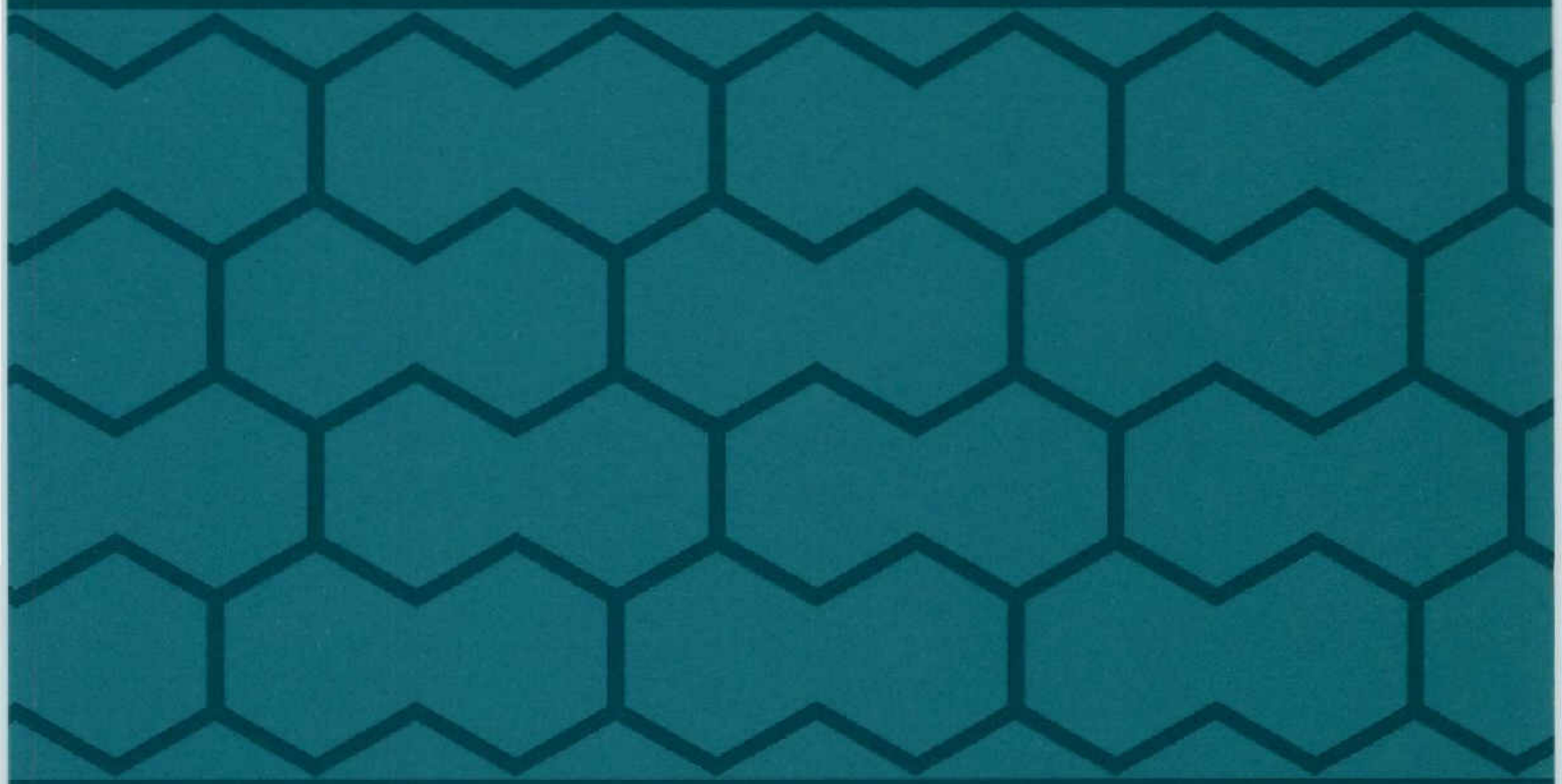
Germacrane Sesquiterpenes

Synthesis and Role in Biosynthesis



Adri Minnaard

Germacrane Sesquiterpenes

Synthesis and Role in Biosynthesis

Adri Minnaard

Promotor: dr. Ae. de Groot, hoogleraar in de bio-organische chemie
Co-promotor: dr. J. B. P. A. Wijnberg, universitair hoofddocent organische chemie

A. J. Minnaard

Germacrane Sesquiterpenes

Synthesis and Role in Biosynthesis

Proefschrift
ter verkrijging van de graad van doctor
op gezag van de rector magnificus
van de Landbouwuniversiteit Wageningen,
dr. C. M. Karssen,
in het openbaar te verdedigen
op woensdag 26 maart 1997
des namiddags te vier uur in de Aula

ISBN 90-5485-668-8

Voorwoord

Dankzij een uniek initiatief van de Landbouwuniversiteit kreeg ik de mogelijkheid een zelf geschreven projectvoorstel uit te werken op een zogenaamde BRAIO-plaats. Het onderwerp, germacraan sesquiterpenen, bleek een gelukkige keuze. De synthese van germacranen was een uitdaging, terwijl met name de stereochemische aspecten van hun rol in de biosynthese erg interessant waren. Tijdens het onderzoek heb ik dankbaar gebruik gemaakt van op de vakgroep reeds ontwikkelde kennis.

Dit is de plaats om een aantal mensen te bedanken die aan de totstandkoming van dit proefschrift hebben meegewerkt. Aede, van meet af aan heb jij je ten volle ingezet voor mijn onderzoek en me alle vrijheid gegeven dit in te vullen. Vaak had je meer vertrouwen in de goede afloop dan ik, en daarvoor ben ik je zeer erkentelijk. Hans, jij bent het nauwst bij mijn onderzoek betrokken geweest. Van jou heb ik geleerd hoe je onderzoek doet. Daarnaast heeft de grondige en secure wijze waarop je mijn teksten hebt nagekeken en becommentarieerd veel aan het resultaat bijgedragen. Marc, ik ben blij je deze tijd als kamer- en zaalgenoot te hebben gehad. Met veel plezier denk ik terug aan de discussies die wij, vaak aangevuld met Hans, hebben gevoerd. Ook met jou, Edwin, was het altijd goed discussiëren en daarmee hebben we veel koffie- en theepauzes benut. Soms waren we het eens. Verder leverden Romano, Rinie, Gonzalo, Erwin, Tamara en Roel hun bijdrage aan de prettige sfeer. André hield de moed erin met een onverwoestbaar humeur en een waardevolle bijdrage aan hoofdstuk vijf. Vladimir, met jou heb ik gedurende negen maanden zeer intensief samengewerkt, met als resultaat hoofdstuk vier. Belangrijker dan dit hoofdstuk zijn echter de fijne kneepjes van het experimentele werk die ik van jou heb geleerd. Karel, jij zult de resultaten van je afstudeervak verspreid over de verschillende hoofdstukken tegenkomen.

Van de collega-AIO's wil ik met name vriend Dennis bedanken voor de samenwerking waarin we, graag en met reden, de moeizaam gesynthetiseerde germacranen weer hebben gemold. Tijdens mijn onderzoek heb ik vaak en nooit tevergeefs een beroep gedaan op de expertise van een groot aantal mensen. Met dank aan: Ben (synthese), Elbert, Pim, Gerrit en Teris (chromatografie), Bep (NMR), Maarten, Hugo en Kees ("de massa"), Rien (element-analyse), Pleun en Ronald (magazijn), Hannie (hygiëne), Elly, Ien en Ineke (secretariaat), Gert en Jurrie (als het vast liep) en Bart (voor beheer en beheersing).

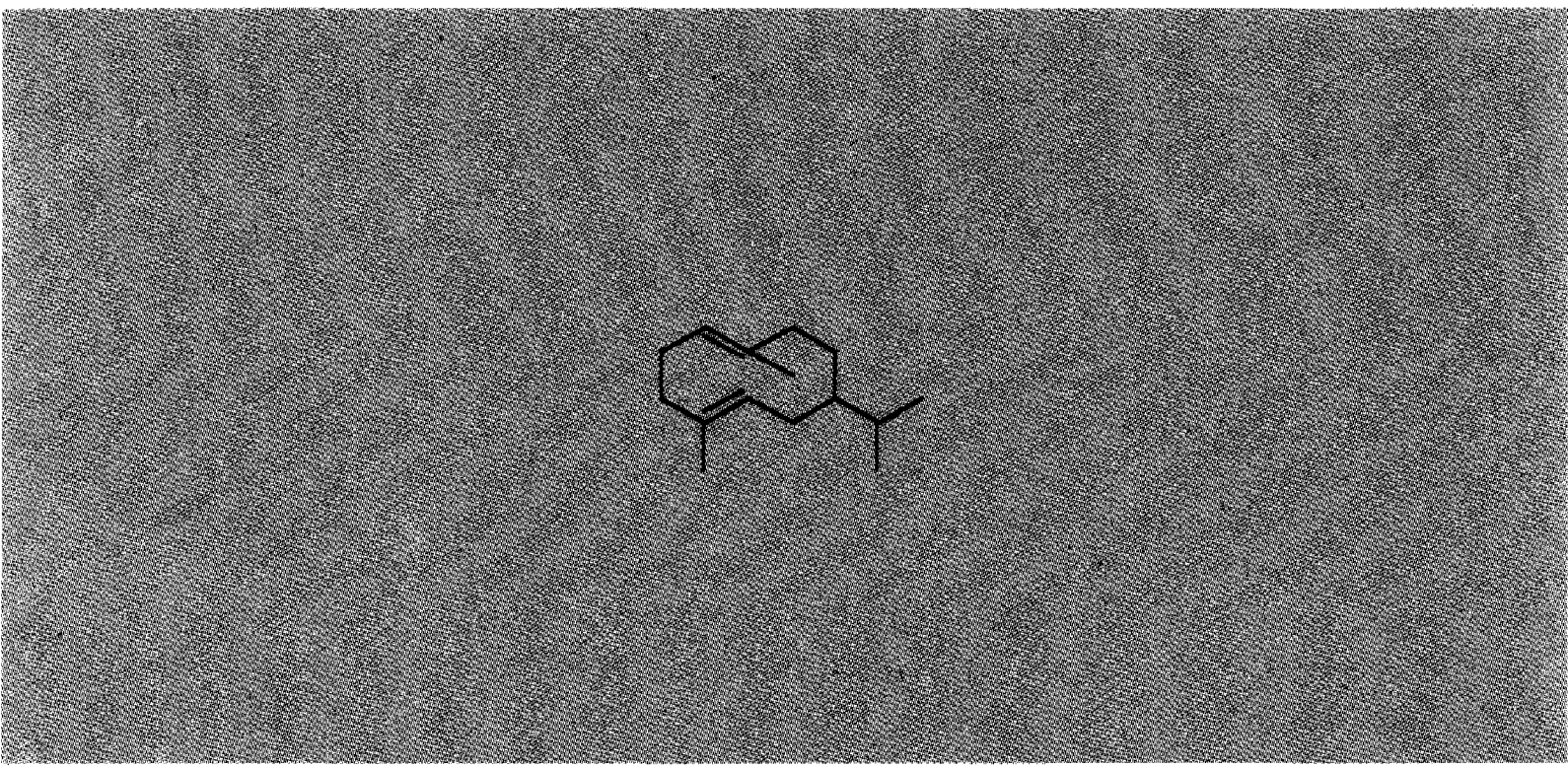
Sies, wat had ik graag dit proefschrift ook aan jou gegeven.

Adri

Aan mijn Vader en Moeder
Aan Christel

Contents

1 Introduction



Abstract: a general introduction to the occurrence and function of terpenes is presented. The place of germacranes 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, repellent, 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.

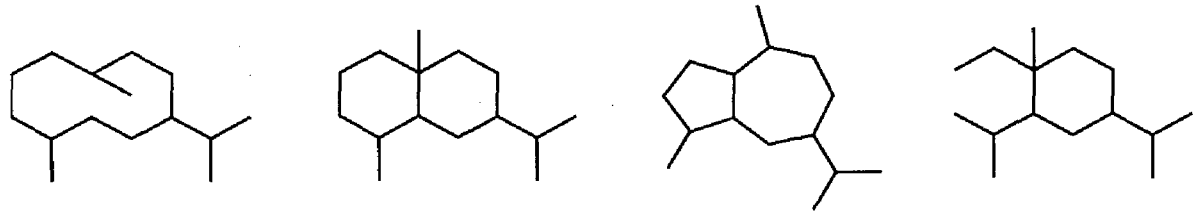
This thesis is concerned with sesquiterpenes (C15 terpenes), especially those of the germacrane class. Sesquiterpenes are typically found in all parts (seed, flowers, foliage, roots, and wood) of higher plants and also occur in mosses, liverworts, algae and lichens, some insects, and fungi.[7] They are found in both terrestrial and marine

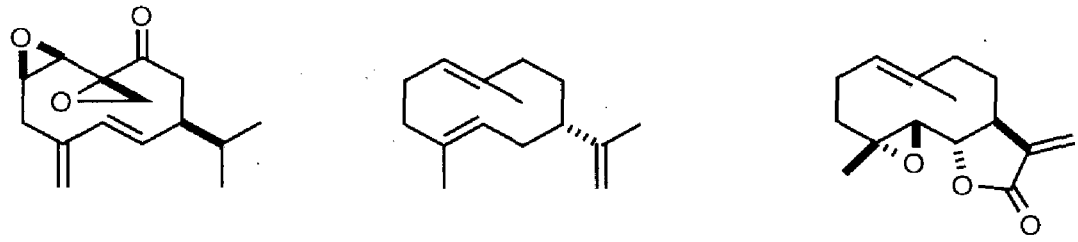
environments.[8] An enormous amount of sesquiterpenes has been isolated and classified according to their carbon skeleton.[9] Some of these classes comprise only a few compounds, other classes several thousands.

Germacrane sesquiterpenes form one of the larger classes of sesquiterpenes. Directly formed from (*E*,*E*)-farnesyl pyrophosphate[10] (§ 1.2), germacranes are the central intermediates in the biosynthesis of several other classes of sesquiterpenes.[11] Eudesmane, guaiane, and elemane 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*).[12] Another example is (–)-germacrene A ((–)-**2**), the alarm pheromone of the spotted alfalfa aphid (*Therioaphis maculata* B.).[13] 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.[14]

Scheme 1.1





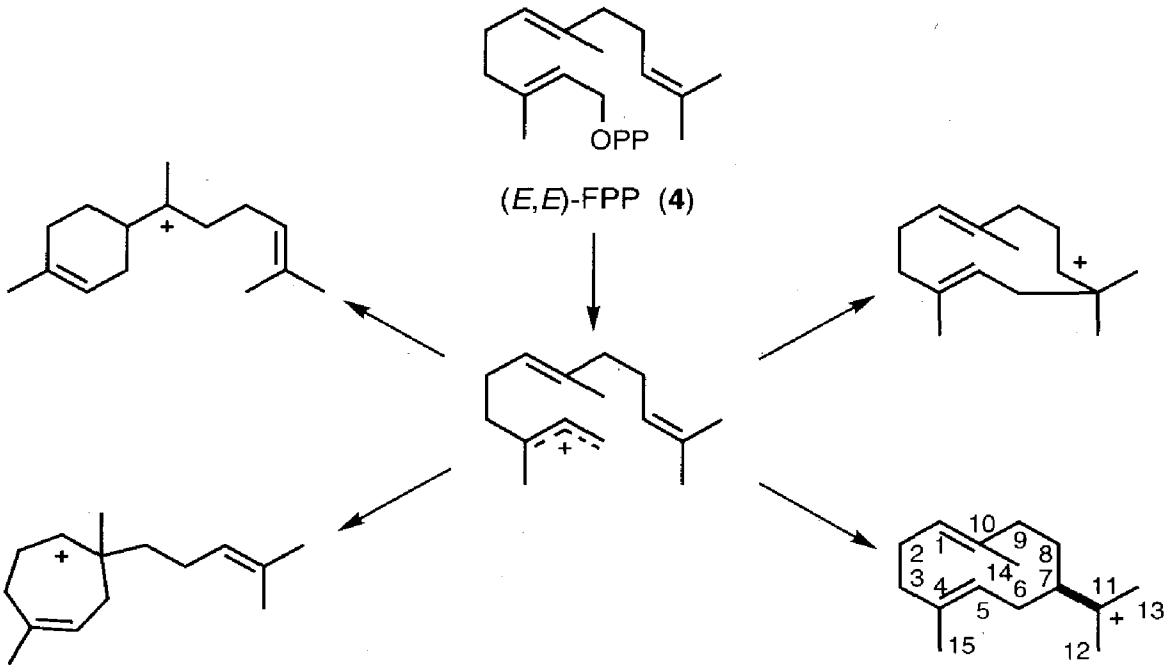
periplanone B (**1**) (–)-germacrene A ((–)-**2**) parthenolide (**3**)

1.2 The Biosynthesis of Germacrane, Eudesmane, and Guaiane Sesquiterpenes

According to the now generally accepted hypothesis of Nobel laureate Ruzicka,[15] the biosynthesis of most of the cyclic sesquiterpenes starts with the ionization of farnesyl pyrophosphate (**4**, FPP, farnesyl diphosphate).[16] 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).[17] In the resulting products, the isopentenyl ("isoprene") units can still be recognized and this is known as the *Isoprene Rule*.[18] Ring closure by attack of the distal double bond in a Markovnikov fashion leads to the germacrane skeleton.[19] Except for the formation of a C(7)–C(11) double bond, this reaction creates a chiral center.[20] 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.[21] These enzymes accept FPP as a substrate and produce germacranes or their cyclization products.

Scheme 1.2

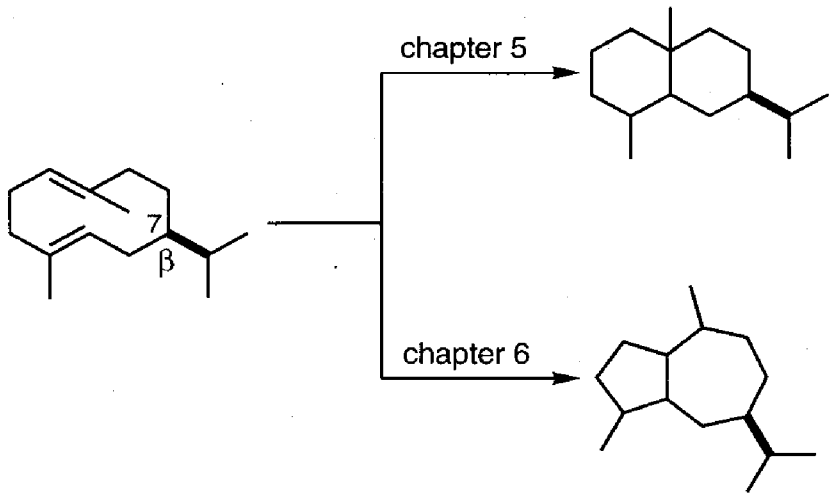


During the conversion of germacranes into eudesmane and guaiane sesquiterpenes, the chiral center at C(7) is generally preserved (Scheme 1.3). In the majority of sesquiterpenes from higher plants, the orientation of the C(7) side chain is β, as depicted, whereas in sesquiterpenes from marine origin and 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.

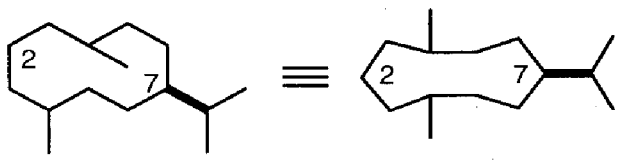
Scheme 1.3



1.3 Structures and Conformations

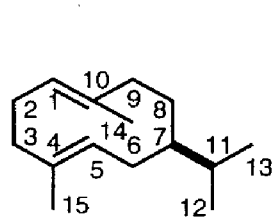
Depicting the carbon skeleton of germacranes in a less usual way (Scheme 1.4), shows that the skeleton possesses a symmetry plane, bisecting C(2) and C(7). In most cases, the C(1)–C(10) and C(4)–C(5) double bonds dissymmetrize the picture. The question *whether* a particular germacrane contains such 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

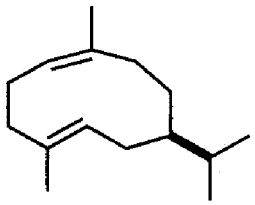


Due to this symmetry, the representation of germacranes caused confusion in the literature because compounds were drawn in two ways. Therefore, drawing conventions were formulated which are now generally accepted (Scheme 1.5).[22]

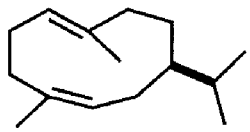
Scheme 1.5



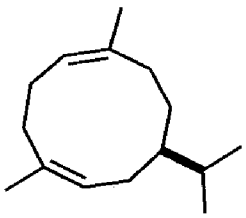
(*E*,*E*)-germacranes



(*Z*,*E*)-germacranes
(melampolides)



(*E*,*Z*)-germacranes
(heliangolides)



(*Z*,*Z*)-germacranes

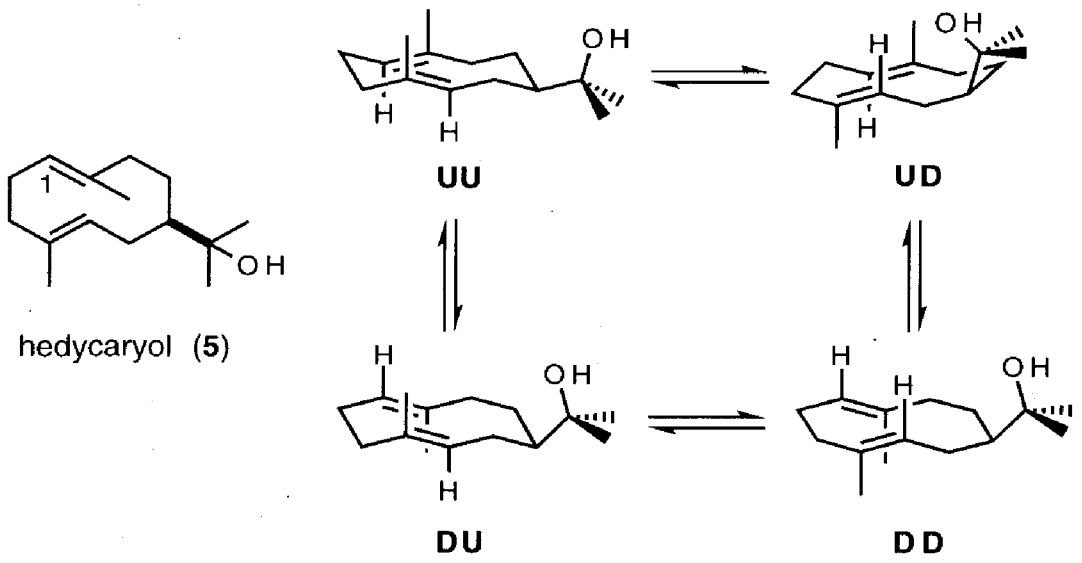
The descriptors *Z* and *E*, when applied to the endocyclic double bonds, indicate the stereochemistry of the ring bonds regardless the normal priority rules. Thus, when in the (*E*,*E*)-germacrane in Scheme 1.5, C(15) is oxidized, it remains an (*E*,*E*)-germacrane although the priority rules define the double bond as *Z*. The C(7) side-chain 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 germacranes has been an area of study for decades and has produced a massive amount of information.[23] The majority of the conformational studies focuses on (*E*,*E*)-germacranes 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.[24] 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 allogermacranes, containing an (*E*,*E*)-cyclodeca-1(10),5-diene system (§ 5.1).

A number of germacranes has been studied in the solid state by X-ray - and neutron diffraction.[25] In solution, many germacranes 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).[26] The existence of different conformations in germacranes 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 germacranes, 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 germacranes. Beside their conformational behavior, one of the most striking properties of (*E,E*)-germacranes is an "anomalous" ultraviolet absorption (λ > 200 nm) due to the interaction of the double bonds in the ring.[27] This phenomenon occurs when the π-lobes of the double bonds have a spatial overlap.[28] Germacranes containing an (*E,E*)-cyclodeca-1(10),5-diene system ("allogermacranes") also show this effect.

Some empirical rules for the interpretation of NMR spectra using $CDCl_3$ 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 a *E* double bond. In the ^{13}C 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.[29] 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.[30]

In connection with the isolation of germacranes 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,[31] argentation chromatography,[32] or even crystallization of the silver nitrate adduct[33] can sometimes be accomplished. On the other hand GC can be a pitfall, because at higher temperatures many germacranes easily undergo a Cope rearrangement to the corresponding elemanes. Germacrene A (**2**) rearranges even at room temperature (§ 2.4.1).

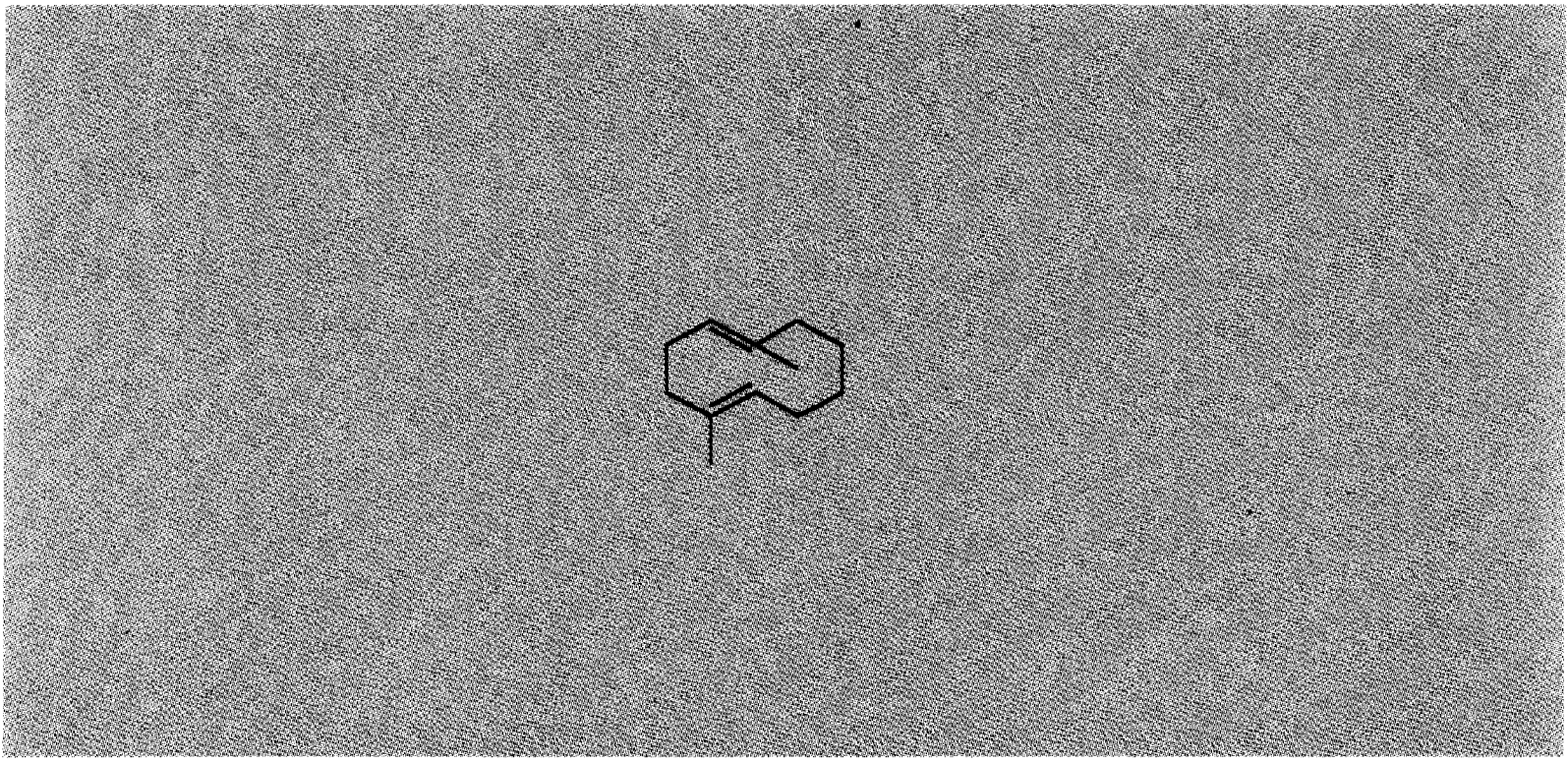
1.4 References and Notes

1. Banthorpe, D. V. In *Natural Products: Their Chemistry and Biological Significance;* Longman Scientific & Technical: Harlow, 1994.
2. Agosta, W. C. *Chemical Communication. The Language of Pheromones;* Scientific American Library: New York, 1992.
3. Harborne, J. B.; Tomas-Barberan, F. A., Eds. *Ecological Chemistry and Biochemistry of Plant Terpenoids;* Clarendon Press: Oxford, 1991.
4. (a) Agosta, W. C. *Bombardier Beetles and Fever Trees;* Addison-Wesley: USA, 1995; Chapter 3. (b) Kesselmans, R. P. W. *Total Synthesis of All Stereoisomers of Eudesm-11-en-4-ol;* Ph.D. Thesis, Agricultural University, Wageningen, The Netherlands, 1992; Chapter 1.
5. Mori, K.; Kuwahara, S.; Igarashi, Y. *Pure & Appl. Chem.* **1990**, *62*, 1307.
6. (a) van Beek, T. A.; de Groot, Ae. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 513. (b) Jermy, T.; *J. Chem. Ecol.* **1990**, *16*, 3151.
7. Reference 1; Chapter 5.
8. Pietra, F. *Chem. Soc. Rev.* **1995**, *24*, 65.
9. Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids;* Chapman & Hall: London, 1991; Vol. 1, Mono- and Sesquiterpenoids.
10. It is not known whether (*E*,*Z*)-, (*Z*,*E*)-, and (*Z*,*Z*)-germacranes 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 Mevalonic Acid Pathway to Terpenoids;* Towers, G. H. N., Stafford, H. A., Eds.; Plenum Press: New York, 1990; Chapter 4.
11. Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089.
12. See **chapter 2** and references cited therein.
13. Bowers, W. S.; Nishino, C.; Montgomery, M. E.; Nault, L. R.; Nielson, M. W. *Science* **1977**, *196*, 680.
14. (a) Hewlett, M. J.; Begley, M. J.; Groenewegen, W. A.; Heptinstall, S.; Knight, D.

W.; May, J.; Salan, U.; Toplis, D. *J. Chem. Soc., Perkin Trans. 1* **1996,** 1979. (b) *Merck Index;* 11th edition; nr. 6996.

15. Ruzicka, L. *Helv. Chim. Acta* **1922,** *5,* 923.
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.
18. Ruzicka, L.; Eschenmosher, A.; Heusser, H. *Experientia* **1953,** *9,* 357.
19. The formation of bicyclogermacranes 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.
21. (a) Reference 11. (b) Back, K.; Chappell, J. *J. Biol. Chem.* **1995,** *270,* 7375.
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.
23. (a) Sutherland, J. K. *Tetrahedron* **1974,** *30,* 1651. (b) Takeda, K. *Tetrahedron* **1974,** *30,* 1525. (c) Watson, W. H.; Kashyap, R. P. *J. Org. Chem.* **1986,** *51,* 2521. (d) Ugliengo, P.; Appendino, G.; Chiari, G.; Viterbo, D. *J. Mol. Struct.* **1990,** *222,* 437.
24. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds;* Wiley Interscience: New York, 1994; pp 1166-1176.
25. Watkins, S. F.; Fischer, N. H.; Bernal, I. *Proc. Nat. Acad. Sci. USA* **1973,** *70,* 2434.
26. Marshall, J. A.; Audia, V. H.; Jenson, T. M.; Guida, W. C. *Tetrahedron* **1986,** *42,* 1703.
27. Jain, T. C.; Banks, C. M. *Can. J. Chem.* **1980,** *58,* 447 and references cited therein.
28. Overlap of the double bonds can be considered as an interplay of through-space *and* through-bond interactions, see: Gleiter, R.; Schäfer, W. *Acc. Chem. Res.* **1990,** *23,* 369.
29. Lange, G. L.; Lee, M. *Magn. Reson. Chem.* **1986,** *24,* 656.
30. Herz, W.; Kalyanaraman, P. S. *J. Org. Chem.* **1975,** *40,* 3486.
31. Southwell, I. A. *Phytochemistry* **1970,** *9,* 2243.
32. For a review, see: van Beek, T. A.; Subrtova, D. *Phytochem. Anal.* **1995,** *6,* 1.
33. Brown, E. D.; Sam, T. W.; Sutherland, J. K.; Torre, A. *J. Chem. Soc., Perkin Trans. 1* **1975,** 2326.

2 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

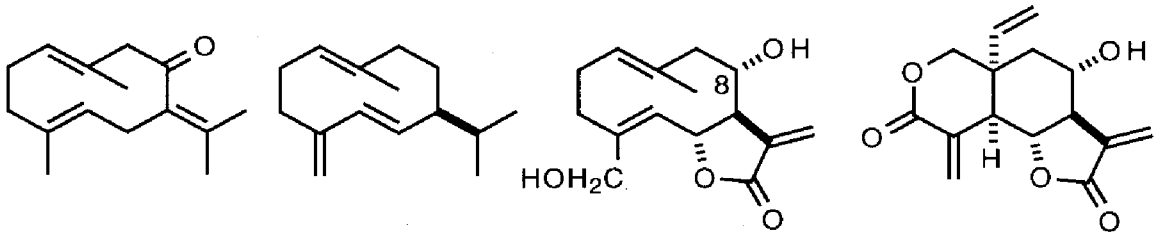
2.1.1 Germacranes as Starting Material in Synthesis

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 germacranes because only a very limited number of germacranes is available in (multi)gram quantities. This means that germacranes 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



germacrone (**1**) germacrene D (**2**) salonitenolide (**3**) vernolepin (**4**)

2.1.2 Strategies for the Synthesis of Germacranes

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 germacranes, 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 germacranes 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.[6] On the other hand, the synthesis of these medium-sized ring systems has functioned as a spring-board to the stereocontrolled synthesis of macrocycles.[7] Herein, we aim at a systematic overview of the synthesis of germacrane sesquiterpenes[8] and focus our attention mainly on the ten-membered ring formation.[9]

Intramolecular carbon-carbon bond formation can be accomplished in several ways. Due to the presence of two double bonds, the ring strain in germacranes 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 germacranes. The smaller rings present in the precursors are easier to construct and their stereochemistry can be controlled. The methods used for cleavage are diverse.

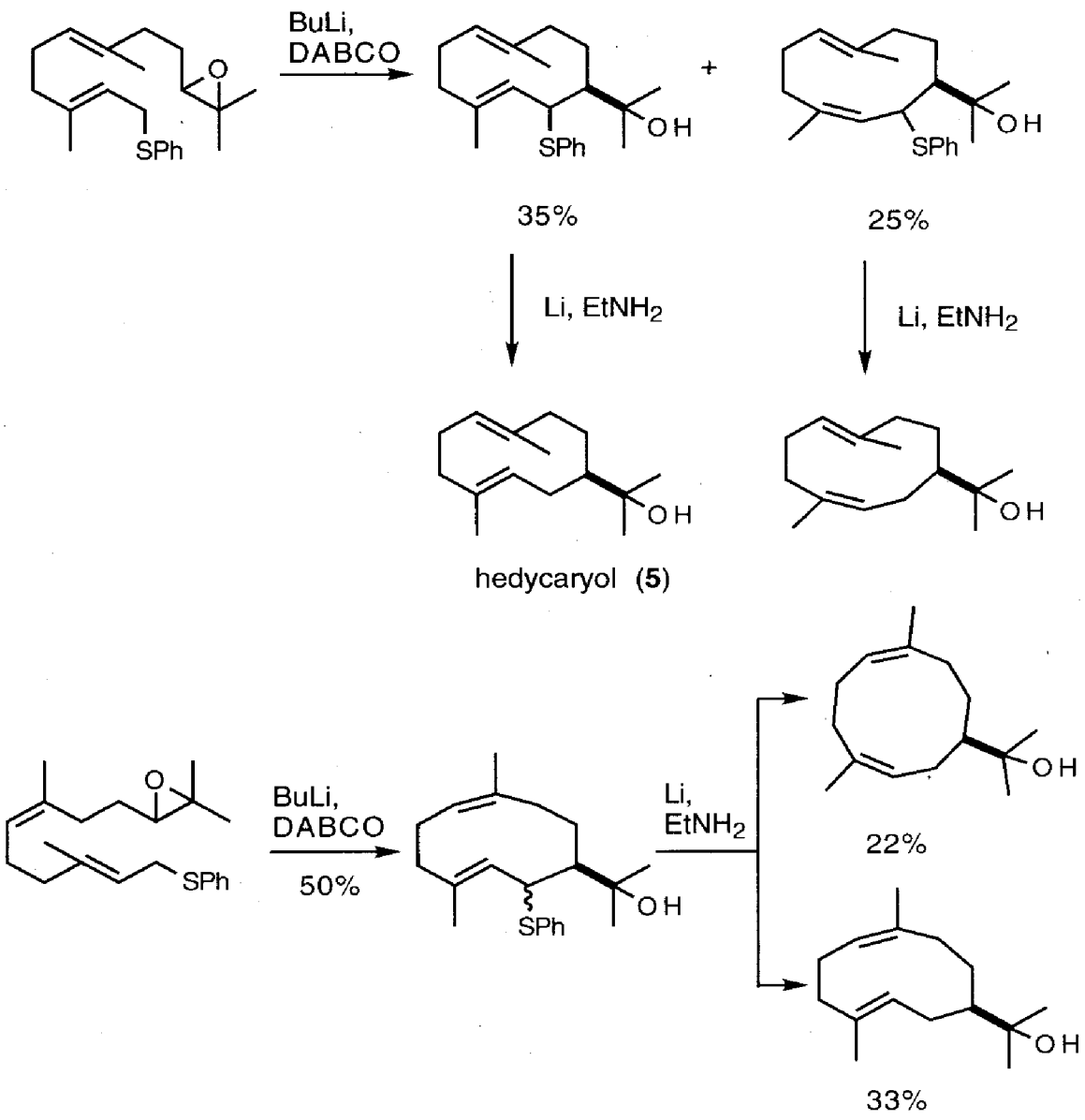
The ring expansions are dominated by the Cope reaction and its variants. The stereochemistry of the double bonds is determined by this [3,3] sigmatropic rearrangement and by the substituted cyclohexane systems involved.

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.[10] 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 hedycaryol (**5**). Acid-catalyzed transannular reactions and thermal Cope rearrangements of these stereoisomers gave more insight into the biosynthesis of the eudesmane and elemane sesquiterpenes.[11]

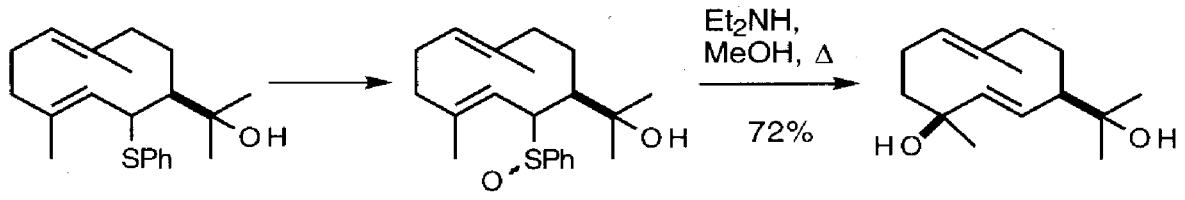
Scheme 2.2



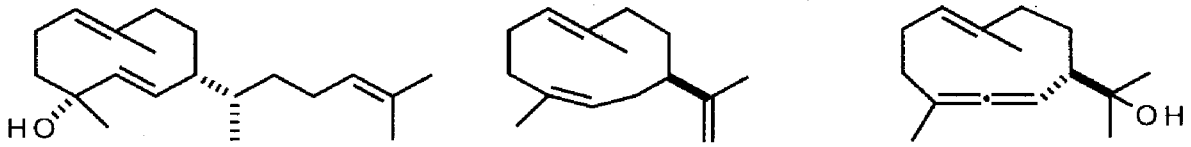
The method has also been used in combination with a [2,3] sigmatropic rearrangement. Obscuronatin (**6**), a diterpene closely related to the germacranes,[12] and the germacrane **7** with a cyclodeca-1(10),5-diene system[13] have been synthesized by this combined method (Scheme 2.3). The latter compound was isolated some years later from a marine soft coral[14] and a liverwort.[15]

The Kodama-Itô method has been applied by Winter et al. to elucidate the structure of helminthogermacrene (**8**) through synthesis.[16] Recently, the method has been revisited in the synthesis of the germacranoid **9** containing an allene function (Scheme 2.3).[17]

Scheme 2.3



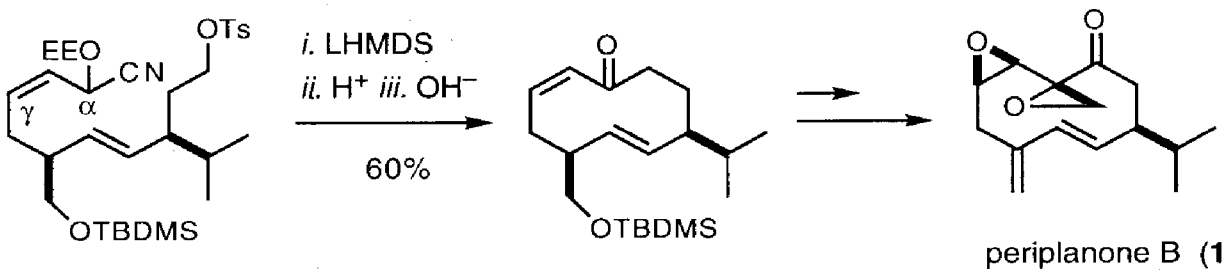
7



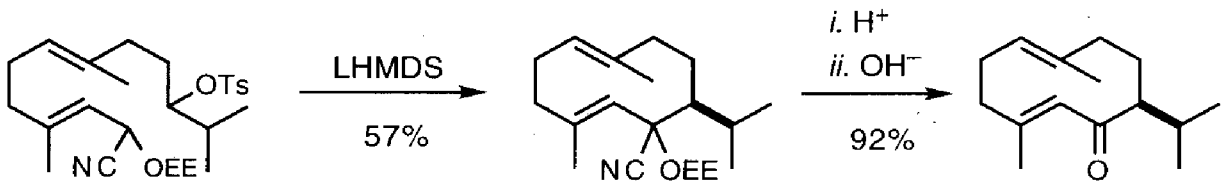
obscuronatin (**6**) helminthogermacrene (**8**) **9**

In 1983 Takahashi et al. have introduced a general method for the construction of (*E,E*)- and (*E,Z*)-2,6-cyclodecadienone systems by intramolecular alkylation of cyanohydrin ethers.[18] The acyclic precursors are built up from farnesyl or geranyl derivatives[19] 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 hexamethyl disilazane (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**)[20] and acoragermacrone (**11**)[21] using this approach. The method has also been used for the synthesis of germacrone (**1**)[22] and, recently, for the synthesis of periplanone analogs.[23] 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.[24]

Scheme 2.4



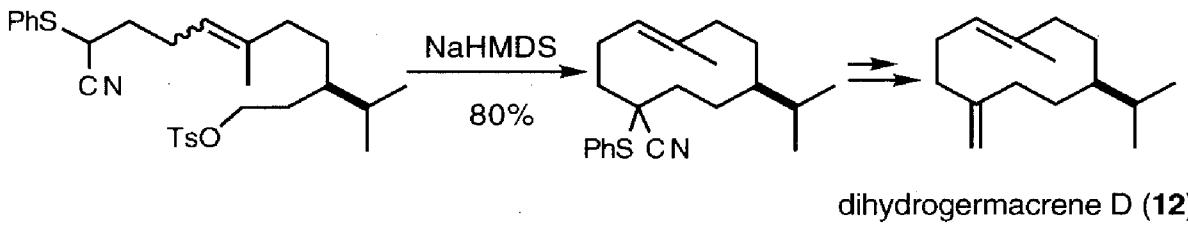
periplanone B (**10**)



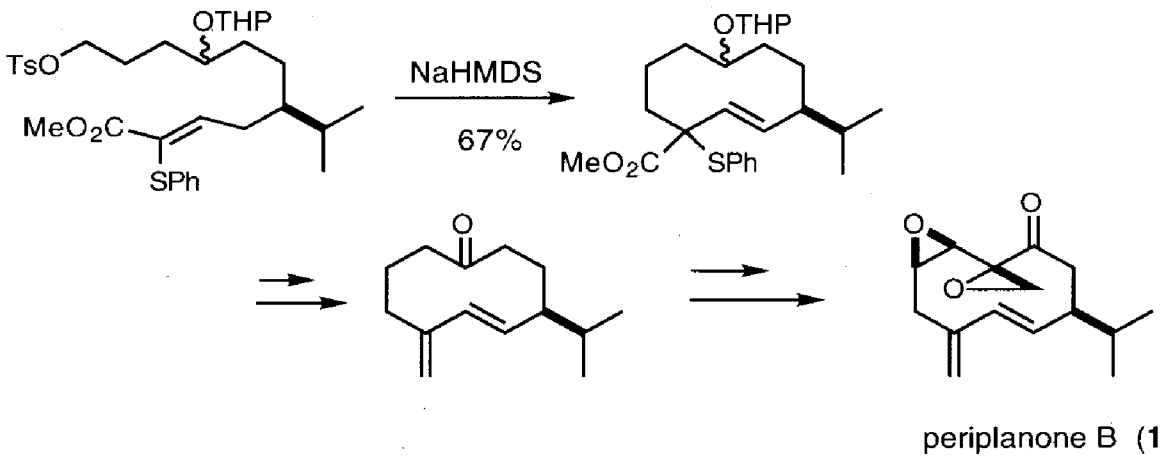
acoragermacrone (**11**)

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 α-phenylthioacrylate has been used in an enantiospecific synthesis of periplanone B (**10**).[26]

Scheme 2.5



dihydrogermacrene D (**12**)

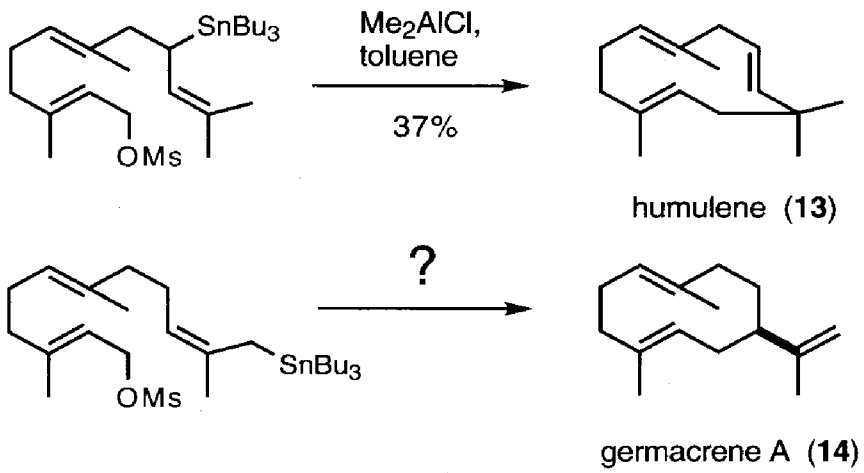


periplanone B (**10**)

Similarly, an ω-tosyloxy-α-phenylsulfenyl ketone, prepared from carvone, has been cyclized to a ten-membered ring.[27]

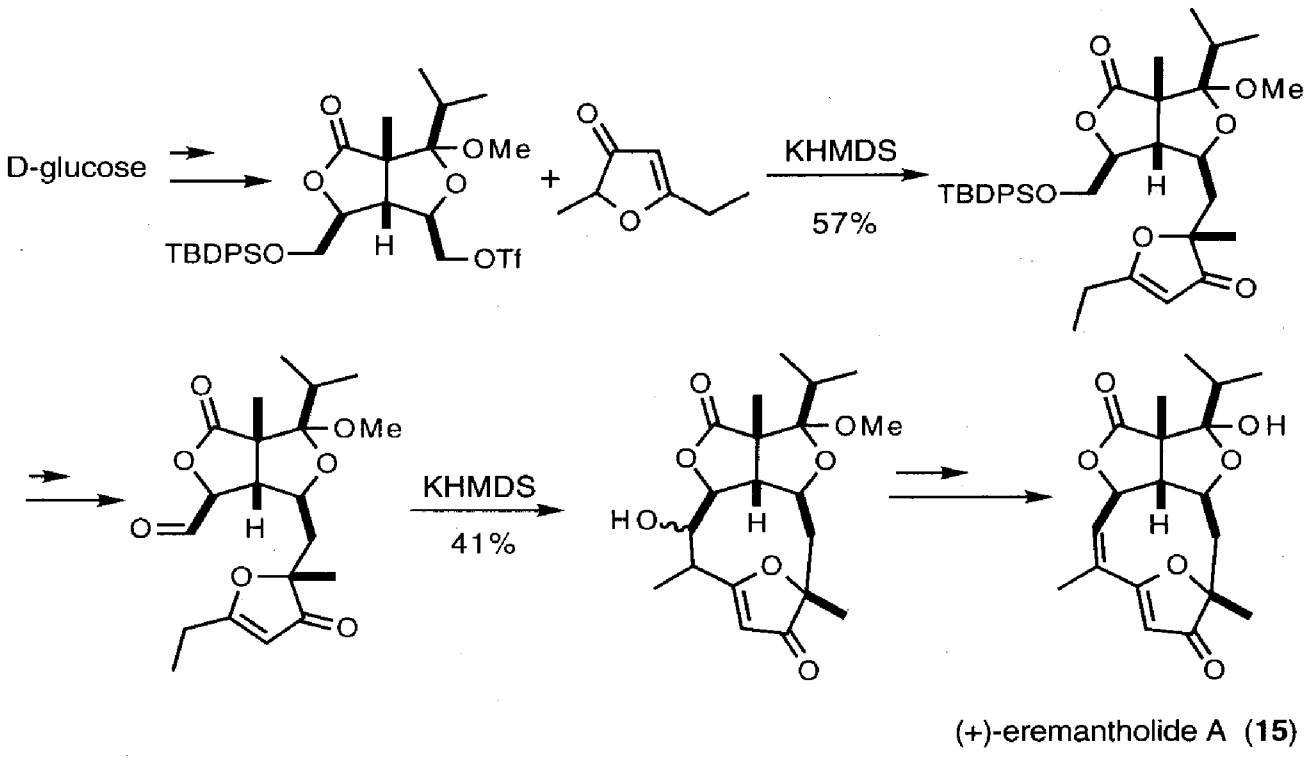
A biomimetic approach has been used by Corey et al. in the synthesis of humulene (**13**), possessing an eleven-membered ring (Scheme 2.6).[28] Whether this cyclization method, applied on a proper precursor, leads to a biomimetic synthesis of germacranes or not is still a question. As Corey already stated in 1965: "The laboratory synthesis of these sesquiterpenes by (such) a biomimetic cyclization has not yet been realized, despite its apparent simplicity".[29]

Scheme 2.6



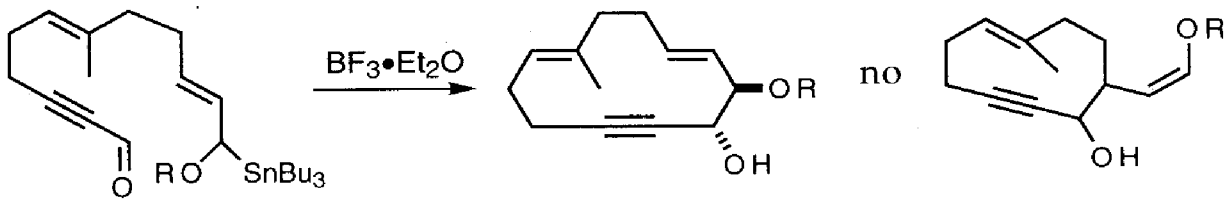
The synthesis of the complex germacrane eremantholide A (**15**) has been a challenge for several research groups.[30] A recent approach to this compound starts from D-glucose and uses an intramolecular vinologous aldol reaction for the construction of the ten-membered ring (Scheme 2.7).[31]

Scheme 2.7



Marshall et al. have developed an efficient cyclization of α-alkoxyallylstannane alkynales for the synthesis of fourteen-membered cembranoid precursors. Application of this method to the synthesis of germacranes fails and gives a twelve-membered ring (Scheme 2.8).[32]

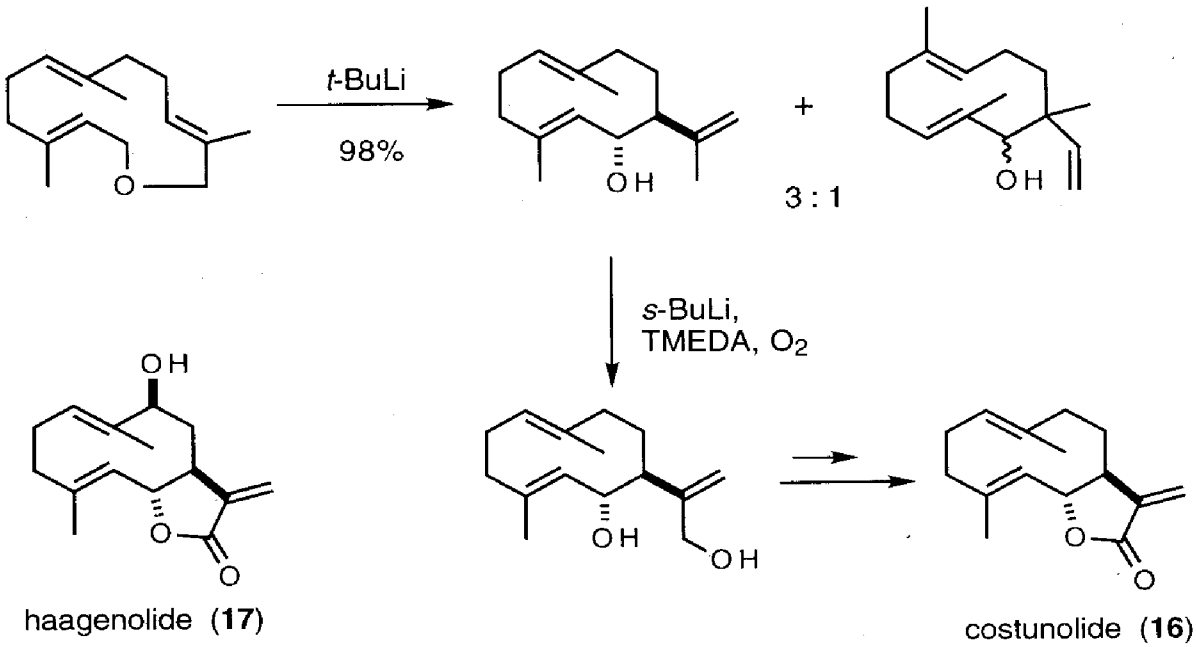
Scheme 2.8



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



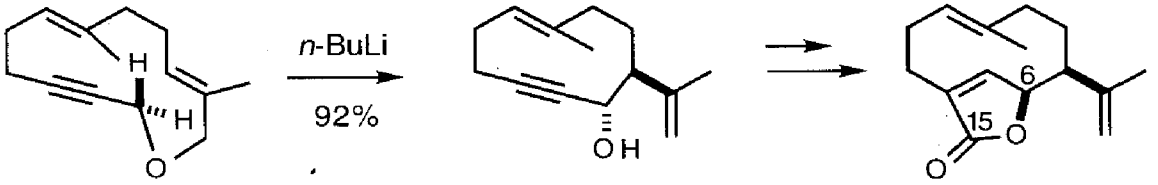
haagenolide (**17**)

costunolide (**16**)

In later work, ring closure leading to the large-ring ether was performed with the aforementioned cyanohydrin ether method[35] (Scheme 2.4) and was used in the synthesis of haagenolide (**17**).[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).[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

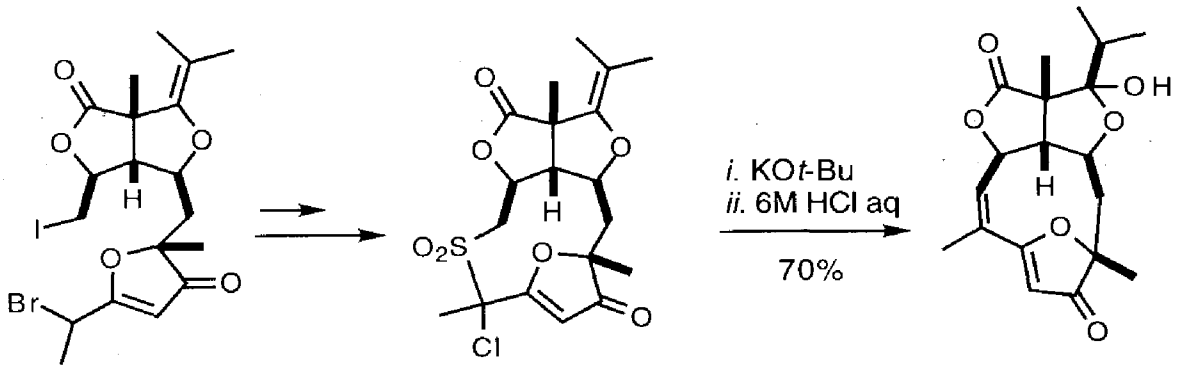


aristolactone (**18**)

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.[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).[39]

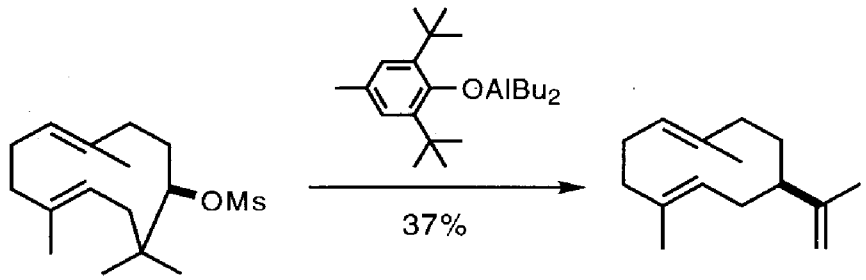
Scheme 2.11



eremantholide A (**15**)

Although not aiming at the synthesis of a particular germacrane, it was found that ring contraction of a humulene derivative gives helminthogermacrene (**8**).[40] Two years later, **8** was isolated from *Helminthosporium sativum*.[41] Ring contraction of another humulene derivative afforded germacrene A (**14**, Scheme 2.12).

Scheme 2.12

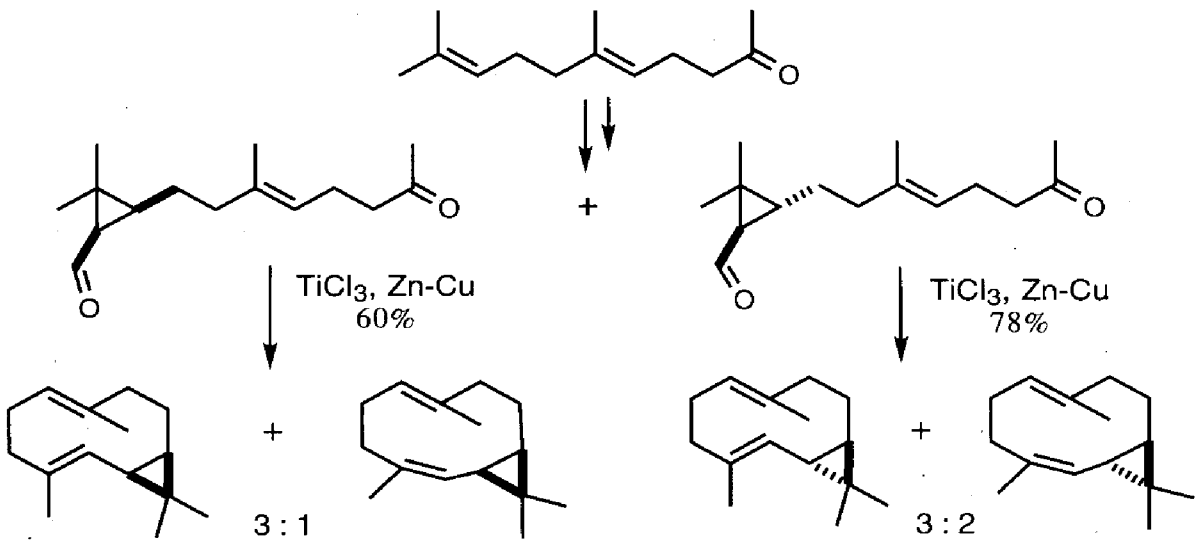


germacrene A (**14**)

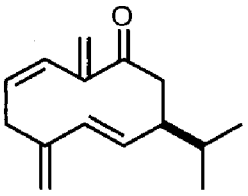
2.2.3 Carbonyl Coupling

Several syntheses of germacranes 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 bicyclogermacrenes (**19**, **20**) and lepidozenes (**21**, **22**) (Scheme 2.13).[42] Very recently, isolepidozene (**21**) has been found in some liverworts.[43]

Scheme 2.13



bicyclogermacrene (**19**) isobicyclogermacrene (**20**) isolepidozene (**21**) lepidozene (**22**)



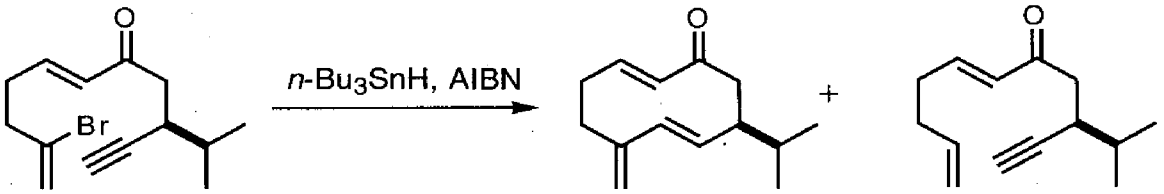
periplanone C (**23**)

Helminthogermacrene (**8**),[44] periplanone C (**23**),[45] and acoragermacrone (**11**)[46] have been prepared similarly. A low valent chromium reagent has been used in the synthesis of costunolide (**16**).[47]

2.2.4 Intramolecular Radical Cyclization

Recently, two reports have been published on an intramolecular radical cyclization approach towards germacrane sesquiterpenes. Parsons et al.[48] 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).

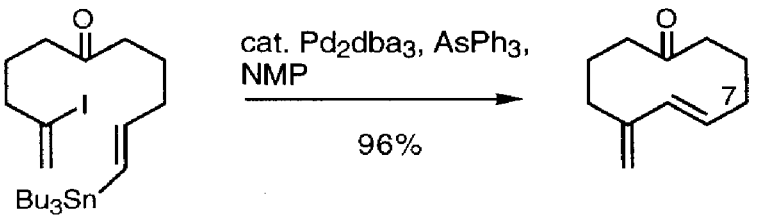
Scheme 2.14



14% 58%

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.[49]

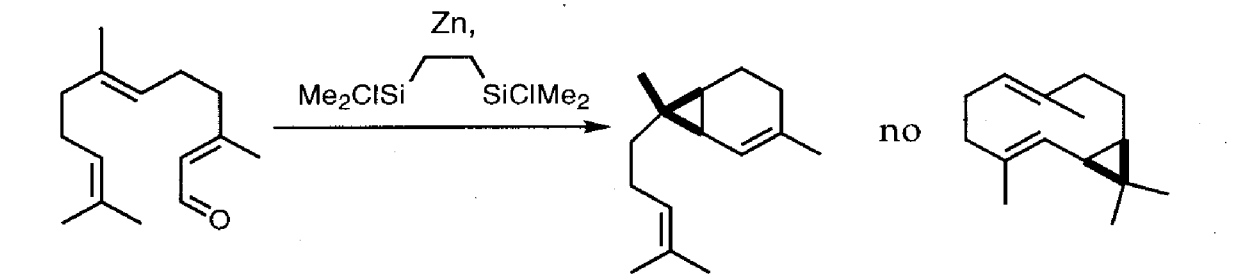
Scheme 2.15



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



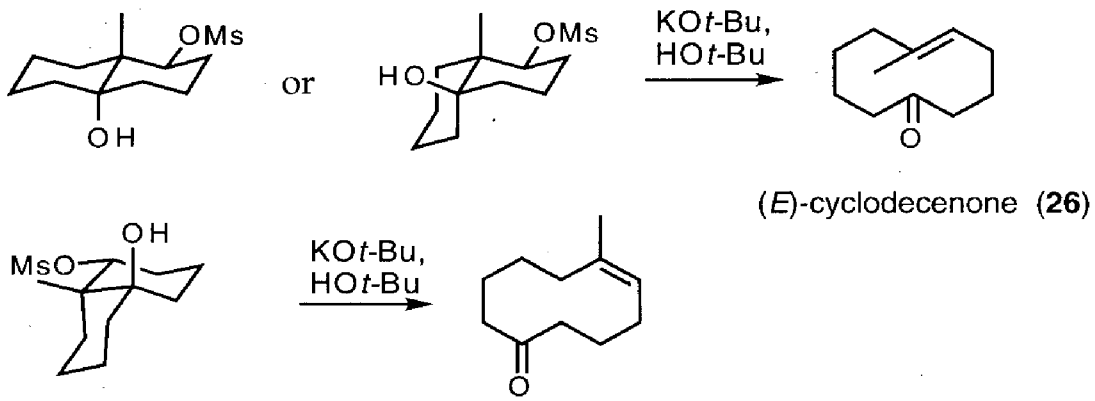
(*E,E*)-farnesal (**24**) sesquicarene (**25**) bicyclogermacrene (**19**)

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/HO*t*-Bu (Scheme 2.17).[51] In a similar way the *Z* isomer (**27**) was prepared.[52]

Scheme 2.17



(*E*)-cyclodecenone (**26**)

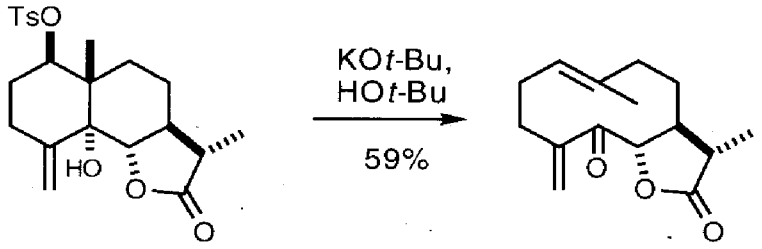
(*Z*)-cyclodecenone (**27**)

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.[53] 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.[54]

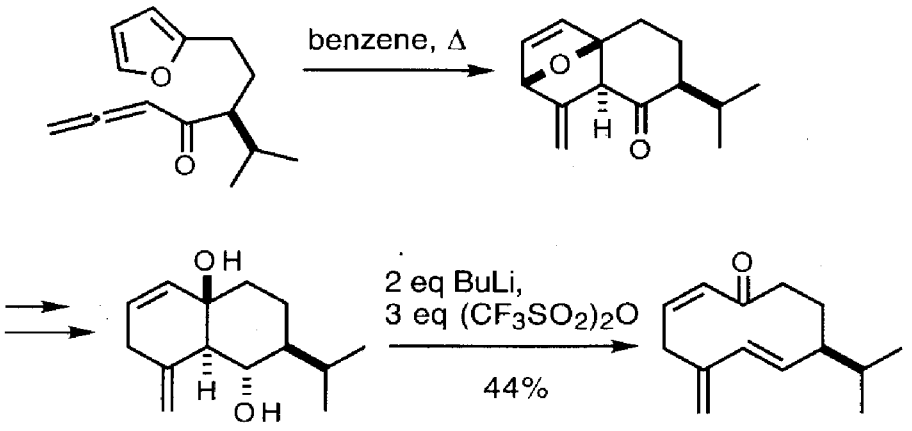
Although not aiming at the synthesis of a germacrane, cyclodecenones were used as intermediates in the synthesis of longipinenes.[55] A cyclodecynone formed by an Eschenmosher fragmentation was used in the biomimetic synthesis of bourbonenolides.[56] In the synthesis of chapliatrin-type compounds[57] and in the biomimetic synthesis of 5α-hydroxy guaianolides,[58] the Wharton fragmentation reaction was used as a key step (Scheme 2.18).

Scheme 2.18



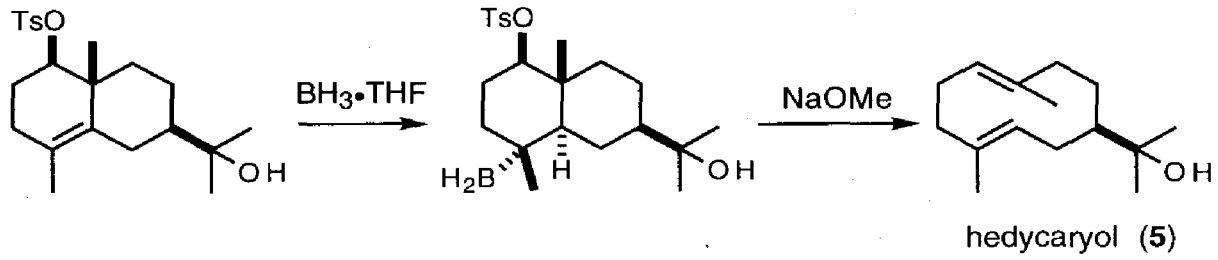
De Clercq et al. developed an elegant route to an intermediate in the synthesis of periplanone B (**10**, Scheme 2.19).[59] Key steps in this approach are an intramolecular Diels-Alder reaction and the Wharton fragmentation reaction.

Scheme 2.19



A reaction closely related to the Wharton fragmentation reaction is the so-called boronate fragmentation reaction developed by Marshall et al..[60] Initially, this reaction was used as a synthetic approach to guaiane sesquiterpenes.[61] Wharton was the first one who applied this method in the synthesis of the germacrane alcohol hedycaryol (**5**, Scheme 2.20).[62] The method has also been used in the synthesis of (*Z*,*E*)-cyclodecadienes.[63] An investigation has been made on the applicability of this method to the construction of germacranolides.[64] Germacrane models constructed this way have recently been used to study the role of enzymes in the biosynthesis of eudesmane and guaiane sesquiterpenes.[65]

Scheme 2.20

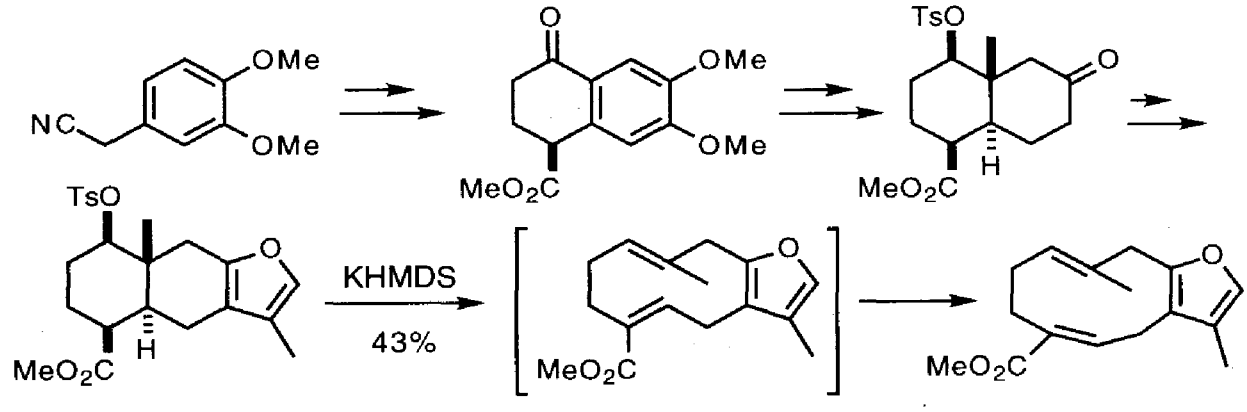


hedycaryol (**5**)

The stereochemistry of the borane addition has been discussed.[66] 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*)-furanogermacrane (Scheme 2.21).[67] The required decalin system was prepared via a dissolving metal reduction and methylation of a substituted tetralone.[68] 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

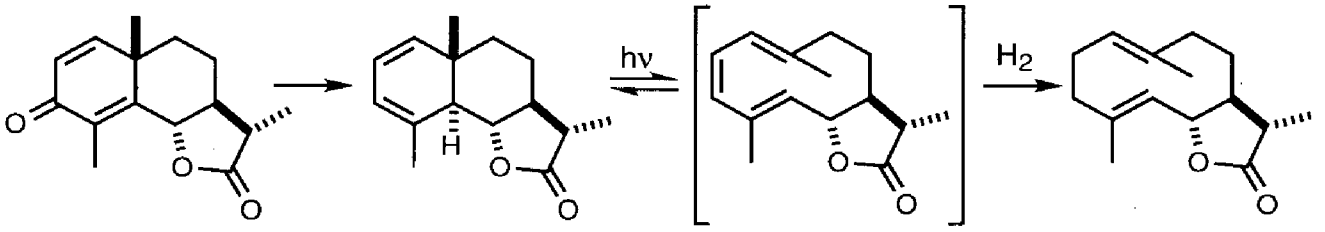


isosericenine (**29**) sericenine (**28**)

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).[69] The starting material was α-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**.

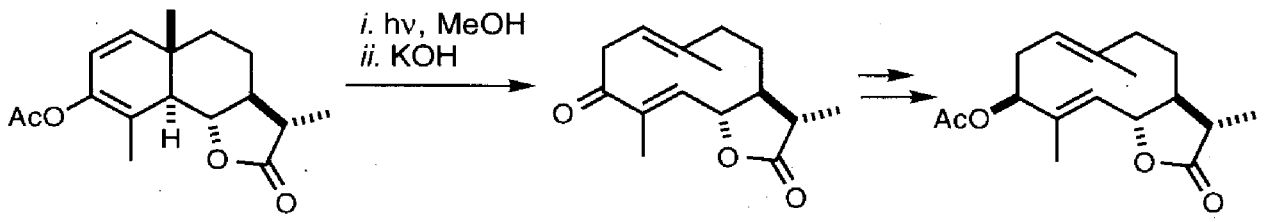
Scheme 2.22



α-santonin (**31**) dihydrocostunolide (**30**)

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).[70] Irradiation of the cross-conjugated dienol acetate and subsequent treatment with KOH afforded the monocyclic enone which could be converted into **32**.

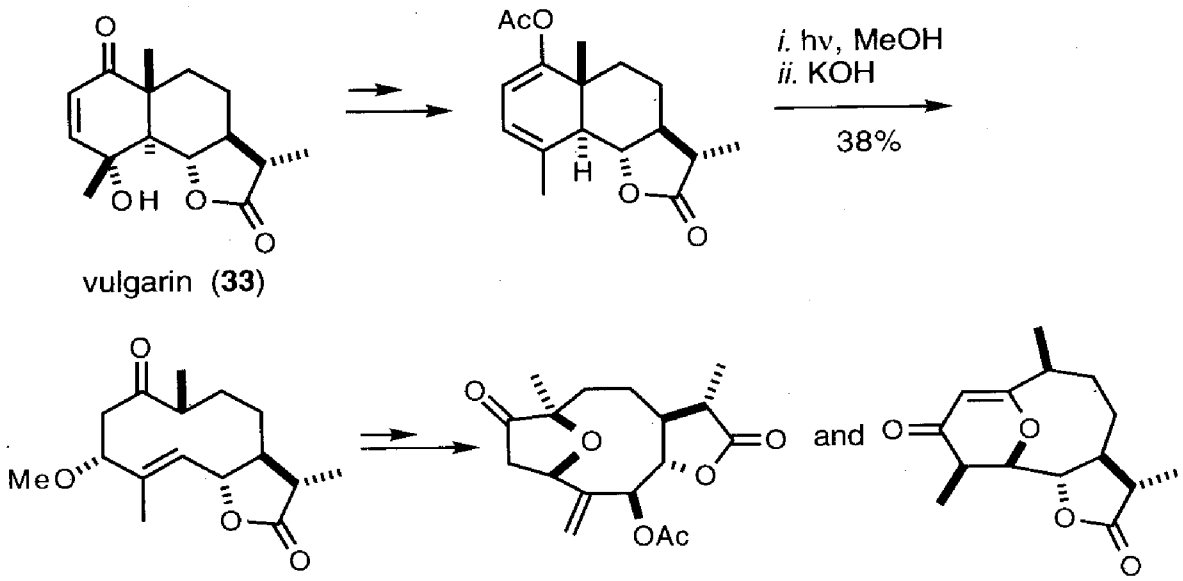
Scheme 2.23



dihydronovanin (**32**)

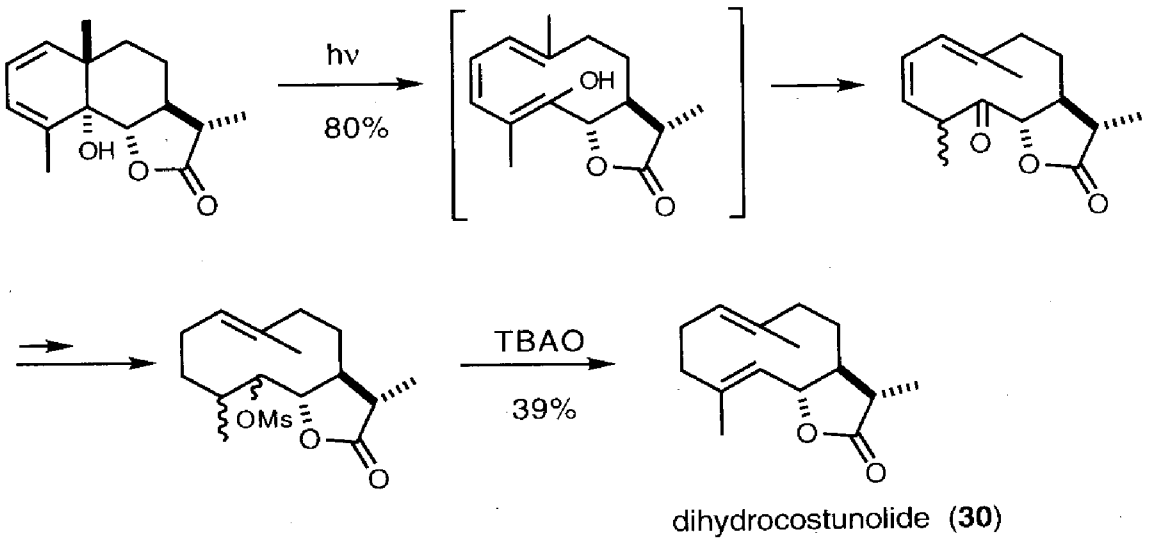
Recently, this method has been applied in the partial synthesis of germacranolides with oxygen bridged rings.[71] Starting from vulgarin (**33**), a dienol acetate was prepared which upon irradiation and KOH treatment gave a ketone which was converted into several bridged intermediates (Scheme 2.24).

Scheme 2.24



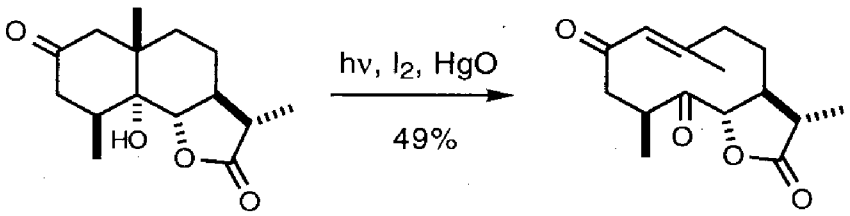
A direct way to avoid the photostationary equilibrium involved irradiation of a dienol prepared from α-santonin (**31**) and gave the corresponding dienone as a mixture of epimers in good yield (Scheme 2.25).[72] Subsequent reduction and mesylation gave a compound which only afforded dihydrocostunolide (**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.[73] This sequence was also used to prepare a chapliatrin-type compound (see § 2.3.1).[74]

Scheme 2.25



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).[75] To our knowledge this monocyclic dione has not yet been applied in germacrane synthesis.

Scheme 2.26

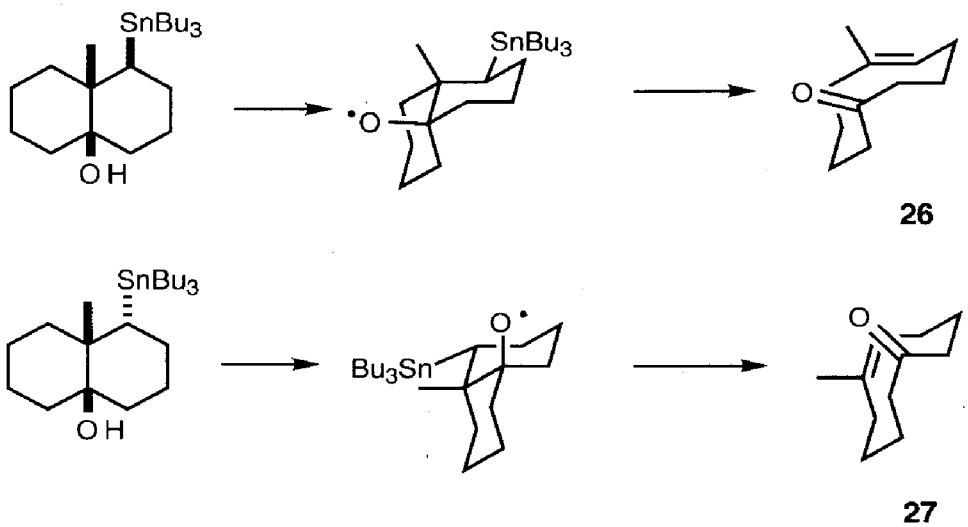


34 **35**

2.3.3 Radical Fragmentation

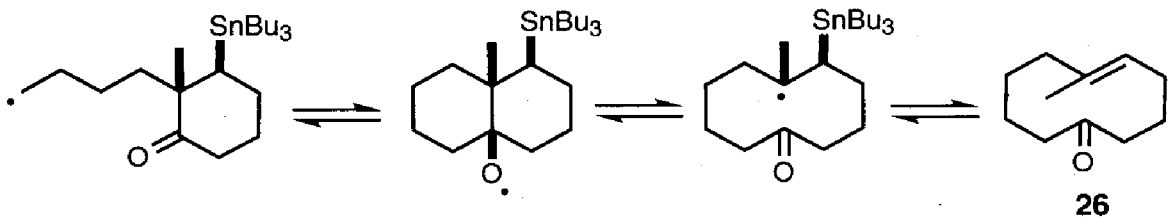
Several synthetically useful ring fragmentations have been developed that rely on the β scission of bridgehead alkoxy radicals.[76] It has well been recognized that the stereochemistry of the starting alcohols determines the geometry of the formed alkene. As in the heterolytic Wharton and Marshall fragmentation 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).[77] The discussion about the rate constants is important here.[78]

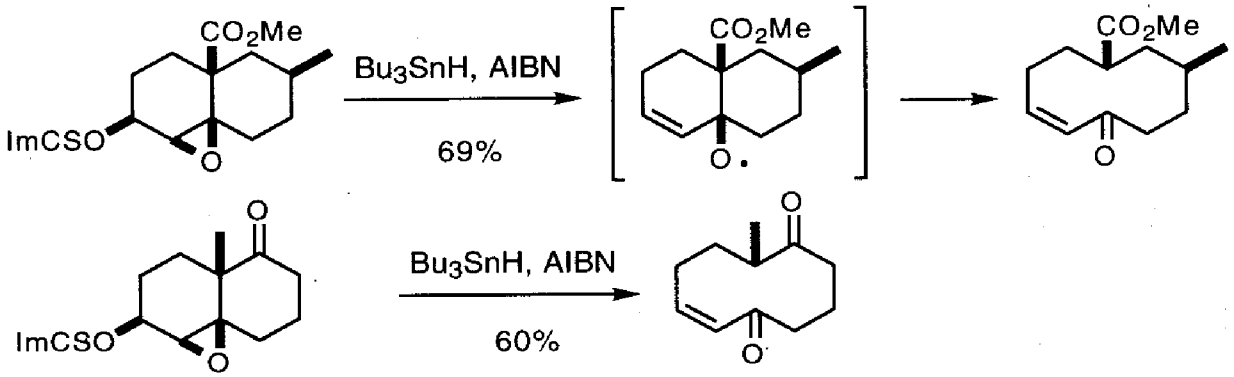
Scheme 2.28



26

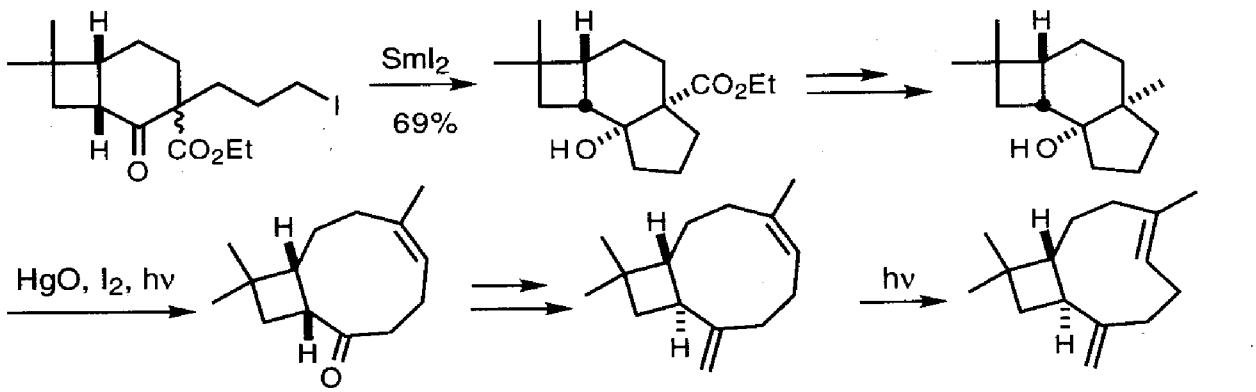
The bridgehead alkoxy radicals can also be formed indirectly as shown in Scheme 2.29. The starting materials for the reaction are easily obtained from Robinson annelation products.[79]

Scheme 2.29



This radical fragmentation is also used in cascade reactions.[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).[81]

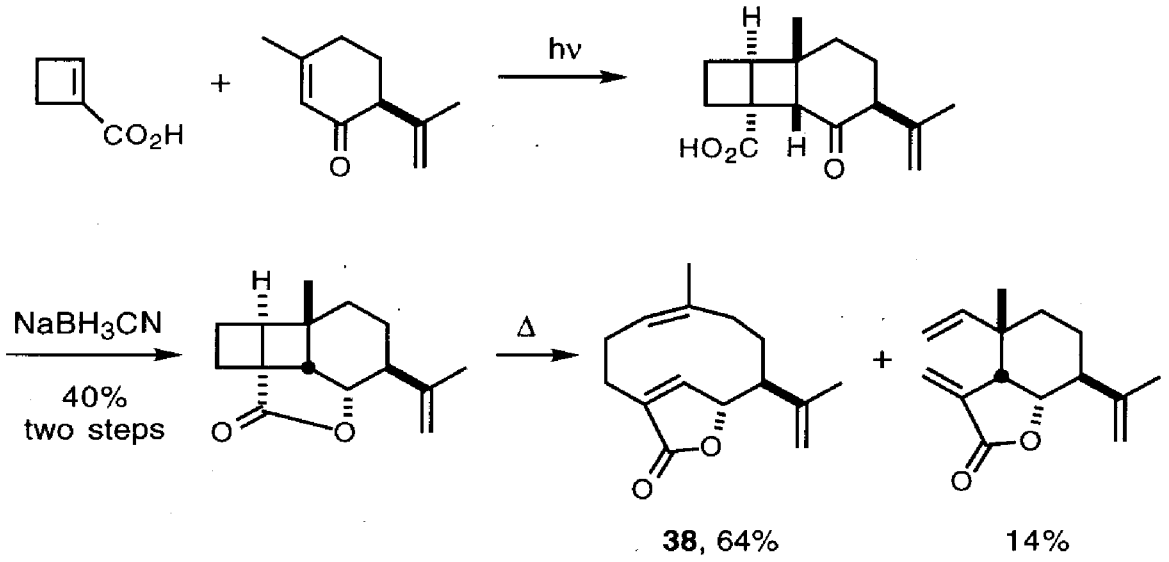
Scheme 2.30



2.3.4 The [2+2] Cycloreversion Reaction

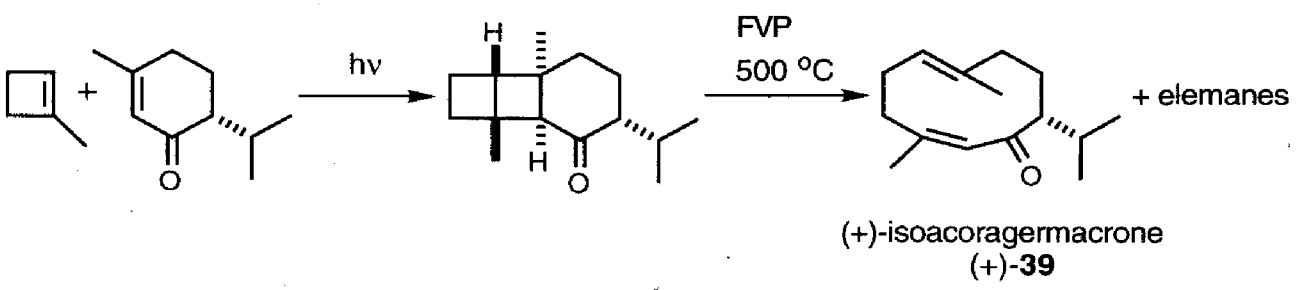
The photochemical [2+2] cycloaddition reaction followed by a thermal [2+2] cycloreversion reaction constitutes another well-known approach to ten-membered ring systems.[82] It was realized that this reaction sequence gave an efficient entry to the melampolide- and heliangolide-type skeletons[83] as the synthesis of the isoaristolactone isomer **38** exemplifies (Scheme 2.31).[84]

Scheme 2.31



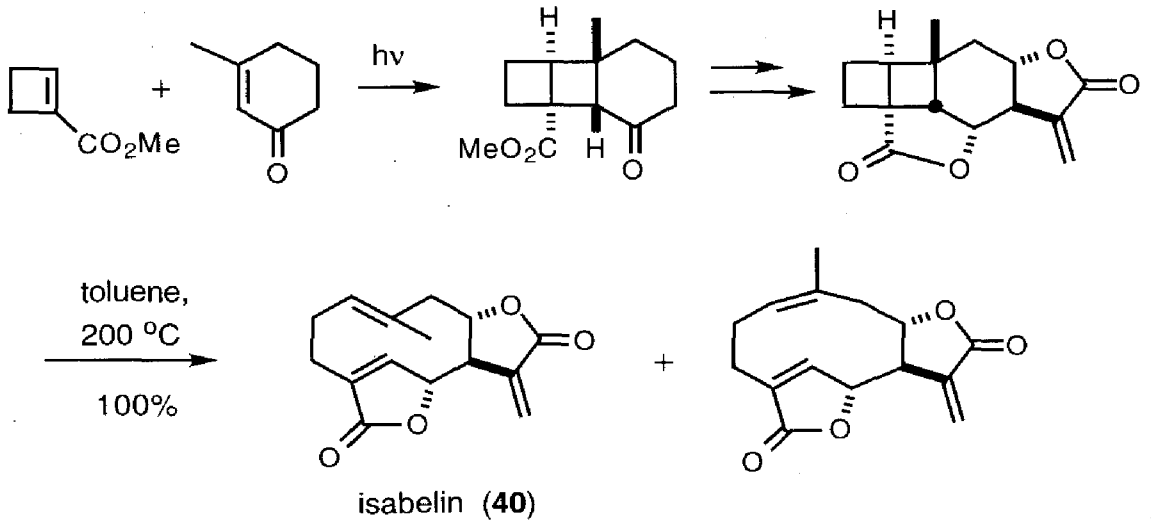
The (*E*,*E*)-germacrane skeleton cannot be prepared easily via this method, partly because the cycloreversion reaction leading to this stereochemistry is not very favorable, and partly because an (*E*,*E*)-germacrane rapidly gives Cope rearrangement to an elemane at the elevated temperatures required for this cycloreversion.[85] In Scheme 2.32 a short synthesis of (+)-isoacoragermacrone (**39**) is shown.[86] This product had already been converted into acoragermacrone (**11**) by Still (§ 2.4.3).

Scheme 2.32



A remarkable synthesis using the cycloreversion reaction is the construction of the (*E,E*)-germacrane isabelin (**40**, Scheme 2.33).[87] 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.

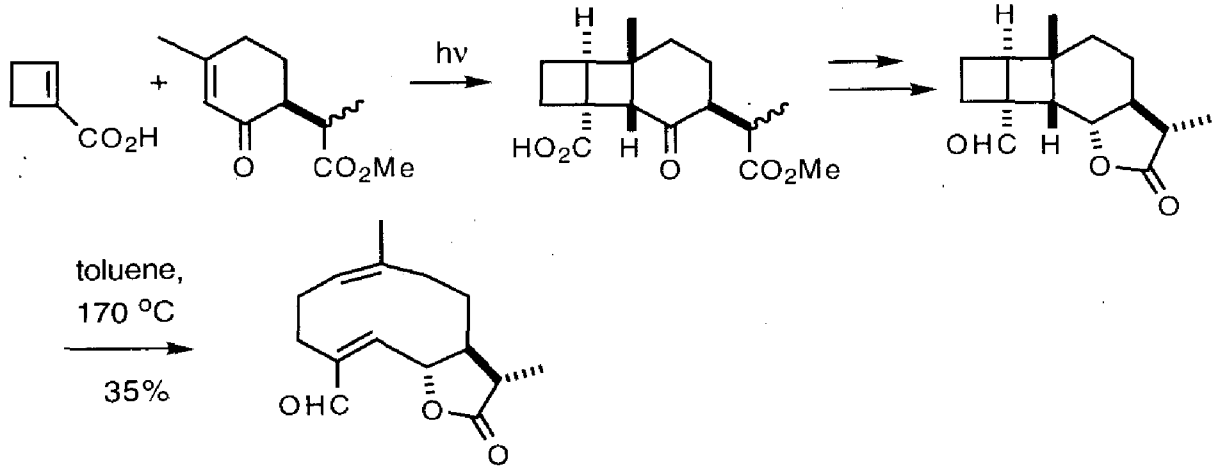
Scheme 2.33



isabelin (**40**)

The synthesis of a functionalized (*Z,E*)-germacranolide (**41**) by this approach is given in Scheme 2.34.[88]

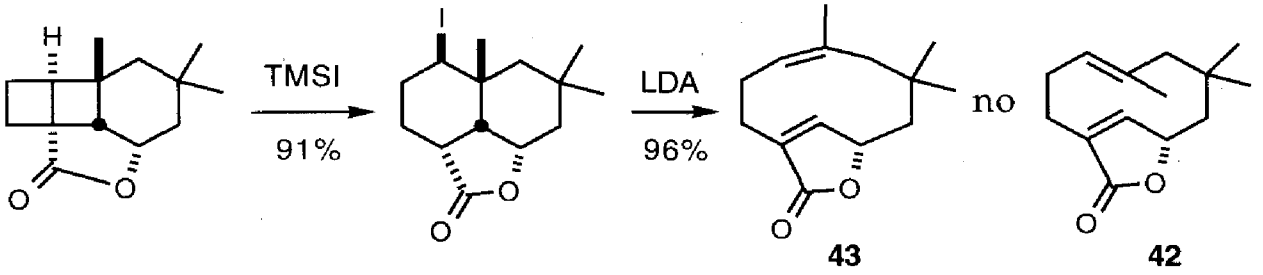
Scheme 2.34



41

Since (*E*,*E*)-germacranes are 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.[89]

Scheme 2.35

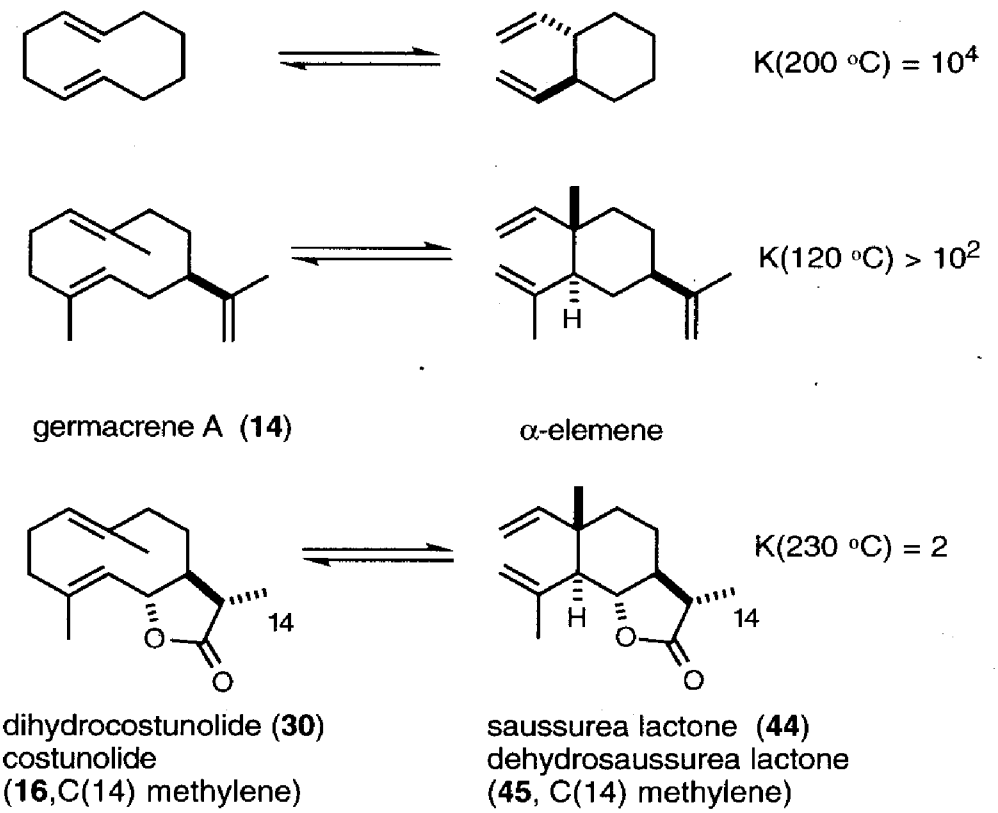


2.4 Ring Expansions

2.4.1 The Cope Rearrangement

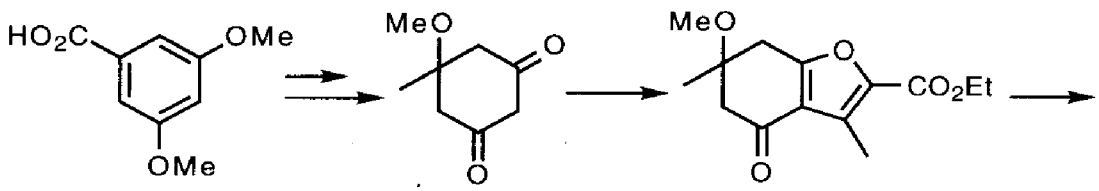
An important reaction for the synthesis of germacrane sesquiterpenes is the Cope rearrangement in which a 1,2-divinylcyclohexane via a [3,3] sigmatropic rearrangement can be converted into a cyclodecadiene. In fact, nature itself delivered the idea: the well-known equilibrium between germacrane and elemane sesquiterpenes. The existence of this equilibrium forms one of the major difficulties in the isolation of pure germacranes from natural sources. The use of purification techniques (GC, distillation) completely converts most of the simple (*E*,*E*)-germacranes, such as hedycaryol (**5**) and germacrene A (**14**), into the corresponding *trans*-1,2-divinylcyclohexane derivatives (elemanes). Extensive research has been done towards the mechanistic details of the Cope rearrangement.[90] 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.[91] The Cope rearrangement of (*Z*,*E*)-germacranes to *cis*-1,2-divinylcyclohexane derivatives proceeds less easily and the equilibrium lies mostly at the germacrane side.[92]

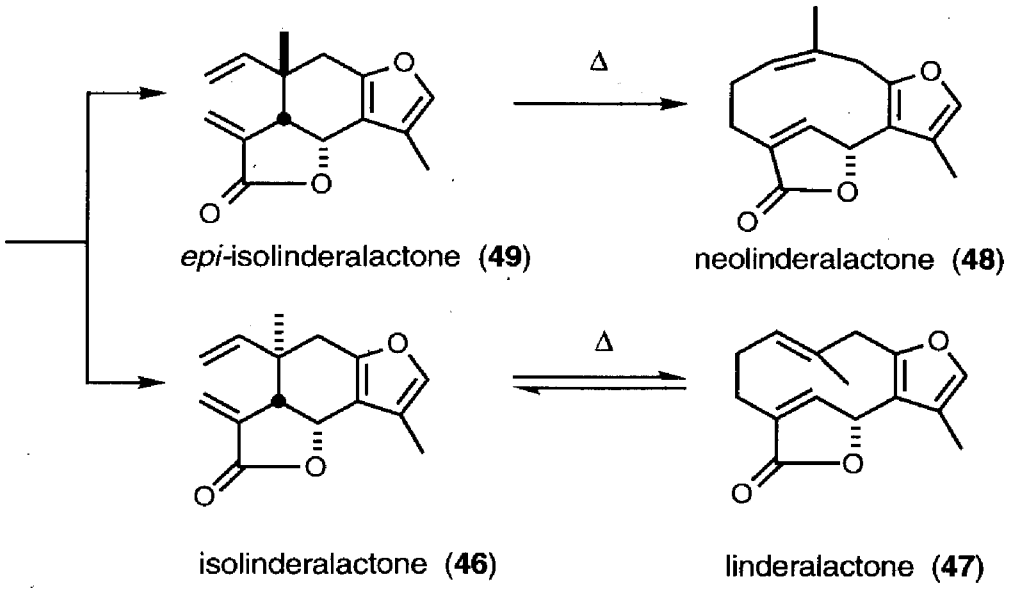
Scheme 2.36



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.[93] A mixture of isolinderalactone (**46**), linderalactone (**47**), and neolinderalactone (**48**) was obtained after thermolysis of a mixture of *epi*-isolinderalactone (**49**) and **46** (Scheme 2.37).[94]

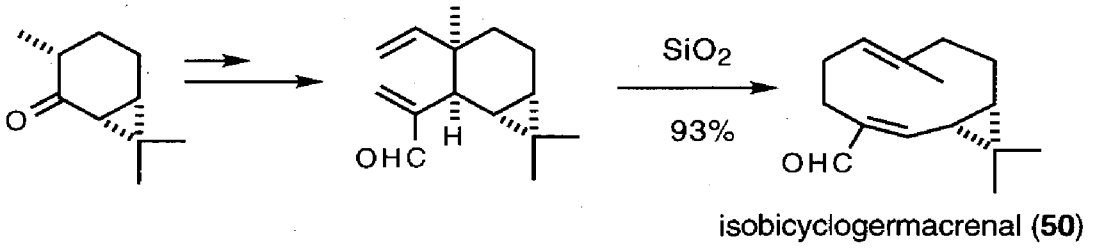
Scheme 2.37





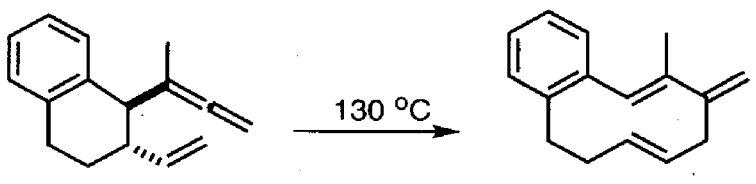
The Cope rearrangement leading to isobicyclogermacrenal (**50**) could not be performed by thermolysis, probably because the cyclopropane ring was not stable under the thermolysis conditions used. With the help of silica gel, however, the Cope rearrangement could be achieved in high yield (Scheme 2.38).[95]

Scheme 2.38



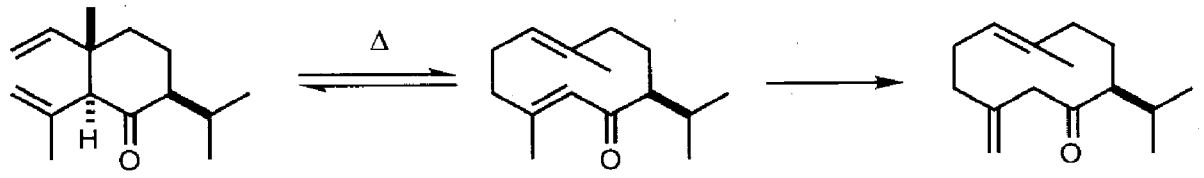
In order to enhance the applicability of the Cope rearrangement in synthesis, many researchers have tried to make the ring expansion thermodynamically more favorable. This can be done, for instance, by changing the carbon hybridization as the Cope rearrangement of the allene derivative **51** proves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

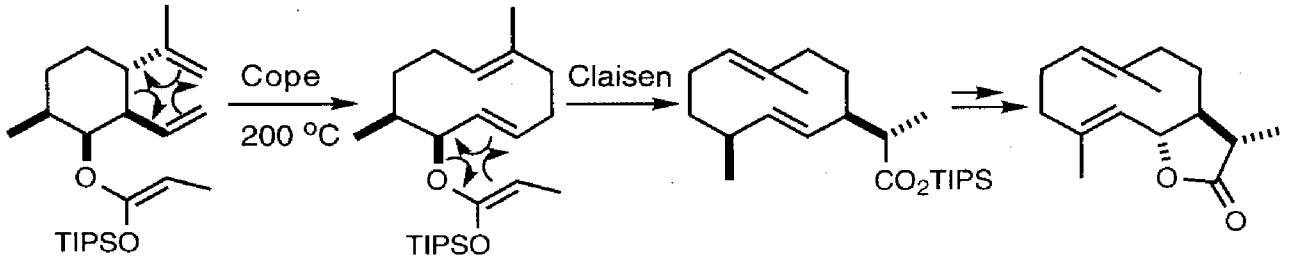


shyobunone (**52**) acoragermacrone (**11**) preisocalamendiol (**53**)

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



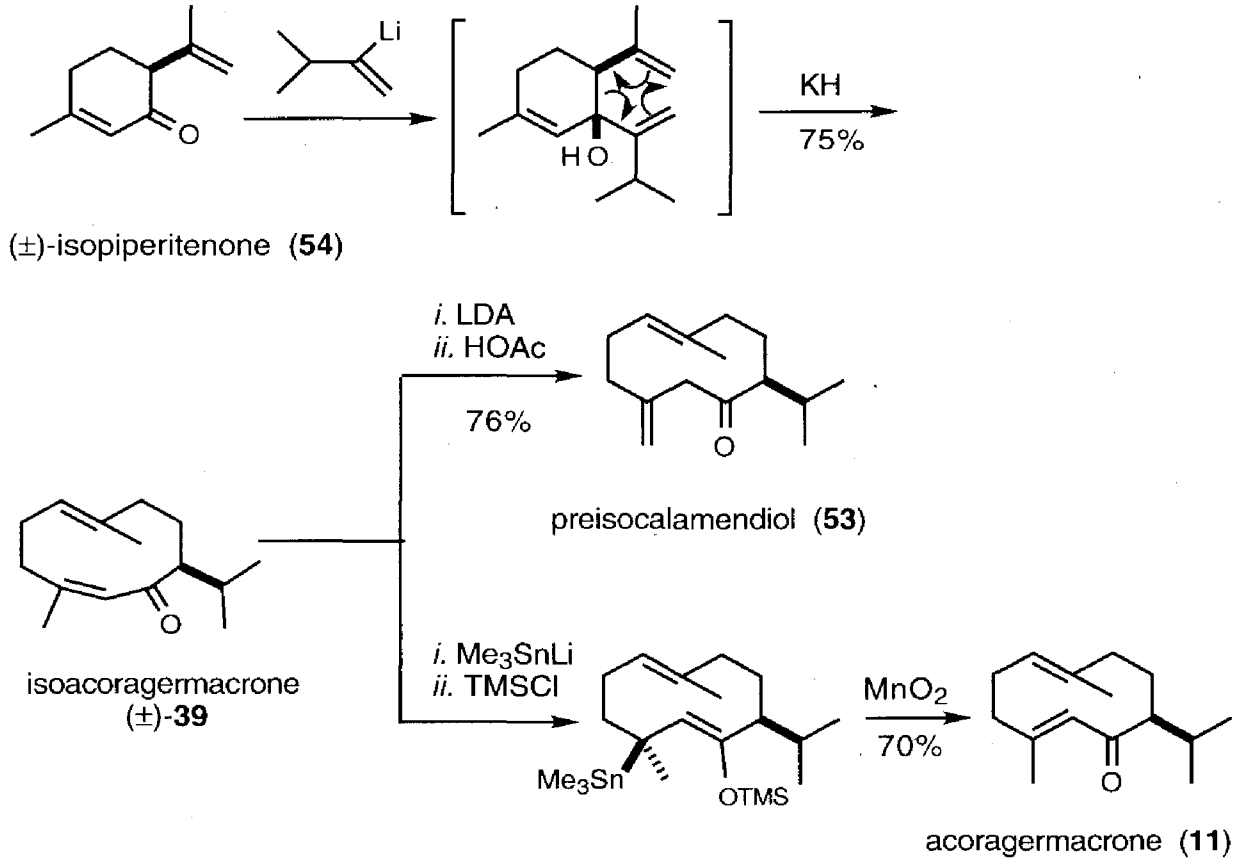
(+)-dihydrocostunolide (**30**)

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 rings[102] 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 acoragermacrone (**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

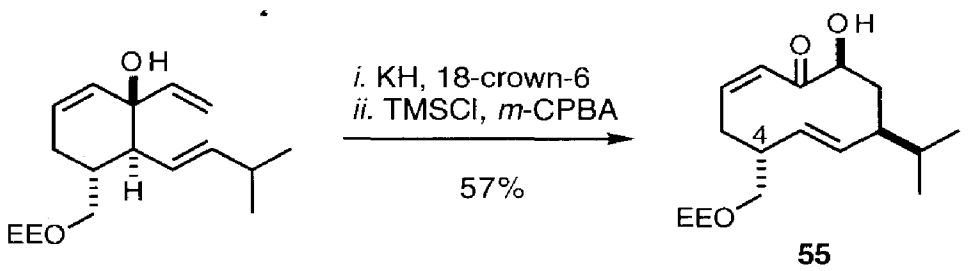
pretreated with iodine.[106] For the synthesis of **11**, the Z double bond of the initial Cope product isoacoragermacrone (**39**) had to be isomerized to *E* by 1,4-addition and subsequent elimination of the bulky Me_3Sn group.

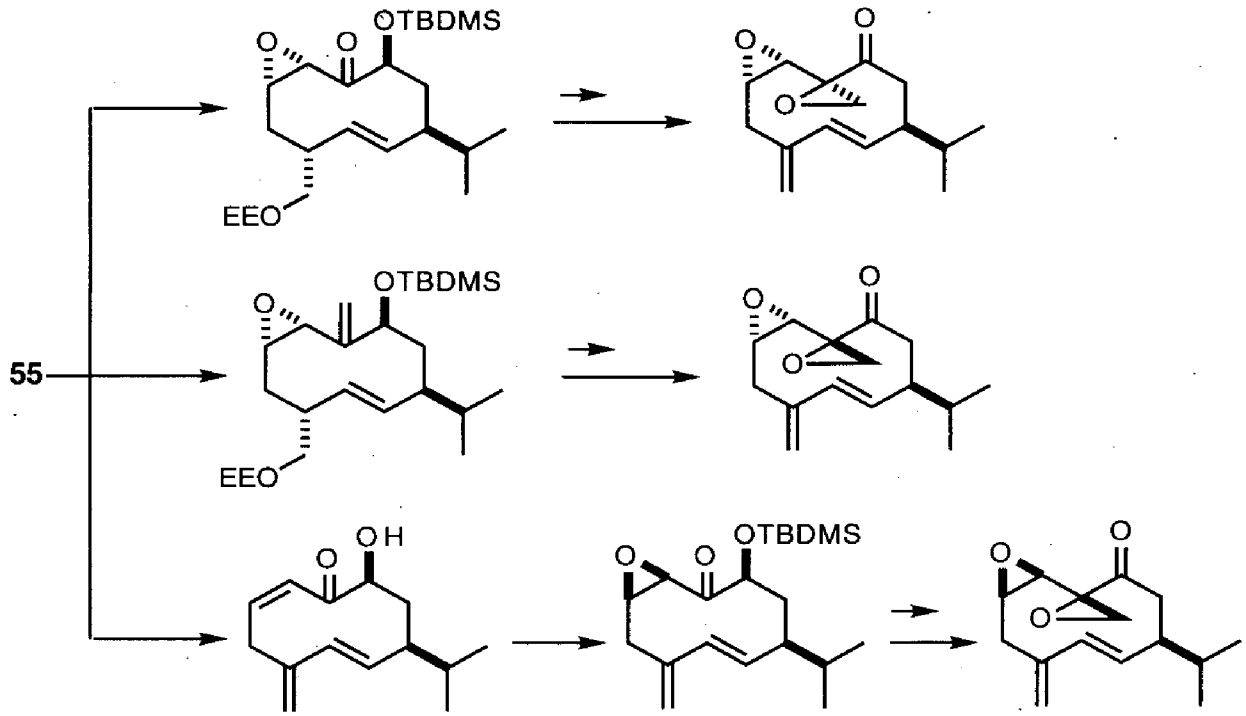
Scheme 2.42



This approach also led to the first synthesis of periplanone B (**10**, Scheme 2.43).[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



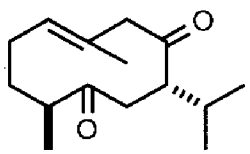


periplanone B (**10**)

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

Starting from (–)-carvone, the enantiomer of (+)-curdione (**56**), an antitumor principle from the Chinese herb *Curcuma aromatica*, has been synthesized in a similar way (Scheme 2.44).[111]

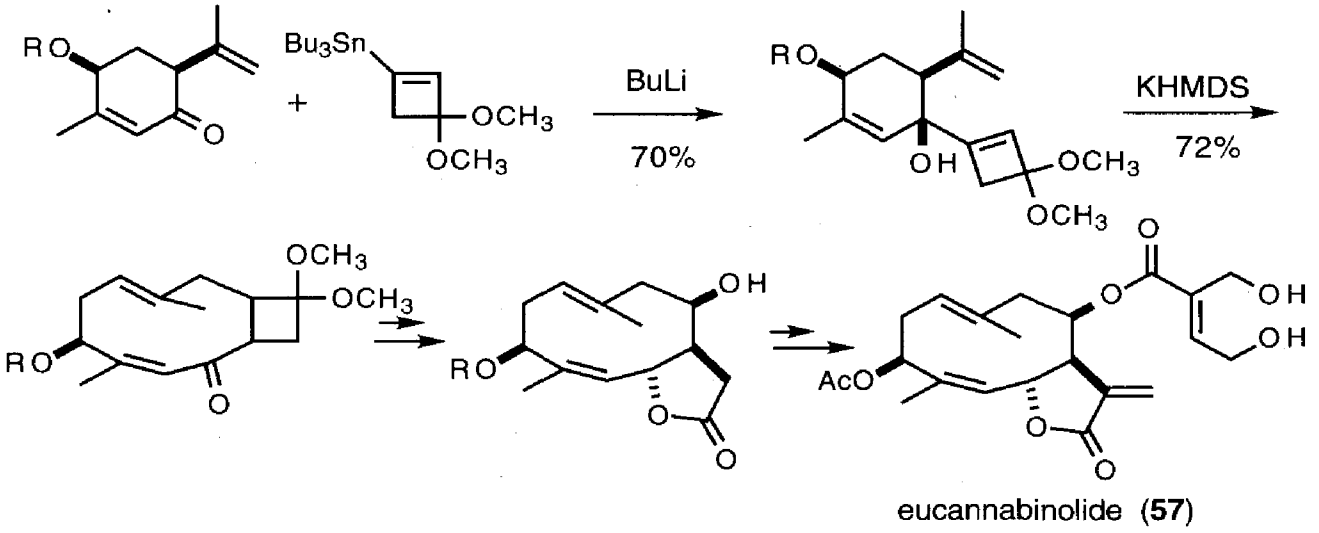
Scheme 2.44



(+)-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).[112]

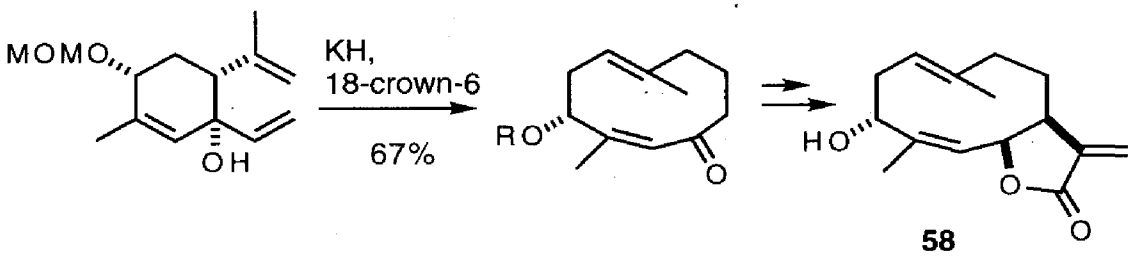
Scheme 2.45



eucannabinolide (**57**)

Using the same approach, heliangolide precursors[113] and a natural occurring heliangolide **58** have been synthesized (Scheme 2.46).[114]

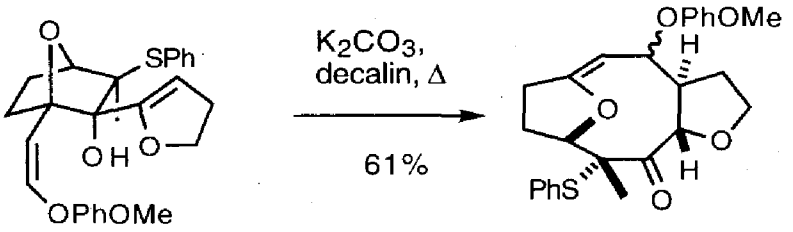
Scheme 2.46



58

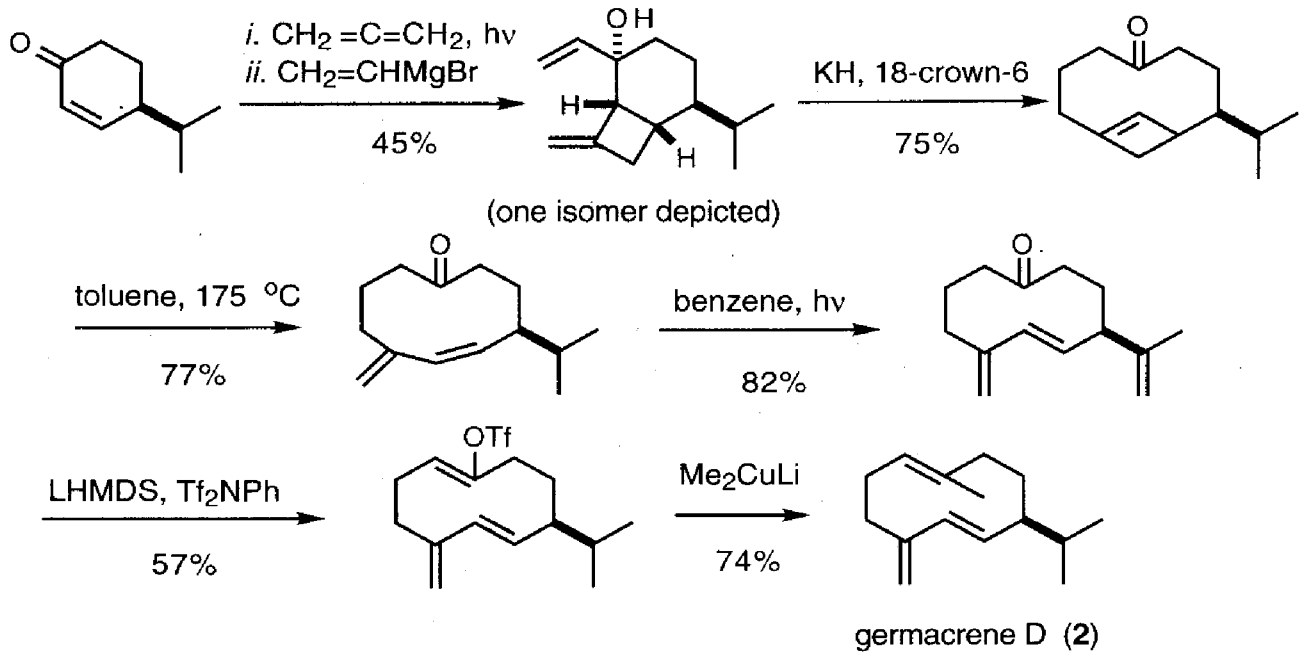
The oxy-Cope rearrangement has also been used to construct the heavily functionalized skeleton of the furanoheliangolides. An example is shown in Scheme 2.47.[115]

Scheme 2.47



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[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**)[117] and, later, also for a short synthesis of germacrene D (**2**, Scheme 2.48).[118]

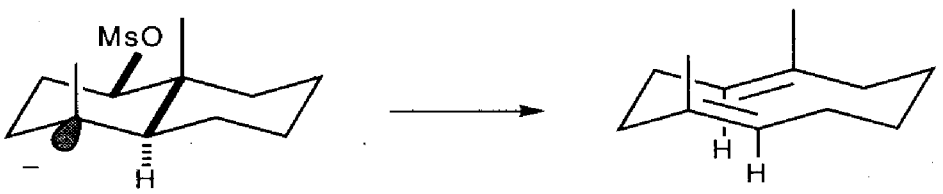
Scheme 2.48



2.5 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.

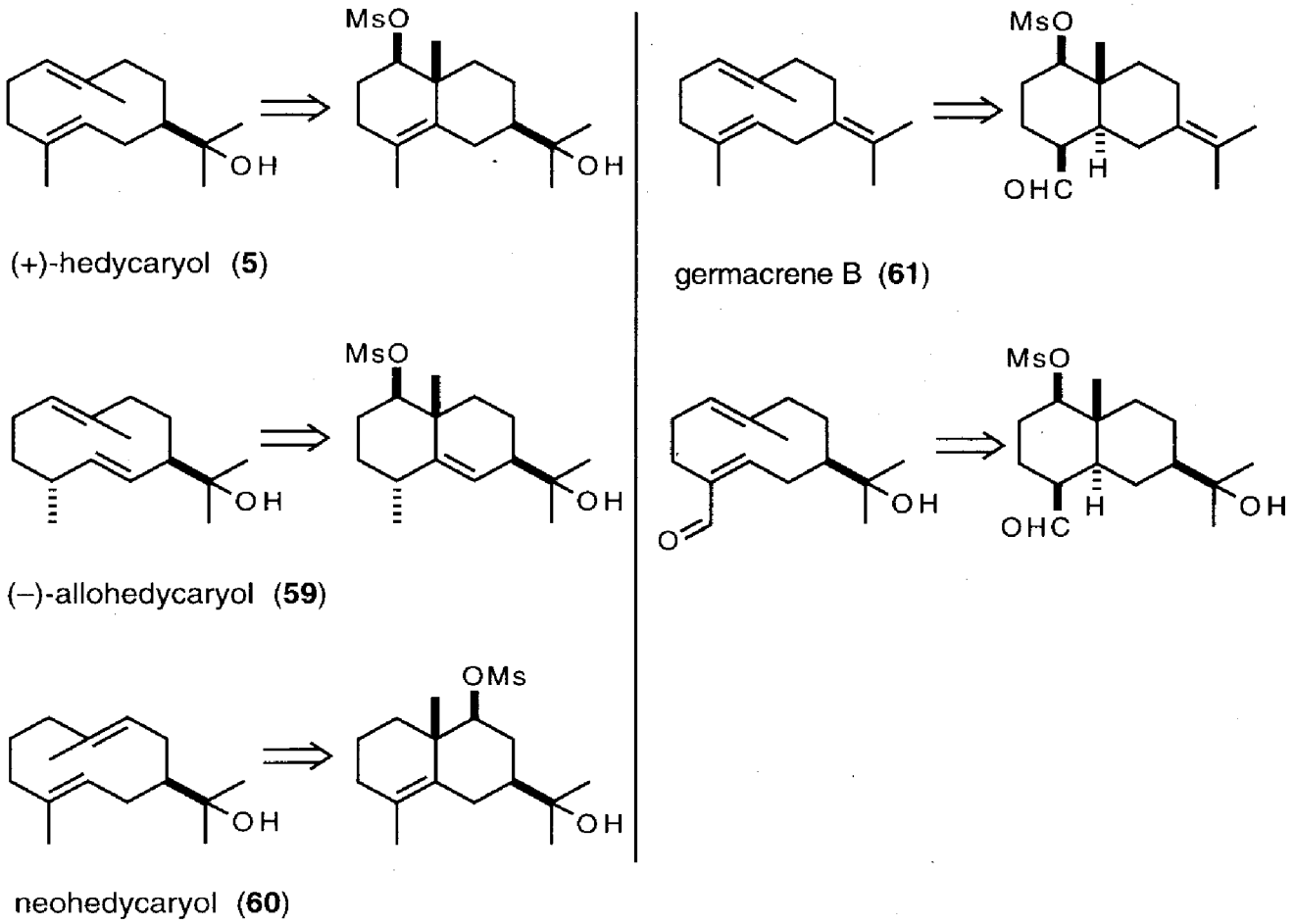
Scheme 2.49



A strong argument in favor of Grob-type fragmentation reactions is the regio- and stereospecific formation of the double bonds. The rigid structure of a trans-fused 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



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 germacranes, 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 germacranes via the enolate-assisted fragmentation reaction is possible.

2.6 References and Notes

1. (a) Reichardt, P. B.; Anderson, B. J.; Clausen, T. P.; Hoskins, L. C. *Can. J. Chem.* **1989**, *67*, 1174. (b) Enev, V.; Tsankova, E. *Tetrahedron Lett.* **1988**, *29*, 1829.
2. (a) Shizuri, Y.; Yamaguchi, S.; Yamamura, S.; Ishihara, M.; Ohba, S.; Saito, Y.; Niwa, M.; Terada, Y.; Miyazaki, M. *Tetrahedron Lett.* **1987**, *28*, 3831. (b) Shizuri, Y.; Matsunaga, K.; Tamaki, K.; Yamaguchi, S.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 1971. (c) Shizuri, Y.; Yamaguchi, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1987**, *28*, 1791. (d) Shizuri, Y.; Matsunaga, K.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 3693.
3. Barrero, A. F.; Oltra, J. E.; Barragán, A. *Tetrahedron Lett.* **1995**, *36*, 311.
4. Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.
5. (a) Especially, see: W. C. Still's MacroModel implementation of the MM2 force field; Moamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440 and references cited therein. (b) McMurry, J. E.; Siemers, N.O. *Tetrahedron Lett.* **1993**, 34, 7891.
6. Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996.
7. (a) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058. (b) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106. (c) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105.
8. Related reviews: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (b) Roxburgh, G. J. *Tetrahedron* **1993**, *49*, 10749. (c) Brown, D. S.; Paquette, L. A. *Heterocycles* **1992**, *34*, 807. (d) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.
9. Related work: Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991.

10. (a) Kodama, M.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1976**, *17*, 1121. (b) Kodama, M.; Yokoo, S.; Yamada, H.; Itô, S. *Tetrahedron Lett.* **1978**, *19*, 3121.
11. Kodama, M.; Yokoo, S.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1979**, *20*, 1687.
12. Kodama, M.; Okumura, K.; Kobayashi, Y.; Tsunoda, T.; Itô, S. *Tetrahedron Lett.* **1984**, *25*, 5781.
13. Kodama, M.; Shimada, K.; Takahashi, T.; Kabuto, C.; Itô, S. *Tetrahedron Lett.* **1981**, *22*, 4271.
14. Izac, R. R.; Bandurraga, M. M.; Wasylyk, J. M.; Dunn, F. W.; Fenical, W. *Tetrahedron* **1982**, *38*, 301.
15. Nagashima, F.; Izumo, H.; Takaoka, S.; Tori, M.; Asakawa, Y. *Phytochemistry* **1994**, *37*, 433.
16. Winter, R. E. K.; Dorn, F.; Arigoni, D. *J. Org. Chem.* **1980**, *45*, 4786.
17. Winter, R. E. K.; Shiang, W. R.; Kolodziej, S. A.; Rath, N. P. *Tetrahedron Lett.* **1992**, *33*, 2941.
18. (a) Takahashi, T.; Nagashima, T.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 1359. (b) Takahashi, T.; Nemoto, H.; Tsuji, J.; Miura, I. *Tetrahedron Lett.* **1983**, *24*, 1121.
19. Takahashi, T.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2005.
20. Takahashi, T.; Kanda, Y.; Nemoto, H.; Kitamura, K.; Tsuji, J.; Fukazawa, Y. *J. Org. Chem.* **1986**, *51*, 3393.
21. Takahashi, T.; Nemoto, H.; Tsuji, J.; Miura, I. *Tetrahedron Lett.* **1983**, *24*, 3485.
22. Takahashi, T.; Kitamura, K.; Nemoto, H.; Tsuji, J.; Miura, I. *Tetrahedron Lett.* **1983**, *24*, 3489.
23. Harada, T.; Takahashi, T.; Takahashi, S. *Tetrahedron Lett.* **1992**, *33*, 369.
24. Usui, S.; Haino, T.; Hayashibara, T.; Hirai, Y.; Fukazawa, Y.; Kodama, M. *Chem. Lett.* **1992**, 527.
25. Kitahara, T.; Mori, K. *J. Org. Chem.* **1984**, *49*, 3281.
26. (a) Kitahara, T.; Mori, M.; Koseki, K.; Mori, K. *Tetrahedron Lett.* **1986**, *27*, 1343. (b) Kitahara, T.; Mori, M.; Mori, K. *Tetrahedron* **1987**, *43*, 2689.
27. Caine, D.; Stanhope, B. *Tetrahedron* **1992**, *48*, 33.
28. Corey, E. J.; Daigneault, S.; Dixon, B. R. *Tetrahedron Lett.* **1993**, *34*, 3675.
29. Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5736.
30. For a first attempt, see: McDougal, P. G.; Oh, Y. -I.; VanDerveer, D. *J. Org. Chem.* **1989**, *54*, 91.
31. (a) Takao, K.; Ochiai, H.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *Tetrahedron Lett.* **1995**, *36*, 1487. (b) Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179.

32. Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1989**, *30*, 309.
33. (a) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315. (b) Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 4316.
34. Reference 33a.
35. Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fukazawa, Y.; Okajima, T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499.
36. Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J. *Heterocycles* **1987**, *25*, 139.
37. (a) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *Tetrahedron Lett.* **1987**, *28*, 723. (b) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883.
38. (a) Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925. (b) Marshall, J. A.; Lebreton, J. *Tetrahedron Lett.* **1987**, *28*, 3323.
39. (a) Boeckman, Jr. R. K.; Heckendorn, D. K.; Chinn, R. L. *Tetrahedron Lett.* **1987**, *28*, 3551. (b) Boeckman, Jr. R. K.; Yoon, S. -K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682.
40. Itoh, A.; Nozaki, H.; Yamamoto, H. *Tetrahedron Lett.* **1978**, *19*, 2903.
41. Winter, R. E. K.; Dorn, F.; Arigoni, D. *J. Org. Chem.* **1980**, *45*, 4786.
42. (a) McMurry, J. E.; Bosch, G. K. *Tetrahedron Lett.* **1985**, *26*, 2167. (b) McMurry, J. E.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885.
43. Hardt, I. H.; Rieck, A.; König, W. A.; Muhle, H. *Phytochemistry* **1995**, *40*, 605.
44. McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1985**, *26*, 2171.
45. McMurry, J. E.; Siemers, N. O. *Tetrahedron Lett.* **1994**, *35*, 4505.
46. Li, W.; Li, Y.; Li, Y. *Synthesis* **1994**, 267.
47. Shibuya, H.; Ohashi, K.; Kawashima, K.; Hori, K.; Murakami, N.; Kitagawa, I. *Chem. Lett.* **1986**, 85.
48. Jonas, D.; Ozlü, Y.; Parsons, P. J. *Synlett* **1995**, 255.
49. Hodgson, D. M.; Boulton, L. T.; Maw, G. N. *Synlett* **1995**, 267.
50. (a) Motherwell, W. B.; Roberts, L. R. *Tetrahedron Lett.* **1995**, *36*, 1121. This kind of cyclizations of precursors derived from farnesol gives invariably six-membered instead of ten-membered rings, see: (b) Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745 and references cited therein.
51. Wharton, P. S. *J. Org. Chem.* **1961**, *26*, 4781.
52. Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254.
53. (a) Wharton, P. S.; Baird, M. D. *J. Org. Chem.* **1971**, *36*, 2932. (b) Mori, M.; Okada, K.; Shimazaki, K.; Chuman, T. *Tetrahedron Lett.* **1990**, *31*, 4037.
54. Clark, D. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1979**, *101*, 3567.

55. Miyashita, M.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1974**, *96*, 1917.
56. Müller, L.; Bohlmann, F. *Liebigs Ann. Chem.* **1985**, 2049.
57. González, A. G.; Galindo, A.; Mansilla, H.; Gutiérrez, A.; Palenzuela, J. A. *J. Org. Chem.* **1985**, *50*, 5856.
58. González, A. G.; Galindo, A.; Palenzuela, J. A.; Mansilla, H. *Tetrahedron Lett.* **1986**, *27*, 2771.
59. (a) Cauwberghs, S.; De Clercq, P. J. *Tetrahedron Lett.* **1988**, *29*, 6501. (b) De Geyter, T.; Cauwberghs, S.; De Clercq, P. J. *Bull. Soc. Chim. Belg.* **1994**, *103*, 433.
60. Marshall, J. A.; Bundy, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 4291.
61. (a) Marshall, J. A.; Huffman, W. F. *J. Am. Chem. Soc.* **1970**, *92*, 6358. (b) Marshall, J. A.; Ruth, J. A. *J. Org. Chem.* **1974**, *39*, 1971. (c) Marshall, J. A.; Huffman, W. F.; Ruth, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 4691. (d) Marshall, J. A. *Synthesis* **1972**, 517.
62. Wharton, P. S.; Sundin, C. E.; Johnson, D. W.; Kluender, H. C. *J. Org. Chem.* **1972**, *37*, 34.
63. Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2212.
64. Sabol, J. S. *Studies on the Applicability of Boronate Fragmentations to Germacranolide Systems;* Ph.D. Thesis, Northwestern University, Evanston, Illinois, 1981.
65. (a) Piet, D. P.; Franssen, M. C. R.; de Groot, A. *Tetrahedron* **1994**, *50*, 3169. (b) Piet, D. P.; Minnaard, A. J.; van der Heijden, K. A.; Franssen, M. C. R.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1995**, *51*, 243. (c) Piet, D. P.; Schrijvers, R.; Franssen, M. C. R.; de Groot, A. *Tetrahedron* **1995**, *51*, 6303. (d) Piet, D. P.; Franssen, M. C. R.; de Groot, A. *Tetrahedron* **1996**, *52*, 11273.
66. Marshall, J. A. *Synthesis* **1971**, 229.
67. Honan, M. C.; Balasuryia, A.; Cresp, T. M. *J. Org. Chem.* **1985**, *50*, 4326.
68. Brown, J. M.; Cresp, T. M.; Mander, L. N. *J. Org. Chem.* **1977**, *42*, 3984.
69. (a) Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1963**, *85*, 4033. (b) Reference 29.
70. Watanabe, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Comm.* **1972**, 698.
71. Hernández, A. S.; Afonso, M. M.; González, A. G.; Galindo, A. *Tetrahedron Lett.* **1992**, *33*, 4747.
72. (a) Fujimoto, Y.; Shimizu, T.; Tatsuno, T. *Tetrahedron Lett.* **1976**, *17*, 2041. (b) Fujimoto, Y.; Shimizu, T.; Ohmori, M.; Tatsuno, T. *Chem. Pharm. Bull.* **1979**, *27*, 923.
73. See also: Raucher, S.; Chi, K. -W.; Hwang, K. -J.; Burks, Jr. J. E. *J. Org. Chem.* **1986**, *51*, 5503.

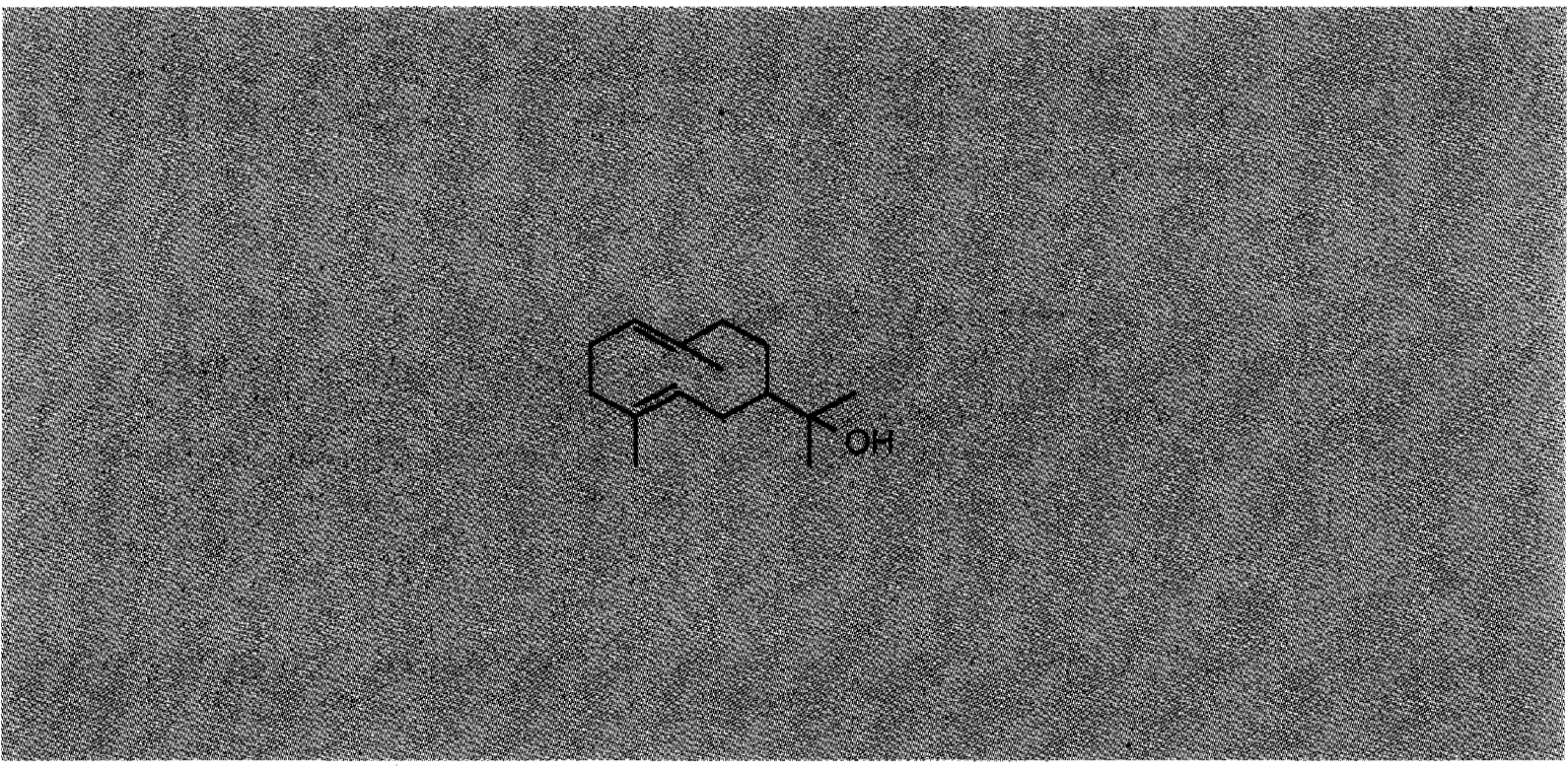
74. Shimizu, T.; Fujimoto, Y.; Tatsuno, T. *Chem. Pharm. Bull.* **1979**, *27*, 934.
75. Harapanhalli, R. S. *Liebigs Ann. Chem.* **1988**, 1009.
76. (a) Macdonald, T. L.; O'Dell, D. E. *J. Org. Chem.* **1981**, *46*, 1501. (b) Beckwith, A. L. J.; Kazlauskas, R.; Syner-Lyons, M. R. *J. Org. Chem.* **1983**, *48*, 4718.
77. (a) Baldwin, J. E.; Adlington, R. M.; Robertson, J. *J. Chem. Soc., Chem. Comm.* **1988**, 1404. (b) Dowd, P.; Choi, S. -C. *Tetrahedron* **1989**, *45*, 77.
78. Baldwin, J. E.; Adlington, R. M.; Robertson, J. *Tetrahedron* **1989**, *45*, 909.
79. (a) Corser, D. A.; Marples, B. A.; Dart, R. K. *Synlett* **1992**, 987. (b) Rawal, V. H.; Zhong, H. M. *Tetrahedron Lett.* **1993**, *34*, 5197.
80. Mowbray, C. E.; Pattenden, G. *Tetrahedron Lett.* **1993**, *34*, 127.
81. Suginome, H.; Kondoh, T.; Gogonea, C.; Singh, V.; Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 69.
82. (a) Lange, G. L.; Huggins, M. -A.; Neidert, E. *Tetrahedron Lett.* **1976**, *17*, 4409. (b) Lange, G. L.; McCarthy, F. C. *Tetrahedron Lett.* **1978**, *19*, 4749. (c) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267.
83. (a) Williams, J. R.; Callahan, J. F. *J. Chem. Soc., Chem. Comm.* **1979**, 404. (b) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4321. (c) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365. (d) Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373. (e) Lange, G. L.; McCarthy, F. C. *Tetrahedron Lett.* **1978**, *19*, 4749.
84. Lange, G. L.; So, S.; Lautens, M.; Lohr, K. *Tetrahedron Lett.* **1981**, *23*, 311.
85. Reference 83c.
86. (a) Williams, J. R.; Callahan, J. F. *J. Org. Chem.* **1980**, *45*, 4475. (b) Williams, J. R.; Callahan, J. F. *J. Org. Chem.* **1980**, *45*, 4479.
87. Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 6340.
88. (a) Lange, G. L.; Lee, M. *Synthesis* **1985**, 117. (b) Lange, G. L.; Lee, M. *J. Org. Chem.* **1987**, *52*, 325.
89. Wender, P. A.; Manly, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 8579.
90. Takeda, K. *Tetrahedron* **1974**, *30*, 1525.
91. (a) Wharton, P. S.; Johnson, D. W. *J. Org. Chem.* **1973**, *38*, 4117. (b) Weinheimer, A. J.; Youngblood, W. W.; Washecheck, P. H.; Karns, T. K. B.; Ciereszko, L. S. *Tetrahedron Lett.* **1970**, *11*, 497. (c) Jain, T. C.; Banks, C. M.; McCloskey, J. E. *Tetrahedron Lett.* **1970**, *11*, 841.
92. Gopolan, A.; Magnus, P. *J. Org. Chem.* **1984**, *49*, 2317.
93. Grieco, P. A.; Nishazawa, M. *J. Org. Chem.* **1977**, *42*, 1717.
94. (a) Reference 92. (b) Gopalan, A.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 1756.
95. Magari, H.; Hirota, H.; Takahashi, T. *J. Chem. Soc., Chem. Comm.* **1987**, 1196.

96. Vedejs, E.; Cammers-Goodwin, A. *J. Org. Chem.* **1994**, *59*, 7541.
97. (a) Kato, K.; Hirata, Y.; Yamamura, S. *J. Chem. Soc., Chem. Comm.* **1970**, 1324. (b) Kato, K.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1971**, *27*, 5987. (c) Iguchi, M.; Nishiyama, A.; Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1969**, *10*, 4295.
98. (a) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 1611. (b) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 880.
99. (a) Raucher, S.; Burks, J. E.; Hwang, K. -J.; Svedberg, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 1853. (b) Chi, K. -W.; Raucher, S. *Bull. Korean Chem. Soc.* **1989**, *10*, 465. (c) Reference 73.
100. Chi, K. -W.; Raucher, S. *Bull. Korean Chem. Soc.* **1991**, *12*, 157.
101. Wilson, S. R. *Org. React. (N.Y.)* **1993**, *43*, 93.
102. (a) Paquette, L. A. *Chem. Soc. Rev.* **1995**, 9. (b) Paquette, L. A.; DeRussy, D. T.; Cottrell, C. E. *J. Am. Chem. Soc.* **1988**, *110*, 890. (c) Janardhanam, S.; Shanmugam, P.; Rajagopalan, K. *Synth. Commun.* **1993**, *23*, 311.
103. (a) Fan, W.; White, J. B. *Tetrahedron Lett.* **1993**, *34*, 957. (b) Jisheng, L.; Gallardo, T.; White, J. B. *J. Org. Chem.* **1990**, *55*, 5426. (b) Sworin, M.; Lin, K. -C. *J. Am. Chem. Soc.* **1989**, *111*, 1815.
104. Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186.
105. Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.
106. Macdonald, T. L.; Natalie, Jr. K. J.; Prasad, G.; Sawyer, J. S. *J. Org. Chem.* **1986**, *51*, 1124.
107. Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493.
108. Hauptmann, H.; Mühlbauer, G.; Walker, N. P. C. *Tetrahedron Lett.* **1986**, *27*, 1315.
109. (a) Kuwahara, S.; Mori, K. *Heterocycles* **1989**, *28*, 167. (b) Mori, K.; Kuwahara, S.; Igarashi, Y. *Pure & Appl. Chem.* **1990**, *62*, 1307.
110. (a) Mori, M.; Okada, K.; Shimazaki, K.; Chuman, T. *Tetrahedron Lett.* **1990**, *31*, 4037. (b) Mori, M.; Okada, K.; Shimazaki, K.; Chuman, T.; Kuwahara, S.; Kitahara, T.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1769. (c) Hashimoto, S.; Miyazaki, Y.; Shiro, M.; Ikegami, S. *Chem. Lett.* **1995**, 1091. (d) Kuwahara, S.; Mori, K. *Tetrahedron* **1990**, *46*, 8083. (e) Kuwahara, S.; Mori, K. *Tetrahedron* **1990**, *46*, 8075.
111. Zhao, R. -B.; Wu, Y. -L. *Acta Chim. Sin. Engl. Ed.* **1989**, 86.
112. Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625.
113. (a) Kuroda, C.; Hirota, H.; Takahashi, T. *Chem. Lett.* **1982**, 249. (b) Kuroda, C.; Nakamura, T.; Hirota, H.; Enomoto, K.; Takahashi, T. *Bull. Chem. Soc. Jpn.*

1985, *58*, 146. (c) Utagawa, A.; Hirota, H.; Ohno, S.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1207.

114. Nakamura, T.; Hirota, H.; Kuroda, C.; Takahashi, T. *Chem. Lett.* **1986**, 1879.
115. Brown, D. S.; Paquette, L. A. *J. Org. Chem.* **1992**, *57*, 4512.
116. (a) Schreiber, S. L.; Santini, C. *Tetrahedron Lett.* **1981**, *22*, 4651. (b) Schreiber, S. L. *Science* **1985**, *227*, 857.
117. Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038.
118. Schreiber, S. L.; Hawley, R. C. *Tetrahedron Lett.* **1985**, *26*, 5971.

3 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**.

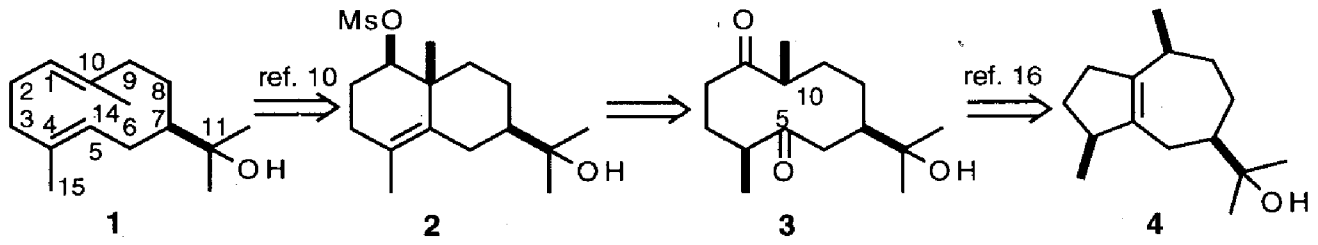
3.1 Introduction*

The germacrane sesquiterpene (+)-hedycaryol (**1**) has been found in several plant species, e.g. *Phebalium ozothamnoides*,[1] *Rubus rosifolius*,[2] *Thujopsis dolabrata*,[3] *Hyssopus officinalis*,[4] and two *Cryptomeria* spp.,[5] and has been used as a chemotype characterizing compound in *Thymus* spp.[6]

Some years before its first isolation from *Hedycarya angustifolia*,[7] hedycaryol was proposed as an important intermediate in the biosynthesis of several classes of sesquiterpene alcohols,[8] and recently, also as a common precursor for several sesquiterpene ethers.[9] The isolation of hedycaryol is rather complicated because the compound is thermally labile and especially sensitive to acids.[10] 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).[11] After a first attempt to synthesize (±)-hedycaryol,[12] two successful syntheses have been reported in the literature, both in low overall yield.[10,13] 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.,[10] 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



3.2 Results and Discussion

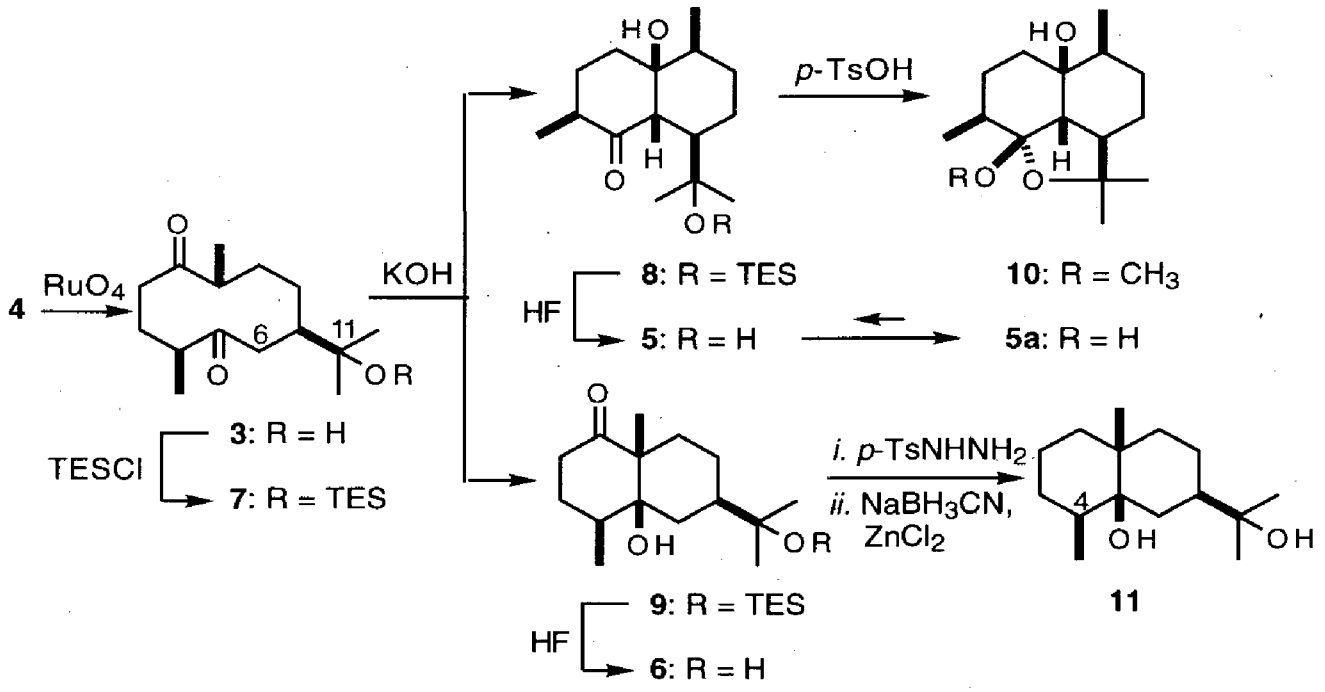
The naturally occurring sesquiterpene (–)-guaiol (**4**) seems to be a suitable starting compound for the synthesis of **2**. It is known that guaiol, which has only been used occasionally in chiral synthesis,[14,15] can be oxidized to the cyclodecane-1,5-dione **3**.[16]

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 H_2 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 $RuO_2/NaIO_4$[17] in a mixture of CCl_4, MeCN, and H_2O 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



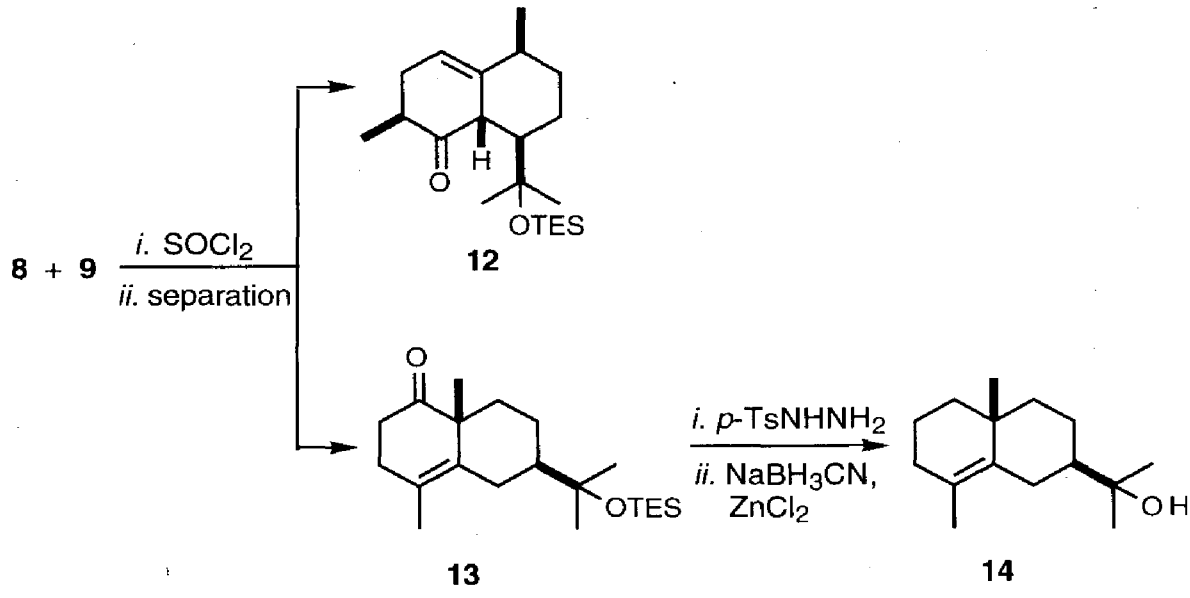
Therefore, it is reasonable to assume that protection of the C(11) hydroxyl group may lead to the formation of compounds with an eudesmane skeleton, e.g. **9**, in addition to, or instead of, cadinane formation. The resulting eudesmane **9** would have all the structural features needed for an effective 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** → **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**.[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**.[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 (δ 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 δ 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

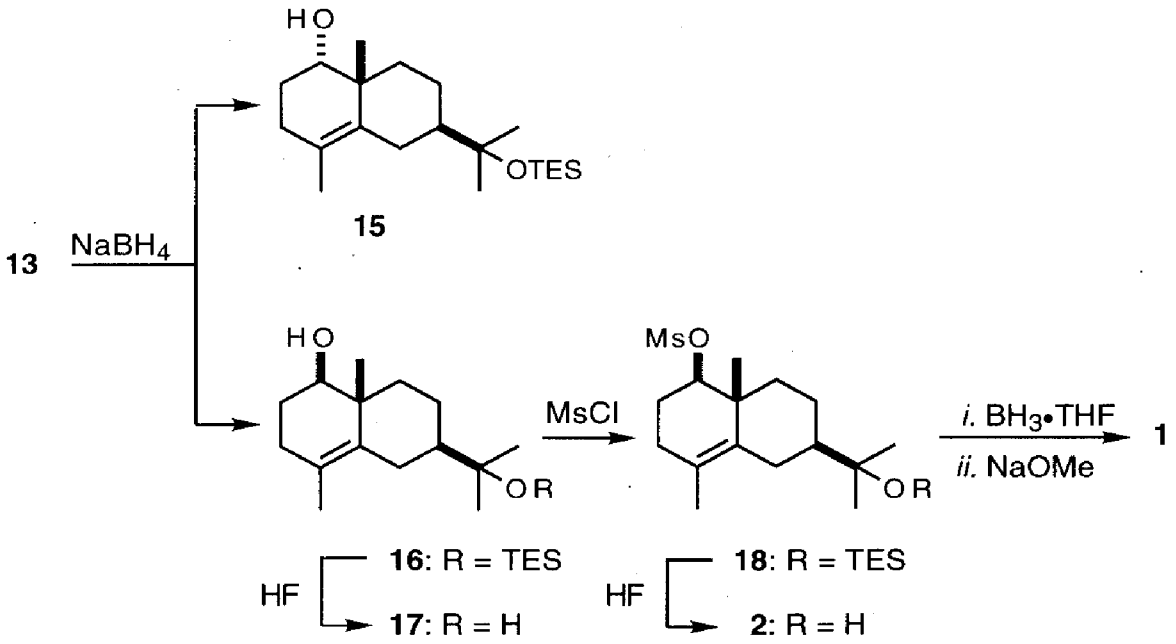


Treatment of **9** with $SOCl_2$ in pyridine gave **13** as the sole product in excellent yield (Scheme 3.3). Furthermore, it was found that after treatment of the above-mentioned 1:2 mixture of **8** and **9** with $SOCl_2$ in pyridine, an easily separable mixture of **12** and **13**, respectively, 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 (+)-hedycaryol, the carbonyl group of **13** had to be reduced to a β-hydroxyl function. The use of $NaBH_4$ 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



Treatment of **16** with MsCl in pyridine followed by desilylation with HF afforded the mesylate **2**. Fragmentation was accomplished using Marshall's procedure[22] to give, after extraction with aqueous $AgNO_3$,[1] pure **1** in 55% yield. It must be noted that during the NMR measurements slow decomposition of **1** was observed in commercial $CDCl_3$, even when this solvent was pretreated with basic alumina. In C_6D_6 solutions **1** appeared to be stable. In the *Chemical Abstracts*, the *S*-configuration is erroneously assigned to (+)-hedycaryol (**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 $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ (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 $MgSO_4$ (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 **17**[21a,b] have been characterized before.

Isolation of (–)-guaiol (4). A solution of 323 g of Guaiac wood oil[23] (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/H_2O (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 H_2 atmosphere as described in the literature,[14] followed by the above-mentioned crystallization procedure using EtOH/H_2O.

[2*S*-(2*R,6*R**,9*S**)]-9-(1-Hydroxy-1-methylethyl)-2,6-dimethyl-1,5-cyclodecanedione (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 CCl_4, and 600 mL of H_2O was added 87.0 g (0.407 mol) of $NaIO_4$ and 0.36 g of $RuO_2.xH_2O$. 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 $Na_2S_2O_3$ and 300 mL of CH_2Cl_2 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 CH_2Cl_2. 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]

[2*S*-(2*R,6*R**,9*S**)]-2,6-Dimethyl-9-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1,5-cyclodecane 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 $NaHCO_3$ 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: $[\alpha]_D$ –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); ^{13}C 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 $C_{19}H_{35}O_3Si$ (M^+–29) *m/z* 339.2355, found *m/z* 339.2355.

[2*S*-(2α,4aα,5α,8α,8aα)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1(2*H*)-naphthalenone (8) and [4*S*-(4α,4aα,6α,8aα)]-Octahydro-4a-hydroxy-4,8a-dimethyl-6-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1(2*H*)-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 NH_4Cl was added. After dilution with H_2O, 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)/Et_2O) 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); $[\alpha]_D$ +54.4° (c 1.21); ^1H NMR (main peaks)[24] 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); ^{13}C NMR (main peaks)[24] 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 $C_{19}H_{35}O_3Si$ (M^+–29) *m/z* 339.2355, found *m/z* 339.2354. Anal. Calcd for $C_{21}H_{40}O_3Si$: C, 68.44; H, 10.94. Found: C, 68.66; H, 11.11. **9**: mp 71 °C (from diisopropyl ether); $[\alpha]_D$ –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); ^{13}C 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), 78.03 (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 $C_{19}H_{35}O_3Si$ (M^+–29) *m/z* 339.2355, found *m/z* 339.2354. Anal. Calcd for $C_{21}H_{40}O_3Si$: C, 68.44; H, 10.94. Found: C, 68.59; H, 11.16.

[2*S*-(2α,4aα,5α,8α,8aα)]-Octahydro-4a-hydroxy-8-(1-hydroxy-1-methylethyl)-2,5-dimethyl-1(2*H*)-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 $NaHCO_3$. 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); $[\alpha]_D$ +48.9° (c 1.59, MeOH) (lit.[18]: +50°, MeOH); HRMS calcd for $C_{15}H_{24}O_2$ (M^+–18) *m/z* 236.1776, found *m/z* 236.1777. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.71; H, 10.37. The ^1H- and ^{13}C NMR spectra of **5** revealed the presence of **5a** in about 80%. **5**: ^1H NMR (main peaks) δ 2.96 (m, 1 H); ^{13}C 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

Hz, 3 H), 1.17 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR δ 12.50 (q), 14.22 (q), 20.09 (t), 24.44 (q), 27.23 (t), 28.94 (q), 31.11 (t), 32.86 (t), 37.80 (d), 38.67 (d), 49.62 (d), 50.77 (d), 73.41 (s), 81.15 (s), 103.82 (s).

[4*S*-(4α,4aα,6α,8aα)]-Octahydro-4a-hydroxy-6-(1-hydroxy-1-methylethyl)-4,8a-dimethyl-1(2*H*)-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); $[\alpha]_D$ –80.6° (c 2.10); ^{1}H 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 (ddd, J = 2.2, 4.4, 15.1 Hz, 1 H), 2.45 (m, 1 H), 2.68 (ddd, J = 7.1, 13.9, 15.1 Hz, 1 H); ^{13}C 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 calcd for $C_{15}H_{26}O_3$ (M^+) *m/z* 254.1882, found *m/z* 254.1882. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.99: H, 10.56.

[2a*R*-(2aα,5β,5aβ,8β,8aβ,8bβ)]-Octahydro-8a-methoxy-2,2,5,8-tetramethyl-2*H*-naphtho[1,8-*bc*]furan-5a(3*H*)-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); $[\alpha]_D$ +43.0° (c 1.37); ^{1}H 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); ^{13}C 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 calcd for $C_{16}H_{28}O_3$ (M^+) *m/z* 268.2038, found *m/z* 268.2038. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.79; H, 10.75.

[2*R*-(2α,4aα,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*-toluenesulfonhydrazide. 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 $NaBH_3CN$, and a solution of 0.085 g (0.63 mmol) of

anhydrous $ZnCl_2$ 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**: $[\alpha]_D$ +37.0° (c 1.15) (lit.[21]: 37.4°, $CHCl_3$); ^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); ^{13}C 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^+, 22), 222 (19), 207 (22), 202 (52), 181 (30), 173 (50), 149 (37), 126 (100), 113 (59); HRMS calcd for $C_{15}H_{28}O_2$ (M^+) *m/z* 240.2089, found *m/z* 240.2088.

[2*S*-(2α,5α,8α,8aα)]-3,5,6,7,8,8a-Hexahydro-2,5-dimethyl-8-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1(2*H*)-naphthalenone (12) and (6*R*-*cis*)-3,5,6,7,8,8a-hexahydro-4,8a-dimethyl-6-[1-methyl-1-[(triethylsilyl)oxy]ethyl]-1(2*H*)-naphthalenone (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 $SOCl_2$ 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)/Et_2O) to give 0.515 g (95%) of pure **13**: $[\alpha]_D$ –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); ^{13}C 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 $C_{20}H_{35}O_2Si$ (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)/Et_2O) afforded 0.254 g of **12**[25] and 0.470 g (44% overall from **7**) of **13**. **12**: ^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); ^{13}C 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),

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 $C_{19}H_{33}O_2Si$ (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**: $[\alpha]_D$ +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]

[1*S*-(1α,6β,8aβ)]- and [1*R*-(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**: $[\alpha]_D$ +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); ^{13}C 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 $C_{20}H_{37}O_2Si$ (M^+–15) *m/z* 337.2563, found *m/z* 337.2563. **16**: $[\alpha]_D$ +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); ^{13}C 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 (t), 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]

[1*R*-(1α,6α,8aα)]-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 $NaHCO_3$ 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**: $[\alpha]_D$ +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); ^{13}C 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 $C_{21}H_{38}OSi$ (M^+–96) *m/z* 334.2691, found *m/z* 334.2692.

[2*R*-(2α,4aα,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); $[\alpha]_D$ +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); ^{13}C 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 $C_{16}H_{28}O_4S$ (M^+) *m/z* 316.1707, found *m/z* 316.1707. Anal. Calcd for $C_{16}H_{28}O_4S$: 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 BH_3·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 NH_4Cl and 10 mL of 25% aqueous NH_3 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 (Na_2SO_4). 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 $AgNO_3$. 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 NH_3, the aqueous layer was extracted with four portions of *t*-butyl methyl ether. The combined organic layers were washed with brine and dried (Na_2SO_4). Evaporation gave 0.365 g (55%) of pure **1**: $[\alpha]_D$ +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]

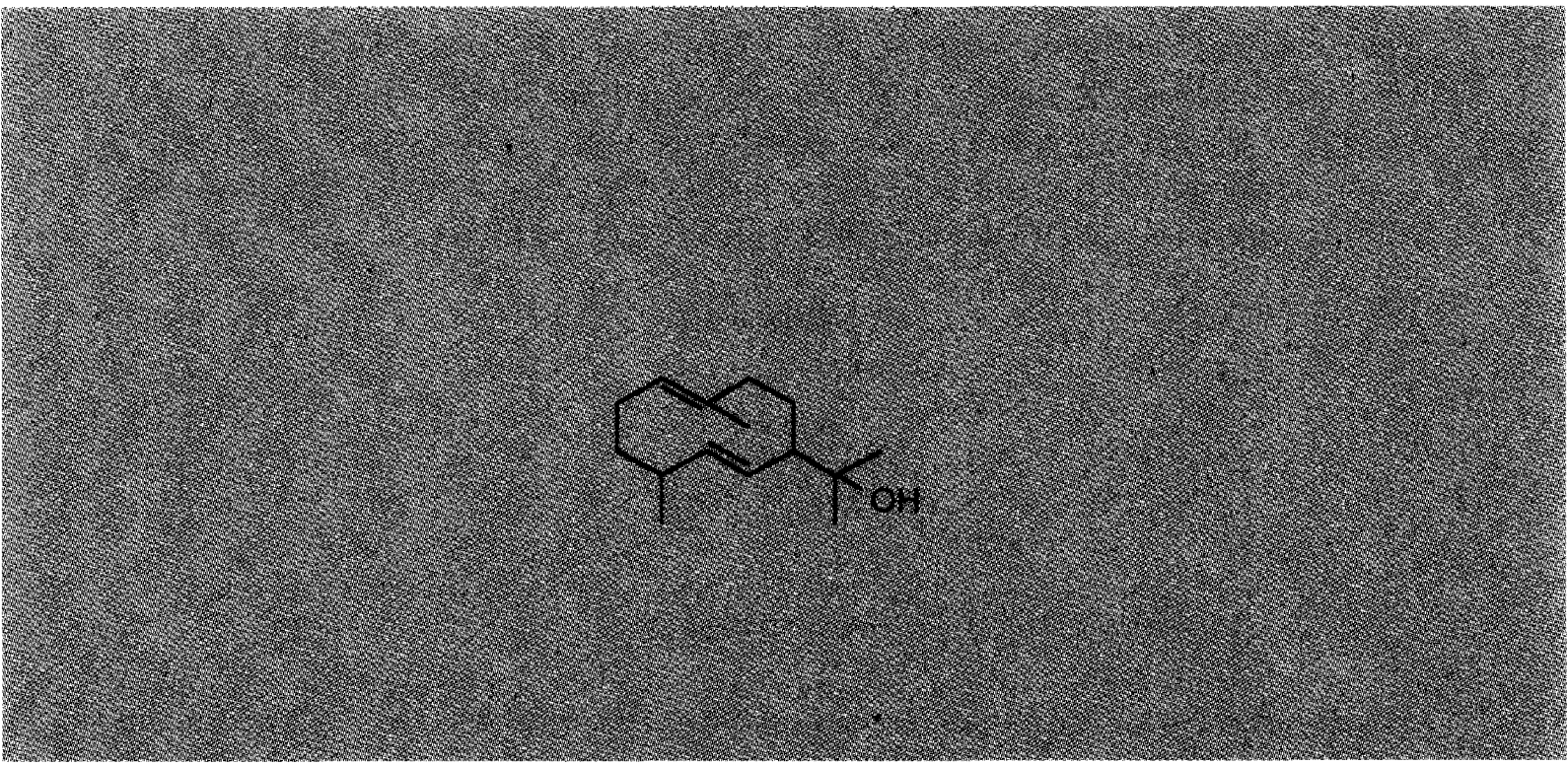
3.4 References and Notes

* This chapter has been published in a revised form: Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1994**, *50*, 4755.

1. Southwell, I. A. *Phytochemistry* **1970**, *9*, 2243.
2. Southwell, I. A. *Aust. J. Chem.* **1978**, *31*, 2527.
3. Hasegawa, S.; Hirose, Y. *Phytochemistry* **1981**, *20*, 508.
4. Schulz, G.; Stahl-Biskup, E. *Flavour Fragrance J.* **1991**, *6*, 69.
5. Nagahama, S.; Tazaki, M.; Kobayashi, H.; Sumimoto, M. *Phytochemistry* **1993**, *33*, 879.
6. (a) Stahl, E. *Planta Med.* **1984**, *50*, 157. (b) Stahl-Biskup, E. *Planta Med.* **1986**, *52*, 36. (c) Stahl-Biskup, E.; Laakso, I. *Planta Med.* **1990**, *56*, 464.
7. Jones, R. V. H.; Sutherland, M. D. *J. Chem. Soc., Chem. Comm.* **1968**, 1229. Note the corrigendum, see: *J. Chem. Soc., Chem. Comm.* **1970**, 892.
8. Hendrickson, J. B. *Tetrahedron* **1959**, *7*, 82.
9. Southwell, I. A.; Tucker, D. J. *Phytochemistry* **1993**, *33*, 857.
10. Wharton, P. S.; Sundin, C. E.; Johnson, D. W.; Kluender, H. C. *J. Org. Chem.* **1972**, *37*, 34.
11. Kodama, M.; Yokoo, S.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1979**, 1687.
12. Corey, E. J.; Broger, E. A. *Tetrahedron Lett.* **1969**, 1779.
13. Kodama, M.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1976**, 1121.

14. van der Gen, A.; van der Linde, L. M.; Witteveen, J. G. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1433.
15. Paknikar, S. K.; Kamat, V. P. *Ind. J. Chem., Sect. B* **1983**, *22*, 1060.
16. Winter, R. E. K.; Zehr, R. J.; Honey, M.; Van Arsdale, W. *J. Org. Chem.* **1981**, *46*, 4309.
17. (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Mehta, G.; Murthy, A. N. *J. Org. Chem.* **1987**, *52*, 2875.
18. Carman, R. M.; Garner, A. C.; Robinson, W. T. *Aust. J. Chem.* **1992**, *45*, 327.
19. Kitagawa, I.; Yamazoe, Y.; Shibuya, H.; Takeda, R.; Takeno, H.; Yosioka, I. *Chem. Pharm. Bull.* **1974**, *22*, 2662.
20. Bates, R. B.; Hendrickson, E. K. *Chem. Ind.* **1962**, 1759.
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 ^{1}H 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); $[\alpha]_D$ +3.6° (c 2.00) (lit. +4.0°); ^{13}C 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: $[\alpha]_D$ +81.2° (c 2.47) (lit. +77.3°); ^{13}C 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).
22. Marshall, J. A.; Huffman, W. F.; Ruth, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 4691.
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.
26. van Beek, T. A.; Kleis, R.; Posthumus, M. A.; van Veldhuizen, A. *Phytochemistry* **1989**, *28*, 1909.

4 The Relative and Absolute Configuration of Allohedycaryol. Enantiospecific Total Synthesis of its Enantiomer

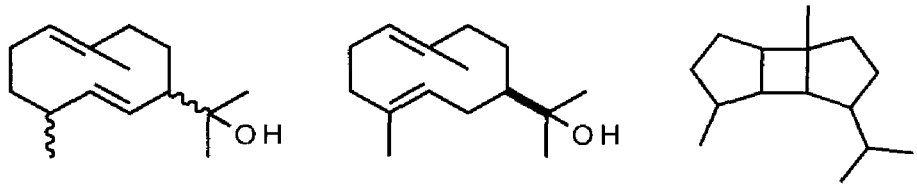


Abstract: the enantiomer of (+)-allohedycaryol (**1**), a germacrane alcohol isolated from giant fennel (*Ferula communis* L.), has been synthesized, thereby elucidating the relative and absolute stereochemistry of the natural product. The synthesis of (–)-allohedycaryol started from (+)-α-cyperone (**5**) 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 allohedycaryol (**1**). The conformation of synthetic (–)-**1** was elucidated via photochemical conversion into a bourbonane system. The synthesis of (–)-allohedycaryol also showed that natural (+)-allohedycaryol 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[1] 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.[2] 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.[3] 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.[4] 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 (+)-hedycaryol (**2**),[5] the name allohedycaryol was proposed for **1**.[3]

Scheme 4.1



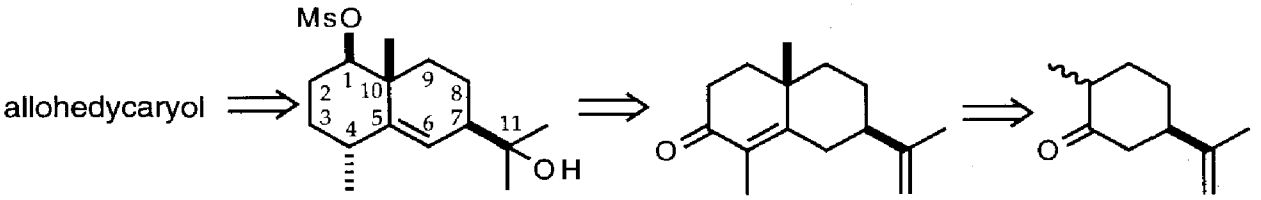
allohedycaryol (**1**) (+)-hedycaryol (**2**) **3**

Germacrane sesquiterpenes, structurally characterized by an (*E,E*)-cyclodeca-1(10),4-diene ring system, are widespread in nature (§ 1.1).[6] 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,[7] allogermacranes are the most likely precursors of bourbonanes, a small class of sesquiterpenes possessing the cyclobuta[1,2:3,4]dicyclopentene skeleton **3**.[8] In contrast to the synthesis of (*E,E*)-germacrane sesquiterpenes and their double bond stereoisomers,[9] little attention has been paid to the synthesis of the regioisomeric allogermacranes (Chapter 2).[10,11]

Because of our interest in the synthesis of germacranes, and because the relative and absolute stereochemistry of allohedycaryol 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 **4** into allohedycaryol by means of a Marshall fragmentation reaction in which both double bonds are regio- and stereospecifically formed.[12] The synthesis of **4** in turn was planned starting from (+)-α-cyperone (**5**) via a number of conversions with the introduction of an equatorial hydroxyl group at C(1)[13] as the most challenging step. An easy access to (+)-α-cyperone was therefore needed and a simple procedure for the synthesis of **5** starting from (+)-dihydrocarvone (**6**) was developed.

Scheme 4.2



4 **5** **6**

Since the absolute and relative stereochemistry of natural allohedycaryol 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 allohedycaryol. We have opted for an equatorial Me group at C(4) and the absolute stereochemistry around C(7) as present in (+)-hedycaryol (**2**). This absolute stereochemistry is normally found in higher plants (vide infra).

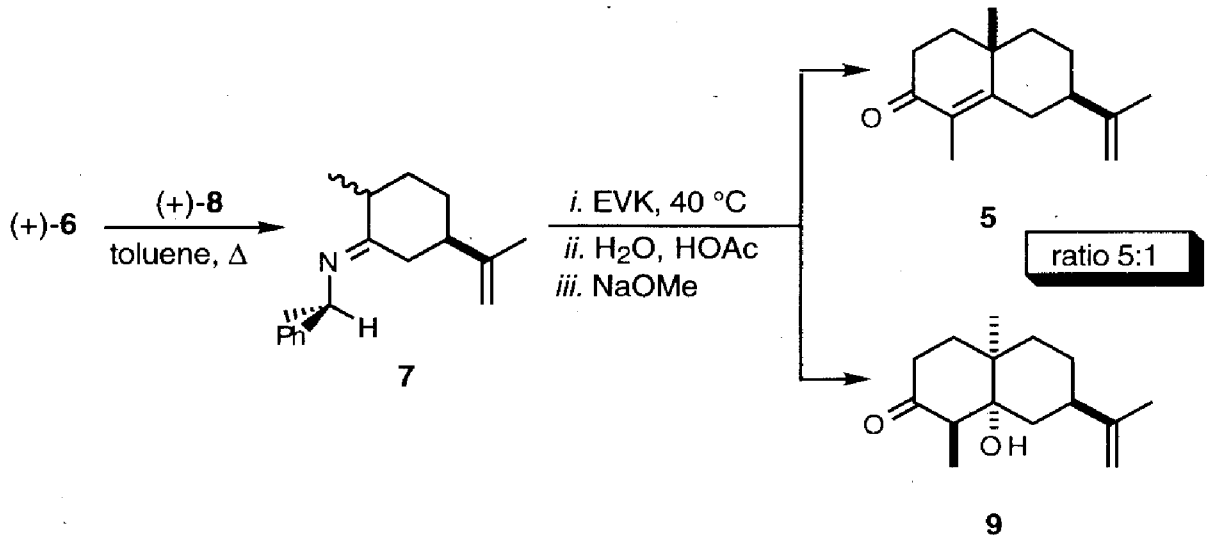
4.2 Results and Discussion

(+)-α-Cyperone (**5**)[14] has been widely used as a starting material for the synthesis of various other fused-ring sesquiterpenes.[15] Whereas (–)-10-*epi*-α-cyperone can be easily synthesized from (+)-dihydrocarvone,[16] the synthetic methods leading to **5** are either rather laborious or give low yields.[17] Because relatively large quantities of **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.[18] The key step in this synthesis was based on the deracemizing alkylation of enantiomerically pure imines derived from racemic cyclanones.[19] In addition, it was shown that in the alkylation of imine **7** derived from **6** with methyl vinyl ketone (MVK) the inherent preference for axial alkylation[15a] was largely overruled by the chiral induction of the imine substituent. We realized that this method could

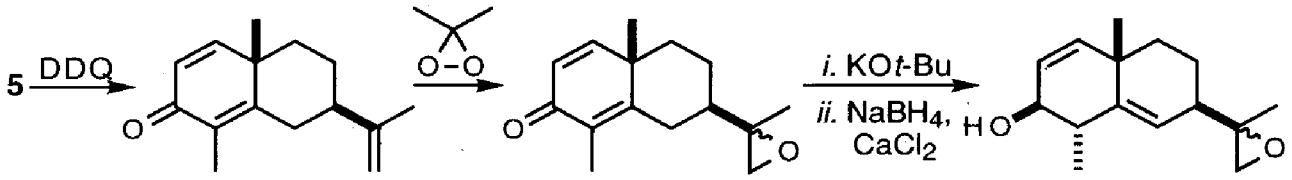
also be used for a short and efficient synthesis of (+)-α-cyperone, simply by replacing MVK by ethyl vinyl ketone (EVK). The synthesis of **5**[20] started with the azeotropic imination of **6** and (*R*)-(+)-1-phenylethylamine (**8**), both commercially available, to afford the imine **7** (Scheme 4.3). 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.[21]

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.[15c] Selective epoxidation of the isopropenyl side-chain in **10** produced **11** as a 1:1 mixture of diastereomers. Treatment of **11** with KO*t*-Bu in dry DMSO and quenching of the resulting enolate with aqueous NH_4Cl gave an unstable deconjugated ketone which was directly reduced with $NaBH_4$ in the presence of $CaCl_2$[22] 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 ($J_{3,4}$) 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.[23] Together with the other NMR data, this observation unequivocally establishes the identity of **12**.

Scheme 4.4



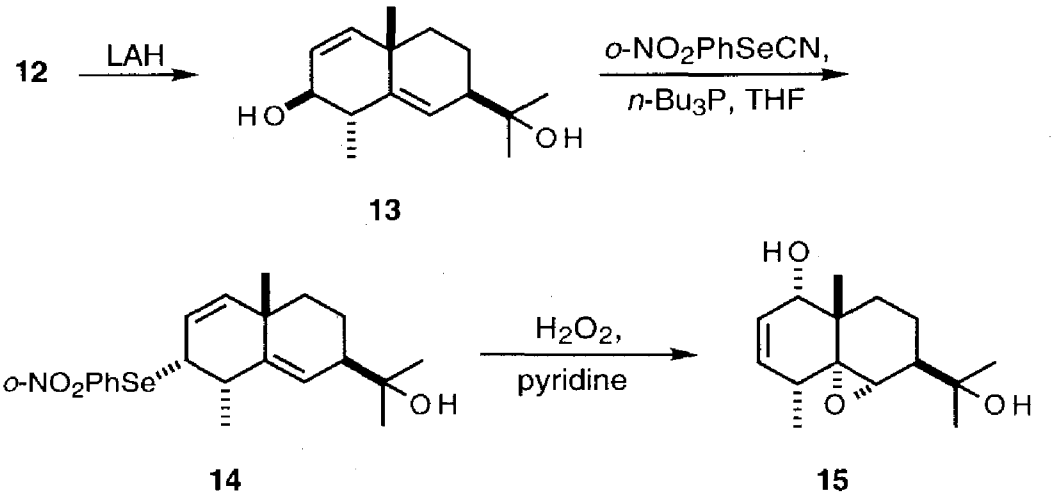
10 **11** **12**

In order to achieve an oxygen function at C(1), some allylic rearrangement experiments[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[25] that treatment of a β-allylic alcohol structurally related to **12** with *t*-BuOOH catalyzed by vanadyl acetylacetonate ($VO(acac)_2$) resulted in the formation of the corresponding β *cis*-epoxy alcohol in reasonable yield. With **12**, however, the *t*-BuOOH/$VO(acac)_2$ reaction only showed oxidation to the corresponding enone.[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.[27]

Another possibility for introducing a hydroxyl function at C(1) involves the stereospecific [2,3] sigmatropic rearrangement of secondary allylic selenoxides.[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[29] (Scheme 4.5). In the ^1H NMR spectrum of the resulting diol **13**, $J_{3,4}$ was found to be 8.5 Hz which confirmed the equatorial α orientation of the Me group at C(4).[23] Treatment of diol **13** with *o*-nitrophenyl selenocyanate in the presence of tri-*n*-butylphosphine afforded the α selenide **14** in 91% yield. Oxidation of **14** with H_2O_2 in the presence of pyridine at –30 °C proceeded smoothly, but gave, in addition to the expected rearrangement, also α epoxidation of the C(5)–C(6) double bond[30] to give **15** as the sole product in 86% yield.[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.

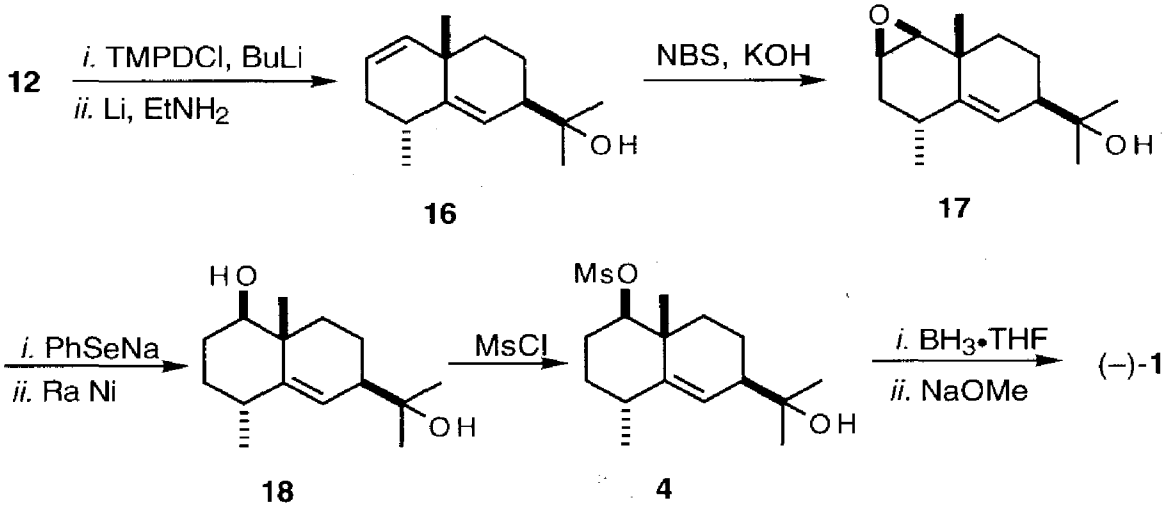
Scheme 4.5



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 $EtNH_2$.[32] 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.[33] 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.

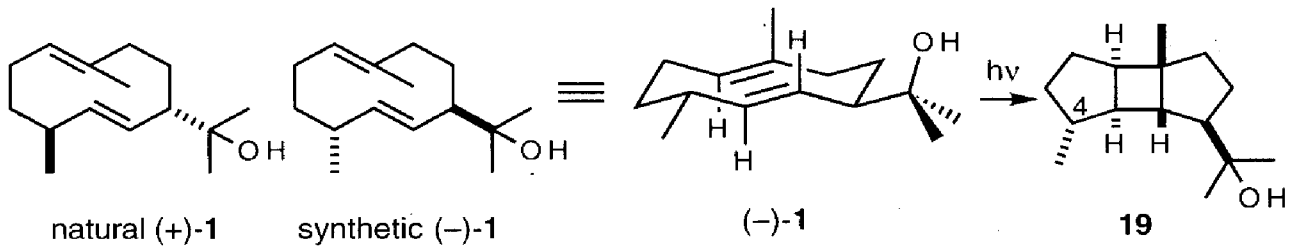
Scheme 4.6



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,[34] but in case of the β epoxide **17** it was found that the diequatorial ring opening prevailed when sodium phenylselenide was used as the nucleophile.[35] After reductive cleavage of the Se–C(2) bond with Raney nickel, the resulting β 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}H NMR spectrum of **4** a one-proton double doublet (J = 11.0, 5.3 Hz) appears at δ 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,[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*.[37] However, the specific rotation obtained for our synthetic product ($[\alpha]_D$ −192°) was opposite to that ($[\alpha]_D$ +181°) reported for natural allohedycaryol,[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 *ent*-configuration,[38] which is remarkable because *ent*-sesquiterpenes are rarely found in higher plants.[39] In addition, the possibility that (+)-hedycaryol (**2**) acts as a direct precursor of (+)-**1** can be ruled out.[40]

Scheme 4.7



natural (+)-**1** synthetic (–)-**1** (–)-**1** **19**

The conformation of allohedycaryol was also investigated. It has been demonstrated[41] that an (*E*,*E*)-cyclodeca-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.[42] (*E*,*E*)-Cyclodeca-1,6-diene ring systems in which one of the double bonds bears a Me group show the same preference.[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.[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 convertion 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**.[43]

4.3 Experimental Section[44]

Materials. All reagents were purchased from Aldrich or Janssen except for *N,N,N′,N′*-tetramethylphosphorodiamidic chloride (TMPDCl) 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**,[17b] **9**,[16] and **10**[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**: $[\alpha]_D$ +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-cyperone (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**: $[\alpha]_D$ –161.5° (c 1.37) (lit.[17b] –149.0°); mp 50–51 °C (from pentane).[45] Anal. Calcd for $C_{15}H_{20}O$: 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]

[4a*S*-[4aα,7α(*R)]] and [4a*S*-[4aα,7α(*S**)]]-5,6,7,8-Tetrahydro-1,4a-dimethyl-7-(2-methyloxiranyl)-2(4a*H*)-naphthalenone (11).** To a stirred solution of 1.95 g (9.03 mmol) of **10** in 120 mL of a 1:1 mixture of CH_2Cl_2 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 $NaHCO_3$ 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 $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ for 20 min. The mixture was extracted with CH_2Cl_2 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: ^{13}C 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]

[1*S*-[1α,2β,4aβ,7β(*R)]] and [1*S*-[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 KO*t*-Bu. The reaction mixture was stirred at rt for 45 min and then poured into ice-water containing 5.0 g of NH_4Cl. The mixture was extracted with CH_2Cl_2 and the combined organic layers were washed with water, dried over Na_2SO_4, 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 $CaCl_2$ in 40 mL of dry EtOH was added dropwise to a stirred solution of 1.1 g (29.1 mmol) of $NaBH_4$ 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 CH_2Cl_2, 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] ^{1}H 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); ^{13}C 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 $C_{15}H_{22}O_2$ (M^+) 234.1620, found 234.1619.

[2*R*-(2α,4aα,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 $MgSO_4$, the mixture was stirred at rt for 5 min and then filtered. The filtrate was evaporated to give 1.20 g (91%) of **13**: $[\alpha]_D$ = –43.1° (c 0.07); ^{1}H 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); ^{13}C 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 (d), 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 $C_{14}H_{21}O_2$ (M^+ – 15) 221.1542, found 221.1545.

[1a*S*-(1aα,2α,4aα,5β,8β,8a*S)]-1a,2,4,4a,5,8-Hexahydro-5-hydroxy-α,α,4a,8-tetramethyl-3*H*-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**: $[\alpha]_D = -409°$ (c 0.30); ^{1}H 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); ^{13}C 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 $C_{21}H_{27}NO_3Se$ (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% H_2O_2 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 $NaHCO_3$ and water, dried over Na_2SO_4, 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**: $[\alpha]_D = +9.4°$ (c 2.06); ^{1}H 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); ^{13}C 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 $C_{15}H_{24}O_3$ (M^+) 252.1725, found 252.1725.

[2*R*-(2α,4aα,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′*-tetramethylethylenediamine (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 $EtNH_2$ at 0 °C. After stirring at 0 °C for 1 h, 100 mL of saturated aqueous NH_4Cl was added and $EtNH_2$ 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 $C_{14}H_{21}O$ (M^+ – 15) 205.1592, found 205.1593.

[1a*R*-(1aα,3α,5β,7aβ,7bα)]-1a,2,3,5,6,7,7a,7b-Octahydro-α,α,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); $[\alpha]_D$ = –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 $C_{15}H_{22}O$ (M^+ – 18) 218.1671, found 218.1669.

[2*R*-(2α,4aα,5α,8β)]-2,3,4,4a,5,6,7,8-Octahydro-5-hydroxy-α,α,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 $CHCl_3$, and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. Flash chromatography (5:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 300 mg (93%) of **18**: $[\alpha]_D$ = –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 $C_{14}H_{23}O_2$ (M^+ – 15) 223.1698, found 223.1697.

[2*R*-(2α,4aα,5α,8β)]-2,3,4,4a,5,6,7,8-Octahydro-α,α,4a,8-tetramethyl-5-[(methylsulfonyl)oxy]-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 $NaHCO_3$ was added dropwise. The reaction mixture was stirred for an additional 5 min and then extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, and evaporated. After removal of the residual pyridine by azeotropic distillation with toluene, 392 mg (99%) of **4** was obtained: $[\alpha]_D$ –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); ^{13}C 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 $C_{15}H_{25}O_4S$ (M^+ – 15) 301.1474, found 301.1472.

(–)-Allohedycaryol (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 BH_3•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 NH_4Cl 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 Na_2SO_4 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 $AgNO_3$. The combined aqueous layers were washed with *t*-butyl methyl ether and then cooled to 0 °C. After addition of 25% NH_3, the aqueous layer was extracted with *t*-butyl methyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation gave 185 mg (68%) of pure **1**: $[\alpha]_D$ = –192° (c 0.92) (lit.[3] +181°); UV (CH_3CN) λ_{max} <200 nm, tail to 260 nm. The NMR and mass spectral data for (–)-**1** corresponded with those reported for natural (+)-**1**.[3]

[1*R*-(1α,3aα,3bβ,6β,6aβ,6bα)]-Decahydro-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%): $[\alpha]_D = -1.3°$ (c 0.95); ^{1}H 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); ^{13}C 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 $C_{15}H_{26}O$ (M^+) 222.1984, found 222.1983.

4.4 References and Notes

* This chapter has been published in a revised form: Zhabinskii, V. N.; Minnaard, A. J.; Wijnberg, J. B. P. A.; De Groot, A. *J. Org. Chem.* **1996**, *61*, 4022.

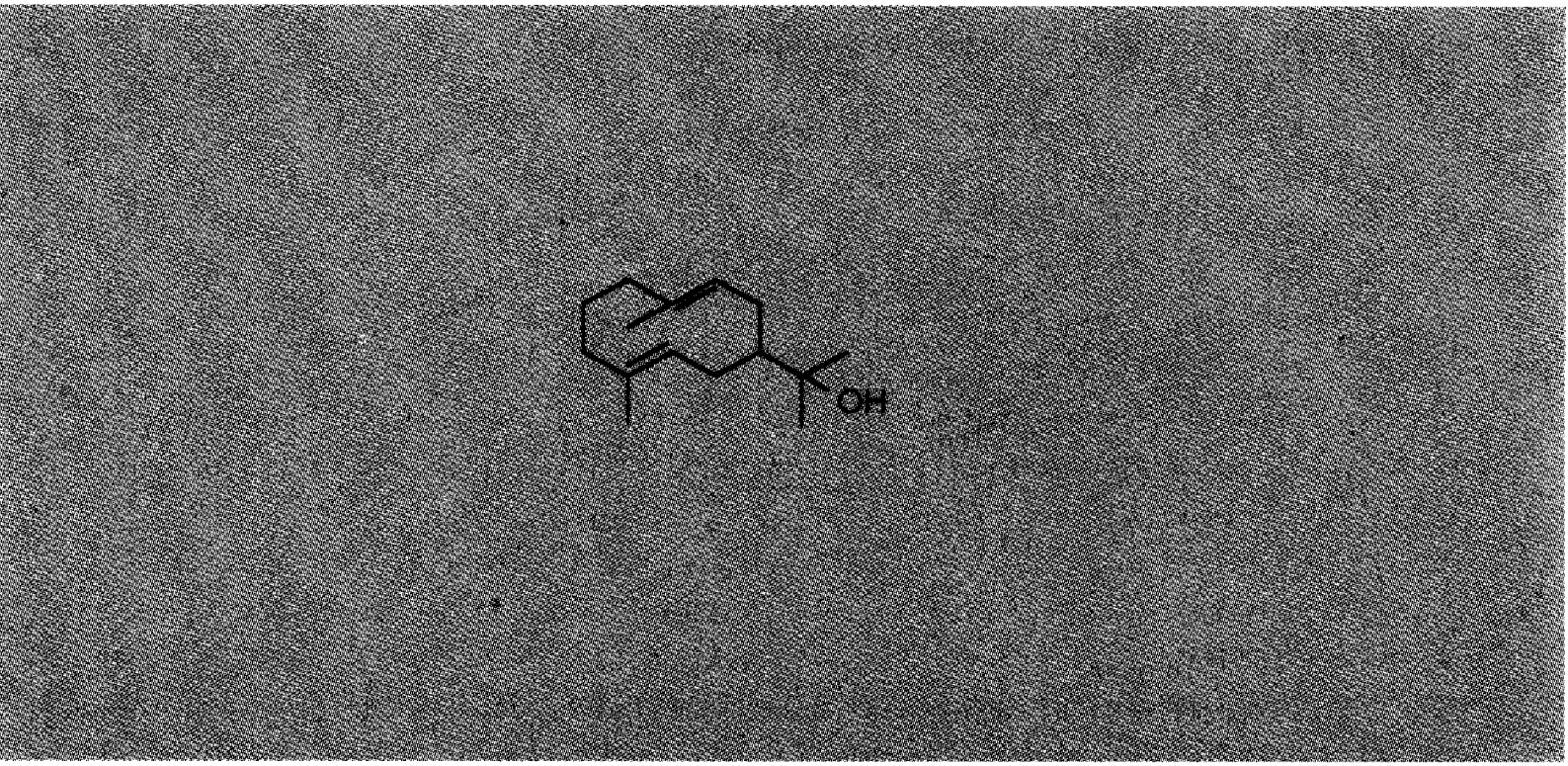
1. Gunther, R. T. In *The Greek Herbal of Dioscorides*; University Press: Oxford, 1934; p 323.
2. For an extensive review, see: Gonzalez, A. G.; Barrera, J. B. *Prog. Chem. Org. Nat. Prod.* **1995**, *64*, 1.
3. Valle, M. G.; Appendino, G.; Nano, G. M.; Picci, V. *Phytochemistry* **1987**, *26*, 253.
4. Kreiser, W. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1991; Vol. 8, pp 39–61.
5. Jones, R. V. H.; Sutherland, M. D. *J. Chem. Soc., Chem. Commun.* **1968**, 1229.
6. Banthorpe, D. V. In *Natural Products: Their Chemistry and Biological Significance*; Longman Scientific & Technical: Harlow, 1994; Chapter 5.
7. Heathcock, C. H.; Badger, R. A.; Starkey, R. A. *J. Org. Chem.* **1972**, *37*, 231.
8. (a) Yoshihara, K.; Ohta, Y.; Sakai, T.; Hirose, Y. *Tetrahedron Lett.* **1969**, 2263. (b) Raldugin, V. A.; Salenko, V. L.; Gamov, N. S.; Titova, T. F.; Khan, V. A.; Pentegova, V. A. *Chem. Nat. Compd. (Engl. Transl.)* **1980**, 154.
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.
10. Kodama, M.; Shimada, K.; Takahashi, T.; Kabuto, C.; Itô, S. *Tetrahedron Lett.* **1981**, *22*, 4271.
11. Schreiber, S. L.; Hawley, R. C. *Tetrahedron Lett.* **1985**, *26*, 5971.

12. Marshall J. A. *Synthesis* **1971**, 229.
13. The numbering system as given in structure **4** will be followed throughout the text of this chapter.
14. Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 1, Mono- and Sesquiterpenoids, p 326.
15. For some representative examples, see: (a) Ho, T.-L. *Enantioselective Synthesis, Natural Products from Chiral Terpenes*; Wiley Interscience: New York, 1992; pp 132–135. (b) Li, Y.; Chen, X.; Shao, S.; Li, T. *Synth. Commun.* **1993**, *23*, 2457. (c) Liu, L.; Xiong, Z.; Nan, F.; Li, T.; Li, Y. *Bull. Soc. Chim. Belg.* **1995**, *104*, 73.
16. Howe, R.; McQuillin, F. J. *J. Chem. Soc.* **1955**, 2423.
17. (a) Reference 15a, pp 198–200 and 272–273. (b) Haaksma, A. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1992**, *48*, 3121. (c) Agami, C.; Kadouri-Puchot, C.; Le Guen, V. *Tetrahedron: Asymm.* **1993**, *4*, 641.
18. Tenius, B. S. M.; de Oliveira, E. R.; Ferraz, H. M. C. *Tetrahedron: Asymm.* **1993**, *4*, 633.
19. (a) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. Review: (b) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymm.* **1992**, *3*, 459.
20. The well-described procedure was followed: Revial, G.; Pfau, M. *Org. Synth.* **1992**, *70*, 35.
21. The use of (*S*)-(−)-1-phenylethylamine resulted in a selective formation of (−)-10-*epi*-α-cyperone in 67% overall yield from (+)-dihydrocarvone. After the completion of this research, two similar syntheses of **5** were published: (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.
22. Krieg, R.; Schönecker, B. *Liebigs Ann. Chem.* **1994**, 1025.
23. Ando, M.; Akahane, A.; Takase, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 283.
24. Narasaka, K. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Science: London, 1994; pp 17–36.
25. Yamakawa, K.; Nishitani, K.; Tominaga, T. *Tetrahedron Lett.* **1975**, 2829.
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) epimer[46] with *t*-BuOOH/$VO(acac)_2$ gave selectively the corresponding α epoxide.
28. Zoretic, P. A.; Chambers, R. J.; Marbury, G. D.; Riebiro, A. A. *J. Org. Chem.* **1985**, *50*, 2981.
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.

30. The epoxidation of olefinic bonds, probably due to the formation of arylperoxyseleninic acid, is a known problem in the selenoxide chemistry, see: (a) Grieco, P. A.; Yokoyama, Y.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 2034. (b) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689.
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]
32. (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (b) Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668.
33. Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1959**, 4136.
34. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 165.
35. Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *J. Org. Chem.* **1993**, *58*, 7204.
36. Southwell, I. A. *Phytochemistry* **1970**, *9*, 2243.
37. We thank Prof. Dr. G. Appendino for supplying copies of the NMR spectra of natural allohedycaryol.
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 (+)-hedycaryol (**2**), see § 3.2.
41. (a) White, D. N. J.; Bovill, M. J. *Tetrahedron Lett.* **1975**, 2239. (b) Neykov, G. D.; Ivanov, P. M.; Orahovats, A. S. *J. Mol. Struct.* **1987**, *153*, 147.
42. Dale, J.; Moussebois, C. *J. Chem. Soc. (C)* **1966**, 264.
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** [^{1}H 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 **12**[46] yielded **16** in 95%.

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

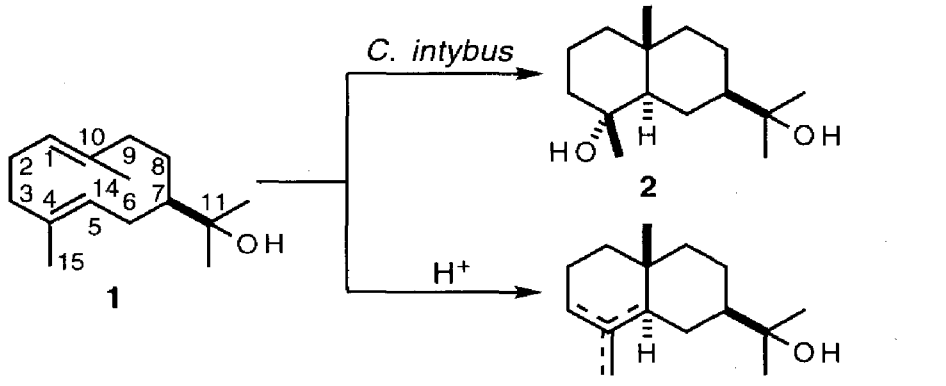


Abstract: the total synthesis of neohedycaryol (**4**), a C(9)–C(10) double bond regioisomer of hedycaryol (chapter 3), was accomplished in 10 steps from the known dione **6**. A Marshall fragmentation of the intermediate mesylate **14** was used to prepare the (*E*,*E*)-cyclodeca-4,9-diene ring present 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**).

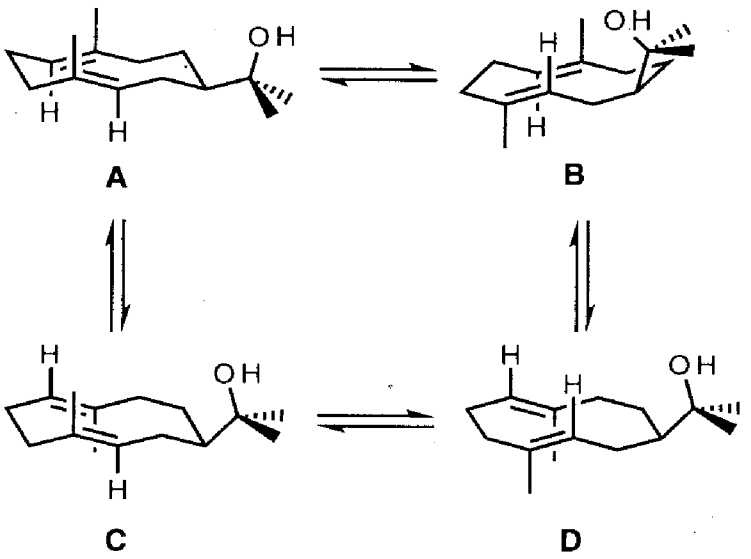
Scheme 5.1



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 unriddle the biosynthesis of *epi*-eudesmanes. In the most straightforward explanation, both the *epi*- and usual eudesmanes are formed from (*E*,*E*)-germacranes.[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.[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.

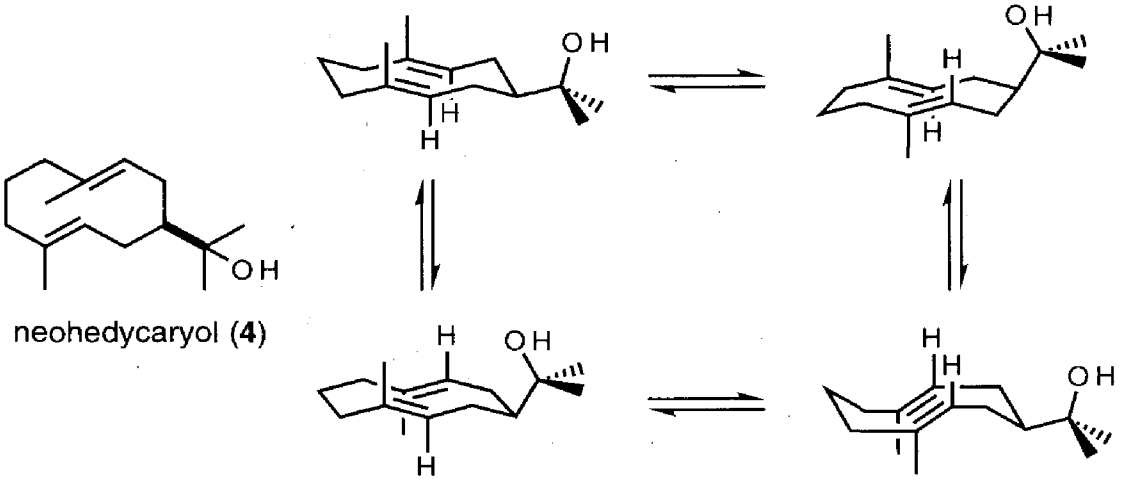
A second explanation for the biosynthesis of *epi*-eudesmanes assumes the cyclization of double bond stereoisomers of (*E*,*E*)-germacranes.[13] It has been shown that acid-catalyzed cyclizations of double bond stereoisomers of **1** do give *epi*-eudesmanes.[11,14] A serious drawback of this hypothesis is the fact that the double bond stereoisomers of simple (*E*,*E*)-germacranes have not been found in nature.[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 neohedycaryol (**4**), might give an eudesmane.[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**.[17] Experimental information, however, failed to appear because **4** was not available. Some years later, a route towards agarofurans based on **4** was postulated.[18] Since

then, **4** has been mentioned several times in connection with the biosynthesis of *epi*-eudesmanes,[19] eremophilanes,[20] and agarofurans.[21]

Although recently two C(5)–C(6) double bond regioisomers of hedycaryol, e.g. allohedycaryol[22] and its C(4) epimer,[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).[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.

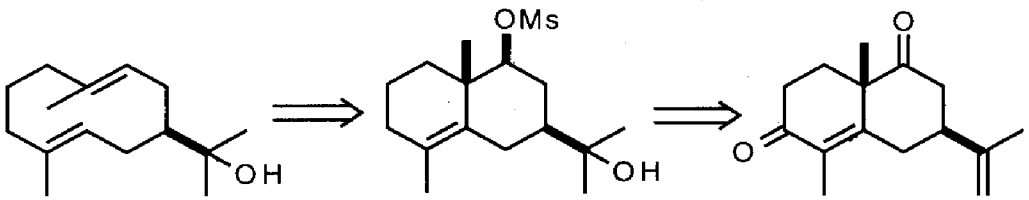
Scheme 5.3: Conformations of neohedycaryol (**4**)



Because of our interest in the biosynthetic-like cyclization reactions of germacrane sesquiterpenes (§ 7.2)[3,25] and their analogues,[26] we decided to synthesize neohedycaryol. As with hedycaryol,[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 neohedycaryol, involved a Marshall fragmentation reaction.[28]

Scheme 5.4



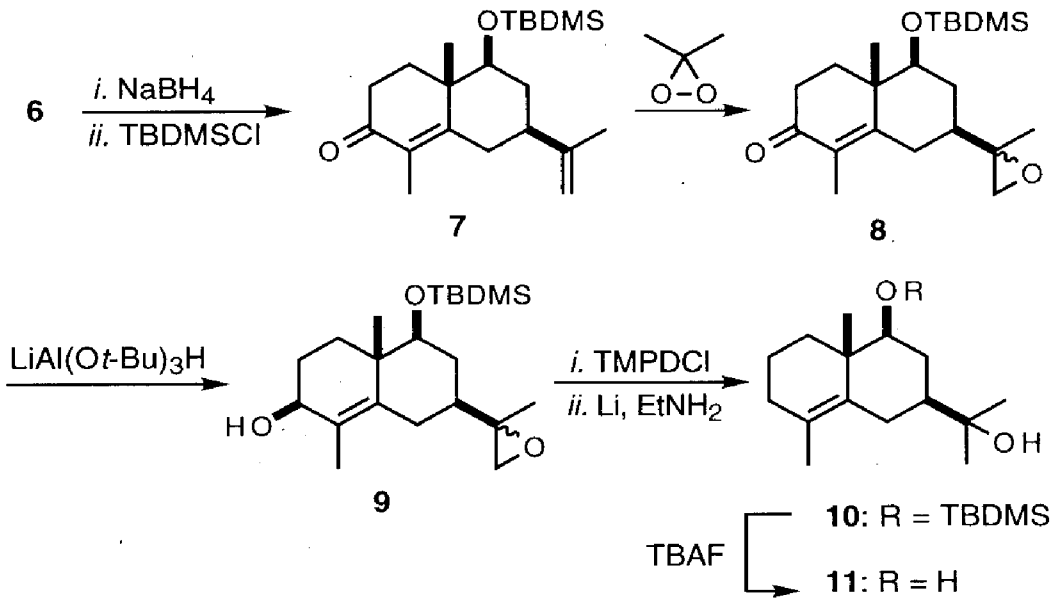
neohedycaryol (**4**) **5** **6**

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 dimethyldioxirane and afforded **8** as a diastereomeric 1:1 mixture.

Reduction of **8** with lithium tri-*tert*-butoxyaluminohydride ($LiAl(O\textit{t}\text{-}Bu)_3H$) provided **9** also as a diastereomeric 1:1 mixture in 87% yield. Since the $LiAl(O\textit{t}\text{-}Bu)_3H$ reduction of a system comparable to **8** proceeds selectively from the α-side,[32] the orientation of the C(3) hydroxyl group of **9** is probably β. In order to remove the oxygen function at C(3), the phosphordiamidate 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.

Scheme 5.5

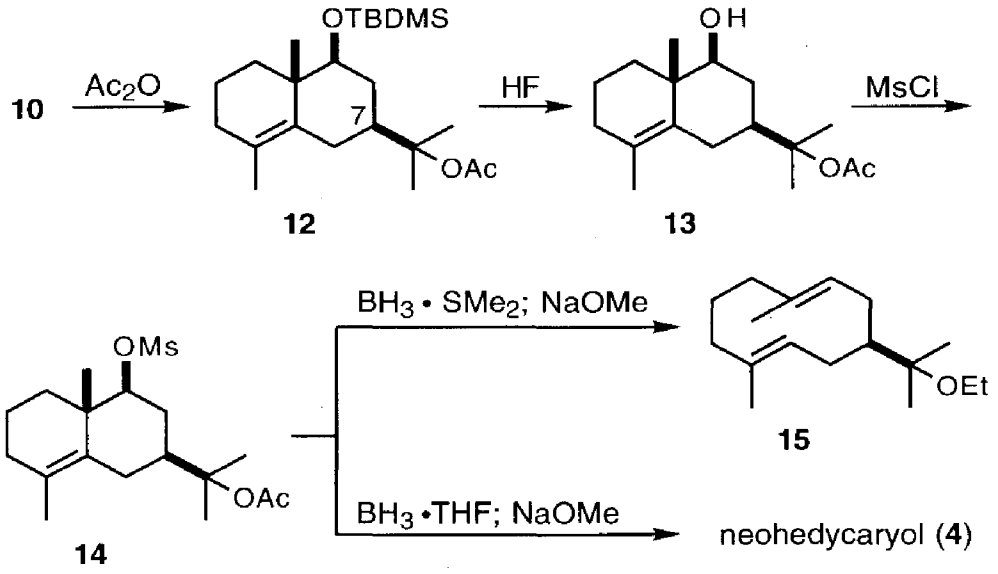


In order to apply the Marshall fragmentation reaction, the C(9) hydroxyl group of **11** had to be converted into a mesylate group, and here we encountered a curious problem. Despite many attempts, we were not able to produce the desired mesylate **5**. For instance, treatment of **11** with MsCl in 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,[34] 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.[35] 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.[36] Strong support for this assumption came from previous studies in our group on trans-fused perhydronaphthalene-[37] and norbornane-1,4-diol monosulfonate esters.[38] 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 alcoholate anion (electron donor) and the sulfonate ester bond (electron acceptor). The extent of these through-bond orbital interactions (TBI)[39] depends on the geometry of the σ-relay (the intervening σ-framework) and is maximized for an all-trans arrangement.[40] From examination of a molecular model

of **5**, it appeared that the σ-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 Ac_2O and a catalytic amount of DMAP in Et_3N[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

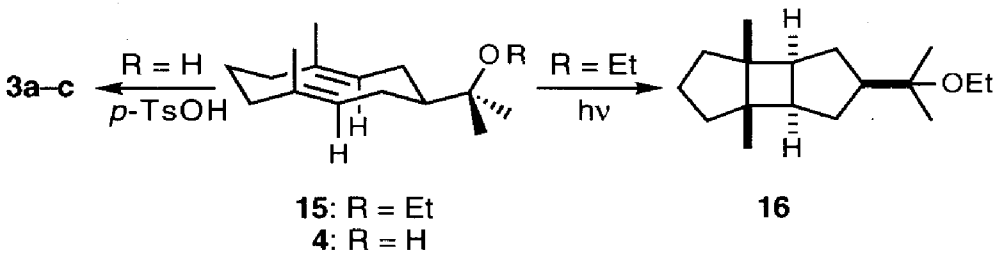


As in the case of (+)-hedycaryol (chapter 3) and (–)-allohedycaryol (chapter 4), the Marshall fragmentation reaction of mesylate **14** was expected to complete the synthesis of neohedycaryol.[43] However, successive treatment of **14** with BH_3·SMe_2 and NaOMe in MeOH gave, instead of expected **4**, 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.[44] In order to minimize the reduction of the acetate group, **14** was treated with BH_3·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 $AgNO_3$ extraction.[45] Although the yield of **4** was poor (11%),[46] all spectral and chromatographic data including the Kováts indices[47] could be obtained.

The ^1H NMR spectrum of **4** points to the preference for one distinct conformation. From its ^{13}C 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.[48] The formation of a 1:2:1 mixture of α-, β-, and γ-eudesmol, respectively, upon treatment of **4** with *p*-TsOH in CH_2Cl_2 proved that **4** reacts exclusively from the elongated chair conformation (Scheme 5.7).[49] 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.[50]

Scheme 5.7



15: R = Et
4: R = H

16

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.[51] It is therefore tempting to consider the possibility that **4** may be a direct in vivo formed precursor[52] of both *ent*- and usual eudesmanes and not, as argued above, of *epi*-eudesmanes.

5.4 Experimental Section[53]

General. Kováts indices were determined on a gas chromatograph equipped with a J&W DB-1 column (60 m × 0.25 mm i.d., film thickness 0.25 μm) and a Restek Stabilwax column (60 m × 0.25 mm i.d., film thickness 0.25 μm). Split ratio 1:100, carrier gas H_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*′-tetramethylphosphorodiamidic chloride (TMPDCl) which was purchased from Fluka. 2-Methyl-5-(1-methylethenyl)-1,3-cyclohexanedione[27] and compound **6**[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.[27] After workup, the remaining residue was dried in a vacuum dessicator on P_2O_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.[27]

(*cis*-3,4,8,8a)-(±)-Tetrahydro-5,8a-dimethyl-3-(1-methylethenyl)-1,6-(2*H*,7*H*)-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.[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 $NaHCO_3$, 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.[29,54]

(4aα,5α,7α)-(±)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-7-(1-methylethenyl)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2(3*H*)-naphthalenone (7). After reduction of **6** with $NaBH_4$ 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 TBDMSCl 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: ^{1}H 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); ^{13}C 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 $C_{17}H_{27}O_2Si$ (M^+ – 57) 291.1780, found 291.1780.

(4aα,5α,7α)-(±)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-5-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-7-(2-methyloxiranyl)-2(3*H*)-naphthalenone (8). To a stirred solution of 10.5 g (30.2 mmol) of **7** in 360 mL of a 1:1 mixture of CH_2Cl_2 and acetone were added 0.755 g (2.86 mmol) of 18-crown-6 and a solution of 11.5 g (137 mmol) of $NaHCO_3$ 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 $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ for 20 min. The mixture was extracted with CH_2Cl_2 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: ^{1}H 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); ^{13}C 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 $C_{17}H_{27}O_3Si$ (M^+ – 57) 307.1730, found 307.1731.

(2α,4aα,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)$_3$AlH 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 $Na_2SO_4 \cdot 10H_2O$ followed by the addition of 2 mL of water and excess $MgSO_4$. 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: ^{1}H 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); ^{13}C 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 $C_{17}H_{29}O_3Si$ (M^+ – 57) 309.1886, 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 $EtNH_2$ at 0 °C. After stirring at 0 °C for 1 h, 20 mL of saturated aqueous NH_4Cl was added and $EtNH_2$ 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] ^{1}H 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); ^{13}C 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 $C_{21}H_{40}O_2Si$ (M^+) 352.2798, found 352.2795.

(2α,4α,4aα)-(±)-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 of 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; ^{1}H 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); ^{13}C 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 $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.55; H, 11.21.

(2α,4α,4aα)-(±)-1,2,3,4,4a,5,6,7-Octahydro-α,α,4,8-tetramethyl-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-naphthalenemethyl acetate (12). To a stirred solution of 0.324 g (0.93 mmol) of **10** in 3 mL of Et_3N was added 0.26 mL (2.80 mmol) of Ac_2O 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 $NaHCO_3$ 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: ^{1}H 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 (dd, *J* = 4.7, 10.8 Hz, 1 H); ^{13}C NMR δ –4.79 (q), –3.91 (q), 18.06 (q), 18.06 (s, obscured), 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 $C_{21}H_{38}OSi$ (M^+ – 60) 334.2692, found 334.2689.

(2α,4α,4aα)-(±)-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 $NaHCO_3$ 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: ^{1}H NMR δ 0.98 (s, 3 H), 1.44 (s, 6 H), 1.60 (br s, 3 H),

1.98 (s, 3 H), 1.2–2.1 (m, 11 H), 2.47 (br d, J = 13.2 Hz, 1 H), 3.33 (dd, J = 4.3, 11.3 Hz, 1 H); ^{13}C NMR δ 17.67 (q), 18.72 (t), 19.69 (q), 22.44 (q), 23.41 (2q), 25.31 (t), 31.27 (t), 32.96 (t), 36.12 (t), 40.07 (s), 44.03 (d), 78.96 (d), 84.25 (s), 127.72 (s), 132.46 (s), 170.50 (s); MS *m/z* (relative intensity) 220 (M^+ – 60, 100), 202 (19), 187 (23), 177 (23), 173 (16), 159 (22), 107 (16), 69 (30), 43 (16); HRMS calcd for $C_{15}H_{24}O$ (M^+ – 60) 220.1827, found 220.1829.

(2α,4α,4aα)-(±)-1,2,3,4,4a,5,6,7-Octahydro-α,α,4,8-tetramethyl-4-[(methylsulfonyl)-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**: ^{1}H NMR (C_6D_6) 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); ^{13}C NMR (C_6D_6) 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 $C_{16}H_{26}O_3S$ (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 BH_3·SMe_2 (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**: ^{1}H NMR (C_6D_6) 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), 3.30 (q, J = 6.9 Hz, 2 H), 5.16 (br d, J = 10.8 Hz, 2 H); ^{13}C NMR (C_6D_6) 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 $C_{17}H_{30}O$ (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 BH_3·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 $AgNO_3$. 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 NH_3, 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); ^{1}H NMR (C_6D_6) 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); ^{13}C NMR (C_6D_6) 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 calcd for $C_{15}H_{26}O$ (M^+) 222.1984, found 222.1977.

Ethyl (2α,3aβ,3bα,6aα,6bβ)-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%): ^{1}H 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); ^{13}C 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 calcd for $C_{16}H_{27}O$ (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 CH_2Cl_2 was added a small crystal of *p*-TsOH·H_2O. After stirring at rt for 7 min, the mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ 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

* This chapter will be published in a revised form: Minnaard, A. J.; Stork, G. A.; Wijnberg, J. B. P. A.; De Groot, A. *J. Org. Chem.* **1997**, in press.

1. The numbering system as given in structure **1** will be followed throughout the text of this chapter.
2. (a) Fischer, N. H. In *Recent Advances in Phytochemistry, Vol. 24: Biochemistry of the Mevalonic Acid Pathway to Terpenoids*; Towers, G. H. N., Stafford, H. A., Eds.; Plenum Press: New York, 1990; Chapter 4. (b) Marco, J. A.; Sanz-Cervera, J. F.; García-Lliso, V.; Domingo, L. R.; Carda, M.; Rodríguez, S.; López-Ortiz, F.; Lex, J. *Liebigs Ann. Chem.* **1995**, 1837 and references cited therein.
3. Piet, D. P.; Minnaard, A. J.; van der Heyden, K. A.; Franssen, M. C. R.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1995**, *51*, 243.
4. Jones, R. V. H.; Sutherland, M. D. *J. Chem. Soc., Chem. Comm.* **1968**, 1229.
5. (a) Wharton, P. S.; Poon, Y. C.; Kluender, H. C. *J. Org. Chem.* **1973**, *38*, 735. (b) Minnaard, A. J. unpublished.
6. This is explained by the Curtin-Hammett principle, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994; pp 647–655.
7. (a) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 1, Mono- and Sesquiterpenoids. (b) Pietra, F. *Chem. Soc. Rev.* **1995**, *24*, 65.
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.
9. For some representative examples, see: (a) Prudent, D.; Perineau, F.; Bessiere, J. M.; Michel, G.; Bravo, R. *J. Essent. Oil Res.* **1993**, *5*, 255. (b) Cañigueral, S.; Vila, R.; Vicario, G.; Tomas, X.; Adzet, T. *Biochem. Syst. Ecol.* **1994**, *22*, 307.
10. Itokawa, H.; Morita, H.; Watanabe, K.; Mihoshi, S.; Iitaka, Y. *Chem. Pharm. Bull.* **1985**, *33*, 1148.
11. Kodama, M.; Shimada, K.; Itô, S. *Tetrahedron Lett.* **1981**, *22*, 1523.
12. Appendino, G.; Gariboldi, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2017.
13. An indication for this pathway is the co-occurrence of (*E*,*Z*)-farnesol (a precursor of (*Z*,*E*)-germacranes) and *epi*-eudesmanes in *Galbanum* species, see: Thomas, A. F.; Ozainne, M. *Helv. Chim. Acta* **1978**, *61*, 2874.
14. Kodama, M.; Yokoo, S.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1979**, 1687.

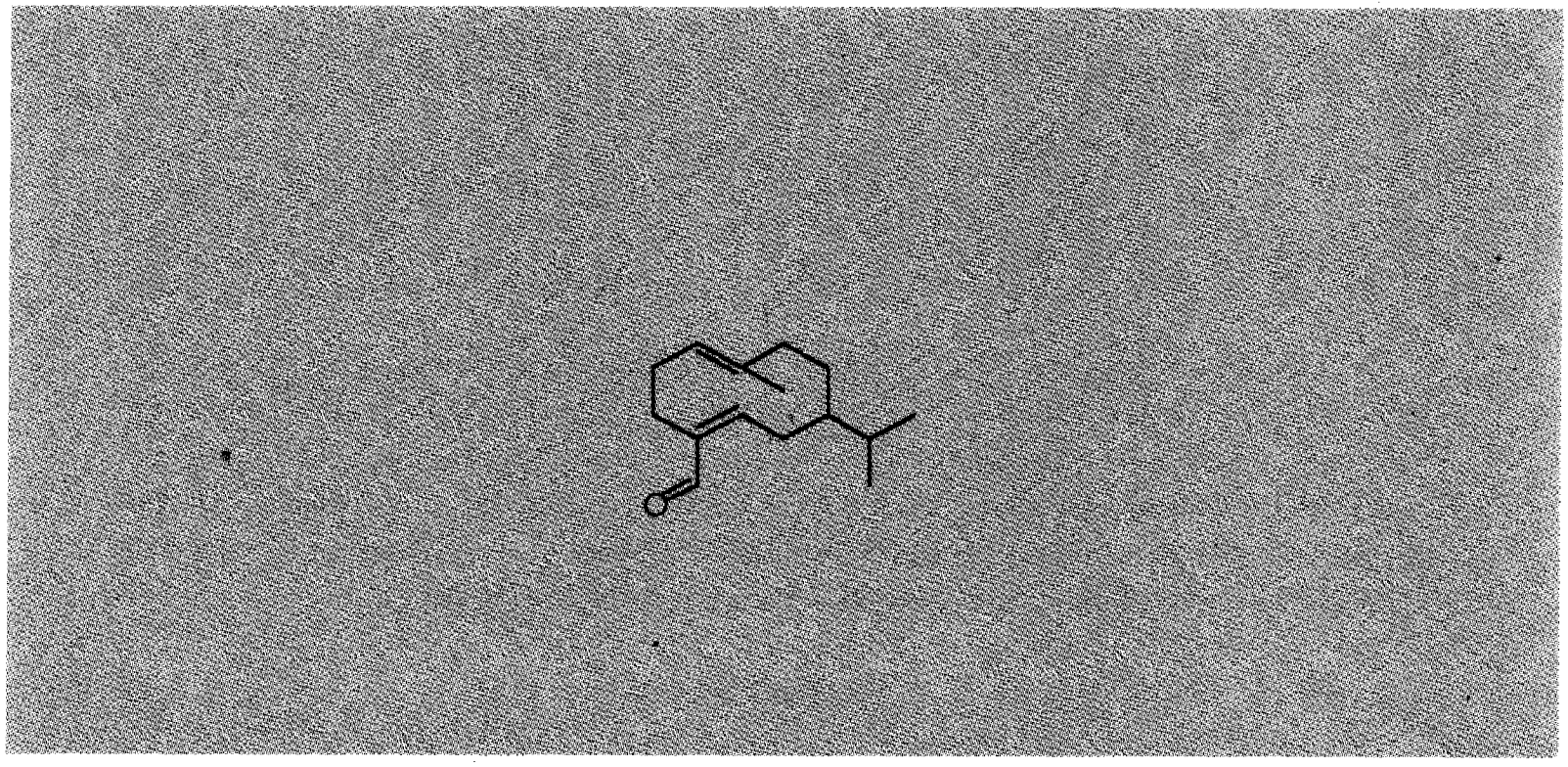
15. All (*E*,*Z*)-germacranes (heliangolides) and (*Z*,*E*)-germacranes (melampolides) possess one or more lactone rings. An exception being helminthogermacrene, see: Winter, R. E. K.; Dorn, F.; Arigoni, D. *J. Org. Chem.* **1980**, *45*, 4786.
16. Hendrickson, J. B. *Tetrahedron* **1959**, *7*, 82.
17. MacSweeney, D. F.; Ramage, R.; Sattar, A. *Tetrahedron Lett.* **1970**, 557.
18. Brüning, R.; Wagner, H. *Phytochemistry* **1978**, *17*, 1821.
19. (a) Southwell, I. A. *Aust. J. Chem.* **1978**, *31*, 2527. (b) Roberts, J. S. The sesquiterpenes. In *Chemistry of Terpenes and terpenoids*; Newman, A. A. Ed.; Academic Press: London, 1972; pp 88–146.
20. (a) Manitto, P. *Biosynthesis of Natural Products*; John Wiley & Sons: New York, 1981; Chapter 5. (b) Teisseire, P. J. *Chemistry of Fragrant Substances*; VCH: New York, 1994; pp 216–218.
21. Southwell, I. A.; Tucker, D. J. *Phytochemistry* **1993**, *33*, 857.
22. Valle, M. G.; Appendino, G.; Nano, G. M.; Picci, V. *Phytochemistry* **1987**, *26*, 253 (see chapter 4).
23. Gansser, D.; Pollak, F. C.; Berger, R. G. *J. Nat. Prod.* **1995**, *58*, 1790.
24. Only the interconversion of the conformations by rotation of the double bonds is considered.
25. Piet, D. P.; Schrijvers, R.; Franssen, M. C. R.; de Groot, A. *Tetrahedron* **1995**, *51*, 6303.
26. (a) Piet, D. P.; Franssen, M. C. R.; de Groot, A. *Tetrahedron* **1994**, *50*, 3169. (b) Piet, D. P.; Franssen, M. C. R.; de Groot, A. *Tetrahedron* **1996**, *52*, 11273.
27. Huffman, J. W.; Hillenbrand, G. F. *Tetrahedron* **1981**, *37*, *Supplement No.1*, 269.
28. Marshall J. A. *Synthesis* **1971**, 229.
29. Agami, C.; Meynier, F.; Puchot, C.; Guilhem, J.; Pascard, C. *Tetrahedron* **1984**, *40*, 1031.
30. Agami, C.; Kadouri-Puchot, C.; Le Guen, V. *Tetrahedron: Asymm.* **1993**, *4*, 641.
31. Li, Y.; Chen, X.; Shao, S.; Li, T. *Ind. J. Chem., Sect. B* **1993**, *32*, 356.
32. Marshall, J. A.; Ruth, J. A. *J. Org. Chem.* **1974**, *39*, 1971.
33. Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.
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 (dd, *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), 27.27 (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

(36), 59 (48).

35. Bundy, G. L. *Synthesis of Cyclodecadienes from Decalylborane Derivatives*; Ph.D. Thesis, Northwestern University, Evanston, Illinois, 1968.
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.
37. (a) Orrū, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199. (b) Orrū, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374. (c) Orrū, R. V. A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4233.
38. Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4240.
39. Paddon-Row, M. N.; Jordan, K. D. In *Modern Models of Bonding and Delocalization*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers: New York, 1988, Chapter 3 and references cited therein.
40. Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, *15*, 245.
41. Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
42. Steglich, W.; Höfle, G. *Angew. Chem., Inter. Ed. Engl.* **1969**, *8*, 981.
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 BH_3-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.
45. Southwell, I. A. *Phytochemistry* **1970**, *9*, 2243.
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.
48. Gleiter, R.; Schäfer, W. *Acc. Chem. Res.* **1990**, *23*, 369.
49. (a) White, D. N. J.; Bovill, M. J. *Tetrahedron Lett.* **1975**, 2239. (b) Neykov, G. D.; Ivanov, P. M.; Orahovats, A. S. *J. Mol. Struct.* **1987**, *153*, 147.
50. Heathcock, C. H.; Badger, R. A.; Starkey, R. A. *J. Org. Chem.* **1972**, *37*, 231.
51. Hardt, I. H.; Rieck, A.; Fricke, C.; König, W. A. *Flavour Fragrance J.* **1995**, *10*, 165.
52. A simple double bond isomerization from (+)-hedycaryol (**1**) to neohedycaryol (**4**) can occur with negligible steric complaint.[16]
53. For a general description of the experimental procedures employed in this research, see § 3.3.

54. Lacoume, B.; Zalkow, L. H. *Tetrahedron Lett.* **1966,** 5881.
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..

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

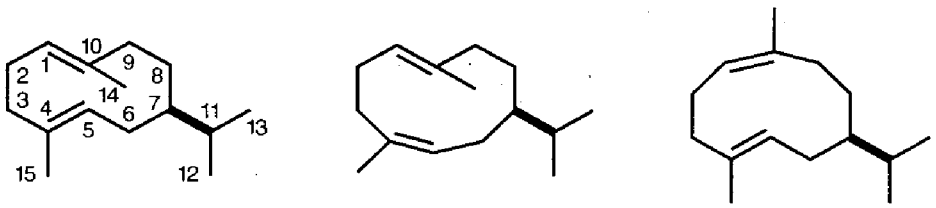


Abstract: enolate-assisted 1,4-fragmentation reactions have been used as the key step in the synthesis of (*E*,*E*)-germacrane sesquiterpenes, starting from racemic Wieland-Miescher ketone derivative **18**. Compound **14** was fragmented using KHMDS in THF, but the reaction was attended by a retro-aldol 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 *E* to *Z* isomerization of the conjugated double bond. With sodium *tert*-amylate as base, however, the (*E*,*E*)-cyclodecadiene **15** was isolated in good yield. This product was converted into germacrene B (**39**). Compound **46**, possessing a protected 2-hydroxy-isopropyl group, gave after fragmentation and reduction 15-hydroxyhedycaryol (**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*)-cyclodecadiene **36** afforded trans-fused guaianes upon acid-induced cyclization.

6.1 Introduction*

As already mentioned in chapter 1, germacranes[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 germacranes possesses the (*E*,*E*)-cyclodeca-1(10),4-diene ring structure **1**[4] as main structural characteristic (Scheme 6.1), but (*E*,*Z*)-germacranes (heliangolides) and (*Z*,*E*)-germacranes (melampolides) depicted by the structures **2** and **3**, respectively, are also frequently found in nature.[2]

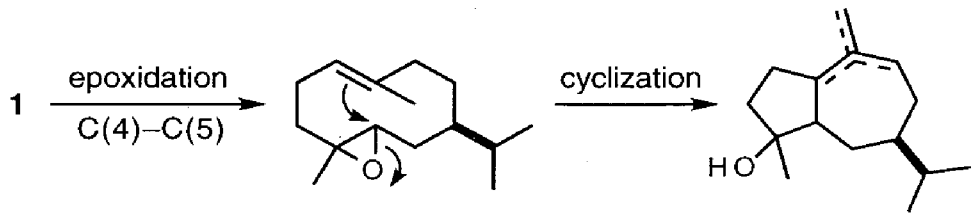
Scheme 6.1



1 **2** **3**

Guaiane sesquiterpenes (**5**), containing a hydroazulene skeleton, are formed from germacranes (**1**) by cyclization of the corresponding C(4)–C(5) epoxides (**4**, 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.

Scheme 6.2



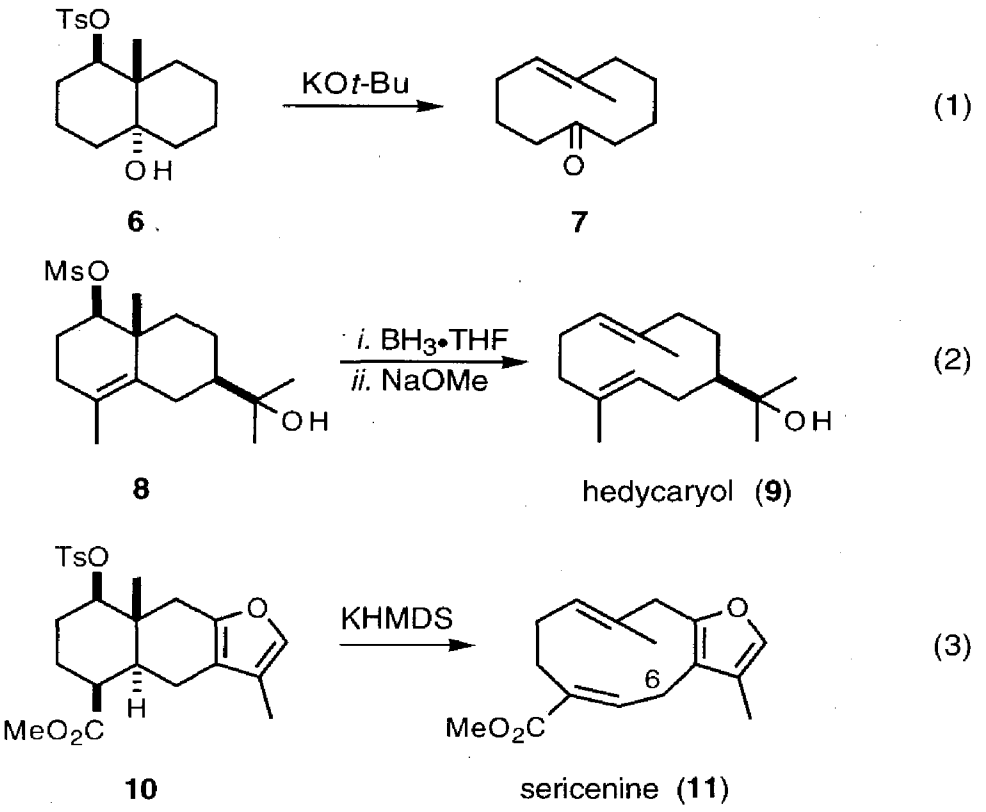
4 **5**

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 perhydronaphthalene-1,3-diol monosulfonate esters (**6**) with strong bases (eq 1, Scheme 6.3).[7] This method has been used several times in sesquiterpene synthesis,[8] 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 germacranes, its application in germacrane synthesis is limited.

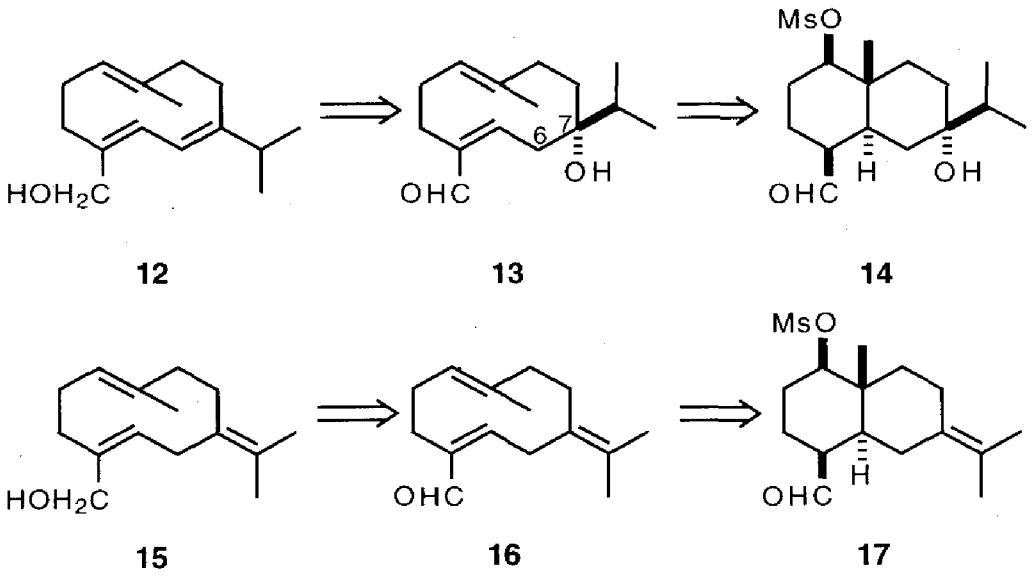
The boronate fragmentation reaction introduced by Marshall circumvents this problem.[9] Both double bonds are formed regio- and stereospecifically and the method has been applied in the synthesis of hedycaryol (**9**)[10] (Scheme 6.3 and chapter 3) and its C(5)–C(6) and C(9)–C(10) double bond isomers allohedycaryol (chapter 4) and neohedycaryol (chapter 5), respectively.[11] Because most functional groups are not compatible with the use of BH_3, and the regio- and stereoselectivity of the BH_3 addition to tetrasubstituted double bonds is usually moderate,[12] 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.,[13] involves an enolate-assisted fragmentation via α deprotonation of an ester function.[14] The synthesis of the heliangolide sericenine (**11**) from ester **10** is the only known example of this approach in germacrane chemistry (eq 3, Scheme 6.3).[15] 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 guaianes 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



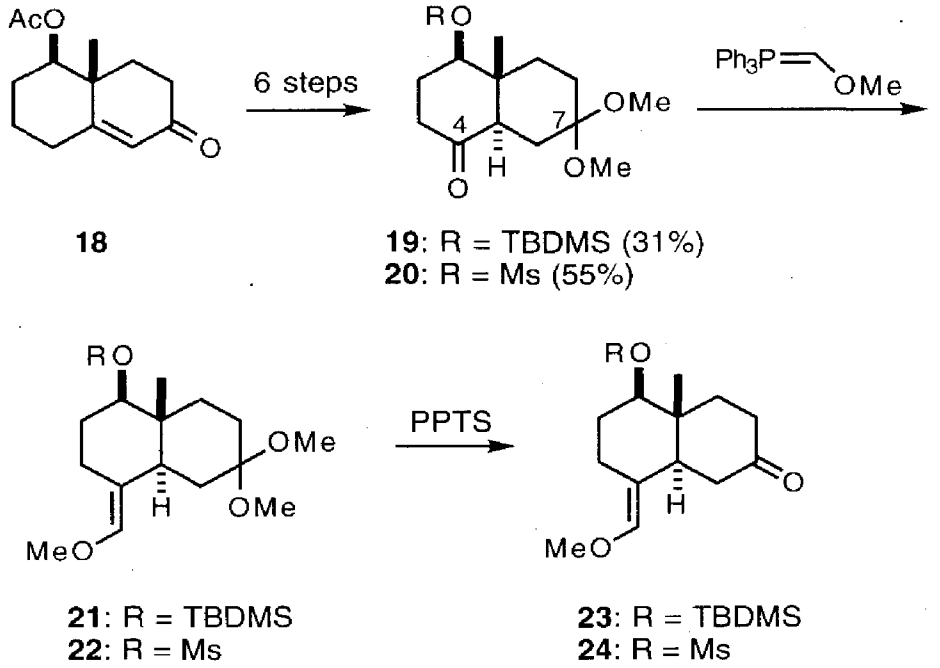
We expected that fragmentation of **14** would lead to a selective formation of the (*E*,*E*)-germacrane derivative **13** without isomerization (*E* → Z) of the C(4)–C(5) double bond. In contrast to the fragmentation reaction of **10**, isomerization is not expected because the carbon atom at the 7-position in **13** possesses sp^3 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 sp^2 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 **18**[16] (Scheme 6.5). By modest adaptions of existing procedures,[17] **18** was converted into the known TBDMS ether **19**[18] 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



18

19: R = TBDMS (31%)
20: R = Ms (55%)

21: R = TBDMS
22: R = Ms

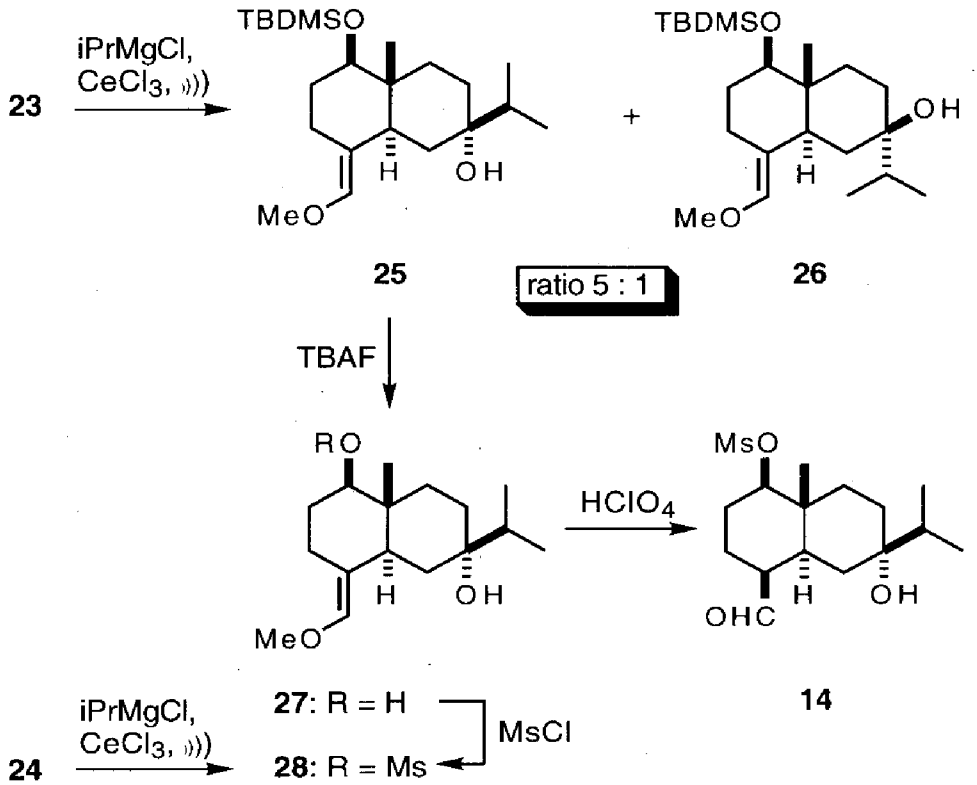
23: R = TBDMS
24: R = Ms

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 chloride[19] 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 KHMDS 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 $CeCl_3$.[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 $CeCl_3$ suspension turned out to be essential.[22]

Scheme 6.6

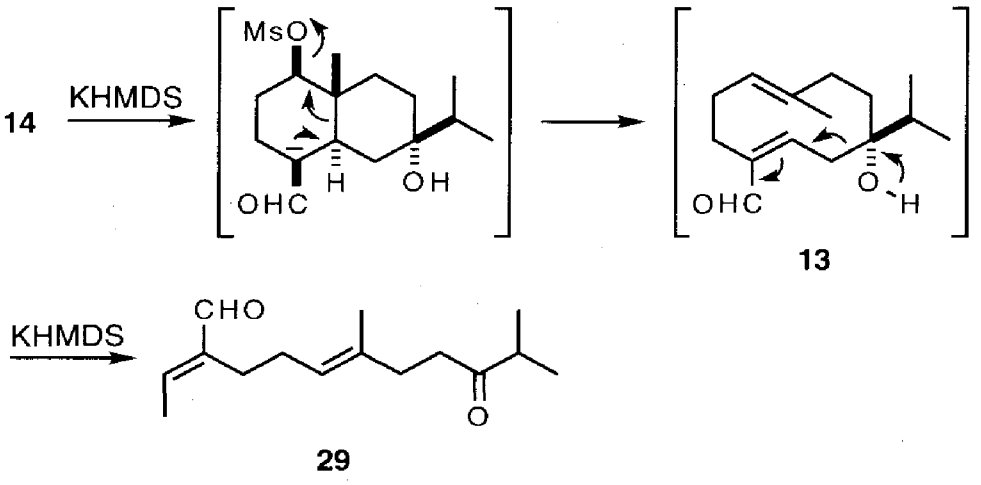


After removal of the TBDMS protecting group in **25** with TBAF in hot DMSO,[23] treatment of the resulting alcohol **27** with MsCl in pyridine afforded the mesylate **28**.[24] Hydrolysis of the masked aldehyde function in **28** with 35% aqueous $HClO_4$ in ether[25] completed the synthesis of **14** 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 KHMDS in THF,[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 ^{1}H NMR spectrum.[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.[28]

Scheme 6.7

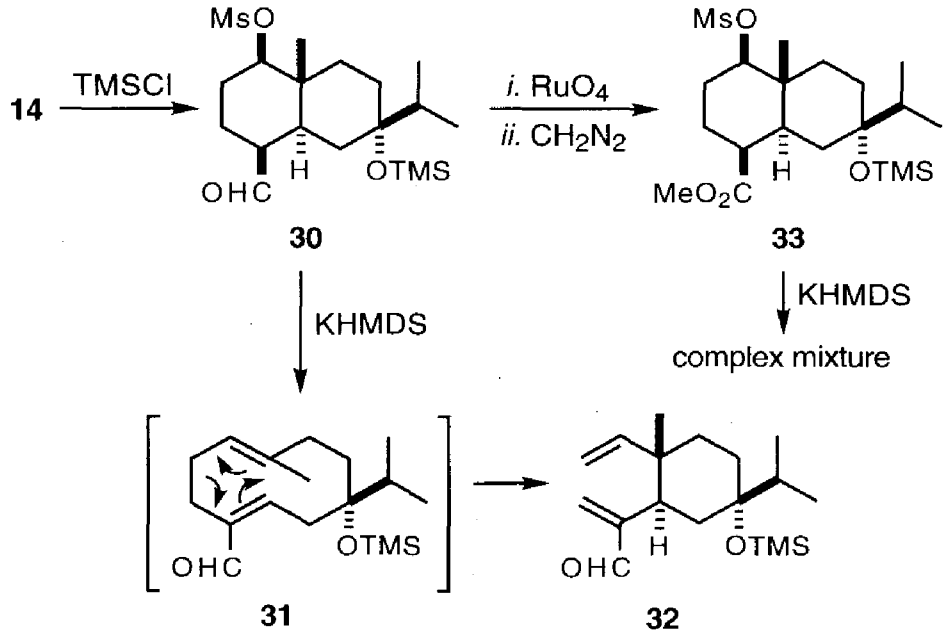


In order to avoid this undesired retro-aldol reaction, the hydroxyl group in **14** was protected as its TMS ether **30**.[29] When **30** was treated with KHMDS in THF, again a fast reaction took place with the rather unstable elemane-like compound **32** as the sole product that could be isolated (Scheme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

It is obvious that the formation of **32** proceeds via a Cope rearrangement of the initially formed intermediate **31**.[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 germacranes, also from natural sources, rather complicated.[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.[32] 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.[33] 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

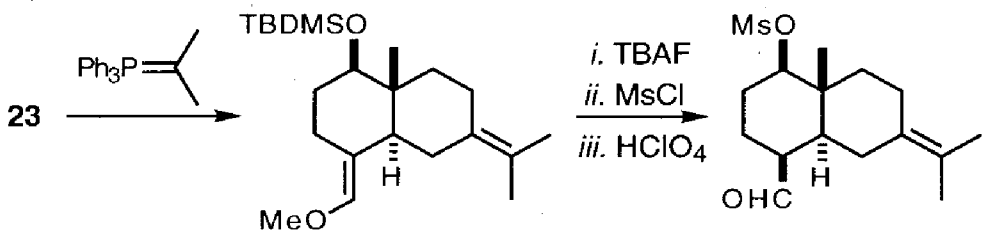


It was known from the literature that an enolate-assisted fragmentation reaction had resulted in an (*E*,*E*)-cyclodeca-1(10),4-diene system with sp^3 hybridization at C(7) and a Me ester instead of an aldehyde function at C(15).[13] Therefore it was hoped that conversion of aldehyde **30** into the 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.[34] Whereas treatment of **30** with PCC in CH_2Cl_2 gave no reaction at all, cleavage of the silyl ether bond and partial decarboxylation were observed with PDC in DMF.[35] Oxidation was finally achieved in moderate yield using the $RuO_4/NaIO_4$ couple,[36] 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 relief 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 (dimethylsulfinyl)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



34 **17**

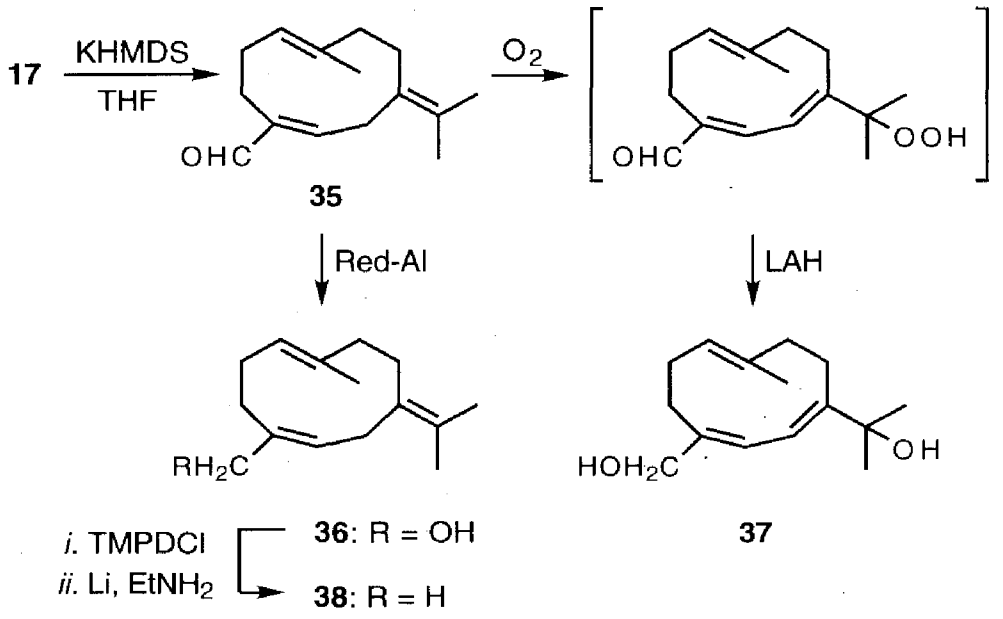
Initially, the fragmentation reaction of **17** was studied in THF with ca one equiv of KHMDS. These reaction conditions led to the formation of a complex product mixture from which only the unstable aldehyde **35** could be isolated in rather poor yield (27%, Scheme 6.10). In a similar fragmentation 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}H NMR spectrum of aldehyde **35** in which a one-proton signal appears at δ 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,[41] reduction of the phosphordiamidate of **36** with Li in $EtNH_2$[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 ^1H 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**[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.[44]

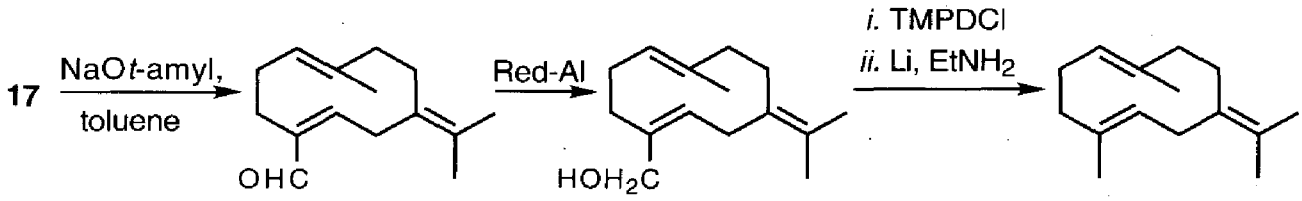
Scheme 6.10



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*-amylate (NaO*t*-amyl) instead of KHMDS. NaO*t*-amyl in benzene or toluene is the most effective base-solvent combination in the fragmentation reactions of 1,4-diol monosulfonate esters[45] and in contrast to hexamethyldisilazane, *tert*-amyl alcohol should not interfere with the reaction. When **17** was treated with one equiv of NaO*t*-amyl in toluene[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 $AgNO_3$ extraction[47] to give **15** in 72% yield, since **36** was not extracted with aqueous $AgNO_3$.[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 $EtNH_2$,[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 hexamethyldisilazane 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.

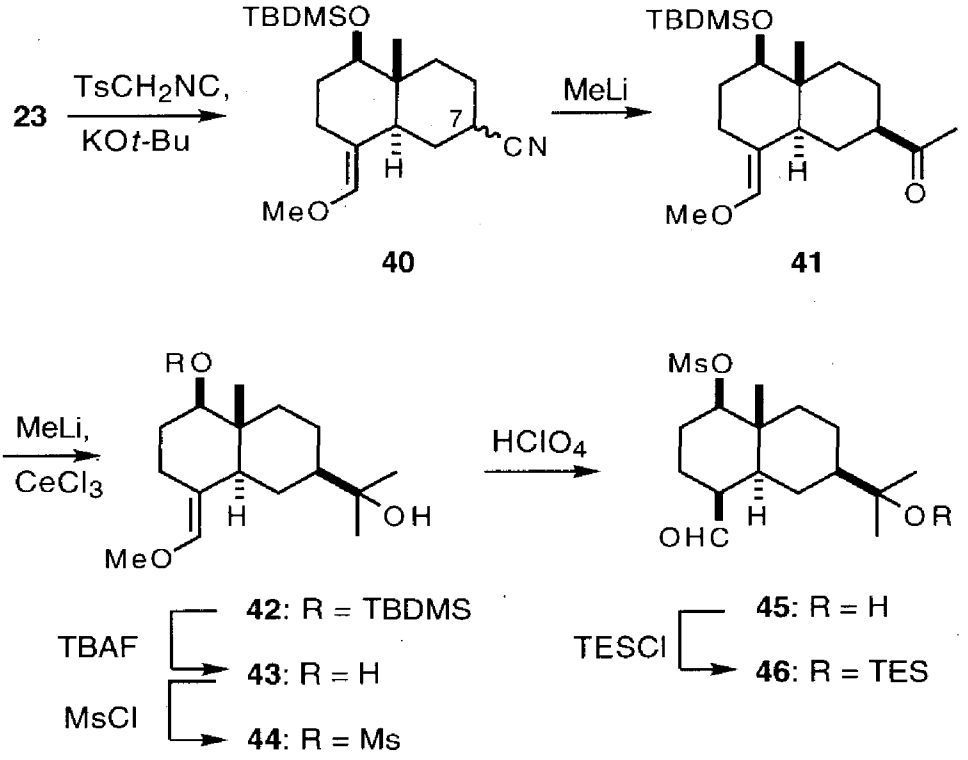
Summarizing the results thusfar, we can state that the enolate-assisted 1,4-fragmentation reaction with NaO*t*-amyl as base is a very useful method for the synthesis of (*E*,*E*)-germacranes with sp^2 hybridization at C(7) as the successful synthesis of germacrene B (**39**) clearly showed. The question 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 subsituents 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-fragmention 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 NaO*t*-amyl as a base, subsequent reduction with Red-Al, and deprotection should then lead to the unnatural germacrane sesquiterpene 15-hydroxyhedycaryol (**48**).

The conversion of the keto group of perhydro-2(3*H*)-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

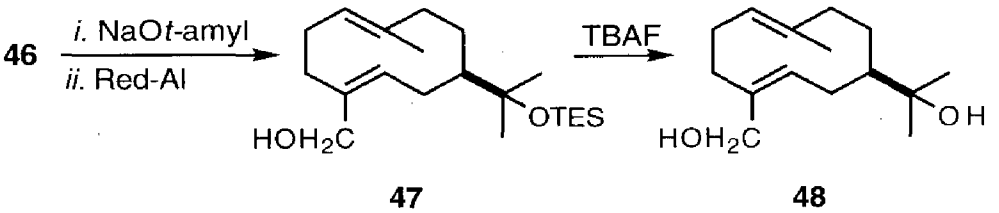
$HClO_4$ in ether afforded aldehyde **45** in excellent yield.
Treatment of **45** with chlorotriethylsilane (TESCl) gave the corresponding TES ether **46** in 56% yield.[60] This protection of the C(11) hydroxyl group was needed to avoid the use of more than 1 equiv of base in the fragmentation step.

Scheme 6.12



The fragmentation reaction of **46** was performed with 1 equiv of NaO*t*-amyl 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 $AgNO_3$ extraction afforded pure 15-hydroxyhedycaryol (**48**) in good yield. Just as for hedycaryol (**9**),[61] the ^1H NMR spectrum of **48** indicates the presence of at least three distinct conformers at room temperature.

Scheme 6.13



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 ^1H 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, $\Delta\nu/J$ = 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]

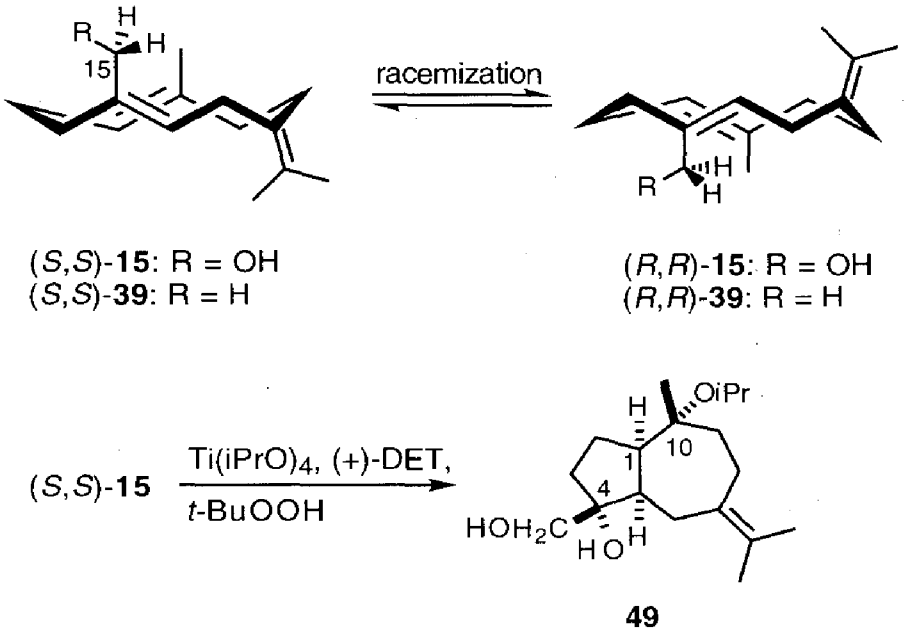
A direct way to establish the chiral stability of **15** involves the asymmetric Sharpless epoxidation,[73] performed as a kinetic resolution. The ee of the recovered starting material can be determined with the aforementioned Eu(hfc)$_3$ method. It is obvious that this ee will depend on the racemization rate. A priori, it was expected that this Sharpless epoxidation would proceed highly diastereoselectively because the π 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°) 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_6D_6. Fortunately, the use of a 1:1:1 mixture of $CDCl_3$, C_6D_6, and C_5D_5N 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.[74b]

Scheme 6.14



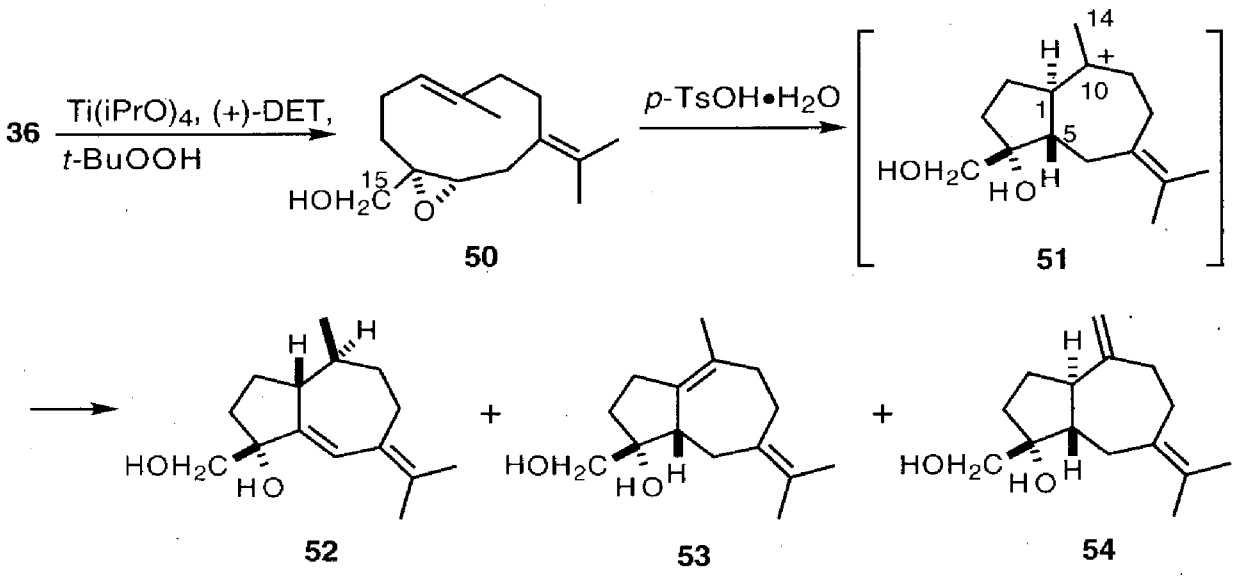
The formation of **49** can simply be explained by epoxide ring opening, transannular cyclization, and incorporation of isopropanol present in the reaction medium. This mechanism is consistent with the findings of Sutherland et al.[62] Because no epimers or elimination products of **49** could be detected, the formation of **49** probably proceeds in a concerted manner. It is possible that in vivo cyclization of germacrene B (**39**) via enzymatic enantioselective epoxidation leads to enantiomerically enriched guaianes.[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 germacrene 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**).[5] The isolation of *trans*-guaianes possessing a cis relationship between C(15) and H-5,[79] 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** ($[\alpha]_D$ –145°).[80] The sharp signals and couplings in the ^{1}H 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 ^{1}H 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 ^{1}H and ^{13}C 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,[81] 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[82] 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.[83] 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.[82b,d]

Purification of the remaining product mixture on $AgNO_3$ impregnated silica gel afforded **53** as main product[84] and a small amount of the exocyclic double bond isomer **54**.[85] 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 $\Delta^{5,6}$-guaianes and pseudoguaianes are also observed in this cyclization reaction.

6.4 Experimental Section[86]

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 P_2O_5 before use. The compounds **18**,[20] **19**,[18b] **38**,[39] and **39**[43] have been characterized before.

(4aα,5α)-(±)-5-Acetoxy-4,4a,5,6,7,8-hexahydro-4a-methyl-2(3*H*)-naphthalenone (18). To a stirred solution of crude (4aα,5α)-(±)-4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3*H*)-naphthalenone (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)[87] in 500 mL of dry pyridine was added dropwise 252 mL of Ac_2O 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,4aα,8aβ)-(±)-Octahydro-7,7-dimethoxy-4a-methyl-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1(2*H*)-naphthalenone (19). To a stirred solution of 87.6 g (398 mmol) of **18** and 250 g NaI in 600 mL of Ac_2O was added dropwise 200 mL of TMSCl over a period of 30 min at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was filtered and concentrated under reduced pressure. The concentrate was carefully mixed with 500 mL of saturated aqueous $NaHCO_3$ and, after addition of 120 g of $Na_2S_2O_3$, stirred at 0 °C 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 $NaHCO_3$ 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 $NaHCO_3$. The mixture was stirred vigorously, and then 1.3 L of 1 M oxone in water was added dropwise at 0 °C. After stirring at 0 °C for 2.5 h, an additional 130 mL of 1 M oxone in water was added dropwise. The reaction mixture was stirred 0 °C 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 CH_2Cl_2. 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 CH_2Cl_2 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 °C and mixed with 250 mL of saturated aqueous $NaHCO_3$. 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 CH_2Cl_2 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 Et_3N, 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 CH_2Cl_2, 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(2*H*)-naphthalenone 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,4aα,8aβ)-(±)-Octahydro-7,7-dimethoxy-4a-methyl-4-[(methylsulfonyl)oxy]-1(2*H*)-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(2*H*)-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 $NaHCO_3$, 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: ^{1}H 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); ^{13}C 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 $C_{14}H_{24}O_6S$ (M^+) 320.1294, found 320.1290.

(4aα,5α,8aβ)-(±)-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: ^{1}H 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); ^{13}C 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),

47.49 (q), 59.45 (q), 79.54 (d), 100.57 (s), 117.54 (s), 139.58 (d); MS *m/z* (relative intensity) 352 (M^+ – 32, 100), 295 (47), 263 (28), 221 (27), 220 (67), 189 (80), 157 (35), 75 (30), 73 (23); HRMS calcd for $C_{21}H_{40}O_4Si$ (M^+) 384.2696, found 384.2699.

(1α,4aβ,8aα)-(±)-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 KHMDS (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); ^{1}H 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); ^{13}C 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 $C_{15}H_{24}O_5S$ (M^+ – 32) 316.1344, found 316.1340. Anal. Calcd for $C_{16}H_{28}O_6S$: C, 55.15; H, 8.10. Found: C, 54.96; H, 8.13.

(4aα,5α,8aβ)-(±)-Octahydro-8-(1-methoxymethylene)-4a-methyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2(3*H*)-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 $NaHCO_3$ 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); ^{1}H 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), 5.44 (br, s 1 H); ^{13}C 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 $C_{19}H_{34}O_3Si$ (M^+) 338.2277, found 338.2274. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.42; H, 10.13. Found: C, 67.53; H, 10.38.

(4aα,5α,8aβ)-(±)-Octahydro-8-(1-methoxymethylene)-4a-methyl-5-[(methylsulfonyl)oxy]-2(3*H*)-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); ^{1}H 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); ^{13}C 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 $C_{14}H_{22}O_5S$ (M^+) 302.1188, found 302.1189. Anal. Calcd for $C_{14}H_{22}O_5S$: C, 55.61; H, 7.33. Found: C, 55.38; H, 7.34.

(2α,4aβ,5β,8aα)- and (2α,4aα,5α,8aβ)-(±)-Decahydro-8-(1-methoxymethylene)-4a-methyl-2-(1-methylethyl)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-naphthalenol (25 and 26). Anhyd $CeCl_3$ (prepared from 3.15 g (8.45 mmol) of $CeCl_3 \cdot 7H_2O$ 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 Et_2O) 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); ^{1}H 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 (dd, *J* = 4.15, 13.5 Hz, 1 H), 2.79 (ddd, *J* = 1.6, 1.6, 13.4 Hz, 1 H), 3.36 (dd, *J* = 4.4, 11.4 Hz, 1 H), 3.54 (s, 3 H), 5.48 (s, 1 H); ^{13}C 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 $C_{22}H_{42}O_3Si$ (M^+) 382.2903, found 382.2900. Anal. Calcd for $C_{22}H_{42}O_3Si$: C, 69.07; H, 11.07. Found: C, 69.03; H, 11.31. **26**: mp 131–133 °C (from pentane); ^{1}H 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); ^{13}C NMR δ –4.77

(q), –3.93 (q), 10.33 (q), 15.93 (q), 16.07 (q), 18.00 (s), 23.79 (t), 25.81 (3 q), 28.84 (d), 31.12 (t), 31.97 (t), 33.45 (t), 34.17 (t), 40.43 (s), 41.61 (d), 59.43 (q), 74.11 (s), 79.99 (d), 117.38 (s), 139.82 (d); MS *m/z* (relative intensity) 382 (M^+, 41), 339 (31), 325 (31), 308 (27), 307 (100), 275 (54), 250 (84), 232 (31), 75 (56), 73 (34), 71 (30), 43 (39); HRMS calcd for $C_{22}H_{42}O_3Si$ (M^+) 382.2903, found 382.2900. Anal. Calcd for $C_{22}H_{42}O_3Si$: C, 69.07; H, 11.07. Found: C, 69.21; H, 11.34.

(1α,4aβ,6β)-(±)-Decahydro-4-(1-methoxymethylene)-8a-methyl-6-(1-methylethyl)-1,6-naphthalenediol (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); ^{1}H NMR δ 0.63 (s, 3 H), 0.93 (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); ^{13}C 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 $C_{16}H_{28}O_3$ (M^+) 268.2038, found 268.2036. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.85; H, 10.73.

(2α,4aβ,5β,8aα)-(±)-Decahydro-8-(1-methoxymethylene)-4a-methyl-2-(1-methylethyl)-5-[(methylsulfonyl)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); ^{1}H 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); ^{13}C 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 $C_{17}H_{28}O_4S$ (M^+ – 18) 328.1708, found 328.1708. Anal. Calcd for $C_{17}H_{30}O_5S$: 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 $CeCl_3$ for 2.5 h as described for **23**. Workup and flash chromatography (2:1 petroleum ether (bp 40–60

°C)/EtOAc) afforded 1.197 g (93%) of pure **28** as the sole product.

(1α,4α,4aα,7β,8aβ)-(±)-Decahydro-7-hydroxy-4a-methyl-7-(1-methylethyl)-4-[(methylsulfonyl)oxy]-1-naphthalenecarboxaldehyde (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 °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_2SO_4, and evaporated. Flash chromatography (1:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.463 g (97%) of **14** as an oil:[89] ^1H NMR δ 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 δ 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 $C_{13}H_{21}O_5S$ (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_4Cl, extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation at rt, the remaining residue (0.057 g) was taken up in 4:1 petroleum ether (bp 40–60 °C)/ether and filtered over a short neutral alumina column to give 0.014 g (20%) of **29**: ^1H NMR δ 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 δ 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.

(1α,4α,4aα,7β,8aβ)-(±)-Decahydro-4a-methyl-7-(1-methylethyl)-7-[(trimethylsilyl)oxy]-4-[(methylsulfonyl)oxy]-1-naphthalenecarboxaldehyde (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 °C. After being stirred at 0 °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: ^{1}H 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); ^{13}C 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 $C_{16}H_{29}O_5SSi$ (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 KHMDS 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] ^{1}H 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* = 10.9, 17.3 Hz, 1 H), 6.01 (br s, 1 H), 6.06 (br s, 1 H), 9.38 (s, 1 H); ^{13}C 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 $C_{15}H_{25}O_2Si$ (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 $HClO_4$, 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 CH_2N_2 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,4aα,7β,8aβ)-(±)-decahydro-4a-methyl-7-(1-methylethyl)-7-[(trimethylsilyl)oxy]-4-[(methylsulfonyl)oxy]-1(2*H*)-naphthalenone: mp 154 °C (from diisopropyl ether); ^{1}H 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); ^{13}C 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 $C_{12}H_{19}O_5S$ (M^+ – 43) 275.0953, found 275.0949. Anal. Calcd for $C_{15}H_{26}O_5S$: C, 56.58; H, 8.23. Found: C, 56.31; H, 8.34.

$RuO_2/NaIO_4$ oxidation. To a well stirred solution of 0.134 g (0.33 mmol) of **30** in a mixture of 3 mL of CH_3CN, 3 mL of CCl_4, and 5 mL of water was added 0.280 g (1.31 mmol) of $NaIO_4$ and 0.011 g of RuO_2 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 CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The black residue was dissolved in 5 mL of ether, and excess CH_2N_2 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); ^{13}C 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 $C_{17}H_{31}O_6SSi$ (M^+ – 43) 391.1611, found 391.1606.

(1α,4aβ,8aα)-(±)-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 (dimethylsulfinyl)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.[91] 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); ^{13}C 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 $C_{22}H_{40}O_2Si$ (M^+) 364.2798, found 364.2793.

(1α,4α,4aα,8aβ)-(±)-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 $C_{17}H_{28}O_4S$ (M^+) 328.1708, found 328.1705. Anal. Calcd for $C_{17}H_{28}O_4S$: 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 $C_{16}H_{26}O_4S$ (M^+) 314.1552, found 314.1547. Anal. Calcd for $C_{16}H_{26}O_4S$: C, 61.11; H, 8.33. Found: C, 61.24; H, 8.61.

(*E,E*)-7-Methyl-4-(1-methylethylidene)-1,7-cyclodecadienecarboxaldehyde (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),

33.51 (t), 36.40 (t), 37.20 (t), 123.61 (d), 128.50 (s), 128.99 (s), 135.70 (s), 140.36 (s), 155.09 (d), 195.94 (d); MS *m/z* (relative intensity) 218 (M^+, 100), 190 (9), 175 (68), 162 (57), 136 (71), 135 (52), 122 (54), 121 (82), 107 (91), 105 (48), 93 (68), 91 (65), 79 (59), 67 (46); calcd for $C_{15}H_{22}O$ (M^+) 218.1671, found 218.1678.

(*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**: ^{1}H 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); ^{13}C 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 $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1772.

(*E,E*)-7-Methyl-4-(1-methylethylidene)-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**: ^{1}H NMR (C_6D_6) 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); ^{13}C NMR (C_6D_6) 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 $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1827.

(*E,Z*)-1,5-Dimethyl-8-(1-methylethylidene)-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 $EtNH_2$ at 0 °C. Stirring was continued at 0 °C for 25 min, and excess aqueous NH_4Cl 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)cyclodecene and 0.030 g (42%) of **38**. *Z*-1,7-Dimethyl-4-(1-methylethylidene)cyclodecene: ^{1}H 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); ^{13}C 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 $C_{15}H_{26}$ (M^+) 206.2035, found 206.2034. **38**: ^{1}H 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 (ddd, *J* = 1.2, 8.2, 8.2 Hz, 1 H); ^{13}C 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 $C_{15}H_{24}$ (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 NaO*t*-amyl (1.55 M in benzene)[92] 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**:[93] ^{1}H NMR (C_6D_6) 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); ^{13}C NMR (C_6D_6)[94] 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 $C_{15}H_{22}O$ (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 NaO*t*-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 NH_4Cl. The reaction mixture was allowed to come to rt and, after addition of Na_2SO_4, 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 $AgNO_3$. 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 NH_3, 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**: ^{1}H NMR (C_6D_6)[95] 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); ^{13}C NMR (C_6D_6)[95] 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 $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1825.

Germacrene B (39). The germacrane alcohol **15** (0.047 g, 0.21 mmol) was treated with TMPDCl and then with Li in $EtNH_2$ 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,4aα,5α,8aβ)- and (2β,4aα,5α,8aβ)-(±)-Decahydro-8-(1-methoxymethylene)-4a-methyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-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 KO*t*-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: ^{1}H 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 $C_{20}H_{35}NO_2Si$ (M^+) 349.2437, found 349.2438.

(2α,4aα,5α,8aβ)-(±)-1-[Decahydro-8-(1-methoxymethylene)-4a-methyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-naphthalenyl]ethanone (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: ^{1}H 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 (dddd, 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 (dd, J = 4.6, 9.8 Hz, 1 H), 3.53 (s, 3 H), 5.54 (br s, 1 H); ^{13}C 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 $C_{21}H_{38}O_3Si$ (M^+) 366.2590, found 366.2584.

(2α,4aα,5α,8aβ)-(±)-Decahydro-8-(1-methoxymethylene)-α,α,4a-trimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-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; ^{1}H 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 (dd, J = 4.2, 11.1 Hz, 1 H), 3.52 (s, 3 H), 5.51 (s, 1 H); ^{13}C 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 $C_{22}H_{42}O_3Si$ (M^+) 382.2903, found 382.2904. Anal. Calcd for $C_{22}H_{42}O_3Si$: C, 69.07; H, 11.07. Found: C, 68.84; H, 11.32.

(2α,4aα,5α,8aβ)-(±)-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); ^{1}H 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); ^{13}C 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 calcd for $C_{16}H_{28}O_3$ (M^+) 268.2038, found 268.2037. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.53; H, 10.71.

(2α,4aα,5α,8aβ)-(±)-Decahydro-8-(1-methoxymethylene)-α,α,4a-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**: ^{1}H 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), 3.50 (s, 3 H), 4.35 (dd, *J* = 4.9, 11.1 Hz, 1 H), 5.53 (br s, 1 H); ^{13}C 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 calcd for $C_{17}H_{30}O_5S$ (M^+) 346.1814, found 346.1813.

(1α,4α,4aα,7β,8aβ)-(±)-Decahydro-7-(1-hydroxy-1-methylethyl)-4a-methyl-4-[(methylsulfonyl)oxy]-1-naphthalenecarboxaldehyde (45). The mesylate **44** (0.131 g, 0.38 mmol) was treated with 35% aqueous $HClO_4$ as described for **28**. Workup and flash chromatography (2:3 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.110 g (87%) of **45**: ^{1}H 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); ^{13}C 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 calcd for $C_{15}H_{22}O$ (M^+ – 114) 218.1671, found 218.1667.

(1α,4α,4aα,7β,8aβ)-(±)-Decahydro-7-[1-[(triethylsilyl)oxy]-1-methylethyl]-4a-methyl-4-[(methylsulfonyl)oxy]-1-naphthalenecarboxaldehyde (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,4aβ,6α,8aα)-(±) Decahydro-4-[1-[(triethylsilyl)oxy]methylene]-6-[1-[(triethylsilyl)-oxy]-1-methylethyl]-1-naphthalenol methanesulfonate: ^{1}H 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); ^{13}C 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 calcd for $C_{28}H_{56}O_5SSi_2$ (M^+) 560.3387, found 560.3389. Further elution afforded 0.322 g (56%) of **46**: mp 105 °C (from diisopropyl ether); ^{1}H 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 (ddd, *J* = 0.8, 4.8, 4.8 Hz, 1 H), 2.37 (ddd, *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); ^{13}C 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 calcd for $C_{21}H_{39}O_5SSi$ (M^+ – 15) 431.2288, found 431.2291. Anal. Calcd for $C_{22}H_{42}O_5SSi$: 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-cyclodecadieneme-thanol (47). The mesylate **46** (0.112 g, 0.25 mmol) was treated with NaO*t*-amyl and Red-Al under oxygen-free conditions as described for **17**. Workup afforded 0.086 g (97%) of almost pure **47**: ^{1}H NMR (C_6D_6, major peaks)[96] 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 calcd for $C_{19}H_{33}OSi$ (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 Na_2SO_4, 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 $AgNO_3$. The combined aqueous layers were washed with *tert*-butyl methyl ether and cooled to 0 °C. After addition of 10 mL of 25% aqueous NH_3, the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were washed with brine, dried on Na_2SO_4, and evaporated to afford 0.017 g (94%) of **48**: ^{1}H NMR (C_6D_6, major peaks)[96] 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 $C_{15}H_{24}O$ (M^+ – 18) 220.1827, found 220.1823.

[1*R*-(1β,3aβ,4β,8aβ)]-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 CH_2Cl_2 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 CH_2Cl_2 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 CH_2Cl_2. 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 $AgNO_3$. The combined aqueous layers were washed with *tert*-butyl methyl ether and cooled to 0 °C. After addition of 15 mL of 25% aqueous NH_3, 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 $AgNO_3$ 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**: $[\alpha]_D$ –52.3° (*c* 0.38), 92% ee;[76] ^1H NMR (1:1:1 $CDCl_3/C_6D_6/C_5D_5N$) 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 ddd, *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); ^{13}C NMR ($CDCl_3$) 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 $C_{18}H_{32}O_3$ (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 $AgNO_3$ extraction was omitted. Flash

chromatography afforded 0.004 g (6%) of **15** and 0.029 g (36%) of **49**: $[\alpha]_D$ –35.5° (*c* 0.69), 56% ee.

(1*R* ,2*S*)-7-Methyl-4-(1-methylethylidene)-(1,2-*b*)-oxiranyl-7-cyclodecenemethanol 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 °C and worked up as described. Flash chromatography (2:1 petroleum ether (bp 40–60 °C)/*tert*-butyl methyl ether) afforded 0.067 g (52%) of **50**: $[\alpha]_D$ –145° (*c* 0.70);[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_2Cl_2 at rt was added 0.01 g (0.05 mmol) of *p*-TsOH•H_2O dissolved in 1.5 mL of dry CH_2Cl_2. After 10 min, water was added and the mixture was extracted with CH_2Cl_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**.[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° (*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**:[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.
2. Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 1, Mono- and Sesquiterpenoids.
3. Banthorpe, D. V. In *Natural Products: Their Chemistry and Biological Significance;* Longman Scientific & Technical: Harlow, 1994; Chapter 5.
4. The numbering system as given in structure **1** will be followed throughout the text of this chapter.
5. For a review, see: Fischer, N. H. Sesquiterpene Lactones: Biogenesis and Biomimetic Transformations. In *Recent Advances in Phytochemistry, Vol. 24: Biochemistry of the Mevalonic Acid Pathway to Terpenoids;* Plenum Press: New York, 1990; Chapter 4.
6. (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis;* VCH: Weinheim, 1996; Chapter 13 and 21. (b) Chapter 2 of this thesis.
7. For a review of the Wharton fragmentation, see: Caine, D. *Org. Prep. Proced. Int.* **1988**, *20*, 1.
8. (a) González, A. G.; Galindo, A.; Mansilla, H.; Gutiérrez, A.; Palenzuela, J. A. *J. Org. Chem.* **1985**, *50*, 5856. (b) Cauwberghs, S.; De Clercq, P. J. *Tetrahedron Lett.* **1988**, *29*, 6501.
9. Marshall, J. A.; Bundy, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 4291.
10. (a) Wharton, P. S.; Sundin, C. E.; Johnson, D. W.; Kluender, H. C. *J. Org. Chem.* **1972**, *37*, 34. (b) Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1994**, *50*, 4755.
11. (a) Zhabinskii, V. A.; Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1996**, *61*, 4022. (b) Minnaard, A. J.; Stork, G. A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1997**, in press.
12. Marshall J. A. *Synthesis* **1971**, 229.

13. Brown, J. M.; Cresp, T. M.; Mander, L. N. *J. Org. Chem.* **1977**, *42*, 3984.
14. The fragmentation reaction induced by α 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.
15. Honan, M. C.; Balasuryia, A.; Cresp, T. M. *J. Org. Chem.* **1985**, *50*, 4326.
16. Wijnberg, J. B. P. A.; Vader, J.; de Groot, A. *J. Org. Chem.* **1983**, *48*, 4380 and references cited therein.
17. Kim, M.; Kawada, K.; Watt, D. S. *Synth. Commun.* **1989**, *19*, 2017.
18. The TBDMS ether **19** has been used a number of times in synthesis, see: (a) Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941. (b) Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585. (c) Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274. (d) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem.* **1995**, *107*, 2017.
19. For an overview of the use of this reagent see: Anderson, C. L.; Soderquist, J. A.; Kabalka, G. W. *Tetrahedron Lett.* **1992**, *33*, 6915.
20. Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
21. (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (b) Denmark, S. E.; Edwards, J. P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 569.
22. Greeves, N.; Lyford, L. *Tetrahedron Lett.* **1992**, *33*, 4759.
23. Orrū, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374.
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 ^1H 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.
25. Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150.
26. (a) Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabayashi, T.; Hayase, Y. *J. Am. Chem. Soc.* **1967**, *89*, 1483. ^1H NMR studies on a system similar to **14** revealed that an axially oriented aldehyde gives rize to a singlet whereas an equatorially

oriented aldehyde appears as a doublet (J = 3.9 Hz), see: (b) García, B.; Skaltsa, H.; Navarro, F. I.; Pedro, J. R.; Lazari, D. *Phytochemistry* **1996**, *41*, 1113.

27. Herz, W.; Kalyanaraman, P. S. *J. Org. Chem.* **1975**, *40*, 3486.
28. For a related example of this reaction see: Walborsky, H. M.; Reddy, S. M. *J. Org. Chem.* **1988**, *53*, 4851.
29. The stereochemistry at C(4) in **30** could be established unambiguously by reduction of its aldehyde function with $NaBH_4$ to the corresponding alcohol: ^{1}H NMR δ 0.10 (s, 9 H), 0.78 (s, 3 H), 0.88 (d, J = 6.8 Hz, 6 H), 1.40–1.97 (m, 14 H), 2.98 (s, 3 H), 3.56 (br d, J = 6.8 Hz, 2 H), 4.31 (dd, J = 7.1, 9.2 Hz, 1 H); ^{13}C NMR δ 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 m/z (relative intensity) 363 (M^+ – 43, 100), 181 (11), 131 (11), 119 (11), 73 (11), 69 (22); HRMS calcd for $C_{16}H_{31}O_5SSi$ (M^+ – 43) 363.1662, found 363.1655. NOE-difference experiments on this alcohol showed a strong NOE between the angular Me group and the carbinol 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.
31. Reichardt, P. B.; Anderson, B. J.; Clausen, T. P.; Hoskins, L. C. *Can. J. Chem.* **1989**, *67*, 1174.
32. Takeda, K. *Tetrahedron* **1974**, *30*, 1525.
33. (a) Bohlmann, F.; Zdero, C. *Phytochemistry* **1979**, *18*, 95. (b) Appendino, G.; Özen, H. C. *Gazz. Chim. Ital.* **1993**, *123*, 93.
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.
35. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
36. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
37. (a) Allen, F. H.; Rogers, D. *J. Chem. Soc., Chem. Comm.* **1967**, 588. (b) Allen, F. H.; Rogers, D. *J. Chem. Soc.* B **1971**, 257.
38. (a) Gersmann, H. R.; Bickel, A. F. *J. Chem. Soc.* B **1971**, 2230. For an example of the autoxidation of a dienolate see: (b) Wydra, R.; Paryzek, Z. *Pol. J. Chem.* **1984**, *58*, 705.
39. Itoh, A.; Nozaki, H.; Yamamoto, H. *Tetrahedron Lett.* **1978**, 2903.
40. Corey, E. J.; Achiwa, K. *J. Org. Chem.* **1969**, *34*, 3667.

41. This complication has been noted before in germacrane chemistry, see: Matsuo, A.; Nozaki, H.; Kubota, N.; Uto, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 203.
42. (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (b) Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668.
43. The hydrogenation of the isolated C(1)–C(10) double bond with Li in $EtNH_2$ was rather unexpected, all the more so because Li/NH_3 reduction of 8-acetoxy-germacrene 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. 1* **1975**, 2326.
44. Lange, G. L.; Lee, M. *Magn. Reson. Chem.* **1984**, *106*, 723.
45. (a) Reference 18a. (b) Bastiaansen, P. M. F. M.; Wijnberg, J. P. B. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4240.
46. The use of more than one equiv of NaO*t*-amyl also led to $E \rightarrow Z$ isomerization of the conjugated C(4)–C(5) double bond.
47. Southwell, I. A. *Phytochemistry* **1970**, *9*, 2243.
48. Cyclic (*E*)-olefins complexate stronger with silver than cyclic (*Z*)-olefins, see: van Beek, T. A.; Subrtova, D. *Phytochem. Anal.* **1995**, *6*, 1.
49. Germacrene 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.
51. Marshall, J. A.; Flynn, K. E. *J. Am. Chem. Soc.* **1984**, *106*, 723.
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.
53. Brown, E. D.; Solomon, M. D.; Sutherland, J. K.; Torre, A. *J. Chem. Soc., Chem. Comm.* **1967**, 111.
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**.
55. Kodama, M.; Yokoo, S.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1979**, 1687.
56. The majority of (*E,E*)-germacranes found in nature possesses one C(7) side chain. See reference 2.
57. Kesselmans, R. P. W.; Wijnberg, J. B. P. A.; Minnaard, A. J.; Walinga, R. E.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 7237 and references cited therein.

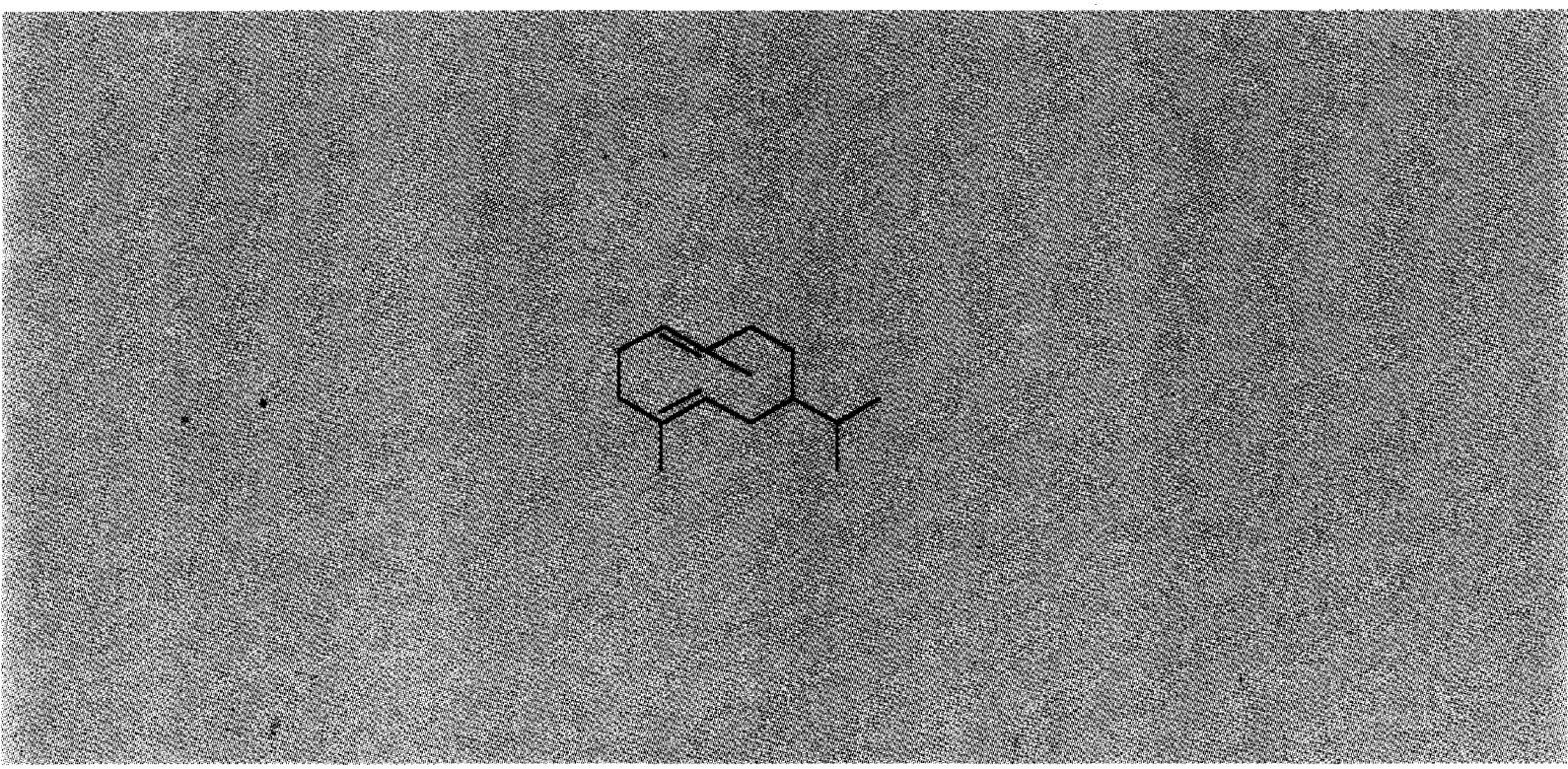
58. Marshall, J. A.; Pike, M. T.; Carroll, R. D. *J. Org. Chem.* **1966**, *31*, 2933.
59. Oldenziel, O. H.; van Leusen, D.; van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.
60. This reaction also gave a by-product with a silyl enol ether function at C(4).
61. (a) Wharton, P. S.; Poon, Y. C.; Kluender, H. C. *J. Org. Chem.* **1973**, *38*, 735. (b) Minnaard, A. J. unpublished results.
62. (a) Allen, F. H.; Brown, E. D.; Rogers, D.; Sutherland, J. K. *J. Chem. Soc., Chem. 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**, 2332. (e) Sam, T. W.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans.* 1 **1975**, 2336.
63. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994; pp 1166-1176.
64. During the rotation of a double bond the vinylic hydrogen, not the Me group, passes through the ring.
65. Watson, W. H.; Kashyap, R. P. *J. Org. Chem.* **1986**, *51*, 2521.
66. Fransen, H. R.; Dormans, G. J. M.; Buck, H. M. *Tetrahedron* **1983**, *39*, 2981.
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.
68. Shirahama, H.; Osawa, E.; Matsumoto, T. *Tetrahedron Lett.* **1979**, 2245.
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. -J. *Tetrahedron Lett.* **1978**, 945.
70. Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089.
71. (+)-Eu(hfc)$_3$ stands for tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III).
72. Siever, R. E.; Kime, K. A. *Aldrichimica Acta* **1977**, *10*, 54. These ^{1}H NMR experiments using (+)-Eu(hfc)$_3$ were also carried out on the (*E,Z*)-isomer **36**. The carbinol 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*)-cycloalkenes, see: (a) Marshall, J. A.; Audia, V. H. *J. Org. Chem.* **1987**, *52*, 1106. (b) Marshall, J. A.; Audia, V. H.; Jenson, T. M.; Guida, W. C. *Tetrahedron* **1986**, *42*, 1703 and references cited therein.
74. (a) Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. *Org. Synth.* **1985**, *63*, 66. (b) Johnson, R. A.; Sharpless, K. B. in *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH Publishers: New York, 1993; Chapter 4.
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 H_2 as carrier gas. Peaks were partly resolved and integrated manually.

77. See § 7.2.
78. Kuroyanagi, M.; Ueno, A.; Koyoma, K.; Natori, S. *Chem. Pharm. Bull.* **1990**, *38*, 55.
79. (a) Bohlmann, F.; Borthakur, N.; Jakupovic, J.; Pickard, J. *Phytochemistry* **1982**, *21*, 1357. (b) Barrero, A. F.; Sánchez, J. F.; Molina, J.; Barrón, A.; Del Mar Salas, M. *Phytochemistry* **1990**, *29*, 3575.
80. The ee of **50** could not be established due to its lability on GC.
81. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Plenum Press: New York, 1990; part A, p 314.
82. (a) Bohlmann, F.; Jacupovic, J. *Phytochemistry* **1979**, *18*, 131. (b) Yu, S.; Fang, N.; Mabry, T. J.; Abboud, K. A.; Simonsen, S. H. *Phytochemistry* **1988**, *27*, 2887. (c) Zdero, C.; Bohlmann, F.; King, R. M. *Phytochemistry* **1990**, *29*, 3201. (d) Gao, F.; Wang, H.; Mabry, T. J. *Phytochemistry* **1990**, *29*, 1601 and references cited therein.
83. (a) González, A. G.; Galindo, A.; Mansilla, H. *Heterocycles* **1989**, *28*, 529. (b) Manitto, P. *Biosynthesis of Natural Products*; John Wiley & Sons: New York, 1981; p 248.
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 (4aα,5α)-(±)-4,4a,5,6,7,-8-hexahydro-5-hydroxy-4a-methyl-2(3*H*)-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 ($NaBH_4$, 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(2*H*)-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 NaO*t*-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 coalescenced.
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**.

7 Discussion



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.

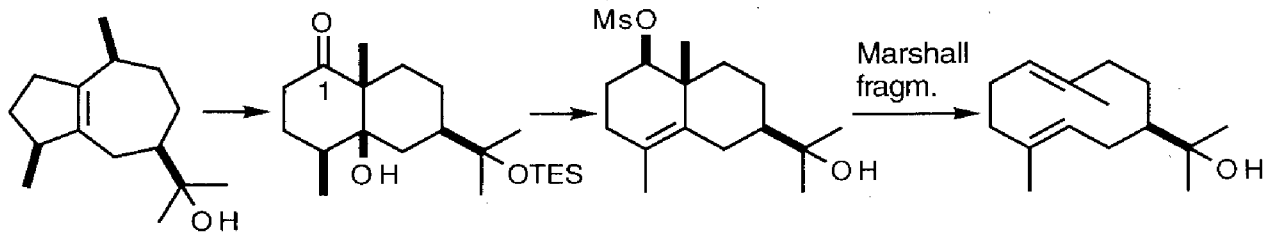
7.1 The Synthesis of Germacrane Sesquiterpenes

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 germacranes 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]

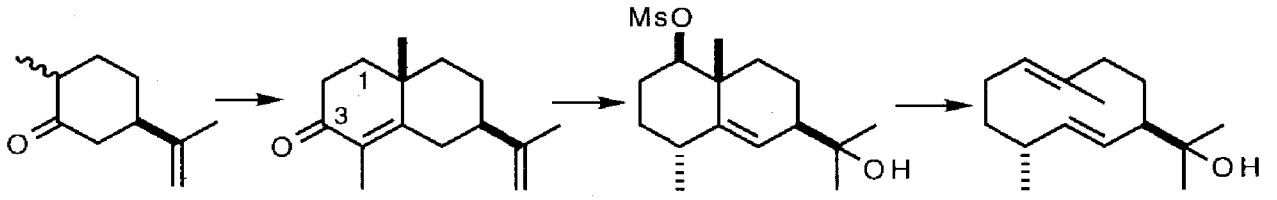
Scheme 7.1



(–)-guaiol (**1**) **2** **3** (+)-hedycaryol (**4**)

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.

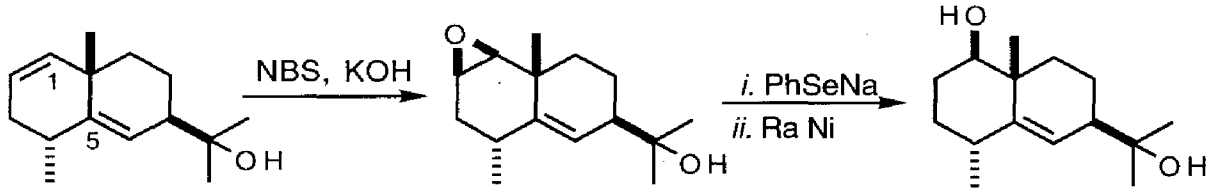
Scheme 7.2



5 (+)-α-cyperone (**6**) **7** (–)-allohedycaryol (**8**)

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.

Scheme 7.3



9 **10** **11**

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 BH_3·THF was required to obtain reproducible yields. In the synthesis of neohedycaryol described in **chapter 5**, we used therefore the more stable BH_3·SMe_2.[5] The use of this reagent in the Marshall fragmentation reaction has also been described by Piet et al..[2]

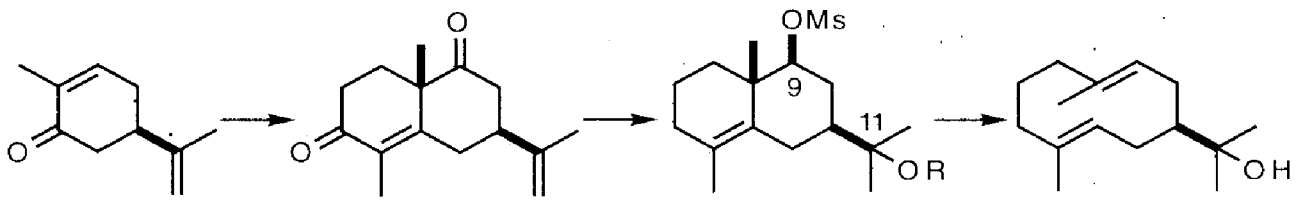
(–)-Carvone (**12**) was used for the synthesis of neohedycaryol (**16**) as described in **chapter 5** (Scheme 7.4). The synthesis of a C(9)-oxidized eudesmane skeleton, in this case **14**, is a longstanding problem[6] and attempts to develop an enantiospecific route failed. We were forced to use a 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, neohedycaryol, 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 (δ^-) 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 (+)-hedycaryol and (–)-allohedycaryol, 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, neohedycaryol.

Scheme 7.4



(–)-carvone (**12**) **13** (racemic) **14**: R = H **15**: R = Ac neohedycaryol (**16**)

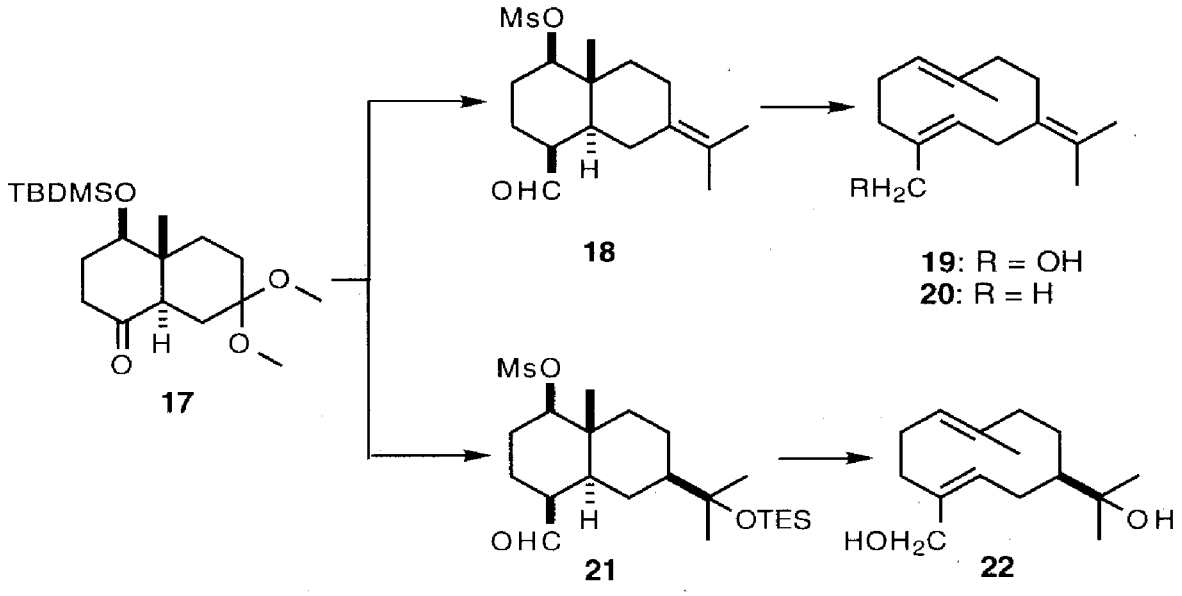
For the enolate-assisted fragmentation reactions described in **chapter 6**, the Wieland-Miescher ketone derivative **17** was chosen as a starting material. Prepared in a number of steps, this compound is frequently used in the synthesis of terpenes. The research in this chapter aimed at the construction of germacranes 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 germacranes 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[8] 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.

Scheme 7.5

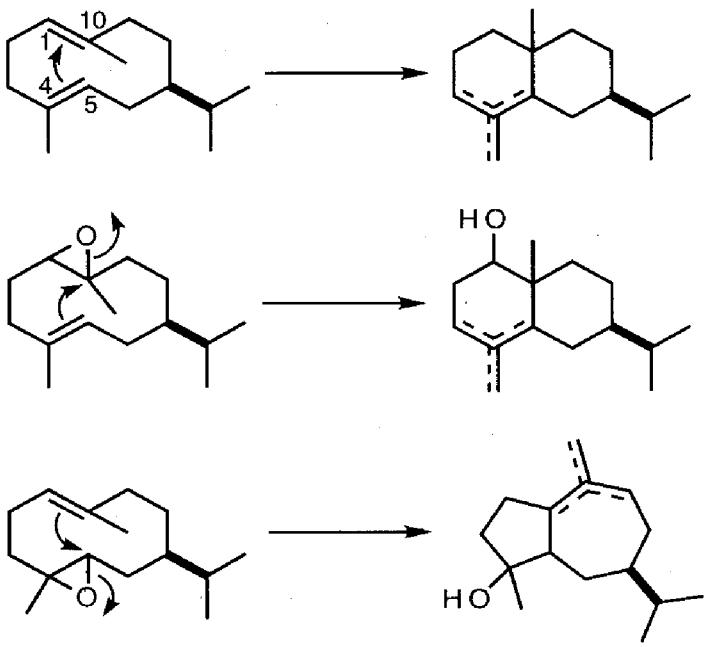


The question posed in the literature whether germacrene B would be enantiomerically stable could be answered in this chapter. Kinetic resolution of **19**, using the aforementioned Sharpless epoxidation, resulted in the recovery of racemic starting material, whereas the isolated guaiane was produced 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 germacranes (Scheme 7.6). Acid-induced cyclization of germacranes or their corresponding mono-epoxides is generally accepted to be biomimetic[9] and represents the biosynthesis of eudesmane and guaiane sesquiterpenes (§ 1.2). An extensive study on this topic has recently appeared in our group.[10] These cyclization reactions are not only restricted to germacrane sesquiterpenes but also occur, for example, in the biosynthesis of taxane diterpenes.[11] 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.[12]

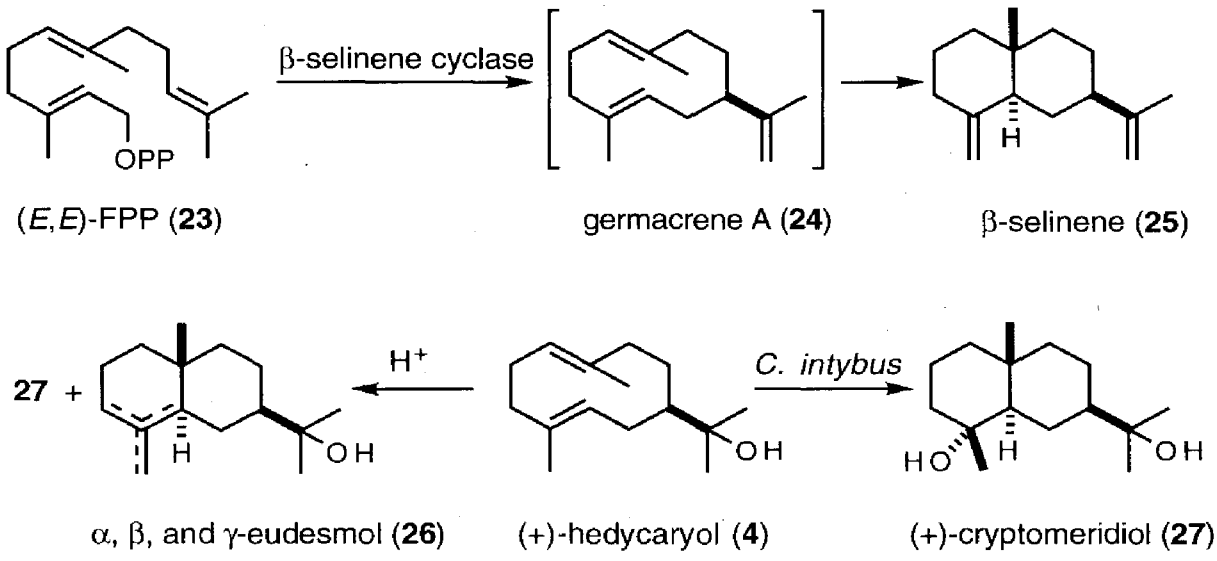
Scheme 7.6



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![13] Biomimetic reactions are valuable tools to show at what stages in biosynthesis, enzymes are interfering with spontaneous non-enzymatic processes.[14]

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.[15] This enzyme converts (*E,E*)-FPP (**23**), presumably via germacrene A (**24**), into β-selinene (**25**, Scheme 7.7).

Scheme 7.7



Because of its thermal lability, germacrene A is not very suitable for chemical or enzymatic studies.[16] 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,[10] 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,[17] 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.[18]

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 empatic 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.[19]

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**). Germacranes like **8**[20] 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[21] and is therefore not included in this thesis.

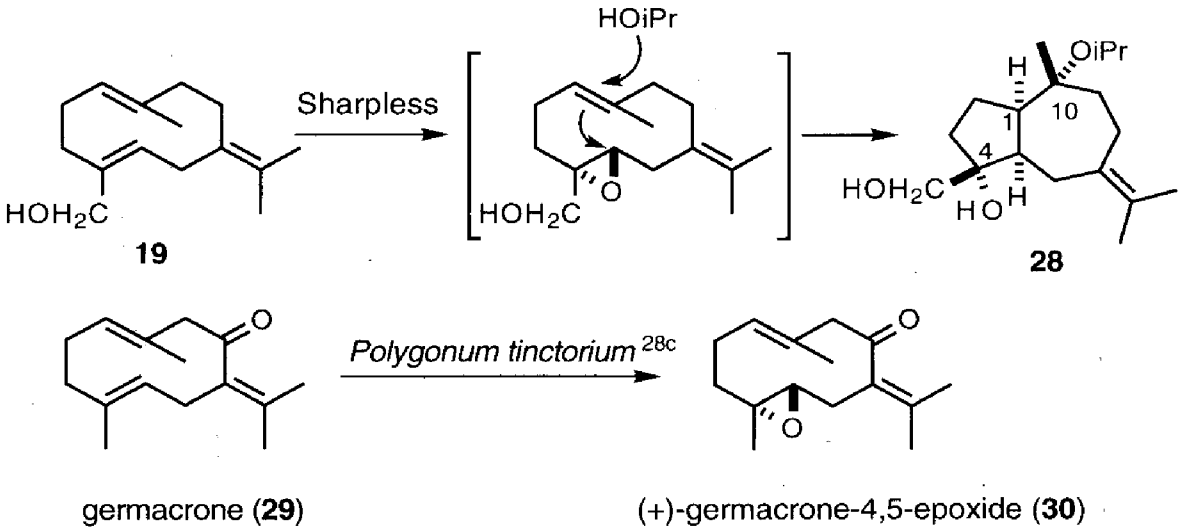
Through synthesis of neohedycaryol (**16**), we were able to show that acid-induced cyclization of both neohedycaryol (**16**) and hedycaryol (**4**) leads to the same products (**26**). Moreover, it was shown that **16** is achiral because of the presence of a symmetry plane. Consequently, acid-induced cyclization of **16** leads to racemic products. Enzymatic cyclization of **16** can, in principle, lead to enantiomerically enriched **26** and **27**.[22] 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 germacranes.[23] The majority of the isolated guaianes possesses a cis-fused ring system with both bridgehead methine protons α oriented.[24] 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 germacranes 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 hedycaryol (**4**), the NMR spectra of **19** and germacrene 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.[25]

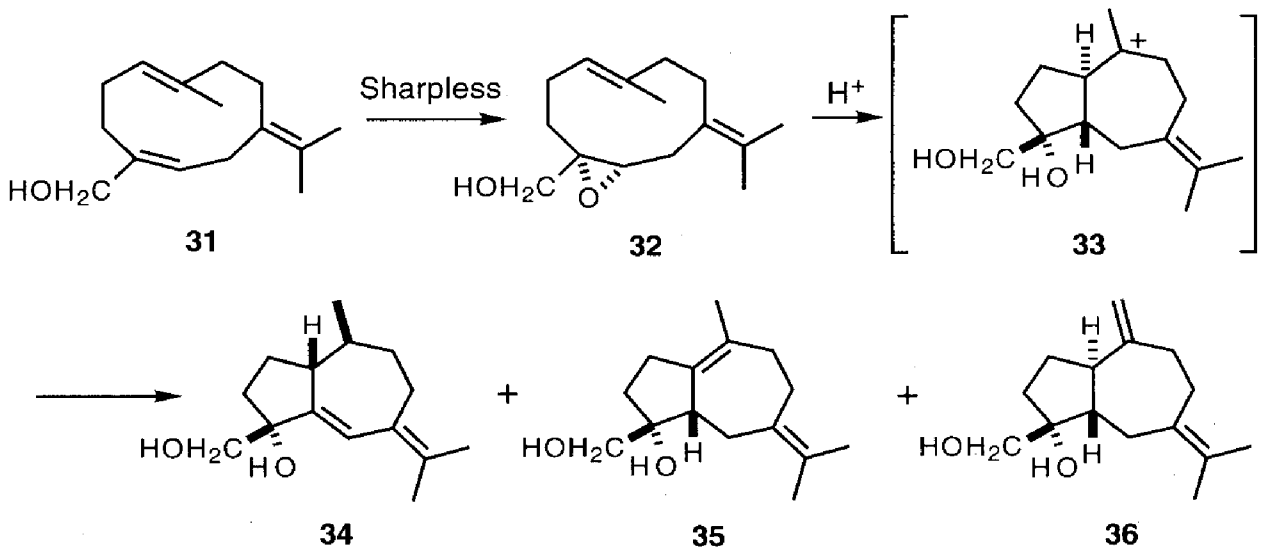
A curious aspect of germacrene B and **19** is their planar chirality. Though rare, natural products which are chiral solely due to the presence of a chiral plane are known.[26] Performed as a kinetic resolution, the Sharpless epoxidation of **19** is highly enantioselective. It is possible that in vivo epoxidation of germacranes is enantioselective as well. Conversion of racemic germacrone (**29**)[27] by plant cell cultures affords enantiomerically enriched germacrone-4,5-epoxide (**30**).[28]

Scheme 7.8



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).[24] This theory fits in the hypothesis discussed earlier and can be replenished by the remark that heliangolides ((*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, heliangolide model **31** was subjected to the Sharpless epoxidation reaction to afford the stable mono-epoxide **32**.

Scheme 7.9



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 unambiquous except for the quencing of the final cation. The 1,2-H shifts leading to the formation of **34** are probably also involved in the biosynthesis of pseudoguaianes[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

1. Ho, T. -L. *Carbocycle Construction in Terpene Synthesis*; VCH Publishers: New York, 1988.
2. For a discussion about the addition of borane in this reaction, see: Piet, D. P.; Minnaard, A. J.; van der Heyden, K. A.; Franssen, M. C. R.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1995**, *51*, 243.
3. Wharton, P. S.; Sundin, C. E.; Johnson, D. W.; Kluender, H. C. *J. Org. Chem.* **1972**, *37*, 34.
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.
5. Hutchins, R. O.; Cistone, F. *Org. Prep. Proced. Int.* **1981**, *13*, 227.
6. Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *J. Org. Chem.* **1993**, *58*, 7204.
7. Bundy, G. L. *Synthesis of Cyclodecadienes from Decalylborane Derivatives*; Ph.D. Thesis, Northwestern University, Evanston, Illinois, 1968.
8. Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH Publishers: New York, 1993; Chapter 4.
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

without interference of the involved enzymes." See: Wanner, M. J.; Koomen, G. J. In *Studies in Natural Products Chemistry*; Atta ur Rahman, Ed.; Elsevier: Amsterdam, 1994; Vol. 14; part 1; p. 739.

10. Piet, D. P. *Transannular Cyclisation Reactions of the Germacrane System Mediated by Enzymes from Cichorium intybus*; Ph.D. Thesis, Agricultural University, Wageningen, The Netherlands, 1996.
11. (a) Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *J. Chem. Soc.* C **1966**, 1933. (b) Torregiani, E.; Rafaiani, G.; Barboni, L.; Appendino, G. *Tetrahedron Lett.* **1995**, *36*, 7127.
12. Comparable observations in alkaloids, isolated from *Nitraria* species, have led to the biomimetic synthesis of these alkaloids. See reference 9; pp 731–768.
13. Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089.
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 *Isopentenoids and Other Natural Products. Evolution and Function*; Nes, W. D. Ed.; ACS Symposium Series 562, Washington DC, 1994; Chapter 3.
15. Belingheri, L.; Cartayrade, A.; Pauly, G.; Gleizes, M. *Plant Science* **1992**, *84*, 129.
16. Weinheimer, A. J.; Youngblood, W. W.; Washecheck, P. H.; Karns, T. K. B.; Ciereszko, L. S. *Tetrahedron Lett.* **1970**, *11*, 497 and § 2.4.1.
17. (a) Reference 14b. (b) Reference 10; chapter 4.
18. Cane, D. E. In *Secondary Metabolites: Their Function and Evolution*; Chadwick, D. J.; Whelan, J. Eds; Ciba Foundation Symposium 171; John Wiley & Sons: Chichester, 1992; pp 163–183.
19. Hendrickson, J. B. *Tetrahedron* **1959**, *7*, 82.
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.
21. Acid-induced cyclization of **8** afforded a mixture of products with a cadinane skeleton; (a) Minnaard A. J.; Zhabinskii, V. A., unpublished results. Cadinanes possessing a 2-hydroxyisopropyl group are, however, extremely rare; (b) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 1, Mono- and Sesquiterpenoids.
22. No effords 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,

Ae. *Tetrahedron* **1995**, *51*, 6303.

24. Fischer, N. H. In *Recent Advances in Phytochemistry, Vol. 24: Biochemistry of the Mevalonic Acid Pathway to Terpenoids;* Plenum Press: New York, 1990; Chapter 4.
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.
26. For a recent example see: Toyota, M.; Yoshida, T.; Kan, Y.; Takaoka, S.; Asakawa, Y. *Tetrahedron Lett.* **1996**, *37*, 4748.
27. Germacrone is isolated as a racemate and probably enantiomerically stable, see: Hill, R. K.; Fracheboud, M. G.; Sawada, S.; Carlson, R. M.; Yan, S. -J. *Tetrahedron Lett.* **1978**, 945.
28. (a) Hikino, H.; Konno, C.; Nagashima, T.; Kohama, T.; Takemoto, T. *Chem. Pharm. Bull.* **1977**, *25*, 6. (b) Sakui, N.; Kuroyanagi, M.; Ishitobi, Y.; Sato, M.; Ueno, A. *Phytochemistry* **1992**, *31*, 143. (c) Sakamoto, S.; Tsuchiya, N.; Kuroyanagi, M.; Ueno, A. *Phytochemistry* **1994**, *35*, 1215. The authors of the papers (b) and (c), however, state erroneously that "germacrone has no chirality". This statement confuses the discussion.
29. (a) González, A. G.; Galindo, A.; Mansilla, H. *Heterocycles* **1989**, *28*, 529. (b) Manitto, P. *Biosynthesis of Natural Products*; John Wiley & Sons: New York, 1981; p 248.

Summary

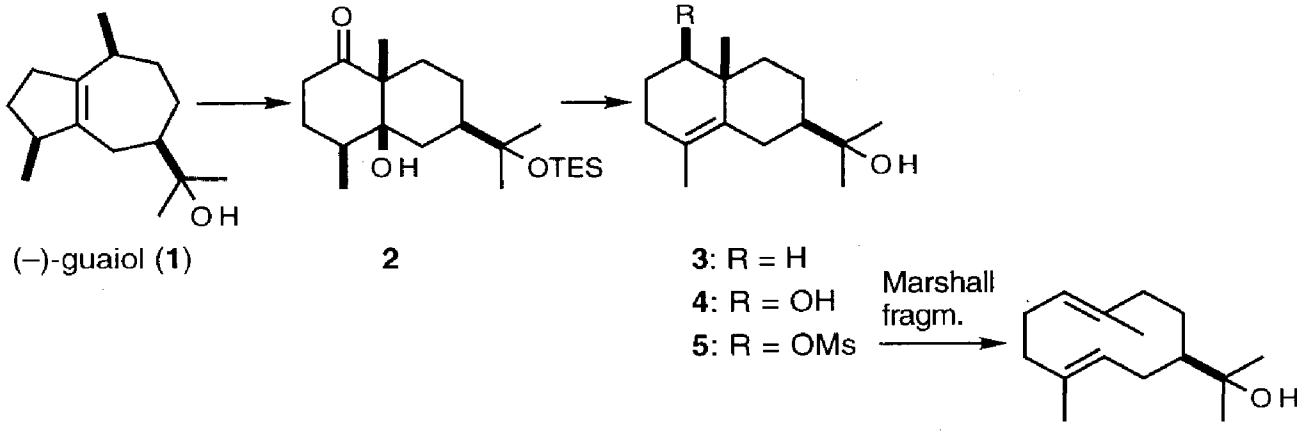
In this thesis, the synthesis of a number of germacrane sesquiterpenes is described. Functionalized decalin systems are prepared, which are used in turn as substrates for Grob-type fragmentation reactions. These fragmentation reactions start either with the hydroboration of a double bond, as in the Marshall 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 germacranes.

The acid-induced cyclization of the germacranes synthesized 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.

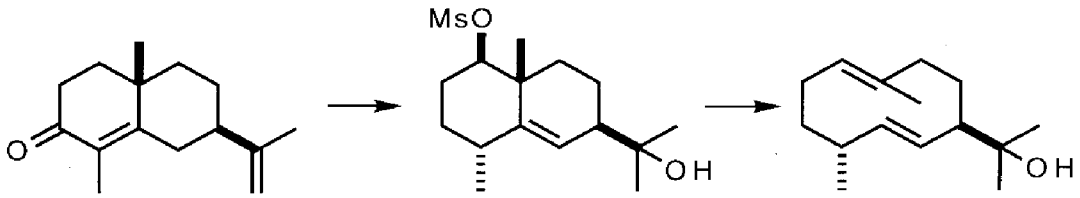
In chapter 2, the literature concerning the synthesis of germacrane sesquiterpenes is reviewed. The synthetic approaches are grouped together according to the applied ten-membered ring forming reactions. The research described in this thesis is mentioned shortly.

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



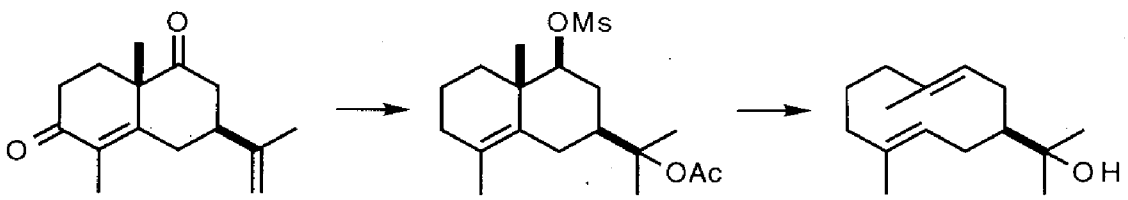
After conversion of **2** into mesylate **5**, a Marshall fragmentation was used to prepare the (*E*,*E*)-cyclodecadiene ring system present in (+)-hedycaryol. Additionally, the applicability of **2** as a starting material in the synthesis of eudesmane sesquiterpenes was illustrated by the synthesis of (+)-γ-eudesmol (**3**) and (+)-4-eudesmene-1β,11-diol (**4**).

In chapter 4, the synthesis of (–)-allohedycaryol (**9**) is described. The synthesis started from (+)-α-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.



(+)-α-cyperone (**7**) **8** (–)-allohedycaryol (**9**)

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.

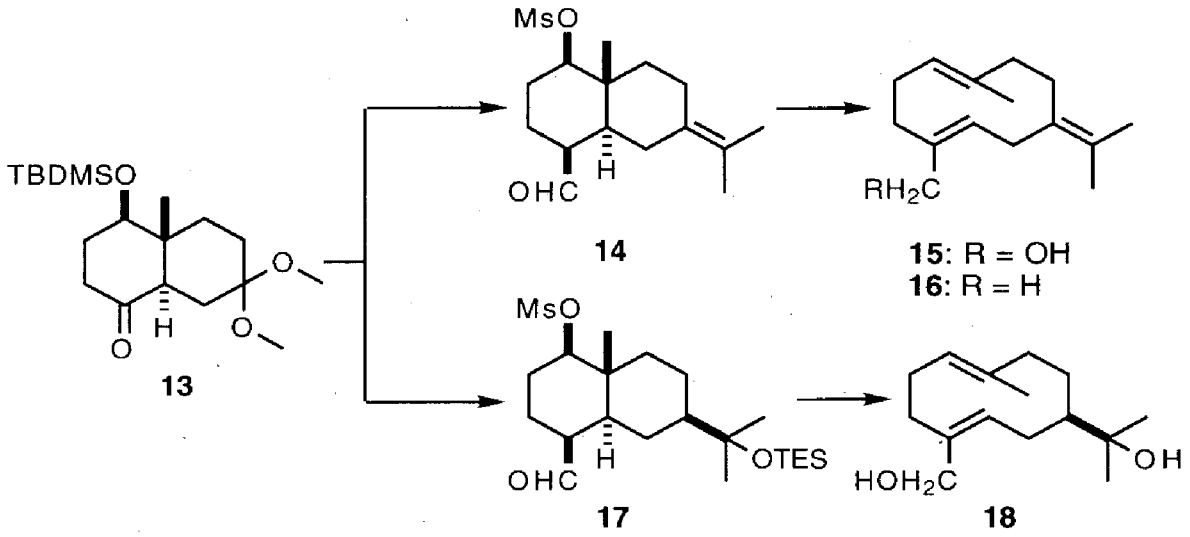


10 (racemic) **11** neohedycaryol (**12**)

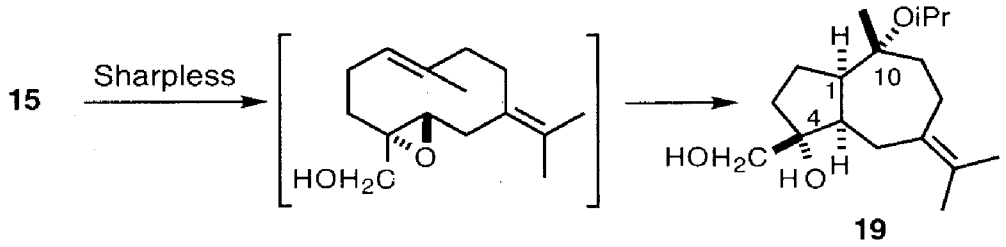
Neohedycaryol exists preferably in the elongated chair conformation as was determined spectroscopically and by chemical transformation and this indicates that

the role of neohedycaryol 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 germacranes. 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-hydroxyhedycaryol (**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.

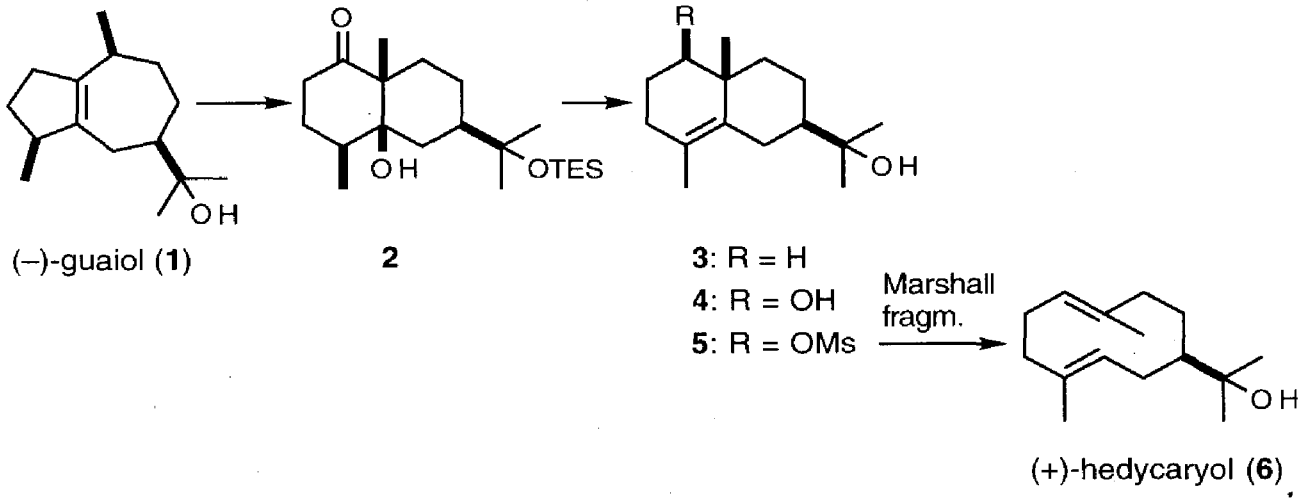
Samenvatting

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 zuurgekatalyseerde 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 structuuropheldering van germacranen.

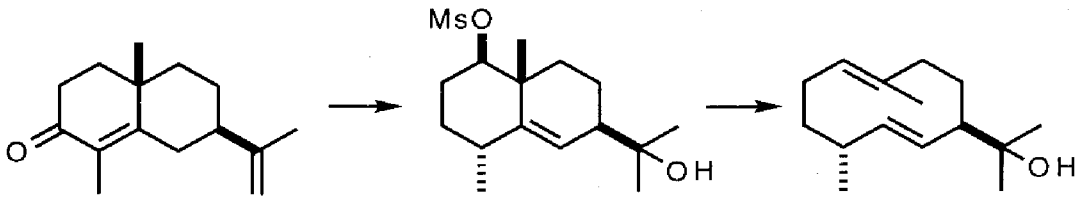
In hoofdstuk 2 wordt de bestaande literatuur over de synthese van germacranen samengevat. De verschillende synthetische benaderingen zijn gegroepeerd aan de hand van de manier waarop de tienring wordt gevormd. Het onderzoek beschreven in dit proefschrift wordt kort toegelicht.



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**

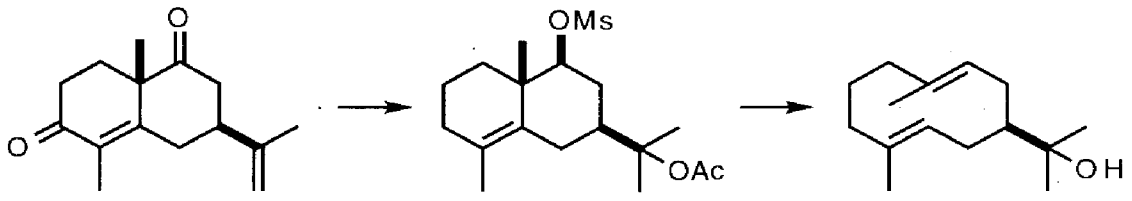
wordt een Marshall-fragmentatie toegepast om het (*E,E*)-cyclodecadieensysteem van hedycaryol te maken. Dat **2** ook bruikbaar is in de synthese van eudesmaan sesquiterpenen wordt geïllustreerd met de synthese van (+)-γ-eudesmol (**3**) en (+)-4-eudesmeen-1β,11-diol (**4**).

In hoofdstuk 4 wordt de synthese van (–)-allohedycaryol (**9**) beschreven. De synthese gaat uit van (+)-α-cyperon (**7**), wat op zijn beurt in goede opbrengst wordt verkregen uit de alkylering van het imine van (+)-dihydrocarvon en (R)-(+)-fenylethylamine. In een aantal stappen wordt **7** omgezet in mesylaat **8**. Marshall-fragmentatie van **8** completeert vervolgens de synthese van (–)-allohedycaryol. De antipode (+)-**9** is geïsoleerd uit reuzenvenkel (*Ferula communis* L.) en door middel van deze synthese is de relatieve en absolute stereochemie van het natuurprodukt opgehelderd. Het blijkt dat natuurlijk (+)-allohedycaryol 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.



(+)-α-cyperon (**7**) **8** (–)-allohedycaryol (**9**)

In hoofdstuk 5 wordt de synthese van neohedycaryol (**12**), een C(9)–C(10) dubbele bindingsisomeer van hedycaryol, 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.

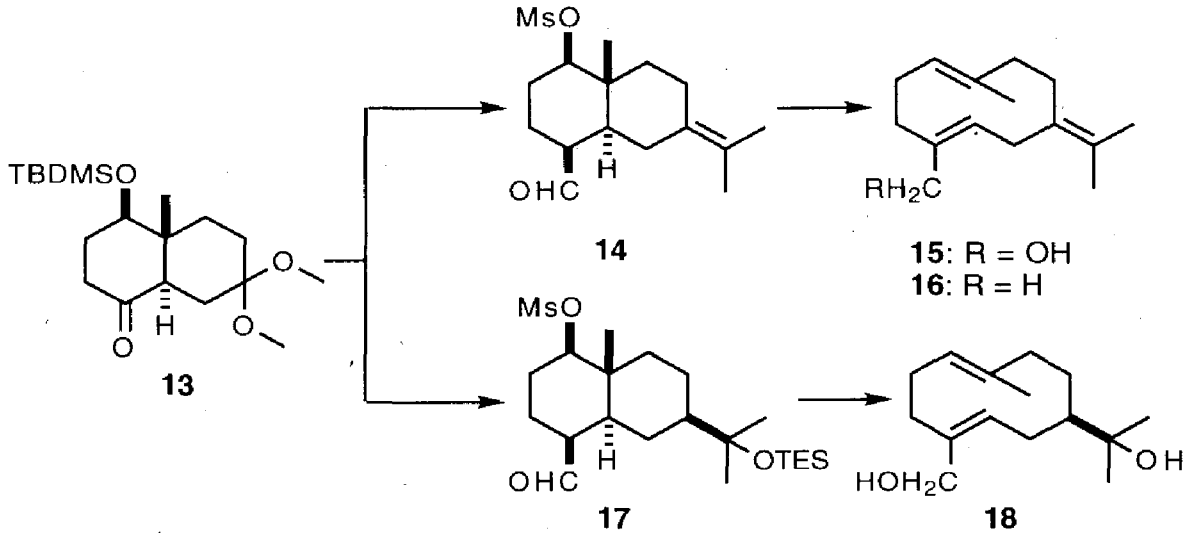


10 (racemisch) **11** neohedycaryol (**12**)

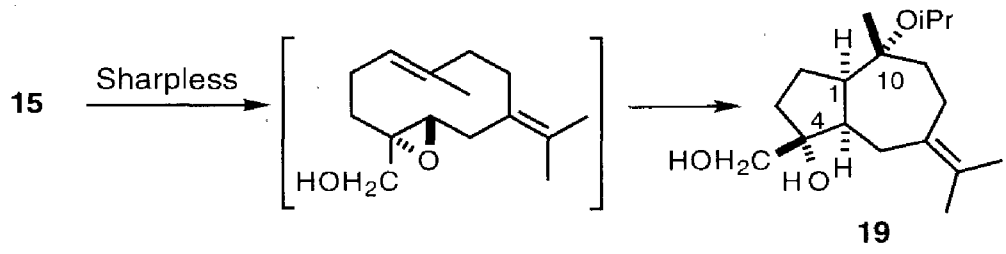
De voorkeur van neohedycaryol voor de verlengde-stoelconformatie is chemisch en spectroscopisch bepaald. Deze conformatie houdt in dat de voorgestelde rol van **12** in de biosynthese van *epi*-eudesmanen waarschijnlijk onjuist is. Het betekent

ook dat **12** niet chiraal is maar in de mesovorm voorkomt.

In hoofdstuk 6 wordt de ontwikkeling van enolaat-geassisteerde fragmentatie-reakties voor de synthese van germacranen beschreven. Behandeling met natrium*tert*-amylaat gevolgd door reductie, zet aldehyde **14** om in (*E,E*)-alcohol **15**. Het gebruik van kaliumhexamethyldisilazaan geeft daarentegen het *E,Z* analoog. De omzetting van **15** in germacreen B (**16**), een algemeen voorkomend germacraan-koolwaterstof, bewijst de *E* geometrie van beide dubbele bindingen in **15**. 15-Hydroxyhedycaryol (**18**) wordt volgens dezelfde methode gesynthetiseerd uit **17**.



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



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.

Curriculum Vitae

Adriaan Jacobus Minnaard werd geboren op 3 februari 1968 te Kruiningen. In 1986 behaalde hij het VWO-diploma aan Het Goese Lyceum in Goes. In hetzelfde jaar begon hij zijn studie aan de Landbouwuniversiteit Wageningen. Tijdens de doctoraalfase koos hij voor de afstudeervakken Organische Chemie onder leiding van ir. R. P. W. Kesselmans en prof. dr. Ae. de Groot, en Fysische Chemie onder leiding van ir. J. Kijlstra en prof. dr. J. Lyklema. De stageperiode werd doorgebracht aan het Imperial College in Londen, Groot-Brittannië, onder leiding van prof. dr. S.V. Ley. In november 1991 werd het doctoraalexamen in de richting Moleculaire Wetenschappen met lof afgelegd. Vanaf 1992 tot 1996 was hij als assistent in opleiding (AIO) werkzaam bij de vakgroep Organische Chemie aan de Landbouwuniversiteit Wageningen. Daar werd het in dit proefschrift beschreven onderzoek verricht onder leiding van dr. J. B. P. A. Wijnberg en prof. dr. Ae. de Groot.
Per 1 januari 1997 is hij werkzaam bij DSM in Geleen.

Stellingen

1. De alkylering van (*E*)-3-penteen-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.

   (a) Coates, R. M.; Shaw, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 5657. (b) Telschow, J. E.; Reusch, W. *J. Org. Chem.* **1975**, *40*, 862. (c) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517. (d) Fuhrhop, J.; Penzlin, G. *Organic Synthesis*; VCH: Weinheim, 1994.

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

   (a) Yoshikawa, M.; Hatakeyama, S.; Tanaka, N.; Fukuda, Y.; Murakami, N.; Yamahara, J. *Chem. Pharm. Bull.* **1992**, *40*, 2582. (b) Lange G. L.; Gottardo, C. *Tetrahedron Lett.* **1994**, *35*, 8513.

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.

   Marcovich, N. E.; Reboredo, M. M.; Aranguren, M. I. *Holz als Roh- und Werkstoff* **1996**, 54, 189.

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 kringlooppapier 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.

   Onder andere 1. (a) Fraga, B. M.; Hernandez, M. G.; Mestres, T.; Terrero, D.; Arteaga, J. M. *Phytochemistry* **1995**, *39*, 617. (b) Kesselmans, R. P. W.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 7232. 2. (a) Su, W. -C.; Fang, J. -M.; Cheng, Y. -S. *Phytochemistry* **1995**, *39*, 603. (b) Itokawa, H.; Nakanishi, H.; Mihashi, S. *Chem. Pharm. Bull.* **1983**, *31*, 1991.

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.

9. Na de invoering van de Tweede Fase in de bovenbouw van het middelbaar onderwijs zal het aantal studenten in het WO, dus ook op de LUW, sterk dalen.

10. Het uitgangspunt dat een wetenschappelijk onderzoek nuttig moet zijn gaat voorbij aan het nut van wetenschappelijk onderzoeken.

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

Met dank aan C. M., J. M., T. M.