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The Synthesis of Germacrane Sesquiterpenes and Related Compounds

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1. Introduction

Because of their unique structural and conformational features, their general occurrence in nature[1] and their central role in the biosynthesis of other sesquiterpenes,[2] germacrane sesquiterpenes have received much attention in modern organic chemistry.

The majority of known germacranes possesses the flexible (*E,E*)-cyclodeca-1(10),4-diene ring unit as the main structural characteristic, but (*Z,E*)-germacranes (melampolides), (*E,Z*)-germacranes (heliangolides) and (*Z,Z*)-germacranes are also frequently found in nature (Figure 1).[3]

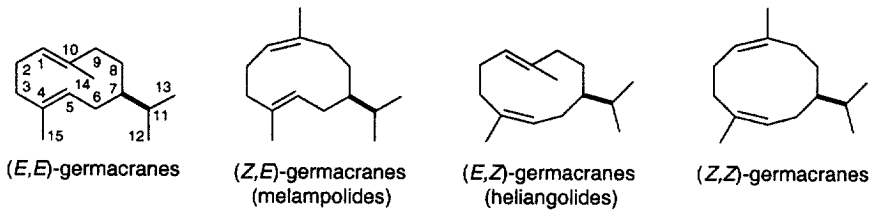
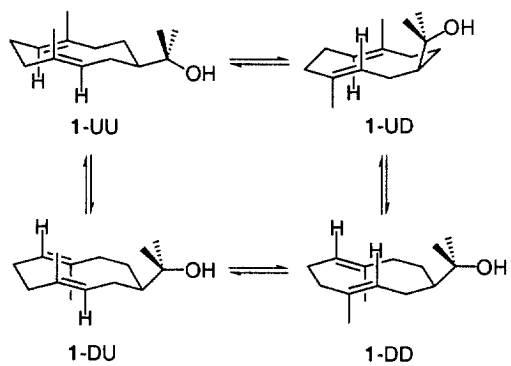


Figure 1

The conformational behaviour of germacranes, in particular the (*E,E*)-germacranes, has been an area of study for decades.[4] These studies have shown that the 10-membered ring of germacranes can adopt four distinct conformations which can be denoted as UU, UD, DU, and DD. U (up) and D (down) refer to the orientation of the C(14) and C(15) methyl groups. These conformers have either a crossed (UU and DD) or parallel relation of the double bonds (UD and DU) and are interconvertible by rotation of each of the double bonds through the ring[5] and inversion of the C(7)–C(8) unit.[6] As indicated in Scheme 1 for hedycaryol (**1**), the conformation of the C(7)–C(8) segment in the 10-membered ring is largely determined by the C(7) substituent which tends to occupy a pseudoequatorial position.



Scheme 1

In the conformations depicted in Scheme 1, the two endocyclic double bonds are approximately perpendicular to the plane of the 10-membered ring, leaving only the outer face of these double bonds available for reactions. For (*E*,*E*)-germacranes, this structural aspect also indicates that these compounds display planar chirality.[7]

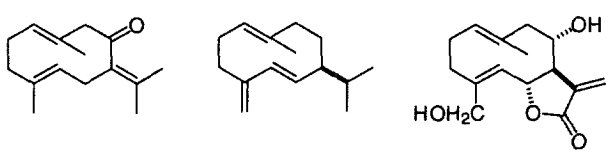
Many (*E*,*E*)-germacranes show temperature-dependent NMR spectra indicative of conformational equilibria in solution. Hedycaryol (**1**), for instance, exists in three different conformations at room temperature.[8] Because these conformations are interconverting at room temperature, transannular cyclization reactions of **1** only proceed via the most stable UU conformation.[9] This type of stereoselectivity in conformationally controlled reactions can often be predicted if the most stable conformation of the compound involved is known.[10] Correct predictions of most stable conformations can be produced by carrying out molecular mechanics calculations, often in combination with NMR and X-ray data.[11] Most of the naturally occurring (*E*,*E*)-germacranolides investigated, exist in the UU conformation. In contrast, the DU and UD conformations seem to be typical for the melampolides and heliangolides. The occurrence of these different germacrane conformations plays an important role in the biosynthesis of other sesquiterpenes.[12]

The synthesis of members of a class of terpenes can often be achieved starting from congeners that occur abundantly in nature. In general, this is not feasible for germacranes because only a few germacranes such as germacrone (**2**), germacrene D (**3**) and salonitenolide (**4**) are available in (multi)gram quantities (Figure 2).

Germacrone (**2**), a commercially available germacrane, can be isolated in large quantities by simple crystallization of the essential oil of *Geranium macrorrhizum* L. The chemistry of this compound has been studied extensively.[13] A serious drawback in the synthetic application of **2** is the lack of a chiral center.

Being the likely precursor in the biosynthesis of periplanones, the widespread germacrene D (**3**) has been used as the starting material for the synthesis of periplanones in order to elucidate their structures.[14]

The germacranolide salonitenolide (**4**) occurs in notable quantities in distinct species of the *Centaurea* genus and has been used to prepare vernolepin-related compounds.[15]



germacrone (**2**) germacrene D (**3**) salonitenolide (**4**)

Figure 2

The total synthesis of germacranes has been a long-standing problem mainly because of difficulties stemming from their thermal instability[16] and the ease with which these compounds undergo transannular cyclizations.[17] In spite of these problems, numerous reports

on germacrane synthesis have been published in the last fourty years. Some of these belong to the most impressive parts of synthetic organic chemistry.[18]

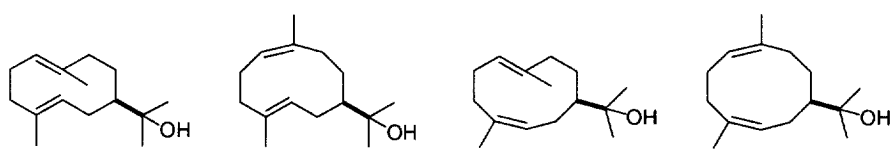
Here, we aim at a systematic presentation of these reports with particular emphasis on the construction of the ten-membered ring system. In the three subsequent sections the main synthetic approaches toward the 10-membered ring system of germacranes, i.e., intramolecular C–C bond formation, ring cleavage of the central bond in decalin systems and ring expansion reactions, are discussed.

2. Intramolecular C-C Bond Formation

Due to the presence of two double bonds, the ring strain in germacranes is markedly lowered compared to cyclodecanes. This fact makes the direct ring closure of appropriately functionalized acyclic precursors a useful method for the construction of the cyclodecadiene skeleton of germacranes. Intramolecular C–C bond formation can be accomplished by several types of ring closures including intramolecular alkylations and aldol condensations, carbonyl coupling reactions, radical cyclizations and cyclopropanation reactions. A special case of intramolecular C–C bond formation is the ring contraction of larger rings.

2.1 Intramolecular Alkylation and Aldol Condensation

One of the most cited methods in germacrane synthesis is the anion-induced intramolecular cyclization of farnesol derivatives, developed by Itô *et al.*[19] The advantage of the Itô strategy is the easy access to the required acyclic precursor, yet cyclization efficiency is only fair, perhaps due to the transannular strain accompanying the formation of the 10-membered ring system. The cyclization step is based on a Biellmann reaction in which an epoxide ring is opened by an allylic anion stabilized by a phenylsulfide group (see Scheme 2). This method has been used for the preparation of all double bond stereoisomers of hedycaryol (**1**) (Figure 3). Acid-catalyzed cyclization reactions and thermal Cope rearrangements of these stereoisomers have provided more insight into the biosynthesis of eudesmane and elemane sesquiterpenes.[20]

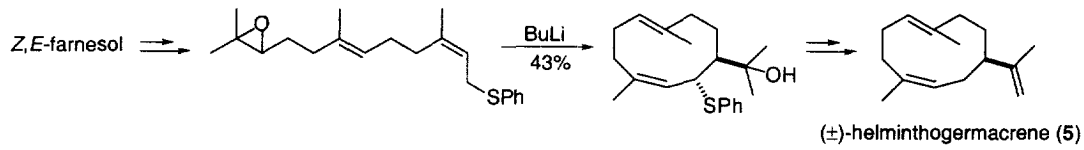


hedycaryol (**1**) 1(10)*Z*-isomer 4*Z*-isomer 1(10)*Z*,4*Z*-isomer

Figure 3

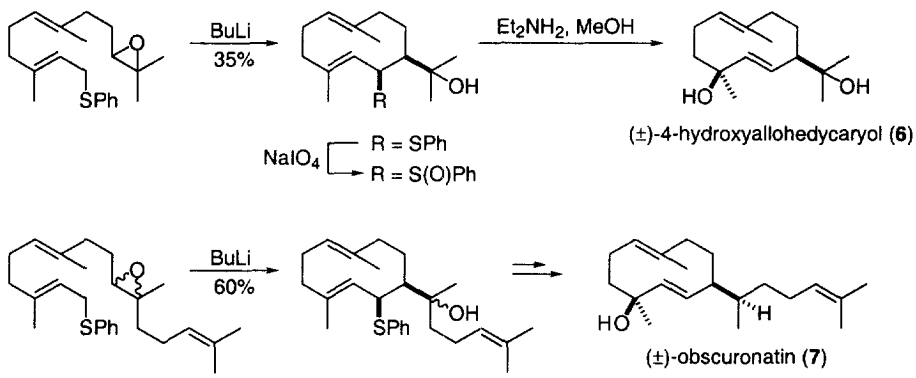
Winter *et al.*[21] have utilized the Itô approach for the synthesis of (±)-helminthogermacrene (**5**) (Scheme 2). More recently, the method has been used again for the synthesis of a

germacranoid containing an allene function.[22]



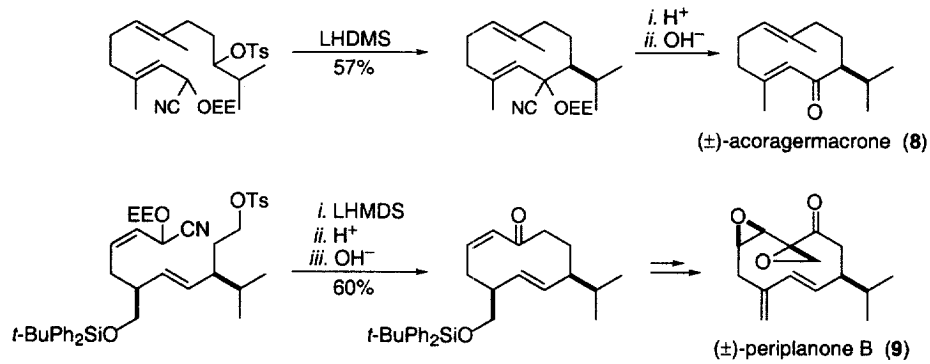
Scheme 2

In combination with a [2,3] sigmatropic rearrangement, Itô's method has been used for the synthesis of (±)-4-hydroxyallohedycaryol (**6**),[23] a germacrane with a (*E*,*E*)-cyclodeca-1(10),5-diene system, and (±)-obscuronatin (**7**),[24] a diterpene closely related to germacranes (Scheme 3).



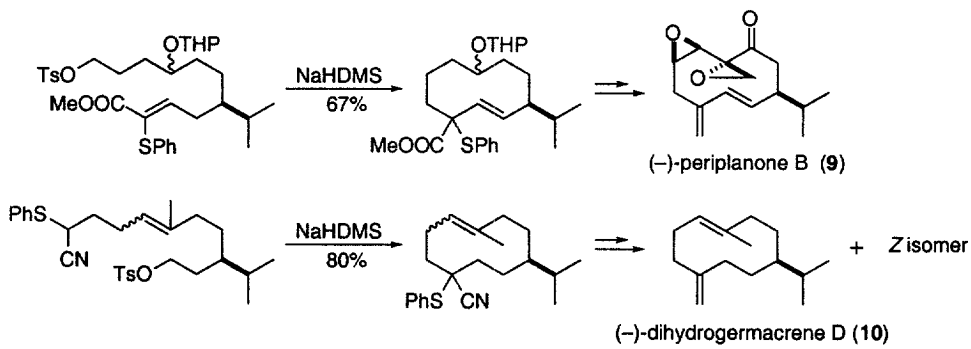
Scheme 3

In 1983, Takahashi *et al.*[25] introduced a general method for the construction of (*E*,*E*)- and (*E*,*Z*)-cyclodecadienone systems. The approach was based on an anion-induced intramolecular alkylation of protected cyanohydrins.[26] The acyclic precursors are built up from geranyl derivatives and contain an allylic cyanohydrin, protected as its 1-ethoxyethyl ether (EEO) and, at the other end of the chain, a primary or secondary tosylate as leaving group. The alkylation step is generally effected with sodium or lithium hexamethyldisilazane (NaHMDS or LHMDS) at elevated temperature. After cyclization to the 10-membered ring system, the protected cyanohydrin function is converted to an enone moiety. Two examples of this approach, the synthesis of (±)-acoragermacrone (**8**)[27] and (±)-periplanone B (**9**),[28] are given in Scheme 4. Also, germacrone (**2**)[29] and two periplanone analogues[30] have been prepared utilizing this method.



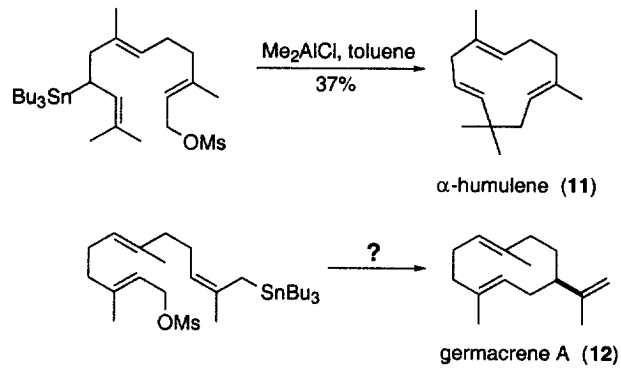
Scheme 4

The same principle has been utilized for the enantiospecific syntheses of (–)-periplanone B (**9**)[31] and (–)-dihydrogermacrene D (**10**)[32] (Scheme 5). Both the key intermediates in these syntheses, an α-phenylthioacrylate and a substituted (phenylthio)acetonitrile, have been synthesized from (+)-menth-1-ene. Similarly, an ω-tosyloxy-α-phenylsulfenyl ketone, prepared from (–)-carvone, has been cyclized to a (*Z*)-cyclodecenone derivative, in good yield.[33] The attempt to convert this compound to optically active helminthogermacrene (**5**) was not successful.



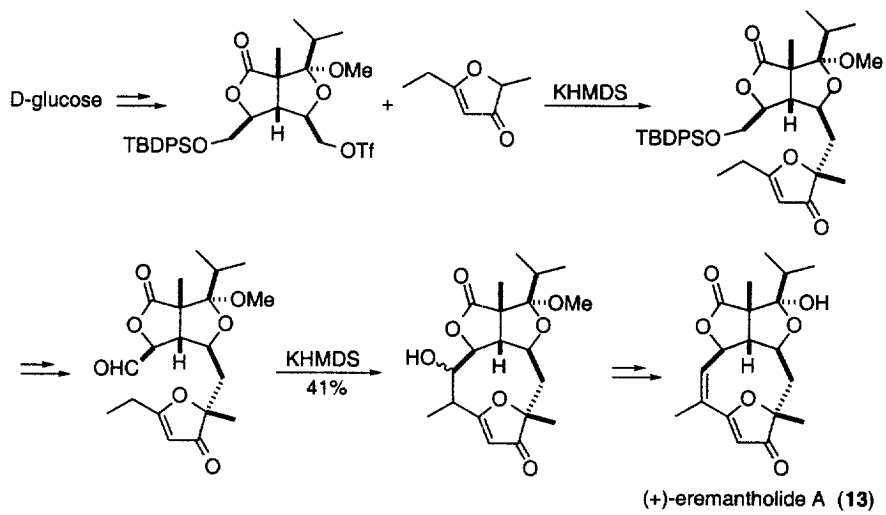
Scheme 5

A biomimetic cation-olefin cyclization route has been used by Corey *et al.*[34] for the synthesis of α-humulene (**11**), a sesquiterpene possessing an 11-membered ring system (Scheme 6). Whether this cyclization method, applied on a proper precursor, can be used for the synthesis of germacrane sesquiterpenes, for example germacrene A (**12**), is still open to question. As Corey already stated in 1965: "The laboratory synthesis of these sesquiterpenes by such a biomimetic cyclization has not yet been realized, despite its apparent simplicity".[35]



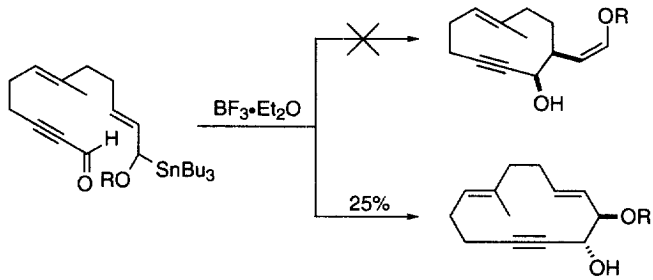
Scheme 6

Owing to its structural uniqueness and cytotoxic properties, the complex germacrane (+)-eremantholide A (**13**) was the target for total synthesis by several groups.[36] A recent approach toward this compound from D-glucose uses an intramolecular vinylogous aldol reaction for the construction of the 10-membered ring present in **13** (Scheme 7).[37]



Scheme 7

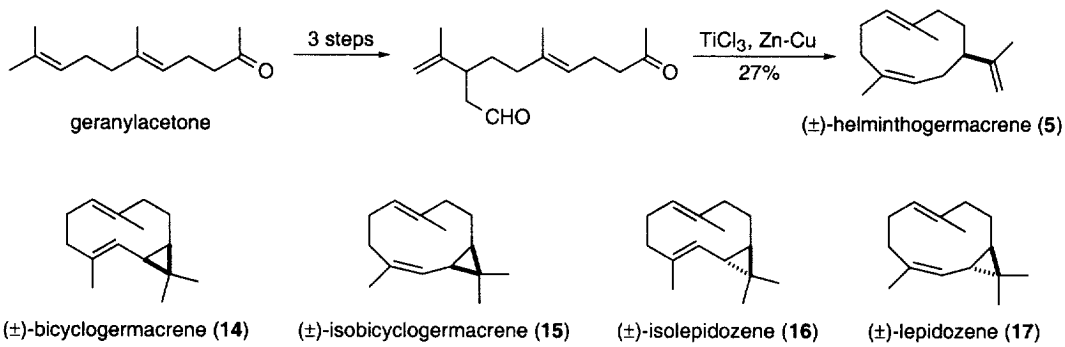
Marshall *et al.*[38] have developed an efficient cyclization of α-alkoxyallylstannane alkynales for the synthesis of 14-membered cembranoid precursors. This cyclization method, however, failed to produce a 10-membered ring system. The only pure product that could be obtained was a cyclododecynol derivative (Scheme 8).[39]



Scheme 8

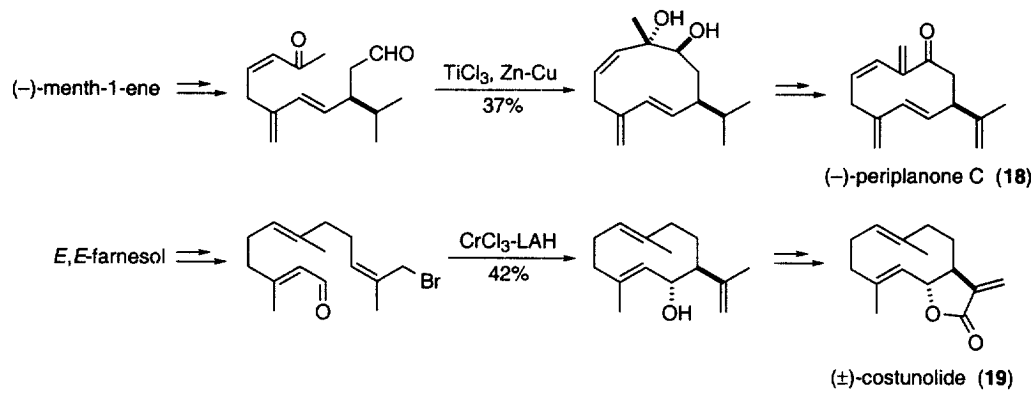
2.2 *Carbonyl Coupling*

Aldehydes and ketones can be converted to dimeric alkenes in high yield by treatment with titanium(III) chloride and a zinc-copper couple.[40] The mechanism consists of initial coupling of two radical species to give a 1,2-dioxygen compound (a titanium pinacolate), which is then deoxygenated. When applied to dicarbonyl compounds, the reaction has been used for the synthesis of cycloalkenes. (±)-Helminthogermacrene (**5**), for instance, was synthesized by this method in four steps starting from the commercially available geranylacetone (Scheme 9).[41] (±)-Bicyclogermacrene (**14**), (±)-isobicyclogermacrene (**15**), (±)-isolepidozene (**16**) and (±)-lepidozene (**17**) have also been prepared by this titanium-induced dicarbonyl-coupling reaction.[42] A similar cyclization reaction applied to a keto ester has been used for the synthesis of (±)-acoragermacrone (**8**).[43]



Scheme 9

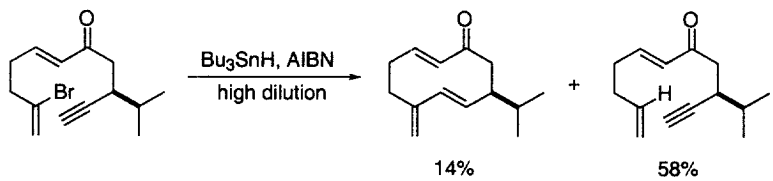
At low temperature, the titanium-induced dicarbonyl coupling reaction ends with the formation of a pinacol. This so-called intramolecular pinacol coupling reaction has been used for the synthesis of (–)-periplanone C (**18**) with (–)-menth-1-ene as the chiral starting material (Scheme10).[44] In a related approach, cyclization of ω-bromofarnesal with a low-valent chromium reagent has been used for the synthesis of (±)-costunolide (**19**).[45]



Scheme 10

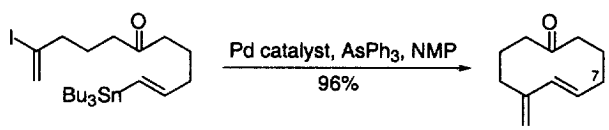
2.3 *Intramolecular Radical Cyclization*

Recently, two reports have been published on an intramolecular radical cyclization approach to germacrane sesquiterpenes. Parsons *et al.*[46] used the addition of an alkenyl radical to an acetylene to construct a periplanone-like ring system lacking the C(14) methyl group (Scheme 11).The efficiency of the cyclization step performed under high dilution conditions was low; reduction of the vinylbromide moiety was the preferred reaction pathway.



Scheme 11

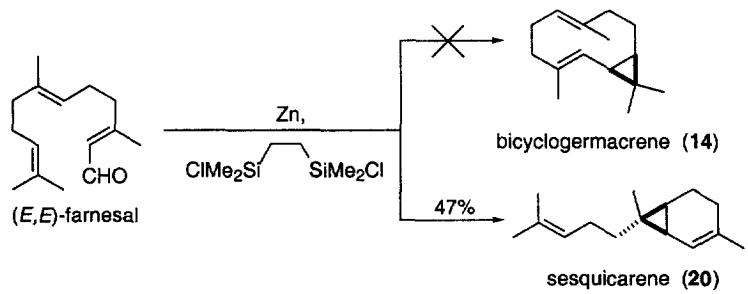
Hodgson *et al.*[47] have demonstrated the utility of an intramolecular Stille cross-coupling reaction under palladium catalysis in the synthesis of a cyclodecadienone system lacking the C(7) isopropyl functionality normally present in germacranes (Scheme 12). Whether this concept is indeed an efficient medium-ring cyclization approach to germacranes, as the authors stated, is open to question.



Scheme 12

2.4 *Intramolecular Cyclopropanation Reaction*

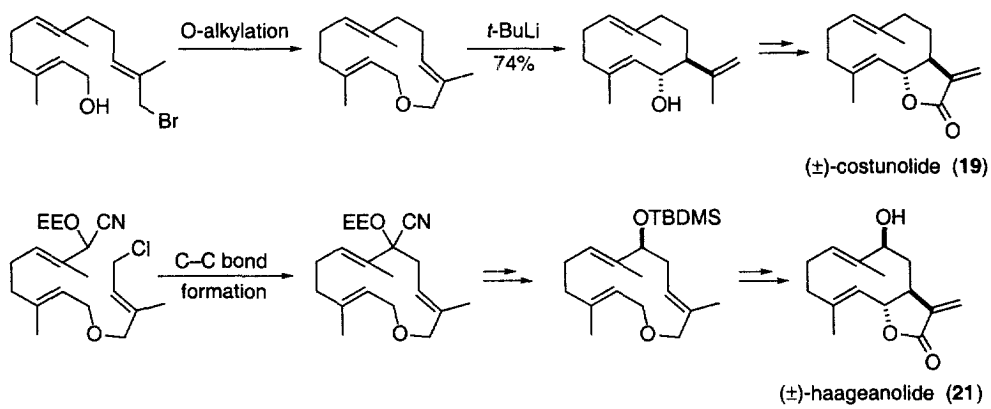
In an attempt to synthesize bicyclogermacrene (**14**), Motherwell and Roberts[48] studied the intramolecular cyclopropanation reaction of an organozinc carbenoid, generated by direct reduction of (*E,E*)-farnesal with zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane (Scheme 13). The only cyclopropanoid product of this reaction, however, turned out to be (±)-sesquicarene (**20**) and not, as expected, bicyclogermacrene (**14**).[49]



Scheme 13

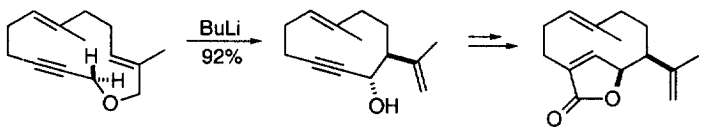
2.5 *Ring Contraction of Larger Rings*

An elegant method for the construction of larger carbocycles has been developed independently by the groups of Takahashi[50] and Marshall.[51] Macrocyclic diallyl or propargyl allyl ethers are subjected to [2,3] Wittig rearrangement to afford carbocyclic rings with substituents appropriate for further elaboration. The successful stereoselective synthesis of the germacranolides, (±)-costunolide (**19**) and (±)-haageanolide (**21**) by Takahashi *et al.*[52] illustrates the usefulness of this methodology in germacrane synthesis (Scheme 14). The synthesis of **19** only differs from that of **21** in the construction of the macrocyclic ether.



Scheme 14

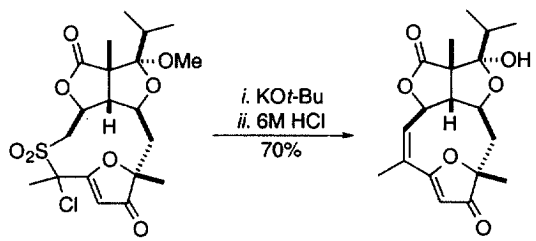
A closely related approach has been used for the synthesis of the bridged germacranolide (±)-aristolactone (**22**).[53] Because the C(6)–O bond and the isopropenyl group at C(7) in **22** are *trans*-related, this method requires Mitsunobu inversion of the hydroxyl group at C(6) after the [2,3] Wittig rearrangement (Scheme 15). This approach also offers the possibility of synthesizing **22** in optically active form, because the two propargylic methylene protons at C(6) in the 13-membered ether derivative are enantiotopic.[54] Using a chiral lithium amide as base instead of butyllithium, the [2,3] Wittig rearrangement afforded the 10-membered propargylic alcohol in 60-80% ee and 70% yield. Further transformation of this alcohol resulted in the enantioselective synthesis of (+)-**22**.



(±)-aristolactone (**22**)

Scheme 15

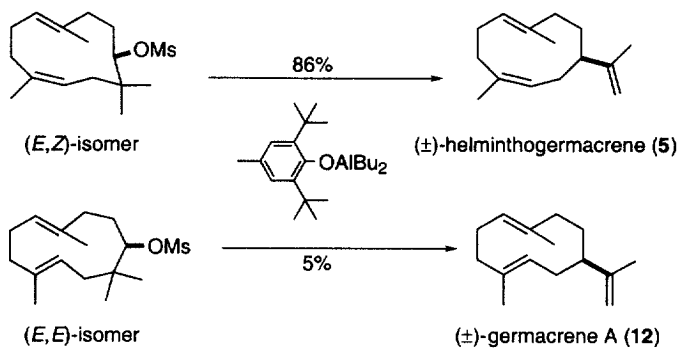
The first enantioselective total synthesis of (+)-eremantholide A (**13**) was accomplished utilizing a Ramberg-Bäcklund rearrangement, a reaction seldom employed in the synthesis of medium-sized rings (Scheme 16).[55]



(+)-eremantholide A (**13**)

Scheme 16

Although not aiming at the synthesis of a particular germacrane, Yamamoto *et al.*[56] found that under the influence of an aluminum reagent of sufficient steric bulk, ring contraction of an (*E,Z*)-humulene derivative took place to afford (±)-helminthogermacrene (**5**) in high yield (Scheme 17). Two years after this publication, **5** was isolated for the first time from a natural source.[21] Ring contraction of the (*E,E*)-isomer gave (±)-germacrene A (**12**), but in this case the yield was very poor.



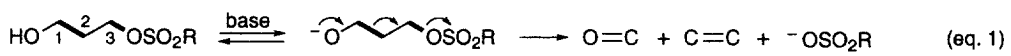
Scheme 17

3. Ring Cleavage Reactions

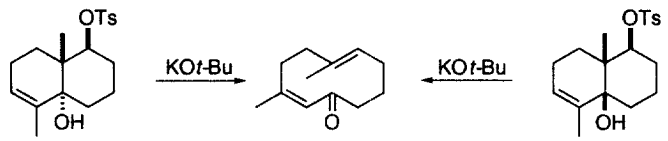
The fragmentation of the central bond in decalin systems has been shown to be a very effective method for the synthesis of germacranes. The decalin precursors are readily available and their stereochemistry can be controlled. The most prominent processes used for the cleavage of the central bond are the Grob-type fragmentation reactions, photolytical cleavage, radical-induced fragmentation and the photoaddition-thermolysis sequence.

3.1 The Grob-type Fragmentation Reactions

The methods with probably the greatest overall synthetic utility for the construction of medium-sized ring systems, especially 10-membered ring systems, are the Grob-type fragmentation reactions. Three closely related Grob-type fragmentation reactions can be distinguished. Firstly, there is the base-induced Wharton reaction[57] in which cyclic 1,3-diol monosulfonate esters undergo olefin-forming fragmentation with the release of an electrofugal carbonyl fragment (eq. 1). In this instance, the base does not play its usual role in elimination reactions but instead serves to abstract a proton from the hydroxyl group, which enables the sulfonate ester group to be removed more easily, since O^- is a powerful electron donor.



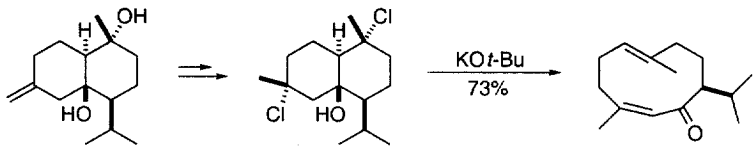
The investigations of Wharton *et al.*[58] on functionalized decalin systems have clearly shown that the stereochemical features of the compound involved are important for the occurrence of the fragmentation process and that the new carbon-carbon double bond is formed stereospecifically. In the case where the bonds undergoing cleavage (C(1)–C(2) and C(3)–OSO_2R in eq. 1) have an antiperiplanar relationship, the fragmentation process is very fast (concerted) and proceeds in high yield. If a gauche relationship exists between these bonds, the compounds react very slowly and usually complex product mixtures are formed.



(*Z,E*)-cyclodecadienone

Scheme 18

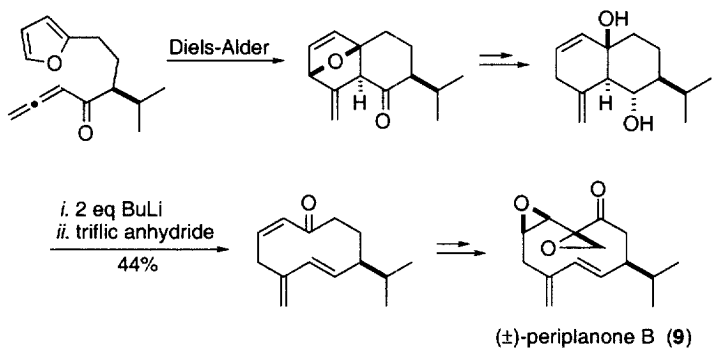
The synthesis of (*Z,E*)-3,6-dimethylcyclodeca-2,6-dienone is a typical example of the Wharton reaction (Scheme 18).[56d] This compound has been used for the synthesis of a simple periplanone B analoque with high biological activity,[59] and very recently, as the starting material for the synthesis of model systems for melampolides.[60] The Wharton reaction has also been applied to bicyclic systems derived from natural eudesmanolides to obtain germacranolides for biosynthetic studies.[61] Similarly, the naturally occurring sesquiterpene isocalamendiol has been converted to isoacoragermacrone (**23**) in good yield (Scheme 19).[62]



isoacoragermacrone (**23**)

Scheme 19

De Clercq *et al.*[63] have developed an elegant route to a known intermediate for the synthesis of (±)-periplanone B (**9**). Key steps in this approach are an intramolecular Diels-Alder reaction of a furan-allene derivative, a radical anion-promoted cleavage of the oxygen-bridge and an *in situ* low-temperature Wharton fragmentation reaction (Scheme 20).

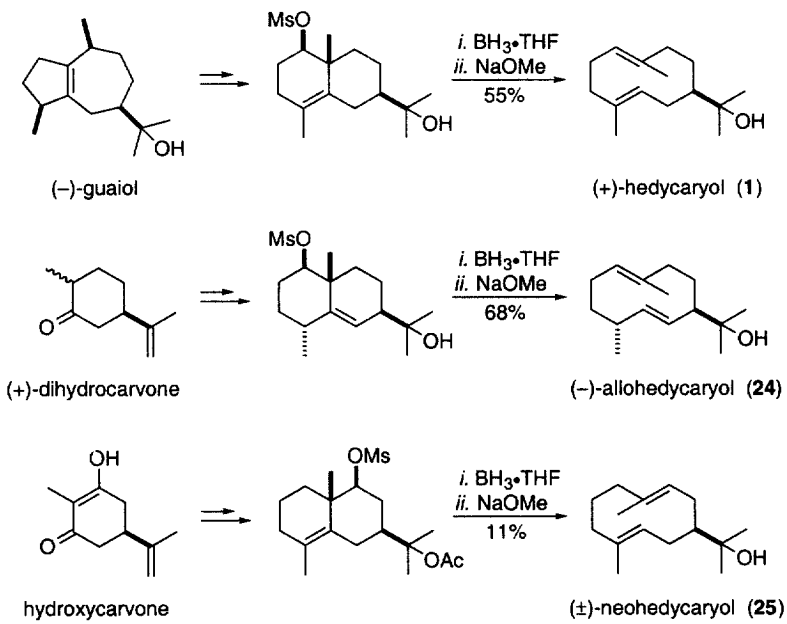


(±)-periplanone B (**9**)

Scheme 20

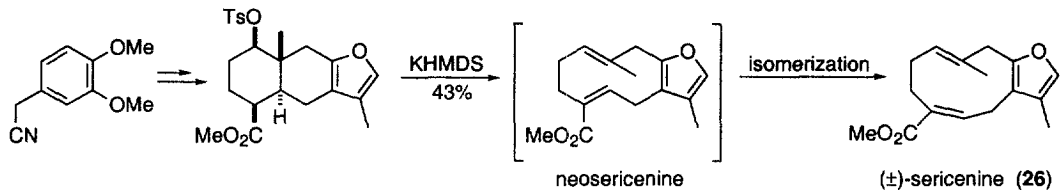
Another Grob-type fragmentation reaction is the so-called boronate fragmentation reaction introduced and extensively studied by Marshall *et al.*[64] In contrast to the Wharton reaction in which only one endocyclic double bond is formed regio- and stereospecifically, the boronate fragmentation reaction results in the regio- and stereospecific formation of two endocyclic double bonds. The necessity of the antiperiplanar alignment of the breaking bonds also exists in the boronate fragmentation reaction. The usually moderate regio- and stereoselectivity of the borane addition to tetrasubstituted double bonds and the fact that several functional groups are not compatible with the use of borane, limit the application of the boronate fragmentation in germacrane synthesis.

The boronate fragmentation reaction has been used for the synthesis of some (*Z*,*E*)-benzocyclodecadiene systems[65] and recently, for the synthesis of simple germacrane models in a study of enzymatic biotransformations.[66] An investigation has been made into the applicability of the boronate fragmentation reaction to germacranolide systems.[67] The first (*E*,*E*)-germacrane that was synthesized by the Marshall approach is (±)-hedycaryol (**1**).[68] Recently, the enantioselective synthesis of (+)-**1** has been accomplished starting from (–)-guaiol (Scheme 21).[69] The enantiomer of natural (+)-allohedycaryol (**24**)[70] and (±)-neohedycaryol (**25**),[71] a possible precursor in the biosynthesis of *epi*-eudesmanes, have also been prepared by this methodology.



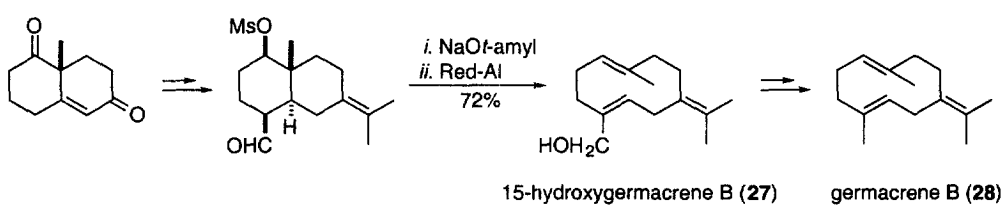
Scheme 21

The third Grob-type fragmentation reaction, developed by Mander *et al.*,[72] involves an enolate-assisted, intraannular 1,4-fragmentation via α-deprotonation of an carbonyl function and has been used to prepare functionalized cyclodecadiene systems.[73] The synthesis of (±)-sericenine (**26**) is the first example of this approach in germacrane synthesis (Scheme 22).[74] Isomerization of the C(4)–C(5) *E* double bond in the initially formed neosericenine[75] under the influence of potassium bis(trimethylsilyl)amide (KHMDS), used as the base for the 1,4-fragmentation reaction, explains the formation of **26** as the sole product in this reaction.



Scheme 22

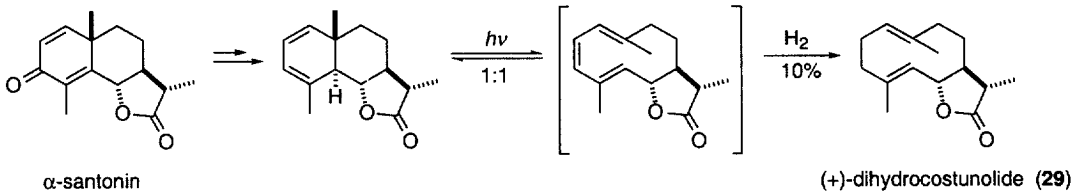
A recent study on the enolate-assisted fragmentation reaction has demonstrated that the isomerization of the C(4)-C(5) *E* double bond can be prevented by the use of one equivalent of sodium *tert*-amylate (NaO*t*-amyl) instead of KHMDS.[76] This new finding has strongly enhanced the synthetic value of the approach and has been applied to the synthesis of (*E*,*E*)-germacranes in which the methyl group at C(4) is oxidized. The synthesis of 15-hydroxygermacrene B (**27**), outlined in Scheme 23, illustrated the usefulness of this adjusted enolate-assisted fragmentation reaction. Because of the instability of the initially formed germacrane aldehyde, *in situ* reduction with Red-Al directly follows the fragmention step. Conversion of **27** to the known germacrene B (**28**), a widespread naturally occurring hydrocarbon, confirmed the *E* geometry of the C(4)–C(5) double bond in **27**. With sodium *tert*-amylate as base, the fragmentation reaction can also be used for the synthesis of (*E*,*E*)-germacranes with sp^3 hybridization at C(7). As the presence of a hydroxylated methyl group at C(4) in compounds like **27** allows the regioselective Sharpless epoxidation of the C(4)–C(5) double bond, this enolate-assisted fragmentation reaction gives easy access to germacrane 4,5-epoxides and facilitates investigations on the biomimetic formation of guaiane sesquiterpenes.[77]



Scheme 23

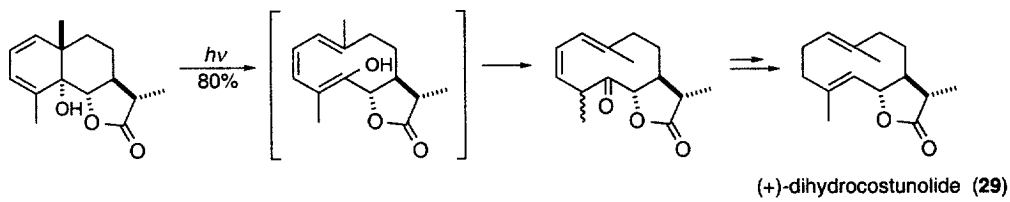
3.2 *Photolytic Cleavage*

In 1963, Corey and Hortmann reported for the first time the synthesis of a germacrane sesquiterpene.[78] They found that irradiation of a bicyclic conjugated diene, readily available from α-santonin, led to an equilibrium mixture of the diene itself together with its monocyclic cyclodecatriene isomer. After hydrogenation of this photolysis mixture, (+)-dihydrocostunolide (**29**) could be obtained in poor yield (Scheme 24).



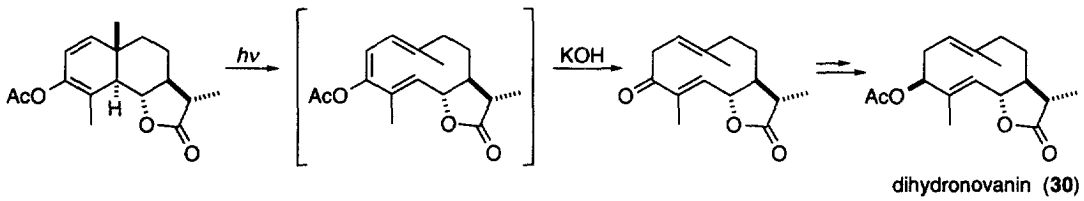
Scheme 24

In order to improve the usefulness of this approach to germacrane synthesis, methods have been developed to affect the photostationary equilibrium. A direct way to upset this equilibrium has been applied in another synthesis of **29** (Scheme 25).[79] Irradiation of the bicyclic dienol, also derived from α-santonin, gave an intermediate cyclodecatrienol which spontaneously underwent ketonization, thereby blocking the equilibrium. The resulting cyclodecadienone, obtained as a mixture of two epimers, was used for further transformation into **29**. It is noteworthy that the introduction of the C(4)–C(5) *E* double bond in **29** required the use of tetrabutylammonium oxalate.[80] Any other base refused to give **29**. Some of the 10-membered ring intermediates in this route toward **29** have served as starting materials in a study on epoxidations of germacranolide-type sesquiterpenes.[81]



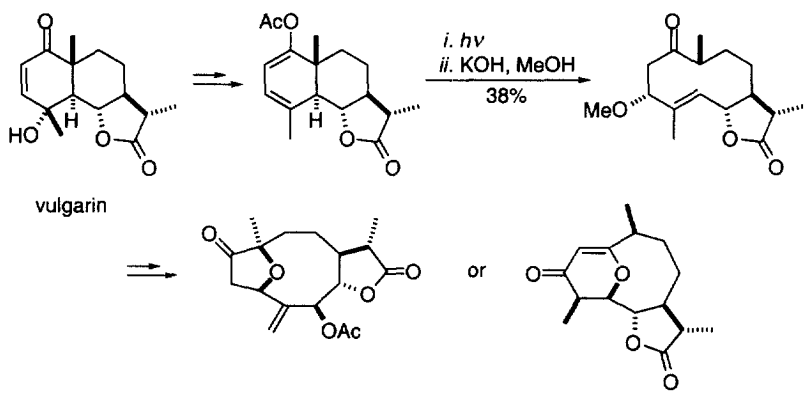
Scheme 25

An indirect way to upset the photostationary equilibrium has been used for the synthesis of dihydronovanin (**30**) (Scheme 26).[82] Irradiation of the cross-conjugated bicyclic dienol acetate resulted in the formation of an intermediate cyclodecatrienol acetate. *In situ* saponification of the acetate group at low temperature afforded the corresponding dienone, which could easily be transformed to **30**. Without saponification, irradiation only produced a 2.5:1 mixture of the starting material and its *cis*-fused isomer, respectively.



Scheme 26

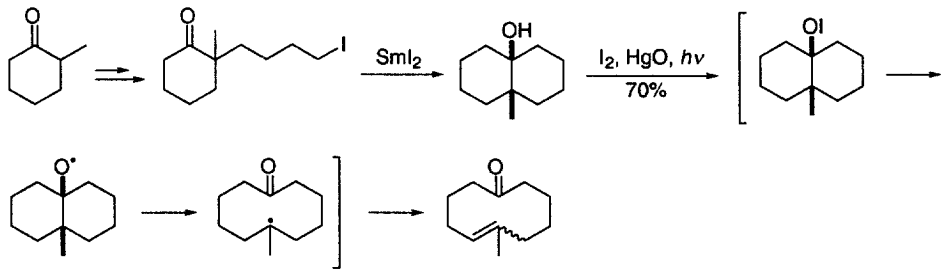
Recently, this methodology has been used for the construction of germacranolides containing ether bridges (Scheme 27).[83] Irradiation of a dienol acetate, readily available from the naturally occurring eudesmanolide vulgarin, and *in situ* treatment of the photolysis adduct with potassium hydroxide provided a functionalized cyclodecanenone derivative in reasonable yield. Further transformation of this compound resulted in the formation of germacranolides with an ether bridge between C(1) and C(5) or C(3) and C(10).



Scheme 27

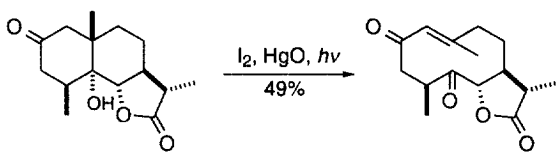
3.3 *Radical-Induced Fragmentation*

Several synthetically useful ring fragmentations have been developed that rely on the β-scission of bridgehead alkoxy radicals. In 1964, Akhtar and Marsh introduced a radical-induced fragmentation reaction as an entry into seco-AB steroids.[84] In later studies, the potential of such methodology for cyclodecan(en)one synthesis has been examined.[85] Based on the original method of Akhtar and Marsh, Suginome *et al.*[86] developed a general method for the synthesis of medium-sized cycloalkan(en)ones involving the selective β-scission of alkoxy radicals generated by photolysis of hypoiodites. In this approach, the hypoiodites were prepared *in situ* by treatment of the corresponding bridgehead alcohols with mercury(II) oxide and iodine (Scheme 28).



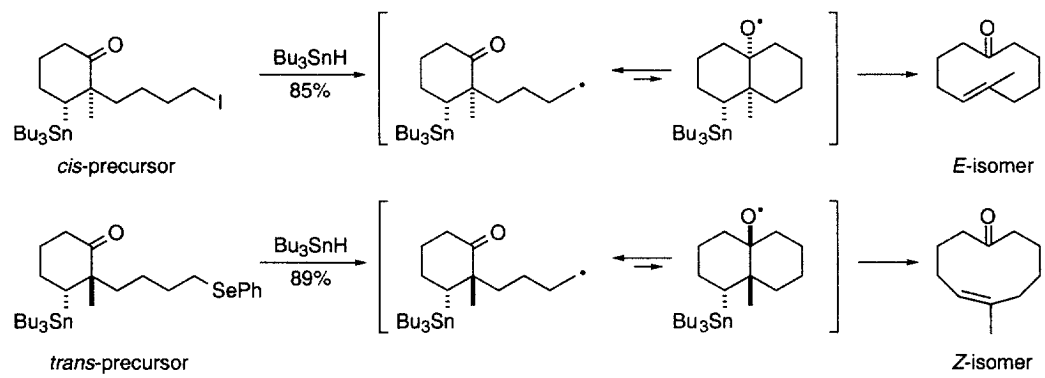
Scheme 28

The formation of a germacranedione in 49% yield from a bridgehead alcohol derived from α-santonin is the only known example of this approach in germacrane synthesis (Scheme 29).[87] Owing to its structural features, this dione promises to be a versatile intermediate in the synthesis of naturally occurring polyoxygenated germacranolides.



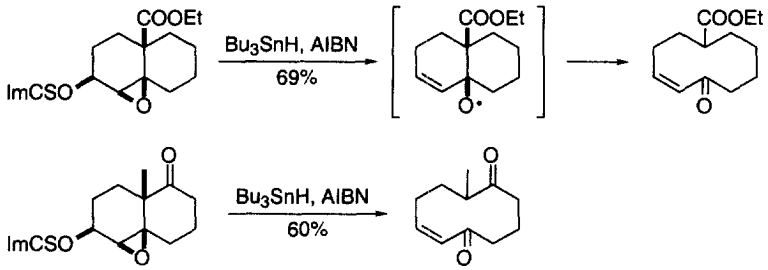
Scheme 29

The radical-induced ring expansion of *cis*- and *trans*-α-substituted-β-stannylcyclohexanones provides another efficient route to *Z*- and *E*-cyclodecenones (Scheme 30).[88] The *cis*-/*trans*-relationship in the precursor controls the alkene geometry of the ring-expanded product which is consistent with a concerted fragmentation process. A comparable radical chain process has been used for the construction of cyclodecanones containing an ester function.[89]



Scheme 30

Thiocarbonylimidazolides derived from simple Robinson annulation products containing a suitably placed ester or keto group can also be converted to functionalized 10-membered ring systems (Scheme 31).[90] In this case, the key step is a radical-induced opening of an epoxide ring followed by β-scission of the resulting alkoxy radical.



Scheme 31

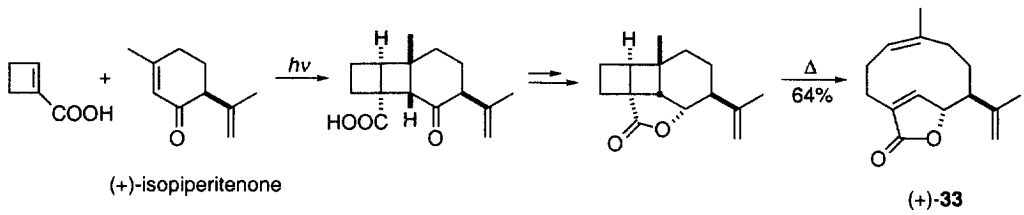
As can be concluded from the examples shown, the use of radical-induced ring expansion reactions for the synthesis of naturally occurring sesquiterpenes with a medium-sized ring skeleton is limited. Only recently, the total synthesis of two fused 4,9-membered ring sesquiterpenes, caryophyllene (**31**) and isocaryophyllene (**32**), has been reported (Figure 4).[86] Except for the synthesis of the germacranolide-like compound depicted in Scheme 29, no other applications in germacrane synthesis are known.

(±)-caryophyllene (**31**) (±)-isocaryophyllene (**32**)

Figure 4

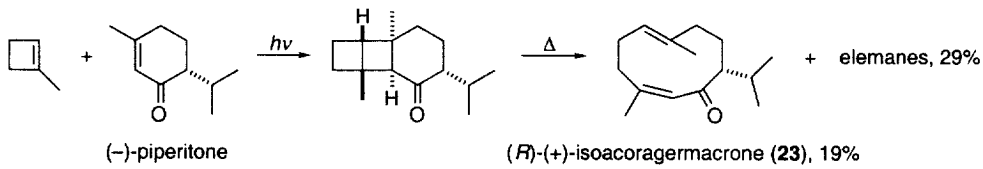
3.4 The Photoaddition-Thermolysis Sequence

The photoaddition-thermolysis sequence developed by the groups of Lange[91] and Wender[92] constitutes another well-known approach to 10-membered ring systems. The sequence involves [2+2] photoaddition of a 2-cyclohexenone derivative to a substituted cyclobutene to give a strained tricyclo[4.4.0.$0^{2,5}$]decane which upon thermolysis produces a 1,5-cyclodecadiene system via a [2+2] cycloreversion reaction. The short enantioselective synthesis of the isoaristolactone isomer (+)-**33** clearly illustrates the utility of this approach in germacrane synthesis (Scheme 32).[93] Several related germacranolides have been similarly synthesized.[94] At higher temperatures and/or prolonged reaction times, the cycloreversion reaction occurred along with transannular cyclization to afford *trans*-fused decalin systems which were used for the synthesis of cadinanes[95] and eudesmanes.[96]



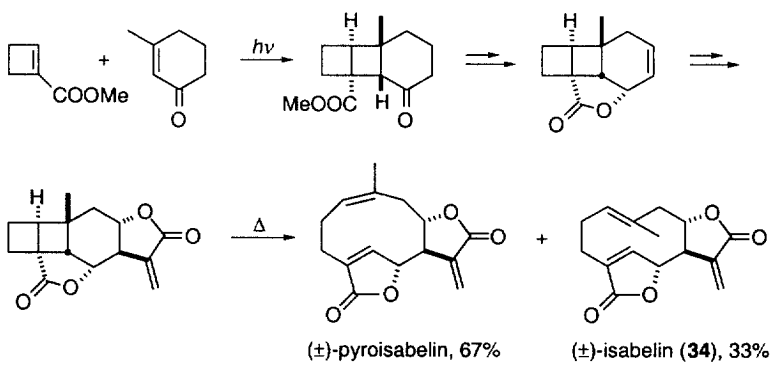
Scheme 32

The cycloreversion reaction applied to the photoadduct of 1-methylcyclobutene and (–)-piperitone resulted in the formation of (*R*)-(+)-isoacoragermacrone (**23**) as a minor product, together with several elemanes (Scheme 33).[97]



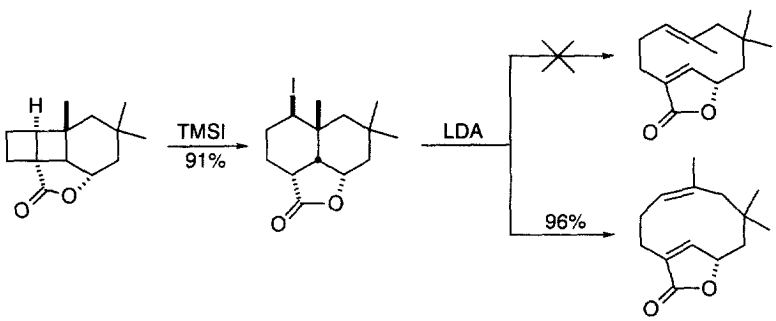
Scheme 33

Because most of the (*E*,*E*)-germacranes readily undergo Cope rearrangement at elevated temperature,[4b] the photoaddition-thermolysis sequence is a less suitable method for the synthesis of these compounds. (±)-Isabelin (**34**), a naturally occurring germacranolide containing two lactone rings, is the only known example of an (*E*,*E*)-germacrane produced in a cycloreversion reaction (Scheme 34).[98] In this specific case, the reaction outcome is controlled by the presence of an additional C(7),C(8) lactone ring.



Scheme 34

In an effort to extend the photoaddition-thermolysis sequence to a more general method for the synthesis of (*E,E*)-cyclodecadienes, the photoaddition reaction was followed by nucleophilic ring opening (Scheme 35).[99] It was expected that a Grob-type fragmentation reaction of the ring-opened product would result in the formation of an (*E,E*)-cyclodecadiene ring system. However, in contrast to the expectations, the (*Z,E*)-isomer was obtained as the sole product.



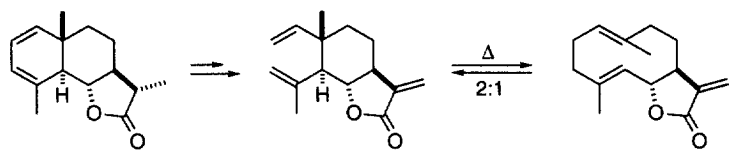
Scheme 35

4. Ring Expansion Reactions

4.1 The Cope Rearrangement

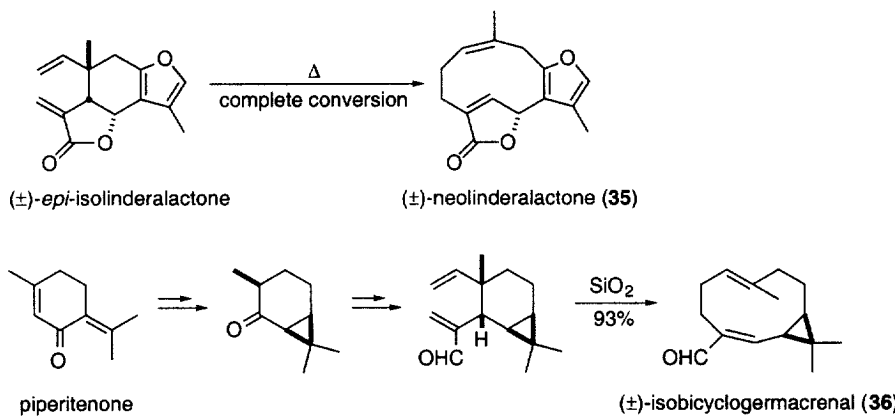
A very important reaction for the synthesis of germacrane sesquiterpenes is the [3,3] sigmatropic Cope rearrangement in which 1,2-divinylcyclohexanes are thermally converted into cyclodecadienes.[100] In fact, nature itself demonstrated the idea: the well-known equilibrium between germacrane and elemane sesquiterpenes. Generally, the position of the equilibrium is determined by the substitution pattern, conjugation effects, ring strain, conformation and other factors.[101] The existence of this equilibrium forms one of the major difficulties in the isolation of pure germacranes from natural sources. The use of conventional purification techniques (GC, distillation), for instance, completely converts most of the simple (*E,E*)-germacranes to the corresponding *trans*-elemane isomers.[102] In some cases, these difficulties can be circumvented by silver nitrate extraction,[103] argentation chromatography[104] or even crystallization of the silver nitrate adduct.[17a]

Due to the reversible nature of the conventional Cope rearrangement,[105] efforts to synthesize germacrane sesquiterpenes from 1,2-divinylcyclohexane precursors have met with only limited success. Grieco and Nishizawa[106] employed the Cope rearrangement for the first total synthesis of (+)-costunolide (**19**) (Scheme 36). Upon thermolysis of (+)-dehydrosaussurea lactone, prepared from (–)-α-santonin, they obtained a 2:1 equilibrium mixture from which **19** could be isolated in modest yield.



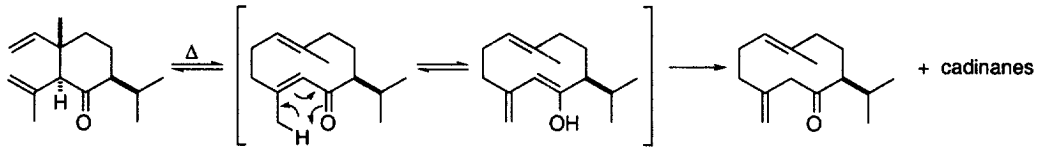
Scheme 36

Although the Cope equilibrium usually lies toward the elemane isomer, a few exceptions to this general behaviour are known (Scheme 37). Upon thermolysis, *epi*-isolinderalactone, an unnatural *cis*-elemane, showed complete conversion to (±)-neolinderalactone (**35**).[105c,d] A silica gel-induced Cope rearrangement gave (±)-isobicyclogermacrenal (**36**) in high yield.[107]



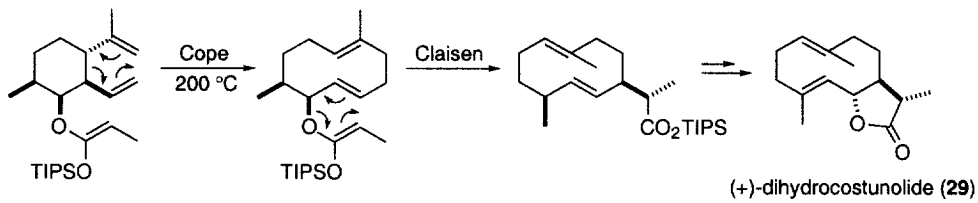
Scheme 37

The formation of preisocalamendiol (**37**) together with two cadinane-like products upon thermolysis of shyobunone, a naturally occurring elemane, can be considered as the first example of a thermal Cope rearrangement in which a consecutive reaction shifts the unfavorable Cope equilibrium toward the germacrane side (Scheme 38).[60,108] Although the initially formed acoragermacrone (**8**) is thermally less stable than its Cope precursor shyobunone,[109] it can undergo rearrangement via a [1,5] hydrogen shift to afford the more stable preisocalamendiol (**37**), thereby irreversibly removing the germacrane isomer from the Cope equilibrium. A thermal transannular Ene reaction of **37** explains the formation of the cadinane-like products in this process. A longer reaction time in combination with a higher reaction temperature leads to the formation of the cadinanes only.



Scheme 38

The Cope rearrangement in conjunction with other reactions is now considered as a method of particular value in the synthesis of natural products.[110] A very elegant example of such a consecutive reaction is the Cope-Claisen rearrangement. As the last step in this tandem process is the irreversible Claisen rearrangement, any unfavourable Cope equilibrium should be transposed to the tandem products.[111] This strategy has been applied successfully in the synthesis of (+)-dihydrocostunolide (**29**) (Scheme 39).[112] The C(1),C(10) epoxide of **29**, used as an precursor for the biomimetic synthesis of eudesmane sesquiterpenes, has been prepared similarly.[113]

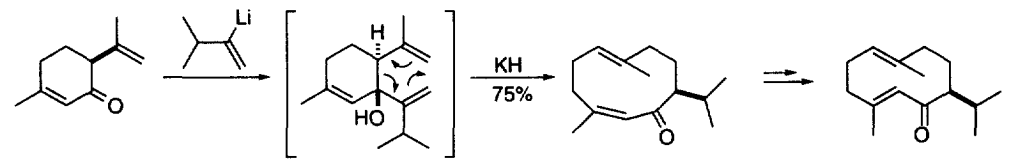


Scheme 39

4.2 The Oxy-Cope Rearrangement

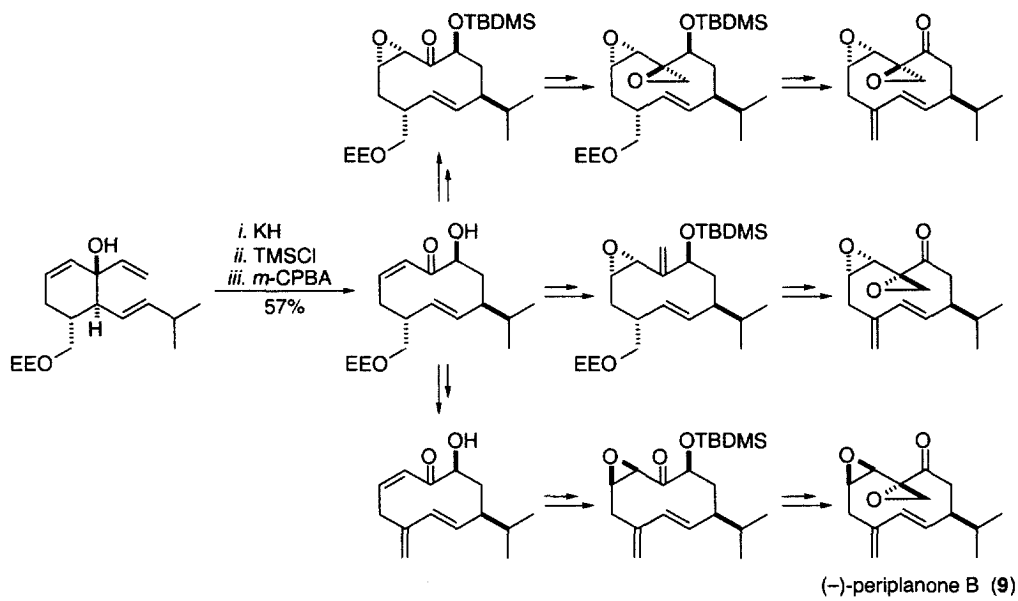
The irreversible rearrangement of 1,2-divinylcycloalkane derivatives with a hydroxyl group at C(1) or C(2) is referred to as the oxy-Cope rearrangement.[114] The oxy-Cope rearrangement when carried out by heating the substrate in a high boiling solvent is often accompanied by other competing reactions and is not very useful for the synthesis of the thermally labile germacranes. The application of a thermal oxy-Cope rearrangement in a synthetic study on oxygen-bridged furanoheliangolides must be considered as an exception.[115]

After the discovery that the use of sodium and, in particular, potassium salts of the oxy-Cope precursors allows the rearrangement to proceed in high yield under mild conditions,[116] the practical value of the oxy-Cope rearrangement for the synthesis of functionalized 10-membered ring systems has been improved significantly.[117] The first successful application of this so-called anionic oxy-Cope rearrangement in germacrane synthesis was reported by Still in 1977.[118] From isopiperitenone, (±)-isoacoragermacrone (**38**) could be synthesized by a very elegant and short method (Scheme 40). Isomerization of **38** to (±)-acoragermacrone (**8**) could be achieved via an organotin addition/oxidation sequence.



Scheme 40

The same strategy has been employed for the first synthesis of (±)-periplanone B (**9**).[119] Based on an ingenious stereocontrol, **9** and two of its stereoisomers could be synthesized, thereby showing the correct relative stereochemistry of **9** (Scheme 41).

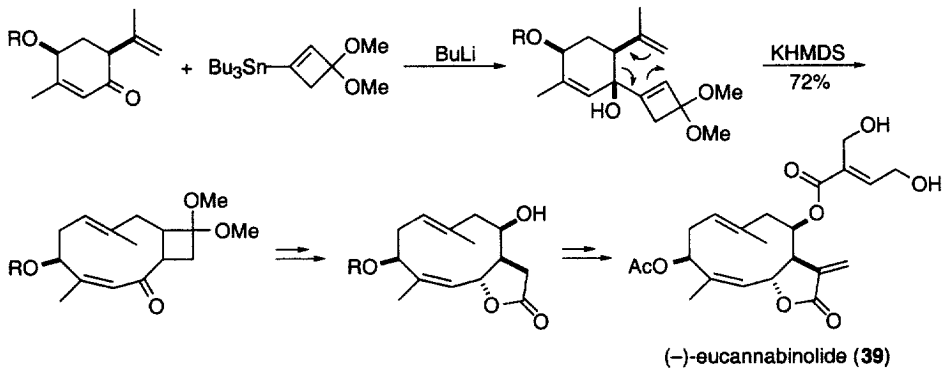


Scheme 41

Except for the preparation of the oxy-Cope precursor, Hauptmann *et al.*[120] followed the same route for their synthesis of **9**. Some years later, Mori's group reported the enantioselective synthesis of the naturally occurring (–)-enantiomer of **9** also utilizing the anionic oxy-Cope rearrangement as the key step.[121] This synthesis laid the foundation for a thorough study on periplanones and their analogues by several Japanese research groups.[122] The same methodology has been used for the synthesis of the enantiomer of the antitumor principle of the Chinese herb *Curcuma aromatica*.[123] Oxy-Cope precursors prepared from (–)-carvone have been used for the enantioselective synthesis of heliangolide-like compounds[124] and a naturally occurring heliangolide.[125]

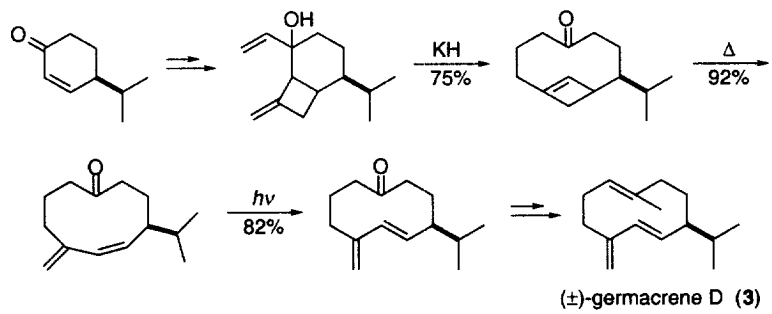
The broad scope of the anionic oxy-Cope rearrangement was further demonstrated by the

enantioselective synthesis of (–)-eucannabinolide (**39**), a structurally complex heliangolide with a strong inhibitory activity *in vivo* against Ehrlich ascites carcinoma (Scheme 42).[126]



Scheme 42

An ingenious route, aiming at the construction of the butadiene unit present in germacrene D (**3**) and periplanones, has been described by Schreiber and Santini[127] and involves a consecutive anionic oxy-Cope rearrangement/cyclobutene ring opening sequence. This method has been used for an efficient synthesis of (±)-periplanone B (**9**),[128] and also for a short synthesis of (±)-germacrene D (**3**) (Scheme 43).[129]



Scheme 43

5. References and Notes

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2. For an extensive review, see: Herz W. Israel J. Chem. 1977;16:32–44.

3. The conventions proposed for describing germacrane sesquiterpenes are followed, see: Rogers D, Moss GP, Neidle S. J. Chem. Soc., Chem. Comm. 1972:142–143. The suffix "olide", as in "germacranolide" is used to indicate the presence of a lactone group.
4. For some representative examples, see: (a) Sutherland JK. Tetrahedron 1974;30:1651–1660. (b) Takeda K. Tetrahedron 1974;30:1525–1534. (c) Watson WH, Kashyap RP. J. Org. Chem. 1986;51:2521–2524.
5. During the rotation of a double bond, the vinylic hydrogen passes through the center of the ring (jump-rope rotation), see: Marshall JA, Audia VH, Jenson TM, Guida WC. Tetrahedron 1986;42:1703–1709.
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8. Unpublished results from this laboratory. See also reference 6.
9. Piet DP, Minnaard AJ, van der Heyden KA, Franssen MCR, Wijnberg JBPA, de Groot A. Tetrahedron 1995;51:243–254.
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11. For example, see: (a) Fransen HR, Dormans GJM, Buck HM. Tetrahedron 1983;39:2981–2987. (b) Ugliengo P, Appendino G, Chiari G, Viterbo D. J. Mol. Struct. 1990;222:437–452.
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13. For example, see: (a) Tsankova E, Enev V. Tetrahedron 1987;43:4425–4432. (b) Enev V, Tsankova E. Tetrahedron Lett. 1988;29:1829–1832.
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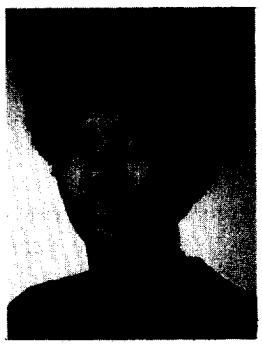
Biographical sketch



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Aede de Groot

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Joannes B. P. A. Wijnberg received his Ph.D. degree in 1979 under the direction of Professor W. N. Speckamp at the University of Amsterdam. He spent a year at the same university, as a postdoctoral fellow with Professor Th. J. de Boer. He then joined the group of Professor A. de Groot at the Wageningen Agricultural University studying natural product synthesis and chemical consequences of long-range orbital interactions in rigid 1,4-diol monosulfonate esters. His current research interests focus on the total synthesis of natural lactarane and marasmane sesquiterpenes, and the isolation and identification of halogenated metabolites from mushrooms.

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Fields of research:

- Total synthesis of natural products, especially sesqui- and diterpenes with fysiologically attractive properties in the field of crop-protection (antifeedants, repellants, pheromones), therapeutics, and flavour and fragrances.
- Synthesis starting from abundantly available chiral natural products, mostly terpenes and steroids (agrification).
- Phytochemistry, isolation and identification of semiochemicals and therapeutics.
- Enzymes in organic synthesis and their application in biotechnology.