Total Synthesis of *cis*-Hydroazulene Sesquiterpenes

Base-Induced and -Directed Elimination and Rearrangement Reactions of Perhydronaphthalene-1,4-diol Monosulfonate Esters

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

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Proefschrift
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Voorwoord

Hoewel slechts één naam op de titelpagina van dit proefschrift prijkt moge het duidelijk zijn dat meer mensen hebben bijgedragen aan het tot stand komen ervan. Diverse mensen hebben mij met raad en daad terzijde gestaan. Zonder de anderen tekort te willen doen wil ik een aantal mensen met name noemen.

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Contents

1 General Introduction

1.1 Historical Background

Since ancient times terpenoids have been used for various purposes, especially for the more pleasant things in life, and for their (supposed) medicinal properties. Myrrh, a gum resin with a sweet smell and a bitter taste, has been known since biblical times.[1] It is obtained from the bark of trees of the genus *Commiphora*, fam. *Burseraceae*, in East Africa and Arabia, and has found its usage in incense and in rare and expensive perfumes, medicines, and dentifrices. The terpenoids found in myrrh include triterpene acids, -esters, and -alcohols, and several furanosesquiterpenes with germacrane, eudesmane, and guaiane frameworks.[2]

Essential oils from various plants are used in the perfume and flavour industry since many centuries. These essential oils, mostly consisting of mono- and sesquiterpenes, were often accredited with miraculous medicinal properties. Spikenard is an example of such an essential oil. It is prepared from the rhizomes of *Nardostachys jatamansi* D. C., fam. *Valerianaceae*, a perennial herb growing at high altitudes in the Himalayas and Nepal.[3,4] For centuries it has been used in the indigenous system of medicin in the treatment of several nervous disorders like hysteria, epilepsy, and convulsions. Since Roman times, spikenard is known to the western world. The Romans also made use of spikenard (*spicae nardi*) in the treatment of nervous illnesses and as the source of an expensive perfumed salve, used as a cosmetic. Jatamansin®, prepared from *N. jatamansi*, is in our time on the market as a sedative.[5] From the sesquiterpene fraction of *N. jatamansi* several guaianes, aristolanes, and maalianes have been isolated, together with valeranone which is noted for its tranquillizing properties.[4b,5]

Nowadays, the oleoresins of pine trees are used as a source of mono- and sesquiterpenes which are utilized in the manufacture of perfumery and specialty chemicals, and a wide range of industrial products including solvents, adhesives, polymers, emulsifiers, and coatings.[6]

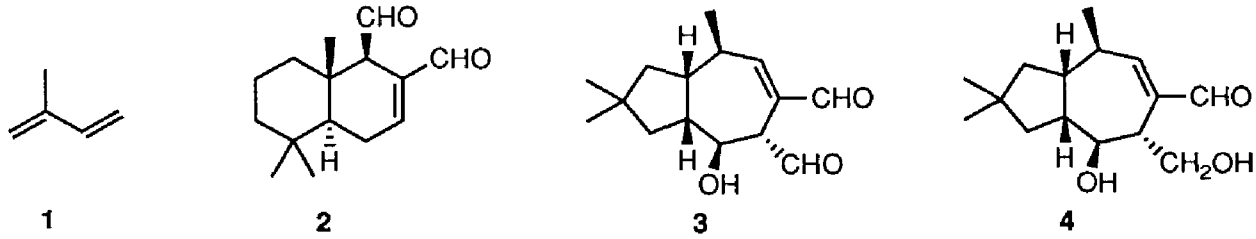
Although the current usage is limited, terpenes might in the future be used in crop protection as many exhibit antifeedant, insect repellant or -attractant, and -growth regulatory properties.[7] Other terpenes are psychotropic, cytotoxic, antifungal, or antitumor compounds and might become used in a diverse array of applications.

1.2 Chemical Background

Terpenes are substances derived from the formal condensation of C_5 isoprenoid units. As a consequence, most terpenes exhibit a carbon content in multiples of this five carbon arrangement. They range in size from the volatile monomeric isoprene **1** (C_5) to the polymer rubber (MW ~ 10^6). Although terpenes are a most diverse group of natural products they lend themselves to simple classification on the basis of their carbon number. This classification divides the terpenes into *hemiterpenes* (1 × C_5), *monoterpenes* (2 × C_5), *sesquiterpenes* (3 × C_5), *diterpenes* (4 × C_5), *sesterpenes* (5 × C_5), and *triterpenes* (6 × C_5).[8]
Terpenoid accumulation has been observed in every plant organ and in a variety of physical forms including essential oils, resins, gums, latex and waxes.[9] Apart from plants, terpenoids are also produced by other organisms like marine sponges, insects (pheromones), and mammals (steroids).[10,11]

All plants employ the isoprenoid pathway in the synthesis of several essential substances like carotenoids and certain plant hormones. In addition to this group of common substances, there exists a diverse array of other terpenoids, classed as so-called secondary metabolites. These secondary metabolites are often characteristic of a narrow range of species. Apart from a chemical, biogenetic, and taxonomic point of view, they have become of interest because of the ecological advantage they (may) impart to the species that produce and accumulate them.[6] A good example in this respect is polygodial **2** (Figure 1.1), isolated from bark extracts of the East African *Warburgia* species,[12] which has a strong insect antifeedant activity. Polygodial **2** is also produced as an antifeedant by the nudibranch *Dendrodoris limbata*, protecting the animal against fish.[13] Another example of biologically active secondary metabolites of terpenoid origin are the lactaranes **3** and **4**, which are isolated from *Lactarius piperatus*, *L. torminosus*, and *Russula queletii*.[14] The compounds were found to be

Figure 1.1



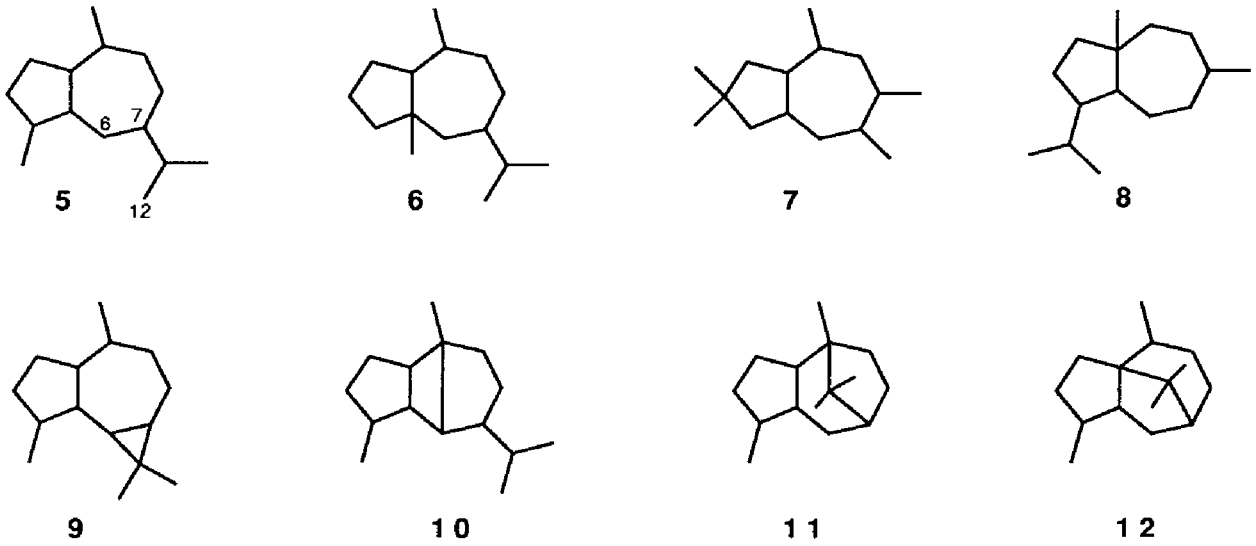
1 **2** **3** **4**

responsible for the pungency of these toadstools. This pungency is believed to serve as a warning signal, protecting the toadstools from being eaten by animals.
Numerous other examples in which secondary metabolites of terpenoid origin play an important role in plant-animal, plant-plant, plant-microbe, and animal-animal interactions have been recorded.[15]

1.3 Sesquiterpenes

Sesquiterpenes form the group of terpenoids possessing a C_{15} framework. About 25% of all known terpenoids belong to the group of sesquiterpenes.[16] Although the sesquiterpenes are found mainly in the essential oils of higher plants, other sources varying from algae[17] and fungi[18] to insects[19] have been described. The sesquiterpenes encompass a wide range of some 200 skeletal types,[6] varying from acyclic to very complex polycyclic structures. Several oxidation states are represented in this class of terpenes, varying from alcohol groups to furans and lactones. The literature on the isolation and characterization of natural sesquiterpenes is overwhelming. A recent review on this subject,[20] covering the literature published during 1987, is based on 262 references and describes the isolation of almost 500 new sesquiterpenes, mainly from higher plants. Of these sesquiterpenes about 140 possess a 5,7-fused ring framework.

Figure 1.2



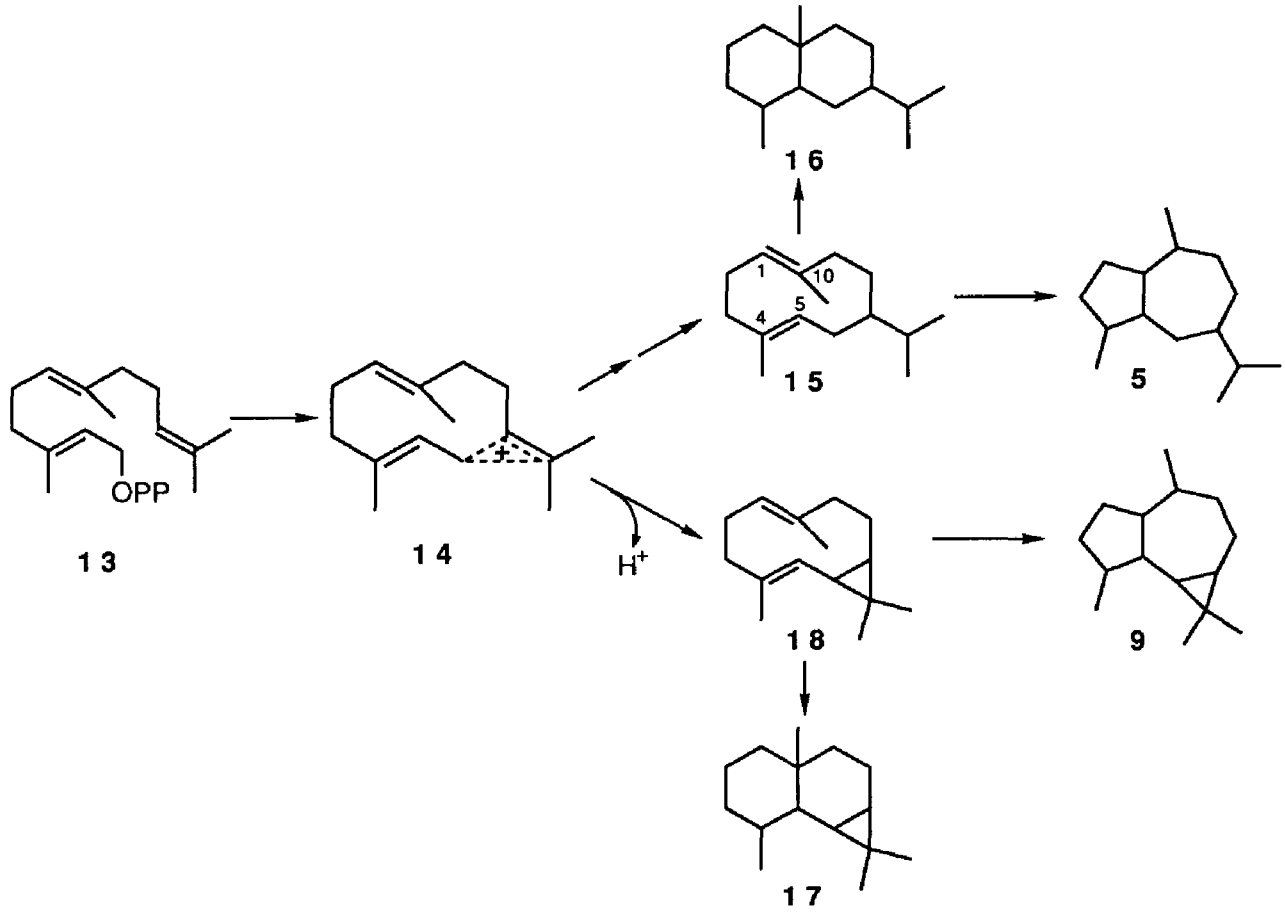
In this thesis the attention will be focused on the synthesis of sesquiterpenes possessing a 5,7-fused hydroazulene ring framework, in particular on (cis-fused)

guaiane (**5**) and aromadendrane (**9**) sesquiterpenes. Other sesquiterpenes belonging to the group of hydroazulene sesquiterpenes are for example the pseudoguaianes **6**, the lactaranes **7**, the carotanes **8**, the bourbanes **10**, and the β- and γ-patchoulanes **11** and **12** (Figure 1.2). The vast majority of isolated guaiane terpenoids are cis-fused guaian-6α,12-olides, in which a lactone is present at the C(6)-C(7) position.

1.4 Biosynthesis

The biosynthetic starting material for the guaiane sesquiterpenes **5** as well as for the eudesmane **16**, maaliane **17**, and aromadendrane sesquiterpenes **9** is the *trans*-farnesyl pyrophosphate (FPP) **13**.[21] The cyclization of **13** will be initiated by an enzyme-mediated solvolysis of the pyrophosphate group,[22] resulting in the formation of an incipient or actual carbocation at the tail position of the farnesyl chain, possibly stabilized by participation of the terminal double bond under formation of the non-classical carbocation **14**.[23] Cyclization of the cation **14** followed by a neutralization of

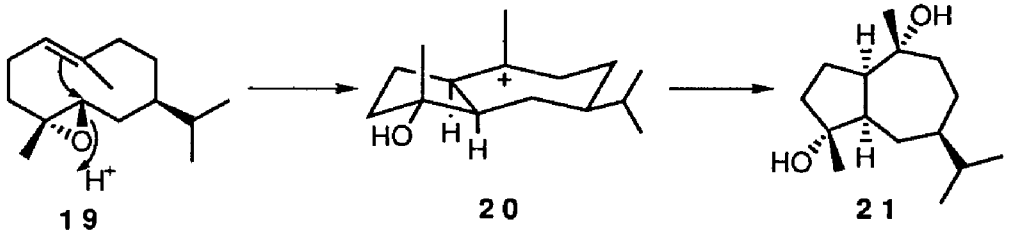
Scheme 1.1



the positive charge then yields the germacra-1(10),4(5)-diene framework **15** which is believed to be the precursor of the eudesmanes **16**[23] as well as the guaiane sesquiterpenes **5**. A 1,3-deprotonation of **14** accounts for the formation of the *gem*-dimethylcyclopropane ring in germacra-1(10),4(5)-diene **18**, the corresponding biosynthetic precursor of the maalianes **17** and the aromadendranes **9**[23] (Scheme 1.1).

Due to the lack of biosynthetic data, *in vitro* transformations of germacrane derivatives have provided indirect evidence for the possible biosynthetic pathways towards guaiane sesquiterpenes.[24]

Scheme 1.2

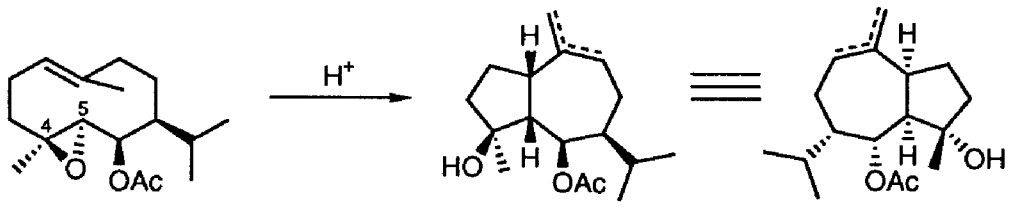


19 **20** **21**

It has been postulated[23a] that an acid catalyzed, anti-Markovnikoff type of cyclization of the *trans,trans*-germacradiene precursor **15** results in the formation of the guaiane framework **5**. This type of reaction has been recorded only with a few 1,5-cyclodecadiene derivatives.[25]

Another plausible suggestion for the biosynthesis of guaianes involves the acid catalyzed cyclization of 4α,5β-epoxides like **19**, which results in the formation of the cis-fused guaiane cation **20**, which can stabilize itself by proton expulsion or reaction with a nucleophile (yielding *e.g.* **21**)[26] (Scheme 1.2). This type of reaction has received a considerable amount of attention and several other examples have been described.[24,27]

Scheme 1.3



22 **23**

The acid-catalyzed cyclization of the isomeric 4β,5α-epoxide **22** was found to yield the cis-fused (α-H) 4α-hydroxy guaiane **23**, (Scheme 1.3),[28] but the framework of this compound is antipodal to the one of the guaiane **21**, except for the isopropyl side chain. This might lead to the conclusion that in biosynthetic processes the chirality of

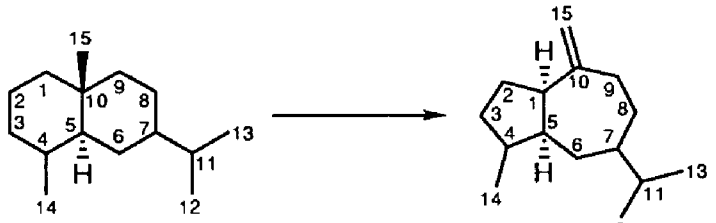
the guaiane skeleton is determined by the stereochemistry of the epoxide in its germacrene precursor.
The cyclization studies of 4,5-epoxy-1,10-germacrenes offer an explanation for the biosynthesis of the cis-fused guaianes **5** and alloaromadendranes **9**[29] that possess an hydroxyl group at C(4) which is positioned *syn* to the ring-fusion protons. For the cis-fused (α-H) hydroazulene sesquiterpenes with a β-hydroxyl group at C(4), which are the topic of this thesis, however, no biomimetic studies have been described sofar.

It is commonly accepted that the *trans*-1,10-germacrene derivatives like **15** and **18**, might serve as biosynthetic precursors for cis-fused guaianes and alloaromadendranes, respectively. The biosynthesis of the trans-fused hydroazulene skeleton, however, has caused some controversy as it can be derived from *trans*-1,10-[30] as well as *cis*-1,10-germacrene derivatives.[27c,31]

1.5 Scope of this Thesis

Several strategies have been developed for the synthesis of the hydroazulene skeleton. In Chapter 2 of this thesis, an overview of these methods is given. Until recently, no generally applicable method for the synthesis of cis-fused hydroazulene sesquiterpenes with an exocyclic methylene unit at C(10) has been developed. In our view, the most promising strategy towards these compounds was the rearrangement of functionalized trans-fused hydronaphthalene precursors. The major advantage of this approach is the highly developed understanding of the stereochemistry and conformational analysis of the hydronaphthalene systems. The bottle-neck in this approach, however, was formed by the rearrangement of the trans-fused hydronaphthalene skeleton to the cis-fused hydroazulene framework with an exocyclic double bond at C(10). Solvolytic methods commonly used for this transformation always result in the formation of mixtures of rearranged double bond isomers. Our aim was to develop a generally applicable selective method for the rearrangement of trans-fused hydronaphthalene precursors to cis-fused hydroazulenes with an exocyclic C(10)-double bond. In Scheme 1.4 this goal is illustrated for the rearrangement of the *trans*-eudesmane skeleton **24** to the *cis*-guaiane framework **25**.

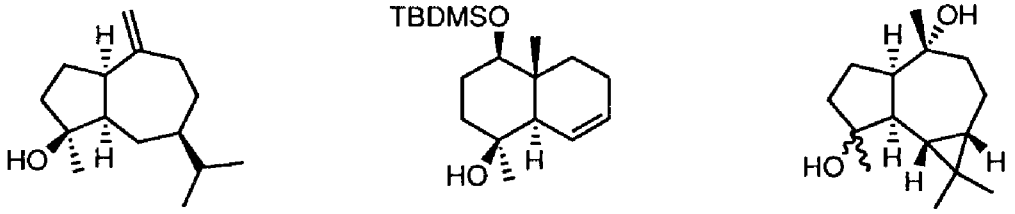
Scheme 1.4*



24 **25**

In Chapter 3, the development of this method is described and the reaction is discussed from a mechanistic point of view. In Chapter 4, an application of our method is described in the total synthesis of the guaiane alcohol **26**[4] (Figure 1.3).
In Chapter 5, the selective introduction of a double bond at the C(6)-C(7) position in the *trans*-hydronaphthalene framework **27** is described. This reaction bears a strong mechanistic resemblance to the rearrangement reaction (Chapter 3) and the mechanistic aspects of the reaction are emphasized in this chapter.
In Chapter 6, the reactions described in the Chapters 3 and 5 are combined to one single synthetic route towards the alloaromadendendrane diols **28** and **29**.[32]
In Chapter 7, some additional attempts to exploit these selective transformations are described.

Figure 1.3**



26 **27** **28** : β-OH
29 : α-OH

* The numbering system of the carbon atoms depicted in Scheme 1.4 is most commonly used in the sesquiterpene literature and is followed throughout the text part of this thesis. For the Experimental Sections the Chemical Abstract nomenclature and numbering system is used.

** All synthetic compounds described in this thesis are racemates. For reasons of readibility, however, this will only be indicated in those cases in which a direct link between the synthetic structure and a natural product exists.

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2 Reported Syntheses of Hydroazulene Sesquiterpenes

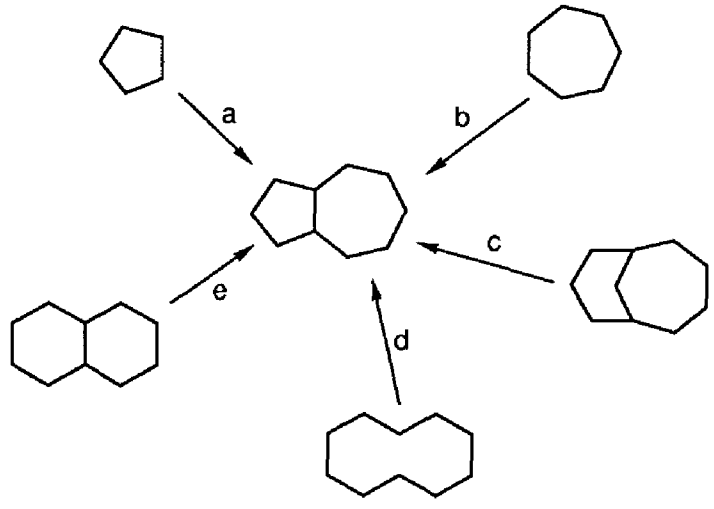
2.1 Introduction

The total synthesis of hydroazulene sesquiterpenes has made a remarkable progress during the last twenty years.[1] The synthetic efforts have been most successful for hydroazulene sesquiterpenes with a pseudoguaiane framework (structure **6**, Figure 1.2). This can be explained by the fact that the angular methyl group at C(5) allows a better stereocontrol in the conformationally labile hydroazulene system. In section 2.2 an overview of the different strategies towards the hydroazulene framework will be given. Reported (total) syntheses of hydroazulene sesquiterpenes *via* rearrangement of substituted hydronaphthalene precursors will be discussed in detail in section 2.3.

2.2 Synthetic Strategies towards the Hydroazulene Framework

Several broad strategies can be recognized for the construction of the hydroazulene framework[2] (Scheme 2.1).

Scheme 2.1



The most frequently employed strategy involves the synthesis of a cyclopentane derivative, followed by the annulation of the cycloheptane ring (route a). This method has been applied in the synthesis of the carotane (-)-daucene[3] and the guaianes (±)-bulnesol,[4,5] (±)-guaiol,[5] (±)-kessanol and its C(8)-epimer,[6] and (±)-gnidi-

dione.[7] Most examples, however, are found in the group of the pseudoguaianes and pseudoguaianolides with the total syntheses of (±)-ambrosin,[8] (±)-aromaticin,[9] (±)-aromatin,[10] (±)-bigelovin,[11] (+)-[12] and (±)-confertin,[10a,c,13] (±)-damsin,[8,13c] (±)-damsinic acid,[13b,14] (±)-helenalin,[15] (±)-linifolin A,[16] (±)-mexicanin I,[16] and (±)-psilostayin C[8] being reported.[17]
Robinson annulation of a cyclohexane ring onto the cyclopentane ring, followed by a one-carbon expansion of the 6-membered ring has been used in the synthesis of the pseudoguaianolides (±)-carpesiolin[18] and (±)-confertin.[19]
A two-carbon ring expansion of a substituted [3.3.0]-bicyclooctane intermediate has been described in the synthesis of the lactaranes (±)-velleral, (±)-vellerolactone, and (±)-pyrovellerolactone.[20]
Another efficient entry into fused 5,7-ring systems starting with the cyclopentane ring is the 2 + 2 photocycloaddition between two cyclopentene rings, followed by a cleavage of the cyclobutane ring.[21,22] This approach has been successfully employed in the synthesis of the guaianes (±)-5-*epi*-kessane and (±)-dehydrokessane,[23] the guaianolides (±)-compressanolide[24] and (±)-estafiatin,[24b,25] and the pseudoguaianolides (±)-carpesiolin,[26] (±)-damsin,[27] (±)-hymenin,[28] (±)-hysterin,[29] (±)-neoambrosin,[28] and (±)-parthenin.[28] A comparable *intra*molecular 2 + 2 photocycloaddition of an alkenyl-cyclopentene derivative, followed by cyclobutane ring cleavage has been used in the synthesis of (±)-β-bulnesene and its C(1)-epimer.[30,31]

The complementary strategy is to add the cyclopentane ring onto a preformed cycloheptane nucleus (route b). This approach has been applied in the synthesis of several hydroazulene sesquiterpene intermediates[32] as well as in the synthesis of the guaianes (±)-cyclocolorenone,[33] (±)-gnididione,[34] (±)-guaiol,[35] patchouli alcohol and patchoulione,[36,37] and (±)-5-*epi*-sclerosporin.[38] Other hydroazulene sesquiterpenes synthesized this way include the guaianolides (±)-dehydrocustoslactone,[39] (±)-estafiatin,[38] and (±)-grosshemin,[40] the pseudoguaianolide (±)-parthenin,[41] and the trinorguaiane (±)-clavukerin A.[42]

The third strategy towards the hydroazulene skeleton is the rearrangement of [4.3.1]-bicyclodecanes (route c).[43] This approach has been used in the synthesis of (±)-bulnesol[44] and (±)-pyrovellerolactone.[45]

The transannular cyclization of appropriately constructed cyclodecanes is another way to build the hydroazulene skeleton (route d). *In vitro* transformations of germacrane derivatives, providing indirect evidence for possible biosynthetic pathways, were described in Chapter 1.[46,47] The pseudoguaianolides (±)-damsin[48] and (±)-4-deoxy-

damsin,[49,50] and the aromadendrane sesquiterpene (±)-globulol[48,51] have been synthesized by cyclization of cyclodecane intermediates. These cyclodecanes were obtained by the fission of the central bond of hydronaphthalene precursors.

The synthetic approach which is relevant for this thesis is the one which starts with a hydronaphthalene precursor (route e). Examples exist in which the 5,7-fused ring system is formed in two separate ringcontraction and -expansion steps from the 6,6-fused ring precursor [(±)-guaiol and its C(7)-epimer,[52] and (+)-daucene, (+)-carotol, and (-)-daucol[53]]. In the following sections, only the (total) syntheses in which the key-step is the one-step skeletal rearrangement of a hydronaphthalene precursor to the hydroazulene framework will be discussed.

2.3 Skeletal Rearrangements of Hydronaphthalenes to Hydroazulenes

2.3.1 Introduction

Among the first syntheses of hydroazulene sesquiterpenes are the skeletal rearrangements of hydronaphthalene precursors. The strength of this approach is quite apparent. Conformational analysis of both the cis- and the trans-fused hydronaphthalene ring system is well established and the stereoselective introduction of substituents can often be achieved with a minimum of difficulty. Stereochemical problems, associated with the conformationally labile hydroazulene system, are often encountered in the other approaches.

The basic strategy towards hydroazulene systems *via* rearrangement of appropriately substituted hydronaphthalene precursors can be divided in three different categories:
i. photochemical rearrangements of cross-conjugated hydronaphthalene dienones
ii. pinacol rearrangements of hydronaphthalene-1,10-diol monosulfonate esters
iii. solvolytic Wagner-Meerwein rearrangements of 10-methyl-hydronaphthalen-1-ol monosulfonate esters

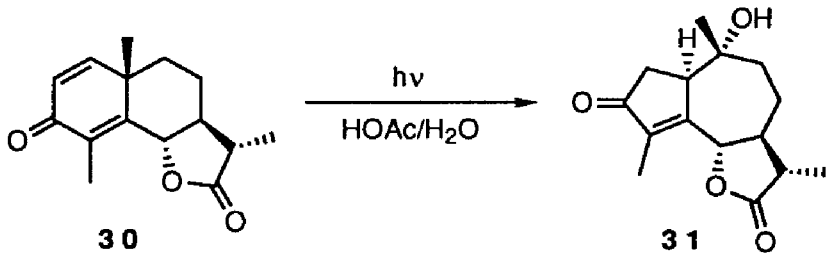
In the following sections, the syntheses of hydroazulene sesquiterpenes based on these different types of rearrangements will be discussed. The examples described will give a good idea of the potentials and the limitations of the different approaches.

2.3.2 Photochemical Rearrangement

The photochemical rearrangement of appropriately functionalized decalin systems is the first methodology discussed here for the preparation of hydroazulene sesquiterpenes. Many of the syntheses following this approach start with the commercially available (-)-α-santonin **30**.[54] The presence of the lactone ring in (-)-α-santonin **30** makes it an ideal precursor for several guaianolides.

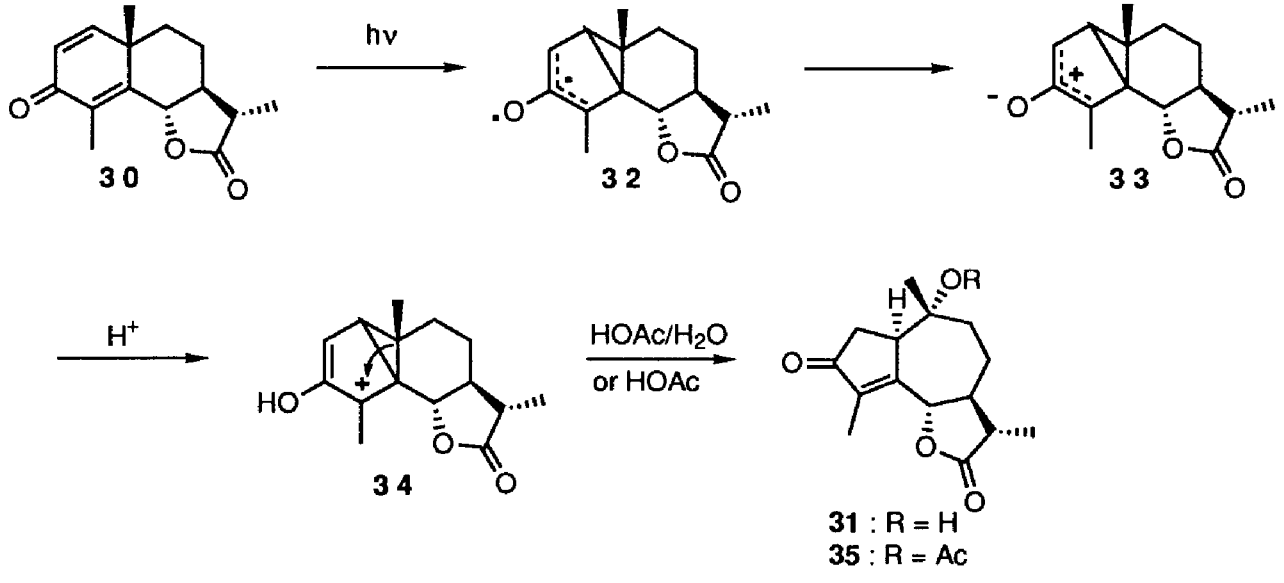
The photochemical rearrangement of (-)-α-santonin **30** was first observed by Barton and co-workers in 1957.[55] They found that (-)-α-santonin **30** rearranged to the isophotosantonic lactone **31** upon irradiation in aqueous acetic acid (Scheme 2.2).

Scheme 2.2



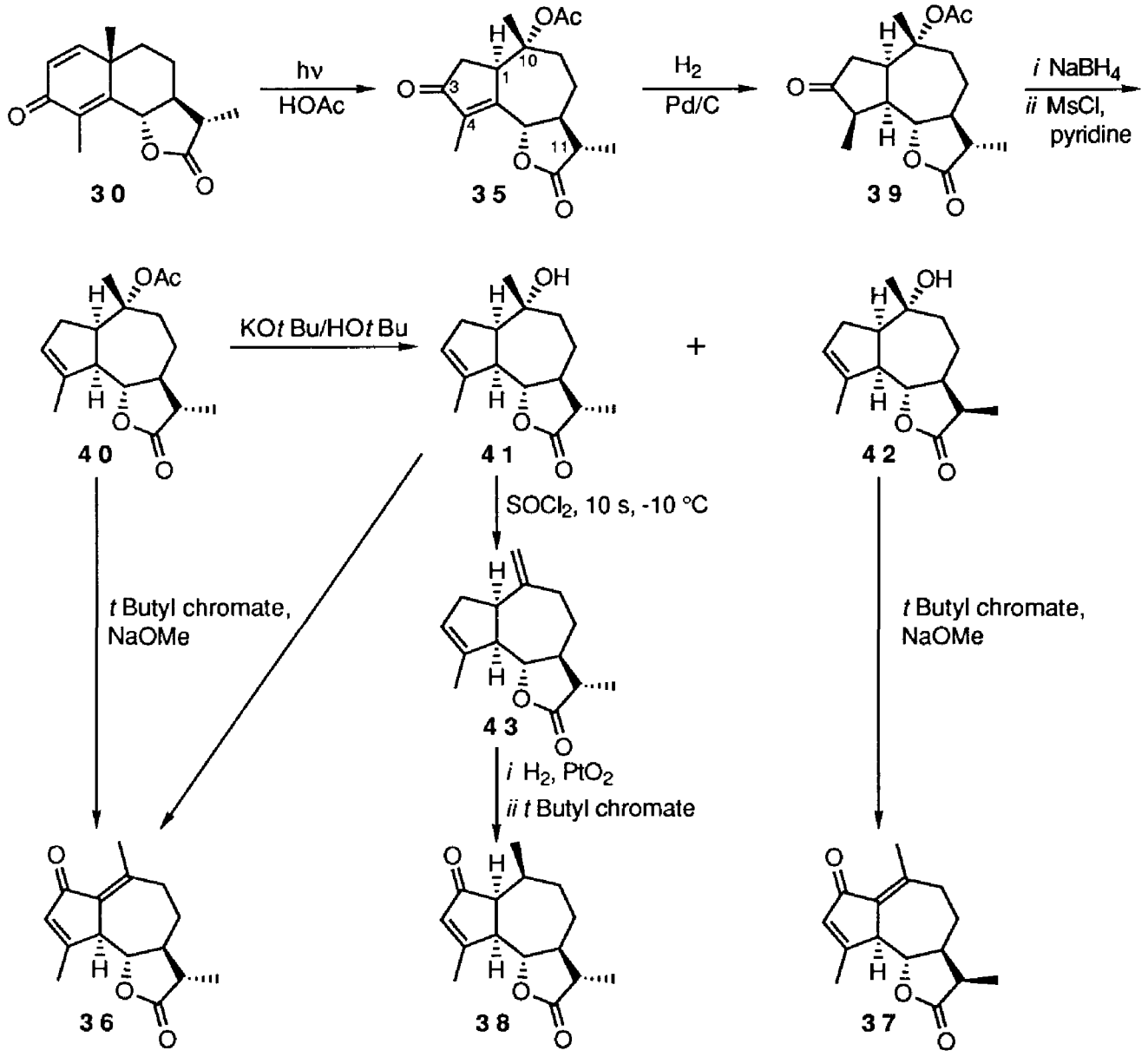
The mechanism of the photochemical rearrangement[56] involves an n → π* electronic transition to the singlet excited state. The singlet undergoes intersystem crossing, followed by 1,5-bonding to give the diradical **32** (Scheme 2.3). This diradical **32** then undergoes π* → n demotion to give the zwitterion **33**, which is protonated to give the

Scheme 2.3



carbocation **34**. Carbocation **34** then cleaves to the 5,7-fused enone **31** or, if glacial acetic acid is used as solvent, the corresponding O-acetyl isophotosantonic lactone **35**.[57]
Later on they demonstrated the general nature of this rearrangement[58] and employed the rearrangement of the related artemisin acetate in the synthesis of geigerin[36,59] and some of its derivatives.

Scheme 2.4



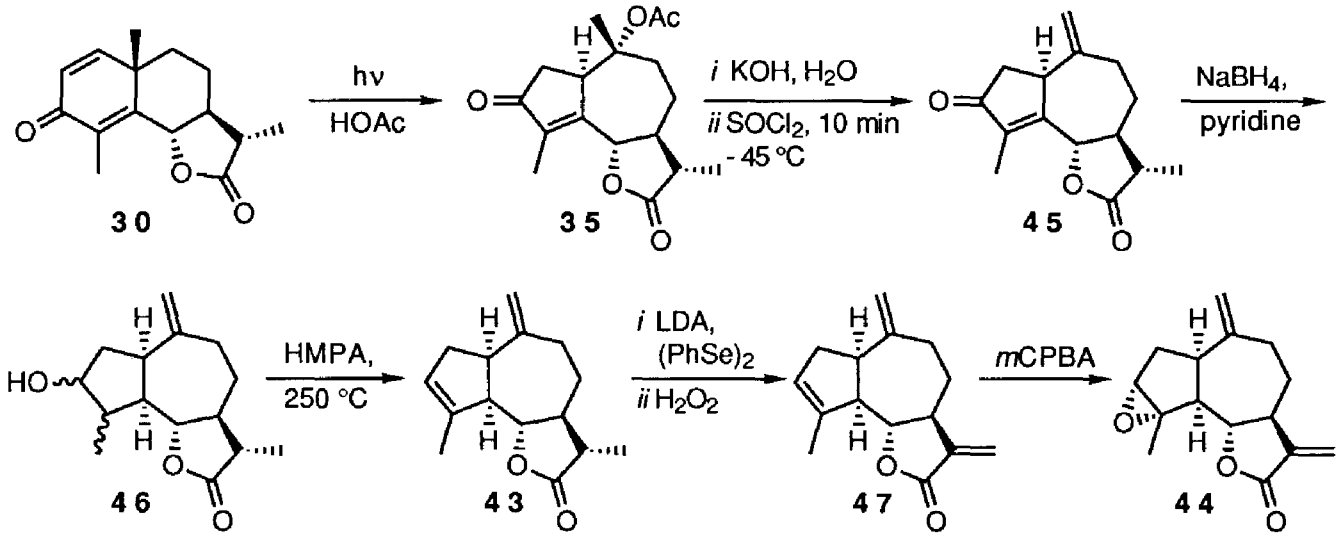
Starting with (-)-α-santonin **30**, Marx *et al.* synthesized (+)-desacetoxymatricarin **36**,[59,60] its C(11)-epimer achillin **37**,[36,60,61] and the related dihydroarbiglovin **38**[36,62] (Scheme 2.4). Photolysis of (-)-α-santonin **30** in glacial acetic acid gave the O-acetyl isophotosantonic lactone **35** in a yield of 30% upon crystallization. Catalytic

hydrogenation (Pd/C) afforded the cis-fused ketone **39**.[63] The following introduction of the C(3)-C(4) double bond proved to be troublesome and the olefin **40** was obtained in 45% upon treatment of **39** with $NaBH_4$ followed by MsCl in pyridine. The problems associated with this transformation find their origin in a partial C(4)-epimerization in **39** and the nonselectivity of the $NaBH_4$ reduction. This resulted eventually in the formation of stable mesylates which could not be eliminated to give **40**.

Allylic oxidation of **40** with *tert*-butyl chromate in acetic acid in the presence of sodium acetate gave (+)-desacetoxymatricarin **36**. Epimerization at C(11) occurred, along with acetate hydrolysis when the lactone **40** was treated with base. The resulting product was an equimolar mixture of the epimers **41** and **42**. Allylic oxidation of **41** again yielded (+)-desacetoxymatricarin **36**, while the C(11)-epimer **42** was transformed into achillin **37**.

Interesting is the transformation of **41** into the cis-fused hydroazulene **43** with an exocyclic double bond. Dehydration with $SOCl_2$ in pyridine at -10 °C for *10 s* resulted in a *ca.* 7:3 mixture of **43** and its $\Delta^{1,10}$ isomer, respectively. When **41** was treated under the same conditions, but for *1 min*, this C(1)-C(10) double bond isomer was found to be the sole product. After catalytic hydrogenation of the exocyclic double bond of **41** over PtO_2, followed by allylic oxidation, dihydroarbiglovin **38** was isolated in 18% yield.

Scheme 2.5

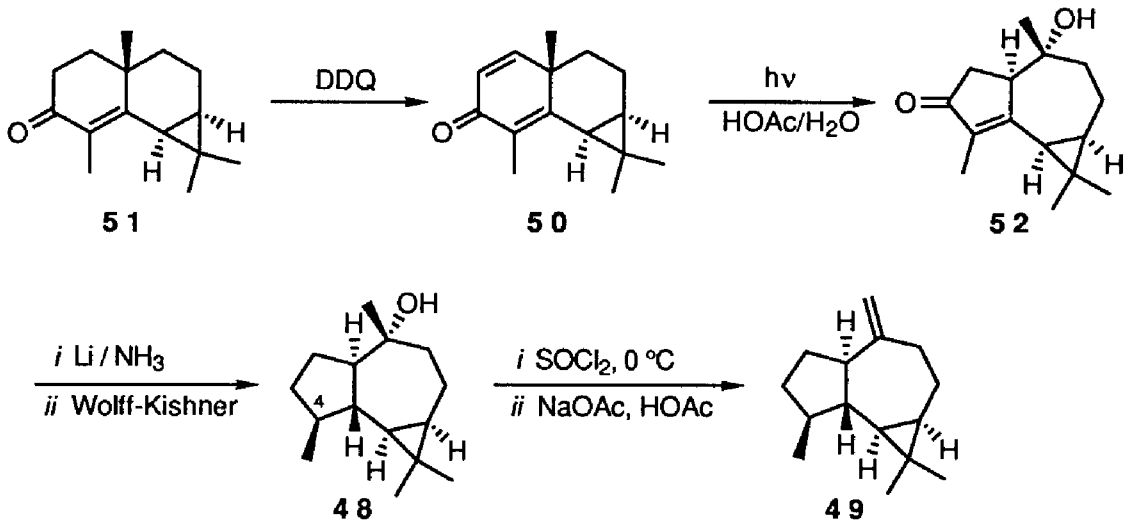


In their synthesis of (-)-estafiatin **44**,[64] Edgar, Greene, and Crabbé employed an alternative reaction sequence towards **43** (Scheme 2.5). The dehydration step was selective and the exo-olefin **45** was obtained in 64% from the O-acetyl isophotosantonic lactone **35**. The most interesting aspect of this synthesis is the reduction of the enone **45** to the cis-fused **46** in *ca.* 70% with a large excess of $NaBH_4$ in pyridine.

Dehydration of **46** also[59] proved to be difficult and **43** was isolated in approximately 25% by the agency of hot HMPA.[65] The final epoxidation of **47** was stereo- and chemoselective giving (-)-estafiatin **44** in 51% yield along with about 10% of the β-epoxide.

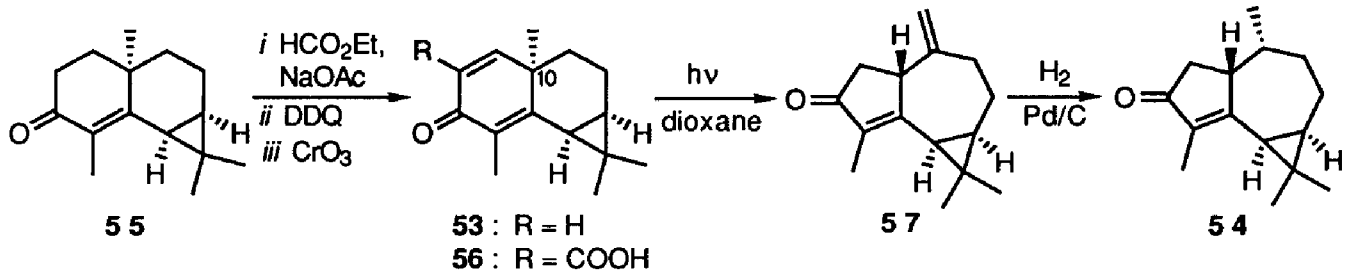
In their synthesis of (-)-4-*epi*-globulol **48** and (+)-4-*epi*-aromadendrene **49**,[66] Caine and Gupton used the photochemical rearrangement of the cross-conjugated cyclohexadienone **50**, which they prepared from (-)-10-*epi*-maalienone **51** by dehydrogenation with DDQ (Scheme 2.6). Dissolving metal reduction of the resulting enone followed by Wolff-Kishner reduction of the carbonyl gave the trans-fused (-)-4-*epi*-globulol **48**, which was dehydrated to (+)-4-*epi*-aromadendrene **49**.

Scheme 2.6

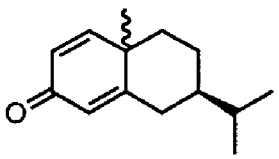


The cross-conjugated dienone **50** readily rearranged when irradiated, but its C(10)-epimer **53** was found to be photochemically stable. For the synthesis of (-)-cyclocolorenone **54**,[67] (-)-maalienone **55** was converted by formylation, dehydrogenation, and oxidation to the dienone acid **56** (Scheme 2.7). This compound readily rearranged with concomitant decarboxylation to the exo-olefin **57** in 60% yield.

Scheme 2.7



55 **53** : R = H; **56** : R = COOH **57** **54**



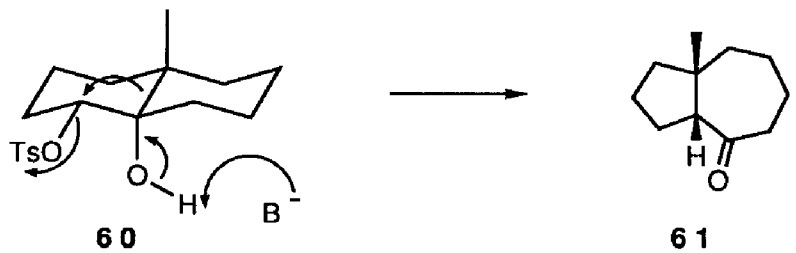
58 : α-Me
59 : β-Me

It is interesting to note that in contrast to the C(10)-epimers **50** and **53**, both the C(10)-epimers **58** and **59**, prepared *via* a Robinson annulation from (-)-carvone, readily rearranged upon irradiation.[68]

2.3.3 Pinacol Rearrangement

The anionic pinacol rearrangement has found limited use in the synthesis of hydroazulene sesquiterpenes. The method was first used for the generation of the hydroazulene skeleton by Mazur and Nussin in 1961.[69] Treatment of the selectively tosylated perhydronaphthalene diol **60** with potassium *tert*-butoxide in *tert*-butyl alcohol at 25 °C or with alumina gave the hydroazulenone **61**, according to the mechanism depicted in Scheme 2.8. A precondition for the rearrangement is an antiperiplanar relationship between the leaving group and the migrating bond.

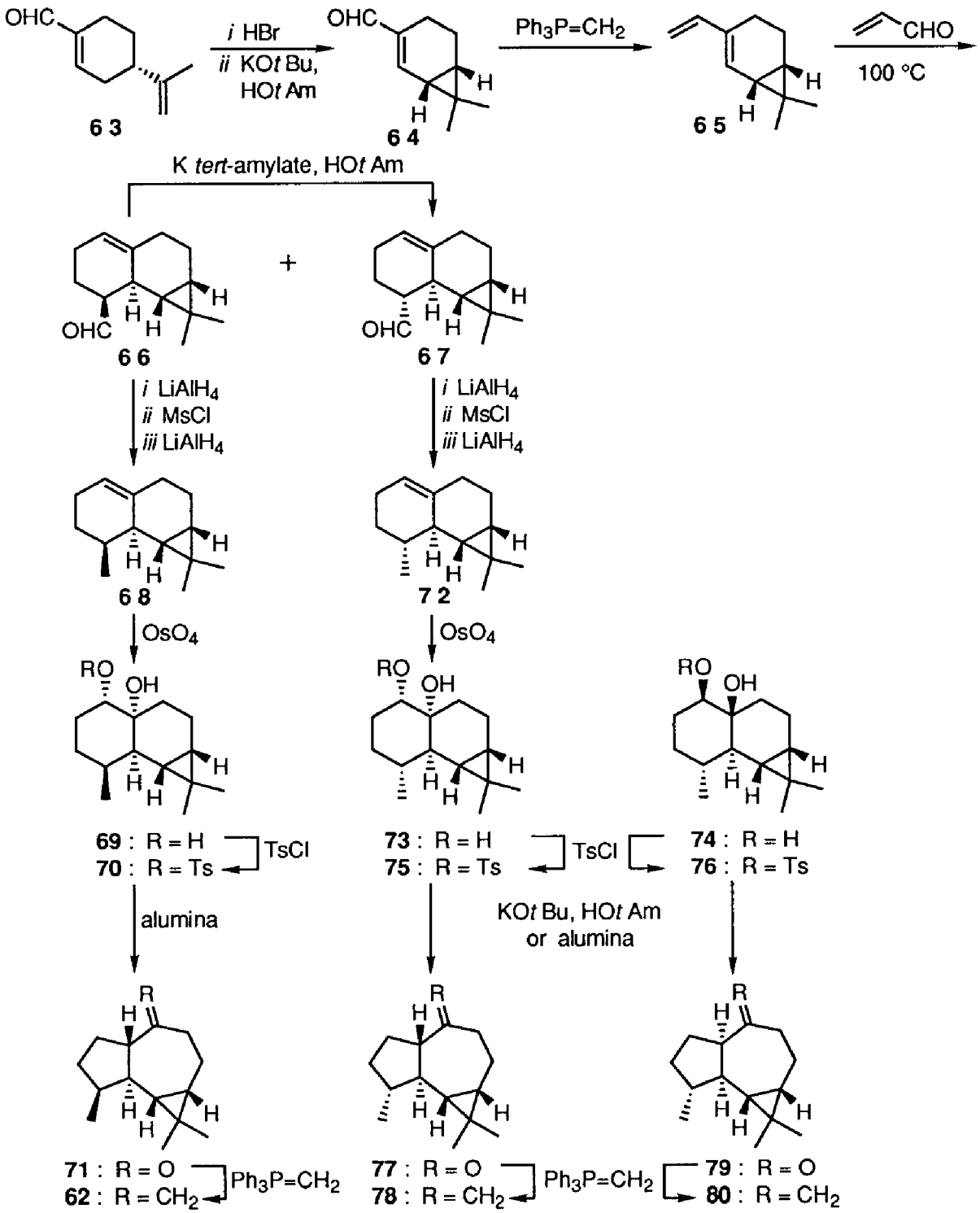
Scheme 2.8



60 **61**

The total synthesis of (-)-aromadendrene **62** and some of its isomers by Büchi and co-workers is the classical example of the use of the pinacol rearrangement in the synthesis of perhydroazulene sesquiterpenes (Scheme 2.9).[70] Starting material was (-)-perillaldehyde **63**. Formation of the *gem*-dimethylcyclopropane ring, followed by a Wittig reaction gave the diene **65**, which reacted with acrolein to give a 5:1 mixture

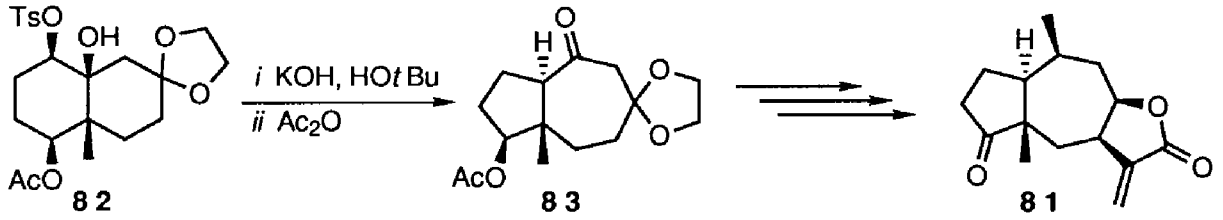
Scheme 2.9



of the aldehydes **66** and **67**, respectively. The major cyclization product **66** was transformed in 7 steps to (-)-aromadendrene **62**. Reduction of the aldehyde to the methyl group by standard methods followed by oxidation with OsO_4 gave a single diol **69** which was selectively tosylated to **70**. When treated with activated alumina in $CHCl_3$, **70** readily underwent the pinacol rearrangement to give apoaromadendrone **71**. By a Wittig reaction, **71** was subsequently converted into (-)-aromadendrene **62**.
Treatment of either of the epimeric aldehydes **66** or **67** with potassium *tert*-amylate in *tert*-amyl alcohol led to an equilibrium mixture of 83% of **67** and 17% of **66**. The more stable epimer **67** was transformed to **72** and the OsO_4 oxidation afforded a mixture of the diols **73** (84%) and **74** (ca. 10%), which were tosylated to **75** and **76** respectively. When the tosylate **75** was treated with 1 equiv of potassium *tert*-butoxide in *tert*-amyl alcohol or chromatographed on alumina, it rearranged to the trans-fused ketone **77**, which in the subsequent Wittig reaction gave (-)-4-*epi*-aromadendrene **78**. The tosylate **76** was transformed to (-)-4-*epi*-alloaromadendrene **80** in a similar reaction sequence.

The key-step in the total synthesis of the pseudoguaianolide (±)-confertin **81** by Heathcock and co-workers[2] was formed by the pinacol rearrangement of **82**, resulting in the ketone **83** (Scheme 2.10). Introduction of the β-methyl group at C(10) and the β *cis*-lactone ring proved to be troublesome and (±)-confertin **81** was eventually isolated in 4.4% overall yield from **82** (14 stages).

Scheme 2.10



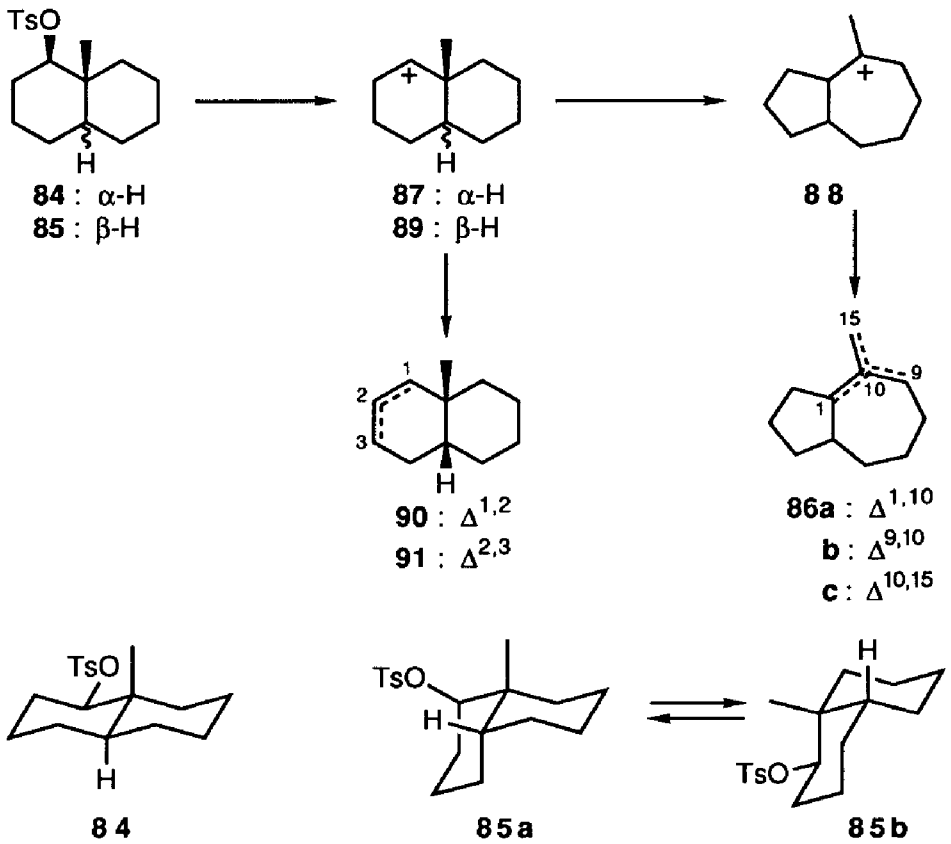
82 **83** **81**

The pinacol rearrangement was also used in the synthesis of the unnatural guaianolide (±)-10-*epi*-4,5-epoxyosmitropsin[71] and a precursor for the hydroazulenic diterpene (±)-portulal.[72]

2.3.4 Solvolytic Wagner-Meerwein Rearrangement

The third type of rearrangement of hydronaphthalene precursors to hydroazulenes is the solvolytic Wagner-Meerwein rearrangement. This approach, developed by Heathcock and co-workers,[73] is based on the discovery that both the *trans*- and the *cis*-10-methylnaphthalenol monotosylates **84** and **85** can undergo solvolytic rearrangement to the hydroazulene products **86** (Scheme 2.11). The rearrangement requires an antiperiplanar relationship between the tosyloxy leaving group and the migrating central bond. In the rigid trans-fused system **84** this requirement is met. On the other hand, the flexible cis-fused system **85** may exist in two conformers and only solvolysis of the nonsteroid conformer **85b** will result in the hydroazulene framework. The steroid conformer **85a** will give rise to the elimination products **90** and **91** with a naphthalene skeleton.[73]

Scheme 2.11

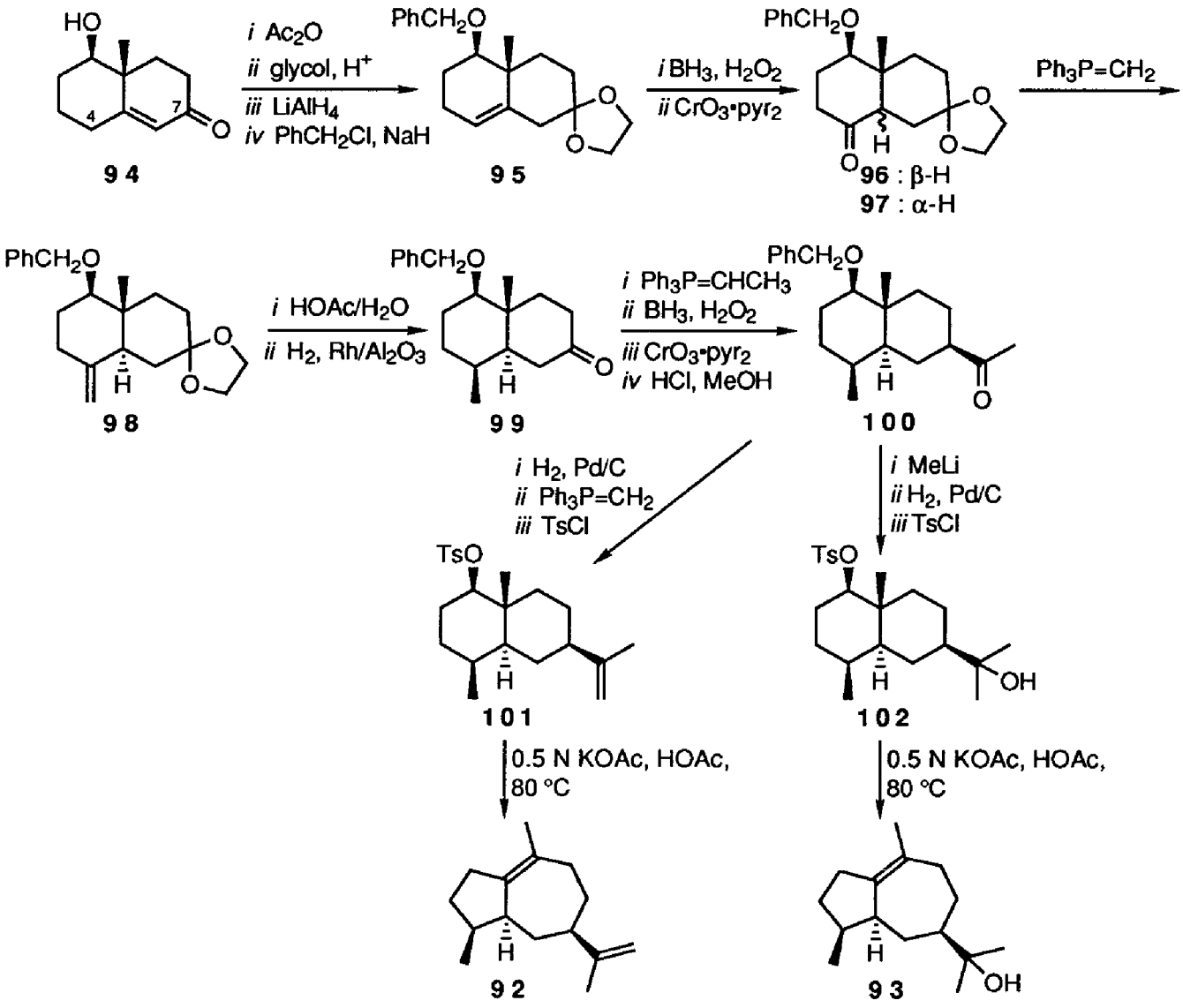


When the trans-fused tosylate **84** is treated under solvolytic conditions (*e.g.* potassium acetate in refluxing acetic acid), ionization of the tosylate bond takes place and the secondary carbocation **87** is formed (Scheme 2.11). By the following 1,2-shift of the central bond the more stable tertiary carbocation **88** is formed. This carbocation **88** may

stabilize itself by proton loss leading to the olefins **86a-c**, in a ratio reflecting their relative stability, or by a reaction with a nucleophile.[46b] If the tosylate group and the central bond are not positioned antiperiplanar as in the *cis*-conformer **85a**, the secondary carbocation **89a** formed by solvolysis will undergo a direct proton loss or a 1,2-shift of a hydride followed by a proton loss, resulting in the olefins **90** and **91**, respectively.[73]

In their synthesis of (±)-α-bulnesene **92** and (±)-bulnesol **93**, Heathcock and Ratcliffe followed the *trans*-decalin route (Scheme 2.12).[74] Ketalization of the carbonyl in **94** caused a migration of the double bond, thereby enabling functionalization of the C(4)-position. Although the *cis*-ketone **96** could easily be epimerized to the *trans*-ketone **97**,

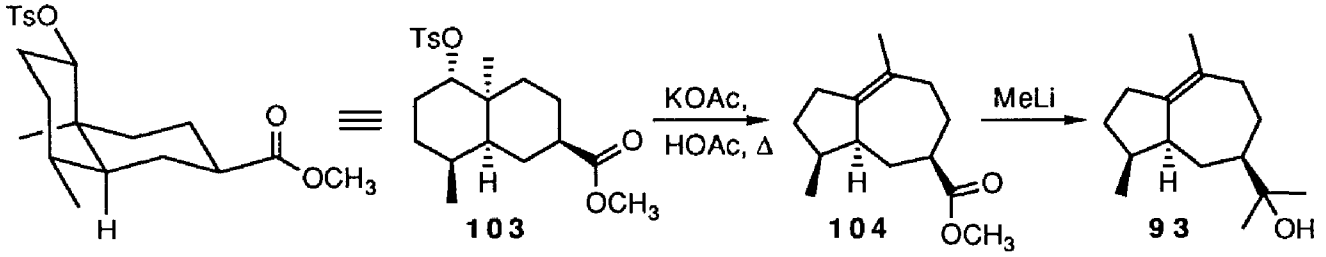
Scheme 2.12



this equilibration step was not necessary as the direct treatment of the 2:1 mixture of **96** and **97** with the Wittig reagent gave only the crystalline trans-fused methylene decalin **98**. The introduction of the β-side chain at C(7) involved an equilibration step of the acyl group to the more stable equatorial position (**100**).[75] Solvolysis of the tosylates **101** and **102** in buffered acetic acid gave (±)-α-bulnesene **92** (16%; 17 steps) and (±)-bulnesol **93** (19%; 17 steps), respectively, as the major products.

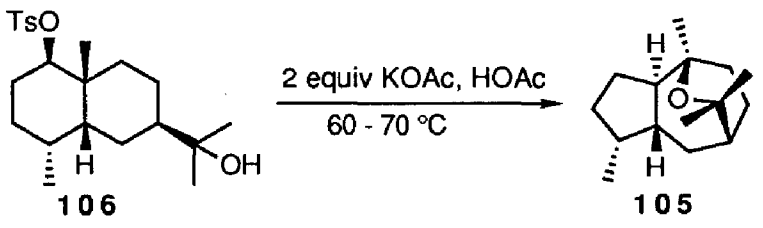
The synthesis of (±)-bulnesol **93** by Yoshikoshi and co-workers is similar to the Heathcock-Ratcliffe synthesis, but proceeds through *cis*-decalin intermediates (Scheme 2.13).[76] The cis-fused tosylate **103** is fixed in the for the rearrangement required nonsteroid conformation and refluxing of the tosylate **103** in buffered acetic acid resulted in the hydroazulene ester **104** which was converted to (±)-bulnesol **93**.
A similar rearrangement of a cis-fused perhydronaphthalene tosylate to α-bulnesene **92** has been described.[36,77]

Scheme 2.13



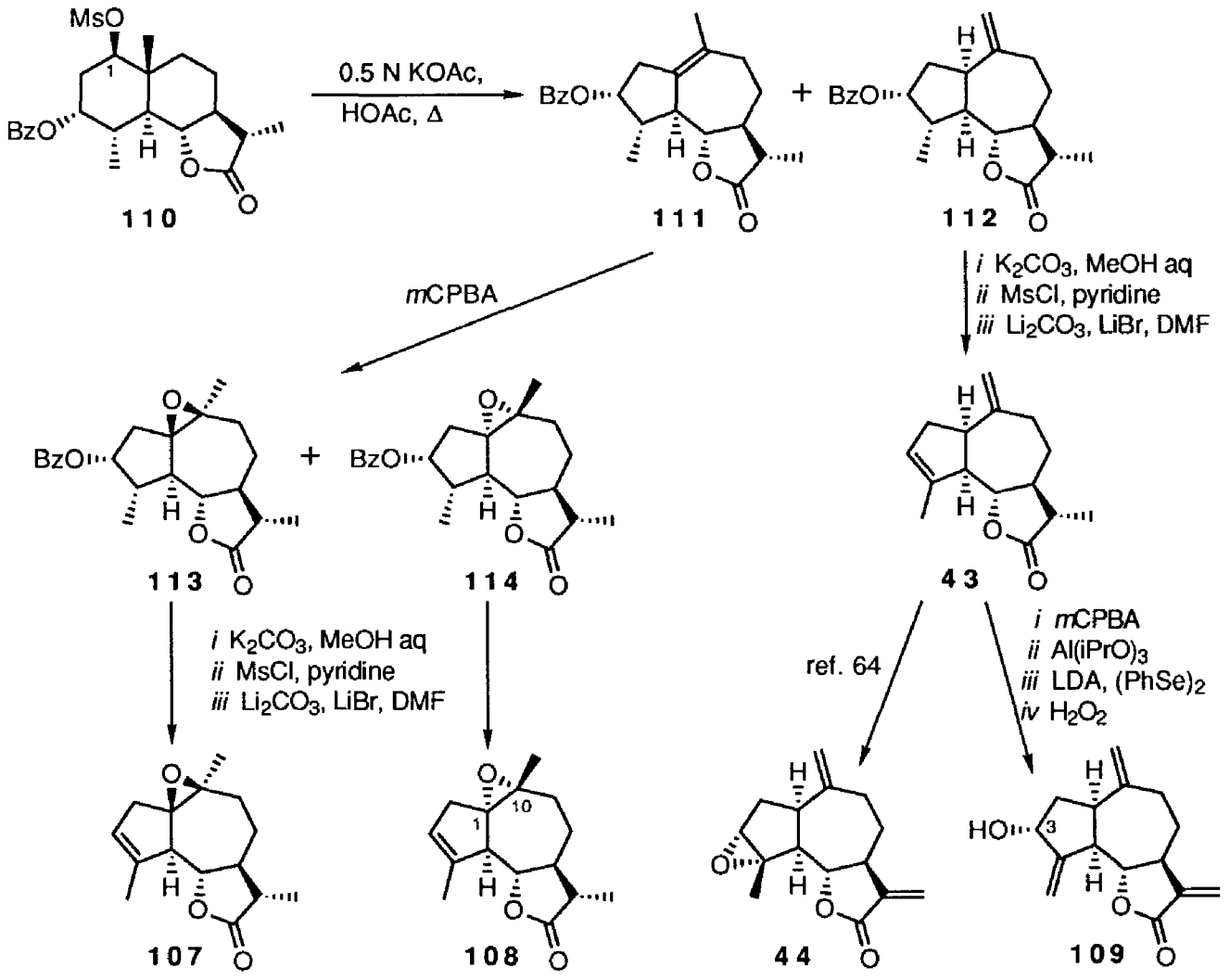
The synthesis of (±)-kessane **105** by Yoshikoshi and co-workers also proceeds via *cis*-decalin precursors (Scheme 2.14).[78] Solvolysis of the tosylate **106**, which is not fixed in its nonsteroid conformation, gave a mixture of three solvolysis products from which (±)-kessane **105**, originating from the intramolecular capture of the intermediary tertiary carbocation (*cf.* **88**) was isolated in 30%.

Scheme 2.14



Ando and co-workers prepared a number of optically active guaianolides by the solvolytic Wagner-Meerwein rearrangement of trans-fused 1β-mesyloxy eudesmanolides derived from (-)-α-santonin **30**.[79] The key-step in their synthesis of (+)-arborescin **107**,[80,81] (+)-1,10-*epi*-arborescin **108**,[80,81] (-)-3-*epi*-zaluzanin C **109**,[82,83] and the Edgar-Greene-Crabbé intermediate **43**[64,81,82] of (-)-estafiatin **44**, was the solvolytic rearrangement of the mesylate **110** which gave a 2:1 mixture of the hydroazulenes **111** and **112**, respectively (Scheme 2.15). Separation of **111** and **112** proved to be difficult, but selective epoxidation resulted in a separable mixture of the isomeric epoxides **113** and **114** (ca. 1:1), and the recovered exo-olefin **112**. Hydrolysis of the β-epoxide **113**, followed by dehydration gave (+)-arborescin **107**, while the α-epoxide **114** was transformed to (+)-1,10-*epi*-arborescin **108**. Hydrolysis, followed by de-

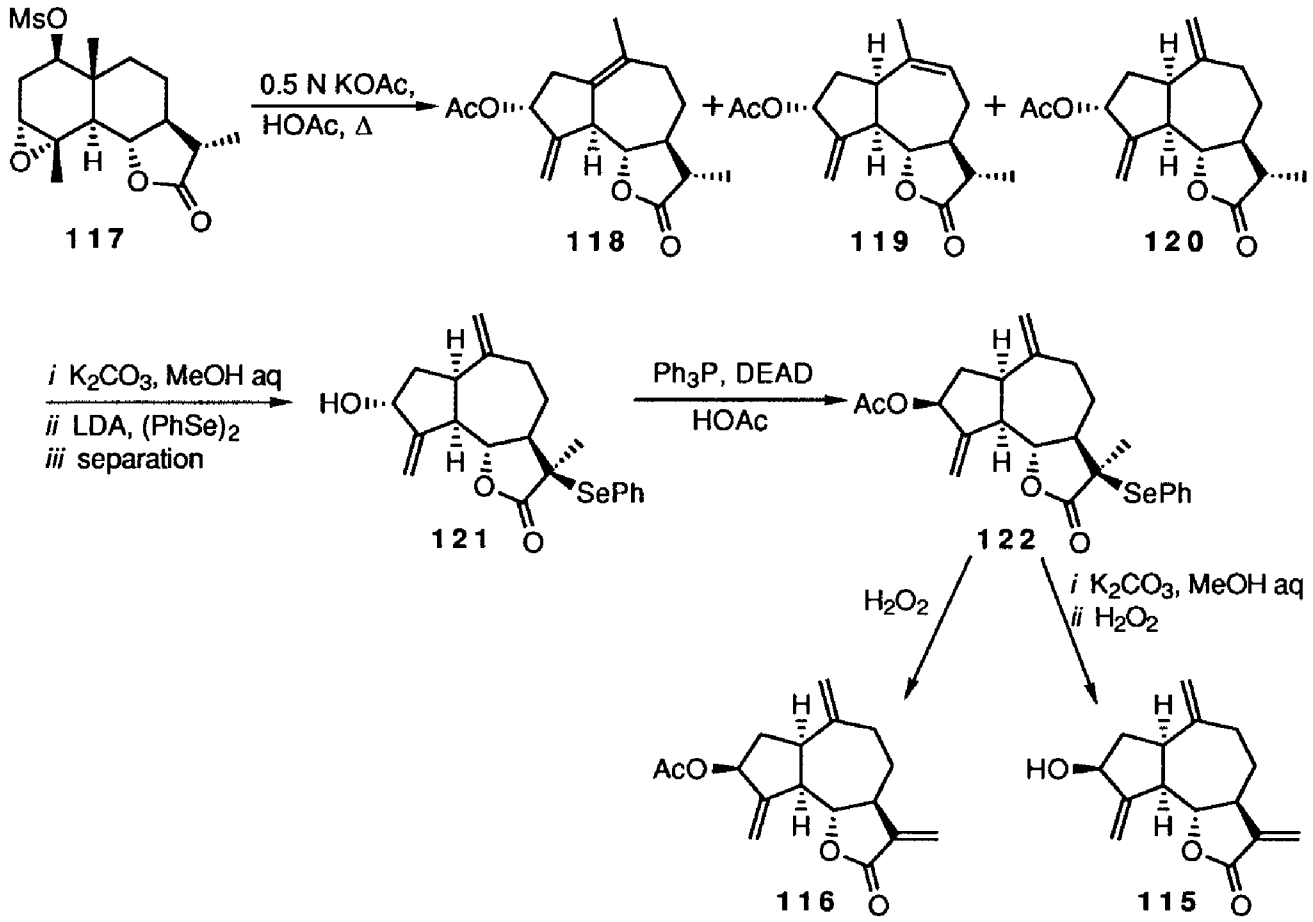
Scheme 2.15



hydration of the exo-olefin **112** gave **43**, from which (-)-estafiatin could be prepared. Stereo- and chemoselective epoxidation of **43** yielded a 3α,4α-epoxide which was treated with aluminum isopropoxide to give the α-allylic alcohol. Phenylselenylation and the successive oxidation of the resulting phenylselenolactone gave the α-methylene-γ-lactone (-)-3-*epi*-zaluzanin C **109**.

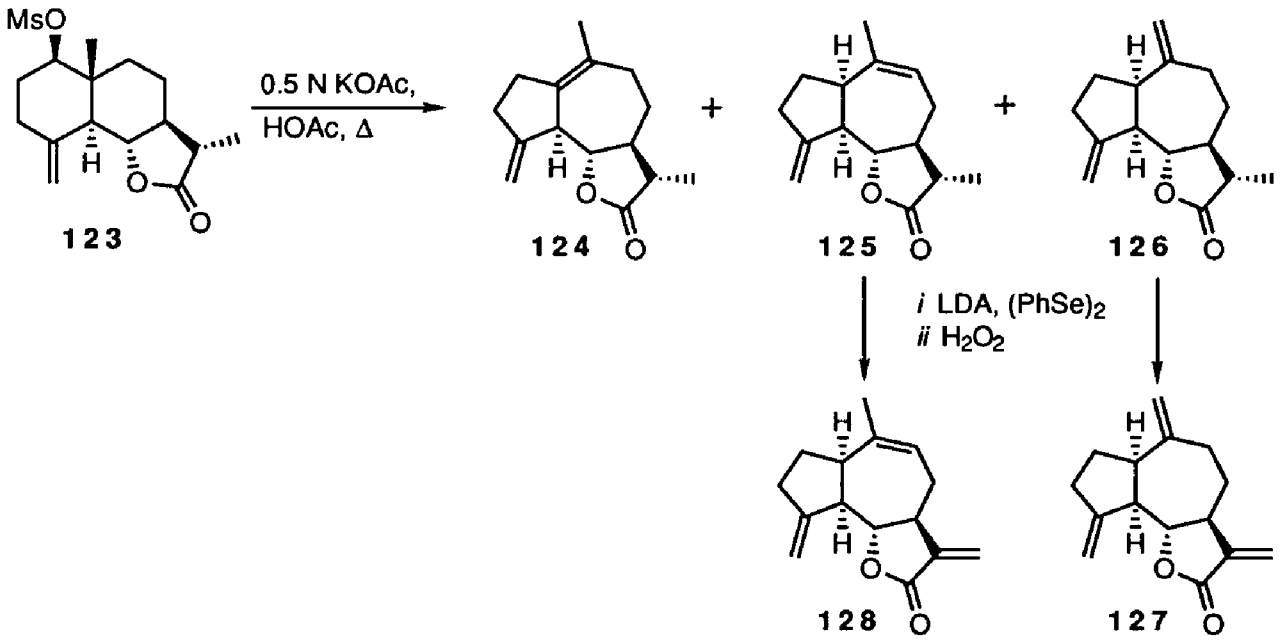
Similarly, the epoxy mesylate **117**, also derived from (-)-α-santonin **30**, was the starting material for the syntheses of (+)-zaluzanin C **115**[82,83] and (+)-zaluzanin D **116**[82,83] (Scheme 2.16). The solvolytic rearrangement of **117** produced a mixture of the double bond isomers **118**, **119**, and **120** in a ratio of 2:1:3, respectively, and a total yield of 75%. The exo-olefin **121** could easily be isolated from the mixture of isomeric compounds after hydrolysis of the acetate group and phenylselenylation. *Via* inversion of the hydroxyl group at C(3) in the Mitsunobu reaction, (+)-zaluzanin C **115** and (+)-zaluzanin D **116** were accessible.

Scheme 2.16



Finally, the solvolytic rearrangement of the mesylate **123** gave a 2:1:2 mixture of the double bond isomers **124, 125,** and **126** (Scheme 2.17).[84] The exo-olefin (+)-mokko lactone **126** could be isolated by selective phenylselenylation of **124** and **125** with 1.5 equiv of LDA and diphenylselenide. Further treatment of the recovered **126** with 2 equiv of LDA and diphenylselenide, followed by oxidative elimination gave (-)-dehydrocostus lactone **127**. The trisubstituted double bond isomer was transformed in the same fashion in (-)-eremanthin **128**.

Scheme 2.17



2.4 References and Notes

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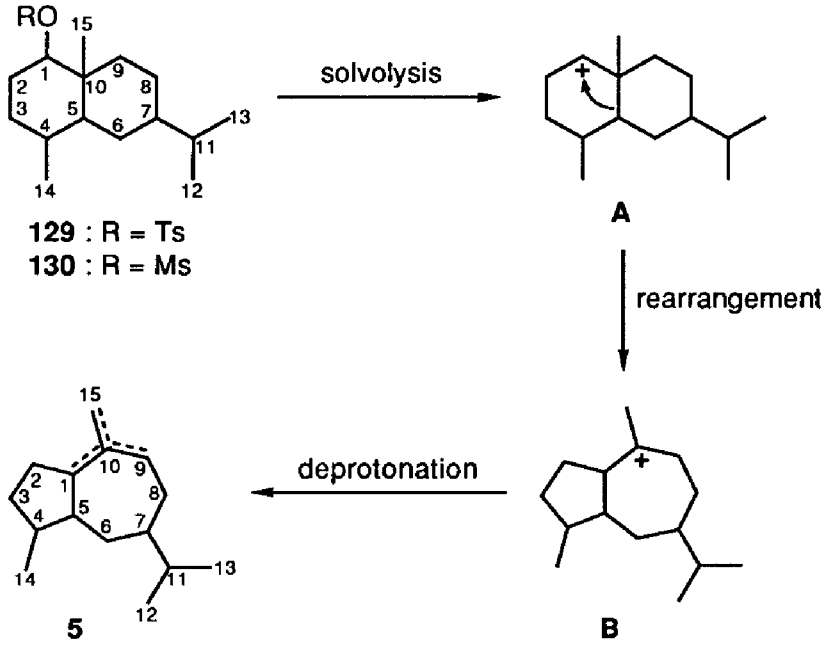
3 Base-Induced and -Directed Rearrangement of Perhydronaphthalene Tosylates

3.1 Introduction

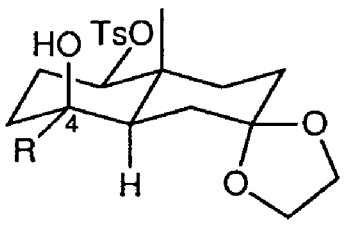
As described in Chapter 2, the rearrangement of appropriately functionalized hydronaphthalene precursors to hydroazulene derivatives is a very attractive strategy for the synthesis of guaianes and other sesquiterpenes bearing a 5,7-fused ring system. Application of this strategy has two major advantages above the other approaches mentioned. In the first place, simple and reliable methods have been developed for the preparation of the hydronaphthalene skeleton. The second and more important factor is the highly developed understanding of the stereochemistry and conformational analysis in hydronaphthalene systems. For this reason, stereoselective syntheses may be designed rather easily in these systems, in contrast to the hydroazulene systems. In the latter, the distinction between axial and equatorial positions is less obvious and influences of substituents on the conformation, especially of the 7-membered ring, are more difficult to predict.

Since a successful method for the preparation of suitably functionalized perhydronaphthalenes for the synthesis of eudesmanes had been developed in our laboratory,[1] it was obvious to investigate the utility of these compounds as intermediates in the synthesis of (cis-fused) guaianes. Solvolysis of the eudesmane sulfonate esters **129** or **130** with concomitant skeletal reorganization will result in the guaiane framework **5**. The driving force for this 1,2-shift of the central bond is the energy the system gains upon going from a secondary carbocation in **A** to a tertiary one in intermediate **B**.
Despite the advantages of the use of hydronaphthalene intermediates in the synthesis of this type of sesquiterpenes, the solvolytic rearrangement has one major drawback. This disadvantage is found in the fact that the rearranged tertiary carbocation **B** has three different positions where the final proton abstraction/loss may take place. (Scheme 3.1). Consequently, solvolytic rearrangement will lead to the formation of mixtures of double bond isomers.[2] Therefore, especially in the case that an exocyclic methylene unit is to be synthesized, the solvolytic rearrangement is not expected to give the desired selectivity, as this isomer is the thermodynamically least favourable one.

Scheme 3.1[3]



In order to synthesize a cis-fused hydroazulene sesquiterpene with an exocyclic C(10)-C(15) double bond *via* rearrangement of a hydronaphthalene intermediate[4], drastic improvement of the selectivity in the deprotonation process was necessary. We expected this selectivity might be attainable if this deprotonation could be directed by the presence of a strategically positioned intramolecular base. We presumed that an axial alcoholate at C(4) might serve this purpose, as it is closely positioned to the former angular methyl group in intermediate **B**. In order to test this assumption, the tosylates **131** and **132** were prepared, both having an axial hydroxyl group at C(4).



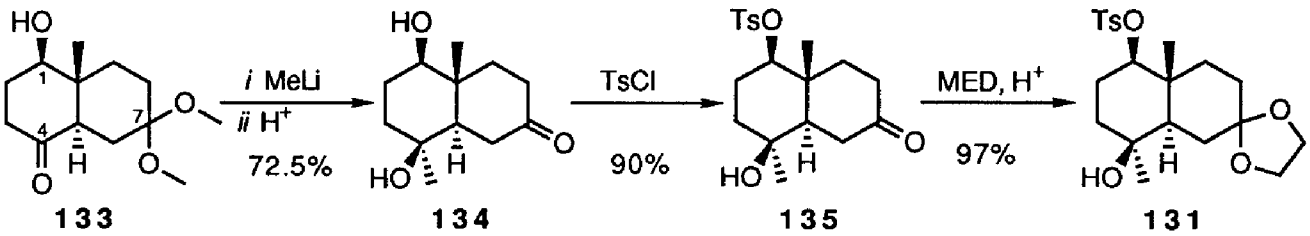
131 : R = CH_3
132 : R = H

In this chapter[5] the syntheses of the tosylates **131** and **132** will be described, followed by the experiments that led to the discovery of the conditions under which a cis-fused hydroazulene with an exocyclic C(10)-C(15) double bond was obtained almost selectively. A mechanism for this reaction will be proposed.

3.2 Synthesis of the Tosylates 131 and 132

The starting material for the synthesis of the tosylates **131** and **132** was the readily available monoacetalized trans-fused dione **133**.[1a] For the preparation of the tosylate **131**, **133** was treated with an excess of MeLi in dry THF at -78 °C, directly followed by hydrolysis of the dimethyl acetal function with aqueous HCl in acetone to give the crystalline diol **134**[6] (Scheme 3.2). The steric hindrance of the angular methyl group

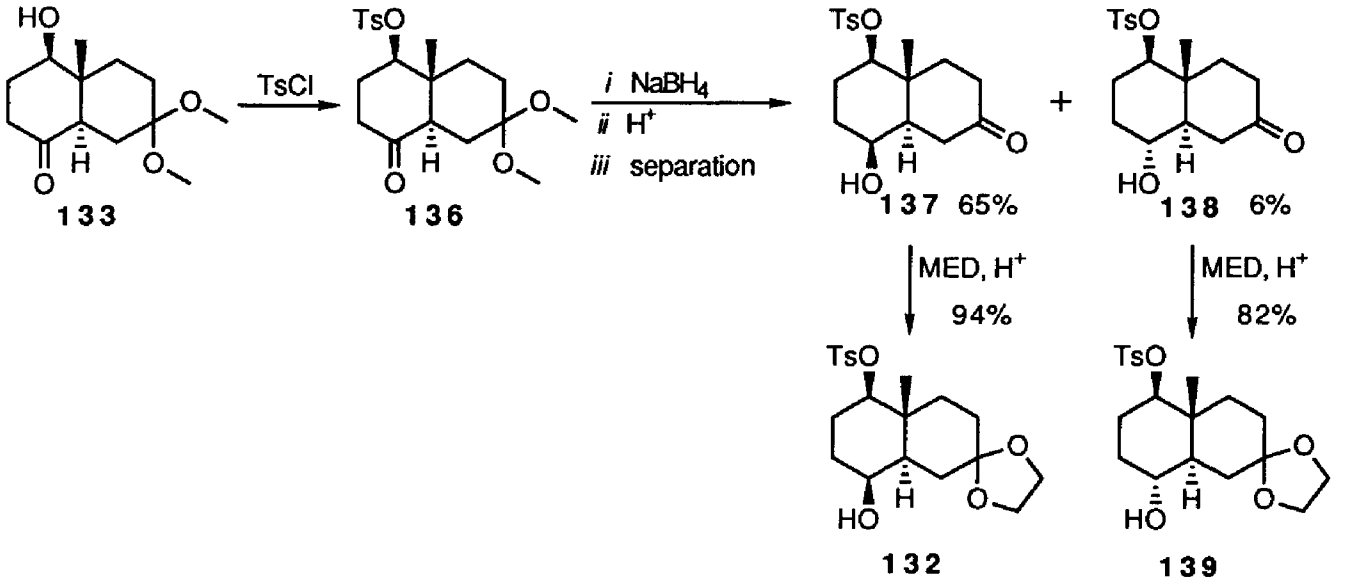
Scheme 3.2



led exclusively to an α-attack on the carbonyl in **133**, and consequently to the desired formation of the axial tertiary β-alcohol at C(4).
Then the secondary alcohol at C(1) was tosylated with TsCl in pyridine and the carbonyl in **135** was protected again, now by treatment with 2-butanone dioxolane (MED).[7] This (protected) carbonyl group at C(7) could eventually be used for the introduction of the isopropyl side chain, which is found in eudesmanes and guaianes at C(7). Protection of the carbonyl was necessary as basic conditions were to be employed in the rearrangement process.

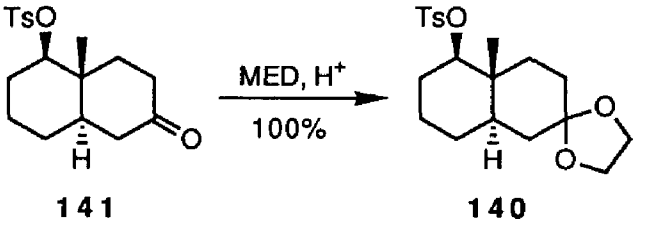
For the synthesis of the tosylate **132**, which has a secondary axial hydroxyl group at C(4), the monoprotected dione **133** had to be reduced in the proper way. Before that the secondary alcohol group at C(1) was first tosylated to give tosylate **136**. The carbonyl at C(4) in **136** was reduced with $NaBH_4$ in EtOH (Scheme 3.3). Again, the steric hindrance of the angular methyl group resulted in a hydride attack primarily on the α-side of the carbonyl, so that the axial secondary alcohol **137** was formed as the major product, along with a small amount of the equatorial alcohol **138**. After hydrolysis of the dimethyl acetal function and chromatographic separation, the tosylates **137** and **138** were treated with MED to give the acetalized secondary alcohols **132** and **139**, respectively.

Scheme 3.3



In order to investigate the rearrangement process in the absence of a hydroxyl group at C(4), the tosylate **140** was prepared straightforward from the known compound **141**[8] (Scheme 3.4).

Scheme 3.4



3.3 Rearrangement Reactions

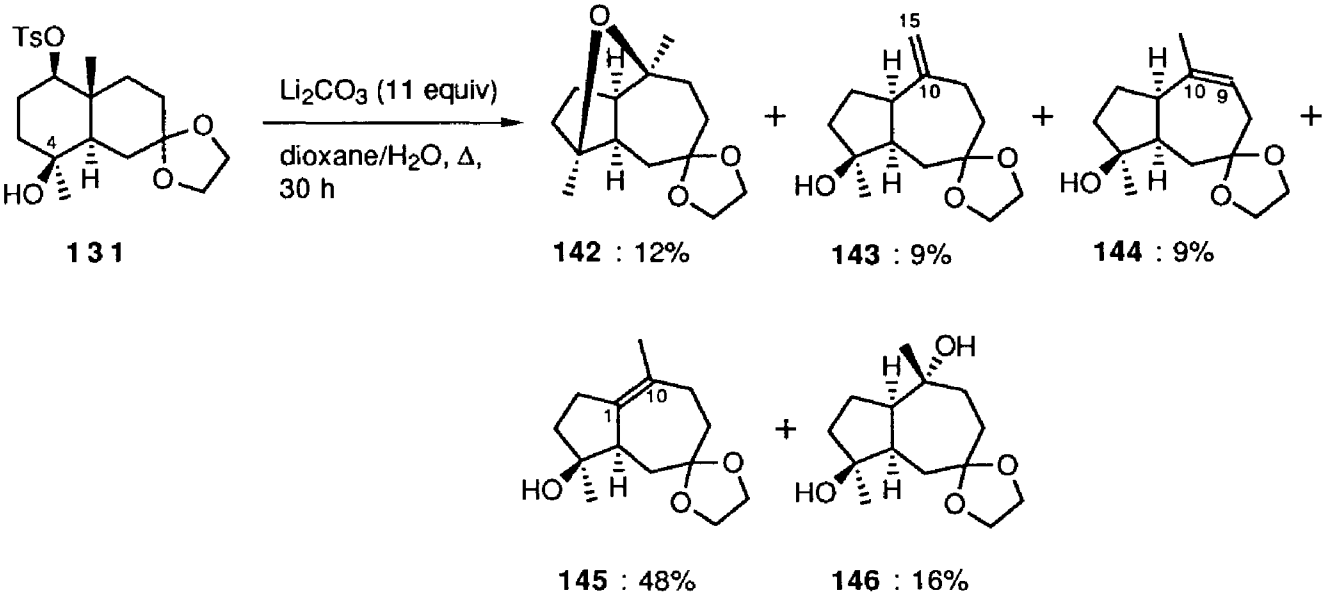
As stated in the introduction, the axial deprotonated hydroxyl group at C(4) was expected to function as an intramolecular base in the deprotonation step of the rearrangement reactions of the tosylates **131** and **132**. It should abstract a proton from C(15) and in this way play a decisive role in the selective formation of the exocyclic methylene unit. Thus, in the rearrangement reactions of the tosylates **131** and **132**, basic conditions had to be employed. The first experiment described here involved the use of a weak base (Li_2CO_3) in refluxing aqueous dioxane, so a solvolytic mechanism

was expected to be operating. It was discovered, however, that under non-solvolytic conditions and with the use of a strong base the rearranged exo 10,15-olefins **143** and **148** were obtained nearly selectively in high yield. Influences of the base concentration and the metal ion on the rearrangement process are described. A mechanism for this non-solvolytic rearrangement process is proposed.

3.3.1 Rearrangement with Lithium Carbonate in Refluxing Aqueous Dioxane

The first rearrangement conditions involved lithium carbonate as a base in refluxing aqueous dioxane.[9] Under these conditions, little if any alkoxide formation is to be expected. A comparable tosylate, with an equatorial hydroxyl group at C(4),[9] was known to give the endo-1,10 olefin as the only double bond isomer, when treated under these conditions for 84 h.
When the tosylate **131** was refluxed in aqueous dioxane with Li_2CO_3, the reaction was completed in 30 h and a mixture of rearranged products was formed (Scheme 3.5).

Scheme 3.5



131

142 : 12%

143 : 9%

144 : 9%

145 : 48%

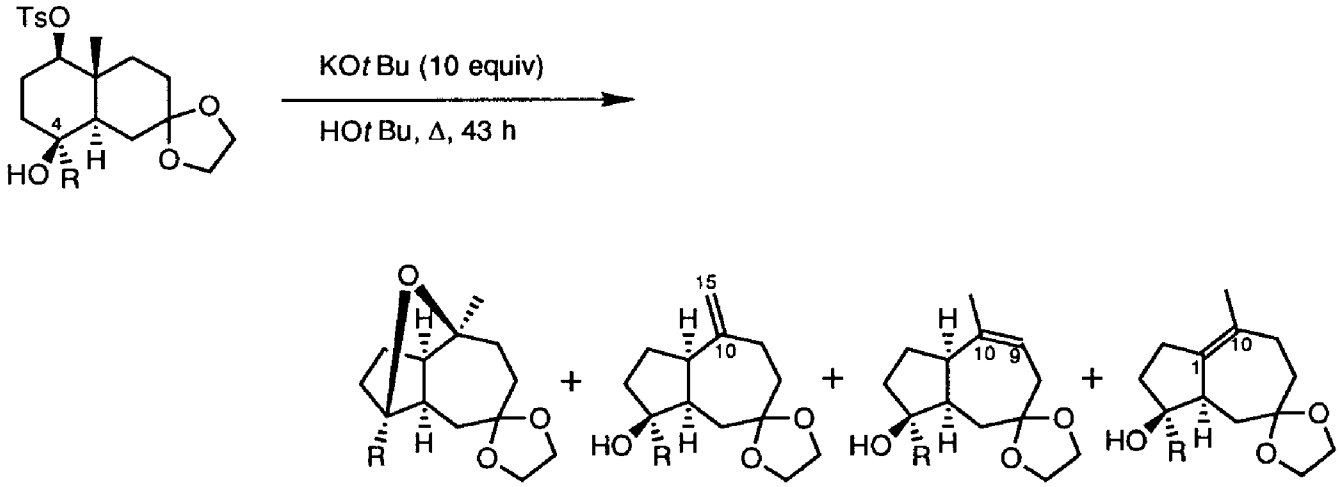
146 : 16%

The presence of the exo 10,15-olefin **143** in this mixture indicated that the axial hydroxyl group at C(4) might have a directing effect on the proton abstraction. Now we decided to investigate the rearrangement reaction under more basic conditions.

3.3.2 Rearrangement with Potassium *tert*-Butoxide in Refluxing *tert*-Butyl Alcohol

When the tosylates **131** and **132** were refluxed in *tert*-butyl alcohol with 10 equiv of potassium *tert*-butoxide, comparable mixtures of rearranged products were obtained in high total yields (90% and 85%, respectively) (Scheme 3.6).

Scheme 3.6



131 : R = CH_3	**142** : 14%	**143** : 53%	**144** : 9%	**145** : 14%
132 : R = H	**147** : 16%	**148** : 44%	**149** : 3%	**150** : 22%

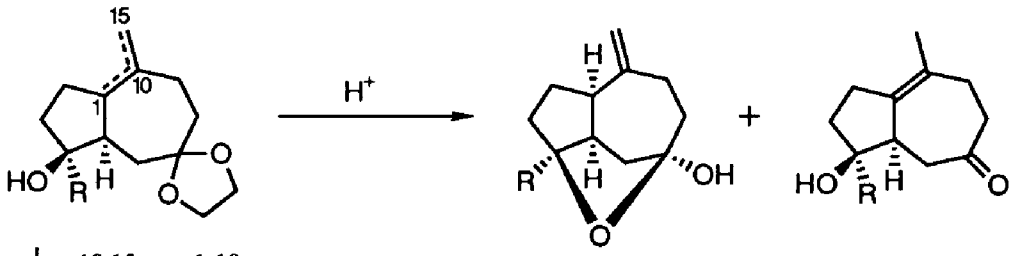
These results show a significant improvement of the selectivity towards the formation of the exocyclic double bond isomers under these conditions. Furthermore, the tosylate **131** with a tertiary β-hydroxyl group is more selective than the tosylate **132** which contains a secondary β-hydroxyl group. Two observations may account for this observation. The first is the fact that a secondary alcoholate is less basic than a tertiary one. As a result, intramolecular proton abstraction is less fast and intermolecular proton loss becomes more important in the case of tosylate **132**. A second explanation is based on steric compression. The tertiary alcohol(ate) in **131** is fixed in its axial position to a greater extent than the secondary one in **132**. Therefore, the tertiary alcoholate will be closer to the angular methyl group and intramolecular deprotonation becomes more apparent.

When a mixture of the rearranged products **148** and **150** was hydrolyzed with HCl in aqueous acetone, the compounds **151** and **152** were isolated (Scheme 3.7).

The IR spectrum of **151** shows no carbonyl absorption, this in contrast to **152** which showed a strong carbonyl absorption near 1700 cm^{-1}. The formation of the cyclic hemiacetal can explain these features and supports the cis-fused hydroazulene

structure of **148**. Similar results were found when **143** and **145** were hydrolyzed to give **153** and **154**, respectively.

Scheme 3.7

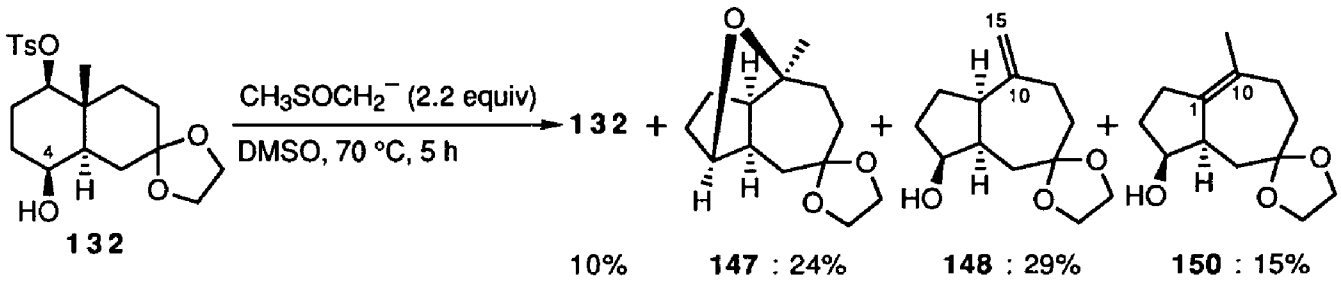


	$\Delta^{10,15}$	$\Delta^{1,10}$		
R = H	**148**	**150**	**151**	**152**
R = CH_3	**143**	**145**	**153**	**154**

3.3.3 Rearrangement with (Dimethylsulfinyl)sodium in Dimethyl Sulfoxide

When the tosylate **132** was treated with 2.2 equiv of (dimethylsulfinyl)sodium in DMSO at 70 °C for 5 h, no improvement of the selectivity was observed. A mixture of the rearranged products **147**, **148**, and **150** was found in a ratio of 5:6:3, respectively (Scheme 3.8).

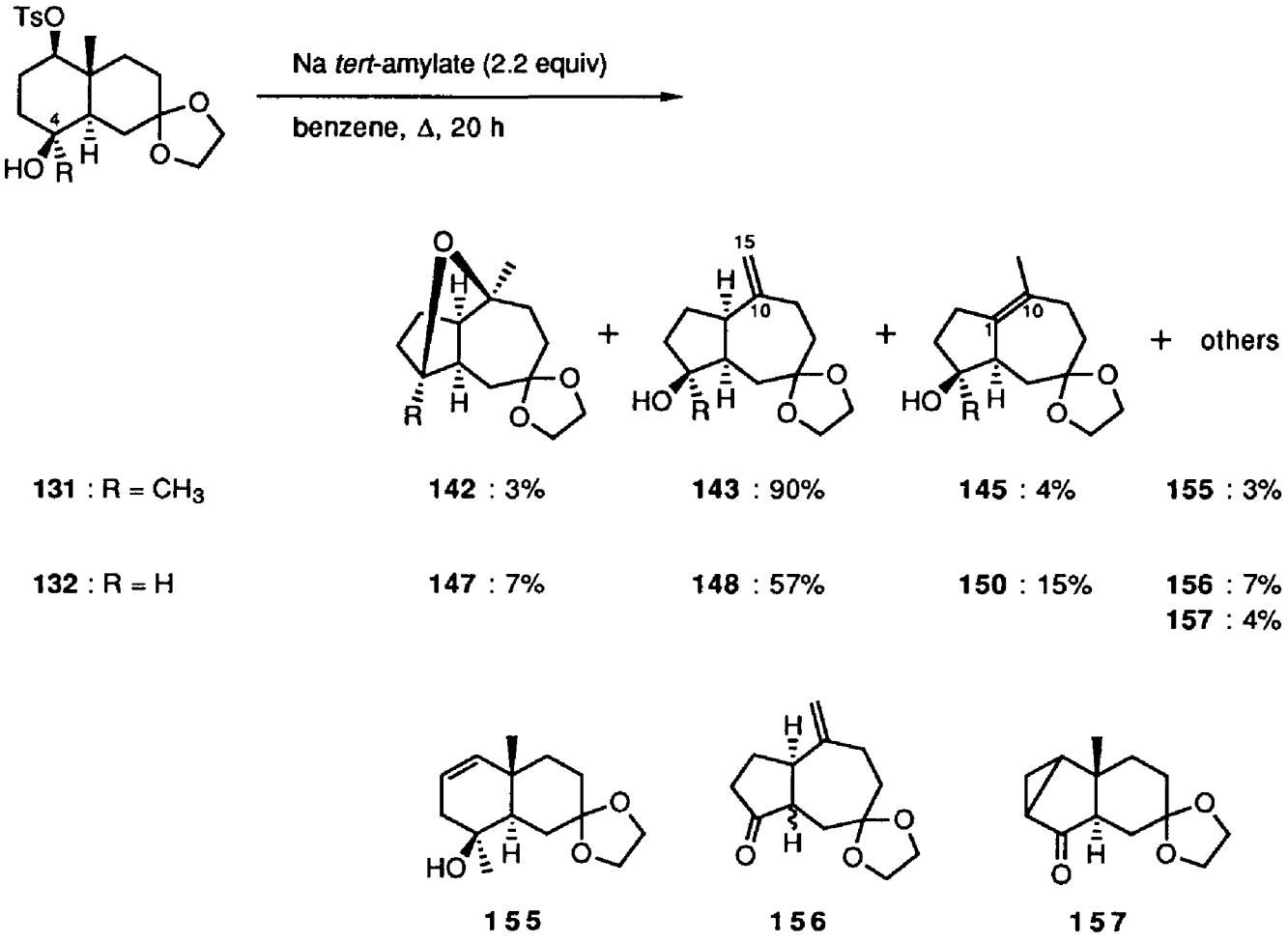
Scheme 3.8



3.3.4 Rearrangement with Sodium *tert*-Amylate in Refluxing Benzene

Eventually, it was discovered[10] that the rearrangement of tosylate **131** could be directed almost selectively to the formation of the exo 10,15-olefin **143** (90% according to GC analysis) by treatment with 2.2 equiv of sodium *tert*-amylate in refluxing benzene (Scheme 3.9). Three side products were identified as the rearranged cyclic ether **142** (3%), the rearranged endo 1,10-olefin **145** (4%), and the unrearranged olefin **155** (3%).

Scheme 3.9



131 : R = CH_3	**142** : 3%	**143** : 90%	**145** : 4%	**155** : 3%
132 : R = H	**147** : 7%	**148** : 57%	**150** : 15%	**156** : 7% **157** : 4%

155 **156** **157**

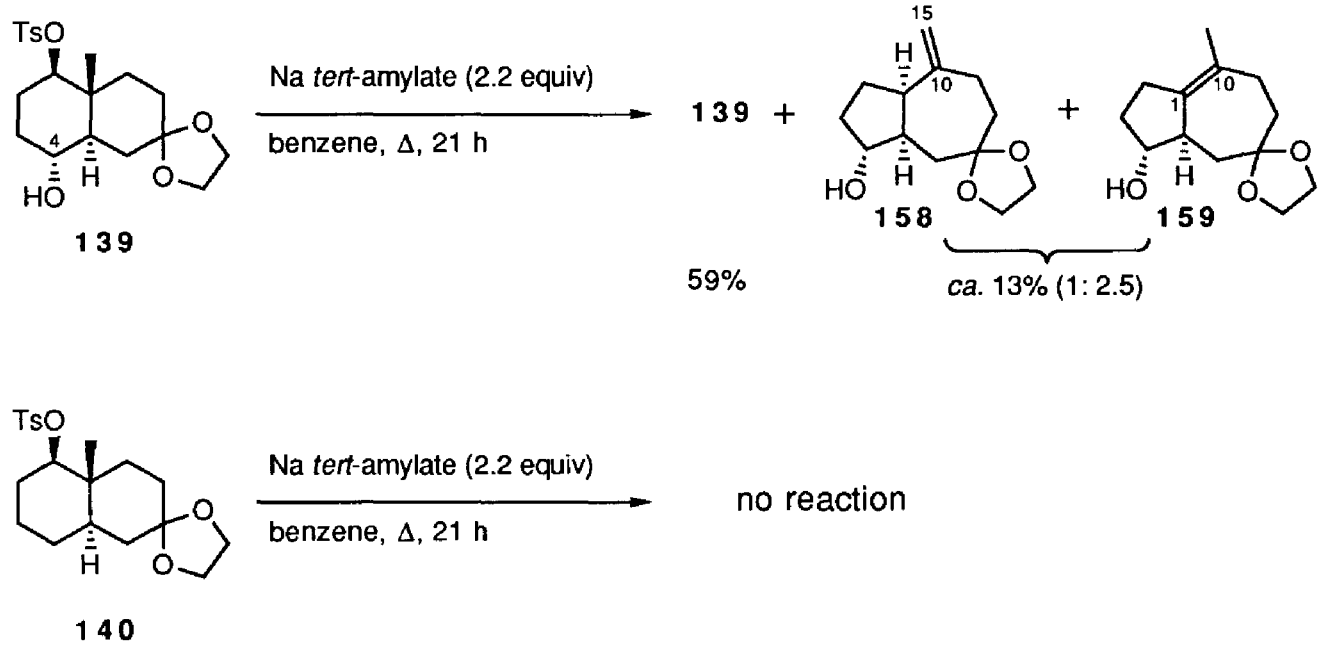
When the secondary β-hydroxy tosylate **132** was treated under these conditions, the rearranged exo 10,15-olefin **148** was again the major product (Scheme 3.9), but now the reaction mixture was somewhat more complex. Apart from the expected cyclic ether **147** and the olefins **148** and **150**, it contained a 2:1 mixture of the rearranged epimeric ketones **156** (7%) and the cyclopropyl derivative **157** (4%).

The formation of the products **156** and **157** can be explained in the following way. Oxidation of **148** by molecular oxygen present in the reaction flask under influence of sodium *tert*-amylate may account for the formation of **156**. Formation of **157** may be attributed to oxidation of the tosylate **132** in a similar way, followed by intramolecular substitution.[11,12]

Again as in the rearrangement reaction with potassium *tert*-butoxide in *tert*-butyl alcohol, a diminished selectivity was found for the secondary β-hydroxy tosylate **132**, when compared to the tertiary alcohol tosylate **131**.

When the tosylate **139**, with an equatorial secondary hydroxyl group at C(4), was treated with 2.2 equiv of sodium *tert*-amylate in refluxing benzene for 21 h, only partial transformation had taken place. After workup and column chromatography, the starting material **139** was recovered in 59%. Only a small amount of products (13%) could be isolated from the reaction mixture (Scheme 3.10). This fraction was, according to GC and ^{1}H NMR analysis, a mixture of mainly two compounds **158** and **159** in a ratio of 1:2.5, respectively. These results indicate that the α-hydroxy tosylate **139** reacts much slower and less selective than the β-hydroxy tosylates **131** and **132**.

Scheme 3.10



Although the conditions used in this rearrangement process (*i.e.* sodium *tert*-amylate in refluxing benzene) made a solvolytic mechanism highly improbable, an experiment was performed to confirm this conjecture. In the tosylate **140**, intramolecular effects will not play any role as the hydroxyl group at C(4) is omitted. That means that only intermolecular, in other words external or solvolytic effects will be looked upon. When this tosylate **140** was treated with 2.2 equiv of sodium *tert*-amylate in refluxing benzene for 21 h, no reaction at all was observed. This means that rearrangement induced by an intermolecular process can be ruled out under the conditions used. Furthermore, no direct elimination of the tosyloxy group occurs under these conditions (*cf.* **155**).

These observations led to the conclusion that the presence of a strategically positioned axial hydroxyl group in the molecule is absolutely essential for a smooth and selective progress of the rearrangement and elimination processes.

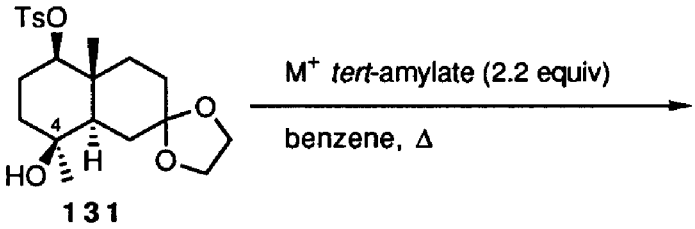
Then the tosylate **131** was treated with 1.1 equiv of pyridine. With this base, no deprotonation of the hydroxyl group at C(4) will take place. After refluxing in benzene for 135 h, no reaction at all had occured and the tosylate **131** was recovered quantitatively after workup. This result proves that deprotonation of the hydroxyl group is absolutely essential for the reaction. In other words, it proves that before any reaction (rearrangement or direct elimination) can take place, the hydroxyl group at C(4) has to be deprotonated.

3.3.5 Role of the Metal Ion in the *tert*-Amylate Rearrangement

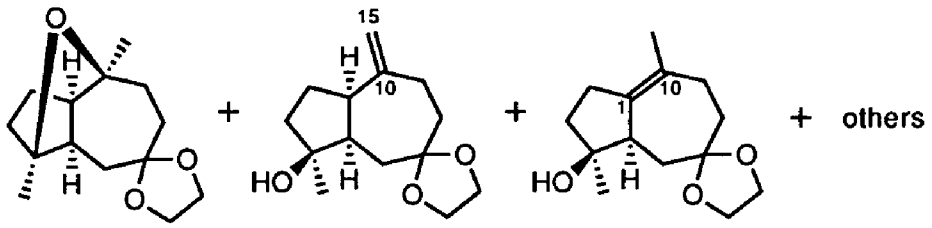
In order to investigate the role of the metal ion in the rearrangement process, the tosylate **131** was also treated with lithium and potassium *tert*-amylate in refluxing benzene. The results of these experiments are given in Scheme 3.11. When potassium *tert*-amylate was used, the selectivity and reaction time (20 h) were about the same as with sodium *tert*-amylate. On the other hand, the use of lithium *tert*-amylate needed a considerably longer reaction time (92 h) and resulted in a lower yield of **143** (59%), while the percentage of **145** increased. Also Grob-like fragmentations,[13] accompanied by a hydride or a methyl shift, leading to **160** and **161**, respectively, were observed.

The higher selectivity and reactivity of potassium and sodium *tert*-amylate when compared to lithium *tert*-amylate can be explained by ion-pairing. The Li^+-O^- bond is stronger (has more covalent character) than the Na^+-O^- or K^+-O^- bond.[14] This makes lithium *tert*-amylate a much weaker base than potassium or sodium *tert*-amylate.[15] Furthermore, it will also result in a lower basicity of the deprotonated hydroxyl group at C(4) in the tosylate **131**, while the inductive power of this alkoxide (see Section 3.4) will be diminished. These effects will result in a slower rearrangement reaction and in a diminished selectivity in the proton abstraction step.

Scheme 3.11

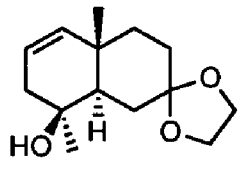


131

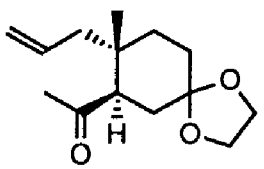


142 **143** **145**

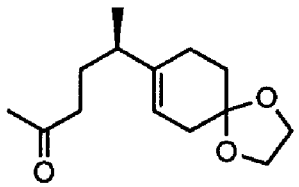
M =	Li	8%	59%	13%	**155** : 2% **160** : 1% **161** : 3%
	Na	3%	90%	4%	**155** : 3%
	K	6%	87%	2%	**155** : 1%



155



160



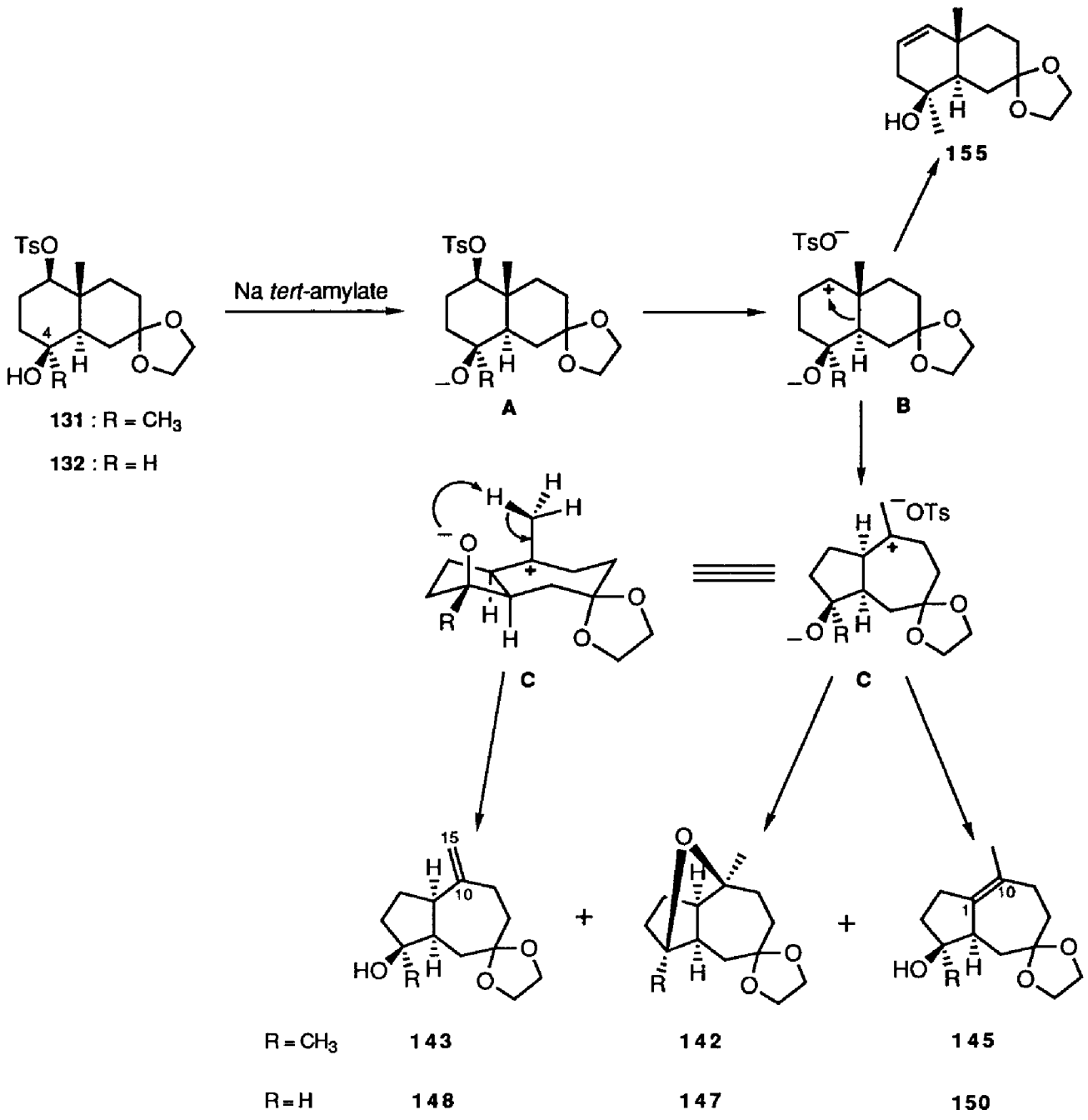
161

3.4 The Mechanism of the Base-Induced and -Directed Rearrangement

The skeletal rearrangement of the tosylates **131** and **132** with sodium *tert*-amylate in refluxing benzene towards the selective formation of **143** and **148**, respectively, as well as the formation of the side products, can now be explained with the following mechanism (Scheme 3.12).

The first step is a deprotonation of the hydroxyl group at C(4) by sodium *tert*-amylate, leading to the intermediate **A**. Heterolysis of the tosylate bond then leads to the formation of the dipolar intermediate **B**. As benzene is used as solvent, it is likely to assume that the tosylate anion is in very close proximity of the secondary carbocation (intimate ion pair).[16,17] The heterolysis of the tosylate bond will be intramolecularly

Scheme 3.12



induced by the deprotonated hydroxyl group at C(4), just as in the Grob fragmentation.[13,18] The inductive power of the O^- group causes an electron delocalization in the σ bonds between itself and the tosylate leaving group. This type of transmission of electronic effects *via* saturated atoms is a very general phenomenon[19] and is called "through bond interaction" (TBI).[20] Especially the donation of electrons to the C(3)-C(2) and the C(5)-C(10) bonds as a result of this TBI-mechanism is important. It enlarges the electron density of these bonds and hence their ability to participate in the ionization process.[21] Both bonds are antiperiplanar to the developing carbocationic 2p orbital at C(1), and therefore the intermediate **B** is stabilized most

effectively by these β-CC bonding electrons.[22] A "through bond" interaction over *both* the C(5)-C(10) and the C(3)-C(2) bond is concluded from the isolation of the Grob-like fragmentation products **161** and **160**, respectively. The observation that the tosylate **139** reacts much slower than the tosylates **131** and **132** may lead to the conclusion that additional acceleration of the ionization process by the axial β-O^--group is obtained by a "through space" interaction.[23,24]

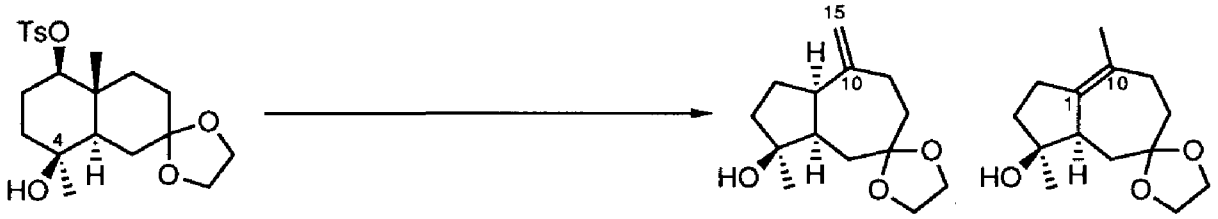
The dipolar intermediate **B** then rapidly rearranges to the thermodynamically more stable intermediate **C**.[8] The original angular methyl group C(15) and the alkoxide at C(4) are close together in this intermediate **C**. As a result, intramolecular proton abstraction is easy and leads to the selective formation of the exo 10,15-olefins **143** and **148**.
The cyclic ethers **142** and **147** are formed from the corresponding intermediates **C** by a direct trapping of the positive charge at C(10) by the proximate alkoxide at C(4).[25] A intermolecular, thermodynamically favourable deprotonation of the intermediates **C** leads to the endo 1,10-olefins **145** and **150**.
Finally, (intramolecular) deprotonation of the intermediate **B** accounts for the formation of the unrearranged olefin **155**.

3.5 Influence of the Sodium *tert*-Amylate Concentration and the Amount of *tert*-Amyl Alcohol on the Rearrangement

In the experiments described so far, sodium *tert*-amylate was prepared *in situ* from 2.2 equiv of NaH and 4.6 equiv of *tert*-amyl alcohol prior to the addition of the substrate. Later on[26] we prepared a solution of sodium *tert*-amylate (3.5 M in toluene) by refluxing *tert*-amyl alcohol with an excess of metallic sodium in toluene. Refluxing was continued until all *tert*-amyl alcohol had reacted (3 d).[27] When this sodium *tert*-amylate solution in refluxing toluene was used in the base-induced rearrangement of the tosylate **185**,[26a,28] a very fast (7 min) but less selective reaction was observed. Although a different substrate and a different solvent (toluene: bp 111 °C) could very well account for the observed differences, we decided to perform a series of experiments with the tosylate **131** and this sodium *tert*-amylate solution, in which we varied the base concentration of the solution and the amount of *tert*-amyl alcohol. As a measure for the selectivity of the proton abstraction step of the reaction of the tosylate **131**, the ratio between the rearranged olefins **143** and **145** was taken (Table 3.1).

The results show that when the sodium *tert*-amylate concentration is higher, the reaction rate is also higher. This is explained by the fact that before any reaction can take place, the hydroxyl group at C(4) in the substrate **131** has to be deprotonated. This deprotonation will be an equilibrium reaction and addition of more sodium *tert*-amylate will shift the equilibrium towards the deprotonated tosylate **131**. At the same time, however, addition of more sodium *tert*-amylate will facilitate intermolecular deprotonation at C(1), resulting in the endo 1,10-olefin **145**.

Table 3.1



131

no	base	solvent	reaction time	**143** : **145**
1	2 equiv Na *tert*-amylate	benzene	300 min	12.4 : 1
2	5 equiv Na *tert*-amylate	benzene	50 min	7.2 : 1
3	10 equiv Na *tert*-amylate	benzene	23 min	6.8 : 1
4	5 equiv Na *tert*-amylate + 5 equiv *tert*-amyl alcohol	benzene	180 min	12.6 : 1
5	2 equiv Na *tert*-amylate + 5 equiv *tert*-amyl alcohol	toluene	90 min	19.0 : 1

Comparison of the entries 2 and 4 shows that addition of *tert*-amyl alcohol to the reaction mixture lowers the reaction rate. This can be explained by a simple shift of the deprotonation equilibrium (*tert*-amylate + **131** $\rightleftharpoons$ *tert*-amyl alcohol + deprotonated **131**) to the left. In reality, however, the situation is more complicated. It is well established that in nonhydroxylic solvents of low polarity like benzene, alkali metal-alkoxide ion-pairing interactions are very important and higher aggregates of ion-paired alkoxides are present.[29] These aggregates of ion pairs appear to be the effective base species.[29] Addition of *tert*-amyl alcohol will result in a co-clustering of the alcohol to the sodium *tert*-amylate aggregates.[30] This co-clustering will lower the basicity of the sodium *tert*-amylate aggregates. Addition of *tert*-amyl alcohol will consequently retard the deprotonation of the hydroxyl group of the substrate **131**, thereby lowering the reaction rate.[31] As the basicity of the solution is diminished, the intramolecular proton abstraction becomes more pronounced, which is reflected in a higher **143**:**145** ratio. The fact that the highest selectivity in this series of experiments

was found when 2 equiv of sodium *tert*-amylate and 5 equiv of *tert*-amyl alcohol were added to the reaction mixture (entry 5) may now be obvious. The relatively short reaction time of this experiment is explained by the fact that this reaction was carried out in refluxing toluene.
Addition of 2 equiv of sodium *tert*-amylate (entry 1) will also result in relatively high quantities of *tert*-amyl alcohol, due to proton exchange with the tosylate **131** and the olefins **143** and **145**. As a consequence, the ratio between the rearranged olefins **143** and **145** will be higher than the one found upon addition of 5 or 10 equiv of sodium *tert*-amylate and equals the one found in entry 4.
The high selectivity found in the rearrangement of the tosylate **131** with 2.2 equiv of sodium *tert*-amylate and 2.4 equiv of *tert*-amyl alcohol (section 3.3.4) also fits very nicely into this picture.

These results show that the highest selectivity is obtained if the basicity of the external base, thus the basicity of the sodium *tert*-amylate aggregates, is somewhat diminished or moderated. Then, intramolecular proton abstraction from C(15) by the alcoholate at C(4) becomes the dominant reaction to a still greater extent. This moderation of the sodium *tert*-amylate basicity is obtained by relatively high amounts of *tert*-amyl alcohol in the reaction mixture.

The choice of an aprotic solvent as benzene also appears to be very important for the selectivity of the proton abstraction step of the reaction. In *tert*-butyl alcohol a lower selectivity was found (see section 3.3.2). It is known that alkali metal alkoxides are stronger bases in aprotic solvents like benzene then in *tert*-butyl alcohol.[30] In the protic *tert*-butyl alcohol the basicity of the alcoholate at C(4) in the substrate is diminished due to H-bridging with the solvent. Consequently, intermolecular deprotonation becomes a more dominant reaction path, which results in a decreased selectivity. Furthermore, a longer reaction time was observed in the rearrangement process with potassium *tert*-butoxide in *tert*-butyl alcohol. This can be explained by the fact that even with an excess of potassium *tert*-butoxide, relatively low equilibrium concentrations of alkoxides are produced in *tert*-butyl alcohol, particularly when tertiary hydroxyl groups are involved.[32]

3.6 Concluding Remarks

The results presented in this chapter show that the rearrangement of appropriately substituted perhydronaphthalenes in refluxing benzene with sodium *tert*-amylate offers a reliable and highly selective access to cis-fused hydroazulene compounds with an exocyclic methylene unit. Under the conditions used, deprotonation of the axial hydroxyl group at C(4) is absolutely essential for the reaction. In the first place, this deprotonation triggers of the series of processes leading to the hydroazulene framework. Secondly, the deprotonated axial hydroxyl group ensures the selective formation of the exocyclic C(10)-C(15) double bond.

3.7 Experimental Section

General

Melting points are uncorrected. Chemical shifts are reported relative to TMS (δ 0.00). IR spectra were recorded on a Jasco A-100 infrared spectrophotometer. MS data were determined at 70 eV on either an AEI MS 902 spectrometer or a VG Micromass 7070 F spectrometer. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. GC analyses were carried out with FID and a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically. Column chromatography was performed on Merck silica gel 60 (70-230 mesh) or ICN alumina B-Super I (activity grade II). Flash chromatography was performed on Merck silica gel 60 (230-400 mesh).

Solvents were dried and freshly distilled by common practice. For all dry reactions, flasks were dried at 150 °C and flushed with dry N_2 just before use, and reactions were carried out under an atmosphere of dry N_2. Product solutions were dried over anhydrous Na_2SO_4, unless otherwise noted, prior to evaporation of the solvent under reduced pressure on a rotary evaporator. 2-Butanone dioxolane (MED) was prepared from 2-butanone as reported.[7] A solution of sodium *tert*-amylate (3.5 M in toluene) was prepared as described elsewhere.[27]

(4aα,5α,8α,8aβ)-Octahydro-5,8-dihydroxy-4a,8-dimethyl-2(1*H*)-naphthalenone (134).

To a solution of 9.92 g (40.99 mmol) of dimethyl acetal **133**[1a] in 350 mL of dry THF, cooled to -78 °C, was added dropwise 90 mL (144.0 mmol) of MeLi (1.6 M in ether). When the addition was complete, the reaction mixture was allowed to stir for 1 h at -78 °C. The excess MeLi was then quenched by the careful addition of saturated

aqueous NH_4Cl. The reaction mixture was washed with 300 mL of brine and the aqueous phase was then continuously back-extracted with CH_2Cl_2. The combined organic layers were dried and evaporated under reduced pressure, and the resulting residue was taken up in a mixture of 50 mL of acetone and 2.5 mL of 15% aqueous HCl. The reaction mixture was allowed to stir at rt for 5.5 h, and then neutralized with Et_3N. Evaporation of the solvent under reduced pressure and chromatography of the residue on silica gel (ether) gave 6.30 g (72.5%) of pure diol **134**: mp 151-153 °C (from EtOAc); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.15 (s, 3 H), 1.25 (s, 3 H), 1.29-2.77 (m, 13 H), 3.30 (m, 1 H); MS, *m/e* (rel intensity) 212 (M^+, 13), 194 (100), 141 (58), 137 (53), 136 (71), 111 (55), 109 (47), 101 (58), 95 (69), 83 (40), 72 (91), 43 (98); calcd for $C_{12}H_{20}O_3$ (M^+) *m/e* 212.1412, found *m/e* 212.1412. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.08; H, 9.29.

(4aα,5α,8α,8aβ)-Octahydro-5,8-dihydroxy-4a,8-dimethyl-2(1*H*)-naphthalenone 5-(4-Methylbenzenesulfonate) (135). To a stirred solution of 2.159 g (10.18 mmol) of diol **134** in 20 mL of pyridine was added 2.548 g (13.36 mmol) of TsCl. The reaction mixture was stirred at rt for 3 d and then concentrated under reduced pressure. The resulting mixture was taken up in 100 mL of CH_2Cl_2 and washed successively with one 50-mL portion of 10% aqueous HCl, two 25-mL portions of saturated aqueous $NaHCO_3$, and one 50-mL portion of brine. The organic layer was dried and the solvent was removed under reduced pressure. The crude product was flash chromatographed on silica gel (2:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 3.432 g (92%) of pure monotosylated ketone **135**: mp 157 °C dec (from petroleum ether (bp 60-80 °C)/EtOAc); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.10 (s, 3 H), 1.23 (s, 3 H), 1.25-2.73 (m, 12 H), 2.43 (s, 3 H), 4.25 (m, 1 H), 7.33 (d, J = 8 Hz, 2 H), 7.80 (d, J = 8 Hz, 2 H); MS, *m/e* (rel intensity) 366 (M^+), 194 (100). Anal. Calcd for $C_{19}H_{26}O_5S$: C, 62.27; H, 7.15. Found: C, 62.09; H, 6.86.

(4'aα,5'α,8'α,8'aβ)-Octahydro-4'a,8'-dimethylspiro[1,3-dioxolane-2,2'(1'*H*)-naphthalene]-5',8'-diol 5'-(4-Methylbenzenesulfonate) (131). To a solution of 2.828 g (7.73 mmol) of monotosylated ketone **135** in a mixture of 15 mL of CH_2Cl_2 and 15 mL of MED were added catalytic amounts of ethylene glycol and *p*-toluenesulfonic acid monohydrate. The reaction mixture was stirred at rt for 24 h, after which time 0.5 mL of Et_3N was added. The reaction mixture was then diluted with 100 mL of CH_2Cl_2 and washed with 50 mL of brine. The organic layer was dried and evaporated under reduced pressure to give the crude monotosylated dioxolane **131**. Recrystallization from methanol and flash chromatography of the mother liquid on silica gel (1:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded 3.066 g (97%) of pure **131**: mp 150 °C dec; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.12 (s, 3 H), 1.14 (s, 3 H), 1.17-2.34 (m, 12 H), 2.45 (s, 3

H), 3.94 (br s, 4 H), 4.27 (m, 1 H), 7.30 (d, J = 8 Hz, 2 H), 7.77 (d, J = 8 Hz, 2 H); MS, *m/e* (rel intensity) 392 (M^+ - 18, 15), 220 (41), 176 (24), 172 (48), 99 (100), 91 (52). Anal. Calcd for $C_{21}H_{30}O_6S$: C, 61.44; H, 7.37. Found: C, 61.36; H, 7.28.

(4aα,5α,8α,8aβ)- and (4aα,5α,8β,8aβ)-Octahydro-5,8-dihydroxy-4a-methyl-2(1*H*)-naphthalenone 5-(4-methylbenzenesulfonates) (137 and 138). A sample of 1.900 g (7.85 mmol) of dimethyl acetal **133**[1a] was treated with TsCl, using conditions similar to those employed for the preparation of the monotosylated diol **135**. After workup the resulting tosylate **136** was taken up in 40 mL of ethanol, cooled to 0 °C, and then 1.00 g (26.46 mmol) of $NaBH_4$ in a mixture of 10 mL of ethanol and 1 mL of 15% aqueous NaOH was added dropwise. When the addition was complete, the reaction mixture was allowed to stir for 2 h at 0 °C, and then the ice bath was removed and stirring was continued for 1 h. The reaction mixture was diluted with 150 mL of water and extracted with four 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 50 mL of brine and dried. The solvent was evaporated under reduced pressure and the remaining residue was taken up in a mixture of 25 mL of acetone and 5 mL of 5% aqueous HCl. The reaction mixture was allowed to stir at rt for 2 h and then diluted with 75 mL of CH_2Cl_2. The organic layer was washed with 50 mL of saturated aqueous $NaHCO_3$ followed by brine, dried, and then evaporated under reduced pressure. The resulting product was chromatographed on silica gel (1:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 1.79 g (65%) of pure β-alcohol **137** along with 0.17 g (6%) of pure α-alcohol **138**.

137: mp 120-122 °C (from diisopropyl ether); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.31 (s, 3 H), 1.33-2.93 (m, 12 H), 2.48 (s, 3 H), 3.67 (m, 1 H), 4.24 (dd, J = 4, 12 Hz, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.79 (d, J = 8 Hz, 2 H); MS, *m/e* (rel intensity) 352 (M^+), 180 (100), 172 (36), 91 (59). Anal. Calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86. Found: C, 61.08; H, 6.65.

138: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.10 (s, 3 H), 1.11-2.83 (m, 12 H), 2.48 (s, 3 H), 3.43 (dt, J = 4.5, 10.5 Hz, 1 H), 4.23 (dd, J = 6.5, 9.5 Hz, 1 H), 7.33 (d, J = 8 Hz, 2 H), 7.74 (d, J = 8 Hz, 2 H); MS, *m/e* (rel intensity) 171 (86), 91 (100).

(4'aα,5'α,8'α,8'aβ)-Octahydro-4'a-methylspiro[1,3-dioxolane-2,2'(1'*H*)-naphthalene]-5'8'-diol 5'-(4-Methylbenzenesulfonate) (132). The β-hydroxyl tosylate **132** was prepared from **137** as described for the synthesis of the tosylate **131**. The workup and chromatography on silica gel (1:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded in a 94% yield pure **132**: mp 124-126 °C (from diisopropylether); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.00-2.27 (m, 12 H), 1.11 (s, 3 H), 2.44 (s, 3 H), 3.67 (m, 1 H), 3.92 (s, 4 H), 4.29 (dd, J = 5, 11 Hz, 1 H), 7.31 (d, J = 8 Hz, 2 H), 7.78 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.69 (q), 21.58 (q), 24.47 (t), 31.68 (t), 32.95 (t), 35.77 (t), 37.17 (t), 39.13 (s), 45.11 (d), 64.59

(t), 64.86 (t), 70.26 (d), 90.72 (d), 109.99 (s), 128.17 (2 d), 130.16 (2 d), 136.73 (s), 144.30 (s); MS, *m/e* (rel intensity) 378 (M^+-18), 171 (100), 91 (95). Anal. Calcd for $C_{20}H_{28}O_6S$: C, 60.58; H, 7.12. Found: C, 60.43; H, 7.07.

(4'aα,5'α,8'β,8'aβ)-Octahydro-4'a-methylspiro[1,3-dioxolane-2,2'(1'*H*)-naphthalene]-5',8'-diol 5'-(4-Methylbenzenesulfonate) (139). The α-hydroxy tosylate **139** was prepared from **138** as described for the synthesis of the tosylate **131**. The workup and chromatography on silica gel (1:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded in a 82% yield pure **139**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.89 (s, 3 H), 1.10-2.17 (m, 12 H), 2.44 (s, 3 H), 3.35 (m, 1 H), 3.97 (s, 4 H), 4.26 (dd, *J* = 6.5, 9.5 Hz, 1 H), 7.33 (d, *J* = 8 Hz, 2 H), 7.78 (d, *J* = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.41 (q), 21.58 (q), 27.41 (t), 31.48 (t), 33.12 (t), 34.35 (t), 36.01 (t), 39.08 (s), 48 32 (d), 64.64 (t), 64.81 (t), 68.54 (d), 89.47 (d), 109.28 (s), 128.19 (2 d), 130.18 (2 d), 136.43 (s), 144.45 (s); MS, *m/e* (rel intensity) 224 (M^+-172, 5), 206 (26), 172 (80), 154 (37), 128 (20), 99 (59), 91 (100); calcd for $C_{20}H_{28}O_6S$ (M^+) *m/e* 396.1606, found *m/e* 396.1611.

(4'aα,5'α,8'aβ)-Octahydro-4'a-methylspiro[1,3-dioxolane-2,2'(1'*H*)-naphthalen]-5'-ol 5'-(4-Methylbenzenesulfonate) (140). The tosylate **140** was prepared from **141**[8] as described for the synthesis of the tosylate **131**. The workup and chromatography on silica gel (3:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded in quantitative yield pure **140**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.88 (s, 3 H), 1.03-1.91 (m, 13 H), 2.43 (s, 3 H), 3.91 (s, 4 H), 4.26 (m, 1 H), 7.32 (d, *J* = 8 Hz, 2 H), 7.79 (d, *J* = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.30 (q), 21.58 (q), 24.72 (t), 27.85 (t), 29.05 (t), 31.63 (t), 35.67 (t), 38.22 (t), 39.05 (s), 42.00 (d), 64.62 (t), 64.77 (t), 90.65 (d), 109.33 (s), 128.14 (2 d), 130.13 (2 d), 136.75 (s), 144.23 (s); MS, *m/e* (rel intensity) 380 (M^+), 208 (6), 112 (26), 99 (100); calcd for $C_{20}H_{28}O_5S$ (M^+) *m/e* 380.1658, found *m/e* 380.1659.

Rearrangement of Tosylate 131

a. With Lithium Carbonate in Refluxing Aqueous Dioxane

To a solution of 0.410 g (1.00 mmol) of tosylate **131** in 15 mL of dioxane was added 7.5 mL of water and 0.802 g (10.85 mmol) of Li_2CO_3. The reaction mixture was heated at reflux for 30 h, allowed to come to rt, and then filtered. The filtrate was diluted with 50 mL of brine and extracted with three 50-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated under reduced pressure. The remaining residue, according to GC analysis a mixture of five products in a ratio of 1.3:1:5.3:1:1.8,

was chromatographed on basic alumina (activity II) (15:1 to 0:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, the cyclic ether **142** (0.028 g, 12%), an inseparable 1:1 mixture of the exo 10,15-olefin **143** and the endo 9,10-olefin **144** (0.043 g, 18%), the endo 1,10-olefin **145** (0.115 g, 48%), and the diol **146** (0.042 g, 16%). Physical and spectroscopic data of the products **142, 144, 145,** and **146** follow.

(1'α,3'aβ,4'α,8'aβ)-Octahydro-1'4'-dimethylspiro[1,3-dioxolane-2,7'(1'*H*)-[1,4]epoxy-azulene] (142): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.23 (s, 3 H), 1.25 (s, 3 H), 1.40-2.14 (m, 11 H), 2.45 (br s, 1 H), 3.92 (s, 4 H); MS, *m/e* (rel intensity) 238 (M^+, 8), 176 (15), 143 (34), 139 (14), 99(100), 87(16), 86 (87), 43 (27); calcd for $C_{14}H_{22}O_3$ (M^+) *m/e* 238.1569, found *m/e* 238.1569.

(3α,3aβ,8aβ)-2,3,3a,4,6,8a-Hexahydro-3,8-dimethylspiro[azulene-5(1*H*),2'-[1,3]dioxolan]-3-ol (144): ^{1}H NMR (main peaks, $CDCl_3$, 90 MHz) δ 1.29 (s, 3 H), 1.75 (br s, 3 H), 3.93 (m, 4 H), 5.46 (br t, *J* = 7.5 Hz, 1 H); MS, *m/e* (rel intensity) 238 (M^+, 16), 165 (10), 139 (10), 119 (12), 99 (100), 93 (11), 86 (12), 81 (21), 79 (11), 43 (13).

***trans*-2,3,3a,4,6,7-Hexahydro-3,8-dimethylspiro[azulene-5(1*H*),2'-[1,3]-dioxolan]-3-ol (145)**: mp 128-130 °C (from petroleum ether (bp 40-60 °C)); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1,28 (s, 3 H), 1.30-2.66 (m, 12 H), 1.65 (br s, 3 H), 3.94 (m, 4 H); MS, *m/e* (rel intensity) 238 (M^+, 28), 220 (36), 130 (30), 119 (42), 118 (40), 105 (28), 99 (100), 91 (41), 86 (64), 43 (48); calcd for $C_{14}H_{22}O_3$ (M^+) *m/e* 238.1569, found *m/e* 238.1568. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.63; H, 9.48.

(3α,3aβ,8β,8aβ)-Octahydro-3,8-dimethylspiro[azulene-5(1*H*),2'-[1,3]-dioxolane]-3,8-diol (146): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.23 (s, 3 H), 1.26 (s, 3 H), 1.42-2.58 (m, 14 H), 3.93 (s, 4 H); MS, *m/e* (rel intensity) 256 (M^+, 2), 238 (37), 223 (13), 209 (16), 194 (30), 143 (28), 139 (31), 115 (70), 100 (62), 99 (100), 43 (69); calcd for $C_{14}H_{24}O_4$ (M^+) *m/e* 256.1674, found *m/e* 256. 1677.

b. With Potassium *tert*-Butoxide in Refluxing *tert*-Butyl Alcohol

To a solution of 0.970 g (8.66 mmol) of potassium *tert*-butoxide in 15 mL of dry *tert*-butyl alcohol was added 0.344 g (0.84 mmol) of tosylate **131**. The mixture was heated at reflux for 43 h, allowed to come to rt, and then poured into 50 mL of water. The aqueous solution was extracted with three 25-mL portions of $CHCl_3$. The combined organic layers were washed with 25 mL of brine, dried over anhydrous K_2CO_3, and then evaporated under reduced pressure. The remaining residue was chromatographed on basic alumina (activity II) (10:1 to 3:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, **142** (0.028 g, 14%) and, according to GC and ^{1}H NMR analysis, a mixture (0.152 g, 76%) of **143, 144,** and **145** in a ratio of 5.8:1:1.5, respectively.

c. With Sodium *tert*-Amylate in Refluxing Benzene

To a mixture of 0.5 mL (4.6 mmol) of dry *tert*-amyl alcohol and 20 mL of dry benzene was added 0.066 g (2.20 mmol, as a 80% dispersion in mineral oil) of NaH. The mixture was heated at reflux for 0.5 h, allowed to come to rt, and then 0.410 g (1.00 mmol) of tosylate **131** was added. The solution was heated at reflux for 20 h and, after cooling to rt, poured into 50 mL of brine. The two-phase mixture was separated, and the aqueous layer was extracted with three 25-mL portions of ether. The combined organic layers were dried over anhydrous K_2CO_3 and evaporated under reduced pressure. The resulting residue, according to GC analysis a mixture of **142** (3%), **143** (90%), **145** (4%), and the unrearranged olefin **155** (3%), was crystallized from petroleum ether (bp 40-60 °C) to give pure **(3α,3aβ,8aβ)-octahydro-3-methyl-8-methylene-spiro[azulene-5(1*H*),2'-[1,3]-dioxolan]-3-ol (143)** (0.187 g, 78.5%): mp 84.5-85 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.27 (s, 3 H), 1.43-2.00 (m, 13 H), 3.92 (s, 4 H), 4.85-4.97 (m, 2 H); MS, *m/e* (rel intensity) 238 (M^+, 18), 220 (18), 181 (15), 165 (15), 133 (17), 119 (20), 105 (17), 99 (100), 93 (18), 91 (22), 86 (55), 79 (18), 43 (38); calcd for $C_{14}H_{22}O_3$ (M^+) *m/e* 238.1569, found *m/e* 238.1568. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C. 70.51; H, 9.43.

d. With Sodium *tert*-Amylate in Refluxing Benzene (Toluene); Influence of the Base Concentration and the Amount of *tert*-Amyl Alcohol

See also Table 3.1. Solutions of 0.205 g (0.5 mmol) of tosylate **131** in 10 mL of dry benzene (entry 5: toluene) were degassed and refluxed under an argon atmosphere. For the experiments 4 and 5, 0.27 mL (2.5 mmol) of dry *tert*-amyl alcohol was added. To these refluxing solutions were added the required quantities of sodium *tert*-amylate (3.5 M in toluene) at once. The reaction mixtures were refluxed until the reactions were completed according to TLC (see: Table 3.1). After cooling to 0 °C and quenching with 10 mL of water, the organic layers were diluted with 40 mL of petroleum ether (bp 40-60 °C), separated, dried, and analyzed with GC. For results, see: Table 3.1.

e. With Potassium *tert*-Amylate in Refluxing Benzene

The tosylate **131** (0.410 g, 1.00 mmol) was treated as described above, under **c**, using KH (0.088 g, 2.20 mmol) instead of NaH. The workup and chromatography on basic alumina (activity II) (15:1 to 4:1 petroleum ether (bp 40-60 °C)/EtOAc) gave, in order of elution, **142** (0.015 g, 6%), **155** (0.002 g, 1%), **143** (0.207 g, 87%), and **145** (0.004 g, 2%).

f. With Lithium *tert*-Amylate in Refluxing Benzene

The tosylate **131** (0.410 g, 1.00 mmol) was treated for 92 h as described above, under **c**, using 1.5 mL (2.25 mmol) of 15% *n*-BuLi in hexane instead of NaH. After the workup, the resulting residue, according to GC analysis a mixture of seven products, was chromatographed on basic alumina (activity II) (12.5:1 to 3:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, **142** (0.019 g, 8%), the cyclohexane derivative **160** (0.003 g, 1%), the cyclohexene derivative **161** (0.007 g, 3%), **155** (0.005 g, 2%), **143** (0.141 g, 59%), and **145** (0.031 g, 13%). Physical and spectroscopic data of the products **155**, **160**, and **161** follow.

(4'aα,8'α,8'aβ)-3',4',4'a,7',8',8'a-Hexahydro-4'a,8'-dimethylspiro[1,3-dioxolane-2,2'-(1'*H*)-naphthalen]-8'-ol (155): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 3 H), 1.21 (s, 3 H), 1.23-1.86 (m, 8 H), 2.11 (dd, *J* = 4.4, 18.5 Hz, 1 H), 2.27 (dt, *J* = 2.7, 18.5 Hz, 1 H), 3.96 (m, 4 H), 5.45 (ddd, *J* = 2.7, 4.4, 10.0 Hz, 1 H), 5.59 (br d, *J* = 10.0 Hz, 1 H); MS, *m/e* (rel intensity) 238 (M^+, 0.2), 220 (5), 142 (26), 99 (100), 86 (19), 43 (14); calcd for $C_{14}H_{22}O_3$ (M^+) *m/e* 238.1569, found *m/e* 238.1570.

(7α,8β)-1-[8-Methyl-8-(2-propenyl)-1,4-dioxaspiro[4.5]dec-7-yl]ethanone (160): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 3 H), 1.21-2.49 (m, 8 H), 2.15 (s, 3 H), 2.76 (dd, *J* = 3.0, 13.0 Hz, 1 H), 3.94 (s, 4 H), 4.99-5.11 (m, 2 H), 5.84 (m, 1 H); MS, *m/e* (rel intensity) 238 (M^+, 2), 195 (18), 167 (58), 139 (12), 111 (12), 99 (100), 93 (10), 87 (31), 86 (36), 81 (18), 43 (52); calcd for $C_{14}H_{22}O_3$ (M^+) *m/e* 238.1569 g, found *m/e* 238.1563.

8-(1R-Methyl-4-oxopentyl)-1,4-dioxaspiro[4.5]dec-7-ene (161): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (d, *J* = 7.3 Hz, 3 H), 1.48-2.60 (m, 11 H), 2.14 (s, 3 H), 3.91 (br s, 4 H), 5.22 (dd, *J* = 4.9, 8.8 Hz, 1 H); MS, *m/e* (rel intensity) 238 (M^+, 4), 181 (3), 119 (3), 118 (7), 105 (5), 100 (13), 99 (100), 91 (6), 86 (6), 79 (6), 55 (6), 43 (14); calcd for $C_{14}H_{22}O_3$ (M^+) *m/e* 238.1569, found *m/e* 238.1565.

Rearrangement of Tosylate 132

a. With Potassium *tert*-Butoxide in Refluxing *tert*-Butyl Alcohol

The tosylate **132** (0.597 g, 1.51 mmol) was treated with potassium *tert*-butoxide as described for the rearrangement of the tosylate **131**. The workup and chromatography on silica gel (3:1 to 2:1 petroleum ether (bp 40-60 °C)/EtOAc) gave, in order of elution, the cyclic ether **147** (0.055 g, 16%) and according to GC and ^{1}H NMR analysis, a mixture (0.233 g, 69%) of the exo 10,15-olefin **148**, the endo 9,10-olefin **149**, and the endo 1,10-olefin **150** in a ratio of 16:1:8, respectively. Physical and spectroscopic data of the products **147** and **149** follow.

(1'α,3'aβ,4'α,8'aβ)-Octahydro-4'-methylspiro[1,3-dioxolane-2,7'(1'*H*)-[1,4]epoxyazulene] (147): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.29 (s, 3 H), 1.31-2.18 (m, 11 H), 2.42 (br s, 1 H), 3.94 (s, 4 H), 3.95 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.46 (t), 27.62 (q), 29.58 (t), 32.72 (t), 36.22 (t), 37.25 (t), 45.76 (d), 46.88 (d), 63.90 (t), 64.43 (t), 81.27 (s), 84.04 (d), 110.49 (s); MS, *m/e* (rel intensity) 224 (M^+, 6), 195 (10), 181 (6), 167 (13), 143 (33), 125 (55), 101 (24), 100 (23), 99 (100), 86 (76), 43 (83); calcd for $C_{13}H_{20}O_3$ (M^+) *m/e* 224.1412, found *m/e* 224.1412.

(3α,3aβ,8aβ)-2,3,3a,4,6,8a-Hexahydro-8-methylspiro[azulene-5(1*H*),2'-[1,3]-dioxolan]-3-ol (149): ^{1}H NMR (main peaks, $CDCl_3$, 90 MHz) δ 5.39 (br t, J = 7.5 Hz, 1 H); MS, *m/e* (rel intensity) 224 (M^+, 30), 206 (33), 165 (44), 141 (48), 125 (18), 123 (21), 118 (20), 99 (100), 91 (15), 87 (39), 86 (95), 81 (33), 79 (27), 73 (23), 43 (22).

b. With (Dimethylsulfinyl)sodium in Dimethyl Sulfoxide

To a stirred solution of 7.5 mL of 0.35 M (dimethylsulfinyl)sodium in DMSO was added dropwise a solution of 0.479 g (1.21 mmol) of tosylate **132** in 7.5 mL of DMSO. The mixture was heated at 70 °C for 5 h, allowed to stir at rt for 16 h, and then poured into 100 mL of water. The aqueous solution was extracted with five 30-mL portions of ether. The combined organic layers were washed with 75 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was chromatographed on silica gel (5:1 to 2:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, **147** (0.066 g, 24%), a mixture (0.119 g, 44%) of **148** and **150** in a ratio of 6:3, according to GC and ^{1}H NMR analysis, and **132** (0.048 g, 10%).

c. With Sodium tert-Amylate in Refluxing Benzene

The tosylate **132** (0.396 g, 1.00 mmol) was treated with sodium *tert*-amylate for 16 h as described for the rearrangement of the tosylate **131** above, under **c**. The workup and chromatography on basic alumina (activity II) (15:1 to 2:1 petroleum ether (bp 40-60 °C)/EtOAc) gave, in order of elution, a 2:1 mixture of the epimeric rearranged ketones **156** (0.016 g, 7%), **147** (0.016 g, 7%), the cyclopropyl derivative **157** (0.009 g, 4%), pure **148** (0.060 g, 27%), and 0.100 g (45%) of a 2:1 mixture of **148** and **150**, respectively. Physical and spectroscopic data of the products **148**, **150**, **156**, and **157** follow.

(3α,3aβ,8aβ)-Octahydro-8-methylenespiro[azulene-5(1*H*),2'-[1,3]dioxolan]-3-ol (148): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.10-2.90 (m, 13 H), 3.90 (s, 4 H), 4.18 (m, 1 H), 4.81 (br s, 1 H), 4.88 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.41 (t), 32.23 (t), 33.49 (2 t), 39.03 (t), 41.58 (d), 46.01 (d), 64.10 (t), 64.26 (t), 75.78 (d), 110.04 (t), 111.30 (s), 151.36 (s); MS, *m/e* (rel intensity) 224 (M^+, 17), 206 (18), 165 (24), 141 (20), 123 (20), 99 (53), 91 (15), 87 (39), 86 (100), 79 (18), 43 (19); calcd for $C_{13}H_{20}O_3$ (M^+) *m/e* 224.1412, found *m/e* 224.1417.

***trans*-2,3,3a,4,6,7-Hexahydro-8-methylspiro[azulene-5(1*H*),2'-[1,3]dioxolan]-3-ol (150)**: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.96 (q), 28.55 (t), 30.00 (t), 35.98 (t), 37.11 (t), 43.38 (t), 45.90 (d), 64.09 (t), 64.14 (t), 76.80 (d), 111.81 (s), 129.17 (s), 137.79 (s); MS, *m/e* (rel intensity) 224 (M^+, 14), 206 (40), 123 (25), 118 (27), 99 (38), 91 (16), 87 (43), 86 (100), 79 (15), 43 (18).

Epimeric ketones 156: IR ($CHCl_3$) 1750, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.13-3.23 (m), 3.94 (br s), 4.80 (m), 4.90 (m); MS (major compound), *m/e* (rel intensity) 222 (M^+, 27), 207 (6), 153 (18), 112 (15), 99 (34), 87 (18), 86 (100), 79 (19), 55 (23); MS (minor compound), *m/e* (rel intensity) 222 (M^+, 24), 207 (7), 153 (20), 112 (15), 99 (45), 87 (22), 86 (100), 79 (19), 55 (26).

(1aα,1bβ,5aα,6aα)-Octahydro-1b-methylspiro[cycloprop[*a*]indene-4(1*H*),2'-[1,3]-dioxolan]-6-one (157): IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.03 (m, 2 H), 1.22 (s, 3 H), 1.25-2.10 (m, 8 H), 2.25 (br d, J = 13.5 Hz, 1 H), 3.93 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.76 (t, J = 165 Hz), 22.78 (q), 26.37 (d, J = 176 Hz), 27.02 (t), 30.81 (t), 32.75 (d, J = 171 Hz), 35.27 (t), 36.21 (t), 46.47 (d), 63.74 (t), 64.23 (t), 107.97 (s), 212.05 (s); MS, *m/e* (rel intensity) 222 (M^+, 5), 126 (9), 100 (7), 99 (100), 86 (16), 79 (5), 55 (19); calcd for $C_{13}H_{18}O_3$ (M^+) *m/e* 222.1256, found *m/e* 222.1257.

Treatment of Tosylate 139 with Sodium *tert*-Amylate in Refluxing Benzene

The tosylate **139** (0.382 g, 0.96 mmol) was treated with sodium *tert*-amylate (2.2 equiv) for 21 h as described for the rearrangement of the tosylate **131** above, under **c**. The workup and chromatography on silica gel (2:1 petroleum ether (bp 40-60 °C)/EtOAc) gave, in order of elution, 0.027 g (13%) of a mixture of mainly **158** and **159** in a ratio, according to GC analysis, of 1:2.5, respectively, and 0.225 g (59%) of the starting material **139**.

158: ^1H NMR (main peaks, $CDCl_3$, 90 MHz) δ 3.95 (s, 4 H), 4.77 (br s, 1 H), 4.88 (br s, 1 H); MS, *m/e* (rel intensity) 224 (M^+, 22), 165 (20), 153 (11), 141 (15), 123 (12), 99 (62), 87 (33), 86 (100), 79 (14), 43 (15).

159: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.05-2.70 (m, 12 H), 1.65 (br s, 3 H), 3.72 (m, 1 H), 3.96 (s, 4 H); MS, *m/e* (rel intensity) 224 (M^+, 8), 206 (52), 191 (12), 144 (13), 123 (24), 99 (45), 87 (39), 86 (100), 79 (14), 43 (17).

Treatment of Tosylate 140 with Sodium *tert*-Amylate in Refluxing Benzene

The tosylate **140** (0.485 g, 1.28 mmol) was treated with sodium *tert*-amylate (2.2 equiv) for 21 h as described for the rearrangement of the tosylate **131** above, under **c**. The workup and chromatography on silica gel (3:1 petroleum ether (bp 40-60 °C)/EtOAc) gave 0.470 g (97%) of the starting material **140**.

Hydrolysis of the Dioxolanes 148, 150, 143, and 145

(1α,3aβ,7α,8aβ)-Octahydro-4-methylene-1,7-epoxyazulen-7(1*H*)-ol (151) and *trans*-2,3,3a,4,6,7-Hexahydro-3-hydroxy-8-methyl-5(1*H*)-azulenone (152). To a solution of 0.100 g (0.45 mmol) of a 2:1 mixture of **148** and **150** in 15 mL of acetone was added 0.5 mL of 15% aqueous HCl. The reaction mixture was allowed to stir at rt for 4.5 h, and then neutralized with 5 mL of saturated aqueous $NaHCO_3$. The reaction mixture was concentrated under reduced pressure and diluted with 50 mL of water. After extraction with three 25-mL portions of CH_2Cl_2, the combined organic layers were washed with 50 mL of brine and dried. Evaporation of the solvent under reduced pressure and flash chromatography of the residue on silica gel (5:1 petroleum ether (bp 40-60 °C)/EtOAc) gave, in order of elution, 0.049 g (61%) of **151** and 0.025 g (31%) of **152**.

151: mp 117-118 °C (from petroleum ether (bp 40-60 °C)); IR ($CHCl_3$) 3580, 3360 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.50-3.13 (m, 12 H), 3.43 (br s, 1 H), 4.77 (br s, 2 H), 4.82 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.09 (t), 30.97 (t), 32.30 (t), 41.00 (t), 41.71 (t), 48.31 (d), 49.31 (d), 87.98 (d), 108.47 (s), 114.18 (t), 151.29 (s); MS, *m/e* (rel intensity) 180 (M^+, 15), 165 (11), 162 (13), 151 (26), 135 (100), 120 (30), 108 (47), 107 (47), 105 (49), 97 (30), 93 (57), 92 (35), 91 (59), 82 (61), 81 (43), 79 (88), 67 (71), 55 (41), 41 (60); calcd for $C_{11}H_{16}O_2$ (M^+) *m/e* 180.1150, found *m/e* 180.1153. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.45; H, 8.75.

152: IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.60-3.07 (m, 12 H), 1.71 (br s, 3 H), 4.22 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.91 (q), 29.12 (t), 31.13 (t), 33.14 (t), 42.07 (t), 43.49 (t), 44.10 (d), 76.49 (d), 128.91 (s), 136.70 (s), 213.57 (s); MS, *m/e* (rel intensity) 180 (M^+, 61), 162 (71), 137 (22), 124 (45), 123 (71), 121 (28), 120 (36), 119 (35), 118 (25), 109 (38), 107 (40), 105 (48), 95 (29), 93 (52), 91 (57), 81 (27), 79 (100), 77 (41), 67 (31), 55 (32), 53 (28), 43 (33), 41 (49); calcd for $C_{11}H_{16}O_2$ (M^+) *m/e* 180.1150, found *m/e* 180.1144.

(1α,3aβ,7α,8aβ)-Octahydro-1-methyl-4-methylene-1,7-epoxyazulen-7(1*H*)-ol (153). The exo 10,15-olefin **143** (0.282 g, 1.18 mmol) was hydrolyzed as described above for the mixture of **148** and **150.** The workup and chromatography on silica gel (4:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded 0.197 g (86%) of pure **153**: mp 104-106 °C (from petroleum ether (bp 60-80 °C)); IR ($CHCl_3$) 3590, 3375 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.41 (s, 3 H), 1.50-2.62 (m, 11 H), 3.01 (m, 1 H), 3.42 (br s, 1 H), 4.77 (br s, 2 H); MS, *m/e* (rel intensity) 194 (M^+, 13), 179 (16), 176 (25), 165 (25), 136 (41), 133 (32), 122 (36), 121 (31), 119 (47), 105 (36), 93 (54), 91 (44), 82 (36), 81 (74), 79 (54), 55 (32), 43 (100). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.23; H, 9.43.

***trans*-2,3,3a,4,6,7-Hexahydro-3-hydroxy-3,8-dimethyl-5(1*H*)-azulenone (154).** The endo 1,10-olefin **145** (0.122 g, 0.51 mmol) was hydrolyzed as described above for the mixture of **148** and **150**. The workup and chromatography on silica gel (4:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded 0.069 g (69%) of pure **154**: IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.33 (s, 3 H), 1.35-3.09 (m, 12 H), 1.71 (br s, 3 H); MS, *m/e* (rel intensity) 194 (M^+, 28), 179 (12), 176 (75), 136 (70), 133 (39), 123 (40), 119 (36), 118 (44), 105 (39), 93 (59), 91 (58), 79 (60), 43 (100); calcd for $C_{12}H_{18}O_2$ (M^+) *m/e* 194.1307, found *m/e* 194.1304.

3.8 References and Notes

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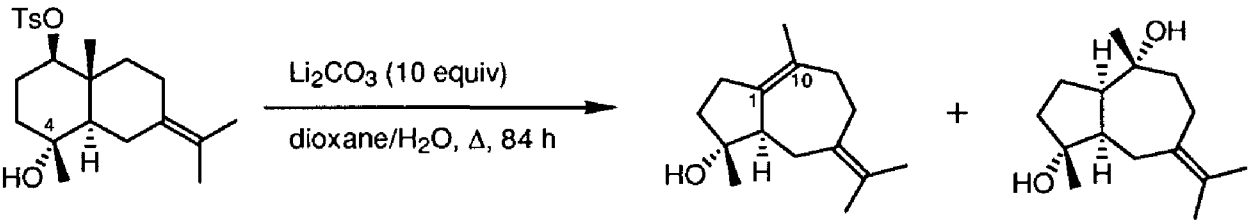

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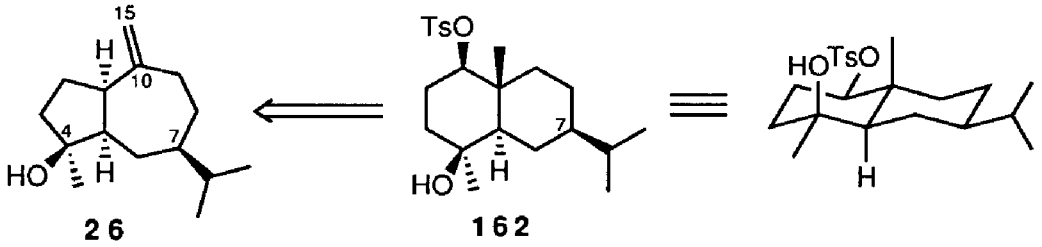
4 Total Synthesis of (±)-5-*epi*-Nardol

4.1 Introduction

As an application of the intramolecular base-induced and -directed rearrangement described in Chapter 3, the guaiane sesquiterpene **26** was synthesized. Guaiane **26** was chosen as a target molecule because its stereochemistry corresponded to the one suggested for the guaiane alcohol (-)-nardol,[1] isolated from *Nardostachys jatamansi* D.C., a medicinal plant from the Himalayas.[2]

The tertiary β-hydroxyl group at C(4) will ensure the selective formation of the cis-fused hydroazulene framework with the exocyclic C(10)-C(15) double bond in the base-induced and -directed rearrangement of the tosylate **162**.[3,4] The β-isopropyl group at C(7) in **26** corresponds to an equatorial isopropyl side chain at C(7) in the perhydronaphthalene precursor **162** (Scheme 4.1). Hence, a thermodynamically controlled introduction of this group ensures stereoselective synthesis at this point. In this way, the advantage of hydronaphthalenes as precursors of hydroazulene sesquiterpenes is nicely illustrated.

Scheme 4.1



26 **162**

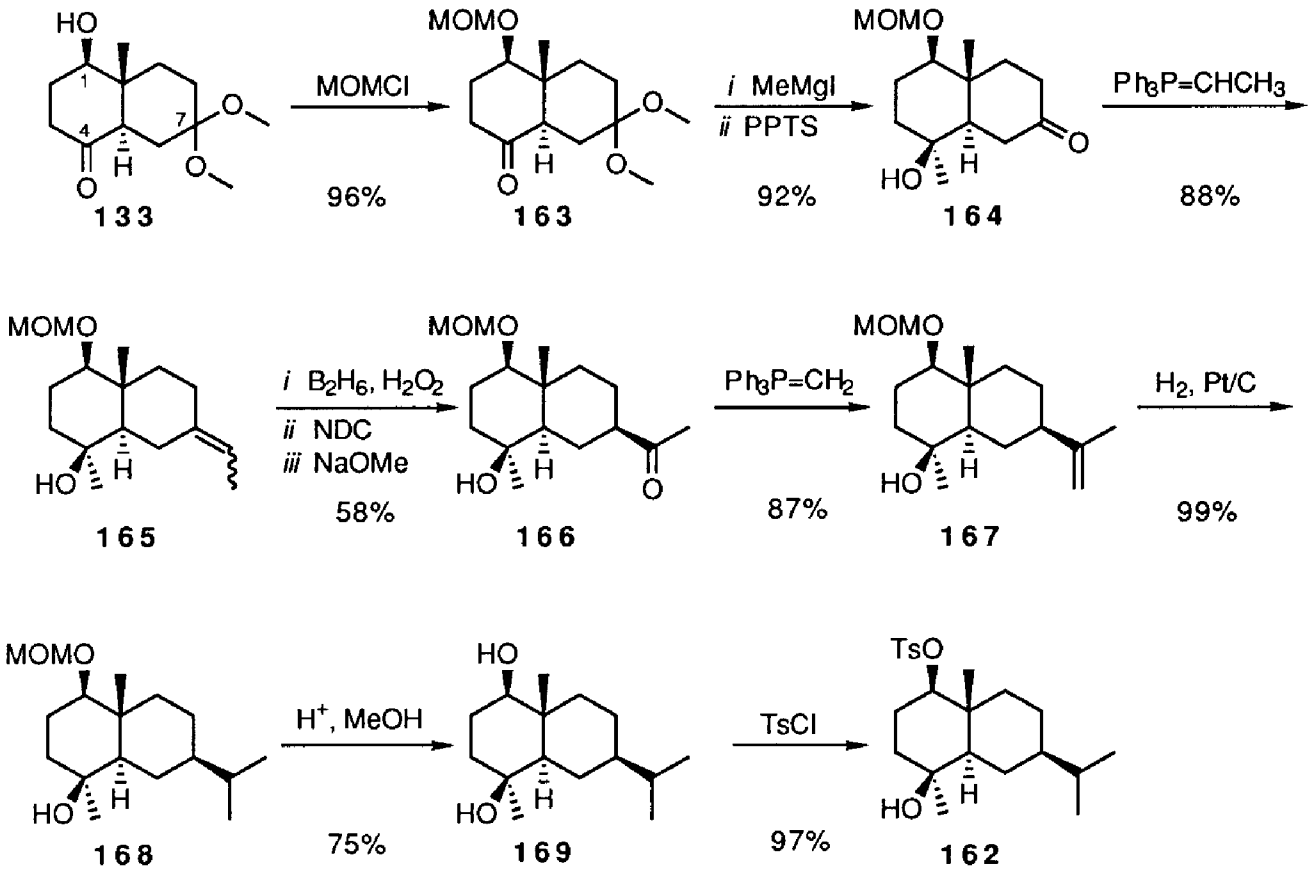
4.2 Synthesis of (±)-5-*epi*-Nardol 26

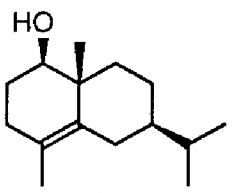
Starting material for the synthesis of the guaiane alcohol **26** was the readily available selectively protected dione **133**[5] (Scheme 4.2). The secondary hydroxyl group of **133** was protected as its methoxy methyl ether (MOM ether)[6] to give compound **163**. A Grignard reaction with an excess of MeMgI in ether[7] and subsequent careful hydrolysis of the dimethyl acetal function with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone gave the crystalline monoprotected diol **164**.

Then the β-isopropyl side chain at C(7) was introduced *via* a Wittig reaction of **164** with ethylenetriphenylphosphorane in DMSO. The resulting product **165** was

obtained as a mixture of geometric isomers. This mixture was oxidatively hydroborated and subsequently oxidized with nicotinium dichromate (NDC) and pyridine in benzene. The resulting 2:1 mixture of the acyl derivative **166** and its C(7) epimer was then equilibrated with sodium methoxide in dry methanol to afford the pure equatorial β-acyl compound **166**. Treatment of **166** with methylenetriphenyl-phosphorane in DMSO produced the corresponding β-isopropenyl compound **167**. The following catalytic reduction of the double bond of **167** under moderate pressure then gave the saturated structure **168**. All substituents in structure **168** are introduced with the required stereochemistry for its conversion into **26**.

Scheme 4.2





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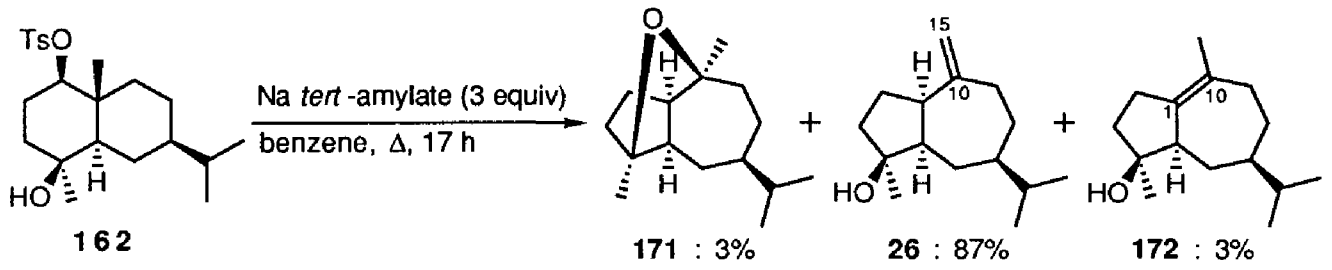
The deprotection and tosylation of the secondary alcohol at C(1) were the next steps in the synthetic route towards guaiane **26**. The hydrolysis of the MOM ether function was carried out in refluxing methanol with a catalytic amount of HCl, yielding the diol **169** in 75%. Apart from **169**, a 41:7:1 mixture of dehydrated products[8] was isolated (15%), in which the olefin **170** was the major compound. The axial position of the tertiary hydroxyl group at C(4) makes it susceptible to acidic conditions.[9]
Finally, the secondary hydroxyl group in **169** was treated with TsCl in pyridine to give

the tosylate **162.**

Then the key step in the synthesis of the guaiane alcohol **26,** the base-induced and -directed skeletal rearrangement of **162,** was performed with sodium *tert*-amylate in refluxing benzene (Scheme 4.3).[4]

Scheme 4.3



After workup and column chromatography **26** was isolated in 87%, *i.e.* 25% overall from **133** (12 steps). The isolated guaiane alcohol **26** contained a small impurity (3%), which was probably the endo 1,10-olefin **172.**[10] Furthermore, the cyclic ether **171** was isolated in 3% yield.

The spectral data of the guaiane alcohol **26** and natural (-)-nardol, isolated from *N. jatamansi* D.C.,[1,2] however, did not agree. Natural nardol is now believed to possess a trans-fused skeleton and to be the C(5)-epimer of structure **26.**[11] Nevertheless, the synthesis of (±)-5-*epi*-nardol **26** is a good illustration of our synthetic strategy towards hydroazulene sesquiterpenes. This strategy involves the synthesis of an appropriately substituted perhydronaphthalene tosylate (**162**), followed by the selective transformation of this perhydronaphthalene to the desired hydroazulene system with an exocyclic C(10)-C(15) double bond in the base-induced and -directed rearrangement reaction.

4.3 Experimental Section

General

Melting points are uncorrected. Chemical shifts are reported relative to TMS (δ 0.00). MS data were determined at 70 eV on either an AEI MS 902 spectrometer or a VG Micromass 7070 F spectrometer. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. GC analyses were carried out with FID and a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. Peak areas were

integrated electronically. Column chromatography was performed on Merck silica gel 60 (70-230 mesh) or ICN alumina B-Super I (activity grade II).
Solvents were dried and freshly distilled by common practice. For all dry reactions, flasks were dried at 150 °C and flushed with dry N_2 just before use, and reactions were carried out under an atmosphere of dry N_2. Product solutions were dried over anhydrous Na_2SO_4, unless otherwise noted, prior to evaporation of the solvent under reduced pressure on a rotary evaporator.

(4α,4aα,8aβ)-Octahydro-7,7-dimethoxy-4-(methoxymethoxy)-4a-methyl-1(2*H*)-naphthalenone (163). To a solution of 5.169 g (21.36 mmol) of keto alcohol **133**[5] in 100 mL of CH_2Cl_2 were added 25 mL of diisopropylethylamine and 7.0 mL (85.6 mmol) of MOMCl. The reaction mixture was stirred at rt for 18 h, and then another 5.6 mL of diisopropylethylamine and 1.6 mL (21.9 mmol) of MOMCl were added. Stirring was continued at rt for an additional 4 h after which time 50 mL of concentrated ammonia and 100 mL of water were added. The two-phase mixture was separated and the aqueous layer was extracted with three 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 75 mL of brine, dried, and evaporated under reduced pressure. The resulting residue was chromatographed on basic alumina (activity II) (3:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 5.846 g (96%) of pure MOM ether **163**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.82 (s, 3 H), 1.13-2.60 (m, 11 H), 3.10 (s, 3 H), 3.20 (s, 3 H), 3.38 (s, 3 H), 3.72 (dd, J = 4, 10 Hz, 1 H), 4.70 (AB q, J = 7 Hz, 2 H); MS, *m/e* (rel intensity) 286 (M^+, 23), 225 (24), 241 (20), 193 (23), 101 (100), 88 (29), 45 (27); calcd for $C_{15}H_{26}O_5$ (M^+) *m/e* 286.1780, found *m/e* 286.1783.

(4aα,5α,8α,8aβ)-Octahydro-8-hydroxy-5-(methoxymethoxy)-4a,8-dimethyl-2(1*H*)-naphthalenone (164). To 100 mL of 0.65 M MeMgI in ether was added dropwise a solution of 4.493 g (15.71 mmol) of MOM ether **163** in 100 mL of dry ether. The reaction mixture was allowed to stir at rt for 15 h and then heated at reflux for 1.5 h. The excess MeMgI was then quenched by the careful addition of saturated aqueous NH_4Cl. After addition of 100 mL of water, the two-phase mixture was separated and the aqueous layer was extracted with four 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 200 mL of brine, dried, and evaporated under reduced pressure. The remaining residue was taken up in 120 mL of acetone, and 12 mL of water and 0.200 g PPTS were added. After stirring at rt for 65 h the reaction mixture was poured into 200 mL of saturated aqueous $NaHCO_3$ and extracted with six 75-mL portions of ether. The combined organic layers were washed with 100 mL of brine, dried, and evaporated under reduced pressure. The resulting product was chromatographed on basic alumina (activity II) (20:1 to 3:1 petroleum ether (bp 40-60 °C)/EtOAc) to give

3.689 g (92%) of pure **164**: mp 88-90 °C (from diisopropylether); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.12 (s, 3 H), 1.15-2.80 (m, 12 H), 1.26 (s, 3 H), 3.21 (dd, *J* = 5, 10 Hz, 1 H), 3.38 (s, 3 H), 4.70 (AB q, *J* = 7 Hz, 2 H); MS, *m/e* (rel intensity) 256 (M^+, 1.8), 224 (28), 194 (52), 185 (97), 179 (45), 166 (79), 155 (63), 137 (53), 124 (52), 116 (100); calcd for $C_{14}H_{24}O_4$ (M^+) *m/e* 256.1674, found *m/e* 256.1677. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.83; H, 9.68.

(1α,4α,4aα,8aβ)-7-Ethylidene-decahydro-4-(methoxymethoxy)-1,4a-dimethyl-1-naphthalenol (165). To a stirred solution of 40 mL of 0.9 M (dimethylsulfinyl)sodium in dry DMSO at rt was added 13.357 g (36.0 mmol) of ethyltriphenylphosphonium bromide. After stirring at rt for 30 min, a solution of 3.689 g (14.41 mmol) of keto alcohol **164** in 25 mL of dry DMSO was added dropwise. The reaction mixture was heated at 55 °C for 1 h and then stirred at rt for 20 h. The reaction mixture was poured into 200 mL of water and extracted with eight 40-mL portions of EtOAc. The combined organic layers were washed with 100 mL of brine, dried, and evaporated under reduced pressure. The remaining residue was chromatographed on basic alumina (activity II) (10:1 to 3:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 3.414 g (88%) of oily **165**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.14 (s, 3 H), 1.19 (s, 3 H), 1.20-2.80 (m, 13 H), 1.60 (br d, *J* = 6.5 Hz, 3 H), 3.14 (dd, *J* = 5, 10.5 Hz, 1 H), 3.37 (s, 3 H), 4.67 (AB q, *J* = 7 Hz, 2 H), 5.21 (br q, *J* = 6.5 Hz, 1 H); MS, *m/e* (rel intensity) 268 (M^+, 4.5), 218 (63), 205 (77), 188 (100), 178 (28), 165 (21), 148 (36), 133 (21), 121 (30), 107 (31), 93 (25), 85 (28), 45 (63); calcd for $C_{16}H_{28}O_3$ (M^+) *m/e* 268.2038, found *m/e* 268.2030.

(2α,4aα,5α,8α,8aβ)-1-(Decahydro-8-hydroxy-5-(methoxymethoxy)-4a,8-dimethyl-2-naphthalenyl)-ethanone (166). To a stirred suspension of 0.853 g (22.55 mmol) of $NaBH_4$ in 10 mL of dry THF was added dropwise 3.36 mL (27.32 mmol) of BF_3 etherate. This solution was added dropwise to a stirred solution of 3.320 g (12.34 mmol) of alcohol **165** in 20 mL of dry THF at 0 °C. The reaction mixture was stirred at 0 °C for 4 h after which time a mixture of 14 mL of THF and 1.4 mL of water was added dropwise, immediately followed by addition of 8.4 mL of 3 N NaOH in water and 8.44 mL of 30% H_2O_2. The reaction mixture was stirred at rt for 65 h and then poured into 150 mL of brine. The two-phase mixture was separated, and the aqueous layer was extracted with four 75-mL portions of ether. The combined organic layers were dried and evaporated under reduced pressure. The resulting oil was dissolved in 4 mL of benzene and this solution was added dropwise to a mixture of 11.51 g (24.8 mmol) of NDC and 3.97 mL (49.6 mmol) of pyridine in 20 mL of benzene. The reaction mixture was stirred at rt for 16 h, and then heated at reflux for 2 h. The mixture was allowed to come to rt, filtered through Celite, and the filter cake was

washed with two 200-mL portions of EtOAc. The solvents were evaporated under reduced pressure and the resulting residue was dissolved in 50 mL of absolute methanol. After addition of 10 mL of 0.43 M sodium methoxide in absolute methanol, the solution was stirred at rt for 20 h and then poured into 150 mL of brine. The aqueous solution was extracted with seven 50-mL portions of ether and the combined organic layers were dried and then evaporated under reduced pressure. The remaining residue was chromatographed on basic alumina (activity II) (5:1 to 3:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 2.038 g (58%) of pure **166**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.07 (s, 3 H), 1.14 (s, 3 H), 1.15-2.60 (m, 13 H), 2.16 (s, 3 H), 3.17 (dd, J = 5, 10 Hz, 1 H), 3.37 (s, 3 H), 3.67 (AB q, J = 7 Hz, 2 H); MS, *m/e* (rel intensity) 284 (M^+, 1.7), 222 (25), 213 (33), 207 (28), 194 (25), 181 (52), 161 (60), 139 (31), 121 (50), 95 (29), 93 (28), 71 (25), 45 (100), 43 (91); calcd for $C_{16}H_{28}O_4$ (M^+) *m/e* 284.1987, found *m/e* 284.1986.

(1α,4α,4aα,7α,8aβ)-Decahydro-4-(methoxymethoxy)-1,4a-dimethyl-7-(1-methylethenyl)-1-naphthalenol (167). To a stirred solution of 25 mL of 1.0 M (dimethylsulfinyl)sodium in dry DMSO was added 7.14 g (20.00 mmol) of methyltriphenylphosphonium bromide. The mixture was stirred at rt for 30 min, and then a solution of 1.988 g (7.00 mmol) of alcohol **166** in 15 mL of dry DMSO was added dropwise. The reaction mixture was stirred at 50 °C for 2 h, allowed to come to rt, and stirring was continued for 17 h. The reaction mixture was diluted with 150 mL of water and extracted with eight 30-mL portions of EtOAc. The combined organic layers were washed with 75 mL of brine and dried. The solvent was evaporated under reduced pressure and the remaining residue was chromatographed on basic alumina (activity II) (15:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 1.721 g (87%) of pure **167**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.03-2.20 (m, 13 H), 1.07 (s, 3 H), 1.14 (s, 3 H), 1.76 (br s, 3 H), 3.17 (dd, J = 4.5, 10 Hz, 1 H), 3.38 (s, 3 H), 4.68 (AB q, J = 7 Hz, 2 H), 4.73 (br s, 2 H); MS, *m/e* (rel intensity) 282 (M^+, 1.9), 267 (23), 205 (24), 192 (45), 179 (78), 162 (38), 149 (28), 135 (31), 121 (42), 107 (45), 101 (35), 95 (43), 81 (29), 71 (26), 45 (100), 43 (61); calcd for $C_{17}H_{30}O_3$ (M^+) *m/e* 282.2195, found *m/e* 282.2193.

(1α,4α,4aα,7α,8aβ)-Decahydro-4-(methoxymethoxy)-1,4a-dimethyl-7-(1-methylethyl)-1-naphthalenol (168). A mixture of 1.691 g (6.00 mmol) of isopropenyl alcohol **167** and 0.195 g of 10% platinum on charcoal in 130 mL of ethanol was hydrogenated in a Parr hydrogenator under 50 psi of H_2 for 70 min. The reaction mixture was filtered through Celite, and the filter cake was washed with 75 mL of EtOAc. The solvents were evaporated under reduced pressure to give 1.688 g (99%) of pure **168**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.89 (d, J = 7 Hz, 6 H), 1.00-2.10 (m, 14 H), 1.03 (s, 3 H), 1.13 (s, 3 H),

3.15 (dd, J = 5.5, 9.5 Hz, 1 H), 3.37 (s, 3 H), 4.67 (AB q, J = 7 Hz, 2 H); MS, *m/e* (rel intensity) 284 (M^+, 1.1), 222 (21), 213 (34), 207 (33), 194 (30), 181 (100), 164 (41), 161 (29), 121 (30), 109 (43), 101 (35), 95 (36), 83 (44), 71 (24), 45 (95), 43 (46); calcd for $C_{17}H_{32}O_3$ (M^+) *m/e* 284.2351, found *m/e* 284.2361.

(1α,4α,4aα,7α,8aβ)-Decahydro-1,4a-dimethyl-7-(1-methylethyl)-1,4-naphthalenediol (169). A solution of 1.663 g (5.85 mmol) of isopropyl alcohol **168** and two drops of concentrated HCl in 20 mL of methanol was heated at reflux for 75 min, allowed to come to rt and then neutralized with 0.3 N KOH in methanol. The reaction mixture was concentrated under reduced presssure, and the resulting residue was taken up in 100 mL of CH_2Cl_2. The organic layer was washed with 50 mL of brine, dried, and evaporated under reduced pressure. Chromatography of the residue on silica gel (5:1 to 2:1 petroleum ether (bp 40-60 °C)/EtOAc) gave in order of elution 0.196 g (15%) of a mixture of dehydrated products (41:7:1; major compound: **170**) and 1.072 g (75%) of pure diol **169**.

169: mp 121 °C (from diisopropylether); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.90 (d, J = 7 Hz, 6 H), 0.95 (s, 3 H), 1.03-2.10 (m, 15 H), 1.14 (s, 3 H), 3.24 (dd, J = 4, 10 Hz, 1 H); MS, *m/e* (rel intensity) 240 (M^+, 0.5), 222 (32), 207 (22), 183 (40), 181 (87), 164 (64), 161 (50), 137 (21), 121 (69), 109 (52), 101 (58), 95 (61), 83 (39), 72 (100), 43 (63); calcd for $C_{15}H_{28}O_2$ (M^+) *m/e* 240.2089, found *m/e* 240.2093.

170: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.70-2.60 (m, 13 H), 0.90 (d, J = 7 Hz, 6 H), 0.99 (s, 3 H), 1.75 (s, 3 H), 3.47 (dd, J = 7.5, 9 Hz, 1 H); MS, *m/e* (rel intensity) 222 (M^+, 24), 204 (99), 189 (84), 178 (53), 161 (56), 135 (73), 119 (53), 105 (100), 93 (72), 55 (47), 41 (53).

(1α,4α,4aα,7α,8aβ)-Decahydro-1,4a-dimethyl-7-(1-methylethyl)-1,4-naphthalenediol 4-(4-Methylbenzenesulfonate) (162). To a stirred solution of 0.918 g (3.82 mmol) of diol **169** in 10 mL of pyridine was added 1.444 g (7.58 mmol) of TsCl. The reaction mixture was stirred at rt for 4 d and then concentrated under reduced pressure. The resulting mixture was taken up in 100 mL of CH_2Cl_2 and washed successively with one 50-mL portion of 10% aqueous H_2SO_4, two 25-mL portions of saturated aqueous $NaHCO_3$, and one 50-mL portion of brine. The organic layer was dried and the solvent was removed under reduced pressure. The crude product was flash chromatographed on silica gel (2:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 1.445 g (97%) of pure **162**: mp 104 °C (from petroleum ether (bp 80-100 °C)); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.86 (d, J = 7 Hz, 6 H), 0.90-1.90 (m, 14 H), 1.01 (s, 3 H), 1.10 (s, 3 H), 2.43 (s, 3 H), 4.26 (m, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.81 (d, J = 8 Hz, 2 H); Anal. Calcd for $C_{22}H_{34}O_4S$: C, 66.97; H, 8.69. Found: C, 67.09; H, 8.77.

(±)-5-*epi*-Nardol (26). To a mixture of 0.5 mL (4.6 mmol) of dry *tert*-amyl alcohol and 20 mL of dry benzene was added 0.090 g (3.00 mmol, as a 80% dispersion in mineral oil) of NaH. The mixture was heated at reflux for 0.5 h, allowed to come to rt, and then 0.394 g (1.00 mmol) of tosylate **162** was added. The solution was heated at reflux for 17 h and, after cooling to rt, poured into 50 mL of brine. The two-phase mixture was separated, and the aqueous layer was extracted with three 25-mL portions of ether. The combined organic layers were dried and evaporated under reduced pressure. Chromatography on silica gel (30:1 to 25:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded in order of elution 0.006 g (3%) of cyclic ether **171** and 0.200 g (90%) of (±)-5-*epi*-nardol **26**:[12] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, J = 6.9 Hz, 6 H), 0.96-2.00 (m, 13 H), 1.27 (s, 3 H), 2.53 (m, 1 H), 2.78 (m, 1 H), 4.80 (br s, 1 H), 4.84 (s, 1 H); MS, *m/e* (rel intensity) 222 (M^+, 16), 204 (69), 191 (49), 161 (95), 135 (31), 121 (100), 109 (54), 95 (62), 81 (58), 71 (46), 43 (64); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found *m/e* 222.1985.
171: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.85 (br d, J = 7.5 Hz, 6 H), 0.90-1.90 (m, 13 H), 1.22 (s, 6 H), 2.16 (bs, 1 H).

4.4 References and Notes

(1) (a) Sastry, S. D.; Maheshwari, M. L.; Bhattachryya, S. C. *Tetrahedron Lett.* **1966**, 1035.
(b) Sastry, S. D.; Maheswari, M. L.; Chakravarti, K. K.; Bhattachryya, S. C. *Perfum. Essent. Oil Rec.* **1967**, *58*, 154.
(2) See also Chapter 1 of this thesis, section 1.1.
(3) Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, Ae. *J. Org. Chem.* **1990**, *55*, 941.
(4) Chapter 3 of this thesis.
(5) Wijnberg, J. B. P. A.; Vader, J.; de Groot, Ae. *J. Org. Chem.* **1983**, *48*, 4380.
(6) Heathcock, C. H.; Tice, C. M.; Germroth, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6081.
(7) MacKenzie, B. D.; Angelo, M. M.; Wolinsky, J. *J. Org. Chem.* **1979**, *44*, 4042.
(8) GCMS analysis of the mixture revealed for all three products M^+ peaks at *m/e* 222.
(9) Garcia-Granados, A.; Molina, A.; Cabrera, E. *Tetrahedron* **1986**, *42*, 81.
(10) Compound **172** could not be isolated, but in analogy with the products formed in the rearrangement of the tosylate **131**, its relative retention time in the GC analysis, and the fact that no additional olefinic signals were observed in the ^{1}H NMR spectrum of **26**, we assigned its structure.
(11) The isolation of the trans-fused "6β,8β-dihydroxynardol-8-cinnamate" from *Echinacea purpurea* has been described. See: Bauer, R. F. X.; Khan, J. A.; Lotter, H.; Wagner, H. *Helv. Chim. Acta* **1985**, *68*, 2355.
(12) According to GC analysis, the purity of **26** was 97%; the 3% impurity was assigned structure **172**.[10]

5 Base-Induced and -Directed Elimination of Perhydronaphthalene Mesylates

5.1 Introduction

In the Chapters 3 and 4, the skeletal rearrangement of trans-fused perhydronaphthalenes to cis-fused hydroazulenes was described. The selectivity in the proton abstraction step of the reaction, leading to the formation of the exocyclic methylene unit was obtained by the action of the strategically positioned, axial alcoholate at C(4). In the present chapter, the use of this group as a directing factor in the elimination reaction leading to the C(6)-C(7) double bond is described.[1]

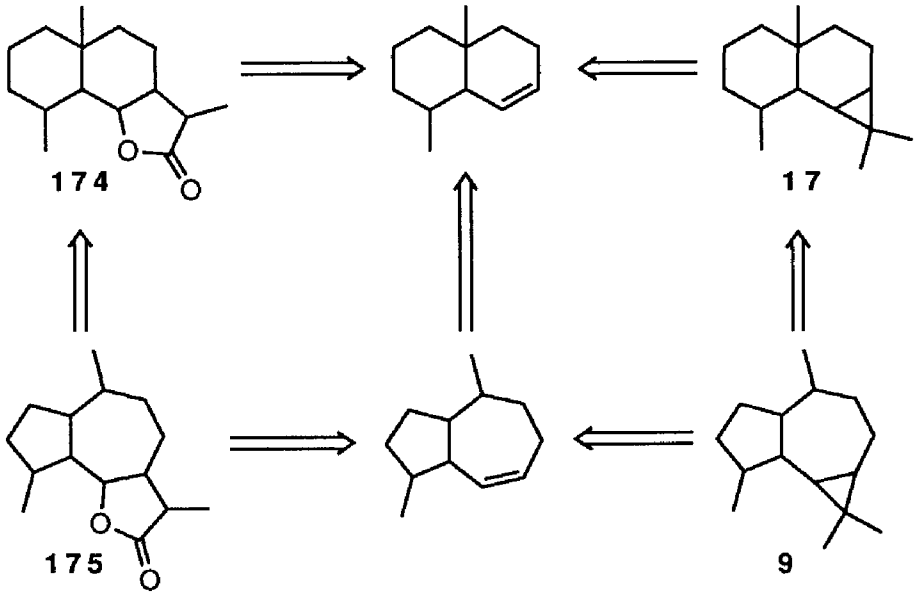
Introduction of an axial leaving group at C(7) should ensure a smooth elimination process because of the *anti* relationship of this leaving group to its β-protons. In the absence of a directing group, elimination reactions in the comparable trans-fused steroid systems mainly lead to the formation of the $\Delta^{2,3}$ double bond isomers[2] (*i.e.* the C(7)-C(8) double bond in the hydronaphthalenes). However, we envisaged that the deprotonated axial hydroxyl group at C(4) could guide the elimination to the selective formation of the C(6)-C(7) double bond isomer (Scheme 5.1).[3]

Scheme 5.1

173 : R = TBDMS **27**

This C(6)-C(7) double bond in isomer **27** is synthetically interesting since it may serve as an entry for other functional groups at this position, which are present in several classes of sesquiterpenes (Scheme 5.2). Elaboration of a lactone from this double bond[4] would lead to the eudesmanolide **174** and guaianolide **175** skeletons. A *gem*-dimethyl-cyclopropane ring at C(6)-C(7), easily introduced *via* a carbene addition,[5] is found in maaliane **17** and aromadendrane **9** sesquiterpenes.

Scheme 5.2



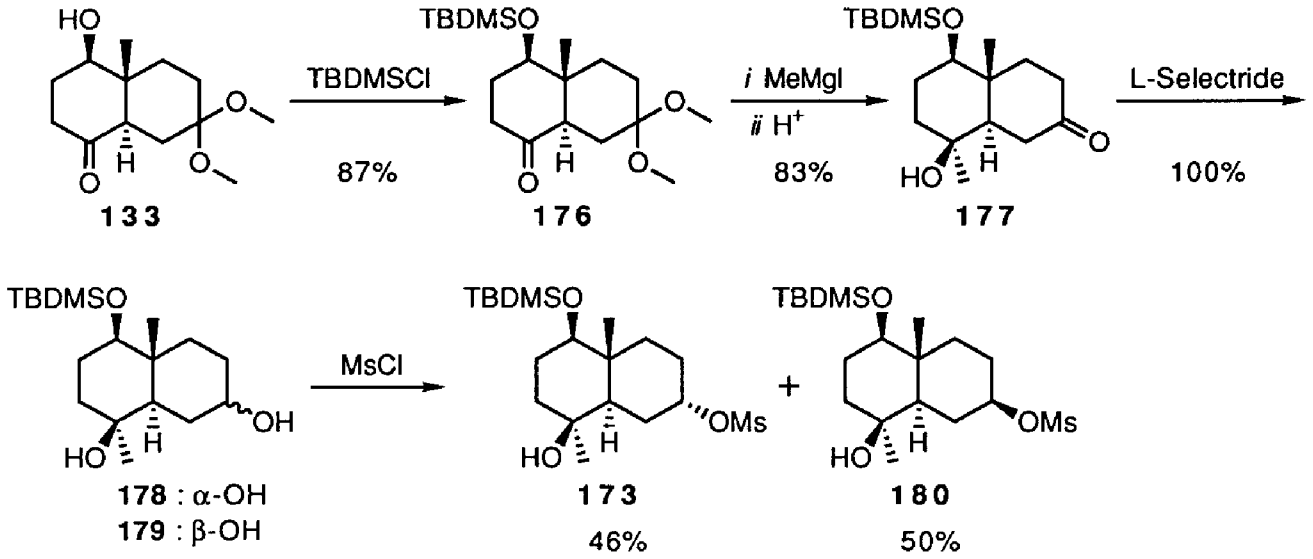
5.2 Synthesis of the Mesylates 173 and 180

Starting material for the synthesis of the α-mesylate **173** was the previously used, readily available monoacetalized trans-fused dione **133**[6,7] (Scheme 5.3). The secondary hydroxyl group of **133** was protected as its TBDMS ether, and the resulting product **176** was treated with an excess of MeMgI in dry ether at rt.[8] Hydrolysis of the dimethyl acetal function with a catalytic amount of HCl in aqueous acetone gave the monoprotected keto diol **177**. The most straightforward approach to an axial leaving group at C(7) would involve a selective reduction of **177** to its corresponding α-alcohol **178**, followed by a sulfonate esterification *e.g.* to the mesylate **173**. L-Selectride, used for stereoselective reductions, seemed the most suitable reagent.[9] Unexpectedly however, treatment of **177** with this reagent in dry THF at -78 °C afforded a 1:1.1 mixture of **178** and the β-alcohol **179**, respectively. This lack of selectivity can probably be attributed to a reaction between the axial alcohol at C(4) and the reagent, resulting in a shielding of the β-side of the C(7)-carbonyl. This shielding will partly lead to an axial, *i.e.* α-attack of the hydride to the carbonyl in **177**. In this respect, it is important to note that stereoselective reductions to the corresponding α-alcohols are observed when the alcohol at C(4) is in an equatorial position or omitted.[9,10]

Other reducing agents were tried but gave, as expected, more of the β-alcohol **179**. $NaBH_4$ reduction, for instance, gave a 1:6.6 mixture of **178** and **179**, respectively, in quantitative yield, while with $LiAlH_4$ and $Li(OtBu)_3BH$ a selective formation of the β-alcohol **179** was obtained. In order to improve the selectivity in the L-Selectride

reduction, we tried to protect the axial hydroxyl group at C(4) as its TMS ether. Due to 1,3-diaxial interactions with the angular methyl group, however, these attempts failed.

Scheme 5.3

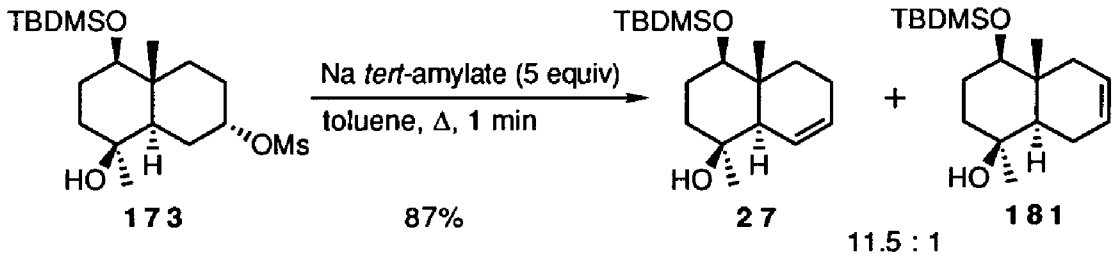


Confronted with this problem, it was decided to investigate not only the usefulness of an axial leaving group for the synthesis of olefin **27**, but also that of an equatorial one at C(7). As the alcohols **178** and **179** were only separated with the greatest difficulty, the 1:1.1 mixture of **178** and **179** obtained in the L-Selectride reduction of **177**, was treated with MsCl at 40 °C for 2 h.[11] After column chromatography, the mesylates **173** and **180** were isolated separately in a combined yield of 96%, overall from **177**.

5.3 Elimination Reactions of the Mesylates 173 and 180

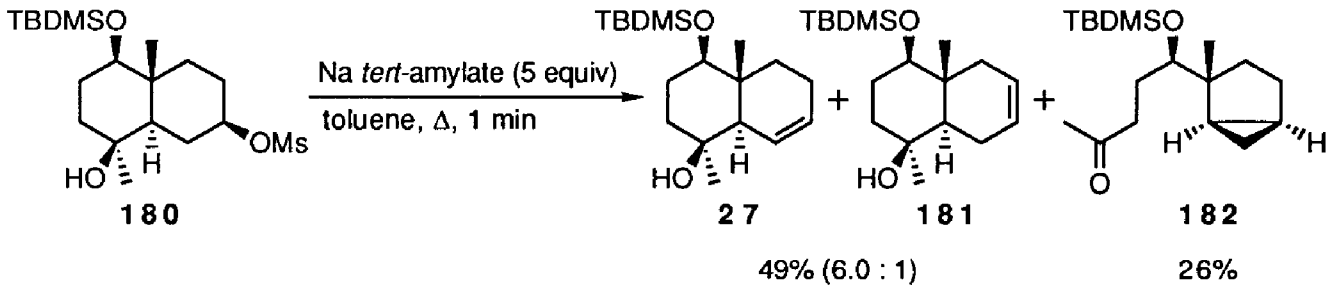
For the elimination reactions of the mesylates **173** and **180**, we decided to employ the same conditions as were used in the rearrangement reactions of the tosylates **131**, **132**, and **162**.[7,12] This decision was inspired by the resemblance between the reactions: in both cases the deprotonated axial hydroxyl group at C(4), separated by three C-C single bonds from the sulfonate leaving group, had to serve as an intramolecular base.
In the rearrangement reactions, sodium *tert*-amylate was prepared *in situ* from NaH and *tert*-amyl alcohol, prior to the addition of the substrate to the reaction mixture. In the elimination reactions described here, 5 equiv of sodium *tert*-amylate (3.5 M in toluene)[13] were added to a refluxing solution of the substrate in toluene.

Scheme 5.4



When the α-mesylate **173** was treated this way with sodium *tert*-amylate in refluxing toluene,[14] the reaction was completed within 1 min and an inseparable mixture of the double bond isomers **27** and **181** was obtained in high yield (Scheme 5.4). According to GC analysis, the mixture consisted for more than 90% of one olefin, which we expected to be the desired olefin **27**. This was confirmed by ^{13}C NMR analysis of the mixture. The olefinic signals of the major olefin **27** appear at δ 124.11 and 129.35, while the corresponding signals of the isomeric, minor olefin **181** resonance at δ 125.30 and 125.47. Furthermore, the allylic bridgehead carbon C(5) in **27** has a chemical shift of 49.95 ppm. In the minor olefin **181**, C(5) gives rise to a doublet at 46.10 ppm. Similar differences in chemical shifts of the olefinic and bridgehead carbon atoms of Δ^2- and Δ^3-steroids have been reported.[15]

Scheme 5.5



For the equatorial β-mesylate **180** a very slow elimination process was expected. To our surprise, however, this reaction was also completed within 1 min upon treatment with 5 equiv of sodium *tert*-amylate in refluxing toluene (Scheme 5.5). After workup and column chromatography a 6.0:1 mixture of **27** and **181** was isolated in a total yield of 49%. Apart from the elimination products, the fragmentation product **182** was isolated in 26%. In its ^{13}C NMR a carbonyl (s at 209.19 ppm) and three cyclopropyl signals (2 d (J_{C-H} = 166.1 and 167.1 Hz) and 1 t (J_{C-H} = 158.5 Hz)) were observed. Furthermore, an inseparable and not fully characterizable mixture of products was

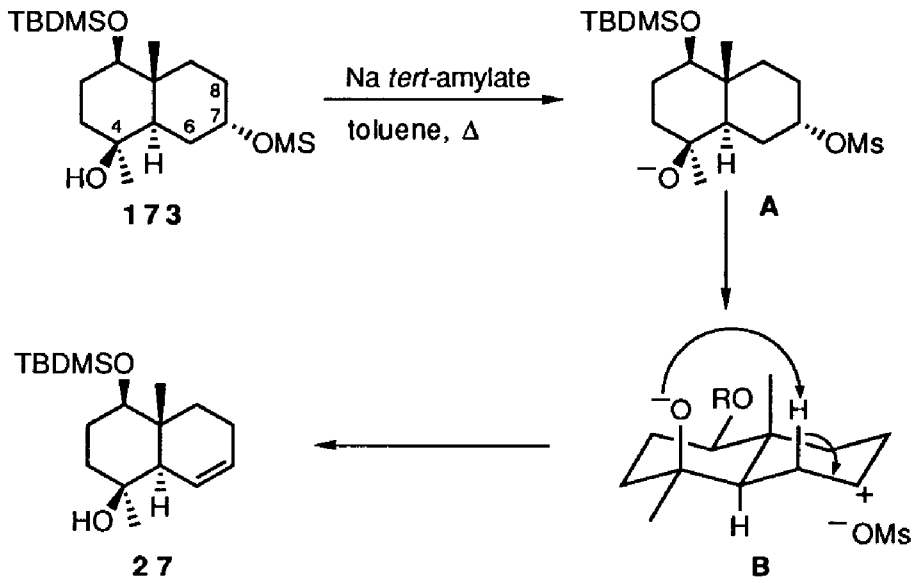
isolated in 5%. In the ^{1}H NMR of this mixture cyclopropyl and olefinic protons were recognizable, as well as the C(1)-H and the TBDMS protecting group. In the MS a M^+-15 peak at *m/e* 587 was found, so it is believed that under the reaction conditions, *i.e.* strong base and high temperature, aldol condensations of **182** have taken place.[16]

5.4 Mechanism of the Base-Induced and -Directed Elimination

5.4.1 Elimination of the α-Mesylate 173

At first, the elimination reaction of the α-mesylate **173** was expected to proceed *via* an E2 mechanism as depicted in Scheme 5.1, with the **27**:**181** ratio roughly reflecting the relative importance of the intra- and intermolecular proton abstraction. Recent discoveries, however, forced us to give up this idea of a concerted E2 mechanism for the elimination of the α-mesylate **173** (*vide infra*). We now believe that the elimination proceeds *via* a dipolar intermediate **B** (Scheme 5.6), just as in the earlier proposed mechanism for the skeletal rearrangement.[7a,b]

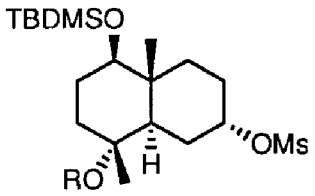
Scheme 5.6



Deprotonation of the axial tertiary hydroxyl group at C(4) by sodium *tert*-amylate results in the formation of intermediate **A**. The deprotonated hydroxyl group at C(4) will then, *via* a "through bond" inductive mechanism,[7a,b,17] bring about the heterolysis of the mesylate ester bond, which results in the formation of intermediate

B. In the nonpolar, aprotic toluene, the mesylate anion will be in close proximity of the carbocation at C(7) in **B** (ion pair).[18,19] The alkoxide substituent at C(4) and the β-H at C(6) are 1,3-diaxially positioned in intermediate **B**, making the formation of **27** *via* an intramolecular deprotonation the most favourable process. Intermolecular proton abstraction from C(8) in intermediate **B** will account for the formation of the minor olefin **181**.[20]

Support for the reaction to proceed *via* the dipolar intermediate **B** was obtained from the behaviour of the α-mesylates **183** and **184**.[10] The α-mesylate **183** reacted with a rate comparable to the one of its C(4)-epimer **173**. On the other hand, the α-mesylate **184**, in which the hydroxyl group at C(4) is protected as its TMS ether, did not react at all, even after prolonged treatment with sodium *tert*-amylate. This indicates that the presence of a deprotonated hydroxyl group at C(4) is absolutely essential for the elimination reaction just as in the case of the rearrangement process.[7a,b]



183 : R = H
184 : R = TMS

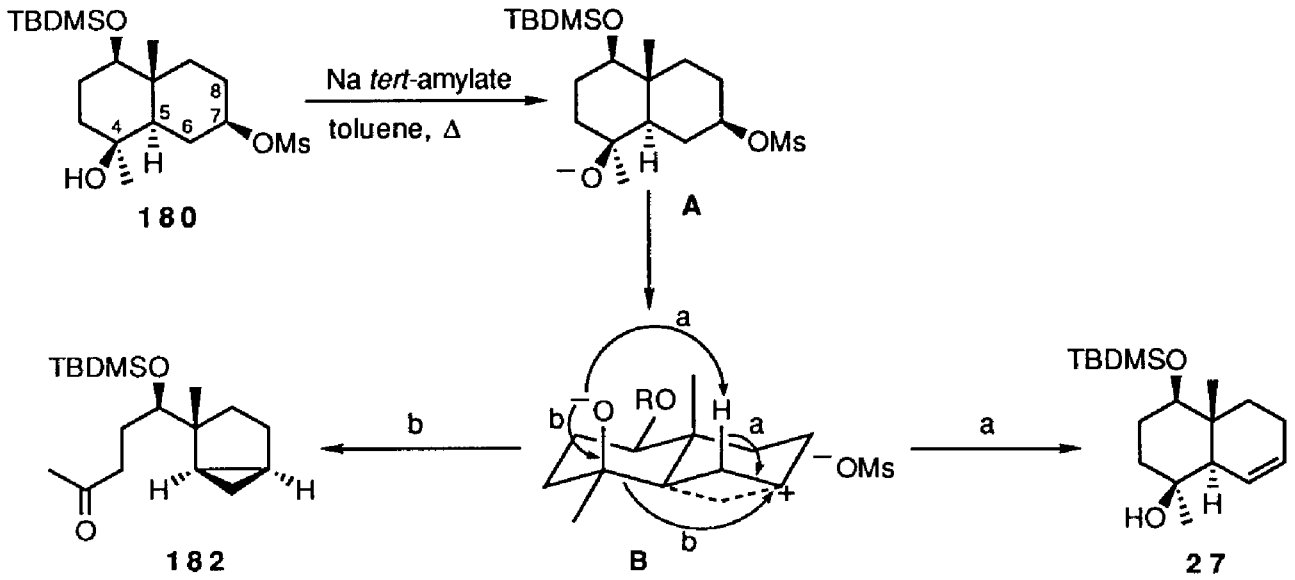
A second, and more direct support[10] for the presence of intermediate **B** in the reaction path was found in an experiment in which the axial α-mesylate **173** was treated with sodium *tert*-amylate and the reaction was quenched before it was completed. After column chromatography, about 10% of the regained mesylate fraction consisted of the equatorial β-mesylate **180**. This observation can be explained by an (internal) return of the mesylate group with inversion of the stereochemistry at C(7) in the dipolar intermediate **B**.

5.4.2 Elimination of the β-Mesylate 180

In the β-mesylate **180**, the protons at C(6) and C(8) are positioned *syn* to the equatorial mesylate leaving group at C(7), so the formation of the olefins **27** and **181** requires a *syn* elimination. Consequently, a slower reaction was expected than for the α-mesylate **173**, which can undergo a facile *anti* elimination. Surprisingly, however, a very fast reaction (< 1 min) was found for this equatorial mesylate **180**.

As in the case of the skeletal rearrangement[7a,b] and the elimination of the α-mesylate **173**, the reaction of this β-mesylate **180** is believed to proceed *via* a dipolar intermediate **B** (Scheme 5.7). Thus, deprotonation of the axial, tertiary hydroxyl group at C(4) by sodium *tert*-amylate results in intermediate **A**. The alcoholate at C(4) induces the heterolysis of the mesylate ester bond. In this β-mesylate **180**, the induction can be divided into two components. In the first place, a "through bond" inductive mechanism (TBI) will be operating over the intervening σ bonds, just as in

scheme 5.7



the α-mesylate **173**. Especially the fact that the electron density of the C(5)-C(6) bond is enlarged is now important for the heterolysis (or ion pair formation[18,19]) of the mesylate ester bond in **180**. This bond is antiperiplanar to the developing carbocationic 2p orbital at C(7) and therefore the intermediate **B** is stabilized most effectively by these β-CC bonding electrons.[21]

In the β-mesylate **180**, the TBI mechanism will be accompanied by an indirect "through space" induction (TSI), which involves 1,3-bridging. This 1,3-bridging will be rather strong for the ionization of the β-mesylate **180**, as the backlobe of the C(4)-C(5) bond overlaps well with the 2p orbital of the carbocationic centre at C(7).[22] The simplified picture **B** shows only the respective orbital axes that converge and intersect. This interplay of "through bond" and indirect "through space" induction will result in a relatively easy formation of the intermediate **B** and therefore in the fast reaction observed for the β-mesylate **180**.

The intermediate **B** has several ways to react further. In the first place it can undergo deprotonation as described for the α-mesylate **173**, with the intramolecular proton abstraction depicted as route a (Scheme 5.7). Secondly, the 1,3-bridging, stabilizing the intermediate **B**, may develop into a complete overlap of the backlobe of the C(4)-C(5) bond with the incipient cationic 2p orbital at C(7). The simultaneous formation of the carbonyl at C(4) and the breaking of the C(4)-C(5) bond then result in the formation of **182** (Scheme 5.7, route b). This type of fragmentation which generates a cyclopropane ring is termed homofragmentation.[23] The process is comparable with the Grob fragmentation,[24] but involves one more σ bond.

So, elimination reactions of both the mesylates **173** and **180** are believed to start with a heterolysis of the mesylate ester bond, intramolecularly induced by the deprotonated hydroxyl group at C(4). The dipolar intermediates **B** then partly follow different reaction paths: intermediate **B** from the axial α-mesylate **173** only undergoes deprotonation reactions, resulting in a mixture of the olefins **27** and **181**. The intermediate **B** from the equatorial β-mesylate **180**, on the other hand, only partly reacts this way. Here, the intramolecular homofragmentation reaction, leading to **182**, competes with the intra- and intermolecular elimination reactions.

5.5 Influence of the Base Concentration on the Formation of the Olefin 27

The yield and selectivity obtained in the elimination reaction of the α-mesylate **173** were good, but for the β-mesylate **180** only a moderate yield of the desired C(6)-C(7) olefin **27** was observed. The yield of the minor C(7)-C(8) olefin **181** in this reaction (7%), however, was the same as the one found in the elimination reaction of the α-mesylate **173**. The moderate yield of the olefin **27** in the elimination reaction of the β-mesylate **180** could therefore be attributed to the competitive homofragmentation reaction, leading to **182**. Suppression of this fragmentation reaction was consequently expected to lead to a more pronounced elimination reaction and in this way to higher yields of the desired C(6)-C(7) olefin **27**.

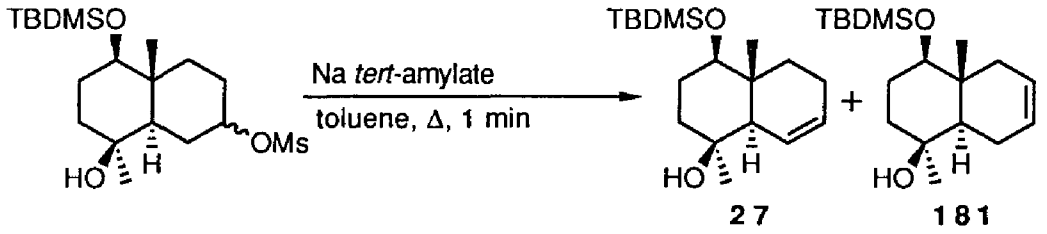
In order to suppress the homofragmentation reaction, the β-mesylate **180** was treated with lithium *tert*-amylate. The lithium ion, in its role as counter ion to the deprotonated hydroxyl group at C(4),[25] was expected to confine the negative charge to the alkoxide to a greater extent than sodium.[26] As a result of this, the backlobe of the C(4)-C(5) bond was expected to be smaller and diminished fragmentation and increased elimination processes were envisaged.
Upon treatment of the β-mesylate **180** with 5 equiv of lithium *tert*-amylate a relatively slow reaction was observed (1 h). This can easily be explained by a slower deprotonation of the C(4)-hydroxyl group since lithium *tert*-amylate is a weaker base than sodium *tert*-amylate. Furthermore, the inductive power of the Li^+-paired alkoxide at C(4) is diminished relative to the Na^+-paired one. After workup and column chromato-graphy, the mixture of olefins **27** and **181** was isolated in 78% yield and the homofragmentation product **182** in 4%. Our assumption that the elimination would be favoured by a suppression of the homofragmentation reaction proved to be correct. Unfortunately, but not completely unexpected,[7a,b,26] a severely diminished

selectivity was observed, due to the reduced basicity of the Li^+-paired alkoxide at C(4). The inseparable mixture of the olefins **27** and **181** was obtained in a ratio of 1.5:1, respectively, according to GC analysis.

Then, a clue for the improvement of the formation of the olefin **27** from the β-mesylate **180** was found. Accidentally, during one of the experiments, the sodium *tert*-amylate (3.5 M in toluene) was *not* added at once to the refluxing solution of β-mesylate **180**. Instead, it was added dropwise, in about 1 min. After workup and column chromatography the mixture of the olefins **27** and **181** was isolated in only 27% yield and in a ratio of 4.25:1, respectively, according to GC analysis. The homofragmentation product **182** and the products derived from **182** by aldol condensations, were isolated in a total yield of 58%. It has been described that the β-mesylate **180** gives a very fast reaction. So in this experiment, the amount of sodium *tert*-amylate, present during the actual reaction, will have been less than the 5 equiv eventually added. This gave way to the idea that the yield and selectivity of the elimination of **180** might be influenced by varying the amount of sodium *tert*-amylate.

The elimination behaviour of the α-mesylate **173** and the β-mesylate **180** with varying amounts of sodium *tert*-amylate was studied. The results of these experiments are presented in Table 5.1. In all cases, a very fast reaction was observed (<1 min).[27]
For the α-mesylate **173**, no influence of the base strength of the solution on the yield and selectivity of the reaction was found. The fact that the intramolecular abstraction of the β-H at C(6) by the alkoxide at C(4) is much faster than an intermolecular deprotonation will account for this observation. Intermolecular formation of either olefin **27** or **181** is then of secondary importance and no significant influences on yield and selectivity of an increasing amount of sodium *tert*-amylate are observed.
For the β-mesylate **180** the situation is different. Here, the yield of the minor C(7)-C(8) olefin **181** also does not vary with an increasing amount of sodium *tert*-amylate. This in contrast to the yield of the desired C(6)-C(7) olefin **27**, which increases drastically upon going from 1.25 to 25 equiv of sodium *tert*-amylate. Apparently, by addition of more sodium *tert*-amylate to the solution, the abstraction of the β-H at C(6) becomes more important at the expense of the intramolecular homofragmentation reaction. This might imply that for the β-mesylate **180**, the intermolecular abstraction of the C(6)-H is of major importance for the formation of the desired C(6)-C(7) olefin **27**. An explanation for this can be found in the so-called "belt aggregate model".[28,29] In the nonpolar, aprotic toluene, sodium *tert*-amylate is mainly present as higher aggregates of alkali metal ion-paired species and, as such, act as the effective base species.[28] In the β-mesylate **180**, a continuous higher aggregate of ion-paired sodium *tert*-amylate can

Table 5.1

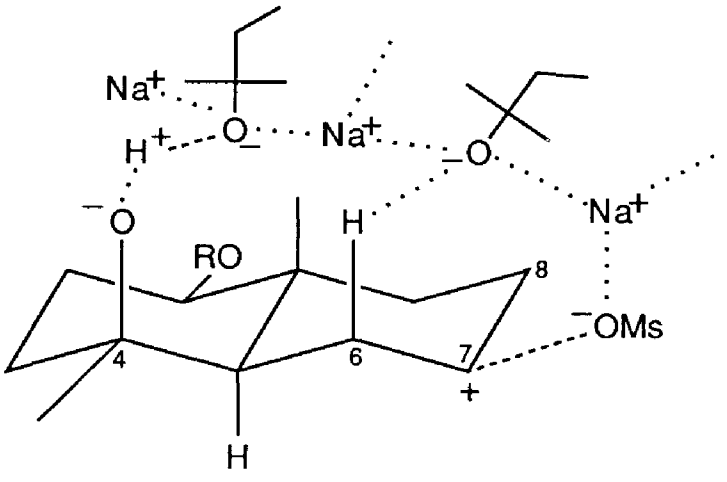


27 **181**

	equiv			total (GC ratio)
173 : α-OMs	1.25	76%	7%	83% (11.4:1)
	5	80%	7%	87% (11.5:1)
	10	80%	7%	87% (11.5:1)
180 : β-OMs	1.25	25%	5%	30% (4.6:1)
	5	42%	7%	49% (6.0:1)
	10	49%	8%	57% (6.6:1)
	25	55%	7%	62% (7.8:1)

be formed between the mesylate leaving group at C(7) and the hydroxyl group/alkoxide at C(4) on the other side of the "belt". After deprotonation of the hydroxyl group at C(4) (Figure 5.1) the resulting alkoxide will induce the heterolysis of the mesylate ester bond. By the coordination of the aggregate of ion-paired sodium *tert*-amylate on the "front side" of the β-mesylate **180**, sodium *tert*-amylate is brought in close proximity of the β-H at C(6) and *inter*molecular proton abstraction will accompany the *intra*molecular abstraction of the C(6)-H to a considerable extent. The observed influence of the amount of sodium *tert*-amylate on the yield of the desired C(6)-C(7) olefin can now be explained in the following manner. In the case that a low amount of sodium *tert*-amylate is added to the reaction mixture, relatively high con-

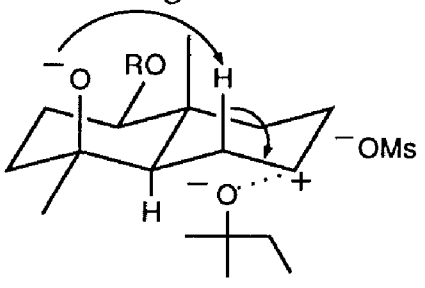
Figure 5.1



centrations of *tert*-amyl alcohol will be formed due to proton exchange between the *tert*-amylate and hydroxyl groups of the substrate **180** and the formed olefins **27** and **181**. Co-clustering of this *tert*-amyl alcohol to the sodium *tert*-amylate aggregates[30] will result in a lower basicity of the aggregates. As a result, less intermolecular abstraction of the β-H at C(6) will take place and consequently, the homofragmentation reaction leading to **182**, will become a more dominant reaction path. When the concentration of sodium *tert*-amylate is higher, relatively less *tert*-amyl alcohol is formed. Consequently, the basicity of the "belt aggregate" is higher. The proton abstraction from C(6) (being a combination of intra- and intermolecular processes) will be able to compete more succesfully with the intramolecular homofragmentation, and higher yields of the desired C(6)-C(7) olefin **27** are obtained.
Similar influences of the amount of sodium *tert*-amylate on the selectivity were found in the proton abstraction step of the skeletal rearrangement reaction of the tosylate **131**.[7b] In that case, however, the intermolecular deprotonation had to be suppressed as much as possible, as it resulted in the isomeric product. Consequently, low sodium *tert*-amylate concentrations and addition of *tert*-amyl alcohol to the reaction mixture resulted in a higher selectivity. In the elimination reaction of the β-mesylate **180**, the situation is partly reversed. The "belt aggregate model" can explain why at higher sodium *tert*-amylate concentrations a higher selectivity is observed. In this model, the intermolecular proton abstraction from C(6) accompanies the intramolecular elimination process and a lowering of the basicity of the solution therefore results in a decreased selectivity.

The increased yield of the C(6)-C(7) olefin **27** at higher sodium *tert*-amylate concentrations may also be explained by a suppression of the homofragmentation reaction. At higher base concentrations, shielding of the positive charge at C(7) by (aggregated) sodium *tert*-amylate on the α-face of the dipolar intermediate **B** (Scheme 5.7) will become more likely (Figure 5.2). This shielding will prevent the formation of the C(5)-C(7) bond, thereby suppressing the competing intramolecular homofragmentation reaction. The intramolecular abstraction of the C(6)-H then becomes more important which results in higher yields of the C(6)-C(7) olefin **27**.

Figure 5.2

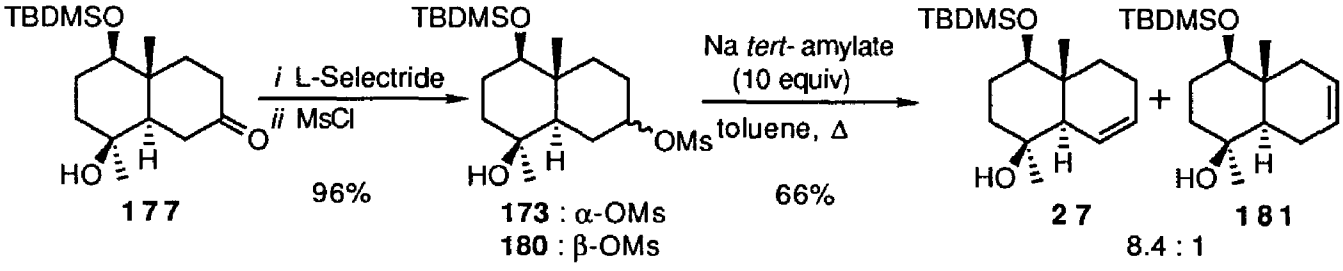


5.6 Concluding Remarks

The results presented in this chapter show that elimination of both the mesylates **173** and **180** results in the formation of the C(6)-C(7) olefin **27**. For the β-mesylate **180** the yield was diminished as a result of the competing homofragmentation reaction, leading to **182**. This reaction could be subdued by increasing the amount of sodium *tert*-amylate in the reaction mixture. Experimental conditions (especially in larger scale reactions), however, limited the amount of sodium *tert*-amylate to about 10 equiv.

Thus, L-Selectride reduction of ketone **177**, directly followed by treatment with MsCl produced a 1:1.1 mixture of the epimeric mesylates **173** and **180**. When this mixture was treated with 10 equiv of sodium *tert*-amylate, a 8.4:1 mixture of the olefins **27** and **181** was prepared in 66% (Scheme 5.8).

Scheme 5.8



5.7 Experimental Section

General

Melting points are uncorrected. Chemical shifts are reported relative to TMS (δ 0.00), with $CHCl_3$ as internal standard (δ 7.23 (^1H) and δ 76.90 (^{13}C)). ^{13}C NMR multiplicities were determined by using a DEPT pulse sequence. MS data were determined at 70 eV on either an AEI MS 902 spectrometer or a Hewlett Packard 5970B series Mass Selective Detector, coupled with a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. GC analyses were carried out with FID and a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically. Flash chromatography was performed on Merck silica gel 60 (230-400 mesh).

Solvents were dried and freshly distilled by common practice. For all dry reactions, flasks were dried at 150 °C and flushed with dry N_2 just before use, and reactions were carried out under N_2, unless otherwise reported. Product solutions were dried over $MgSO_4$ prior to evaporation of the solvent under reduced pressure on a rotary evaporator. Sodium *tert*-amylate (3.5 M in toluene) was prepared as described elsewhere.[13]

(4α,4aα,8aβ)-4-[(*tert*-Butyldimethylsilyl)oxy]octahydro-7,7-dimethoxy-4a-methyl-1(2*H*)-naphthalenone (176). To a solution of 16.56 g (68.4 mmol) of the alcohol **133**[6,7] in 90 mL of DMF were added 11.64 g (171 mmol) of imidazole and 12.87 g (85.5 mmol) of TBDMSCl. The reaction mixture was stirred at rt for 3 d, and then poured into 300 mL of water. The two-phase mixture was separated, and the aqueous layer was extracted with five 100-mL portions of CH_2Cl_2. The combined organic layers were washed with 150 mL of brine, dried, and evaporated under reduced pressure. The resulting product was flash chromatographed on silica gel (10:1 to 1:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 21.28 g (87%) of silyl ether **176**: mp 69.5-70.5 °C (from absolute EtOH); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.05 (s, 6 H), 0.70 (s, 3 H), 0.80 (s, 9 H), 1.00-2.60 (m, 11 H), 3.04 (s, 3 H), 3.12 (s, 3 H), 3.73 (dd, J = 6, 10 Hz, 1 H); MS, *m/e* (rel intensity) 356 (M^+, 23), 341 (3), 325 (25), 299 (100), 267 (41), 193 (41), 175 (36), 101 (42); calcd for $C_{19}H_{36}O_4Si$ (M^+) *m/e* 356.2383, found *m/e* 356.2400. Anal. Calcd for $C_{19}H_{36}O_4Si$: C, 64.00; H, 10.17. Found: C, 64.19; H, 10.44.

(4aα,5α,8α,8aβ)-5-[(*tert*-Butyldimethylsilyl)oxy]octahydro-8-hydroxy-4a,8-dimethyl-2(1*H*)-naphthalenone (177). To 360 mL of 0.62 M MeMgI in ether was added dropwise a solution of 19.79 g (55.6 mmol) of silyl ether **176** in 360 mL of dry ether. The reaction mixture was stirred at rt for 42 h, after which time the excess MeMgI was quenched by careful addition of saturated aqueous NH_4Cl. After addition of 500 mL of water, the two-phase mixture was separated and the aqueous layer was extracted with five 150-mL portions of CH_2Cl_2. The combined organic layers were washed with 300 mL of brine, dried, and evaporated under reduced pressure. The remaining residue was taken up in 500 mL of acetone, and 10 mL of water and three drops of concentrated HCl were added. After stirring at rt for 20 min, 5 mL of saturated aqueous $NaHCO_3$ was added. The reaction mixture was concentrated under reduced pressure, taken up in 500 mL of water, and extracted with five 200-mL portions of CH_2Cl_2. The combined organic layers were washed with 200 mL of brine, dried, and evaporated under reduced pressure. Recrystallization from diisopropyl ether and flash chromatography of the mother liquid on silica gel (10:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded 15.06 g (83%) of pure **177**: mp 143-145 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.00 (s, 3 H), 0.03

(s, 3 H), 0.83 (s, 9 H), 0.90-2.80 (m, 12 H), 1.10 (s, 3 H), 1.20 (s, 3 H), 3.26 (dd, J = 4, 10 Hz, 1 H); MS, *m/e* (rel intensity) 311 (M^+-15, 1.6), 293 (1), 269 (31), 251 (13), 177 (100), 159 (18), 135 (41), 131 (31), 119 (22), 75 (46); calcd for $C_{17}H_{31}O_3Si$ (M^+-15) *m/e* 311.2042, found *m/e* 311.2049. Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.20; H, 10.49. Found: C, 66.11; H, 10.67.

(1α,4α,4aα,7β,8aβ)- and (1α,4α,4aα,7α,8aβ)-4-[(*tert*-Butyldimethylsilyl)oxy]decahydro-1,4a-dimethyl-1,7-naphthalenediols (178 and 179). To a solution of 3.26 g (10.0 mmol) of ketone **177** in 80 mL of dry THF was added dropwise 25 mL of 1 M L-Selectride in THF at -78 °C. The solution was warmed to 0 °C over 1 h, and then a mixture of 10 mL of water and 35 mL of EtOH was added. After stirring for 20 min, 10 mL of 6 M NaOH and 25 mL of 30% H_2O_2 were added and stirring was continued for 16 h. The mixture was then concentrated under reduced pressure and the resulting residue was taken up in 150 mL of water. The aqueous layer was extracted with four 100-mL portions of ether. The combined organic layers were dried and evaporated under reduced pressure to afford 3.28 g (100%) of a 1:1.1 mixture of **178** and **179**, respectively, according to GC analysis. Analytical samples of **178** and **179** were obtained by flash chromatography on silica gel (8:1 petroleum ether (bp 40-60 °C)/EtOAc). Physical and spectral data of **178** and **179** follow.

178: mp 119-121 °C (from petroleum ether (bp 80-100 °C)); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.02 (s, 6 H), 0.70-2.10 (m, 13 H), 0.84 (s, 9 H), 0.97 (s, 3 H), 1.09 (s, 3 H), 3.26 (dd, J = 4, 10 Hz, 1 H), 4.17 (m, $W_{1/2}$ = 9 Hz, 1 H); MS, *m/e* (rel intensity) 271 (M^+-57, 5), 253 (25), 179 (8), 161 (100), 131 (15), 119 (15), 105 (13), 75 (20); calcd for $C_{14}H_{27}O_3Si$ (M^+-57) *m/e* 271.1729, found *m/e* 271.1733. Anal. Calcd for $C_{18}H_{36}O_3Si{\cdot}H_2O$: C, 62.38; H, 11.05. Found: C, 62.26; H, 11.09.

179: mp 189-191 °C (from petroleum ether (bp 100-140 °C)); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.00 (s, 6 H), 0.70-2.10 (m, 13 H), 0.86 (s, 9 H), 1.02 (s, 3 H), 1.10 (s, 3 H), 3.13 (dd, J = 4, 10 Hz, 1 H), 3.55 (m, $W_{1/2}$ = 21 Hz, 1 H); MS, *m/e* (rel intensity) 271 (M^+-57, 6), 253 (8), 179 (15), 161 (100), 131 (23), 119 (16), 105 (16), 75 (22); calcd for $C_{14}H_{27}O_3Si$ (M^+-57) *m/e* 271.1729, found *m/e* 271.1725. Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04. Found: C, 66.06; H, 11.22.

(1α,4α,4aα,7β,8aβ)- and (1α,4α,4aα,7α,8aβ)-4-[(*tert*-Butyldimethylsilyl)oxy]decahydro-1,4a-dimethyl-1,7-naphthalenediol 7-(Methanesulfonates) (173 and 180). To a stirred solution of 3.28 g (10.0 mmol) of a 1:1.1 mixture of **178** and **179** in 75 mL of dry pyridine was added 1.22 mL (15.75 mmol) of MsCl. The reaction mixture was stirred for 2 h at 40 °C and then concentrated under reduced pressure. The resulting residue was taken up in 200 mL of CH_2Cl_2 and washed successively with 50-mL portions of

10% aqueous H_2SO_4, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried and the solvent was removed under reduced pressure. The remaining residue was flash chromatographed on silica gel (8:1 to 2:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, 2.042 g (50%) of β-mesylate **180** and 1.856 g (46%) of α-mesylate **173**. Spectral and physical data of the mesylates **173** and **180** follow.

173: mp 45 °C dec (from petroleum ether (bp 40-60 °C)); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.75-2.15 (m, 12 H), 0.85 (s, 9 H), 0.99 (s, 3 H), 1.12 (s, 3 H), 2.98 (s, 3 H), 3.25 (dd, J = 4.1, 11.4 Hz, 1 H), 5.07 (m, $W_{1/2}$ = 9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -5.04 (q), -4.17 (q), 11.82 (q), 17.81 (s), 25.60 (3 q), 26.61 (2 t), 26.88 (t), 29.38 (q), 33.38 (t), 38.32 (q), 39.02 (s), 39.26 (t), 43.30 (d), 70.67 (s), 79.01 (d), 80.20 (d); MS, *m/e* (rel intensity) 349 (M^+-57, 4), 311 (1.5), 254 (11), 161 (100), 131 (15), 119 (14), 105 (28), 75 (19); calcd for $C_{15}H_{29}O_5SSi$ (M^+-57) *m/e* 349.1505, found *m/e* 349.1494. Anal. Calcd for $C_{19}H_{38}O_5SSi$: C, 56.11; H, 9.42. Found: C, 56.01; H, 9.52.

180: mp 91-93 °C (from diisopropyl ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ -0.03 (s, 3 H), 0.00 (s, 3 H), 0.83 (s, 9 H), 0.92-2.17 (m, 12 H), 1.01 (s, 3 H), 1.11 (s, 3 H), 2.98 (s, 3 H), 3.15 (dd, J = 4.0, 11.5 Hz, 1 H), 4.63 (m, $W_{1/2}$ = 22 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -5.10 (q), -4.18 (q), 12.41 (q), 17.79 (s), 25.58 (3 q), 26.89 (t), 27.56 (t), 27.97 (t), 29.67 (q), 37.42 (t), 38.62 (s), 38.73 (q), 39.19 (t), 48.50 (d), 70.76 (s), 79.24 (d), 82.26 (d); MS, *m/e* (rel intensity) 311 (M^+-95, 1.5), 254 (13), 161 (100), 131 (10), 119 (13), 105 (25), 75 (17); calcd for $C_{18}H_{35}O_2Si$ (M^+-95) *m/e* 311.2406, found *m/e* 311.2408. Anal. Calcd for $C_{19}H_{38}O_5SSi$: C, 56.11; H, 9.42. Found: C, 56.30; H, 9.68.

Elimination Reactions of the Mesylates 173 and 180 with Sodium *tert*-Amylate in Refluxing Toluene.

a. The α-Mesylate 173

A solution of 1.051 g (2.59 mmol) of α-mesylate **173** in 40 mL of dry toluene was degassed and refluxed under an argon atmosphere. To this refluxing solution was added 3.7 mL (5 equiv) of sodium *tert*-amylate (3.5 M in toluene) at once. The reaction mixture was refluxed for a total of 11 min[31] and then, after cooling to 0 °C, 10 mL of water and 40 mL of brine were added. The two-phase mixture was separated and the aqueous layer was extracted with six 50-mL portions of petroleum ether (bp 40-60 °C). The combined organic layers were dried and evaporated under reduced pressure. The remaining residue was flash chromatographed on silica gel (50:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 0.697 g (87%) of a 11.5:1 mixture of double bond isomers **27** and **181**, respectively, according to GC analysis. Almost pure

samples of **27** and **181** were obtained by flash chromatography on silica gel (100:1 petroleum ether (bp 40-60 °C)/EtOAc).

(1α,4α,4aα,8aβ)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4,4a,5,6,8a-octahydro-1,4a-dimethyl-1-naphthalenol (27): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.80-2.15 (m, 10 H), 0.86 (s, 9 H), 0.98 (s, 3 H), 1.18 (s, 3 H), 3.25 (dd, J = 4.1, 11.3 Hz, 1 H), 5.64-5.82 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -4.87 (q), -3.98 (q), 12.03 (q), 18.05 (s), 23.09 (t), 25.84 (3 q), 27.34 (t), 29.21 (q), 35.09 (t), 38.36 (s), 38.71 (t), 49.95 (d), 70.89 (s), 78.50 (d), 124.11 (d), 129.35 (d); MS, *m/e* (rel intensity) 253 (M^+-57, 2), 161 (100), 131 (20), 119 (10), 105 (20), 75 (19); calcd for $C_{14}H_{25}O_2Si$ (M^+-57) *m/e* 253.1624, found *m/e* 253.1617.

(1α,4α,4aα,8aβ)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4,4a,5,8,8a-octahydro-1,4a-dimethyl-1-naphthalenol (181): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.75-2.12 (m, 10 H), 0.86 (s, 9 H), 0.96 (s, 3 H), 1.10 (s, 3 H), 3.23 (dd, J = 3.9, 11.4 Hz, 1 H), 5.49-5.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -4.86 (q), -3.91 (q), 12.09 (q), 18.06 (s), 22.51 (t), 25.83 (3 q), 27.11 (t), 29.76 (q), 38.17 (s), 39.14 (t), 41.19 (t), 46.10 (d), 70.73 (s), 79.97 (d), 125.30 (d), 125.47 (d); MS, *m/e* (rel intensity) 295 (M^+-15, 0.4), 253 (17), 161 (100), 131 (18), 119 (27), 105 (67), 75 (37); calcd for $C_{14}H_{25}O_2Si$ (M^+-57) *m/e* 253.1624, found *m/e* 253.1630.

b. The β-Mesylate 180

The β-mesylate **180** (0.406 g, 1.00 mmol) was treated with 5 equiv of sodium *tert*-amylate in toluene as described above for the elimination of the α-mesylate **173**. Workup and flash chromatography on silica gel (50:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded in order of elution 0.016 g (5%) of "aldol-condensated"-**182**, 0.082 g (26%) of **182** and, 0.152 g of a mixture (49%) of **27** and **181** in a ratio of 6.0:1, respectively, according to GC analysis. Physical and spectral data of "aldol-condensated"-**182** and **182** follow.

"aldol-condensated"-**182**: ^{1}H NMR (main peaks, $CDCl_3$, 90 MHz) δ 0.00 (s), 0.00-0.45 (m), 0.84 (s), 3.23-3.50 (m), 5.30-5.56 (m), 6.05 (s); MS, *m/e* (rel intensity) 587 (M^+-15, 0.3), 545 (10), 507 (23), 413 (10), 375 (5), 305 (26), 253 (32), 239 (100); calcd for $C_{36}H_{66}O_3Si_2$ (M^+) *m/e* 587.4316, found *m/e* 587.4312.

(5R)-5-[(*tert*-Butyldimethylsilyl)oxy]-5-[(1'α,2'α,5'α)-2'-methylbicyclo[3.1.0]hexan-2'-yl]-pentanone (182): ^{1}H NMR ($CDCl_3$, 200 MHz) δ -0.02-0.13 (m, 1 H), 0.02 (s, 3 H), 0.03 (s, 3 H), 0.21-0.35 (m, 1 H), 0.62-1.25 (m, 3 H), 0.88 (s, 9 H), 0.93 (s, 3 H), 1.47-2.03 (m, 5 H), 2.12 (s, 3 H), 2.37-2.73 (m, 2 H), 3.37 (dd, J = 3.6, 6.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -4.13 (q), -3.31 (q), 6.07 (t, J_{C-H} = 158.5 Hz), 17.59 (d, J_{C-H} = 166.1 Hz), 18.43 (s), 20.99 (3 q), 24.58 (d, J_{C-H} = 167.1 Hz), 26.18 (3 q), 26.98 (t), 27.19 (t), 30.05 (q), 31.10 (t), 41.25 (t), 48.32 (s), 77.00 (d), 209.19 (s); MS, *m/e* (rel intensity) 295 (M^+-15, 0.4), 253 (19), 239 (19), 215 (100), 199 (3), 173 (5), 145 (12), 115 (5), 95 (12), 73 (36); calcd for $C_{14}H_{25}O_2Si$ (M^+-57) *m/e*

253.1624, found *m/e* 253.1623.

c. A mixture of α-Mesylate 173 and β-Mesylate 180

In a similar way, a 1:1.1 mixture of **173** and **180** gave a 8.4:1 mixture of **27** and **181**, in 66% yield, upon treatment with 10 equiv of sodium *tert*-amylate.

d. Influence of the Base Concentration

See also Table 5.1. To refluxing solutions of the α-mesylate **173** and the β-mesylate **180** (0.067 M in toluene) were added the required quantities of sodium *tert*-amylate (3.5 M in toluene) at once. The reaction mixtures were refluxed for a total of 11 min.[31] After quenching, workup, and column chromatographic separation as described above under **a.**, mixtures of the olefins **27** and **181** were isolated in the yields reported in Table 5.1. Product ratios were determined by GC analysis.

Elimination Reaction of the β-Mesylate 180 with Lithium *tert*-Amylate in Refluxing Toluene.

To a solution of 0.55 mL (5 mmol) of dry *tert*-amyl alcohol in 10 mL of dry toluene was added 3.13 mL (5 mmol) of *n*-BuLi (1.6 M in hexanes). The mixture was degassed and refluxed under an argon atmosphere. To this refluxing solution was added 0.406 g (1.00 mmol) of β-mesylate **180** in 5 mL of dry toluene. The reaction mixture was refluxed for 1 h. Workup and column chromatography as described above under **a.** afforded, in order of elution 0.012 g (4%) of the fragmentated product **182** and 0.242 g (78%) of a mixture of the olefins **27** and **181**, in a GC ratio of 1.5:1, respectively.

5.8 References and Notes

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(b) Forthcoming thesis of R. V. A. Orru, Agricultural University Wageningen.
(11) In analogy with the skeletal rearrangement,[7] preparation of the corresponding tosylates from **178** and **179** was tried at first. Tosylation of the axial alcohol in **178**, however, proved to be a very slow reaction, in contrast to the preparation of the mesylates **173** and **180**. No major differences were expected in behaviour between tosylates and mesylates; see: Bentley, T. W.; Llenwellyn, G. *Prog. Phys. Org. Chem.* **1990**, *17*, 121.
(12) Sodium *tert*-amylate in a refluxing nonpolar, aprotic solvent.[14]
(13) Conia, M. J.-M. *Bull. Soc. Chim.* **1950**, *17*, 537.
(14) Toluene was used instead of benzene. Shorter reaction times were found, but some pilot experiments showed that yields and product ratios were not affected by this change of solvent.
(15) (a) Tori, K.; Komeno, T.; Sangaré, M.; Septe, B.; Delpech, B.; Ahond, A.; Lukacs, G. *Tetrahedron Lett.* **1974**, 1157.
(b) Blunt, J. W.; Stothers, J. B. *Org. Magn. Reson.* **1977**, *9*, 439.
(c) Eggert, H.; Djerassi, C. *J. Org. Chem.* **1981**, *46*, 5399.
(16) Caine, D. *Org. Prep. Proced. Int.* **1988**, *20*, 1.
(17) This type of transmission of electronic effects *via* saturated atoms is a very general phenomenon; For an overview, see: Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 369; and references cited therein.
(18) Bartsch, R. A. *Acc. Chem. Res.* **1975**, *8*, 239.
(19) Definition of an ion pair is: "an extended bond with considerable ionic character"; see: Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 239.
(20) Partial intermolecular formation of **27** can not be ruled out.
(21) Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P. v. R. *J. Org. Chem.* **1988**, *53*, 661.
(22) Grob, C. A. *Acc. Chem. Res.* **1983**, *16*, 426.
(23) (a) Fischer, W.; Grob, C. A.; Hanreich, R.; von Sprecher, G.; Waldner, A. *Helv. Chim. Acta* **1981**, *64*, 2298.
(b) Flury, P.; Grob, C. A. *Helv. Chim. Acta* **1983**, *66*, 1971.
(24) (a) Grob, C. A. *Angew. Chem.* **1969**, *81*, 343.
(b) March, J. *Advanced Organic Chemistry*, 3th ed.; Wiley-Interscience: New York, 1985; p 927.
(25) In nonpolar media like toluene, ion-paired charges will be the dominant species present.[18]

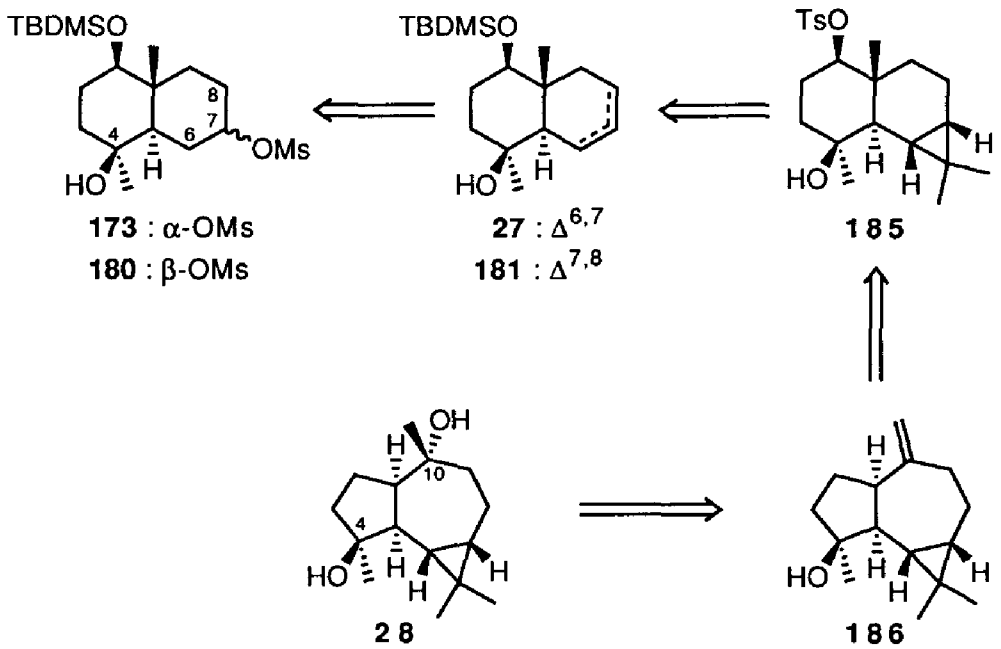
(26) The Li^+-O^- bond is stronger (has more covalent character) than the Na^+-O^- bond; see: Paquette, L. A.; Gilday, J. P. *J. Org. Chem.* **1988**, *53*, 4972.
(27) Rate effects of the amount of sodium *tert*-amylate[7b] should be studied at a lower temperature, using *e.g.* benzene as the solvent.
(28) Bartsch, R. A.; Závada, J. *Chem. Rev.* **1980**, *6*, 453.
(29) Schlosser, M.; Jan, G.; Byrne, E.; Sicher, J. *Helv. Chim. Acta* **1973**, *56*, 1530.
(30) Pearson, D. E.; Buehler, C. A. *Chem. Rev.* **1974**, *74*, 453.
(31) According to TLC analysis the reaction was completed within 1 min.

6 Total Synthesis of (±)-Alloaromadendrane-4β,10α-diol and (±)-Alloaromadendrane-4α,10α-diol

6.1 Introduction

The base-induced and -directed rearrangement[1] and elimination[2] reactions of substituted *trans*-perhydronaphthalene-1,4-diol monosulfonate esters have been described in the Chapters 3 and 5, respectively. We envisaged that by incorporation of the two reactions into one single synthetic route, cis-fused aromadendranes **9** (*i.e.* alloaromadendranes) and guaianolides **175** could be accessible (see Scheme 5.2). The chief characteristic of this strategy is the central role of the axial tertiary hydroxyl group at C(4) in the two key steps of such a total synthesis: *i.* the selective formation of the C(6)-C(7) double bond and *ii.* the skeletal rearrangement. The C(6)-C(7) double bond was to be used for the introduction of the desired functionality at this position, while in the latter reaction the *cis* 5,7-fused ring framework with the exocyclic double bond would be obtained.

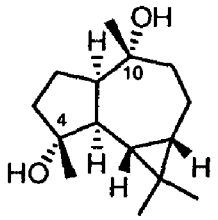
Scheme 6.1



Recently the isolation of an (+)-alloaromadendrane-4,10-diol from *Ambrosia peruviana* Willd.,[3] a slightly aromatic herb found mainly in the Caribbean and from *A. elatior* L., growing in Argentina,[4] has been described. The compound was found to be a selective inhibitor of the growth of the fungus *Cladosporium herbarium* and a

stimulator of the root and shoot growth in lettuce seedlings at low concentrations. The aromadendrane skeleton and the *cis* 5,7-fused ring junction of this compound were identified by chemical and spectroscopic means. The stereochemistry of the hydroxyl groups at C(4) and C(10) was assigned by correlating features of molecular models with data from its NMR spectra and comparison with the NMR spectra of the four isomeric trans-fused aromadendrane-4,10-diols obtained from natural spathulenol.[5] On this basis, the natural product isolated from *A. peruviana* was assigned the stereochemistry shown in structure **28** (Scheme 6.1).

Our synthetic plan for diol **28**,[2] outlined in Scheme 6.1, was inspired by the possibility of a base-induced and -directed rearrangement of the tosylate **185** to the cis-fused hydroazulene **186** with an exocyclic double bond.[1,6] Selective epoxidation of this double bond from the less hindered α-side, followed by reduction would result in the introduction of the α-hydroxyl group at C(10). For the synthesis of compound **185**, annulation of the cyclopropane ring at C(6)-C(7) was necessary. This should be possible starting the olefin **27** with the double bond at this position. The selective formation of this olefin **27** in the base-induced and -directed elimination of (a mixture of) the mesylates **173** and **180** has been described in Chapter 5.



29

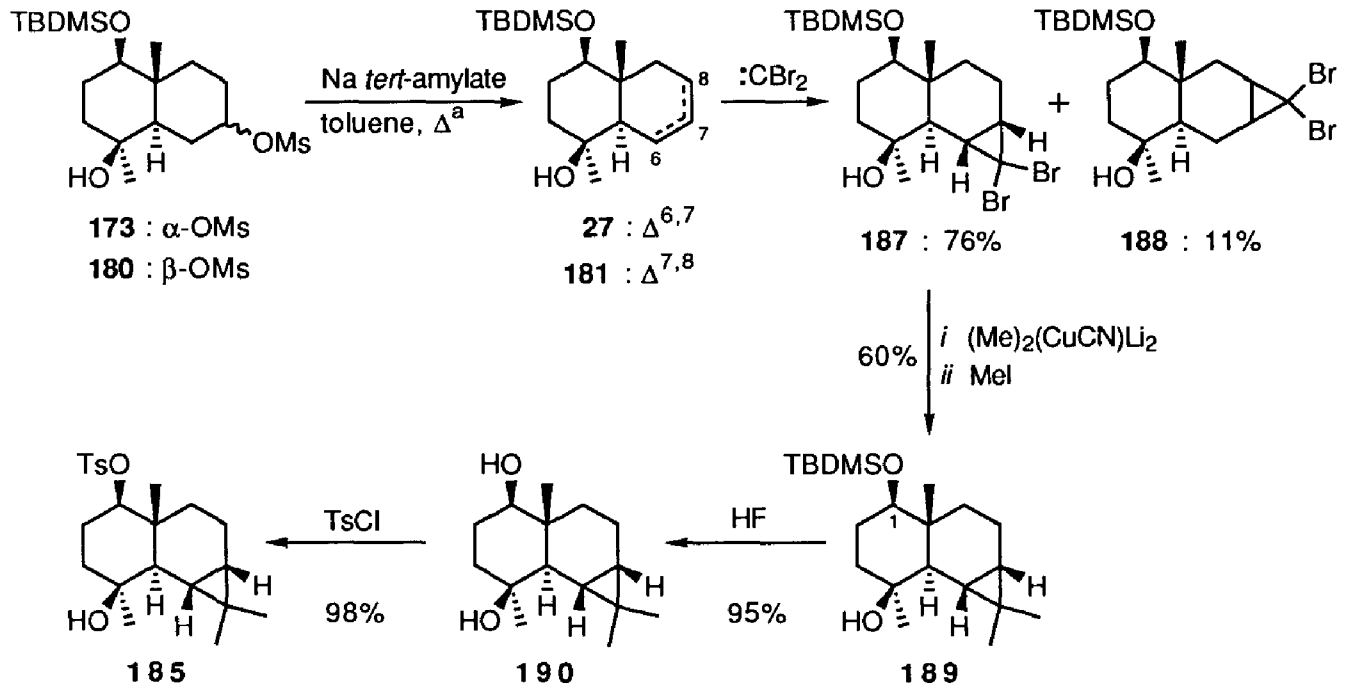
In this chapter the total synthesis of this (±)-alloaromadendrane-4β,10α-diol **28** is described. Furthermore, the synthesis of its C(4)-epimer, (±)-alloaromadendrane-4α,10α-diol **29**, *via* a dehydration, epoxidation, reduction sequence from **186** is described and a revision of the structure of the natural compound is proposed.

6.2 Synthesis of Alloaromadendren-4β-ol 186

The key intermediate in the synthetic routes towards (±)-alloaromadendrane-4β,10α-diol **28**[2] and towards its C(4)-epimer (±)-alloaromadendrane-4α,10α-diol **29** was the rearranged exo 10,15-olefin alloaromadendren-4β-ol **186**. Starting material for the synthesis of **186** was an inseparable 7:1 mixture of the olefins **27** and **181**, respectively. This mixture was accumulated from the elimination experiments described in Chapter 5 with the mesylates **173** and **180**. The first step in our route towards **186** was the introduction of the *gem*-dimethylcyclopropane ring. This functionality is most commonly prepared by dimethylation of *gem*-dihalocyclopropane derivatives.[7,8] The reaction of dibromocarbene, prepared from bromoform and sodium *tert*-amylate, with the 7:1 mixture of the double-bond isomers **27** and **181** in toluene afforded the

corresponding dibromides **187** and **188**, which could easily be separated by column chromatography and were isolated in 76 and 11% yield, respectively (Scheme 6.2). Steric demands of the dibromocarbene were expected to result in an addition to the less hindered α-side of the double bond in **27**, and the product **187** was assigned the indicated stereochemistry. ^{1}H NOE difference experiments of the diol **29** later on confirmed this assumption.[9] For the isomeric olefin **181** also an α-approach of the dibromocarbene to the double bond is to be expected. For the resulting dibromide, however, the relative stereochemistry at C(7)-C(8) was not ascertained, and therefore left undecided in structure **188**.

Scheme 6.2



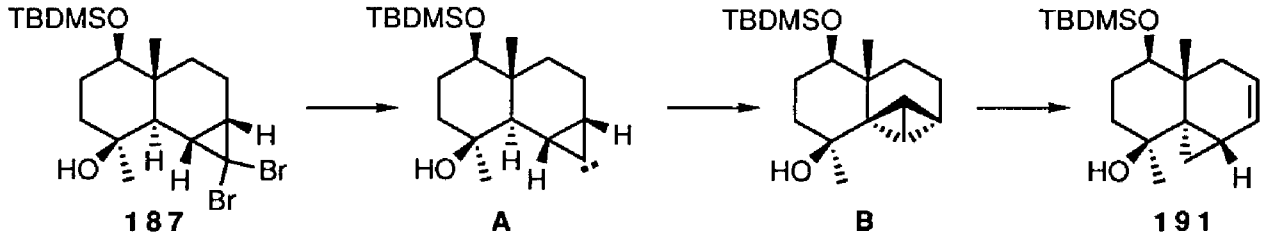
[a] see Chapter 5

The reaction of the dibromide **187** with the higher order organocuprate, prepared from copper(I) cyanide and methyllithium, followed by addition of methyl iodide,[7c] afforded the *gem*-dimethylcyclopropane compound **189** in 60% yield. Quenching of the reaction mixture with saturated aqueous NH_4Cl before addition of methyl iodide resulted in the formation of the dimethylated **189** and two monomethylated products[10] in a GC ratio of 5.5:3:1, respectively. By addition of methyl iodide, the formation of these monomethylated products could be suppressed completely. The formation of the monomethylated products and the fact that this side reaction could be prevented by the addition of methyl iodide suggests that the substitution reaction proceeds, at least partly, *via* an intermediary monomethylcyclopropane anion.[7c,11]

The relatively low yield of the *gem*-dimethylcyclopropane compound **189** (60%) was caused by another side reaction in which Br_2 was eliminated.[12] According to GC analysis of the crude reaction mixture, the product of this side reaction was formed in 36%. After column chromatography, however, this product could only be isolated in 12% yield and was tentatively assigned the structure **191** on basis of its NMR spectral data. The observed multiplicities in the ^{13}C NMR spectrum (4 s, 4 d, 4 t, and 7 q) rule out other skeletal arrangements than the one proposed. The endocyclic double bond was concluded from the 2 d at δ 121.71 and 128.71 in the ^{13}C NMR spectrum. The corresponding olefinic protons resonance as a br t at 5.36 ppm and a ddd at 5.97 ppm, which is consistent with the C(7)-C(8) double bond. The presence of a cyclopropane ring in **191** was affirmed by the fact that a dd (J = 4.7, 9.3 Hz, 1 H) and a t (J = 4.7 Hz, 1 H) at δ 0.67 and 0.96, respectively, are observed in its ^1H NMR spectrum. The relatively small J (4.7 Hz) is characteristic for the geminal coupling between the cyclopropane protons at C(11).[13]

The reaction is believed to proceed through a carbenoid related to the free cyclopropylidene **A**, which can be formed in a reaction between the *gem*-dibromocyclopropane derivative **187** and methyllithium present in the reaction medium.[14,15] Intramolecular insertion into the C(5)-H bond then leads to the bicyclo[1.1.0]butane system in **B**,[14] which undergoes an isomerization leading to **191**.[16]

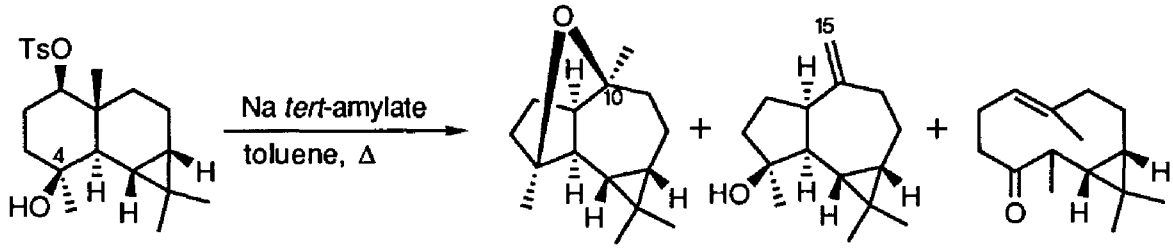
Scheme 6.3



The next steps in our synthetic route towards alloaromadendrane-4β-ol **186** were the cleavage of the TBDMS protecting group of **189** with HF in aqueous acetonitril[17] followed by tosylation of the generated secondary alcohol at C(1). These reactions offered no problems and the tosylated maaliane derivative **185** was isolated in 93% overall yield from **189**.

The base-induced and -directed skeletal rearrangement of the tosylate **185** was performed as previously described,[1,6,18] with sodium *tert*-amylate in refluxing toluene (Scheme 6.4). After workup and column chromatography, **186** was isolated in 70% yield. Two minor products were identified as the cyclic ether **192** (7%) and the germacrane-like compound **193** (7%).

Scheme 6.4

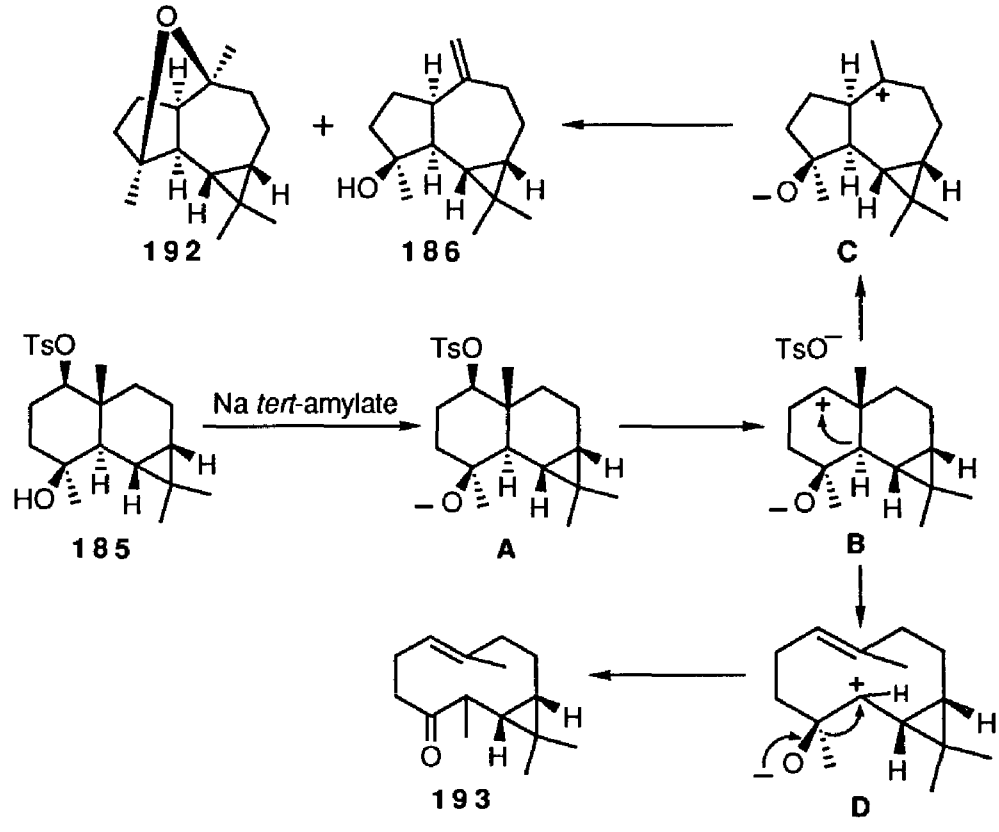


185 **192** : 7% **186** : 70% **193** : 7%

Selective proton abstraction from C(15) in the rearranged intermediate **C** by the tertiary alkoxide at C(4) results in the formation of the exocyclic double bond in **186** (Scheme 6.5). The formation of **192** can be explained by the direct trapping of the positive charge at C(10) in the rearranged dipolar intermediate **C** by the proximate alkoxide. The formation of these compounds is in agreement with the reaction pattern observed before.[1b,6,18]

The germacrane-like structure **193**, however, originates from a reaction path not observed before (Scheme 6.5). The reaction starts with the formation of the dipolar intermediate **B** by a "through bond" inductive mechanism.[1b,6] In the reactions that have been described so far,[1,6,18] the only way for intermediate **B** to gain stability was

Scheme 6.5



192 **186** **C** **185** **A** **B** **193** **D**

the 1,2-shift of the central bond. As a result of this rearrangement, the system goes from the secondary carbocation **B** to the thermodynamically more stable tertiary carbocation **C**, and the hydroazulene framework is formed. Apart from this rearrangement, however, the intermediate **B** from the tosylate **185** has an alternative route to gain stability. Fragmentation of the central bond results in the formation of the 10-membered ring intermediate **D** with a C(1)-C(10) double bond. In the intermediate **D**, the carbocationic center at C(5) is positioned adjacent to the cyclopropane ring. As the orbitals involved in the CC bonding in the cyclopropane ring are more p-like (about 83% p-character[19]) than normal sp^3 orbitals (75% p-character), the internal bonds of the cyclopropane ring are intermediate in character between σ and π.[20] Consequently, intermediate **D** is a thermodynamically more stable carbocation then the intermediate **B**. The subsequent formation of the carbonyl at C(1) and the concomitant 1,2-shift of the methyl group then results in the formation of the germacrane-like compound **193**.

The formation of germacrane-like structures has not been encountered before in the rearrangement reactions of the tosylates **131**, **132**, and **162**.[1,6,18] This is a strong indication that the formation of **193** proceeds *via* the carbocationic intermediate **D** and that **193** is not formed in a concerted fashion from the intermediate **B**. Although the methyl shift will initially result in an α-position of this methyl group, the relative stereochemistry at C(5) in structure **193** is not specified as the strong basic reaction conditions may very well cause epimerization at this position.

6.3 Skeletal Structure of Alloaromadendren-4β-ol 186

Since the alloaromadendren-4β-ol **186** was the key intermediate in the synthetic routes towards both the (±)-alloaromadendrane-4,10-diols **28** and **29**, we decided to investigate its structure more thoroughly, in particular with respect to the position of the *gem*-dimethylcyclopropane ring. In Chapter 5, the positions of the double bonds in **27** and the isomeric olefin **181** were assigned by comparing the ^{13}C NMR spectral data of these olefins with those of the comparable Δ^2- and Δ^3-steroids. As a result of the severe overlap in the ^1H NMR spectra of these compounds no independent, additionally confirming evidence for the assigned structures could be obtained. The ^1H NMR spectrum of the hydroxy alloaromadendrane derivative **186**, however, was less crowded and therefore easier to interpret. By combining the results of COSY and HETCOR experiments, the position of the cyclopropane ring in **186** could be established and, in this indirect way, the structure of the olefin **27** was confirmed.

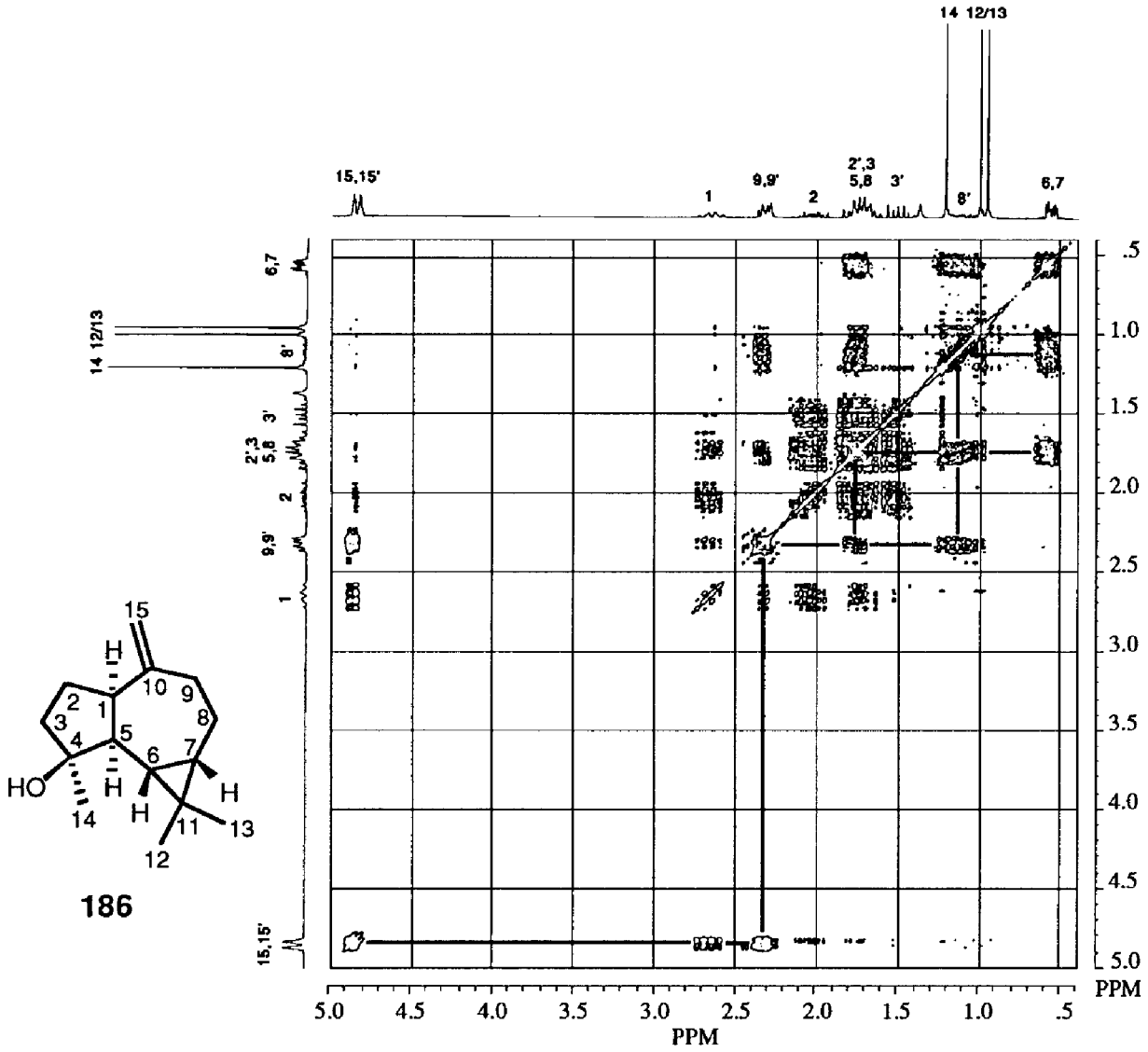
Table 6.1 **^{13}C NMR Spectral Data, Assignments and HETCOR Spectrum of Alloaromadendren-4β-ol 186**

	^{13}C		^{1}H-^{13}C HETCOR cross peaks observed
δ (ppm)	mult	assignment	δ (ppm); [mult]
15.85	q	C(12)/C(13)	0.96 (s)
17.17	s	C(11)	---
21.43	t	C(8)	1.00-1.25 (m) + 1.60-1.90 (m)
21.79	d	C(6)[a]	0.50-0.67 (m)
25.31	d	C(7)[a]	0.50-0.67 (m)
26.85	t	C(2)	1.60-1.90 (m) + 1.95-2.15 (m)
26.85	q	C(14)	1.22 (s)
28.74	q	C(12)/C(13)	1.01 (s)
37.88	t	C(9)	2.25-2.40 (m)
40.40	t	C(3)	1.45-1.60 (m) + 1.60-1.90 (m)
44.62	d	C(1)	2.67 (br q)
47.26	d	C(5)	1.60-1.90 (m)
80.26	s	C(4)	---
108.63	t	C(15)	4.83 (br s) + 4.87 (br s)
150.65	s	C(10)	---

[a] see text

In Table 6.1 the ^{13}C NMR spectral data and assignments as well as the observed ^{1}H-^{13}C HETCOR cross peaks of **186** are presented. Figure 6.1 shows the COSY spectrum. The assignments of the ^{1}H and ^{13}C resonances were obtained by combining the results from the HETCOR and COSY spectra. Assignment of the geminal methyl carbons C(12) and C(13) was not possible with the techniques used. Furthermore, the resonances of the cyclopropane methine carbons C(6) and C(7) were assigned only tentatively on the basis of the respective cross sections from the HETCOR spectrum.

Figure 6.1 COSY Spectrum of Alloaromadendren-4β-ol 186



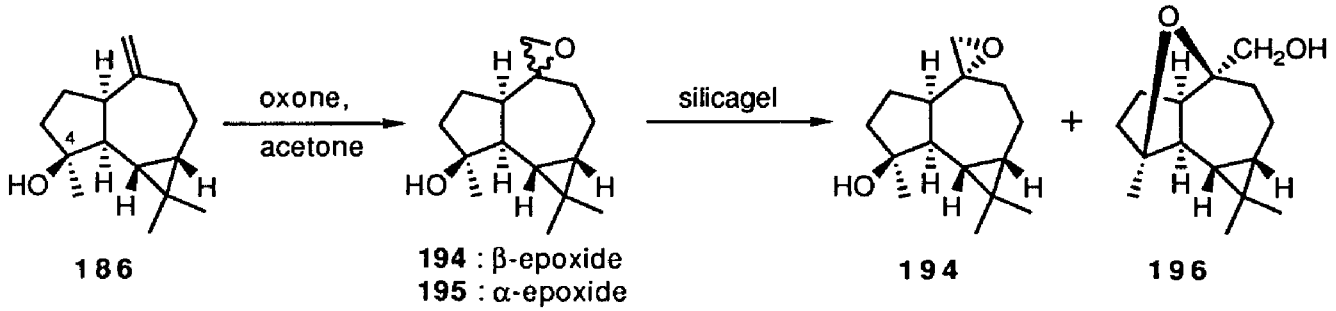
The C(6)-C(7) position of the cyclopropane ring was confirmed in the following manner. The signal of the olefinic methylene carbon at 108.63 ppm was correlated with the two br s at 4.83 and 4.87 ppm in the ^{1}H NMR spectrum, which have a total integral of 2 H. These signals of the C(15)-protons show two major cross peaks in the COSY spectrum. The first one results from a correlation with the br q at 2.67 ppm, which is coupled to the methine carbon at 44.62 ppm (HETCOR). This br q has an integral of 1 H (^{1}H NMR), so it originates from the H(1). A second cross peak in the COSY spectrum is found between the olefinic signals and the m at δ 2.25-2.40. This m has an integral of 2 H and is connected to the signal of the methylene carbon at 37.88 ppm, according to the HETCOR spectrum. From this it was concluded that the m at δ 2.25-2.40 is originating from the two protons at C(9). In the COSY spectrum, this signal from the C(9)-protons shows two cross peaks, one with the cluster of peaks at 1.60-1.90

ppm, and one with the m between 1.00 and 1.25 ppm, but no cross peak is found with the signal of the cyclopropyl protons which resonance as a overlapping m of 2 H at δ 0.50-0.67. Consequently, the cyclopropane ring is not positioned adjacent to C(9) at the C(7)-C(8) position. Therefore, the double bond in the olefin **27** was also not present at this position, and the structure assigned to this compound was correct. The two cross peaks found in the COSY spectrum for the C(9)-protons will then originate from coupling with the two C(8)-protons, one of which resonances in the cluster of peaks between 1.60 and 1.90 ppm, while the other gives rise to the m between 1.00 and 1.25 ppm. As expected for structure **186**, a correlation peak is found between this latter H(8) and the cyclopropane ring protons at 0.50-0.67 ppm. A second cross peak for the cyclopropane ring protons is found at about 1.75 ppm, so it is correlated with the cluster of peaks between δ 1.60 and 1.90. The fact that the intensity of this second cross peak seems to be higher than that of the first one, is in agreement with the fact that, apart from one H(8), also the ring junction proton at C(5) was found to resonance between 1.60 and 1.90 ppm.

6.4 Synthesis of (±)-Alloaromadendrane-4β,10α-diol 28

The synthesis of (±)-alloaromadendrane-4β,10α-diol **28** required a selective epoxidation of the olefin **186**, followed by reduction of the resulting epoxide. When **186** was treated with *in situ* generated dimethyldioxirane,[21] a mixture of two products was formed in a ratio of 4.3:1, according to GC analysis. Attempts to separate this mixture on silica gel led to the isolation of the minor β-epoxide **194**, while the major epoxidation product **195** was found to be completely converted into the cyclic ether **196** (Scheme 6.6).

Scheme 6.6

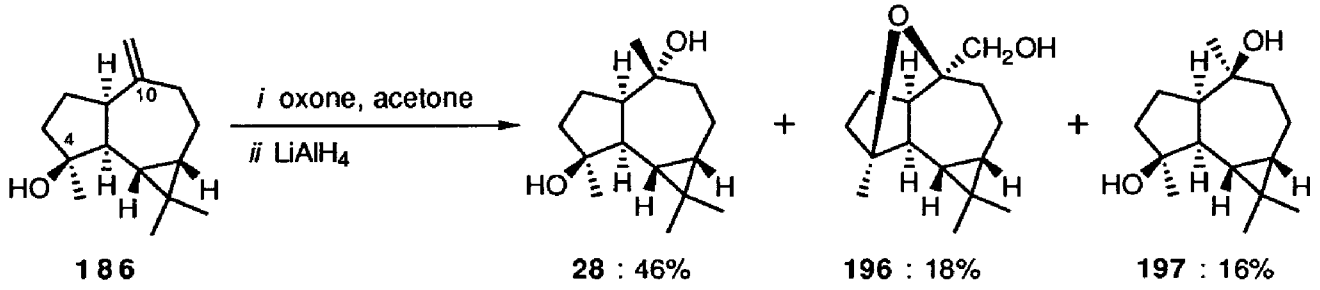


186 **194** : β-epoxide **195** : α-epoxide **194** **196**

This opening of the epoxide ring of **195** by an intramolecular nucleophilic attack of the tertiary hydroxyl group at C(4) was facilitated by the slightly acidic character of the silica gel. The formation of **196** corroborated the cis-fused ring junction of the 5,7-ring system and we could conclude with confidence that the epoxidation of the double bond in **186** had occurred, as expected, primarily from the less-hindered α-face of the molecule. In order to suppress the undesired formation of **196**, we decided to reduce the crude mixture of the epoxides **194** and **195** with $LiAlH_4$ without previous chromatographic purification.

In this way, epoxidation of the olefin **186** with *in situ* generated dimethyldioxirane,[21] followed by reduction of the mixture of epoxides with $LiAlH_4$ gave a mixture of three products with the (±)-alloaromadendrane-4β,10α-diol **28** as main product in 46% yield from **186** (Scheme 6.7).

Scheme 6.7



186 **28** : 46% **196** : 18% **197** : 16%

The two minor products were identified as the cyclic ether **196** and the (±)-alloaromadendrane-4β,10β-diol **197**. On the basis of these results, one can conclude again that our synthetic product **28** possesses a cis-fused 5,7-ring junction and that the relative stereochemistry of the two hydroxyl groups at C(4) and C(10) is *trans* as shown in structure **28**.

Comparison of the ^{13}C NMR spectral data of (±)-alloaromadendrane-4β,10α-diol **28** with those of the natural (+)-alloaromadendrane-4,10-diol showed significant differences (Table 6.1). Even more notable differences between **28** and the natural (+)-alloaromadendrane-4,10-diol were observed in the ^1H NMR spectra of both compounds. In the ^1H NMR spectrum of the natural product, the two cyclopropane ring protons at C(6) and C(7) give rise to a t (J = 9.7 Hz) and a ddd (J = 5.8, 9.7, 11.6 Hz) at δ 0.00 and 0.62, respectively.[3] Furthermore, the methyl groups give rise to s at δ 1.02, 1.03, 1.19, and 1.33. In the ^1H NMR spectrum of our synthetic product **28** the protons at C(6) and C(7) give rise to an overlapping m at δ 0.48-0.68, while the signals due to the methyl groups appear at 0.95, 1.03, 1.24, and 1.32 ppm.

Table 6.1 ^{13}C NMR Spectral Data of the Natural (+)-Alloaromadedrane-4,10-diol and the Synthetic (±)-Alloaromadendrane-4,10-diols 28, 197, and 29.

mult	natural product[a]	28	197	29
s	18.6	19.49	20.31	18.63
	74.3	74.72	74.79	74.32
	82.1	79.87	79.47	82.05
d	25.3	22.71	22.20	25.20
	28.8	26.25	25.38	28.73
	47.8	45.22	46.49	47.57
	54.0	50.37	46.76	53.80
t	18.7	20.71	22.20	18.67
	25.1	25.59	25.62	25.07
	37.4	39.16	39.72	37.34
	37.9	41.47	42.22	37.90
q	16.4	15.45	15.43	16.19
	25.6	27.39	23.74	25.53
	28.5	28.30	28.58	28.50
	32.2	28.86	29.29	32.09

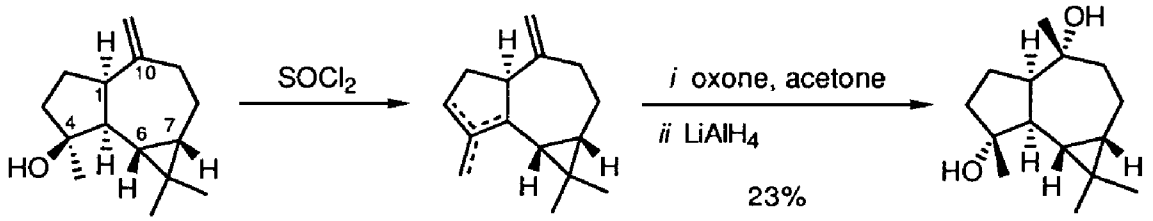
[a] taken from ref 2.

Consequently, the natural product and the synthetic alloaromadendrane-4,10-diol **28** must have differences in their stereochemistry. Comparison of the ^{1}H and ^{13}C NMR spectral data of the 4β,10β-diol **197** with those of the natural product also showed significant differences (Table 6.1 and Experimental Section). As we had no reason to doubt the stereochemistry of our synthetic alloaromadendrane-4,10-diols **28** and **197**, we concluded that the stereochemistry of the natural product differed from the one proposed.[3] We were strengthened in this opinion by the fact that the stereochemical assignment of the natural product was based solely on correlating features of molecular models with data from its NMR spectra and the NMR spectra of the four isomeric trans-fused aromadendrane-4,10-diols derived from natural spathulenol. No independently obtained evidence was presented to confirm the assigned structure.[3]

6.5 Synthesis of (±)-Alloaromadendrane-4α,10α-diol 29

As the natural product was easily silylated to its di-OTMS derivative,[3] we had reason to believe that in this structure the hydroxyl groups at C(4) and C(10) are positioned on the less hindered α-face of the molecule. This means that in the natural product the hydroxyl group at C(4) probably has a stereochemistry, different from the one proposed. In order to test this assumption, the olefin **186** was converted into the (±)-alloaromaden-drane-4α,10α-diol **29** *via* a dehydration, epoxidation, reduction sequence (Scheme 6.8).

Scheme 6.8



186 **198** **29**

Treatment of **186** with thionyl chloride in pyridine at -15 °C afforded an uncharacterized, highly volatile mixture of double bond isomers **198** in a ratio of 6:3:1, according to GC analysis. Reaction of this mixture with *in situ* prepared dimethyldioxirane[22] gave a complex mixture of epoxides. Again, as in the case of the epoxidation of **186** (Scheme 6.7), epoxidation was expected to occur preferentially from the less hindered α-face of the molecule. The mixture of epoxides was then treated with $LiAlH_4$ to give diol **29** in an overall yield of 23% from **186**.

As this diol **29** differs clearly from the diols **28** and **197**, **29** must have the opposite stereochemistry at C(4). The relative stereochemistry at C(10) was ascertained by ^1H NOE difference spectroscopy. By irradiation of the t for H(6) at δ -0.03, NOE's with the methyl groups at δ 1.30, 1.16, and 1.01/0.99 were observed. Since no NOE exists between H(6) and the α-methyl group of the *gem*-dimethylcyclopropane ring,[22] this observation led to the conclusion that one of the NOE signals must originate from an interaction with the methyl group at C(10). Consequently, this methyl group is positioned on the β-side of the molecule, and the synthesized product **29** is the 4α,10α-diol. Affirmative to this conclusion is the fact that upon irradiation of the m at δ 2.45, which is believed to be descended from H(1),[3] no NOE with any of the methyl groups was observed.

The ^1H NMR spectral data of our synthetic (±)-alloaromadendrane-4α,10α-diol **29** agree very well with those of the natural product. For the cyclopropane ring protons

H(6) and H(7), a t (J = 9.6 Hz) at -0.03 and a ddd (J = 5.2, 9.6, 11.3 Hz) at 0.60 ppm are observed, respectively. The methyl groups in **29** give rise to s at δ 0.99, 1.01, 1.16, and 1.30, which is in agreement with these signals in the ^{1}H NMR of the natural (+)-alloaromadendrane-4,10-diol.[3] Furthermore, the ^{13}C NMR spectrum of (±)-alloaromadendrane-4α,10α-diol **29** is in full agreement with the one reported for the natural product[3] (Table 6.1).
In conclusion, the natural product isolated from *Ambrosia peruviana* Willd. and *A. elatior* L. possesses the stereochemistry shown in structure **29**, and not the one proposed in structure **28**.

6.6 Concluding Remarks

The total synthesis of (±)-alloaromadendrane-4β,10α-diol **28** is a good illustration of our strategy towards cis-fused 5,7-ring sesquiterpenes that are functionalized at the C(6)-C(7) position. In this strategy the axial tertiary hydroxyl group at C(4) plays a central role in the two key steps of the synthetic route towards these compounds: *i.* the selective introduction of the C(6)-C(7) double bond[23] and *ii.* the skeletal rearrangement.[6]

6.7 Experimental Section

General

Melting points are uncorrected. Chemical shifts are reported relative to TMS (δ 0.00), with $CHCl_3$ as an internal standard [δ 7.23 (^{1}H) and δ 76.90 (^{13}C)]. ^{13}C NMR multiplicities were determined by using a DEPT pulse sequence. ^{1}H NOE difference experiments were performed at 200 MHz, using a τ_m of 2 s. MS data were determined at 70 eV on either an AEI MS 902 spectrometer or a Hewlett Packard 5970B series Mass Selective Detector, coupled with a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. GC analyses were carried out with FID and a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically. Flash chromatography was performed on Merck silica gel 60 (230-400 mesh).

Solvents were dried and freshly distilled by common practice. For all dry reactions, flasks were dried at 150 °C and flushed with dry N_2 just before use, and reactions were carried out under N_2, unless otherwise reported. Product solutions were dried over $MgSO_4$ prior to evaporation of the solvent under reduced pressure on a rotary evaporator. Bromoform was filtered over ICN alumina B-Super I (activity grade Super I) just before use. Sodium *tert*-amylate (3.5 M in toluene) was prepared as described elsewhere.[24]

(1aα,3aα,4α,7α,7aβ,7bα)-1,1-Dibromo-4-[(*tert*-butyldimethylsilyl)oxy]decahydro-3a,7-dimethyl-1*H*-cyclopropa[*a*]naphthalen-7-ol (187). To a solution of 1.514 g (4.88 mmol) of a 7:1 mixture of **27** and **181** in 40 mL of dry toluene was added 14 mL of sodium *tert*-amylate (3.5 M in toluene). To this mixture was added a solution of 2.13 mL (24.4 mmol) of $HCBr_3$ in 10 mL of dry toluene dropwise under vigorous stirring. When the addition was complete, the reaction mixture was allowed to stir for an additional 20 min, after which time 200 mL of brine was added. The two-phase mixture was separated and the aqueous layer was extracted with five 100-mL portions of petroleum ether (bp 40-60 °C). The combined organic layers were dried and evaporated under reduced pressure. The remaining residue was flash chromatographed on silica gel (70:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 1.786 g (76%) of dibromide **187**, which solidified on standing, and 0.263 g (11%) of the isomeric dibromide **188**. Physical and spectroscopic data of **187** and **188** follow.

187: mp 81-83 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ -0.01 (s, 3 H), 0.02 (s, 3 H), 0.45-2.20 (m, 12 H), 0.87 (s, 9 H), 0.92 (s, 3 H), 1.26 (s, 3 H), 3.15 (dd, J = 4, 10 Hz, 1 H); MS, *m/e* (rel intensity) 427 (13), 425 (24), 423 (M^+-57, 12), 335 (16), 333 (30), 331 (15), 254 (22), 253 (16), 252 (23), 251 (12), 131 (100); calcd for $C_{15}H_{25}O_2Br_2Si$ (M^+-57) *m/e* 422.9992, found *m/e* 422.9984. Anal. Calcd for $C_{19}H_{34}O_2Br_2Si$: C, 47.30; H, 7.10. Found: C, 47.04; H, 7.12.

188: mp 106-107 °C (from diisopropyl ether); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.00 (s, 6 H), 0.50-2.57 (m, 12 H), 0.86 (s, 9 H), 0.90 (s, 3 H), 1.05 (s, 3 H), 3.12 (dd, J = 4, 10 Hz, 1 H); MS, *m/e* (rel intensity) 427 (38), 425 (73), 423 (M^+-57, 38), 335 (22), 333 (47), 331 (23), 254 (17), 253 (21), 252 (18), 251 (18), 145 (36), 131 (100), 95 (51), 75 (100); calcd for $C_{15}H_{25}O_2Br_2Si$ (M^+-57) *m/e* 422.9992, found *m/e* 422.9990. Anal. Calcd for $C_{19}H_{34}O_2Br_2Si$: C, 47.30; H, 7.10. Found: C, 47.35; H, 7.25.

(1aα,3aα,4α,7α,7aβ,7bα)-4-[(*tert*-Butyldimethylsilyl)oxy]decahydro-1,1,3a,7-tetramethyl-1*H*-cyclopropa[*a*]naphthalen-7-ol (189). To a suspension of 4.28 g (47.9 mmol) of dry copper(I) cyanide in 90 mL of dry ether was added 54.4 mL (87 mmol) of MeLi (1.6 M in ether) at -78 °C. The mixture was gradually warmed to 0 °C over 45 min. The mixture was then cooled to -15 °C and a solution of 2.097 g (4.35 mmol) of dibromo

compound **187** and 1.9 mL (4.35 mmol) of HMPA in 80 mL of dry ether was added dropwise. Stirring was continued for an additional 45 min, after which time 15 mL of MeI was added. The mixture was stirred for another 5 min and then poured into a mixture of 90 mL of saturated aqueous NH_4Cl and 10 mL of concentrated NH_4OH. The two-phase mixture was separated and the aqueous layer was extracted with five 50-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated under reduced pressure. The remaining residue was flash chromatographed on silica gel (60:1 petroleum ether (bp 40-60 °C)/EtOAc) to give in order of elution 0.926 g (60%) of pure dimethylated product **189**, which solidified on standing, and 0.169 g (12%) of **191**. Physical and spectroscopic data of **189** and **191** follow.

189: mp 64-65 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ -0.06 (s, 3 H), -0.04 (s, 3 H), 0.10-2.20 (m, 12 H), 0.80 (s, 12 H), 0.93 (s, 3 H), 0.98 (s, 3 H), 1.06 (s, 3 H), 3.08 (dd, *J* = 4, 10 Hz, 1 H); MS, *m/e* (rel intensity) 352 (M^+, 0.2), 295 (1.6), 203 (100), 149 (12), 147 (13), 131 (17), 123 (10), 119 (8), 105 (12), 75 (20); calcd for $C_{17}H_{31}O_2Si$ (M^+-57) *m/e* 295.2093, found *m/e* 295.2096. Anal. Calcd for $C_{21}H_{40}O_2Si$: C, 71.53; H, 11.43. Found: C, 71.22; H, 11.66.

191: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.00 (s, 3 H), 0.03 (s, 3 H), 0.67 (dd, *J* = 4.7, 9.3 Hz, 1 H), 0.86 (s, 12 H), 0.96 (t, *J* = 4.7 Hz, 1 H), 1.10-2.15 (m, 11 H), 3.47 (dd, *J* = 4.2, 10.3 Hz, 1 H), 5.36 (br t, *J* = *ca* 9 Hz, 1 H), 5.97 (ddd, *J* = 3.3, 5.6, 9.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -4.84 (q), -3.94 (q), 14.36 (d), 15.99 (t), 18.00 (s), 18.55 (q), 25.79 (3 q), 26.66 (q), 28.26 (t), 35.73 (s), 35.90 (s), 37.38 (t), 37.67 (t), 73.37 (s), 78.53 (d), 121.71 (d), 128.71(d). MS, *m/e* (rel intensity) 322 (M^+, 3), 304 (3), 289 (2), 265 (5), 247 (27), 157 (39), 131 (88), 105 (51), 75 (100).

(1aα,3aα,4α,7α,7aβ,7bα)-Decahydro-1,1,3a,7-tetramethyl-1*H*-cyclopropa[*a*]naphthalene-4,7-diol (190). To a solution of 0.881 g (2.50 mmol) of monoprotected diol **189** in 40 mL of acetonitrile was added 2.5 mL of 40% aqueous HF. The mixture was stirred for 100 min and then poured into 150 mL of saturated aqueous $NaHCO_3$. After extraction of the aqueous layer with six 50-mL portions of CH_2Cl_2, the combined organic layers were dried and evaporated under reduced pressure. Flash chromatography of the resulting residue on silica gel (5:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded 0.563 g (95%) of diol **190** as white crystals: mp 149-150 °C (from diisopropyl ether); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.50-0.75 (m, 2 H), 0.88 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.12 (s, 3 H), 1.25-2.15 (m, 11 H), 3.13 (dd, *J* = 4, 10 Hz, 1 H); MS, *m/e* (rel intensity) 238 (M^+, 6), 220 (39), 205 (16), 202 (15), 187 (16), 163 (43), 162 (100), 135 (27), 123 (30), 121 (30); calcd for $C_{15}H_{26}O_2$ (M^+) *m/e* 238.1933, found *m/e* 238.1930. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.19; H, 11.04.

(1aα,3aα,4α,7α,7aβ,7bα)-Decahydro-1,1,3a,7-tetramethyl-1*H*-cyclopropa[*a*]naphthalene-4,7-diol 4-(4-Methylbenzenesulfonate) (185). A solution of 0.559 g (2.35 mmol) of diol **190** and 0.896 g (4.70 mmol) of TsCl in 25 mL of dry pyridine was stirred for 3.5 d. The reaction mixture was diluted with 250 mL of CH_2Cl_2 and washed successively with one 100-mL portion of 10% aqueous H_2SO_4, two 50-mL portions of saturated aqueous $NaHCO_3$, and one 100-mL portion of brine. The organic layer was dried and the solvent was removed under reduced pressure. The crude product was flash chromatographed on silica gel (15:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 0.903 g (98%) of tosylate **185** as white crystals: mp 120-121 °C (from diisopropyl ether); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.35-0.80 (m, 2 H), 0.86 (s, 3 H), 0.95-2.30 (m, 10 H), 1.05 (s, 3 H), 1.07 (s, 3 H), 1.13 (s, 3 H), 2.44 (s, 3 H), 4.20 (dd, J = 4, 10 Hz, 1 H), 7.30 (d, J = 8 Hz, 2 H), 7.76 (d, J = 8 Hz, 2 H); MS, *m/e* (rel intensity) 392 (M^+, 1.8), 374 (15), 220 (45), 202 (68), 172 (100), 91 (56); Anal. Calcd for $C_{22}H_{32}O_4S$: C, 67.31; H, 8.21. Found: C, 67.23; H, 8.03.

Alloaromadendren-4β-ol (186). A solution of 0.392 g (1.00 mmol) tosylate **185** in 16 mL of dry toluene was degassed and refluxed under an argon atmosphere. To this refluxing solution was added 0.57 mL (2 equiv) of sodium *tert*-amylate (3.5 M in toluene) at once. The reaction mixture was refluxed for 30 min and then, after cooling to 0 °C, 10 mL of water and 40 mL of brine were added. The two-phase mixture was separated and the aqueous layer was extracted with five 40-mL portions of petroleum ether (bp 40-60 °C). The combined organic layers were dried and evaporated under reduced pressure. The remaining residue was flash chromatographed on silica gel (150:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, 0.015 g (7%) of cyclic ether **192**, 0.155 g (70%) of olefin **186**, and 0.015 g (7%) of compound **193**. ^1H-^{13}C HETCOR and COSY-45 experiments were performed with the olefin **186**. For the ^1H-^{13}C HETCOR spectrum the parameters were: relaxation delay = 1 s, delays used in the pulse sequence = 3.5 and 1.8 ms, 90° carbon pulse = 6.3 μs. Spectral width in t_1 = 900 Hz, in t_2 = 5000 Hz. A total of 256 experiments with 64 transients each was done. Sine-bell window functions without phase shift were used for the Fourier transformation. The parameters for the COSY-45 experiment were as follows: relaxation delay = 0.1 s, 90° pulse = 6.3 μs, a spectral width of 475 Hz in t_1 and of 950 Hz in t_2 was used, and one experiment with 8 transients was performed. Before fourier transformation, zero filling and a squared sine-bell window function without phase shift were applied in both dimensions. Spectroscopic and physical data of **186**, **192**, and **193** follow.

186: mp 57.5-59 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.50-0.67 (m, 2 H), 0.90-1.87 (m, 7 H), 0.96 (s, 3 H), 1.01 (s, 3 H), 1.22 (s, 3 H), 1.93-2.18 (m, 1 H), 2.25-2.40 (m, 2 H), 2.67 (br q, J = 10.1 Hz, 1 H), 4.83 (br s, 1 H), 4.87 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.85 (q), 17.17

(s), 21.43 (t), 21.79 (d), 25.31 (d), 26.85 (t), 26.85 (q), 28.74 (q), 37.88 (t), 40.40 (t), 44.62 (d), 47.26 (d), 80.26 (s), 108.63 (t), 150.65 (s); ^1H-^{13}C HETCOR: see Table 6.1; COSY: see Figure 6.1; MS, *m/e* (rel intensity) 220 (M^+, 6), 205 (10), 202 (100), 187 (59), 159 (26), 146 (49), 117 (45), 107 (51), 93 (40), 91 (37), 43 (49); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1835. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.60; H, 11.29.

192: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.48-0.75 (m, 2 H), 0.99 (s, 3 H), 1.04 (s, 3 H), 1.10 (s, 3 H), 1.20-1.82 (m, 8 H), 1.24 (s, 3 H), 1.86 (br s, 1 H), 2.06 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.47 (q), 17.31 (s), 18.41 (q), 20.83 (t), 22.49 (d), 23.50 (t), 24.97 (d), 28.83 (q), 29.37 (q), 35.09 (t), 40.87 (t), 46.90 (d), 51.33 (d), 81.83 (s), 85.43 (s); MS, *m/e* (rel intensity) 220 (M^+, 15), 205 (6), 202 (5), 187 (6), 177 (10), 162 (100), 147 (50), 134 (37), 119 (67), 109 (32), 85 (48), 43 (47); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1828.

193: mp 57-59 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.21-0.36 (m, 1 H), 0.80-1.40 (m, 3 H), 0.86 (s, 3 H), 0.95 (d, J = 7 Hz, 3 H), 1.01 (s, 3 H), 155 (br s, 3 H), 1.60-1.92 (m, 2 H), 2.10-2.72 (m, 5 H), 5.18-5.31 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.44 (q), 15.77 (s), 16.54 (q), 19.70 (q), 25.17 (t), 26.99 (t), 27.20 (d), 27.79 (d), 29.54 (q), 36.87 (t), 41.07 (t), 45.67 (d), 122.12 (d), 138.02 (s), 216.93 (s); MS, *m/e* (rel intensity) 220 (M^+, 50), 205 (6), 202 (2), 177 (38), 149 (44), 148 (35), 110 (54), 95 (100), 82 (65), 43 (32); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1830. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.58; H, 10.91.

(±)-Alloaromadendrane-4β,10α-diol (28). To a solution of 0.060 g (0.27 mmol) of olefin **186** in 5 mL of CH_2Cl_2 were added 5 mL of acetone, 5 mL of water, 0.005 g of 18-crown-6 and 0.100 g of $NaHCO_3$. The mixture was stirred vigorously and 1.36 mL of 0.29 M Oxone (0.79 mmol of $KHSO_5$) in water was added dropwise at 0 °C. Stirring was continued for an additional 80 min, after which time 5 mL of 10% aqueous $Na_2S_2O_3$ and 10 mL of saturated aqueous $NaHCO_3$ were added. The aqueous layer was extracted with seven 25-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated under reduced pressure. The remaining residue, according to GCMS and ^1H NMR analysis, a 4.3:1 mixture of the epoxides **195** [^1H NMR (main peaks, $CDCl_3$) δ 0.94 (s, 3 H), 1.02 (s, 3 H), 1.18 (s, 3 H), 2.50 (d, J = 4 Hz, 1 H), 2.95 (d, J = 4 Hz, 1 H); MS, *m/e* (rel intensity) 236 (M^+, 0.1), 221 (1), 218 (4), 203 (3), 187 (4), 175 (6), 163 (8), 145 (16), 133 (14), 121 (15), 105 (28), 81 (60), 55 (30), 43 (100)] and **194** [^1H NMR (main peaks, $CDCl_3$) δ 0.94 (s, 3 H), 1.04 (s, 3 H), 1.15 (s, 3 H), 2.40 (d, J = 4 Hz, 1 H), 2.88 (d, J = 4 Hz, 1 H); MS, *m/e* (rel intensity) 236 (M^+, 0.3), 221 (0.4), 218 (2), 203 (2), 187 (3), 175 (6), 160 (8), 145 (21), 134 (17), 105 (27), 81 (44), 55 (27), 43 (100)], respectively, was taken up in 5 mL of dry ether and an excess $LiAlH_4$ was added. The mixture was stirred at rt for 17 h, diluted with 75 mL of CH_2Cl_2, and then carefully quenched with a few drops of saturated aqueous Na_2SO_4. The mixture was dried and concentrated under reduced

pressure. The remaining residue was flash chromatographed on silica gel (6:1 to 2:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, 0.011 g (16%) of 4β,10β-diol **197**, 0.012 g (18%) of the cyclic hydroxy ether **196**, and 0.030 g (46%) of 4β,10α-diol **28**. Physical and spectroscopic data of **28**, **196**, and **197** follow.

28: mp 120-120.5 °C (from n-hexane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.48-0.68 (m, 2 H), 0.95 (s, 3 H), 1.00-1.95 (m, 11 H), 1.03 (s, 3 H), 1.24 (s, 3 H), 1.32 (s, 3 H), 2.23 (br q, J = 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): see Table 6.1; MS, *m/e* (rel intensity) 238 (M^+, 0.3), 220 (3), 205 (5), 202 (3), 187 (4), 177 (4), 162 (11), 149 (9), 147 (14), 139 (100), 121 (26), 81 (39), 43 (52); calcd for $C_{15}H_{26}O_2$ (M^+) *m/e* 238.1933, found *m/e* 238.1928. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.30; H, 11.20.

196: mp 137-138 °C (from diisopropyl ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.49 (d, J = 9.4 Hz, 1H), 0.60-0.77 (m, 1 H), 0.90-1.89 (m, 10 H), 0.97 (s, 3 H), 1.01 (s, 3 H), 1.24 (s, 3 H), 2.19 (br s, 1 H), 3.31 (d, J = 9.5 Hz, 1 H), 3.37 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.41 (q), 17.48 (s), 18.15 (q), 20.67 (t), 22.08 (d), 23.26 (t), 25.38 (d), 29.35 (q), 35.57 (t), 36.17 (t), 44.65 (d), 50.94 (d), 68.96 (t), 83.81 (s), 85.76 (s); MS, *m/e* (rel intensity) 236 (M^+, 3), 218 (32), 205 (16), 160 (40), 147 (58), 145 (62), 134 (100), 105 (38), 91 (33), 43 (46); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1775. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 76.51; H, 10.37.

197: mp 109 °C (from n-hexane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.60-0.75 (m, 1 H), 0.87 (br d, J = 7.4 Hz, 1 H), 0.93-1.47 (m, 3 H), 0.96 (s, 3 H), 1.05 (s, 3 H), 1.09 (s, 3 H), 1.20 (s, 3 H), 1.64-2.00 (m, 8 H), 2.20 (dt, J = 8.9, 11.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): see Table 6.1; MS, *m/e* (rel intensity) 238 (M^+, 0.3), 220 (7), 205 (4), 202 (4), 192 (5), 187 (4), 177 (5), 162 (7), 147 (10), 139 (100), 121 (60), 81 (34), 43 (36); calcd for $C_{15}H_{26}O_2$ (M^+) *m/e* 238.1933, found *m/e* 238.1930. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.24; H, 11.22.

(±)-Alloaromadendrane-4α,10α-diol (29). To a solution of 0.100 g (0.45 mmol) of olefin **186** in 5 mL of dry pyridine was added 0.2 mL (1.0 mmol) of $SOCl_2$ at -15 °C. The mixture was stirred for 10 min and then poured into 100 mL of aqueous 20% H_2SO_4. The aqueous solution was extracted with five 50-mL portions of CH_2Cl_2. The combined organic layers were dried and the solvent was evaporated at atmospheric pressure. The remaining residue, a mixture of three products in a ratio of 6:3:1 according to GC analysis, was epoxidized and reduced as described above for olefin **186**. Workup and flash chromatography on silica gel (2:1 petroleum ether (bp 40-60 °C)/EtOAc) gave 0.025 g (23%) of pure **29**: mp 79-80 °C (from n-hexane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ -0.03 (t, J = 9.6 Hz, 1 H), 0.60 (ddd, J = 5.2, 9.6, 11.3 Hz, 1 H), 0.99 (s, 3 H), 1.01 (s, 3 H), 1.10-2.11 (m, 11 H), 1.16 (s, 3 H), 1.30 (s, 3 H), 2.45 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): see Table 6.1; MS, *m/e* (rel intensity) 238 (M^+, 1.7), 220 (18), 205 (18),

202 (21), 187 (19), 177 (11), 162 (100), 147 (52), 134 (24), 119 (51), 107 (48), 93 (49), 81 (33); calcd for $C_{15}H_{24}O$ (M^+-18) *m/e* 220.1827, found *m/e* 220.1825. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.77; H, 11.30.

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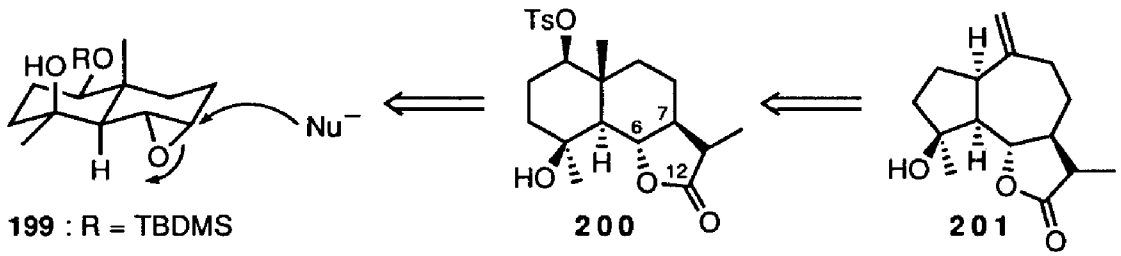
7 Miscellaneous Results

7.1 Studies towards the Stereoselective Formation of the Lactone Ring

As described in Chapter 1, the vast majority of isolated guaiane terpenoids are cis-fused guaian-6α,12-olides, in which a *trans*-lactone is present at the C(6)-C(7) position.[1] This functionality was believed to be relatively easy prepared *via* a nucleophilic β-attack on the sterically less demanding C(7) position of the α-epoxide **199** (Scheme 7.1).[2] The base-induced and -directed rearrangement of the eudesmanolide **200** would subsequently lead to a cis-fused guaianolide **201** with an exocyclic methylene unit.[3]

Scheme 7.1

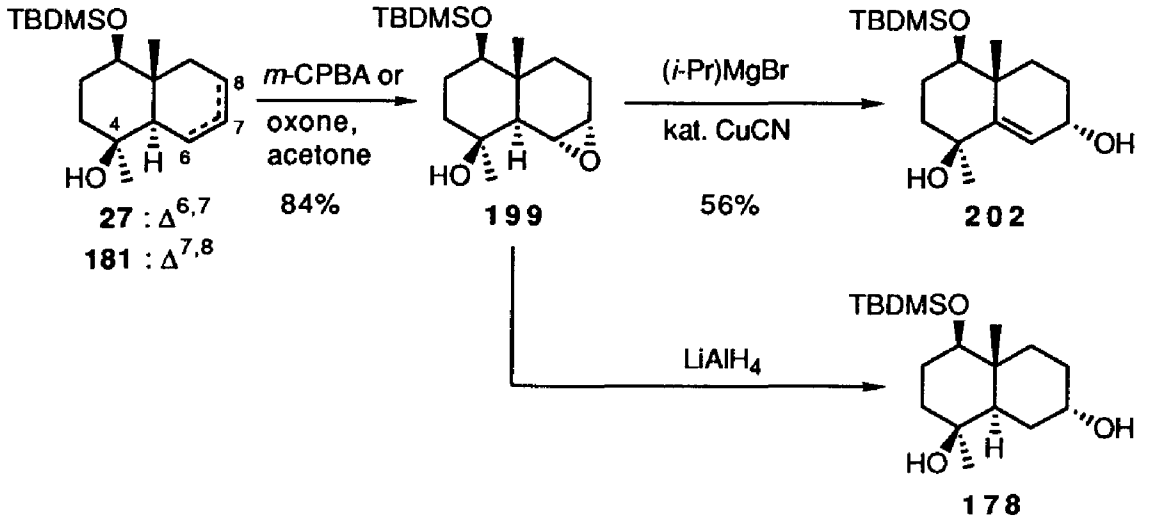


Epoxidation of an inseparable 8.4:1 mixture of the olefins **27** and **181**, respectively,[4] with *m*-CPBA or *in situ* generated dimethyldioxirane[5] gave the pure α-epoxide **199** in 84% yield after column chromatography (Scheme 7.2). Reaction of **199** with $Li_2(i\text{-}C_3H_5)_2CuCN$[6] gave a complex mixture of products. The copper(I) cyanide catalyzed Grignard reaction[7] of the epoxide **199** with isopropyl-magnesium bromide also failed. Instead, the allyl alcohol **202** was formed as the only product in 56% isolated yield. Upon reduction of the epoxide **199** with $LiAlH_4$, a hydride attack on the less hindered C(7) position was expected. After oxidation of the generated C(6) hydroxyl group, alkylation of the C(7) position, *e.g. via* the kinetic enol silylether, would then be possible.

Treatment of the epoxide **199** with $LiAlH_4$, however, resulted in the formation of the known diol **178**.[8] It is believed that a reaction between the reagent and the hydroxyl group at C(4) accounts for this regioselective epoxide opening, the more so as in this way the epoxide is reduced through the preferred transition state involving diaxial opening.[9]

Consequently, elaboration of a 6α,7β-lactone starting with the double bond in **27** is not as easy as it might appear at first sight. A selective β-epoxidation of the double bond in

Scheme 7.2

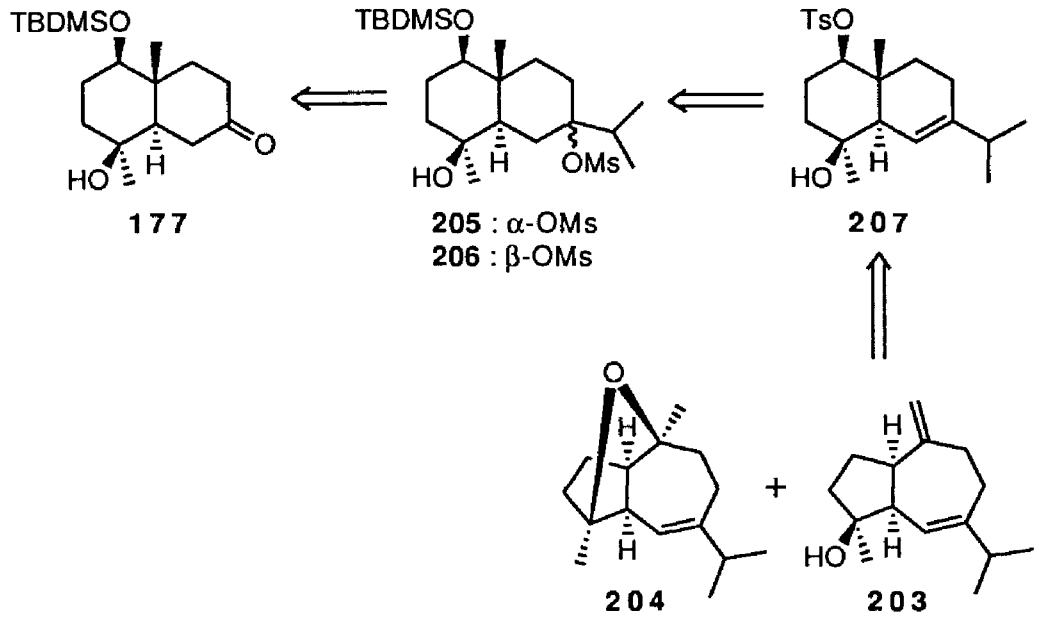


27, which seems to be a prerequisite for the regioselective epoxide opening, will cause major problems due to steric hindrance of the angular methyl group. Furthermore, the nucleophilic opening at C(7) of the 6β,7β-epoxide ring will result in a stereochemistry opposite to the one in **200** and **201**. The synthesis of the 6α,7β-lactone ring will then include the oxidation of the hydroxyl group at C(6), the equilibration of the side chain at C(7) to the equatorial position, and a subsequent selective reduction of C(6) carbonyl group to the α-hydroxyl group.

7.2 Studies towards (±)-Alismol 203

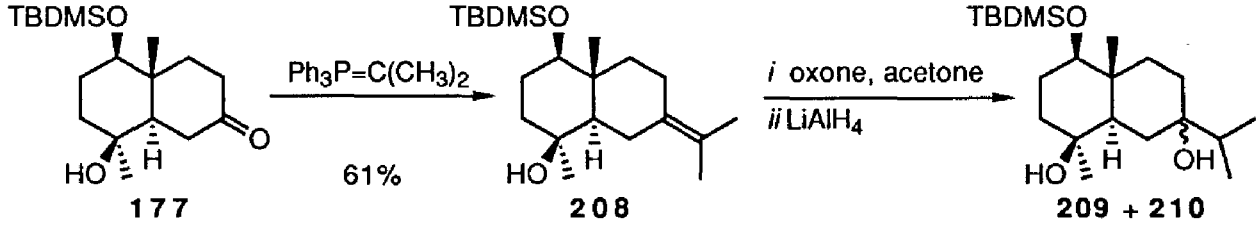
From the rhizome of *Alisma plantago-aquatica* L. var. *orientale* Samuelsson, which has been used in oriental medicine for diuretic and anti-inflammatory purposes, the guaiane sesquiterpenes (+)-alismol **203** and (+)-alismoxide **204** have been isolated.[10,11] Synthesis of these compounds would be another illustration of the use of our base-induced and -directed elimination[8] and rearrangement[3] processes. It was envisaged that elimination of both the mesylates **205** and **206** would result in the selective formation of the trisubstituted C(6)-C(7) double bond (Scheme 7.3). The following rearrangement of the *iso*-oplodiol tosylate **207** would then result in the selective formation of **203**, with **204** as side product.[3,12] The presence of the double bond at the C(6)-C(7) position in **207** was not expected to cause major problems in the rearrangement process towards **203**. The tosylate derived from **27** was known to give

Scheme 7.3



the normal reaction pattern when treated with sodium *tert*-amylate in refluxing benzene, with no formation of germacrane-like products (cf. **193**, Scheme 6.5).
Treatment of **177** with *iso*-propylenetriphenylphosphorane in DMSO produced the corresponding *iso*-propylidene compound **208** (Scheme 7.4). Epoxidation of the double bond with *in situ* generated dimethyldioxirane[5] resulted in a 1:1.3 mixture of epoxides in almost quantitative yield, which was reduced to the epimeric alcohols **209** and **210**.[13] Both alcohols proved to be stable upon treatment with MsCl under various conditions,[14] thereby frustating the synthetic plan outlined in Scheme 7.3.

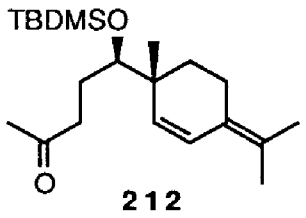
Scheme 7.4



Attempts to isomerize the exocyclic double bond of **208** to the C(6)-C(7) position with the combination sodium *tert*-amylate/15-crown-5 in refluxing toluene failed. Similar attempts by treatment of **208** with potassium *tert*-butoxide in DMSO at 60 °C[15] resulted in the cleavage of the TBDMS protecting group.

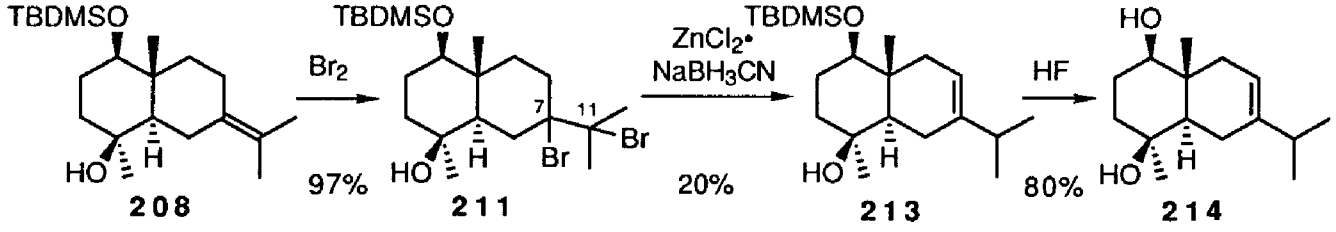
7.3 Synthesis of (±)-Oplodiol 214

In order to introduce a good leaving group at C(7) the olefin **208** was treated with Br_2 to give a single dibromide **211** in high yield (Scheme 7.5). The stereochemistry at C(7) in **211** could not be established. Upon treatment with 10 equiv of sodium *tert*-amylate in refluxing toluene, **211** gave a highly unstable product, which was assigned structure **212** on the basis of its ^1H and ^{13}C NMR spectra.[16] Therefore, apart from fragmentation also elimination of the bromine at C(11) had occurred. In order to prepare a compound with only a good leaving group at C(7), we tried to reduce selectively the tertiairy bromide at C(11) in **211**.



212

Scheme 7.5



For this reduction a reaction with zinc-modified cyanoboro-hydride in ether was tried. This reagent, prepared by mixing zinc(II) chloride and sodium cyanoborohydride in a 1:2 molar ratio, reduces tertiary halides to the corresponding hydrocarbons.[17] We hoped that it would be possible to reduce the sterically less hindered bromide at C(11). Treatment of the dibromide **211** with this reagent resulted in the partial formation of a product within 1 h, but on prolonged reaction this product seemed to react further according to TLC. So, although the reaction was not completed yet, it was decided to stop it. After workup and column chromatography, the initial reaction product was isolated in 20%, together with 42% of the recovered **211**. The following deprotection of the secondary hydroxyl group with HF in aqueous acetonitril offered no problems but the isolated olefinic diol **214** was, according to its ^1H and ^{13}C NMR spectral data, identical to (+)-oplodiol,[18,19,20] an eudesmane isolated from *Oplopanax japonicus* (Nakai) Nakai[19] and from *Pulicaria paludosa*.[20]

The results above show that also other factors, which are not completely understood at this moment, complicate the expected reaction sequences and patterns and further research is necessary to solve these problems.

7.4 Experimental Section

General

Chemical shifts are reported relative to TMS (δ 0.00), with $CHCl_3$ as an internal standard [δ 7.23 (^1H) and δ 76.90 (^{13}C)]. ^{13}C NMR multiplicities were determined by using a DEPT pulse sequence. MS data were determined at 70 eV on either an AEI MS 902 spectrometer or a Hewlett Packard 5970B series Mass Selective Detector, coupled with a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. GC analyses were carried out with FID and a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically. Flash chromatography was performed on Merck silica gel 60 (230-400 mesh).
Solvents were dried and freshly distilled by common practice. For dry reactions, flasks were dried at 150 °C and flushed with dry N_2 just before use, and reactions were carried out under N_2. Product solutions were dried over $MgSO_4$ prior to evaporation of the solvent under reduced pressure on a rotary evaporator.

(1α,4α,4aα,6β,7β,8aβ)-4-[(*tert*-Butyldimethylsilyl)oxy]decahydro-1,4a-dimethyl-6,7-epoxy-1-naphthalenol (199). To a solution of 0.155 g (0.50 mmol) of a 8.4:1 mixture of the olefins **27** and **181** in 10 mL of CH_2Cl_2 were added 10 mL of acetone, 10 mL of water, 0.020 g of 18-crown-6 and 0.750 g of $NaHCO_3$. The mixture was stirred vigorously and 7.00 mL of 0.29 M Oxone (2.03 mmol of $KHSO_5$) in water was added dropwise at 0 °C. Stirring was continued for an additional 60 min, after which time 10 mL of 10% aqueous $Na_2S_2O_3$ and 100 mL of saturated aqueous $NaHCO_3$ were added. The aqueous layer was extracted with seven 25-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated under reduced pressure. The remaining residue was flash chromatographed on silica gel (15:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 0.137 g (84%) of crystalline **199**: mp 95-95.5 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ -0.02 (s, 3 H), 0.00 (s, 3 H), 0.80-2.15 (m, 10 H), 0.85 (s, 9 H), 0.95 (s, 3 H), 1.34 (s, 3 H), 3.13 (dd, J = 4.1, 11.3 Hz, 1 H), 3.20 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -5.14 (q), -4.20 (q), 13.20 (q), 17.80 (s), 20.46 (t), 25.60 (3 q), 26.75 (t), 28.97 (q), 31.75 (t), 37.57 (s), 39.00 (t), 51.21 (d), 51.58 (d), 51.90 (d), 70.64 (s), 77.40 (d); MS *m/e* (rel intensity) 269 (M^+-57, 8), 251 (17), 225 (5), 177 (15), 159 (55), 131 (27), 119 (20), 105 (23), 93 (27), 75 (100), 55 (19), 43 (52); calcd for $C_{14}H_{25}O_3Si$ (M^+-57) *m/e* 269.1573, found *m/e* 269.1574. Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.20; H, 10.49. Found: C, 66.35; H, 10.80.

(1α,4α,4aα,7β)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4,4a,5,6,7-octahydro-1,4a-dimethylnaphthalene-1,7-diol (202). To 7 mL of 0.60 M *i*-PrMgBr in ether was added 0.038 g (0.42 mmol) of CuCN at 0 °C. After 15 min a solution of 0.136 g (0.42 mmol) of epoxide

199 in 7 mL of dry ether was added dropwise. The reaction mixture was refluxed for 1 h, after which time the excess *i*-PrMgBr was quenched by careful addition of saturated aqueous NH_4Cl. After addition of 50 mL of water, the two-phase mixture was separated and the aqueous layer was extracted with five 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 40 mL of brine, dried, and evaporated under reduced pressure. The remaining residue was flash chromatographed on silica gel (10:1 to 3:1 petroleum ether (bp 40-60 °C)/EtOAc) to afford 0.076 g (56%) of crystalline **202**: mp 142-144 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.00 (s, 6 H), 0.75-2.20 (m, 10 H), 0.83 (s, 9 H), 1.13 (s, 3 H), 1.30 (s, 3 H), 3.24 (dd, J = 4, 10 Hz, 1 H), 4.10 (m, $W_{1/2}$ = 10 Hz, 1 H), 5.82 (d, J = 5 Hz, 1 H); MS, *m/e* (rel intensity) 269 (M^+-57, 0.5), 251 (20), 177 (31), 159 (100), 133 (20), 117 (25), 105 (21), 75 (75), 73 (56), 43 (69); calcd for $C_{14}H_{25}O_3Si$ (M^+-57) *m/e* 269.1573, found *m/e* 269.1573. Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.20; H, 10.49. Found: C, 66.22; H, 10.51.

(1α,4α,4aα,8aβ)-4-[(*tert*-Butyldimethylsilyl)oxy]decahydro-1,4a-dimethyl-7-(1-methylethylidene)-1-naphthalenol (208). To a stirred solution of 30 mL of 0.83 M (dimethylsulfinyl)sodium in dry DMSO was added 10.80 g (25.00 mmol) of *iso*-propyltriphenylphosphonium iodide. The mixture was stirred at rt for 30 min, and then a solution of 3.26 g (10.00 mmol) of alcohol **177**[3] in 20 mL of dry DMSO was added dropwise. The reaction mixture was stirred at 55 °C for 1.5 h, allowed to come to rt, and stirring was continued for an additional 24 h. The reaction mixture was diluted with 250 mL of water and extracted with six 100-mL portions of EtOAc. The combined organic layers were washed with 75 mL of brine and 25 mL of $Na_2S_2O_3$, and dried. The solvent was evaporated under reduced pressure and the remaining residue was flash chromatographed on silica gel (40:1 to 4:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 2.148 g (61%) of pure **208**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.02 (s, 6 H), 0.80-2.80 (m, 12 H), 0.87 (s, 9 H), 1.06 (s, 3 H), 1.15 (s, 3 H), 1.75 (br s, 6 H), 3.20 (dd, J = 4.5, 10 Hz, 1 H); MS *m/e* (rel intensity) 295 (M^+-57, 5), 203 (100), 159 (18), 147 (39), 133 (28), 119 (33), 105 (30), 95 (50), 81 (23), 75 (67), 55 (24), 43 (44); calcd for $C_{17}H_{31}O_2Si$ (M^+-57) *m/e* 295.2093, found *m/e* 295.2089.

(1α,4α,4aα,8aβ)-7-Bromo-7-(1-bromo-1-methylethyl)-4-[(*tert*-butyldimethylsilyl)oxy]-decahydro-1,4a-dimethyl-1-naphthalenol (211). To a stirred solution of 0.173 g (0.49 mmol) of olefin **208** was added dropwise 1.23 mL of Br_2 (0.4 M in CH_2Cl_2). After stirring for 5 min, the reaction mixture was evaporated under reduced pressure and flash chromatographed on silica gel (2:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 0.244 g (97%) of pure **211**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.00 (s, 6 H), 0.75-2.60 (m, 12 H), 0.83 (s, 9 H), 0.96 (s, 3 H), 1.05 (s, 3 H), 2.00 (br s, 6 H), 3.30 (dd, J = 4, 10 Hz, 1 H).

(1α,4α,4aα,8aβ)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4,4a,5,8,8a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-naphthalenol (213). To a stirred solution of 0.033 g (0.24 mmol) of dry $ZnCl_2$ in 5 mL of ether was added 0.030 g (0.48 mmol) of $NaBH_3CN$. The mixture was stirred at rt for 20 min and then 0.244 g (0.48 mmol) dibromide **211** was added in 2 mL of ether. The reaction mixture was stirred for 75 min and then quenched with 10 mL of saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated under reduced pressure and flash chromatographed on silica gel (150:1 to 10:1 petroleum ether (bp 40-60 °C)/EtOAc) to give in order of elution 0.033 g (20%) of olefin **213** [^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.03 (s, 6 H), 0.85-2.45 (m, 11 H), 0.93 (s, 9 H), 0.97 (2 d, J = 7 Hz, 6 H), 1.02 (s, 3 H), 1.13 (s, 3 H), 3.30 (dd, J = 4, 11 Hz, 1 H), 5.36 (m, 1 H)] and 0.101 g (42%) of dibromide **211**.

(±)-Oplodiol (214). To a solution of 0.033 g (0.09 mmol) of monoprotected diol **213** in 5 mL of acetonitrile was added 0.5 mL of 40% aqueous HF. The mixture was stirred for 35 min and then poured into 30 mL of saturated aqueous $NaHCO_3$. After extraction of the aqueous layer with five 15-mL portions of EtOAc, the combined organic layers were dried and evaporated under reduced pressure. Flash chromatography of the resulting residue on silica gel (5:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded 0.018 g (80%) of diol **214**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85-2.28 (m, 12 H), 0.93 (s, 3 H), 0.99 (br d, J = 6.9 Hz, 6 H), 1.15 (s, 3 H), 3.30 (dd, J = 3.8, 12.0 Hz, 1 H), 5.31 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.46 (q), 20.97 (q), 21.53 (q), 22.80 (t), 26.52 (t), 29.61 (q), 34.73 (d), 37.42 (s), 39.21 (t), 40.45 (t), 46.01 (d), 70.72 (s), 79.64 (d), 115.82 (d), 141.65 (s); MS, *m/e* (rel intensity) 238 (M^+, 7), 220 (39), 205 (10), 202 (10), 187 (58), 161 (73), 159 (100), 145 (27), 135 (34), 119 (62), 94 (59), 43 (74); calcd for $C_{15}H_{26}O_2$ (M^+) *m/e* 238.1933, found *m/e* 238.1935.

7.5 References and Notes

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(11) The structures of **203** and **204** are the enantiomers of the natural forms.[10]
(12) See also Chapters 4 and 6 of this thesis.
(13) The stereochemistry of the epoxides and the alcohols **209** and **210** could not be ascertained.
(14) MsCl, pyridine; MsCl, Et_3N, pyridine; *n*-BuLi, THF, then MsCl; NaH, toluene, then MsCl; NaH, 15-crown-5, toluene, then MsCl.
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(16) ^1H NMR ($CDCl_3$, 200 MHz) δ 0.01 (s, 6 H), 0.75-2.70 (m, 8 H), 0.85 (s, 9 H), 0.92 (s, 3 H), 1.67 (s, 3 H), 1.70 (s, 3 H), 2.07 (s, 3 H), 3.45 (dd, J = 4.0, 11.5 Hz, 1 H), 5.45 (d, J = 11.3 Hz, 1 H), 6.32 (d, J = 11.3 Hz, 1 H); ^{13}C NMR (main peaks, $CDCl_3$, 50 MHz) δ 124.74 (d), 126.54 (s), 126.74 (s), 133.28 (d), 208.62 (s).
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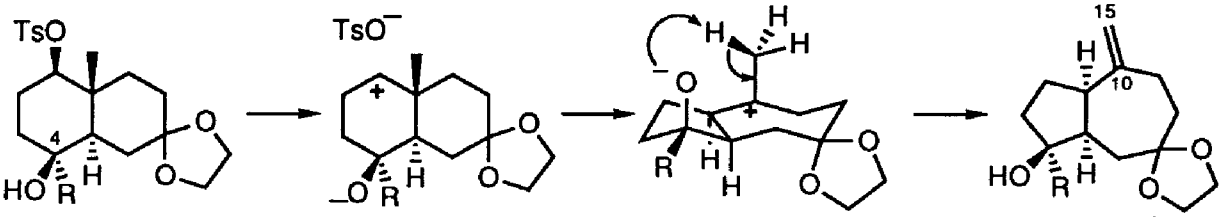
8 Summary

The total synthesis of a number of cis-fused hydroazulene sesquiterpenes is described in this thesis. In this synthetic study, ample attention is paid to the mechanistic aspects of the base-induced and -directed rearrangement and elimination reactions of perhydronaphthalene-1,4-diol monosulfonate esters. These reactions form the key steps in the synthetic routes that were followed.

A general introduction into the chemistry of terpenes, with emphasis laid on the sesquiterpenes with a hydroazulene skeleton, is given in Chapter 1.

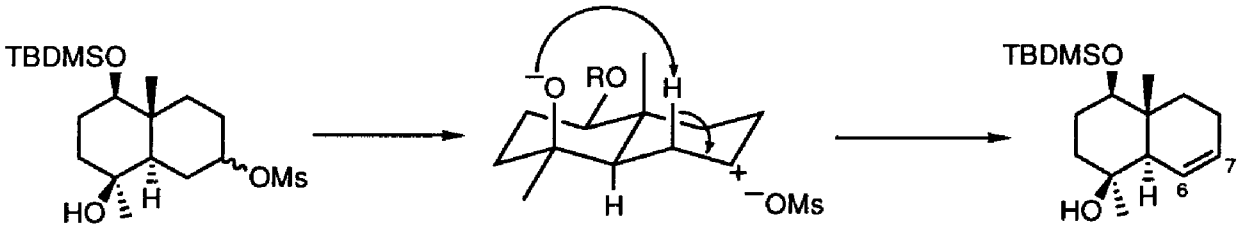
In Chapter 2, an overview of the literature on the synthesis of these hydroazulene sesquiterpenes is presented. The different synthetic strategies towards the hydroazulene skeleton and their use in natural product synthesis are mentioned in first part of this chapter. The rearrangement reaction of the hydronaphthalene skeleton to the hydroazulene framework is described in more detail. The photochemical, the pinacol, and the solvolytic Wagner-Meerwein rearrangement are discussed successively. Upon solvolytic Wagner-Meerwein rearrangement of the hydronaphthalene framework towards the hydroazulene framework, a mixture of double bond isomers is formed in a ratio reflecting the relative stability of the products. This is a serious drawback of this method for the selective synthesis of hydroazulene sesquiterpenes with an exocyclic C(10)-C(15) double bond.

In Chapter 3 the utility of trans-fused hydronaphthalene precursors for the synthesis of cis-fused hydroazulene sesquiterpenes with an exocyclic C(10)-C(15) double bond is examined. For this purpose the tosylates **131** and **132** were prepared, and their behaviour under basic conditions was studied. Upon treatment with sodium *tert*-amylate, the tosylate **131**, which has a tertiary axial hydroxyl group at C(4), rearranged with high selectivity (90%) to the desired cis-fused exo 10-olefinic hydroazulene **143**. When the tosylate **132** with a secondary axial hydroxyl group at C(4), was treated this way, a lower selectivity (57%) in the formation of the corresponding hydroazulene **148** was observed. A mechanism for the rearrangement reaction is proposed. According to this mechanism the reaction starts with the deprotonation of the axial hydroxyl group at C(4). The generated alkoxide then induces the heterolysis of the tosylate ester bond, thereby leading to the formation of a secondary carbocation (ion pair). The system then rearranges to a more stable tertiary carbocation by a 1,2-shift of the central bond, thereby forming the hydroazulene skeleton. The subsequent intramolecular proton abstraction from the former angular methyl group by the axial alkoxide at C(4) directs the elimination reaction to the selective formation of the isomer with the exocyclic C(10)-C(15) double bond.



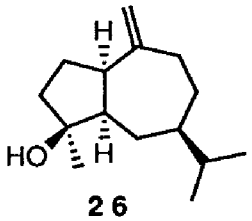
131 : R = CH_3
132 : R = H

143 : R = CH_3
148 : R = H



173 : α-OMs
180 : β-OMs

27

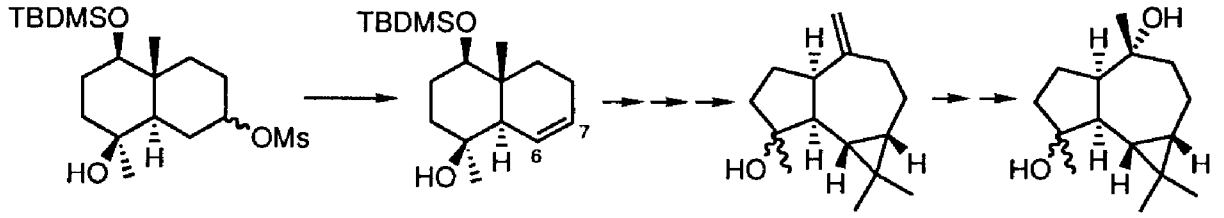


26

As an application of this base-induced and -directed rearrangement the total synthesis of the guaiane sesquiterpene (±)-5-*epi*-nardol **26** is described in Chapter 4.

In Chapter 5 the selective introduction of a double bond at the C(6)-C(7) position in the hydronaphthalene system is described. Compound **27** was formed selectively by treatment of both the axial mesylate **173** and the equatorial mesylate **180** with sodium *tert*-amylate in refluxing toluene. The mechanism proposed for this base-induced and -directed elimination bears strong resemblance with the one proposed for the rearrangement. The hydroxyl group at C(4) is deprotonated by the base and the thereby formed alkoxide induces the heterolysis of the mesylate ester bond. By abstraction of the C(6) proton, the alkoxide C(4) then directs the reaction to the selective formation of **27**. Apart from proton abstraction also homofragmentation was found to take place in the equatorial mesylate **180**, thereby reducing the yield of **27**. By increasing the sodium *tert*-amylate concentration this homofragmentation could be suppressed.

In Chapter 6 the total synthesis of the (±)-alloaromadendrane-4,10-diols **28** and **29** is described. The C(6)-C(7) double bond of **27** was used for the annulation of the cyclo-



173 : α-OMs
180 : β-OMs

27

186

28 : β-OH
29 : α-OH

propane ring. Selective epoxidation of the C(10)-C(15) double bond in the rearranged product **186**, followed by reduction gave **28**. Inversion of the stereochemistry at C(4) by dehydration of **186**, selective epoxidation and reduction resulted in the natural product **29**.

In Chapter 7, studies towards a 6α,7β-lactone ring and (±)-alismol, and the synthesis of (±)-oplodiol are described.

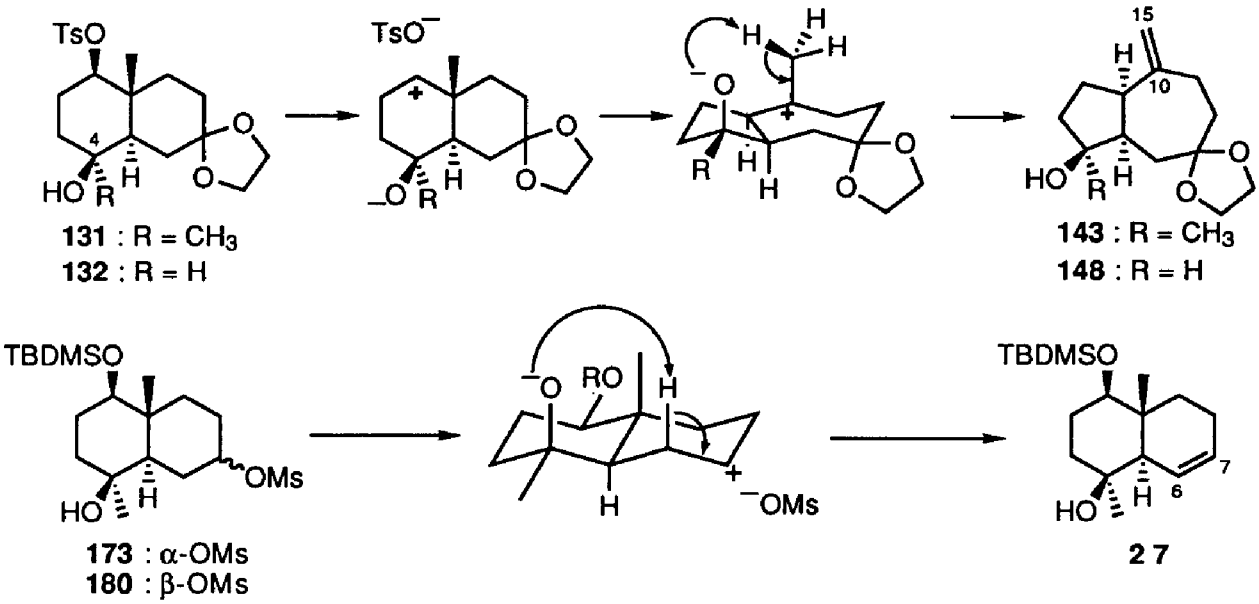
9 Samenvatting

In dit proefschrift worden de totaalsyntheses van een aantal cis-verknoopte hydroazuleen sesquiterpenen beschreven. In deze synthetische studie wordt ruime aandacht geschonken aan de mechanistische aspecten van de base-geïnduceerde en -gestuurde omleggings- en eliminatiereacties van perhydronaftaleen-1,4-diol monosulfonaat esters. Deze reacties vormen de sleutelstappen in de gevolgde syntheseroutes.

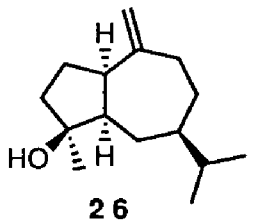
In hoofdstuk 1 wordt een algemene inleiding gegeven in de chemie van terpenen, waarbij de nadruk gelegd wordt op de sesquiterpenen met een hydroazuleen skelet.

In hoofdstuk 2 wordt een literatuuroverzicht van de synthese van deze hydroazuleen sesquiterpenen gegeven. In het eerste deel van dit hoofdstuk worden de verschillende synthetische strategieën die leiden tot het hydroazuleen skelet kort aangestipt alsmede de toepassingen hiervan in natuurproduktsynthese. De omleggingsreacties van het hydronaftaleen skelet naar het hydroazuleen skelet worden vervolgens in meer detail beschreven. Achtereenvolgens komen de fotochemische, de pinacol- en de solvolytische Wagner-Meerwein omlegging aan de orde. Bij de solvolytische Wagner-Meerwein omlegging van het hydronaftaleen skelet naar het hydroazuleen skelet ontstaat een mengsel van dubbele band isomeren in een verhouding die de relatieve stabiliteit van de produkten weerspiegelt. Hierdoor is de methode minder geschikt voor de selectieve synthese van hydroazuleen sesquiterpenen met een exocyclische C(10)-C(15) dubbele binding.

In hoofdstuk 3 wordt de bruikbaarheid van trans-verknoopte hydronaftaleen uitgangsstoffen in de synthese van cis-verknoopte hydroazuleen sesquiterpenen met een exocyclische C(10)-C(15) dubbele binding nader onderzocht. Met dit doel werden de tosylaten **131** en **132** gesynthetiseerd en hun gedrag onder basische omstandigheden bestudeerd. Tosylaat **131**, met een tertiaire axiale hydroxyl groep op C(4), bleek door behandeling met natrium *tert*-amylaat in refluxende benzeen met hoge selectiviteit (90%) om te leggen tot het gewenste cis-verknoopte hydroazuleen **143** met de exocyclische C(10)-C(15) dubbele binding. Voor het tosylaat **132**, met een secundaire axiale hydroxyl groep op C(4), werd het overeenkomstige hydroazuleen **148** met een lagere selectiviteit (57%) gevormd. Een mechanisme voor de omleggingsreactie wordt voorgesteld. Volgens dit mechanisme wordt eerst de axiale hydroxylgroep op C(4) gedeprotoneerd door de base. Het ontstane alkoxide induceert de heterolyse van de tosylaat ester binding waardoor een secundair carbokation (ion paar) ontstaat. Het systeem legt vervolgens om naar een stabieler tertiair carbokation door een 1,2-shift van de centrale binding waarbij het hydroazuleen skelet wordt gevormd. De intramoleculaire protonabstractie van de voormalige angulaire methylgroep door het



axiale alkoxide op C(4) stuurt daarna de reactie naar de selectieve vorming van het exocyclische dubbele band isomeer.

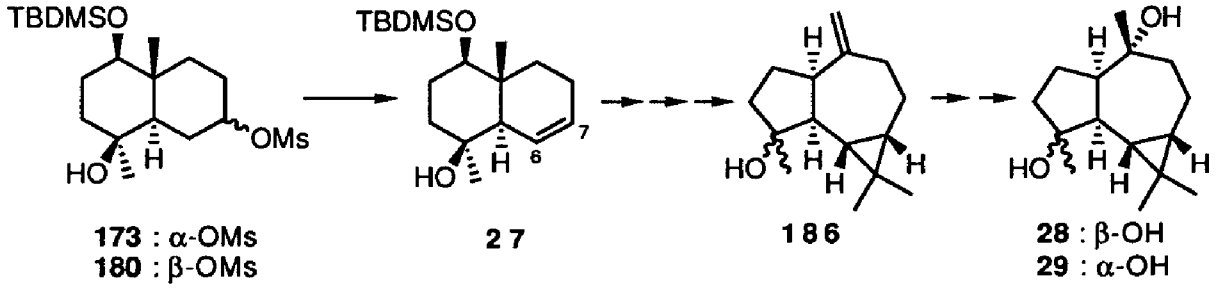


26

Als een toepassing van deze base-geïnduceerde en -gestuurde omlegging wordt de totaalsynthese van de guaiaan sesquiterpeen (±)-5-*epi*-nardol **26** beschreven in hoofdstuk 4.

In hoofstuk 5 wordt selectieve invoering van een dubbele binding op de C(6)-C(7) positie van het hydronaftaleen systeem beschreven. Verbinding **27** werd door behandeling van zowel het axiale mesylaat **173** als het equatoriale mesylaat **180** met natrium *tert*-amylaat in refluxende tolueen selectief gevormd. Het mechanisme dat voor deze base-geïnduceerde en -gestuurde eliminatie werd opgesteld vertoont grote overeenkomst met dat van de omleggingsreactie. Het door deprotonering ontstane alkoxide op C(4) induceert de heterolyse van mesylate ester binding, waarna hetzelfde alkoxide de reactie stuurt naar de selectieve vorming van **27** door het proton op C(6) te abstraheren. In het equatoriale mesylaat **180** bleek behalve protonabstractie ook homofragmentatie op te treden waardoor de opbrengst aan **27** verminderde. Door verhoging van de natrium *tert*-amylaat concentratie kon deze homofragmentatie worden onderdrukt.

In hoofdstuk 6 wordt de totaalsynthese van de (±)-alloaromadendraan-4,10-diolen **28** en **29** beschreven. De C(6)-C(7) dubbele binding in **27** werd gebruikt voor de annelering van de cyclopropaanring. Selectieve epoxidatie van de C(10)-C(15) dubbele binding het omgelegde produkt **186**, gevolgd door reductie gaf **28**. Omkering van de stereochemie op C(4) door dehydratatie van **186**, selectieve epoxidatie en reductie resulteerde in het natuurprodukt **29**.



173 : α-OMs
180 : β-OMs

27

186

28 : β-OH
29 : α-OH

In hoofdstuk 7 worden pogingen om te komen tot de synthese van een 6α,7β-lacton en (±)-alismol beschreven. Deze pogingen hebben geleid tot de synthese van (±)-oplodiol.

Curriculum Vitae

Louis Henri Dieudonné Jenniskens werd op 10 november 1962 geboren te Maastricht. In 1981 behaalde hij het diploma Gymnasium-β aan het Stedelijk Lyceum en HAVO te Maastricht. In hetzelfde jaar begon hij zijn studie aan de toenmalige Landbouwhogeschool te Wageningen. In 1985 werd met lof het kandidaatsexamen van de studierichting Levensmiddelentechnologie behaald in de differentiaties Levensmiddelenchemie en Levensmiddelenmicrobiologie. Tijdens de doctoraalfase koos hij voor een hoofdvak Levensmiddelenchemie (prof. dr. ir. A. G. J. Voragen) en een verzwaard hoofdvak Organische Chemie (dr. J. B. P. A. Wijnberg en prof. dr. Ae. de Groot). Stageperiodes werden doorgebracht bij de Keuringsdienst van Waren te Maastricht en bij de Agricultural Research Organization "the Volcani Center" te Bet Dagan, Israel. In januari 1988 werd het doctoraalexamen Levensmiddelentechnologie (oude stijl) met lof afgelegd. Van 1 januari 1988 tot 1 maart 1992 was hij als assistent in opleiding verbonden aan de vakgroep Organische Chemie van 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.

Stellingen

1. De omschrijving "efficiënt" die Harada *et al.* geven aan hun methode voor de synthese van optisch zuiver Wieland-Miescher keton, (-)-(8aR)-3,4,8,8a-tetrahydro-8a-methyl-1,6(2*H*,7*H*)-naphthalenedione, is in hoge mate discutabel.

Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53.

2. De synthese en uiteindelijke isolatie van de γ-cholesterylester van glutaminezuur door Quentin en Pleurdeau is meer aan het toeval dan aan doordachte chemie te danken.

Quentin, G.; Pleurdeau, A. *Eur. Polym. J.* **1985**, *21*, 741

3. Het resultaat van de enzymatische halogenering van anisool met behulp van *Corallina* broomperoxidase biedt voldoende garantie tegen toepasing van deze methode door derden. Het octrooi van Ito *et al.* op het procédé wekt dan ook bevreemding.

Itoh, N.; Hasan, A. K. M. Q.; Izumi, Y.; Yamada, H. *Eur. J. Biochem.* **1988**, *172*, 477.
Ito, S.; Yamada, H.; Izumi, Y. *Chem. Abstr.* **1989**, *110*, 191280. Octrooi.

4. De bepaling door Miskiel en Pazur van de immunologische determinanten van arabische gom en mesquite gom voor IgG-antilichamen opgewekt in konijnen, is aan ernstige kritiek onderhevig.

Miskiel, F.J.; Pazur, J. H. *Carbohydr. Polymers* **1991**, *16*, 17.

5. García Martínez *et al.* gaan er ten onrechte vanuit dat de omzetting van (-)-(1R)-2,2-dimethyl-3-oxotrifluoromethylsulfonyloxynorboraan tot (-)-(1R)-3-(1-methyl-ethylideen)cyclopentaancarbonzuur en de overeenkomstige ethylester in gebufferde 60% waterige ethanol een solvolyse reactie is.

García Martínez, A.; Teso Vilar, E.; Osío Barcina, J.; Manrique Alonso, J.; Rodríguez Herrero, E.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1992**, *33*, 607.

6. Het is onwaarschijnlijk dat Lecas-Nawrocka *et al.* de verbinding 5-[2,6-dinitrofenyl]-3,7,13,17-tetraethyl-2,8,12,18-tetramethylporfyrine als bijprodukt uit hun reactie hebben verkregen.

Lecas-Nawrocka, A; Boitrel, B.; Rose, E. *Tetrahedron Lett.* **1992**, *33*, 481.

7. Door het roodschilderen van fietspaden lijkt de overheid de fietser nog eens duidelijk op zijn gevaarlijke positie in het verkeer te willen wijzen.

8. De slechtste baan na een promotie is de stormbaan.

L. H. D. Jenniskens 2 oktober 1992

Total Synthesis of *cis*-Hydroazulene Sesquiterpenes; Base-Induced and -Directed Elimination and Rearrangement Reactions of Perhydronaphthalene-1,4-diol Monosulfonate Esters