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TOTAL SYNTHESIS OF POLYCARBOCYCLIC SESQUITERPENES

A SURVEY OF NOVEL METHODS AND REACTIONS

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INTRODUCTION

The polycarbocyclic sesquiterpenes represent a large body of naturally occurring substances which are usually subdivided according to their carbon framework.[1] The wide diversity in structural type, in functionality pattern and in stereochemistry offers a variety of target molecules to the synthetic chemist. The structural characteristics as well as the biological properties have indeed for decades stimulated active synthetic research in this area. The consequence has been a flood of publications describing total synthesis of many members in the different series. Among others, two excellent and exhaustive reviews covering, respectively, the periods up to the middle of 1970[2a] and 1970–1979[2b] have been published by Heathcock *et al.*

The object of this report is to review novel or improved approaches to the main classes of polycarbocyclic sesquiterpenes disclosed since 1973 and up to the end of 1983. In selecting material for inclusion, it was not always possible to distinguish new methods or reactions falling strictly within the scope of the title; evidently several methods have emanated from discoveries in other areas or from work on model compounds. We have therefore limited ourselves to those methods found in publications, describing total syntheses of polycarbocyclic sesquiterpenes. Relay- and hemisyntheses and work on model compounds have, as a general rule, not been included. The report concentrates practically exclusively on the construction of fused and bridged polycarbocyclic systems carrying 5-, 6- and 7-membered rings. Methods for attaching cyclopropane and cyclobutane rings are not discussed, except when these small rings are formed concomitant with one of the above mentioned carbocycles. Also approaches to aromatic sesquiterpenes are not covered.

Among the different features of a total synthesis, the phase during which the carbocyclic framework is assembled represents in general the most salient aspects of the sequence. We have therefore made the decision to centre the discussion around the key-steps involved in constructing the polycyclic system. Only in some cases we will indicate the transformations leading to the crucial precursor and the

subsequent steps to individual natural substances. In this way it is possible to cover the work published during the last 10 years within a reasonable space. This will allow the reader to compare the different strategies which have evolved during the crucial stages for assembling the same or closely related carbocyclic frameworks. With this goal in mind we have also incorporated novel applications of well-established methodologies in order to allow an appreciation of the evolution in synthetic methodology. The overall efficiency of the different multi-step sequences leading to the natural products is therefore not a point of debate in this report.

The large diversity in structural type and in the synthetic methodology on the one hand and the varying number of publications for the several classes of polycarbocyclic sesquiterpenes on the other hand, does not allow us to organize the different sections in the same way. A description of the structural characteristics within all subclasses is far beyond the coverage of this report. In order to help the reader to orientate himself a limited amount of structural information is provided. The structures of recently discovered natural substances will be presented in context with the new methods developed for their synthesis. Because of the overall objective of this report an attempt has been made to group, in the different sections, a number of methods under a common heading. Annulation methods, during which a ring is attached on a pre-existing system, are generally recognized as such when the two new carbon–carbon bonds are formed in timely related processes. They can be simultaneous, consecutive, or separated by only a few refunctionalization steps necessary for the final cyclization. When a large number of steps separate both carbon–carbon bond formations, the concept of annulation is no longer adequate and emphasis will then be laid up on the cyclization process. In another important strategy for constructing polycarbocyclic systems, the crucial step(s) involve(s) modification of a preformed different polycyclic framework. During such approaches, frequently, use is made of strained molecules as intermediates which greatly facilitates the structural rearrangement. Many recent efficient syntheses offer illustrations of this principle.

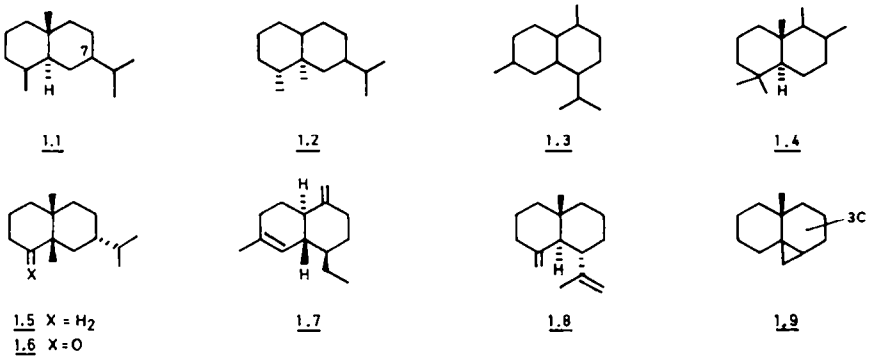
The last section is devoted to some selected formations of functionalized side chains, which are subsequently involved in cyclization processes or are present as such in natural substances. Because of our arbitrary decision to review carbon–carbon bond formations, syntheses involving mainly functional group transformations on previously known polycarbocycles cannot be included.

I. FUSED SYSTEMS

1. *The bicyclo*[4.4.0]*decane or decalin group*

The bicyclo[4.4.0]decane framework is found in four main subclasses, the eudesmanes **1.1**, eremophilanes **1.2**, cadinanes **1.3** and drimanes **1.4**, and in valerane **1.5**, valeranone **1.6**, the norcadinane, khusitene **1.7** and in β-gorgonene **1.8**. It is also present in some polycyclic sesquiterpenes; approaches towards the tricyclic system **1.9** will be included in this section when a cyclohexane ring is formed together with the cyclopropane ring. Formation of natural substances containing a benzene ring is not discussed.

The Robinson annulation and related methods. Upon comparing approaches reviewed in refs. 2*a* and 2*b* respectively, one realizes that prior to 1970 almost invariably the angularly substituted decalin nucleus has been constructed via Robinson annulation and that only recently a gradual shift towards other methods is observed. The problems associated with the efficiency, the regio- and stereocontrol of

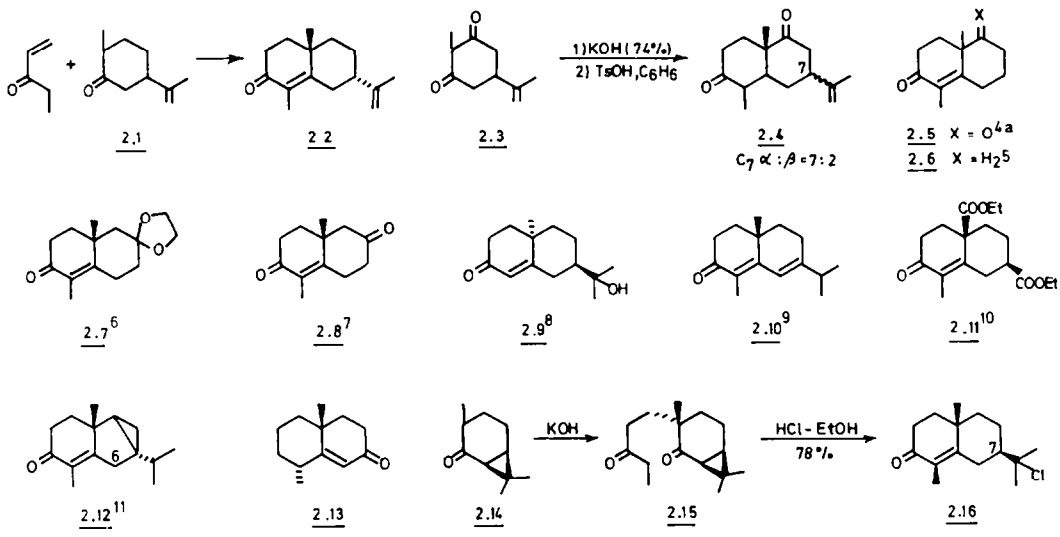


1.1 1.2 1.3 1.4

1.5 X = H_2
1.6 X = O

1.7 1.8 1.9

Scheme 1.

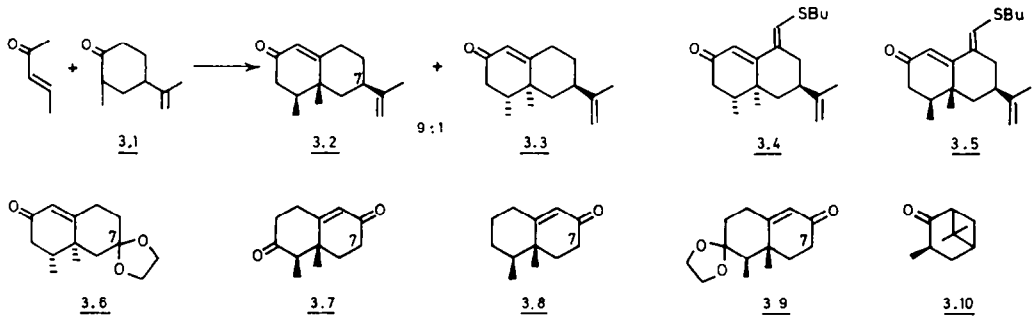


Scheme 2.

both steps in this annulation, have been adequately discussed elsewhere[3] and cannot be dealt with at length in this report. A limiting factor is related to the stereochemistry of the initial alkylation step when 2,x-dialkylcyclohexanones are the substrates. Robinson annulation of 2,5-disubstituted cyclohexanones, e.g. **2.1**, affords mainly the diastereoisomer **2.2** with both substituents axial. Therefore applications for the synthesis of eudesmanes, with an equatorial β C-7 substituent, were directed via intermediates in which the desired three-carbon side chain was introduced at a later stage, with the possibility for C-7 equilibration to the more stable configuration. Intermediates, obtained via direct Robinson annulation and which are still being used or newly constructed since 1973, are the bicyclic enones **2.5** to **2.13**.[4–11] Huffman and Hillenbrand[12] have recently demonstrated that annulation involving the anion of the more acidic **2.3** affords mainly the trans isomer **2.4**α although previously the sole formation of **2.4**β had been claimed.[13] An efficient approach to the 7-β eudesmane series has been reported by Caine and Gupton.[14] Steric hindrance of the endo methyl group on the cyclopropane ring in (−)-2-carone (**2.14**) ensures exclusive alkylation from the α-face. Subsequent acid treatment of **2.15** causes cyclopropane ring opening and aldolization to **2.16**. In a somewhat similar concept the bicyclic ketone thujone has been used as a chiral synthon for the synthesis of eudesmanes via **2.12**.[11] Subsequent to C-6 functionalization the cyclopropane ring is opened.

It is generally observed that reaction of cyclohexanone enolates with alkyl vinyl ketones in aprotic medium produces the adducts in low yields because of polymerization of the enone and/or polyalkylation. Stork and Ganem[15] have circumvented these problems using α-silylvinyl ketones; the silicon atom stabilizes the initial Michael adduct. This method has been used to construct, inter alia, **2.6** (60%) and **3.9** (44%). A remarkable improvement, recently described by Ziegler and Hwang[16] is illustrated by the synthesis of **2.2**. The thermodynamic enolate of **2.1**, formed with 0.9 equiv. LDA in THF at 20°, reacts with ethyl vinyl ketone (−78° → 20°) to the bicyclic ketol (92%), dehydration with KOH–EtOH then produces **2.2** (93%). Although the reaction of **2.1** with methyl vinyl ketone is less efficient, this procedure also represents a substantial improvement. Application of the eudesmane precursor **2.13** has in the past been thwarted by the failure of the Robinson annulation to provide a viable route to this enone. The acid-catalyzed annulation produced preferentially the bridged enone upon aldol cyclization. Still and Van Middlesworth[17] have now observed that reaction of 2,6-dimethylcyclohexanone and methyl vinyl ketone can be stopped at the 1,5-diketone stage (50–58%) when conducted at 0° in H_2SO_4–benzene. High yield (87%) had previously been reported for the NaOEt-catalyzed cyclization of this 1,5-diketone to **2.13**.

Also the evolution of eremophilane syntheses has heavily drawn on the Robinson annulation. Earlier investigations have shown that the crucial *cis* relationship of the C-4 and C-5 methyl groups is obtained under kinetically controlled conditions; e.g. reaction of **3.1** with 3-penten-2-one affords (±)-7-epinootkatone **3.2** and (±)-nootkatone **3.3** in a 9:1 ratio.[18] Piers[19] has shown that additional substitution on the cyclohexanone influences the conformation and hence the result of the annulation; depending on the conditions **3.4** and **3.5** can be obtained in ratios up to 1 : 1.[20] It may be noted that the



Scheme 3.

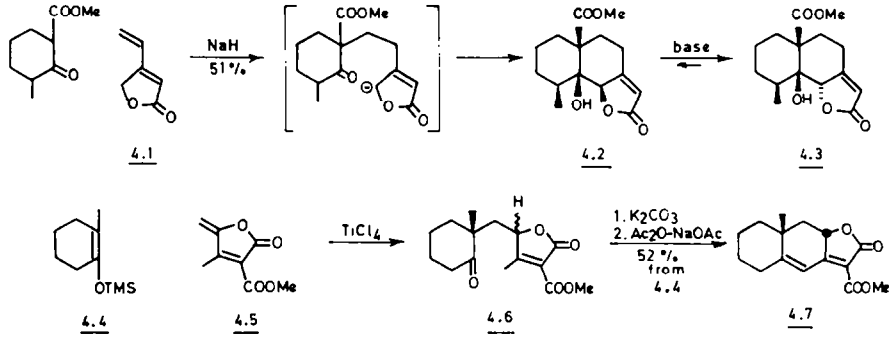
annulation procedure is unsuccessful when the cyclohexanone carries a 4-acrylic ester group.[21] The problem for obtaining β C-7 substitution can be solved by the intermediacy of **3.6**,[22] **3.7**,[23] **3.8**[24] or **3.9**.[25] Several of these decalins have already been described previously. Zoretic *et al.*[24] have shown that acid-catalyzed (H_2SO_4–benzene, reflux) Robinson annulation of 2,3-dimethylcyclohexanone affords **3.8** as the major isomer (ratio > 9 : 1, 30%), this represents an improvement compared to the base-catalyzed procedure on the same cyclohexanone. Two groups[26] have recently reported the synthesis of the important (+)-nootkatone (**3.3**) starting from nopinone (**3.10**). In order to ensure stereoselectivity a large number of transformations separate the initial "alkylation" and cyclization steps.

Novel annulation methods have been described, which enable construction of ring B together with elements of a γ-lactone or furan ring. These approaches, which provide highly functionalized eudesmanolide precursors, feature 1,6-additions and vinylogous aldol type cyclizations. Yoshikoshi *et al.*[27] described the novel annulation reagent **4.1**, which however only reacts with weak basic enolate anions derived from β-keto esters and 1,3-diketones. In the case shown, subsequent condensation produces the diastereoisomers **4.2** (kinetic product) and **4.3** in a 2 : 1 ratio.

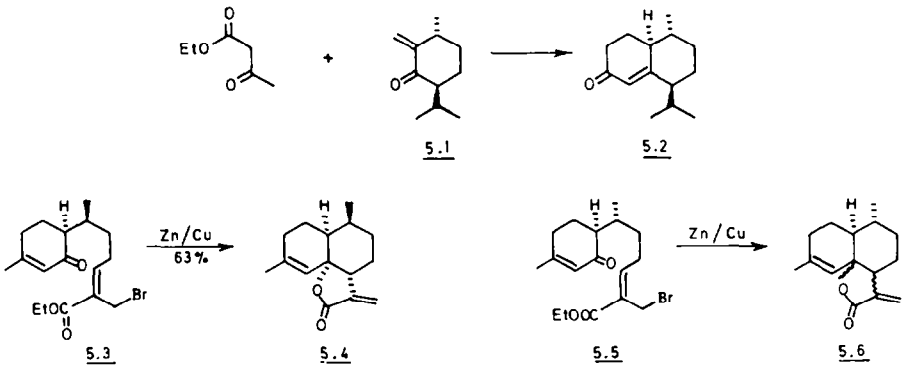
Schultz and Godfrey[28] developed an efficient 3-step synthesis of the interesting annulation reagent **4.5**. 1,6-Addition of **4.5** on the enol ether **4.4** leads to **4.6**. Base-catalyzed aldolization and dehydration with concomitant C-8 equilibration provides the linear tricyclic lactone **4.7**.

The cadinane intermediate **5.2** has been constructed via annulation of **5.1** with ethyl acetoacetate; the equilibration conditions assure formation of **5.2** as the more thermodynamically stable product.[29] In an approach to lactonic cadinanes, Dreiding[30] applied an intramolecular Reformatsky-type reaction for the simultaneous formation of the cyclohexane and α-methylene-butyrolactone rings. *Cis*-fused lactones are formed; starting from **5.3** only **5.4** is isolated, while **5.5** produces both α (45%) and β (21%) lactones **5.6**.

Diels–Alder reactions. The intermolecular version[31] for assembling angularly methylated decalins from substituted cyclohexenones as dienophiles has found limited application in the past. This is due to the known reluctance of α- and, especially β-alkyl substituted cyclohexenones to react with dienes. The problem can be circumvented via an angular methoxy-carbonyl substituent[32] (e.g. **6.1**; R = H or Me); however, its transformation into a methyl group considerably lowers the overall efficiency. An improved application makes use of the more reactive Danishefsky diene; e.g. **6.2** is formed in 50–60% yield at 200°.[33] Kitahara *et al.*[34] observed a dramatic increase in the yield (93%) for the formation of **6.3** when the reaction is catalyzed by aluminium chloride (0.1 equiv. to dienophile).



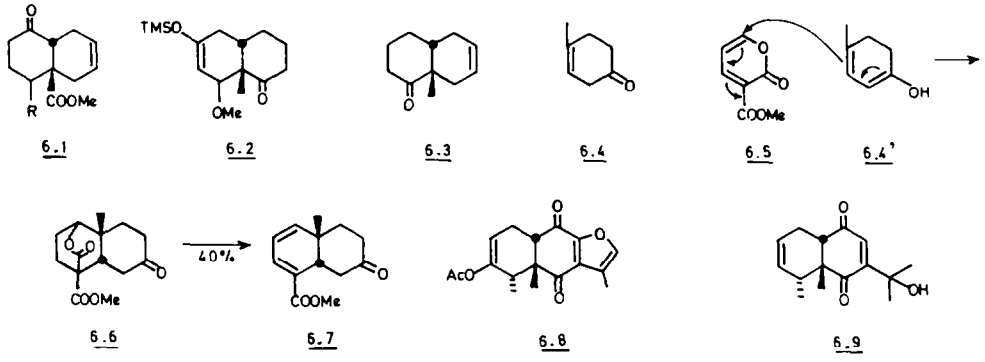
Scheme 4.



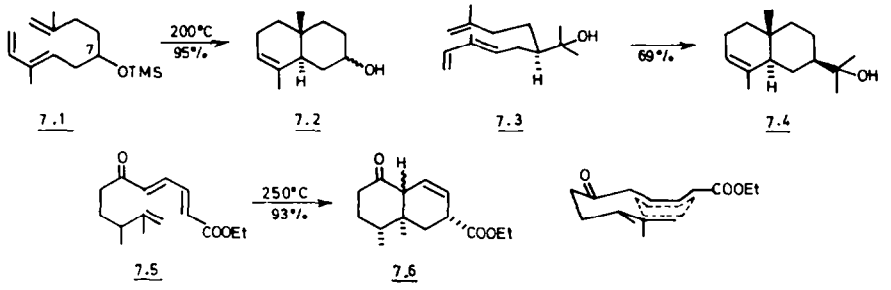
Scheme 5.

Another solution for the synthesis of angularly methylated decalins has been provided by Corey and Watt.[35] The exceptional "inverse electron demand" Diels–Alder reaction between the α-pyrone **6.5** and **6.4** affords **6.6**, which upon extrusion of CO_2 leads to **6.7**. The remarkable regioselectivity appears to be due to the intervention of the enol form **6.4'** as the true dienophilic partner. Consistent with this argument, cyclohexenes lacking the carbonyl function in **6.4** fail to react as they do not possess the electron-donating power of the dienol **6.4'**. The eremophilane precursors **6.8**[36a] and **6.9**[36b] have been constructed by Bohlmann *et al.* from the appropriate *p*-quinones and substituted dienes.

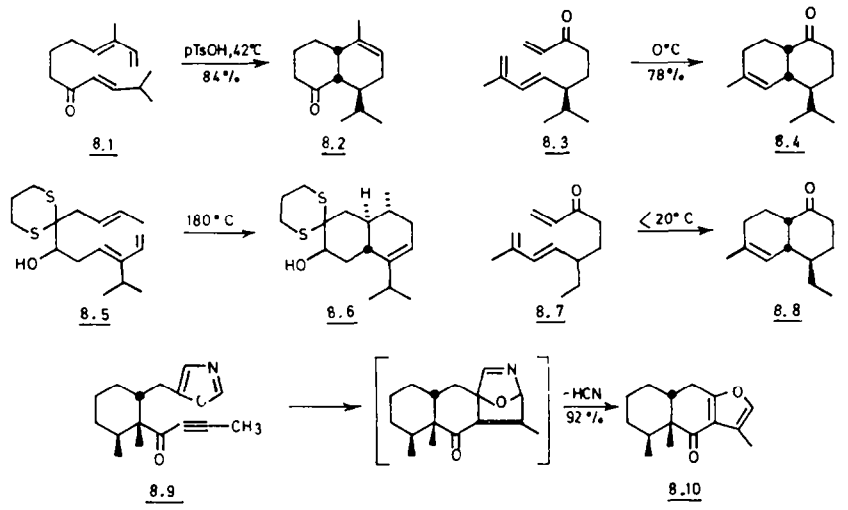
The intramolecular Diels–Alder reaction for assembling decalins has found increased application during the last decade. Its advantages over the intermolecular version with respect to regio- and especially stereochemical problems are presently well documented.[37] However, it should be noted that the overall efficiency is somewhat overshadowed by the problems in assembling the triene precursor. Indeed, despite considerable progress, stereospecific olefin synthesis is generally still more difficult than stereocontrol in cyclic systems. Several reports have described the formation of angularly methylated decalin systems. The eudesmane precursor **7.1** undergoes smooth cyclization to predominantly *trans*-fused epimers **7.2** (3:5 ratio OH axial:equatorial).[38] In the transition state leading to *cis*-fused



Scheme 6.



Scheme 7.

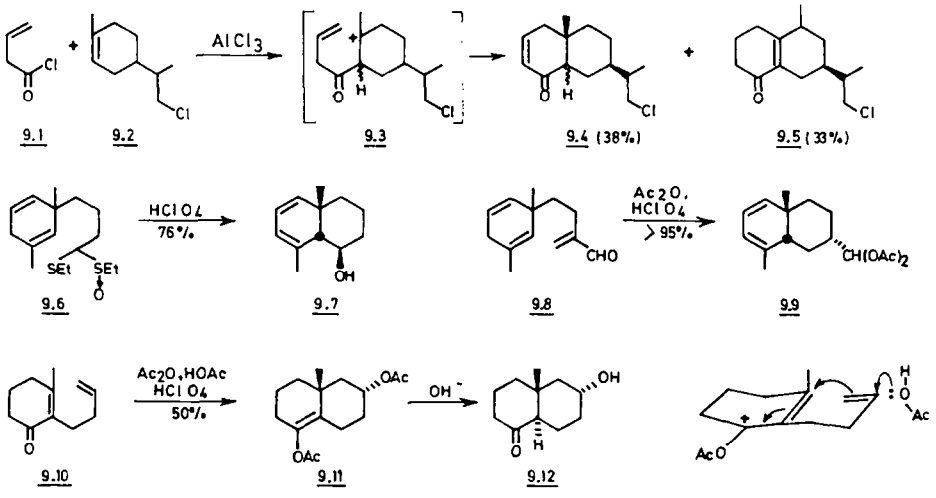


Scheme 8.

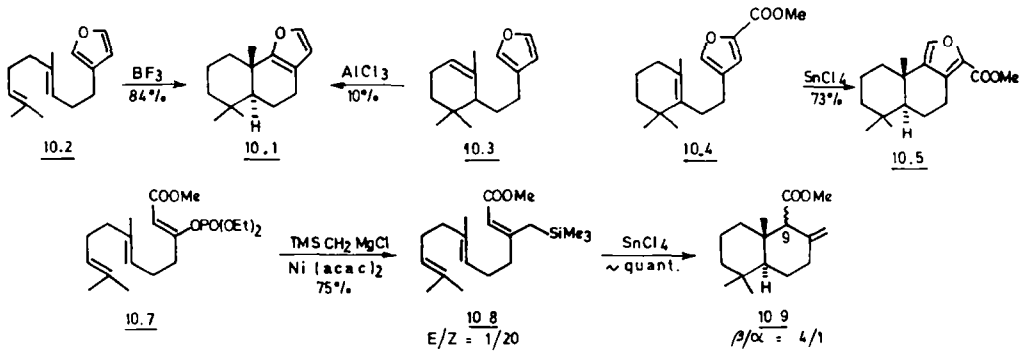
products there is a severe nonbonded interaction between the vinylic methyl on the diene and the 7-hydrogen atom. Taber and Saleh[39] have recently shown that upon replacing the TMS ether in **7.1** by a hydroxypropyl group (**7.3**) the 7-equatorial isomer **7.4** (α-eudesmol) dominates. Because of the ready availability of the acyclic triene **7.5** the approach developed by Näf *et al.*[40] represents an efficient route to eremophilanes and valencanes. Depending on the conditions, cyclization of **7.5** gives either a 1 : 1 mixture of fusion isomers **7.6** or only the *cis*-isomer by rapid epimerization of the kinetic *trans*-adduct. A transition state is assumed in which the secondary methyl group is in the more stable equatorial position.

The cadinane nuclei **8.2**,[41] **8.4**[42] and **8.6**[43] have been assembled starting respectively from trienes **8.1**, **8.3** (via *endo* transition states) and **8.5**. In Vig's (±)-khusitene synthesis, spontaneous cyclization of **8.7** leads to **8.8** as the most probable major isomer.[44] An interesting route to C-6 oxygenated furano-eremophilanes, described by Jacobi *et al.*[45] is based on the bis-heteroannulation strategy, involving the intramolecular version of Diels–Alder reactions on oxazoles. The acetylenic oxazole **8.9** cyclizes to a primary adduct which extrudes HCN, to produce (±)-ligularone (**8.10**). Also the corresponding acetylenic alcohol undergoes facile Diels–Alder reaction (84%).

Cationic olefin cyclizations and related reactions. Since the pioneering work of Stork,[46] Eschenmoser,[47] Johnson[48] and Van Tamelen[49] on biomimetic cyclizations of polyenes, the first applications in the decalin sesquiterpene area were mostly directed towards the drimane subclass.[2a] More recently the synthesis of eudesmanes has been addressed. Wolinski *et al.*[50] described a new annulation via a consecutive acylation–cycloalkylation procedure. Reaction of **9.1** and **9.2** affords



Scheme 9.



Scheme 10.

stereoselectively the desired enone **9.4** next to **9.5**, which most likely arises via hydride and methyl shifts from the cation formed upon ring closure of **9.3**. The highly stereoselective formation of **9.7**[51a] and **9.9**[51b] has been reported by Marshall *et al.*; reaction of **9.6** presumably proceeds via the aldehyde.

Decalin **9.12**[52] is of interest; it provides an entry to eudesmanes with different functionality patterns than when starting from ketone **2.5**. The cyclization, triggered by an enone, is carried out under conditions ensuring efficient nucleophilic capture of the bicyclic cation, rather than deprotonation to an alkene.

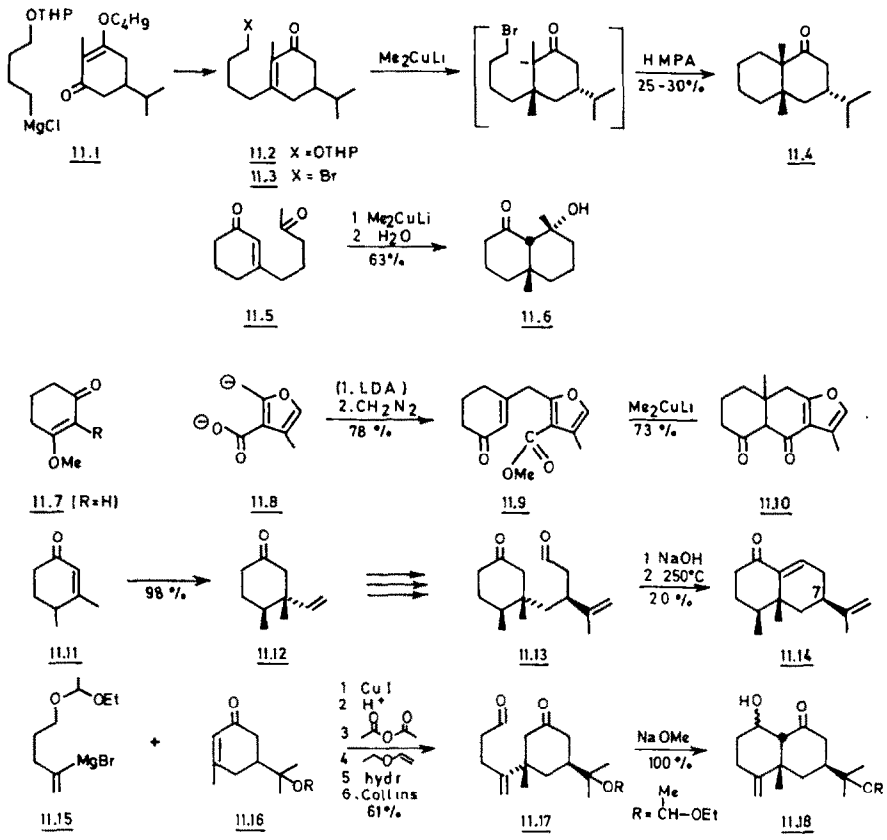
Pallescensin A (**10.1**), a non-isoprenoid sesquiterpene, has been obtained from **10.2**[53] and **10.3**.[54] Cyclization of **10.3** produces **10.1** as the minor product next to the *cis*-fused isomer (ratio 1 : 2). The related Friedel–Crafts reaction of **10.4** is stereoselective; the ester function guarantees formation of the drimane skeleton **1.4** after decarboxylation of **10.5**.[55] Recently Weiler *et al.*[56] extended Fleming's cyclization of allylsilanes to the synthesis of the drimane class. They demonstrated that the allylsilane group activates conjugated esters in polyene cyclizations; e.g. **10.8** (>95% *Z*) produces isomers **10.9** in almost quantitative yield. Carboxylated *Z*-allylsilanes, such as **10.8** are obtained predominantly upon Ni(II) catalyzed coupling of *Z*-enol phosphonates (e.g. **10.7**) of β-keto-esters with Grignard reagents.

1,4-*Additions to cyclohexenones and enolate trapping* (Scheme 11). The intramolecular variant of Stork's regiospecific alkylation[57,58] of an enolate, generated by conjugate addition to a cyclohexenone, has been at the origin of several approaches. The problem for constructing the angular *cis*-dimethyl substitution pattern of **1.5** has been addressed by Posner *et al.*[59] Cuprate addition to **11.3** (from **11.1** via **11.2**) introduces the methyl group *trans* to the isopropyl group; in the second step of the one-pot reaction, cycloalkylation produces **11.4**. An application involving an intramolecular aldolization has been described by Näf *et al.*[60] (**11.5** to **11.6**). Takahashi[61] constructs **11.10** via internal keto-ester condensation, subsequent to cuprate addition. The substrate **11.9** is obtained from dianion **11.8** which gives 1,2-addition reaction with enol ethers of cyclic 1,3-diketones such as **11.7** (R = H). It can be noted that reaction of **11.7** (R = Me) with **11.8** has been employed in furano-eremophilane synthesis. Although the syntheses of eremophilone reported by Ziegler[62] and by Ficini[63] do not feature one-pot β and α bond formation as in the above cited examples they can be described here. The highly stereoselective 1,4-addition on respectively **11.11** and **11.16** and the final aldol cyclization are separated by a number of steps. In the Ziegler route the major preoccupation concerns the C-7 stereochemistry (**11.13** → **11.14**). Ficini's approach centers around ring A formation in **11.18**.

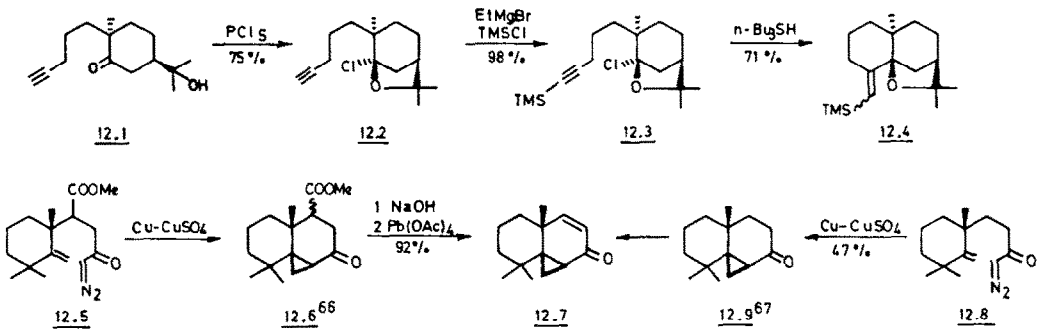
Cyclization involving radical or carbenoid intermediates (Scheme 12). Büchi and Wuest[64] reported an interesting β-agarofuran synthesis, involving radical promoted[65] cyclization of acetylenic silane **12.3** producing **12.4** as a 4 : 1 mixture. Cyclization of **12.2** failed, presumably because of the presence of the acetylenic hydrogen. In two syntheses[66,67] of tricyclic sesquiterpenes possessing a fused cyclopropane ring, the skeleton is constructed via an intramolecular α-ketocarbene–olefin insertion of, respectively, **12.5** and **12.8**. In McMurry's approach[66] the efficient oxidative decarboxylation of the carboxylic acid (from **12.6**) in γ-position of the keto function is worth noting.

Bicyclo[4.4.0]*decanes from other polycarbocyclic systems.* New synthetic routes centre around the skeletal modification of preconstructed, different polycarbocyclic systems which have generally been assembled by a direct annulation process.

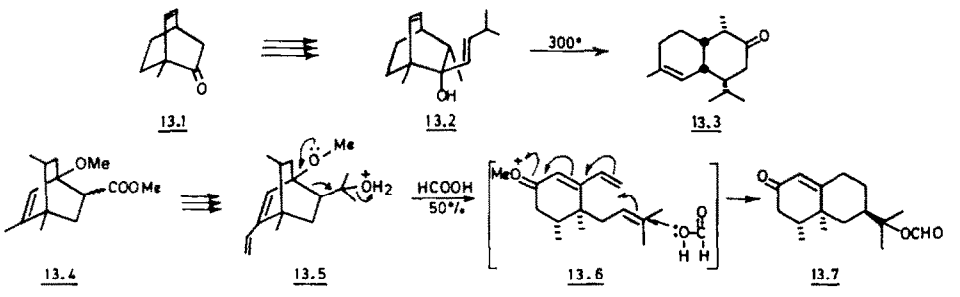
From bicyclo[2.2.2]*octanes.* In two imaginative approaches, the precursors **13.1** and **13.4** have been constructed via Diels–Alder reaction on cyclohexadienes. Gregson and Mirrington[68] described an application of the oxy-Cope rearrangement for the construction of the cadinane skeleton **13.3**.



Scheme 11.



Scheme 12.



Scheme 13.

Unfortunately, this conceptually interesting method suffers from a lack of stereoselectivity during the synthesis of **13.2**. The key-transformation in the Dastur[69] (±)-nootkatone synthesis involves acid-catalyzed ring opening of **13.5** followed by instant recyclization via a cationic-olefin mechanism. The relative stereochemistry of the three chiral centers is ensured by: (1) Diels–Alder addition of methyl acrylate *trans* to the secondary methyl (→**13.4**); (2) cyclization of **13.6** through a transition state with the oxy-isopropyl in equatorial position in order to minimize interaction with the methyl group.

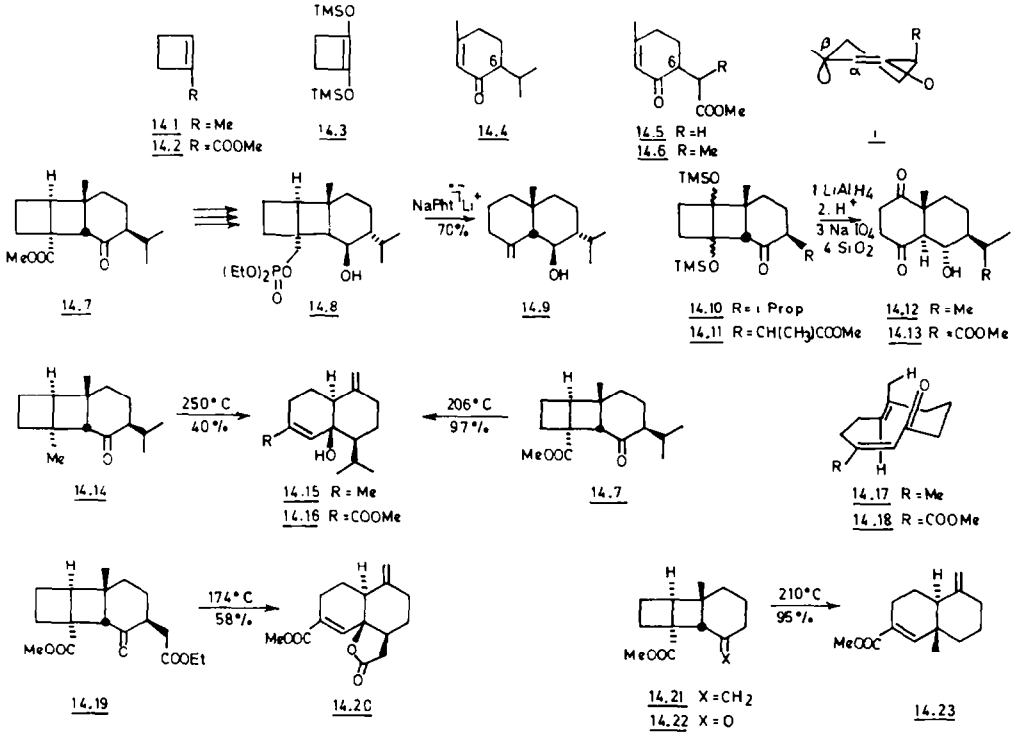
From photochemically assembled precursors. The facile and versatile manipulation of the cyclobutane ring has been at the origin of several approaches in which the carbon atoms were initially assembled by the enone–alkene photocycloaddition reaction.[70]

For the synthesis of the eudesmane and cadinane skeleton, piperitone (**14.4**) and the 2-cyclohexenones **14.5** and **14.6** are obvious starting materials to which the four carbon atoms of cyclobutenes **14.1**, **14.2** or **14.3** are annulated upon irradiation at 350 nm. The yields observed with these 3-methylcyclohexenones are consistently within the range of 65–80%; the anti-adducts are formed predominantly.[71]

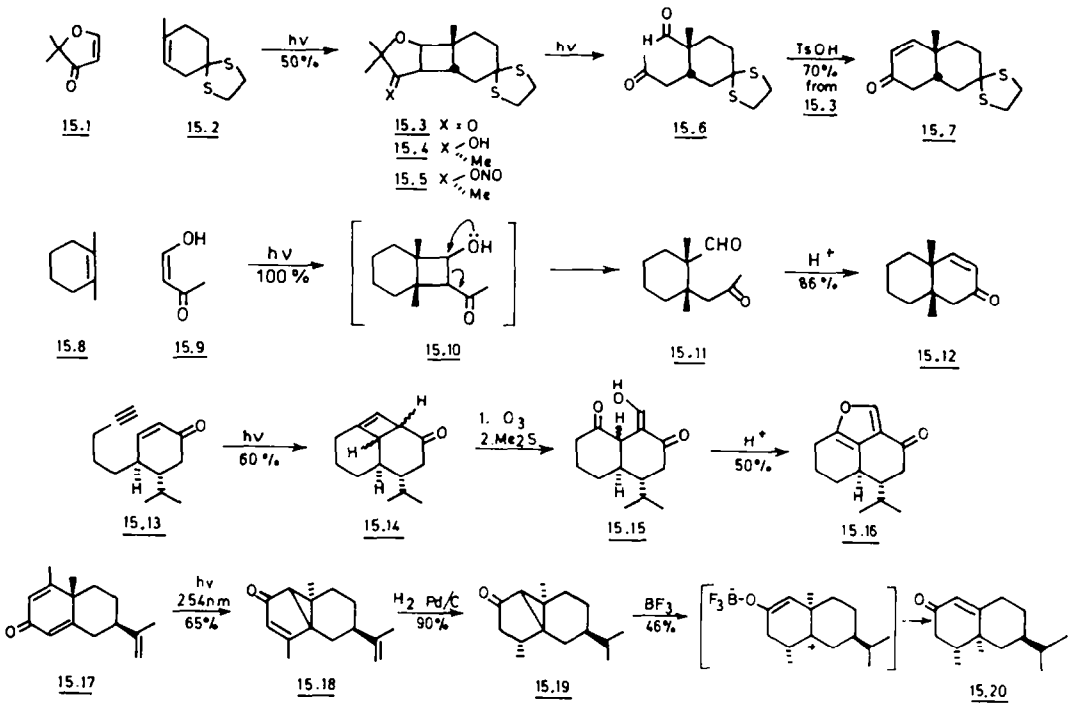
Starting from the unsymmetrically substituted olefins **14.1** and **14.2**, the highly regioselective formation of adducts **14.7**,[72,73] **14.14**[74] and **14.19**[74] is remarkable and indicates that electronic effects are superseded by steric factors. The addition occurs predominantly *trans* to the 6-substituent, when the latter is a sterically demanding group as in **14.4** and **14.6**.[75] This is in accord with Wiesner's rule[76] and assumes an excited state *i* with a pyramidal β-carbon atom and reacting in its most stable conformation. The effect of the size of the 6-substituent is illustrated by the different stereoselectivity observed upon reaction of **14.3** with, respectively, **14.5** and **14.6**;[75a] adduct **14.11** is the major isomer (ratio 9 : 1) while the less space demanding group in **14.5** does not induce stereocontrol. However the sole formation of adduct **14.19** has been observed upon cycloaddition of **14.5** with **14.2**.[74c]

Adducts **14.7**, **14.10** and **14.11** are suitable eudesmane precursors. In the Wender–Lechleiter[72a] synthesis of 10-epijunenol (**14.9**) the 2,5-bond in **14.8** is cleaved upon reduction with lithium naphthalene radical anion. Vandewalle *et al.* have shown that **14.10**[71] and **14.11**[75] provide an entry into 1-oxygenated natural substances. Hydride reduction, TMS ether hydrolysis, periodate α-diol cleavage and isomerization of the *cis*-fused products provides intermediates **14.12** and **14.13** in 50–60% overall yield.

Several groups[72–74] have studied the thermal rearrangement of the tricyclic photoadducts given in Scheme 14. Initial metathetical thermolysis of **14.14**[74a] and **14.7**[72c,d] produces cyclodecadienones **14.17**



Scheme 14.

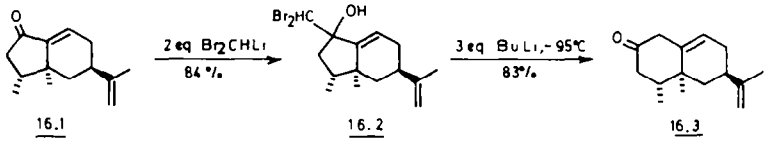


Scheme 15.

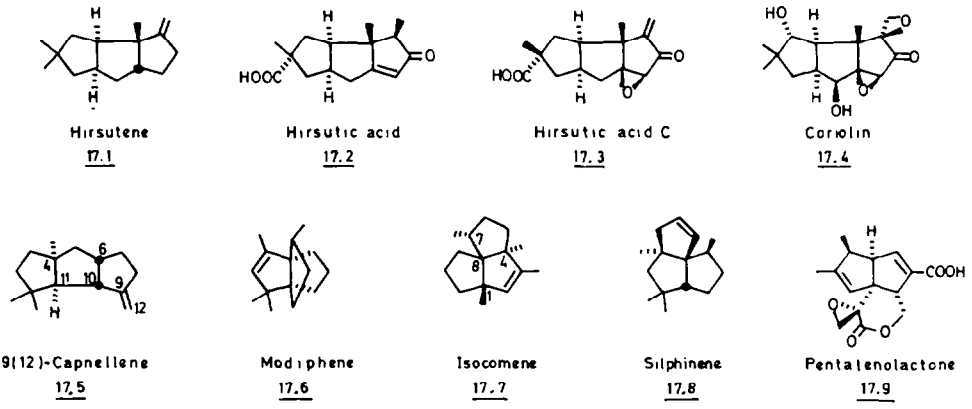
and **14.18** which, under the condition of their generation, undergo an ene-type ring closure leading to the cadinane precursors **14.15** and **14.16**. The significant difference in yield suggests that, relative to the methyl group the ester unit may serve to facilitate the cycloreversion, activate the keto-function and stabilize the product.[72c,d] Similarly, thermolysis of **14.19** gives the lactone **14.20**, plus 15% of the uncyclized hydroxy-ester.[74c] The same sequence has been applied on the methylene analogue **14.21** (from photoadduct **14.22**) and provides in high yield **14.23**, an intermediate in the Wender–Eck[72d] synthesis of warburganal.

Baldwin *et al.*[77] studied the synthetic potential of photo-cycloadducts obtained from furanone **15.1**; irradiation with **15.2** affords **15.3** plus 15% of the HH isomer. The construction of **15.7** was accomplished by the light-induced oxidative fragmentation of the nitrite ester **15.5** and aldolization of **15.6**. Alternatively **15.7** could also be formed by a process initiated by Beckman fragmentation of the oxime of **15.3**.[77b] Cycloaddition with **15.1** is in fact an alternative for the de Mayo[78] reaction, involving the enol form of β-diketones, and has also been applied by Baldwin[79] for the construction of the valerane skeleton **15.12**. These approaches provide a solution to the problem of constructing fused cyclohexenones with a functionality pattern as in **15.7** and **15.12** (see also Scheme 12). The Koft–Smith synthesis[80] of the cadinane, hibiscone C, is the first example of an intramolecular photocycloaddition of enones to acetylenic moieties. Irradiation of **15.13** gives a mixture of *cis–trans* (1 : 1.5) adducts **15.14**. Subsequent ozonolysis to **15.15** and ring closure produce the furano compound **15.16**. The Barton[81] photochemical rearrangement of cross conjugated dienones, has been applied for the construction of tricyclodecanone **15.19**.[82] BF_3-mediated opening of the cyclopropyl ketone, followed by a 1,2-shift of the methyl group leads to dihydronootkatone **15.20**.

Cyclopentane ring expansion of hydrindanones. Recently, Hiyama and Nozaki[83] have described a versatile ring-expansion procedure based on a β-oxido-carbenoid intermediate. Organolithium reaction on **16.1** affords **16.2** which, upon treatment with butyllithium, produces the carbenoid which selectively inserts into the olefinic and carbonyl carbon atoms of **16.1**.



Scheme 16.

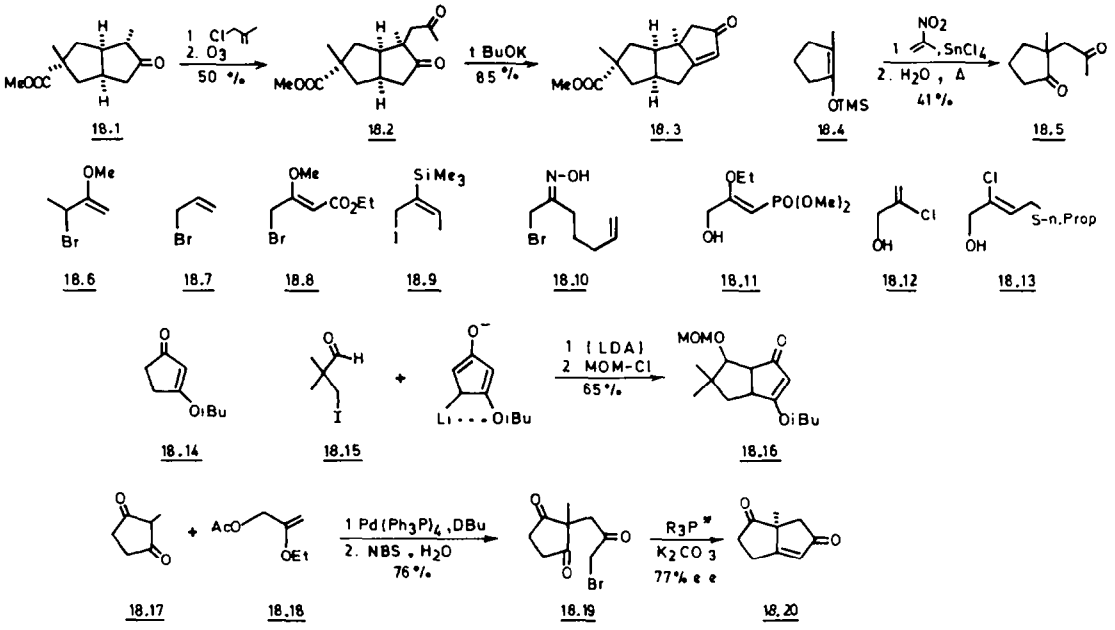


Scheme 17.

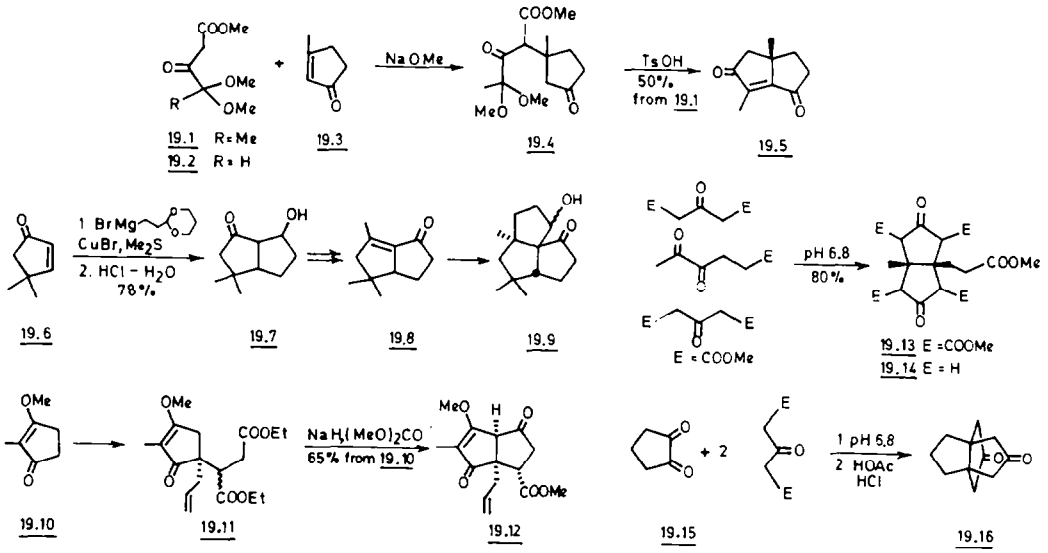
2. *The bicyclo*[3.3.0]*octane or di- and triquinane group*

The recent isolation of a number of sesquiterpenes based on fused cyclopentane rings has greatly stimulated the development of synthetic methods in this area.[84] The most inspiring target molecules are shown in Scheme 17.

Annulation methods. Matsumoto's 1974 total synthesis of **17.2**, is the first reported successful approach to a naturally occurring triquinane.[85] The route centres essentially on aldol cyclization of 1,4-diketones. In contrast to the 3-oxo-butyl side chain in the Robinson annulation, the 2-oxy-propyl side chain, required for a three-carbon annulation, is mostly introduced via a side chain containing a latent carbonyl function. Matsumoto formed 1,4-diketone **18.2** upon alkylation of ketone **18.1** with methallyl chloride and subsequent ozonolysis. Since then new methods became available for the formation of 2-oxo-alkyl side chains. Michael addition of silyl enol ethers, such as **18.4** to nitroolefins and subsequent mild hydrolysis affords 1,4-diketone **18.5** which can then be submitted to alkaline aldol cyclization.[86] Other electrophilic three-carbon alkylating agents possessing a latent carbonyl function are: **18.6**,[87] **18.7**,[88] **18.8**,[89,90] **18.9**[91] and **18.10**.[92] Phosphonate **18.11**[93] is used in an intramolecular Wadsworth–Emmons reaction. **18.12**[94] and **18.13**[95] have been introduced via Claisen rearrangement. An interesting three-carbon annulation described by Koreeda and Mislankar is based on the facile generation of dianions of 3-hetero-substituted 2-cyclopenten-1-ones.[96] Reaction of the dianion of **18.14** with **18.15**, followed by trapping of the aldol product with methoxymethyl chloride, produces **18.16**, a precursor for **17.4**. Trost and Curran[97] studied the use of optically active phosphines for



Scheme 18.



Scheme 19.

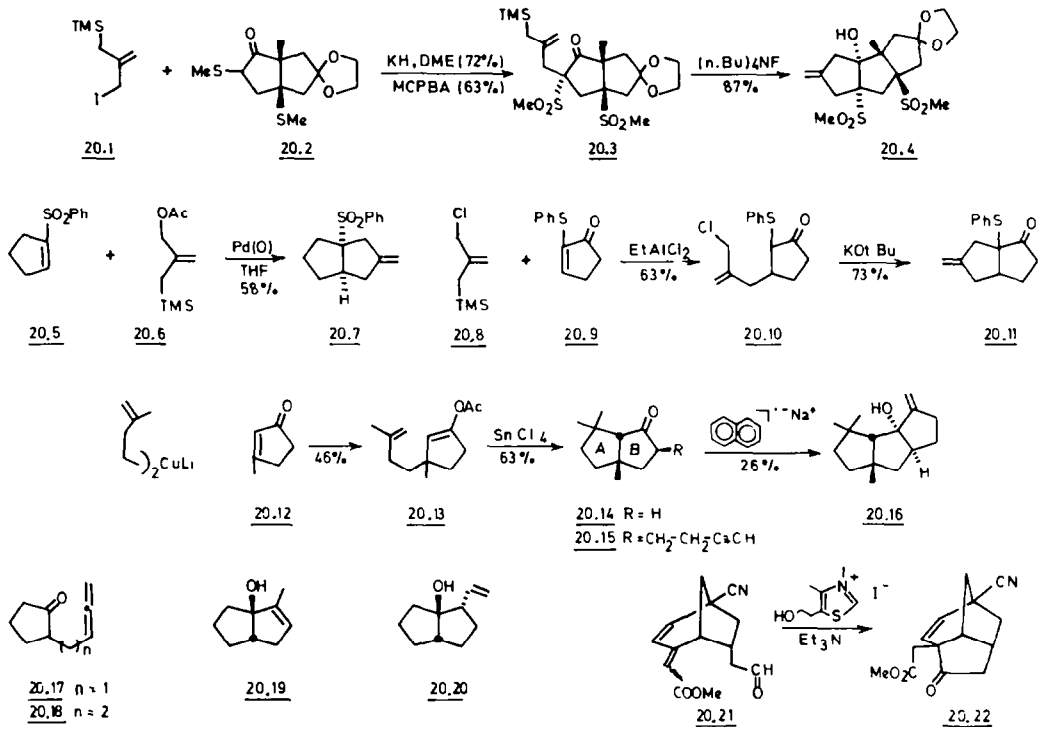
asymmetric induction in the intramolecular Wittig reaction. The side chain in **18.19** is introduced via Pd(0) directed C-alkylation of **18.17**. Cyclization of the ylid formed with (+)-*R*-cyclohexyl-O-anisylmethyl phosphine, gives (+)-*S*-**18.20** (with up to 77% *e.e.*). Brooks *et al.*[98] prepared the *R*-enantiomer of **18.20** by microbial reduction of a 2,2-disubstituted 1,3-cyclopentanedione and subsequent aldolization.

Danishefsky and Etheredge[99] described the new annulation reagent **19.1** for the construction of enediones of type **19.5**. Michael reaction between **19.1** and **19.3** gives the α-diketo equivalent **19.4** which by treatment with *p*-TsOH undergoes decarboxylation and cyclization to **19.5**. It is worth noting that, starting from the α-keto-aldehyde equivalent **19.2**, the cyclization step fails. Central in the Leone–Bay–Paquette[100] synthesis of (±)-**17.8** stands the annulation procedure originally described by Marfat and Helquist.[101] The tandem conjugate addition, acid-promoted aldolization process is repeated during the transformation of **19.8** into **19.9**.[100,102] The method is suitable for the construction of vicinal quaternary centres.

Annulations based on keto-ester condensation have also been described. In Schlessinger's total synthesis[103] of **17.9**, the diquinane nucleus is produced starting from vinylogous ester **19.10**. Propenylation of the enolate anion, deprotonation with LDA and conjugate addition to diethyl fumarate gives **19.11** as a 1 : 1 epimeric mixture. Base-induced cyclization provides only the most stable isomer **19.12** (COOMe; equatorial), thus indicating epimerization during the process. Dauben and Walker[104] constructed the diquinane **19.13** via Weiss–Cook condensation[105] of dimethyl acetonedicarboxylate with an α-diketone; subsequent hydrolysis and decarboxylation yields **19.14** (76%). The modiphene intermediate **19.16** has also been obtained from **19.15** via this condensation.[106]

Several cyclopentane ring formations are grouped in Scheme 20. Trost *et al.*[107] developed a new three-carbon annulation based on **20.1**. With sufficiently thermally stable enolate anions (as from **20.2**) good yields of alkylation products are observed; the final step involves a fluoride-induced cyclization to **20.4**. The annulating agent **20.6** reacts only with olefins bearing electron-withdrawing groups (**20.5** → **20.7**).[108] An alternative[109] is based on the nucleophilicity of allylsilanes toward enones in the presence of a Lewis acid. $EtAlCl_2$-promoted reaction of **20.8** and **20.9** provides **20.10** which is cyclized to **20.11**. While cyclohexenone gave an excellent result, cyclopentenone fails to react; in the latter case phenylthio-activation is necessary.

En route to hydroxylated capnellenols, Pattenden and Teague[110] have assembled the triquinane skeleton via annulation of rings A and C on B. The first annulation involves conjugate addition, trapping as the enol acetate and subsequent cyclization of **20.13**. Ring C is then constructed via alkylation with 2,4-dichloro-1-butene and transformation of the vinylic chloride to the acetylene in **20.15**. Cyclization is effected using Stork's procedure;[111] best results are obtained upon titration of **20.15** with sodium naphthalene radical anion. A recent report[112] from the same laboratory showed that electrolysis of terminal allenic ketones **20.17** and **20.18** resulted in reductive cyclization, through the

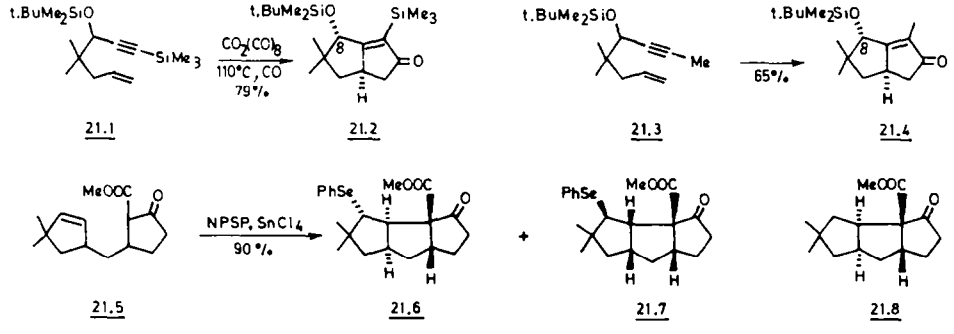


Scheme 20.

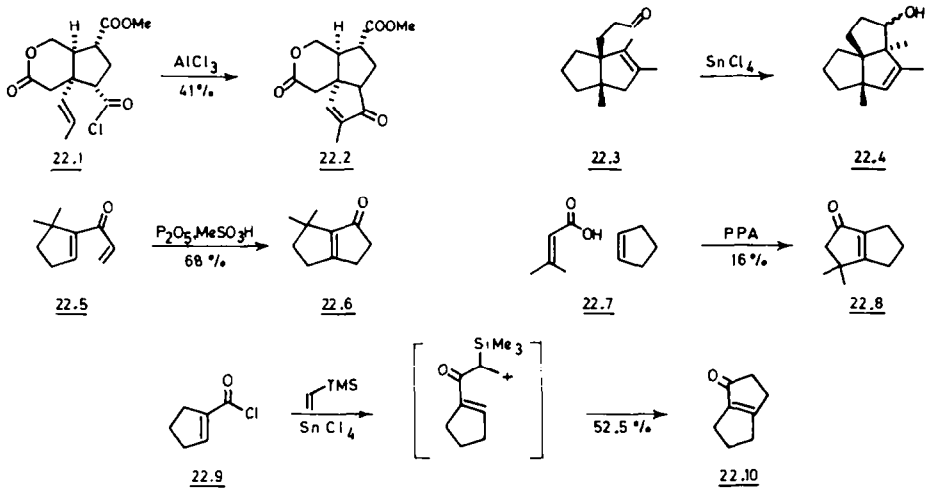
exo-mode, producing respectively **20.19** (42%) and **20.20** (23%). During their synthesis of (±)**17.2**, Trost *et al.*[113] effected ring closure of **20.21** to **20.22** using Stetter's method.[114] The *in situ* formation of an acyl anion equivalent for the intramolecular Michael reaction is achieved with the thiazonium salt in the presence of a base.

Exon and Magnus[115] have examined the stereoselectivity of intramolecular alkene–alkyne dicobalt-octacarbonyl-mediated cyclopentenone formation. Substrate **21.1** yields **21.2** (79%) and 3% of the C-8 epimer (ratio 26 : 1). On the other hand, starting from **21.3** a 3.3 : 1 isomeric mixture, in favour of **21.4**, is obtained. This remarkable difference in stereoselectivity implies that the terminal group, which is three carbon atoms removed from both new stereocentres, must exert the major influence on the stereochemical outcome. The origin of this effect is not known. Ley's strategy centres around an organoselenium-mediated cyclization.[116] Intermediate **21.5**, obtained (74%) via cuprate-conjugate addition on methyl-2-oxocyclopentane carboxylate, smoothly cyclizes upon treatment with N-phenylselenophtalimide and $SnCl_4$. The cyclization is not stereoselective and produces a 1 : 1 mixture of the anti- and syn-adducts **21.6** and **21.7**. The phenylseleno group in **21.6** is then removed by reduction with Raney-nickel producing the (±)-hirsutene precursor **21.8**.

Some recent applications for constructing diquinanes based on acid-catalyzed cycloacylation, cycloalkylation and on the Nazarov reaction are shown in Scheme 22. Lactone **22.2** is an intermediate



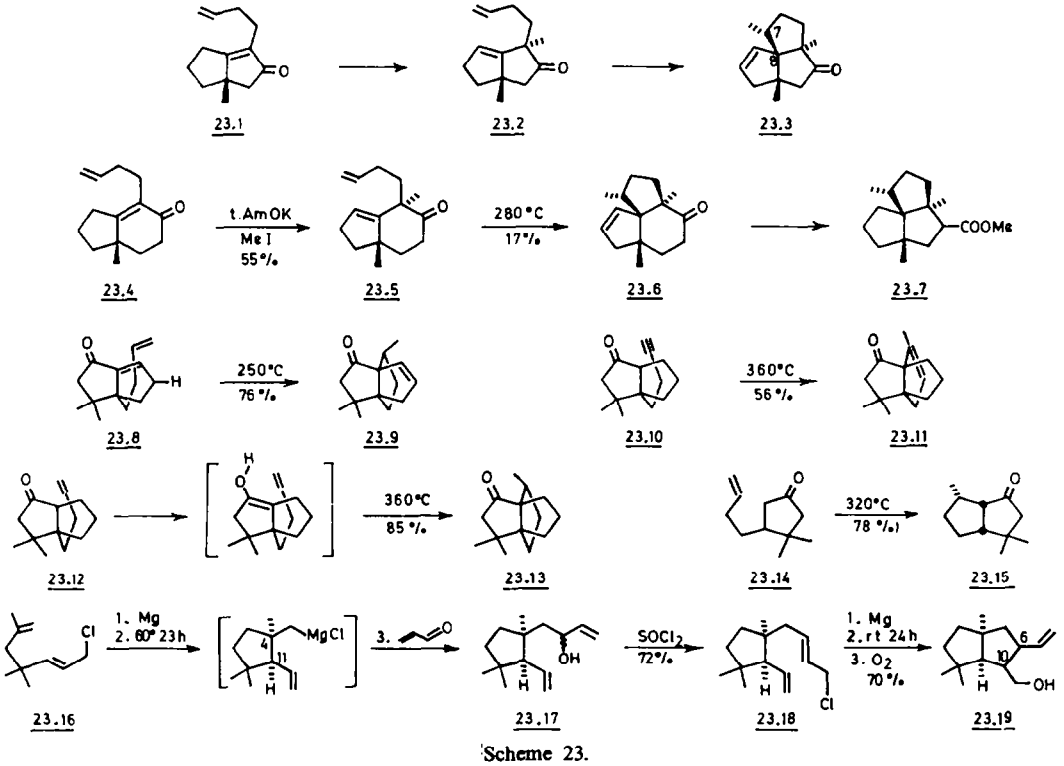
Scheme 21.



Scheme 22.

in the pentalenolactone synthesis of Danishefsky.[117] Compounds **22.4**[118] and **22.6**[119] are intermediates in Paquette's approaches to triquinanes. Me_2CuLi addition to **22.6** provides an alternative synthesis of **20.14**. The isomer **22.8** is a precursor for **17.6** used by Paquette and by Oppolzer (Scheme 23). The rather difficult accessibility of divinylketones (e.g. **22.5**) as substrates for the Nazarov cyclization reaction[120] is a drawback. Magnus *et al.*[121] have reported the use of vinyltrimethylsilane as an ethylene equivalent in reactions with α,β-unsaturated acid chlorides (such as **22.9**) in the presence of a Lewis acid. The dienone intermediate is formed via the β-silyl carbenium ion and then enters into the Nazarov reaction yielding **22.10**.

Thermal cyclizations. The intramolecular ene-reaction[122] has been applied by Oppolzer for the synthesis of (±)-**17.7** and (±)-**17.6**. The strategy towards **17.7**[123] is based on the formation of the 7,8-bond in **23.3**. However, attempted methylation of **23.1** at the α-position, expected because of the bulky angular C-1 methyl group, fails. It was shown that deprotonation of **23.1** is disfavoured by specific

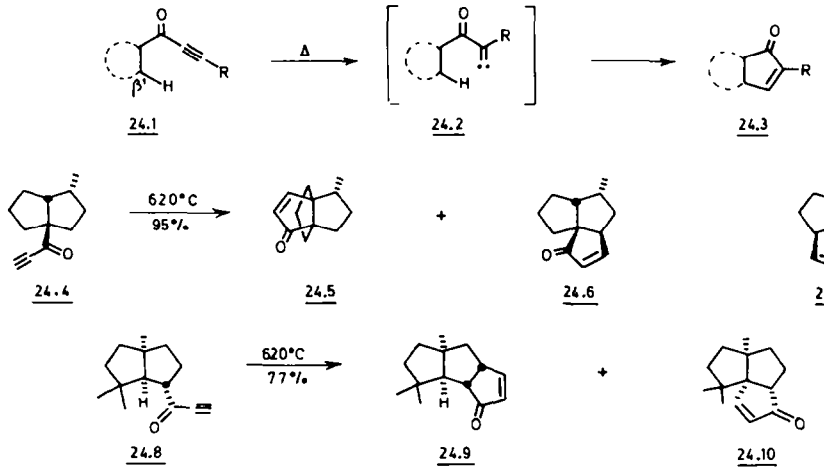


Scheme 23.

constraints of the pentalene system. The synthesis was therefore conducted via the homologous indenone **23.4** which affords **23.5** upon methylation. The crucial ene-reaction gives **23.6** in low yield, which indicates the steric congested nature of the transition state. Subsequently, the triquinane **23.7** is formed by photo-induced Wolff rearrangement of the α-diazo derivative of **23.6**. Oppolzer's efficient synthesis[124] of **17.6** centres around the ene-reaction on the 1,6-diene **23.8**, obtained from **22.8** via conjugate addition, enolate trapping with PhSeBr and the oxidation–elimination procedure. The stereochemistry of **23.9** is based on the observation that 1,6-dienes containing the H-donor site *cis* with regard to the enophilic chain furnish on thermal cyclization, exclusively 5-membered rings with *cis*-positioned H-donor and acceptor sites. In Paquette's[125] synthesis of **17.6**, the skeleton is formed via the Conia cyclization.[126] The precursors **23.10** and **23.12** were obtained from **22.8** by conjugate addition using the Yamamoto procedure.[127] Although, starting from the acetylene **23.10**, the exocyclic olefin is the kinetic product, facile isomerization to **23.11** occurs. Thermolysis of **23.12** leads to the epimodhephene skeleton **23.13**, as mechanistically the process is an ene-reaction on the enol form. The same group[91] also reported the synthesis of stereohomogeneous **23.15**. The Oppolzer and Bättig[128] synthesis of **17.5** centres around the intramolecular "type I-magnesium ene"-reaction.[129] The congested 4,11 bond in cyclopentane **23.17** is formed upon heating the alkenylmagnesium chloride obtained from **23.16**, followed by addition of acrolein. A second thermal reaction at the stage of **23.18** occurs smoothly at room temperature; subsequent trapping with O_2 gives a 3:2 mixture of 6,10-*cis,trans* **23.19**.

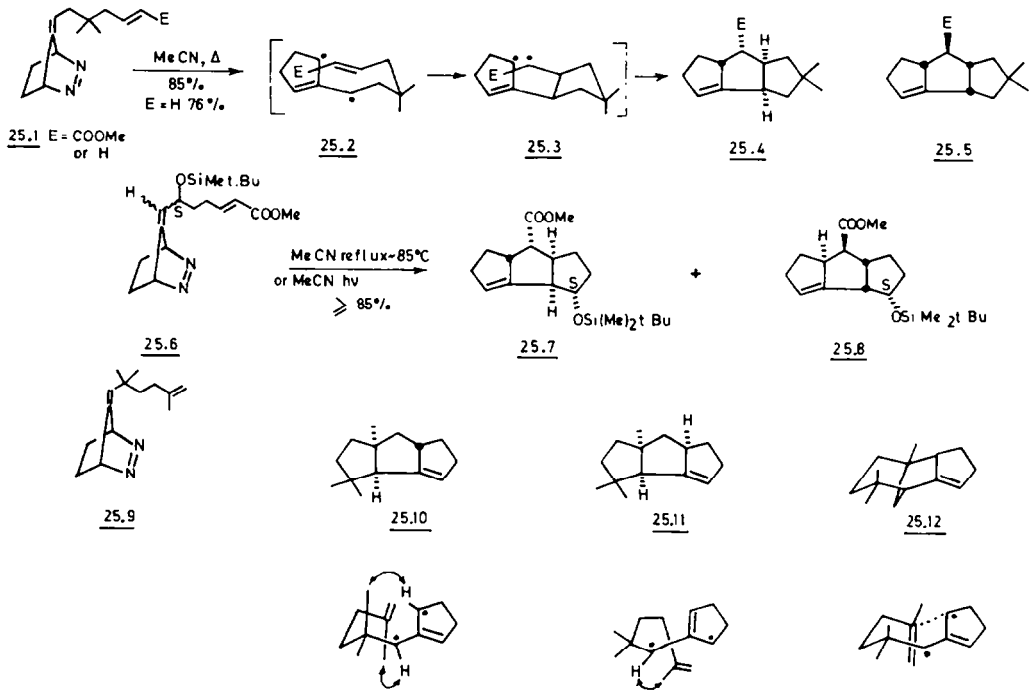
Dreiding developed the α-alkynone cyclization for the formation of fused 5-membered ring systems.[130] Alkynyl alkyl ketones **24.1**, having at least one β′-H atom, thermally cyclize to 2-cyclopentenones **24.3**. The process forms a new C—C bond at a non-activated β′-C atom and causes a [1.2]-shift of an acetylenic substituent and is therefore explained by the intermediacy of an alkylidene-carbene **24.2**, which inserts into the β′C—H bond. The regioselectivity is in order of tertiary > secondary > primary β′-C atoms but is also subject to conformational factors and steric inhibition thus resulting in the formation of isomers when several β′-H atoms are available. This is illustrated by the cyclization of **24.4**,[131] giving **24.5**, **24.6** and **24.7** in a 2:1:1 ratio and of **24.8**[132] giving **24.9** and **24.10** in a 45:55 ratio.

Intramolecular diyl trapping. Little *et al.*[133] have reported a highly interesting approach (Scheme 25) towards the *anti–cis* linear triquinane framework of **17.1** and **17.5**. The key-step is the intramolecular variant of the diyl trapping reaction,[134] forming two 5-membered rings in the process. The precursor diazenes (e.g. **25.1**) are obtained via Diels–Alder reaction of a fulvene with azodicarboxylate esters. Expulsion of nitrogen yields the 1,3-diyl **25.2** which is trapped by the double bond; the step-wise fashion explains best the experimental observations.[135a] The stereoselectivity can be rationalized by assuming a pseudochain conformation for the acyclic chain in **25.2** with an *endo*-methoxycarbonyl group permitting energy lowering secondary orbital interactions, which explains the different observed ratio. Indeed, starting from **25.1**, for respectively E = COOMe[133a] and E = H,[133b] the ratios of **25.4** and **25.5** are 9:1 and 5:1. With **25.6** asymmetric induction in the 1,3-diyl trapping reaction was studied.[135b]



24.1 24.2 24.3 24.4 24.5 24.6 24.7 24.8 24.9 24.10

Scheme 24.

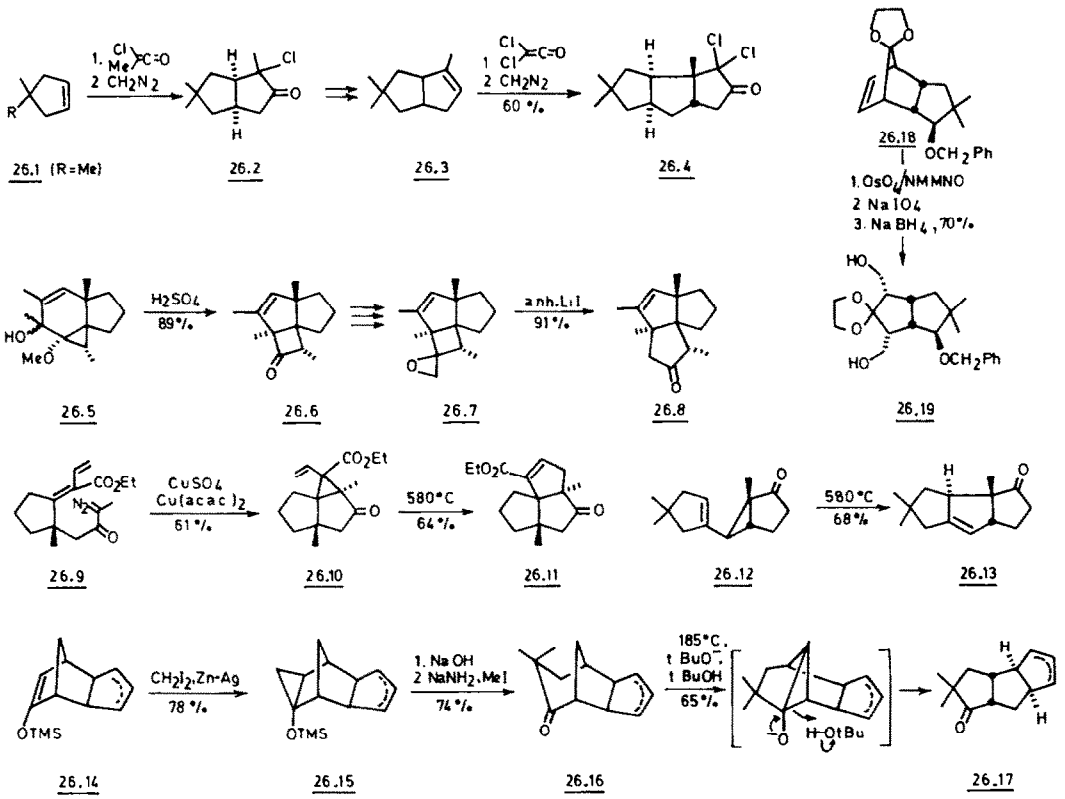


Scheme 25.

Both diastereoisomers give the same result; under reflux conditions the diastereoisomeric ratio **25.7** : **25.8** is 11.8 : 1. Fragmentation of **25.6** upon irradiation has a dramatic effect; the ratio in favour of **25.7** is now 26 : 1. Starting from **25.9** a reversal of the above described regiochemical mode is observed, the major product being the bridged tricycle **25.12**.[136] The transition states leading to **25.10** and **25.11** suffer respectively from two and one H-methyl nonbonded interactions (Scheme 25).

Bicyclo[3.3.0]*octanes from other polycarbocyclic systems.* A short route to the hirsutane group, based on iterative three-carbon annulation, has been developed by Greene.[137] The method centres around chloro-ketene [2+2]cyclo addition and subsequent regioselective (directed by the chlorine atom) diazomethane ring expansion (**26.1** → **26.2** and **26.3** → **26.4**). Starting from **26.1** (R = COOMe) reaction with dichloroketene produces the bicyclic intermediate with the *exo*-carboxylic group as the major product (ratio 3 : 1). Recently Paquette and Annis[118b] applied Greene's strategy, starting with regioselective cycloaddition to a silyl enol ether. The synthesis of **17.7** reported by Wenkert and Arrhenius[138] starts from **26.5**, obtained from 2-methylcyclopentanone in 9 steps, via Robinson annulation, stereodirected cyclopropanation and functionalization of the 6-membered ring. The crucial step involves an α-oxycyclopropyl carbinol-to-cyclobutane rearrangement of **26.5** to **26.6**. Cyclobutanone ring expansion using the Trost methodology finally gives then **26.8**. Hudlicky *et al.*[139b] constructed the isocomene skeleton by internal cyclopropanation of the exocyclic acrylate **26.9** (1 : 1 *E*–*Z* isomers) and subsequent vinylcyclopropane rearrangement to **26.11**. Previously a report of the same laboratory[139a] described the synthesis of **17.1** via the same process; **26.12** is obtained by internal cyclopropanation of the corresponding diazo-ethyl ketone, its thermolysis provides the anti-*cis* linear triquinane **26.13** next to 10% of syn-*cis* isomer. Stothers *et al.*[140a] described an approach to **17.1** in which the key-step is based on the rearrangement by homoenolisation of **26.16**. Starting from dicyclopentadiene and via homoketonisation of **26.15**, the intermediate is obtained as a 3 : 1 mixture of double bond isomers. Rearrangement of **26.16** proceeds smoothly to the *cis-anti-cis* skeleton **26.17** of hirsutene. The mechanism shown is assumed to occur via β-enolization; previously the same group had also given evidence of γ-enolization in related systems.[140b] The methane indene **26.18** (from the dimer of the acetal of cyclopentadienone) has been used to construct **26.19**, as precursor for **17.4**.[141]

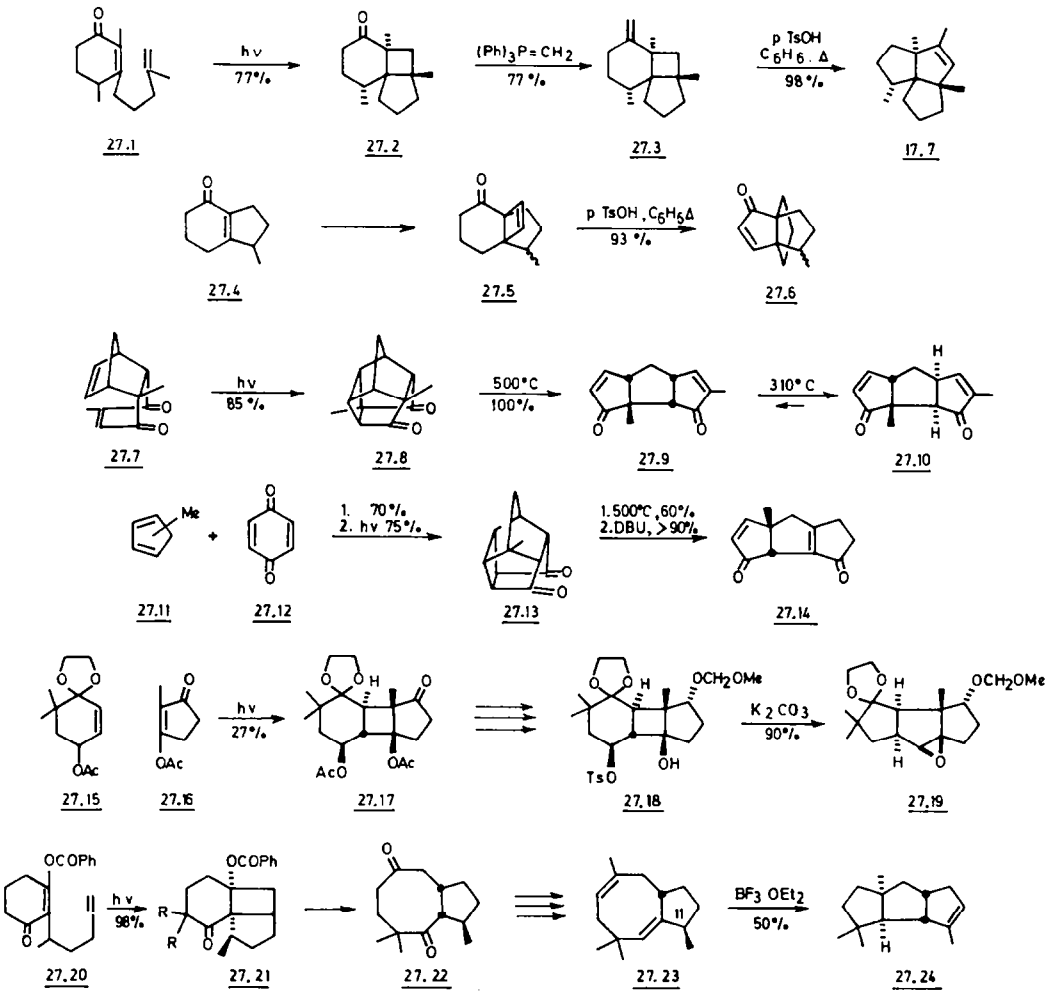
Skeleton rearrangement of photocycloaddition products. The ready availability of 4-membered rings from enone–alkene photocycloadditions has been at the origin of several approaches. An efficient application of this strategy is found in Pirrung's synthesis[142] of **17.7**. Irradiation of **27.1** provides **27.2** as the only isomer, with the correct configuration of three contiguous quaternary centres. Wittig reaction



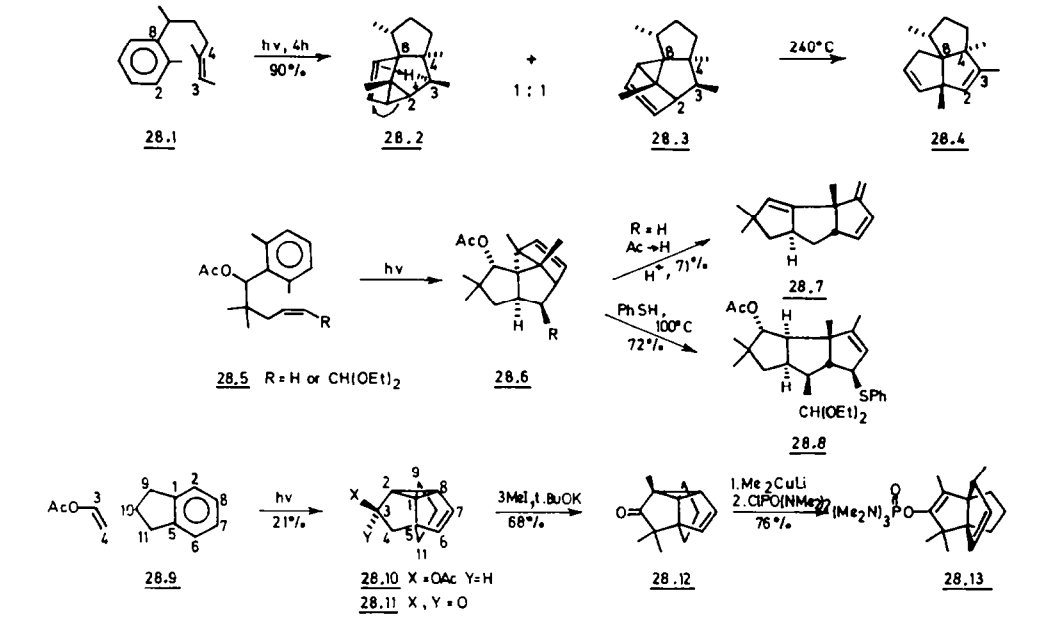
Scheme 26.

under forcing conditions and Wagner–Meerwein rearrangement of **27.3** leads to **17.7**. In the Smith–Jerris synthesis[143] of **17.6** the tricyclic intermediate **27.5** is obtained upon irradiation of **27.4** with ethyne or better with 1,2-dichloroethene (and subsequent reductive removal of chlorine); the cycloaddition is only moderately in favour of the desired *anti*-adduct (57 : 43). Cargill rearrangement of **27.5**, via initial shift of the vinylic bond, followed by a second [1.2] alkyl shift produces **27.6**. An interesting and versatile construction of the linear triquinanes involving a photo-thermal metathetic sequence has been described by Mehta *et al.*[144] Irradiation of **27.7** (the *endo* Diels–Alder adduct of cyclopentadiene and 2,5-dimethyl-*p*-benzoquinone), followed by thermolysis of the cyclobutane ring in **27.8** provides **27.9**. Thermal isomerization, involving double bond shift to the fused position leads to an equilibrium with **27.10**, a precursor for **17.1** and **17.4**. Essentially the same sequence starting from **27.11** enables construction of **27.14** a precursor of **17.5**.[145] The key-step in the Tatsuta *et al.* synthesis[146] of **17.1** and **17.4** is the solvolytic rearrangement of tosylate **27.18** to epoxide **27.19**. The approach starts with the photocycloaddition between **27.15** and **27.16**. Pattenden's biogenetically patterned synthesis of the capnellene framework involves transannular cationic–olefin cyclization of **27.23**, the C-11 epimer of the naturally occurring precapnelladiene.[147] The key-step is the intramolecular photocycloaddition of **27.20**. Double methylation, base promoted hydrolysis and retro-aldol reaction yields **27.22** which is then selectively converted to **27.23**.

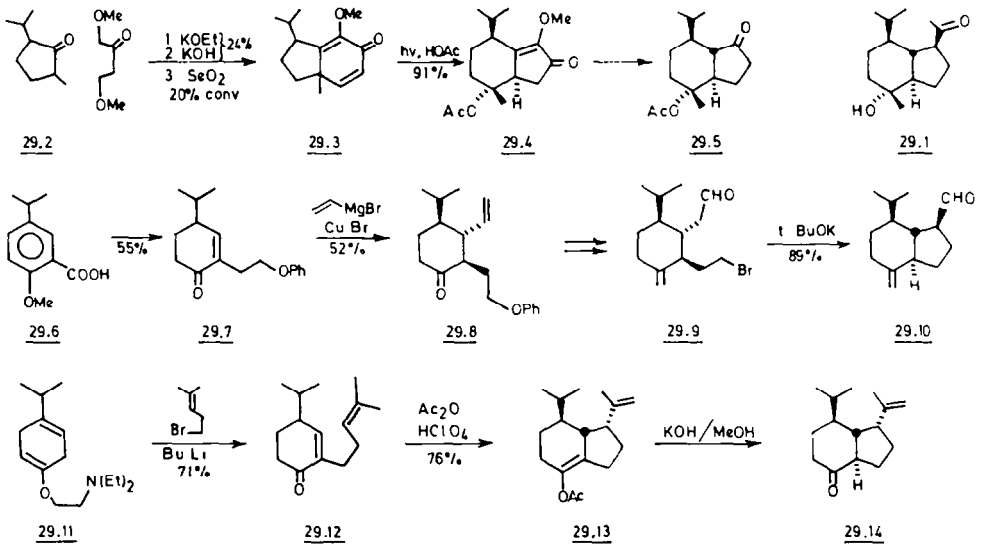
Highly potential precursors for annulated 5-ring systems can be obtained via the intramolecular variant of the arene–olefin *meta* photocycloaddition[148] (Scheme 28). Wender's application provides presently the most efficient and versatile approach to triquinanes.[149,150] Irradiation of **28.1** gives a 1 : 1 ratio of the photochemically interconvertible adducts **28.2** and **28.3**.[149a] A thermally induced homo 1,5-sigmatropic H-shift in **28.2** provides (±)-dehydroisocomene **28.4** (82%); the latter is also obtained (46%) from **28.3**, via initial vinylcyclopropane isomerization to **28.2**. Starting from bromotoluene, **17.7** is obtained in five steps. Similarly **28.5** can be converted to **28.6** as the major adduct.[150] The alcohol from **28.6** (R = H) is transformed via dehydrative rearrangement to **28.7**, while radical cleavage of **28.6** [R = $CH(OEt)_2$] gives **28.8**. Both **28.7** and **28.8** are precursors for **17.4**. The intermolecular *meta* addition[149b] of **28.9** with vinylacetate gives **28.10** which is transformed into **28.11**, a precursor for **17.6**. Interestingly, upon methylation of **28.11**, three methyl groups are introduced, this is made possible by



Scheme 27.



Scheme 28.



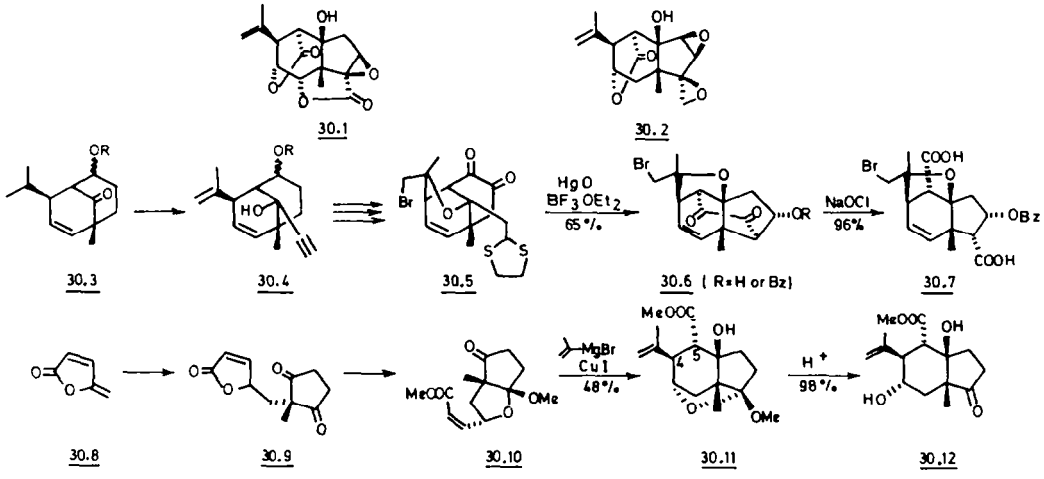
Scheme 29.

the fact that the enolate of **28.11** and of already methylated derivatives, exhibit the dynamic behaviour of semibullvalenes. Finally nucleophilic cyclopropane ring opening followed by enolate trapping produces **28.13**.

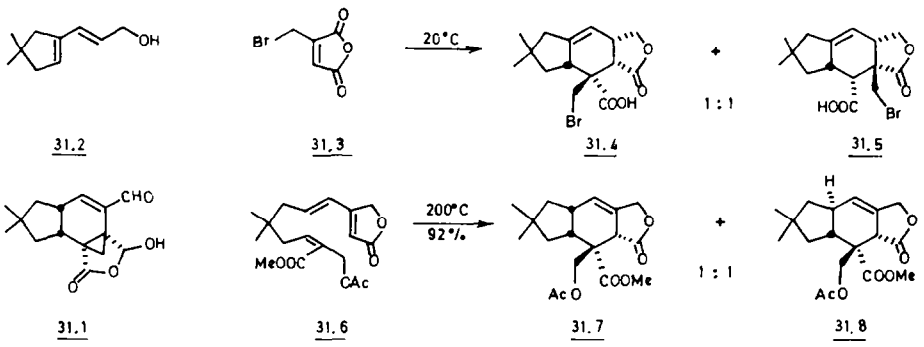
3. *The bicyclo*[4.3.0]*nonane or hydrindane group*

There are only few sesquiterpenes based on this structure, even when tricyclic compounds having an additional cyclopropane or cyclobutane ring are included. Therefore we will group the different approaches towards a specific skeleton. Obviously some of the 5- and 6-membered annulating methods described in the foregoing sections can be applied. Oplopanone **29.1** is a *trans*-fused hydrindane with a β-oriented substituent at C-3; both stereochemical features represent the most stable configuration. The Caine–Tuller synthesis[151] centres around the photochemical rearrangement[81] of cross-conjugated dienone **29.3**, itself produced by Robinson annulation followed by oxidation. Transformation of **29.4** leads to the thermodynamically stable *trans*-fused hydrindanone **29.5**. The Taber–Korsmeyer synthesis[152] is based on the internal alkylation of the aldehyde **29.9** affording the most stable isomer **29.10**. The sequence starts with reductive alkylation of **29.6** and subsequent 1,4-addition on **29.7**. Alternatively, Köster and Wolf[153] apply the directed alkylation on **29.11** for constructing **29.12**, which is then cyclized, stereoselectively, to **29.13**. Hydrolysis under equilibration conditions affords *trans*-fused **29.14** as the major isomer (ratio 3:2).

The remarkable total synthesis of picrotoxinin **30.1** reported by Corey and Pearce[154] features a number of transformations from which only those directly involved in the construction of the skeleton



Scheme 30.



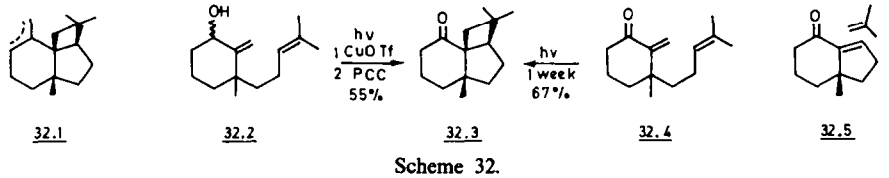
Scheme 31.

are selected. Alkylation of the dimethylhydrazone of (−)-carvone and aldol cyclization produces **30.3**. Elaboration of **30.5** proceeds via **30.4** and subsequent bromoether formation, introduction of a protected aldehyde function and keto-enolate oxidation (O_2). Dithiolane cleavage and aldol cyclization establishes the hydrindane nucleus in **30.6**. It is worth noting that oxidative double-lactonization of **30.7** could only be affected with lead tetraacetate in acetonitrile. Inubushi *et al.*[155] constructed the hydrindane nucleus of coriamyrtin (**30.2**) upon 1,4-addition on acrylate **30.10** followed by cyclization via enolate trapping by the carbonyl function. The first step is not selective as the C-4,C-5-diastereoisomer of **30.11** is formed in 36% yield. The intermediacy of **30.10** is necessary because the same reaction sequence on butenolide **30.9** produces the incorrect stereochemistry.

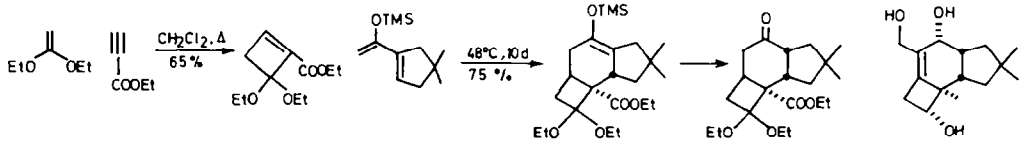
In recent syntheses of marasmic acid (**31.1**) the framework is constructed via a Diels–Alder reaction. In the Greenlee–Woodward[156] approach, the smooth reaction between **31.2** and **31.3** suggests an internal process, subsequent to ester formation; both adducts **31.4** and **31.5** are suitable for further transformation. The Boeckman–Ko[157] synthesis centres around cyclization of **31.6**, both the *cis* (*endo*) and the *trans* (*exo*) hydrindenes **31.7** and **31.8** are produced. Traces of acid increase the proportion of **31.8**; clearly secondary orbital interactions are energetically insufficient to overcome unfavourable nonbonded interactions. The preferred formation of *trans*-hydrindene **31.8** is in accord with previous observations.

The tricyclic skeleton of the panasinsenes **32.1** (*exo* or *endo* double bond) has been constructed by intramolecular [2 + 2] photocycloaddition reactions. McMurry and Choy[158] apply the intramolecular version of the Salomon process on **32.2** involving cuprous triflate catalyzed photochemical addition of an olefin to an allylic alcohol. Johnson and Meanwell[159] showed that, although slow, the intramolecular process starting from enone **32.4** produces **32.3**. It is worth noting that McMurry[158] has observed that the intermolecular variant on enone **32.5** with isobutylene did not afford **32.3**.

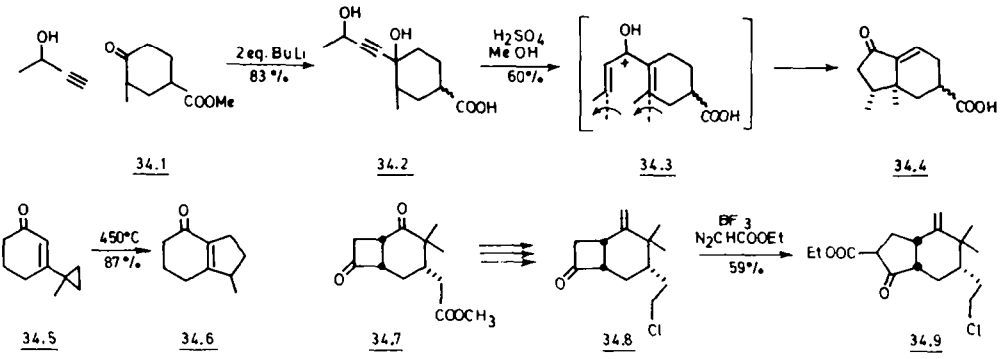
In a recent illudol (**33.1**) synthesis, Semmelhack *et al.*[160] constructed the skeleton **33.4** by Diels–Alder reaction between **33.2** and **33.3**; because of the thermal instability of the dienophile, minimum temperature conditions are required.



Scheme 32.



Scheme 33.



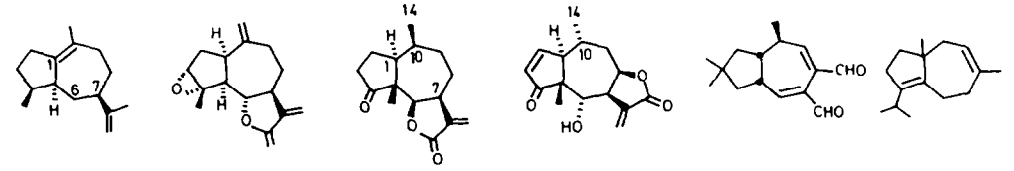
Scheme 34.

The formation of some hydrindanes which are intermediates in the synthesis of other sesquiterpene skeletons is given in Scheme 34. The eremophilane precursor **16.1** has been obtained from **34.4**. Other novel applications of the Nazarov reaction have already been described in Scheme 22; Hiyama *et al.*[83b,c] reported an efficient alternative for the divinylketone intermediate starting from **34.1**. Cyclization of **34.2** is completely regio- and stereoselective. This suggests the cation **34.3** as the thermodynamically favourable intermediate for electrocyclic conrotatory ring closure. The hydrindenone **34.6**, an intermediate for the synthesis of (±)-zizaene (Section III.2) has been obtained upon thermal rearrangement of the β-cyclopropyl-α,β-unsaturated ketone **34.5**.[161] Ring expansion of cyclobutanone **34.8** affords the khusimone precursor **34.9**.[162] Diketone **34.7** is the hydrolyzed, minor product (ratio 5 : 8) formed during photocycloaddition of the corresponding cyclohexenone and 1,1-diethoxy-ethene.

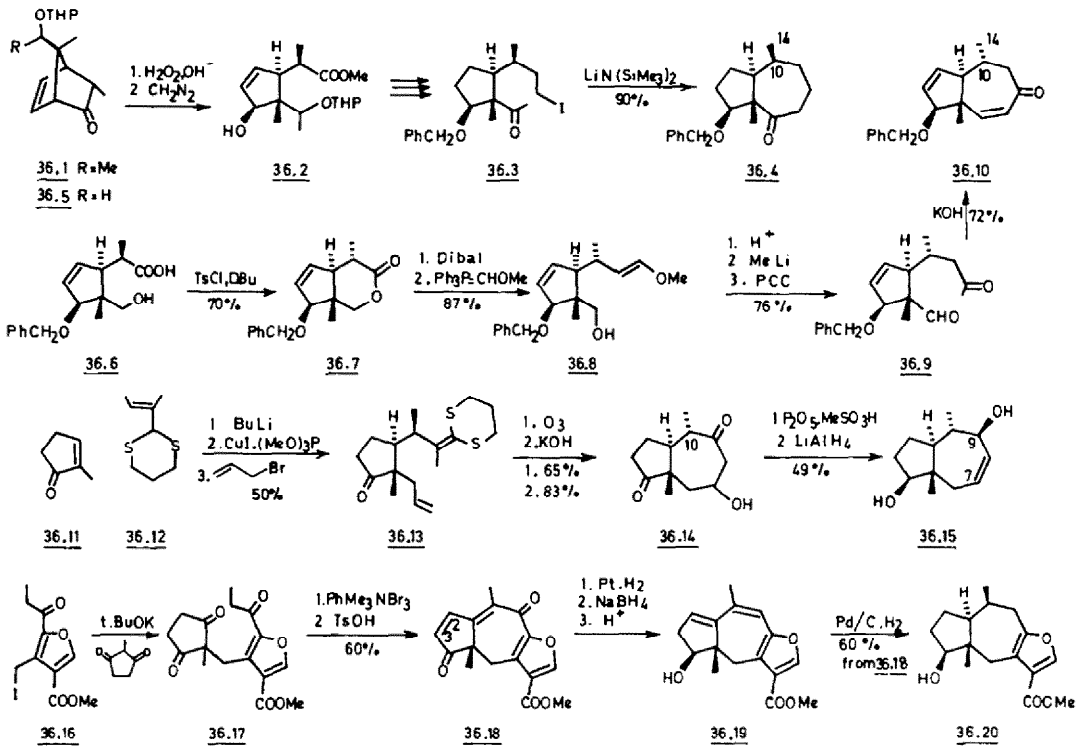
4. *The bicyclo*[5.3.0]*decane or perhydroazulene group*

Despite their early detection, marked progress in the total synthesis of perhydroazulenic sesquiterpenes has only been made during the last 10 years. This is largely due to stereochemical problems associated with the conformationally labile system. The two largest subgroups are based on the guaiane (e.g. **35.1** and **35.2**) and on the pseudoguaiane (e.g. **35.3** and **35.4**) framework, while some compounds have a substitution pattern as in **35.5** and **35.6**. The isopropyl group of a guaiane can also be part of a cyclopropane ring closed at C-6. This section will be devoted mainly to the two large subgroups and more especially to the pseudoguaianolides (e.g. **35.3** and **35.4**) for which synthetic efforts were most successful. This can be explained by the fact that the angular methyl group allows better stereocontrol. The pseudoguaianolides are *trans*-fused, possess a β C-7 configuration and the lactone ring *cis*- or *trans*-fused at C-6 or C-8; they are subdivided according to the orientation of the C-14 methyl group (**35.3** and **35.4**). As has first been shown by Marshall[163] and as is illustrated throughout this section, catalytic hydrogenation of a double bond at respectively C-10 and C-7 leads in general predominantly to the β-configuration. On the other hand intermediates allowing equilibration at C-10 provide an entry into the α series (e.g. **35.4**). Among the first approaches towards perhydroazulenes rank skeleton rearrangements of decalin precursors; new applications will be described in Scheme 42. We will however review first the recent, most frequently employed strategy in which the 7-membered ring is constructed on the cyclopentane ring.

Annulation of the cycloheptane ring. Scheme 36 groups three approaches in which the 7-membered ring is closed upon aldolization. Central in Grieco's[164,165] large contribution to the



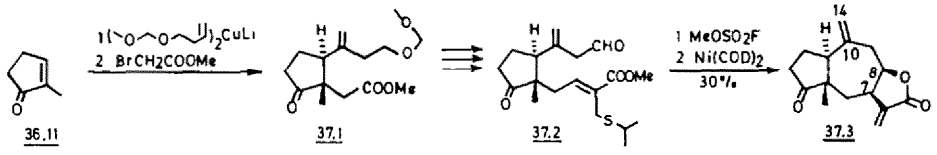
Scheme 35.



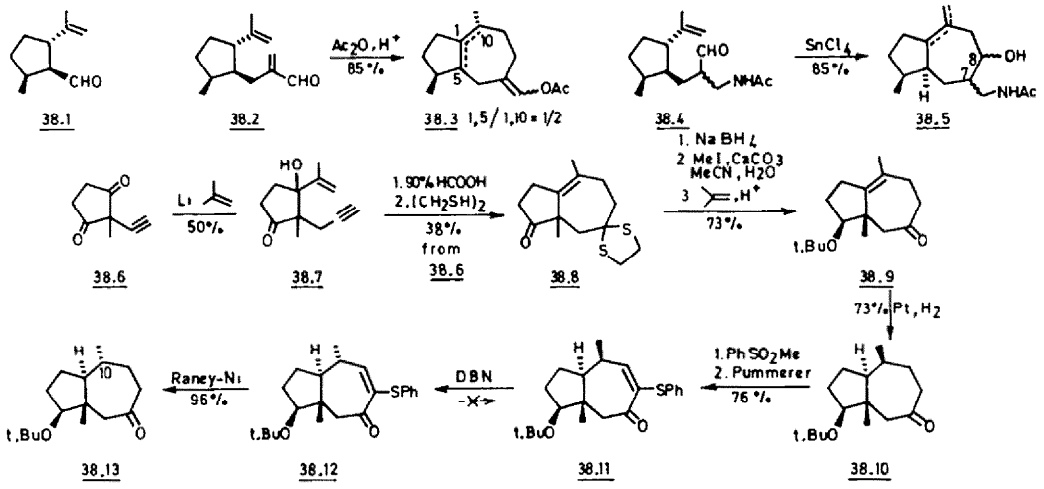
Scheme 36.

pseudoguaianolides are the cyclopentanoids **36.2** and **36.6**. The intermediate **36.2** (for the C-10 β-series) is obtained via **36.1** from norbornadiene in 25% overall yield.[164] Functional group transformation and chain extention provides **36.3** which is cyclized to **36.4**. Alternatively the α C-10 subclass is accessible via **36.6** (from **36.5**).[165] Inversion at C-10 involves the intermediacy of **36.7**; complete isomerization of the 14-methyl group occurs because of the severe 1,3-diaxial methyl–methyl interaction in the initially produced lactone. Transformation to **36.9** and aldol cyclization provides **36.10**. Both **36.4** and **36.10** are valuable intermediates. The Ziegler–Fang[166] approach involves 1,4-addition on **36.11** of the lithium anion of **36.12** and subsequent alkylation for attaching the elements of the 7-membered ring. Ozonolysis produces the keto-aldehyde, which upon cyclization leads to the more stable α C-10 configuration (**36.14**). The stereoselective reduction at C-9 is essential because the C-7-substituent is subsequently introduced on **36.15** via Claisen rearrangement. Schultz and Motyka[167] developed the annulation reagent **36.16** for attaching the C-atoms of the cycloheptane and lactone ring on 2-methyl-1,3-cyclopentanedione. The enole form of **36.17** inhibits aldol cyclization; therefore the double bond was first introduced and the reaction to **36.18** was carried out on the cyclopentenedione intermediate. Hydrogenation of the 2,3-bond, reduction of both keto functions and dehydration produces **36.19**. Selective hydrogenation leads to the β C-10 series, subsequently the furan ring in **36.20** can be transformed to a β-*cis* fused γ-lactone.

Semmelhack's[168] strategy involves intramolecular coupling of an allylic metal species obtained via the sulfonium salt of **37.2**, with an aldehyde function and concomitant lactonization. Optimum results were obtained with Ni(0); **37.3** is formed next to the 7,8(α)-diastereoisomer (15%). The substrate **37.2** was constructed via **37.1**. Unfortunately, selective reduction of the 10,14-double bond in **37.3** was not possible.



Scheme 37.

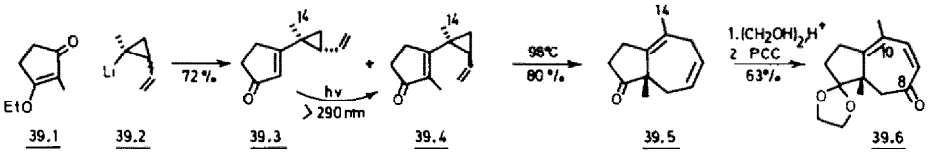


Scheme 38.

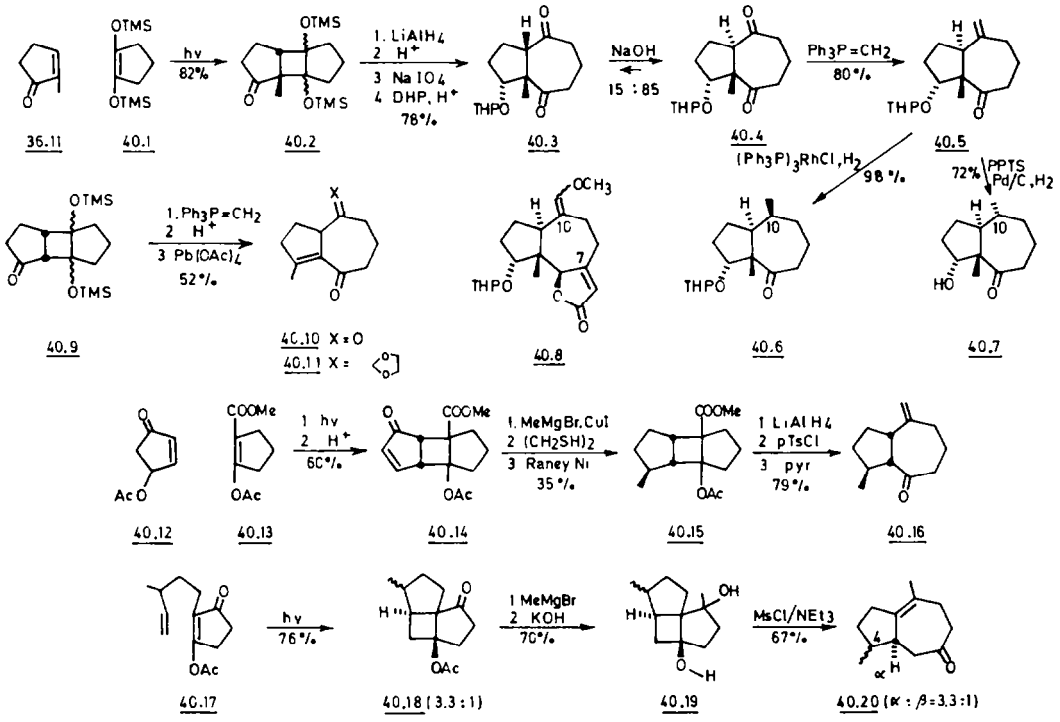
The approach to guaianes reported by Andersen *et al.*[169] centres around the cationic–olefin cyclization of **38.2** and **38.4** which are obtained from photocitral **38.1**. Cyclization of **38.2** provides the 1 : 2 mixture of double bond isomers **38.3** while **38.4** leads to three major products **38.5**; the *exo* isomer is stereohomogeneous (α C-7 and C-8). Lansbury *et al.*[170] developed a 3-step pseudoguaiane skeleton formation via **38.6**, obtained upon propargylation of 2-methyl-1,3-cyclopentanedione **18.8**. Cyclization of **38.7** produces a 7-membered ring; competitive 6-membered ring formation is disfavoured because of the intermediacy of a primary vinyl cation. The resulting diketone is selectively transformed into **38.8**, allowing the formation of a β C-4 substituent which enhances the stereoselectivity (> 90%) of the hydrogenation step to **38.10**. Entry into the α C-10 isomer **38.13** is achieved via **38.11**; DBN-mediated equilibration gives **38.12** next to the β,γ-enone in a 3 : 1 ratio. Attempted epimerization of the cycloheptenone, lacking the phenylthio group, led completely to the β,γ-enone.

The thermal rearrangement of divinylcyclopropanes for cycloheptane annulation has been studied independently by Piers,[171] Marino[172] and Wender[173] in 1976. Wender *et al.*[174] have extended the method for pseudoguaianolide total synthesis. It was observed that for C-14 methylated cyclopropanes only the *cis*-isomer **39.4** leads to **39.5**. Isomer **39.3**, the major product from **39.1** (ratio 4 : 1), gave at 140° a homo[1,5]sigmatropic shift. This problem could be circumvented upon photoisomerization of **39.3**. Irradiation provides a mixture, enriched in **39.4**, which upon selective pyrolysis gives **39.5** and unreacted **39.3**. Oxidation of the acetal of **39.5** provides predominantly **39.6**, an intermediate for β C-10 pseudoguaianolides.

Photocycloaddition between two cyclopentene rings followed by cyclobutane ring cleavage provides an efficient entry into fused 5,7-ring systems (Scheme 40). Vandewalle *et al.*[175] constructed the pseudoguaianolide intermediate **40.4** via cycloaddition between **36.11** and **40.1**; after reduction of the keto function in adduct **40.2**, diol cleavage affords the *cis*-fused skeleton. Equilibration of the ether **40.3** provides predominantly the *trans*-fused isomer **40.4**; the ratio is probably influenced by the destabilizing effect of the *endo* oriented group in **40.3**. After selective Wittig reaction, entry into both C-10 α and β series is possible. Wilkinson catalyst produces exclusively **40.6**;[175c] although less efficiently, Pt-catalysts give comparable results. Surprisingly, reversal of the stereochemical outcome is observed when the hydrogenation is conducted on the corresponding alcohol of **40.5** with Pd–C as catalyst; the α,β ratio is 8 : 2.[176a] Although the reason is unknown, seemingly the free α C-4 hydroxyl group is a



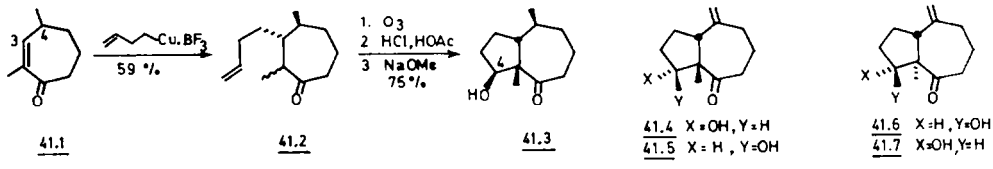
Scheme 39.



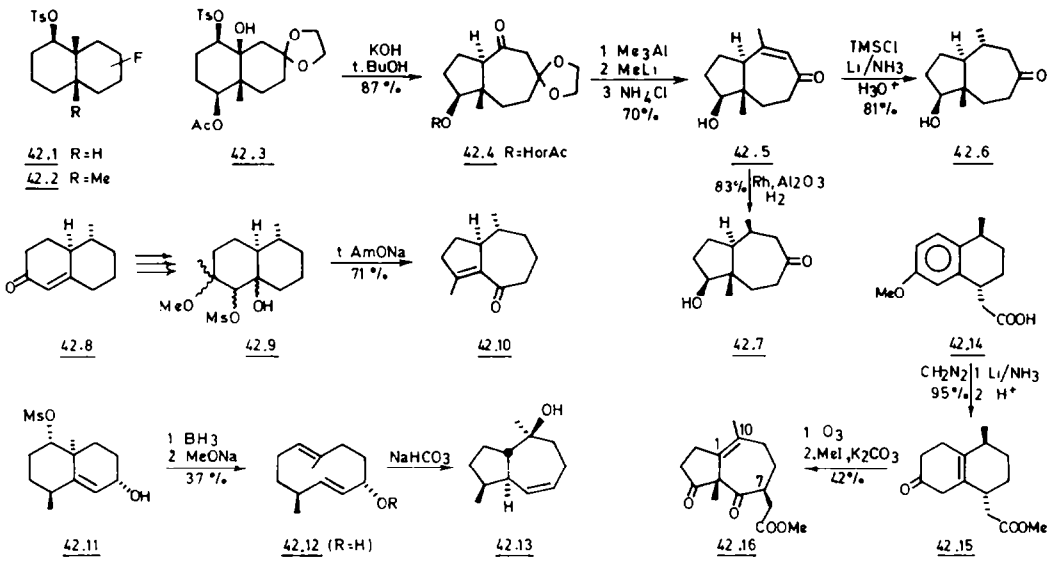
Scheme 40.

determining factor. It is worth mentioning that, hydrogenation on Pt–C of the enol ether **40.8** leads, with cleavage of the THP ether, also to a C-10 epimeric mixture in favour of the α-isomer (7 : 3), while only the β-configuration at C-7 is formed.[176c] Analogously, initial photoaddition of **40.1** with cyclopentenone provides, via **40.9**, a 3 step entry into the guaiane framework **40.10**. The monoketal **40.11** is the key-intermediate[177] which allowed the first direct total synthesis of guaianolides (e.g. **35.4**).[177c] Liu and Lee[178] constructed the pseudoguaiane framework upon photocycloaddition with the unsymmetrical olefin **40.13**. The expected adduct is formed predominantly and affords enone **40.14** upon subsequent acid treatment. After introduction of the 4-methyl group removal of the keto function and reduction of both esters, fragmentation is effected upon preparing the primary tosylate. The same ring expansion has been applied by Oppolzer and Wylie in their β-bulnesene synthesis.[179] The intramolecular photoaddition in **40.17** produces **40.18** as an epimeric mixture (ratio 3 : 3 : 1). Fragmentation of **40.19** via the presumed mesylate yields the C-4 epimers **40.20**.

Annulation of the cyclopentane ring. The unique approach based on this strategy has been reported by Heathcock *et al.*[180] Using Yamamoto's reagent the 3,4-*trans*-configuration in precursor **41.2** is obtained predominantly (ratio 5 : 1). Acid-catalyzed aldolization only produces the *cis*-fused isomer **41.3** as the kinetic product. The C-4 epimeric *endo* alcohol is also formed under equilibrating conditions; the *trans*-fused products are not observed, although they are usually more stable than the *cis* isomers. This suggests an energetically unfavourable transition state for the formation of *trans*-perhydroazulenes by intramolecular aldolization. In this context, it is of interest to mention the base-induced isomerization of **41.4** and **41.6**[181] which afford predominantly **41.5** and **41.7**, respectively, under kinetic conditions in the presence of chelating lithium cations. In hydroxylic medium **41.5** is the preferred kinetic product, while under equilibration conditions **41.5** and **41.6** predominate.



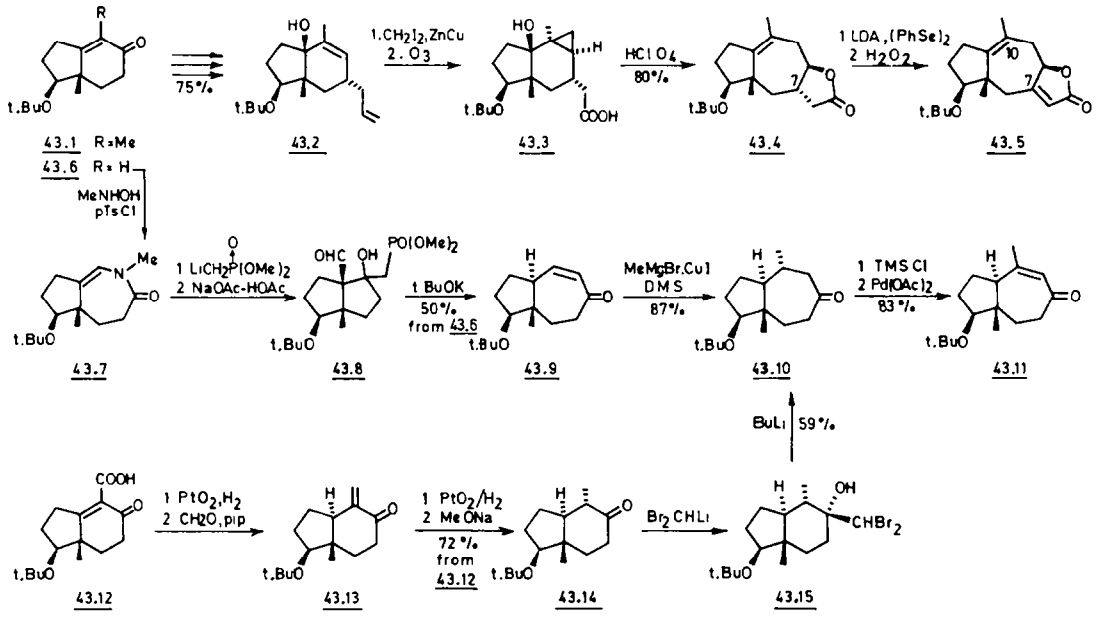
Scheme 41.



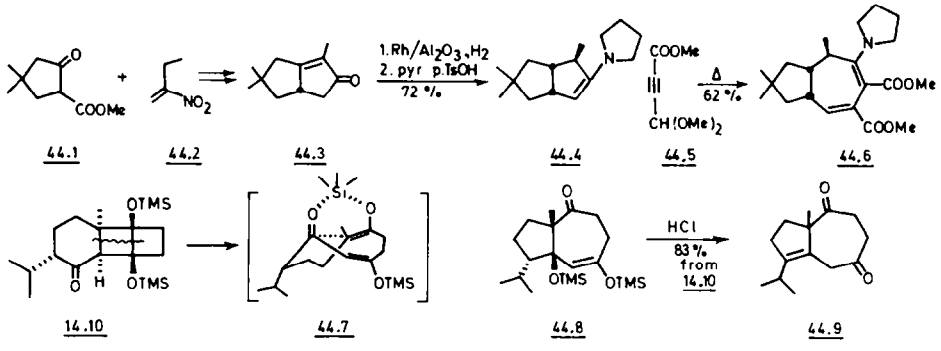
Scheme 42.

Bicyclo[5.3.0]*decanes from other polycarbocyclic systems.* Earlier approaches to perhydroazulenes relied heavily on the rearrangement of decalin precursors.[182] Barton's[81] photochemical transformation of cross-conjugated dienones found use in relay syntheses. Other processes, involving solvolytic [1.2] shifts, have been developed by Mazur[183] (pinacol rearrangement) and Heathcock[184] (Wagner–Meerwein rearrangement). Heathcock *et al.*[185] have recently reported that, in contrast to **42.1**, solvolysis of angularly dimethylated precursors as **42.2** fails to produce a viable route to the pseudoguaiane skeleton. Alternatively, the pinacol rearrangement of **42.3** provides **42.4** (R = H) together with the *cis* isomer in a 4 : 1 ratio, reflecting the equilibrium. Transformation of **42.4** (R = Ac) into **42.5** (see also **43.11**) and subsequent chemical reduction or catalytic hydrogenation allows an entry into both C-10 α and β pseudoguaianolides **42.6** and **42.7**. In an approach to guaianolides, Posner *et al.*[186] applied the anionic pinacol rearrangement on a mixture of isomeric **42.9**; concomitant β-elimination provides **42.10**. The substrates **42.9** were obtained from the known **42.8**. Transformation of decalins to perhydroazulenes via a 10-membered ring has also been effected. In an application of his boronate fragmentation reaction,[187a] Marshall[187b] opened **42.11** to **42.12**, the *p*-nitrobenzoate of which undergoes solvolytic cyclization to **42.13**. The first total synthesis of a naturally occurring pseudoguaianolide has been described by Kretchmer and Thompson.[188] Construction of the intermediate **42.16** is based on the ozonolysis of **42.15**, aldol ring closure of the resulting triketone and subsequent methylation. The process is non-stereoselective and affords also the α C-7 isomer (21%). In a further stage hydrogenation on Pd–C leads to the β configuration at C-10.

Three approaches involving ring expansion of a hydrindane precursor are shown in Scheme 43. Marshall–Ellison[189] constructed the key-intermediate **43.3** starting with Robinson annulation on **18.18**; it is noteworthy that the Wharton method for the formation of **43.2** from **43.1** failed and that a longer alternative had to be used. Solvolysis of **43.3** produces directly the lactone **43.4** with incorrect α C-7 configuration. Inversion is realized via **43.5**, which upon hydrogenation (Pd–C) provides the desired C-7,C-10 β isomer. Schlessinger *et al.*[190] have reported an efficient entry into pseudoguaianolides starting from **43.6**. The Barton[191] variant of the Beckman rearrangement leads to **43.7**; reaction of the phosphonate anion on the carbonyl of this lactam is followed by rearrangement via ring opening and ring closure to the N—Me imine analogue of **43.8**. The desired *trans*-fused geometry of **43.9** is determined during this process. Base-induced retro aldol ring opening and intramolecular Wadsworth–Emmons condensation provides then **43.9**. Complete stereoselective transformation to **43.10** is effected as shown; alternative addition of Me_2CuLi complex led to a 4 : 1 isomeric mixture. The β C-10 series can also be obtained upon trapping of the intermediate enolate of **43.10** as a TMS ether and oxidative reintroduction of the double bond.[190b] Subsequent catalytic hydrogenation of **43.11**, as shown for **42.5**, affords the β C-10 isomer. An alternative synthesis of **43.10** has been reported by Kim *et al.*[192] Hydrogenation of the unstable enone **43.13** produces an epimeric mixture which upon base-



Scheme 43.



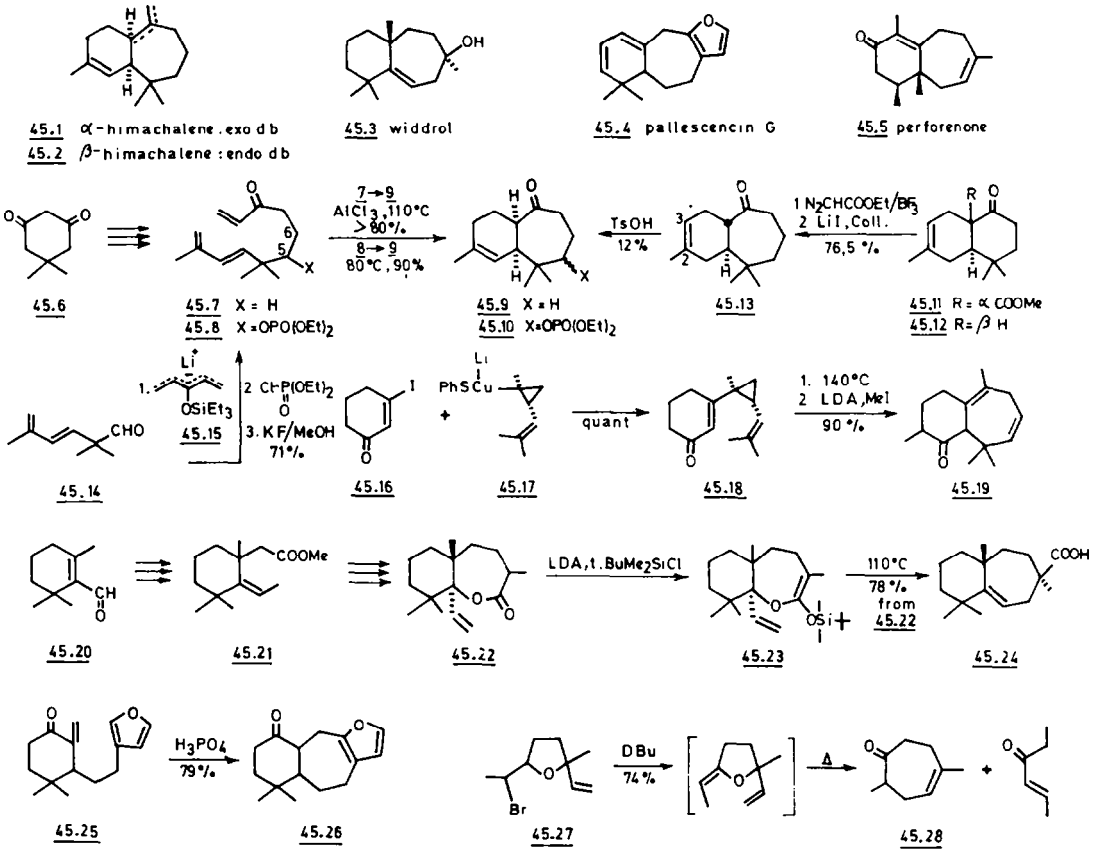
Scheme 44.

equilibration gives the most stable equatorial isomer **43.14**. Application of Nozaki's β-oxido-carbenoid ring expansion (see Scheme 16) leads via **43.15** to **43.10**.

The vellerane skeleton has been constructed by Froborg and Magnusson[193] from the enamine **44.4** which has been obtained from **44.1** (see also Scheme 18). Thermal cycloaddition of **44.4** with acetylenic ester **44.5** and subsequent cyclobutene ring opening produces **44.6**, which has been transformed into **35.5**. A recent approach to daucene **35.6**[194b] is based on the metathetical thermolysis of photoadduct **14.10**. The initially formed cyclodecadienones, such as **44.7**, undergo a spontaneous transannular reaction under the condition of their formation.[194a] The reaction involves an oxygen to oxygen migration of a silyl group leading to **44.8** as one of two major isomers. Both produce the diketone **44.9** upon acid treatment.

5. *The bicyclo*[5.4.0]*undecane group*

Some representatives of this small group of sesquiterpenes are shown in Scheme 45. The *cis*-fused framework of α-himachalene **45.1** has been formed upon intramolecular Diels–Alder reaction of **45.7** and **45.8**. Wenkert and Naemura[195] constructed the triene **45.7** in a multistep sequence. A more convergent synthesis of **45.8** has been presented by Oppolzer and Snowden[196a] and involves formation of the 5,6-bond by their method for attaching a functionalized 5-carbon chain[196b] (**45.14** + **45.15** → **45.8**). The Liu–Browne[197] approach centres around diazoacetate ring expansion of **45.12** which produces, **45.13** after decarboxylation. Acid-catalyzed equilibration of **45.13** leads to a mixture of 4



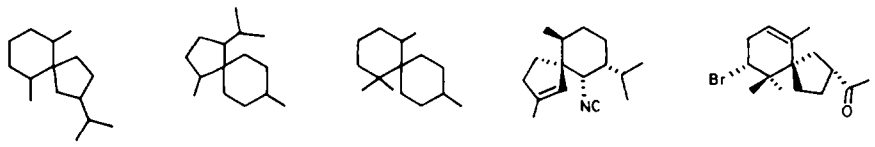
Scheme 45.

isomers (*cis–trans* and 1,2–2,3 double bond) in which **45.9** is a minor component. The ester **45.11**, precursor for **45.12**, is formed by a fairly regioselective, $SnCl_4$-mediated Diels–Alder reaction. Thermal rearrangement of divinylcyclopropanes[171–173] (see also Scheme 39) has been applied by Piers and Ruediger[198] for the synthesis of **45.2**. Heating **45.18** and subsequent methylation produces **45.19**. Danishefsky *et al.*[199b] developed a method for the construction of cycloalkenes based on the Claisen rearrangement of lactonic silyl enolates, as a variant of Ireland's[200] rearrangement. In the synthesis of **45.3**,[199a] thermolysis of **45.23** leads stereospecifically to **45.24**, through a boatlike transition state. Subsequently the carboxyl function in **45.24** is replaced, with retention of configration, by a hydroxyl group. The precursor **45.22** was obtained in a multi-step sequence from cyclocitral **45.20**. Matsumoto and Usui[201] synthesized **45.4** upon applying a Friedel–Craft type cyclization of **45.25** (see also Scheme 10). Perforenone (**45.5**) has been obtained by Gonzalez *et al.*;[202] Robinson annulation of **45.28** produces in 29% yield a 2 : 1 mixture of isomers with **45.5** as the major compound. The formation of cycloheptenone **45.28** involving a Claisen rearrangement is of interest.

II. SPIROCYCLIC SYSTEMS

1. *The* [5.4]*decane and* [5.5]*undecane group*

Most spirocyclic sesquiterpenes fall within three classes: the spirovetivanes (**46.1**) the acoranes (**46.2**) and the chamigrenes (**46.3**) (Scheme 46).[203a] Axisonitrile (**46.4**) and spirolaurenone (**46.5**) are unusual sesquiterpenes of marine origin. Since the pioneering work of Marshall[203b] spirocompounds have attracted considerable synthetic activity.[204] We will further essentially focus on the construction of the spiro[4.5]decane and spiro[5.5]undecane nuclei. Next to the problem of constructing the quaternary centre,[205] one has also to cope with the relative stereochemistry of substituents on the same ring (*cf* acoranes **46.2**). The major stereochemical problem, however, is establishing the correct sense of chirality of the spirocarbon relative to the centres present in one or both rings. Obviously, when dealing



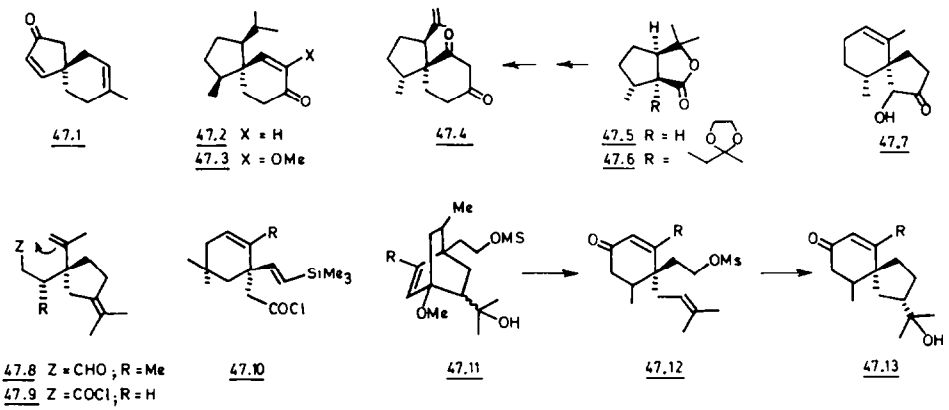
46.1 46.2 46.3 46.4 46.5

Scheme 46.

with pseudosymmetric 6-membered rings, the problem may present itself as a regiochemical one. Several strategies have been used for the construction of the spirosystem. We will distinguish four conceptually different approaches. (1) The strategy involves the synthesis of a *gem*-disubstituted monocycle and subsequent construction of the second ring. (2) The *gem*-disubstituted monocycle is obtained via spiroannulation followed by fragmentation. (3) The desired spirosystem is directly constructed via bond formation at the spirocentre. (4) A tricyclic system is synthesized first and subsequent specific bond breaking releases the desired spirosystem.

Indirect construction of the spirosystem. The problem resides here mainly in the creation of an adequate quaternary centre on one ring.[205] The eventual obtention of the full spirosystem is then realized via classical ring closure reactions which are summarized in Scheme 47: aldolization (**47.1**,[206–208] **47.2**,[209] **47.3**[210]), Claisen condensation (**47.4**[211]), acyloin condensation (**47.7**[212]) and π-cation cyclizations (**47.8**,[213] **47.9**,[214] **47.10**,[215] **47.13**[216]). The stereospecific synthesis of (−)-α-acoradiene was recently reported by Solas and Wolinsky[211] starting from puleganolide (**47.5**); the required stereochemistry at the three adjacent centres on the 5-membered ring is obtained via alkylation to **47.6**, followed by base-induced elimination of the lactone. Cyclopentenone annulation via $TiCl_4$-mediated intramolecular acylation of vinylsilane **47.10** has been described by Burke *et al.*,[215] although not directly in relation to spiroterpene synthesis. Masamune's synthesis of spirovetivanes centres about the acid fragmentation of suitable bicyclo[2.2.2]octenes (**47.11**) to cyclohexenones (**47.12**) which further undergo ring closure via π-cyclization.[216] While formic acid treatment gives the cyclohexenone derivatives **47.12** in high yield, use of oxalic acid in aqueous acetone directly leads to the spirosystem; it is interesting to note that when R is methyl the α-configuration at the hydroxy-isopropyl group in **47.13** is obtained stereoselectively with the dehydration product.[216a]

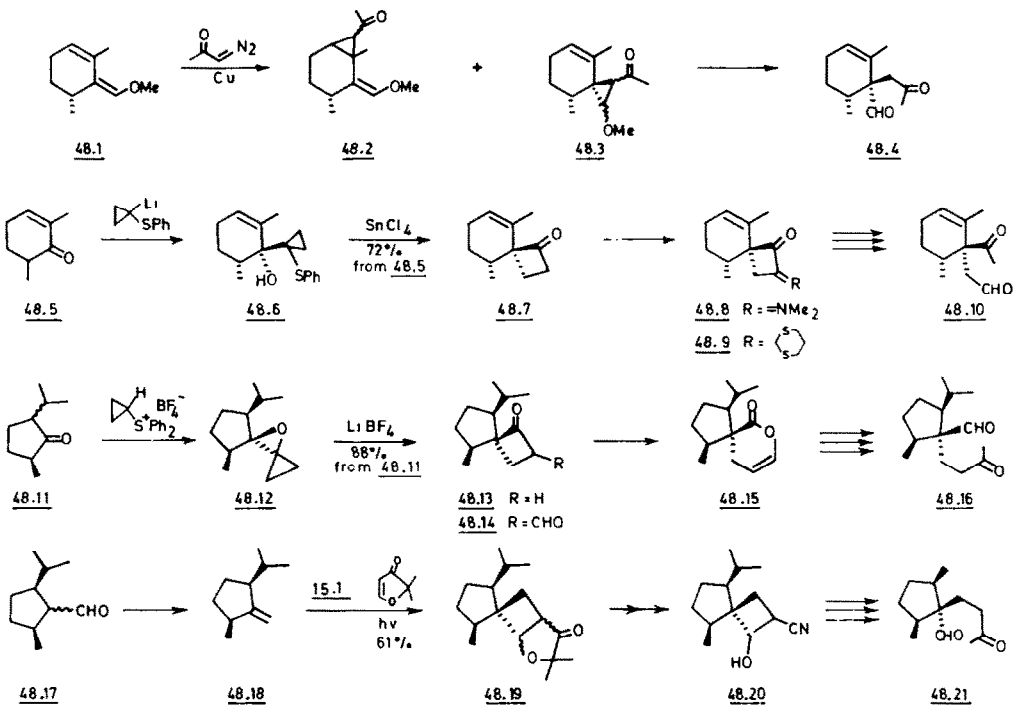
Spiroannulation–fragmentation sequence ("secoalkylation"). A number of interesting approaches to the spiro[4.5]decane nucleus involve prior formation of a spirocompound which is subsequently fragmented giving suitable side chains for final aldol ring closure to the requisite spirosystem (Scheme 48). Wenkert *et al.*[217] applied a β-oxycyclopropyl ketone formation–acid fragmentation sequence to a formal synthesis of β-vetivone. Treatment of the conjugated dienyl ether **48.1** with diazoacetone under copper-catalyzed thermal decomposition gives a 3:1 mixture of **48.2** and **48.3**; subsequent acid treatment gives with rearranged products originating from **48.2**, the stereohomogeneous diketone **48.4** (9% from **48.1**). Trost *et al.* have applied their cyclobutanone spiroannulation method[218] for the



47.1 47.2 X = H; 47.3 X = OMe 47.4 47.5 R = H; 47.6 R = 47.7

47.8 Z = CHO; R = Me 47.9 Z = COCl; R = H 47.10 47.11 47.12 47.13

Scheme 47.

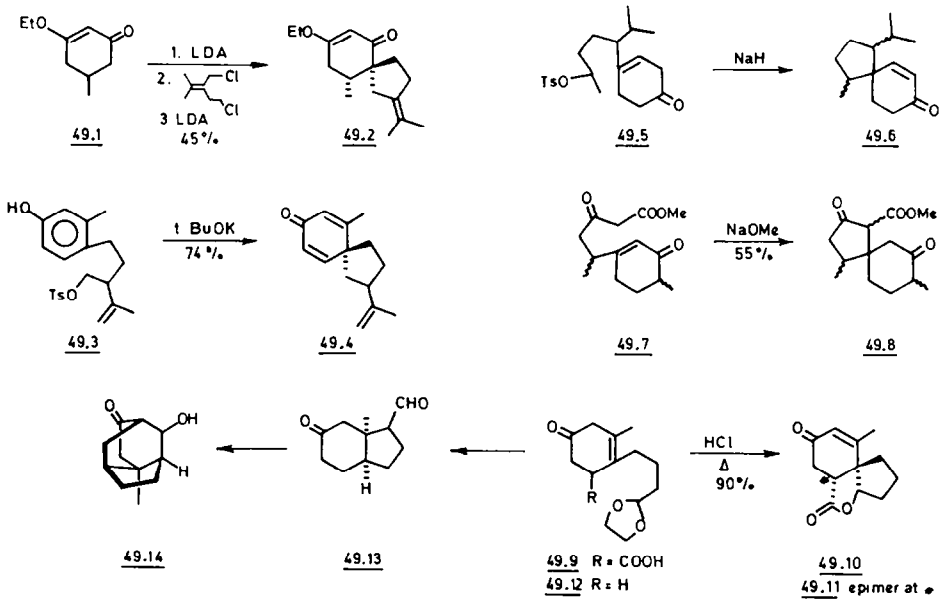


Scheme 48.

synthesis of spirovetivanes[219] and acorenone B.[220] Reaction of 1-lithiocyclopropylphenylsulfide with enone **48.5** gives **48.6**, and further cyclobutanone **48.7** upon stereospecific acid rearrangement.[219] Further transformation to **48.10** involved 5 steps: after activation of the α-cyclobutanonemethylene group to **48.8** (Bredereck's reagent) and solvolysis in the presence of trimethylenedithiotosylate, **48.9** is obtained (50%), which is further cleaved to the corresponding dithiane acid. Cyclopentanone **48.11** reacts as an isomeric mixture with the ylide derived from cyclopropyldiphenylsulfonium fluoroborate (reversible ylide generation conditions) to a stereohomogeneous oxaspiropentane **48.12**. Again a stereospecific rearrangement (lithium fluoroborate) yields cyclobutanone **48.13**.[220] Note that the stereochemical outcome of both approaches is complementary. Eight steps are further required for obtaining **48.16**: acid fragmentation of α-formylcyclobutanone **48.14** leads to an acid-aldehyde which cyclizes directly to **48.15**.

In an extension of the use of [2+2] photochemical cycloadditions of cyclic β-alkoxyenones for the preparation of cyclohexenones, Baldwin has reported the synthesis of (−)-acorenone.[221] Irradiation of alkene **48.18**, obtained in optically active form from (+)-limonene via **48.17** (11 steps, 17% overall), with enone **15.1** affords photoadduct **48.19**, the result of exclusive head-to-tail addition. A further 6-step sequence is required for the transformation to **48.21**, involving base fragmentation of **48.20**, obtained upon treatment of the corresponding oxime of **48.19** with thionyl chloride.[222]

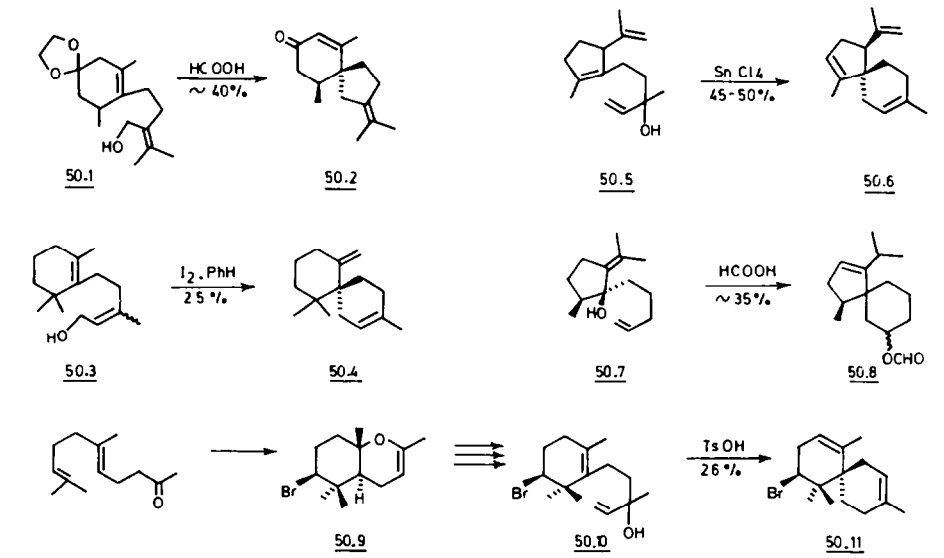
Direct construction of the spirosystem. The direct formation of carbocyclic spirocompounds via intramolecular alkylation has been reviewed in 1974.[204a] The stereoselective spiroannulation of **49.1** to **49.2** has been described by Stork *et al.*[223] and is based on the previous finding that enol ethers of 1,3-cyclohexanediones can efficiently be alkylated via their kinetic enolates.[224] Winstein and Baird's[225] $Ar_{1,5}$-cyclization, which already found application in the spirosesquiterpene area,[226,227] was used by Torii *et al.* for the conversion of **49.3** to **49.4**.[228] γ-Alkylation of enone **49.5** provides the spirocyclic system **49.6**.[229] Pinder *et al.* succeeded to effect internal Michael addition of **49.7** to **49.8**.[230] Yamada's[231] syntheses of spirovetivanes rest on the acid-catalyzed aldol reaction of **49.9** to lactone **49.10**. This lactone is the thermodynamically preferred product. Short reaction times allow for the isolation of epimer **49.11**. The latter is the product which one would expect from reaction opposite to the carboxyl group. It is interesting to note that when **49.12** is hydrolyzed under more vigorous conditions, the saturated tricyclic aldol **49.14** is formed via internal Michael addition to the conjugated enone aldol cyclization of intermediate **49.13**.



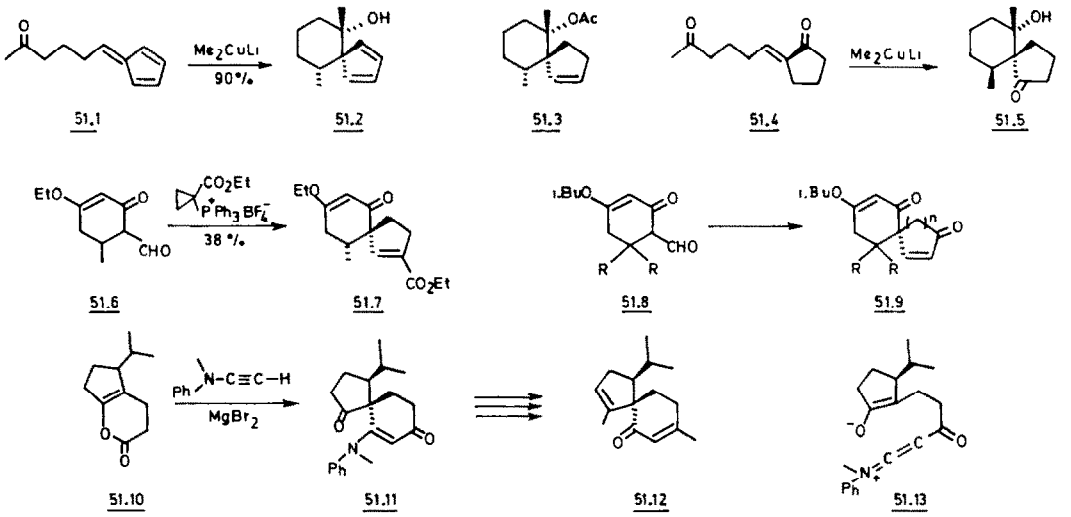
Scheme 49.

Different cation–olefin cyclizations have been used for the formation of spirocarbocyclic systems (Scheme 50). McCurry *et al.*[232] obtained cyclohexenone **50.2** by acid treatment of **50.1**; it was thereby anticipated that the 1-alkoxybutadiene, intermediate in the acetal hydrolysis, would be sufficiently nucleophilic at the 4-position to parallel Winstein's $Ar_{1,5}$-cyclization and to disfavour decalin formation. Predictably, alkylation of the allylic cation occurs *trans* to the methyl group (β-vetivone = epi-**50.2**). Since Kitahara's[233] synthesis of α-chamigrene (**50.3** → **50.4**) other classical π-cyclizations have been used, such as the transformations of **50.5** into **50.6**,[234] and **50.7** into **50.8**.[235] The synthesis of 10-bromo-α-chamigrene has been reported by Wolinsky and Faulkner.[236] Bromonium ion induced cyclization[237] of geranylacetone leads to **50.9**, which is further transformed to allylic alcohol **50.10**. Acid treatment of the latter gives a mixture containing 10-bromo-α-chamigrene (**50.11**). The same compound has been obtained later along similar lines.[238]

An interesting β-vetivone synthesis has been reported by Büchi *et al.*, involving Me_2CuLi addition to the fulvene **51.1**, followed by reaction of the lithium cyclopentadienide with the carbonyl group to



Scheme 50.



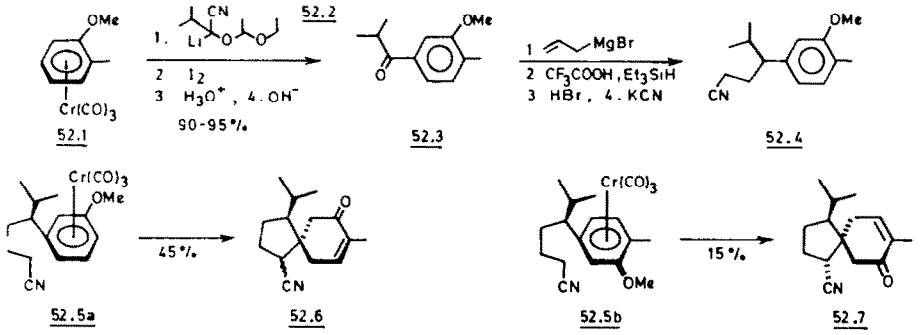
Scheme 51.

yield the single alcohol **51.2**.[239] Surprisingly, diimide reduction of the corresponding acetate gives a single dihydro compound **51.3** (57% yield). At the same time Näf *et al.*[240] described the stereoselective formation of aldol product **51.5** arising from conjugate addition to the enedione **51.4**. Dauben and Hart[241] have extended Fuchs method[242] for the synthesis of cyclopentene carboxylates using carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate to the synthesis of several spirovetivanes. Treatment of a HMPT solution of the sodium enolate of formylketone **51.6** gives a single spiroderivative **51.7**. It is of interest here to mention subsequent work of de Groot and Jansen[243] who obtained good yields of Robinson annulated **51.9** (n = 2) via addition of methylvinylketone to the sodium enolate of **51.8** and ring closure with pyrrolidine–acetic acid in methanol (R = alkyl). The 5-membered enone **51.9** (n = 1) was obtained from **51.8** (R = H) and iodoacetone followed by cyclization (27%).

A novel spiroannelating method has been described by Ficini *et al.*[244] The ynamine acylation of the enol lactone **51.10** gives stereoselectively and in good yield the spirocompound **51.11**. A lesser degree of stereoselectivity (~ 4 : 1) is obtained with less sterically demanding substituents (Me versus *i*-Pr). The intermediacy of **51.13** in the reaction has been suggested. Enamine derivative **51.11** is further transformed into **51.12** via double Wittig reaction and acid hydrolysis.

The potential use of arene–metal complexes in the synthesis of spiro[4.5]decenones has recently been described by Semmelhack *et al.*,[245a] and applied to the synthesis of acorenone and acorenone B.[245b] The process is based on the observation that carbon nucleophiles attack π-anisolechromium tricarbonyl at the meta position,[246] and that the resulting η^5-cyclohexadienyl complexes of chromium can subsequently be protonated and freed from chromium to give 1-substituted cyclohexa-1,3-dienes.

For the construction of the acorane spirosystem this concept has been used at two different stages (Scheme 52). Reaction of *o*-methylanisole and chromium hexacarbonyl in dioxane gives **52.1** in 95%



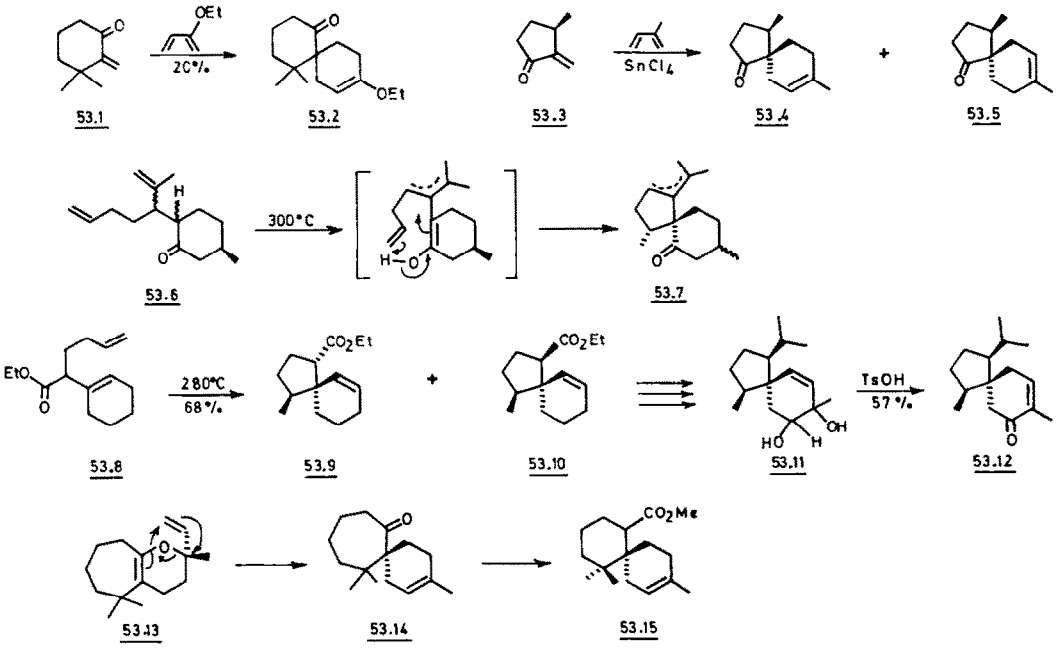
Scheme 52.

yield. Subsequent reaction with **52.2** followed by oxidation and cyanohydrin acetal removal yields **52.3**. The elaboration of the side chain in **52.4** involved "ionic hydrogenation"[247] of the tertiary alcohol obtained upon allylmagnesium bromide reaction on **52.3**. Via reaction of anisole **52.4** with chromium hexacarbonyl the two diastereoisomers **52.5a** and **52.5b** are obtained in 84% yield (ratio 3:2). Both isomers were separated and treated with LDA at $-78°$; after hydrolytic work-up there was obtained a diastereoisomeric mixture (8:1) of **52.6** from **52.5a** and a single spiroenone **52.7**. In both cases does the alkylation proceed via *exo*-addition to the coordinated arene.

Since Yoshikoshi's[248] report on the use of the Diels–Alder reaction to form the spirocentre of chamigrenes (*cf* **53.1** to **53.2**), this reaction has found little application in the synthesis of spirocyclic sesquiterpenes.[204c] In work related to the synthesis of acoranes Marx and Norman[249] reported a 7:3 isomeric ratio of **53.4** and **53.5**, respectively, for the $SnCl_4$-catalyzed Diels–Alder reaction of enone **53.3**, obtained in optically pure form from (+)-pulegone. The thermal cycloaddition reaction shows less stereoselectivity and also gives rise to the formation of substantial amounts of regioisomers (~ 30%).

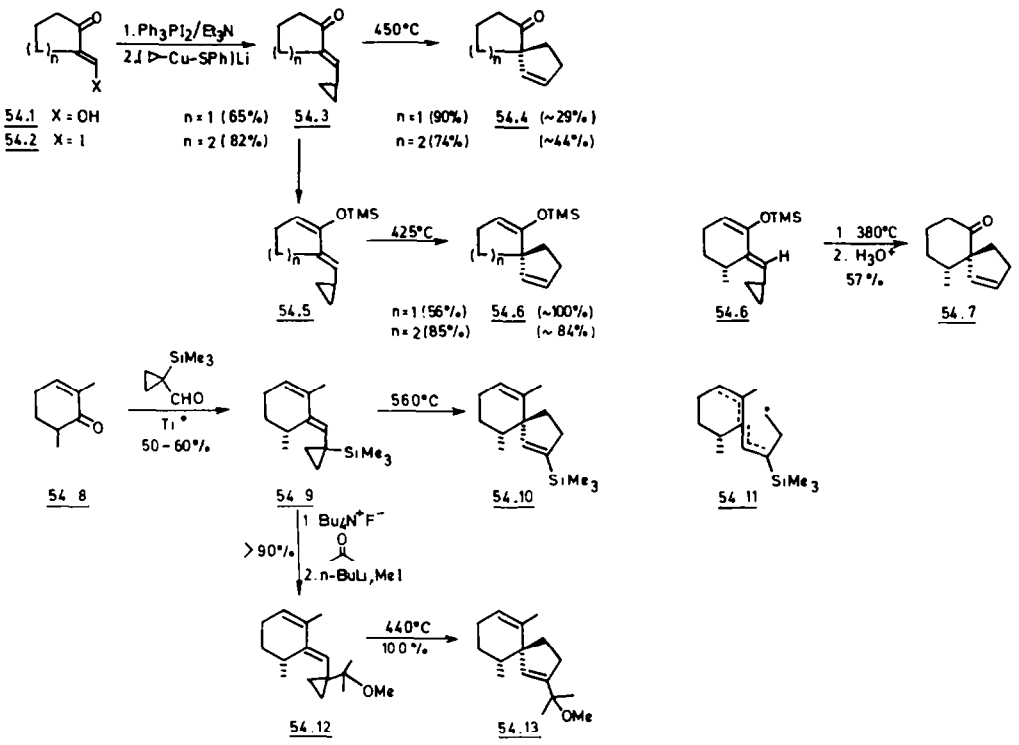
The application of the intramolecular ene cyclization of cyclic ketones which contain a 1-butenyl residue[250] constituted the first synthetic approach to the acorane sesquiterpenes (**53.6** to **53.7**).[251,204b] The stereoselective formation of spirocompounds via kinetically controlled intramolecular ene-reaction[252] has been used by Oppolzer *et al.*[253] for the synthesis of acoranes. The thermal cyclization of **53.8** proceeds exclusively via *endo* transition state and gives a 1.7:1 ratio of spirocyclohexenes **53.9** and **53.10**, respectively; with regard to the *cis*-relationship between the methyl group and the olefinic bond 100% stereoselectivity is obtained. Further synthesis to **53.12** also involved an interesting pinacol-type hydrogen shift of the cation obtained upon acid treatment of diol **53.11**. A total synthesis of β-chamigrene, involving Claisen rearrangement of the vinyl substituted cycloheptapyran **53.13** to **53.14**, followed by ring contraction to **53.15**, has also been reported.[254]

Vinylcyclopropane–cyclopentene rearrangement has been applied by Piers *et al.*[255] to the synthesis of spirovetivanes. They discovered that, whereas the vinylcyclopropyl ketones **54.3** afforded poor yields of the desired spiroketones **54.4** upon thermolysis, a better result is obtained when the ketone is first transformed to the corresponding TMS enol ether (*cf* **54.5** to **54.6**). The cyclopropyl derivatives **54.3** are obtained from the vinyl iodides **54.2** and lithium phenylthiocyclopropyl cuprate. Thermolysis of methyl-substituted **54.6** gives a diastereoisomeric mixture in favour of **54.7** (2.5:1).[255b] Paquette's[256] recent synthesis of α-vetispirene centres around a similar rearrangement involving, however, a substituted cyclopropyl group. The trimethylsilyl derivative **54.9**, obtained from enone **54.8** via titanium reductive coupling,[257] is thermolyzed to give a 4:1 mixture of spirodienes in favour of **54.10**,



53.1 53.2 53.3 53.4 53.5 53.6 53.7 53.8 53.9 53.10 53.11 53.12 53.13 53.14 53.15

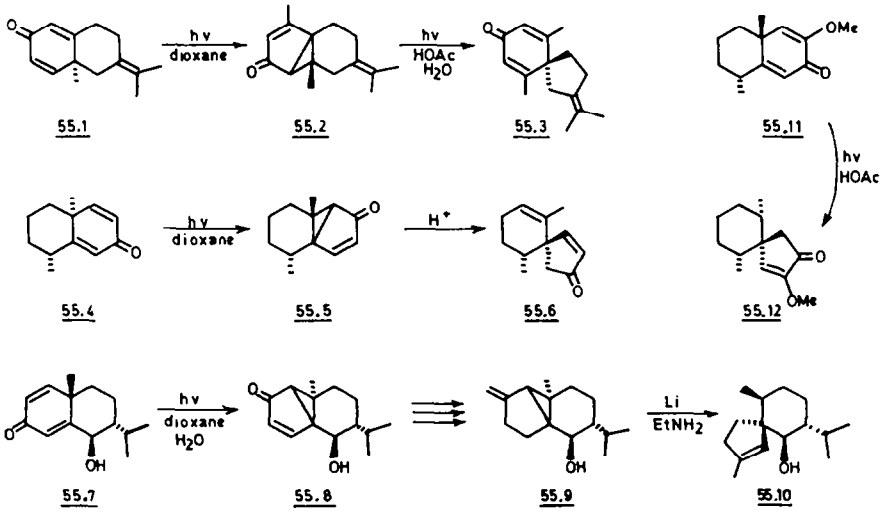
Scheme 53.



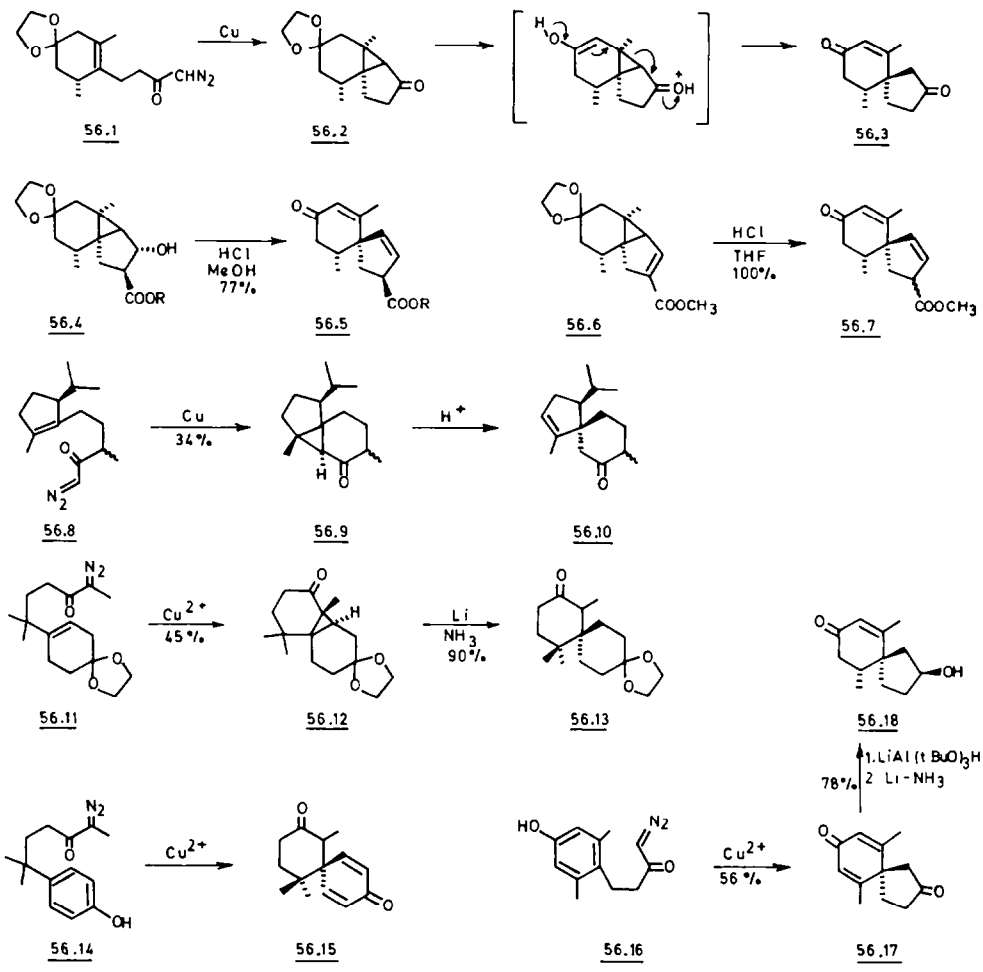
Scheme 54.

implying preferential recombination of biradical **54.11** along the less hindered face of the 6-membered ring. The alkyl-substituted cyclopropyl derivative **54.12** was obtained according to Sakurai's method;[258] here a regioselective alkylation to **54.12**, without methylenecyclopropane formation, is observed. A 5:1 ratio is obtained in favour of **54.13** upon pyrolysis of diene **54.12**.

Generation of the spirocyclic system via specific bond cleavage in tricyclic systems. The study of the acid-catalyzed cleavage[259] of cyclopropyl ketones related to lumisantonin[260–262] lies at the basis of the first recorded spirosesquiterpene synthesis.[263a] Several syntheses have since then appeared based upon the photochemical isomerization of cyclohexadienones (**55.1**, **55.4**, **55.7**, **55.11**) to cyclopropyl ketones. Cleavage of the 3-membered ring is effected either by light-induced acid catalysis (**55.2** to **55.3**),[263b] by normal acid cleavage (**55.5** to **55.6**)[264] or by dissolved metal reduction (**55.9** to **55.10**).[265] Caine's[266] synthesis of α-vetisperene involves the direct photochemical rearrangement of **55.11** to spirocompound



Scheme 55.

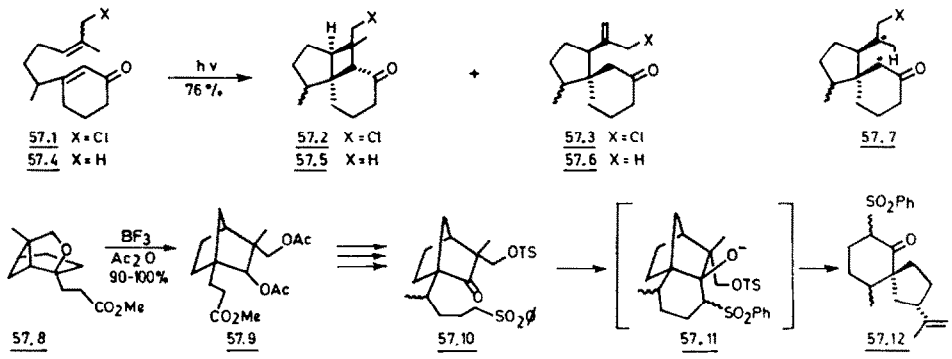


Scheme 56.

55.12 upon photolysis in acetic acid. Note that the reduction of the conjugated cyclopropyl derivative **55.9** with lithium in ethylamine proceeds with inversion of the configuration at the methyl, in line with the result obtained for the reduction of similar conjugated cyclopropyl ketones.[267] Spirocompound **55.10** is a precursor for axisonitrile (**46.4**).

An alternative approach to the construction of cyclopropyl cycloalkanones involves the use of the intramolecular reaction of diazoketones to olefins.[268] This approach was originally applied by Deslongchamps *et al.*[269] for the synthesis of epihinesol. Copper-catalyzed cyclopropane formation from **56.1** gives a 9:1 ratio in favour of **56.2**.[269,270] Acid-catalyzed retro-aldolization furnishes spirocyclohexenone **56.3** in 90% yield. Cyclopropane bond cleavage was also effected on **56.4** and **56.6**, obtained via transformation of ketone **56.2**. Treatment of **56.6** under mild acid conditions gave a mixture of unconjugated esters **56.7**. A similar strategy was used by White *et al.*[271] for the synthesis of (−)-acorenone B. Olefin **56.8**, available in optically active form from (+)-limonene, in refluxing benzene containing copper powder gave ketone **56.9**, only diastereoisomeric at the methyl group. Subsequent exposure to hydrochloric acid in chloroform gave directly olefin **56.10**. In the course of the synthesis of α-chamigrene the use of a soluble complexed form of copper(II), i.e. bis(N-n-propylsalicylidenaminato) copper(II), was found necessary to effect thermal decomposition of **56.11** to **56.12**. The direct construction of a spirodienone system from a phenol precursor has been reported by Iwata *et al.* (**56.14** to **56.15**, **56.16** to **56.17**).[272] Enone **56.18** is further obtained as a result of a stereo- and regioselective dissolved metal reduction implying intramolecular protonation via the hydroxyl group on the 5-membered ring.

α-Acoradiene has recently been synthesized by Oppolzer *et al.*[273] following an intramolecular photoaddition–reductive fragmentation sequence (Scheme 57). Irradiation of enone **57.1** yields a



Scheme 57.

mixture of **57.2** and **57.3**, which on reductive cleavage furnishes spiroketones **57.6** in 59% yield (ratio 10 : 3). The direct formation of ring opened product **57.6** had been noted previously by Hoye *et al.*[274] upon irradiation of **57.4** to **57.5**, and should arise from H-transfer in radical **57.7**. It is interesting to note that the possible formation of spirocompound **57.6** via retroene reaction of **57.5** (*cis*-1-acyl-2-alkylcyclobutane derivative) has been investigated without success.[274] On the other hand, Fetizon *et al.*[275] reported the Norrish type II fragmentation of **57.5** to **57.6** in 55% yield.

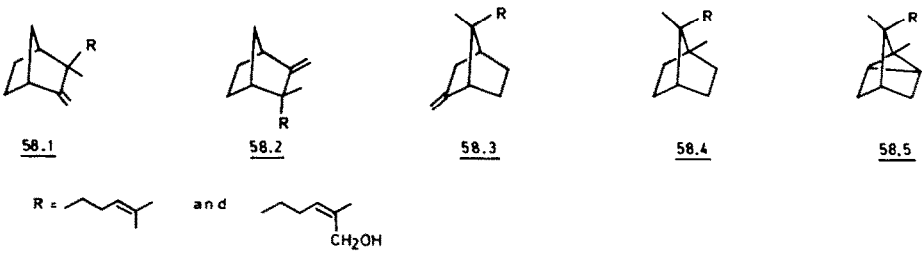
Two rearrangements characterize the synthesis of (+)-hinesol by Magnus *et al.*[276] The acid-catalyzed rearrangement of **57.8**, available from (+)-nopinone, gives **57.9**; upon treatment of keto tosylate **57.10** with sodium hydride in DMSO β-keto sulfone **57.12** is formed via fragmentation of the intermediate alkoxide **57.11**.

III. BRIDGED SYSTEMS

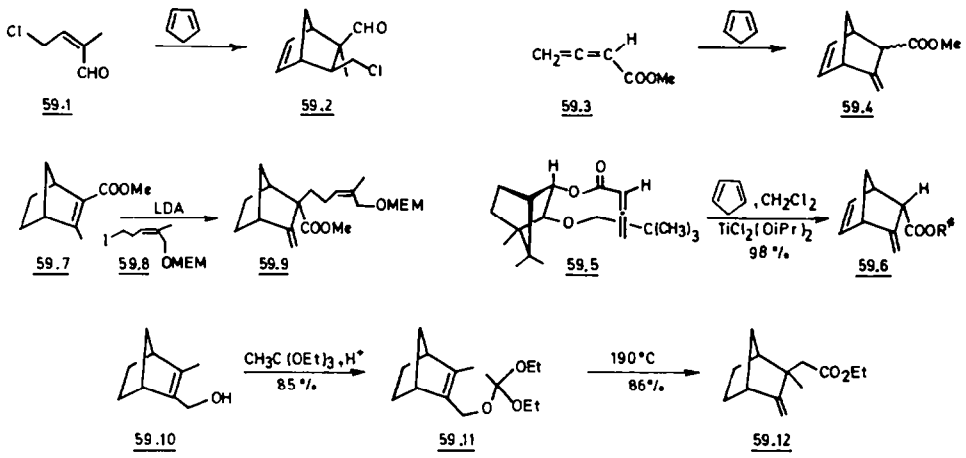
1. *The bicyclo*[2.2.1]*heptane and bicyclo*[3.1.1]*heptane groups*

A number of sesquiterpenes possess a bicyclo[2.2.1]heptane (**58.1–58.4**) or related tricyclo[2.2.1.0]heptane skeleton (Scheme 58). Not surprisingly, most syntheses related to **58.1** centre about a Diels–Alder reaction between cyclopentadiene and an appropriate dienophile (Scheme 59). Baumann and Hoffmann[277] reported the Diels–Alder reaction with (*Z*)-4-chloro-2-methyl-2-pentenal (**59.1**), which gives exclusively the *exo* addition product **59.2**. Bertrand *et al.*[278] use the allenic ester **59.3**. The obtained adducts **59.4** are reduced at the more reactive norbornene double bond using Brown's nickel boride catalyst[279] and further alkylated to give products of type **58.1**. Using this approach, Oppolzer and Chapuis[280] have reported a highly enantioselective synthesis of (−)-β-santalene. An efficient π-facial selection was obtained in the initial cycloaddition step using the camphor derived ester **59.5**. In the presence of a titanium catalyst a 98% yield of almost exclusive endo adduct **59.6** (98 : 2 ratio) in 99% optical purity was obtained. β-Santalol has been obtained through alkylation of **59.7** with iodide **59.8**.[281] The synthesis of ester **59.12** via Claisen rearrangement of **59.11** has been reported by the same authors.[282]

A number of acid-catalyzed rearrangements of readily available bicyclo[2.2.1]heptanes have been used for the obtention of the desired substitution pattern (Scheme 60). Money's 1973 syntheses[283] in this area centre about the Wagner–Meerwein rearrangements of the tosylates obtained from **60.1** [from



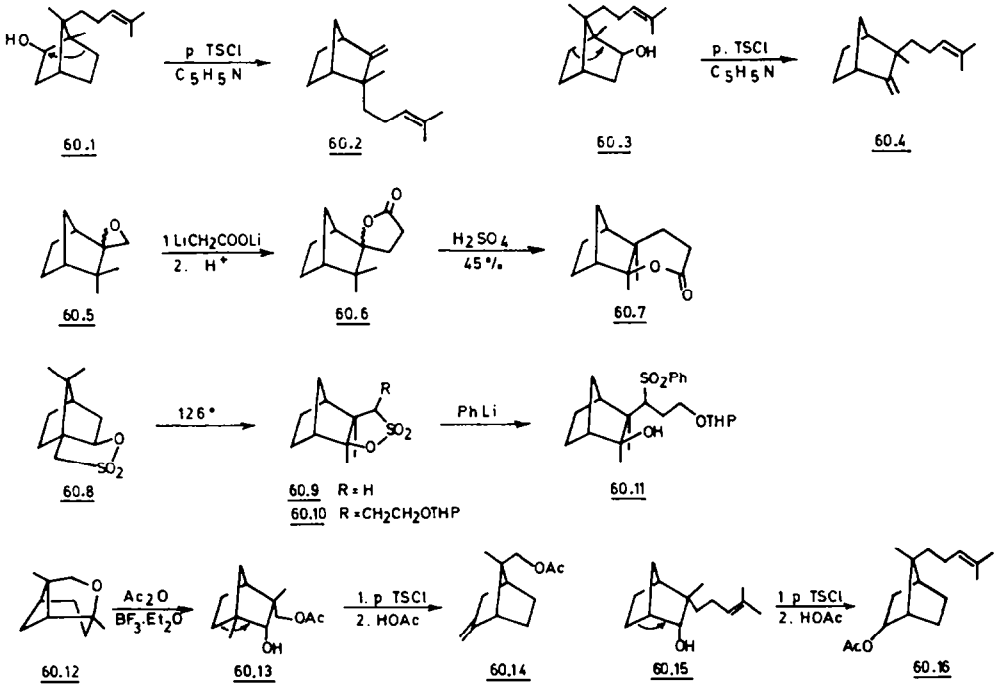
Scheme 58.



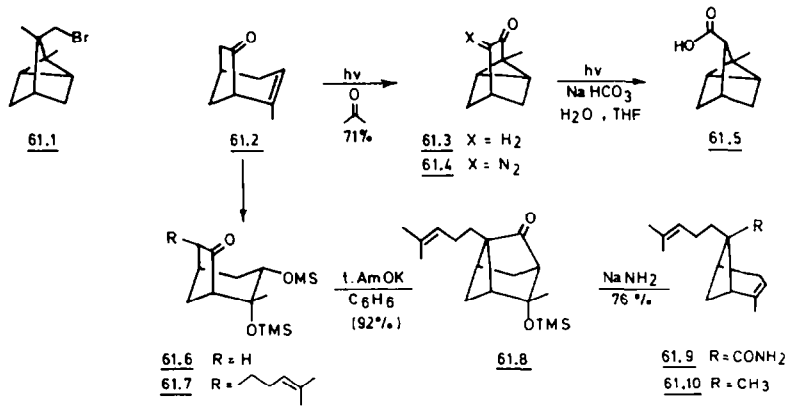
Scheme 59.

(+)-9-bromocamphor] and **60.3** [from (−)-8-iodocamphor] yielding (+)-epi-β-santalene (**60.2**) and (−)-β-santalene (**60.4**), respectively. Christenson and Willis[284a] described the rearrangement of spirolactones **60.6** in acid medium[284b] to **60.7**. Epoxides **60.5** resulted from the epoxidation of racemic camphene. Camphenesultone (**60.9**), obtained by pyrolysis of **60.8** (from camphorsulfonic acid), is the central product in Wolinsky's work.[285] Desulfurization of alkylated **60.10** proceeds via ring opening to sulfone **60.11** followed by sodium amalgam treatment (49% overall).[285b] The synthesis of (+)-sesquifenchene (**58.3**) by Bessiere *et al.*[286] is characterized by two consecutive skeletal rearrangements. Ether **60.12** yields alcohol **60.13** upon treatment with BF_3-etherate; the tosylate then undergoes Wagner–Meerwein rearrangement to **60.14** upon solvolysis. In one of Grieco's sesquifenchene syntheses an analogous rearrangement (**60.15** to **60.16**) is reported.[287]

Syntheses of α-santalene and α-santalol (*cf* **58.5**) almost invariably start from the readily available (−)-π-bromotricyclene (**61.1**). A notable exception is the Monti–Larsen[288] synthesis of α-santalene. The desired tricyclene nucleus (**61.5**) is obtained via photoisomerization of **61.2** to ketone **61.3**, followed



Scheme 60.

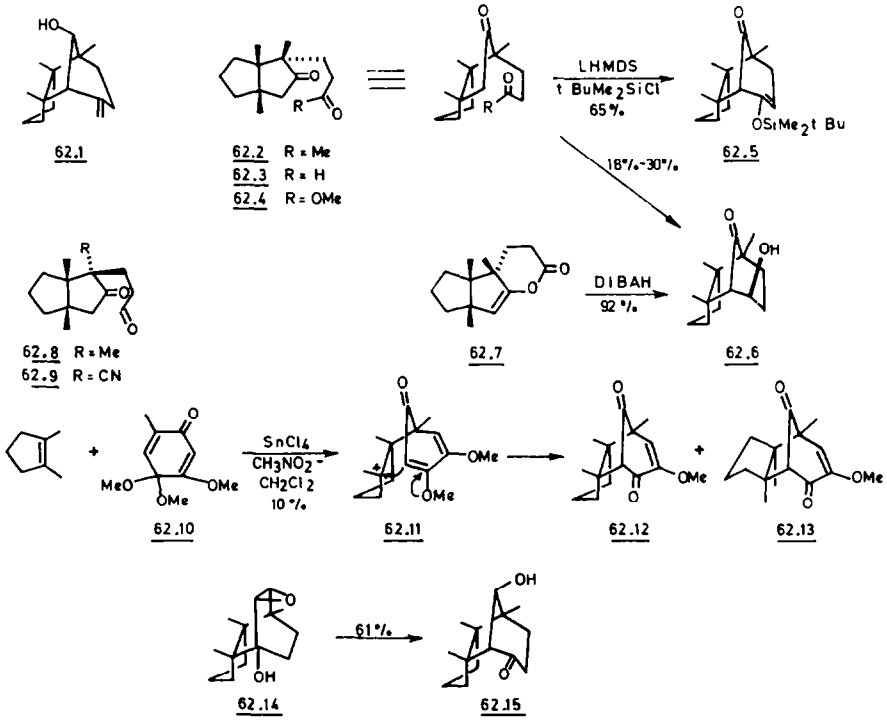


Scheme 61.

by photochemical Wolff rearrangement of the corresponding diazoketone **61.4**; further alkylation with 5-iodo-2-methyl-2-pentene proceeds via the dianion of acid **61.5**. An improved synthesis of *α-trans*-bergamotene (**61.10**)[289] has been reported by the same authors.[290] Ketone **61.6** is alkylated to **61.7** and subsequent ring closure effected with potassium t-amylate. Haller–Bauer fragmentation yields **61.9**, which is correctly patterned for further transformation into *α-trans*-bergamotene (**61.10**).

2. *The tricarbocyclic systems*

Five syntheses of gymnomitrol (**62.1**) have been reported in 1979.[291–296] The relative location of the functionalities on the 4,8-methanoperhydroazulene framework suggests an aldol or Claisen condensation as a key step (Scheme 62). Three successful approaches were realized along this line.[291–293] Following this protocol the synthesis of a *cis*-bicyclo[3.3.0]octanone possessing three contiguous quaternary centres (*cf* **62.2–62.4**) is mandatory; we will return to this specific problem in Section V. Both the groups of Coates[291] and Paquette[292] have attempted unsuccessfully to effect the aldol cyclization of the methyl ketone **62.2** under various acid and basic conditions; the difficulties associated with the projected aldol would be of kinetic origin.[292] After extensive experimentation

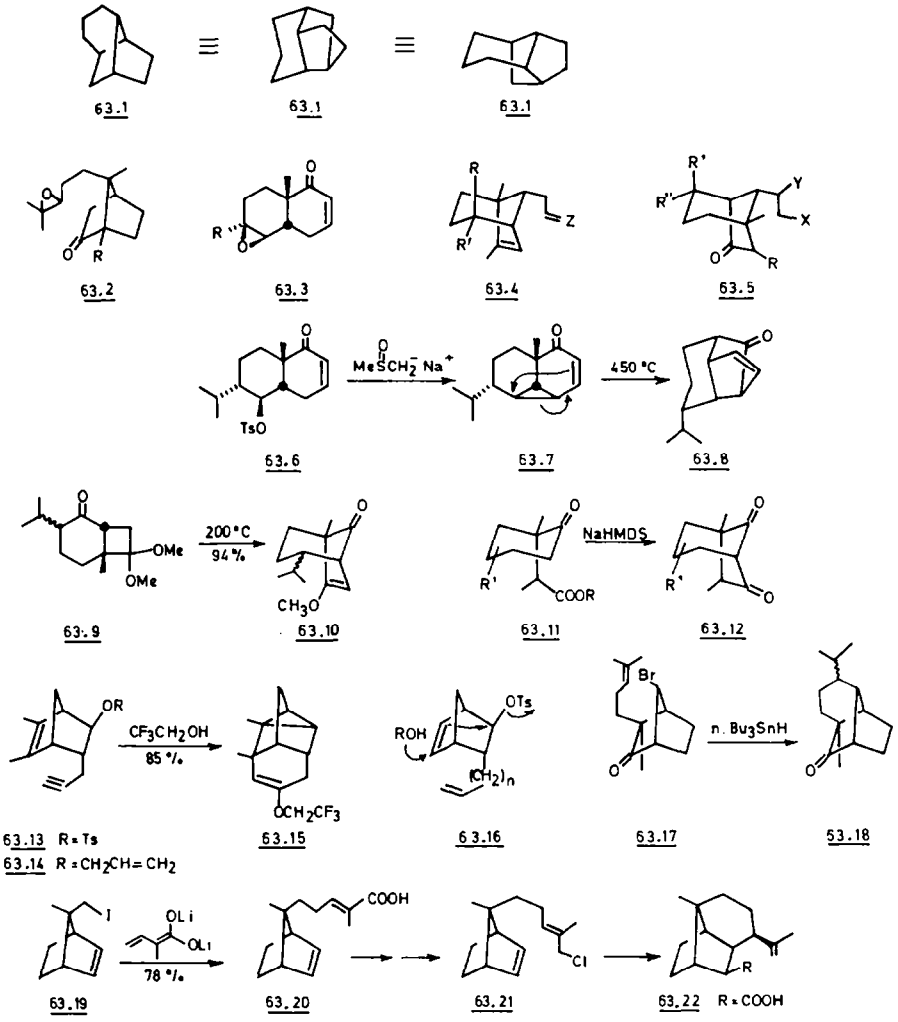


Scheme 62

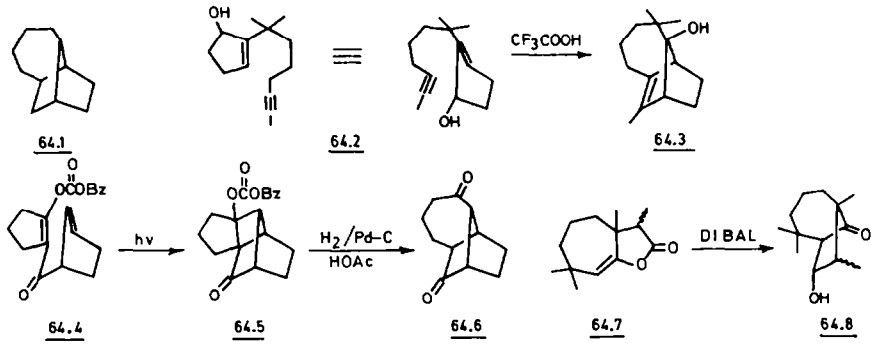
aldehyde **62.3** was found to cyclize under basic conditions leading to an equilibrium mixture of **62.3** and **62.6** (18% isolated yield with Na_2CO_3 in methanol–water;[291] 30% isolated yield 2% KOH in methanol).[292] It is interesting to note that the epimeric keto aldehydes **62.8** and **62.9** cyclize readily. The moderate success obtained for the direct aldol reaction of **62.3** prompted Coates *et al.*[291] to have recourse to enol lactone reductive cyclization; upon treatment of **62.7** with DIBAH the desired alcohol **62.6** was obtained in high yield (92% crude). The approach of Welch *et al.*[293] involves the condensation of keto ester **62.4** which leads to **62.5**.

Buchi's method for the preparation of bicyclo[3.2.1]octanes via acid-catalyzed addition of *p*-quinonemonoketals to olefins, leads eventually to gymnomitrol, albeit in low yield (Scheme 62).[294] Condensation of quinone ketal **62.10** with 1,2-dimethylcyclopentene gives the two diastereoisomers **62.12** and **62.13** (ratio 3.3 : 1, respectively) in 10% yield. This low yield is ascribed to crowding in the transition state next to additional angle strain created by the cyclopentane. A pinacol-type rearrangement of a bicyclo[2.2.2]octane is the key reaction in the synthesis of Kodama *et al.*[295] Epoxide **62.14** undergoes the required skeletal rearrangement to **62.15** on alumina chromatography.

A preferred key-step for the formation of the carbocyclic skeleton of the copa- and ylangosesquiterpenes (*cf* **63.1**) has been the intramolecular alkylation of a correctly functionalized bicyclic precursor, such as **63.2**,[296,297] **63.3**,[298a] **63.4**[299] and **63.5**.[300] Interestingly, the intramolecular alkylation of **63.6** does not yield the product from α-alkylation (**63.8**), but rather cyclopropane derivative **63.7**.[298b] McMurry and Silvestri[298b] converted the latter into desired enone **63.8** via vinylcyclopropane rearrangement. Both Matsumoto[301] and Piers[299,300] form the tricyclic framework starting from a bicyclo[3.2.1]octanone. In Matsumoto's synthesis the required skeleton is formed by



Scheme 63.



Scheme 64.

acid-catalyzed (GPLC Shimalite column) rearrangement of photoadduct **63.9**, which is obtained from racemic piperitone. Both separate adducts eliminated methanol and rearranged to give the same 1 : 1 mixture of epimers **63.10**. Piers *et al.*[299,300] use the Dieckmann condensation with sodium hexamethyldisilazane as the base (**63.11** to **63.12**).

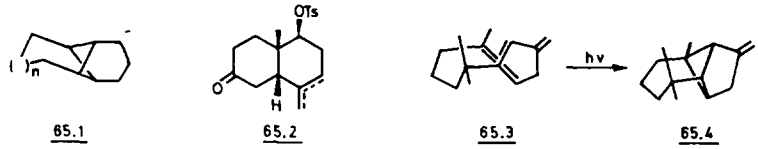
Baldwin's approach to cyclosativene involves a π-cationic cyclization.[302] Trifluorethanolysis of the acetylene **63.13** leads to the required skeleton **63.15**. The removal of the ether in **63.14** in the presence of the terminal acetylene was effectively done by successive treatment of a liquid ammonia solution of **63.14** with methyllithium and sodium. Note that the outcome of the cyclization is greatly affected by the length of the chain (*cf* n in **63.16**): n = 0 and n = 2 only tricarbocyclic ethers are obtained. The diastereoisomeric ketones **63.18** were obtained by Bakuzis *et al.*[303] via treatment of bromide **63.17** with tri-n-butylstannane.

The sinularene synthesis of Oppolzer *et al.*[304] centres about the intramolecular type-I-magnesium-ene reaction in which the carbanion, resulting from ene reaction of the Grignard derivative of **63.21**, is reacted with carbon dioxide to **63.22**. Whereas the disalts of dienolate dianions usually lead to α-alkylation, the tiglic acid derivative gives γ-alkylated **63.20** in high yield upon reaction with the known norbornene **63.19**.

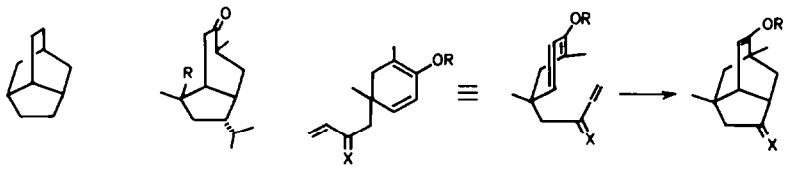
Since 1973 a few syntheses in the longi-series (**64.1**) have been recorded. Johnson *et al.*[305] obtained the carbon framework of longifolene directly via π-cyclization of cyclopentenol **64.2**. The expeditive synthesis of Oppolzer *et al.*[306] centres about the retro aldol cleavage of photoadduct **64.5** to diketone **64.6**. Enone **64.4** was obtained via acylation of the morpholine enamine of cyclopentanone with 3-cyclopentene carbonyl chloride. A crucial intermediate in Welch's syntheses[307] in this area is aldol product **64.8**, which is obtained through the reductive cyclization of enol lactone **64.7**.

Syntheses in the copa-series (**65.1**) have formed the 4-membered ring through intramolecular alkylation of a *cis*-decalin keto tosylate (**65.2**)[308] and via sensitized photoisomerization of triene **65.3**.[309] A few sesquiterpenes possessing the tricyclo[4.3.1.$0^{3,7}$]decane nucleus (*cf* **66.1**) are known. Corey's syntheses[310] centre about the cyclization of a properly functionalized bicyclic precursor (**66.2** and **66.3**). Other approaches proceed via intramolecular Diels–Alder reaction of the 1,3-cyclohexadienes **66.4**,[311] **66.5**[312] and **66.6**.[313] The activating effect of the carbonyl group (*cf* **66.5**) is noteworthy since at the moment of cycloaddition the carbonyl and olefinic π-systems must be nearly orthogonal.

In view of the bicyclo[2.2.2]octane moiety present in seychellene (**67.1**), patchuli alcohol (**67.2**) and norpatchoulenol (**67.3**) the intramolecular Diels–Alder reaction is a logical key-step. Four synthetic approaches along this line have been reported. Compared to the cases shown in Scheme 66 the dienes are less activated and harsher conditions are necessary for reaction, except in the case of **67.8**. In this case



Scheme 65.



66.1 | 66.2 R = CHO; 66.3 R = CH_2OTs | 66.4 R = $SiMe_3$, X = H,OTHP; 66.5 R = Me, X = O; 66.6 R = $PO(OEt)_2$, X = H,OH | 160°C; 60°C; 140°C | 87%; 89%

Scheme 66.

Frater[314] isolated a 3 : 1 mixture of isomers **67.9** and **67.10**, the latter being eventually transformed into seychellene. The reasons for this rate enhancement and lack of regioselectivity are unclear. Yoshikoshi *et al.*[315] obtained diene **67.6** by *in situ* Cope elimination at 430° in a GPLC apparatus of the dimethylamine oxide, obtained from **67.5**. Both Oppolzer *et al.*[316] and Näf–Ohloff *et al.*[317] started from cyclohexadienone **67.16** for the synthesis of dienes **67.11** and **67.13**. The former group uses 3-triethylsilyloxypentadienyl lithium for the introduction of the required enone side chain.[316] With regard to the configuration at the starred carbon in **67.13** and **67.14** Näf and Ohloff[317] observed a complete diastereoselectivity. Only diastereoisomer **67.13** leads to adduct formation, due to the presence of a severe 1,3-diaxial methyl–methyl interaction in **67.14**. Furthermore, the presence of base was found necessary for successful reaction. This may be an example of "alkoxide accelerated cycloaddition". Base-catalyzed interconversion of **67.14'** into the reactive isomer **67.13'** via alkoxide accelerated electrocyclic reaction has also been suggested.[318]

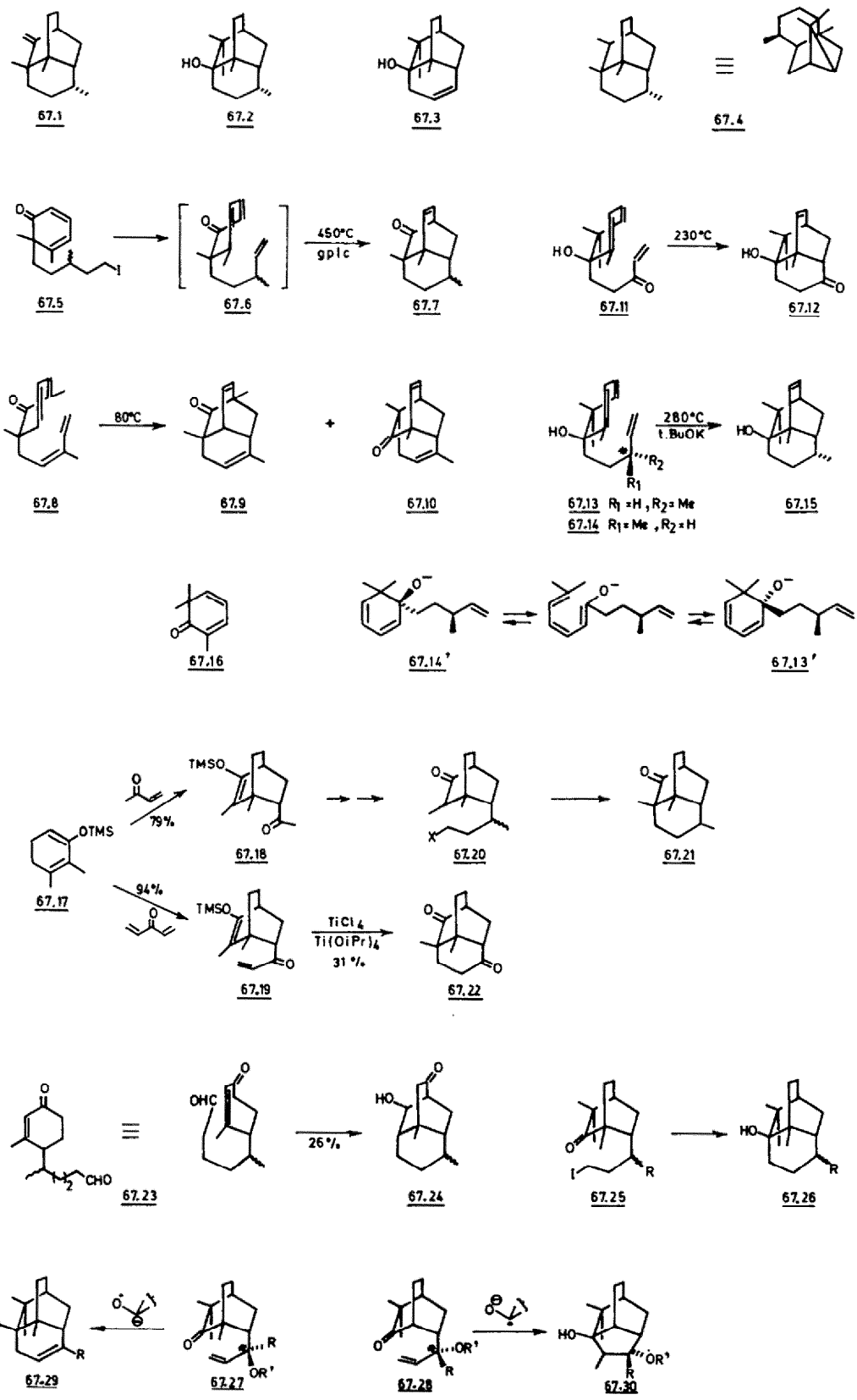
The approaches of Jung and McCombs[319] use the potential of alkyl-substituted siloxydienes in the intermolecular Diels–Alder reaction (*cf* **67.17**). The *endo* isomers **67.18** and **67.19** are predominantly formed in good yield. Ketone **67.20**, obtained from **67.18**, gives a quantitative yield upon cyclization in base.[320] The intramolecular Michael addition of enone **67.19** proved difficult to realize: only with a mixture of titanium tetrachloride and titanium tetraisopropoxide in methylene chloride is a reasonable yield of **67.22** observed.

The strategy of Yamada *et al.*[321] for the synthesis of seychellene (**67.1**) is based on the tandem intramolecular Michael–aldol cyclization of aldehyde **67.23** to **67.24** (ratio 8 : 1). The bridgehead alcohol present in patchouli alcohol (**67.2**) was originally obtained by Danishefsky and Dumas[322] via reductive cyclization of an appropriate keto halogenide. Both Mirrington[323] and Teisseire[324] have elaborated on the same reaction type (*cf* **67.25** to **67.26**). An interesting variation has recently been reported.[325] Treatment of **67.27** (R = Me or H) with sodium in THF leads to olefin **67.29** via nucleophilic addition of the intermediate radical carbanion. The epimeric **67.28** with incorrect ether configuration for S_N2' displacement, however, undergoes radical cyclization to **67.30**. The best cyclization yields were obtained for the methoxymethyl ether derivative (R').

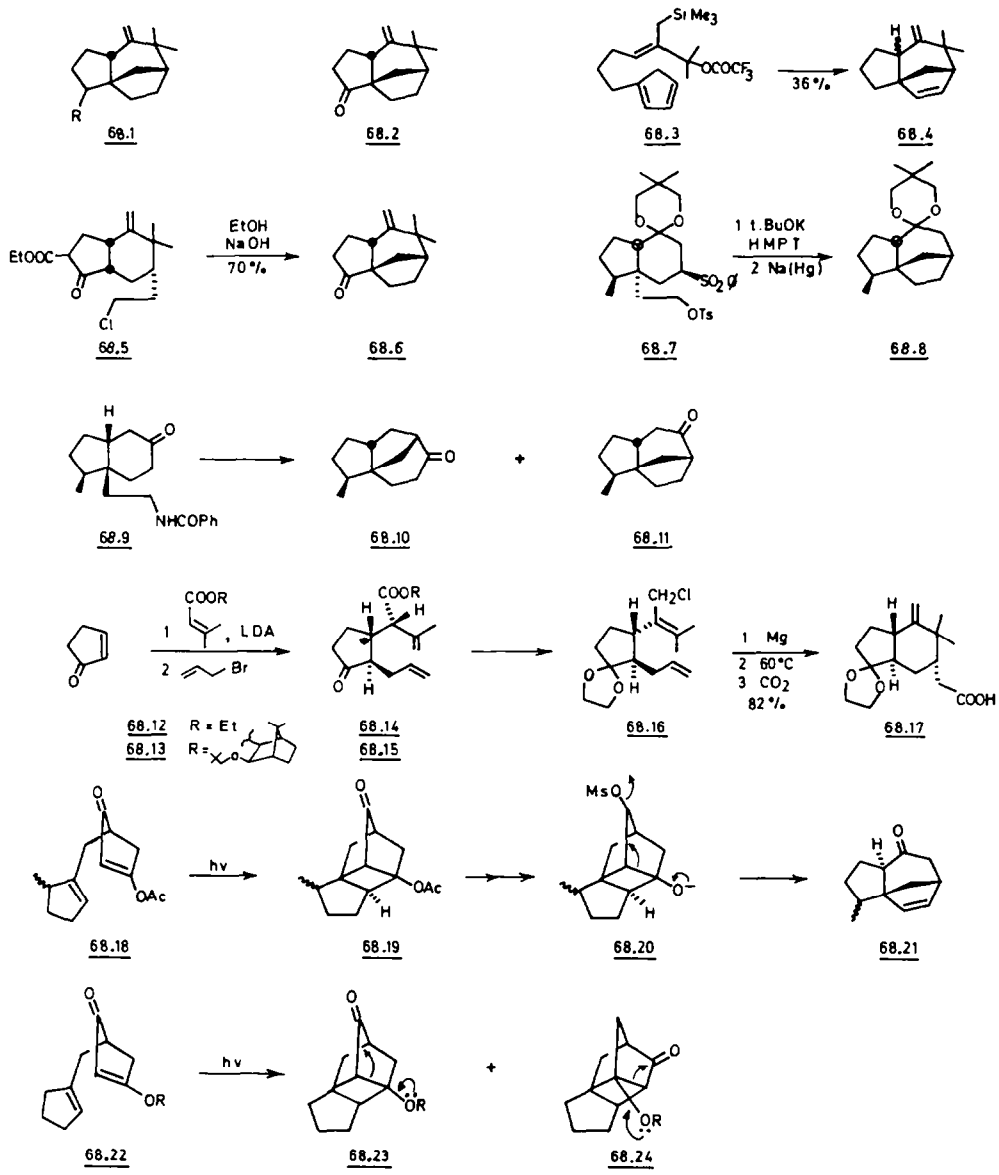
Since 1973 the zizaene-type sesquiterpenes (*cf* **68.1**) and the nor-derivative khusimone (**68.2**) have attracted considerable synthetic interest. An interesting, although low yielding, approach to the zizaene skeleton has been reported by Hoffmann *et al.*[326] and involves an intramolecular allyl cationic cycloaddition; crude **68.3** is passed at −30° down a neutral alumina column, coated with $ZnCl_2$, and gives a mixture of **68.4** (ratio ~1 : 1).

Adequately functionalized bicyclo[4.3.0]nonanes have been used for obtaining the desired skeleton. In the approach of Liu and Chan[327] alkylation is effected on **68.5**. Piers and Banville[161] obtained acetal **68.8** via alkylation of sulfone **68.7** and desulfurization. Prezizaene, epimeric with zizaene (**68.1**, R = β-methyl) has been obtained by Vettel and Coates[328] via cyclization–rearrangement of the diazoketone, obtained from **68.9**, which led to a mixture of ketones **68.10** (29%) and **68.11** (34%). The synthesis of khusimone (**68.2**) by Oppolzer and Pitteloud[329a] centres about the regio- and stereoselective type-II-magnesium-ene reaction of the Grignard derivative of **68.16** to bicyclic precursor **68.17**. The introduction of the side chain involves 1,4-addition of the lithium enolate of **68.12** (R = Et), followed by *in situ* alkylation with allyl bromide (50% yield). The same sequence applied to **68.13** leads predominantly to chiral **68.15** (37% isolated yield), representing a 48% asymmetric induction of the starred centre.[329b]

Intramolecular photochemical cycloaddition, followed by appropriate fragmentation, has also been applied for obtaining the zizaene nucleus. In the synthesis of Barker and Pattenden[330] irradiation


67.1
67.2
67.3
67.4
67.5
67.6
450°C
gplc
67.7
67.11
230°C
67.12
67.8
80°C
67.9
67.10
67.13 R1 =H , R2 = Me
67.14 R1 = Me , R2 = H
280°C
t.BuOK
67.15
67.16
67.14'
67.13'
OTMS
67.17
79%
TMSO
67.18
67.20
67.21
94%
67.19
TiCl4
Ti(OiPr)4
31 %
67.22
67.23
OHC
26 %
67.24
67.25
67.26
67.29
67.27
67.28
67.30

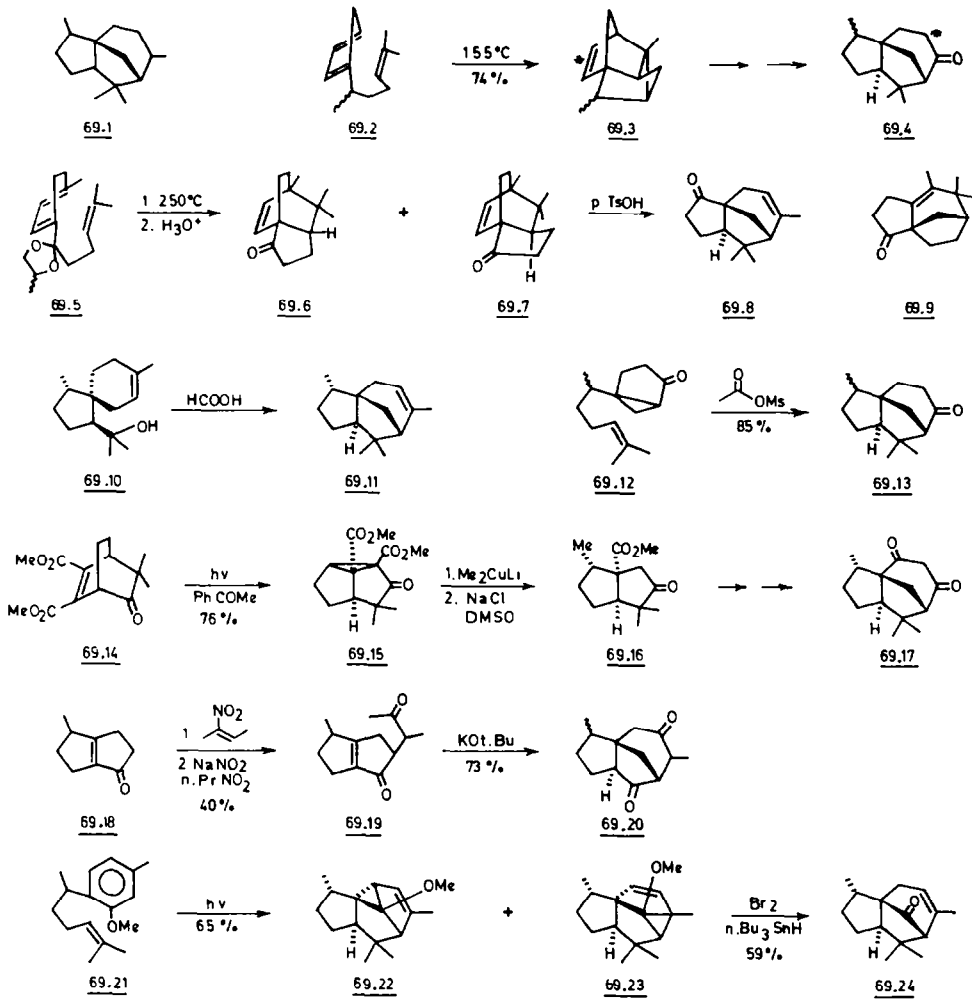
Scheme 67.



Scheme 68.

of enol acetate **68.18** leads to a mixture of two adducts; the major adduct **68.19** is further transformed to mesylate **68.20** which upon Grob fragmentation gives **68.21**. Previously Oppolzer and Burford[331] have reported a similar sequence in which photoadducts **68.23** and **68.24** (ratio 1:3, respectively) were transformed into diketones via retro-aldol-type fragmentation.

Different approaches have been followed in the synthesis of cedranoid sesquiterpenes (*cf* **69.1**). Breitholle and Fallis[332] have used the intramolecular Diels–Alder reaction of **69.2** to obtain **69.3**, in which the unsaturated 5-membered ring is further enlarged to **69.4**. The Diels–Alder approach of Büchi *et al.*[333] leads to bicyclo[2.2.2]octenes **69.6** and **69.7** (ratio 1:3, respectively) which are separated and rearranged in acid. Wheareas isomer **69.6** gives isokushimone (**69.9**) in high yield, the other isomer **69.7** leads to a mixture of **69.9** (15%) and **69.8** (40%). Cationic π-cyclizations starting from spirocompounds have been used at different occasions in the past (*cf* **69.10** to **69.11**).[334–337] Cyclization of **69.12** with acetyl methanesulfonate to **69.13** has been reported by Corey and Balanson.[338] The approach used by Stevens and Yates[339] involves the synthesis of Stork's intermediate **69.17**.[340] Diester **69.14** on irradiation in acetophenone as solvent and photosensitizer gives the oxa-di-π-methane product **69.15**, which on further treatment with Me_2CuLi and decarboxylation gives **69.16**. Horton and Pattenden[341] construct diketone **69.20** via a sequence involving Michael addition of the enolate derived from **69.18**

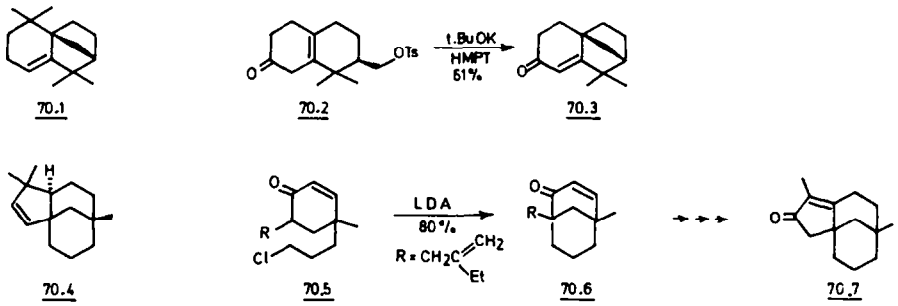


Scheme 69.

with 2-nitrobut-2-ene, and intra-Michael addition of **69.19**. A spectacular 4-step synthesis of cedrene (**69.11**) has been developed by Wender and Howbert[342] using the intramolecular variant of the 1,3-photoaddition of olefins to arenes. Although 26 cycloadducts are formally possible only **69.22** and **69.23** (1 : 1 ratio) are found upon irradiation of **69.21**, the result of high mode selectivity (*meta* cycloadducts), regioselectivity (addition across alkyl or alkoxyl groups of the arene), *endo/exo* selectivity and stereoinduction by the secondary methyl group. Both adducts were converted to enone **69.24** in 59% yield.

Piers and Zbozny[343] have reported a synthesis of isolongifolene (**70.1**) based upon the intramolecular alkylation of cyclohexenone **70.2** which gives the product of γ-alkylation **70.3**. The synthesis of clovene (**70.4**) by Schultz and Dittami[344] proceeded via α′-alkylation of enone **70.5**. The resulting enone **70.6** was further transformed into cyclopentenone **70.7**, an intermediate in Raphael's clovene synthesis.[345]

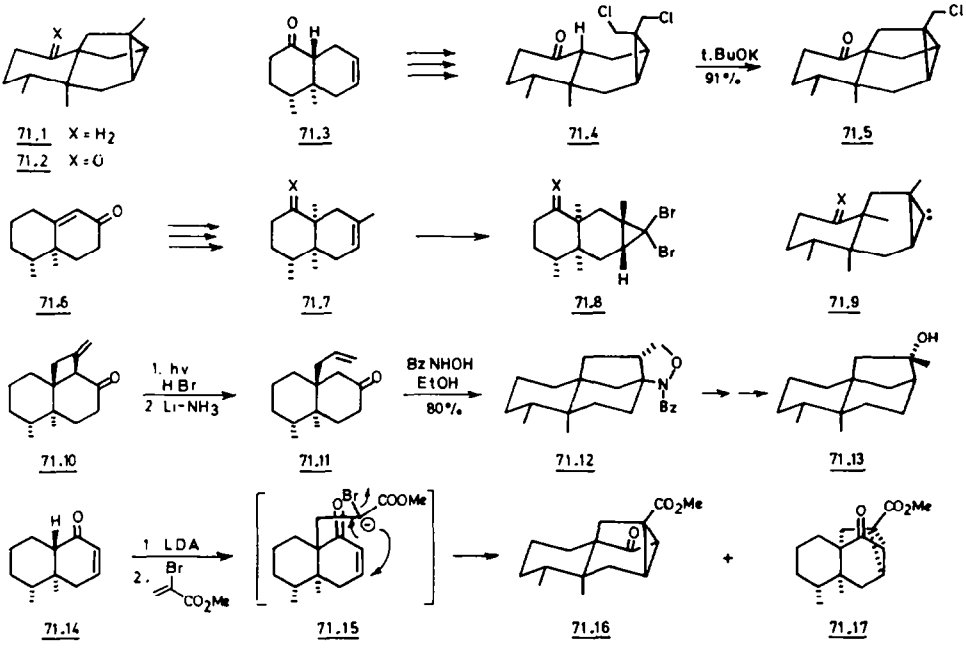
The tetracarbocyclic sesquiterpenes ishwarane (**71.1**) and ishwarone (**71.2**) constitute an interesting synthetic challenge. In the synthesis of Piers and Hall[346] **71.4** is obtained from olefin **71.3** via dimethyl diazomalonate addition and subsequent transformation of the diester; dichloride **71.4** is then ring closed in base. Cory *et al.*[347] have obtained both sesquiterpenes starting from olefin **71.7** (X = H_2 or O). Dibromocarbene addition leads to **71.8** (X = O), which on further treatment with methyllithium leads to ishwarone (**71.2**). Carbene generation in the presence of methyllithium (X = H_2; carbontetrabromide, methyllithium, −70°), however, gives directly ishwarane (**71.1**) upon raising the temperature to −30°. In both cases the regiospecific one-step carbon insertion proceeds via **71.9**. The olefins **71.3** and **71.7** (X = O) are not available via direct Diels–Alder reaction and were obtained via



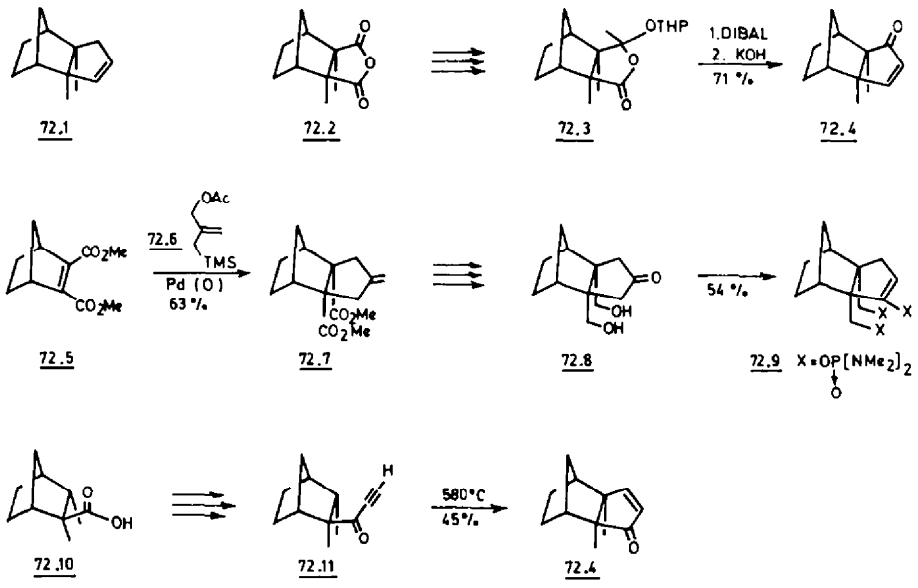
Scheme 70.

alkylative sequences. Intramolecular nitrone–olefin cycloaddition was applied by Funk *et al.*[348] for the preparation of secoishwaranol (**71.13**). A single isoxazolidine (**71.12**) is obtained by treatment of ketone **71.11** with benzylhydroxylamine in ethanol. A reductive fragmentation sequence was used to obtain **71.11** from cycloadduct **71.10**, an intermediate in the Kelly synthesis.[349] The direct construction of the tetracyclic ishwarane skeleton via bicycloannulation has been reported by Hagiwara *et al.*[350] Michael addition of the enolate derived from **71.14** on α-bromoacrylate gives intermediate **71.15**, which forms *in situ* the required 3-membered ring via internal Michael attack to the enone moiety, followed by an intramolecular displacement of the bromine atom. Unfortunately, the reaction gives a low yield of desired **71.16** (20%) and isomeric **71.17** (12%).

The synthesis of albene (**72.1**) by Baldwin and Barden[351] features the cyclopentenone annulation sequence **72.3** to **72.4**; the protected keto aldehyde, obtained upon reduction of **72.3**, gives **72.4** in good yield when treated with methanolic potassium hydroxide. Anhydride **72.2** was prepared via the known photochemical cycloaddition with benzophenone as sensitizer. A transition metal-mediated protocol was applied by Trost and Renaut.[352] The formal [3+2] cycloaddition of **72.6** to unsaturated diester **72.5** gives **72.7**; tetrakis(triisopropyl phosphite)palladium, prepared *in situ* from triisopropyl phosphite and palladium acetate, was the catalyst of choice. Complete deoxygenation of **72.9**, obtained from keto diol **72.8** via the phosphoramidate method, was effected by lithium in ethylamine (82% yield). Dreiding *et al.*[353] have used the thermal rearrangement of α-acetylenic ketones to 2-cyclopentenones for the synthesis of albene (**72.1**). Thermolysis of **72.11** gives predominantly (> 90%) enone **72.4** which can be isolated in 45% yield.



Scheme 71.

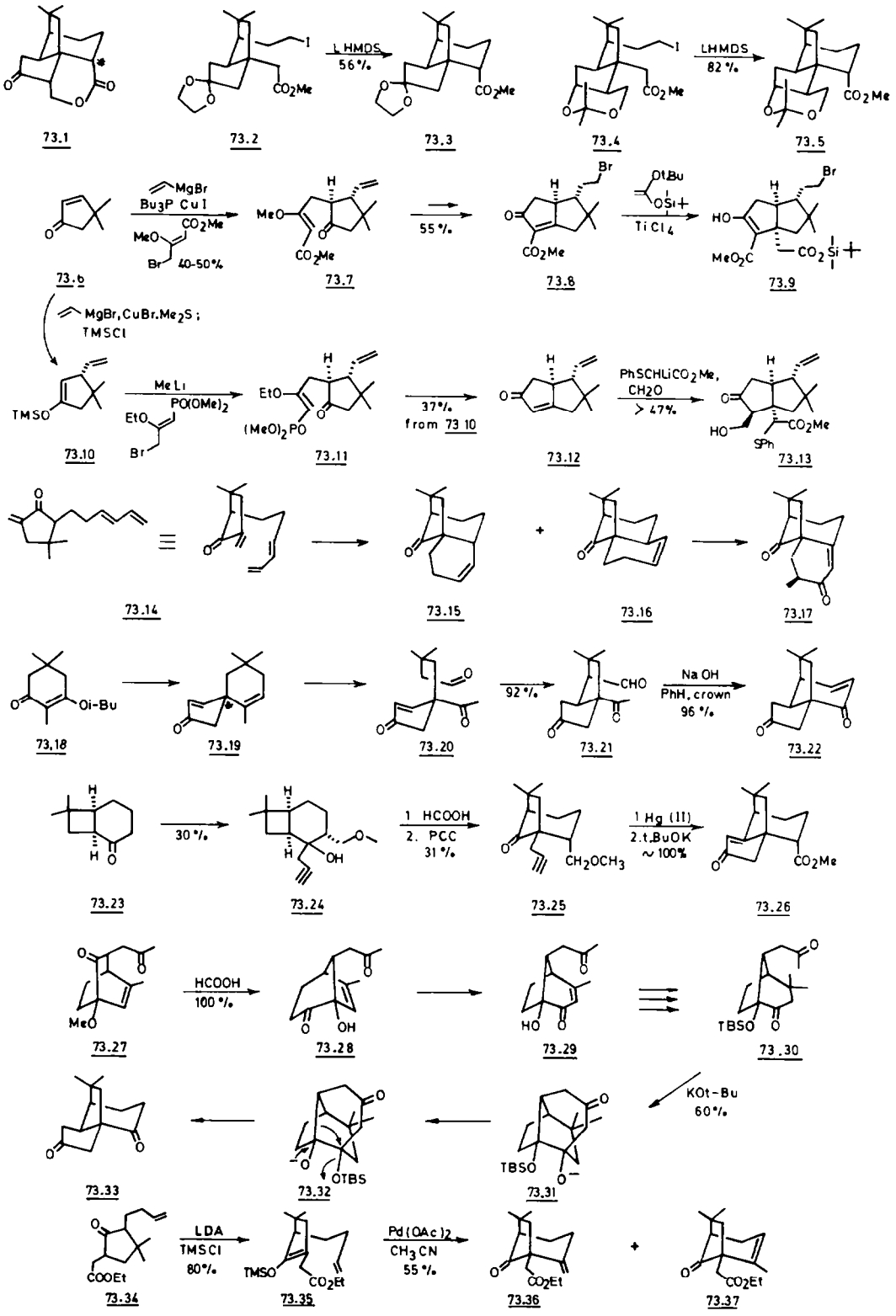


Scheme 72.

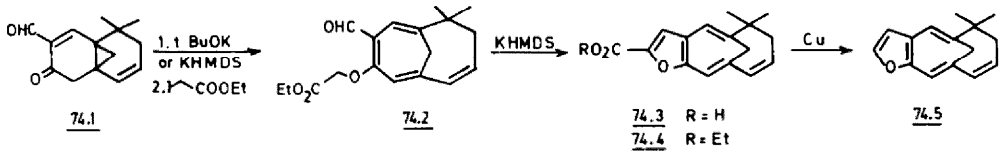
Since its discovery in 1978 quadrone (**73.1**) has attracted considerable synthetic interest. Both Danishefsky *et al.*[354] and Helquist *et al.*[355] have assembled the carbocyclic skeleton by intramolecular alkylative formation of the 6-membered ring starting from a properly constituted *cis*-fused diquinane (**73.2** to **73.3**, and **73.4** to **73.5**, respectively). In both cases the axial carbomethoxy group is obtained; the reasons for this specificity remain to be clarified. In Danishefsky's approach **73.7** is obtained from 4,4-dimethylcyclopentenone via conjugate addition and trapping with the γ-electrophilic equivalent of acetoacetate.[356] Diquinane **73.9**, precursor of **73.2**, is obtained from **73.8** via Mukaiyama reaction.[357] Helquist's route proceeds through **73.12**, which was obtained via Piers cyclopentenone annulation procedure;[93] this enone is treated with the lithium enolate of methyl phenylmercaptoacetate followed by formaldehyde to yield **73.13**, which is further transformed to **73.4**.

The groups of Schlessinger[358] and Vandewalle[359] have independently reported an almost identical Diels–Alder approach to quadrone. While the former group reported the sole formation (48% yield) of *exo*-adduct **73.16** upon heating of **73.14** in toluene–acetonitrile at 120°, Vandewalle *et al.*[359] observed the formation of **73.15** and **73.16** (ratio 1:3; 60% conversion) in refluxing toluene. Both groups converted **73.16** (and **73.15**)[360] into the desired *cis*-decalin system (*cf* eventual configuration at starred carbon in **73.1**) via allylic oxidation (CrO_3, 3,5-dimethylpyrazole) and alkylation (LDA, CH_3I) to **73.17**, followed by catalytic hydrogenation.

The synthesis of Burke *et al.*[360] centres about the site selective Michael addition of **73.20** to **73.21**, followed by internal aldolization to **73.22**. Aldehyde **73.21** is obtained selectively when using morpholine and *p*-toluenesulfonic acid in benzene. Spirocycle **73.19** is synthesized using intramolecular vinylsilane acylation (*cf* **47.10**). In the synthesis of Yoshii *et al.*[361] the enol ether of **73.23** is treated with chloromethyl methyl ether in the presence of zinc–copper couple and diiodomethane, followed by propargylaluminium sesquibromide, to give **73.24**. Cyclobutylcarbinyl cation rearrangement of **73.24** leads, after saponification and oxidation, to a mixture from which ketone **73.25** is isolated in 31% yield. The presence of a substituted bicyclo[3.2.1]octane moiety in quadrone's skeleton prompted Monti and Dean[362] to investigate a rearrangement route starting from bicyclo[2.2.2]octenone **73.27**. Acid-catalyzed rearrangement affords the more stable dione **73.29** quantitatively; under controlled conditions **73.28** can be isolated. A tandem aldol-pinacol transformation, involving silyl migration (**73.31** to **73.32**), leads directly to diketone **73.33** upon treatment of **73.30** with potassium t-butoxide. The synthesis of Kende *et al.*[363a] centres about the Pd(II)-mediated cycloalkenylation[363b] of TMS ether **73.35** which gives a 8:1 ratio of **73.36** and **73.37**, respectively. The rate-determining step would involve a nucleophilic attack of the enol ether double bond upon the palladium coordinated exocyclic olefin. The desired enolate anion for the synthesis of **73.35** was uniquely obtained via treatment of **73.34** with 0.95 equiv. of LDA.



Scheme 73.



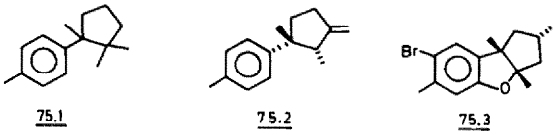
Scheme 74.

The synthesis of the unstable marine furanosesquiterpene spiniferin-1 (**74.5**) has recently been described by Marshall and Conrow.[364] The 1,6-methano[10]annulene structure suggests a norcaradiene-cycloheptatriene-type electrocyclic rearrangement as a possible route.[365] This was effected on **74.1** through the use of base; alkylation of the enolate with ethyl iodoacetate gave **74.2** which on further base-treatment led to a mixture of acid **74.3**, ester **74.4** and minor amounts of spiniferin-1 (**74.5**).

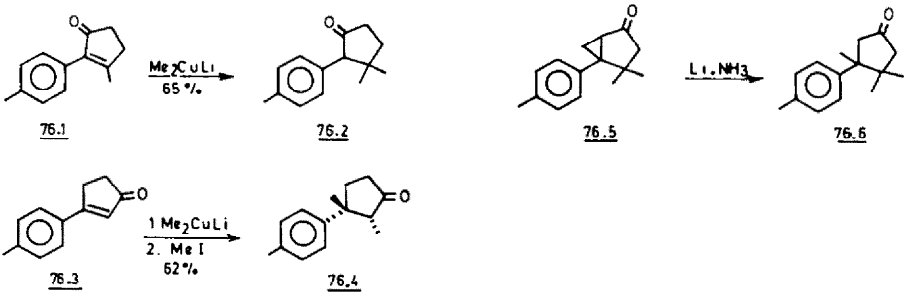
IV. ISOLATED RINGS

The synthesis of cuparanes (**75.1**) requires the creation of two adjacent quaternary centres on a 5-membered ring, one of which bears a *p*-methylphenyl group (Scheme 75). Since 1973 a number of different approaches have been reported. In several syntheses quaternization has involved methylation α to a carbonyl or conjugative addition to a cyclopentenone (**76.1** to **76.2**,[366] **76.3** to **76.4**[367]). Casares and Maldonado[368] reported the interesting transformation of **76.5** to β-cuparenone (**76.6**). Instead of benzylic radical formation, the peripheral bond is reductively cleaved in accord with the concept of orbital overlap.

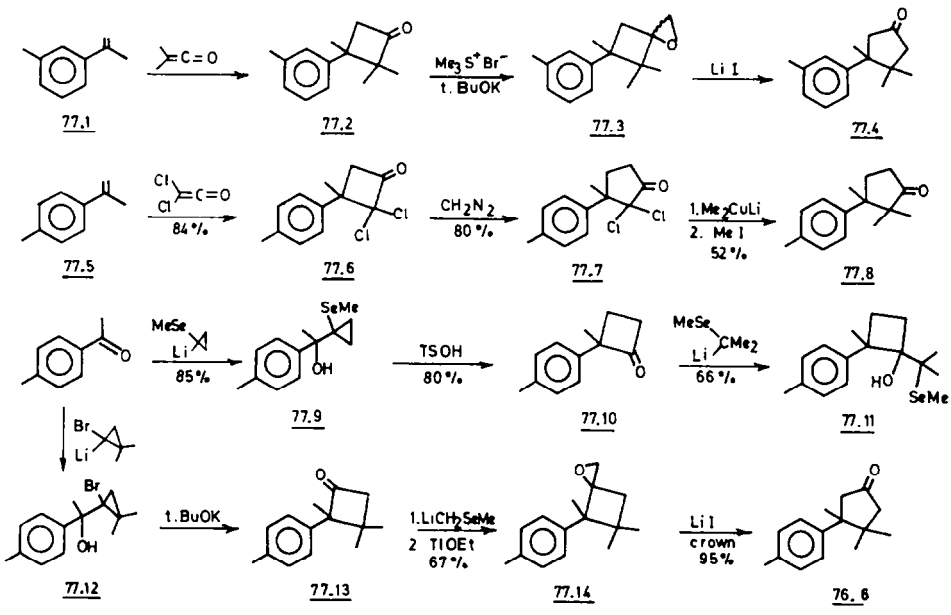
In several approaches the required skeleton has been formed through ring expansion (Scheme 77). Leriverend *et al.*[369] obtained cyclopentanone **77.4** upon stereoselective rearrangement of exocyclic epoxides **77.3** with anhydrous lithium iodide. A less stereoselective opening of a similar epoxide has led to the formation of a mixture of α- and β-cuparenone.[369c] Cyclobutanone **77.2** resulted from regioselective thermal cycloaddition of **77.1** and *in situ* generated dimethylketene. In recent work reported by Greene *et al.*[370] the use of dichloroketene enables the synthesis of **77.6**, which is subsequently ring enlarged to cyclopentanone **77.7**. Geminal substitution via cleavage-methylation leads to α-cuparenone (**77.8**). The latter product has been obtained by Krief *et al.*[371] via acid rearrangement of cyclobutanol **77.11**. Cyclobutanone **77.10** resulted in turn from the acid rearrangement of the methylseleno cyclopropane **77.9**. The same authors reported the almost quantitative conversion of epoxide **77.14** to β-cuparenone with lithium iodide and 12-crown-4. Cyclobutanone **77.13** was directly formed upon base treatment of **77.12** and does not arise from the acidic rearrangement of an intermediate oxaspiropentane.[372]



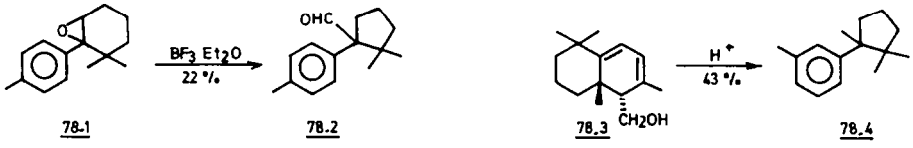
Scheme 75.



Scheme 76.



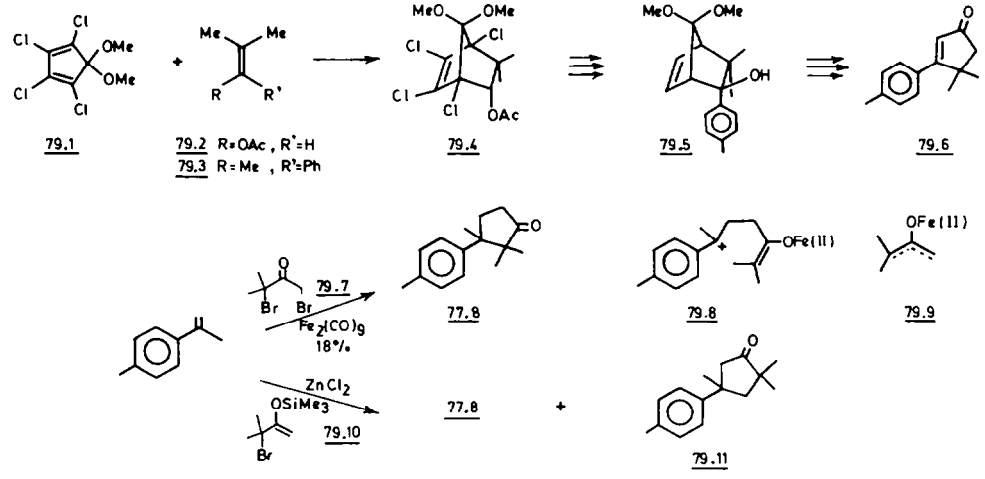
Scheme 77.



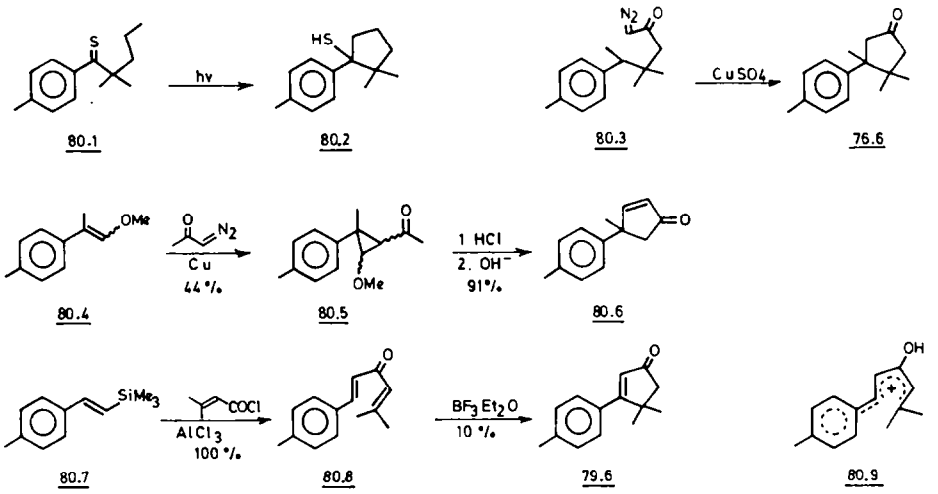
Scheme 78.

The cuparane skeleton has also been obtained by ring contraction of epoxide **78.1** (Scheme 78). The remarkable rearrangement of alcohol **78.3** to herbetene (**78.4**) has been observed by Fratér[374] and supposedly involves the intermediacy of cyclopropyl carbinyl ions.

Jung and Radcliffe[375] have used "three-carbon annulation" for the synthesis of β-cuparenone (Scheme 79). Unfortunately, tetrasubstituted olefin **79.3** did not enter Diels–Alder reaction with cyclopentadiene derivative **79.1**. However, reaction of the latter with **79.2** does yield the *endo*-adduct **79.4** (35% after several days). In a further sequence the product was transformed to **79.5**, which was successively oxidatively cleaved, hydrolyzed and decarboxylated to **79.6**. Noyori *et al.*[376] have



Scheme79.



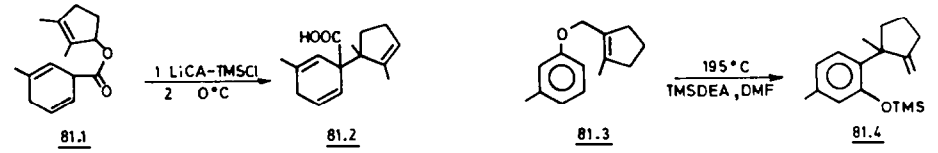
Scheme 80.

described a very expeditious synthesis of α-cuparenone (**77.8**) based on the $Fe_2(CO)_9$-promoted coupling between α,α'-dibromo ketone **79.7** and an arylated olefin. If not very efficient, the reaction is highly stereoselective (94 : 6) due to the relative stability of intermediate **79.8**, formed by electrophilic attack of **79.9** on the olefinic substrate. The [3 + 2]cycloaddition of enol ether **79.10** to the same styrene derivative has also been reported to yield α-cuparenone (27% yield) next to regiosomer **79.11** (16%).[377]

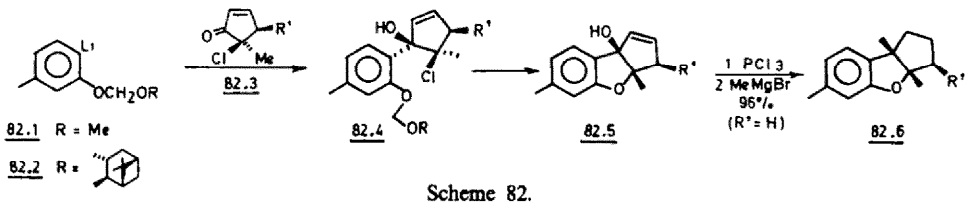
In a synthesis of cuparene De Mayo *et al.*[378] have used the interesting photocyclization of thione **80.1** to thiol **80.2**, followed by elimination to the corresponding cyclopentene (mercuric acetate; 65% overall). β-Cuparenone has been obtained directly via intramolecular ketocarbene insertion into the benzylic C—H bond of **80.3**.[379] Wenkert *et al.*[217] applied β-oxocyclopropyl ketone fragmentation for the synthesis of α-cuparenone. Thermal decomposition of diazoacetone in enol ether **80.4** in the presence of copper bronze gave **80.5**. Hydrolysis and aldol ring closure of the resulting keto aldehyde gave enone **80.6**. It is interesting to note that application of the Nazarov reaction for constructing the cuparane skeleton from **80.8** did not prove very successful. Paquette *et al.*[380] subjected the latter dienone, readily obtained from vinylsilane **80.7**, to a variety of acid conditions and only observed formation of the desired cyclopentenone **79.6** (10% yield) with borontrifluoride etherate. The stability of intermediate cation **80.9** has been invoked for this somewhat surprising result.

The Claisen rearrangement has also found application in this area (Scheme 81). Chandrasekaran and Turner[381] reported the [3,3]sigmatropic rearrangement of the silyl ester enolate derived from **81.1** to acid **81.2**, which was subsequently decarboxylated (lead tetraacetate, cupric acetate) to a precursor of herbetene (**78.4**). The overall sequence from 3-methylbenzoic acid proceeds in 52% yield. The classical Claisen rearrangement of phenol ether **81.3** is advantageously carried out in the presence of N-trimethylsilyldiethylamine which directly leads to ether **81.4** in good yield; without etherification of the resulting phenol, furan ring closure to the exocyclic double bond is observed.[382]

The synthesis of laurene (**75.2**) and related products via olefination of the corresponding 2,3,3-trisubstituted cyclopentanones is rendered difficult by the concomitant epimerization at the methyl group.[383] We will return to this problem in Section V. The halogenated marine sesquiterpenes allolaurinteral (related to laurene **75.2**) and aplysin (**75.3**) were synthesized by Ronald *et al.*[384] following Scheme 82. Reaction of lithio derivative **82.1** with cyclopentenone **82.3** gives unstable chlorohydrine **82.4**. The mixed phenolic acetal serves as a directing and stabilizing group for aromatic metallation.

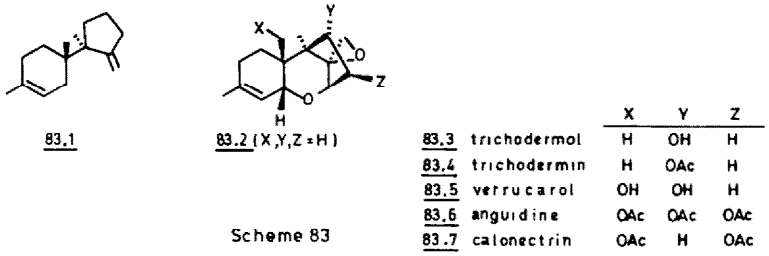


Scheme 81.



Scheme 82.

The use of chiral **82.2** [*cf*(−)-isopinocampheol] enables diastereoisomeric resolution: diastereoisomer **82.4** (R′ = Me, R = isopinocamphyl), obtained in 37% yield, eventually yields natural (−)-aplysin. Solvolysis of **82.4** in methanol containing potassium hydroxide gives **82.5**. The introduction of a methyl group is performed on the corresponding chloride with methylmagnesium bromide; this introduction appears to take place with retention of configuration and could involve an ion-pair process.

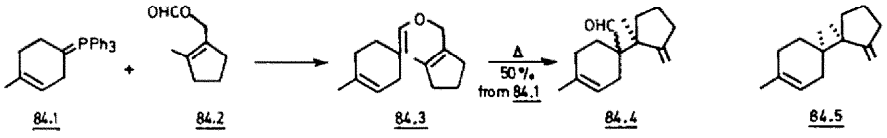


		X	Y	Z
83.3	trichodermol	H	OH	H
83.4	trichodermin	H	OAc	H
83.5	verrucarol	OH	OH	H
83.6	anguidine	OAc	OAc	OAc
83.7	calonectrin	OAc	H	OAc

Scheme 83

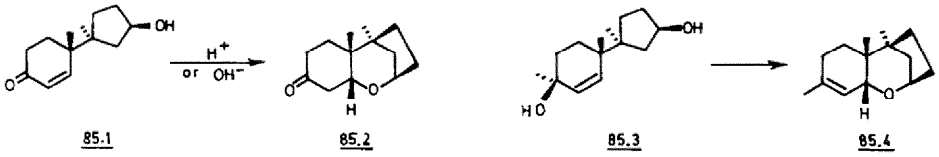
Scheme 83.

The trichothecane antibiotic sesquiterpenes, a class of fungal metabolites, possess the common tetracyclic 12,13-epoxytrichothec-9-ene skeleton (**83.2**) and are biogenetically related to trichodiene (**83.1**). Syntheses of the latter require control over two adjacent chiral quaternary centres which are free to rotate about a common C—C single bond. Lack of control results in the concomittant formation of bazzanene, as in the recently reported study of Suda (Scheme 84).[385] In this work Claisen rearrangement of enol ether **84.3**, directly obtained from the Wittig reaction on formate **84.2** gives a mixture of aldehydes **84.4**. Subsequent Wolff–Kishner reduction led to a 1 : 1 mixture of trichodiene (**83.1**) and bazzanene (**84.5**).

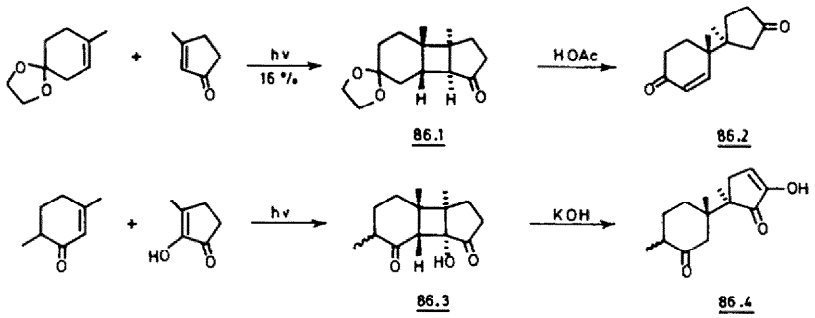


Scheme 84.

In 1974 Masuoka *et al.*[386] reported the stereoselective formation of **85.2** and **85.4** from the bicyclic precursors **85.1** and **85.3** (Scheme 85). Several approaches aiming at trichothecanes have used this ring closure type (*vide infra*). Obviously, a stereoselective synthesis along this line necessitates control of at least three centres. As in the case of trichodiene (**83.1**) two vicinal quaternary centres on different rings must be created with the correct relative configuration. In many syntheses this is accomplished via stereochemically controlled operations in a bi- or tricyclic system which is subsequently fragmented. These fragmentation approaches are discussed first.



Scheme 85.



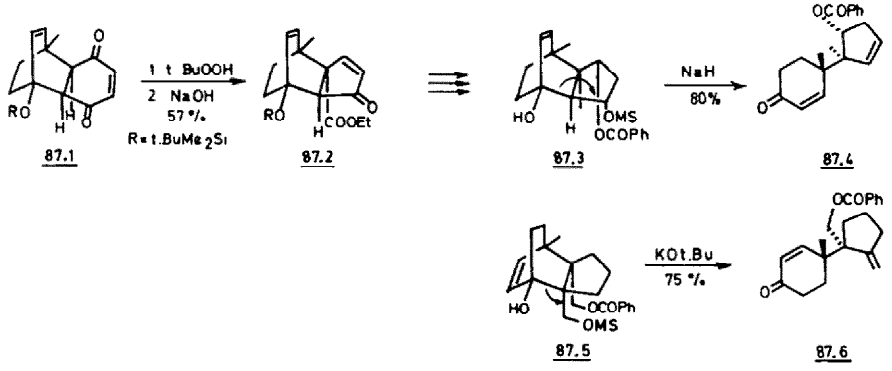
Scheme 86.

Masuoka and Kamikawa[387] used the acid fragmentation of photoadduct **86.1** to **86.2** in the synthesis of 12,13-epoxytrichothec-9-ene (**83.2**). Yamakawa *et al.*[388] isolated photoadduct **86.3** among several other products; reverse aldol reaction leads to α-diketone **86.4**, a precursor for norketotrichodiene.

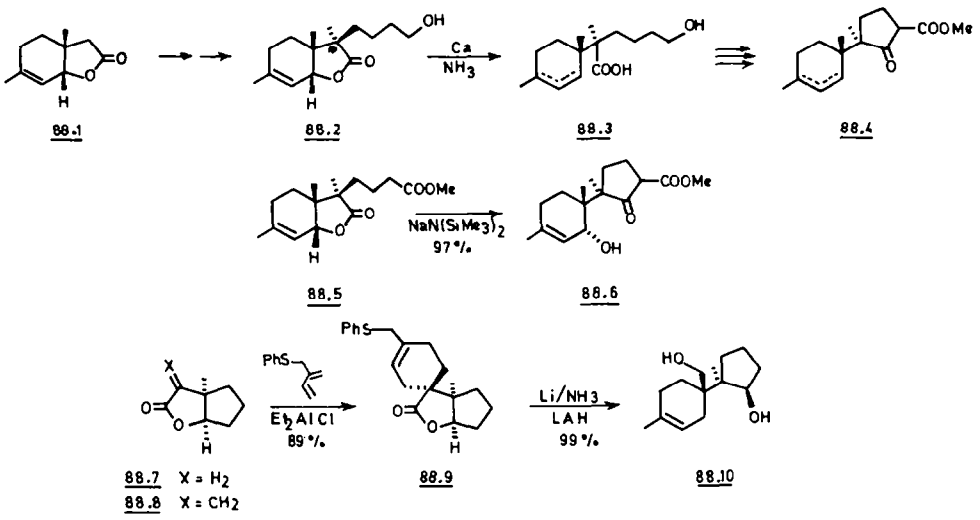
The bicyclo[2.2.2]octene substructure has also served the same basic purpose in two examples. Still and Tsai[389] reported a synthesis of trichodermol in which bicyclic enone **87.4** is obtained via anionic fragmentation of **87.3**. The latter was obtained via cyclopentenone **87.2**, which resulted from epoxidation and Herz–Favorskii ring contraction of Diels–Alder adduct **87.1**. The conversion of tricyclic alcohol **87.5** to enone **87.6** via a similar fragmentation has also been described by Kodama *et al.*[390]

Two groups have reported stereoselective syntheses of trichodiene (**83.1**) starting from a *cis*-fused bicyclic lactone. Welch *et al.*[391] converted **88.1** stereoselectively into **88.2** or its epimer (starred carbon) depending on the order of sequential alkylation. Hydrogenolysis with calcium in liquid ammonia gives a mixture of tri- and disubstituted olefins (**88.3**) in good yield. Dieckmann condensation of the corresponding diester led to cyclopentanones **88.4** in high yield. The ester **88.5** gave directly keto ester **88.6** upon treatment with sodium bis(trimethylsilyl)amide. Schlessinger and Schultz[392] obtained the vicinal quaternary centres with the desired configuration via Lewis acid catalyzed Diels–Alder reaction of 2-(phenylthio)methyl-1,3-butadiene on the α-methylene lactone **88.8**.

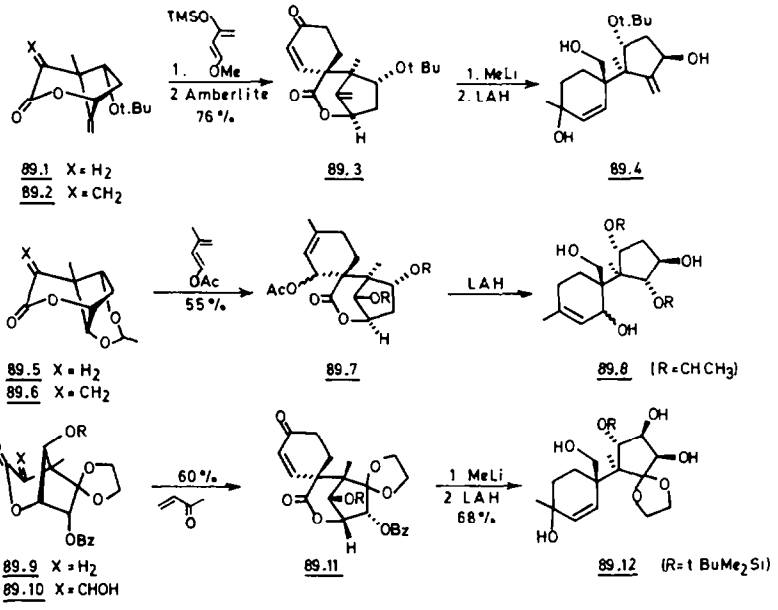
Following model studies of Roush[393] the oxabicyclo[3.2.1]octanone framework has been used to obtain stereoselectively the three chiral centres necessary for eventual trichothecane synthesis according to Scheme 85. Again Schlessinger *et al.*[394] applied Diels–Alder quaternization on a α-methylene lactone (**89.2**). Hydrolysis of the adduct gave **89.3** as the sole unsaturated enone, which was further transformed to verrucarol (**83.5**). A similar strategy has recently been applied by Roush and D'Ambra.[395] In both syntheses the α-methylene lactones were obtained directly from **89.1** and **89.5**, respectively (Section V). An enantioselective synthesis of anguidine has been described by Brooks *et al.*[396] starting from lactone **89.9**, obtained in optically active form via asymmetric microbial reduction of 2-allyl-2-methyl-1,3-cyclopentanedione. Stereoselective quaternization was realized via an aldol sequence on **89.10**. The efficient ring closure of **89.12** required here the protection of the primary hydroxyl group in contrast to the above cases **89.4** and **89.8**.



Scheme 87.



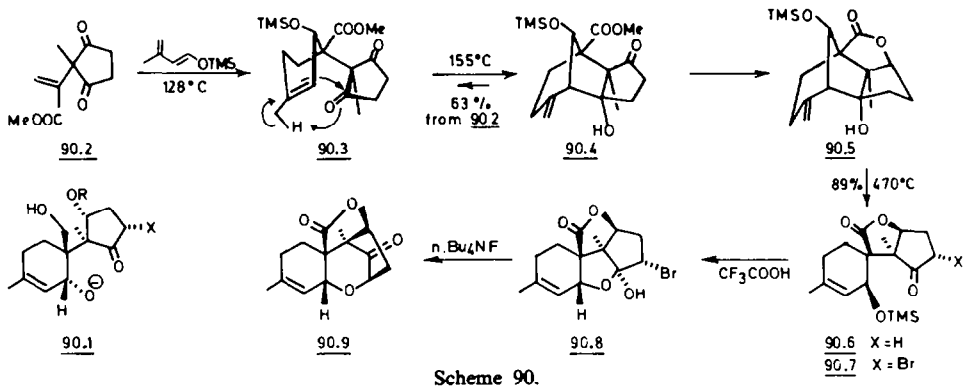
Scheme 88.



Scheme 89.

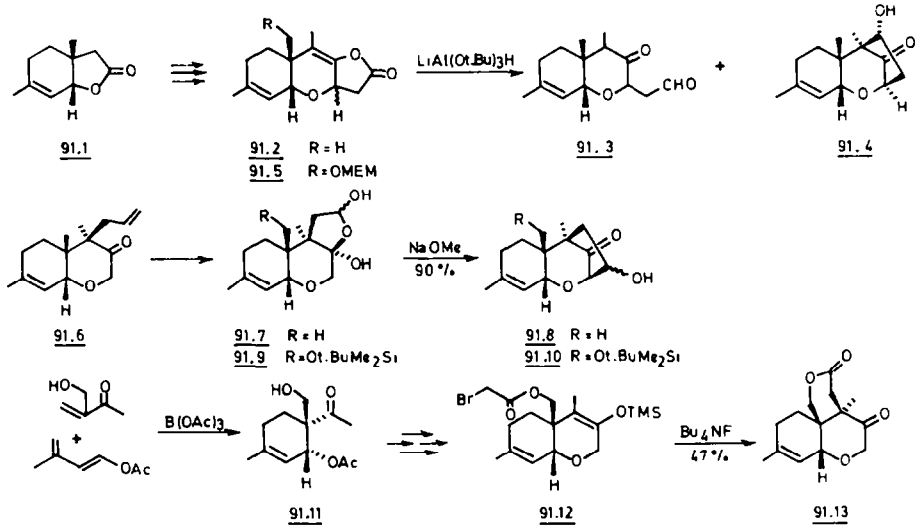
Trost and McDougal[397] have reported a synthesis of verrucarol (**83.5**) whereby the trichothecane nucleus originates from nucleophilic displacement of a properly oriented leaving group, an approach that requires stereochemical control over one supplementary centre (*cf* **90.1**). Diels–Alder adduct **90.3** was found to undergo a mild ene reaction to **90.4**; only one of the two diastereotopic carbonyl groups can align itself in the proper orientation. After elaboration to lactone **90.5** a retroene reaction yields **90.6**. The sequence **90.3** to **90.6** thus represents a diastereotopic differentiation and a method of protection. Inversion at the trimethylsilyloxy group in **90.7** is realized via hemiketal **90.8**, presumably via trapping of the allylic carbonium ion by the hydrated form of the ketone. Eventual ring closure to **90.9** has been effected by fluoride initiated rearrangement.

The 5-membered ring of the trichothecane skeleton has also been formed by intramolecular aldolization. The first synthesis in the area, the Colvin–Raphael synthesis[398] of trichodermin (**83.4**), is based on this approach. Lithium aluminium tri-t-butoxyhydride converted exocyclic enol lactone **91.2** into **91.4** (< 10% yield) next to aldehyde **91.3**. The latter, however, could not be induced to yield further aldol product **91.4**. In line with the configuration-holding property of the coordinating metal, which



Scheme 90.

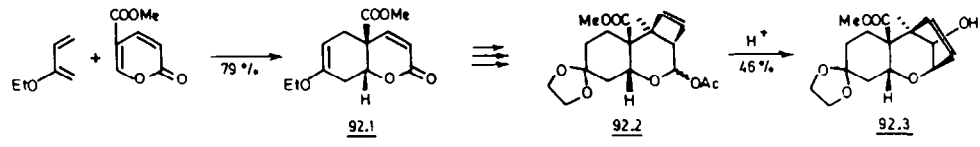
was previously observed upon reductive rearrangement of exocyclic enol lactones,[399] the correct configuration of the hydroxyl group is obtained. However, application of the same strategy on **91.5** (*cf* verrucarol **83.5**) proved unrewarding.[400] The conceptually different aldol ring closure has been more successful. Fujimoto *et al.*[401] reported the high yield conversion of **91.7** to **91.8**; the former is obtained as the hydrated form of the keto-aldehyde which results from the oxidative cleavage of **91.6**. The analogous conversion (**91.9** to **91.10**) was reported by Kraus *et al.*[402] in their synthesis of calonectrin (**83.7**); a 6 : 1 ratio of diastereoisomeric alcohols was obtained. The stereoselective formation of the two adjacent chiral quaternary centres was realized via intramolecular alkylation of the enolate derived from **91.12**. The cyclohexene ring was formed via Diels–Alder reaction; $B(OAc)_3$-catalyzed reaction gave predominantly the *endo*-adduct **91.11** (3.5 : 1) in modest yield.



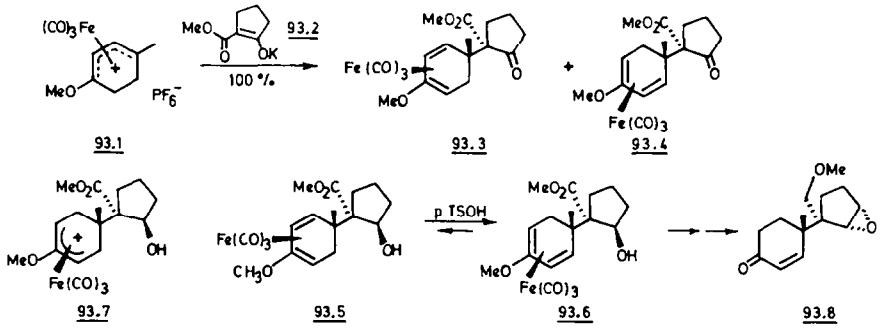
Scheme 91.

The acid rearrangement of a cyclobutenyl carbinol (from **92.2**) to the bridged cyclopentenol **92.3** has been reported by White *et al.*[403] in a model study for verrucarol (**83.5**). Lactone **92.1** is obtained in good yield upon Diels–Alder reaction of 2-ethoxybutadiene with methyl coumalate.

Of special interest is the method for controlled formation of two contiguous quaternary centres developed by Pearson *et al.*[404] The hexafluorophosphate **93.1** was found to react regio- and



Scheme 92.

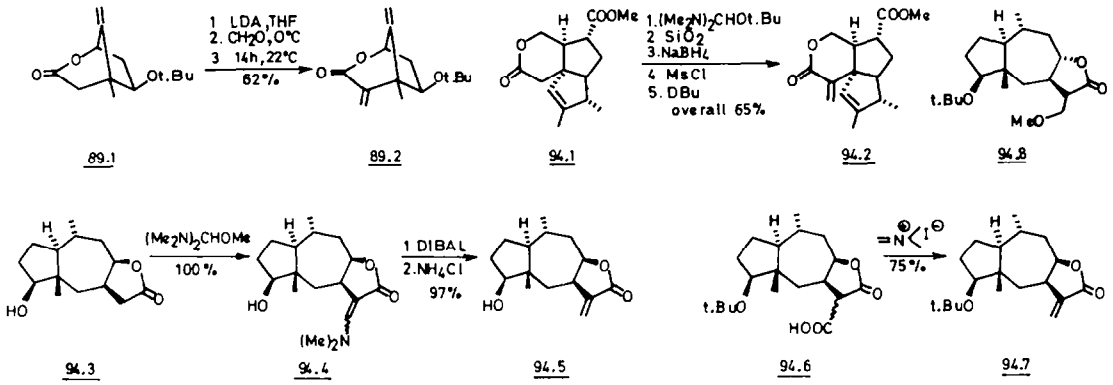


Scheme 93.

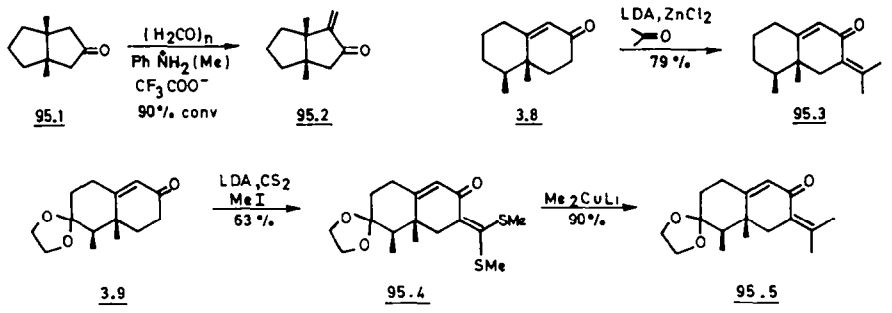
stereospecifically at the methylated dienyl terminus with stabilized enolate anions. Reaction with the potassium enolate **93.2** gives a quantitative yield of two diastereoisomers **93.3** and **93.4**. The protective property of the $Fe(CO)_3$ group toward a dienol ether is apparent in **93.5** and **93.6**, which were obtained by sodium borohydride reduction of **93.3** and **93.4**, respectively; unprotected diene is known to form a tetrahydrofuran derivative upon cyclization with the secondary hydroxyl group. A further useful property of the diene–$Fe(CO)_3$ system is the possibility for equilibration of **93.5**, which involves initial protonation on the metal followed by proton transfer to the symmetrical allyl complex **93.7**; reversal of the sequence can then give either **93.5** or **93.6**. The conversion of the latter product to **93.8** also involved several oxidative conditions which did not effect decomposition of the iron complex.

V. INTRODUCTION OF FUNCTIONALIZED SIDE CHAINS

In this section some transformations of general interest are discussed which are related to the construction of functionalized side chains, such as the introduction of a α-methylene unit on a lactone, of an α-alkylidene group on a cyclic ketone, of an acrylic ester moiety, the construction of fused butenolide and furan units, alternatives for the Wittig alkylation, and quaternization reactions on a cyclic substrate. A complete survey of each topic being obviously beyond the scope of this report the focus will reside here on the novelty or the usefulness of the described reaction (sequence). The formation of α-methylene lactones has been reviewed in 1975 by Grieco[405] and by Gammill *et al.*[406] Since then several new methods for the α-methylenation of lactones have been proposed, but only a few of them have been used during total synthesis work. The original Grieco–Hiroi[407] 3-step method (α-hydroxymethylation and subsequent elimination of the mesylate) has been modified by Schlessinger *et al.*[394] and by Roush *et al.*[395] (Scheme 94). It was observed that reaction of the enolate of **89.1** with monomeric formaldehyde at temperatures higher than previously described gives directly **89.2** and not the expected hydroxymethyl lactone.[394] During the synthesis of **17.9**, Danishefsky *et al.* described a novel 5-step sequence, starting with reaction of **94.1** with Brederick's reagent.[117] Subsequently, Ziegler



Scheme 94.



95.1 95.2 3.8 95.3 3.9 95.4 95.5

Scheme 95.

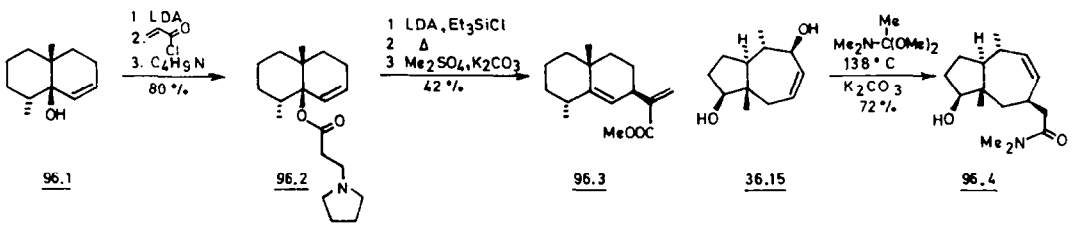
et al.[166] reported a highly efficient modification, which involves reduction of the intermediate vinylogous carbamate,[408] as is shown in sequence **94.3** to **94.5**. A lithium liq. ammonia reduction of vinylogous carbamates has also been used.[392] A modification of the Parker–Johnson[409] methodology has been described by Lansbury *et al.*;[170c] carboxylation of **94.3** with Stiles reagent leads to **94.6** which upon treatment with Eschenmoser's salt[410] is converted into **94.7**. It should be noted that, in the vernolepin synthesis, Danishefsky *et al.*[411] have treated directly lactone enolates with Eschenmoser's salt. Elimination of the β-methoxy group in **94.8** gives better results when "unsolvated" KOtBu in THF is used.[170c]

In 1978 Gras[412] described, on model compounds, the introduction of an α-methylene unit upon treatment of enolates with s-trioxane and N-methylanilinium trifluoroacetate. Recently Paquette and Han[292] observed that this method gives better results when paraformaldehyde is used (*cf* **95.1** to **95.2**). House's method[413] for intercepting the intermediate keto alkoxide, as a metal chelate, during aldol reactions has substantially improved the formation of dehydrofukinone **95.3**.[32a] Although several other methods were investigated, Bohlmann and Otto[25] observed that only the Corey–Chen methodology,[414] via the α-dithiomethylene ketone **95.4**, provides a viable route to **95.5**.

An interesting method for the direct introduction of the acrylic ester moiety, reported by Still and Schneider,[17a] is based on the Ireland–Claisen rearrangement.[415] The intermediate β-pyrrolidinopropionate **96.2** is readily prepared from **96.1** (from **2.8**). The silylketene formation, rearrangement and elimination steps represent a one-flask procedure. During the synthesis of (+)-confertin the Eschenmoser variant of the Claisen rearrangement has been employed for constructing **96.4**.[166]

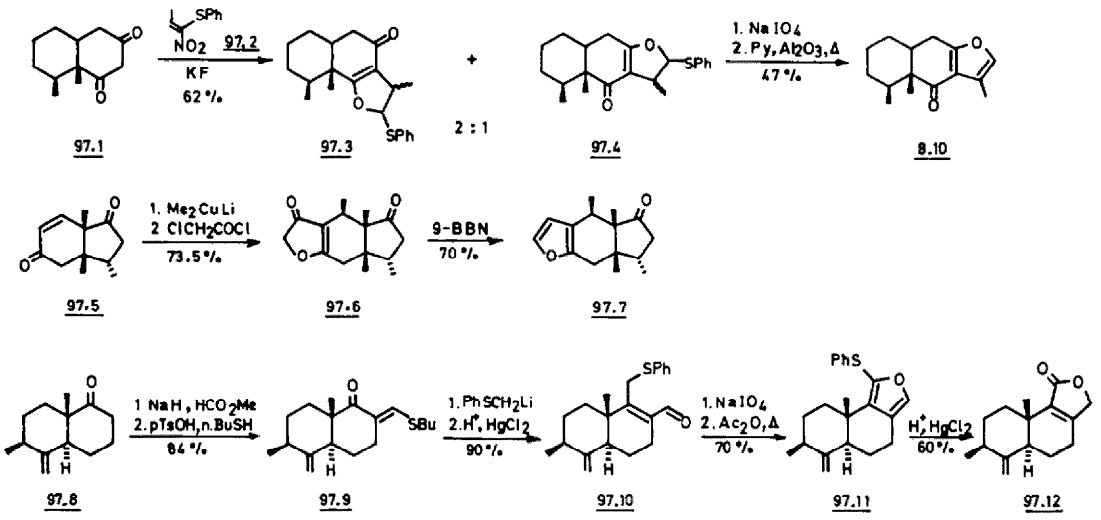
In Scheme 97 three methods are given which are suitable for the formation of fused butenolide or furan units. Michael reaction of **97.1** with the unsaturated nitro compound[416] **97.2** produces a mixture of **97.3** and **97.4** (2:1); the latter is then transformed into (±)-ligularone (**8.10**). Gariboldi *et al.*[417b] studied the acylation with chloroacetyl chloride. Trapping of the enolate after complete stereoselective cuprate addition on **97.5** provides the β-furanone **97.6**, a precursor of **97.7**. de Groot *et al.*[418] reported a new annulation method for butenolides (e.g. **97.12**) via hydrolysis of thiophenyl furan **97.11** which is formed as shown.

The lack of reactivity of hindered ketones with Wittig-reagents has stimulated the search for alternative methods. They are summarized in Scheme 98. Kende and Blacklock[419] observed poor reaction of **98.1** towards phosphor ylids, the Peterson reaction or TOSMIC. The homologation to **98.2** could be achieved by the Magnus–Roy[420] method involving addition of lithium



96.1 96.2 96.3 36.15 96.4

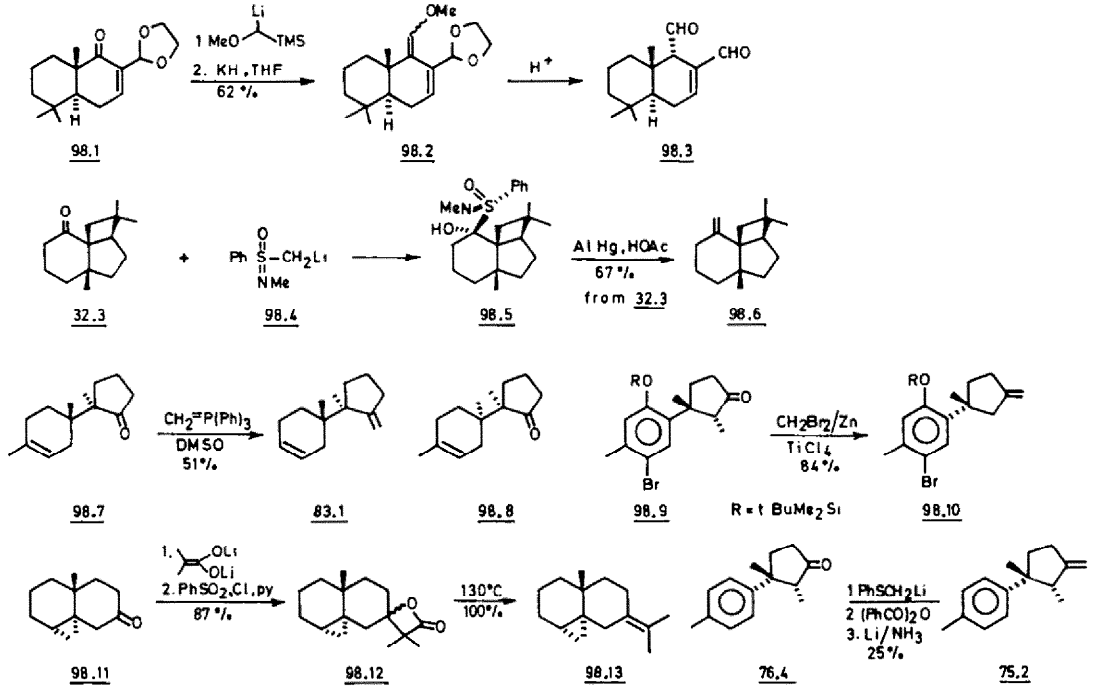
Scheme 96.



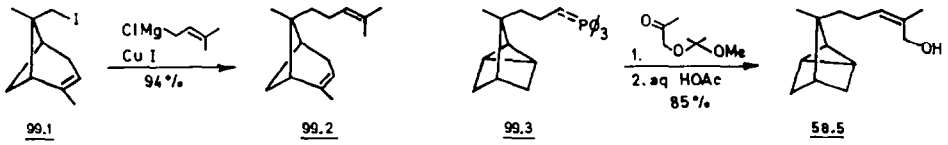
Scheme 97.

methoxy(trimethylsilyl)methylide followed by elimination of TMSOH. Johnson and Meanwell observed that reaction of **32.3** with **98.4** exhibits remarkable diastereoselectivity as practically exclusively (> 30:1) diastereoisomer **98.5** is produced.[159] This finding has been exploited in a methylenation–resolution procedure starting with the *S* enantiomer of **98.4**.

Despite previous unsuccessful reports Welch *et al.* converted trichoenone **98.7** to trichodiene (**83.1**) with 10 equiv. of Wittig reagent in scrupulously dried DMSO; under identical conditions, however, isomer **98.8** is unreactive.[391] The same transformation of **98.7** to **83.1** has been reported by Schlessinger and Schultz,[392] the reaction is carried out in a sealed tube for 60 hr at 80° (75% yield). The synthesis of **98.10** and **75.2** is rendered difficult due to epimerization at the ketone stage during Wittig reactions and to lack of reactivity with most other olefination procedures. Ketone **98.9** could however be methylenated, without epimerization, upon applying Nozaki's[421] method. McMurry and von



Scheme 98.



99.1 99.2 99.3 58.5

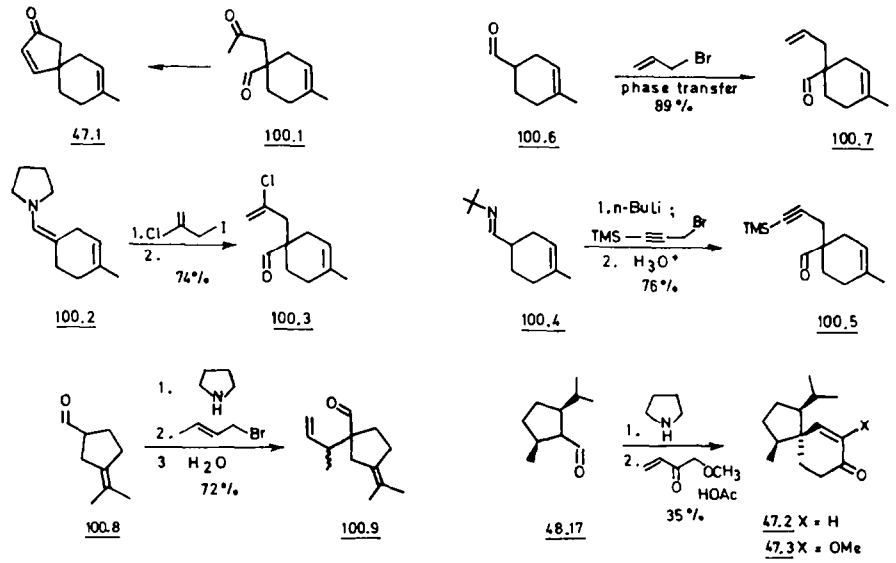
Scheme 99.

Beroldingen[422] have solved the problem for preparing **75.2** via Coates' method.[423] The unreactivity of **98.11** in Wittig reactions led Moss and Chen[424] to effect its transformation to **98.13** by initial reaction with the dianion of isobutyric acid to form **98.12**.

The attachment of an isoprene unit to a neopentyl carbon is a classical problem in the synthesis of several bicyclic bridged sesquiterpenes (Section III.1). Whereas the method of choice has often involved the use of π-(1,1-dimethylallyl)nickel bromide,[425] Linstrumelle *et al.*[426] have recently reported the regioselective alkylation of the Grignard derivative of γ,γ-dimethylallyl chloride at the primary carbon under copper-catalyzed conditions; thus, iodopinene **99.1** gives α-*cis*-bergamotene (**99.2**) in high yield. The direct Wittig-type synthesis of *Z*-trisubstituted olefins has been described by Still *et al.*;[427] the utility of the process is illustrated with a synthesis of α-santalol (**58.5**), obtained with more than 99% stereoisomeric purity.

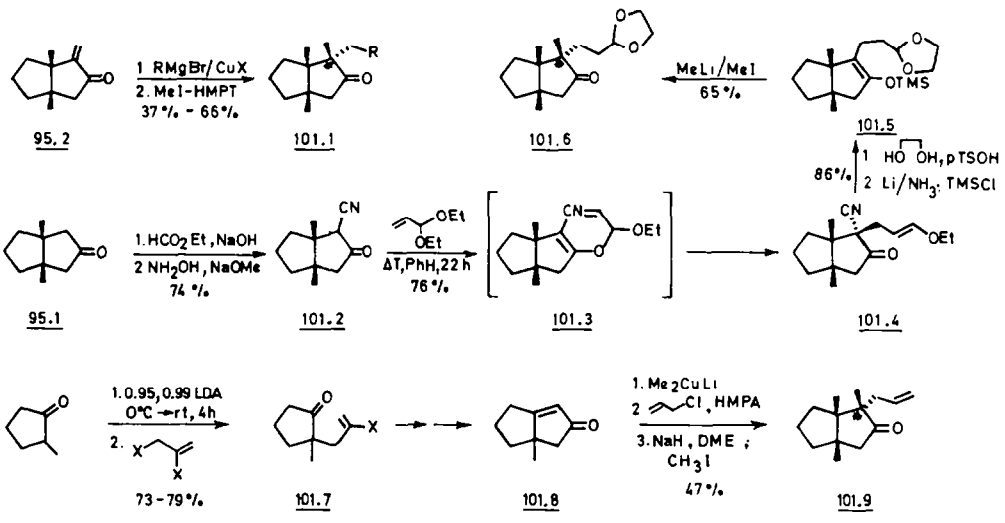
In connection with the synthesis of spirocyclic sesquiterpenes (Section II) at several occasions an alkylation α to an aldehyde has been required. It is of interest here to compare the different methods that were used for the synthesis of **100.1**. Martin and Chou[206] applied the classical Stork enamine alkylation (**100.2** to **100.3**), whereas McCrae and Dolby[207] had recourse to the Wittig–Stork metalloenamine method[428] (**100.4** to **100.5**). In both cases was the desired methyl ketone **100.1** obtained via acidic Hg(II) treatment. A more direct route to **100.1** has recently been reported by Ho,[208] and involves the direct alkylation of aldehyde **100.6** with allyl bromide under conditions of phase transfer catalysis,[429] followed by Wacker's oxidation. Enamine alkylation has also been applied for the synthesis of **100.9**[213] and **47.3**;[210] enone **47.2** was, however, directly obtained from aldehyde **48.17** (methyl vinyl ketone, KOH, dioxane at 70°) allbeit in low yield (~ 20%).[209]

Crucial in three syntheses of gymnomitrol (**62.1**) is the obtention of a quaternary centre on a *cis*-fused diquinane with the correct stereochemistry (starred centre in **101.1**, **101.6** and **101.9**). Paquette's approach involved the 1,4-addition of functionalized Grignard reagents on the relatively uncongested methylenic carbon of **95.2**, followed by *in situ* methylation.[292] The synthesis of Coates *et al.* implies the reductive alkylation of an α-cyano ketone (*cf* **101.4** to **101.6**). Of special interest here is the conversion of **101.2** to **101.4** presumably involving acetal exchange with the enol form of **101.2** to give ethoxyallyl enol



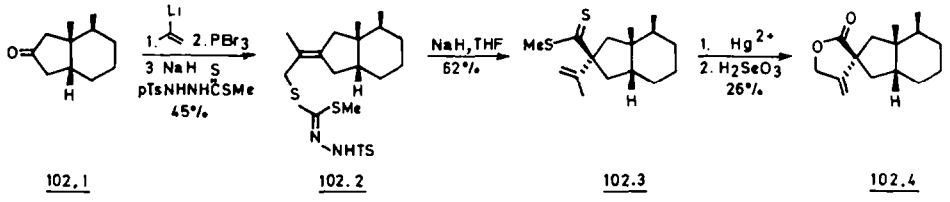
47.1 100.1 100.6 100.7 100.2 100.3 100.4 100.5 100.8 100.9 48.17

Scheme 100.



Scheme 101.

ether **101.3**, followed by [3,3]sigmatropic rearrangement.[291] Welch's approach centres about the classical 1,4-addition–alkylation sequence, followed by introduction of the quaternary methyl via direct alkylation (**101.8** to **101.9**).[293] The regioselective alkylation of 2-methylcyclopentanone to **101.7** was effected via enolate equilibration and quenching with the electrophile; this method was found superior to the House enol acetate or the Stork TMS enol ether methods.



Scheme 102.

Within the context of a total synthesis of bakkenolide-A (**102.4**) Evans *et al.*[430] have reported the interesting transformation of **102.1** to **102.4** involving the highly stereoselective [2,3]sigmatropic rearrangement of the carbenoid or the conjugated base derived from carbamate **102.2** to dithioester **102.3**.[431]

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