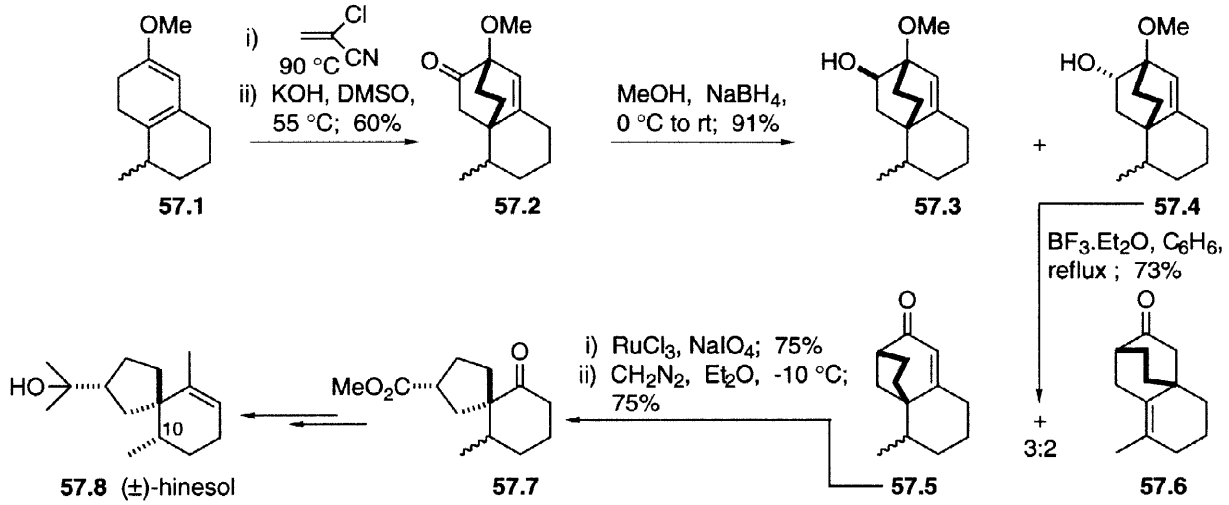
Scheme 56



56.1 **56.2**

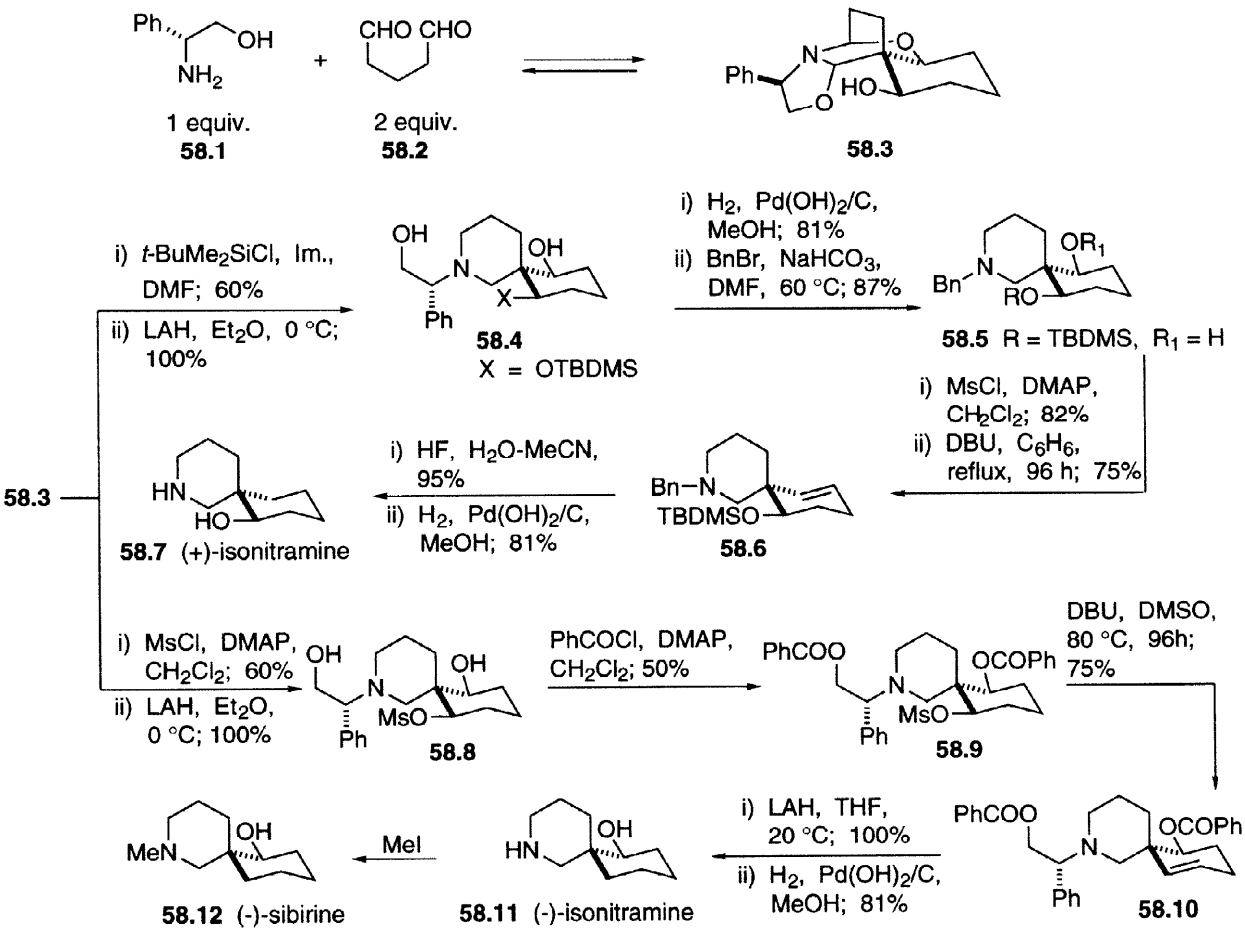
Another type of acid catalyzed rearrangement of an alcohol has been used by Janaki and Subba Rao[75] to make (±)-hinesol and (±)-10-*epi*-hinesol (Scheme 57). In this work, ketone **57.2**, prepared from the dihydrotetralin derivative **57.1** by Diels-Alder reaction and hydrolysis, afforded a 1:3 mixture of alcohols **57.3** and **57.4** when subjected to sodium borohydride reduction. On treatment with boron trifluoride etherate, the *endo* isomer **57.4** underwent rearrangement to a 3:2 mixture of **57.5** and **57.6**. Oxidative cleavage of **57.5** furnished a ketoacid which, on methylation, gave **57.7**, and this was then converted into a mixture (which does not appear to have been separated) of the natural product (±)-hinesol (**57.8**) and its C(10) epimer.

Scheme 57



Husson *et al.*[76] synthesized (+)- and (-)-isonitramine enantiospecifically by way of the common intermediate **58.3** (Scheme 58), which was prepared as shown (**58.1** + **58.2** → **58.3**). The synthesis is based on the recognition that breaking appropriate bonds in **58.3** would release the spiropiperidine ring, and further elaboration would then lead to the individual enantiomers **58.7** and **58.11** of isonitramine. The (+)-enantiomer

Scheme 58



was synthesized by ring opening of **58.3** to give **58.4**. The nitrogen protecting group was then removed by hydrogenolysis and replaced by a benzyl group (**58.4** → **58.5**). Dehydration of **58.5**, desilylation and, finally, hydrogenolysis, afforded (+)-isonitramine (**58.7**).

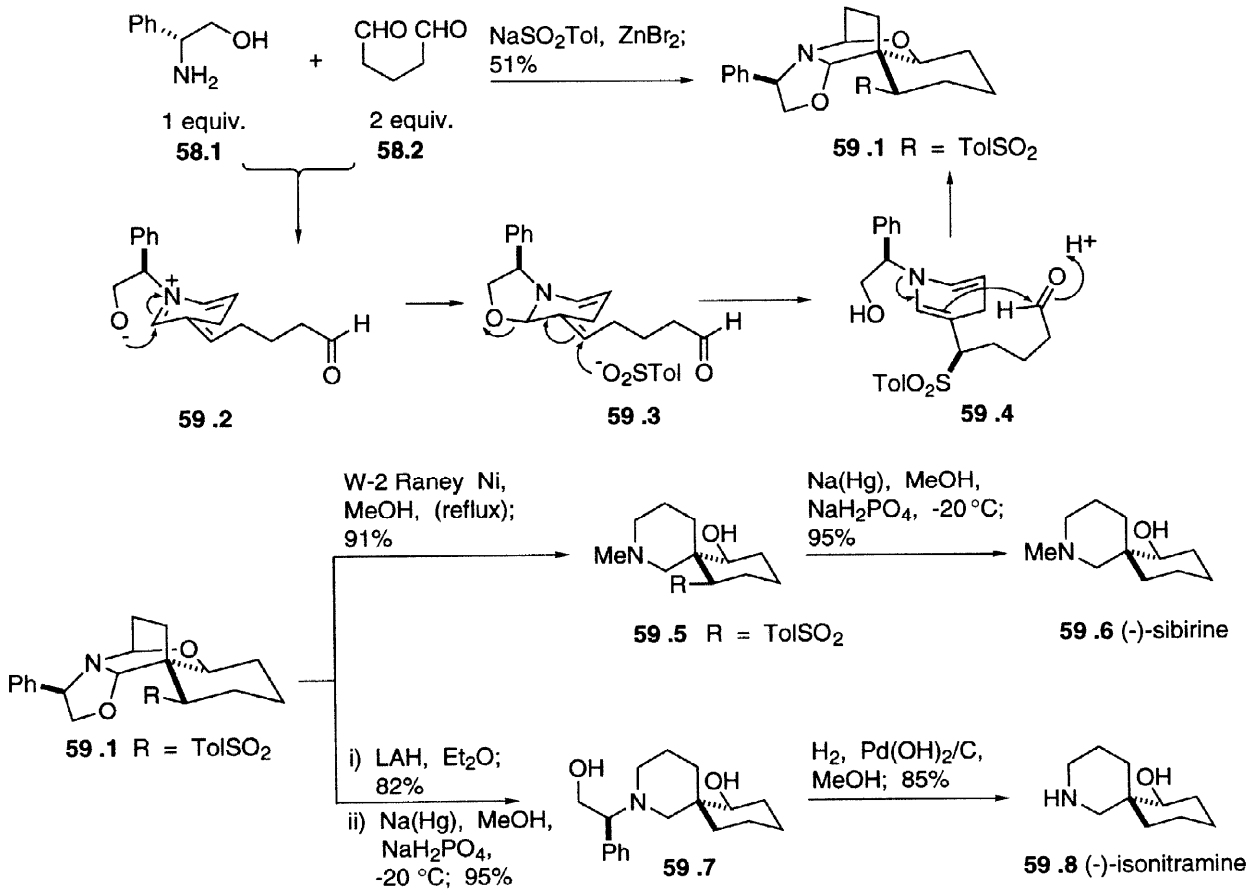
The other enantiomer (**58.11**) was made by similar reactions, but these were employed in a different order. This enantiomer could be converted easily into the unnatural enantiomer (**58.12**) of sibirine by reaction with methyl iodide.

A more concise synthesis of (-)-sibirine and (-)-isonitramine was developed by Husson *et al.*[77] They condensed **58.1** and **58.2** in the presence of sodium *p*-toluenesulfinate as a nucleophilic source. This modification results in replacement of the hydroxyl of **58.3** by an easily removable *p*-TolS(O)$_2$ group (Scheme 59). After diastereoselective addition of the sulfinate (**59.3** → **59.4**), the addition of the enamine unit of **59.4** to the aldehyde proceeds via a chairlike transition state in which the sulfone and the newly formed C-O bond are in a diequatorial arrangement (**59.4** → **59.1**).

Compound **59.1** was then easily converted into (-)-sibirine and (+)-isonitramine by simple chemical transformations, as shown in Scheme 59.

The natural enantiomer, (+)-isonitramine, can be prepared by a similar route starting from (*S*)-(+)-phenylglycinol.

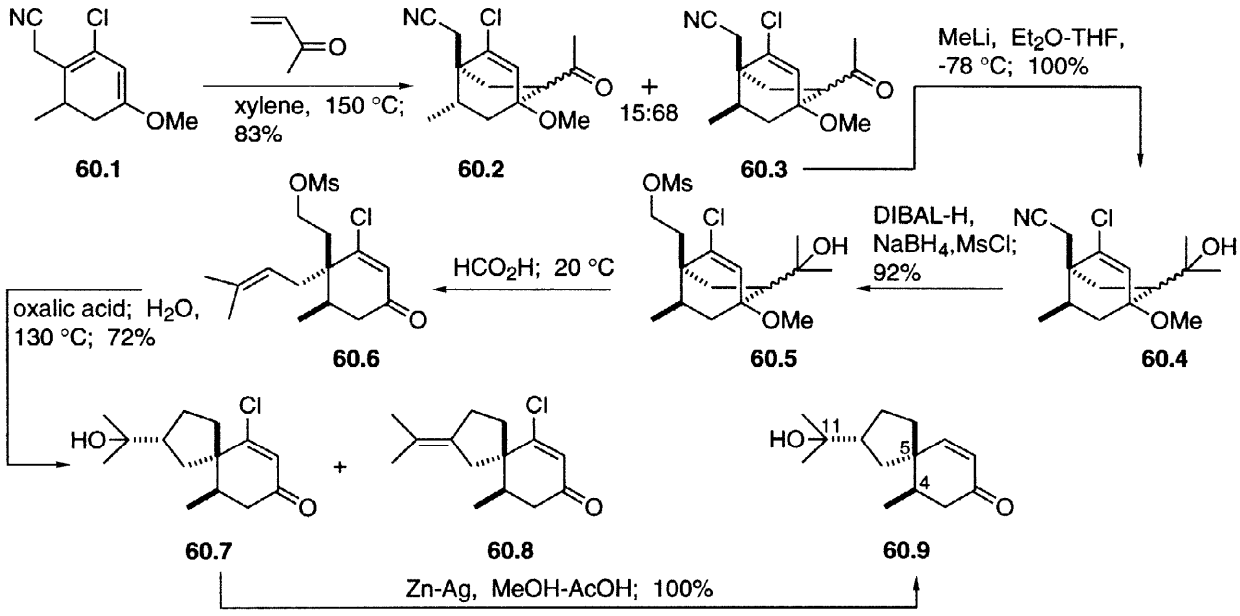
Scheme 59



In a stereoselective synthesis of (±)-11-hydroxy-15-norsolavetivone (**60.9**) (Scheme 60),[78] the desired relative stereochemistry at C(5) and C(4) (see **60.9**) was generated at an early stage by Diels-Alder reaction

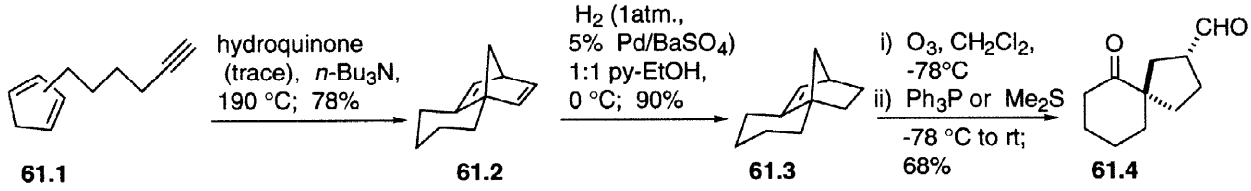
(**60.1** → **60.3**). Diels-Alder adducts **60.2** and **60.3** were obtained as a separable mixture of isomers, by reaction of nitrile **60.1** with methyl vinyl ketone. The major adducts (**60.3**), when treated with methyllithium, were easily converted into the alcohols **60.4**. The derived monomesylates gave **60.6** on treatment with formic acid. At that point, cyclization, by heating with oxalic acid in the presence of water, afforded **60.7** as the major product (72:19), and dechlorination with Zn/Ag couple then gave (±)-11-hydroxy-15-norsolavetivone (**60.9**).

Scheme 60



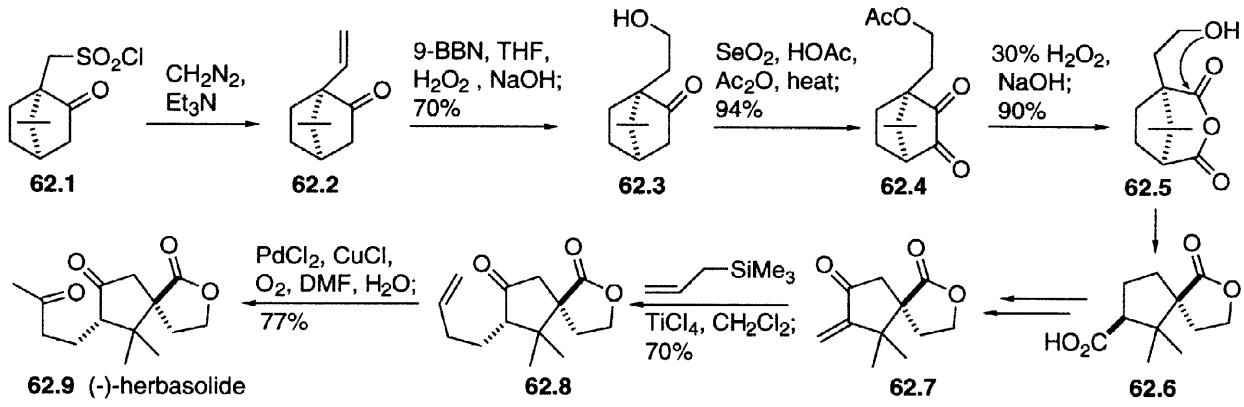
In another route to spiro[4.5]decanes, a Diels-Alder reaction was again used to control the relative configuration of the asymmetric centers (Scheme 61).[79] Substrate **61.1**, prepared as a 1:1 mixture of 1- and 2-substituted cyclopentadienes, underwent smooth intramolecular cycloaddition at high temperature to provide **61.2** exclusively. Selective hydrogenation of the less hindered double bond (**61.2** → **61.3**), and ozonolysis, followed by reductive workup, afforded the functionalized spiro[4,5]decane system **61.4**.

Scheme 61



Intramolecular acylation has been used to convert an optically pure bridged system into a spirocyclic natural product. This approach was used by Ho and Liang[80] in the synthesis of (-)-herbasolide (**62.9**) (the enantiomer of the natural product), starting from optically pure (+)-10-camphorsulfonyl chloride (Scheme 62). The latter was transformed into **62.2** by a Ramberg-Bäcklund reaction. Hydroboration, followed by selenium dioxide oxidation in acetic acid, then gave the camphorquinone **62.4**. Treatment with alkaline hydrogen peroxide afforded spirolactone **62.6** via cyclic anhydride **62.5**, which then lactonized (**62.5** → **62.6**). Compound **62.7**, obtained from **62.6** by several straightforward steps, was converted into (-)-herbasolide by sequential Sakurai-Hosomi reaction (**62.7** → **62.8**) and Wacker oxidation (**62.8** → **62.9**).

Scheme 62



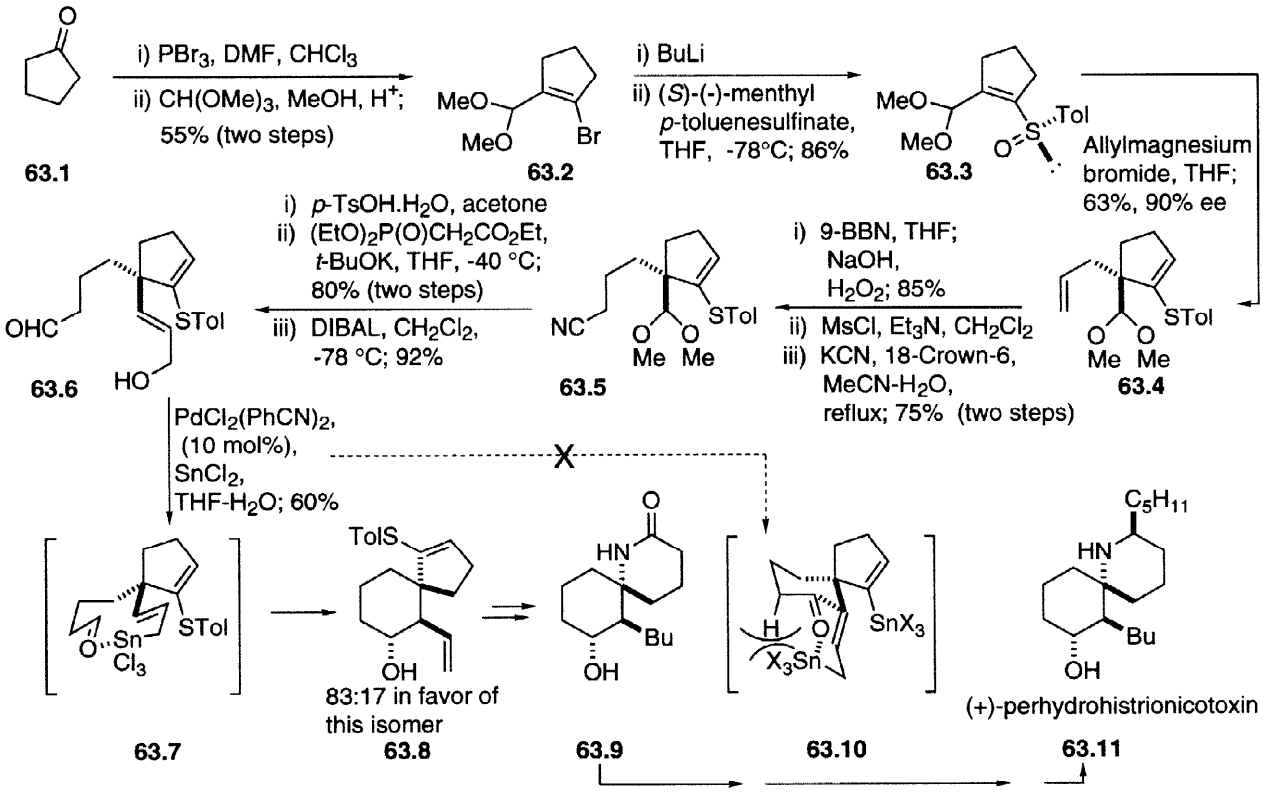
5 Ring closure of geminally disubstituted cyclic systems

Many approaches to spiro structures are best regarded as routes to compounds with quaternary carbons carrying two functionalized chains that are then joined so as to generate the second ring of the spiro system.

5a Allylation of vinyl sulfoxides and ring closure

Perhydrohistrionicotoxin (**63.11**) has been a longstanding synthetic target due to its complicated structure and potentially useful pharmacological properties. In a fairly recent formal synthesis[81] by Iwata's group, a key spirocyclic intermediate (**63.8**) was prepared by palladium-catalyzed ring closure (**63.6** → **63.8**). Formation of this intermediate sets the relative stereochemistry of the three contiguous asymmetric centers, as explained below.

Scheme 63



Cyclopentanone was converted into **63.2** (Scheme 63) and then into sulfoxide **63.3** (ee >90%). Treatment of **63.3** with allylmagnesium bromide provided the geminally disubstituted vinyl sulfide **63.4** (ee 90%) by way of a Pummerer-like reaction. The vinyl sulfide was elaborated by several conventional steps into aldehyde **63.6**, and this was converted into the allyltin **63.7**, which underwent a palladium-catalyzed cyclization (**63.7** → **63.8**). The cyclization was diastereoselective and gave **63.8** as the major isomer (83:17). Further elaboration of **63.8** gave **63.9**, which had previously been converted into **63.11**.

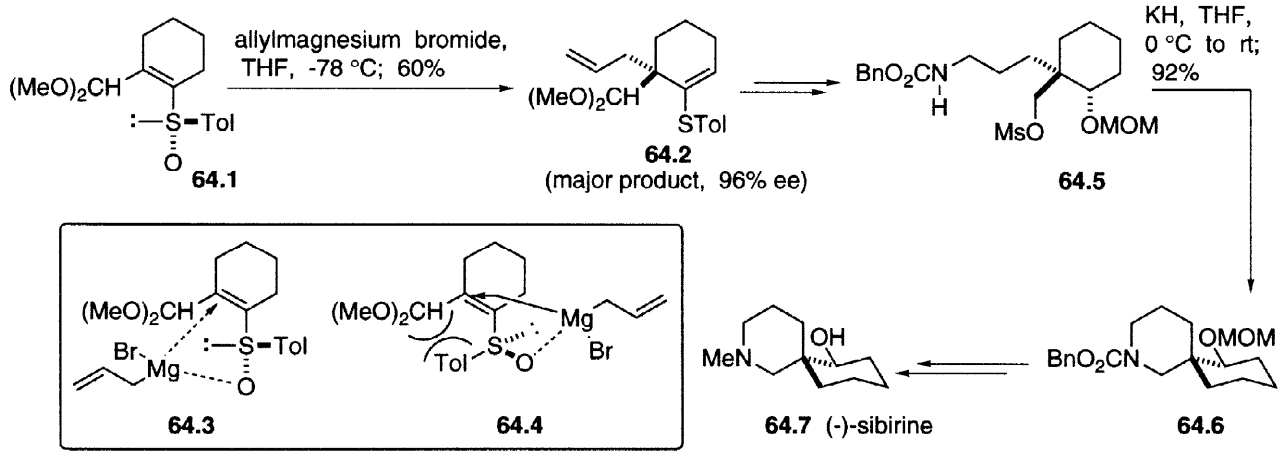
The stereoselectivity in the palladium catalyzed reaction can be understood by recognizing that the transition state **63.10** is sterically congested, and is less favored than **63.7**.

In related work, a chiral sulfoxide (**64.1**, Scheme 64) similar to the chiral sulfoxide **63.3**, was used[82] in the synthesis of (-)-sibirine. The key transformation for this purpose was the conjugate addition-Pummerer reaction **64.1** → **64.2** (96% ee). The enantioselectivity of this process can be explained on the basis of transition state **64.3**, which is clearly more favored than the alternative (**64.4**).[82]

Compound **64.2** was easily converted (Scheme 64) into (–)-sibirine (**64.7**) by functional group manipulation via **64.5** and **64.6**.

The course of the initial reaction with allylmagnesium bromide is easily changed by altering the substitution of the vinyl sulfoxide. Thus, when chiral sulfoxide **65.1** (Scheme 65) was used instead of **64.1**, the

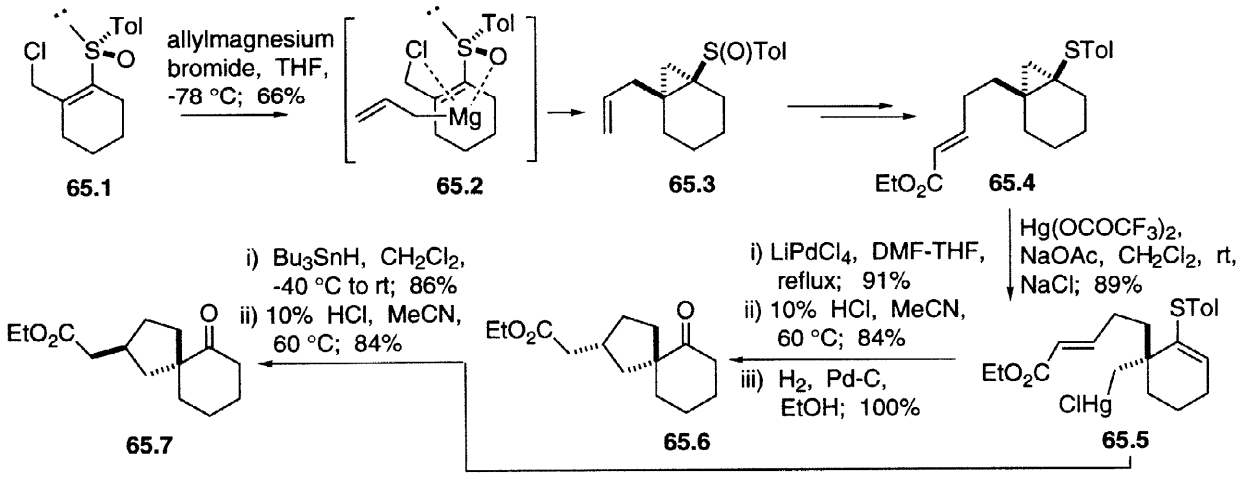
Scheme 64



cyclopropane **65.3** was formed as a single stereoisomer on reaction with allylmagnesium bromide.[83] In this case, reaction evidently proceeded via a transition state resembling **65.2**.[83] Compound **65.3** was converted into **65.4** and, on treatment with mercuric(II) trifluoroacetate, **65.4** underwent ring opening to **65.5** in high yield. Radical cyclization then produced **65.7** as the major isomer.

In further work, it was found that when **65.5** was treated with a palladium catalyst, the major product was the diastereomeric spiro compound **65.6**. In principle, compounds **65.6** and **65.7** could serve as key intermediates for enantioselective synthesis of sesquiterpenes of the spirovetivane and kaurane classes.

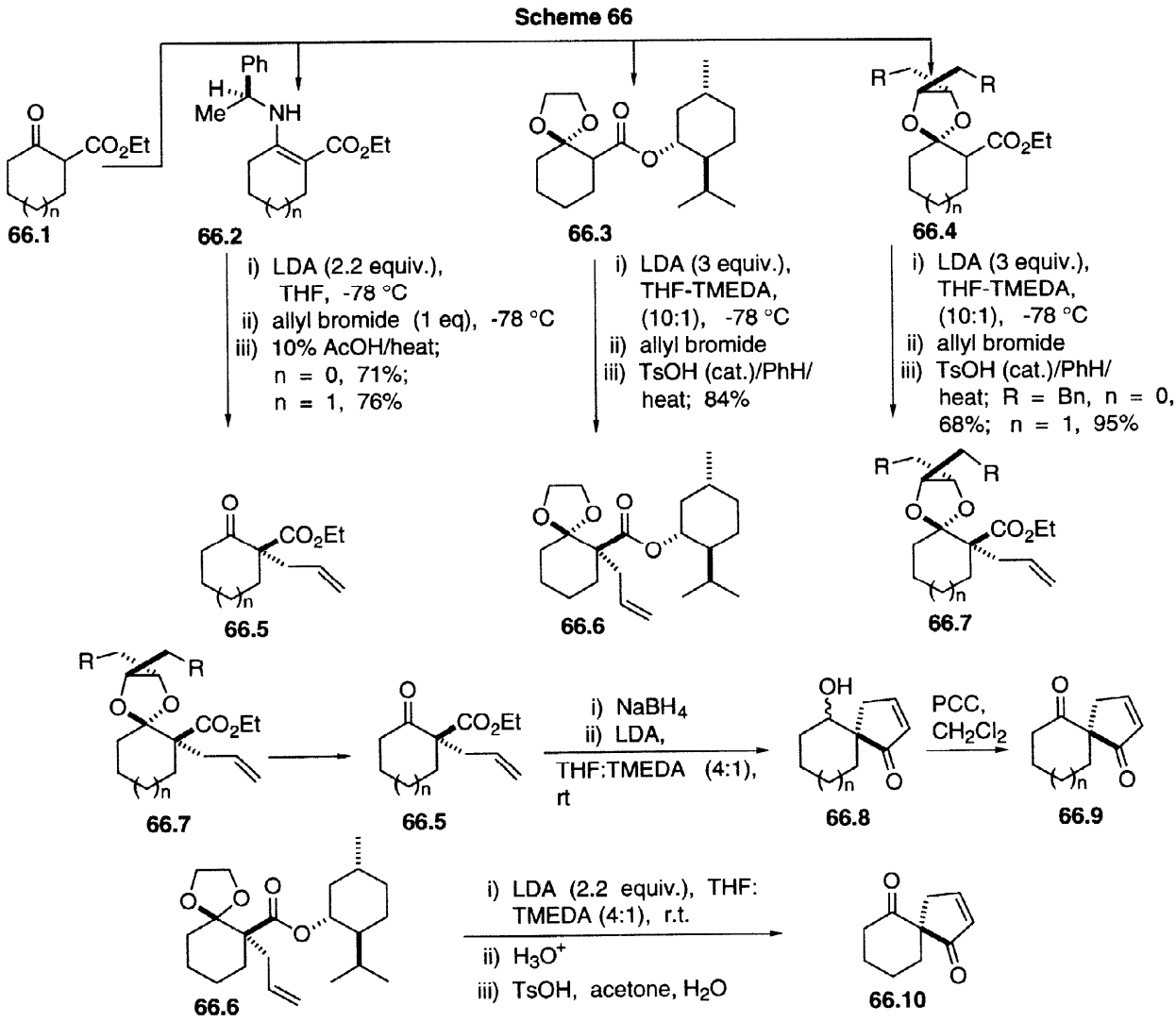
Scheme 65



5b *Asymmetric allylation of β-dicarbonyl compounds and ring closure*

Asymmetric allylation of derivatives of β-ketoesters **66.1** has been used by Chitkul *et al.*[84] (Scheme

Scheme 66

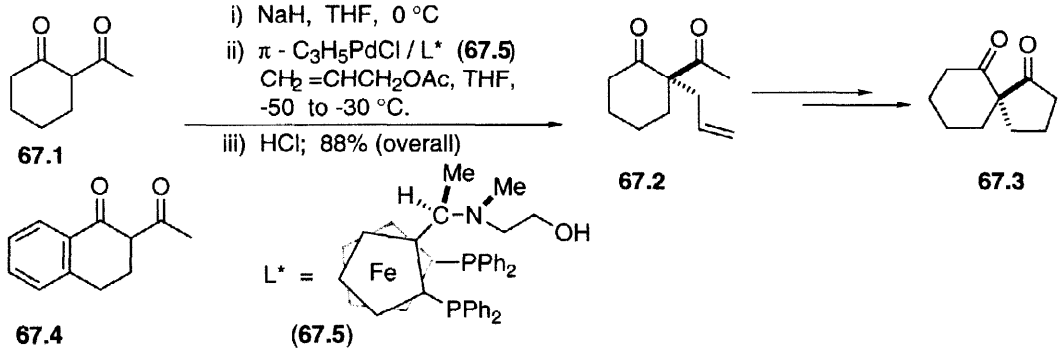


66) in a route to optically active diones. For this purpose, the β-ketoesters **66.1** were converted first into optically active enamines (**66.2**), a menthyl ester (**66.3**), or ketals (**66.4**). Each of these was then allylated (**66.2** → **66.5**; **66.3** → **66.6**; **66.4** → **66.7**). It was found that the presence of HMPA or TMEDA enhanced the enantioselectivity in the case of ketals **66.4**. Among the various ketals of type **66.4** studied (R = Ph, OMe, OBn), best results were obtained for n = 1, R = OBn (yield 95%, ee = 88%). Cyclization of **66.7** was effected by conversion into ketones **66.5** (Scheme 66), reduction by sodium borohydride and then treatment with LDA. This sequence gave bicyclic alcohols **66.8**, which were oxidized to the spirodiones **66.9** (n = 0, 69% ee; n = 1, 88% ee). Compound **66.6** could be cyclized directly by the action of LDA, and gave **66.10** on deacetalization.

Spirodione **67.3** (Scheme 67) was constructed by Hayashi *et al.*[85] using a procedure for catalytic asymmetric allylation of active methine compounds. Highest enantioselectivity was observed with 0.5-1.0% of a palladium complex with the chiral phosphine ligand **67.5**. For example, when the sodium enolate of β-diketone **67.1**, or the tetralone **67.4**, was reacted with allyl acetate in the presence of this catalyst-ligand system, allylation occurred, to give a product with an ee of 73% (for **67.1** → **67.2**) and an ee of 82% (in the case of **67.4**).

The enantioselectivity is attributed to hydrogen bonding of the terminal hydroxyl group of the ligand to the prochiral enolate derived from **67.1** or **67.4**. In this way a specific facial relationship is set between the allyl system (which, like the chiral ligand, is coordinated to the palladium) and the enolate. The allylated product **67.2** was elaborated into optically active **67.3** by simple steps that involved cleavage of the double bond, followed by aldol condensation of the resulting aldehyde.

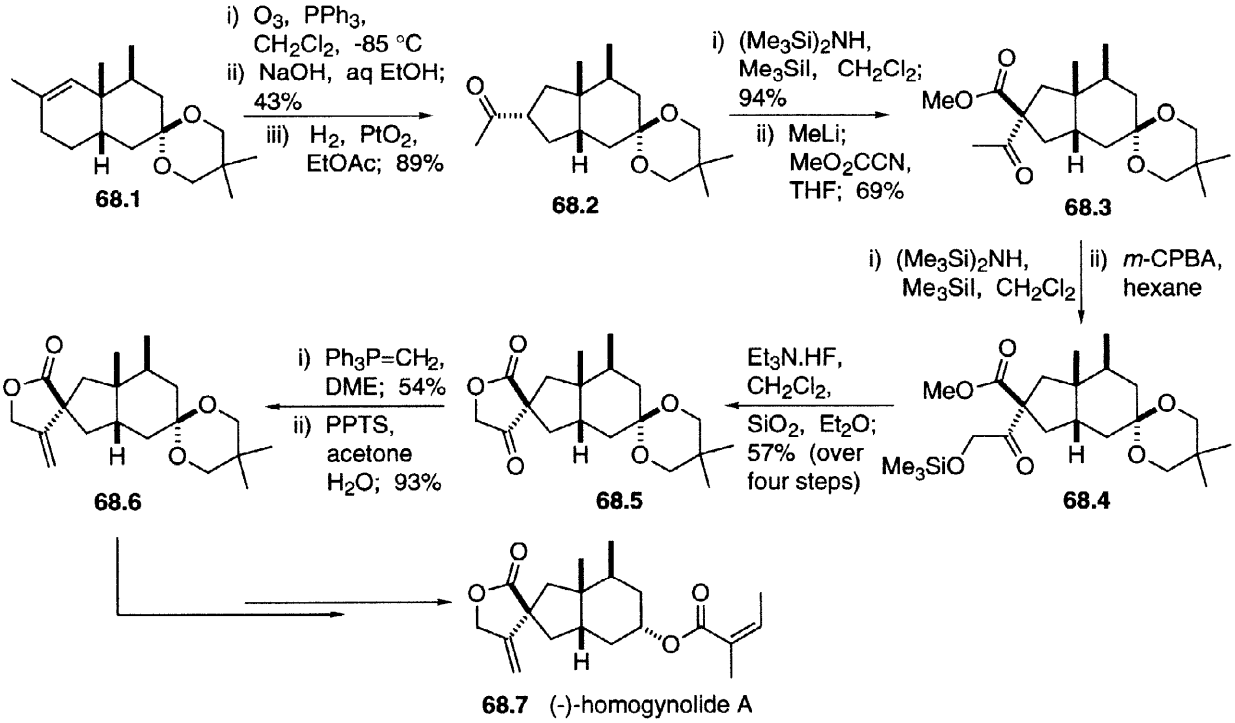
Scheme 67



5c Intermolecular acylation and lactonization

In a stereoselective synthesis of the bakkenolide (-)-homogynolide (Scheme 68),[86] Mori and Matsushima subjected olefin **68.1** to ozonolytic cleavage, aldol condensation, and hydrogenation, so as to form the ring-contracted ketone **68.2**. The spirocenter was then created by stereoselective introduction of a methoxycarbonyl group, via the thermodynamically more stable silyl enol ether, and from the less hindered convex face (**68.2** → **68.3**). Further elaboration of **68.3** was effected by introduction of a hydroxyl group by epoxidation of the derived silyl enol ether, followed by rearrangement of the epoxide to silyloxy ketone **68.4**. Desilylation of **68.4**, and lactonization over silica, afforded **68.5**. Wittig methylenation and deketalization, then gave **68.6**. From this stage the procedure of reference 7 was followed, to obtain the natural product.

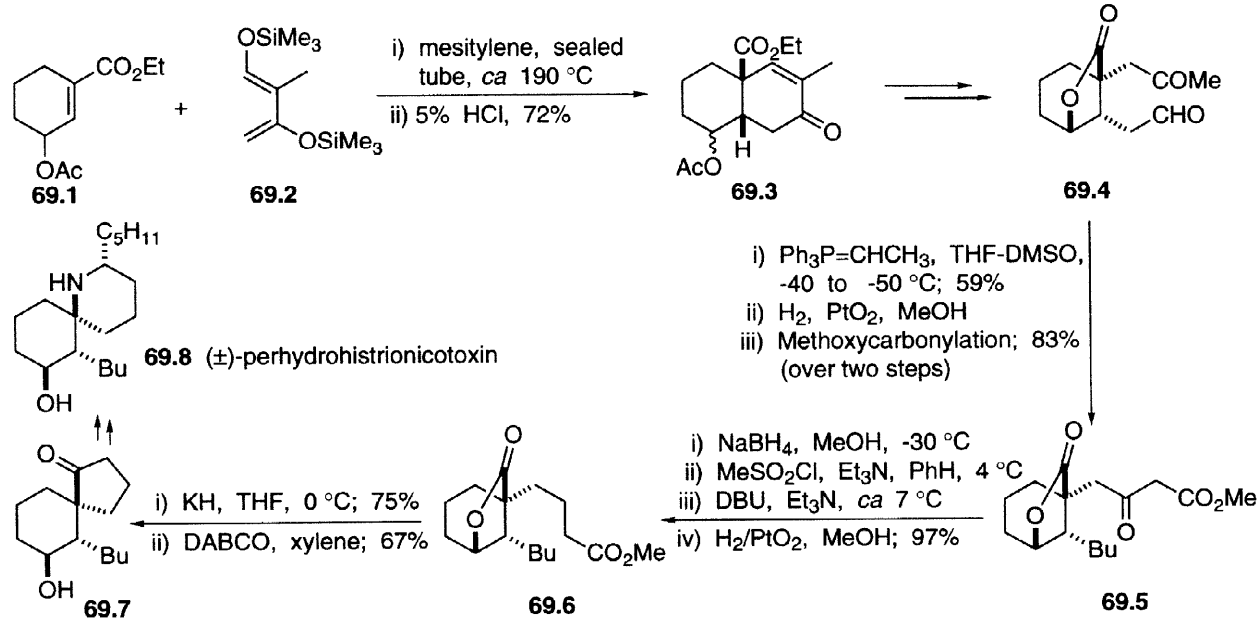
Scheme 68



5d Diels-Alder reaction and Dieckmann condensation

In a formal synthesis of perhydrohistrionicotoxin (**69.8**), Ibuka *et al.*[87] developed a route via intermediate **69.6**, which was prepared either by Diels-Alder reaction (Scheme 69) or by conjugate addition to an appropriately substituted enone (see later, Scheme 74).[88]

Scheme 69



In the Diels-Alder approach, reaction of ester **69.1** and diene **69.2** afforded an inseparable mixture (9:1) of diastereomers **69.3**. Both were processed by a multistep sequence, during which separation was effected

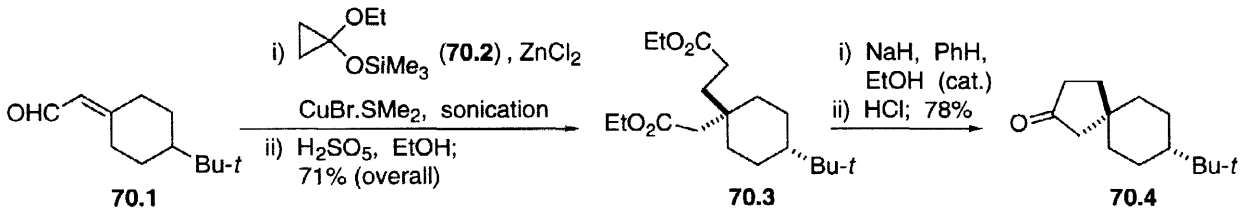
and the enone ring was cleaved. These operations gave **69.4**. Wittig reaction then led to a 30:7 mixture of geometrical isomers, which was hydrogenated and acylated to provide the β-ketoester **69.5**. Further reduction, in several steps, gave **69.6**, and then Dieckmann condensation, followed by decarboxylation, furnished the required spiro intermediate **69.7**, which is a precursor of (±)-perhydrohistrionicotoxin.

5e Conjugate addition and Dieckmann condensation

Sequential conjugate addition and Dieckmann condensation is the basis of Provencal and Leahy's[89] approach to spirocyclopentanones. Scheme 70 shows a typical example of the methodology. The unsaturated aldehyde **70.1**, prepared from the corresponding cyclohexanone by Peterson olefination, was subjected to copper-catalyzed conjugate addition of a reagent made from the cyclopropane **70.2**, followed by treatment with Caro's acid. These operations provided diester **70.3**, and sequential Dieckmann condensation, hydrolysis, and decarboxylation then furnished **70.4**, as a single isomer.

The stereochemical control observed in this sequence is the result of preferential *equatorial* attack of the cuprate reagent on the starting unsaturated aldehyde.

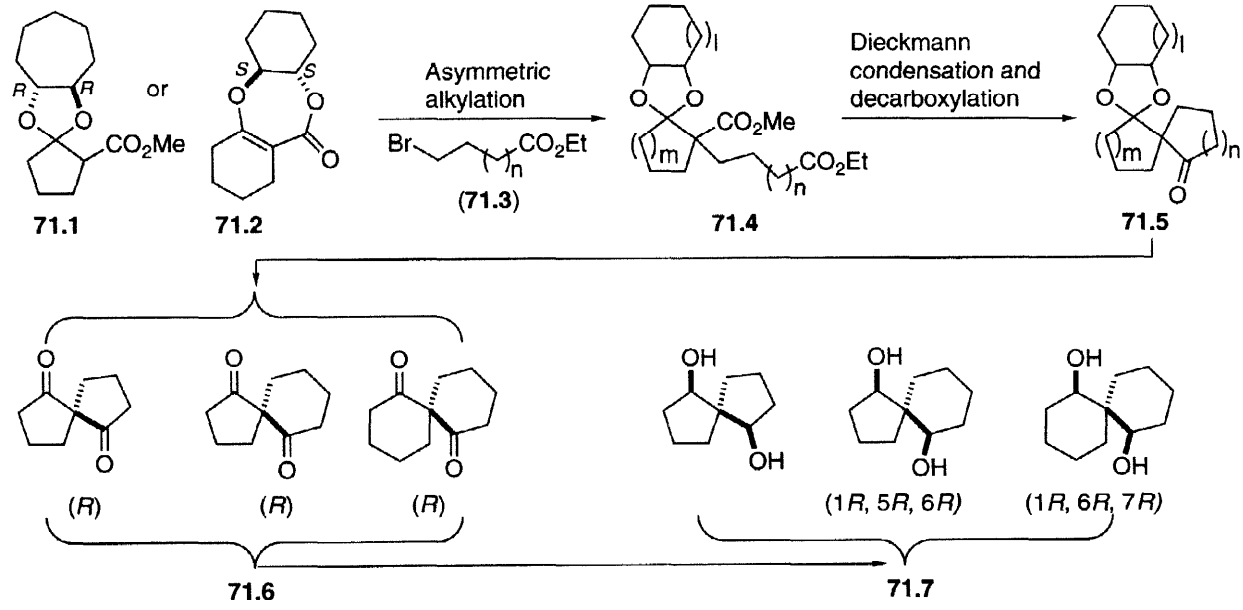
Scheme 70



5f Asymmetric alkylation and Dieckmann condensation

Optically active spirocyclic diones, which can display homoconjugation effects, have attracted attention as synthetic targets. A very efficient strategy to construct these compounds has been developed,[90] which utilizes cycloalkane 1,2-diols as chiral auxiliaries (Scheme 71). For example, when acetal **71.1** was

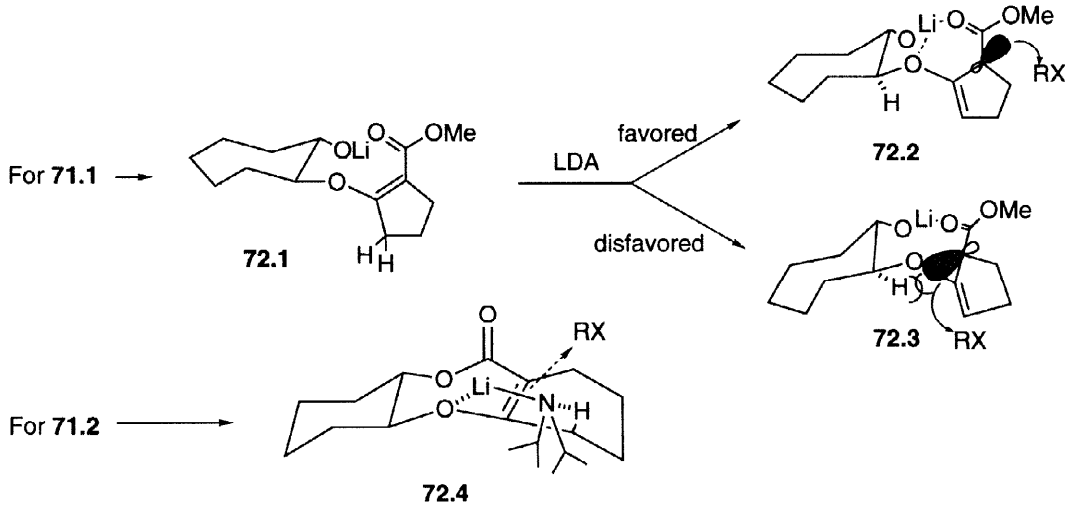
Scheme 71



alkylated with a bromoester (**71.3**) under kinetic conditions, it gave rise to the generic diester **71.4** with complete diastereoselectivity. A similar transformation could be done with **71.2**, but in this case an additional step was needed to reach **71.4**. Dieckmann condensation of **71.4**, followed by decarboxylation, produced spiroketones **71.5**. These can be processed to optically pure spirodiones **71.6** by acetal cleavage, and the diones can be reduced diastereoselectively to the corresponding spirodiols (**71.7**).

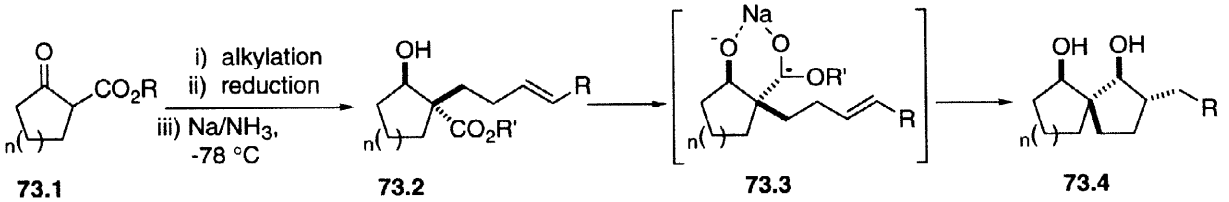
The stereochemical bias of the alkylation steps is interpreted in terms of transition states **72.2** (for **71.1**) and **72.4** (for **71.2**), as shown in Scheme 72.

Scheme 72



Spirodiols structurally related to **71.7** have also been synthesized by Cossy *et al.*[91] from hydroxy esters **73.2** (Scheme 73), which, in turn, were generated from **73.1** by alkylation and sodium borohydride reduction. Treatment of each hydroxy ester with sodium in ammonia, generated an intermediate of type **73.3**. This underwent 5-*exo*-trigonal cyclization to give spirodiols **73.4** in good yield. When the proximal terminus of the olefin carried a methyl group, the product of competing Bouveault-Blanc reduction of the ester was isolated, and cyclization was not observed.

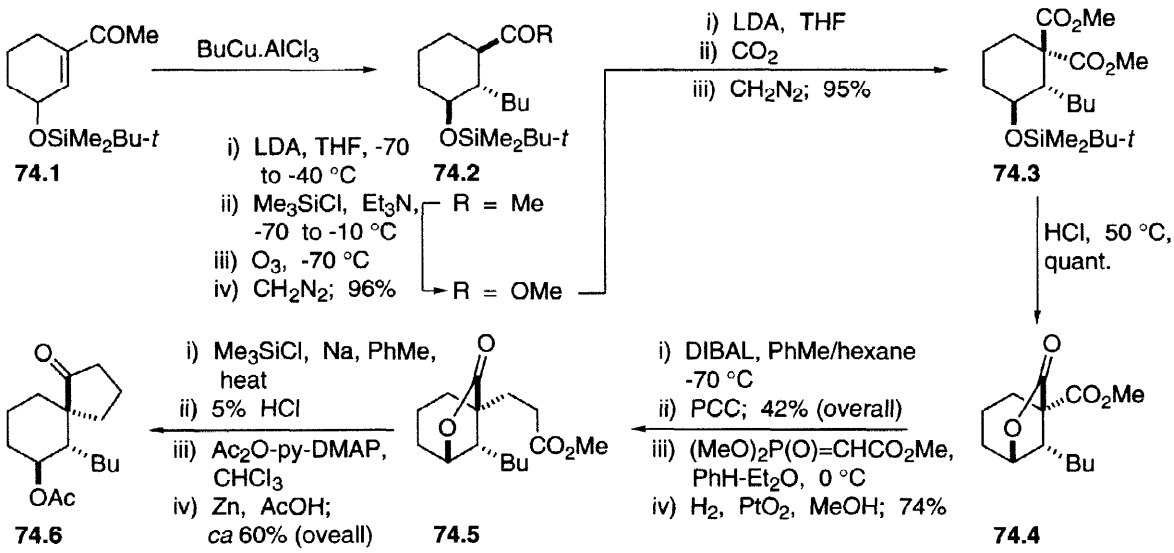
Scheme 73



5g Conjugate addition and acyloin condensation

In another approach to perhydrohistrionicotoxin, Ibuka *et al.*[88] obtained spiroketone **74.6** (synthetically equivalent to **69.7**) by conjugate addition of BuCu.$AlCl_3$ to **74.1** (Scheme 74). Thereafter, a sequence of standard operations summarized in the Scheme led to **74.6**, which was elaborated further into an intermediate that had previously been converted into (±)-perhydrohistrionicotoxin.

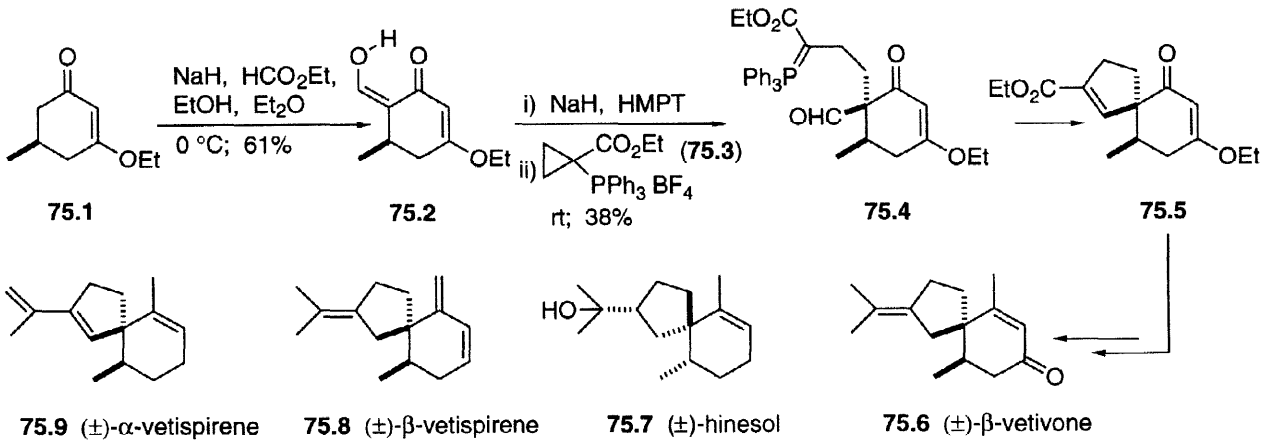
Scheme 74



5h Alkylation and ring closure by Wittig reaction

In an innovative use of a Wittig reagent — in this case the cyclopropyl derivative **75.3** (Scheme 75) — Dauben[92] found a general method to prepare a functionalized spiro [4.5] framework which could be elaborated further into various sesquiterpenes. The key step involves attack of the enolate derived from **75.2** on the cyclopropyl ring of the phosphonium salt, with formation of an ylide; this then undergoes Wittig olefination (**75.2** → **75.4** → **75.5**). The initial attack on the cyclopropane is from the face opposite to the methyl group in **75.2**, and this facial selectivity then sets the relative stereochemistry of the newly created spirocenter. The utility of this reaction was demonstrated (Scheme 75) by the synthesis of α-vetispirene, β-vetispirene, β-vetivone and hinesol, via the common intermediate **75.5**.

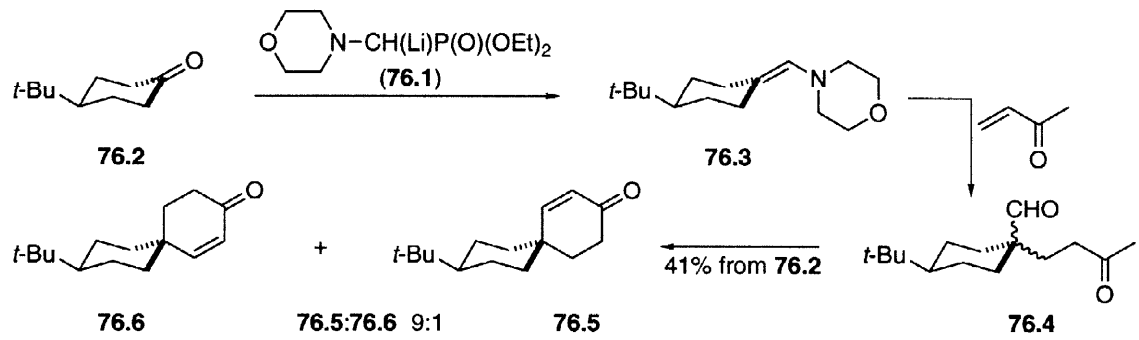
Scheme 75



5i Michael addition and intramolecular aldol condensation

In Martin's approach[93] (Scheme 76) to the diastereoselective construction of spiro [5.5] systems, morpholine enamines, which were easily prepared from the corresponding ketone and phosphonate **76.1**, were treated with methyl vinyl ketone. In the case shown, hydrolysis of the intermediate product gave ketoaldehyde **76.4**, which undergoes spontaneous cycloaldolization and dehydration to spiro compounds **76.5** and **76.6** (9:1).

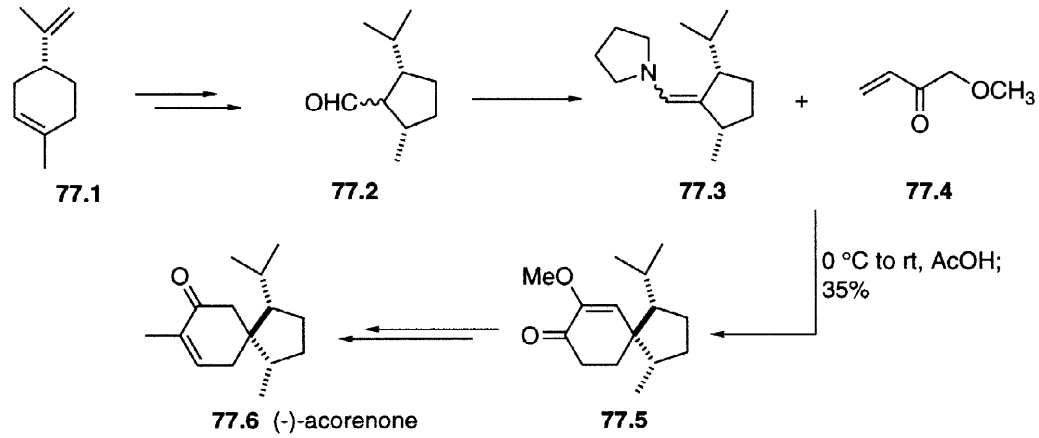
Scheme 76



Sequential Michael addition and aldol condensation have also been used (Scheme 77) by Lange's group in the first synthesis[94] of (-)-acorenone (**77.6**). One of the required components was enamine **77.3**, which was made from aldehyde **77.2**, itself available from (+)-limonene (**77.1**). The crucial step involved Michael addition to **77.4** from the less sterically hindered face of **77.3**, and subsequent cycloaldolization in the presence of acetic acid. This sequence of reactions produced (+)-**77.5**, which was then elaborated into (-)-acorenone.

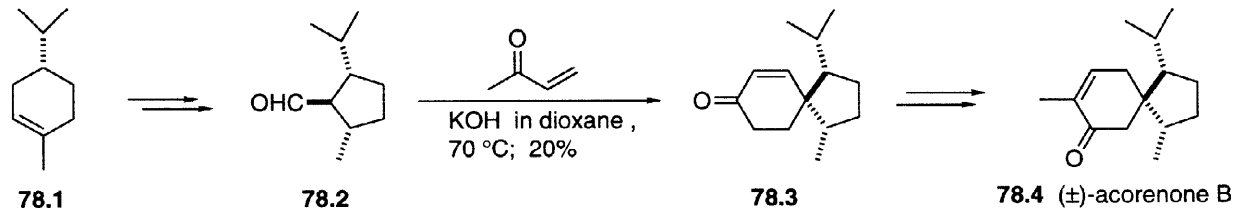
In an enantioselective synthesis (Scheme 78) of the sesquiterpenes (±)-acorenone and (±)-acorenone B (**78.4**), the key spiro intermediate **78.3**[95] was generated by Robinson annulation of **78.2**, itself obtained from optically pure (+)-*p*-menth-1-ene (**78.1**). The stereoselectivity of the annulation can be understood by

Scheme 77



assuming that attack of methyl vinyl ketone (**78.2** → **78.3**) occurs on the less hindered face of the enolate derived from **78.2**.[95] Enone **78.3** was elaborated by simple operations into the two natural products, of which only (±)-acorenone B is shown in the Scheme.

Scheme 78

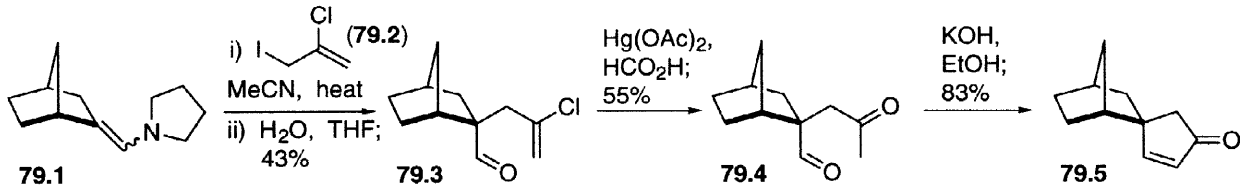


5j Alkylation and intramolecular aldol condensation

A process conceptually related to the methods of Schemes 76, 77 and 78 is Burnell and Valenta's[96]

alkylation-aldol sequence shown in Scheme 79. Alkylation of norbornanone with iodide **79.2**, by the enamine method, occurs stereoselectively, to give aldehyde **79.3**. Conversion of the vinyl chloride moiety to a ketone, and aldol condensation then generates the spiro compound **79.5**.

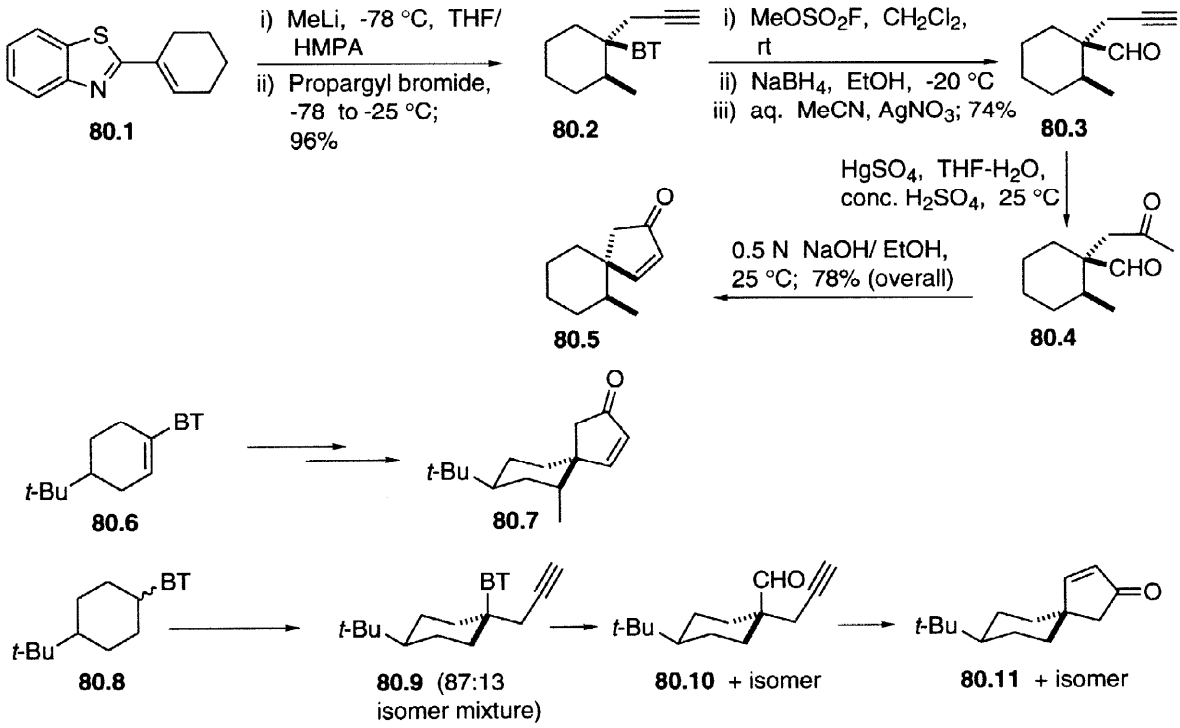
Scheme 79



5k Use of benzothiazoles: conjugate addition and intramolecular aldol condensation

Corey and Boger[97] used a 2-benzothiazole (BT) derivative of cyclohexene to construct a variety of spiro [4.5] and [4.6] rings in a stereocontrolled manner. The versatility of this approach is shown in the examples of Scheme 80. Addition of methyllithium to **80.1**, followed by treatment with propargyl bromide, produced **80.2**, which was converted into aldehyde **80.3**, using standard conditions for modifying the heterocycle. Hydration of the triple bond, catalyzed by Hg(II), gave **80.4**, and this underwent intramolecular aldol condensation to provide spiroenone **80.5**, with two asymmetric centers whose relative stereochemistry was set during the initial alkylation (**80.1** → **80.2**). In a similar fashion, **80.6** was converted into **80.7**.

Scheme 80



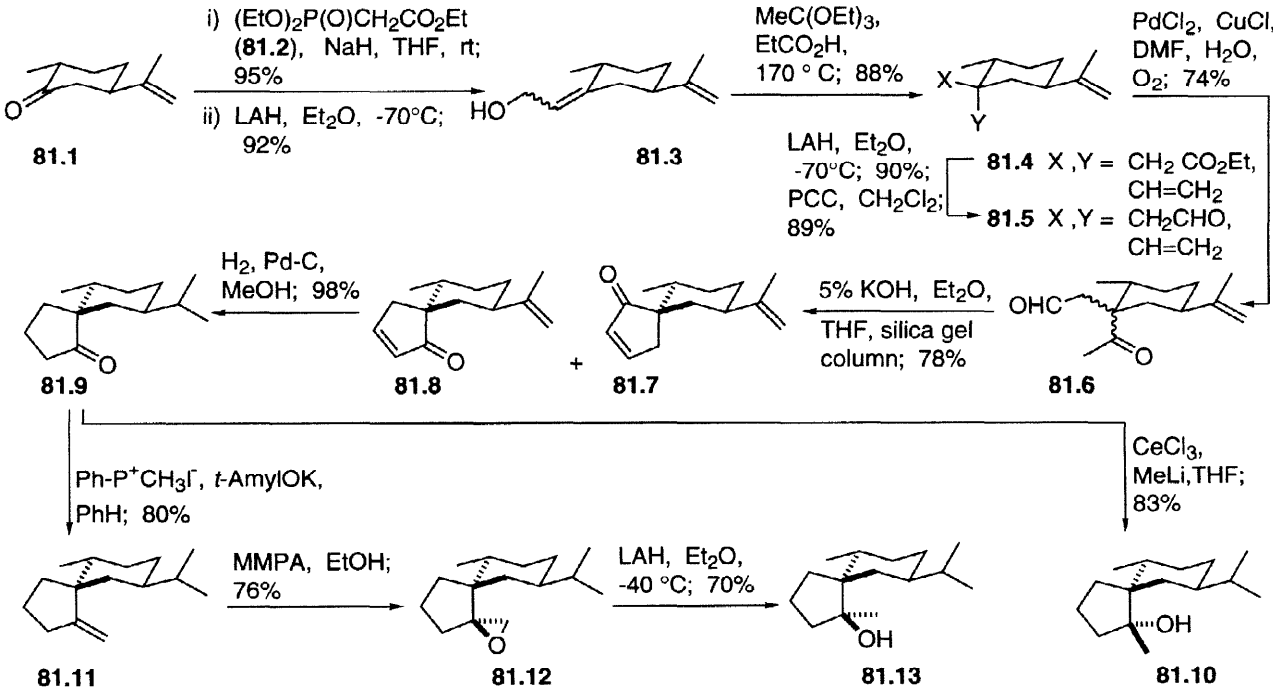
When compound **80.8** was treated first with butyllithium, followed by propargyl bromide, an 87:13 mixture of benzothiazoles **80.9** was obtained. Without separation here, or in the following stages, the material was converted into **80.10** by modification of the BT group, and intramolecular aldol condensation then gave **80.11**.

5l *Claisen rearrangement and aldol condensation*

In an enantiospecific synthesis of (+)-dihydroerythrodiene (**81.11**), (+)-dihydrospirojatamol (**81.13**), and (+)-dihydroepispirojatamol (**81.10**) by Srikrishna *et al.*[98] the crucial spirocenter was constructed by Claisen rearrangement. *Trans*-dihydrocarvone (**81.1**), obtained from (*R*)-carvone, gave the allyl alcohols **81.3** by reaction with triethyl phosphonoacetate, followed by hydride reduction. Treatment of **81.3** with triethyl orthoacetate in the presence of a catalytic amount of acid at high temperature produced an inseparable diastereomeric mixture (*ca* 3.5:1) of the diene esters **81.4**. Reduction and PCC oxidation yielded the corresponding aldehydes **81.5**. Wacker oxidation of **81.5** then produced ketoaldehydes **81.6**, which underwent intramolecular aldol condensation to give chromatographically separable spiroenones **81.7** and **81.8** (57:81). Catalytic hydrogenation of the major product (**81.8**) yielded **81.9**, which was then methylenated by Wittig reaction to give (+)-dihydroerythrodiene (**81.11**). Treatment of **81.9** with methyllithium/cerium trichloride gave (+)-dihydroepispirojatamol (**81.10**) in a highly stereoselective manner. Stereoselective epoxidation of **81.11** to **81.12**, followed by reduction, furnished (+)-dihydrospirojatamol (**81.13**). The stereoselectivity of the steps **81.11** → **81.12** and **81.9** → **81.10** is controlled by steric interactions generated by the secondary methyl group attached directly to the cyclohexane ring.

The Claisen rearrangement has also been applied in an analogous manner to carbohydrate-derived ketones.[99]

Scheme 81

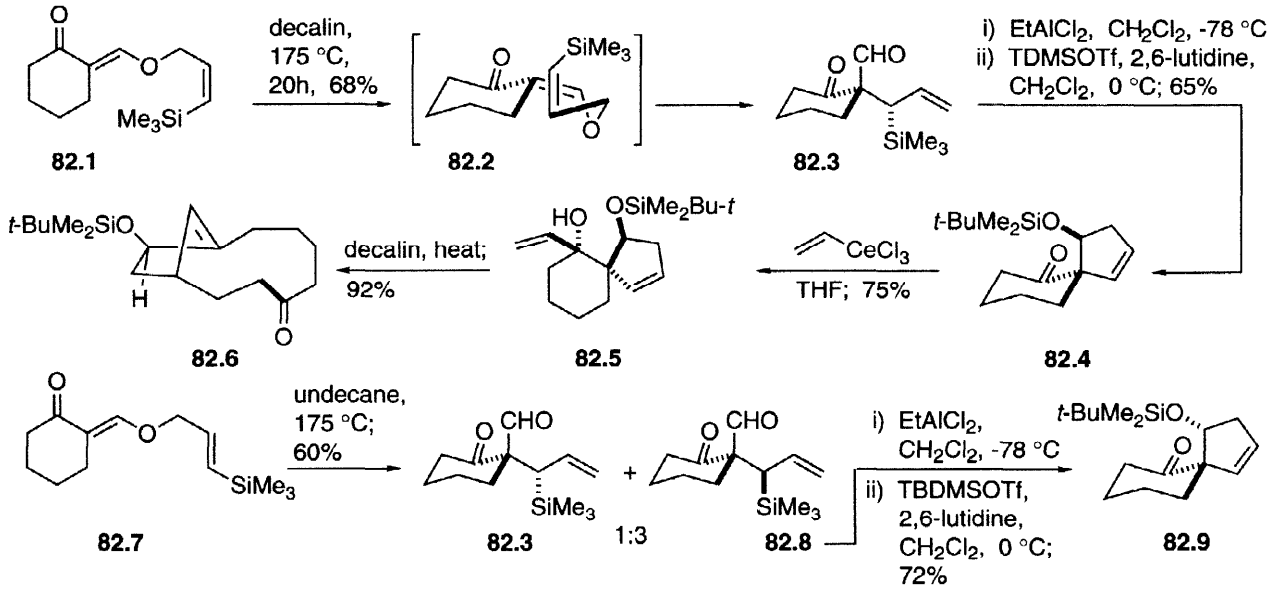


5m *Claisen rearrangement and intramolecular Sakurai-Hosumi reaction*

A number of complex natural products of the 8,9-seco-*ent*-kaurane family are known to possess antitumor activity, and among the synthetic endeavors in this area, approaches have been published that rely on the stereoselective formation of spirocyclic intermediates. For example, Ladouceur and Paquette, in their construction of the A/B subunit of these cytotoxins, used the process summarized in Scheme 82 as the central

theme.[100] When the *Z*-vinyl silane **82.1** was heated in decalin for 20 h, a [3,3]-sigmatropic shift occurred via a chairlike transition state, providing aldehyde **82.3** exclusively. In contrast, the *E*-isomer **82.7**, under similar conditions, gave a 3:1 mixture of aldehydes **82.3** and **82.8**. With the separable aldehydes in hand, Lewis acid catalyzed intramolecular 5-*exo*-trigonal cyclization of **82.3** and **82.8** and silylation provided the protected aldols **82.4** and **82.9**, respectively. Nucleophilic addition of a vinylcerium reagent to the carbonyl of compound **82.4** furnished **82.5** stereoselectively. This material underwent oxy-Cope rearrangement to **82.6**, which represents the core structure of 8,9-seco-*ent*-kauranes.

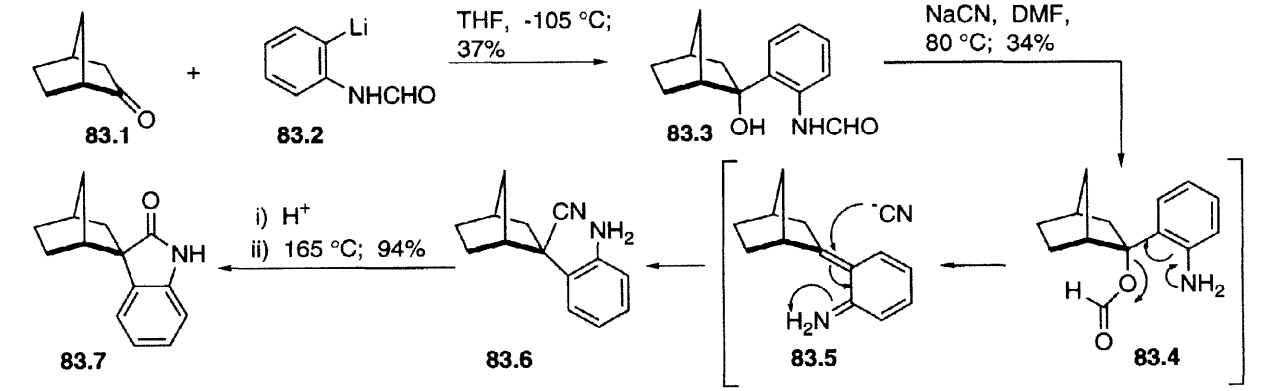
Scheme 82



5n Formation of oxindoles

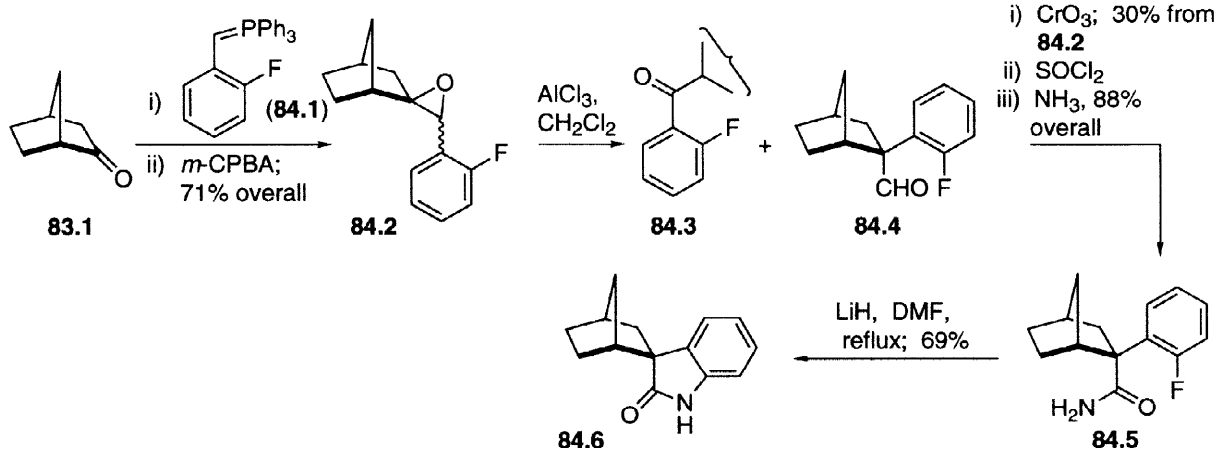
During exploratory studies on approaches to gelsemine, Fleming and coworkers[101] developed a route (Scheme 83) to stereochemically complimentary oxindoles that are fused in a spiro manner to norbornane, which was arbitrarily chosen as a model for part of the [3.2.1] bicyclic substructure of the natural product. In the first route, norbornanone was converted into hydroxy formamide **83.3**. This compound was next treated with cyanide ion, which attacked the norbornyl system from the *exo*-direction, affording nitrile **83.6** exclusively. Hydrolysis then gave oxindole **83.7**. In the second route, the fluorine-containing aldehyde **84.4**

Scheme 83



was first constructed from norbornanone by the procedure shown in Scheme 84. Aldehyde **84.4** was converted into the corresponding amide by standard methods and, when the amide was heated in the presence of potassium hydride, the cyclized product **84.6** was formed by the unusual process of displacement of fluoride from the unactivated benzene ring.

Scheme 84



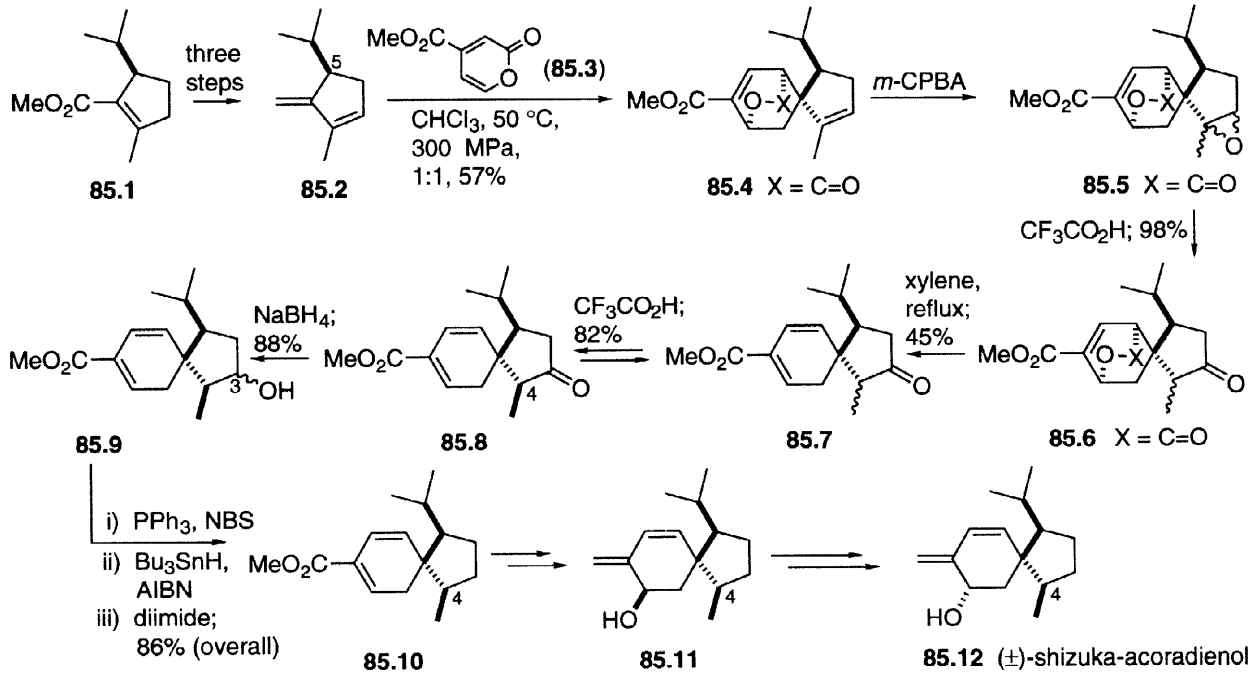
6 Cycloaddition methods

A variety of cycloadditions, such as [4 + 2], [2 + 2], 2 + 1], [3 + 2], as well as ene reactions, have been used to form spiro compounds — either directly or after cleavage of one of the newly-formed bonds.

6a Intermolecular Diels-Alder reaction

The stereo- and regioselectivity of [4 + 2] cycloaddition was effectively used in the synthesis of (±)-shizuka-acoradienol (**85.12**).[102] The relative configuration of two of the adjacent asymmetric centers was set

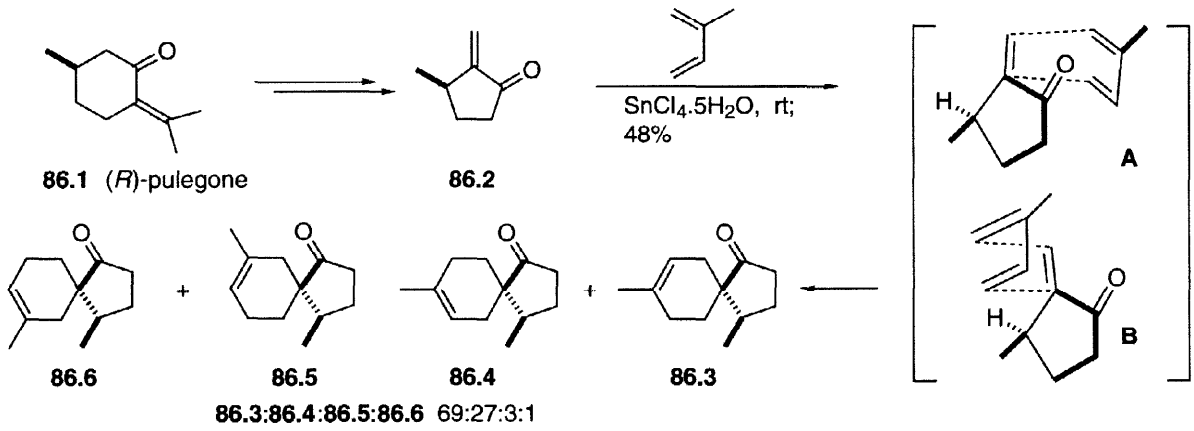
Scheme 85



during the cycloaddition, which was controlled, in turn, by the substituent at C(5) in **85.2** (Scheme 85). High pressure Diels-Alder reaction of **85.2** and **85.3** formed the cycloadduct **85.4**, which was epoxidized on both faces to give **85.5**. Treatment of the epoxides with acid, followed by thermal decarboxylation, produced **85.7**. On equilibration, this compound yielded the spiroketone **85.8** (with the desired relative configuration) as the major (5:1) isomer. Reduction of this mixture of C(4) epimers to the corresponding alcohols, followed by deoxygenation afforded **85.10**, which was separated by HPLC from its minor C(4) epimer. The target (**85.12**) was then easily reached by straightforward modification of **85.10**. During the deoxygenation sequence (**85.9** → **85.10**) some elimination occurred, so as to generate a double bond in the five-membered ring, but this double bond was easily saturated with diimide.

The stereoselectivity of [4 + 2] cycloaddition was also exploited by Marx and Norman[103] to synthesize (-)-acorone and several related spirosesquiterpenes (Schemes 86 and 87). Enone **86.2**, generated from (*R*)-pulegone (**86.1**), underwent Lewis acid catalyzed Diels-Alder reaction with isoprene to give **86.3**, **86.4**, **86.5**, and **86.6** (69:27:3:1). The stereochemistry of the cycloadducts can be rationalized by considering transition states **A** and **B**. Transition state **A** is favored over transition state **B**. Product **86.3**, formed by attack of isoprene from the opposite face to the methyl in **86.2**, meets the stereochemical requirements for γ-acoradiene.

Scheme 86



The other major product (**86.4**), possessing the same relative configuration at the spirocenter as δ-acoradiene, is formed via transition state **B**.

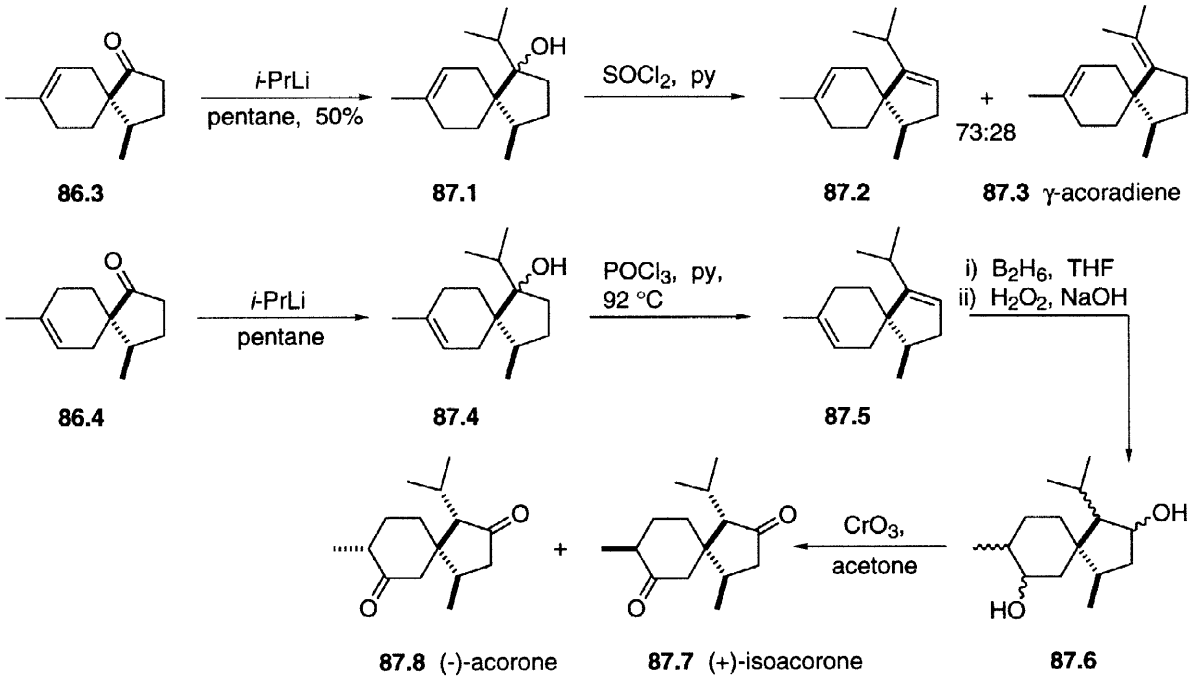
The remaining steps of the synthesis (Scheme 87) involved nucleophilic addition of isopropyllithium, followed by dehydration, to produce **87.2** and γ-acoradiene (**87.3**) from **86.3**, and **87.5** from **86.4**. Hydroboration-oxidation of the endocyclic diene **87.5** gave a 1:1 mixture of isomers (**87.6**), and chromic oxidation then afforded **87.7** and **87.8**. Equilibration (sodium methoxide) of these two ketones gives a 7:3 mixture in which **87.8** predominates. The two ketones were easily separated by chromatography.

Exactly the same principle of Diels-Alder addition to an exocyclic double bond has served to prepare simple spirooxindoles[104] and spiroindanones.[105]

The Diels-Alder reaction has also been used (Scheme 88) to prepare spirolactones **88.5** and **88.6** by reacting the β-isopropyl-α-methylene-β-lactone **88.1** with 1,3-dienes (**88.2**). Good yields and high stereoselectivities were observed.[106] The stereoselectivity is controlled by the isopropyl group in the β-lactone, and the *exo* transition state (**88.4**) is preferred over the *endo* (**88.3**), notwithstanding the absence of secondary orbital effects in **88.4**.

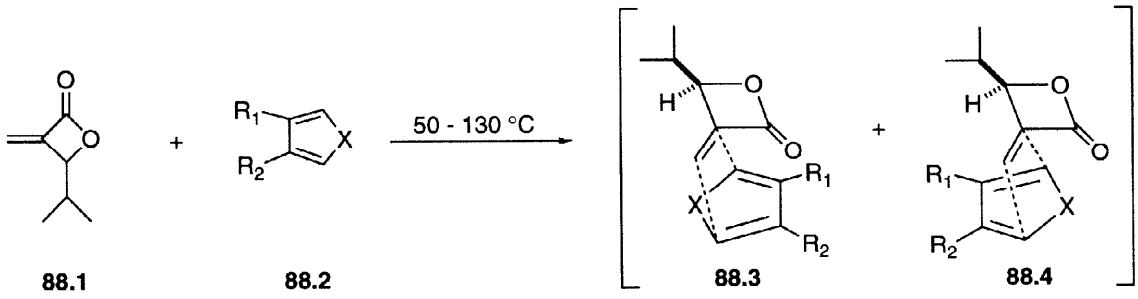
A cycloaddition method to construct racemic and also optically pure spirolactones was developed by Barluenga *et al.*[107] This method (Scheme 89) involves a stereospecific *exo*-selective [4 + 2] reaction between α,β-unsaturated exocyclic chromium carbene complex **89.2** and butadienes **89.1a-g** to give spiro compounds **89.3a-d**. In the case of **89.1e-g**, the products were **89.4-89.6**, respectively, derived from silica gel hydrolysis

Scheme 87

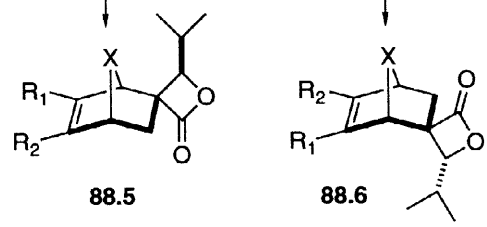


of the initial adducts. Metal-free spirolactones were obtained from **89.3** by treatment with silica gel (for enamine hydrolysis), followed by oxygen, in the presence of light (to replace the chromium unit by oxygen).

Scheme 88

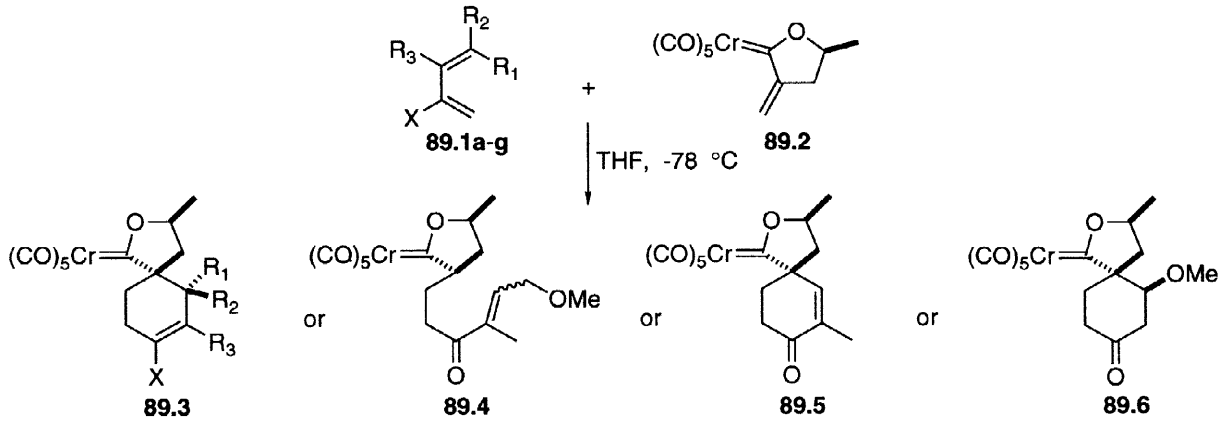


88.2	88.6 / 88.5	%
butadiene	-	54
isoprene	-	52
cyclopentadiene	-	94
furan	71:29	52
1,3-cyclohexadiene	70:30	73
anthracene	80:20	66



The low stereoselectivity observed for **89.5** and **89.6** (see Scheme 89), along with the fact that the open chain compound **89.4** was formed, suggests a stepwise mechanism involving zwitterionic intermediates.

Scheme 89



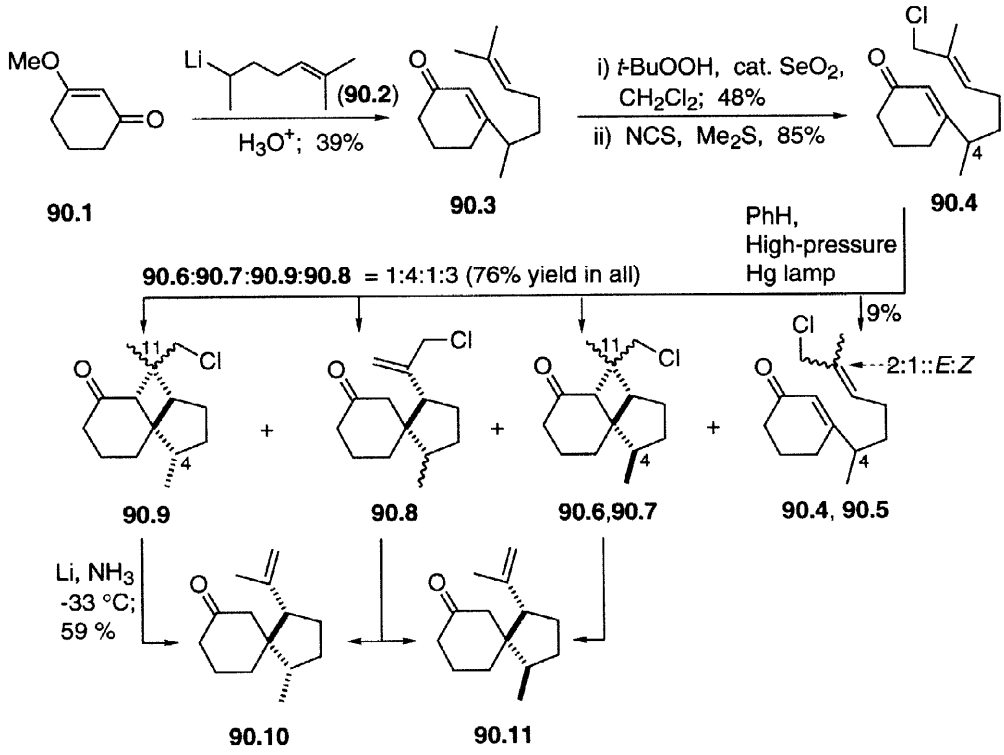
	R_1	R_2	R_3	X	% yield	product	de
a)	H	CH_2OCH_3	CH_3	1-morpholino	80	**89.3**	>97:3
b)	H		CH_2-$(CH_2)_2$-CH_2	1-morpholino	82	**89.3**	>97:3
c)	H	H	CH_3	1-morpholino	91	**89.3**	>97:3
d)	H	$CH_2OTBDMS$	CH_3	1-morpholino	85	**89.3**	>97:3
e)	CH_2OCH_3	H	CH_3	1-morpholino	30	**89.4**	2:1
f)	H	1-morpholino	CH_3	1-morpholino	54	**89.5**	3:1
g)	H	OCH_3	H	$OSiMe_3$	37	**89.6**	7.5:1

When enantiomerically pure **89.2** was reacted with **89.1a-d**, optically pure **89.3a-d** were obtained.

6b Intermolecular [2 + 2] cycloaddition

[2 + 2] Cycloaddition, followed by cleavage of a perimeter bond of the resulting cyclobutane, has

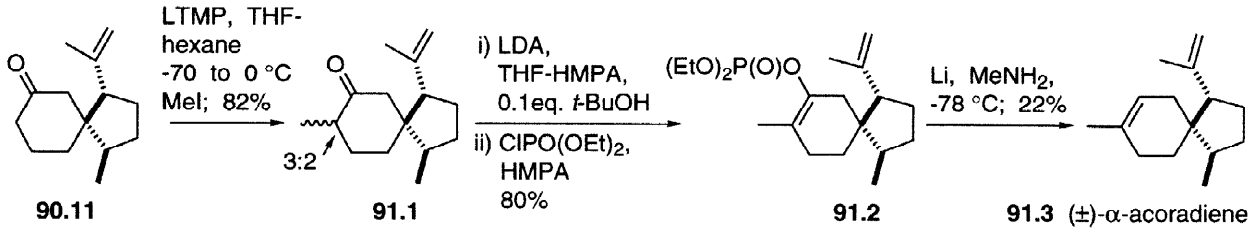
Scheme 90



provided a synthetic route to several members of the acorane family.

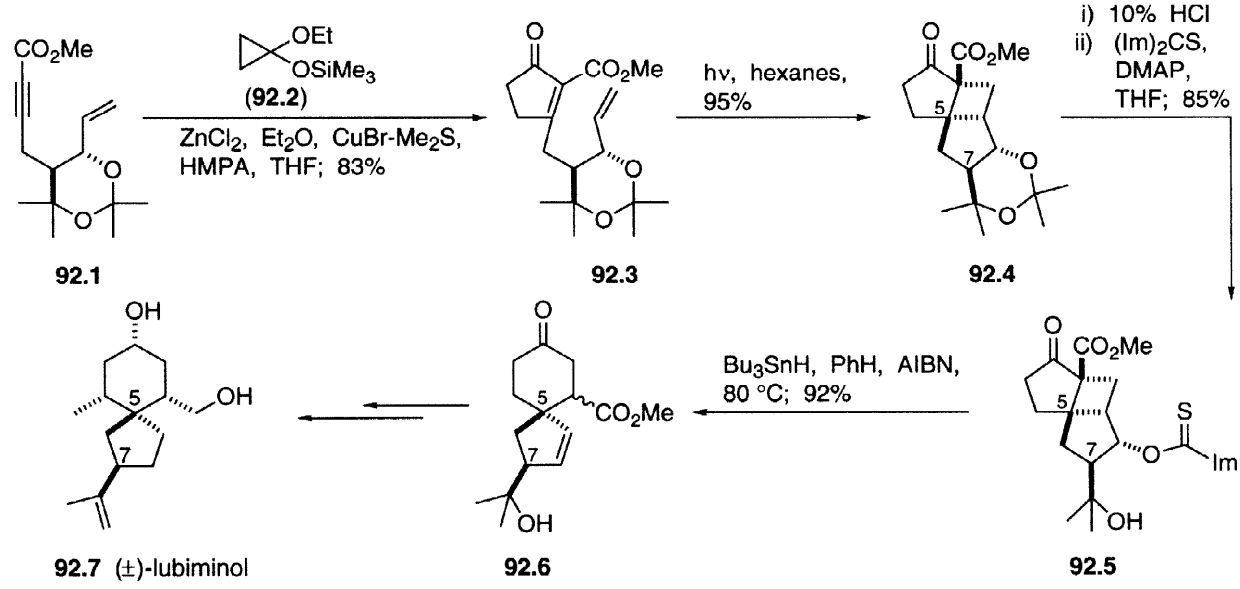
In a stereoselective synthesis of (±)-α-acoradiene (Schemes 90 and 91) carried out by the Oppolzer group,[108] the starting material for the key photoaddition step was prepared from enone **90.1**, which was first treated with the organolithium **90.2**. Acid hydrolysis of the intermediate then gave **90.3**, as expected. Allylic oxidation with selenium dioxide, and treatment of the resulting alcohol with *N*-chlorosuccinimide-dimethyl sulfide, gave the *E*-allyl chloride **90.4**. Irradiation of **90.4** with a high-pressure mercury lamp produced a 2:1 mixture of **90.4** and **90.5**, together with a 1:4:1:3 mixture of **90.6-90.9**. Lithium/ammonia reduction of this last mixture afforded the separable spiro compounds **90.10** and **90.11** in a 3:10 ratio. The stereochemistry of the eventual spirocenter is controlled during the photolysis by the substituent at C(4) (see **90.4**). Alkylation of **90.11**, which was the major product of the dissolving metal reduction, gave **91.1** (Scheme 91). This was deoxygenated via its enol phosphate (**91.2**), to (±)-α-acoradiene (**91.3**).

Scheme 91



Four-membered rings can also be opened by stannane-mediated radical chemistry, and in this case the stereochemical outcome is again set by the method of generating the four-membered ring. For example, in the synthesis by Crimmins *et al.*[109] of the phytoalexin (±)-lubiminol (**92.7**) (Scheme 92), the key steps involved formation of **92.3** via conjugate addition-cyclization of **92.1** and **92.2**, followed by irradiation. The photochemical step proceeded diastereoselectively to give cycloadduct **92.4** exclusively, thereby establishing the C(5)-C(7) relative stereochemistry of the final product (**92.7**). Hydrolysis of the photoadduct (**92.4**), and subsequent derivatization with 1,1'-thiocarbonyldiimidazole, provided **92.5**, and the stage was now set for

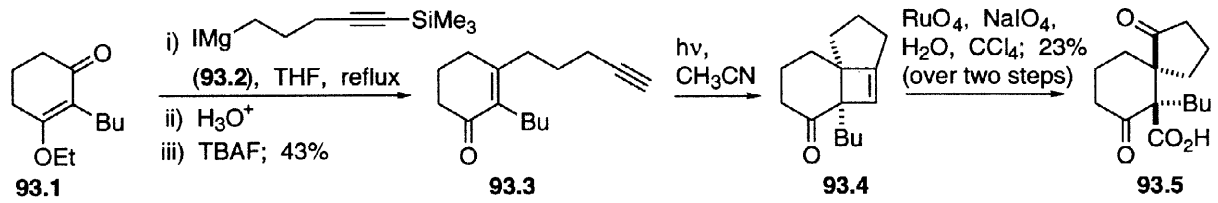
Scheme 92



radical fragmentation-radical ring expansion, leading to **92.6**. This compound contains the spiro [4.5] skeleton of the natural product **92.7**, which was easily reached by standard operations.[109]

In model studies for the synthesis of perhydrohistrionicotoxin (Scheme 93), Koft and Smith[110] developed a route to a spiroketone that involves intramolecular [2 + 2] photoaddition. In this approach the key starting material (**93.3**) was constructed by treating enone **93.1** with Grignard reagent **93.2**, followed by

Scheme 93

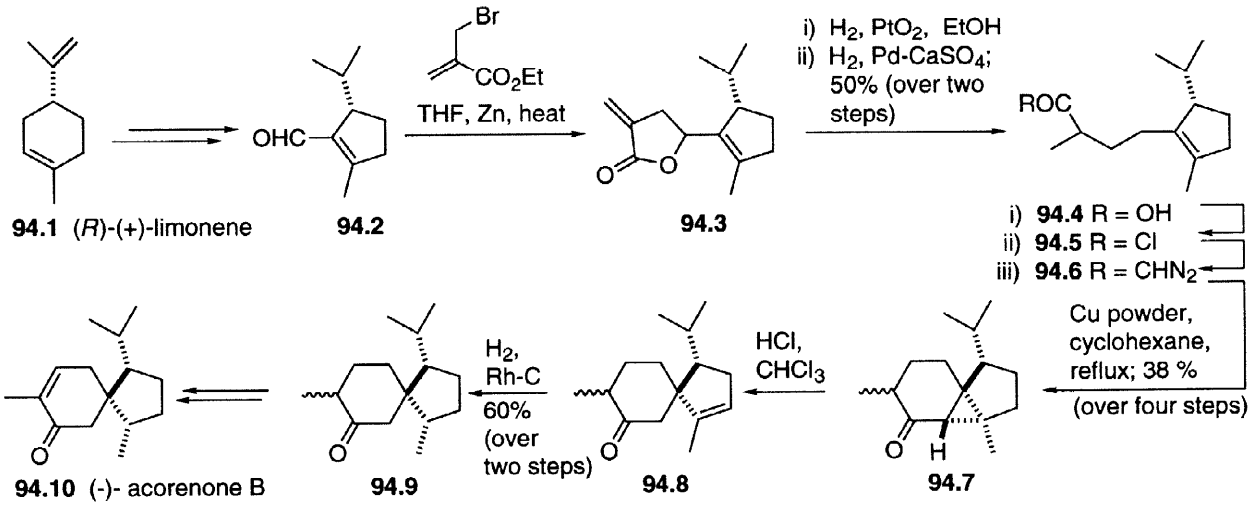


hydrolysis and removal of the silyl group. Irradiation of **93.3** furnished **93.4**, and the desired spiroketone **93.5** was then liberated by oxidative cleavage of the cycloadduct. In principle, decarboxylation and Beckmann rearrangement of **93.5** should have led to an intermediate in a previously published route to perhydrohistrionicotoxin but, in the event, these simple steps could not be achieved in a satisfactory manner. Nonetheless, the approach seems useful for stereoselective construction of functionalized spiro[4.5]decanones.

6c Intermolecular [2 + 1] cycloaddition (cyclopropanation)

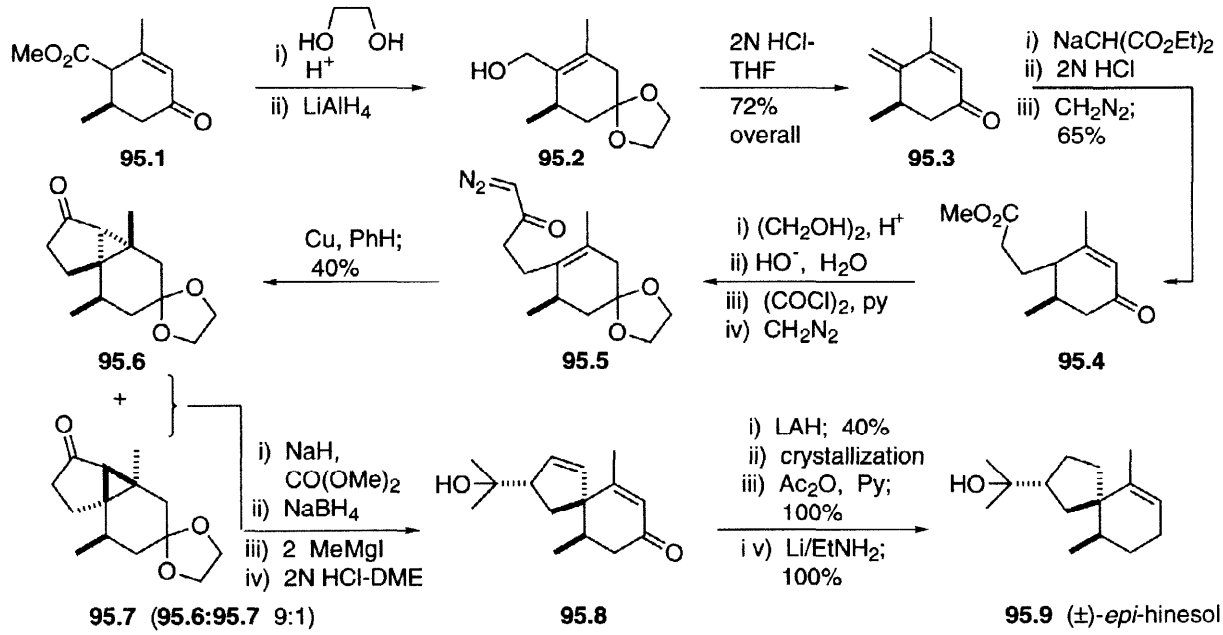
In a route (Scheme 94) to (-)-acorenone B, based on cyclopropanation, White *et al.* converted[111] optically pure (*R*)-(+)-limonene (**94.1**) into aldehyde **94.2**, which underwent a Reformatsky reaction leading to the α-methylenelactone **94.3**. Selective reduction and hydrogenolysis afforded carboxylic acid **94.4**. This was then converted into diazo ketone **94.6** via the acid chloride **94.5**. Decomposition of **94.6** produced a carbenoid which attacked the cyclic olefin intramolecularly from the face opposite the isopropyl group. In this way **94.7** was produced stereoselectively. Cleavage of the tricyclic intermediate under acidic conditions gave **94.8**, and reduction then introduced the third asymmetric center, to afford **94.9**. Finally, the ketone was desaturated by bromination and elimination to (-)-acorenone B (**94.10**).

Scheme 94



Another example which uses [2 + 1] cycloaddition to set the stereochemistry of the spirocenter is found in the synthesis of (±)-*epi*-hinesol (**95.9**) reported by Deslongchamps *et al.*[112] (Scheme 95). Protection of racemic ester **95.1** as a ketal, followed by reduction, gave **95.2**, which, on deketalization, afforded dienone **95.3**. Michael addition of diethyl malonate, acid catalyzed hydrolysis, and decarboxylation then gave **95.4**, which was converted by standard methods into diazo ketone **95.5**. Decomposition of **95.5** by treatment with copper powder gave a 1:9 mixture of cyclopropyl ketones **95.7** and **95.6**. This mixture was then converted into spiroketone **95.8** by the straightforward sequence shown in the Scheme. Reduction of **95.8**, purification by crystallization, followed by acetylation, hydrogenolysis of the resulting allylic acetate, and lithium/ammonia reduction, completed the synthesis of (±)-*epi*-hinesol (**95.9**).

Scheme 95



6d [3 + 2] Cycloaddition

The spirobicyclic sesquiterpenes (±)-spirojatamol (**96.8**) and (±)-erythrodiene (**96.6**) have been synthesized by [3 + 2] cycloaddition methodology.

Tokunaga *et al.*[20a] used intramolecular 1,3-dipolar cycloaddition of nitrone **96.1** (Scheme 96) to construct the key intermediate (**96.2**). When nitrone **96.1**, easily prepared from 4-isopropylcyclohex-2-enone, was heated for 22 h at 180 °C in toluene, the two products **96.2** and **96.3** were produced (in a ratio of 3:2). Although the level of stereoselectivity is poor, the required product (**96.2**) was easily separated. Hydrogenolysis of **96.2**, and oxidation with *m*-CPBA, afforded nitro alcohol **96.4**, and further oxidation with tetrapropylammonium perrruthenate furnished the spirodiketone **96.5**. When the diketone was subjected to the methylenation procedure of Nozaki and Lombardo,[20b,c] (±)-erythrodiene (**96.6**) was obtained.

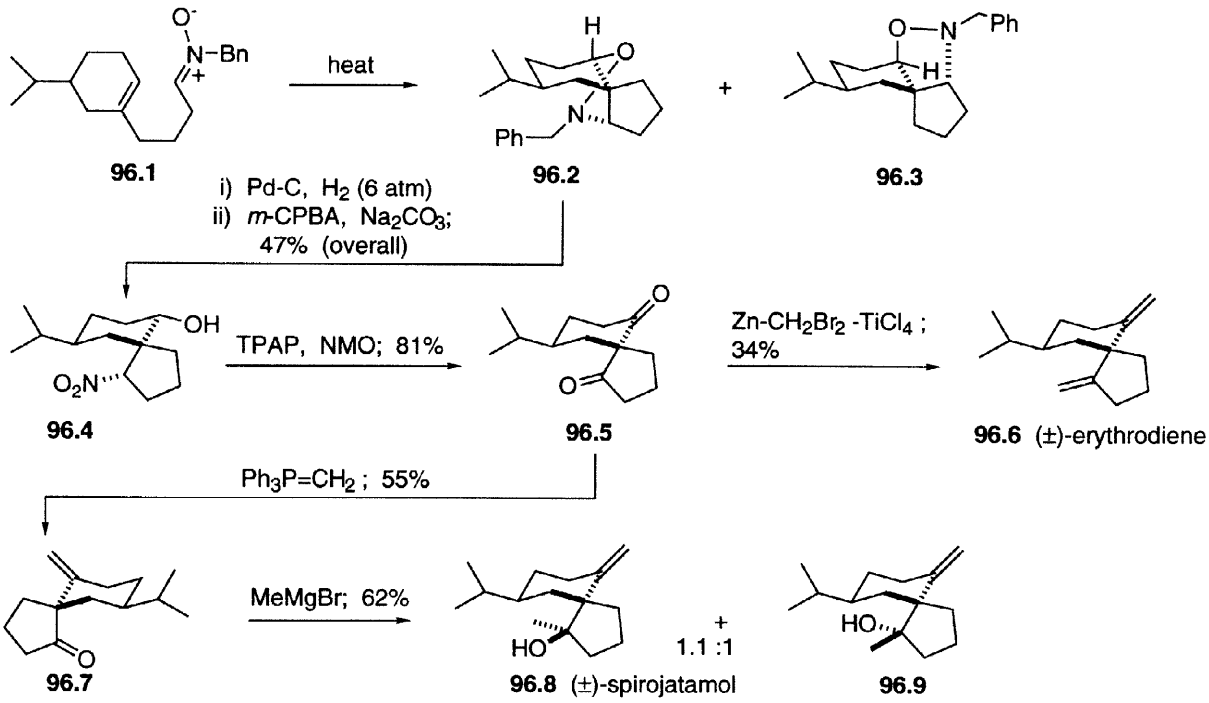
The spirodiketone **96.5** could also be elaborated into (±)-spirojatamol (**96.8**), as shown in the Scheme. Wittig reaction converted **96.5** into the olefinic ketone **96.7**, and this, with methylmagnesium bromide, gave a mixture of diastereomeric tertiary alcohols, of which the major isomer was (±)-spirojatamol (**96.8**).

Knolker *et al.*[113] used Lewis acid promoted [3 + 2] cycloaddition of hindered allyl silanes, such as **97.1**, with 2-alkylidenecycloalkanones of various ring sizes (**97.2**) to synthesize spirocyclopentanes (**97.3**)

diastereoselectively (Scheme 97).

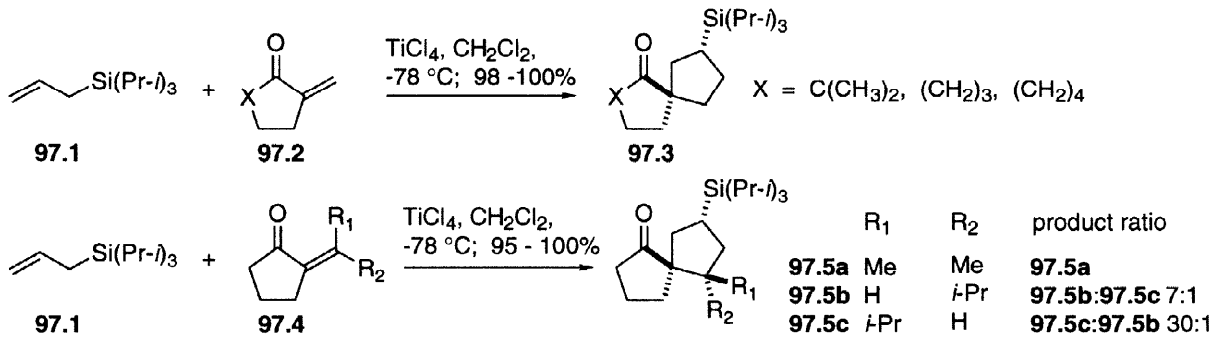
In order to introduce an additional asymmetric center, this method was extended to disubstituted *exo*-

Scheme 96



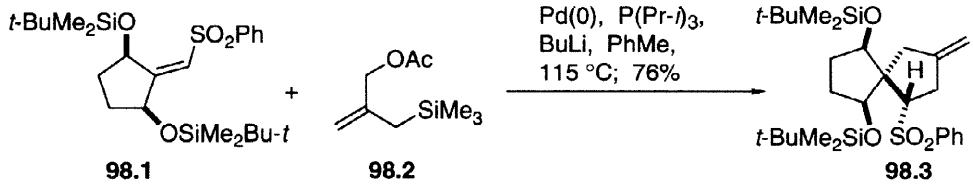
methylene compounds (**97.4**). The spirocycles **97.5a-c** were formed with the same relative stereochemistry as before [carbonyl *anti* to the Si(Pr-*i*)$_3$]. The low stereoselectivity observed in the formation of **97.5b** is probably due to steric congestion produced by the presence of both the silyl and isopropyl groups on the same face of the cyclopentane ring.

Scheme 97



Trost *et al.*[114] developed a [3 + 2] cycloaddition route (Scheme 98) to compounds related to the synthetically challenging core spirocyclic ring of the ginkgolides. Palladium-catalyzed cycloaddition of the sterically congested sulfone **98.1** to the substituted propene **98.2** proceeded diastereoselectively to give **98.3** in 76% yield. The excellent stereoselectivity observed in this reaction is attributed to steric factors, as the corresponding reaction in which one of the silyloxy groups of **98.1** was replaced by an hydroxyl gave a 4.2:1 mixture of diastereomers.

Scheme 98



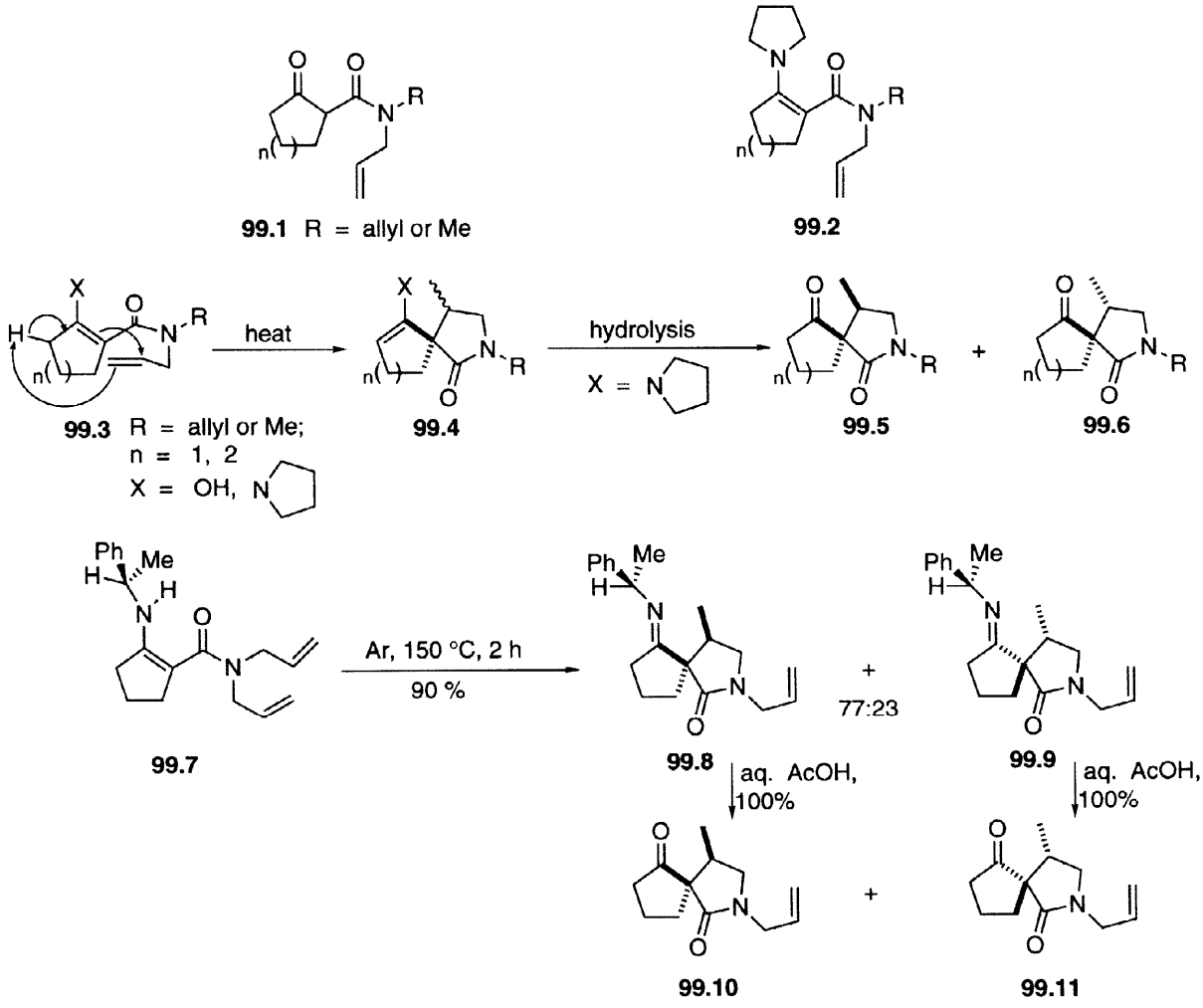
98.1 **98.2** **98.3**

6e Ene reaction

Thermal rearrangement (Scheme 99) of a variety of β-ketoamides (**99.1**) and β-enaminoamides (**99.2**) has been studied in Cossy's group as a route to spirolactams.[115,116] The thermal rearrangement proceeds via a carba-ene mechanism (see **99.3**) to give spirolactams **99.4**. Hydrolysis of the enamine function in **99.4** (X = pyrrolidino unit) or formation of the ketone from the enols **99.4** (X = OH), furnished a mixture of **99.5** and **99.6**. In general, the product **99.5** is favored over **99.6** (*ca* 85-93:15-7). Similar carba-ene reactions occur when a propargyl instead of an allyl pendant is used.

With a chiral enamine (**99.7**), a 77:23 mixture of readily separable diastereomers **99.8** and **99.9** was produced. Hydrolysis of **99.8** and of **99.9** proceeded quantitatively to give the enantiomeric spirodiketones **99.10** and **99.11**, respectively.

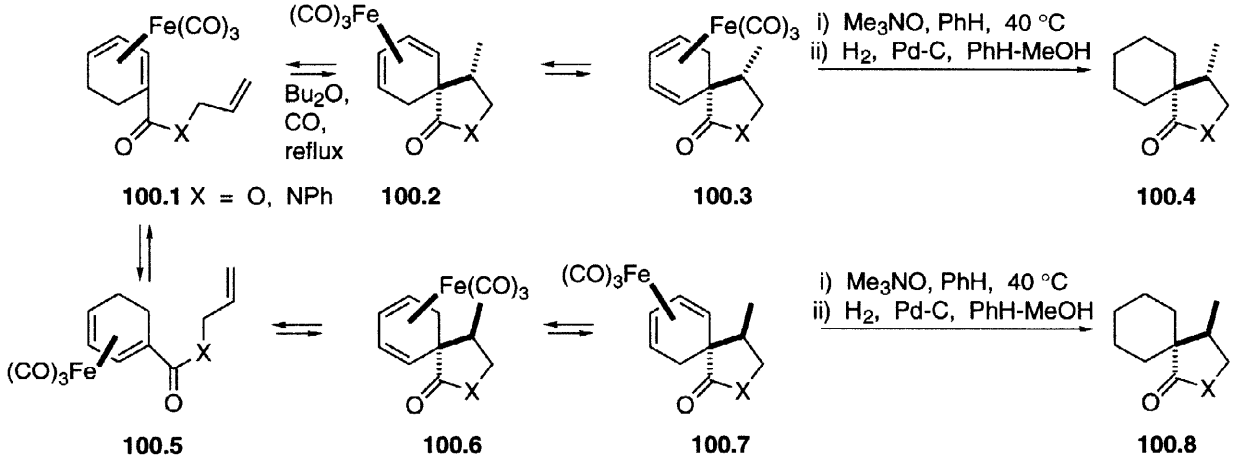
Scheme 99



The above method constitutes an effective means of forming spiro [4.5] and [4.4] compounds with reasonable stereocontrol over the two newly created asymmetric centers.

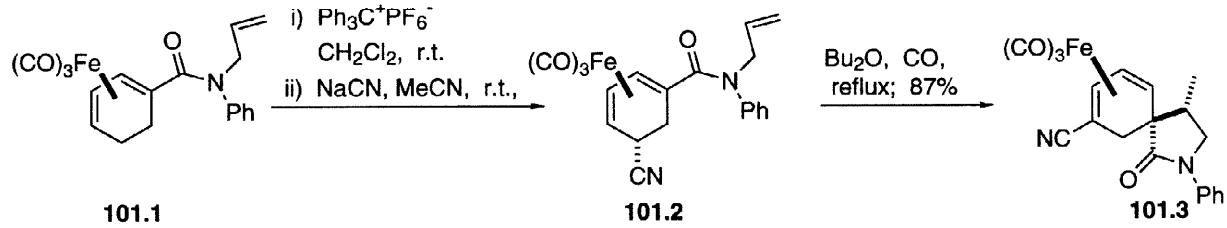
In a formally related reaction (Scheme 100), iron-complexed allyl amides or esters **100.1** were found by Pearson *et al.*[117] to undergo thermally induced spirocyclization. The cyclization is stereospecific, but the products (**100.3** and **100.7**) and the starting materials undergo competing rearrangement of the complexed

Scheme 100



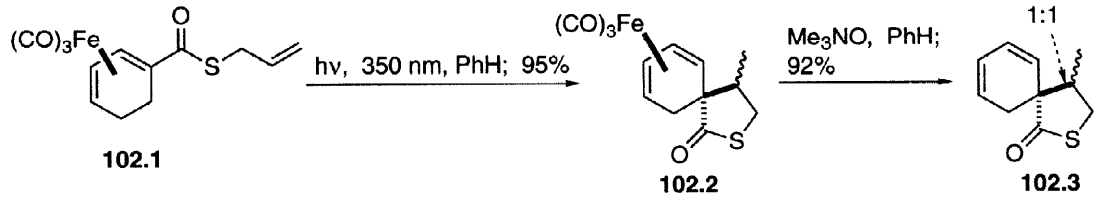
diene unit (see equilibria in Scheme 100). When the substituent at C(5) of the diene was electron-withdrawing (CN) (see **101.2** in Scheme 101), however, these competing processes were suppressed, and reaction proceeded as shown, to afford enantiomerically pure product, starting from optically pure amide **101.1**.[117]

Scheme 101



Due to the inherent difficulties in reducing or opening lactam rings — a process that would be required in order to use the above optically pure materials in natural product synthesis — the possibility of making the corresponding thiol lactones (**102.1** → **102.3**) was also examined[118] but, unfortunately, yields were poor, except for the allyl thioester shown in Scheme 102.

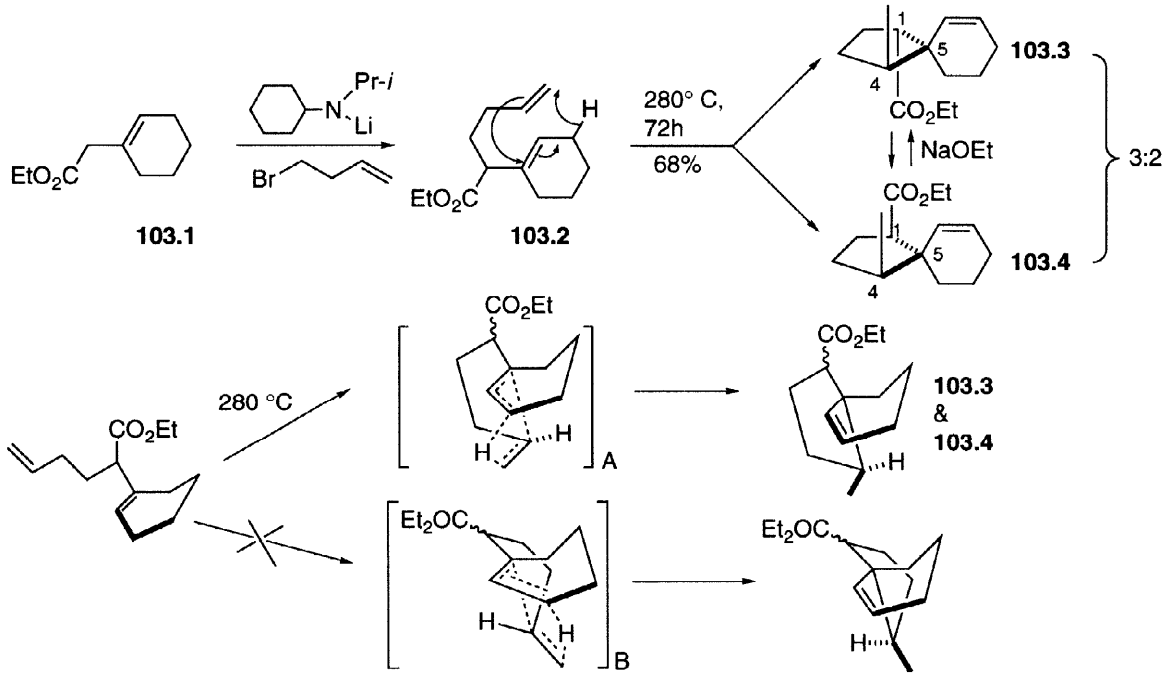
Scheme 102



Several members of the acorane family of sesquiterpenes have been constructed by intramolecular thermal ene reaction with excellent stereocontrol. In an example of such work (Schemes 103 and 104),

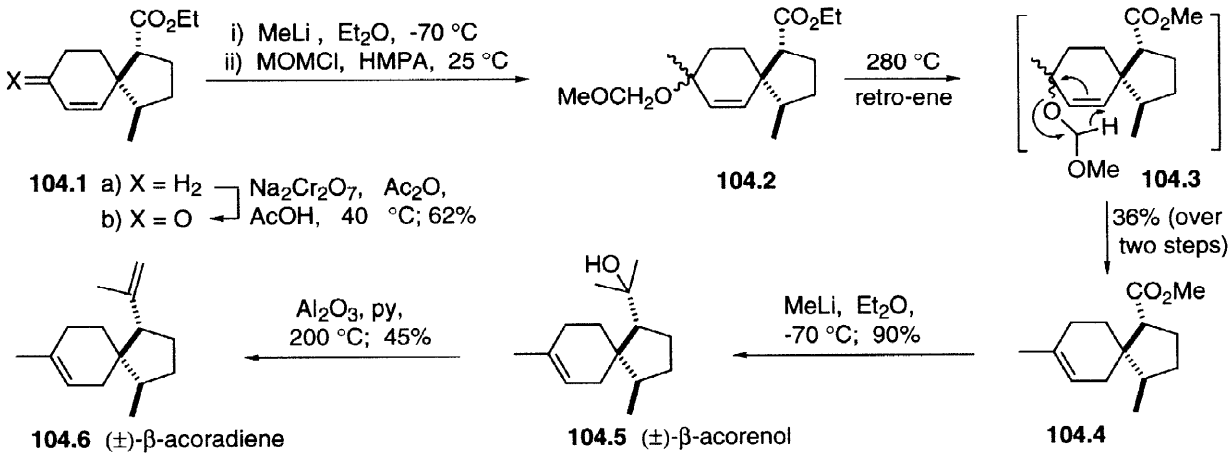
Oppolzer *et al.*[119] alkylated **103.1** to produce **103.2**, which was the substrate for the ene reaction. Thermally induced ring closure of **103.2** proceeded by way of the more favored transition state **A**, giving rise to esters **103.3** and **103.4**. These possess the same relative configuration at C(4) and C(5).

Scheme 103



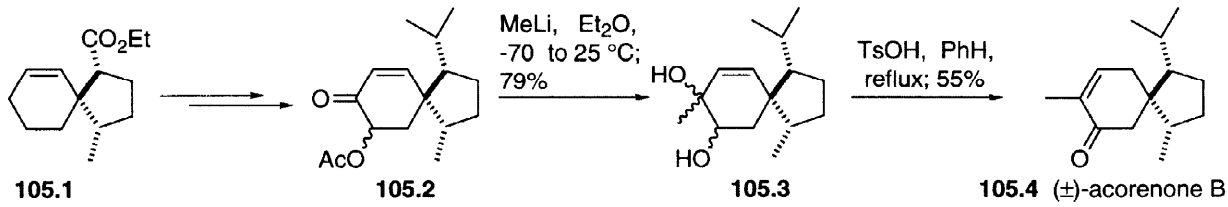
Allylic oxidation (Scheme 104) of the *trans* isomer **104.1** (≡**103.3**) (it is convenient to show a different enantiomer from that in the previous Scheme), followed by selective reaction with methyllithium, gave a mixture of alcohols, which were protected as their MOM ethers (**104.2**). These underwent retro-ene reaction on heating (**104.2** → **104.4**). Further treatment with methyllithium furnished (±)-β-acorenol (**104.5**) and, on subsequent dehydration, (±)-acoradiene (**104.6**).

Scheme 104



The intermediate **103.4** (see Scheme 103) was also elaborated (Scheme 105) into (±)-acorenone B. For this purpose, **105.1** (≡**103.4**) (it is convenient to show a different enantiomer from that in Scheme 103) was

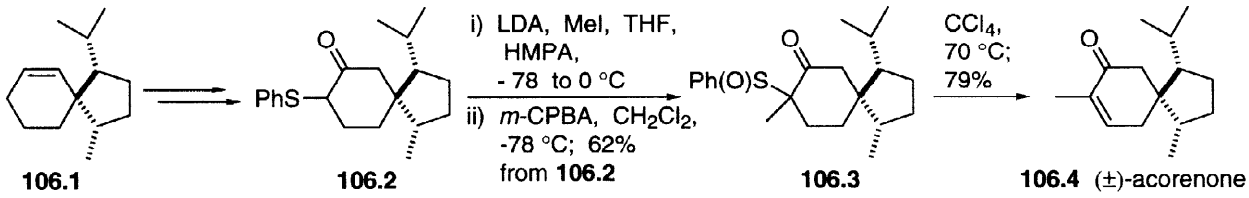
Scheme 105



converted in several steps into the acetoxy ketone **105.2**. Addition of methyllithium (**105.2** → **105.3**) and, finally, treatment with acid, gave (±)-acorenone B (**105.4**).

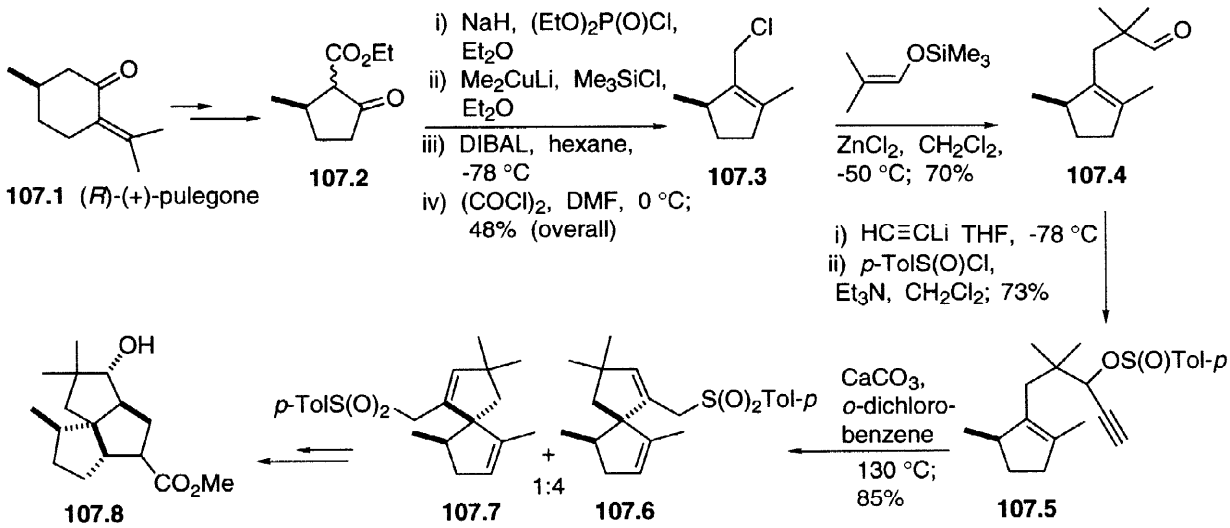
Compound **106.1** (see Scheme 106), an intermediate in the above route to **105.4**, was converted into ketosulfide **106.2**. The methyl group and the enone function of (±)-acorenone were then introduced by alkylation, and sulfoxide elimination, as shown in Scheme 106.

Scheme 106



Recently, the intramolecular Alder-ene reaction was used by Bintz-Giudecelli *et al.*[120] in a synthesis of the pentalenic acid derivative **107.8** (Scheme 107). Ketoester **107.2**, obtained from (*R*)-(+)-pulegone, was converted into chloride **107.3**. Treatment with the trimethylsilyl enol ether of isobutyraldehyde in the presence

Scheme 107



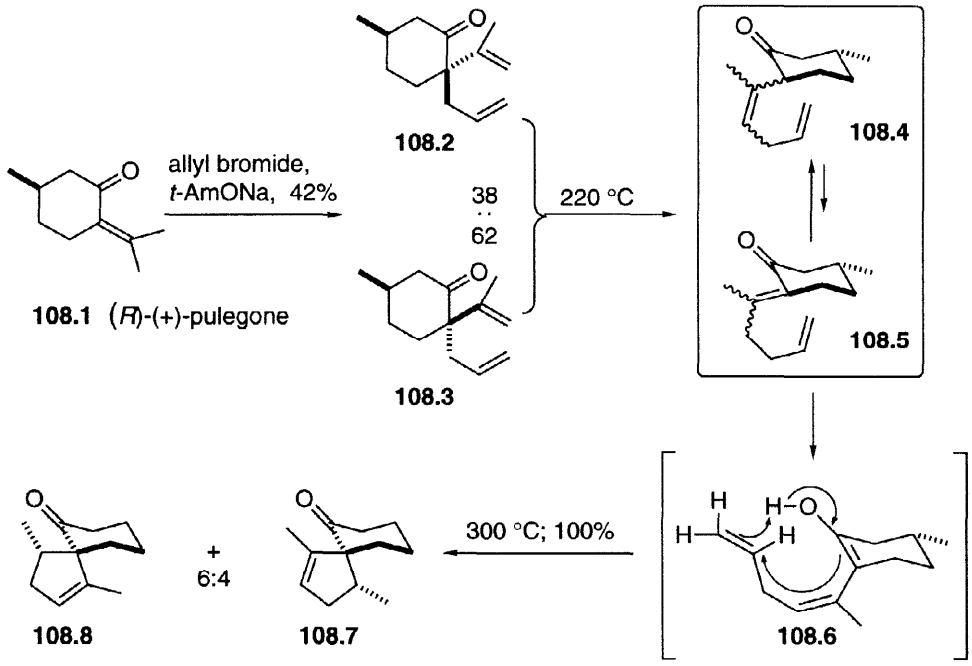
of zinc chloride gave aldehyde **107.4**, which was condensed with lithium acetylide. The resulting alcohol was protected as the sulfinate ester **107.5**, and heating in *o*-dichlorobenzene then afforded spiro compound **107.6** as the major product (**107.6**:**107.7** = 4:1). From **107.6** the pentalenic acid precursor **107.8** was obtained by a series of standard reactions.

6f Conia-type cyclization

Thermal cyclization of enolizable ketones has been studied extensively by Conia;[121] such processes can be used for the preparation of spiro compounds (Scheme 108), although the level of stereocontrol is low.

Pulegone was allylated to obtain diastereomers **108.2** and **108.3** (38:62) which, on thermolysis, provided a mixture of **108.4** and **108.5**. Further heating led to a Conia-type cyclization via **108.6** to yield a 3:2 separable mixture of **108.8** and **108.7**.

Scheme 108



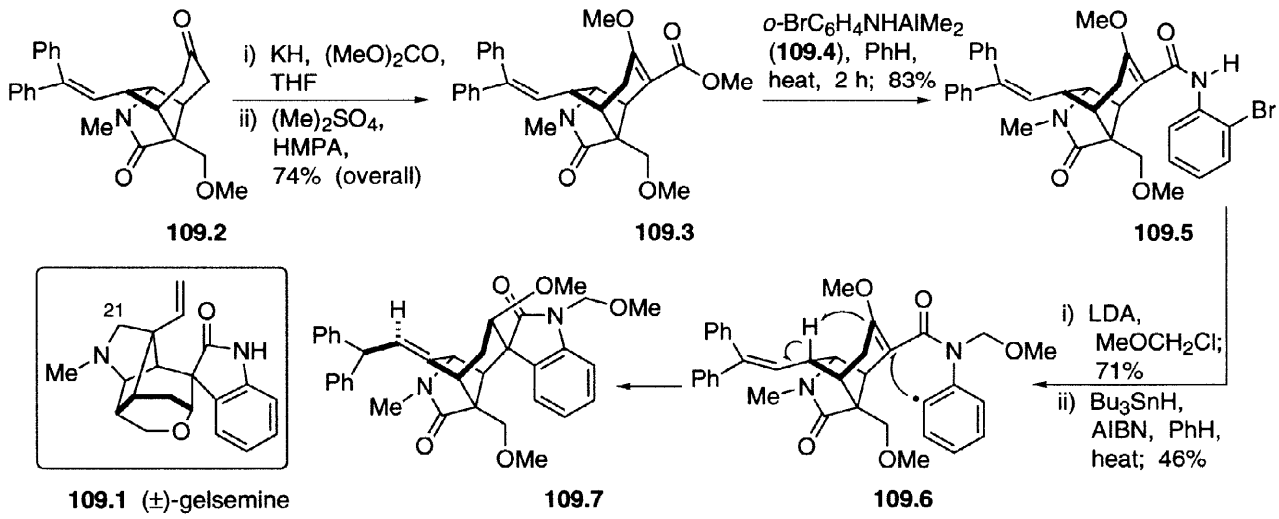
7 Radical cyclization methods

The technique of radical cyclization has been applied in the stereocontrolled generation of spirocenters, although not as extensively as the methods discussed above. The most widely used procedure is based on stannane chemistry, but more recently, cyclization techniques, in which the initial radical is generated oxidatively, have been used.

7a Radical spirocyclization

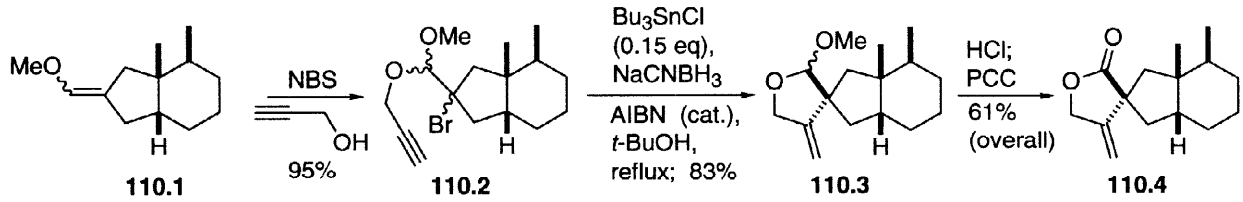
An example of stannane-mediated radical ring closure is found in Hart's[122] synthesis of the oxindole portion of the alkaloid gelsemine (**109.1**, Scheme 109). Acylation and methylation of ketone **109.2** served to convert the material into ester **109.3**, and this, on treatment with the dimethylaluminum amide (**109.4**) derived from *o*-bromoaniline, was converted into the bromophenyl amide **109.5**. Treatment with tributyltin hydride and AIBN under standard conditions then induced stereoselective 5-*exo*-trigonal radical cyclization so as to furnish oxindole **109.7**. The asymmetry of the spirocenter is controlled by the fact that approach of the radical to the double bond is facially selective. Compound **109.7** is a key intermediate in the synthesis of the oxindole segment of gelsemine, and a closely related sequence was subsequently used to make (±)-21-oxogelsemine, which had previously been converted into gelsemine in a single step.[122b]

Scheme 109



In work on the synthesis of bakkenolides, Srikrishna and his colleagues also used[123] 5-*exo*-trigonal radical cyclization (Scheme 110) to produce the spirolactone unit. Bromoacetals **110.2** underwent highly

Scheme 110

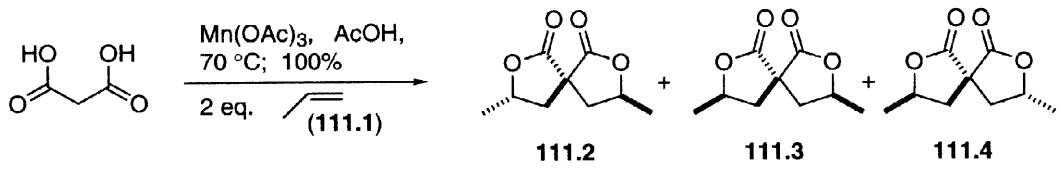


stereoselective radical cyclization to produce spiroacetals **110.3**, which were easily converted into (±)-bakkenolide A (**110.4**), a substance isolated from the buds of *Petasites japonicus*. Related experiments with similar substrates showed that this method for spirocyclization does not always proceed with high stereoselectivity.[123b,c]

Another technique of radical chemistry for making spiro compounds is based on an oxidative process, mediated by Mn(III).[124] This method involves oxidation of enolized β-dicarbonyl compounds, and has been used to form products with high regioselectivity, but usually modest stereoselectivity.

An early example is found in Firstad and Herschberger's approach[124] to spirolactones (Scheme 111). When manganese(III) acetate, an alkene, such as **111.1**, and malonic acid (0.67:2:1 mol respectively) were heated to 70 °C in glacial acetic acid, a mixture of diastereomeric spirodilactones **111.2**-**111.4** was produced.[124] Best yields were obtained for unhindered terminal alkenes, followed by 1,1-disubstituted

Scheme 111

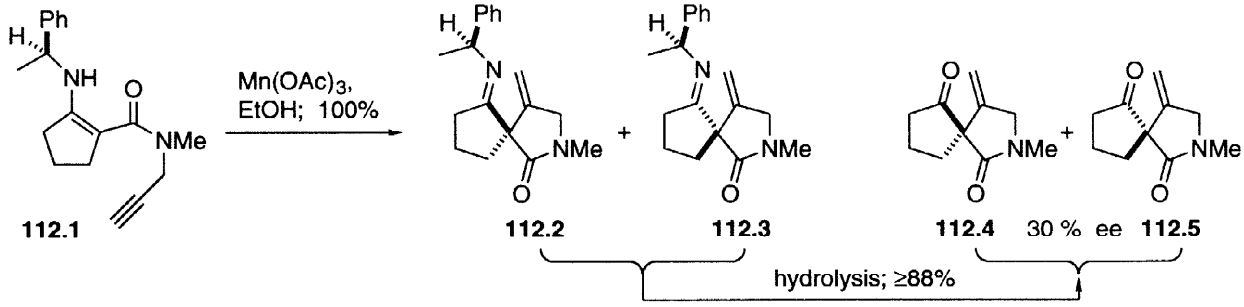


alkenes. Of the possible stereoisomers, the so-called unsymmetrical (**111.3**) was the major product, followed by the symmetrical *anti* isomer (**111.4**). This reaction was studied independently, in slightly earlier work by

Kurosawa *et al.*[125]

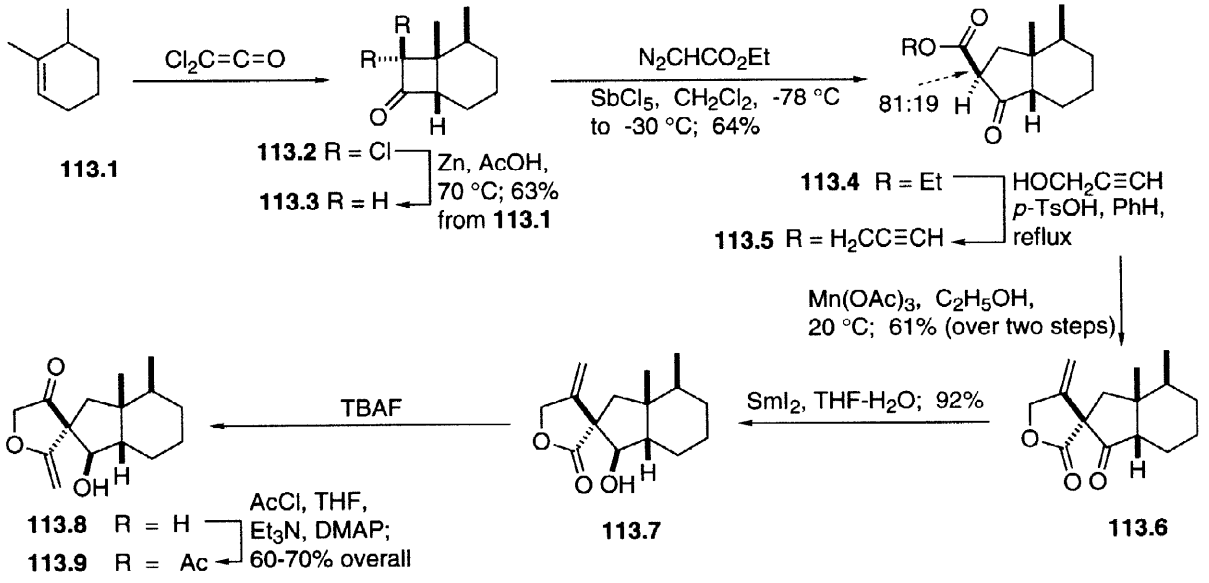
In an effort to synthesize the biologically active spiroalkaloids nitramine, isonitramine and sibirine, Cossy *et al.*[126] developed a different method to prepare chiral lactams (Scheme 112), again using manganese(III) acetate. Compound **112.1**, generated from the corresponding β-ketoamide and (*R*)-(+)-α-methylbenzylamine, when heated with 1 equivalent of manganese(III) acetate in ethanol, produced a 6.5:3.5 mixture of the imines **112.2** and **112.3**. These were separated and hydrolyzed with aqueous acetic acid to the corresponding optically active ketones (ee 30%) **112.4** and **112.5**.

Scheme 112



The potential of oxidative methods based on manganese(III) acetate to generate spirocenters in a highly stereocontrolled manner has been demonstrated (Scheme 113) by Greene *et al.*[127] in the synthesis of (±)-9-acetoxyfukinanolide (**113.9**), a bakkenolide isolated, like **110.4**, from *Petasites japonicus* maxim.[128] The synthesis involved dichloroketene addition to **113.1**, followed by dehalogenation (**113.1** → **113.2** → **113.3**). Ring expansion with ethyl diazoacetate then produced **113.4**, and transesterification afforded **113.5**. Treatment with manganese(III) acetate in degassed ethanol led to stereoselective 5-*exo*-digonal cyclization to the β-methylene-γ-butyrolactone **113.6**. In this step the stereoselectivity is evidently controlled by the shape of the

Scheme 113



rest of the molecule. Stereoselective reduction of **113.6** gave **113.7**. This compound was next treated with tetrabutylammonium fluoride, and it underwent a thermodynamically controlled retroaldol-aldol reaction that

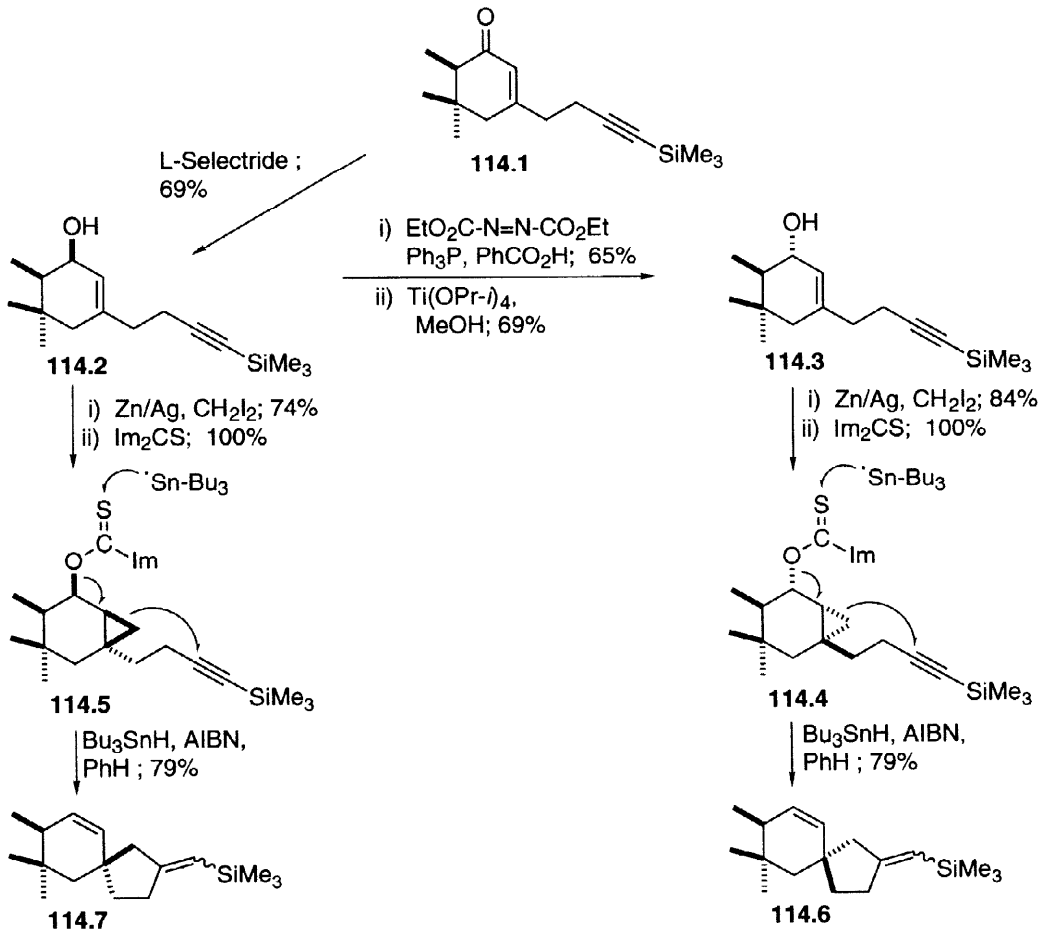
afforded the spirolactone **113.8** with the desired relative stereochemistry at the newly created spirocenter. Finally, acetylation gave (±)-9-acetoxyfukinanolide.

7b Radical ring opening

Motherwell *et al.*[129] have developed a different approach for controlling the stereoselectivity of a radical ring closure that leads to a spiro compound. They use hydroxyl-directed Simmons-Smith cyclopropanation of an allylic alcohol possessing a suitably located multiple bond. As shown in Scheme 114, the resulting cyclopropane is made to undergo radical ring opening, and the new radical then cyclizes onto the multiple bond in the pendant.

This principle was illustrated in the following way. Allylic alcohol **114.2** was prepared from enone **114.1** by alkylation of the kinetic lithium enolate and stereoselective reduction with L-Selectride (**114.1** → **114.2**). Configurational inversion at the hydroxyl-bearing carbon by Mitsunobu reaction proceeded cleanly to give alcohol **114.3**. Both diastereomeric alcohols were cyclopropanated, and the corresponding thiocarbonylimidazolide derivatives were then prepared (**114.2** → **114.5**; **114.3** → **114.4**). Generation of the radical by the standard Barton-McCombie deoxygenation procedure gave the spirocycles **114.7** and **114.6** in

Scheme 114



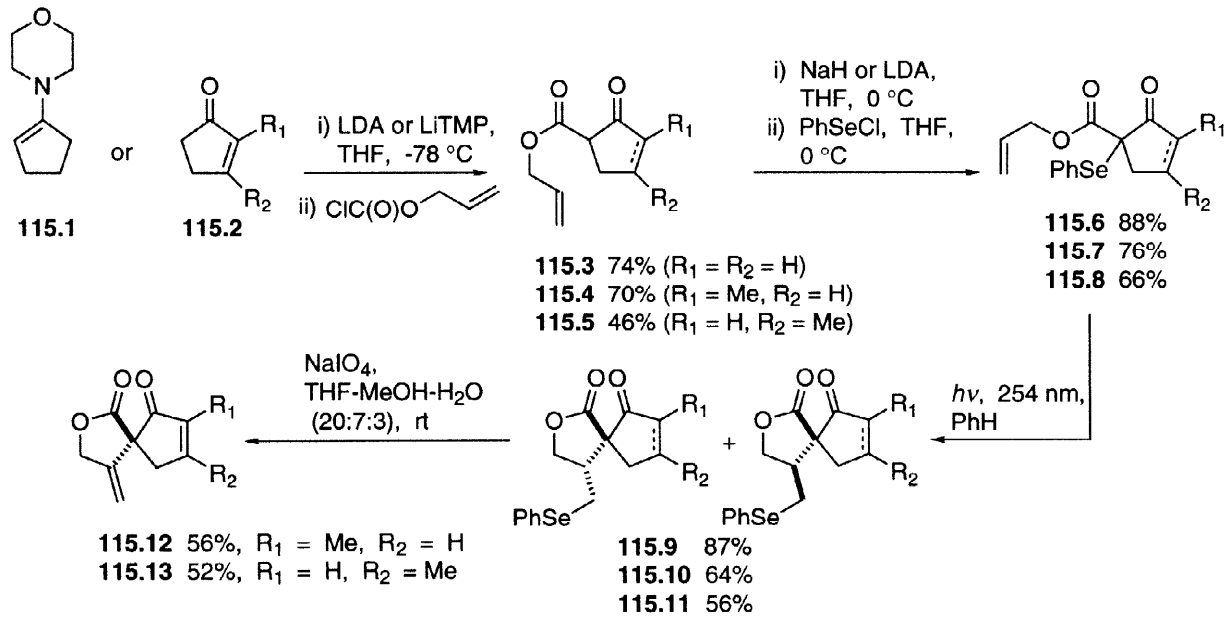
good yield. These compounds differed, of course, only in their relative stereochemistry at the spirocenter, and the stereocontrol was imposed by the well-established hydroxyl-directed cyclopropanation. In the radical ring

opening of the cyclopropane, a perimeter bond of the cyclopropane is opened because of stereoelectronic factors imposed by the shape of the bicyclic starting material.

7c *Radical group transfer reactions*

Radical-mediated group transfer reactions have also been used to form spiro compounds, and this approach has seen service in Back's group for the construction of substances related to bakkenolides **115.14**-**115.16**.[130] In this technique, a selenium group activated by adjacent carbonyls has been used as the unit that undergoes transfer. The method is illustrated (Scheme 115) by the synthesis of spiro ring systems **115.12** and **115.13**. The morpholine enamine of cyclopentanone or the kinetic enolates of 2-methyl- or 3-methyl-cyclopent-2-enones (**115.2**) were acylated to furnish **115.3**-**115.5**, respectively. On selenenylation, these compounds gave the corresponding selenides **115.6**-**115.8**, and UV irradiation then led to the spirolactones **115.9**-**115.11** as pairs of diastereomers in the ratio of >20:1, 5:1 and 10:1, respectively. Oxidation of the major diastereomers of selenides **115.10** and **115. 11**, and elimination of the derived selenoxides, produced spirolactones **115.12** and **115.13**, which represent the spiro [4.4] systems of the natural products homogynolide A and homogynolide B (**115.15** and **115.16**). The saturated selenide **115.9** was not processed further.

Scheme 115



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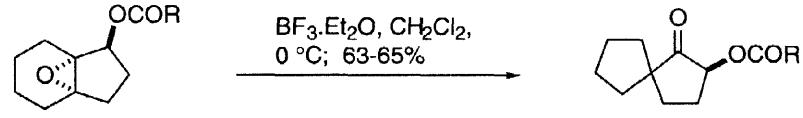

i R = *p*-nitrophenyl
ii COR = (-)-camphanoyl

iii

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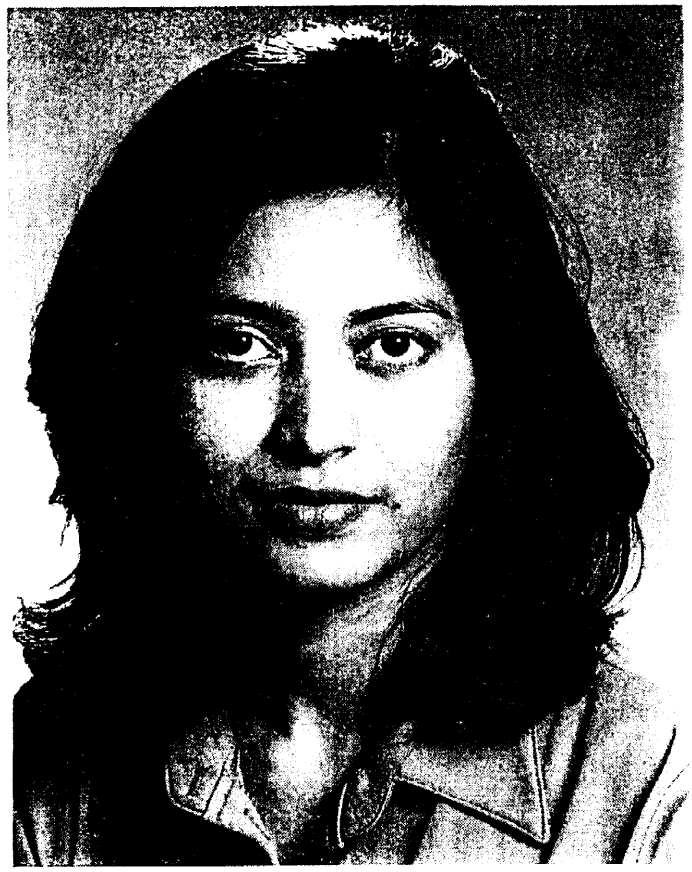
Biographical sketch



Mousumi Sannigrahi

Mousumi Sannigrahi obtained a B.Sc. from the Indian Institute of Technology, Kharagpur, India, and an M.Sc. in theoretical chemistry from the University of New Brunswick, Canada. During her M.Sc. program, under the supervision of Dr. F. Grein, she studied mechanisms of various 1,3-dipolar cycloadditions, using *ab initio* methods. Currently, as a doctoral candidate at the University of Alberta, she is working under the supervision of Dr. D. L. J. Clive in the area of natural product synthesis based on radical cyclization methodology.