Germacrane Sesquiterpenes
Synthesis and Role in Biosynthesis

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Voorwoord

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Contents

1 Introduction
   1.1 General Introduction  2
   1.2 The Biosynthesis of Germacrane, Eudesmane, and Guaiane Sesquiterpenes  3
   1.3 Structures and Conformations  5
   1.4 References and Notes  8

2 The Synthesis of Germacrane Sesquiterpenes
   2.1 Introduction  12
      2.1.1 Germacrane as Starting Material in Synthesis  12
      2.1.2 Strategies for the Synthesis of Germacrane  12
   2.2 Intramolecular Carbon-Carbon Bond Formation  13
      2.2.1 Intramolecular Alkylation and Aldol Condensation  13
      2.2.2 Ring-Contraction of Larger Rings  18
      2.2.3 Carbonyl Coupling  20
      2.2.4 Intramolecular Radical Cyclization  21
      2.2.5 Intramolecular Carbene Cyclization  22
   2.3 Ring Cleavage of Bicyclic and Tricyclic Compounds  22
      2.3.1 The Grob-type Fragmentation Reactions  22
      2.3.2 Photolytic Cleavage  25
      2.3.3 Radical Fragmentation  27
      2.3.4 The [2+2] Cycloreversion Reaction  29
   2.4 Ring Expansions  31
      2.4.1 The Cope Rearrangement  31
      2.4.2 The Cope-Claisen Rearrangement  34
      2.4.3 The oxy-Cope Rearrangement  34
   2.5 Scope of The Thesis  38
   2.6 References and Notes  40

3 The Synthesis of (+)-Hedycaryol, Starting from Natural (−)-Guaiol
   3.1 Introduction  48
   3.2 Results and Discussion  48
   3.3 Experimental Section  52
   3.4 References and Notes  59
4 The Relative and Absolute Configuration of Allohedycaryol. Enantiospecific Total Synthesis of Its Enantiomer

4.1 Introduction 62
4.2 Results and Discussion 63
4.3 Experimental Section 68
4.4 References and Notes 74

5 The Total Synthesis of Neohedycaryol. Its Role in the Biosynthesis of Eudesmane Sesquiterpenes

5.1 Introduction 78
5.2 Results and Discussion 81
5.3 Concluding Remarks 84
5.4 Experimental Section 85
5.5 References and Notes 91

6 The Synthesis of Germacrane Sesquiterpenes Using Enolate-Assisted 1,4-Fragmentation Reactions

6.1 Introduction 96
6.2 Results and Discussion 99
6.3 The Biomimetic Synthesis of Guaiane Sesquiterpenes 108
6.4 Experimental Section 112
6.5 References and Notes 130

7 Discussion

7.1 The Synthesis of Germacrane Sesquiterpenes 138
7.2 The Biosynthesis of Eudesmane and Guaiane Sesquiterpenes 142
7.3 References and Notes 147

Summary 151

Samenvatting 155

Curriculum Vitae 159
1

Introduction

Abstract: a general introduction to the occurrence and function of terpenes is presented. The place of germacrane in the biosynthesis of sesquiterpenes is discussed, together with their chemical characteristics.
1.1 General Introduction

Terpenes, also known as terpenoids, isopentenoids, or isoprenoids, form one of the main classes of secondary metabolites. All terpenes are built up from the five-carbon unit isopentenyl pyrophosphate\(^1\) and are therefore subdivided into hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterpenes (C25), triterpenes (C30), carotenoids (C40), and polyisoprenoids. Because of their importance, and for historical reasons, steroids (degraded triterpenes) are commonly considered as a separate class.

Terpenes and steroids are widespread in both the animal and plant kingdom, and in micro-organisms. As most other secondary metabolites, they are often characteristic for a certain species or for a small group of species. Especially in plants, the occurrence of terpenes is used as a tool in taxonomic studies. Two important functions of terpenes, at least for the organism producing them, can be described as chemical communication\(^2\) and chemical defence.\(^3\)

Hormones, often from terpenoid or steroid origin, play an important role in the communication between cells in an organism. Obvious examples are the steroid hormones in mammals. Pheromones, partly from terpenoid origin, play this role too, but function as messengers between organisms of the same species. Because the communication with hormones and pheromones has to be under rapid control, only minute amounts of these compounds are produced and stored. An example of chemical communication between individuals of different species is the production of fragrances, often mixtures of mono- and sesquiterpenes, by flowering plants.

Terpenes used for defensive purposes are often produced in larger amounts. Chemical defence is, next to physical protection with thorns or hairs, for plants an important way to avoid herbivory. The terpenes act as toxin, repellant, antifeedant etc.. Insects also use chemical defence. Well-known are the "chemical weapons" of termites and ants.\(^4\)

It is easy to understand that man employs the natural functions of terpenes, for instance to improve agriculture. Examples are the use of pheromones in order to monitor and control insect populations,\(^5\) and the use of insect antifeedants as natural pesticides.\(^6\) However, the application of terpenes is not restricted to their original functions. Since ancient times, terpenes are applied as food additives and as medicines, mostly in the form of plant extracts or the whole plant.

This thesis is concerned with sesquiterpenes (C15 terpenes), especially those of the germaacrane class. Sesquiterpenes are typically found in all parts (seed, flowers, foliage, roots, and wood) of higher plants and also occur in mosses, liverworts, algae and lichens, some insects, and fungi.\(^7\) They are found in both terrestrial and marine
environments. An enormous amount of sesquiterpenes has been isolated and classified according to their carbon skeleton. Some of these classes comprise only a few compounds, other classes several thousands.

Germacrane sesquiterpenes form one of the larger classes of sesquiterpenes. Directly formed from (E,E)-farnesyl pyrophosphate (§ 1.2), germacranes are the central intermediates in the biosynthesis of several other classes of sesquiterpenes. Eudesmane, guaiane, and elemene sesquiterpenes are directly formed from germacranes. The carbon skeletons of these compounds are depicted in Scheme 1.1.

Apart from their place in the biosynthetic pathways, several germacranes have a demonstrable physiological activity. Well-known is the germacrane periplanone B (1), a component of the sex pheromone of the American cockroach (Periplaneta americana). Another example is (−)-germacrene A (−-2), the alarm pheromone of the spotted alfalfa aphid (Theroiapnis maculata B.). Germacrane sesquiterpenes with a known pharmaceutical function are rare. The germacrane parthenolide (3) isolated from feverfew (Tanacetum parthenium L., Dutch: moederkruid), however, has recently got attention because of its application as a migraine prophylactic.

Scheme 1.1

1.2 The Biosynthesis of Germacrane, Eudesmane, and Guaiane Sesquiterpenes

According to the now generally accepted hypothesis of Nobel laureate Ruzicka, the biosynthesis of most of the cyclic sesquiterpenes starts with the ionization of farnesyl pyrophosphate (4, FPP, farnesyl diphosphate). The resulting allylic cation
is attacked by one of the other two double bonds (Scheme 1.2), and the process ends with proton loss or the capture of an external nucleophile (water). In the resulting products, the isopentenyl ("isoprene") units can still be recognized and this is known as the Isoprene Rule. Ring closure by attack of the distal double bond in a Markovnikov fashion leads to the germacrane skeleton. Except for the formation of a C(7)–C(11) double bond, this reaction creates a chiral center. The role of enzymes in this step has become an important research topic in the last decade. Several FPP cyclases have now been purified but the nature of their active sites is still obscure. These enzymes accept FPP as a substrate and produce germacranes or their cyclization products.

During the conversion of germacrane s into eudesmane and guaiane sesquiterpenes, the chiral center at C(7) is generally preserved (Scheme 1.3). In the majority of sesquiterpenes from higher plants, the orientation of the C(7) side chain is β, as depicted, whereas in sesquiterpenes from marine origin and from liverworts the α orientation predominates. Exceptions are known, and the discovery of such an exception will be discussed in chapter 4. The biosynthesis of eudesmanes and guaianes is studied in chapter 5 and chapter 6, respectively.

It is important to note that the absolute configuration of isolated sesquiterpenes is seldom determined, and the detection of sesquiterpenes by GC-MS is normally not accompanied by measurement of their optical rotation. Due to advances in the
development of chiral GC and chiral HPLC, determination of the enantiomeric purity of terpenes has been facilitated. However, these methods are often hampered by the lack of racemic reference material which is necessary to determine the separation of the enantiomers.

Scheme 1.3

1.3 Structures and Conformations

Depicting the carbon skeleton of germacrane in a less usual way (Scheme 1.4), shows that the skeleton possesses a symmetry plane, bisecting C(2) and C(7). In most cases, the C(1)–C(10) and C(4)–C(5) double bonds dissymmetrize the picture. The question whether a particular germacran contains such a symmetry plane depends on its three-dimensional structure. This possibility, and its implications for further biosynthetic steps, will be treated in chapter 5.

Scheme 1.4

Due to this symmetry, the representation of germacrane caused confusion in the literature because compounds were drawn in two ways. Therefore, drawing conventions were formulated which are now generally accepted (Scheme 1.5).22
The descriptors Z and E, when applied to the endocyclic double bonds, indicate the stereochemistry of the ring bonds regardless the normal priority rules. Thus, when in the (E,E)-germacrane in Scheme 1.5, C(15) is oxidized, it remains an (E,E)-germacrane although the priority rules define the double bond as Z. The C(7) sidechain is drawn in the bottom right corner of the molecule and oriented β, except when the absolute stereochemistry is known to be the opposite.

Whereas the potential symmetry plane in the two-dimensional representation of the germacrane skeleton is normally trivial, the stereochemistry in the three-dimensional representation is not. The conformational behavior of germacrane has been an area of study for decades and has produced a massive amount of information. The majority of the conformational studies focuses on (E,E)-germacrane and their corresponding epoxides because the presence of one or two E double bonds in the ten-membered ring makes this ring chiral, just as in (E)-cyclooctene. The π-lobes of the E double bonds are positioned more or less in the plane of the ten-membered ring, and this gives rise to 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) Me groups (Scheme 1.6). The array C(6)-C(7)-C(8)-C(9) is the third stereoelement in the ring but the conformation of this array is mainly determined by the C(7) substituent which tends to a pseudo-equatorial position as shown here for hedycaryol (5). A comparable situation exists for the allogermacrane, containing an (E,E)-cyclodeca-1(10),5-diene system (§ 5.1).

A number of germacrane has been studied in the solid state by X-ray - and neutron diffraction. In solution, many germacrane show broadened NMR signals or even multiple NMR signals indicative of conformational equilibria. In these equilibria, one of the double bonds is rotating and the vinylic hydrogen passes through the centre of the ring (jump-rope rotation). The existence of different conformations in germacrane plays an important role in the biosynthesis of
eudesmanes and guaianes mentioned above. (+)-Hedycaryol (5), the subject of chapter 3, possesses several interconverting conformations at room temperature.

Scheme 1.6

When the cyclization of FPP ends with the formation of a C(7)–C(11) double bond (Scheme 1.2), the product has no chiral center. Also some other germacrane, often possessing a C(7)–C(8) furan ring, are devoid of chiral centers. These compounds are nevertheless chiral because of the presence of E double bonds. The conformation and chirality of such compounds is studied in chapter 6.

Several interesting characteristics have been noticed which sometimes can be helpful to simplify the structure elucidation of germacrane. Beside their conformational behavior, one of the most striking properties of (E,E)-germacrane is an "anomalous" ultraviolet absorption (λ > 200 nm) due to the interaction of the double bonds in the ring. This phenomenon occurs when the π-lobes of the double bonds have a spatial overlap. Germacrane containing an (E,E)-cyclodeca-1(10),5-diene system ("allogermacrane") also show this effect.

Some empirical rules for the interpretation of NMR spectra using CDCl₃ as solvent have also been developed. Thus, a Me group connected to a Z double bond normally resonates at lower field in the ¹H NMR spectrum than one connected to an E double bond. In the ¹³C NMR spectrum the resonance for a Me group attached to an Z double bond has a δ value greater than 20 ppm and in the case of a E double bond a δ value smaller than 20 ppm. When C(14) or C(15) bears an aldehyde function, distinction can be made between the conjugated Z or E double bond. The aldehyde proton resonates at a δ value > 9.8 ppm in the case of an E double bond.
whereas a Z double bond gives rise to signals in the range of 9.2–9.5 ppm.\textsuperscript{30}

In connection with the isolation of germacrane in pure form (from natural sources or reaction mixtures), some remarks can also be made. When one or more double bonds are present, silver nitrate extraction,\textsuperscript{31} argentation chromatography,\textsuperscript{32} or even crystallization of the silver nitrate adduct\textsuperscript{33} can sometimes be accomplished. On the other hand GC can be a pitfall, because at higher temperatures many germacrane easily undergo a Cope rearrangement to the corresponding eleanes. Germacrene A (2) rearranges even at room temperature (§ 2.4.1).

1.4 References and Notes

7. Reference 1; Chapter 5.
10. It is not known whether (E,Z)-, (Z,E)-, and (Z,Z)-germacrane are formed from (Z,E)-, (E,Z)-, and (Z,Z)-FPP, respectively, or by isomerization of double bonds in a later stage, see: Fischer, N. H. In Recent Advances in Phytochemistry, Vol. 24: Biochemistry of the Malval Acid Pathway to Terpenoids; Towers, G. H. N., Stafford, H. A., Eds.; Plenum Press: New York, 1990; Chapter 4.
12. See chapter 2 and references cited therein.
chapter 1


16. Exceptions are the drimane sesquiterpenes in which cyclization is induced by protonation of a double bond, a route also followed for most di- and higher terpenes, see reference 1, p 318.

17. For clarity, this picture is simplified and does not depict possible isomerizations of (E,E)-FPP to (Z,E)-FPP or nerolidyl pyrophosphate, prior to cyclization, see: (a) Cane, D. E. Acc. Chem. Res. 1985, 18, 220. (b) Reference 10.


19. The formation of bicyclogermacrarnes proceeds in an analogous manner.

20. When isomerization of FPP to nerolidyl pyrophosphate takes place, prior to cyclization, a chiral center is formed and preserved during cyclization.


22. (a) Rogers, D.; Moss, G. P.; Neidle, S. J. Chem. Soc., Chem. Comm. 1972, 142. (b) Reference 10. (c) The suffix "olide", as in "germacranolide" is used to indicate the presence of a lactone group.


chapter 1
The Synthesis of Germacrane Sesquiterpenes

Abstract: the literature concerned with the synthesis of germacrane sesquiterpenes is reviewed and the scope of the thesis is presented. The attention is focused on the construction of the ten-membered ring.
2.1 Introduction

2.1.1 Germacrane as Starting Material in Synthesis
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 germacrane because only a very limited number of germacrane is available in (multi)gram quantities. This means that germacrane are not very suitable as a starting material in synthesis. However, there are exceptions. Germacrone (1, Scheme 2.1), 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 well-studied.¹ A serious drawback in the synthetic application of 1 is the lack of a chiral center.

Being the likely precursor in the biosynthesis of periplanones, the also widespread germacrene D (2) has been used as a starting material in synthesis in order to elucidate the structure of the periplanones and to mimic their biological activity. Germacrene D is not very stable and often isolated as a racemate.²

Salonitenolide (3, or one of its C(8)-esters cnicin and acetylcnicin) occurs quite abundantly in *Centaurea* species and has been used to prepare vernolepin (4).³

![Scheme 2.1](image)

**Scheme 2.1**

2.1.2 Strategies for the Synthesis of Germacrane
In ring systems derived from cyclohexane, the axial-equatorial preference is often used for stereochemical control in synthesis. The application of this type of control is much more difficult in medium-sized rings. Nevertheless, reactions on these ring systems are sometimes surprisingly stereoselective.⁴ This selectivity can often be predicted, providing that the conformation of the compound involved is known. This has led to the use of molecular mechanics, often in combination with NMR and X-ray data.⁵ It is now widely accepted that, although medium-sized rings can often adopt a number of stable conformations, only a few of these conformations
are actually present at room temperature. For the germacrane, especially those with two \( E \) double bonds, these predictions normally result in one of the conformations discussed in § 1.3. Because the plane of the \( E \) double bonds in the ring is perpendicular to the plane of the ring, only one side is available for reactions. This has been used frequently in synthesis (vide infra).

The synthesis of germacrane has been a long-standing problem. Difficulties arise because of the ring strain and the possibility of transannular reactions. Nevertheless, a number of approaches has been developed to overcome these problems and some of them belong to the most impressive parts of synthetic organic chemistry. On the other hand, the synthesis of these medium-sized ring systems has functioned as a spring-board to the stereocontrolled synthesis of macrocycles. Herein, we aim at a systematic overview of the synthesis of germacrane sesquiterpenes and focus our attention mainly on the ten-membered ring formation.

Intramolecular carbon-carbon bond formation can be accomplished in several ways. Due to the presence of two double bonds, the ring strain in germacrane is markedly lowered compared to cyclodecane. This makes ring closure a useful method. A special case is the contraction of larger rings.

The ring cleavage or fragmentation of bicyclic and tricyclic compounds has shown to be a very effective method for the synthesis of germacrane. The smaller rings present in the precursors are easier to construct and their stereochemistry can be controlled. The methods used for cleavage are diverse.

The ring expansions are dominated by the Cope reaction and its variants. The stereochemistry of the double bonds is determined by this [3,3] sigmatropic rearrangement and by the substituted cyclohexane systems involved.

2.2 Intramolecular Carbon-Carbon Bond Formation

2.2.1 Intramolecular Alkylation and Aldol Condensation
One of the most cited methods in germacrane synthesis is the anionic cyclization approach of Kodama and Itô. 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 (Scheme 2.2). The method has been used to prepare all double bond stereoisomers of hedyacaryol (5). Acid-catalyzed transannular reactions and thermal Cope rearrangements of these stereoisomers gave more insight into the biosynthesis of the eudesmane and elemene sesquiterpenes.
The method has also been used in combination with a [2,3] sigmatropic rearrangement. Obscuronatin (6), a diterpene closely related to the germacrane, and the germacrane 7 with a cyclodeca-1(10),5-diene system have been synthesized by this combined method (Scheme 2.3). The latter compound was isolated some years later from a marine soft coral and a liverwort.

The Kodama-Itô method has been applied by Winter et al. to elucidate the structure of helminthogermacrene (8) through synthesis. Recently, the method has been revisited in the synthesis of the germacranoid 9 containing an allene function (Scheme 2.3).
In 1983 Takahashi et al. have introduced a general method for the construction of (E,E)- and (E,Z)-2,6-cyclooctadiene systems by intramolecular alkylation of cyanohydrin ethers. The acyclic precursors are built up from farnesyl or geranyl derivatives and contain an allylic cyanohydrin protected as its ethoxyethyl ether (EEO). The leaving group at the other end of the chain is a primary or secondary tosylate. The alkylation step is generally effected with sodium - or lithium hexamethyldisilazane (NaHMDS or LHMDS) at elevated temperature and proceeds in high yield. After cyclization, the cyanohydrin is converted into the ketone function by careful treatment, first with acid and then with base. Scheme 2.4 shows the synthesis of periplanone B (10) and acoragermacrone (11) using this approach. The method has also been used for the synthesis of germacrone (1) and, recently, for the synthesis of periplanone analogs. No γ-alkylation occurs during the alkylation step because an E double bond in the resulting eight-membered ring is energetically unfavorable. Recent studies reveal that this preference for α-alkylation changes when the resulting eight-membered ring only contains a Z double bond.
A closely related approach using a (phenylthio)acetonitril has been used for the synthesis of dihydrogermacrene D (12)\(^{25}\) as shown in Scheme 2.5, whereas an \(\alpha\)-phenylthioacrylate has been used in an enantiospecific synthesis of periplanone B (10).\(^{26}\)

Similarly, an \(\omega\)-tosyloxy-\(\alpha\)-phenylsulfenyl ketone, prepared from carvone, has been cyclized to a ten-membered ring.\(^{27}\)

A biomimetic approach has been used by Corey et al. in the synthesis of humulene (13), possessing an eleven-membered ring (Scheme 2.6).\(^{28}\) Whether this cyclization method, applied on a proper precursor, leads to a biomimetic synthesis of germacrane or not is still a 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."\(^{29}\)
The synthesis of the complex germacrane eremantholide A (15) has been a challenge for several research groups.\textsuperscript{30} A recent approach to this compound starts from D-glucose and uses an intramolecular vinologous aldol reaction for the construction of the ten-membered ring (Scheme 2.7).\textsuperscript{31}
Marshall et al. have developed an efficient cyclization of \( \alpha \)-alkoxyallylstannane alkynes for the synthesis of fourteen-membered cembranoid precursors. Application of this method to the synthesis of germacrane fails and gives a twelve-membered ring (Scheme 2.8).\(^{32}\)

Scheme 2.8

2.2.2 Ring-Contraction of Larger Rings
An elegant method for the construction of larger carbocycles using a Wittig rearrangement has been developed independently by the groups of Takahashi and Marshall in 1986.\(^{33}\) A diallylic or an allylic propargylic cyclic ether is contracted to give the desired carbocycle with trans-related vicinal hydroxyl and isopropenyl substituents. The usefulness of the method was demonstrated with the synthesis of costunolide (16), in which the large-ring ether was formed with a high dilution method (Scheme 2.9).\(^{34}\)

Scheme 2.9
In later work, ring closure leading to the large-ring ether was performed with the aforementioned cyanohydrin ether method\(^\text{35}\) (Scheme 2.4) and was used in the synthesis of haagenolide (17).\(^\text{36}\)

A closely related approach was used in the synthesis of aristolactone (18), a germacrane possessing a lactone ring connecting C(15) and C(6).\(^\text{37}\) Because the C(6)–O bond and the isopropenyl group at C(7) in aristolactone possess the cis relationship, this approach requires the reversal of the stereochemistry at C(6) (Scheme 2.10).

![Scheme 2.10](image)

After it was realized that the cyclic ether involved possesses planar chirality, which means that the propargylic CH\(_2\) protons are enantiotopic, this method has also been employed in the enantioselective synthesis of 18. Using an optically active base, the [2,3] Wittig ring contraction could be effected in 60-80% ee.\(^\text{38}\)

The first enantioselective synthesis of eremantholide A (15) was effected using a Ramberg-Bäcklund rearrangement, an approach seldom used in the synthesis of medium-sized rings (Scheme 2.11).\(^\text{39}\)

![Scheme 2.11](image)
Although not aiming at the synthesis of a particular germacrane, it was found that ring contraction of a humulene derivative gives helminthogermacrene (8). Two years later, 8 was isolated from Helminthosporium sativum. Ring contraction of another humulene derivative afforded germacrone A (14, Scheme 2.12).

**Scheme 2.12**

![Scheme 2.12](image)

germacrene A (14)

2.2.3 Carbonyl Coupling

Several syntheses of germacrane are based on metal-mediated ring closure. The most frequently used method is the titanium-induced carbonyl coupling reaction. Usually, the syntheses start with the easily available geranylacetone as shown in the synthesis of a series of bicyclogermacrane (19, 20) and lepidozenes (21, 22) (Scheme 2.13). Very recently, isolepidozone (21) has been found in some liverworts.

**Scheme 2.13**

![Scheme 2.13](image)

bicyclogermacrene (19) isobicyclogermacrene (20) isolepidozone (21) lepidozone (22)
Helminthogermacrene (8), periplanone C (23), and acoragermacrene (11) have been prepared similarly. A low valent chromium reagent has been used in the synthesis of costunolide (16).

2.2.4 Intramolecular Radical Cyclization
Recently, two reports have been published on an intramolecular radical cyclization approach towards germacrane sesquiterpenes. Parsons et al. used the addition of an alkenyl radical to an acetylene to form a germacrane ring system, lacking the C(14) Me group, in low yield (Scheme 2.14).

Scheme 2.14

An intramolecular Stille cross-coupling has also been used as a ring closing strategy towards an intermediate in the synthesis of periplanone B analogs (Scheme 2.15). It is, however, likely that the results strongly depend on the amount of ring strain in the transition state leading to the product. In this approach the C(7) isopropyl group is lacking.
2.2.5 Intramolecular Carbene Cyclization
A recent and very direct attempt to synthesize bicyclogermacrene (19) used the organozinc carbenoid derived from (E,E)-farnesal (24, Scheme 2.16). The product of this reaction, however, turned out to be sesquicarene (25) instead of 19.\(^{50}\)

Scheme 2.16

\[(E,E)\text{-farnesal (24)} \xrightarrow{\text{Zn}, \text{Me}_2\text{ClSi}, \text{SiClMe}_2} \text{sesquicarene (25)} \quad \text{bicyclogermacrene (19)}\]

2.3 Ring Cleavage of Bicyclic and Tricyclic Compounds

2.3.1 The Grob-type Fragmentation Reactions
A well-known method for medium-sized ring formation, especially for the synthesis of germacrane sesquiterpenes, is the Grob-type fragmentation reaction developed by Wharton. As early as in 1961, Wharton synthesized (E)-cyclodecenone (26) from the corresponding 1,3-diol monomesylate by treatment with KO\(_t\)-Bu/HOt-Bu (Scheme 2.17).\(^{51}\) In a similar way the Z isomer (27) was prepared.\(^{52}\)

Scheme 2.17

\[
\begin{array}{c}
\text{OMs} \\
\text{OH}
\end{array}
\xrightarrow{\text{KOT-Bu, HOR-Bu}}
\begin{array}{c}
\text{msO} \\
\text{OH}
\end{array}
\]

\[(E)\text{-cyclodecenone (26)} \quad (Z)\text{-cyclodecenone (27)}\]

The compounds shown in Scheme 2.17 have been used to study the conformation and reactivity of these systems, and can also be considered as simple models for
germacranes, especially for the periplanones. The double bond formation is stereospecific because the reaction proceeds via a transition state in which the leaving group and the central (breaking) bond are aligned in an antiperiplanar way. The negative charge needs neither to be located at oxygen nor to be exocyclic (vide infra) and formally the fragmentation can be classified as intraannularly, interannularly, or extraannularly depending on the location of the negative charge.

Although not aiming at the synthesis of a germacrane, cyclodecenones were used as intermediates in the synthesis of longipinenes. A cyclodecynone formed by an Eschenmosher fragmentation was used in the biomimetic synthesis of bourbonenolides. In the synthesis of chapliatrin-type compounds and in the biomimetic synthesis of 5α-hydroxy guaianolides, the Wharton fragmentation reaction was used as a key step (Scheme 2.18).

De Clercq et al. developed an elegant route to an intermediate in the synthesis of periplanone B (10, Scheme 2.19). Key steps in this approach are an intramolecular Diels-Alder reaction and the Wharton fragmentation reaction.

Scheme 2.18

[Diagram of the reaction schemes]

Scheme 2.19

[Diagram of the reaction schemes]
A reaction closely related to the Wharton fragmentation reaction is the so-called boronate fragmentation reaction developed by Marshall et al. Initially, this reaction was used as a synthetic approach to guaiane sesquiterpenes. Wharton was the first one who applied this method in the synthesis of the germacrene alcohol hedycaryl (5, Scheme 2.20). The method has also been used in the synthesis of (Z,E)-cyclodecadienes. An investigation has been made on the applicability of this method to the construction of germacranoles. Germacrene models constructed this way have recently been used to study the role of enzymes in the biosynthesis of eudesmane and guaiane sesquiterpenes.

Scheme 2.20

The stereochemistry of the borane addition has been discussed. Solvolytic assistance seems to facilitate the subsequent fragmentation to some extent.

An enolate-assisted intraannular fragmentation has been used for the synthesis of sericenine (28), an (E,Z)-furanogermacrene (Scheme 2.21). The required decalin system was prepared via a dissolving metal reduction and methylation of a substituted tetralone. Under the basic conditions applied, the initially formed (E,E)-germacrane isosericenine (29), also a natural product, isomerizes quickly via its dienolate to 28.

Scheme 2.21
2.3.2 Photolytic Cleavage

In 1963, Corey and Hortmann synthesized for the first time a germacrane sesquiterpene, i.e., dihydrocostunolide (30, Scheme 2.22). The starting material was \( \alpha \)-santonin (31) which was converted in several steps into a conjugated diene. Irradiation with UV-light gave a photostationary equilibrium between the bicyclic diene and a monocyclic triene. Catalytic reduction of this equilibrium mixture afforded 30.

\[\text{Scheme 2.22}\]

This approach was used several times in germacrane synthesis and methods were developed to affect the photostationary equilibrium as the synthesis of dihydronovanin (32) exemplifies (Scheme 2.23). Irradiation of the cross-conjugated dienol acetate and subsequent treatment with KOH afforded the monocyclic enone which could be converted into 32.

\[\text{Scheme 2.23}\]

Recently, this method has been applied in the partial synthesis of germacranolides with oxygen bridged rings. Starting from vulgarin (33), a dienol acetate was prepared which upon irradiation and KOH treatment gave a ketone which was converted into several bridged intermediates (Scheme 2.24).
A direct way to avoid the photostationary equilibrium involved irradiation of a dienol prepared from α-santonin (31) and gave the corresponding dienone as a mixture of epimers in good yield (Scheme 2.25). Subsequent reduction and mesylation gave a compound which only afforded dihydrocostunolide (30) upon treatment with tetrabutylammonium oxalate (TBAO) in acetone (five days). The fruitful use of this reagent has been reported by several authors in attempts to introduce the E double bond. This sequence was also used to prepare a chapliatrin-type compound (see § 2.3.1).
In a different approach, the sensitized photolytic cleavage of the C(5) α-hydroxy ketone 34 gave dione 35 in 49% yield (Scheme 2.26).\textsuperscript{75} To our knowledge this monocyclic dione has not yet been applied in germacrane synthesis.

**Scheme 2.26**

2.3.3 Radical Fragmentation
Several synthetically useful ring fragmentations have been developed that rely on the β scission of bridgehead alkoxy radicals.\textsuperscript{76} It has well been recognized that the stereochemistry of the starting alcohols determines the geometry of the formed alkene. As in the heterolytic Wharton and Marshall fragmentation reactions (vide infra), this is consistent with a concerted mechanism as shown in Scheme 2.27.

**Scheme 2.27**

This radical fragmentation in combination with the addition of an alkyl radical to a ketone leads directly to cycloalkenones (Scheme 2.28).\textsuperscript{77} The discussion about the rate constants is important here.\textsuperscript{78}
The bridgehead alkoxy radicals can also be formed indirectly as shown in Scheme 2.29. The starting materials for the reaction are easily obtained from Robinson annelation products.\textsuperscript{79}

This radical fragmentation is also used in cascade reactions.\textsuperscript{80} No example of the use of these radical fragmentations in the synthesis of germacrane sesquiterpenes is known yet. Very recently, a closely related total synthesis of the nine-membered ring sesquiterpenes caryophyllene (36) and isocaryophyllene (37) has been accomplished (Scheme 2.30).\textsuperscript{81}
2.3.4 The [2+2] Cycloreversion Reaction
The photochemical [2+2] cycloaddition reaction followed by a thermal [2+2] cycloreversion reaction constitutes another well-known approach to ten-membered ring systems.\(^8\) It was realized that this reaction sequence gave an efficient entry to the melampolide- and heliangolide-type skeletons\(^8\) as the synthesis of the isoaristolactone isomer \(38\) exemplifies (Scheme 2.31).\(^4\)

Scheme 2.31

\[
\begin{align*}
\text{CO}_2\text{H} & \quad + \quad \text{hv} \\
\text{I} & \quad \text{hv} \\
\text{NaBH}_3\text{CN} & \quad \Delta \\
40\% \quad \text{two steps} & \quad \text{38, 64\%} \quad + \quad 14\%
\end{align*}
\]

The \((E,E)\)-germacrane skeleton cannot be prepared easily via this method, partly because the cycloreversion reaction leading to this stereochemistry is not very favorable, and partly because an \((E,E)\)-germacrane rapidly gives Cope rearrangement to an elemene at the elevated temperatures required for this cycloreversion.\(^8\) In Scheme 2.32 a short synthesis of \((+)-\)isoacoragermacrone \((39)\) is shown.\(^8\) This product had already been converted into acoragermacrone \((11)\) by Still (§2.4.3).

Scheme 2.32

\[
\begin{align*}
\text{hv} & \quad \text{PVP} \quad 500 \, ^\circ\text{C} \\
\text{I} + & \quad \text{hv} \\
\text{FVP} & \quad \text{500 \, ^\circ\text{C}} \\
\text{(+)-isoacoragermacrone} & \quad \text{(+)-39}
\end{align*}
\]
A remarkable synthesis using the cycloreversion reaction is the construction of the \((E,E)\)-germacrane isabelin (40, Scheme 2.33). In this case, the main product is the \(E,E\) system probably because the C(7),C(8) lactone ring determines largely the conformation of the intermediate diradical and the resulting ten-membered ring. The conformation of 40 probably prevents also Cope rearrangement.

**Scheme 2.33**

\[
\begin{align*}
\text{toluene,} & \quad 200^\circ\text{C} \\
& \quad 100\% \\
\text{isabelin (40)}
\end{align*}
\]

The synthesis of a functionalized \((Z,E)\)-germacranolide (41) by this approach is given in Scheme 2.34.

**Scheme 2.34**

\[
\begin{align*}
\text{toluene,} & \quad 170^\circ\text{C} \\
& \quad 35\%
\end{align*}
\]
Since \((E,E)\)-germacrane is not easily accessible by this method, the photoadduct has been subjected to nucleophilic ring opening. The resulting decalin might be a good starting material for the synthesis of the \((E,E)\)-germacrane 42 via heterolytic fragmentation (§ 2.3.1). Strangely enough, only the \((Z,E)\)-germacrane 43 was obtained (Scheme 2.35) and despite thorough research, the reaction course could not been established.\(^9\)

\textbf{Scheme 2.35}

2.4 Ring Expansions

2.4.1 The Cope Rearrangement

An important reaction for the synthesis of germacrane sesquiterpenes is the Cope rearrangement in which a 1,2-divinylcyclohexane via a [3,3] sigmatropic rearrangement can be converted into a cyclodecadiene. In fact, nature itself delivered the idea: the well-known equilibrium between germacrane and elemene sesquiterpenes. The existence of this equilibrium forms one of the major difficulties in the isolation of pure germacrane from natural sources. The use of purification techniques (GC, distillation) completely converts most of the simple \((E,E)\)-germacranes, such as hedycaryol (5) and germacrone A (14), into the corresponding \textit{trans}-1,2-divinylcyclohexane derivatives (elemenes). Extensive research has been done towards the mechanistic details of the Cope rearrangement.\(^9\) Generally, the equilibrium strongly depends on the ring substituents; especially the commonly occurring lactone ring has a strong influence. In Scheme 2.36 some examples are given.\(^9\) The Cope rearrangement of \((Z,E)\)-germacranes to \textit{cis}-1,2-divinylcyclohexane derivatives proceeds less easily and the equilibrium lies mostly at the germacrane side.\(^9\)
The Cope rearrangement as such has been used several times in synthesis. Thermolysis of dehydrosaussurea lactone (45), synthesized from α-santonin (31), gave costunolide (16) in 21% yield along with 42% of starting material. A mixture of isolinderalactone (46), linderalactone (47), and neolinderalactone (48) was obtained after thermolysis of a mixture of \textit{epi}-isolinderalactone (49) and 46 (Scheme 2.37).
The Cope rearrangement leading to isobicyclogermacrenal (50) could not be performed by thermolysis, probably because the cyclopropane ring was not stable under the thermolysis conditions used. With the help of silica gel, however, the Cope rearrangement could be achieved in high yield (Scheme 2.38).95

Scheme 2.38

In order to enhance the applicability of the Cope rearrangement in synthesis, many researchers have tried to make the ring expansion thermodynamically more favorable. This can be done, for instance, by changing the carbon hybridization as the Cope rearrangement of the allene derivative 51 proves (Scheme 2.39).96

Scheme 2.39
Another method to affect the equilibrium involves a double bond shift during the thermolysis (Scheme 2.40).97

Scheme 2.40

shyobunone (52) \[ \xrightarrow{\Delta} \] acoragmacronone (11) \[ \rightarrow \] preisocalamendiol (53)

2.4.2 The Cope-Claisen Rearrangement
A very elegant way to shift the equilibrium to the germacrane side uses the so-called tandem Cope-Claisen rearrangement. In this reaction, the Cope rearrangement triggers the Claisen rearrangement, the latter being de facto irreversible.98 This concept forms the basis of a synthetic route towards (+)-dihydrocostunolide (30) starting from (−)-carvone (Scheme 2.41).99 This route has also been used for the biomimetic synthesis of eudesmane sesquiterpenes.100

Scheme 2.41

2.4.3 The oxy-Cope Rearrangement
1,2-Divinylcyclohexane derivatives possessing a hydroxyl group at C(1) or C(2) can easily undergo ring expansion.101 This so-called oxy-Cope rearrangement has successfully been applied in the synthesis of medium-sized rings102 and bicyclic systems.103 The first example of the use of this reaction in germacrane synthesis has been reported by Still in 1977.104 Starting from (±)-isopiperitenone (54), preisocalamendiol (53) and acoragmacronone (11) could be synthesized in an elegant and short way using the Evans modification of the Cope rearrangement (Scheme 2.42).105 More recently, the Evans modification has been improved by using KH
pretreated with iodine.\textsuperscript{106} For the synthesis of 11, the Z double bond of the initial Cope product isoacoragemacrone (39) had to be isomerized to E by 1,4-addition and subsequent elimination of the bulky Me\textsubscript{3}Sn group.

Scheme 2.42

\[
\begin{array}{c}
\text{cis-}2,3\text{-dimethyl-1,4-cyclohexadiene} \\
\text{Li} \\
\text{KH} 75\% \\
\end{array}
\]

(±)-isopiperitenone (54)

\[
\begin{array}{c}
\text{LDA} \\
\text{HOAc} \\
76\% \\
\end{array}
\]

preisocalamendiol (53)

\[
\begin{array}{c}
\text{Me3SnLi} \\
\text{TMSCI} \\
\text{MnO}_2 70\% \\
\end{array}
\]

acoragemacrone (11)

This approach also led to the first synthesis of periplanone B (10, Scheme 2.43).\textsuperscript{107} Based on an ingenious stereocontrol, 10 and two of its stereoisomers could be synthesized, thereby settling the correct relative stereochemistry of periplanone B (10).

Scheme 2.43

\[
\begin{array}{c}
\text{KH, 18-crown-6} \\
\text{TMSCI, } m\text{-CPBA} \\
57\% \\
\end{array}
\]

55
Hauptmann et al. have used the same principle in their synthesis of 10.\textsuperscript{108} Several years later, the C(4)-cis isomer of Still's intermediate \textbf{55} (Scheme 2.43) was used for an enantioselective synthesis of \((-\))-periplanone B (10) by Mori's group.\textsuperscript{109} This synthesis laid the basis for a thorough study of the periplanones.\textsuperscript{110}

Starting from \((-\))-carvone, the enantiomer of \((+\))-curdione (56), an antitumor principle from the Chinese herb \textit{Curcuma aromatica}, has been synthesized in a similar way (Scheme 2.44).\textsuperscript{111}

\textbf{Scheme 2.44}

\((+\)-curdione (56)

The broad scope of the oxy-Cope rearrangement was demonstrated by the synthesis of the structurally complex heliangolide eucannabinolide (57, Scheme 2.45).\textsuperscript{112}
Using the same approach, heliangolide precursors\textsuperscript{113} and a natural occurring heliangolide 58 have been synthesized (Scheme 2.46).\textsuperscript{114}

The oxy-Cope rearrangement has also been used to construct the heavily functionalized skeleton of the furanoheliangolides. An example is shown in Scheme 2.47.\textsuperscript{115}
An ingenious route, aiming at the synthesis of the butadiene unit present in germacrene D (2) and periplanones, has been presented by Schreiber and Santini\textsuperscript{116} and involves an oxy-Cope rearrangement followed by a cyclobutene ring opening. This method was used for an efficient synthesis of periplanone B (10)\textsuperscript{117} and, later, also for a short synthesis of germacrene D (2, Scheme 2.48).\textsuperscript{118}

\begin{center}
\textbf{Scheme 2.48}
\end{center}

2.5 \textbf{Scope of The Thesis}

It has been shown in the preceding paragraphs that for the synthesis of germacrane sesquiterpenes, a number of approaches has been developed to overcome the ring strain and to introduce the double bonds. In § 2.3.1 the use of different manifestations of the Grob fragmentation reaction in decalin systems is discussed. A schematic representation of this reaction is given in Scheme 2.49. This thesis will elaborate on this concept.

\begin{center}
\textbf{Scheme 2.49}
\end{center}
A strong argument in favor of Grob-type fragmentation reactions is the regionand stereospecific formation of the double bonds. The rigid structure of a transfused decalin system assures the orbital overlap, needed for a rapid and unambiguous fragmentation reaction. This is a prerequisite for a successful synthesis because the introduction of a double bond in a ten-membered ring can hardly be directed. Another advantage of this rigidity is the possibility to predict the stereochemistry of transformations in decalin systems, also based on a massive amount of experience.

In most cases, the fragmentation reaction is placed at the end of the synthetic route. This strategy divides the synthesis of a germacrane into two parts. The first part is concerned with the construction of the correctly functionalized decalin system, while the second part is concerned with the fragmentation of that decalin to give the desired germacrane. For the germacranes discussed in this thesis, the decalin precursors are depicted in Scheme 2.50.

**Scheme 2.50**

\[ (+)-hedycaryol (5) \Rightarrow \]

\[ \text{MsO} \]

\[ (-)-allohedycaryol (59) \Rightarrow \]

\[ \text{MsO} \]

\[ \text{OMs} \]

\[ \text{germacrene B (61)} \Rightarrow \]

\[ \text{MsO} \]

\[ \text{OHC} \]

\[ \text{OH} \]

\[ \text{neohedycaryol (60)} \Rightarrow \]

\[ \text{MsO} \]

\[ \text{OHC} \]

\[ \text{OH} \]

\[ \text{OH} \]
The synthesis of (+)-hedycaryol (5), (−)-allohedycaryol (59), and neohedycaryol (60) with the Marshall fragmentation (§ 2.3.1) as key step, is discussed in chapter 3, chapter 4, and chapter 5, respectively. The construction of germacrane, with C(15) functionalized is described in chapter 6. As key step, an enolate-assisted fragmentation reaction is used and the scope of the reaction is studied. Because the substrates selected for this fragmentation reaction only differ in the nature of the C(7) side chain, a general route towards germacrane via the enolate-assisted fragmentation reaction is possible.

2.6 References and Notes

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chapter 2

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The Synthesis of (+)-Hedycaryol, Starting from Natural (−)-Guaiol

Abstract: (+)-hedycaryol (1), a generally occurring germacrane sesquiterpene, has been synthesized starting from (−)-guaiol (4). The hydroazulene system of (−)-guaiol was converted in three steps into a decalin system which contained all the structural features needed for the synthesis of (+)-hedycaryol. A Marshall fragmentation reaction was used to prepare the (E,E)-cyclodecadiene ring system present in 1. Additionally, (+)-γ-eudesmol (14) and (+)-4-eudesmene-1β,11-diol (17) have been synthesized, starting from 4.
3.1 Introduction

The germacrane sesquiterpene (+)-hedycaryol (1) has been found in several plant species, e.g. *Phebalium ozothamnoides*, *Rubus rosifolius*, *Thujaopsis dolabrata*, *Hyssopus officinalis*, and two *Cryptomeria* spp., and has been used as a chemotype characterizing compound in *Thymus* spp.

Some years before its first isolation from *Hedycarya angustifolia*, hedycaryol was proposed as an important intermediate in the biosynthesis of several classes of sesquiterpene alcohols, and recently, also as a common precursor for several sesquiterpene ethers. The isolation of hedycaryol is rather complicated because the compound is thermally labile and especially sensitive to acids. Under the influence of elevated temperatures, hedycaryol rearranges to elemol and, upon treatment with acid, it cyclizes to a mixture of α-, β-, and γ-eudesmol (see chapter 5). After a first attempt to synthesize (±)-hedycaryol, two successful syntheses have been reported in the literature, both in low overall yield. No synthesis of natural (+)-hedycaryol is known.

Because of our interest in the biomimetic cyclization reactions of the conformationally flexible germacrane sesquiterpenes, we were looking for an efficient synthesis of enantiomerically pure (+)-hedycaryol (1). As shown by Wharton et al., the Marshall fragmentation reaction is very promising in this connection because both double bonds are formed regio- and stereospecifically (§ 2.3.1). This approach needs the synthesis of enantiomerically pure eudesmane derivative 2 (Scheme 3.1).

![Scheme 3.1](image)

3.2 Results and Discussion

The naturally occurring sesquiterpene (−)-guaiol (4) seems to be a suitable starting compound for the synthesis of 2. It is known that guaiol, which has only been used occasionally in chiral synthesis, can be oxidized to the cyclodecane-1,5-dione 3.
When a selective intramolecular aldol condensation reaction of 3, leading to C(5)–C(10) bond formation can be accomplished, it is possible to synthesize 2 and thus also 1. This approach will be demonstrated in this chapter.

A simple method to obtain large quantities of pure 4 from the commercially available Guaiac wood oil turned out to be crystallization of the crude oil from acetone and subsequent recrystallization of the remaining crystalline mass from water/ethanol mixtures. An extra crop of 4 was obtained when the mother liquor, which consisted mainly of bulnesol, was treated with H₂ and Pd/C.¹⁴ During this reaction bulnesol isomerized to a mixture of 4 and iso-guaiol.

Although ozonolysis of 4 gave good yields (72–74%) of the dione 3,¹⁶ the oxidative cleavage of the central double bond was performed with RuO₂/NaIO₄¹⁷ in a mixture of CCl₄, MeCN, and H₂O at room temperature. In this way 3 could be obtained in 95% yield (Scheme 3.2). It is known that dione 3 easily cyclizes to the cadinane 5.¹⁶ The stereochemistry of 5 was recently revised,¹⁸ and the suggestion was made that the C(11) hydroxyl group plays an important role in the selective deprotonation at C(6) in the cyclization process.

Scheme 3.2

Therefore, it is reasonable to assume that protection of the C(11) hydroxyl group may lead to the formation of compounds with an eudesmane skeleton, e.g. 9, in addition to, or instead of, cadinane formation. The resulting eudesmane 9 would have all the structural features needed for an effective synthesis of 2.
To confirm this assumption, it was necessary to protect the hydroxyl group at C(11) in 3 as its triethylsilyl (TES) ether (3 \rightarrow 7). The key step in our approach, the intramolecular aldol condensation reaction of 7, indeed gave the eudesmane 9 as the main product. Upon treatment with KOH in EtOH, the triethylsilyl ether 7 afforded a ca 1:2 mixture of 8 and 9, respectively, from which 9 could be isolated in 55% yield after careful column chromatography.

Despite an extensive search for other conditions, the yield of 9 could not be improved. Stronger bases clearly favored the formation of 8, as did the use of other solvents. For instance KOH in THF gave exclusively 8. The structure of 8 could be assigned after cleavage of its silyl ether bond with HF in MeCN, which led to the known cadinane 5.\textsuperscript{18} It is interesting to note that in solution 5 exists in equilibrium with its lactol form 5a, according to the NMR spectral data. This explains the quantitative formation of the cyclic acetal 10 upon a short treatment of a methanolic solution of both 5 and 8 with \( p \)-TsOH.

The stereochemistry at the ring junction of the eudesmane 9 as shown in Scheme 3.2 was deduced from its conversion into the reported cis-fused compound 11.\textsuperscript{19} However, the stereochemistry of the Me group at C(4) in this compound was unknown. To assign this orientation, cleavage of the TES ether bond in 9 was necessary. In the \( ^1 \)H NMR spectrum of the desilylated product 6 the doublet (\( \delta 0.96 \)) due to the Me group at C(4) is no longer obscured by other signals. By irradiation of this doublet, the signal of the C(4) proton appears as a double doublet at \( \delta 2.39 \) with couplings of 12.3 and 4.5 Hz. This means that the Me group at C(4) is equatorially oriented.

Scheme 3.3
Treatment of 9 with SOCl₂ in pyridine gave 13 as the sole product in excellent yield (Scheme 3.3). Furthermore, it was found that after treatment of the above-mentioned 1:2 mixture of 8 and 9 with SOCl₂ in pyridine, an easily separable mixture of 12 and 13, respectively, was obtained. In this way the troublesome separation of 8 and 9 by means of column chromatography could be avoided, and a better overall yield of 13 (44% from 7) was obtained.

Additional support for the assigned structure of 13 was obtained through synthesis of the known natural sesquiterpene (+)-γ-eudesmol (14).²⁰ Via reduction of the corresponding tosylhydrazone, which was accompanied by silyl ether bond cleavage, 14 was formed in 40% yield from 13.

To complete the synthesis of (+)-hedycaryl, the carbonyl group of 13 had to be reduced to a β-hydroxy group. The use of NaBH₄ in EtOH gave, after separation, 17% of the α-alcohol 15 and 73% of the desired β-alcohol 16 (Scheme 3.4). Cleavage of the triethylsilyl ether bond in 16 with HF afforded (+)-4-eudesmene-1β,11-diol (17), a sesquiterpene recently isolated from Cryptomeria japonica.²¹

Scheme 3.4

```
\[ \begin{align*}
\text{13} & \xrightarrow{\text{NaBH}_4} \text{15} \\
\text{16: } & R = \text{TES} \\
\text{17: } & R = \text{H} \\
\text{18: } & R = \text{TES} \\
\text{2: } & R = \text{H} \\
\end{align*} \]
```

Treatment of 16 with MsCl in pyridine followed by desilylation with HF afforded the mesylate 2. Fragmentation was accomplished using Marshall's procedure²² to give, after extraction with aqueous AgNO₃,¹ pure 1 in 55% yield. It must be noted that during the NMR measurements slow decomposition of 1 was observed in commercial CDCl₃, even when this solvent was pretreated with basic alumina. In C₆D₆ solutions 1 appeared to be stable. In the Chemical Abstracts, the S-configuration is erroneously assigned to (+)-hedycaryl (1) probably because a
corrigendum of reference 7 has been overlooked. The R-configuration of natural (+)-1 has been ascertained by this synthesis, because the absolute configuration of (−)-guaiol is known.

Thus, starting from the readily available (−)-guaiol (4), (+)-hedycaryol (1) has been synthesized in a 7 steps reaction sequence in an overall yield of 16%. The conformational behavior of 1, and its role in the biosynthesis of eudesmane sesquiterpenes will be discussed in chapter 5.

3.3 Experimental Section

General. Melting points were determined on a Mettler FP80 HT melting point apparatus and are uncorrected. Optical rotations were obtained from CHCl₃ solutions on a Perkin-Elmer 241 polarimeter. ¹H and ¹³C NMR spectra were determined in CDCl₃ (unless indicated otherwise) at 200 MHz and 50 MHz, respectively, on a Bruker AC-E 200 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). Mass spectral data were determined on an AEI MS 902 spectrometer. FT-IR spectra were determined on a BIO-RAD FTS-7 infra-red spectrometer. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. GC analyses were carried out on a Varian Vista 6000 or a Fisons GC 8000 gas chromatograph with a flame ionization detector and a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically with a Fisons integrator DP700. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh), unless otherwise noted. The silica gel used for column chromatography was Merck silica gel 60 (70–230 mesh). Solvents were dried and distilled fresh by common practice. For all dry reactions, flasks were dried at 140 °C and flushed with dry nitrogen just before use, and reactions were carried out under an atmosphere of dry nitrogen. Product solutions were dried over anhydrous MgSO₄ (unless otherwise noted) prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

Materials. The compounds 1,⁶a, 3,¹⁶ 5,¹⁸ 14,²⁶ and 17²¹a,b have been characterized before.

Isolation of (−)-guaiol (4). A solution of 323 g of Guaiac wood oil⁵ (guaiol content ca 37% according to GC) in 430 mL of acetone was stored for two days at −20 °C. The formed crystals were isolated by suction filtration and dried under reduced pressure to give 125 g of crude guaiol, (GC purity 70%). Recrystallization from a 3:1 mixture of EtOH/H₂O (380 mL) afforded 83 g of pure guaiol as white crystals, (GC purity >97%). A second crop (7 g) of guaiol was obtained from the mother liquor after
treatment with Pd/C in a H₂ atmosphere as described in the literature,¹⁴ followed by
the above-mentioned crystallization procedure using EtOH/H₂O.

[2S-(2R*,6R*,9S*)]-9-(1-Hydroxy-1-methylethyl)-2,6-dimethyl-1,5-cyclodecane-
dione (3). To a vigorously stirred solution of 60.0 g (0.262 mol) of 4 in a mixture of
350 mL of MeCN, 350 mL of CCl₄, and 600 mL of H₂O was added 87.0 g (0.407 mol) of
NaIO₄ and 0.36 g of RuO₂·xH₂O. The flask was closed air-tight, and the reaction
mixture was stirred at rt until completion (45 min, according to GC). After dropwise
addition of 20 mL of isopropanol, the mixture was stirred for an additional 30 min.
Then 200 mL of saturated aqueous Na₂S₂O₃ and 300 mL of CH₂Cl₂ were added. The
mixture was stirred for 10 min and filtered. The two-phase filtrate was separated,
and the aqueous layer was extracted with three portions of CH₂Cl₂. The combined
organic layers were washed with brine, dried, and evaporated. The remaining
residue was column chromatographed on silica gel (70–230 mesh, 2:1 petroleum
ether (bp 40–60 °C)/EtOAc) to give 63.2 g (95%) of 3 as white crystals. Physical and
spectroscopic data were consistent with those reported in the literature.¹⁶

[2S-(2R*,6R*,9S*)]-2,6-Dimethyl-9-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1,5-cyclo-
decane dione (7). To a stirred solution of 38.3 g (0.151 mol) of 3 and 35.0 g (0.515 mol)
of imidazole in 300 mL of DMF was added 27.8 mL (0.166 mol) of TESCl. After
stirring at rt for 4.5 h, the reaction mixture was poured into an ice-cooled mixture of
saturated aqueous NaHCO₃ and petroleum ether (bp 40–60 °C). The two-phase
mixture was separated, and the aqueous layer was extracted with four portions of
petroleum ether (bp 40–60 °C). The combined organic layers were washed with brine
and dried. Evaporation gave 53.3 g of crude 7 which, according to NMR, contained
some residual triethylsilanol. A sample (5.96 g) of crude 7 was purified by flash
chromatography (20:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 5.72 g (92%) of 7
as a colorless oil: [α]D −13.2° (c 1.67); ¹H NMR δ 0.61 (q, J = 8.0 Hz, 6 H), 0.98 (t, J = 8.0
Hz, 9 H), 1.06 (d, J = 5.9 Hz, 3 H), 1.07 (d, J = 6.8 Hz, 3 H), 1.07 (s, 3 H), 1.28 (s, 3 H),
1.48–2.02 (m, 8 H), 2.09 (m, 1 H), 2.38 (m, 1 H), 2.67 (m, 1 H), 2.93–3.12 (m, 2 H); ¹³C
NMR δ 6.48 (3 t), 6.87 (3 q), 17.66 (q), 19.23 (q), 24.90 (q), 26.84 (t), 28.39 (q), 29.79 (t),
30.50 (t), 33.91 (t), 40.78 (d), 45.11 (t), 45.11 (d), 50.05 (d), 75.35 (s), 216.60 (s), 218.48 (s);
mass spectrum, m/z (relative intensity) 339 (M⁺–29, 14), 321 (3), 263 (4), 219 (7), 218
(6), 173 (100), 116 (26), 104 (13), 88 (11), 76 (13); HRMS calcd for C₁₉H₃₅O₃Si (M⁺–29)
m/z 339.2355, found m/z 339.2355.
[2S-(2α,4αα,5α,8α,8αα)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-[1-methyl-1-[(triethylsilyloxy)ethyl]-1(2H)-naphthalenone (8) and [4S-(4α,4αα,6α,8αα)]-Octahydro-4a-hydroxy-4,8a-dimethyl-6-[1-methyl-1-[(triethylsilyloxy)ethyl]-1(2H)-naphthalenone (9). To a stirred solution of 49.3 g (ca 0.13 mol) of crude 7 in 200 mL of EtOH was added a solution of 3.0 g (53 mmol) of KOH in 50 mL of EtOH. The reaction mixture was stirred at rt for 1.5 h, and then 35 mL of saturated aqueous NH₄Cl was added. After dilution with H₂O, the reaction mixture was extracted with five portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Crystallization of the resulting residue from diisopropyl ether and careful chromatography of the mother liquor (3:1 petroleum ether (bp 40–60 °C)/Et₂O) gave 14.0 g (30%) of pure 8, 3.5 g of a mixture of 8 and 9, and 26.0 g (55%) of pure 9. 8: mp 106-107 °C (from diisopropyl ether); [α]D +54.4° (c 1.21); 1H NMR (main peaks) δ 0.57 (q, J = 7.7 Hz, 6 H), 0.89 (t, J = 7.7 Hz, 9 H), 0.93 (d, J = 7.1 Hz, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 1.18 (s, 6 H); 13C NMR (main peaks) δ 6.25 (3 t), 6.83 (3 q), 13.24 (q), 21.82 (t), 28.36 (t), 28.81 (q), 31.65 (t), 214.96 (s); mass spectrum, m/z (relative intensity) 339 (M⁺–29, 12), 321 (12), 310 (9), 263 (6), 229 (29), 173 (100), 116 (27), 104 (15), 88 (15), 76 (15); HRMS calcd for C₁₉H₃₅O₃Si (M⁺–29) m/z 339.2355, found m/z 339.2354. Anal. Calcd for C₂₁H₄₀O₃Si: C, 68.44; H, 10.94. Found: C, 68.66; H, 11.11. 9: mp 71 °C (from diisopropyl ether); [α]D –62.1° (c 1.77); 1H NMR δ 0.59 (q, J = 7.8 Hz, 6 H), 0.95 (d, J = 5.4 Hz, 3 H), 0.96 (t, J = 7.8 Hz, 9 H), 1.17 (s, 3 H), 1.19 (s, 3 H), 1.21 (s, 3 H), 1.28–2.08 (m, 10 H), 2.26–2.54 (m, 2 H), 2.67 (m, 1 H); 13C NMR δ 6.57 (3 t), 6.91 (3 q), 14.13 (q), 14.51 (q), 21.17 (t), 27.01 (q), 27.62 (q), 28.78 (t), 31.94 (d), 32.80 (t), 34.04 (t), 37.37 (t), 46.00 (d), 53.72 (s), 74.27 (s), 78.83 (s), 215.85 (s); mass spectrum, m/z (relative intensity) 310 (M⁺–58, 4), 292 (7), 174 (17), 173 (100), 169 (6), 116 (17), 104 (7), 88 (7), 76 (9); HRMS calcd for C₁₉H₃₅O₃Si (M⁺–29) m/z 339.2355, found m/z 339.2354. Anal. Calcd for C₂₁H₄₀O₃Si: C, 68.44; H, 10.94. Found: C, 68.59; H, 11.16.

[2S-(2α,4αα,5α,8α,8αα)]-Octahydro-4a-hydroxy-8-(1-hydroxy-1-methylethyl)-2,5-dimethyl-1(2H)-naphthalenone (5). To a solution of 0.40 g (1.08 mmol) of 8 in 5 mL of MeCN was added 0.13 mL of 40% aqueous HF. The reaction mixture was stirred at rt for 15 min and then poured into saturated aqueous NaHCO₃. After extraction of the aqueous layer with four portions of EtOAc, the combined organic layers were dried and evaporated. Crystallization of the resulting residue from acetone gave 0.248 g (90%) of 5: mp 224–225 °C (lit.18: 223–225 °C); [α]D +48.9° (c 1.59, MeOH) (lit.18: +50°, MeOH); HRMS calcd for C₁₅H₂₄O₂ (M⁺–18) m/z 236.1776, found m/z 236.1777. Anal. Calcd for C₁₅H₂₆O₃: C, 70.83; H, 10.30. Found: C, 70.71; H, 10.37. The 1H- and 13C NMR spectra of 5 revealed the presence of 5a in about 80%. 5: 1H NMR (main peaks) δ 2.96 (m, 1 H); 13C NMR (main peaks) δ 13.03, 21.57, 23.55, 30.24, 32.41, 38.20, 40.63, 49.93, 56.84, 78.78. 5a: 1H NMR (main peaks) δ 0.97 (d, J = 6.4 Hz, 3 H), 1.03 (d, J = 7.0
[4S-(4α,4α,6α,8α)]-Octahydro-4a-hydroxy-6-(1-hydroxy-1-methylethyl)-4,8a-dimethyl-1(2H)-naphthalenone (6). A sample (0.307 g, 0.83 mmol) of 9 was desilylated with HF as described above. Workup and flash chromatography (2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.193 g (91%) of 6: mp 111 °C (from diisopropyl ether); [α]D −80.6° (c 2.10); 1H NMR δ 0.96 (d, J = 6.7 Hz, 3 H), 1.18 (s, 3 H), 1.22 (s, 6 H), 1.25–2.10 (m, 11 H), 2.30 (dd, J = 2.2, 4.4, 15.1 Hz, 1 H), 2.45 (m, 1 H), 2.68 (dd, J = 7.1, 13.9, 15.1 Hz, 1 H); 13C NMR δ 14.21 (q), 14.64 (q), 21.27 (t), 26.62 (q), 26.97 (q), 28.73 (t), 31.94 (d), 32.85 (t), 33.90 (t), 37.39 (t), 44.71 (d), 53.67 (s), 71.94 (s), 77.97 (s), 215.90 (s); mass spectrum, m/z (relative intensity) 254 (M+, 9), 236 (50), 178 (44), 153 (69), 141 (63), 137 (55), 70 (62), 60 (62), 43 (50), 28 (100); HRMS calcld for C15H26O3 (M+) m/z 254.1882, found m/z 254.1882. Anal. Calcld for C15H26O3: C, 70.83; H, 10.30. Found: C, 70.99; H, 10.56.

[2aR-(2α,5β,5aβ,8β,8aβ,8bβ)]-Octahydro-8a-methoxy-2,2,5,8-tetramethyl-2H-naphtho[1,8-bc]furan-5a(3H)-ol (10). To a stirred solution of 0.50 g (1.36 mmol) of 8 in 5 mL of MeOH was added a catalytic amount of p-TsOH. After stirring at rt for 10 min, water was added to the reaction mixture followed by extraction with three portions of EtOAc. The combined organic layers were washed with brine and dried. Evaporation gave 0.357 g (98%) of 10: mp 96–98 °C (from diisopropyl ether); [α]D +43.0° (c 1.37); 1H NMR δ 0.87 (d, J = 6.3 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 1.12 (s, 3 H), 1.15–1.97 (m, 11 H), 1.20 (s, 3 H), 2.23 (s, OH), 2.28 (d, J = 13.8 Hz, 1 H), 3.25 (s, 3 H); 13C NMR δ 12.89 (q), 14.16 (q), 20.25 (t), 23.71 (t), 27.21 (q), 29.03 (q), 31.14 (t), 33.04 (t), 37.65 (d), 38.90 (d), 41.63 (d), 48.24 (q), 48.98 (d), 73.59 (s), 80.08 (s), 106.79 (s); mass spectrum, m/z (relative intensity) 268 (M+, 35), 250 (18), 236 (88), 218 (100), 203 (29), 186 (41), 149 (60), 142 (43); HRMS calcld for C16H28O3 (M+) m/z 268.2038, found m/z 268.2038. Anal. Calcld for C16H28O3: C, 71.60; H, 10.52. Found: C, 71.79; H, 10.75.

[2R-(2α,4α,8α,8aα)]-Decahydro-8a-hydroxy-α,α,4a,8-tetramethyl-2-naphthalenemethanol (11). To a stirred solution of 0.307 g (0.83 mmol) of 9 in 3 mL of dry MeOH was added 0.174 g (0.94 mmol) of p-toluenesulfonylhydrazide. The reaction mixture was refluxed for 45 min and then cooled to rt. After the addition of 5 mL of dry MeOH, 0.065 g (1.03 mmol) of NaBH₃CN, and a solution of 0.085 g (0.63 mmol) of
anhydrous ZnCl₂ in 15 mL of dry MeOH, the mixture was refluxed for another 2 h. The reaction mixture was allowed to come to rt, poured into 0.5% aqueous NaOH, and extracted with four portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (2:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.097 g (49%) of 11: [α]D +37.0° (c 1.15) (lit: 21: 37.4°, CHCl₃); ¹H NMR δ 0.88 (d, J = 6.8 Hz, 3 H), 1.00 (s, 3 H), 1.10–1.83 (m, 14 H), 1.22 (s, 6 H), 1.93–2.14 (m, 2 H); ¹³C NMR δ 14.69 (q), 21.09 (t), 22.01 (t), 22.51 (q), 26.65 (q), 26.86 (q), 30.30 (t), 31.93 (t), 32.23 (d), 32.76 (t), 36.05 (t), 37.40 (s), 45.03 (d), 72.28 (s), 74.94 (s); mass spectrum, m/z (relative intensity) 240 (M⁺, 2), 222 (19), 207 (22), 202 (52), 181 (30), 173 (50), 149 (37), 126 (100), 113 (59); HRMS calcd for C₁₅H₂₈O₂ (M⁺) m/z 240.2089, found m/z 240.2088.

[2S-(2α,5α,8α,8αax)]-3,5,6,7,8,8a-Hexahydro-2,5-dimethyl-8-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1(2H)-naphthalene (12) and (6R-cis)-3,5,6,7,8,8a-hexahydro-4,8a-dimethyl-6-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1(2H)-naphthalene (13). To a stirred solution of 10.5 g (28.5 mmol) of 9 in 100 mL of pyridine was added 2.3 mL (31.4 mmol) of SOCl₂ at −10 °C. After stirring for 15 min, the reaction mixture was poured into ice-water and extracted with four portions of petroleum ether (bp 40–60 °C). The combined organic layers were washed with brine, dried, and evaporated. After removal of the residual pyridine by azeotropic distillation with toluene, 9.7 g of crude 13 was obtained as a yellow oil. This crude 13 could be used in the next reactions without further purification. A sample (0.527 g) of crude 13 was flash chromatographed (30:1 petroleum ether (bp 40–60 °C)/Et₂O) to give 0.515 g (95%) of pure 13: [α]D −7.5° (c 1.26); ¹H NMR δ 0.61 (q, J = 7.6 Hz, 6 H), 1.00 (t, J = 7.6 Hz, 9 H), 1.10–1.57 (m, 3 H), 1.22 (s, 3 H), 1.25 (s, 6 H), 1.64–1.96 (m, 3 H), 1.73 (br s, 3 H), 2.27–2.77 (m, 5 H); ¹³C NMR δ 6.65 (3 t), 6.94 (3 q), 18.61 (q), 21.82 (q), 22.31 (t), 26.29 (t), 26.66 (q), 27.94 (q), 31.97 (t), 34.85 (t), 35.96 (t), 47.08 (s), 50.49 (d), 74.65 (s), 123.59 (s), 134.78 (s), 216.25 (s); mass spectrum, m/z (relative intensity) 321 (M⁺–29, 3), 219 (13), 218 (69), 201 (8), 174 (17), 173 (100), 159 (31), 145 (19), 116 (34); HRMS calcd for C₂₀H₃₅O₂Si (M⁺−15) m/z 335.2406, found m/z 335.2405.

In a similar way, a crude mixture of 8 and 9, obtained from treatment of 0.939 g (2.55 mmol) of 7 with KOH in EtOH, gave an easily separable mixture of 12 and 13. Flash chromatography (30:1 petroleum ether (bp 40–60 °C)/Et₂O) afforded 0.254 g of 12²⁵ and 0.470 g (44% overall from 7) of 13. ¹H NMR δ 0.58 (q, J = 7.5 Hz, 6 H), 0.91 (t, J = 7.5 Hz, 9 H), 0.99 (d, J = 7.1 Hz, 3 H), 1.07 (d, J = 6.0 Hz, 3 H), 1.17 (s, 6 H), 1.20–2.10 (m, 5 H), 2.30–2.60 (m, 3 H), 2.88 (br d, J = 13.8 Hz, 1 H), 2.97 (m, 1 H), 5.38 (br d, J = 5.2 Hz, 1 H); ¹³C NMR δ 6.46 (3 t), 6.92 (3 q), 13.78 (q), 17.66 (q), 22.78 (t), 26.26 (q), 27.16 (q), 33.28 (t), 37.10 (d), 37.28 (t), 39.10 (d), 51.37 (d), 57.61 (d), 75.65 (s), 116.94 (d),
chapter 3

145.61 (s), 215.40 (s); mass spectrum, m/z (relative intensity) 321 (M+–29, 32), 292 (35), 263 (42), 218 (53), 174 (47), 173 (100), 159 (37), 116 (74), 104 (81); HRMS calcd for C_{19}H_{33}O_{2}Si (M+–29) m/z 321.2249, found m/z 321.2248.

(+)-γ-Eudesmol (14). This compound was prepared from 13 (0.15 g, 0.43 mmol) as described for the synthesis of 11. The workup and flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.038 g (40%) of 14: [α]_{D}^{20} +91.5° (c 1.55, CHCl_{3}) (lit.20 +66.7°, neat). The spectroscopic data of 14 were consistent with those reported in the literature.26

[1S-(1α,6β,8aβ)]- and [1R-(1α,6α,8aα)]-1,2,3,5,6,7,8,8a-Octahydro-4,8a-dimethyl-6-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1-naphthalenol (15 and 16). To a stirred solution of 3.01 g (8.60 mmol) of 13 in 20 mL of EtOH was added 0.36 g (9.40 mmol) of NaBH_{4} at 0 °C. After stirring at rt for 1 h, ice-water was added to the reaction mixture followed by extraction with four portions of EtOAc. The combined organic layers were washed successively with 0.01 M aqueous HCl, saturated aqueous NaHCO_{3}, and brine. After drying and evaporation, the remaining residue was flash chromatographed (15:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.515 g (17%) of 15 and 2.21 g (73%) of 16, both as colorless oils. 15: [α]_{D} +57.0° (c 1.95); 1H NMR δ 0.61 (q, J = 8.0 Hz, 6 H), 0.99 (t, J = 8.0 Hz, 9 H), 1.08 (s, 3 H), 1.10–2.30 (m, 11 H), 1.21 (s, 3 H), 1.23 (s, 3 H), 1.66 (br s, 3 H), 2.72 (dt, J = 1.4, 13.9 Hz, 1 H), 3.52 (m, W_{1/2} = 12.5 Hz, 1 H); 13C NMR δ 6.67 (3 t), 6.94 (3 q), 18.84 (q), 22.51 (t), 24.24 (q), 25.48 (t), 26.13 (t), 26.77 (q), 27.81 (t), 27.82 (q), 33.16 (t), 39.01 (s), 50.70 (d), 74.73 (d), 74.73 (s), 122.84 (s), 133.07 (s); mass spectrum, m/z (relative intensity) 305 (9), 220 (41), 202 (53), 187 (24), 173 (100), 159 (47), 145 (20), 116 (35), 77 (24); HRMS calcd for C_{20}H_{37}O_{2}Si (M+–15) m/z 337.2563, found m/z 337.2563. 16: [α]_{D} +51.6° (c 1.36); 1H NMR δ 0.62 (q, J = 8.1 Hz, 6 H), 1.00 (t, J = 8.1 Hz, 9 H), 1.04 (s, 3 H), 1.05–2.30 (m, 11 H), 1.22 (s, 3 H), 1.24 (s, 3 H), 1.63 (br s, 3 H), 2.69 (dt, J = 2.0, 13.6 Hz, 1 H), 3.49 (t, J = 7.5 Hz, 1 H); 13C NMR δ 6.67 (3 t), 6.94 (3 q), 17.02 (q), 18.67 (q), 22.65 (t), 26.15 (t), 26.69 (q), 26.90 (q), 27.85 (q), 31.71 (t), 38.77 (t), 39.26 (s), 50.48 (d), 74.83 (s), 78.20 (d), 123.12 (s), 134.09 (s); mass spectrum, m/z (relative intensity) 231 (4), 220 (75), 219 (28), 202 (19), 173 (100), 116 (30), 69 (53); HRMS calcd for C_{21}H_{38}OSi (M+–18) m/z 334.2691, found m/z 334.2692.

(+)-4-Eudesmene-1β,11-diol (17). To a stirred solution of 0.294 g (0.84 mmol) of 16 in 4 mL of MeCN at rt was added 4 drops of 40% aqueous HF. After 1 h stirring, water was added and the mixture was extracted with EtOAc, washed with brine and dried. The crude product was crystallized in diisopropyl ether to afford 0.172 g (87%) of 17: mp: 135 °C (lit.21b 136–137 °C). The spectral data of 17 corresponded with those reported in the literature.21a,b
[1R-(1α,6α,8αα)]-1,2,3,5,6,7,8,8a-Octahydro-4,8a-dimethyl-6-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1-naphthalenol methanesulfonate (18). To a stirred solution of 1.70 g (4.83 mmol) of 16 in 15 mL of pyridine was added 0.5 mL (6.41 mmol) of MsCl at 0 °C. After stirring at rt for 1.5 h, 20 mL of saturated aqueous NaHCO₃ was added. The reaction mixture was stirred for an additional 5 min, and then extracted with four portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. After removal of the residual pyridine by azeotropic distillation with toluene, 2.06 g of crude 18 was obtained which could be used in the next step without further purification. A sample (0.539 g) of crude 18 was flash chromatographed (10:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.496 g (91%) of pure 18: [α]D +57.2° (c 1.73); ¹H NMR δ 0.60 (q, J = 8.0 Hz, 6 H), 0.98 (t, J = 8.0 Hz, 9 H), 1.05–2.35 (m, 10 H), 1.10 (s, 3 H), 1.22 (s, 3 H), 1.26 (s, 3 H), 1.62 (br s, 3 H), 2.68 (dt, J = 2.4, 14.0 Hz, 1 H), 3.04 (s, 3 H), 4.56 (t, J = 7.8 Hz, 1 H); ¹³C NMR δ 6.65 (3 t), 6.92 (3 q), 17.94 (q), 18.49 (q), 22.39 (t), 25.10 (t), 26.05 (t), 26.69 (q), 27.77 (q), 31.28 (t), 38.41 (q), 38.71 (t), 38.71 (s), 50.23 (d), 74.65 (s), 89.73 (d), 123.28 (s), 133.44 (s); mass spectrum, m/z (relative intensity) 334 (M⁺–96, 4), 305 (6), 202 (80), 187 (26), 174 (100), 159 (58), 116 (39), 104 (34); HRMS calcd for C₂₁H₃₈OSi (M⁺–96) m/z 334.2691, found m/z 334.2692.

[2R-(2α,4αα,5α)]-1,2,3,4,4a,5,6,7-Octahydro-α,α,4a,8-tetramethyl-5-[(methylsulfonyl)oxy]-2-naphthalenemethanol (2). To a stirred solution of 1.72 g (ca 3.7 mmol) of the crude 18 in 10 mL of MeCN was added 0.67 mL of 40% aqueous HF over 0.5 h. After stirring for 1 h at rt, water was added and the mixture was extracted four times with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The crude oil was purified by flash chromatography (3:2 petroleum ether (bp 40–60 °C)/EtOAc) to give 1.142 g (98%) of 2 as pale yellow crystals: mp 82 °C (from diisopropyl ether); [α]D +80.5° (c 1.25); ¹H NMR δ 1.11 (s, 3 H), 1.23 (s, 6 H), 1.63 (br s, 3 H), 1.10–1.87 (m, 6 H), 1.95–2.35 (m, 6 H), 2.68 (br d, J = 13.6 Hz, 1 H), 3.05 (s, 3 H), 4.56 (t, J = 7.7 Hz, 1 H); ¹³C NMR δ 18.01 (q), 18.59 (q), 22.42 (t), 25.03 (t), 26.14 (t), 26.36 (q), 27.09 (q), 31.25 (t), 38.52 (q), 38.52 (t), 38.52 (s), 49.24 (d), 72.32 (s), 89.55 (d), 123.81 (s), 132.76 (s); mass spectrum, m/z (relative intensity) 298 (8), 220 (27), 202 (47), 187 (41), 159 (100), 145 (25), 131 (34), 106 (25), 60 (25); HRMS calcd for C₁₆H₂₈O₄S (M⁺) m/z 316.1707, found m/z 316.1707. Anal. Calcd for C₁₆H₂₈O₄S: C, 60.73; H, 8.92. Found: C, 60.49; H, 9.12.

(+) Hedycaryol (1). To a stirred solution of 0.946 g (2.99 mmol) of 2 in 10 mL of dry THF was added dropwise 18 mL of BH₃·THF (1 M in THF) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and additionally at rt for 2 h. The reaction mixture was then cooled to 0 °C, after which 3 mL of MeOH was added dropwise,
immediately followed by dropwise addition of 40 mL of NaOMe (2 M in MeOH). The reaction mixture was allowed to come to rt and stirred overnight. After addition of a mixture of 40 mL of saturated aqueous NH₄Cl and 10 mL of 25% aqueous NH₃ to the cooled reaction mixture, 100 mL of petroleum ether (bp 40–60 °C) was added. Stirring was continued for an additional 30 min after which the mixture was extracted with four portions of petroleum ether (bp 40–60 °C). The combined organic layers were washed with brine and dried (Na₂SO₄). Evaporation afforded a pale yellow oil which was dissolved in a mixture of 30 ml of hexane and 10 mL of t-butyl methyl ether. This solution was extracted with four portions of 20% aqueous AgNO₃. The combined aqueous layers were washed with one portion of t-butyl methyl ether and then cooled on an ice-bath. After addition of 70 mL of 25% aqueous NH₃, the aqueous layer was extracted with four portions of t-butyl methyl ether. The combined organic layers were washed with brine and dried (Na₂SO₄). Evaporation gave 0.365 g (55%) of pure 1: [α]D +24.2° (c 2.57) (lit.¹: +24.5°); FT IR (film) 3404, 2969, 2928, 2853, 1656, 1449, 1383, 1366, 1127, 845 cm⁻¹; The ¹H NMR and the mass spectral data corresponded with those reported in the literature.⁶a

3.4 References and Notes

* This chapter has been published in a revised form: Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. Tetrahedron 1994, 50, 4755.
21. (a) Su, W. -C.; Fang, J. -M.; Cheng, Y. -S. Phytochemistry 1995, 39, 603. By cleavage of the triethylsilyl ether bond with HF, 13 and 15 were converted into the corresponding known unnatural C(1) oxidized γ-eudesmols. The 1H NMR and the mass spectral data were consistent with those reported in the literature. See: (b) Itokawa, H.; Nakanishi, H.; Mihashi, S. Chem. Pharm. Bull. 1983, 31, 1991. 1-oxo-γ-eudesmol: mp 77-78 °C (from diisopropyl ether) (lit. 78-80 °C); [α]D +3.6° (c 2.00) (lit. +4.0°); 13C NMR δ 18.64 (q), 21.90 (q), 22.34 (t), 26.37 (q), 26.37 (t), 27.09 (q), 31.89 (t), 34.66 (t), 35.84 (t), 46.94 (s), 49.45 (d), 72.17 (s), 124.04 (s), 134.09 (s), 216.02 (s). 1α-hydroxy-γ-eudesmol: [α]D +81.2° (c 2.47) (lit. +77.3°); 13C NMR δ 18.86 (q), 22.50 (t), 24.22 (q), 25.40 (t), 26.26 (t), 26.37 (q), 26.75 (q), 27.80 (t), 32.99 (t), 38.94 (s), 49.72 (d), 72.73 (s), 74.57 (d), 123.33 (s), 132.40 (s).
23. Guaiac wood oil was obtained from Quest International, Naarden, The Netherlands.
24. In the NMR spectra of this compound strong coalescence was observed due to conformational flexibility.
25. This compound was contaminated with traces of a double bond isomer.
Abstract: the enantiomer of (+)-allohedcaryol (1), a germacrane alcohol isolated from giant fennel \textit{(Ferula communis} L.), has been synthesized, thereby elucidating the relative and absolute stereochemistry of the natural product. The synthesis of (−)-allohedcaryol started from (+)-α-cyperone (5) which was available in relatively large quantities via alkylation of the imine derived from (+)-dihydrocarvone and (R)-(−)-1-phenylethylamine. In a number of steps 5 was converted into mesylate 4 with a regio- and stereoselective epoxidation as the key step. A Marshall fragmentation of 4 was used to prepare the \((E,E)\)-cyclodeca-1(10),5-diene ring present in allohedcaryol (1). The conformation of synthetic (−)-1 was elucidated via photochemical conversion into a bourbonane system. The synthesis of (−)-allohedcaryol also showed that natural (+)-allohedcaryol has the opposite absolute stereochemistry to that normally found in higher plants.
4.1 Introduction

Through the ages, plant species belonging to the genus *Ferula* (Umbelliferae) have been used in folk medicine and are now known as rich sources of secondary metabolites. A long list of sesquiterpene alcohols and lactones as well as coumarines has been reported. Recently, a new main component has been isolated from the essential oil obtained from the roots of *F. communis* L. (giant fennel, Dutch: reuzenvenkel), a plant toxic to livestock and widespread in the Mediterranean area. The compound was originally thought to be a bisabolane sesquiterpene alcohol but through synthesis of this alcohol, it turned out that the proposed bisabolane structure was incorrect. Then the germacrane structure 1 with unknown relative and absolute stereochemistry was assigned to this new natural product (Scheme 4.1). Being a double bond regioisomer of the germacrane alcohol (+)-hedycaryl (2), the name allohedycaryl was proposed for 1.

![Scheme 4.1](image)

Germacrane sesquiterpenes, structurally characterized by an (E,E)-cyclodeca-1(10),4-diene ring system, are widespread in nature (§ 1.1). Allogermacranes, in which an (E,E)-cyclodeca-1(10),5-diene ring system is present, are not very abundant in nature and may play a different role in the biosynthesis of sesquiterpenes. Since the (E,E)-cyclodeca-1(10),5-diene unit is known to undergo a smooth photochemical [2+2] cycloaddition, allogermacranes are the most likely precursors of bourbonanes, a small class of sesquiterpenes possessing the cyclobuta[1,2;3,4]dicyclopentene skeleton 3. In contrast to the synthesis of (E,E)-germacrane sesquiterpenes and their double bond stereoisomers, little attention has been paid to the synthesis of the regioisomeric allogermacranes (Chapter 2).

Because of our interest in the synthesis of germacrane, and because the relative and absolute stereochemistry of allohedycaryl was unsettled, we decided to investigate its enantiospecific synthesis following the strategy outlined in Scheme...
4.2. The key step in this approach is the conversion of mesylate \textbf{4} into allohedycaryl by means of a Marshall fragmentation reaction in which both double bonds are regio- and stereospecifically formed.\textsuperscript{12} The synthesis of \textbf{4} in turn was planned starting from (+)-\(\alpha\)-cyperone (\textbf{5}) via a number of conversions with the introduction of an equatorial hydroxyl group at C(1)\textsuperscript{13} as the most challenging step. An easy access to (+)-\(\alpha\)-cyperone was therefore needed and a simple procedure for the synthesis of \textbf{5} starting from (+)-dihydrocarvone (\textbf{6}) was developed.

\begin{center}
\textbf{Scheme 4.2}
\end{center}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {allohedycaryl};
\node (B) at (2,0) {\(\text{MsO}\)};
\node (C) at (2,-1) {4};
\node (D) at (4,-1) {\textbf{5}};
\node (E) at (6,-1) {\textbf{6}};
\node (F) at (2,-2) {OH};
\draw[->] (A) -- (B);
\draw[->] (B) -- (C);
\draw[->] (C) -- (D);
\draw[->] (D) -- (E);
\end{tikzpicture}
\end{center}

Since the absolute and relative stereochemistry of natural allohedycaryl was unknown, we realized that the synthetic route depicted in Scheme 4.2 might lead to the formation of the enantiomer or, at worst, to the formation of a diastereomer of allohedycaryl. We have opted for an equatorial Me group at C(4) and the absolute stereochemistry around C(7) as present in (+)-hedycaryl (2). This absolute stereochemistry is normally found in higher plants (vide infra).

\subsection*{4.2 Results and Discussion}

(+)-\(\alpha\)-Cyperone (\textbf{5})\textsuperscript{14} has been widely used as a starting material for the synthesis of various other fused-ring sesquiterpenes.\textsuperscript{15} Whereas (−)-10-epi-\(\alpha\)-cyperone can be easily synthesized from (+)-dihydrocarvone,\textsuperscript{16} the synthetic methods leading to \textbf{5} are either rather laborious or give low yields.\textsuperscript{17} Because relatively large quantities of \textbf{5} were needed for our study, we were looking for a more efficient method for the preparation of this compound.

Recently, an improved synthesis of enantiomerically pure naphthalenones was reported.\textsuperscript{18} The key step in this synthesis was based on the deracemizing alkylation of enantiomerically pure imines derived from racemic cyclanones.\textsuperscript{19} In addition, it was shown that in the alkylation of imine \textbf{7} derived from \textbf{6} with methyl vinyl ketone (MVK) the inherent preference for axial alkylation\textsuperscript{15a} was largely overruled by the chiral induction of the imine substituent. We realized that this method could
also be used for a short and efficient synthesis of (+)-α-cyperone, simply by replacing MVK by ethyl vinyl ketone (EVK). The synthesis of 5 started with the azeotropic imination of 6 and (R)-(+)1-phenylethylamine (8), both commercially available, to afford the imine 7 (Scheme 4.3). The alkylation of 7 was performed in THF at 40 °C with a slight excess EVK. After hydrolysis of the imine, the product was dissolved in MeOH and treated with NaOMe at room temperature to give an easily separable mixture of 5 and the ketol 9 in a ratio of ca 5:1, respectively. Flash chromatography afforded pure 5 in 47% overall yield from (+)-dihydrocarvone.

Scheme 4.3

With easy access to 5, we could start with our synthetic route towards allohedycaryol (Scheme 4.4). Dehydrogenation of 5 with DDQ in dry dioxane afforded (−)-1,2-dehydro-α-cyperone (10) in good yield. Selective epoxidation of the isopropenyl side-chain in 10 produced 11 as a 1:1 mixture of diastereomers. Treatment of 11 with KOT-Bu in dry DMSO and quenching of the resulting enolate with aqueous NH₄Cl gave an unstable deconjugated ketone which was directly reduced with NaBH₄ in the presence of CaCl₂ to afford the stable allylic alcohol 12. In the ¹H NMR spectrum of 12, also a 1:1 diastereomeric mixture, the coupling constant between α H-3 and β H-4 (J₃,₄) was found to be 8.8 Hz, which indicates that the Me group at C(4) and the hydroxyl group at C(3) possess an equatorial α and β orientation, respectively. Together with the other NMR data, this observation unequivocally establishes the identity of 12.
In order to achieve an oxygen function at C(1), some allylic rearrangement experiments\textsuperscript{23,24} were performed with 12, but the results were poor. We therefore focused our attention on the stereoselective Sharpless epoxidation of the C(1)–C(2) double bond in 12. It was found in the literature\textsuperscript{25} that treatment of a β-allylic alcohol structurally related to 12 with t-BuOOH catalyzed by vanadyl acetylacetonate (VO(acac))\textsubscript{2} resulted in the formation of the corresponding β cis-epoxy alcohol in reasonable yield. With 12, however, the t-BuOOH/VO(acac)\textsubscript{2} reaction only showed oxidation to the corresponding enone.\textsuperscript{26} Apparently, the equatorial β hydroxyl group in 12 is not properly positioned for assistance in the epoxidation reaction and oxidation of the alcohol function will be preferred.\textsuperscript{27}

Another possibility for introducing a hydroxyl function at C(1) involves the stereospecific [2,3] sigmatropic rearrangement of secondary allylic selenoxides.\textsuperscript{28} To determine the applicability of the above [2,3] sigmatropic rearrangement to the 3β-allylic alcohol system in 12, the epoxide ring in the side-chain had to be reduced first\textsuperscript{29} (Scheme 4.5). In the \textsuperscript{1}H NMR spectrum of the resulting diol 13, \textit{J}_{3,4} was found to be 8.5 Hz which confirmed the equatorial α orientation of the Me group at C(4).\textsuperscript{23} Treatment of diol 13 with \textit{o}-nitrophenyl selenocyanate in the presence of tri-\textit{n}-butylphosphine afforded the α selenide 14 in 91% yield. Oxidation of 14 with H\textsubscript{2}O\textsubscript{2} in the presence of pyridine at \textdegree C proceeded smoothly, but gave, in addition to the expected rearrangement, also α epoxidation of the C(5)–C(6) double bond\textsuperscript{30} to give 15 as the sole product in 86% yield.\textsuperscript{31}

Because none of the above approaches yielded a workable result, we were forced to develop an alternative route for the conversion of 12 into the mesylate 4. From examination of molecular models, it appeared that the C(5)–C(6) double bond in 12 is sterically more shielded than the C(1)–C(2) double bond. It was therefore expected that the selective epoxidation of the C(1)–C(2) double bond without participation of the hydroxyl group at C(3) would be possible. Based on these considerations, a synthetic pathway was devised in which the hydroxyl group at C(3) of 12 was removed prior to the epoxidation of the C(1)–C(2) double bond.
Because reduction of the mesylate ester of 12 only gave elimination products, the removal of the C(3) hydroxyl group of 12 was performed via reduction of its phosphordiamidate with Li in EtNH₂. This reaction proceeded smoothly and was attended with reductive opening of the epoxide ring in the side-chain to provide the diene 16 in about 60% overall yield from 12 (Scheme 4.6).

At this stage, we had to introduce an epoxide ring at the sterically less favored β side of the C(1)–C(2) double bond. For this purpose, we chose a strategy based on the trans-diaxial bromohydrin formation. Treatment of 16 with N-bromosuccinimide (NBS) in aqueous dioxane followed by ring closure with methanolic KOH afforded the β epoxide 17 as the sole product in 61% yield. As expected (vide supra), epoxidation of the C(5)–C(6) double bond did not take place.
The regioselective opening of the epoxide ring in 17 was the next step. Normally, nucleophilic attack on an epoxide ring gives rise to diaxial ring opening,\textsuperscript{34} but in case of the \( \beta \) epoxide 17 it was found that the diequatorial ring opening prevailed when sodium phenylselenide was used as the nucleophile.\textsuperscript{35} After reductive cleavage of the Se–C(2) bond with Raney nickel, the resulting \( \beta \) C(1)-alcohol 18 was treated with MsCl in pyridine to afford the desired mesylate 4 in 92% overall yield from 17. In the \(^1\text{H}\) NMR spectrum of 4 a one-proton doublet (\( J = 11.0, 5.3 \text{ Hz} \)) appears at \( \delta 4.29 \), which is consistent with the presence of an equatorial mesylate group at C(1).

Completion of the synthesis of allohedycaryol was accomplished by successive treatment of 4 with excess fresh BH\(_3\)-THF and NaOMe in MeOH. After purification by aqueous AgNO\(_3\) extraction,\textsuperscript{36} allohedycaryol was obtained as a colorless oil in 68% yield. The synthetic material was spectroscopically identical to the natural product isolated from \( F. \) communis.\textsuperscript{37} However, the specific rotation obtained for our synthetic product \((\alpha)_D – 192^\circ\) was opposite to that \((\alpha)_D +181^\circ\) reported for natural allohedycaryol,\textsuperscript{3} which meant that we had synthesized the antipode of the natural product as structure \((-\)-1 illustrates (Scheme 4.7). Consequently, structure \((+)-1\) represents the relative and absolute configuration of natural allohedycaryol. This also means that natural \((+)-1\) possesses the \textit{ent}-configuration,\textsuperscript{38} which is remarkable because \textit{ent}-sesquiterpenes are rarely found in higher plants.\textsuperscript{39} In addition, the possibility that \((+)-\)hedycaryol (2) acts as a direct precursor of \((+)-1\) can be ruled out.\textsuperscript{40}

\textbf{Scheme 4.7}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_4.7}
\end{center}

The conformation of allohedycaryol was also investigated. It has been demonstrated\textsuperscript{41} that an \( (E,E)\)-cyclodec-1,6-diene ring preferably adopts an "elongated chair" conformation. This is not surprising because such a conformation is essentially Pitzer-strain free and all the Van der Waals radii are respected.\textsuperscript{42} \( (E,E)\)-Cyclodec-1,6-diene ring systems in which one of the double bonds bears a Me group show the same preference.\textsuperscript{41b} It is most likely that allohedycaryol also will exist in
the elongated chair conformation all the more so because in this conformation both the C(4) Me group and the C(7) 2-hydroxyisopropyl group adopt the pseudo-equatorial orientation as the three dimensional structure (−)-1 in Scheme 4.7 indicates. The preference for one distinct conformation was supported by the NMR spectra of our synthetic (−)-1. Further information about the conformation of allohedycaryol was obtained from the UV spectrum of (−)-1, in which the absorption maximum at <200 nm shows strong tailing toward the red (260 nm). This tailing indicates that both double bonds are lying parallel and close to each other.\textsuperscript{41b} The rather close proximity of the double bonds in (−)-1 was further proved by irradiation of (−)-1 in MeCN solution with a low-pressure Hg lamp. This resulted in a smooth conversion of 1 into 19 in almost quantitative yield. The structure of 19 was established with $^1$H NMR spectroscopy using Eu(fod)$_3$ as a shift reagent. With increasing concentration of the shift reagent, the angular Me group shifted markedly to lower field ($\Delta \delta = 0.56$ ppm) which proves a cis relationship between the 2-hydroxyisopropyl group and the angular Me group. The doublet of the α C(4) Me group was hardly shifted by varying the concentration of the shift reagent. It is of interest to note that most of the naturally occurring bourbonane sesquiterpenes possess the same relative stereochemistry as found for 19.\textsuperscript{43}

4.3 Experimental Section\textsuperscript{44}

Materials. All reagents were purchased from Aldrich or Janssen except for N,N,N′,N′-tetramethylphosphorodiamidic chloride (TMPDCI) which was purchased from Fluka. The $^1$H NMR experiments using Eu(fod)$_3$ as a shift reagent were performed at 400 MHz. The compounds 5,\textsuperscript{17b} 9,\textsuperscript{16} and 10\textsuperscript{17b} have been characterized before.

(+)−α-Cyperone (5). To a solution of 10.0 g (65.8 mmol) of (+)-dihydrocarvone (6) in 70 mL of dry toluene was added 9.3 mL (72.2 mmol) of (R)-(−)-1-phenylethylamine (8). The reaction mixture was refluxed under Dean-Stark conditions until completion (14 h) and concentrated under reduced pressure. The remaining crude imine 7 was dissolved in 75 mL of dry THF and 7.9 mL (79 mmol) of EVK was added. After stirring in the dark at 40 °C for 3 d, 25 mL of 10% aqueous AcOH was added. The reaction mixture was vigorously stirred for 1 h and then poured into 50 mL of brine. After extraction with five portions of petroleum ether (bp 40−60 °C), the combined organic layers were washed successively with 0.2 M aqueous HCl, saturated aqueous NaHCO$_3$, and brine. The solution was dried and evaporated. The remaining residue was dissolved in 100 mL of MeOH and 4 mL of 1
M NaOMe in MeOH was added dropwise. The reaction mixture was stirred at rt for 30 h, diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (50:1 petroleum ether (bp 40–60 °C)/EtOAc) gave, in order of elution, 1.10 g (11%) of 6 and 6.74 g (47%) of 5: [α]D +92.2° (c 2.04) (lit.17b +91.1°). The spectroscopic data for 5 were identical with those reported in the literature.17b Further elution (2:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 1.4 g (9%) of the known ketol 9.16

(−)-1,2-Dehydro-α-cyprone (10). A mixture of 1.33 g (6.10 mmol) of 5 and 1.93 g (8.50 mmol) of DDQ in 50 mL of dry dioxane was refluxed for 24 h. The reaction mixture was allowed to come to rt and filtered. The filtrate was evaporated under reduced pressure and the remaining residue was purified by column chromatography (5:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 1.01 g (76%) of 10: [α]D −161.5° (c 1.37) (lit.17b −149.0°); mp 50–51 °C (from pentane).45 Anal. Calcd for C15H20O: C, 83.28; H, 9.32. Found: C, 83.31; H, 9.47. The spectroscopic data for 10 were identical with those reported in the literature.17b

[4aS-[4aa,7α(R*)]] and [4aS-[4aa,7α(S*)]]-5,6,7,8-Tetrahydro-1,4a-dimethyl-7-(2-methyloxiranyl)-2(4aH)-naphthalenone (11). To a stirred solution of 1.95 g (9.03 mmol) of 10 in 120 mL of a 1:1 mixture of CH2Cl2 and acetone 0.240 g (0.91 mmol) of 18-crown-6 was added followed by a solution of 3.6 g (43 mmol) of NaHCO3 in 48 mL of water. The mixture was cooled to 0 °C and a solution of 6.6 g (10.7 mmol) of Oxone in 30 mL of water was added dropwise. The reaction mixture was vigorously stirred at 0 °C for 3.5 h and then treated with an excess of saturated aqueous Na2S2O3 and saturated aqueous NaHCO3 for 20 min. The mixture was extracted with CH2Cl2 and the combined organic layers were washed with water, dried, and evaporated to afford 1.98 g (94%) of 11 as a 1:1 diastereomeric mixture: 13C NMR δ 10.52 (q), 18.08 (q), 18.51 (q), 22.75 (t), 23.25 (t), 23.45 (d), 29.36 (t), 29.78 (t), 37.30 (d), 40.15 (s), 45.07 (d), 45.37 (d), 53.11 (t), 53.44 (t), 58.74 (s), 126.16 (d), 129.48 (s), 156.32 (d), 156.37 (d), 158.56 (s), 186.26 (s). The 1H NMR and mass spectral data for 11 corresponded with those reported in the literature.15c

[1S-[1α,2β,4aβ,7β(R*)]] and [1S-[1α,2β,4aβ,7β(S*)]]-1,2,4a,5,6,7-Hexahydro-1,4a-dimethyl-7-(2-methyloxiranyl)-2-naphthalenol (12). To a stirred solution of 1.98 g (8.53 mmol) of 11 in 50 mL of dry DMSO was added 3.0 g (24.6 mmol) of KOT-Bu. The reaction mixture was stirred at rt for 45 min and then poured into ice-water containing 5.0 g of NH4Cl. The mixture was extracted with CH2Cl2 and the combined organic layers were washed with water, dried over Na2SO4, and
evaporated. The so-obtained crude deconjugated ketone was used directly for next step reaction. A solution of 1.94 g (17.5 mmol) of anhydrous CaCl₂ in 40 mL of dry EtOH was added dropwise to a stirred solution of 1.1 g (29.1 mmol) of NaBH₄ in 40 mL of dry EtOH at -25 °C. The solution was stirred at this temperature for 30 min and then a solution of the crude deconjugated ketone in a mixture of 20 mL of dry EtOH and 10 mL of dry THF was added. After stirring at -25 °C for an additional 1.5 h, the reaction mixture was treated with 10 mL of acetone and allowed to come to rt. The solution was concentrated under reduced pressure, diluted with water, and then treated with AcOH until a clear solution was formed. After extraction with CH₂Cl₂, the combined organic layers were washed with water, dried, and evaporated. The residue was purified by flash chromatography (5:1 petroleum ether (bp 40–60 °C)/EtOAc) to afford 1.35 g (67%) of 12 as a 1:1 diastereomeric mixture:⁴⁶ ¹H NMR (major peaks) δ 2.54–2.61 (m, 2 H), 3.60 (d, J = 8.8 Hz, 1 H), 5.25, 5.46 (br s, br s, 1:1 ratio, 1 H), 5.43 (br d, J = 10.0 Hz, 1 H), 5.50 (br d, J = 10.0 Hz, 1 H);¹³C NMR δ 13.78 (q), 17.32 (q), 18.53 (q), 20.85 (t), 20.96 (t), 26.61 (q), 35.81 (t), 35.88 (t), 36.31 (s), 39.82 (d), 42.21 (d), 43.91 (d), 52.47 (t), 53.26 (t), 59.50 (s), 59.55 (s), 60.35 (t), 75.60 (d), 118.14 (d), 119.05 (d), 127.97 (d), 128.06 (d), 138.01 (d), 144.85 (s), 145.01 (s); MS m/z (relative intensity) 234 (M⁺, 36), 201 (90), 177 (62), 159 (98), 143 (100), 131 (70), 119 (86), 105 (83), 91 (73), 43 (69); HRMS calcd for C₁₅H₂₂O₂ (M⁺) 234.1620, found 234.1619.

[2R-(2α,4αα,7α,8β)]-2,3,4,4a,7,8-Hexahydro-7-hydroxy-α,α,4a,8-tetramethyl-2-naphthalenemethanol (13). A mixture of 1.30 g (5.56 mmol) of 12 and 0.60 g (15.8 mmol) of LAH in 25 mL of dry THF was stirred at rt for 1 h. The excess LAH was destroyed by careful addition of 2 mL of water at 0 °C. After addition of 5.0 g of MgSO₄, the mixture was stirred at rt for 5 min and then filtered. The filtrate was evaporated to give 1.20 g (91%) of 13: [α]D = -43.1° (c 0.07);¹H NMR δ 1.07 (s, 3 H), 1.10 (s, 3 H), 1.13 (d, J = 6.5 Hz, 3 H), 1.16 (s, 3 H), 1.29–1.72 (m, 6 H), 2.08 (m, 1 H), 2.24 (m, 1 H), 3.64 (dd, J = 8.5, 4.8 Hz, 1 H), 5.35–5.47 (m, 3 H);¹³C NMR δ 13.87 (q), 20.16 (t), 25.75 (q), 26.52 (q), 28.02 (q), 36.30 (t), 36.30 (s), 40.13 (d), 47.58 (s), 73.05 (s), 75.95 (d), 119.15 (d), 127.67 (d), 138.74 (d), 144.93 (s); MS m/z (relative intensity) 178 (M⁺ – 58, 41), 163 (18), 160 (39), 149 (13), 145 (100), 135 (12), 121 (10), 105 (10), 91 (8), 59 (41); HRMS calcd for C₁₄H₂₁O₂ (M⁺ – 15) 221.1542, found 221.1545.

[1a5-(1αα,2α,4αα,5β,8β,8αS)]-1a2,4,4a,5,8-Hexahydro-5-hydroxy-α,α,4a,8-tetramethyl-3H-naphth[1,8a-b]oxirene-2-methanol (15). To a solution of 236 mg (1.0 mmol) of 13 and 342 mg (1.5 mmol) of o-nitrophenyl selenocyanate in 10 mL of dry THF was added 0.40 mL (1.61 mmol) of tri-n-butyl phosphine. The mixture was allowed to stand at rt for 20 h and then concentrated at reduced pressure. The
concentrate was purified by column chromatography (20:1 to 5:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 397 mg (91%) of α selenide 14: [α]D = −409° (c 0.30); 1H NMR δ 1.10 (s, 3 H), 1.14 (s, 3 H), 1.18 (d, J = 6.8 Hz, 3 H), 1.21 (s, 3 H), 1.25–1.75 (m, 5 H), 2.24 (m, 1 H), 2.92 (m, 1 H), 4.03 (dd, J = 5.3, 4.3 Hz, 1 H), 5.43 (d, J = 9.5 Hz, 1 H), 5.49 (br s, 1 H), 5.87 (dd, J = 9.5, 5.5 Hz, 1 H), 7.24 (dt J = 8.1, 1.3 Hz, 1 H), 7.45 (dt, J = 8.2, 1.5 Hz, 1 H), 7.67 (dd, J = 8.1, 1.1 Hz, 1 H), 8.12 (dd, J = 8.2, 1.5 Hz, 1 H); 13C NMR δ 16.71 (q), 20.01 (t), 25.63 (q), 26.36 (q), 28.08 (q), 35.20 (d), 35.90 (q), 36.90 (s), 47.25 (d), 49.20 (d), 72.93 (s), 120.02 (d), 124.75 (d), 125.50 (d), 126.01 (d), 130.81 (d), 133.07 (d), 133.42 (s), 139.15 (d), 143.49 (s), 147.94 (s); MS m/z (relative intensity) 421 (M+, 1), 219 (7), 201 (9), 161 (100), 159 (10), 145 (21), 119 (17), 105 (16), 69 (19), 59 (45); HRMS calcd for C21H27NO3Se (M+) 421.1156, found 421.1157. To a solution of 390 mg (0.926 mmol) of 14 and 0.3 mL of pyridine in 25 mL of THF was added dropwise 2.4 mL (25 mmol) of 35% H2O2 at −30 °C. The reaction mixture was stirred at −30 °C for 1 h and then allowed to come to rt. After addition of water, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO3 and water, dried over Na2SO4, and evaporated. The remaining residue was purified by column chromatography (2:1 to 1:2 petroleum ether (bp 40–60 °C)/EtOAc) to afford 202 mg (86%) of 15: [α]D = +9.4° (c 2.06); 1H NMR δ 0.83 (d, J = 7.2 Hz, 3 H), 1.02 (m, 1 H), 1.08 (s, 3 H), 1.19 (s, 3 H), 1.24 (m, 1 H), 1.26 (s, 3 H), 1.81–2.23 (m, 4 H), 2.68 (br q, J = 7.2 Hz, 1 H), 3.18 (s, 1 H), 3.54 (br s, 1 H), 5.53 (dd, J = 10.0, 2.0 Hz, 1 H), 5.90 (ddd, J = 10.0, 5.1, 2.8 Hz, 1 H); 13C NMR δ 12.83 (q), 18.86 (t), 20.97 (q), 25.28 (q), 27.46 (t), 28.81 (q), 30.75 (d), 36.76 (s), 45.49 (d), 53.66 (d), 63.92 (s), 72.26 (s), 73.33 (d), 127.55 (d), 133.18 (d); MS m/z (relative intensity) 252 (M+, 10), 219 (45), 193 (64), 123 (67), 122 (43), 110 (46), 107 (45), 95 (49), 59 (100), 43 (54); HRMS calcd for C15H24O3 (M+) 252.1725, found 252.1725.

[2R-(2α,4αα,8β)]-2,3,4,4a,7,8-Hexahydro-α,α,4a,8-tetramethyl-2-naphthalenemethanol (16). To a stirred solution of 8.77 g (37.5 mmol) of 12 in a mixture of 40 mL of dry THF and 10 mL of N,N,N',N'-tetramethylethlyenediamine (TMEDA) was added dropwise 20 mL of BuLi (2.5 M in hexane) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min and then 7.5 mL (52 mmol) of N,N,N',N'-tetramethylphosphorodiamidic chloride was added. After stirring at −78 °C for 5 min, the cooling bath was removed and the reaction mixture was allowed to come to rt and stirred for an additional 1 h. The reaction mixture was then added, via syringe, to a solution of 3.0 g (428 mmol) of Li in 200 mL of EtNH2 at 0 °C. After stirring at 0 °C for 1 h, 100 mL of saturated aqueous NH4Cl was added and EtNH2 was allowed to evaporate by standing at rt overnight. Addition of water to the remaining layer was followed by extraction with EtOAc. After drying and
evaporation of the combined organic layers, column chromatography (4:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 5.60 g (68%) of 16 (GC purity >85%);[47] \(^1\)H NMR δ 1.06 (d, J = 6.6 Hz, 3H), 1.10 (s, 3H), 1.16 (s, 3H), 1.22 (s, 3H), 1.38–1.74 (m, 6 H), 2.10–2.24 (m, 2 H), 2.42 (m, 1 H), 5.31 (dd, J = 10.0, 2.3 Hz, 1 H), 5.37 (br s, 1 H), 5.50 (ddd, J = 10.0, 5.2, 2.3 Hz, 1 H); \(^13\)C NMR δ 17.70 (q), 20.29 (t), 25.85 (q), 27.27 (q), 27.98 (q), 30.88 (d), 36.43 (s), 36.74 (t), 37.14 (t), 47.71 (d), 73.07 (s), 116.11 (d), 123.33 (d), 137.72 (d), 148.47 (s); MS m/z (relative intensity) 205 (M⁺ – 15, 2), 162 (66), 161 (9), 147 (100), 133 (14), 119 (11), 105 (17), 91 (12), 81 (12), 59 (51); HRMS calcd for C₁₄H₂₁O (M⁺ – 15) 205.1592, found 205.1593.

\[1aR-(1a\alpha,3a,5\beta,7a\beta,7b\alpha)]-1a,2,3,5,6,7a,7b-Octahydro-\alpha,\alpha,3,7a-tetramethyl-naphth[1,2-b]oxirene-5-methanol (17).\] To a stirred solution of 5.43 g (24.7 mmol) of 16 in a mixture of 200 mL of dioxane and 40 mL of water was added dropwise a solution of 5.21 g (29.3 mmol) of NBS in 50 mL of dioxane at 0 °C. The reaction mixture was stirred at 5–10 °C for 30 min and then 8.0 g (143 mmol) of KOH in 50 mL of MeOH was added. After stirring at rt for another 1 h, the reaction mixture was diluted with EtOAc, washed with water, dried, and evaporated. Flash chromatography of the remaining residue (9:1 to 3:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 3.55 g (61%) of 17 as white crystals: mp 148–149 °C (from EtOH); [α]D = –99.8° (c 0.46); \(^1\)H NMR δ 0.96 (d, J = 6.6 Hz, 3 H), 1.10 (s, 3 H), 1.15 (s, 3 H), 1.19 (s, 3 H), 1.24–1.39 (m, 2 H), 1.49–1.77 (m, 4 H), 2.08–2.36 (m, 3 H), 2.75 (d, J = 3.8 Hz, 1 H), 3.22 (br d, J = 3.8 Hz, 1 H), 5.27 (br s, 1 H); \(^13\)C NMR δ 17.23 (q), 20.20 (t), 22.63 (q), 25.71 (q), 26.77 (d), 27.87 (q), 33.64 (s), 35.33 (t), 36.43 (t), 47.25 (d), 54.20 (d), 61.34 (d), 72.90 (s), 116.30 (d), 146.96 (s); MS m/z (relative intensity) 218 (M⁺ – 18, 25), 178 (100), 163 (70), 145 (54), 134 (49), 121 (81), 119 (45), 105 (48), 93 (30), 59 (88); HRMS calcd for C₁₅H₂₂O (M⁺ – 18) 218.1671, found 218.1669.

\[2R-(2α,4αα,5α,8β)]-2,3,4,4a,5,6,7,8-Octahydro-5-hydroxy-\alpha,\alpha,4a,8-tetramethyl-2-naphthalenemethanol (18).\] To an ethanolic solution of NaOEt, prepared from 75 mg (3.26 mmol) of Na and 20 mL of dry EtOH, were successively added 500 mg (3.18 mmol) of benzeneselenol and 318 mg (1.35 mmol) of 17. The reaction mixture was refluxed for 7 h, allowed to come to rt, and then treated with 5.0 g of Raney nickel for 1 h. After filtration of the solid material, the filtrate was concentrated under reduced pressure, dissolved in CHCl₃, and washed with water. The organic layer was dried over Na₂SO₄ and evaporated. Flash chromatography (5:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 300 mg (93%) of 18: [α]D = –71.7° (c 0.06); \(^1\)H NMR δ 0.97 (d, J = 6.8 Hz, 3 H), 0.99 (s, 3 H), 1.11 (s, 3 H), 1.18 (s, 3 H), 1.22–1.40 (m, 2 H), 1.50–2.20 (m, 10 H), 3.21 (dd, J = 11.0, 4.6 Hz, 1 H), 5.41 (br s, 1 H); \(^13\)C NMR δ 17.80
(q), 18.43 (q), 20.33 (t), 25.66 (q), 27.87 (q), 30.45 (t), 32.30 (d), 33.27 (t), 36.64 (t), 40.27 (s),
47.74 (d), 72.96 (s), 80.14 (d), 119.57 (d), 147.16 (s); MS m/z (relative intensity) 223 (M+ – 15, 1),
180 (31) 162 (100), 147 (48), 133 (14), 123 (35), 105 (23), 91 (15), 81 (13), 59 (51);
HRMS calcd for C14H23O2 (M+ – 15) 223.1698, found 223.1697.

[2R-(2α,4αα, 5α,8β)]-2,3,4,4a,5,6,7,8-Octahydro-α,α,4a,8-tetramethyl-5-[(methylsulfonyloxy)-2-naphthalenemethanol (4). To a stirred solution of 298 mg (1.25 mmol)
of 18 in 6 mL of pyridine was added a solution of 300 mg (2.63 mmol) of MsCl in 3 mL of pyridine at 0 °C. After stirring at 0 °C for 1 h, saturated aqueous NaHCO3 was added dropwise. The reaction mixture was stirred for an additional 5 min and then extracted with CH2Cl2. The combined organic layers were washed with water, dried over Na2SO4, and evaporated. After removal of the residual pyridine by azeotropic distillation with toluene, 392 mg (99%) of 4 was obtained: [α]D –25.2° (c 0.47); 1H NMR δ 0.99 (d, J = 6.4 Hz, 3 H), 1.08 (s, 3 H), 1.10 (s, 3 H), 1.18 (s, 3 H), 1.25–2.30 (m, 11 H), 2.98 (s, 3 H), 4.29 (dd, J = 11.0, 5.3 Hz, 1 H), 5.51 (br s, 1 H); 13C NMR δ 18.15 (q),
18.86 (q), 20.08 (t), 25.54 (q), 27.97 (q), 28.75 (t), 32.01 (d), 32.75 (t), 36.64 (t), 38.82 (q),
39.83 (s), 47.64 (d), 72.74 (s), 90.88 (d), 121.53 (d), 145.06 (s); MS m/z (relative intensity)
258 (M+ – 58, 2), 204 (7), 162 (100), 147 (40), 133 (11), 120 (11), 119 (11), 105 (18), 91 (12),
59 (28); HRMS calcd for C15H25O4S (M+ – 15) 301.1474, found 301.1472.

(–)-Allohedecaryol (1). To a stirred solution of 385 mg (1.22 mmol) of 4 in 5 mL of dry THF was added 8 mL 1 M BH3•THF at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and additionally at rt for 2 h. After cooling to 0 °C, 1.5 mL of MeOH was added dropwise, immediately followed by 16 mL of NaOMe (2 M in MeOH). The reaction mixture was allowed to come to rt and stirred overnight. After addition of 20 mL of saturated aqueous NH4Cl and 10 mL of 25% aqueous ammonia to the cooled reaction mixture, petroleum ether (bp 40–60 °C) was added. Stirring was continued for an additional 30 min after which the two-phase mixture was separated. The aqueous layer was extracted with petroleum ether (bp 40–60 °C) and the combined organic layers were dried over Na2SO4 and evaporated. The remaining residue was dissolved in a mixture of 15 mL of hexane and 5 mL of t-butyl methyl ether and extracted with 20% aqueous AgNO3. The combined aqueous layers were washed with t-butyl methyl ether and then cooled to 0 °C. After addition of 25% NH3, the aqueous layer was extracted with t-butyl methyl ether. The combined organic layers were washed with brine and dried over Na2SO4. Evaporation gave 185 mg (68%) of pure 1: [α]D = –192° (c 0.92) (lit.³ +181°); UV
(CH3CN) λmax <200 nm, tail to 260 nm. The NMR and mass spectral data for (–)-1 corresponded with those reported for natural (+)-1.³
[1R-(1α,3αα,3ββ,6β,6αβ,6βα)]-Decahydrop-α,α,3a,6-tetramethyl-cyclobuta[1,2:3,4]-dicyclopentene-1-methanol (19). A solution of 26 mg (0.12 mmol) of ()-1 in 4 mL of MeCN placed in a sealed quartz cuvet was irradiated for 14 h using a CAMAG Universal UV-lamp 29230. The reaction progress was monitored by GC. After completion, the solvent was evaporated under reduced pressure to give 25 mg (96%) of 19 (GC purity >98%): [α]D = −1.3° (c 0.95); 1H NMR δ 0.75 (d, J = 7.2 Hz, 3 H), 0.86 (s, 3 H), 1.13 (s, 6 H), 1.24 (br s, OH), 1.39–1.66 (m, 7 H), 1.73–1.96 (m, 5 H), 2.28 (ddd, J = 6.3, 6.3, 2.8 Hz, 1 H); 13C NMR δ 20.28 (q), 20.57 (q), 24.55 (t), 28.27 (q), 28.48 (q), 28.84 (t), 33.31 (t), 38.57 (d), 43.19 (s,t), 44.84 (d), 50.39 (d), 51.70 (d), 61.93 (d), 71.81 (s); MS m/z (relative intensity) 222 (M+, 1), 161 (8), 149 (13), 140 (8), 122 (11), 107 (14), 95 (8), 82 (100), 67 (18), 59 (40); HRMS calcd for C15H26O (M+) 222.1984, found 222.1983.

4.4 References and Notes

9. For example, all stereoisomers of (±)-2 have been synthesized, see § 2.2.1. During the synthesis of (±)-2 a by-product was formed to which structure 1 was assigned, see: Kodama, M.; Matsuki, Y.; Itô, S. Tetrahedron Lett. 1976, 1121.
13. The numbering system as given in structure 4 will be followed throughout the text of this chapter.
20. The well-described procedure was followed: Revial, G.; Pfau, M. Org. Synth. 1992, 70, 35.
26. Recently, a similar result has been found during the t-BuOOH/VO(acac)2 epoxidation of a steroidal allylic alcohol: Kocovsky, P. J. Chem. Soc., Perkin Trans. 1 1994, 1759.
27. In contrast to 12, treatment of its C(3) epimer46 with t-BuOOH/VO(acac)2 gave selectively the corresponding α epoxide.
29. It was expected that ring opening of the side-chain epoxide in 12 would occur
during the formation of the allylic selenide. For example, see: Clive, D. L. J. Tetrahedron 1978, 34, 1049.


31. The observation that the use of pyridine did not prevent the epoxidation of the C(5)–C(6) double bond suggests an intramolecularly directed process.²⁸


37. We thank Prof. Dr. G. Appendino for supplying copies of the NMR spectra of natural allohedycaryl.

38. The conventions proposed for describing germacrane sesquiterpenes are followed, see § 1.3.

39. Prof. Dr. G. Appendino attended us to an article in which the isolation of α-ferulene, another ent-sesquiterpene from F. communis, has been reported: Carboni, S.; Da Settimo, A.; Malaguzzi, V.; Marsili, A.; Pacini, P. L. Tetrahedron Lett. 1965, 3017.

40. In the Chemical Abstracts, the S-configuration is erroneously assigned to (+)-hedycaryl (2), see § 3.2.


43. Reference 14, p 636.

44. For a general description of the experimental procedures employed in this chapter, see § 3.3.

45. Previously, compound 10 was reported as an oil.¹⁵c,¹⁷b

46. This reaction also gave a small amount (ca 5%) of the C(3) epimer of 12 [¹H NMR (main peaks) δ 2.49–2.61 (m, 2 H), 3.82 (dd, J = 5.1, 3.6 Hz, 1 H), 5.22–5.52 (m, 2 H), 5.72 (m, 1 H)].

47. In a smaller scale experiment using freshly distilled TMEDA, the yield of 16 was 82%. The same reduction procedure applied on the C(3) epimer of 12⁴⁶ yielded 16 in 95%.
The Total Synthesis of Neohedycaryol. Its Possible Role in the Biosynthesis of Eudesmane Sesquiterpenes

Abstract: the total synthesis of neohedycaryol (4), a C(9)-C(10) double bond regioisomer of hedycaryol (chapter 3), was accomplished in 10 steps from the known dione 6. A Marshall fragmentation of the intermediate mesylate 14 was used to prepare the (E,E)-cyclodeca-4,9-diene ring present in neohedycaryol. During the synthesis of 14, a pronounced example of through-bond interactions (TBI) was observed. The preferred elongated chair conformation of neohedycaryol was determined spectroscopically and by chemical conversion into α-, β-, and γ-eudesmol. These findings indicate that the role of neohedycaryol as a precursor in the biosynthesis of epi-eudesmanes as proposed in the literature is unlikely. The preference of neohedycaryol for the elongated chair conformation further means that the compound occupies a meso form. This implies that neohedycaryol may act as a precursor in the biosynthesis of both ent- and usual eudesmanes.
5.1 Introduction*

Germacrane sesquiterpenes\(^1\) and their 1,10-monoepoxides are generally considered as direct precursors of eudesmane sesquiterpenes (§ 1.2).\(^2\) Strong evidence for the involvement of these monocyclic compounds in the biosynthesis of eudesmanes comes from enzyme- and acid-mediated cyclization reactions. For instance, incubation of (+)-hedycaryol (1) with a root suspension of chicory (Cichorium intybus) gave selectively cryptomeridiol (2),\(^3\) while a mixture of α-, β-, and γ-eudesmol (3a, b, and c, respectively) was obtained upon treatment of 1 with acid\(^4\) (Scheme 5.1). The formation of these eudesmanes can easily be explained by enzymatic or chemical protonation of the C(1)–C(10) double bond followed by cyclization (formation of the C(5)–C(10) bond) and subsequent incorporation of water (in case of 2) or proton loss (in case of 3a, b, and c).

**Scheme 5.1**

![Scheme 5.1](image)

The stereochemical aspects of these cyclization reactions are also important. Although \(^1\)H NMR experiments clearly show that 1 exists in at least three different conformations at room temperature,\(^5\) cyclization of 1 only affords the trans-fused eudesmane skeleton with a cis relationship between the C(10) Me group and the C(7) side chain. Because the different conformers are interconverting at room temperature as depicted in Scheme 5.2, it is obvious that 1 only cyclizes via the conformer A in which both vinylic Me groups are pointing upwards.\(^6\)

The greater part of the eudesmanes isolated from higher plants possesses the same relative and absolute configuration as present in the structures 2 and 3.\(^7\) A small number of eudesmanes, however, has an aberrant configuration at C(5) and/or C(10).\(^8\) These so-called epi-eudesmanes have been found in plant species together with the usual eudesmanes.\(^9\)
Scheme 5.2: Conformations of (+)-hedycaryol (1)

Several hypotheses have appeared in the literature to unravel the biosynthesis of epi-eudesmanes. In the most straightforward explanation, both the epi- and usual eudesmanes are formed from (E,E)-germacranes.\textsuperscript{10} From the conformations of 1 depicted in Scheme 5.2, it can easily be deduced that cyclization of the conformations B, C, and D will lead to 5-epi-, 10-epi-, and 5-epi-10-epi-eudesmanes, respectively. In the literature, two examples are known in which (E,E)-germacranes yielded epi-eudesmanes.\textsuperscript{11,12} In both cases, however, the (E,E)-cyclodeca-1(10),4-diene ring bears a β substituent at C(6) as a result of which conformation A will be less favorable.

A second explanation for the biosynthesis of epi-eudesmanes assumes the cyclization of double bond stereoisomers of (E,E)-germacranes.\textsuperscript{13} It has been shown that acid-catalyzed cyclizations of double bond stereoisomers of 1 do give epi-eudesmanes.\textsuperscript{11,14} A serious drawback of this hypothesis is the fact that the double bond stereoisomers of simple (E,E)-germacranes have not been found in nature.\textsuperscript{15}

In a third explanation, the one we will concentrate on, the cyclization of a double bond regioisomer of (E,E)-germacranes has been proposed. It was already recognized in 1959 by Hendrickson that cyclization of the C(9)-C(10) double bond regioisomer of hedycaryol, subsequently named neochedycaryol (4), might give an eudesmane.\textsuperscript{16} This suggestion was picked up by McSweeney et al. who reasoned that cyclization to both epi- and usual eudesmanes would proceed via different conformations of 4.\textsuperscript{17} Experimental information, however, failed to appear because 4 was not available. Some years later, a route towards agarofurans based on 4 was postulated.\textsuperscript{18} Since
then, 4 has been mentioned several times in connection with the biosynthesis of *epi*-eudesmanes,\textsuperscript{19} eremophilanes,\textsuperscript{20} and agarofurans.\textsuperscript{21}

Although recently two C(5)-C(6) double bond regioisomers of hedycaryol, e.g. allohedycaryol\textsuperscript{22} and its C(4) epimer,\textsuperscript{23} have been isolated from higher plants, 4 has not been found in nature until now. This does not imply that 4 does not exist. It may have escaped isolation due to its supposed instability; the ten-membered ring is prone to cyclization because the double bonds are close to each other and cyclization can occur via relatively stable tertiary carbocations. In this context, it is important to note that the three-dimensional model of 4 reveals several interesting stereochemical aspects. The (E,E)-cyclodeca-4,9-diene system of 4 can be considered as a cyclohexane ring elongated with two double bonds (Scheme 5.3). There are two conformations in which the double bonds are lying parallel (comparable with the chair and boat conformation of cyclohexane) and two conformations in which the double bonds are crossed (the twist conformations of cyclohexane).\textsuperscript{24} It also appeared that in the parallel conformations, 4 has on the average a symmetry plane and this means that the compound occupies a meso form. The two crossed forms are enantiomers of each other.

**Scheme 5.3: Conformations of neochedycaryol (4)**

Because of our interest in the biosynthetic-like cyclization reactions of germacrane sesquiterpenes (§ 7.2)\textsuperscript{3,25} and their analogues,\textsuperscript{26} we decided to synthesize neochedycaryol. As with hedycaryol,\textsuperscript{3} it was expected that the acid-catalyzed cyclization of 4 would provide more information about its possible role in the biosynthesis of eudesmanes.
In our synthetic approach to 4, the known dione 6\(^27\) was used as the starting material (Scheme 5.4). A number of apparently simple reactions was needed to prepare the mesylate 5 from 6. The key step in this approach, the conversion of 5 into neochedycaryol, involved a Marshall fragmentation reaction.\(^28\)

**Scheme 5.4**

\[
\text{neochedycaryol (4)} \quad \Rightarrow \quad \text{OMs} \quad \Rightarrow \quad \text{O} \\
\]

\[
\text{5} \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 

5.2 Results and Discussion

Following the procedure described by Agami et al.\(^29\) the synthesis of 6 started with the addition of ethyl vinyl ketone (EVK) to hydroxycarvone which was easily prepared from (R)-(−)-carvone.\(^27\) In our hands, both the reported enantioselective\(^30\) and the acid-catalyzed ring closure\(^31\) of the addition product, a 3:2 mixture of two triketones, did not yield any workable result. It was then decided to achieve cyclization with a substoichiometric amount of pyrrolidine in refluxing benzene. In this way, racemic 6 was obtained in 38% yield. Reduction of the C(9) carbonyl group of 6 with NaBH\(_4\) and protection of the resulting alcohol as its TBDMS ether gave 7 in good yield (Scheme 5.5). Selective epoxidation of the double bond in the side chain of 7 was effected with dimethylidioxirane and afforded 8 as a diastereomeric 1:1 mixture.

Reduction of 8 with lithium tri-tert-butoxyluminohydride (LiAl(Ot-Bu))\(_3\)H provided 9 also as a diastereomeric 1:1 mixture in 87% yield. Since the LiAl(Ot-Bu))\(_3\)H reduction of a system comparable to 8 proceeds selectively from the \(\alpha\)-side,\(^32\) the orientation of the C(3) hydroxyl group of 9 is probably \(\beta\). In order to remove the oxygen function at C(3), the phosphorimidate of 9 was reduced with Li in EtNH\(_2\).\(^33\) In this way, not only the C(3)--O bond was reduced but also the epoxide ring was opened to give almost pure 10 in high yield. Cleavage of the C(9) Si--O bond with TBAF in hot DMSO afforded the diol 11 in pure form after recrystallization from EtOH.
In order to apply the Marshall fragmentation reaction, the C(9) hydroxyl group of 11 had to be converted into a mesylate group, and here we encountered a curious problem. Despite many attempts, we were not able to produce the desired mesylate 5. For instance, treatment of 11 with MsCl in dry pyridine at −10 °C showed the complete disappearance of the starting material on TLC but workup and purification only afforded a small amount of a compound which contained Cl as deduced from its mass spectrum. In its $^1$H NMR spectrum, an one-proton signal appears as a double doublet at δ 3.74 with couplings of 4.4 and 12.2 Hz, indicating the replacement of the C(9) hydroxyl group by Cl with retention of configuration. In sharp contrast with this unexpected result, no problems were reported for the mesylation of a homoallylic alcohol similar to 11 but lacking the C(7) substituent. It was therefore assumed that the difficulties encountered with the mesylation of 11 were due to the presence of the C(7) 2-hydroxyisopropyl group. Strong support for this assumption came from previous studies in our group on trans-fused perhydropyridazine and norbornene-1,4-diol monosulfonate esters. It has been demonstrated that deprotonation of the alcohol function of these compounds leads to a strongly enhanced leaving group ability of the sulfonate ester group, almost certainly as a result of long-range orbital interactions through the four σ-bonds between the alcohoholate anion (electron donor) and the sulfonate ester bond (electron acceptor). The extent of these through-bond orbital interactions (TBI) depends on the geometry of the σ-relay (the intervening σ-framework) and is maximized for an all-trans arrangement. From examination of a molecular model
of 5, it appeared that the \(\sigma\)-relay between the tertiary hydroxyl group at C(11) and the mesylate group at C(9) possesses such an all-trans arrangement. This should mean that deprotonation of the C(11) hydroxyl group strongly enhances the leaving group ability of the mesylate group. Because the synthesis of mesylate 5 requires the use of pyridine,\(^{41}\) hydrogen bond formation between pyridine and the C(11) alcohol function will lead to partial negative charge on the C(11) oxygen, thereby increasing the leaving group ability of the mesylate group. Consequently, the mesylate group of 5 will be very susceptible to nucleophilic replacement as the reaction outcome of our initial mesylation experiments clearly showed (vide supra).

Having thus explained the anomalous behavior of mesylate 5, the solution was obvious: protection of the C(11) hydroxyl function as its acetate to prevent hydrogen bond formation. In order to confirm this hypothesis, 10 was treated with \(\text{Ac}_2\text{O}\) and a catalytic amount of DMAP in Et\(_3\text{N}\)\(^{42}\) to afford 12 in 82% yield (Scheme 5.6). After removal of the TBDMS protecting group, treatment of the resulting alcohol 13 with MsCl in pyridine now proceeded without any problems and gave the mesylate 14 in 89% yield! The NMR and mass spectral data of 14 are fully consistent with the assigned structure.

### Scheme 5.6

\[
\begin{align*}
\text{10} & \xrightarrow{\text{Ac}_2\text{O}} \text{12} & \text{12} & \xrightarrow{\text{HF}} \text{13} & \text{13} & \xrightarrow{\text{MsCl}} \text{14}
\end{align*}
\]

As in the case of (+)-hedycaryl (chapter 3) and (−)-allohedycaryl (chapter 4), the Marshall fragmentation reaction of mesylate 14 was expected to complete the synthesis of neohedycaryl.\(^{43}\) However, successive treatment of 14 with BH\(_3\)-SMe\(_2\) and NaOMe in MeOH gave, instead of expected 4, the corresponding ethyl ether 15 as the sole product in moderate yield (36%). Apparently, the C(11) acetate group was
reduced to the corresponding ethyl ether. In order to minimize the reduction of the acetate group, 14 was treated with BH₃·THF at 0 °C for only a relatively short time. In this way, after treatment with NaOMe in MeOH, a complex mixture of 4 and several unidentified products was obtained. Fortunately, isolation of pure 4 from this mixture was easily effected with aqueous AgNO₃ extraction. Although the yield of 4 was poor (11%), all spectral and chromatographic data including the Kováts indices could be obtained.

The ¹H NMR spectrum of 4 points to the preference for one distinct conformation. From its ¹³C NMR spectrum, it follows that 4 possesses a symmetry plane which means that the crossed conformations (see Scheme 5.3) can be excluded. The UV spectrum of 4, in which the absorption maximum at < 200 nm shows strong tailing toward the red (270 nm), is in line with this conclusion. The formation of a 1:2:1 mixture of α-, β-, and γ-eudesmol, respectively, upon treatment of 4 with p-TsOH in CH₂Cl₂ proved that 4 reacts exclusively from the elongated chair conformation (Scheme 5.7). The NMR data and the almost quantitative formation of 16 upon irradiation (3.5 h) of 15 in MeCN solution with a low-pressure Hg lamp indicate that 15 also exists in the elongated chair conformation.

![Scheme 5.7](image)

**Scheme 5.7**

5.3 Concluding Remarks

These findings show that neohedycaryol (4) preferentially exists in the elongated chair conformation at room temperature. Consequently, its cyclization can only result in the usual stereochemistry of eudesmanes found in higher plants as confirmed by the formation of α-, β-, and γ-eudesmol upon acid treatment. For this reason, 4 is a less likely precursor in the biosynthesis of epi-eudesmanes and probably also of agarofurans.

The preferred elongated chair conformation further indicates that 4 occupies the meso form. As a consequence, 4 can only produce racemic eudesmanes under non-enzymatic circumstances, while pure enantiomers may be generated enzymatically. If both pathways are followed in biosynthesis, then enantiomeric mixtures of
eudesmanes with one enantiomer in excess will be formed. The co-occurrence of both enantiomers of eudesmanes in the same plant supports this hypothesis.\textsuperscript{51} It is therefore tempting to consider the possibility that 4 may be a direct in vivo formed precursor\textsuperscript{52} of both ent- and usual eudesmanes and not, as argued above, of epi-eudesmanes.

5.4 Experimental Section\textsuperscript{53}

**General.** Kováts indices were determined on a gas chromatograph equipped with a J&W DB-1 column (60 m x 0.25 mm i.d., film thickness 0.25 µm) and a Restek Stabilwax column (60 m x 0.25 mm i.d., film thickness 0.25 µm). Split ratio 1:100, carrier gas H\textsubscript{2}, inlet pressure 20 psi, linear velocity 35 cm/sec; temperature program 50 °C (0 min hold) to 238 °C (8 min hold) at 4 °C/min; injector temperature 220 °C; detector temperature 260 °C; FID detection.

**Materials.** All reagents were purchased from Aldrich or Janssen except for N,N,N',N'-tetramethylethylphosphorodiamidic chloride (TMPDCl) which was purchased from Fluka. 2-Methyl-5-(1-methylethenyl)-1,3-cyclohexanedione\textsuperscript{27} and compound 6\textsuperscript{29,54} have been characterized before.

**2-Methyl-5-(1-methylethenyl)-1,3-cyclohexanedione.** Epoxycarvone (46 g, 277 mmol) was treated with 1 M aqueous NaOH at 65 °C for 65 min following a previously described procedure.\textsuperscript{27} After workup, the remaining residue was dried in a vacuum desiccator on P\textsubscript{2}O\textsubscript{5} overnight to give 44 g (96%) of 2-methyl-5-(1-methylethenyl)-1,3-cyclohexanedione (GC purity 98%). Its spectroscopic data corresponded with those reported in the literature.\textsuperscript{27}

**(cis-3,4,8,8a)-(-)-Tetrahydro-5,8a-dimethyl-3-(1-methylethenyl)-1,6-(2H,7H)-naphthalenedione (6).** A 3:2 mixture of two epimeric triketones was prepared in 81% yield from 2-methyl-5-(1-methylethenyl)-1,3-cyclohexanedione and EVK as described.\textsuperscript{29} To a solution of 17.3 g (69.2 mmol) of this mixture in 125 mL of benzene was added 0.81 mL (9.8 mmol) of pyrrolidine. The reaction mixture was heated at reflux and, after 7 and 18 h, two other 0.81 mL portions of pyrrolidine were added. The total reflux time amounted to 4 d. The mixture was allowed to come to rt, poured into water, and extracted with petroleum ether (bp 40–60 °C). The combined organic layers were washed successively with 1 M aqueous HCl, saturated aqueous NaHCO\textsubscript{3}, and brine. After drying and evaporation, the remaining residue was flash chromatographed (6:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 6.1 g (38%) of 6. The spectroscopic data of 6 corresponded with those reported in the literature.\textsuperscript{29,54}
(4α,5α,7α)-(±)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-7-(1-methylethenyl)-5-[(1,1-dimethylthethyl)dime-thylsilyloxy]-2(3H)-naphthalenone (7). After reduction of 6 with NaBH₄ following a previously described procedure,³⁰ the resulting alcohol (8.82 g, 37.7 mmol) was added to a solution of 6.42 g (94.4 mmol) of imidazole and 7.08 g (46.9 mmol) of TBDMS-Cl in 50 mL of DMF. The mixture was stirred at rt for two d and then poured into 200 mL of water. After extraction with petroleum ether (bp 40–60 °C), the combined organic layers were washed with brine and dried. Flash chromatography (20:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 10.53 g (80%) of 7 as an oil: ¹H NMR δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 1.13 (s, 3 H), 1.76 (br s, 6 H), 1.6–1.8 (m, 3 H), 1.99–2.08 (m, 3 H), 2.36–2.44 (m, 2 H), 2.66 (dd, J = 1.6, 9.7 Hz, 1 H), 3.40 (dd, J = 5.1, 10.7 Hz, 1 H), 4.77 (br s, 2 H); ¹³C NMR δ −4.91 (q), −3.91 (q), 11.30 (q), 16.00 (q), 17.00 (s), 20.41 (q), 25.78 (3 q), 32.34 (t), 33.55 (t), 33.89 (t), 35.58 (t), 41.55 (d), 41.97 (s), 78.57 (d), 109.71 (t), 130.21 (s), 147.97 (s), 160.11 (s), 199.10 (s); MS m/z (relative intensity) 291 (M⁺ – 57, 100), 211 (39), 75 (20), 73 (27); HRMS calcd for C₁₇H₂₇O₂Si (M⁺ – 57) 291.1780, found 291.1780.

(4α,5α,7α)-(±)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-5-[(1,1-dimethylthethyl)dime-thylsilyloxy]-7-(2-methyloxyiranyl)-2(3H)-naphthalenone (8). To a stirred solution of 10.5 g (30.2 mmol) of 7 in 360 mL of a 1:1 mixture of CH₂Cl₂ and acetone were added 0.755 g (2.86 mmol) of 18-crown-6 and a solution of 11.5 g (137 mmol) of NaHCO₃ in 200 mL of water. The mixture was cooled to 0 °C and a solution of 20.7 g (33.6 mmol) of Oxone in 100 mL of water was added dropwise. The reaction mixture was vigorously stirred at 0 °C for 3 h and then treated with an excess of saturated aqueous Na₂S₂O₃ and saturated aqueous NaHCO₃ for 20 min. The mixture was extracted with CH₂Cl₂ and the combined organic layers were washed with water, dried, and evaporated to afford 11.0 g of crude 8, which was used directly for the next step. A sample (0.125 g, 0.34 mmol) of crude 8 was flash chromatographed (10:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.115 g (93%) of 8 as a 1:1 mixture of diastereomers: ¹H NMR δ 0.01 (s, 3 H), 0.04 (s, 3 H), 0.86 (s, 9 H), 1.10 (s, 3 H), 1.30 (s, 3 H), 1.75 (br s, 3 H), 1.2–2.1 (m, 6 H), 2.35–2.42 (m, 2 H), 2.57–2.72 (m, 3 H), 3.34 (dd, J = 4.7, 10.7 Hz, 1 H); ¹³C NMR δ −4.93 (q), −3.90 (q), 11.32 (q), 15.93 (q), 17.87 (q), 17.97 (s), 18.12 (q), 25.77 (3 q), 28.87 (t), 29.33 (t), 32.26 (t), 32.75 (t), 33.49 (t), 33.81 (t), 40.35 (d), 40.57 (d), 42.06 (s), 53.13 (t), 53.32 (t), 58.49 (s), 78.12 (d), 130.40 (s), 130.66 (s), 159.04 (s), 198.86 (s); MS m/z (relative intensity) 307 (M⁺ – 57, 46), 249 (98), 227 (35), 215 (40), 204 (44), 86 (52), 75 (94), 73 (100); HRMS calcd for C₁₇H₂₇O₂Si (M⁺ – 57) 307.1730, found 307.1731.
(2α,4α,5α,7α)-(±)-2,3,4,4a,5,6,7,8-Octahydro-1,4a-dimethyl-5-[[1,1-dimethylethyl]dimethylsilyl]oxy]-7-(2-methyloxiranyl)-2-naphthalenol (9). To a stirred solution of 8.34 g (32.8 mmol) of Li(t-BuO)₃AlH in 100 mL of THF was added dropwise a solution of 3.27 g (8.98 mmol) of 8 in 60 mL of THF at 0 °C. After being stirred at rt for 1.5 h, the reaction mixture was quenched with 13.5 g of Na₂SO₄·10H₂O followed by the addition of 2 mL of water and excess MgSO₄. The mixture was stirred for an additional 0.5 h and filtered. The filtrate was evaporated, and the remaining residue was purified by flash chromatography (6:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 2.85 g (87%) of 9 as a 1:1 mixture of diastereomers: ²H NMR δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 9 H), 0.99 (s, 3 H), 1.28 (br s, 3 H), 1.0–2.4 (m, 12 H), 2.35–2.62 (m, 3 H), 3.24 (dd, J = 4.7, 10.7 Hz, 1 H), 3.94 (m, 1 H); ¹³C NMR δ –4.90 (q), –3.88 (q), 15.55 (q), 18.02 (q), 18.15 (s), 18.29 (q), 25.81 (3 q), 26.96 (t), 27.45 (t), 28.39 (t), 31.74 (t), 32.76 (t), 33.25 (t), 41.31 (s), 41.74 (d), 41.91 (d), 53.43 (t), 58.87 (s), 70.90 (d), 76.99 (d), 79.42 (d), 129.88 (s), 129.96 (s), 137.00 (s); MS m/z (relative intensity) 309 (M⁺ – 57, 5), 291 (40), 227 (89), 177 (46), 159 (51), 75 (65), 73 (100); HRMS calcd for C₁₇H₂₉O₃Si (M⁺ – 57) 309.1884, found 309.1884.

(2α,4α,4aα)-(±)-1,2,3,4,4a,5,6,7-Octahydro-α,α,4,8-tetramethyl-4-[[1,1-dimethyl-ethyl]dimethylsilyl]oxy]-2-naphthalenemethanol (10). To a stirred solution of 0.746 g (2.04 mmol) of 9 in a mixture of 16 mL of THF and 4 mL of TMEDA was added 2.84 mL of BuLi (1.6 M in hexane) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min, and then 2.4 mL (16.0 mmol) of TMPDCl was added. After stirring at −78 °C for another 5 min, the reaction mixture was allowed to come to rt and stirred for an additional 1 h. The reaction mixture was then slowly added, via syringe, to a solution of 0.90 g (129 mmol) of Li in 50 mL of EtNH₂ at 0 °C. After stirring at 0 °C for 1 h, 20 mL of saturated aqueous NH₄Cl was added and EtNH₂ was allowed to evaporate by standing at rt overnight. The remaining layer was extracted with ether, and the combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.63 g (88%) of 10.⁵⁵ ¹H NMR δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.88 (s, 9 H), 0.94 (s, 3 H), 1.18 (s, 6 H), 1.60 (br s, 3 H), 1.2–2.0 (m, 11 H), 2.54 (ddd, J = 2.4, 2.4, 13.4 Hz, 1 H), 3.26 (dd, J = 4.6, 10.8 Hz, 1 H); ¹³C NMR δ –4.83 (q), –3.87 (q), 14.08 (s), 18.02 (2 q), 18.86 (t), 19.72 (q), 25.59 (t), 25.87 (3 q), 26.79 (q), 32.36 (t), 33.14 (t), 36.72 (t), 41.52 (s), 46.71 (d), 72.26 (s), 79.44 (d), 126.88 (s), 133.51 (s); MS m/z (relative intensity) 352 (M⁺, 1), 293 (52), 229 (31), 203 (100), 161 (51), 147 (31), 73 (61), 59 (12); HRMS calcd for C₂₁H₄₀O₂Si (M⁺) 352.2798, found 352.2795.
(2α,4α,4αα)-(±)-1,2,3,4,4a,5,6,7-Octahydro-4-hydroxy-α,α,4,8-tetramethyl-2-naphthalenemethanol (11). To a stirred solution of 0.62 g (1.76 mmol) of 10 in 10 mL of DMSO was added 4 mL of TBAF (1 M in THF). The reaction mixture was placed in an oil bath at 100 °C and stirred for 45 min. The resulting brown mixture was cooled to rt and poured into 120 mL of water. The mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (2:1 petroleum ether (bp 40–60 °C)/EtOAc) and crystallization from EtOH gave 0.310 g (74%) of pure 11: mp 147 °C; 1H NMR δ 0.98 (s, 3 H), 1.27 (s, 6 H), 1.62 (br s, 3 H), 1.27–2.0 (m, 12 H), 2.58 (ddd, J = 2.6, 2.6, 13.8 Hz, 1 H), 3.32 (dd, J = 4.5, 10.9 Hz, 1 H); 13C NMR δ 17.68 (q), 18.77 (q), 19.81 (t), 25.58 (t), 26.86 (q), 27.28 (q), 31.70 (t), 33.02 (t), 36.20 (t), 40.06 (s), 46.89 (d), 72.38 (s), 79.31 (d), 127.51 (s), 132.93 (s); MS m/z (relative intensity) 238 (M+, 100), 223 (47), 195 (50), 187 (33), 159 (40), 147 (33), 145 (30), 105 (39), 59 (34). Anal. Calcd for C15H26O2: C, 75.58; H, 11.00. Found: C, 75.55; H, 11.21.

(2α,4α,4αα)-(±)-1,2,3,4,4a,5,6,7-Octahydro-α,α,4,8-tetramethyl-4-[(1,1-dimethyl-ethyl)dimethylsilyloxy]-2-naphthalenemethyl acetate (12). To a stirred solution of 0.324 g (0.93 mmol) of 10 in 3 mL of Et3N was added 0.26 mL (2.80 mmol) of Ac2O followed by 0.010 g (0.08 mmol) of DMAP at 0 °C. The mixture was allowed to come to rt, stirred for two d, and then poured into water. After extraction with EtOAc, the combined organic layers were washed with saturated aqueous NaHCO3 and brine, dried, and evaporated. Flash chromatography (50:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.303 g (82%) of 12 as an oil: 1H NMR δ 0.00 (s, 6 H), 0.87 (s, 9 H), 0.92 (s, 3 H), 1.40 (s, 3 H), 1.42 (s, 3 H), 1.58 (br s, 3 H), 1.1–1.7 (m, 7 H), 1.8–2.05 (m, 3 H), 2.02 (s, 3 H), 2.42 (ddd, J = 2.3, 2.3, 10.5 Hz, 1 H), 3.26 (ddd, J = 4.7, 10.8 Hz, 1 H); 13C NMR δ −4.79 (q), −3.91 (q), 18.06 (q), 18.06 (s, observed), 18.90 (t), 19.71 (q), 22.43 (q), 23.43 (q), 23.47 (q), 25.50 (t), 25.92 (3 q), 32.15 (t), 33.18 (t), 36.67 (t), 40.68 (s), 43.63 (d), 79.18 (d), 84.49 (s), 127.28 (s), 133.10 (s), 170.34 (s); MS m/z (relative intensity) 334 (M+−60, 34), 277 (100), 229 (24), 211 (20), 203 (80), 161 (29), 75 (27), 73 (32); HRMS calcd for C21H38OSi (M+−60) 334.2692, found 334.2689.

(2α,4α,4αα)-(±)-1,2,3,4,4a,5,6,7-Octahydro-4-hydroxy-α,α,4,8-tetramethyl-2-naphthalenemethyl acetate (13). To a stirred solution of 0.349 g (0.89 mmol) of 12 in 4 mL of MeCN were added two drops of 40% aqueous HF every h over a period of 6 h. After this time, the reaction mixture was diluted with EtOAc and washed with saturated aqueous NaHCO3 and brine. After drying and evaporation, the remaining residue was flash chromatographed (3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.193 g (78%) of 13 as an oil: 1H NMR δ 0.98 (s, 3 H), 1.44 (s, 6 H), 1.60 (br s, 3 H),...
(2α,4α,4αα)-(±)-1,2,3,3,4,4a,5,6,7-Octahydro-α,α,4,8-tetramethyl-4-[(methylsulfonil)oxy]-2-naphthalenemethyl acetate (14). To a stirred solution of 0.089 g (0.32 mmol) of 13 in 2 mL of pyridine was added 0.037 mL (0.48 mmol) of MsCl at 0 °C. The mixture was allowed to come to rt, stirred for 50 min, and poured into water. After extraction with petroleum ether (bp 40–60 °C), the combined organic layers were washed with brine, dried, and evaporated. Removal of residual pyridine by azeotropic distillation with toluene afforded 0.101 g (89%) of almost pure 14: 1H NMR (CD6) δ 1.09 (s, 3 H), 1.39 (s, 3 H), 1.43 (s, 3 H), 1.54 (br s, 3 H), 1.72 (s, 3 H), 1.2–2.3 (m, 10 H), 2.31 (s, 3 H), 2.44 (br d, J = 13.2 Hz, 1 H), 4.42 (dd, J = 4.8, 11.2 Hz, 1 H); 13C NMR (CD6) δ 18.42 (q), 18.65 (t), 19.48 (q), 21.56 (q), 23.03 (2 q), 24.99 (t), 29.91 (t), 32.75 (t), 36.01 (t), 37.67 (q), 39.64 (s), 44.12 (d), 82.76 (s), 88.29 (d), 128 (s, obscured), 131.00 (s), 169.5 (s); MS m/z (relative intensity) 298 (M⁺ – 60, 2), 203 (63), 202 (92), 187 (100), 160 (29), 159 (91), 145 (38), 105 (26), 43 (47); HRMS calcd for C16H26O3S (M⁺ – 60) 298.1603, found 298.1603.

Ethyl (E,E)-α,α,4,8-tetramethyl-3,8-cyclodecadienemethanoate (15). To a stirred solution of 0.101 g (0.28 mmol) of 14 in 3 mL of THF was added 0.75 mL of BH3-SMe2 (2 M in THF) at 0 °C. The reaction mixture was stirred at rt overnight. The resulting white cloudy mixture was cooled to 0 °C and 1 mL of MeOH was added dropwise, immediately followed by 3 mL of NaOMe (2 M in MeOH). The reaction mixture was allowed to come to rt and stirred overnight. After addition of water, the mixture was extracted with tert-butyl methyl ether. The combined organic layers were washed with brine, dried, and evaporated. Column chromatography (10:1 hexane/tert-butyl methyl ether) gave 0.025 g (36%) of 15: 1H NMR (CD6) δ 1.13 (s, 6 H), 1.16 (t, J = 6.9 Hz, 3 H), 1.65 (br s, 6 H), 0.9–1.85 (m, 3 H), 2.1–2.56 (m, 8 H), 3.50 (q, J = 6.9 Hz, 2 H), 5.16 (br d, J = 10.8 Hz, 2 H); 13C NMR (CD6) δ 15.86 (2 q), 16.13 (q), 17.22 (t), 23.17 (2 q), 30.13 (2 t), 42.21 (2 t), 46.97 (d), 55.60 (t), 76.28 (s), 130.90 (2 d), 131.32 (2 s); MS m/z (relative intensity) 250 (M⁺, 14), 204 (72), 189 (51), 175 (25), 161 (75), 96 (62), 87 (100), 59 (70); HRMS calcd for C17H30O (M⁺) 250.2297, found 250.2292.
(E,E)-α,α,4,8-Tetramethyl-3,8-cyclodecadienemethanol (neohedycaryol, 4). To a stirred solution of 0.062 g (0.17 mmol) of 14 in 2 mL of THF was added 0.86 mL of BH₃·THF (1 M in THF) at 0 °C. The mixture was allowed to come to rt and stirred for 2 h. After cooling to 0 °C, 1 mL of MeOH was added dropwise, immediately followed by 3 mL of NaOMe (2 M in MeOH). The mixture was allowed to come to rt and stirred overnight. After addition of water, the mixture was extracted with petroleum ether (bp 40–60 °C). The combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in 3 mL of tert-butyl methyl ether and extracted four times with 2 mL of 20% aqueous AgNO₃. The combined aqueous layers were washed with 1 mL of tert-butyl methyl ether and cooled to 0 °C. After addition of 10 mL of 25% aqueous NH₃, the mixture was extracted with tert-butyl methyl ether. The combined organic layers were washed with brine, dried, and evaporated to give 0.004 g (11%) of 4: UV (MeCN) λ_max < 200 nm, tail to 270 nm; Kováts indices: 2341 (Stabilwax) and 1689 (DB-1); ¹H NMR (C₆D₆) δ 1.07 (s, 6 H), 1.64 (br s, 6 H), 0.75–1.75 (m, 4 H), 2.0–2.55 (m, 8 H), 5.14 (br d, J = 10.8 Hz, 2 H); ¹³C NMR (C₆D₆) δ 15.84 (2 q), 17.13 (t), 27.16 (2 q), 30.27 (2 t), 42.20 (2 t), 50.39 (d), 74.4 (s), 130.67 (2 d), 131.33 (2 s); MS m/z (relative intensity) 222 (M⁺, 15), 204 (62), 189 (36), 161 (100), 119 (40), 107 (35), 105 (54), 96 (73), 81 (80), 59 (63), 43 (34); HRMS calc'd for C₁₅H₂₆O (M⁺) 222.1984, found 222.1977.

Ethyl (2α,3αβ,3βα,6αα,6ββ)-decahydro-α,α,3b,6a-tetramethyl-2-cyclobuta[1,2:3,4]-dicyclopentenemethanoate (16). A solution of 0.008 g (0.03 mmol) of 15 in 4 mL of MeCN placed in a sealed quartz cuvet was irradiated for 3.5 h using a CAMAG Universal UV-lamp 29230. The reaction progress was monitored by GC. After completion, the solvent was evaporated to give 0.007 g (90%) of 16 (GC purity >96%): ¹H NMR δ 0.87 (s, 6 H), 1.15 (t, J = 7.0 Hz, 3 H), 1.17 (s, 6 H), 0.9–2.05 (m, 13 H), 3.38 (q, J = 7.0 Hz, 2 H); ¹³C NMR δ 16.24 (q), 18.79 (2 q), 23.43 (t), 23.76 (2 q), 28.84 (2 t), 42.96 (2 t), 43.24 (2 d), 45.40 (2 s), 51.50 (d), 56.00 (t), 75.58 (s); MS m/z (relative intensity) 204 (M⁺ – 46, 31), 189 (13), 161 (20), 96 (36), 87 (100), 81 (16), 59 (39), 43 (11); HRMS calc'd for C₁₆H₂₇O (M⁺ – 15) 235.2062, found 235.2057.

α-, β-, and γ-Eudesmol (3a, b, and c). To a stirred solution of 0.001 g (0.005 mmol) of 4 in 1 mL of CH₂Cl₂ was added a small crystal of p-TsOH·H₂O. After stirring at rt for 7 min, the mixture was diluted with CH₂Cl₂, washed with saturated aqueous NaHCO₃ and brine, and dried. After evaporation, the remaining residue was analyzed by GC and GC-MS. The product mixture consisted of α-eudesmol (3a), β-eudesmol (3b), and γ-eudesmol (3c) in a ratio of 1:2:1, respectively.56 Kováts indices on Stabilwax and DB-1, respectively: 3a 2224 and 1643; 3b 2233 and 1638; 3c 2171 and 1620.
5.5 References and Notes

1. The numbering system as given in structure 1 will be followed throughout the text of this chapter.


8. The 7-epi-eudesmanes are the antipodes of 5-epi-10-epi-eudesmanes and, consequently, possess the ent-configuration. For example, see: van Beek, T. A.; Kleis, R.; Posthumus, M. A.; van Veldhuizen, A. Phytochemistry 1989, 28, 1909.


15. All (E,Z)-germacranes (heliangolides) and (Z,E)-germacranes (melampolides) possess one or more lactone rings. An exception being helminthogermacrene, see: Winter, R. E. K.; Dorn, F.; Arigoni, D. J. Org. Chem. 1980, 45, 4786.
24. Only the interconversion of the conformations by rotation of the double bonds is considered.
34. $^1$H NMR δ 1.04 (s, 3 H), 1.15 (s, 6 H), 1.65 (br s, 3 H), 1.1–2.1 (m, 11 H), 2.55 (ddd, J = 2.2, 2.2, 12.5 Hz, 1 H), 3.74 (ddd, J = 4.4, 12.2 Hz, 1 H); $^{13}$C NMR δ 18.76 (q), 18.84 (t), 19.85 (q), 25.52 (t), 26.87 (q), 27.25 (q), 33.17 (t), 34.37 (t), 37.36 (t), 40.68 (s), 48.98 (d), 72.28 (s), 72.69 (d), 128.58 (s), 133.01 (s); MS m/z (relative intensity) 258 (M$^+$ + 2, 3), 256 (M$^+$, 9), 240 (33), 238 (100), 225 (7), 223 (21), 197 (20), 195 (60), 187 (34), 159
chapter 5

(36), 59 (48).


36. Initially, it was thought that just the presence of the homoallylic double bond frustrated the mesylation of 11, see: Shoppee, C. W.; Summers, G. H. R. J. Chem. Soc. 1952, 3361.


43. It was expected that the use of NaOMe in the Marshall fragmentation reaction would lead to cleavage of the acetate ester bond.

44. The BH₃-reduction of sterically hindered acetate groups to ethyl ethers has been described before, see: Dias, J. R.; Pettit, G. R. J. Org. Chem. 1971, 36, 3485.


46. The Marshall fragmentation reaction of a mesylate similar to 14 but lacking the C(7) substituent also proceeded in low yield (25%), see reference 35.

47. The Kováts indices in combination with GC-MS may be very helpful to detect 4 in complex mixtures of natural origin.


52. A simple double bond isomerization from (+)-hedecycaryl (1) to neohedecycaryl (4) can occur with negligible steric complaint.¹⁶

53. For a general description of the experimental procedures employed in this research, see § 3.3.

55. GC analysis revealed the presence of a small amount (<10%) of another compound, probably a double bond isomer of 10.

56. Reference 8, van Beek et al..
The Synthesis of Germacrane Sesquiterpenes Using Enolate-Assisted 1,4-Fragmentation Reactions

Abstract: enolate-assisted 1,4-fragmentation reactions have been used as the key step in the synthesis of (E,E)-germacrane sesquiterpenes, starting from racemic Wieland-Miescher ketone derivative 18. Compound 14 was fragmented using KHMDS in THF, but the reaction was attended by a retro-aldol reaction. Protection of the C(7) hydroxyl group avoided this retro-aldol reaction but the fragmentation product immediately underwent a Cope rearrangement. With an isopropylidene side chain, fragmentation was followed by L to Z isomerization of the conjugated double bond. With sodium tert-amylate as base, however, the (E,E)-cyclooctadiene 15 was isolated in good yield. This product was converted into germacrone B (39). Compound 46, possessing a protected 2-hydroxyisopropyl group, gave after fragmentation and reduction 15-hydroxyhedycaryl (48) in high yield. The planar chirality of 15-hydroxygermacrene B 15 was studied by NMR spectroscopy. An asymmetric Sharpless epoxidation reaction showed that 15 racemizes quickly at room temperature. The resulting epoxide of 15 underwent a transannular cyclization reaction to afford the cis-fused guaiane 49 in high ee. The epoxide of (E,Z)-cyclooctadiene 36 afforded trans-fused guaianes upon acid-induced cyclization.
6.1 Introduction*

As already mentioned in chapter 1, germacrane\(^1\) form one of the largest classes of sesquiterpenes\(^2\) which are biosynthetically produced by enzymatic cyclization of farnesyl pyrophosphate.\(^3\) The majority of known germacrane possesses the \((E,E)\)-cyclodeca-1(10),4-diene ring structure \(1^4\) as main structural characteristic (Scheme 6.1), but \((E,Z)\)-germacrane (heliangolides) and \((Z,E)\)-germacrane (melampolides) depicted by the structures 2 and 3, respectively, are also frequently found in nature.\(^2\)

\[\text{Scheme 6.1}\]

Guaiane sesquiterpenes \((5)\), containing a hydroazulene skeleton, are formed from germacrane \((1)\) by cyclization of the corresponding C(4)–C(5) epoxides \((4,\text{Scheme 6.2})\). Both trans- and cis-fused guaianes are known from natural sources, but direct evidence about the influence of the conformational and configurational features of the germacrane ring on the formation of guaianes is scarce,\(^5\) mainly because selective chemical epoxidation of the C(4)–C(5) double bond is difficult to realize.

\[\text{Scheme 6.2}\]

Because of their unique structure and general occurrence, germacrane sesquiterpenes have received much attention in modern organic chemistry.\(^6\) The main synthetic approaches towards the cyclodeca-1(10),4-diene ring system can be classified as intramolecular C–C bond formation, ring expansion reactions, and ring cleavage of bicyclic and tricyclic compounds (chapter 2).
In connection with the ring cleavage of bicyclic compounds, three different but closely related Grob-type reactions have to be mentioned. First, the Wharton fragmentation in which 5-cyclodecenones (7) are formed upon treatment of perhydroronaphthalene-1,3-diol monosulfonate esters (6) with strong bases (eq 1, Scheme 6.3). This method has been used several times in sesquiterpene synthesis, but suffers from the fact that only one C–C double bond is formed regio- and stereospecifically. Because problems are encountered in the conversion of the keto group into the second double bond present in the large majority of germacrane, its application in germacrane synthesis is limited.

The boronate fragmentation reaction introduced by Marshall circumvents this problem. Both double bonds are formed regio- and stereospecifically and the method has been applied in the synthesis of hedycaryol (9) (Scheme 6.3 and chapter 3) and its C(5)–C(6) and C(9)–C(10) double bond isomers allohedycaryol (chapter 4) and neochedycaryol (chapter 5), respectively. Because most functional groups are not compatible with the use of BH₃, and the regio- and stereoselectivity of the BH₃ addition to tetrasubstituted double bonds is usually moderate, the synthetic value of the boronate fragmentation in germacrane chemistry is limited as well.

Scheme 6.3
The third reaction, developed by Mander et al., involves an enolate-assisted fragmentation via α deprotonation of an ester function. The synthesis of the heliangelide sericenine (11) from ester 10 is the only known example of this approach in germacrane chemistry (eq 3, Scheme 6.3). The formation of an (E,Z)-germacrane ring system in this reaction resulted from isomerization of the conjugated double bond in the initially formed (E,E)-germacrane under the basic conditions applied. We realized that, if this isomerization of the C(4)–C(5) double bond could be prevented, the enolate-assisted 1,4-fragmentation would form an ideal method for the synthesis of (E,E)-germacranes. First, because of the regio- and stereospecific formation of both double bonds and, second, because the method creates the opportunity to synthesize germacranes in which the C(15) Me group is oxidized. The presence of such an oxidized C(15) Me group allows the regioselective epoxidation of the C(4)–C(5) double bond via allylic epoxidation and this will strongly facilitate the investigations on the biomimetic formation of guaiane sesquiterpenes. In addition, the asymmetric Sharpless epoxidation creates the possibility to develop a synthetic route toward enantiomerically enriched guianes in which chirality is introduced at a very late stage of the reaction sequence. Therefore, we decided to synthesize the aldehydes 14 and 17 (Scheme 6.4).

**Scheme 6.4**

We expected that fragmentation of 14 would lead to a selective formation of the (E,E)-germacrane derivative 13 without isomerization (E → Z) of the C(4)–C(5) double bond. In contrast to the fragmentation reaction of 10, isomerization is not expected because the carbon atom at the 7-position in 13 possesses sp³ hybridization which makes H-6 less acidic. Reduction of the aldehyde function in 13 and subsequent
elimination of water affording a conjugated diene system should then complete the synthesis of 15-hydroxygermacrene C (12). Similarly, fragmentation of 17 followed by reduction of the formed aldehyde 16 would lead to 15-hydroxygermacrene B (15). We realized that sp² hybridization at C(7) in 16 could lead to isomerization of the C(4)–C(5) double bond, but it was hoped that the use of only one equiv of strong base would suppress this undesired isomerization.

6.2 Results and Discussion

For the synthesis of the aldehyde 14, two slightly different reaction pathways were followed starting from the easily accessible racemic acetate 18¹⁶ (Scheme 6.5). By modest adaptations of existing procedures,¹⁷ 18 was converted into the known TBDMS ether 19¹⁸ and also into the mesylate 20, both in a six-step reaction sequence without the need of interim purification (see § 6.4). In this way, 19 and 20 were obtained in 31% and 55% overall yield, respectively, from acetate 18.

![Scheme 6.5](image)

Because the introduction of the isopropyl side chain at C(7) was not compatible with the presence of an aldehyde function at C(4), a methyl enol ether function was selected as a masked aldehyde. Whereas treatment of 19 with (methoxymethyl)triphenylphosphonium chloride¹⁹ and (dimethylsulfinyl)sodium in dry DMSO afforded the methyl enol ether 21 in high yield, application of these reaction conditions on mesylate
20 completely failed. Only the use of KHMD5 in THF in this reaction gave a moderate yield (48%) of the desired product 22. The problems encountered with this Wittig reaction, when applied on 20, can be explained by competitive abstraction of H-5 which leads to γ-elimination of the mesylate group, thereby forming a three-membered ring.20 The next step, hydrolysis of the dimethyl acetal function in 21 and 22 with PPTS in aqueous acetone,16 proceeded without problems and afforded 23 and 24, respectively, in almost quantitative yield.

At this stage of the reaction sequence, the isopropyl group at C(7) was introduced. Because addition of iPrMgCl to the keto group of 23 failed, probably as a result of enolization and reduction, iPrMgCl was transmetallated with CeCl3.21 With this cerium analog, 23 gave an easily separable 5:1 mixture of 25 and 26, respectively, in excellent yield (Scheme 6.6). In order to obtain reproducible high yields in this reaction, ultrasonic treatment of the CeCl₃ suspension turned out to be essential.22

Scheme 6.6

After removal of the TBDMS protecting group in 25 with TBAF in hot DMSO,23 treatment of the resulting alcohol 27 with MsCl in pyridine afforded the mesylate 28.24 Hydrolysis of the masked aldehyde function in 28 with 35% aqueous HClO₄ in ether25 completed the synthesis of 14 in which the aldehyde group most likely possesses an axial orientation.26 This route toward aldehyde 14 requires 12 steps from acetate 18 and
proceeds in ca 20% overall yield. In contrast to 23, the organocerium reaction mentioned above applied on 24 proceeded selectively and gave the mesylate 28 in 93% yield. Although this second route toward aldehyde 14 was slightly shorter (10 steps), the overall yield of 14 starting from acetate 18 was about the same.

With aldehyde 14 now in hand, we could start investigating the enolate-assisted 1,4-fragmentation reaction. Upon treatment of 14 with KHMD5 in THF,\textsuperscript{15} a fast reaction took place resulting in a product which partly decomposed during flash chromatography. Instead of the expected ten-membered ring system 13, the isolated product turned out to be the linear compound 29 (Scheme 6.7). The stereochemistry of the enal function in 29 follows from its \textsuperscript{1}H NMR spectrum.\textsuperscript{27} The formation of 29 can easily be explained by a vinologous retro-aldol reaction of the initially formed fragmentation product 13 under the basic reaction conditions used.\textsuperscript{28}

![Scheme 6.7](image)

In order to avoid this undesired retro-aldol reaction, the hydroxyl group in 14 was protected as its TMS ether 30.\textsuperscript{29} When 30 was treated with KHMD5 in THF, again a fast reaction took place with the rather unstable elemane-like compound 32 as the sole product that could be isolated (Scheme 6.8).

It is obvious that the formation of 32 proceeds via a Cope rearrangement of the initially formed intermediate 31.\textsuperscript{30} This [3,3]-sigmatropic rearrangement is a characteristic feature of (E,E)-cyclodeca-1(10),4-diene systems (§ 2.4) and makes the isolation of germacrane, also from natural sources, rather complicated.\textsuperscript{31} Because the Cope rearrangement can only take place via a chair-like transition state, the fast and selective formation of 32 may be an indication that intermediate 31 easily can adopt this chair-like conformation. The nature of the C(7) side chain has a profound impact on the conformational behavior of these compounds, so the rate of the Cope rearrangement
strongly depends on the stereochemistry at C(7) and structural features of the side chain. Another structural characteristic of 31 that might favor the Cope rearrangement is the aldehyde function at C(15). This has been concluded from the observation that natural germacrane aldehydes undergo Cope rearrangement at a much lower temperature than their corresponding alcohols or C(15) unfunctionalized derivatives. Thus, the presence of a C(15) aldehyde function combined with the structural features around C(7) might explain the easy Cope rearrangement of 31 to 32.

Scheme 6.8

It was known from the literature that an enolate-assisted fragmentation reaction had resulted in an (E,E)-cycloeca-1(10),4-diene system with sp\(^3\) hybridization at C(7) and a Me ester instead of an aldehyde function at C(15). Therefore it was hoped that conversion of aldehyde 30 into the corresponding Me ester 33 would hamper the Cope rearrangement. In order to check this possibility, the conversion of 30 into ester 33 was studied. Oxidation of 30 with chromium reagents was not successful. Whereas treatment of 30 with PCC in CH\(_2\)Cl\(_2\) gave no reaction at all, cleavage of the silyl ether bond and partial decarboxylation were observed with PDC in DMF. Oxidation was finally achieved in moderate yield using the RuO\(_4\)/NaIO\(_4\) couple, and the crude acid was directly converted into 33 with diazomethane. Unfortunately, treatment of 33 with KHMDS in THF only resulted in a complex product mixture and we decided to terminate this approach toward 15-hydroxygermacrene C (12).

Since none of the above approaches permitted isolation of an (E,E)-germacrane system, we decided to introduce an isopropylidene group at C(7). We opted for this
group because the introduction of an additional \(sp^2\) center in the ten-membered ring will partly relieve the strain,\(^{37}\) thereby diminishing the tendency towards Cope rearrangement. The introduction of the isopropylidene side chain at C(7) was easily achieved by treatment of 23 with isopropyltriphenylphosphonium iodide and (dimethylsulfanyl)sodium in DMSO to give 34 in high yield (Scheme 6.9). Further conversion of 34 into the crystalline aldehyde 17 was accomplished with standard procedures.

![Scheme 6.9](image)

Initially, the fragmentation reaction of 17 was studied in THF with ca one equiv of KHMDS. These reaction conditions led to the formation of a complex product mixture from which only the unstable aldehyde 35 could be isolated in rather poor yield (27\%, Scheme 6.10). In a similar fragmentation reaction of 17, the reaction mixture was in situ reduced with LAH at 0 °C. However, instead of the expected alcohol 36, this one pot reaction gave diol 37 (in 38\% yield) as the sole product that could be isolated.

From the first experiment it was concluded that, despite the fact that only one equiv of KHMDS was used, isomerization of the initially formed C(4)–C(5) \(E\) double bond immediately followed the fragmentation of 17. Support for this conclusion was obtained from the \(^{1}\text{H}\) NMR spectrum of aldehyde 35 in which a one-proton signal appears at \(\delta 9.28\) indicating the presence of an aldehyde group connected to a \(Z\) double bond.\(^{27}\) The formation of 37 in the second experiment can easily be explained by autoxidation of the trienol form of 35\(^{38}\) followed by reduction of the resulting hydroperoxide. This mechanism was supported by an experiment in which the fragmentation of 17 was performed under argon with a degassed solution of KHMDS in toluene. After quenching the reaction mixture with Red-Al instead of LAH, the \((E,Z)\)-germacrane alcohol 36 was obtained as the sole product in 77\% yield. Under these oxygen-free conditions, diol 37 was not formed at all.

Additional support for the \(Z\) geometry of the C(4)–C(5) double bond in 36 was obtained by its conversion into the known \((E,Z)\)-germacrane 38.\(^{39}\) Whereas treatment of 36 with SO\(_3\)•pyridine and in situ reduction of the resulting sulfate\(^{40}\) led to complex
product mixtures, partly caused by shifting of the C(4)–C(5) double bond,\textsuperscript{41} reduction of the phosphordiamidate of 36 with Li in EtNH\textsubscript{2}\textsuperscript{42} was more successful and provided a separable 1:1 mixture of the (E,Z)-germacrane 38 and another product similar to 38 but with one of the double bonds being reduced. The \textsuperscript{1}H NMR data of 38 were identical with those reported in the literature, and this finding unequivocally establishes the identity of 38. Reduction of the E C(1)–C(10) double bond in 38\textsuperscript{43} might explain the formation of the other product. This assumption was based on the empirical NMR rules developed for the structure elucidation of germacrane sesquiterpenes.\textsuperscript{44}

\begin{center} Scheme 6.10 \end{center}

![Scheme 6.10](image)

The fragmentation reactions of 17 with KHMDS as base also show that, regardless of the amount of KHMDS employed in these reactions, the \(E \rightarrow Z\) isomerization of the C(4)–C(5) conjugated double bond could not be avoided. It was therefore assumed that hexamethyldisilazane formed during these reactions would act as a basic catalyst for the isomerization and we decided to use sodium tert-amy late (NaOt-amy l) instead of KHMDS. NaOt-amy l in benzene or toluene is the most effective base-solvent combination in the fragmentation reactions of 1,4-diol monosulfonate esters\textsuperscript{45} and in contrast to hexamethyldisilazane, tert-amy l alcohol should not interfere with the reaction. When 17 was treated with one equiv of NaOt-amy l in toluene\textsuperscript{46} under oxygen-free conditions, a fast reaction took place resulting in the formation of the unstable (E,E)-germacrane aldehyde 16 and trace amounts of 35 (Scheme 6.11). The same reaction, but now combined with the in situ Red-Al reduction, afforded the corresponding alcohol 15 together with a small amount of 36. Purification was easily
achieved with aqueous AgNO₃ extraction⁴⁷ to give 15 in 72% yield, since 36 was not extracted with aqueous AgNO₃.⁴⁸ Support for the E geometry of the C(4)–C(5) double bond in 15 was obtained by its conversion into germacrene B (39).⁴⁹ Via a short treatment (5 min) of the phosphordiamidate of 15 with Li in EtNH₂,⁵⁰ 39 was obtained in 53% yield.

**Scheme 6.11**

Significant differences between the aldehydes 35 and 16 and between the alcohols 36 and 15 were observed in the ¹H NMR spectra of these compounds. The ¹H NMR spectrum of 35 shows the aldehyde singlet at δ 9.28, while the corresponding signal in the ¹H NMR spectrum of 16 appears at δ 9.93. These observations obey the empirical rules mentioned above.⁴⁴ Distinction between 36 and 15 can be made by comparing the multiplicities of the C(15) carbinol protons in their ¹H NMR spectra. A broad singlet was found for 36 and an AB-system for 15. Marshall and Flynn observed similar differences in the ¹H NMR spectra of related betweenanenes.⁵¹

Although no Cope rearrangement products were found in the fragmentation reactions of 17,⁵² this rearrangement can be used to make chemical distinction between 36 and 15. On the basis of their structures, it was expected that only 15 would show Cope rearrangement at elevated temperatures. A similar behavior has been observed for germacrene B.⁵³ Thus, when 15 was subjected to GC analysis, a "hump" was obtained suggesting that the compound was partly converted into its Cope rearrangement product on GC. When the injection temperature was raised to 250 °C, the "hump" changed into a sharp peak indicating complete conversion at that temperature. On the other hand, 36 appeared to be stable at higher temperatures as was concluded from its well-shaped peak on GC.

Although the results described above clearly show that both 35 and 16 (or 36 and 15, after reduction with Red-Al) can be synthesized selectively and in good yield from 17 by changing the base (KHMDS vs NaO-t-amyl), the reason for this difference in reaction outcome remains unknown. Our initial idea that hexamethylsilazane might act as a basic catalyst for the isomerization of 16 to 35 proved to be incorrect. This was concluded from an experiment in which 16 was exposed to hexamethyldisilazane in
toluene$^{54}$ at room temperature for 1 h. Although 16 partly decomposed, isomerization to 35 was not observed.

Summarizing the results thusfar, we can state that the enolate-assisted 1,4-fragmentation reaction with NaOt-amyl as base is a very useful method for the synthesis of (E,E)-germacranes with sp$^2$ hybridization at C(7) as the successful synthesis of germacrone B (39) clearly showed. The question raised, however, whether this method could also be employed for the synthesis of (E,E)-germacranes with sp$^3$ hybridization at C(7). We had already demonstrated that fragmentation of aldehydes with two bulky substituents at C(7), such as aldehyde 30, easily gave Cope rearrangement products. On the other hand, an (E,E)-germacrane like hedycaryol (9) with only one bulky substituent at C(7) is stable at room temperature and undergoes Cope rearrangement only at (slightly) elevated temperatures.$^{10a,55}$ These two facts combined led to the assumption that it should be possible to employ the enolate-assisted 1,4-fragmentation for the synthesis of (E,E)-germacranes in which only one C(7) substituent is present.$^{56}$ In order to test this hypothesis, we decided to synthesize the aldehyde 46 with a protected 2-hydroxyisopropyl side chain at C(7). Fragmentation of 46 using NaOt-amyl as a base, subsequent reduction with Red-Al, and deprotection should then lead to the unnatural germacrine sesquiterpene 15-hydroxyhedycaryol (48).

The conversion of the keto group of perhydro-2(3H)-naphthalenones into a 2-hydroxyisopropyl group has been studied extensively. Most of the procedures developed for this purpose use either borane$^{57}$ or strong acids.$^{16}$ The use of these reagents, however, is not compatible with the presence of an enol ether. Marshall et al.$^{58}$ followed another approach and converted the keto group into a nitrile function. The reaction sequence employed for this conversion involved reduction, tosylation, and nucleophilic displacement. The nitrile function in turn was converted into an 2-hydroxyisopropyl group by addition of MeLi, hydrolysis of the resulting imine, and again addition of MeLi. We decided to follow this approach, except that the three-step reaction sequence to convert the C(7) keto group into a nitrile was replaced by a direct one-step procedure using tosylmethyl isocyanide (TosMIC).$^{59}$

For the synthesis of aldehyde 46, the TBDMS ether 23 was the starting material (Scheme 6.12). Treatment of 23 with TosMIC gave 40 as an epimeric mixture of two nitriles. Addition of MeLi to 40 afforded, after basic hydrolysis, selectively compound 41 possessing an equatorial acyl group.$^{58}$ The introduction of the second Me group was performed with the cerium analog of MeLi to avoid enolization of the acyl group in 41. In this way, 42 was obtained in excellent yield. After cleavage of the TBDMS ether function in 42 with TBAF, treatment of the resulting alcohol 43 with MsCl afforded the mesylate 44. Subsequent hydrolysis of the enol ether function in 44 with 35% aqueous
HClO₄ in ether afforded aldehyde 45 in excellent yield. Treatment of 45 with chlorotriethylsilane (TESCl) gave the corresponding TES ether 46 in 56% yield. This protection of the C(11) hydroxyl group was needed to avoid the use of more than 1 equiv of base in the fragmentation step.

The fragmentation reaction of 46 was performed with 1 equiv of NaOt-amy1 in toluene and afforded, after reduction and workup, almost pure 47 in high yield (Scheme 6.13). No Cope rearrangement products were found. Removal of the TES protecting group in 47 was achieved by treatment with TBAF in THF, and the following purification by aqueous AgNO₃ extraction afforded pure 15-hydroxyhedycaryol (48) in good yield. Just as for hedycaryol (9), the ¹H NMR spectrum of 48 indicates the presence of at least three distinct conformers at room temperature.
6.3 The Biomimetic Synthesis of Guaiane Sesquiterpenes

Previous studies by Sutherland et al. on the biomimetic cyclization of \((E,E)\)-germacranes have shown that germacrene B epoxides undergo acid-catalyzed cyclization to eudesmane and guaiane sesquiterpenes.\(^{62}\) In these transannular cyclization reactions, the conformational features of the \((E,E)\)-germacrane involved are important. First, the double bonds in \((E,E)\)-germacranes form chiral planes because these double bonds are positioned more or less perpendicular to the plane of the ten-membered ring (§ 1.3).\(^{63}\) Second, because the Me groups C(14) and C(15) can be located at both sides of the ten-membered ring, \((E,E)\)-germacranes can exist in four distinct conformations. The C(6)–C(7)–C(8)–C(9) array is the third stereoelement in the ten-membered ring but the geometry of this array is mostly determined by the substituent at C(7) which tends to a pseudo-equatorial position. As pointed out by Wharton,\(^{61a}\) three interconversion operations can therefore be described: rotation of the C(1)–C(10) double bond, rotation of the C(4)–C(5) double bond, and a change in the C(6)–C(7)–C(8)–C(9) array.\(^{64}\) For both germacrene B (39) and 15-hydroxygermacrene B (15), the situation is somewhat more complex. Although 15 and 39 do not contain a chiral center, these compounds are chiral because of the presence of two \(E\) double bonds in the ten-membered ring. As a consequence, the three stereoelements mentioned above count for eight possible conformers of 15 and 39: four diastereomers and their enantiomers.

For simplicity, only the interconversion of the conformations by rotation of the endocyclic double bonds will be considered. According to MM2\(^{65}\) and MNDO\(^{66}\) calculations on 39, the so-called crown conformation in which the endocyclic double bonds possess the crossed orientation is energetically most stable, but the energy difference with other conformers is small. The preference of 39 for the crown conformation is supported by the X-ray analysis of the 1:1 adduct of 39 with AgNO\(_3\).\(^{37}\) This X-ray analysis also revealed the presence of both the enantiomers (S,S)-39 and (R,R)-39 (1:1 ratio) in the adduct.\(^{67}\) In other studies it was suggested that resolution of germacrene B would be possible under strictly controlled conditions but that the resolved enantiomer should be susceptible to racemization.\(^{68}\) It is therefore intriguing to study the chiral stability of germacrene B (39) and related compounds\(^{69}\) in more detail, all the more so because it is assumed that the formation of 39 in vivo is probably enantioselective.\(^{70}\)

The successful synthesis of 15-hydroxygermacrene B (15) allowed us to study its conformational behavior and enantiomer composition by NMR experiments. The signals in the NMR spectra of 15 and 39 at rt are broadened but singular. Information about the conformational behavior of 15 was obtained from \(^1\)H NMR experiments at
low temperatures. Beside line broadening the number of signals increased, indicating
the presence of more than one conformer. Although this observation does not imply
that 15 racemizes at rt, it shows that at this temperature an averaged $^1$H NMR spectrum
is obtained.

The enantiopure shift reagent (+)-Eu(hfc)$_3$ was used to determine the enantiomer
composition of 15.$^{71}$ In the normal $^1$H NMR spectrum of 15, the carbinol protons
appear as an AB system ($J = 11.7$ Hz, $\Delta v/J = 5.4$). After addition of Eu(hfc)$_3$, the signals
are strongly shifted and doubled. This latter effect results from the racemic nature of
15.$^{72}$

A direct way to establish the chiral stability of 15 involves the asymmetric Sharpless
epoxidation,$^{73}$ performed as a kinetic resolution. The ee of the recovered starting
material can be determined with the aforementioned Eu(hfc)$_3$ method. It is obvious that
this ee will depend on the racemization rate. A priori, it was expected that this
Sharpless epoxidation would proceed highly diastereoselectively because the $\pi$
lobe of the C(4)–C(5) double bond at the interior of the ten-membered ring of 15 is effectively
shielded and not available for reaction. It was also expected that the resulting epoxide
would be prone to cyclization because of the presence of titanium species acting as
Lewis acids. As discussed in § 6.1, this cyclization of the C(4)–C(5) epoxide of 15
represents an important step in the biosynthesis of guaiane sesquiterpenes (Scheme
6.2).

The Sharpless epoxidation of 15 was carried out following well-described procedures
with (+)-diethyl tartrate (DET) as the chiral ligand.$^{74}$ The reaction was designed as a
kinetic resolution using 0.55 equiv of tert-butyl hydroperoxide (t-BuOOH) and
stoichiometric amounts of the titanium complex. Aqueous AgNO$_3$ extraction and
chromatographical purification were applied to regain unreacted starting material
(46%). $^1$H NMR experiments with Eu(hfc)$_3$ indicated that this recovered 15 was
racemic,$^{75}$ which indicates that ring inversion of 15 is rapid at room temperature.
Consequently, 15 and most likely also germacrene B (39) are not enantiomerically stable
at room temperature.

Together with small amounts of unidentified products, this asymmetric Sharpless
epoxidation of 15 with 0.55 equiv of t-BuOOH produced the optically active guaiane 49
([$\alpha$]$_D$ $-$52$^o$) in 17% yield. Chiral GC showed that 49 was formed in 92% ee.$^{76}$ Initially, the
elucidation of the stereochemistry of 49 was troublesome because of overlapped signals
in its $^1$H NMR spectrum in CDCl$_3$ and in C$_6$D$_6$. Fortunately, the use of a 1:1:1 mixture of
CDCl$_3$, C$_6$D$_6$, and C$_5$D$_5$N as solvent resulted in unobscured signals for both the
bridgehead protons H-1 and H-5. NOE-difference experiments showed a clear NOE
between these two protons, thereby establishing the cis fusion of the guaiane skeleton.
The NOE observed between H-1 and the isopropoxy group ascertained the
stereochemistry at C(10). Because the C(15) carbinol group and H-5 necessarily possess the trans orientation, the stereochemistry of 49 is as depicted in Scheme 6.14. The assignment of the absolute configuration of 49 is based on the Sharpless model for allylic alcohol epoxidations.  

**Scheme 6.14**

![Scheme 6.14](image)

(S,S)-15: R = OH  
(S,S)-39: R = H  
(R,R)-15: R = OH  
(R,R)-39: R = H

The formation of 49 can simply be explained by epoxide ring opening, transannular cyclization, and incorporation of isopropanol present in the reaction medium. This mechanism is consistent with the findings of Sutherland et al.62 Because no epimers or elimination products of 49 could be detected, the formation of 49 probably proceeds in a concerted manner. It is possible that in vivo cyclization of germacrone B (39) via enzymatic enantioselective epoxidation leads to enantiomerically enriched guaiaines.77

Summarizing these results, the stereochemistry found for 49 indicates that 15 reacts from the S,S conformation. Although other stereochemical courses for the cyclization of (E,E)-germacranes can not be excluded,78 in this particular case the relation between an (E,E)-germacrane and a cis-guaiane has been established. Furthermore, it is demonstrated that 15 and probably also germacrone B racemize quickly at rt. Consequently, these compounds can not be added to the list of enantiomerically stable (E)-cycloalkenes.63 The formation of 49 in 56% ee upon Sharpless epoxidation of 15 performed with 1.1 equiv of t-BuOOH at −23 °C indicates that, during the reaction, the racemization of 15 can not keep up with the epoxidation of the preferably reacting enantiomer which is therefore not completely replenished.
Beside guaianes possessing a cis-fused ring system, a number of trans-fused guaianes has been found in nature. It has been postulated that the biosynthesis of trans-guaianes proceeds via the C(4)–C(5) epoxides of melampolides (3). The isolation of trans-guaianes possessing a cis relationship between C(15) and H-5, however, points to a heliangolide precursor (2) containing a Z C(4)–C(5) double bond. In order to study the cyclization of C(4)–C(5) epoxy heliangolides, (E,Z)-alcohol 36 was converted into its mono-epoxide and subjected to cyclization. Although chiral, like 15, 36 is expected to racemize quickly at rt because the barrier for rotation of the E-(1,10) double bond is low.

The Sharpless epoxidation of 36 (Scheme 6.15), carried out with excess t-BuOOH, was slow compared to 15 and afforded, after workup, the stable epoxide 50 ([α]_D
–145°). The sharp signals and couplings in the ¹H NMR spectrum indicate that 50 is present as one conformer. Acid treatment of 50 afforded in a fast reaction a mixture of essentially four products in a 1:1:1:4 ratio as judged by GC. Careful chromatography on silica gel afforded a pure compound which ¹H NMR spectrum showed typically a vinylic one-proton signal at δ 5.32 and a Me doublet at δ 1.02. These data together with other ¹H and ¹³C NMR data are consistent with structure 52. The formation of 52 probably proceeds via the intermediate carbocation 51 and two 1,2-H shifts (C(1)→C(10) and C(5)→C(1)) followed by elimination of a proton at C(6). Because tandem 1,2-H shifts are suprafacial and occur most likely via a concerted process, the orientation of both bridgehead protons in cation 51 is trans. This information, combined with the cis relationship between H-5 and the C(15) carbinol group establishes the stereochemistry of 52, as depicted.

Scheme 6.15
A number of guaianes with a C(5)–C(6) double bond and a cis relationship between H-1 and the C(14) Me group has been found in plants and the formation of these guaianes probably involves these 1,2-H shifts. A similar route has been suggested for the biosynthesis of the pseudoguaianes. In this biosynthesis the 1,2-H shifts are followed by a C(4)→C(5) shift of the C(15) Me or carbinol group. The latter shift is not expected in the cyclization of 50 because of the cis relationship between C(15) and H-5. Trans-fused guaianes, pseudoguaianes, and guaianes with a C(5)–C(6) double bond co-occur in the same plant species.

Purification of the remaining product mixture on AgNO₃ impregnated silica gel afforded 53 as main product and a small amount of the exocyclic double bond isomer 54. Assuming that all three products are derived from the same intermediate cation 51, the stereochemistry of 54 is probably as depicted.

These results show, that trans-fused guaianes are obtained using 50 as a model for the biosynthetic cyclization of 4,5-epoxy-heliangolides (2). The 1,2-H shifts which probably occur in the biosynthesis of Δ⁵,⁶-guaianes and pseudoguaianes are also observed in this cyclization reaction.

6.4 Experimental Section

Materials. All reagents were purchased from Aldrich or Janssen except for N,N,N′,N′-tetramethylphosphorodiamidic chloride (TMPDCl) which was purchased from Fluka. (Methoxymethyl)triphenylphosphonium chloride and isopropyltriphenylphosphonium iodide were dried in a vacuum dessicator over P₂O₅ before use. The compounds 18, 19, 38, and 39 have been characterized before.

(4α,5α)-(±)-5-Acetoxy-4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalene (18). To a stirred solution of crude (4α,5α)-(±)-4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalene (prepared from 2-methylcyclohexane-1,3-dione (100 g, 0.79 mol) and freshly distilled methyl vinyl ketone (129 mL, 1.58 mol) following known procedures) in 500 mL of dry pyridine was added dropwise 252 mL of Ac₂O at 10–15 °C. When the addition was complete, the reaction mixture was stirred at rt for 3 d. Standard workup gave an oil which was taken up in 500 mL of diisopropyl ether and left overnight to crystallize. The crystals were filtered off to give 60.9 g of pure 18. The mother liquor was concentrated and dissolved in a mixture of 150 mL of diisopropyl ether and 50 mL of petroleum ether (bp 40–60 °C). After standing overnight at 0 °C, a second crop (9.7 g) of pure 18 was obtained. The remaining mother liquor was concentrated and afforded, after flash chromatography (4:1 petroleum ether (bp 40–60 °C)/EtOAc) and crystallization from diisopropyl ether, a third portion (17.0 g) of pure
18. The total yield of pure 18 amounted to 87.6 g (50% overall from 2-methylcyclohexane-1,3-dione). The spectroscopic data of 18 are identical with those reported in the literature.20

(4α,4αα,8αβ)-(±)-Octahydro-7,7-dimethoxy-4a-methyl-4-[[1(1,1-dimethylethyl)dimethylisilyl]oxy]-1(2H)-napthalenone (19). To a stirred solution of 87.6 g (398 mmol) of 18 and 250 g NaI in 600 mL of Ac₂O was added dropwise 200 mL of TMSCl over a period of 30 min at 0 ºC. After being stirred at 0 ºC for 1 h, the reaction mixture was filtered and concentrated under reduced pressure. The concentrate was carefully mixed with 500 mL of saturated aqueous NaHCO₃ and, after addition of 120 g of Na₂S₂O₅, stirred at 0 ºC for 1 h. The aqueous layer was then extracted with three 500 mL portions of EtOAc. The combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried, and evaporated to leave 103 g of a brown oil. To a solution of this oil in 850 mL of MeOH was added 250 g of NaHCO₃. The mixture was stirred vigorously, and then 1.3 L of 1 M oxone in water was added dropwise at 0 ºC. After stirring at 0 ºC for 2.5 h, an additional 130 mL of 1 M oxone in water was added dropwise. The reaction mixture was stirred 0 ºC for another 1 h and then filtered. After removal of MeOH under reduced pressure, the remaining aqueous phase was extracted with four 500 mL portions of CH₂Cl₂. The combined organic layers were washed with brine, dried, and evaporated to leave 71 g of a yellow solid. To a stirred solution of this solid in a mixture of 280 mL of CH₂Cl₂ and 800 mL of ether was added 5 mL of 47% aqueous HBr. After being stirred at rt for 45 min, the reaction mixture was cooled to 0 ºC and mixed with 250 mL of saturated aqueous NaHCO₃. The two-phase mixture was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to leave 67 g of a brown solid. To a stirred solution of this solid in 1.4 L of CH₂Cl₂ was added 105 mL of trimethyl orthoformate and 1.4 g of TsOH. After being stirred at rt for 2.5 h, the reaction mixture was quenched with 15 mL of Et₃N, washed with brine, dried, and evaporated to leave 82 g of a brown oil. To a stirred solution of this oil in 1 L of dry MeOH was added dropwise 200 mL of 0.076 M NaOMe in dry MeOH. The reaction mixture was stirred at rt overnight and concentrated under reduced pressure to a volume of ca 250 mL. After addition of 2 L of CH₂Cl₂, the organic layer was washed with 200 mL of water and 400 mL of brine, dried, and evaporated to leave 55 g of a dark brown oil. This oil was taken up in 400 mL of diisopropyl ether and filtered. Evaporation of the filtrate afforded 50 g of crude octahydro-4-hydroxy-7,7-dimethoxy-4a-methyl-1(2H)-napthalenone as a light brown oil.88 This oil was dissolved in 270 mL of dry DMF, and then 35.0 g (515 mmol) of imidazole and 37.4 g (248 mmol) of TBDMSCl were added. The reaction mixture was stirred at rt overnight and then poured into 600 mL of ice-water. The aqueous layer was
extracted with five 250 mL portions of petroleum ether (bp 40–60 °C). The combined organic layers were washed with brine, dried, and evaporated to leave ca 70 g of crude 19. Flash chromatography (20:1 to 3:1 petroleum ether (bp 40–60 °C)/EtOAc) and recrystallization from dry EtOH afforded 44.4 g (31% overall from 18) of pure 19. The spectroscopic data of 19 are identical with those reported in the literature.18b

(4α,4αα,8αβ)-(±)-Octahydro-7,7-dimethoxy-4a-methyl-4-[(methylsulfonyl)oxy]-1(2H)-naphthalenone (20). The procedures described above for the synthesis of 19 were employed with the exception of the silylation step which was replaced by the following mesylation procedure. To a stirred solution of 14.9 g of crude octahydro-4-hydroxy-7,7-dimethoxy-4a-methyl-1(2H)-naphthalenone in 100 mL of pyridine was added 11 mL (143 mmol) of MsCl at 0 °C. The reaction mixture was allowed to come to rt, stirred for 4 h, and concentrated under reduced pressure. The concentrate was taken up in EtOAc, mixed with saturated aqueous NaHCO₃, and stirred for 10 min. After addition of water and separation of the two-phase mixture, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (3:1 to 1:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 16.13 g (55% overall from 18) of 20 as an oil: ¹H NMR δ 0.82 (s, 3 H), 0.90–2.51 (m, 11 H), 3.02 (s, 3 H), 3.06 (s, 3 H), 3.16 (s, 3 H), 4.81 (dd, J = 4.5, 11.5 Hz, 1 H); ¹³C NMR δ 11.29 (q), 26.79 (t), 27.39 (t), 27.90 (t), 33.25 (t), 38.10 (t), 38.79 (q), 41.37 (s), 47.43 (q), 47.74 (q), 51.07 (d), 85.68 (d), 99.56 (s), 208.04 (s); MS m/z (relative intensity) 320 (M⁺, 23), 289 (54), 224 (25), 193 (46), 114 (41), 101 (100), 88 (28), 84 (40); HRMS calcd for C₁₄H₂₄O₆S (M⁺) 320.1294, found 320.1290.

(4αα,5α,8αβ)-(±)-Decahydro-2,2-dimethoxy-8-(1-methoxymethylene)-4a-methyl-5-[[1,1-dimethylethyl]dimethylsilyl]oxy]naphthalene (21). To 210 mL of 0.40 M (dimethylsulfinyl)sodium in DMSO was added with stirring 100 mL of THF at rt. The solution was cooled to 0 °C and, after addition of a slurry of 30.0 g (85 mmol) of (methoxymethyl)triphenylphosphonium chloride in 50 mL of DMSO, stirred at 0 °C for 1 h. To the dark red reaction mixture was then added, via syringe, a solution of 14.81 g (41.6 mmol) of 19 in 40 mL of THF. Stirring was continued at 0 °C for 0.5 h and at rt for 1 h. The reaction mixture was poured into ice-water and extracted with ether. The combined organic layers were washed with brine, dried and evaporated. Flash chromatography (100:1 to 12:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 14.25 g (89%) of 21 as a clear oil: ¹H NMR δ 0.00 (s, 6 H), 0.66 (s, 3 H), 0.84 (s, 9 H), 1.05–1.94 (m, 10 H), 2.76 (ddd, J = 2.0, 4.5, 11.0 Hz, 1 H), 3.11 (s, 3 H), 3.19 (s, 3 H), 3.30 (dd, J = 4.3, 10.9 Hz, 1 H), 3.51 (s, 3 H), 5.47 (br s, 1 H); ¹³C NMR δ –4.75 (q), –3.93 (q), 9.57 (q), 18.03 (s), 23.75 (t), 25.85 (3 q), 28.34 (t), 29.67 (t), 31.07 (t), 33.59 (t), 40.44 (s), 41.15 (d), 47.45 (q),
(1α,4αβ,8αα)-(±)-Decahydro-6,6-dimethoxy-4-(1-methoxymethylene)-8a-methyl-1-naphthalenol methanesulfonate (22). To a stirred suspension of 6.08 g (17.2 mmol) of (methoxymethyl)triphenylphosphonium chloride in 45 mL of THF was added dropwise 35.4 mL of KHMS (15% in toluene) at −40 °C. When the addition was complete, the reaction mixture was stirred at 0 °C for 20 min. To the resulting deep red solution was added, via syringe, a solution of 1.891 g (5.91 mmol) of 20 in 10 mL of THF. After being stirred at 0 °C for 15 min, the reaction mixture was allowed to come to rt and then stirred for an additional 4 h. The brown reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.977 g (2.81 mmol, 48%) of 22: mp 118 °C (from diisopropyl ether); 1H NMR δ 0.75 (s, 3 H), 1.07–2.08 (m, 10 H), 2.85 (dd, J = 2.2, 9.0 Hz, 1 H), 2.97 (s, 3 H), 3.09 (s, 3 H), 3.18 (s, 3 H), 3.52 (s, 3 H), 4.42 (dd, J = 4.9, 11.2 Hz, 1 H), 5.51 (br s, 1 H); 13C NMR δ 10.17 (q), 23.33 (t), 27.70 (t), 28.44 (t), 29.49 (t), 32.91 (t), 38.77 (q), 39.43 (s), 41.31 (d), 47.46 (q), 47.59 (q), 59.57 (q), 89.99 (d), 99.94 (s), 115.08 (s), 140.61 (d); MS m/z (relative intensity) 316 (M+ − 32, 100), 285 (37), 271 (14), 221 (21), 220 (15), 205 (17), 189 (23), 173 (11), 101 (12), 85 (20), 83 (26), 79 (12); HRMS calcd for C15H24O5S (M+ − 32) 316.1344, found 316.1340. Anal. Calcd for C16H28O6S: C, 55.15; H, 8.10. Found: C, 54.96; H, 8.13.

(4αα,5αα,8αβ)-(±)-Octahydro-8-(1-methoxymethylene)-4a-methyl-5-[[1,1-dimethyl-ethyl]dimethylsilyloxy]-2(3H)-naphthalenone (23). To a solution of 16.2 g (42.2 mmol) of 21 in 250 mL of acetone and 25 mL of water was added 5 g of PPTS. After being stirred at rt for 1 h, the reaction mixture was diluted with EtOAc, washed with saturated aqueous NaHCO3 and brine, and dried. Evaporation and flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 13.98 g (98%) of 23 as a white solid: mp 101 °C (from diisopropyl ether); 1H NMR δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 0.88 (s, 3 H), 1.10–1.69 (m, 6 H), 2.03–2.50 (m, 4 H), 2.82 (dd, J = 3.9, 10.5 Hz, 1 H), 3.31 (dd, J = 4.7, 10.7 Hz, 1 H), 3.54 (s, 3 H), 3.77 (br s, 1 H); 13C NMR δ −4.87 (q), −3.92 (q), 9.41 (q), 17.99 (s), 23.62 (t), 25.79 (3 q), 30.71 (t), 36.80 (t), 37.64 (t), 39.69 (t), 40.27 (s), 45.26 (d), 59.59 (q), 79.31 (d), 116.41 (s), 140.33 (d), 211.64 (s); MS m/z (relative intensity) 338 (M+, 21), 282 (24), 281 (100), 206 (48), 189 (21), 171 (30), 75 (33), 73 (16); HRMS calcd for C19H34O3Si (M+) 338.2277, found 338.2274. Anal. Calcd for C19H34O3Si: C, 67.42; H, 10.13. Found: C, 67.53; H, 10.38.
(4α,5α,8αβ)-(-)-Octahydro-8-(1-methoxymethylene)-4a-methyl-5-[(methylsulfonyl)oxy]-2(3H)-naphthalenone (24). The mesylate 22 (1.396 g, 4.01 mmol) was treated with PPTS for 1.5 h as described for 21. Workup and flash chromatography (2:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 1.123 g (93%) of 24 as a white solid: mp 107 °C (from diisopropyl ether/acetone); 1H NMR δ 0.98 (s, 3 H), 1.52–1.90 (m, 3 H), 2.02–2.42 (m, 7 H), 2.93 (ddd, J = 2.3, 2.3, 10.5 Hz, 1 H), 3.00 (s, 3 H), 3.56 (s, 3 H), 4.44 (dd, J = 4.9, 11.4 Hz, 1 H), 5.51 (br s, 1 H); 13C NMR δ 10.02 (q), 23.23 (t), 28.18 (t), 35.87 (t), 37.03 (t), 39.01 (q), 39.20 (t), 39.24 (s), 45.13 (d), 59.80 (q), 88.84 (d), 114.01 (s), 141.50 (d), 209.80 (s); MS m/z (relative intensity) 302 (M+, 94), 207 (40), 206 (100), 191 (24), 174 (23), 159 (17), 135 (20), 132 (17), 131 (18), 119 (23), 105 (18), 79 (17); HRMS calcd for C14H22O5S (M+) 302.1188, found 302.1189. Anal. Calcd for C14H22O5S: C, 55.61; H, 7.33. Found: C, 55.38; H, 7.34.

(2α,4αβ,5β,8α)- and (2α,4αβ,5α,8αβ)-(-)-Decahydro-8-(1-methoxymethylene)-4a-methyl-2-(1-methylthyl)-5-[[1,1-dimethylthyl(dimethylsilyl)oxy]-2-naphthalenol. (25 and 26). Anhyd CeCl3 (prepared from 3.15 g (8.45 mmol) of CeCl3⋅7H2O according to the procedure of Imamoto et al.)21 and 20 mL of THF were mixed at 0 °C and stirred at rt overnight under argon. The flask was then placed in an ultrasonic bath for 1.5 h. To the resulting fine dispersion was added, via syringe, 8.3 mL of iPrMgCl (ca 1 M in Et2O) at 0 °C. The mixture was stirred at 0 °C for 2.5 h and then, via syringe, a solution of 0.940 g (2.78 mmol) of 23 in 10 mL of THF was added. After being stirred at 0 °C for another 0.5 h, the reaction mixture was treated with concentrated aqueous KF and extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (20:1 to 12:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.859 g (81%) of 25 and 0.170 g (16%) of 26, both as white solids. 25: mp 77–78 °C (from pentane); 1H NMR (500 MHz) δ 0.03 (s, 6 H), 0.63 (s, 3 H), 0.86 (s, 9 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.97 (s, OH), 1.34–1.70 (m, 10 H), 2.10 (ddd, J = 4.15, 13.5 Hz, 1 H), 2.79 (ddd, J = 1.6, 1.6, 13.4 Hz, 1 H), 3.36 (ddd, J = 4.4, 11.4 Hz, 1 H), 3.54 (s, 3 H), 5.48 (s, 1 H); 13C NMR δ –4.78 (q), –3.96 (q), 9.11 (q), 16.78 (q), 16.84 (q), 18.02 (s), 23.77 (t), 25.83 (3 q), 28.98 (t), 31.09 (t), 31.27 (t), 32.31 (t), 39.00 (d), 39.65 (d), 40.37 (s), 59.38 (q), 73.30 (s), 79.61 (d), 118.35 (s), 139.33 (d); MS m/z (relative intensity) 382 (M+, 3), 364 (58), 322 (29), 321 (100), 232 (34), 189 (50), 163 (21), 132 (28), 123 (20), 75 (30), 73 (24); HRMS calcd for C22H42O3Si (M+) 382.2903, found 382.2900. Anal. Calcd for C22H42O3Si: C, 69.07; H, 11.07. Found: C, 69.03; H, 11.31. 26: mp 131–133 °C (from pentane); 1H NMR δ 0.02 (s, 6 H), 0.72 (s, 3 H), 0.85 (s, 9 H), 0.85 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.95–1.86 (m, 11 H), 2.01 (septet, J = 6.8 Hz, 1 H), 2.77 (dd, J = 2.2, 9.8 Hz, 1 H), 3.27 (dd, J = 4.2, 10.9 Hz, 1 H), 3.53 (s, 3 H), 5.52 (br s, 1 H); 13C NMR δ –4.77
(1α,4αβ,6β)-(±)-Decahydro-4-(1-methoxymethylene)-8a-methyl-6-(1-methylthyl)-1,6-naphthalenedioliol (27). To a solution of 0.865 g (2.26 mmol) of 25 in 15 mL of dry DMSO was added at once 5.13 mL of TBAF (1.1 M in THF) at 100 °C. The resulting brown reaction mixture was stirred at 100 °C for 80 min, poured into water, and extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (2:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.522 g (87%) of 27: mp 99 °C (from pentane/diisopropyl ether); 1H NMR δ 0.63 (s, 3 H), 0.95 (d, J = 6.8 Hz, 6 H), 1.10 (br s, OH), 1.32–1.80 (m, 11 H), 2.12 (dd, J = 5.0, 10.8 Hz, 1 H), 2.82 (ddd, J = 2.1, 2.1, 13.6 Hz, 1 H), 3.39 (dd, J = 4.3, 11.0 Hz, 1 H), 3.54 (s, 3 H), 5.48 (br s, 1 H); 13C NMR δ 8.93 (q), 16.80 (2 q), 23.76 (t), 28.84 (t), 30.38 (t), 30.97 (t), 31.66 (t), 38.98 (d), 39.43 (d), 39.76 (s), 59.41 (q), 73.21 (s), 79.18 (d), 117.87 (s), 139.58 (d); MS m/z (relative intensity) 268 (M⁺, 2), 250 (15), 208 (14), 207 (100), 175 (17), 131 (14), 69 (5); HRMS calcd for C₁₆H₂₈O₃ (M⁺) 268.2038, found 268.2036. Anal. Calcd for C₁₆H₂₈O₃: C, 71.60; H, 10.52. Found: C, 71.85; H, 10.73.

(2α,4αβ,5β,8αα)-(±)-Decahydro-8-(1-methoxymethylene)-4a-methyl-2-(1-methylthyl)-5-[(methylsulfonfonyl)oxy]-2-naphthalenol (28). a. To a stirred solution of 0.194 g (0.72 mmol) of 27 in 3 mL of pyridine was added 0.084 mL (1.09 mmol) of MsCl at rt. The reaction mixture was stirred at rt for 1.5 h and, after addition of water, extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (3:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.247 g (99%) of 28: mp 101 °C (from diisopropyl ether); 1H NMR δ 0.66 (s, 3 H), 0.86 (d, J = 6.8 Hz, 6 H), 1.20–2.01 (m, 11 H), 2.18 (br d, J = 9.8 Hz, 1 H), 2.81 (dd, J = 2.1, 9.1 Hz, 1 H), 2.93 (s, 3 H), 3.49 (s, 3 H), 4.41 (dd, J = 4.8, 11.2 Hz, 1 H), 5.47 (br s, 1 H); 13C NMR δ 9.74 (q), 16.76 (2 q), 23.38 (t), 28.48 (t), 28.64 (t), 30.65 (t), 31.72 (t), 38.57 (q), 38.82 (d), 39.41 (d), 39.63 (s), 59.45 (q), 72.79 (s), 90.49 (d), 115.84 (s), 140.37 (d); MS m/z (relative intensity) 328 (M⁺ – 18, 12), 287 (7), 286 (19), 285 (100), 207 (7), 189 (11), 157 (10), 83 (8); HRMS calcd for C₁₇H₂₈O₄S (M⁺ – 18) 328.1708, found 328.1708. Anal. Calcd for C₁₇H₃₀O₅S: C, 58.93; H, 8.73. Found: C, 59.14; H, 8.93.

b. The mesylate 24 (1.126 g, 3.73 mmol) was treated with iPrMgCl and CeCl₃ for 2.5 h as described for 23. Workup and flash chromatography (2:1 petroleum ether (bp 40–60
\( ^{1}C /\text{EtOAc} \) afforded 1.197 g (93\%) of pure 28 as the sole product.

(1\( \alpha \),4\( \alpha \),4a\( \alpha \),7\( \beta \),8\( a\( \beta \))-\( \pm \)-Decahydro-7-hydroxy-4a-methyl-7-(1-methylethyl)-4-[(methylsulfonfonyl)oxy]-1-naphthalencarboxaldehyde (14). To a stirred solution of 0.500 g (1.44 mmol) of 28 in 20 mL of ether was added dropwise 4 mL of 35\% aqueous HClO\(_4\) at 0 \( ^{\circ} \)C. The solution was allowed to come to rt and stirred for 1 h. After addition of water, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO\(_3\) (twice) and brine, dried over Na\(_2\)SO\(_4\), and evaporated. Flash chromatography (1:1 petroleum ether (bp 40–60 \( ^{\circ} \)C)/EtOAc) gave 0.463 g (97\%) of 14 as an oil.\(^{89} \) \( ^{1}H \) NMR \( \delta 0.68 \) (s, 3 H), 0.86 (d, \( J = 6.8 \) Hz, 6 H), 1.30–2.32 (m, 14 H), 2.92 (s, 3 H), 4.30 (dd, \( J = 6.0 \), 10.4 Hz, 1 H), 9.82 (br s, 1 H); \( ^{13}C \) NMR \( \delta 11.39 \) (q), 16.63 (q), 16.72 (q), 23.03 (t), 25.49 (t), 29.51 (t), 32.91 (t), 33.60 (t), 38.65 (d), 38.76 (q), 39.07 (s), 40.31 (d), 49.86 (d), 73.29 (s), 89.64 (d), 203.74 (d); MS \( m/z \) (relative intensity) 289 (M\(^+\) - 43, 100), 261 (37), 193 (98), 163 (31), 147 (52), 105 (30), 83 (30), 81 (44), 57 (37), 55 (38), 43 (52); HRMS calcd for C\(_{13}\)H\(_{21}\)O\(_{5}\)S (M\(^+\) - 43) 289.11097, found 289.11095.

\((E,\,E)\)-2-Ethylidene-6,10-dimethyl-9-oxo-5-undecenal (29). To a stirred solution of 1.46 mL of KHMDS (0.5 M in toluene) in 4 mL of dry THF was added dropwise, via syringe, a solution of 0.097 g (0.29 mmol) of 14 in 2 mL of THF at rt. The reaction mixture was stirred at rt for 10 min and, after addition of saturated aqueous NH\(_4\)Cl, extracted with EtOAc. The combined organic layers were washed with brine and dried over Na\(_2\)SO\(_4\). After evaporation at rt, the remaining residue (0.057 g) was taken up in 4:1 petroleum ether (bp 40–60 \( ^{\circ} \)C)/ether and filtered over a short neutral alumina column to give 0.014 g (20\%) of 29: \( ^{1}H \) NMR \( \delta 1.07 \) (d, \( J = 6.9 \) Hz, 6 H), 1.56 (br s, 3 H), 1.97 (d, \( J = 7.1 \) Hz, 3 H), 2.00–2.51 (m, 8 H), 2.56 (septet, \( J = 6.9 \) Hz, 1 H), 5.10 (dd, \( J = 5.8 \), 6.5 Hz, 1 H), 6.56 (dd, \( J = 7.1 \), 14.1 Hz, 1 H), 9.34 (s, 1 H); \( ^{13}C \) NMR \( \delta 14.87 \) (q), 16.02 (q), 18.22 (2 q), 23.61 (t), 26.61 (t), 33.39 (t), 38.92 (t), 40.84 (d), 123.75 (d), 134.85 (s), 144.25 (s), 150.10 (d), 194.97 (d), 214.81 (s); MS \( m/z \) (relative intensity) 236 (M\(^+\), 46), 193 (33), 150 (76), 138 (45), 135 (100), 133 (50), 121 (47), 109 (41), 107 (59), 81 (63), 71 (88), 43 (60); HRMS calcd for C\(_{15}\)H\(_{24}\)O\(_{2}\) (M\(^+\)) 236.1776, found 236.1772.

(1\( \alpha \),4\( \alpha \),4a\( \alpha \),7\( \beta \),8\( a\( \beta \))-\( \pm \)-Decahydro-4a-methyl-7-(1-methylethyl)-7-[(trimethylsilyl)oxy]-4-[(methylsulfonfonyl)oxy]-1-naphthalencarboxaldehyde (30). To a stirred solution of 0.525 g (1.58 mmol) of 14 in 15 mL of pyridine was added 0.34 mL (1.6 mmol) of hexamethyldisilazane and 0.63 mL (4.8 mmol) of TMSCl at 0 \( ^{\circ} \)C. After being stirred at 0 \( ^{\circ} \)C for 3 h, the reaction mixture was poured into ice-water and extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO\(_3\) and brine,
dried, and evaporated. Flash chromatography (3:2 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.510 g (80%) of 30 as an oil: 1H NMR δ 0.12 (s, 9 H), 0.74 (s, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 1.42–1.60 (m, 6 H), 1.72 (septet, J = 6.8 Hz, 1 H), 1.81–2.38 (m, 6 H), 2.97 (s, 3 H), 4.31 (dd, J = 6.0, 10.6 Hz, 1 H), 9.86 (d, J = 0.7 Hz, 1 H); 13C NMR δ 2.66 (3 q), 11.75 (q), 17.48 (q), 17.56 (q), 23.12 (t), 25.51 (t), 28.61 (t), 32.52 (t), 33.91 (t), 38.37 (q), 38.79 (d), 39.09 (s), 40.49 (d), 49.94 (d), 78.58 (s), 89.94 (d), 203.69 (d); MS m/z (relative intensity) 361 (M+ – 43, 100), 347 (15), 333 (40), 171 (15); HRMS calcd for C16H29O5Si (M+ – 43) 361.1505, found 361.1506.

(±)-2-[2-Ethenyl-2-methyl-5-(1-methylethyl)-5-[(trimethylsilyl)oxy]-1-cyclohexyl]-2-propenal (32). The TMS ether 30 (0.157 g, 0.39 mmol) was treated with KHMSD for 15 min as described for 14. After workup, the remaining residue (0.120 g) was flash chromatographed (10:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.043 g (36%) of 32:90 1H NMR δ 0.13 (s, 9 H), 0.85 (s, 3 H), 0.91 (d, J = 6.8 Hz, 6 H), 1.03–2.0 (m, 7 H), 3.21 (dd, J = 3.2, 13.4 Hz, 1 H), 4.71 (dd, J = 1.4, 17.3 Hz, 1 H), 4.77 (dd, J = 1.4, 10.9 Hz, 1 H), 5.68 (dd, J = 11.9, 17.3 Hz, 1 H), 6.01 (br s, 1 H), 6.06 (br s, 1 H), 9.38 (s, 1 H); 13C NMR δ 2.56 (3 q), 14.20 (q), 17.44 (q), 17.54 (q), 28.72 (t), 34.42 (t), 34.68 (t), 36.38 (d), 38.72 (d), 39.46 (s), 78.42 (s), 110.26 (t), 134.88 (t), 149.19 (d), 151.95 (s), 194.22 (d); MS m/z (relative intensity) 265 (M+ – 43, 19), 86 (51), 84 (100), 51 (27), 50 (92); HRMS calcd for C15H25O2Si (M+ – 43) 265.1624, found 265.1623.

Oxidation reactions of aldehyde 30. PDC oxidation. To a solution of 0.095 g (0.23 mmol) of 30 in 2 mL of DMF was added 0.530 g (1.41 mmol) of PDC. The reaction mixture was stirred at rt overnight, poured into 20 mL of brine, and extracted with ether. After addition of 1 mL of 1 M aqueous HClO4, the aqueous layer was again extracted with ether. The combined organic layers were dried and evaporated. The remaining residue was dissolved in 2 mL of ether and cooled to 0 °C. After addition of excess CH2N2 in ether, the reaction mixture was stirred at rt for 1 h. Evaporation and flash chromatography (2:1 to 1:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.030 g (39%) of 14 and 0.020 g (27%) of (4α,4α,7β,8αβ)-(±)-decahydro-4a-methyl-7-(1-methylethyl)-7-[(trimethylsilyl)oxy]-4-[(methylsulfonyl)oxy]-1(2H)-naphthalenone: mp 154 °C (from diisopropyl ether); 1H NMR δ 0.81 (s, 3 H), 0.88 (s, OH), 0.93 (d, J = 6.8 Hz, 6 H), 1.42–1.90 (m, 7 H), 2.08–2.59 (m, 4 H), 2.77 (dd, J = 4.1, 11.6 Hz, 1 H), 3.06 (s, 3 H), 4.88 (dd, J = 4.4, 11.5 Hz, 1 H); 13C NMR δ 10.98 (q), 16.63 (2 q), 28.00 (2 t), 28.52 (t), 32.11 (t), 38.27 (t), 38.69 (q), 38.69 (d), 41.49 (s), 49.58 (d), 72.76 (s), 86.24 (d), 209.36 (s); MS m/z (relative intensity) 275 (M+ – 43, 82), 193 (21), 179 (100), 133 (25), 101 (40), 43 (20); HRMS calcd for C12H19O5S (M+ – 43) 275.0953, found 275.0949. Anal. Calcd for C15H26O5S: C, 56.58; H, 8.23. Found: C, 56.31; H, 8.34.
RuO₂/NaIO₄ oxidation. To a well stirred solution of 0.134 g (0.33 mmol) of 30 in a mixture of 3 mL of CH₃CN, 3 mL of CCl₄, and 5 mL of water was added 0.280 g (1.31 mmol) of NaIO₄ and 0.011 g of RuO₂ at 0 °C. The resulting yellow mixture was stirred at 0 °C for 4 h, and then 2 mL of isopropanol was added. After being stirred for 5 min, the reaction mixture was poured into water and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, and evaporated. The black residue was dissolved in 5 mL of ether, and excess CH₂N₂ was added at 0 °C. The reaction mixture was allowed to come to rt and stirred for 75 min. Evaporation and flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.082 g (58%) of Me ester 33 as an oil: ¹H NMR δ 0.11 (s, 9 H), 0.78 (s, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 1.71 (septet, J = 6.8 Hz, 1 H), 1.32–2.40 (m, 12 H), 2.99 (s, 3 H), 3.66 (s, 3 H), 4.34 (dd, J = 4.9, 11.6 Hz, 1 H); ¹³C NMR δ 2.68 (3 q), 11.17 (q), 17.51 (q), 17.59 (q), 25.84 (t), 26.29 (t), 28.26 (t), 34.62 (t), 34.73 (t), 38.40 (d), 38.79 (q), 38.92 (s), 40.52 (d), 41.33 (d), 51.32 (q), 78.77 (s), 90.96 (d), 174.84 (s); MS m/z (relative intensity) 391 (M⁺ – 43, 100), 331 (10), 295 (5), 235 (10), 73 (13); HRMS calcd for C₁₇H₃₁O₆S₅Si (M⁺ – 43) 391.1611, found 391.1606.

(1α,4α₈,αα₆)-(±)-Decahydro-4-(1-methoxymethylene)-8a-methyl-6-(1-methylethylidene)-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]naphthalene (34). To a stirred solution of 150 mL of 0.50 M (dimethylsulfonyl)sodium in DMSO was added a slurry of 32.5 g (75.2 mmol) of isopropyltriphenylphosphonium iodide in 30 mL of DMSO at rt. The reaction mixture was stirred at rt for 1.5 h. To the resulting deep red solution was added, via syringe, a solution of 9.90 g (29.3 mmol) of 23 in 60 mL of THF. After being stirred at rt overnight, the reaction mixture was poured into ice-water and extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Repeated flash chromatography (50:1 petroleum ether (bp 40–60 °C)/tert-butyl methyl ether) gave 8.897 g (83%) of 34: ¹H NMR δ 0.00 (s, 6 H), 0.75 (s, 3 H), 0.85 (s, 9 H), 1.57 (br s, 6 H), 0.93–1.96 (m, 8 H), 2.41–2.58 (m, 2 H), 2.77 (dd, J = 4.2, 9.7 Hz, 1 H), 3.23 (dd, J = 5.0, 10.9 Hz, 1 H), 3.55 (s, 3 H), 5.55 (s, 1 H); ¹³C NMR δ –4.76 (q), –3.90 (q), 9.86 (q), 18.08 (s), 19.99 (q), 20.09 (q), 23.77 (t), 25.36 (t), 25.91 (3 q), 27.10 (t), 31.15 (t), 38.26 (t), 40.88 (s), 46.29 (d), 59.55 (q), 79.92 (d), 118.50 (s), 120.70 (s), 131.25 (s), 139.64 (d); MS m/z (relative intensity) 364 (M⁺, 50), 307 (70), 232 (100), 231 (61), 145 (30), 84 (31), 75 (54), 73 (36); HRMS calcd for C₂₂H₄₀O₂Si (M⁺) 364.2798, found 364.2793.

(1α,4α₈,αα₆,8αβ)-(±)-Decahydro-4a-methyl-7-(1-methylethylidene)-4-[(methylsulfonyl)oxy]-1-naphthalenecarboxaldehyde (17). The TBDMS ether 34 (8.897 g, 24.4 mmol) was desilylated with TBAF for 45 min as described for 25. Workup and flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 5.429 g (89%) of the
corresponding alcohol: mp 131 °C (from diisopropyl ether); \(^1\)H NMR δ 0.76 (s, 3 H), 1.65 (br s, 6 H), 1.00–1.18 (m, 2 H), 1.35–1.98 (m, 7 H), 2.43–2.58 (m, 2 H), 2.82 (ddd, \(J = 2.2, 4.6, 11.2\) Hz, 1 H), 3.28 (dd, \(J = 4.1, 11.0\) Hz, 1 H), 3.57 (s, 3 H), 5.58 (br s, 1 H); \(^13\)C NMR δ 9.59 (q), 19.97 (q), 20.07 (q), 23.67 (t), 25.06 (t), 26.87 (t), 30.36 (t), 37.42 (t), 40.23 (s), 45.97 (d), 59.50 (q), 79.53 (d), 117.87 (s), 121.20 (s), 130.63 (s), 139.91 (d); MS m/z (relative intensity) 250 (M\(^+\), 100), 232 (8), 218 (11), 207 (16), 168 (54), 153 (71), 135 (40), 93 (20); HRMS calcd for C\(_{16}\)H\(_{26}\)O\(_2\) (M\(^+\)) 250.1933, found 250.1929. Anal. Calcd for C\(_{16}\)H\(_{26}\)O\(_2\): C, 76.75; H, 10.47. Found: C, 76.36; H, 10.66. A solution of this alcohol (7.114 g, 28.5 mmol) in pyridine was treated with MsCl as described for 27. Workup and flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 9.24 g (99%) of the corresponding mesylate: mp 103 °C (from pentane/diisopropyl ether); \(^1\)H NMR δ 0.81 (s, 3 H), 1.14 (ddd, \(J = 4.1, 9.3, 9.3\) Hz, 1 H), 1.60 (br s, 6 H), 1.60–2.00 (m, 7 H), 2.40–2.56 (m, 2 H), 2.83 (ddd, \(J = 2.3, 2.3, 9.1\) Hz, 1 H), 2.93 (s, 3 H), 3.30 (s, 3 H), 4.30 (dd, \(J = 4.9, 11.2\) Hz, 1 H), 5.53 (br s, 1 H); \(^13\)C NMR δ 10.42 (q), 19.99 (q), 20.07 (q), 23.33 (t), 24.83 (t), 26.65 (t), 28.49 (t), 37.52 (t), 38.67 (q), 39.88 (s), 46.26 (d), 59.54 (q), 90.42 (d), 115.86 (s), 121.81 (s), 129.66 (s), 140.74 (d); MS m/z (relative intensity) 328 (M\(^+\), 41), 285 (22), 246 (16), 232 (33), 217 (14), 189 (20), 135 (43), 73 (100); HRMS calcd for C\(_{17}\)H\(_{28}\)O\(_4\)S (M\(^+\)) 328.1708, found 328.1705. Anal. Calcd for C\(_{17}\)H\(_{28}\)O\(_4\)S: C, 62.16; H, 8.59. Found: C, 61.86; H, 8.79. A solution of this mesylate (2.38 g, 7.26 mmol) in ether was treated with 35% HClO\(_4\) for 3.5 h as described for 28. Workup and recrystallization from diisopropyl ether/acetone afforded 2.228 g (98%) of 17: mp 126 °C; \(^1\)H NMR δ 0.89 (s, 3 H), 1.14 (ddd, \(J = 4.2, 9.4, 9.4\) Hz, 1 H), 1.38 (m, 1 H), 1.65 (s, 3 H), 1.68 (s, 3 H), 1.60–1.99 (m, 5 H), 2.24–2.46 (m, 3 H), 2.55–2.76 (m, 2 H), 2.98 (s, 3 H), 4.29 (dd, \(J = 6.9, 9.3\) Hz, 1 H), 9.96 (d, \(J = 1.0\) Hz, 1 H); \(^13\)C NMR δ 11.83 (q), 20.03 (q), 20.07 (q), 22.92 (t), 24.98 (t), 25.51 (t), 29.22 (t), 38.83 (q), 39.21 (t), 39.51 (s), 46.96 (d), 50.42 (d), 89.61 (d), 122.42 (s), 129.49 (s), 203.40 (d); MS m/z (relative intensity) 314 (M\(^+\), 10), 218 (11), 189 (9), 147 (8), 136 (9), 135 (100), 107 (8); HRMS calcd for C\(_{16}\)H\(_{26}\)O\(_2\)S (M\(^+\)) 314.1552, found 314.1547. Anal. Calcd for C\(_{16}\)H\(_{26}\)O\(_2\)S: C, 61.11; H, 8.33. Found: C, 61.24; H, 8.61.

\((E,E)-7\)-Methyl-4-(1-methylethylidene)-1,7-cyclodecadiene-carboxaldehyde (35). To a stirred solution of 0.053 g (0.17 mmol) of 17 in 2 mL of THF was added 0.37 mL of KHMDS (0.5 M in toluene) at −78 °C. The reaction mixture was stirred at −78 °C for 10 min and, after removal of the dry-ice bath, for an additional 25 min. After addition of ether, the reaction mixture was washed with water and brine, dried, and evaporated. Column chromatography on neutral alumina (5:1 petroleum ether (bp 40–60 °C)/tert-butyl methyl ether) afforded 0.010 g (27%) of 35: \(^1\)H NMR δ 1.34 (s, 3 H), 1.65 (s, 3 H), 1.73 (s, 3 H), 1.95–2.36 (m, 8 H), 2.98 (m, 2 H), 5.13 (dd, \(J = 7.8, 7.8\) Hz, 1 H), 6.49 (dd, \(J = 8.5, 8.5\) Hz, 1 H), 9.28 (s, 1 H); \(^13\)C NMR δ 18.96 (q), 20.48 (q), 21.19 (q), 23.10 (t), 25.99 (t), 121
(E,E,E)-4-Hydroxymethyl-α,α,8-trimethyl-1,3,7-cyclodecatrienemethanol (37). The mesylate 17 (0.053 g, 0.17 mmol) was treated with KHMDS in the same way as described above, except that at completion of the fragmentation reaction, the reaction mixture was treated with 0.010 g of LAH at 0 °C for 20 min and subsequently quenched with solid Glauber's salt. After filtration and evaporation of the filtrate, flash chromatography (3:2 petroleum ether (bp 40–60 °C)/tert-butyl methyl ether) afforded 0.015 g (38%) of 37: ¹H NMR δ 1.36 (s, 6 H), 1.38 (s, 3 H), 1.4–2.3 (m, 10 H), 3.97 (d, AB system, J = 13.0 Hz, 1 H), 4.02 (d, AB system, J = 13.0 Hz, 1 H), 4.70 (dd, J = 3.8, 9.7 Hz, 1 H), 5.84 (d, J = 4.6 Hz, 1 H), 6.11 (d, J = 4.6 Hz, 1 H); ¹³C NMR δ 16.93 (q), 28.02 (t), 28.10 (t), 30.26 (t), 30.33 (2 q), 39.37 (t), 66.57 (t), 74.09 (s), 123.11 (d), 125.19 (d), 126.34 (d), 134.54 (s), 139.23 (s), 146.27 (s); MS m/z (relative intensity) 236 (M⁺, 3), 218 (60), 205 (11), 203 (37), 200 (8), 187 (43), 145 (71), 91 (100), 59 (88), 43 (42); calcd for C₁₅H₂₂O₂ (M⁺) 236.1776, found 236.1772.

(E,E)-7-Methyl-4-(1-methylthylidene)-1,7-cyclodecadienemethanol (36). To a degassed solution of 0.111 g (0.35 mmol) of 17 in 3 mL of toluene was added with stirring 0.74 mL of KHMDS (0.5 M in toluene) at –40 °C. After being stirred at –40 °C for 30 min, the reaction mixture was gradually warmed to 0 °C over a period of 20 min. The yellowish reaction mixture was cooled to –78 °C, and then excess Red-Al (65% in toluene) was added dropwise. After being stirred at –78 °C for 10 min, the reaction mixture was allowed to come to rt and carefully quenched with 1 mL of water. The reaction mixture was then diluted with EtOAc, dried, and evaporated. The remaining residue (0.091 g) was flash chromatographed (5:1 hexane/tert-butyl methyl ether) to afford 0.059 g (77%) of 36: ¹H NMR (C₆D₆) δ 1.51 (d, J = 1.2 Hz, 3 H), 1.65 (s, 3 H), 1.71 (s, 3 H), 1.95–2.3 (m, 9 H), 2.79 (m, 2 H), 3.93 (s, 2 H), 5.25 (br m, 1 H), 5.65 (dd, J = 8.2, 8.2 Hz, 1H); ¹³C NMR (C₆D₆) δ 18.47 (q), 20.32 (q), 20.96 (q), 25.94 (t), 26.91 (t), 33.53 (t), 34.76 (t), 37.92 (t), 67.40 (t), 123.84 (d), 126.29 (d), 126.67 (s), 131.54 (s), 135.17 (s), 135.73 (s); MS m/z (relative intensity) 220 (M⁺, 26), 205 (12), 202 (26), 189 (48), 136 (38), 133 (37), 121 (66), 107 (36), 93 (44), 91 (49), 31 (100); HRMS calcd for C₁₅H₂₄O (M⁺) 220.1827, found 220.1827.

(E,Z)-1,5-Dimethyl-8-(1-methylthylidene)-1,5-cyclodecadiene (38). To a stirred solution of 0.078 g (0.35 mmol) of 36 and 0.7 mL of N, N, N', N'-tetramethyl-
ethylenediamine in 3 mL of THF was added dropwise 0.26 mL of BuLi (1.6 M in hexane) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min, and then 0.075 mL (0.52 mmol) of TMPDCl was added. After being stirred at −78 °C for 5 min, the reaction mixture was allowed to come to rt and stirred for an additional 1 h. The reaction mixture was then added, via syringe, to a solution of 0.09 g (12.9 mmol) of Li in 25 mL of EtNH₂ at 0 °C. Stirring was continued at 0 °C for 25 min, and excess aqueous NH₄Cl was added. The reaction mixture was stirred for another 40 min and extracted with pentane. The combined organic layers were washed with brine, dried, and carefully evaporated. Repeated flash chromatography (pentane) gave 0.017 g (23%) of Z-1,7-dimethyl-4-(1-methylethenyl)cyclodecane and 0.030 g (42%) of 38. Z-1,7-Dimethyl-4-(1-methylethylidene)cyclodecane: ¹H NMR δ 0.81 (d, J = 6.6 Hz, 3 H), 1.67 (br s, 9 H), 0.9–2.3 (m, 10 H), 2.45 (ddd, J = 4.0, 4.0, 11.9 Hz, 1 H), 2.89 (m, 2 H), 5.20 (dd, J = 8.7, 8.7 Hz, 1 H); ¹³C NMR δ 20.40 (2 q), 21.58 (t), 22.15 (q), 22.70 (q), 26.88 (t), 28.10 (d), 28.61 (t), 29.46 (t), 30.89 (t), 36.77 (t), 124.79 (d), 125.31 (s), 131.65 (s), 134.95 (s); MS m/z (relative intensity) 206 (M⁺, 72), 191 (18), 163 (43), 135 (33), 121 (50), 109 (52), 107 (70), 95 (73), 93 (59), 81 (100), 41 (65); HRMS calcd for C₁₅H₂₆ (M⁺) 206.2035, found 206.2034. 38: ¹H NMR δ 1.54 (d, J = 1.2 Hz, 3 H), 1.66 (s, 3 H), 1.70 (s, 6 H), 2.02–2.25 (m, 8 H), 2.67 (m, 2 H), 5.18 (dd, J = 7.8, 7.8 Hz, 1 H), 5.31 (dd, J = 1.2, 8.2, 8.2 Hz, 1 H); ¹³C NMR δ 18.44 (q), 20.48 (q), 21.06 (q), 24.41 (q), 25.11 (t), 30.96 (t), 33.39 (t), 34.84 (t), 37.91 (t), 123.69 (d), 125.24 (d), 126.70 (s), 131.49 (s), 131.65 (s), 135.71 (s); MS m/z (relative intensity) 204 (M⁺, 55), 189 (35), 161 (35), 147 (20), 136 (21), 133 (35), 121 (100), 107 (50), 105 (47), 93 (54), 41 (35); HRMS calcd for C₁₅H₂₄ (M⁺) 204.1878, found 204.1876.

(Z,E)-7-Methyl-4-(1-methylethylidene)-1,7-cyclodecadienecarboxaldehyde (16). To a degassed solution of 0.122 g (0.39 mmol) of 17 in 4 mL of toluene was added with stirring 0.25 mL of NaOt-amyl (1.55 M in benzene) at −78 °C. The reaction mixture was stirred at −78 °C for 10 min and then allowed to come to 0 °C. After being stirred at 0 °C for an additional 35 min, the reaction mixture was poured into water and extracted with tert-butyl methyl ether. The combined organic layers were washed with brine and dried. Evaporation afforded 0.082 g (97%) of almost pure 16: ¹H NMR (C₆D₆) δ 1.23 (s, 3 H), 1.52 (s, 3 H), 1.57 (s, 3 H), 1.9–2.45 (m, 7 H), 2.7–3.0 (m, 2 H), 3.12 (ddd, J = 1.6, 5.3, 12.3 Hz, 1 H), 4.70 (dd, J = 4.9, 11.7 Hz, 1 H), 5.58 (dd, J = 5.7, 9.9 Hz, 1 H), 9.93 (s, 1 H); ¹³C NMR (C₆D₆) δ 16.96 (q), 20.09 (q), 20.36 (q), 26.81 (t), 30.08 (t), 31.21 (t), 31.98 (t), 40.70 (t), 125.72 (d), 130.65 (s), 136.28 (s), 138.07 (s), 150.89 (d), 188.53 (d); MS m/z (relative intensity) 218 (M⁺, 66), 203 (28), 189 (25), 175 (44), 136 (100), 135 (75), 123 (55), 122 (51), 121 (63), 107 (83), 105 (52), 96 (57), 93 (53), 91 (61), 79 (54); HRMS calcd for C₁₅H₂₂O (M⁺) 218.1671, found 218.1677.
(Z,E)-7-Methyl-4-(1-methylethylidene)-1,7-cyclodecadienemethanol (15). To a degassed solution of 0.285 g (0.91 mmol) of 17 in 5 mL of dry toluene was added with stirring 0.59 mL of NaOt-amyl (1.55 M in benzene) at -78 °C. After being stirred at -78 °C for 15 min, the reaction mixture was allowed to come to rt, stirred at that temperature for 15 min, and then cooled to 0 °C. Stirring was continued at 0 °C for an additional 20 min, after which the reaction mixture was cooled again to -78 °C. After dropwise addition of 1 mL of Red-Al (65% in toluene) followed by stirring at -78 °C for 15 min, excess Red-Al was destroyed by careful addition of saturated aqueous NH4Cl. The reaction mixture was allowed to come to rt and, after addition of Na2SO4, stirred for 20 min. The resulting suspension was diluted with EtOAc and filtered over a short silica gel column. After thorough evaporation, the remaining residue was dissolved in 15 mL of tert-butyl methyl ether and extracted with five portions of 20% aqueous AgNO3. The combined aqueous layers were washed with tert-butyl methyl ether and then cooled to 0 °C. After addition of 15 mL of 25% aqueous NH3, the aqueous layer was extracted with tert-butyl methyl ether. The combined organic layers were washed with brine, dried, and evaporated to afford 0.143 g (72%) of 15: 1H NMR (C6D6) δ 1.37 (br s, 3 H), 1.64 (s, 3 H), 1.67 (s, 3 H), 1.7-2.7 (m, 10 H), 3.00 (m, 1 H), 3.81 (d, AB system, J = 11.8 Hz, 1 H), 4.13 (d, AB system, J = 11.8 Hz, 1 H), 4.78 (m, 2 H); 13C NMR (C6D6) δ 16.86 (q)*, 20.15 (q), 20.48 (q), 26.39 (t), 32.13 (t), 32.77 (t)*, 34.57 (t), 40.42 (br t), 59.71 (t), 126.18 (d), 131.39 (d), 132.81 (s), 135.13 (s), 136.81 (s); MS m/z (relative intensity) 220 (M+, 31), 205 (18), 202 (46), 189 (82), 137 (91), 133 (63), 122 (72), 121 (100), 119 (79), 107 (96), 105 (81), 93 (87), 91 (87), 81 (93), 79 (70); HRMS calcd for C15H24O (M+) 220.1827, found 220.1825.

Germacrene B (39). The germacrene alcohol 15 (0.047 g, 0.21 mmol) was treated with TMPDCl and then with Li in EtNH2 for 5 min as described for 36. Workup and flash chromatography (pentane) gave, in order of elution, 0.013 g of a mixture of hydrogenated products and 0.023 g (53%) of pure germacrene B (39). The NMR and mass spectral data for 39 corresponded with those reported for natural germacrene B.43

(2α,4αα,5α,8αβ)- and (2β,4αα,5α,8αβ)-(t)-Decahydro-8-(1-methoxymethylene)-4a-methyl-5-[(1,1-dimethylethyl)dimethylsilyloxy]-2-naphthalenecarbonitrile (40). To a stirred solution of 1.158 g (3.42 mmol) of 23, 0.870 g (4.46 mmol) of TosMIC, and 0.34 mL (5.82 mmol) of dry EtOH in 20 mL of dry DME was added 0.667 g (8.6 mmol) of KOt-Bu at 0 °C. After being stirred at 0 °C for 5 min, the reaction mixture was warmed to 35 °C and stirred at this temperature overnight. After addition of water, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (20:1 petroleum ether (bp 40–60
°C)/EtOAc) gave 0.883 g (74%) of 40 as a 1:1 mixture of two diastereomers: 1H NMR (major peaks) δ 0.00, 0.01, 0.02, 0.04 (s, s, s, s, 1:1:1:1 ratio, 6 H), 0.66, 0.69 (s, s, 1:1 ratio, 3 H), 0.84, 0.85 (s, s, 1:1 ratio, 9 H), 3.52, 3.53 (s, s, 1:1 ratio, 3 H), 5.42, 5.47 (s, s, 1:1 ratio, 1 H); HRMS calcd for C20H35NO2Si (M+) 349.2437, found 349.2438.

(2α,4αα,5α,8αβ)-(±)-1-[Decahydro-8-(1-methoxymethylene)-4a-methyl-5-[(1,1-dimethylethyl)dimethylsilyloxy]-2-naphthalenyl]ethane (41). To a stirred solution of 1.526 g (4.37 mmol) of 40 in 50 mL of ether was added dropwise 8.2 mL of MeLi (1.6 M in ether) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and, after addition of water, extracted with ether. The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (30:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 1.311 g (82%) of 41 as an oil: 1H NMR δ 0.02 (s, 6 H), 0.66 (s, 3 H), 0.85 (s, 9 H), 1.09 (ddd, J = 3.9, 13.2, 13.2 Hz, 1 H); 1.2–1.85 (m, 8 H), 1.96 (ddd, J = 3.3, 3.3, 12.9 Hz, 1 H), 2.14 (s, 3 H), 2.34 (ddd, J = 3.3, 3.3, 12.9, 12.9 Hz, 1 H), 2.78 (dd, J = 4.6, 9.8 Hz, 1 H), 3.26 (ddd, J = 4.6, 9.8 Hz, 1 H), 3.53 (s, 3 H), 5.54 (br s, 1 H); 13C NMR δ –4.84 (q), –3.97 (q), 10.11 (q), 17.96 (s), 23.51 (t), 23.90 (t), 24.63 (t), 25.78 (3 q), 28.06 (q), 30.94 (t), 37.57 (t), 40.48 (s), 44.64 (d), 51.61 (d), 59.37 (q), 79.69 (d), 117.15 (s), 139.91 (d), 211.80 (s); MS m/z (relative intensity) 366 (M+), 35, 310 (20), 309 (100), 234 (73), 185 (35), 159 (23), 135 (16), 119 (19), 75 (46); HRMS calcd for C21H38O3Si (M+) 366.2590, found 366.2584.

(2α,4αα,5α,8αβ)-(±)-Decahydro-8-(1-methoxymethylene)-α,α,4a-trimethyl-5-[(1,1-dimethylethyl)dimethylsilyloxy]-2-naphthalenemethanol (42). The acyl compound 41 (1.19 g, 3.25 mmol) was treated with the cerium analog of MeLi at –78 °C for 15 min as described for 23. Workup and crystallization from heptane afforded 1.222 g (98%) of 42: mp 121 °C; 1H NMR δ 0.00 (s, 6 H), 0.63 (s, 3 H), 0.84 (s, 9 H), 1.16 (s, 3 H), 1.18 (s, 3 H), 0.9–1.7 (m, 11 H), 1.91 (ddd, J = 3.2, 3.2, 13.0 Hz, 1 H), 2.75 (m, 1 H), 3.24 (ddd, J = 4.2, 11.1 Hz, 1 H), 3.52 (s, 3 H), 5.51 (s, 1 H); 13C NMR δ –4.81 (q), –3.96 (q), 10.32 (q), 18.00 (s), 22.44 (t), 23.70 (t), 23.70 (t), 25.83 (3 q), 26.57 (q), 27.60 (q), 31.08 (t), 37.25 (t), 40.52 (s), 45.47 (d), 49.25 (d), 59.36 (q), 72.73 (s), 79.94 (d), 118.14 (s), 139.64 (d); MS m/z (relative intensity) 382 (M+, 32), 325 (100), 307 (31), 250 (97), 232 (36), 123 (38), 85 (35), 83 (54), 75 (46); HRMS calcd for C22H42O3Si (M+) 382.2903, found 382.2904. Anal. Calcd for C22H42O3Si: C, 69.07; H, 11.07. Found: C, 68.84; H, 11.32.

(2α,4αα,5α,8αβ)-(±)-Decahydro-5-hydroxy-8-(1-methoxymethylene)-α,α,4a-trimethyl-2-naphthalenemethanol (43). The TBDMS ether 42 (0.734 g, 1.92 mmol) was treated with TBAF as described for 25. Workup and flash chromatography (3:2 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.432 g (84%) of 43 as white crystals: mp
174 °C (from acetone); 1H NMR δ 0.67 (s, 3 H), 1.19 (s, 3 H), 1.20 (s, 3 H), 1.0–1.82 (m, 12 H), 1.96 (ddd, J = 2.8, 2.8, 11.1 Hz, 1 H), 2.83 (ddd, J = 2.5, 2.5, 11.9 Hz, 1 H), 3.32 (dd, J = 4.2, 15.0 Hz, 1 H), 3.55 (s, 3 H), 5.55 (br s, 1 H); 13C NMR δ 10.10 (q), 22.20 (t), 23.60 (t), 23.60 (t), 26.75 (q), 27.54 (q), 30.42 (t), 36.52 (t), 39.98 (s), 45.25 (d), 49.09 (d), 59.11 (q), 73.02 (s), 79.61 (d), 118.05 (s), 140.00 (d); MS m/z (relative intensity) 268 (M+, 100), 250 (45), 178 (18), 160 (59), 145 (41), 59 (54); HRMS calc'd for C16H28O3 (M+) 268.2038, found 268.2037. Anal. Calc'd for C16H28O3: C, 71.60; H, 10.52. Found: C, 71.53; H, 10.71.

(2α,4αα,5α,8αβ)-(±)-Decahydro-8-(1-methoxymethylene)-α,α,4α-trimethyl-5-[(methylsulfonyl)oxy]-2-naphthalenemethanol (44). The alcohol 43 (0.571 g, 2.13 mmol) was treated with MsCl for 2 h as described for 27. Workup and flash chromatography (3:2 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.716 g (97%) of 44: 1H NMR δ 0.70 (s, 3 H), 1.13 (s, 3 H), 1.14 (s, 3 H), 1.0–2.1 (m, 12 H), 2.82 (ddd, J = 2.8, 2.8, 11.3 Hz, 1 H), 2.94 (s, 3 H), 3.05 (s, 3 H), 4.35 (dd, J = 4.9, 11.1 Hz, 1 H), 5.53 (br s, 1 H); 13C NMR δ 10.86 (q), 21.95 (t), 23.32 (t), 23.32 (t), 26.60 (q), 27.66 (q), 28.45 (t), 36.59 (t), 38.77 (q), 39.55 (s), 45.52 (d), 48.76 (d), 59.50 (q), 72.48 (s), 90.54 (d), 115.59 (s), 140.78 (d); MS m/z (relative intensity) 346 (M+, 3), 293 (15), 250 (6), 229 (27), 203 (58), 161 (41), 86 (63), 84 (100), 49 (82); HRMS calc'd for C17H30O5S (M+) 346.1814, found 346.1813.

(1α,4αα,4αα,7β,8αβ)-(±)-Decahydro-7-(1-hydroxy-1-methylethyl)-4α-methyl-4-[(methylsulfonyl)oxy]-1-naphthalencarboxaldehyde (45). The mesylate 44 (0.131 g, 0.38 mmol) was treated with 35% aqueous HClO4 as described for 28. Workup and flash chromatography (2:3 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.110 g (87%) of 45: 1H NMR δ 0.76 (s, 3 H), 1.18 (s, 3 H), 1.19 (s, 3 H), 1.1–1.45 (m, 4 H), 1.6–1.95 (m, 8 H), 2.21 (dd, J = 3.4, 4.9 Hz, 1 H), 2.37 (ddd, J = 1.7, 1.7, 13.6 Hz, 1 H), 2.98 (s, 3 H), 4.29 (dd, J = 6.1, 10.4 Hz, 1 H), 9.89 (d, J = 1.0 Hz, 1 H); 13C NMR δ 12.23 (q), 22.18 (t), 22.87 (t), 25.45 (t), 26.06 (t), 26.66 (q), 27.67 (q), 38.34 (t), 38.83 (q), 39.18 (s), 46.20 (d), 49.83 (d), 50.46 (d), 72.29 (s), 89.66 (d), 203.56 (d); MS m/z (relative intensity) 332 (M+, 2), 314 (8), 218 (15), 178 (100), 149 (63), 135 (39), 107 (35), 59 (58); HRMS calc'd for C15H22O (M+ – 114) 218.1671, found 218.1667.

(1α,4αα,4αα,7β,8αβ)-(±)-Decahydro-7-[1-[(triethylsilyl)oxy]-1-methylethyl]-4α-methyl-4-[(methylsulfonyl)oxy]-1-naphthalencarboxaldehyde (46). To a stirred solution of 0.430 g (1.29 mmol) of 45 in 3 mL of DMF was added 0.175 g (2.57 mmol) of imidazole and 0.32 mL (1.94 mmol) of TESCl at rt. After being stirred at rt for 90 min, the reaction mixture was diluted with water and extracted with petroleum ether (bp 40–60 °C). The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (7:1 petroleum ether (bp 40–60 °C)/EtOAc) gave first 0.137 g (19%) of
(1α,4αβ,6α,8αα)-(±) Decahydro-4-[1-[[[triethylsilyl]oxy]methylene]-6-[1-[[[triethylsilyl]oxy]-1-methylethyl]-1-naphthalenol methanesulfonate: 1H NMR δ 0.58 (q, J = 7.4 Hz, 6 H), 0.60 (q, J = 7.4 Hz, 6 H), 0.65 (s, 3 H), 0.92 (t, J = 7.4 Hz, 9 H), 0.97 (t, J = 7.4 Hz, 9 H), 1.18 (s, 3 H), 1.22 (s, 3 H), 1.1–2.15 (m, 11 H), 2.95 (m, 1 H), 2.99 (s, 3 H), 4.42 (dd, J = 4.7, 11.2 Hz, 1 H), 5.89 (br s, 1 H); 13C NMR δ 4.43 (t), 5.79 (t), 6.41 (t), 6.55 (t), 6.59 (t), 6.80 (t), 6.88 (3 q), 7.17 (3 q), 10.84 (q), 21.88 (t), 23.23 (t), 23.23 (t), 27.16 (q), 28.43 (q), 28.64 (t), 36.82 (t), 38.81 (q), 39.68 (s), 45.62 (d), 49.62 (d), 74.92 (s), 91.05 (d), 119.49 (s), 132.82 (d); MS m/z (relative intensity) 560 (M+ 4), 464 (2), 435 (3), 291 (7), 217 (73), 189 (49), 173 (65), 103 (100), 75 (82); HRMS calc for C28H56O5Si2 (M+ 560.3387, found 560.3389. Further elution afforded 0.322 g (56%) of 46: mp 105 °C (from diisopropyl ether); 1H NMR δ 0.54 (q, J = 7.5 Hz, 6 H), 0.77 (s, 3 H), 0.93 (t, J = 7.5 Hz, 9 H), 1.18 (s, 3 H), 1.19 (s, 3 H), 1.1–1.5 (m, 3 H), 1.63–1.95 (m, 8 H), 2.19 (dd, J = 0.8, 4.8, 4.8 Hz, 1 H), 2.37 (dd, J = 1.5, 1.5, 13.5 Hz, 1 H), 2.98 (s, 3 H), 4.31 (dd, J = 7.4, 9.1 Hz, 1 H), 9.91 (d, J = 1.0 Hz, 1 H); 13C NMR δ 6.80 (3 t), 7.13 (3 q), 12.05 (q), 21.87 (t), 22.88 (t), 25.50 (t), 26.03 (t), 27.57 (q), 28.05 (q), 38.40 (t), 38.82 (q), 39.21 (s), 46.18 (d), 50.72 (d), 50.72 (d), 74.60 (s), 89.83 (d), 203.53 (d); MS m/z (relative intensity) 431 (M+ – 15, 1), 417 (5), 403 (1), 321 (3), 173 (100), 115 (20); HRMS calc for C21H39O5Si (M+ – 15) 431.2288, found 431.2291. Anal. Calcd for C22H42O5Si: C, 59.16; H, 9.48. Found: C, 59.06; H, 9.54.

(Z,E)-(±)-4-[1-[[Triethylsilyl]oxy]-1-methylethyl]-7-methyl-1,7-cyclodecadienemethanol (47). The mesylate 46 (0.112 g, 0.25 mmol) was treated with NaOt-amyl and Red-Al under oxygen-free conditions as described for 17. Workup afforded 0.086 g (97%) of almost pure 47: 1H NMR (CD6, major peaks) δ 0.67 (q, J = 7.9 Hz, 6 H), 1.09 (t, J = 7.9 Hz, 9 H), 1.13 (s, 6 H); MS m/z (relative intensity) 305 (M+ – 47, 1), 220 (8), 202 (3), 173 (100), 115 (26), 87 (9), 75 (10); HRMS calc for C19H33OSi (M+ – 47) 305.2301, found 305.2293.

(Z,E)-(±)-4-Hydroxymethyl-α,α,8-trimethyl-3,7-cyclodecadienemethanol (48). To a stirred solution of 0.027 g (0.077 mmol) of 47 in 1 mL of THF was added 0.1 mL of TBAF (1 M in THF) at rt. After stirring at rt for 4 h, another 0.05 mL of TBAF was added, and stirring was continued at rt overnight. After addition of tert-butyl methyl ether, the reaction mixture was washed with water and brine, dried on Na2SO4, and evaporated. The remaining residue was dissolved in 3 mL of tert-butyl methyl ether and extracted with four 1 mL portions of 20% aqueous AgNO3. The combined aqueous layers were washed with tert-butyl methyl ether and cooled to 0 °C. After addition of 10 mL of 25% aqueous NH3, the aqueous layer was extracted with tert-butyl methyl ether. The combined organic layers were washed with brine, dried on Na2SO4, and evaporated to afford 0.017 g (94%) of 48: 1H NMR (CD6, major peaks) δ 1.08 (s, 3 H), 1.12 (s, 3 H);
MS m/z (relative intensity) 220 (M⁺ – 18, 45), 205 (7), 202 (24), 189 (84), 177 (66), 162 (44), 159 (79), 147 (56), 133 (98), 119 (56), 107 (67), 105 (84), 93 (89), 91 (60), 81 (60), 79 (57), 59 (100); HRMS calcd for C₁₅H₂₄O (M⁺ – 18) 220.1827, found 220.1823.

[1R-(1β,3αβ,4β,8αβ)]-Decahydro-1-hydroxymethyl-4-methyl-7-(1-methylethylidene)-4-[(1-methylethyl)oxy]-1-azulenol (49). To a stirred solution of 0.134 mL (0.45 mmol) of Ti(iPrO)₄ in 2 mL of dry CH₂Cl₂ was added 0.090 mL (0.52 mmol) of (+)-DET at –23 °C. The solution was stirred for 5 min, and then a solution of 0.100 g (0.45 mmol) of 15 in 2 mL of CH₂Cl₂ was added. After stirring at –23 °C for an additional 30 min, 0.045 mL of t-BuOOH (5–6 M in decane) was added. Stirring was continued at –23 °C for 1 h, and then a mixture of 8 mL of acetone and 0.5 mL of water was added. After being stirred at –23 °C for another 30 min and at 0 °C for 3 h, the reaction mixture was filtered, and the filtrate was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried, and evaporated at rt. The remaining residue was dissolved in 10 mL of tert-butyl methyl ether and added to a mixture of 5 mL of brine and 0.2 g of NaOH at 0 °C. The two-phase mixture was stirred at 0 °C for 1 h. After separation and drying, the organic layer was evaporated at rt to afford 0.115 g of the crude product mixture. This mixture was dissolved in 10 mL of tert-butyl methyl ether and extracted with five portions of 20% aqueous AgNO₃. The combined aqueous layers were washed with tert-butyl methyl ether and cooled to 0 °C. After addition of 15 mL of 25% aqueous NH₃, the aqueous layer was extracted with tert-butyl methyl ether. The combined organic layers were washed with brine, dried, and evaporated at rt to afford 0.037 g (37%) of the starting material 15. The tert-butyl methyl ether solution remaining after aqueous AgNO₃ extraction was washed with brine, dried, and evaporated. Flash chromatography (3:1 to 3:2 petroleum ether (bp 40–60 °C)/tert-butyl methyl ether) gave, in order of elution, 0.009 g (9%) of 15 and 0.022 g (17%) of 49: [α]D₅ –52.3° (c 0.38), 92% ee;⁷⁶ ¹H NMR (1:1:1 CDC₃/C₆D₆/C₅D₅N) δ 1.07 (d, J = 6.5 Hz, 3 H), 1.11 (d, J = 6.5 Hz, 3 H), 1.11 (s, 3 H), 1.46–1.66 (m, 4 H), 1.75 (br s, 3 H), 1.81 (m, 2 H), 1.90 (br s, 3 H), 1.92–2.00 (m, 2 H), 2.21 (dd, J = 5.8, 12.4 Hz, 1 H), 2.62 (d, J = 12.8 Hz, 1 H), 2.87 (ddd, J = 5.3, 14.1, 17.0 Hz, 1 H), 3.07 (br dddd, J ≈ 6, 6, 13 Hz, 1 H), 3.73 (d, AB system, J = 10.8 Hz, 1 H), 3.82 (septet, J = 6.5 Hz, 1 H), 3.91 (d, AB system, J = 10.8 Hz, 1 H); ¹³C NMR (CDCl₃) δ 20.06 (q), 20.27 (q), 24.64 (t), 25.20 (q), 25.30 (q), 26.85 (t), 27.00 (t), 28.59 (q), 31.54 (t), 32.50 (t), 47.93 (d), 50.22 (d), 62.40 (d), 66.85 (t), 77.05 (s), 84.91 (s), 122.63 (s), 130.86 (s); MS m/z (relative intensity) 296 (M⁺, 1), 236 (70), 218 (28), 205 (100), 187 (66), 147 (25), 122 (67), 107 (27), 43 (32); HRMS calcd for C₁₈H₃₂O₃ (M⁺) 296.2351, found 296.2355.

The same procedure was employed by using 0.062 g (0.28 mmol) of 15 and 0.062 mL of t-BuOOH (5–6 M in decane), except that the AgNO₃ extraction was omitted. Flash
chromatography afforded 0.004 g (6\%) of 15 and 0.029 g (36\%) of 49: [\(\alpha\)]D \(-35.5^\circ\) (c 0.69), 56\% ee.

\((1R,2S)-7\)-Methyl-4-(1-methylethylidene)-(1,2-b)-oxiranyl-7-cyclodecenemethanol\n
The procedure used for the epoxidation of 15 was employed by using 0.123 g (0.56 mmol) of 36 and 0.28 mL of \(t\)-BuOOH (5–6 M in decane). The reaction mixture was stored overnight at \(-20^\circ\)C and worked up as described. Flash chromatography (2:1 petroleum ether (bp 40–60 °C)/\textit{tert}-butyl methyl ether) afforded 0.067 g (52\%) of 50: [\(\alpha\)]D \(-145^\circ\) (c 0.70),\textsuperscript{84} \(^1^H\) NMR 1.31 (ddd, \(J = 4.8, 13.5, 13.5\) Hz, 1 H), 1.65 (s, 6 H), 1.73 (s, 3 H), 1.80–2.30 (m, 8 H), 2.51 (m, 1 H), 2.83 (br d, \(J = 15.0\) Hz, 1 H), 3.07 (br d, \(J = 10.0\) Hz, 1 H), 3.55 (dd, AB system, \(J = 6.8, 12.2\) Hz, 1 H), 3.83 (dd, AB system, \(J = 4.3, 12.2\) Hz, 1 H), 5.30 (dd, \(J = 8.0, 8.0\) Hz, 1 H); \(^{13}C\) NMR 17.02 (q), 20.63 (q), 21.53 (q), 22.78 (t), 27.99 (t), 33.82 (t), 34.18 (t), 38.63 (t), 60.60 (d), 64.07 (t), 64.73 (s), 122.83 (d), 128.11 (s), 129.82 (s), 135.88 (s); MS m/z (relative intensity) 236 (M\(^+\), 18), 221 (36), 205 (70), 147 (100), 135 (94), 121 (73), 107 (96), 93 (87), 55 (80); HRMS calcd for C\(_{15}\)H\(_{24}\)O\(_2\) (M\(^+\)) 236.1776, found 236.1778.

Acid-induced cyclization of 50. To a stirred solution of 0.040 g (0.17 mmol) of 50 in 5 mL of dry CH\(_2\)Cl\(_2\) at rt was added 0.01 g (0.05 mmol) of \(p\)-TsOH+H\(_2\)O dissolved in 1.5 mL of dry CH\(_2\)Cl\(_2\). After 10 min, water was added and the mixture was extracted with CH\(_2\)Cl\(_2\), washed with saturated aqueous NaHCO\(_3\) and brine, dried, and evaporated to afford 0.040 g of a crude product mixture. Repeated flash chromatography on silica gel (3:1 hexane/EtOAc) afforded 0.002 g of 52. Flash chromatography of the remaining mixture using silica gel impregnated with 7\% of AgNO\(_3\) afforded 0.010 g of 53 and 0.002 g of 54.\textsuperscript{85} 52: \(^1^H\) NMR 1.02 (d, \(J = 7.0\) Hz, 3 H), 1.20 (m, 1 H), 1.60 (br s, OH, 2 H), 1.68 (br s, 3 H), 1.71 (br s, 3 H), 1.60–2.70 (m, 9 H), 3.61 (dd, AB system, \(J = 4.8, 10.6\) Hz, 1 H), 3.72 (br d, AB system, \(J = 10.6\) Hz, 1 H), 5.32 (d, \(J = 0.9\) Hz, 1 H); \(^{13}C\) NMR 19.71 (q), 20.10 (2 q), 29.16 (t), 30.15 (t), 32.81 (t), 34.91 (d), 41.51 (t), 50.08 (d), 68.35 (t), 82.88 (s), 119.56 (d), 123.68 (s), 132.05 (s), 152.27 (s); MS m/z (relative intensity) 236 (M\(^+\), 57), 218 (54), 205 (100), 187 (86), 149 (30), 145 (32), 131 (30), 121 (32), 91 (32), 55 (33), 41 (30); HRMS calcd for C\(_{15}\)H\(_{24}\)O\(_2\) (M\(^+\)) 236.1776, found 236.1776. 53: [\(\alpha\)]D \(+48^\circ\) (c 0.49); \(^1^H\) NMR 1.56 (s, 3 H), 1.60 (s, 6 H), 1.55–2.60 (m, 13 H), 3.46 (d, AB system, \(J = 11.0\) Hz, 1 H), 3.65 (d, AB system, \(J = 11.0\) Hz, 1 H); \(^{13}C\) NMR 20.33 (2 q), 22.21 (q), 28.82 (t), 29.47 (t), 31.94 (t), 35.17 (t), 36.07 (t), 47.35 (d), 68.49 (t), 83.12 (s), 122.71 (s), 128.99 (s), 132.07 (s), 137.40 (s); MS m/z (relative intensity) 236 (M\(^+\), 46), 218 (20), 205 (100), 187 (30), 149 (15), 123 (6), 105 (16), 97 (39); HRMS calcd for C\(_{15}\)H\(_{24}\)O\(_2\) (M\(^+\)) 236.1776, found 236.1777. 54: \textsuperscript{97} \(^1^H\) NMR 1.20 (ddd, \(J = 3.8, 11.7, 11.7\) Hz, 1 H), 1.60 (br s, OH, 2 H), 1.65 (br s, 3 H), 1.67 (br s, 3 H), 1.60–2.15 (m, 5 H), 2.25–2.65 (m, 6 H), 3.50 (dd, AB system, 5.3, 10.7 Hz,
1 H), 3.62 (dd, AB system, 3.2, 10.7 Hz, 1 H), 4.72 (br s, 2 H); $^{13}$C NMR 20.25 (2 q), 26.68 (t), 30.96 (t), 31.69 (t), 36.35 (t), 36.62 (t), 49.08 (d), 53.34 (d), 69.58 (t), 82.10 (s), 107.23 (t), 124.87 (s), 130.62 (s), 152.58 (s); MS m/z (relative intensity) 236 (M$^+$, 15), 218 (17), 206 (15), 205 (100), 187 (37), 145 (11), 131 (12), 105 (11), 91 (14); HRMS calcd for C$_{15}$H$_{24}$O$_2$ (M$^+$) 236.1776, found 236.1777.

6.5 References and Notes

* This chapter will be published in a condensed form: Minnaard, A. J.; Wijnberg, J. B. P. A.; De Groot, A.
1. The conventions proposed for describing germacrane sesquiterpenes are followed, see: §1.3.
4. The numbering system as given in structure 1 will be followed throughout the text of this chapter.
14. The fragmentation reaction induced by $\alpha$ deprotonation of a ketone in a bicyclo[5.4.0]undecane derivative has been used to construct an eleven-membered ring system, see: (a) Clark, D. A.; Fuchs, P. L. J. Am. Chem. Soc. 1979, 101, 3567. Recently, a peculiar result has been published. The ester-enolate assisted fragmentation of a cis-fused decalin system afforded a cyclodecadiene with a double bond stereochemistry that can not be explained by the stereochemical rules valid for this reaction, see: (b) Wender, P. A.; Manly, C. J. J. Am. Chem. Soc. 1990, 112, 8579.
24. The stereochemistry at C(7) in 28 could be ascertained with NMR experiments. With the use of the shift reagent Eu(fod)$_3$ in $^1$H NMR measurements, the close proximity of H-5 and the hydroxyl group at C(7) was demonstrated. NOE-difference studies showed a clear NOE between H-1 and H-5. A NOE between H-5 and the isopropyl group at C(7) was not observed.
26. (a) Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabayashi, T.; Hayase, Y. J. Am. Chem. Soc. 1967, 89, 1483. $^1$H NMR studies on a system similar to 14 revealed that an axially oriented aldehyde gives rise to a singlet whereas an equatorially
oriented aldehyde appears as a doublet \( (J = 3.9 \text{ Hz}) \), see: (b) García, B.; Skaltsa, H.; Navarro, F. I.; Pedro, J. R.; Lazari, D. Phytochemistry 1996, 41, 1113.


29. The stereochemistry at C(4) in 30 could be established unambiguously by reduction of its aldehyde function with NaBH₄ to the corresponding alcohol: \(^1\text{H} \) NMR \( \delta \) 0.10 (s, 9 H), 0.78 (s, 3 H), 0.88 (d, \( J = 6.8 \text{ Hz} \), 6 H), 1.40–1.97 (m, 14 H), 2.98 (s, 3 H), 3.56 (br d, \( J = 6.8 \text{ Hz} \), 2 H), 4.31 (dd, \( J = 7.1, 9.2 \text{ Hz} \), 1 H); \(^{13}\text{C} \) NMR \( \delta \) 2.67 (3q), 13.53 (q), 17.45 (q), 17.58 (q), 24.69 (t), 25.93 (t), 28.43 (t), 33.56 (t), 35.30 (t), 38.42 (q), 38.61 (d), 38.61 (s), 39.91 (d), 41.70 (d), 60.87 (t), 78.68 (s), 91.44 (d); MS \text{m/z} \) (relative intensity) 363 (M\(^+\) – 43, 100), 181 (11), 131 (11), 119 (11), 73 (11), 69 (22); HRMS calcd for C\(_{16}\)H\(_{31}\)O\(_5\)SSi (M\(^+\) – 43) 363.1662, found 363.1655. NOE-difference experiments on this alcohol showed a strong NOE between the angular Me group and the carbonyl group at C(4), thereby establishing the axial orientation of the substituent at C(4).

30. Cleavage of the C(2)–C(3) bond via a 1,4-fragmentation reaction would result in the same product, but it has been shown that this process is very unlikely, see: Marshall, J. A.; Babler, J. H. J. Org. Chem. 1969, 34, 4186.


34. The angular methyl group seems to thwart the formation of the bulky tetragonal chromate ester. The same effect probably counts for the slow hydrolysis of esters in related systems, see: Haslam, E. Tetrahedron 1980, 36, 2409.


chapter 6


43. The hydrogenation of the isolated C(1)–C(10) double bond with Li in EtNH₂ was rather unexpected, all the more so because Li/NH₃ reduction of 8-acetoxygermacrene B only gave germacrene B and no products in which one of the double bonds was hydrogenated, see: Brown, E. D.; Sam, T. W.; Sutherland, J. K.; Torre, A. J. Chem. Soc., Perkin Trans. I 1975, 2326.


46. The use of more than one equiv of NaOtt-amyl also led to E → Z isomerization of the conjugated C(4)–C(5) double bond.


49. Germacrane B is a widespread naturally occurring hydrocarbon and has previously been synthesized from natural germacrone, see reference 43 and references cited therein.

50. Longer reaction times led to a mixture of 39 and hydrogenated products with the latter compounds in excess.


52. After completion of this research, we noticed that in a recent synthesis of a nine-membered 3-ene-1,5-diyne system the same tactic has been employed. Thus, an exocyclic double bond was introduced to avoid rapid Cope rearrangement, see: Iida, K.; Hirama, M. J. Am. Chem. Soc. 1994, 116, 10310.


54. The outcome of the fragmentation reaction did not depend on the solvent used. Fragmentation of 17 with KHMDS in toluene or THF both afforded 35.


56. The majority of (E,E)-germacrane found in nature possesses one C(7) side chain. See reference 2.

60. This reaction also gave a by-product with a silyl enol ether function at C(4).
Minnaard, A. J. unpublished results.
Comm. 1967, 1116. (b) Sutherland, J. K. Tetrahedron 1974, 30, 1651. (c) Reference 43.
(d) Brown, E. D.; Sutherland, J. K.; Sam, T. W. J. Chem. Soc., Perkin Trans. 1 1975,
63. Eliel, E. L.; Wilen, S. H.; Mander, L. N. Stereochemistry of Organic Compounds; Wiley
64. During the rotation of a double bond the vinylic hydrogen, not the Me group,
passes through the ring.
67. Prefixes like S,S denote the chirality associated with the C(1)-C(10) and the C(4)-
C(5) double bond, respectively. See: Cahn, R. S.; Ingold, C.; Prelog, V. Angew.
Chem. 1966, 78, 413.
69. Germacrone has been partly resolved by asymmetric reduction and back
oxidation, see: Hill, R. K.; Fracheboud, M. G.; Sawada, S.; Carlson, R. M.; Yan, S.
71. (+)-Eu(hfc)₃ stands for tris[3-(heptafluoropropylhydroxymethylene)-(+)camph-
orato]-europium(III).
72. Siever, R. E.; Kime, K. A. Aldrichimica Acta 1977, 10, 54. These ¹H NMR
experiments using (+)-Eu(hfc)₃ were also carried out on the (E,Z)-isomer 36. The
carbonyl protons in 36 shifted strongly but stayed one singlet.
73. Marshall et. al. have used the same method in the synthesis of optically active
betweenanenes and related (E)-cyclolkenes, see: (a) Marshall, J. A.; Audia, V. H. J.
74. (a) Hill, J. G.; Sharpless, K. B.; Exxon, C. M.; Regenye, R. Org. Synth. 1985, 63, 66. (b)
Johnson, R. A.; Sharpless, K. B. in Catalytic Asymmetric Synthesis; Ojima, I. Ed.;
75. In different runs the optical rotation did not exceed 5°.
76. A gas chromatograph was used, equipped with a Supelco 30 m BETA-DEX™-120
fused silica capillary column, 0.25 mm i.d. and 0.25 μm film thickness, using H₂ as carrier gas. Peaks were partly resolved and integrated manually.

77. See § 7.2.
80. The ee of 50 could not be established due to its lability on GC.
84. The ee of 50 and its cyclization products could not be determined. Chiral GC of 53 afforded a single peak. The enantioselectivity of the Sharpless epoxidation of allylic alcohols almost invariably approaches 100%. See reference 74b; p 104.
85. The C(9)–C(10) double bond isomer of 53 and 54, presumably detected in the ¹H NMR spectrum of the crude product mixture, was lost during purification.
86. For a general description of the experimental procedures employed in this research, see § 3.3.
87. The reaction sequence employed for the synthesis of crude (4αα,5α)-(±)-4,4a,5,6,7,-8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone from 2-methylcyclohexane-1,3-dione and MVK involved (a) Michael addition (1 mol % of hydroquinone, water, 50 °C, 2 d), (b) cyclization (0.15 equiv of pyrrolidine, toluene, 100 °C), and (c) reduction (NaBH₄, EtOH, 0 °C). In all cases, the crude product of each individual step was used for the next reaction. See: (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* 1974, 39, 1612. (b) Marshall, J. A.; Seitz, D. E.; Snyder, W. R.; Goldberg, B. *Synth. Commun.* 1974, 4, 79. (c) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* 1960, 2680.
88. The ¹H NMR spectrum of crude octahydro-4-hydroxy-7,7-dimethoxy-4a-methyl-1(2H)-naphthalenone was identical with that reported in reference 18a.
89. Aldehyde 14 was susceptible to air oxidation and had to be stored under nitrogen in the refrigerator.
90. The NMR spectra of 32 revealed the presence of a trace amount of an isomer.
91. Shorter reaction times led to lower yields.
92. A stock solution of NaOt-Amyl (1.55 M in benzene) was prepared as described, see: Conia, M. J.-M. Bull. Soc. Chim. Fr. 1950, 17, 537.
93. The $^1$H NMR spectrum of 16 revealed the presence of trace amounts of 35.
94. Coalescence was observed for the marked signals. One singlet in the $^{13}$C NMR spectrum was obscured.
95. In the NMR spectra of 15 the peaks are slightly coalesced.
96. In the NMR spectra of this compound strong coalescence was observed. The $^1$H NMR spectrum pointed to the presence of at least three different conformers.
97. The $^1$H NMR spectrum of 54 revealed the presence of a small amount of 52.
Abstract: in this chapter, the results of the research described in chapter 3–6 are discussed. In the first paragraph, the syntheses are commented. The biomimetic cyclization reactions described in chapter 5 and 6 are discussed in the second paragraph, and compared with the literature. Based on this information, suggestions are made about the role of enzymes in these cyclization reactions.
7.1 The Synthesis of Germacrane Sesquiterpenes

At the moment that the research described in this thesis started, both the Marshall fragmentation reaction and the enolate-assisted fragmentation reaction had been used only once in the synthesis of germacrane sesquiterpenes (§ 2.3.1). The scope of both methods, however, turned out to be considerable as the synthesis of several naturally occurring germacrane sesquiterpenes presented in this thesis shows.

A great part of the thesis describes the construction and functionalization of decalin systems (eudesmane systems in fact), required for these fragmentation reactions. Although the substrates for the Marshall fragmentation reaction described in chapter 3, 4, and 5 are comparable (§ 2.5), it turned out necessary to develop different synthetic routes towards each of them.

(-)-Guaiol (1), obtained by crystallization from guaiac wood oil, was chosen as starting material for the synthesis of (+)-hedycaryol (4) described in chapter 3. The hydroazulene ring system of 1 was converted in 3 steps into the 5-hydroxyeudesmane 2. As shown in this chapter, this approach is also valuable for the synthesis of naturally occurring eudesmane sesquiterpenes. Especially, eudesmanes oxidized at C(1) which are frequently found in nature are difficult to synthesize in other ways (see also chapter 4).\(^1\) Probably due to a moderate regioselectivity in the addition of borane to 3,\(^2\) the Marshall fragmentation reaction afforded (+)-4 only in 55% yield. Essentially the same yield has been obtained by Wharton et al. in the synthesis of (±)-4.\(^3\)

**Scheme 7.1**

For the synthesis of (-)-allohedycaryol (8) described in chapter 4, (Scheme 7.2) an efficient synthesis of (+)-α-cyperone (6) was developed via the alkylation of the imine derived from (+)-dihydrocarvone (5) and (R)-(—)-1-phenylethylamine.\(^4\) (+)-α-Cyperone (6) has been used as a starting material in the synthesis of a number of other sesquiterpenes. For our purpose, a net functionality transfer from C(3) to C(1) in 6 was needed.
The ultimate answer to this problem turned out to be rather straightforward, although reaching that point a considerable amount of our energy was required. The key to the solution is the easy accessibility of the C(1)–C(2) double bond compared to the C(5)–C(6) double bond in 9 (Scheme 7.3). When this feature was exploited using a net epoxidation of the sterically less favored β side, the desired epoxide 10 could be obtained in 61% yield. Based on a recent observation in the literature, it was expected that this epoxide function could be opened di-equatorially to give, after reduction of the obtained intermediate, diol 11. This turned out to be the case.

The Marshall fragmentation reaction of 7 gave a higher yield than that of 3. This is probably due to the higher regioselectivity of the addition of borane to the trisubstituted double bond in 7. Excess fresh BH₃·THF was required to obtain reproducible yields. In the synthesis of neochedarcyol described in chapter 5, we used therefore the more stable BH₃·SMe₂. The use of this reagent in the Marshall fragmentation reaction has also been described by Piet et al.2

(−)-Carvone (12) was used for the synthesis of neochedarcyol (16) as described in chapter 5 (Scheme 7.4). The synthesis of a C(9)-oxidized eudesmane skeleton, in this case 14, is a longstanding problem and attempts to develop an enantiospecific route failed. We were forced to use a known method in which chirality is lost. Although
not elegant, this loss of chirality was of no importance in this research because the final product, neochedycaryl, turned out to be achiral! Due to its elongated chair conformation, a symmetry plane is present in 16.

The impossibility to obtain mesylate 14 from the corresponding diol was initially puzzling. We were guided, however, by the fact that the synthesis of a similar compound, lacking the 2-hydroxyisopropyl group, was reported to be uncomplicated.\(^7\) It appeared that the leaving group ability of the mesylate function formed, was strongly enhanced by through-bond electron donation of the hydroxyl group at C(11) which carries negative charge (\(\delta^-\)) due to hydrogen bond formation with pyridine present in the reaction medium. By protecting the C(11) hydroxyl group as its acetate, hydrogen bond formation was avoided and mesylate 15 could be isolated in high yield. This solution to the problem was very satisfactory and allowed completion of the synthesis of 16.

Compared to (+)-chedycaryl and (-)-allochedycaryl, the yield of the fragmentation reaction affording 16 is low. This is partly due to interference of the C(11) acetate group. Another possibility is that the regioselectivity of the addition of borane to 15 is poor due to polarization of the double bond by the homo-allylic mesylate group.\(^7\) Once again, an aqueous silver nitrate extraction turned out to be extremely useful for the purification of the final product, neochedycaryl.

**Scheme 7.4**

For the enolate-assisted fragmentation reactions described in chapter 6, the Wieland-Miescher ketone derivative 17 was chosen as a starting material. Prepared in a number of steps, this compound is frequently used in the synthesis of terpenes. The research in this chapter aimed at the construction of germacrane devoid of chiral centers, so racemic starting material was used.

In the first instance, the study of the enolate-assisted fragmentation reaction was frustrated because the initially formed products reacted immediately further. Nevertheless, by the characterization of the isolated products, we concluded that the
fragmentation reaction itself was a rapid and unambiguous process. After the introduction of an isopropylidene side chain and, especially, the discovery that the E → Z isomerization of the fragmentation product could be suppressed by the use of sodium tert-amylate as the base, the desired break-through was a fact. The usefulness of this approach was further illustrated by the synthesis of 15-hydroxyhedycaryol (22). The velocity of the fragmentation reaction and the excellent yield of this product show the efficiency of the enolate-assisted fragmentation reaction in germacrane synthesis.

15-Hydroxygermacrene B (19) was employed to study the biomimetic cyclization of germacrane to guaianes. Until now, this conversion was difficult to perform because it requires the regioselective epoxidation of the C(4)–C(5) double bond. In case of 19, however, the presence of a hydroxyl group at C(15) allowed a regio- and enantioselective epoxidation and afforded, after cyclization, a cis-fused guaiane system in high ee (§ 7.2). The reactivity of the intermediate epoxide precluded its isolation and caused immediate cyclization. The present isopropanol plaid the role of water in the natural process by quenching the intermediate carbocation. Similarly, the E,Z-analog of 19 was subjected to Sharpless epoxidation and afforded a stable epoxide. The ee of this product could not be determined but the enantioselectivity of the Sharpless epoxidation is virtually always very high. Acid induced cyclization of this epoxide afforded several products derived from a trans-fused guaiane cation.

\[ \text{Scheme 7.5} \]
The question posed in the literature whether germacrene B would be enantiomerically stable could be answered in this chapter. Kinetic resolution of 19, using the aforementioned Sharpless epoxidation, resulted in the recovery of racemic starting material, whereas the isolated guaiane was produced in high ee. This result shows that racemization of 19 occurs at a considerable speed at rt and this conclusion can safely be extrapolated to germacrene B (20).

7.2 The Biosynthesis of Eudesmane and Guaiane Sesquiterpenes

An important topic in this thesis is the influence of the configuration and conformation on the product outcome of the transannular cyclization of germacrane (Scheme 7.6). Acid-induced cyclization of germacrane or their corresponding mono-epoxides is generally accepted to be biomimetic and represents the biosynthesis of eudesmane and guaiane sesquiterpenes (§ 1.2). An extensive study on this topic has recently appeared in our group. These cyclization reactions are not only restricted to germacrane sesquiterpenes but also occur, for example, in the biosynthesis of taxane diterpenes. Most of the time, the acid-induced cyclization is fast and results in eudesmanes or guaianes with a stereochemistry identical to that found in the majority of the natural products.
The observations mentioned above are important for the discussion about the role of enzymes in these cyclization reactions. In general, enzymes are involved in both the rate and the product control of reactions. In the biosynthesis of sesquiterpenes, however, it is difficult to imagine how an enzyme can control these energetically favorable cyclization reactions which proceed via highly reactive carbocations. Biomimetic reactions are valuable tools to show at what stages in biosynthesis, enzymes are interfering with spontaneous non-enzymatic processes.

The biosynthesis of eudesmanes from germacranes is studied in chapter 5. In connection with this conversion, it is important to note that the partial purification of one enzyme, β-selinene cyclase, has been reported. This enzyme converts \( (E,E) \)-FPP (23), presumably via germacrene A (24), into β-selinene (25, Scheme 7.7).

![Scheme 7.7](image)

Because of its thermal lability, germacrene A is not very suitable for chemical or enzymatic studies. For this purpose, the thermally more stable hedycaryol (4) is a better substrate. Cyclization of (+)-4 by a suspension of chicory roots, supposedly possessing sesquiterpene cyclase activity, affords selectively (+)-cryptomeridiol (27). Acid-induced cyclization of (+)-4 leads to a mixture of products consisting of 27 and α, β, and γ-eudesmol (26). Although hedycaryol possesses three interconverting conformations at room temperature (§ 5.1), acid-induced and enzyme-mediated cyclization take place from only one conformer.

So, the observed difference between the biomimetic and biosynthetic transannular cyclization of (+)-hedycaryol is, in this case, the selectivity in the termination of the reaction. This is comparable with the activity of β-selinene.
cyclase which produces selectively β-selinene (25). *These results suggest that the role of a sesquiterpene cyclase in this reaction is mainly concerned with the initiation and termination of the cyclization reaction, and less or not at all with the course of the cyclization itself.*

Once the cyclization has been initiated by protonation, the reaction is presumably very fast and dictated by the inherent reactivity of the substrate. In connection with product control, it is questionable whether in the termination of the reaction, an enzyme can accelerate the formation of one product compared to other, unwanted, products. Therefore, it might well be that the enzymatic regulation of the product outcome in the termination of these reactions is effected in part by diminishing the speed of side-reactions. In the case of β-selinene cyclase, product control can partly be effected by the exclusion of water from the active site, thereby eliminating the role of water as nucleophile and as a base. This offers, however, no explanation for the regioselectivity in the formation of the double bond. The selective formation of 27 by the cichory root suspension possibly involves stabilization of the resulting carbocation at C(4) by aromatic amino acid side chains, thereby slowing down the formation of a double bond and allowing the nucleophilic attack of water. This description of the role of sesquiterpene cyclases seems to find some support in the literature.

In the light of the foregoing, the occurrence of *epi*-eudesmanes possessing an aberrant stereochemistry at C(10) or C(5) is very interesting. The biosynthesis of normal eudesmanes and *epi*-eudesmanes from the *same* germacrane requires empathic interference of the cyclase(s) involved. As mentioned in *chapter* 5, *epi*-eudesmanes are not formed by acid-catalyzed cyclization of hedycaryol. An alternative explanation, which limits the role of the sesquiterpene cyclase involved, would be the formation of *epi*-eudesmanes from neohedycaryol (16), already suggested in the literature in 1959.

Although 16 is not found in nature until now, an additional argument for its existence is the isolation of (+)-allohedycaryol (8), which structure has been proven through synthesis of its enantiomer (chapter 4). Germacrane like 8 are probably formed by a C(4)–C(5) double bond shift in the corresponding 1(10),4-germacrane. This would imply that allohedycaryol and neohedycaryol are both formed from hedycaryol by shifting the C(4)–C(5) and the C(1)–C(10) double bond, respectively. However, allohedycaryol possesses the ent-configuration and, consequently, its biosynthesis requires *ent*-hedycaryol. The transannular cyclization of allohedycaryol probably does not represent a biosynthetic step and is therefore not included in this thesis.
Through synthesis of neochedycaryl (16), we were able to show that acid-induced cyclization of both neochedycaryl (16) and hedycaryl (4) leads to the same products (26). Moreover, it was shown that 16 is achiral because of the presence of a symmetry plane. Consequently, acid-induced cyclization of 16 leads to racemic products. Enzymatic cyclization of 16 can, in principle, lead to enantiomerically enriched 26 and 27. Further studies have to wait for the detection of 16 in natural sources, which has been strongly facilitated by its synthesis.

Compared to the biosynthesis of eudesmanes, the biosynthesis of guaianes has received less attention in the literature because the availability of germacrane C(4)–C(5) epoxides is limited. Some information has been obtained from germacrane epoxides from natural origin or from mixtures of epoxides, formed by nonselective epoxidation of germacrane. The majority of the isolated guaianes possesses a cis-fused ring system with both bridgehead methine protons α oriented. A number of exceptions possesses a trans-fused ring system.

The biomimetic cyclization of germacrane-4,5-epoxides is studied in chapter 6. The enolate-assisted fragmentation reaction gives access to germacrane with a C(15) carbinol group. The presence of a hydroxyl group at C(15) allows the selective epoxidation of the C(4)–C(5) double bond (Scheme 7.8). Application of a Sharpless epoxidation reaction on 19 gave information about the stereochemistry of the cyclization process because the configuration of the resulting guaiane could be established independently. In contrast to hedycaryl (4), the NMR spectra of 19 and germacrane B (20) suggest that these compounds exist in one conformation at rt. Nevertheless, we were able to show that 19 racemizes quickly at rt, which implies that rotation of both ring double bonds takes place. In the presence of the Lewis acid-titanium species used, the intermediate epoxide immediately cyclized to the guaiane skeleton 28. Apparently, epoxidation and cyclization take place from the crown conformation in which the endocyclic double bonds possess the crossed orientation. This results in the cis stereochemistry present in the majority of isolated guaianes.

A curious aspect of germacrane B and 19 is their planar chirality. Though rare, natural products which are chiral solely due to the presence of a chiral plane are known. Performed as a kinetic resolution, the Sharpless epoxidation of 19 is highly enantioselective. It is possible that in vivo epoxidation of germacrane is enantioselective as well. Conversion of racemic germacrone (29) by plant cell cultures affords enantiomerically enriched germacrone-4,5-epoxide (30).
It has been postulated in the literature that the biosynthesis of trans-fused guaianes possessing a trans relationship between C(15) and H-5 proceeds via melampolides ((Z,E)-germacranes). This theory fits in the hypothesis discussed earlier and can be replenished by the remark that heliagonalides ((E,Z)-germacranes) are likely precursors of trans-fused guaianes with a cis relationship between C(15) and H-5. In order to test this hypothesis, heliagonalide model 31 was subjected to the Sharpless epoxidation reaction to afford the stable mono-epoxide 32.
As in the biomimetic cyclization of hedycaryol (4), acid-induced cyclization of 32 afforded a rather complex mixture of products due to the nonselective termination of the reaction. With extensive chromatography the three major products could be purified of which diene 34 disclosed the stereochemical course of the reaction. The cyclization of 32 requires stronger acidic conditions compared to (E,E)-germacranes and small amounts of unidentified by-products are formed. Nevertheless, the cyclization is unambiguous except for the quenching of the final cation. The 1,2-H shifts leading to the formation of 34 are probably also involved in the biosynthesis of pseudoguaianes\textsuperscript{29} and $\Delta^{5,6}$-guaianes.

Summarizing the results, we can state that the biosynthesis of trans-fused and cis-fused guaianes can be mimicked by the acid-induced cyclization of 32 and the C(4)–C(5) epoxide of 16, respectively. The formation of 34 from 32 also suggests a biosynthetic route to rearranged guaianes. These cyclization experiments support the aforementioned hypothesis that the influence of the involved sesquiterpene cyclase(s) on the course of these cyclization reactions is limited.

7.3 References and Notes

4. Apparently, we were not the only one who saw the benefits of this method because two similar procedures appeared in the literature shortly after the publication of our results. (a) Tenius, B. S. M.; Rohde, A. R.; Victor, M. M.; Viegas Jr, C. *Synth. Commun.* 1996, 26, 197. (b) Xiong, Z.; Yang, J.; Li, Y. Tetrahedron: Asymm. 1996, 7, 2607.
9. The following definition of "biomimetic" is used: "A biomimetic step follows the biosynthetic route used in nature as closely as possible in the laboratory
12. Comparable observations in alkaloids, isolated from Nitraria species, have led to the biomimetic synthesis of these alkaloids. See reference 9; pp 731–768.
14. Impressive observations of this kind have been made in the biomimetic synthesis of steroids, a field more thoroughly studied. See: (a) Johnson, W. S. Angew. Chem. 1976, 88, 33. (b) Abe, I.; Rohmer, M.; Prestwich, G. D. Chem. Rev. 1993, 93, 2189. (c) Buntel, C. J.; Griffin, J. H. In Isopenetenoïds and Other Natural Products. Evolution and Function; Nes, W. D. Ed.; ACS Symposium Series 562, Washington DC, 1994; Chapter 3.
17. (a) Reference 14b. (b) Reference 10; chapter 4.
20. Recently, the C(4)-epimer of 8 with unknown absolute configuration has been isolated, see: Gansser, D.; Pollak, F. C.; Berger, R. G. J. Nat. Prod. 1995, 58, 1790.
22. No efforts have been made to test this hypothesis by cyclization of 16 with a chicory root suspension.
23. The C(4)–C(5) epoxide of germacrone (29, Scheme 7.8) has been used in cyclization studies, see: Piet, D. P.; Schrijvers, R.; Franssen, M. C. R.; de Groot,


25. Guaianes with a structure closely related to 28 have been isolated but it is not clear whether they are formed from germacrene B or from other germacrane precursors.


chapter 7
Summary

In this thesis, the synthesis of a number of germacrane sesquiterpenes is described. Functionalized decalin systems are prepared, which are used in turn as substrates for Grob-type fragmentation reactions. These fragmentation reactions start either with the hydroboration of a double bond, as in the Marshall fragmentation, or with the α deprotonation of an aldehyde, as in the enolate-assisted fragmentation. Both fragmentation reactions result in the regio- and stereospecific formation of two $E$ double bonds as present in the ten-membered ring of germacrane.

The acid-induced cyclization of the germacrane synthetized in this way mimics the biosynthesis of eudesmane and guaiane sesquiterpenes and is used to study the role of enzymes in these cyclization reactions.

In chapter 1, a general introduction into the biosynthesis and physiological role of terpenes is presented. The biosynthesis of germacrane sesquiterpenes and their subsequent conversion into eudesmane and guaiane sesquiterpenes is further worked out. Attention is paid to important aspects of isolation, purification, and structure elucidation.

In chapter 2, the literature concerning the synthesis of germacrane sesquiterpenes is reviewed. The synthetic approaches are grouped together according to the applied ten-membered ring forming reactions. The research described in this thesis is mentioned shortly.

In chapter 3, the synthesis of $\dagger$-hedycaryol (6), a generally occurring germacrane alcohol, is described. The hydroazulene skeleton of the starting material $\dagger$-guaiol (1) was therefore transformed to the decalin system 2 in 3 steps.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{Diagram.png}};
\end{tikzpicture}
\end{center}

\begin{center}
(\textit{-}-guaiol (1)) \quad 2 \quad 3: R = H \\
4: R = OH \\
5: R = OM \text{Marshall fragm.} \\
(\textit{+}-hedycaryol (6))
\end{center}
After conversion of 2 into mesylate 5, a Marshall fragmentation was used to prepare the \((E,E)\)-cyclodecadiene ring system present in (+)-hedycaryol. Additionally, the applicability of 2 as a starting material in the synthesis of eudesmane sesquiterpenes was illustrated by the synthesis of (+)-\(\gamma\)-eudesmol (3) and (+)-4-eudesmene-1\(\beta\),11-diol (4).

In chapter 4, the synthesis of \((-\)-allohedycaryol (9) is described. The synthesis started from (+)-\(\alpha\)-cyperone (7) which was efficiently prepared via alkylation of the imine derived from (+)-dihydrocarvone and \((R)\)-\(+\)-1-phenylethylamine. In a number of steps, 7 was converted into mesylate 8. A Marshall fragmentation of 8 completed the synthesis of allohedycaryol. This successful synthesis of \((-\)-9 allowed the elucidation of the relative and absolute stereochemistry of its antipode isolated from giant fennel (Ferula communis L.). It turned out that natural (+)-9 has the opposite absolute stereochemistry to that normally found in higher plants. The conformation of 9 was elucidated via photochemical conversion into a bourbonane system.

In chapter 5, the total synthesis of neohedycaryol (12), the C(9)–C(10) double bond regioisomer of hedycaryol (6), is described. The synthesis started from the known dione 10, prepared as a racemate from carvone. Again, a Marshall fragmentation was used to prepare the \((E,E)\)-cyclodecadiene ring. During the synthesis of 11, a pronounced example of through-bond interactions (TBI) was observed.

Neohedycaryol exists preferably in the elongated chair conformation as was determined spectroscopically and by chemical transformation and this indicates that
the role of neohedycaryl as a precursor in the biosynthesis of epi-eudesmanes, as proposed in the literature, is unlikely. This also means that 12 is not chiral and occupies a meso form.

In chapter 6, enolate-assisted fragmentation reactions are developed for the synthesis of germacrane. After treatment with sodium tert-amylate and subsequent reduction, aldehyde 14 afforded the (E,E)-alcohol 15. The use of potassium hexamethyldisilazane instead of sodium tert-amylate as a base gave the corresponding E,Z analog. The presence of two E double bonds in 15 was proven by conversion of 15 into germacrene B (16). With the same approach, 15-hydroxyhedycaryl (18) was also efficiently synthesized.

The biosynthesis of guaiane sesquiterpenes was mimicked by asymmetric Sharpless epoxidation of allylic alcohol 15 to afford guaiane 19 in high ee. The cis-fused ring system in 19 is found in most of the isolated guaianes. Epoxidation and cyclization of the (E,Z)-analog of 15 afforded trans-fused guaianes.

In chapter 7, the results presented in chapter 3 through 6 are discussed. The results of the biomimetic cyclization reactions suggest that the role of sesquiterpene cyclases is mainly concerned with the initiation and termination of these cyclization reactions, and less or not at all with the course of the cyclization itself.
Samenvatting

In dit proefschrift wordt de synthese van een aantal germacraan sesquiterpenen beschreven. Voor dit doel zijn verbindingen met een gefunctionaliseerd decalineskelet gesynthetiseerd als substraten voor Grob-type fragmentatiereakties. Deze fragmentatiereakties beginnen hetzij met de hydroborering van een dubbele binding, zoals in de Marshall-fragmentatie, hetzij met de α deprotonering van een aldehyde, zoals in de enolaat-geassisteerde fragmentatie. Als resultaat van deze reakties worden regio- en stereospecifiek de twee E dubbele bindingen gevormd die aanwezig zijn in de tienring van germacranen.

De zuurgekatalyserte cyclisatie van de gesynthetiseerde germacranen bootst de biosynthese van eudesmaan - en guaiaan sesquiterpenen na. Dit verschijnsel wordt gebruikt om de rol van enzymen in deze cyclisatiereakties te bestuderen.

In hoofdstuk 1 wordt een algemene introductie in de biosynthese en fysiologische functie van terpenen gegeven. Daarna wordt de biosynthese van germacraan sesquiterpenen en hun omzetting in eudesmaan - en guaiaan sesquiterpenen verder uitgewerkt. Verder wordt aandacht besteed aan belangrijke aspecten van de isolatie, zuivering en structuurherkennings van germacranen.

In hoofdstuk 2 wordt de bestaande literatuur over de synthese van germacranen samengevat. De verschillende synthetische benaderingen zijn gegroepeerd aan de hand van de manier waarop de tienring wordt gevormd. Het onderzoek beschreven in dit proefschrift wordt kort toegelicht.

\[
\begin{align*}
(-)-guaiol (1) & \\
2 & \\
3: R = H & \\
4: R = OH & \\
5: R = OMs & \\
& \text{Marshall fragm.} \\
& \text{(+)-hedycaryol (6)}
\end{align*}
\]

In hoofdstuk 3 wordt de synthese van (+)-hedycaryol (6), een algemeen voorkomend germacraanalkohol, beschreven. In de eerste 3 stappen van deze synthese wordt het hydroazuleenskelet van de uitgangsstof (-)-guaiol (1) getransformeerd tot het decalineskelet 2. Na omzetting van 2 in het mesylaat 5
wordt een Marshall-fragmentatie toegepast om het \((E,E)\)-cyclodecadieensysteem van hedycaryl te maken. Dat 2 ook bruikbaar is in de synthese van eudesmaan sesquiterpenen wordt geïllustreerd met de synthese van \((+)-\gamma\)-eudesmol (3) en \((+)-4\)-eudesmeen-\(1\beta,11\)-diol (4).

In hoofdstuk 4 wordt de synthese van \((-)\)-allohedycaryl (9) beschreven. De synthese gaat uit van \((+)-\alpha\)-cyperon (7), wat op zijn beurt in goede opbrengst wordt verkregen uit de alkylering van het imine van \((+)-\text{dihydrocarvon}\) en \((R)-(+)\)-fenylethylamine. In een aantal stappen wordt 7 omgezet in mesylaat 8. Marshall-fragmentatie van 8 completeert vervolgens de synthese van \((-)\)-allohedycaryl. De antipode \((+)\)-9 is geïsoleerd uit reuzenvenkel (Ferula communis L.) en door middel van deze synthese is de relatieve en absolute stereochemie van het natuurproduct opgehelderd. Het blijkt dat natuurlijk \((+)\)-allohedycaryl niet de absolute stereochemie heeft die normaal in hogere planten wordt gevonden. De conformatie van 9 is opgehelderd via fotochemische cyclisatie tot een bourbonaan skelet.

\[
\begin{align*}
&(+)\-\alpha\-\text{cyperon (7)} & & \text{MsO} & & \text{OH} & & \text{OH} \\
&\text{8} & & \text{(-)allohedycaryl (9)}
\end{align*}
\]

In hoofdstuk 5 wordt de synthese van neochedycaryl (12), een C(9)-C(10) dubbele bindingsisomeer van hedycaryl, beschreven. De synthese gaat uit van het bekende racemische dion 10 dat gemaakt wordt uit carvon. Weer wordt een Marshall-fragmentatie gebruikt voor de vorming van de \((E,E)\)-cyclodecadieenring. Tijdens de synthese van 11 werd op een uitgesproken voorbeeld van "through-bond" interactie (TBI) gestuit.

\[
\begin{align*}
&(10 \text{ racemisch}) & & \text{OMs} & & \text{OAc} & & \text{OH} \\
&\text{11} & & \text{neochedycaryl (12)}
\end{align*}
\]

De voorkeur van neochedycaryl voor de verlengde-stoelconformatie is chemisch en spectroscopisch bepaald. Deze conformatie houdt in dat de voorgestelde rol van 12 in de biosynthese van \emph{epi}-eudesmanen waarschijnlijk onjuist is. Het betekent
ook dat 12 niet chiraal is maar in de mesovorm voorkomt.

![Chemical structure diagram]

Met de asymmetrische Sharpless-epoxidatie van 15 wordt de biosynthese van guiaan sesquiterpenen nagebootst. Dit resulteert in de vorming van guiaan 19 in hoge enantiomere overmaat. Het cis-verknoopte ringsysteem is karakteristiek voor de meeste natuurlijke guaienanen. Evenzo leidt epoxidatie en cyclisatie van het (E,Z)-analogon van 15 tot trans-verknoopte guaiananen.

![Chemical structure diagram]

In hoofdstuk 7 worden de resultaten van hoofdstuk 3 tot en met 6 besproken. De resultaten van de biomimetische cyclisatiereakties duiden erop dat de betrokken sesquiterpeencyclase(s) voornamelijk verantwoordelijk zijn voor de initiatie en terminatie van de cyclisatiereaktie en niet of nauwelijks voor het stereochemische verloop ervan.
samenvatting
Curriculum Vitae

Stellingen

1. De alkylering van (E)-3-penten-2-on met het enaminoketon bereid uit methyl cyclohexaan-1,3-dion en pyrrolidine, heeft een ander verloop dan door Coates et. al. wordt verondersteld.


2. Hoewel in het algemeen de totaalsynthese van een natuurprodukt als een overtuigend strukturbewijs wordt gezien, is dit bij de synthese van alismol door Lange et. al. niet het geval.


3. In de publicatie van Marcovich et. al. over de modificatie van zaagsel door maleïnezuuranhydride wordt ten onrechte niet aangegeven hoeveel zaagsel voor de experimenten is gebruikt.


4. De enzymen die betrokken zijn bij de cyclisatie van germacraan sesquiterpenen beïnvloeden in veel gevallen de initiatie en terminatie van de reaktie maar niet het stereochemische verloop ervan.

Dit proefschrift.

5. Ook estetische overwegingen staan het gebruik van kringloppapier niet meer in de weg.

Dit proefschrift.

6. Een beter literatuuronderzoek door de betrokken auteurs zou het aantal "nieuwe" verbindingen dat gerapporteerd wordt in het tijdschrift Phytochemistry aanmerkelijk reduceren.

7. Vegetarisme is geen luxe.

8. De waarneming dat chimpansees elkaar omarmen bij vreugde en bij verdriet, weerspiegelt het gedrag van voetballers tijdens een wedstrijd.


11. De uitbreiding van de telecommunicatie zal het personenverkeer niet doen afnemen.

Stellingen behorende bij het proefschrift: "Germacrane Sesquiterpenes, Synthesis and Role in Biosynthesis".

Wageningen, 26 maart 1997. 

A. J. Minnaard

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