TOTAL SYNTHESIS OF ALL STEREOISOMERS OF EUDESM-11-EN-4-OL

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TOTAL SYNTHESIS OF ALL STEREOISOMERS OF EUDESM-11-EN-4-OL

Proefschrift
ter verkrijging van de graad van doctor
in de landbouw- en milieuwetenschappen
op gezag van de rector magnificus,
dr. H. C. van der Plas
in het openbaar te verdedigen
op maandag 18 mei 1992
des namiddags te vier uur in de Aula
van de Landbouwuniversiteit te Wageningen

STELLINGEN

1 De bepaling van het L-guluronzuur- en D-mannuronzuurgehalte volgens Krull en Cote is aan ernstige kritiek onderhevig.
- Krull, L.H.; Cote, G.L. *Carbohydrate Polymers* 1992, *17*, 205.

2 De door Clarke et al. beschreven zure hydrolyse van polysachariden met behulp van trifluorazijnzuur is niet uit te voeren.
- Clarke, A.J.; Sarabia, V.; Keenleyside, W.; MacLachlan, P.R.; Whitfield, C. *Analytical Biochemistry* 1991, *199*, 68.

3 Het sesquiterpeen Caudatol wordt door Jolad et al. ten onrechte beschreven als een guanolide.
- Jolad, S.D.; Hoffmann, J.J.; Bates, R.B.; Calders, S.; McLaughlin, S.P. *Phytochemistry*, 1990, *29*, 3024.

4 Gerhard A. de Ruiter et al. gaan er ten onrechte van uit dat *Rhizopus oryzae* en *R. arrhizus* verschillende schimmel species zijn.
- de Ruiter, G.A.; van der Lugt, A.W.; Voragen, A.G.J.; Rombouts, F.M. *Carbohydrate Research*, 1991, *215*, 47.

5 De conclusie dat de pathogene schimmel *Ascochyta caulina* weinig perspectief biedt bij het bestrijden van *Chenopodum album* is voorbarig.
- Eggers,Th.; Thun, K. *Z. PflKrankh. PflSchutz, Sonderh.* 1988, *XI*, 225.

6 Zetmeel is de belangrijkste voedingsvezel in de voeding.

7 Het poneren van meer dan het minimum aantal wetenschappelijke stellingen is eerder een maat voor (on)collegiaal gedrag dan voor een brede wetenschappelijke belangstelling.

8 Het financieringstekort van de overheid zou lager uitvallen wanneer de overheid voor uitbetaling van haar ambtenaren hetzelfde principe hanteert als voor de uitbetaling van A.I.O.'s.

9 Het stookgedrag van de landbouwuniversiteit noopt tot aanpassing van het begrip kamertemperatuur.

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11 De meeste verslaggevers van Studio Sport hebben moeite om de sportbeelden accuraat en objectief van commentaar te voorzien.

12 Als Bounty het paradijs op aarde is, zullen veel mensen de hel verkiezen.

13 Het zou mooi zijn geweest wanneer de aardbeving in Limburg van 13 april j.l. ook politiek Den Haag wakker geschud zou hebben.

R.P.W. Kesselmans, Wageningen 18 mei 1992.

Stellingen behorende bij het proefschrift "Total Synthesis of All Stereoisomers of Eudesm-11-en-4-ol"

aan mijn ouders

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Hugo Jongejan, Bep van Veldhuizen en Kees Teunis, bedankt voor het nauwkeurige en snelle meten van mijn 'stofjes'.

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RON

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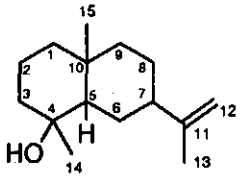
1. INTRODUCTION

1.1 STRUCTURE

The term eudesm-11-en-4-ol refers to a group of compounds with the common structure **1**. These compounds belong to a subgroup of sesquiterpenes known as eudesmanes.

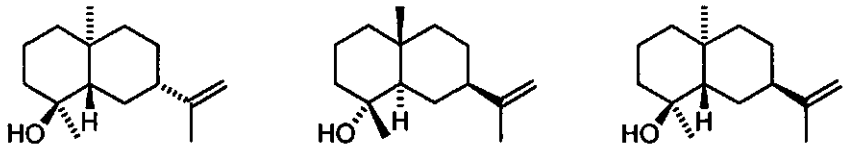
Figure 1.1



1

The first eudesm-11-en-4-ol was isolated in 1963 from the steam volatile oil of the grass *Bothriochloa intermedia*.[1] The authors assigned structure **2** to this compound, which they called (+)-intermedeol. The determination of the structure was based on chemical evidence and IR spectroscopy. However, when in 1967 the enantiomer of compound **2**, (-)-selin-11-en-4α-ol **I**, was isolated from the essential oil of *Podocarpus dacrydioides*,[2] it appeared that intermedeol was not enantiomeric. Therefore, the proposed structure **2**, tentatively assigned to intermedeol, had to be revised. Synthetic studies showed that intermedeol is correctly represented by structure **II**.[3]

Figure 1.2

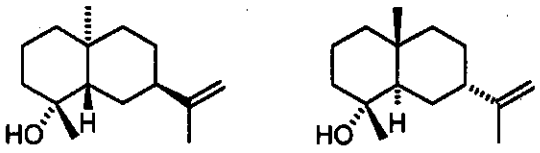


2 **I** **II**

As part of a composition study of grapefruit oil, the isolation of another eudesm-11-en-4-ol, (+)-paradisiol **IV**, was reported.[4] Again, the structure assigned to paradisiol proved to be incorrect. The isolated compound was in fact intermedeol **II**.[5] In 1979 the isolation of isointermedeol **3**, the

enantiomer of (+)-intermedeol II, was mentioned.[6] However, on the basis of spectral comparison and the small differences in the physical data, Huffman[7] concluded that the isolated isointermedeol was an impure sample of (+)-intermedeol II.

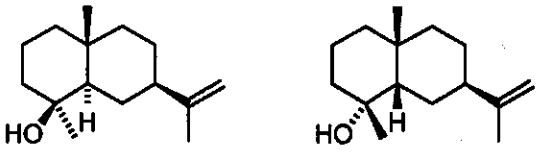
Figure 1.3



IV 3

Until now, two more eudesm-11-en-4-ols have been isolated and identified unequivocally. These are the *trans*-fused (+)-neointermedeol III, first found in *Bothriochloa* grasses,[8] and the *cis*-fused (+)-amiteol V, isolated from the secretion of termite soldiers (*Amitermes excellens*).[9]

Figure 1.4



III V

1.2 OCCURRENCE AND BIOLOGICAL ACTIVITY

1.2.1 Plant species

Stereoisomers of eudesm-11-en-4-ol have been found in a wide range of plant species. A selection of these species is shown in table 1.1.

Intermedeol II and neointermedeol III have been isolated and identified from *Bothriochloa* grasses (Graminae).[1,8] Many of these grasses are rich in essential oil, which imparts to the grass a pleasant smell and taste. These features make them particularly attractive to cattle as fodder. There is also evidence that these grasses are resistant to the ravages of some plaque insects such as the fall army worm (*Spodoptera frugiperda*).[10a] The volatile oil of the *Bothriochloa intermedia* can contain up to 90% intermedeol II, while in

Table 1.1. Occurrence of Eudesm-11-en-4-ols in Plant species

Plant species	compound (% in volatile oil) I	II	III
Grasses:			
Bothriochloa glabra[10]	-	+	80%
B. intermedia (300754)[1,8,10]	-	90%	-
B. intermedia (5752)[10]	-	+	68%
B. bladhi[14]	-	12%	4%
B. insculpta[10]	-	+	+
Cymbopogon flexuosus[6]	-	51%	-
Herbs:			
Humulus lupulus[15]	1%	-	-
Senecio amplexicaulus[16]	-	11%	-
Artemisia schmidtiana[17]	-	-	2.4%
Carthamus Lanatus[11]	-	16%	-
Shrumbs and Trees:			
Podocarpus dacrydioides[2]	+	-	-
Myrica gale[12]	15%	-	-
Euginia uniflora[13]	2%	-	-
Geigeria burkei[18]	-	-	14%
Fruits:			
Citrus paradisi swingle[4,5]	-	+	-
Psidium guajava[19]	3.3%	-	-
Liverwort:			
Riccardia jackii[20]	+	-	-

Key: - = not detected or reported; + = reported, but no percentages were given

other accessions[10c] neointermedeol III is the major compound.[10]

Intermedeol II is also the major compound (51%) of the essential oil of the perrenial grass *Cymbopogon flexuosus*.[6] This oil, having a scent of violets and lemon, is used in the soap industry. Furthermore, it was used by the Vietnamese for treating cholera and rheumatics. Also in the indian

safflower oil (*Carthamus lanatus*) intermedeol **II** is an essential component.[11]

Beside intermedeol **II** and neointermedeol **III**, a third *trans*-fused eudesmane alcohol, selin-11-en-4α-ol **I**, has been isolated from plant species. The essential oil of the leaves of *Myrica gale* contains for almost 15% selin-11-en-4α-ol **I**.[12] The leaves of this small shrub are considered to be aromatic and to have astringent properties. They are used in medicine for treating dysentry, and as an antiparaciticum especially against moths. As a traditional medicine they were used for treating skin diseases. Selin-11-en-4α-ol **I** occurs also in the leave oil of *Euginia uniflora*,[13] which again is used in medicine. The crushed pungent and scented leaves of this shrubby tree repel insects.

1.2.2 Termites

The most spectacular occurrence of eudesm-11-en-4-ols is established in the secretion of termite soldiers (Table 1.2). The soldier caste has to defend the termite colony against predators, specially ants. These soldiers have provided a variety of morphological adaptions and chemical weapons.[21]

Table 1.2. Occurrence of Eudesm-11-en-4-ols in the Defensive Secretion of Termite Soldiers

	compounds (% in secretion)		
Termitidae (Isoptera)	**II**	**III**	**V**
Amitermes excellens	-	+	67%
Subulitermes bailey	-	10-40%	-
Subulitermes oculatissimus	-	+	-
Subulitermes parvellus sp A & B	-	+	-
Velocitermes velox	+	-	-

Key: - = not detected or reported; + = reported, but no percentages were given

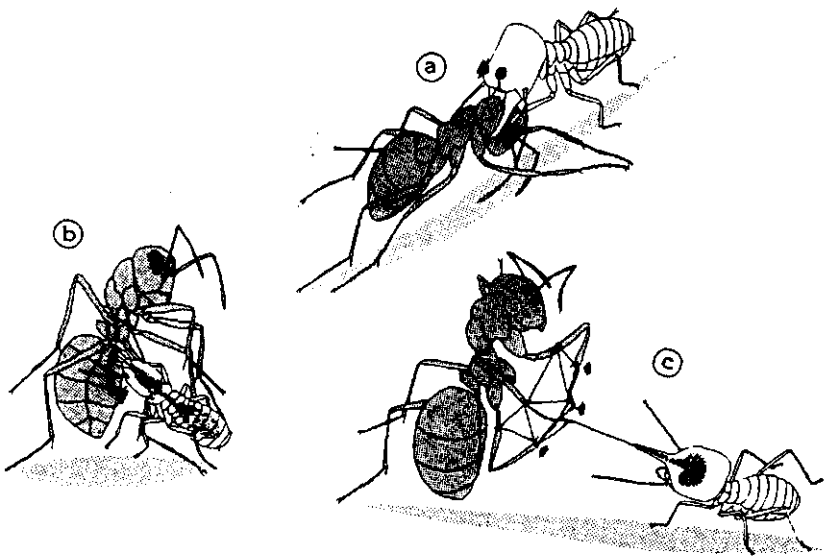
Three fundamental types of mechanisms are recognized[22] (Figure 1.5):

a. Daubing which involves application of a secretion from the frontal gland through an elongated labrum.

b. Biting with simultaneous addition of a toxic substance from the frontal gland (*Amitermes*).

c. Squirting which involves ejection by the soldiers of a viscous, sticky secretion from a specialized elongated rostrum called the nasus. In this way physical contact between termite and enemy is avoided. The soldiers have even lost their mandibles through evolutionary processes, and are entirely committed to their chemical defence (*Subulitermes, Nasutitermes*).

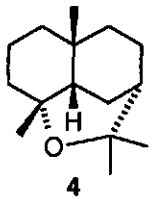
Figure 1.5



(a) Daubing; (b) Biting; (c) Squirting.

The chemical weapons, which consist of several terpenes, are employed as antihealants, repellents, glues, and irritants. Examination of the defence secretion of *A. excellence* revealed the presence of amiteol **V** (67%), neointermedeol **III**, and a closely related *cis*-fused eudesmane, the evuncifer ether **4**.[9] This ether is the major compound of the formidicially active secrections of *A. evuncifer* (90%) and *A. messinae* (90%).[23] The *trans*-fused eudesmanes intermedeol **II** and neointermedeol **III** have been isolated from the secretion of *S. bailey* (10-40%)[24] and *Velocitermes velox* (*Nasutitermes*),[25] respectively.

Figure 1.6



4

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2. STRATEGIES USED IN THE SYNTHESIS OF THE EUDESMANES

2.1 APPROACHES TO THE EUDESMANE SKELETON

The object of this paragraph is to summarize the main approaches to the eudesmane skeleton. The methods reported are limited to those found in publications describing the total syntheses of eudesmanes. The discussion is centered around the key steps involved in the construction of the fused ringsystem. In some cases the synthesis of the precursor and its transformation to the eudesmanes will be described. The paragraph is organized in sections, each dealing with a number of methods under a common heading i.e. annulation, cycloaddition, intramolecular cyclization reactions, and transformations of natural sesquiterpenes.

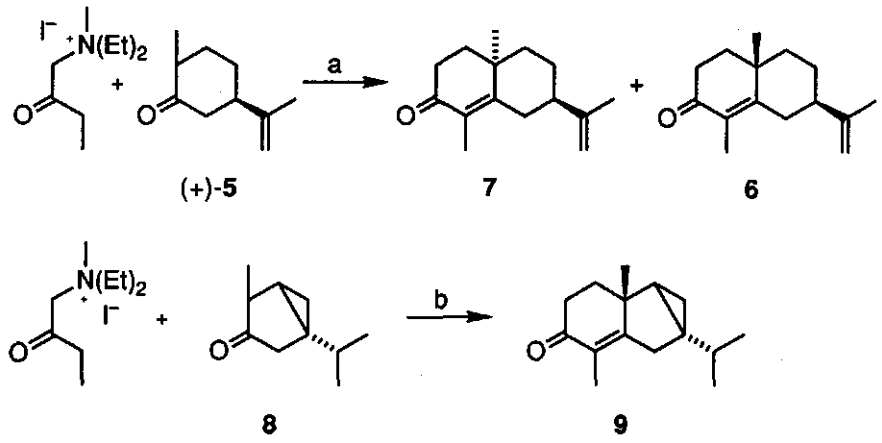
2.1.1 Annulation Reactions

Prior to 1970 almost invariably the eudesmane skeletons were constructed involving the Robinson annulation reaction as key step.[1,2,3] Because of the thermodynamic control, 2-substituted cyclohexanones invariably give angularly substituted decalin systems as major products. With 2,5-dialkylcyclohexanones, the major products are those in which the two alkyl groups remain or become trans to each other, regardless of the initial ratio of isomers present in the cyclohexanones.

Thus, (+)-dihydrocarvone **5** afforded 3% of (+)-α-cyperone **6** and as main product (-)-7-*epi*-cyperone **7** in which the angular methyl group was trans to the (axial) 1-methylethenyl group.[4] Also (-)-thujone **8** afforded a synthon **9** in which the angular methyl group was trans to the (axial) C-7 substituent[5] (Scheme 2.1). In this last procedure additional steps were necessary for the cleavage of the cyclopropane ring to obtain an eudesmane derivative.

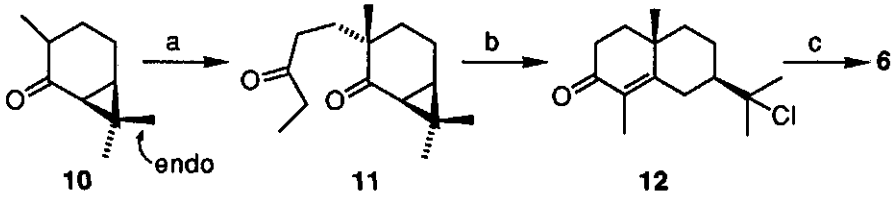
However, in many natural eudesmanes the equatorial C-7 substituent and the angular methyl group are cis to each other. An efficient approach to these β C-7 eudesmanes has been reported by Caine.[6] Steric hindrance of the endo methyl of (-)-carone **10** ensured exclusive alkylation from the less hindered α face. Subsequent treatment of **11** with HCl caused cyclopropane ring opening, aldolcondensation, and dehydration. Dehydrohalogenation of **12** gave (+)-α-cyperone **6** in good yield (Scheme 2.2).

Scheme 2.1[a]



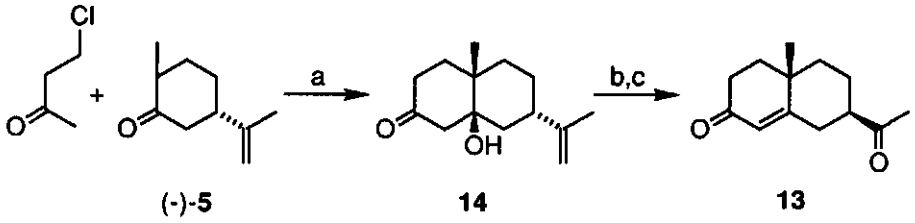
[a] (a) $NaNH_2$, ether; (b) KOH, EtOH, Δ.

Scheme 2.2[a]



[a] (a) Ethyl vinyl ketone, KOH, EtOH, ether; (b) HCl-EtOH; (c) NaOAc, AcOH, 100 °C.

Scheme 2.3[a]



[a] (a) NaH, THF; (b) ozone, CH_2Cl_2, CH_3OH; (c) HCl, AcOH.

2. STRATEGIES USED IN THE SYNTHESIS OF THE EUDESMANES

2.1 APPROACHES TO THE EUDESMANE SKELETON

The object of this paragraph is to summarize the main approaches to the eudesmane skeleton. The methods reported are limited to those found in publications describing the total syntheses of eudesmanes. The discussion is centered around the key steps involved in the construction of the fused ringsystem. In some cases the synthesis of the precursor and its transformation to the eudesmanes will be described. The paragraph is organized in sections, each dealing with a number of methods under a common heading i.e. annulation, cycloaddition, intramolecular cyclization reactions, and transformations of natural sesquiterpenes.

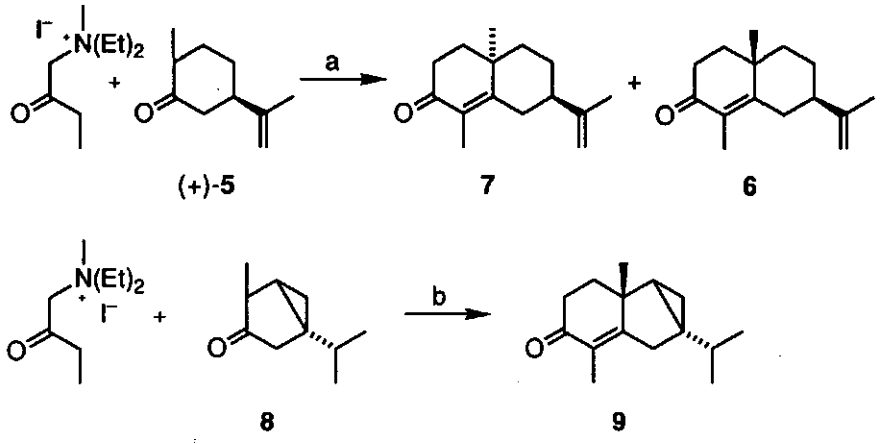
2.1.1 Annulation Reactions

Prior to 1970 almost invariably the eudesmane skeletons were constructed involving the Robinson annulation reaction as key step.[1,2,3] Because of the thermodynamic control, 2-substituted cyclohexanones invariably give angularly substituted decalin systems as major products. With 2,5-dialkylcyclohexanones, the major products are those in which the two alkyl groups remain or become trans to each other, regardless of the initial ratio of isomers present in the cyclohexanones.

Thus, (+)-dihydrocarvone **5** afforded 3% of (+)-α-cyperone **6** and as main product (-)-7-*epi*-cyperone **7** in which the angular methyl group was trans to the (axial) 1-methylethenyl group.[4] Also (-)-thujone **8** afforded a synthon **9** in which the angular methyl group was trans to the (axial) C-7 substituent[5] (Scheme 2.1). In this last procedure additional steps were necessary for the cleavage of the cyclopropane ring to obtain an eudesmane derivative.

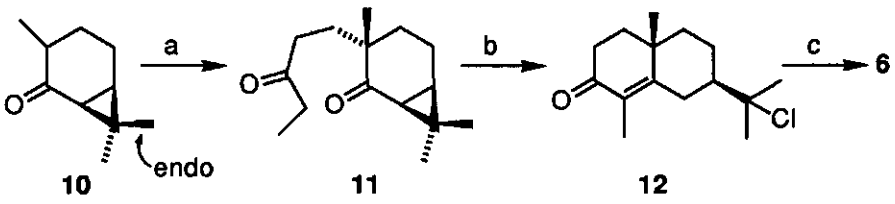
However, in many natural eudesmanes the equatorial C-7 substituent and the angular methyl group are cis to each other. An efficient approach to these β C-7 eudesmanes has been reported by Caine.[6] Steric hindrance of the endo methyl of (-)-carone **10** ensured exclusive alkylation from the less hindered α face. Subsequent treatment of **11** with HCl caused cyclopropane ring opening, aldolcondensation, and dehydration. Dehydrohalogenation of **12** gave (+)-α-cyperone **6** in good yield (Scheme 2.2).

Scheme 2.1[a]



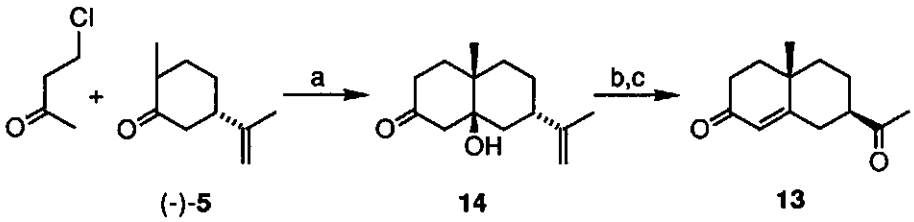
[a] (a) $NaNH_2$, ether; (b) KOH, EtOH, Δ.

Scheme 2.2[a]



[a] (a) Ethyl vinyl ketone, KOH, EtOH, ether; (b) HCl-EtOH; (c) NaOAc, AcOH, 100 °C.

Scheme 2.3[a]

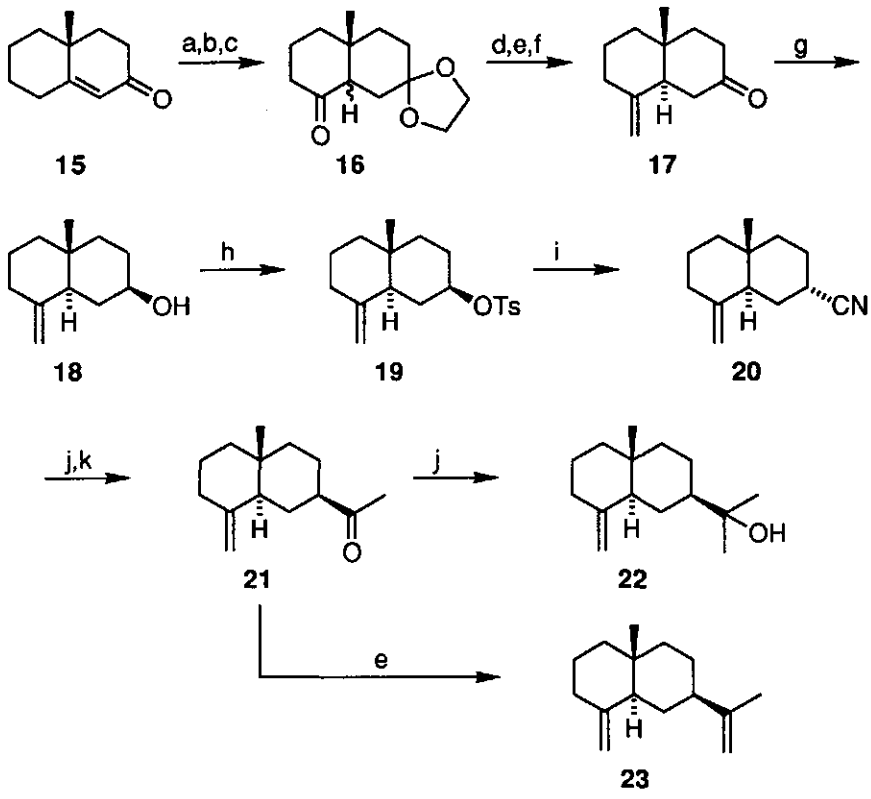


[a] (a) NaH, THF; (b) ozone, CH_2Cl_2, CH_3OH; (c) HCl, AcOH.

Ando synthesized both α and β C-7 substituted intermediates *via* the Robinson annulation reaction starting from (-)-dihydrocarvone **5**.[7] For the synthesis of the β C-7 compound **13**, the Robinson annulation product **14** was isolated in 51% based upon consumed **5**. Ozonolysis of the double bond gave an α-acetyl group which was equilibrated in the dehydration reaction to the desired β position (Scheme 2.3).

Other applications for the synthesis of eudesmanes were directed *via* intermediates in which the three-carbon side chain was introduced at a later stage,[1,2,3,8] with the possibility for C-7 equilibration to the more stable

Scheme 2.4[a]



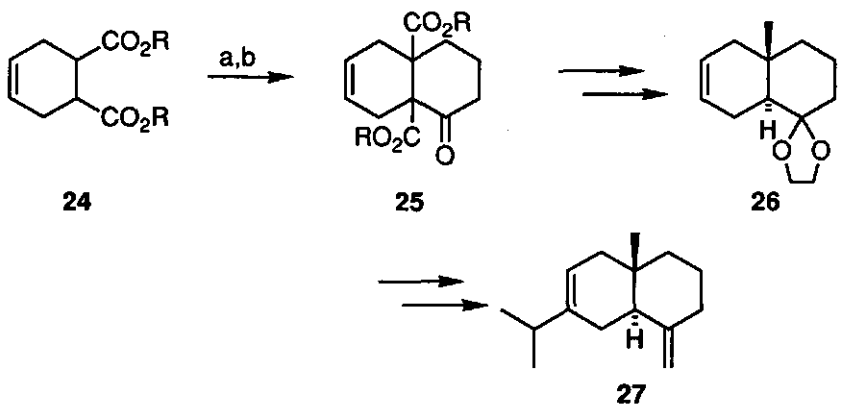
[a] (a) glycol, *p*-TsOH, toluene; (b) B_2H_6, THF; H_2O_2, NaOH; (c) Jones reagent, acetone; (d) $NaOCH_3$, CH_3OH (e) $Ph_3P{=}CH_2$, DMSO; (f) HCl, acetone/water; (g) $LiAlH_4$, ether; (h) *p*-TsCl, pyridine; (i) NaCN, N-methyl-pyrrolidone; (j) CH_3Li, ether; (k) hydrolysis.

β configuration. An example of this approach has been described by Marshall[9] (Scheme 2.4). In this approach the Robinson annulation product **15** was converted into enone **17** in a six steps reaction sequence. The enone **17** was reduced with $LiAlH_4$ and the resulting alcohol **18** was converted into the α nitril **20** *via* substitution of the β *p*-toluenesulfonate ester **19**. The related β acetyl **21** was obtained through treatment of the α nitril **20** with CH_3Li and subsequent hydrolysis. Treatment of **21** with CH_3Li gave β-eudesmol **22**, while Wittig olefination of **21** gave β-selinene **23**.

In our laboratory a more efficient transformation of **15** to **17** was developed,[10] which will be discussed in chapter 4.

Garratt and Porter reported an annulation reaction of the vicinal diester **24** and ethyl 4-bromobutanoate to the decalin **25**[11] (Scheme 2.5). Removal

Scheme 2.5[a]



24 **25** **26**

27

[a] (a) LDA, HMPA, THF, -78°C; (b) $Br(CH_2)_3COOEt$, THF.

of the C-5 ester group and conversion of the other one into an angular methyl substituent gave a carbon skeleton **26** suitable for elaboration into an eudesmane. The ethylene ketal can be converted into the exocyclic methylene group. The double bond provides a site for an indirect alkylation. In this way vetiselinene **27** was synthesized from **25** in an eleven steps reaction sequence in an overall yield of only 1.9 %.

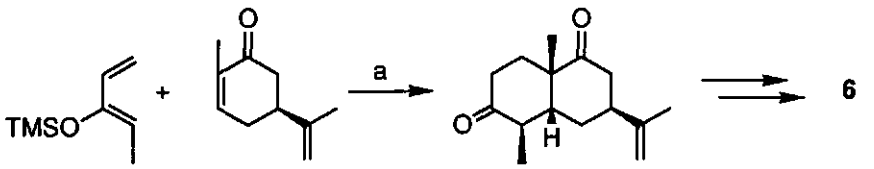
An annulation method *via* a consecutive acylation-cycloalkylation step has been used in the synthesis of neointermedeol **III** (see paragraph 2.2.3).

2.1.2 Cycloaddition Reactions

2.1.2.1 [4+2]Cycloaddition Reactions

The intermolecular Diels-Alder reaction for assembling angularly methylated decalins from substituted cyclohexenones has found limited application in the past. This is due to the known reluctance of α- and especially β-alkyl substituted cyclohexenones to react with dienes. The synthesis of (+)-α-cyperone **6** *via* an intermolecular Diels-Alder reaction as the key step has been provided by Haaksma[12] (Scheme 2.6). The Lewis acid catalyzed Diels-Alder reaction between (+)-carvone **28** and the silyloxydiene **29** followed by hydrolysis afforded the *cis*-fused decalin **30**. Compound **30** was converted into **6** in a seven steps reaction sequence. The overall yield of (+)-α-cyperone was 37% starting from (+)-carvone.

Scheme 2.6[a]



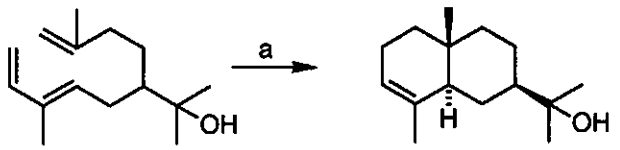
29 **28** **30**

[a] (a) $EtAlCl_2$, toluene; H^+.

On the other hand, the intramolecular Diels-Alder reaction for assembling the eudesmane skeleton has found increasing applications. It should be noted that the overall efficiency is somewhat overshadowed by the problems encountered in the synthesis of the required triene precursors. However, the benefits of the intramolecular Diels-Alder reaction are enormous. It effects an one step cyclization of an acyclic triene to a fused bicyclic system. It offers heightened reactivity of the substrates in comparison with the intermolecular reaction components as a consequence of entropic activation. Often the geometric constrains imposed on suchs systems cause the adoption of unusual transition states, and normally inaccesible stereoisomers may be produced. For example, triene **31** underwent smooth cyclization to a mixture

of four stereoisomers with α-eudesmol **32** as the major product[13] (Scheme 2.7).

Scheme 2.7[a]

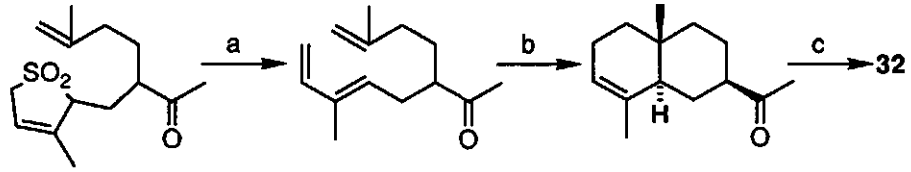


31 **32**

[a] (a) methylene blue, toluene, 195°.

Another approach *via* an intramolecular Diels-Alder reaction was reported by Chou.[14] The pyrolysis of the isoprenyl sulfone derivative **33** at 350 °C yielded the triene **34**. Diels-Alder reaction of triene **34** gave the *trans*-fused decalin **35**, which was converted into α-eudesmol **32** (Scheme 2.8).

Scheme 2.8[a]



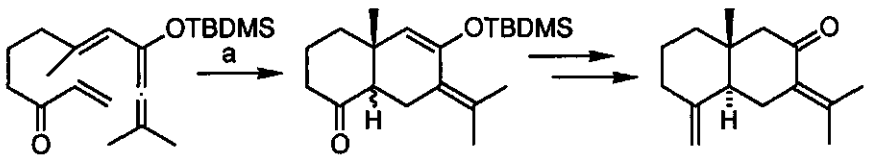
33 **34** **35**

[a] (a) 350°C; (b) toluene, sealed tube, 170°C; (c) CH_3MgBr, THF.

Conjugated allenes may act as dienes, but the Diels-Alder reaction of such substrates has a drawback with respect to the stereoselectivity. The intramolecular Diels-Alder reaction of enone silyloxyvinylallene **36** afforded the enol silylether **37** as a 1:1 mixture of *cis*- and *trans*-isomers[15] (Scheme 2.9). The use of enantiomerically pure acyclic precursors in intramolecular Diels-Alder reactions was described by Caine and Stanhope.[16] In this sequence (+)-carvone **28** was converted into a mixture of geometric isomers of α-phenylsulphonyl-ketone **39** which underwent Diels-Alder reaction to a mixture of oxo-selinenes **40** (Scheme 2.10). A Wolff-Kishner reduction

afforded a mixture of selinenes **41** which could be separated by preparative GC.

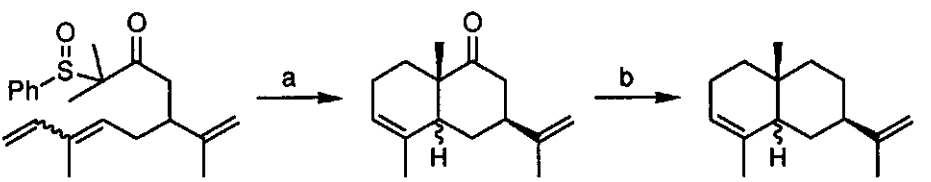
Scheme 2.9[a]



36 **37** **38**

[a] (a) $EtAlCl_2$, CH_2Cl_2.

Scheme 2.10[a]



39 **40** cis/trans = 1/2 **41**

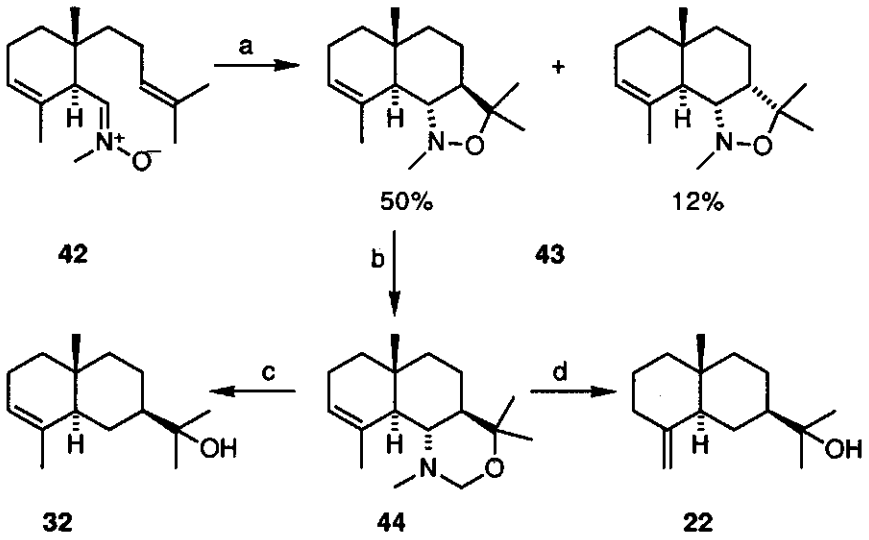
[a] (a) hydroquinone, toluene, sealed tube, 150°C; (b) triethylene glycol, N_2H_4, KOH.

2.1.2.2 [3+2]Cycloaddition Reactions

The [3+2]cycloadditions used for the construction of decalins, are dominated by the concerted 1,3-dipolar additions. The usefulness of these reactions is quite limited, since elimination of the heteroatom(s) must be accomplished afterward, and an intramolecular version is usually required. The serviceability of this reaction is the addition of nitrones to double bonds to yield isoxazolidines. The synthesis of α- and β-eudesmol **32** and **22**, which have been synthesized from the nitrone **42**,[17] is an example of this [3+2]cycloaddition (Scheme 2.11). Intramolecular nitrone-olefin cycloaddition of **42** afforded a mixture of C-7 stereoisomers of isoxazolidine **43**, of which the major isomer *via* the oxazine intermediate **44** could be

converted into **32** and **22**. Interesting was that the quaternization in anhydrous sulfolane and subsequent reduction led to mainly α-eudesmol **32**. The same reaction sequence gave rise to β-eudesmol **22** when the quaternary ammonium salt was formed in technical sulfolane.

Scheme 2.11[a]



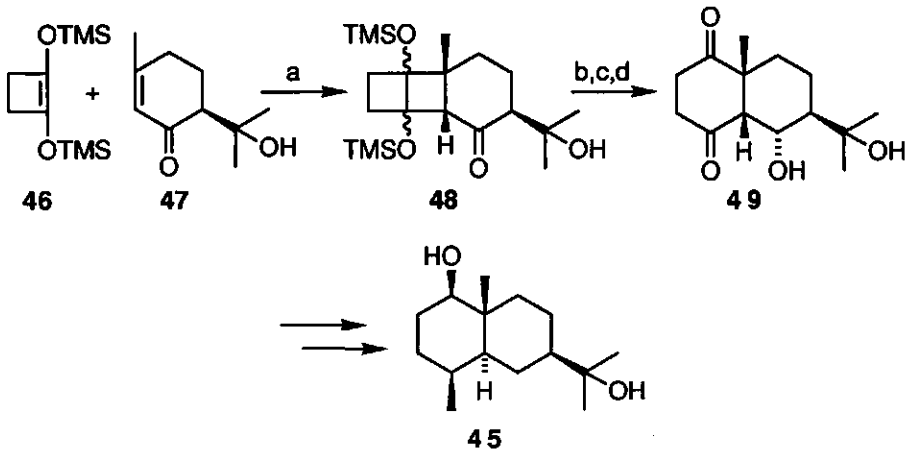
[a] (a) toluene, 90°C; (b) CH_3I; NaOH, CH_3OH; (c) anhydrous sulfolane, CH_3I; Li, NH_3 ; (d) technical sulfolane, CH_3I; Li, NH_3.

2.1.2.3 [2+2]Cycloaddition Reactions

The facile manipulation of the cyclobutane ring has been originated several approaches in which the eudesmane skeleton has been constructed *via* an enone-alkene [2+2]photocycloaddition/α-diol cleavage reaction sequence.[18,19,20]

For the synthesis of (+)-balonitol **45**,[18] 1,2-bistrimethylsilyloxycyclobutene **46** was annulated to the optically active 3-methylcyclohex-2-enone derivative **47** upon radiation at 350 nm to afford the adduct **48** (Scheme 2.12). Sequential reduction, desilylation, and α-diol cleavage transformed **48** into the dione **49**. A five steps reaction sequence was used to convert **49** into (+)-balonitol **45**.

Scheme 2.12[a]



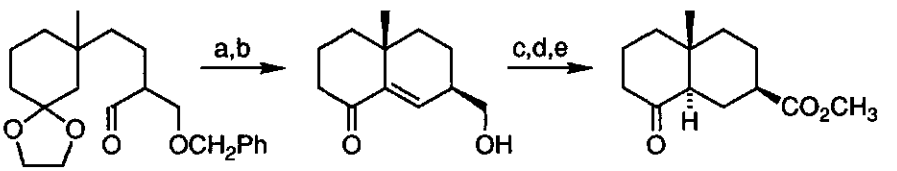
46 47 48 49 45

[a] (a) hυ, pentane; (b) $LiAlH_4$, ether; (c) HCl, ether, water; (d) O_2, CH_3OH.

2.1.3 Intramolecular Cyclization Reactions

In this section several approaches *via* intramolecular cyclizations are described. Kawamata[21] reported the intramolecular aldol condensation of acetal aldehyde **50**. Subsequent cleavage of the benzyl ether afforded enone **51** in only 28% yield (Scheme 2.13). The enone **51** was converted into ester **52**, which was used as an intermediate in the synthesis of β-eudesmol **22**.[22] The possibility to convert β-eudesmol **22** into neointermedeol **III**, as the authors suggest, is far from ideal (see paragraph 2.2.3).

Scheme 2.13[a]

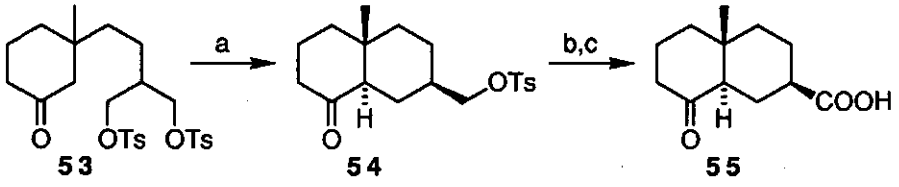


50 51 52

[a] (a) HCl, THF; (b) 10%-Pd/C, EtOH-EtOAc; (c) PCC, CH_2Cl_2; (d) Jones reagent, acetone; (e) CH_2N_2, ether.

The base catalyzed cyclization of ditosylate **53** afforded diastereo-selectively the β C-7 substituted ketone **54**[23] in 56% yield (Scheme 2.14). This compound was converted into keto acid **55**, which was used in the synthesis of β-eudesmol **22**.[22]

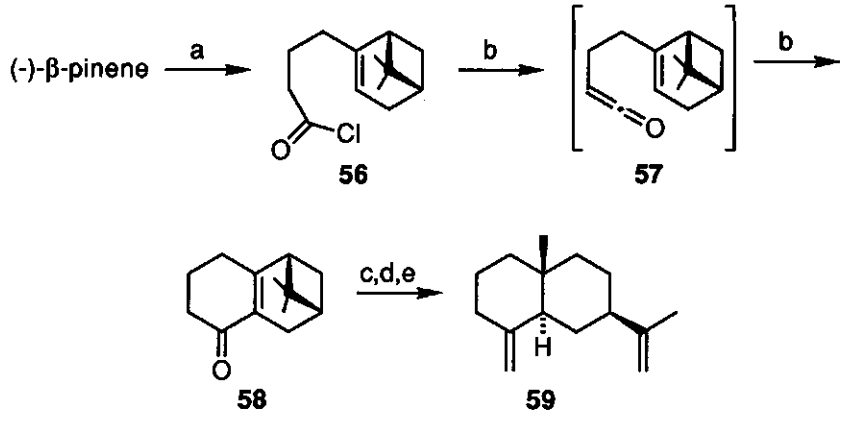
Scheme 2.14[a]



[a] (a) Na-*t*-pentoxide, benzene; (b) NaOAc, DMF, K_2CO_3, CH_3OH; (c) PDC, CH_2Cl_2.

The cyclization of the ene adduct **56** from (-)-β-pinene and acryloyl chloride was mediated by an intramolecular ene reaction involving ketene **57**.[24] The product **58**, which had undergone conjugation, was used as a precursor for (+)-β-selinene **59**. Thermolytic cleavage of **58** followed by

Scheme 2.15[a]



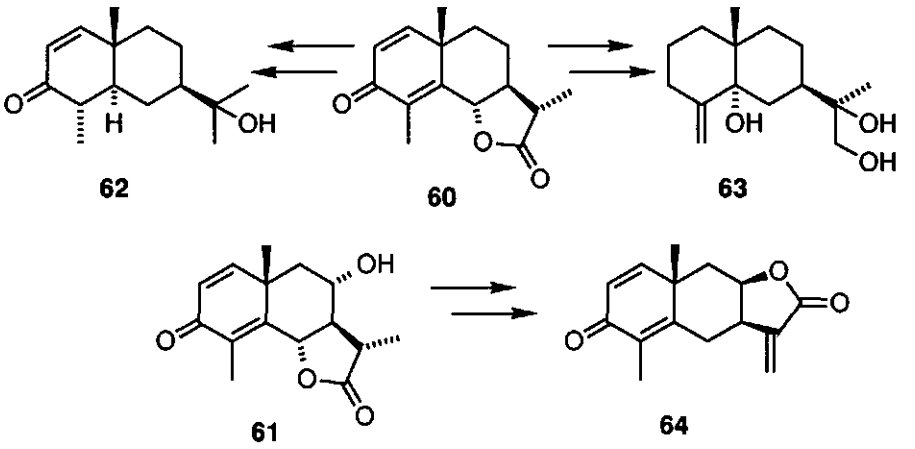
[a] (a) acryloyl chloride, 70°C; (b) Bu_3N, 150 °C; (c) 265°C; (d) $(CH_3)_2Li_2Cu(I)I$, ether; (e) $Ph_3P{=}CH_2$.

methyllithium cuprate addition and a Wittig reaction completed the reaction sequence (Scheme 2.15). Pure **59** could be isolated from the product mixture with preparative GC.

2.1.4 Transformations of Natural Sesquiterpenes

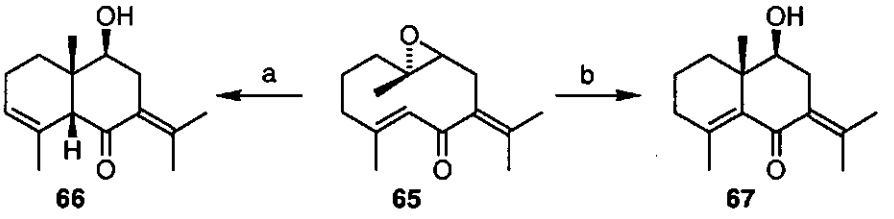
The eudesmanolides (-)-α-santonin **60** and (-)-artemisin **61** have been used in the synthesis of several eudesmanes e.g. (+)-4-*epi*-aubergenone **62**,[25] (+)-kudtriol **63**,[26] and the eudesmanolide (+)-yomogin **64**[27] (Scheme 2.16).

Scheme 2.16



Cyclization of germacrene derivatives offers an attractive method to construct the eudesmane skeleton. This method has found little application because of the scarcity of suitable germacrene derivatives. Isogermacrone

Scheme 2.17[a]

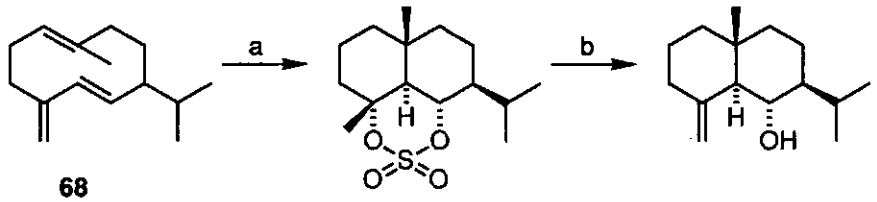


[a] (a) BF_3·ether, etherate; (b) NaOEt.

epoxide **65** underwent acid- and base-induced transannular cyclization to yield the eudesmane compounds **66** and **67**, respectively[28] (Scheme 2.17).

Reaction of germacrene-D **68** with H_2SO_4 afforded an eudesmane-4,6-diol cyclic sulfate **69**[29] in only 4.5% yield (Scheme 2.18). Treatment of **69** with alcoholic KOH gave junenol **70**.

Scheme 2.18[a]



68 **69** **70**

[a] (a) concd. H_2SO_4, ether, 5°C; (b) 10% KOH, EtOH.

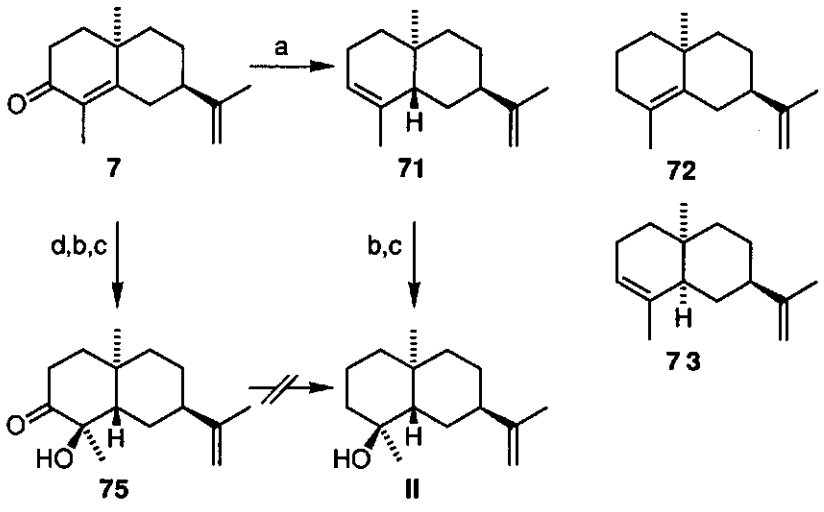
2.2 REPORTED SYNTHESIS OF EUDESM-11-EN-4-OLS

2.2.1 Total Synthesis of Intermedeol II

Two different research groups have synthesized intermedeol **II** at about the same time in almost the same way. Both groups started with (-)-7-*epi*-cyperone **7** which was synthesized from (-)-carvone. In the first approach a Wolff-Kishner reduction of **7** gave a mixture of the dienes **71**, **72**, and **73**[30] (Scheme 2.19). The diene **71**, necessary for the synthesis of **II**, could be isolated from this mixture in only 13% yield. Epoxidation of **71** followed by reduction gave a mixture of alcohols from which an analytical sample of **II** could be isolated after preparative GC. Huffman et al.[31] synthesized **71** starting from **7** in a more convenient way (Scheme 2.20), but again the conversion of **71** into intermedeol **II** was very problematic.

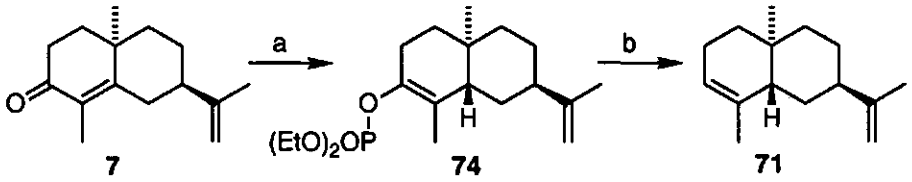
A second approach tried by both groups ended with ketone **75**. All efforts to remove the carbonyl group of **75** led to decomposition (Scheme 2.19).

Scheme 2.19[a]



[a] (a) triethylene glycol, N_2H_4, KOH; (b) *m*-CPBA, CH_2Cl_2; (c) $LiAlH_4$, THF; (d) Li, NH_3, *t*-BuOH, Ac_2O.

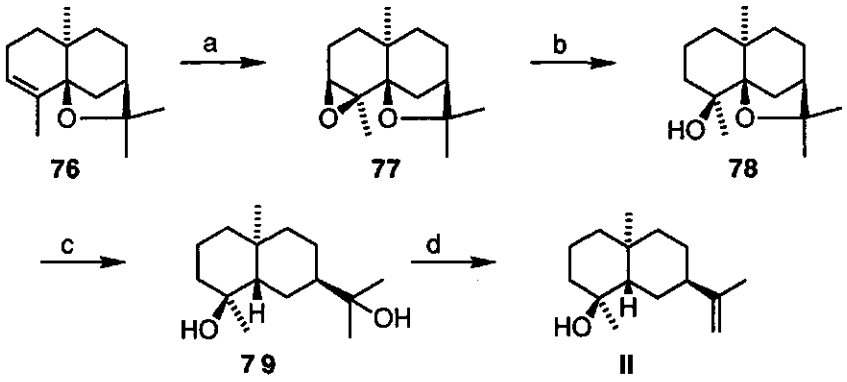
Scheme 2.20[a]



[a] (a) Li, NH_3, ether; $(EtO)_2P(O)Cl$; (b) Na, NH_3, *t*-BuOH.

A third method, reported by Huffman,[31] started from α-agarofuran **76** (Scheme 2.21). The reaction sequence involved conversion of **76** into the epoxide **77**. Reduction of **77** with $LiAlH_4$ gave the alcohol **78**. The latter compound afforded diol **79** after reduction with Li in $EtNH_2$. Partial dehydration of **79** gave a mixture of five compounds from which an analytical sample of **II** could be isolated after preparative GC in poor yield.

Scheme 2.21[a]

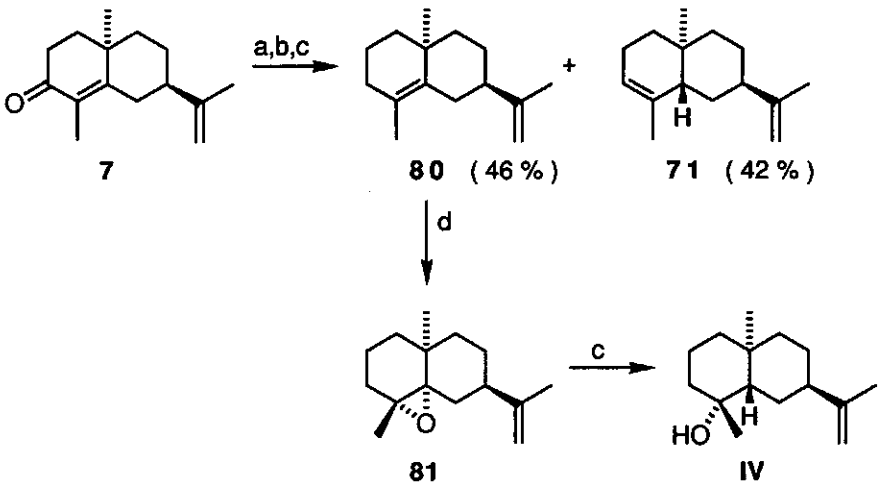


[a] (a) *m*-CPBA, CH_2Cl_2; (b) $LiAlH_4$, ether; (c) Li, $EtNH_2$; (d) 2% quinoline on Al, 192°C.

2.2.2 Total Synthesis of Paradisiol IV

(-)-7-*epi*-Cyperone **7** has also been used in the synthesis of paradisiol **IV**.[31] In a three steps reaction sequence **7** was converted into a ca. 1:1 mixture of the dienes **71** and **80**. After separation, **80** was converted *via* the epoxide **81** into paradisiol IV in 33% overall yield (Scheme 2.22).

Scheme 2.22[a]



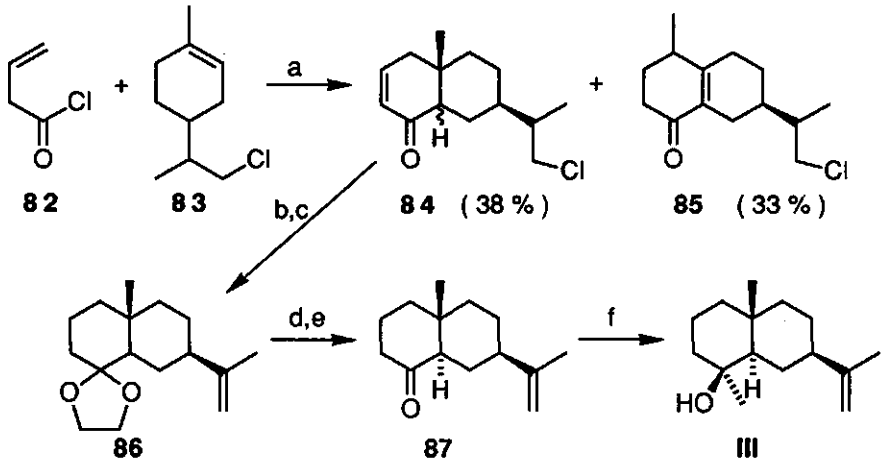
[a] (a) $LiAlH_4$, THF; (b) Ac_2O, pyridine; (c) Li, NH_3, ether; (d) *m*-CPBA, CH_2Cl_2.

2.2.3 Total Synthesis of Neointermedeol **III**

An original annulation method used in the synthesis of eudesmanes is reported by MacKenzie[32] (Scheme 2.23). Condensation of vinylacetylchloride **82** with (+)-9-chloro-1-*p*-menthene **83**, followed by distillation and chromatography, gave the enones **84** (38%) and **85** (33%). Catalytic hydrogenation of **84** followed by ketalization, dehydrohalogenation, and hydrolysis afforded ketone **87**. (-)-Neointermedeol **III** was obtained from **87** upon treatment with CH_3MgI in an overall yield of 29% from **84**.

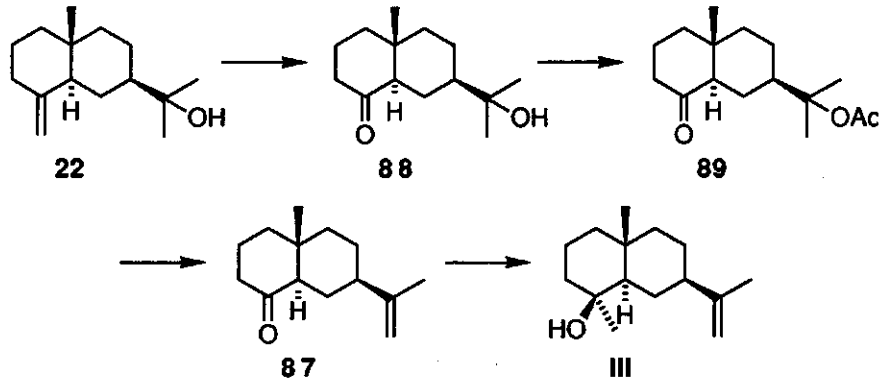
Another synthesis of **III** started with β-eudesmol **22**[33] (Scheme 2.24). Ozonolysis of **22** afforded the ketone **88** which was converted into the acetate **89**. Pyrolysis of the acetate **89** at 400 °C gave the ketone **87** which upon treatment with CH_3MgCl produced **III**. No yields and reaction conditions were reported in this article.

Scheme 2.23[a]



[a] (a) $AlCl_3$, CH_3NO_2; (b) H_2/Pt, AcOH; (c) glycol, benzene, H^+; (d) *t*-BuOK, DMSO; (e) H^+, H_2O, dioxane; (f) CH_3MgI, ether.

Scheme 2.24

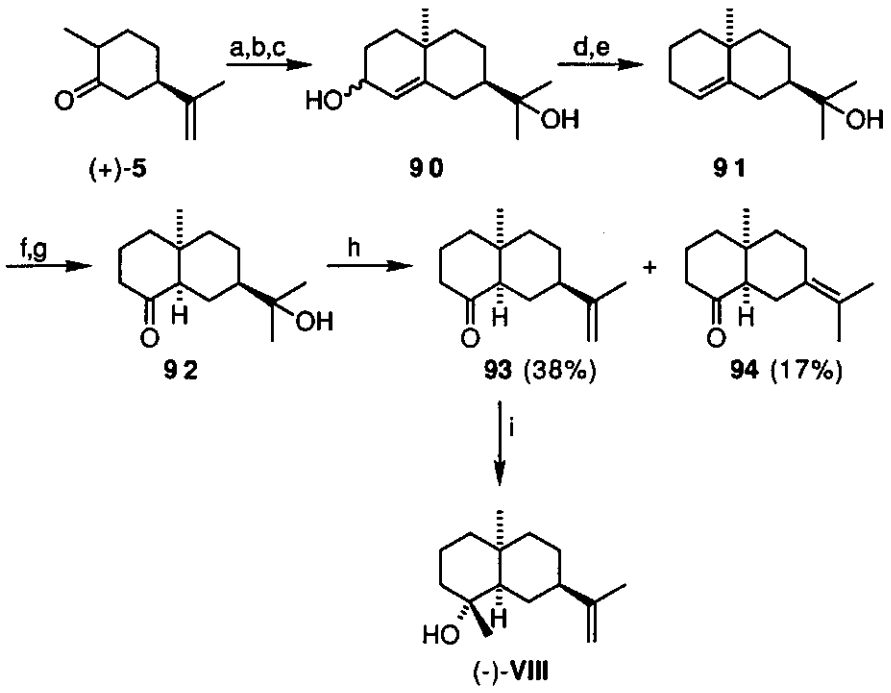


2.2.4 Total Synthesis of 5-*epi*-Paradisiol **VIII**

In an attempt to synthesize amiteol **V**, Baker et al.[34] reported the synthesis of 5-*epi*-paradisiol **VIII** (Scheme 2.25). In an eight steps reaction sequence (+)-dihydrocarvone **5** was converted into a 2:1 mixture of ketones **93** and **94**, respectively, in an overall yield of 3.5%. After separation by means of

preparative HPLC, a Grignard reaction of ketone **87** with CH_3MgI gave **VIII** in 33% yield, beside 52% of the starting material.

Scheme 2.25[a]



[a] (a) $NaNH_2$, $ClCH_2CH_2COCH_3$, THF; concd HCl, EtOH; (b) *m*-CPBA, CH_2Cl_2; (c) $LiAlH_4$, ether; (d) Ac_2O, pyridine; (e) Li, NH_3; (f) B_2H_6, THF; H_2O_2, NaOH; (g) PCC, CH_2Cl_2; (h) $SOCl_2$, pyridine, 0°C; (i) CH_3MgI.

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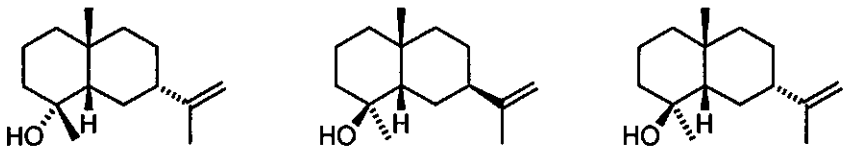
3. SCOPE OF THIS THESIS

The existing confusion around the structure elucidation of the natural stereoisomers of eudesm-11-en-4-ol, the poor availability of physical and spectral data, and their interesting biological activities have been among the reasons to initiate a synthetic program to all stereoisomers of eudesm-11-en-4-ol. This program includes the synthesis of the unnatural *cis*-fused 7-*epi*-amiteol **VI**, 5-*epi*-neointermedeol **VII**, and 5-*epi*-paradisiol **VIII** (Figure 3.1).

Figure 3.1

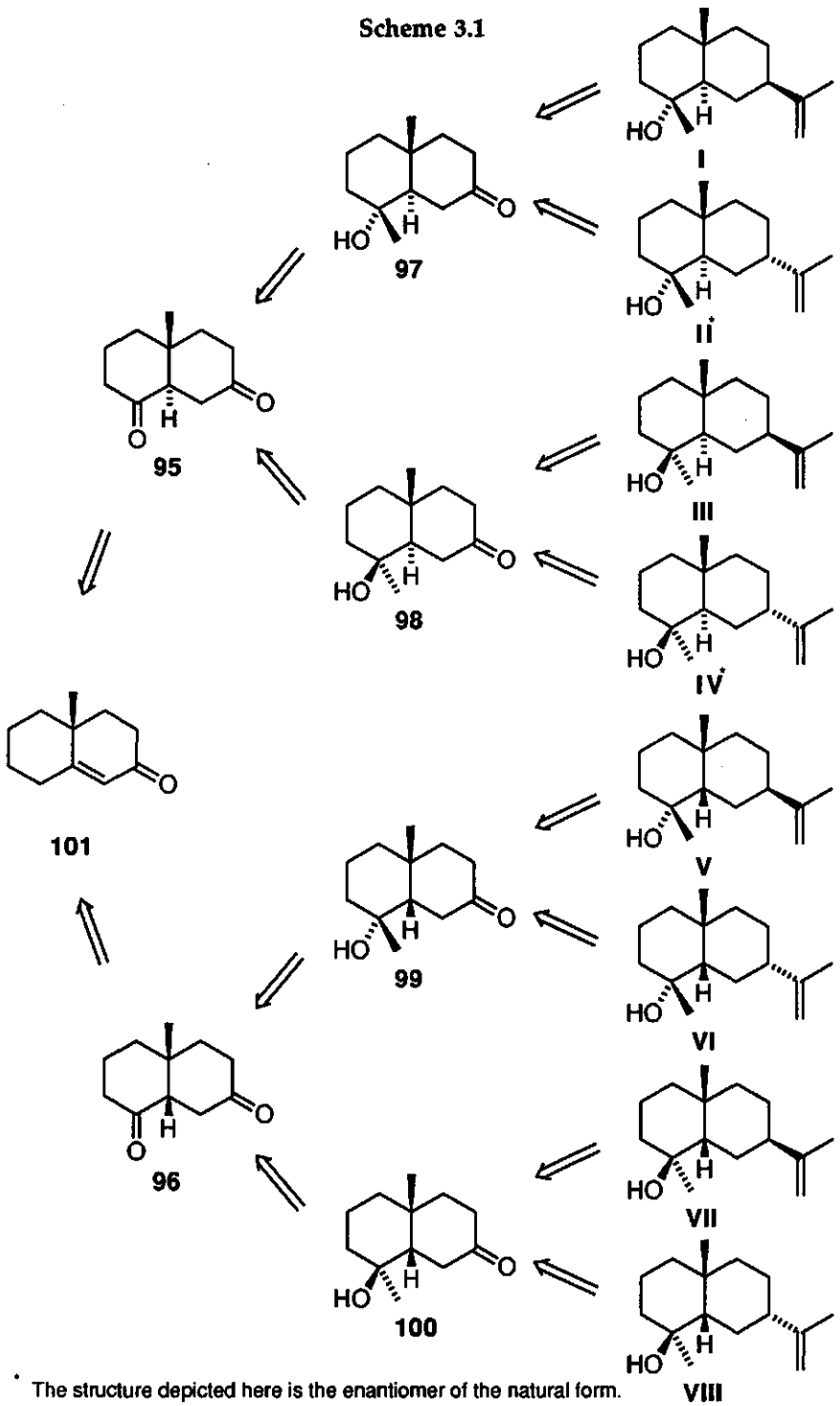


VI **VII** **VIII**

Most of the reported total syntheses of eudesm-11-en-4-ols proceed in low overall yields (see paragraph 2.2). Therefore, a general and more efficient synthesis of the eudesm-11-en-4-ols is desirable.

At our laboratory an easy synthesis of the *trans*- and *cis*-fused diones **95** and **96**, respectively, has been developed. These diones are attractive starting materials in the synthesis of all eight stereoisomers of eudesm-11-en-4-ol. The strategy for their synthesis is outlined in scheme 3.1, which is also given on a supplementary sheet at the end of this thesis. The synthesis starts from enone **101**. A large scale synthesis of the diones **95** and **96**, and the stereocontrol on the C-5 bridgehead center is described in chapter 4. The C-7 carbonyl group in both diones can be selectively protected, and this feature allows a stereoselective introduction of the methylgroup at C-4 (Chapter 5). Well-established procedures are available for the introduction of a thermodynamically more stable equatorial 1-methylethenyl group in the *trans*- and *cis*-fused hydroxy ketones **97-100**. The solution for the problem expected for the introduction of an axial 1-methylethenyl group in these compounds, especially in the *cis*-fused hydroxy ketones **99** and **100**, is given in chapter 6. NMR and MM2 studies of the conformational behavior of the *cis*-fused compounds **V**, **VI**, **VII**, and **VIII** are described in chapter 7. In chapter 8 all spectral and physical data of the eudesm-11-en-4-ols are collected.

Scheme 3.1



* The structure depicted here is the enantiomer of the natural form.

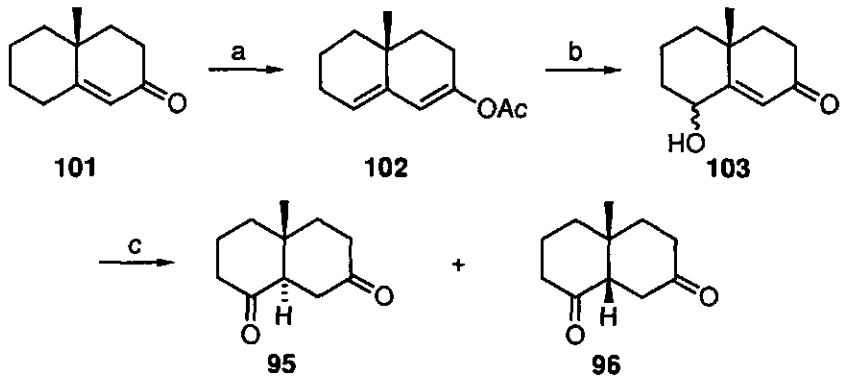
4. SYNTHESIS OF THE *TRANS*- AND *CIS*-FUSED HEXAHYDRO-4a-METHYL-1(2*H*),7(8*H*)-NAPHTHALENEDIONES

A general and efficient method for the stereoselective synthesis of the *trans*- and *cis*-fused diones **95** and **96** has been developed.[1] These diones are used as starting materials in the synthesis of all stereoisomers of eudesm-11-en-4-ol.

4.1 STEREOSELECTIVE SYNTHESIS OF THE *TRANS*- AND *CIS*-FUSED DIONES

The easily accessible enone **101** was prepared according to the alkaline Robinson annulation from 2-methylcyclohexanone and methyl vinyl ketone.[2] Treatment of **101** with acetic anhydride, NaI, and $(CH_3)_3SiCl$ afforded dienol acetate **102**[3] which was oxidized with Oxone in a mixture of methanol and water, buffered with $NaHCO_3$.[4] The resulting mixture of α and β alcohols was isomerized with HBr in ether (Scheme 4.1). Flash chromatography gave the *trans*-fused dione **95** and *cis*-fused dione **96** in 42% and 18% overall yield, respectively. This reaction sequence was performed on 0.5 mol scale.

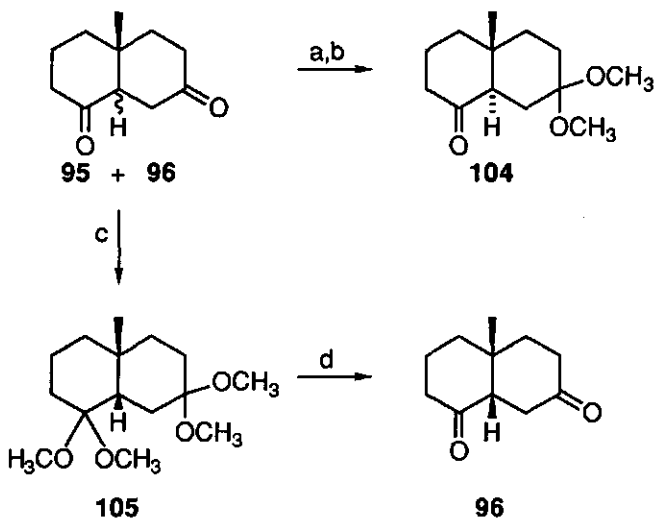
Scheme 4.1[a]



[a] (a) NaI, $(CH_3)_3SiCl$, Ac_2O; (b) Oxone, $NaHCO_3$, H_2O, CH_3OH; (c) HBr, ether.

Treatment of a mixture of **95** and **96** with trimethyl orthoformate in ***ether*** in the presence of a catalytic amount of acid gave a selective C-7 acetalization of both compounds. Subsequent epimerization with base afforded exclusively the C-7 monoacetalized *trans*-fused dione **104**[1a] (Scheme 4.2). This dione was used in the synthesis of the *trans*-fused eudesm-11-en-4-ols.

Scheme 4.2[a]



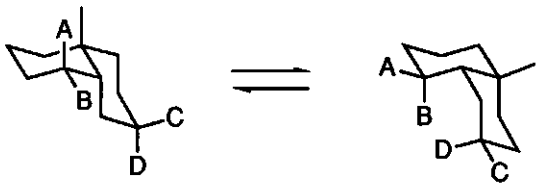
[a] (a) $(CH_3O)_3CH$, *p*-TsOH, ether; (b) $NaOCH_3$, CH_3OH; (c) $(CH_3O)_3CH$, H_2SO_4, CH_3OH; (d) PPTS, acetone, H_2O.

Treatment of the *trans*-fused dione **95** with trimethyl orthoformate in ***methanol*** in the presence of a catalytic amount of acid at room temperature for 3-5 days gave exclusively the *cis*-fused tetramethyl diacetal **105** in 70% yield (Scheme 4.2). Mild hydrolysis of **105** with PPTS in aqueous acetone for 1 h afforded the *cis*-fused dione **96** in quantitative yield. In this way the thermodynamically stable *trans*-fused dione **95** was transformed to the less favorable *cis*-fused dione **96**.

A further investigation of the *cis*-fused tetramethyl diacetal **105** was necessary to find an explanation for this transformation. It is well established that *cis*-fused decalin systems can occur in either the steroid **106a** or the nonsteroid **106b** conformation, or as an equilibrium mixture between both conformations.[5] Substituents which have the equatorial position in the

steroid conformer **106a**, are axially positioned in the nonsteroid conformer **106b**, and *vice versa* (Chart 4.1).

Chart 4.1

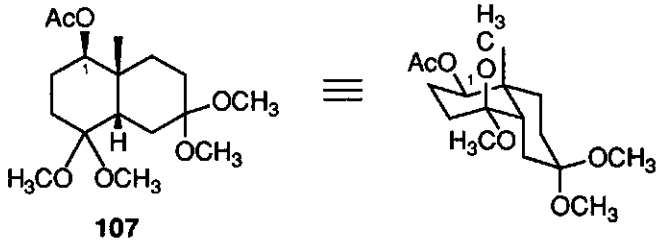


106 a (steroid) **106 b** (non-steroid)
105 a : A, B, C, D = OCH_3 **105 b** : A, B, C, D = OCH_3

The determination of the conformation of **105** with NMR was very difficult. However,force valence field calculations (MM2)[6] showed a conformational energy difference of 28 kJ/mol in favor of the steroid conformer **105a**. This means that the population of the nonsteroid conformer **105b** is reduced to less than 0.1% (Chart 4.1).

The C-1 substituted analogue of **105**, the acetate **107**, was synthesized to obtain additional support for these calculations. The couplings of 4.3 Hz and 11.9 Hz at δ 5.50 measured for the C-1 proton of **107** proves that this proton possesses the axial position. These observations correspond with the steroid conformation of **107** (Figure 4.1).

Figure 4.1

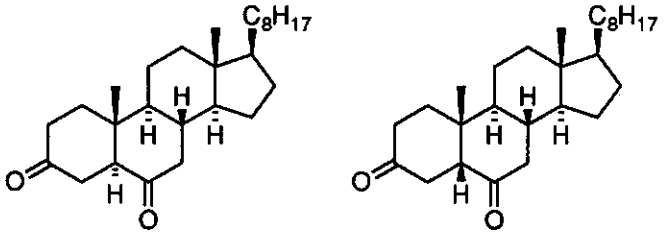


107

Also the fact that *trans*-fused cholestane-3,6-dione **108** could be transformed under the same reaction conditions to *cis*-fused dione **109**, which can only exist in the steroid conformation,[7] supports the MM2

calculations. On account of these data, it is reasonable to assume that **105** occurs in the steroid conformation.

Figure 4.2



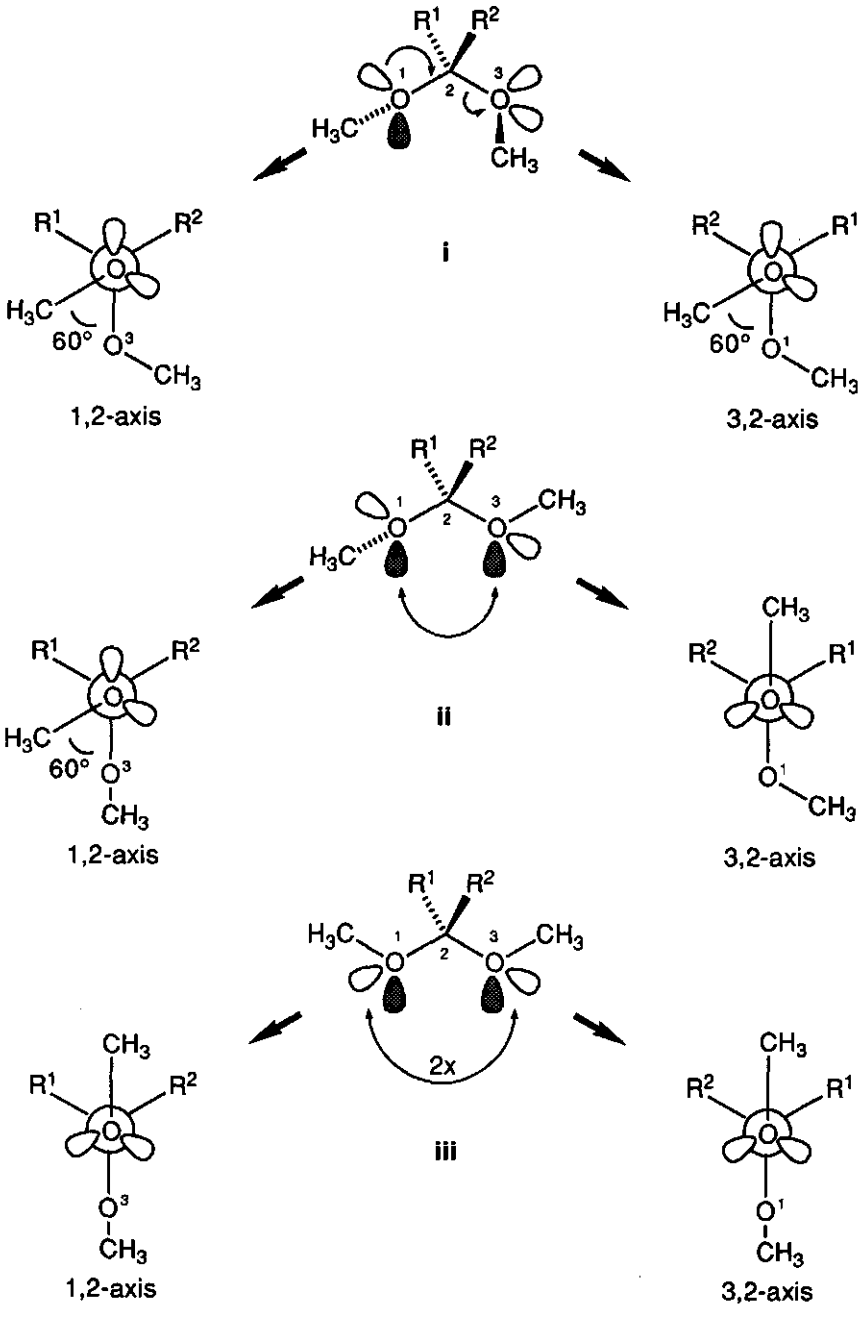
108 **109**

Somewhat surprisingly was that the calculated free energy difference between the *trans*-fused tetramethyl diacetal **110** and **105a** amounted 8 kJ/mol in favor of **105a**. When the methoxy groups in the MM2 calculations in **105a** and **110** were replaced by ethyl groups the *trans*-fused system was favored by 16 kJ/mol. These remarkable differences must be due to the anomeric effect of the C-4 dimethyl acetal function.

In general, the origin of the anomeric effect can be considered as stabilizing or destabilizing.[8,9] The dimethyl acetal group can take three basic staggered conformations **i-iii** (Figure 4.3). The stabilizing electronic effect of a dimethyl acetal group occurs when an electron pair of an oxygen atom has an antiperiplanar orientation toward the other methoxy group as depicted in conformer **i**. Stabilization will then be gained by partial transfer of an electron pair of one oxygen to the other, as shown by the arrows in **i**. The destabilizing electronic effect is due to repulsion by electron pair - electron pair interactions which is represented by the arrows in the conformers **ii** and **iii**. The conformation **i** has two stabilizing anomeric effects. Newman-projections across the 1,2- and 3,2-axis show antiperiplanarity between both the methoxy groups and electron pairs. As a result, the CH_3O^1-C^2-O^3 and CH_3O^3-C^2-O^1 torsial angles are both 60°.

The conformation **ii** has one stabilizing and one destabilizing anomeric effect. The stabilizing anomeric effect is shown by the Newman-projection across the 1,2-axis with a CH_3O^1-C^2-O^3 torsial angle of 60 °C. The destabilizing effect is due to electron pair - electron pair repulsion as represented by the arrow. The Newman-projection across the 3,2-axis shows the lack of

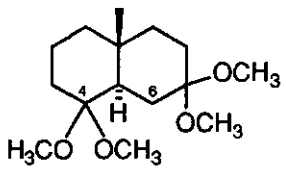
Figure 4.3



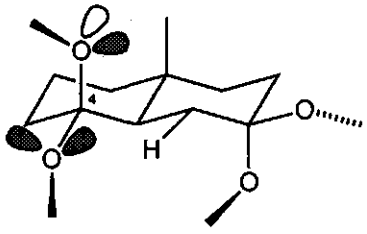
antiperiplanarity between the methoxy group and an electron pair of O-3. As a consequence, this CH_3O^3-C^2-O^1 torsial angle is 180°. Conformation **iii** possesses two electron pair - electron pair repulsions, thus two destabilizing effects. The Newman-projections across the 1,2- and 3,2-axis show that both torsial angles are 180°.

MM2 calculations reveal that **110a** is the most stable conformation of **110**. In this calculated conformation **110a** the dimethyldiacetal group at C-4 has torsial angles of 66° (stabilizing) and 173° (destabilizing) (Figure 4.4). This means that its conformation corresponds with conformer **ii**. The two other possible conformations **110b** and **110c** which both correspond with the electronically more favorable conformer **i**, show van der Waals repulsions between the α C-4 methoxy group and the α C-6 proton (**110b**) and between the β C-4 methoxy group and the β C-6 proton (**110c**) (Figure 4.4). These steric effects make **110b** and **110c** less favorable.

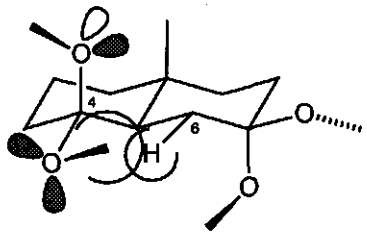
Figure 4.4



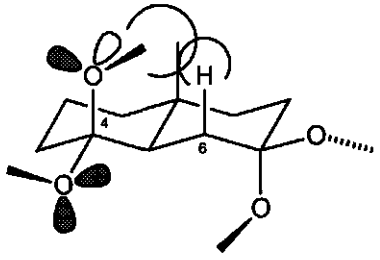
110



110 a



110 b

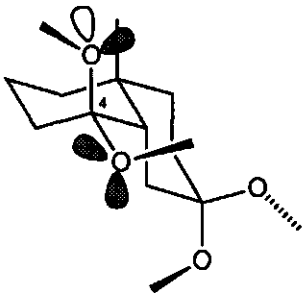


110 c

In contrast, the C-4 dimethyl acetal group in **105a** is not hindered by C-6 protons. Both methoxy groups can adopt the ideal conformation as depicted

in conformer **i**. The calculated torsial angles are 65° and 58° (both stabilizing) (Figure 4.5).

Figure 4.5

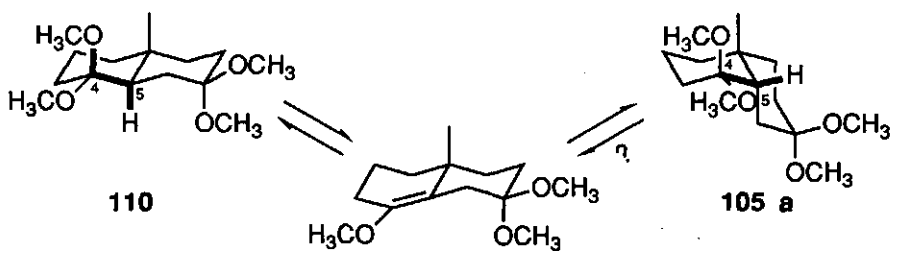


105 a

A kinetic effect can also play an important role in the transformation of **95** into **96**. The formation of **105a** can be explained in terms of an elimination-addition mechanism.[1c] The *trans*-fused **110** is equilibrated to **105a** *via* an acid-catalyzed anti elimination of the α C-5 proton and the β C-4 methoxy group (**110** to **111**) and renewed addition of methanol (**111** to **105a**). In the latter compound **105a** the β C-5 proton and the methoxy groups at C-4 lack the antiperiplanar orientation, which will decrease the rate of elimination of the reverse reaction (Scheme 4.3).

Further investigation will be necessary to establish whether the dynamic or kinetic effect, or a combination of both, is responsible for this *trans-cis* transformation.

Scheme 4.3



110 **111** **105 a**

In these reaction sequences the steoreoselective synthesis of *trans*- and *cis*-fused diones **95** and **96** are described. These compounds are ideal intermediates in the synthesis of all stereoisomers of eudesm-11-en-4-ol because of the differences in reactivity between the C-1 and C-7 carbonyl group (vide supra).

4.2 EXPERIMENTAL SECTION

NMR spectra were recorded on a Varian EM-390 at 90 MHz (^{1}H). Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). NMR multiplicities are recorded by use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad; J, coupling constant; Hz, hertz. Mass spectral data were determined on an AEI MS 902 spectrometer. Gas-liquid chromatography (GC) analyses were carried out on a Varian Vista 6000 gaschromatograph with a flame ionization detector and a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically with a Spectra-Physics integrator SP 4290. Column chromatography was performed using ICN alumina B-Super I. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Solvents were dried and distilled fresh by common practice. Product solutions were dried over anhydrous sodium sulfate, unless otherwise noted, prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

(4aα,8aβ)-(±)-Hexahydro-4a-methyl-1(2*H*),7(8*H*)-naphthalenedione (95) and (4aα,8aα)-(±)-Hexahydro-4a-methyl-1(2*H*),7(8*H*)-naphthalenedione (96). To a stirred mixture of 68.66 g (0.42 mol) of enone **101**[2] and 250 g (1.67 mol) of NaI in 600 mL of acetic anhydride, cooled to 0 °C, was added dropwise 208 mL (1.63 mol) of $(CH_3)_3SiCl$. The reaction mixture was stirred at 0 °C for 1 h, after which time the solvents were evaporated under reduced pressure. The remaining residue was taken up in 500 mL of saturated aqueous $NaHCO_3$, cooled to 0 °C, and 120 g of $Na_2S_2O_3$ was added. The mixture was allowed to stir at 0 °C for 1 h, after which time the evolution of carbon dioxide had ceased. The aqueous mixture was extracted with three 500-mL portions of EtOAc. The combined organic layers were dried and evaporated under reduced pressure to give 69 g of dienol acetate **102** (^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.00-2.60 (m, 10 H), 1.10 (s, 3 H), 2.15 (s, 3 H), 5.41 (t, 1 H), 5.70 (s, 1 H)). The crude **102** was taken up in a mixture of 900 mL of CH_3OH, and then 90.0 g

(1.07 mol) of $NaHCO_3$ was added. The reaction mixture was cooled to 0 °C, and then a solution of 430 g of Oxone in 1300 mL of water was added dropwise. After stirring at room temperature for 1 h, the reaction mixture was filtered, and the CH_3OH was evaporated under reduced pressure. The remaining aqueous mixture was extracted with five 250-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated under reduced pressure to give 69 g of a mixture of the α and β alcohols **103** (α alcohol: ^1H NMR ($CDCl_3$, 90 MHz) (major peaks) δ 1.23 (s, 3 H), 4.33 (m, 1 H); β alcohol: ^1H NMR ($CDCl_3$, 90 MHz) (major peaks) δ 1.47 (s, 3 H), 5.80 (s, 1 H)). The crude mixture **103** was taken up in 500 mL of ether, and 2.0 mL of concd HBr was added. The reaction mixture was stirred at room temperature for 2 h, and then diluted with 500 mL of saturated aqueous $NaHCO_3$. The two-phase mixture was separated, and the aqueous layer was extracted with three 300-mL portions of CH_2Cl_2. The combined organic layers were washed with 250 mL of brine, dried, and evaporated under reduced pressure. The remaining residue was flash chromatographed on silica gel (10:1 - 1:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, 32.04 g (42%) of *trans*-fused dione **95** and 13.32 g (18%) of *cis*-fused dione **96**. Spectroscopic data of **95** and **96** are shown below.

95: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.04 (s, 3 H), 1.15-2.79 (m, 13 H); mass spectrum *m/e* (relative intensity) 180 (M^+, 52), 151 (100), 123 (48), 97 (22), 67 (28), 55 (23), 41 (27).

96: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.33 (s, 3 H), 1.34-2.87 (m, 13 H); mass spectrum *m/e* (relative intensity) 180 (M^+, 100), 110 (45), 97 (73), 82 (40), 81 (27), 67 (37), 55 (53), 41 (38).

(4aα,8aβ)-(±)-Hexahydro-7,7-dimethoxy-4a-methyl-1(2*H*)-naphtalenone (104). The *trans*-fused dimethyl acetal **104** was synthesized from either a mixture of **95** and **96** or pure **95** as described.[1a]

Transformation of 95 into 96. To a stirred solution of 6.21 g (34.5 mmol) of *trans*-fused dione **95** in 30 mL of CH_3OH and 8 mL of trimethyl orthoformate, cooled to 0 °C, was added dropwise a solution of 0.15 mL (2.7 mmol) of concd H_2SO_4 in 10 mL of CH_3OH. After the solution was stirred at room temperature for 6 days, 0.58 mL (7.2 mmol) of pyridine was added. The reaction mixture was allowed to stir for 30 min, concentrated under reduced pressure, and then diluted with 200 mL of water. The aqueous solution was extracted with three 250-mL portions of CH_2Cl_2. The combined organic layers

were dried over K_2CO_3 and evaporated. The remaining residue was chromatographed on basic alumina (activity IV) (10:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 6.85 g of the corresponding *cis*-fused tetramethyl diacetal **105** (^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.73-2.67 (m, 13 H), 1.08 (s, 3 H), 3.14 (s, 3 H), 3.18 (s, 6 H), 3.22 (s, 3 H)). The so-obtained diacetal **105** was taken up in 200 mL of acetone, and 20 mL of water and 0.500 g (2.0 mmol) of PPTS were added. The reaction mixture was stirred at room temperature for 20 h and then diluted with 200 mL of saturated aqueous $NaHCO_3$. After evaporation of the acetone under reduced pressure, the remaining aqueous solution was extracted with three 250-mL portions of CH_2Cl_2. The organic layers were washed with brine and dried over a 1:1 mixture of Na_2SO_4 and K_2CO_3. Evaporation afforded 4.32 g (70%) of the *cis*-fused dione **96**, which was used without further purification for the next reactions.

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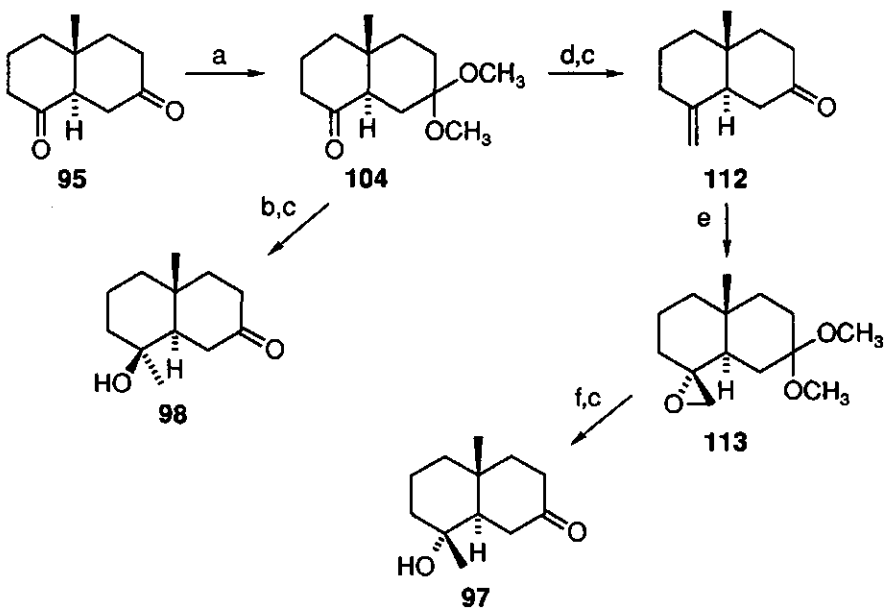
5. STEREOSPECIFIC SYNTHESIS OF THE *TRANS*- AND *CIS*-FUSED OCTAHYDRO-8-HYDROXY-4a,8-DIMETHYL-2(1*H*)-NAPHTHALENONES. CONFORMATIONAL ANALYSIS OF THE *CIS*-FUSED COMPOUNDS

In this chapter the conversion of the diones **95** and **96** into the corresponding hydroxy ketones **97, 98** and **99, 100**, respectively, is described. The stereochemistry and conformational analysis of the *cis*-fused hydroxy ketones **99** and **100** was determined by high-field NMR spectroscopy in combination with molecular mechanics calculations.

5.1 PREPARATION OF THE *TRANS*-FUSED HYDROXY KETONES

The carbonyl function at C-7 of the *trans*-fused dione **95** could be selectively protected with trimethyl orthoformate in the presence of *p*-TsOH at room temperature in ether as a solvent to give the *trans*-fused dimethyl

Scheme 5.1[a]



[a] (a) $(CH_3O)_3CH$, *p*-TsOH, CH_2Cl_2; (b) CH_3MgI, ether; (c) HCl, acetone, H_2O; (d) $Ph_3P{=}CH_2$, DMSO; (e) $(CH_3O)_3CH$, *p*-TsOH, CH_3OH, then MMPP; (f) $LiAlH_4$, THF.

acetal **104**.[1,2] Treatment of **104** with CH_3MgI and subsequent hydrolysis of the acetal function afforded the β-hydroxy ketone **98** in 80% yield as the sole product (Scheme 5.1). It is obvious that steric hindrance of the angular methyl group at C-10 prevents a β-attack of the Grignard reagent.

For the synthesis of the α-hydroxy ketone **97** the *trans*-fused dimethyl acetal **104** was treated with $Ph_3P{=}CH_2$ in DMSO. Isolation of a pure product was only possible after hydrolysis of the acetal function and in this way the olefinic ketone **112** was obtained.[3] A solution of **112** in CH_3OH was treated with MMPP in the presence of trimethyl orthoformate and a catalytic amount of acid to prevent a Baeyer-Villiger oxidation. The so-obtained crude epoxy acetal **113** was reduced with $LiAlH_4$, and after hydrolysis of the acetal function **97** was isolated in an overall yield of 69%.

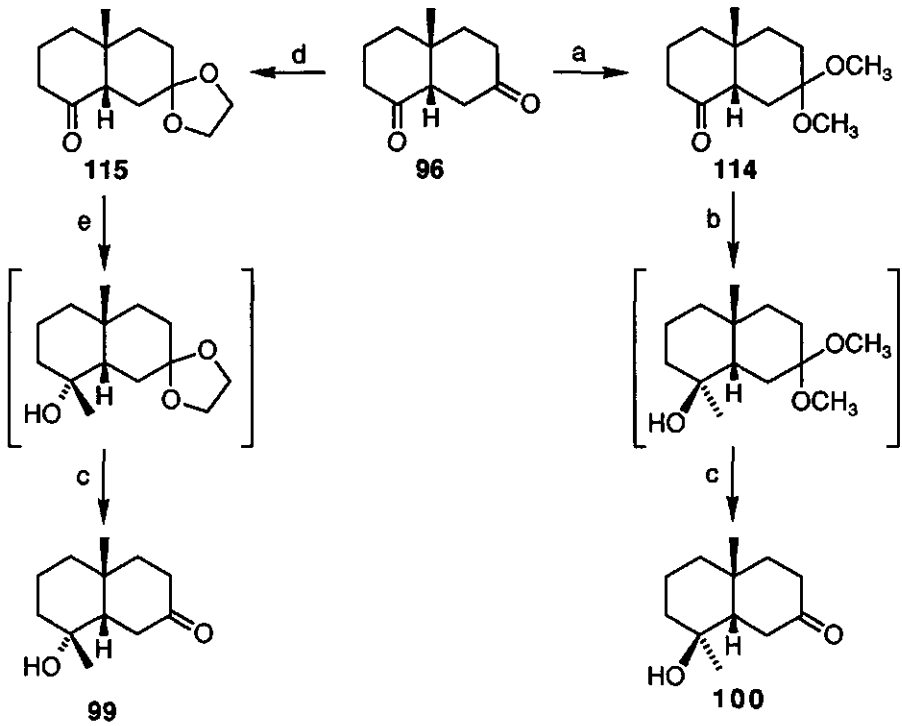
5.2 PREPARATION OF THE *CIS*-FUSED HYDROXY KETONES

The *cis*-fused dione **96** could be selectively protected with trimethyl orthoformate or 2-butanone dioxolane (MED) to afford **114** or **115**, respectively. When the *dimethyl* acetal **114** was treated with CH_3MgI in ether as a solvent at room temperature, no addition products could be detected. Only partial epimerization at C-5 was observed. Probably, the carbonyl group in **114** was converted into its enolate which upon hydrolysis gave the original ketone **114** together with its 5-epimer **95**. On the other hand, treatment of **114** with CH_3Li in THF as a solvent at -78 °C, under which conditions enolization is much less important,[4] followed by hydrolysis of the acetal function afforded exclusively the *cis*-fused β-hydroxy ketone **100** in 81% yield (Scheme 5.2). Treatment of the *ethylene* acetal **115** with CH_3Li in ether at room temperature gave, after hydrolysis, a 1:3 mixture of **99** and **100**, respectively. An almost complete reversal of the stereochemistry at C-4 was observed when **115** was treated with CH_3MgI in ether at room temperature. Hydrolysis of the ethylene acetal function gave the *cis*-fused α-hydroxy ketone **99** in 78% yield together with a small quantity (10%) of **100**.

In order to explain these results, we assume that the conformational equilibrium **A** (steroid) $\rightleftharpoons$ **B** (nonsteroid), as depicted in Chart 5.1, plays an important role in the selectivity of the addition reaction to **114** and **115**.

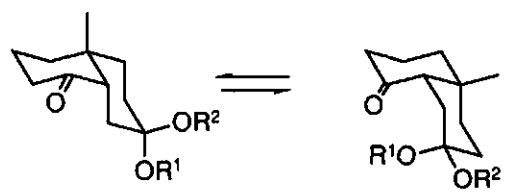
The more bulky dimethyl acetal group in **114** forces this compound into its steroid conformation **114A**. The ethylene acetal group in **115** exerts a lesser destabilizing effect on the nonsteroid conformation **115B**, as a result of

Scheme 5.2[a]



[a] (a) $(CH_3O)_3CH$, *p*-TsOH, CH_2Cl_2; (b) CH_3Li, THF, -78 °C; (c) HCl, acetone, H_2O; (d) MED, *p*-TsOH, CH_2Cl_2; (e) CH_3MgI, ether.

Chart 5.1



A (steroid) **B** (nonsteroid)

114 : $R^1 = R^2 = CH_3$

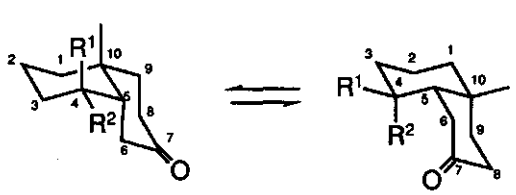
115 : $R^1 + R^2 = CH_2 - CH_2$

which **115** can exist as the equilibrium mixture **115A** $\rightleftharpoons$ **115B** at room temperature.[5] The selective formation of **100**, starting from **114**, must arise from an α attack of CH_3Li on the steroid conformer **114A**. This result indicates that the methyl group at C-10 controls the approach to the carbonyl group. Similar arguments can be used for the predominant formation of **100** starting from **115**. Treatment of **114** with CH_3MgI in ether at room temperature does not give any addition products, which leads to the conclusion that the carbonyl function in **114A** is too sterically hindered for reaction with the lesser nucleophilic and more bulky CH_3MgI. The observation that the *cis*-fused ethylene acetal **115** upon treatment with CH_3MgI under the same circumstances gives preferably the formation of **99** indicates that the addition of CH_3MgI must proceed from the β face of the nonsteroid conformer **115B**.[6,7]

5.3 CONFORMATIONAL ANALYSIS OF THE *CIS*-FUSED HYDROXY KETONES

For the structure elucidation of the *cis*-fused hydroxy ketones **99** and **100** two issues were important. Firstly, the configuration of the methyl and hydroxy group around C-4 had to be established. Secondly, since most *cis*-decalins are conformationally mobile,[8] the conformation of **99** and **100** had to be determined (**A** (steroid) or **B** (nonsteroid), see Chart 5.2). In order to solve these problems, the relevant ^1H and ^{13}C resonances of **99** and **100** were assigned using 1-D and 2-D NMR methods. Thus, ^1H assignments were established *via* ^1H - ^1H COSY measurements. The results are listed in Table 5.1.

Chart 5.2



A (steroid) **B** (nonsteroid)

99 : $R^1 = CH_3$, $R^2 = OH$
100 : $R^1 = OH$, $R^2 = CH_3$

Table 5.1. ^{1}H NMR Data (400 MHz) for Compounds 99 and 100[a]

proton on carbon no.[b]	100[c]	99[c]	99[d]
1[e]	1.6, m	1.57, m	1.52, m
	1.2, m	1.35, m	1.20, m
2	1.65, m, H_{ax}	1.80, m, H_{ax}	2.03, m, H_{ax}
	1.45, m, H_{eq}	1.35, m, H_{eq}	1.39, m, H_{eq}
3[e]	1.60, m	1.57, m	1.52, m
	1.35, m	1.35, m	1.20, m
5	1.72, dd	1.53, dd	1.26, dd (J = 1.8, 6.6 Hz)
6	2.45, dd	2.51, m	2.67, dd (J = 1.8, 15.8 Hz)
	2.36, dd		2.36, dd (J = 6.6, 15.8 Hz)
8	2.36, m	2.42, m	2.62, m(J = 1.9, 5.7, 15.5 Hz)
		2.30, m	2.39, m (J = 7.3, 13.0, 15.5 Hz)
9	1.90, m, H_{ax}	2.65, m, H_{ax}	2.94, m, H_{ax}
	1.45, m, H_{eq}	1.25, m, H_{eq}	1.16, m, H_{eq}
CH_3(10)	1.10, s	1.17, s	1.05, s[e]
CH_3(4)	1.25, s	1.22 s	1.06, s[e]
OH	–[f]	0.87, br s	0.76, br s

[a] Chemical shifts in ppm relative to the $CDCl_3$ singlet (δ 7.23) or C_6D_6 singlet (δ 7.40). [b] See Chart II. [c] Recorded in $CDCl_3$. [d] Recorded in C_6D_6. [e] Assignments for these protons are interchangeable. [f] Obscured by other resonances.

In principle, the conformation of **99** and **100** can be determined from the coupling constants $J_{H(5)H(6ax)}$ and $J_{H(5)H(6eq)}$, that is, if these compounds have one rigid conformation. As can be seen in Table 5.1, even at 400 MHz no coupling constant could be determined due to chemical shift equivalency of H(6) and H(8), except for **99** in C_6D_6. From these coupling constants, it can be estimated that **99** must possess the nonsteroid conformation **B** since the steroid conformation **A** requires a 180° angle between H(5) and H(6ax). This

would result in a coupling constant of at least 9 Hz, whereas the largest coupling constant measured is 6.6 Hz.

The nonsteroid conformation **B** for **99** is supported by three other facts: (i) Low-temperature ^{13}C measurements show that this compound exists essentially in one conformation (vide infra), which is a prerequisite for conformational analysis by coupling constants. (ii) A NOE-effect between H(2ax) and H(9ax) was observed, which is only possible in the nonsteroid conformation. (iii) Molecular mechanics calculations of the conformational equilibrium [**A** $\rightleftharpoons$ **B**], using the consistent valence force field,[9] showed a free energy difference of 18 kJ/mol for **99** (**99(B)** being the more stable conformer), and 4 kJ/mol for **100** in favor of **100(A)** as the stable conformer. In terms of conformational equilibria this means that the population of **99(A)** is reduced to less than 0.1%, rendering it essentially unobservable by ^{13}C NMR. The population of **100(A)** is approximately 80-90% depending upon the accuracy of the calculations.

Table 5.2. ^{13}C NMR Data (100 MHz) for Compounds 99 and 100 in $CDCl_3$[a]

carbon no.[b]	**99**[c]	**100**[c]	**100** (major)[d]	**100** (minor)[d]
1[e]	39.8	35.4		
2	17.3	18.8	19.2	17.9
3[e]	40.8	38.8		
4	71.9	73.0		
5	51.8	52.5	52.5	51.4
6	38.0	39.3		
7	213.0	212.9		
8	37.4	37.1		
9	32.1	36.1		
10	32.5	33.3		
CH_3(10)	29.0	29.3		
CH_3(4)	30.4	26.9	23.6	30.5

[a] Chemical shifts in ppm relative to the $CDCl_3$ triplet at δ 77.0. [b] See Chart II. [c] At 298 K. [d] At 221 K. [e] Assignments are interchangeable.

The results of the calculations are supported by ^{13}C NMR measurements. The assignments were established by 2-D NMR ^{1}H-^{13}C chemical shift

correlation measurements, and the results are listed in Table 5.2. Comparison of the data in Table 5.2 with those for two similar compounds (which only lack the hydroxy group at C-4) shows a good overall agreement.[10]

As expected, the measurements at lower temperatures (298 K down to 221 K) showed that the spectrum of **99** was essentially temperature independent, whereas for **100** exchange phenomena were observed. At 221 K, a major and minor form were seen (approximately 4:1). Comparison of the chemical shifts of the minor form with those for **99** shows that it has the nonsteroid conformation. Thus **100** preferentially adopts the steroid conformation **A**, in accordance with the calculations.

This left only the configuration around C-4 to be established. This was accomplished by NOE difference measurements with multiple irradiation.[11] Since **100** is in conformational equilibrium at room temperature, NOE data for this compound are hard to interpret because it would remain uncertain from which form the NOE effect originated.[12] Therefore, NOE difference measurements were only performed for **99**. Once the configuration around C-4 for this compound is known, it is assumed that, because of the chemical history of **99** and **100**, the other configuration can be assigned to **100**. Irradiation of the C-6 protons of **99** at δ 2.51 gives NOEs with both methyl groups at C-10 and C-4, as well as with H(5). Irradiation of H(9ax) at δ 2.65 gives NOEs with H(9eq), H(8eq), the hydroxyl proton, and with H(2ax). These data confirm that **99** exists in the nonsteroid conformation **B**, and are consistent with the assignment $R^1 = CH_3$, $R^2 = OH$ for **99**. This leaves $R^1 = OH$, $R^2 = CH_3$ for compound **100**.

In this chapter we have shown that stereocontrol on the C-4 stereoisomeric center in the *trans*- and *cis*-fused hydroxy ketones can be achieved. The conversion of the hydroxy ketones into the corresponding eudesm-11-en-4-ols will be described in the next chapter.

5.4 EXPERIMENTAL SECTION

Melting points were determined on an Olympus HSA melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Philips PU 9706 infrared spectrophotometer, and peak positions are expressed in cm^{-1}. NMR spectra were recorded on a Varian EM-390 at 90 MHz (^1H), a Bruker 200 E at 200 MHz (^1H) and at 50 MHz (^{13}C), and a Bruker AM-400 at 400 MHz (^1H) and at 100 MHz (^{13}C). Chemical shifts are reported

in parts per million (δ) relative to tetramethylsilane (δ 0.0). NMR multiplicities are recorded by use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad; *J*, coupling constant; Hz, hertz. COSY, ^{1}H-^{13}C correlation and NOE experiments were carried out on a Bruker AM-400. Typical parameters for the COSY-45 experiments are as follows: 90° pulse = 6 μs (5 mm selective probe), a spectral width of 900 Hz in t_1 and t_2 was used, and 128 experiments with 8 transients each were done. Before fourier transformation, zero filling was used once, and no window functions were applied. For the ^{1}H-^{13}C heteronuclear shift correlation spectra: 90° carbon pulse = 6 μs, 90° proton pulse = 11 μs (5 mm dual probe). Spectral width in t_1 = 800 Hz, in t_2 = 3787.9 Hz with a size of 256·1 K. A total of 128 experiments with 128 transients each were done. Delays used in the pulse sequence were 3.3 and 2.2 ms. Sine-bell window functions without phase shift were used for the fourier transformation. Mass spectral data were determined on either an AEI MS 902 spectrometer or a VG Micromass 7070 F spectrometer at 70 eV. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. Gas-liquid chromatography (GC) analyses were carried out on a Varian Vista 6000 gaschromatograph with a flame ionization detector and a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically with a Spectra-Physics integrator SP 4290. Column chromatography was performed using ICN alumina B-Super I or ICN alumina N-super I. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh).

Solvents were dried and distilled fresh by common practice. For all dry reactions, flasks were dried at 150 °C and flushed with dry nitrogen just before use, and reactions were carried out under an atmosphere of dry nitrogen. Product solutions were dried over anhydrous sodium sulfate, unless otherwise noted, prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. 2-Butanone dioxolane (MED) was prepared from 2-butanone as reported.[13]

(4aα,8α,8aβ)-(±)-Octahydro-8-hydroxy-4a,8-dimethyl-2(1*H*)-naphthalenone (98). To 200 mL of 0.6 M CH_3MgI in ether was added dropwise a solution of 7.51 g (33.2 mmol) of dimethyl acetal **104** in 100 mL of dry ether. The reaction mixture was allowed to stir at room temperature for 1 h. The excess CH_3MgI was then quenched by the careful addition of saturated aqueous NH_4Cl. After addition of 150 mL of water, the two-phase mixture was separated and the aqueous layer was extracted with three 100-mL portions of ether. The

combined organic layers were washed with brine, dried, and evaporated. The remaining residue was taken up in a mixture of 100 mL of acetone, and 4 mL of 5% aqueous HCl was added. The reaction mixture was stirred at room temperature for 45 min and diluted with 100 mL of saturated aqueous $NaHCO_3$. After evaporation of the acetone under reduced pressure, the remaining aqueous solution was extracted with three 100-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (3:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 5.90 g (80%) of **98**: mp 130-131 °C (from diisopropyl ether); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90-2.00 (m, 10 H), 1.06 (s, 3 H), 1.15 (s, 3 H), 2.10-2.60 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.75 (q), 17.75 (t), 29.69 (q), 33.29 (s), 37.90 (t), 38.01 (t), 40.38 (t), 40.66 (t), 42.12 (t), 50.49 (d), 71.25 (s), 213.03 (s); mass spectrum *m/e* (relative intensity) 196 (M^+, 84), 181 (30), 178 (16), 167 (37), 164 (21), 153 (49), 148 (100), 138 (47), 111 (81), 109 (74); calcd for $C_{12}H_{20}O_2$ (M^+) *m/e* 196.1463, found 196.1460. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.69; H, 10.27.

(4aα,8aβ)-(±)-Octahydro-4a-methyl-8-methylene-2(1*H*)-naphthalenone (112). The enone **112** was prepared from **95** as desribed.[2a]

(1α,4aβ,8aα)-(±)-Octahydro-7,7-dimethoxy-4a-methylspiro[naphthalen-1(2*H*),2'-oxirane] (113). To a stirred solution of 6.41 g (36.0 mmol) of methylene ketone **112** in 200 mL of CH_3OH were added 20 mL of trimethyl orthoformate and 0.222 g (1.13 mmol) of *p*-TsOH. The solution was allowed to stir at room temperature for 30 min, and then 20.2 g (40.8 mmol) of MMPP (magnesium monoperoxyphthalate) was added. The reaction mixture was stirred at room temperature for an additional 17 h, after which time 350 mL of 10% aqueous $Na_2S_2O_3$ and 200 mL of saturated aqueous $NaHCO_3$ were added. The aqueous solution was extracted with five 200-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over a 1:1 mixture of Na_2SO_4 and K_2CO_3, and evaporated. The crude epoxide **113** (8.00 g) (^1H NMR ($CDCl_3$, 90 MHz) δ 0.70-2.10 (m, 13 H), 0.87 (s, 3 H), 2.57 (m, 2 H), 3.10 (s, 3 H), 3.16 (s, 3 H)) was used without further purification for the next reaction.

(4aα,8β,8aβ)-(±)-Octahydro-8-hydroxy-4a,8-dimethyl-2(1*H*)-naphthalenone (97). To a stirred suspension of 2.94 g (77.0 mmol) of $LiAlH_4$ in 150 mL of dry THF, cooled to 0 °C, was added dropwise a solution of 8.00 g of crude epoxide

113 in 100 mL of dry THF. The reaction mixture was allowed to stir at room temperature for 24 h and then heated at reflux for 11 h. The excess $LiAlH_4$ was quenched at 0 °C by the careful addition of saturated aqueous Na_2SO_4. After addition of 300 mL of water, the two-phase mixture was separated, and the aqueous layer was extracted with four 150-mL portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue (8.91 g) was hydrolyzed as described for the synthesis of **97**. The workup and flash chromatography (4:1 - 2:1 petroleum ether (bp 40-60 °C)/EtOAc) gave 4.80 g (69% overall from **112**) of **97**: mp 55-56.5 °C (lit.[14] mp 57-58.5 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00-1.90 (m, 10 H), 1.06 (s, 3 H), 1.11 (s, 3 H), 2.05-2.65 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.72 (q), 20.03 (t), 21.83 (q), 34.28 (s), 37.74 (t), 38.04 (t), 39.93 (t), 42.66 (t), 43.32 (t), 53.76 (d), 71.61 (s), 212.03 (s); mass spectrum *m/e* (relative intensity) 196 (M^+, 100), 181 (21), 178 (23), 167 (38), 163 (19, 153 (53), 138 (56), 111 (98), 109 (96); calcd for $C_{12}H_{20}O_2$ (M^+) *m/e* 196.1463, found 196.1465.

(4aα,8aα)-(±)-Octahydro-7,7-dimethoxy-4a-methyl-1(2*H*)-naphthalenone (114). To a stirred solution of 6.23 g (34,6 mmol) of *cis*-fused dione **96** in 100 mL of CH_2Cl_2 were added 10 mL of trimethyl orthoformate and 0.340 g (1.78 mmol) of *p*-TsOH. The reaction mixture was stirred at room temperature for 45 min, after which time 0.160 g (2.35 mmol) of imidazole was added. The reaction mixture was allowed to stir for an additional 10 min and then concentrated under reduced pressure. The remaining residue was chromatographed on neutral alumina (activity II) (10:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 7.47 g (96%) of **114**: ^1H NMR ($CDCl_3$, 90 MHz) δ 0.77-2.67 (m, 13 H), 0.97 (s, 3 H), 3.17 (s, 3 H), 3.22 (s, 3 H). This material was sensitive to atmospheric moisture, and satisfactory analytical values could not be obtained.

(4aα,8α,8aα)-(±)-Octahydro-8-hydroxy-4a, 8-dimethyl-2(1*H*)-naphthalenone (100). To a stirred solution of 40 mL (64.0 mmol) of CH_3Li (1.6 M in ether), cooled to -78 °C, was added dropwise over a period of 30 min a solution of 2.25 g (10.0 mmol) of crude **114** in 100 mL of dry THF. When the addition was complete, the reaction mixture was allowed to stir at -78 °C for an additional 30 min. The excess CH_3Li was then quenched by 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 three 100-mL portions of EtOAc. The combined organic layers were washed with brine,

dried, and evaporated. The crude product (^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.65-2.10 (m, 14 H), 1.16 (s, 3 H), 1.20 (s, 3 H), 3.15 (s, 3 H), 3.20 (s, 3 H)) was hydrolyzed as described for the synthesis of **98**. The workup and flash chromatography (3:1 petroleum ether (bp 40-60 °C)/EtOAc) gave 1.59 g (81%) of **100**: ^{1}H NMR, see Table 5.1; ^{13}C NMR, see Table 5.2; mass spectrum *m/e* (relative intensity) 196 (M^+, 81), 181 (26), 178 (22), 167 (28), 161 (14), 154 (53), 138 (48), 111 (100), 109 (94); calcd for $C_{12}H_{20}O_2$ (M^+) *m/e* 196.1463, found 196.1464. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73,61; H, 10.08.

(4'aα,8'aα)-(±)-Octahydro-4'a-methylspiro[1,3-dioxolane-2,2'(8'*H*)-naphthalen]-8'-one (115). To a stirred solution of 5.57 g (30.9 mmol) of *cis*-fused dione **96** in 100 mL of CH_2Cl_2 were added 20 mL of MED, a catalytic amount of ethylene glycol, and 0.160 g (0.84 mmol) of *p*-TsOH. The reaction mixture was stirred at room temperature for 45 min, after which time 0.078 g (1.15 mmol) of imidazole was added. The reaction mixture was allowed to stir for an additional 10 min and then concentrated under reduced pressure. The remaining residue was flash chromatographed (5:1 - 2:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, 4.79 g (69%) of **115** and 0.58 g (10%) of the starting material **96**. The compound **115** had spectral characteristics identical with those reported in the literature.[15]

(4aα,8β,8aα)-(±)-Octahydro-8-hydroxy-4a,8-dimethyl-2(1*H*)-naphthalenone (99). The ethylene acetal **115** (4.79 g, 21.4 mmol) was treated with CH_3MgI for 3 h as described for the synthesis of **98**. After the workup, the crude reaction product (^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.80-2.70 (m, 14 H), 0.98 (s, 3 H), 1.17 (s, 3 H), 3.95 (m, 4 H)) was hydrolyzed for 18 h as described for the synthesis of **98**. The workup and flash chromatography (5:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded 3.25 g (78%) of **99** along with 0.42 g (10%) of **100**.

99: mp 117-119 °C (from diisopropyl ether); IR (CCl_4)[16] 3620, 3600, 1710 cm^{-1}; ^{1}H NMR, see Table 5.1; ^{13}C NMR, see Table 5.2; mass spectrum *m/e* (relative intensity) 196 (M^+, 100), 181 (17), 178 (22), 167 (24), 163 (12), 154 (52), 138 (46), 111 (98), 109 (89); calcd for $C_{12}H_{20}O_2$ (M^+) *m/e* 196.1463, found 196.1463. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.25; H, 10.43.

5.5 REFERENCES AND NOTES

(1) See chapter 4.

(2) (a) Wijnberg, J. B. P. A.; Vader, J.; de Groot, Ae. *J. Org. Chem.* **1983**, *48*, 4380. (b) Wijnberg, J. B. P. A.; Jongedijk, G.; de Groot, Ae. *Ibid.* **1985**, *50*, 2650. (c) Wijnberg, J. B. P. A.; Kesselmans, R. P. W.; de Groot, Ae. *Tetrahedron Lett.* **1986**, 27, 2415.

(3) The olefinic ketone **112** could also be prepared in good yield from a mixture of **95** and **96**.[2a]

(4) Buhler, J. D. *J. Org. Chem.* **1973**, *38*, 904.

(5) (a) According to molecular mechanics calculation **114A** is 4 kJ more stable then **114B**, while **115A** is only 0.4 kJ more stable then **115B**.[5b] (b) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(6) Treatment of **115** with CH_3Li and MgI_2 in ether at room temperature afforded a 3:1 mixture of **99** and **100**, respectively. This result indicates that either the reaction of **115** with in situ generated CH_3MgI has taken place[7a] or that MgI_2 coordinates **115** to the nonsteroid conformation (**115B**).[7b]

(7) (a) Wakefield, B. J. *Organolithium Methods*; Academic Press Limited: London, 1988, 159. (b) Tamura, Y.; Annoura, H.; Fujioka, H. *Tetrahedron Lett.* **1987**, *28*, 5681.

(8) Browne, L. M.; Klinck, R. E.; Stothers, J. B. *Org. Magn. Reson.* **1979**, *12*, 561.

(9) Lifson, S.; Hagler, A. T.; Dauber, P. *J. Am. Chem. Soc.* **1979**, *101*, 5111.

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(13) Bauduin, G.; Pietrasanta, Y. *Tetrahedron* **1973**, *29*, 4225.

(14) Brown, E. D.; Sam, T. W.; Sutherland, J. K.; Torre, A. *J. Chem. Soc., Perkin Trans 1* **1975**, 2326.

(15) Marshall, J. A.; Pike, M. T.; Carroll, R. D. *J. Org. Chem.* **1966**, *31*, 2933.

(16) Dilution of the hydroxy ketone caused a decrease in intensity of the absorption band for bonded OH stretching and a concominant increase in the intensity of the free hydroxyl absorption, which leads to the conclusion that **99** has no intramolecular hydrogen bonds.

6. TOTAL SYNTHESIS OF THE EUDEM-11-EN-4-OLS I-VIII. FIRST TOTAL SYNTHESIS OF AMITEOL

In this chapter, the total synthesis of all stereoisomers **I-VIII** of eudesm-11-en-4-ol starting from the hydroxy ketones **97-100** is described. In the synthesis of the *trans*-fused decalins **I-IV** it was anticipated that the conversion of the carbonyl group of the hydroxy ketones **97** and **98** into the eudesmanes **II** and **IV** with a less favorably orientated 1-methylethenyl substituent could lead to some difficulties. The conformational mobility of the *cis*-fused decalin structure makes the stereochemical outcome difficult to predict for the eudesmanes **V-VIII**.

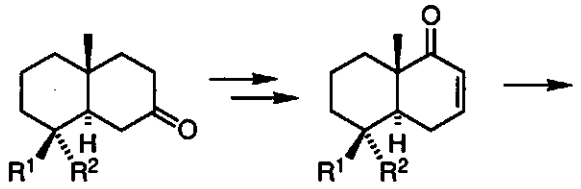
6.1 SYNTHESIS OF THE *TRANS*-FUSED EUDESM-11-EN-4-OLS I-IV

For conformationally fixed *trans*-fused compounds an elegant solution to the problem of producing an axial 1-methylethenyl group has been reported.[1] This method could not be applied in our approach because the strongly acidic conditions in this reaction led to dehydration of the tertiary alcohol group. Therefore, the introduction of the axial alkenyl group *via* a stereoelectronic controlled 1,4-addition of a cuprate reagent to the α,β-unsaturated ketones **116** and **117** was investigated (Scheme 6.1). These compounds were prepared from the corresponding hydroxy ketones *via* reported methods.[2] Conjugate addition of $Li_2(i\text{-}C_3H_5)_2Cu(I)CN$[3] to **116** gave **118** as a single stereoisomer. Two methods were employed for the conversion of **118** into **IV**.

A Wolff-Kishner reduction gave **IV** in low yield. The other method involved the reduction of the carbonyl group to an alcohol followed by a deoxygenation reaction.[4] The disadvantage of this method is the nonselective reduction of the carbonyl group which gave almost equal amounts of the α- and β-alcohols. The α-alcohol could not be converted into the corresponding xanthate in the deoxygenation reaction, while the application of this reaction to the β-alcohol gave **IV** in poor yield.

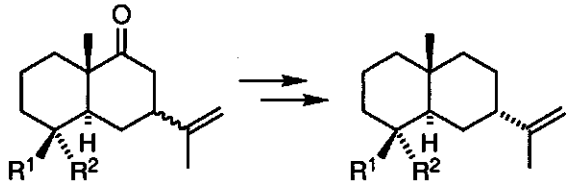
The conversion of **117** into **II** was even less satisfactory. With the unprotected tertiary alcohol group in **117**, the cuprate addition proceeded only when forced reaction conditions were applied and the ketone **119**, with an *equatorial* β 1-methylethenyl group, was isolated as the reaction product.

Scheme 6.1



98: $R^1 = OH; R^2 = CH_3$ **116**: $R^1 = OH; R^2 = CH_3$

97: $R^1 = CH_3; R^2 = OH$ **117**: $R^1 = CH_3; R^2 = OH$



118: $R^1 = OH; R^2 = CH_3$; α-alkenyl **IV**: $R^1 = OH; R^2 = CH_3$

119: $R^1 = CH_3; R^2 = OH$; β-alkenyl **II**: $R^1 = CH_3; R^2 = OH$

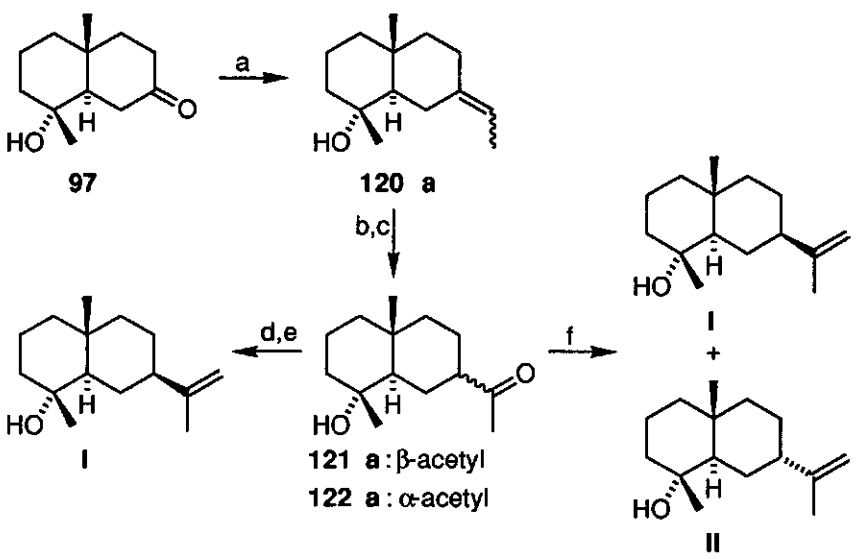
Protection of the tertiary alcohol group in **117** as its TMS ether successively followed by cuprate addition, reduction, deoxygenation, and deprotection finally did give **II**, but again in a low yield.

On the other hand, a well-established procedure is available for the introduction of a thermodynamically more stable equatorial 1-methylethenyl substituent starting from the carbonyl group in *trans*- and *cis*-fused decalones.[5,6] This synthetic sequence is exemplified in Scheme 6.2 and involves the conversion of a carbonyl group into an ethylidene substituent, oxidative hydroboration, oxidation, and a base-catalyzed equilibration, resulting in an equatorially orientated acetyl substituent. A subsequent Wittig olefination then generates the desired 1-methylethenyl group. This reaction sequence was successfully employed in the synthesis of the eudesmane alcohols **I**, **III**, **V**, and **VIII**. During the synthesis of **I** we noticed that the oxidative hydroboration of the olefin **120a** gave an adduct with an axial substituent at C-7 as the main product, probably as a result of the preferentially equatorial attack of the BH_3 reagent.[7] This selectivity can be

used in a straightforward route to the remaining eudesmane alcohols **II**, **IV**, **VI**, and **VII**, as is demonstrated in this chapter.

For the synthesis of **I** and **II** the *trans*-fused hydroxy ketone **97** was the starting material (Scheme 6.2). Treatment of **97** with $Ph_3P{=}CHCH_3$ in DMSO yielded **120a** as a 1:1 mixture of geometric isomers. Oxidative hydroboration (BH_3·THF; NaOH, H_2O_2) of **120a**, directly followed by oxidation with PDC in CH_2Cl_2 gave a 1:2.3 mixture of **121a** and **122a**, respectively.[8] Equilibration of this mixture with KOH in CH_3OH afforded **121a** as the sole product. From these results it was concluded that BH_3 attacks **120a** preferentially from the β side. Pure **I** was obtained upon treatment of **121a** with $Ph_3P{=}CH_2$ in DMSO in an overall yield of 53% starting from **97**. For the preparation of **II**, the original 1:2.3 mixture of **121a** and **122a** was subjected to silyl-Wittig olefination reaction conditions ($(CH_3)_3SiCH_2Li$, THF; KH, THF)[9] to afford a 1:2.3 mixture of **I** and **II**, respectively. It is obvious that during this reaction no epimerization occurs.[10] Although the separation of **I** and **II** was not easy to perform, careful chromatography gave pure **II** in an overall yield of 39% from **97**.

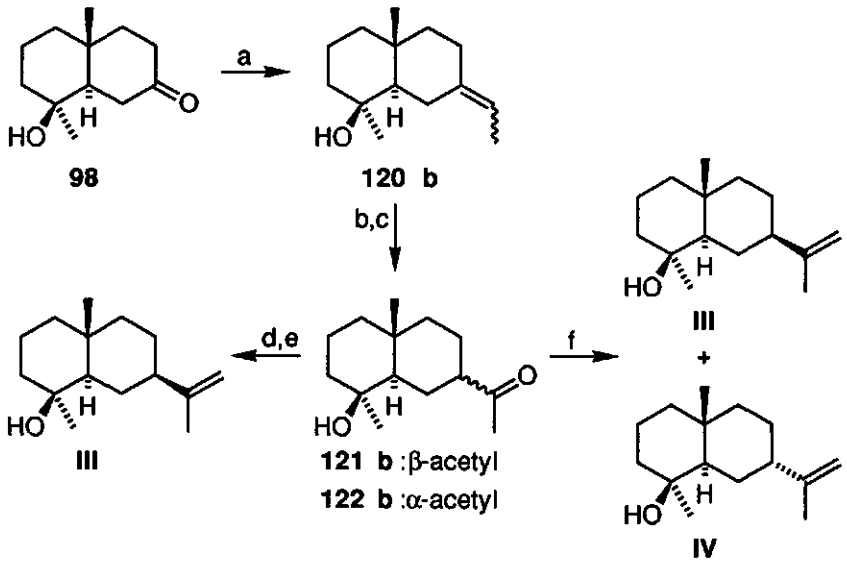
Scheme 6.2[a]



[a] (a) $Ph_3P{=}CHCH_3$, DMSO; (b) BH_3·THF; H_2O_2, NaOH; (c) PDC, CH_2Cl_2; (d) KOH, CH_3OH; (e) $Ph_3P{=}CH_2$, DMSO; (f) $(CH_3)_3SiCH_2Li$, THF; KH, THF.

Starting from the hydroxy ketone **98**, the procedure outlined above, i.e., **98** ⟶ **120b** ⟶ **121b** + **122b** (ratio 1.3:1),[11] followed by equilibration and a Wittig reaction afforded **III** in an overall yield of 58%. Without the interim equilibration step an 1.3:1 mixture of **III** and **IV**, respectively, was obtained after the silyl-Wittig reaction. This mixture could be separated and **IV** was isolated in an overall yield of 33% from **98** (Scheme 6.3).

Scheme 6.3[a]

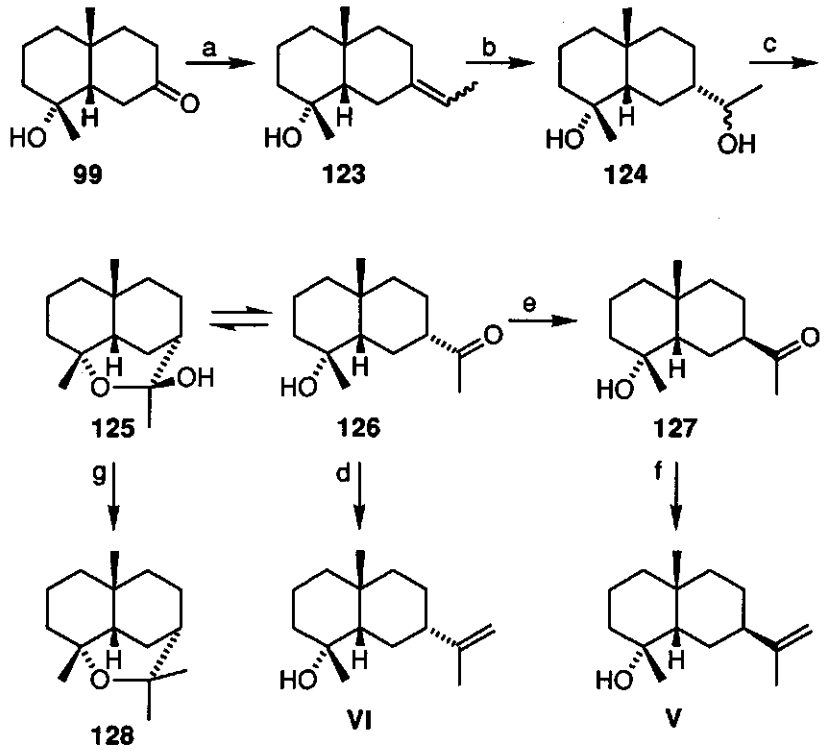


[a] (a) $Ph_3P{=}CHCH_3$, DMSO; (b) BH_3·THF; H_2O_2, NaOH; (c) PDC, CH_2Cl_2; (d) KOH, CH_3OH; (e) $Ph_3P{=}CH_2$, DMSO; (f) $(CH_3)_3SiCH_2Li$, THF; KH, THF.

6.2 SYNTHESIS OF THE *CIS*-FUSED EUDEM-11-EN-4-OLS V-VIII

In a similar reaction sequence as applied to the synthesis of **I-IV**, the *cis*-eudesmane alcohols **V-VIII** could be prepared from the hydroxy ketones **99** and **100**. Treatment of **99** with $Ph_3P{=}CHCH_3$ in DMSO afforded **123** as a 1:1 mixture of geometric isomers. The oxidative hydroboration (BH_3·THF; NaOH, H_2O_2) of the olefinic alcohol **123** provided a diastereomeric 1:1 mixture of only two diols to which structure **124** was assigned (Scheme 6.4).

Scheme 6.4[a]



[a] (a) $Ph_3P{=}CHCH_3$, DMSO; (b) $BH_3{\cdot}THF$; H_2O_2, NaOH; (c) NDC, pyridine, CH_2Cl_2; (d) $(CH_3)_3SiCH_2Li$, THF; KH, THF; (g) (e) *t*-BuOK, DMSO; (f) Zn, CH_2I_2, $TiCl_4$, THF; (g) $BF_3{\cdot}O(C_2H_5)_2$, $(CH_3)_2Li_2Cu(I)CN$, ether.

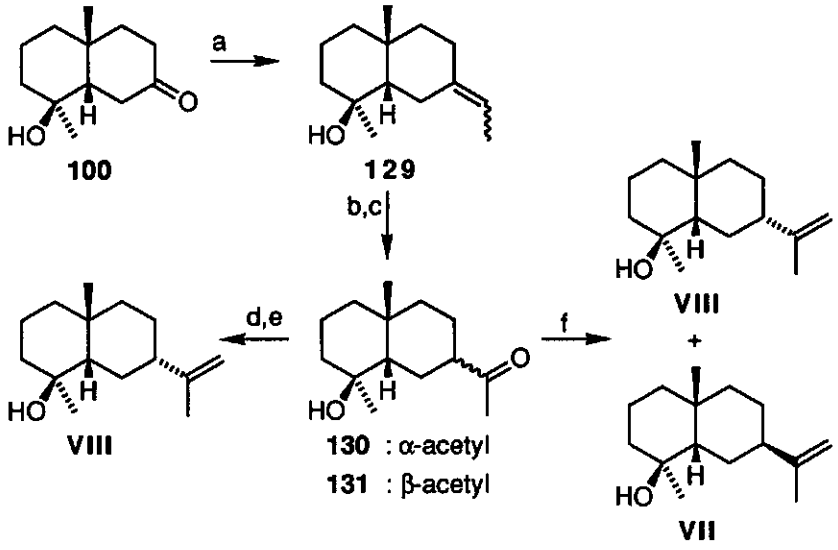
Since we assume that **123** consists in the nonsteroid conformation, just as **99**,[12] one would expect the borane reagent to approach the double bond in **123** from the more open convex face of the molecule. This can explain the selective formation of **124**. The structure of **124** was further confirmed after treatment with NDC and pyridine in CH_2Cl_2,[13] which gave the crystalline lactol **125** in 90% yield. Furthermore, the IR, ^1H NMR, and ^{13}C NMR spectral data of **125** show the presence of the α-acetyl alcohol **126** in about 20%. Thus, in solution the lactol **125** exists in equilibrium with its open form **126**. This observation led us to examine the base-catalyzed equilibration of the lactol

125 in order to prepare a suitable intermediate for the synthesis of **V**. The best result was obtained when **125** was treated with 2 equiv of *t*-BuOK in DMSO at room temperature for a short period (1 min). In this way an easily separable mixture of the β-acetyl alcohol **127** (59%) and **125** (25%) was produced. Longer reaction times gave lower yields of **127**, probably as a result of aldol condensation reactions.[14] Treatment of **127** with zinc powder and CH_2I_2 under the influence of titanium(IV) chloride in dry THF[15] gave (±)-**V** as the sole product in 74% yield (27% overall from **99**).[16] Reaction of **125** with 4 equiv of $Ph_3P{=}CH_2$ in DMSO also afforded (±)-**V**, but now together with its C-7 epimer **VI** in isolated yields of 45 and 42%, respectively. Clearly, during this Wittig reaction partial epimerization at the C-7 position of **126** had occurred. On the the other hand, after a silyl-Wittig olefination reaction of the lactol **125** no epimerization at all was observed and **VI** was produced in an overall yield of 61% starting from **99**.

The lactol **125** is also a highly suitable intermediate for the synthesis of the (±)-evuncifer ether (**128**), the main component of the defensive secretion of *Armitermes evuncifer*.[17] Recently, a method has been reported in which a direct reaction of δ-lactols with modestly nucleophilic organometals in the presence of a Lewis acid provided substituted tetrahydropyrans.[18] The application of a modified version of this method to **125**, using $Li_2(CH_3)_2Cu(I)CN$ in place of dimethylzinc, afforded **128** in 64% yield[19] (39% overall from **99**).

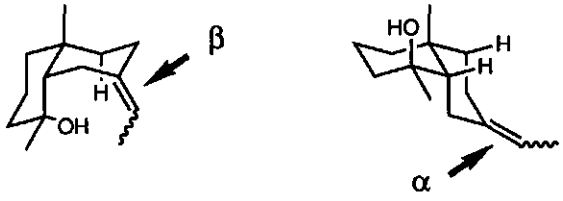
The unnatural *cis*-fused eudesmane alcohols, **VII** and **VIII**, were prepared from the hydroxy ketone **100** in a similar fashion as described for the synthesis of **V** and **VI** starting from **99** (Scheme 6.5). When **100** was subjected to a Wittig reaction with $Ph_3P{=}CHCH_3$ in DMSO the olefinic alcohol **129** was produced as a 3:1 mixture of geometric isomers. The oxidative hydroboration of **129**, which is thought to exist predominantly in the steroid conformation,[12] gave a mixture of at least three diols, which without further purification was oxidized with PDC to afford an inseparable mixture of the epimeric acetyl compounds **130** and **131** in a ratio of 1:2.3, respectively. It is obvious that the conformation of the *cis*-fused compounds **123** and **129** plays an important role in directing the incoming hydroborating reagent. The hydroboration of **123** (nonsteroid) proceeds stereoselectively from the β side. On the other hand, in the hydroboration of **129** (predominantly steroid) the favored attack is from the α side (Figure 6.1).

Scheme 6.5[a]



[a] (a) $Ph_3P{=}CHCH_3$, DMSO; (b) BH_3·THF; H_2O_2, NaOH; (c) PDC, CH_2Cl_2; (d) KOH, CH_3OH; (e) $Ph_3P{=}CH_2$, DMSO; (f) $(CH_3)_3SiCH_2Li$, THF; KH, THF.

Figure 6.1

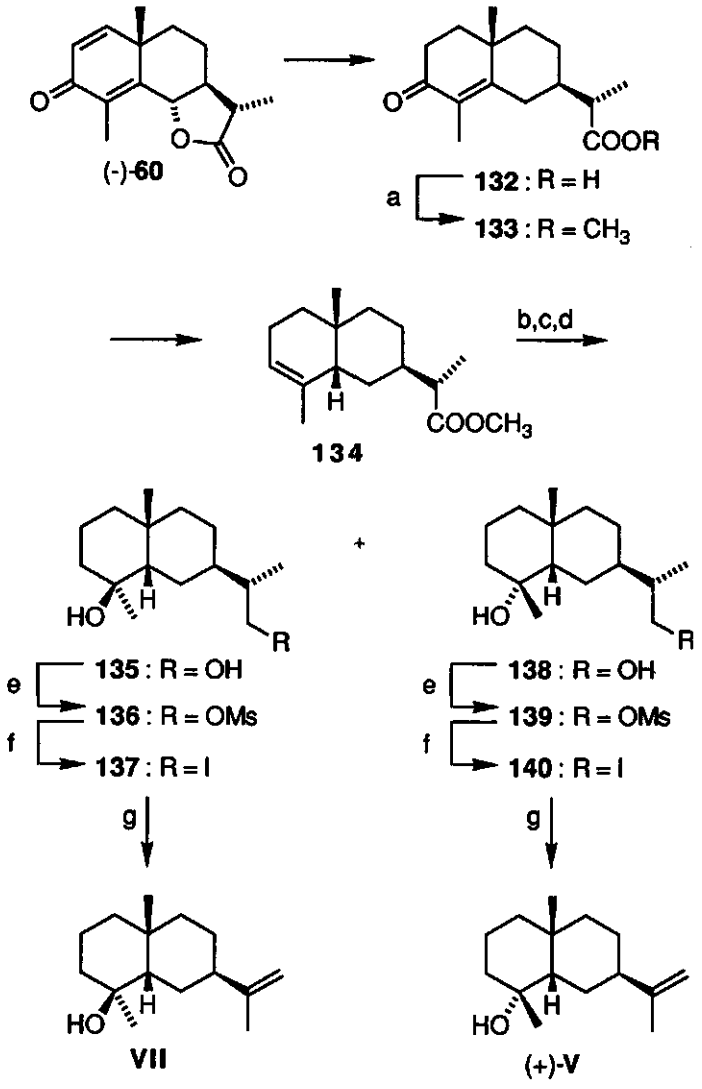


123 **129**

The 1:2.3 mixture of **130** and **131** was equilibrated with KOH in CH_3OH to a 19:1 mixture. Treatment of this 19:1 mixture with $Ph_3P{=}CH_2$ in DMSO and recrystallization of the resulting product gave pure **VIII** in an overall yield of 52% from **100**. The spectroscopic data of **VIII** were identical with those of a *cis*-fused eudesmane alcohol synthesized previously.[20] The structure of this latter product has been determined by X-ray crystallography thus supporting

the stereochemical assignments of the epimeric acetyl alcohols **130** and **131** (vide supra).

Scheme 6.6[a]



[a] (a) $(CH_3)_3SiCl$, CH_3OH; (b) Oxone, acetone, 10-crown-6, $NaHCO_3$, H_2O, CH_2Cl_2; (c) $LiAlH_4$, THF; (d) separation; (e) MsCl, pyridine; (f) NaI, acetone; (g) *t*-BuOK, *t*-BuOH.

For the preparation of **VII**, the original 1:2.3 mixture of **130** and **131** was subjected to silyl-Wittig olefination reaction conditions to afford a mixture of **VII** and **VIII** in high yield. According to GC and ^{1}H NMR analysis, this mixture consisted of 70% of **VII** as the main product and 30% of **VIII**. Unfortunately, **VII** was separated only with difficulty from the minor product **VIII**. After careful chromatography a sample of 93% pure (±)-**VII** could be obtained in a moderate yield of 55%. To prepare pure **VII**, we examined a more effective synthesis starting from the commercially available (-)-α-santonin. *Via* a slightly modified version of a known procedure[21] (-)-α-santonin was converted into the *cis*-fused olefinic ester **134**, i.e., (-)-α-santonin ⟶ **132** ⟶ **133** ⟶ **134** (Scheme 6.6). Epoxidation of **134** with in situ generated dimethyldioxirane[22] and subsequent reduction with $LiAlH_4$ led to a mixture of diols which could be readily separated. The major diol **135**, isolated in 70% yield, was converted into the corresponding iodide **137** *via* its monomesylate **136**. The iodide **137** could be dehydrohalogenated with *t*-BuOK in refluxing *t*-BuOH to afford the desired optically active unnatural (+)-**VII** in an overall yield of 75% from diol **135**. In an analogous fashion, i.e., **138** ⟶ **139** ⟶ **140** ⟶ **V**, the minor diol **138** gave natural (+)-**V** in an overall yield of 58%.

6.3 EXPERIMENTAL SECTION

Melting points were determined on an Olympus HSA melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Philips PU 9706 infrared spectrophotometer, and peak positions are expressed in cm^{-1}. NMR spectra were recorded on a Varian EM-390 at 90 MHz (^{1}H), and a Bruker 200 E at 200 MHz (^{1}H) and at 50 MHz (^{13}C). Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). NMR multiplicities are recorded by use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad; *J*, coupling constant; Hz, hertz. Mass spectral data were determined on either an AEI MS 902 spectrometer or a Hewlett Packard 5970B series MSD coupled with a Hewlett Packard 5890A gas chromatograph with a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 μm. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. Gas-liquid chromatography (GC) analyses were carried out on a Varian Vista 6000 gas chromatograph with a flame ionization detector and a DB-17 fused silica capillary column, 30 m x 0.25

mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically with a Spectra-Physics integrator SP 4290. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh).

Solvents were dried and distilled fresh by common practice. For all dry reactions, flasks were dried at 150 °C and flushed with dry nitrogen just before use, and reactions were carried out under an atmosphere of dry nitrogen. Product solutions were dried over anhydrous $MgSO_4$, unless otherwise noted, prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

(1α,4aβ,8aα)-(±)-Decahydro-7-ethylidene-1,4a-dimethyl-1-naphthalenol (120a). To a stirred solution of 75 mL of 0.44 M (dimethylsulfinyl)sodium in dry DMSO at room temperature was added 12.5 g (33.0 mmol) of $Ph_3PCH_2CH_3Br$. After the solution was stirred at room temperature for 30 min, a solution of 2.06 g (10.5 mmol) of hydroxy ketone **97** in 25 mL of dry DMSO was added dropwise. The reaction mixture was stirred at room temperature for 15 h and then poured into 400 mL of water. The aqueous solution was extracted with eight 100-mL portions of EtOAc. The combined organic layers were washed with 200 mL of brine, dried, and evaporated. The remaining residue was flash chromatographed (10:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 1.98 g (91%) of **120a**, which was a mixture of two geometric isomers in a ratio of 1:1, according to GCMS and ^1H NMR analysis: ^1H NMR ($CDCl_3$, 90 MHz) (major peaks) δ 0.96 (s, 3 H), 1.14 (s, 3 H), 5.19 (m, 1 H); mass spectrum (first isomer) *m/e* (relative intensity) 208 (M^+, 23), 190 (39), 175 (32), 121 (38), 93 (28), 81 (30), 67 (30), 43 (100); mass spectrum (second isomer) *m/e* , (relative intensity) 208 (M^+, 20), 190 (37), 175 (30), 121 (37), 93 (28), 81 (29), 67 (30), 43 (100).

(2α,4aα,8β,8aβ)-(±)-1-(Decahydro-8-hydroxy-4a,8-dimethyl-2-naphthalenyl)ethanone (121a) and (2α,4aβ,8α,8aα)-(±)-1-(Decahydro-8-hydroxy-4a,8-dimethyl-2-naphthalenyl)ethanone (122a). To a stirred solution of 1.85 g (8.9 mmol) of olefin **120a** in 75 mL of dry THF, cooled to 0 °C, was added dropwise 35 mL (35 mmol) of BH_3·THF (1.0 M in THF). The reaction mixture was stirred at room temperature for 21 h, and then heated at reflux for 1h. The reaction mixture was cooled to 0 °C, after which a mixture of 35 mL of THF and 3.5 mL of water was added dropwise, immediately followed by addition of 21 mL of 3 N NaOH in water and 21 mL of 30% H_2O_2. The reaction mixture was stirred at room temperature for 15 h and then

heated at reflux for 1 h. The reaction mixture was allowed to come to room temperature and poured into 200 mL of brine. The two-phase mixture was separated, and the aqueous layer was extracted with four 100-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated. The resulting oil was dissolved in 250 mL of CH_2Cl_2, and then 10.3 g (27.4 mmol) of PDC was added. The reaction mixture was allowed to stir at room temperature for 20 h and filtered through Celite, and the filter cake was washed with two 100-mL portions of CH_2Cl_2. The solvent was evaporated under reduced pressure, and the resulting residue was flash chromatographed (5:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 1.59 g (80%) of a mixture of **121a** and **122a** in a ratio of 1:2.3, respectively, according to GCMS and ^1H NMR analysis: ^1H NMR ($CDCl_3$, 90 MHz) (major peaks) δ 0.89 (s, 3 H), 1.07 (s, 3 H), 2.16 (s, 3 H), 2.68 (m, $W_{1/2}$ = 12 Hz, 1 H). **121a**: mass spectrum *m/e* (relative intensity) 224 (M^+, 6), 206 (14), 191 (7), 163 (11), 137 (16), 121 (10), 95 (10), 71 (23), 43 (100). **122a**: mass spectrum *m/e* (relative intensity) 206 (M^+ - 18, 33), 191 (30), 163 (11), 147 (13), 121 (7), 81 (19), 71 (18), 43 (100), 41 (20).

(±) Selin-11-en-4α-ol (I). To a stirred solution of 0.76 g (3.4 mmol) of a 1:2.3 mixture of **121a** and **122a** in 150 mL of absolute CH_3OH was added 2.0 g (36 mmol) of KOH. The reaction mixture was stirred at room temperature for 41 h and then poured into 200 mL of brine. After evaporation of CH_3OH under reduced pressure, the remaining aqueous solution was extracted with five 100-mL portions of EtOAc. The combined organic layers were dried and evaporated. The remaining residue was flash chromatographed (4:1 - 1:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 0.59 g (78%) of pure **121a**: mp 86-87 °C (from diisopropyl ether); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.75-2.60 (m, 15 H), 0.87 (s, 3 H), 1.09 (s, 3 H), 2.13 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.41 (q), 19.94 (t), 22.63 (q), 22.80 (t), 23.50 (t), 28.23 (q), 34.39 (s), 40.78 (t), 43.27 (t), 43.72 (t), 52.19 (d), 53.96 (d), 71.99 (s), 212.08 (s); calcd for $C_{14}H_{24}O_2$ (M^+) *m/e* 224.1776, found 224.1773. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.66; H, 10.88. The procedure described for the synthesis of **120a** was employed by using 50 mL of 0.26 M (dimethylsulfinyl)sodium in dry DMSO, 4.64 g (13.0 mmol) of Ph_3PCH_3Br, and 0.59 g (2.6 mmol) of **121a** in 25 mL of dry DMSO. After stirring at 50 °C for 7 h, the workup and flash chromatography (25:1 petroleum ether (bp 40-60 °C)/EtOAc) gave 0.55 g (94%) of I: mp 61-62 °C (from diisopropyl ether); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.75-2.00 (m, 15 H), 0.83 (s, 3 H), 1.06 (s, 3 H), 1.68 (br s, 3 H), 4.65 (br s, 2 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.61 (q), 20.03 (t), 21.00 (q), 22.58 (q), 25.89 (t), 26.74 (t), 34.49 (s), 40.96 (t), 43,23 (t), 44.55 (t), 46.19 (d), 54.69 (d), 72.10 (s), 108.06 (t), 150.49 (s); mass spectrum *m/e* (relative intensity) 222 (M^+, 31), 204 (100), 189 (43), 137 (54), 135 (85), 109 (49), 81 (64), 71 (54), 43 (50) ; calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found 222.1984. Anal. Calcd for $C_{15}H_{26}O$: C, 81.08; H, 11.78. Found: C, 80.71; H, 11.72. Our synthetic (±)-**I** exhibited spectra identical with those of (-)-selin-11-en-4α-ol.[23]

(±)-Intermedeol (II). To a stirred solution of 10 mL of 0.5 M $(CH_3)_3SiCH_2Li$ in 1:1 pentane/THF, cooled to -78 °C, was added dropwise a solution of 0.061 g (0.27 mmol) of a 1:2.3 mixture of **121a** and **122a** in 15 mL of dry THF. When the addition was complete, the reaction mixture was allowed to stir for 30 min at -78 °C. The excess $(CH_3)_3SiCH_2Li$ was then quenched by the careful addition of saturated aqueous NH_4Cl. After addition of 25 mL of water, the two-phase mixture was separated, and the aqueous layer was extracted with three 20-mL portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was taken up in 15 mL of dry THF and added dropwise to a suspension of 0.090 g (2.25 mmol) KH in 10 mL of dry THF. The reaction mixture was stirred at room temperature for 30 min and then diluted with 25 mL of water. The two-phase mixture was separated, and the aqueous layer was extracted with three 20-mL portions of EtOAc. The combined orgxanic layers were washed with brine, dried, and evaporated. The remaining mixture was flash chromatographed (20:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, 0.032 g (53%) of pure **II** and 0.028 g (46%) of a 2:1 mixture of **I** and **II**, respectively.

II: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.80-1.89 (m, 13 H), 0.90 (s, 3 H), 1.06 (s, 3 H), 1.72 (br s, 3 H), 2.03 (m, 1 H), 2.40 (m, 1 H), 4.84 (br s, 1 H), 4.88 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.38 (q), 20.06 (t), 22.21 (q), 22.65 (q), 22.65 (t), 23.40 (t), 35.21 (s), 39.25 (d), 40.24 (t), 41.25 (t), 43.42 (t), 49.08 (d), 72.01 (s), 110.72 (t), 146.61 (s); mass spectrum *m/e* (relative intensity) 222 (M+, 1), 207 (13), 204 (77), 189 (70), 174 (13), 167 (33), 161 (100), 147 (23), 133 (29), 122 (53), 105 (27); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found 222.1984. Our synthetic (±)-**II** exhibited spectra identical with those of (+)-intermedeol.[24]

(1α,4aα,8aβ)-(±)-Decahydro-7-ethylidene-1,4a-dimethyl-1-naphthalenol (120b). The olefin **120b** was prepared in 86% yield from the hydroxy ketone **98** (3.00 g, 15.3 mmol) as described for the synthesis of **120a**. According to GCMS

and ^{1}H NMR analysis, **120b** was a mixture of two geometric isomers in a ratio of 7:3: ^{1}H NMR ($CDCl_3$, 90 MHz) (major peaks) δ 1.11 (s, 3 H), 1.19 (s, 3 H), 5.18 (m, 1 H); mass spectrum (major isomer) *m/e* (relative intensity) 208 (M^+, 1.5), 190 (60), 175 (51), 161 (21), 147 (17), 134 (17), 119 (35), 108 (24), 93 (26), 67 (27), 43 (100); mass spectrum (minor isomer) *m/e* (relative intensity) 208 (M^+, 2.1), 190 (53), 175 (46), 161 (20), 147 (16), 134 (16), 119 (32), 108 (23), 93 (24), 67 (28), 43 (100).

(2α,4aα,8α,8aβ)-(±)-1-(Decahydro-8-hydroxy-4a,8-dimethyl-2-naphthalenyl)ethanone (121b) and (2α,4aβ,8β,8aα)-(±)-1-(Decahydro-8-hydroxy-4a,8-dimethyl-2-naphthalenyl)ethanone (122b). An inseparable mixture of **121b** and **122b** was prepared in 90% yield from the olefin **120b** (2.62 g, 12.6 mmol) as described for the oxidative hydroboration and subsequent oxidation of **120a.** According to GCMS and ^{1}H NMR analysis, the ratio of **121b** and **122b** was 1.3:1, respectively: ^{1}H NMR ($CDCl_3$, 90 MHz) (major peaks) δ 1.09 (s, 3 H), 1.18, 1.26 (s, 3 H), 2.20 (s, 3 H). **121b**: mass spectrum *m/e* (relative intensity) 224 (M^+, 0.1), 209 (9), 206 (26), 191 (15), 181 (2), 163 (9), 147 (9), 71 (20), 43 (100). **122b**: mass spectrum *m/e* (relative intensity) 224 (M^+, 4), 209 (18), 206 (7), 191 (6), 181 (8), 163 (10), 137 (11), 71 (21), 43 (100).

(±)-Neointermedeol (III). A sample of the 1.3:1 mixture of alcohol **121b** and **122b** (2.00 g, 8.93 mmol) was equilibrated and treated with $Ph_3P{=}CH_2$ as described for the synthesis of I to give 1.49 g (75%) of III: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95-2.05 (m, 15 H), 1.03 (s, 3 H), 1.12 (s, 3 H), 1.71 (br s, 3 H), 4.66 (m, 1 H), 4.69 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.03 (t), 18.66 (q), 20.69 (q), 25.76 (t), 26.81 (t), 30.23 (q), 33.66 (s), 41.24 (t), 41.56 (t), 43.85 (t), 46.67 (d), 51.84 (d), 71.92 (s), 108.31 (t), 150.75 (s); mass spectrum *m/e* (relative intensity) 222 (M^+, 16), 207 (82), 204 (100), 188 (54), 171 (29), 145 (61), 105 (91), 81 (51), 71 (41), 43 (49); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found 222.1989. Anal. Calcd for $C_{15}H_{26}O$: C, 81.01; H, 11.78. Found: C, 80.76; H, 11.82. Our synthetic (±)-III exhibited spectra identical with those of (+)-neointermedeol.[25]

(±)-Paradisiol (IV). A sample of the 1.3:1 mixture of **121b** and **122b** (0.072 g, 0.32 mmol) was treated with $(CH_3)_3SiCH_2Li$ and KH as described for the synthesis of II. The workup and flash chromatography (20:1 petroleum ether (bp 40-60 °C)/EtOAc) gave, in order of elution, 0.036 g (53%) of **III** and 0.030 g (42%) of **IV**.

IV: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-2.00 (m, 15 H), 1.06 (s, 3 H), 1.13 (s, 3 H), 1.71 (br s, 3 H), 4.78 (br s, 1 H), 4.88 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.81 (t), 18.31 (q), 22.38 (t), 22.59 (q), 23.13 (t), 29.78 (q), 34.14 (s), 39.13 (d), 39.38 (t), 41.01 (t), 41.61 (t), 45.82 (d), 71.83 (s), 110.37 (t), 146.90 (s); mass spectrum *m/e* (relative intensity) 222 (M+, 8), 207 (14), 204 (26), 189 (20), 161 (23), 135 (16), 123 (21), 109 (23), 81 (47), 43 (100); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found 222.1986. Our synthetic (±)-**IV** exhibited spectra identical with those of (+)-paradisiol.[24]

(1α,4aβ,8aβ)-(±)-Decahydro-7-ethylidene-1,4a-dimethyl-1-naphthalenol (123). The olefin **123** was prepared in 86% yield from the hydroxy ketone **99** (6.00 g, 30.6 mmol) as described for the synthesis of **120a**. According to GCMS and ^{1}H NMR analysis, **123** was a mixture of two geometric isomers in a ratio of 1:1: ^{1}H NMR ($CDCl_3$, 90 MHz) (major peaks) δ 1.03 (s, 3 H), 1.20, 1.23 (s, s, 1:1 ratio, 3 H), 5.28 (m, 1 H); mass spectrum (first isomer) *m/e* (relative intensity) 208 (M^+, 0.4), 193 (7), 190 (85), 175 (61), 161 (35), 147 (26), 133 (34), 119 (60), 93 (50), 43 (100); mass spectrum (second isomer) *m/e* (relative intensity) 208 (M^+, 0.4), 193 (7), 190 (82), 175 (60), 161 (35), 147 (25), 133 (35), 119 (61), 93 (51), 43 (100).

(2α,4aβ,8α,8aβ)-(±)-1-(Decahydro-8-hydroxy-4a,8-dimethyl-2-naphthalenyl)ethanol (124). The diol **124** was prepared in 79% yield from **123** (5.49 g, 24.3 mmol) as described for the oxidative hydroboration of **120a**. According to GCMS and ^{1}H NMR analysis, **124** was a 1:1 mixture of two diastereoisomers. Pure samples of the two diastereoisomers were obtained after flash chromatography (2:1 petroleum ether (bp 40-60 °C)/EtOAc).

124 (first diastereoisomer): mp 143-144 °C (from diisopropyl ether); IR ($CHCl_3$) 3670, 3600, 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.73-1.89 (m, 16 H), 0.98 (s, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.39 (s, 3 H), 3.56 (m, $W_{1/2}$ = 16 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.04 (t), 20.37 (q), 23.12 (t), 26.00 (t), 29.13 (t), 30.29 (q), 31.03 (q), 33.97 (s), 34.98 (t), 42.35 (t), 44.80 (d), 52.51 (d), 71.81 (d), 72.71 (s); mass spectrum *m/e* (relative intensity) 190 (M^+ - 36, 27), 175 (12), 161 (13), 150 (15), 123 (43), 121 (26), 95 (29), 81 (45), 71 (37), 67 (32), 43 (100).

124 (second diastereoisomer): mp 147-149 °C (from diisopropyl ether); IR ($CHCl_3$) 3670, 3600, 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.73-1.89 (m, 16 H), 0.98 (s, 3 H), 1.14 (d, J = 6 Hz, 3 H), 1.39 (s, 3 H), 3.56 (m, $W_{1/2}$ = 16 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.18 (t), 20.48 (q), 23.28 (t), 26.12 (t), 29.28 (t), 30.44 (q), 31.16 (q), 34.11 (s), 35.12 (t), 42.51 (t), 44.94 (d), 52.65 (d), 71.92 (d), 72.84

(s); mass spectrum *m/e* (relative intensity) 190 (M^+ - 36, 27), 175 (16), 161 (22), 150 (21), 133 (17), 123 (48), 121 (34), 95 (27), 81 (58), 71 (46), 67 (41), 43 (100).

(±)-(3α,4aβ,5α,8aα)-Octahydro-2-hydroxy-2,5,8a-trimethyl-3,5-ethano-2*H*-1-benzopyran (125). To a stirred solution of 4.21 g (18.6 mmol) of diol **124** in 150 mL of CH_2Cl_2 was added 11.6 g (24 mmol) of NDC and 20.8 mL (240 mmol) of pyridine. The reaction mixture was stirred at room temperature for 70 min, after which time the mixture was filtered through Celite. The filter cake was washed with two 100-mL portions of CH_2Cl_2. The combined organic layers were washed successively with 75 mL of 10% aqueous HCl and 100 mL of a saturated aqueous $NaHCO_3$, dried, and evaporated. The remaining residue was flash chromatographed (10:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 3.78 g (90%) of **125**: mp 101-102 °C (from diisopropyl ether); mass spectrum m/e (relative intensity) 224 (M+, 2), 209 (21), 206 (15), 191 (11), 164 (34), 149 (35), 109 (100); calcd for $C_{14}H_{24}O_2$ (M^+) *m/e* 224.1776, found 224.1778. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.91; H, 11.06. The IR, ^1H NMR, and ^{13}C NMR spectra of **125** revealed the presence of **126** in about 20%.

125: IR (CCl_4) 3600 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.68-2.37 (m, 15 H), 0.93 (s, 3 H), 1.32 (s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.52 (t), 21.11 (t), 24.84 (t), 28.23 (t), 28.77 (q), 29.17 (q), 29.74 (q), 32.42 (s), 34.54 (d), 40.55 (t), 41.21 (t), 42.78 (d), 73.91 (s), 99.26(s).

126: IR (CCl_4) 1710 cm^{-1}; ^1H NMR (main peaks) ($CDCl_3$, 200 MHz) δ 0.97 (s), 1.37 (s), 2.09 (s); ^{13}C NMR (main peaks) ($CDCl_3$, 50 MHz) δ 20.02 (t), 23.91 (t), 25.64 (t), 30.29 (q), 31.21 (q), 33.84 (s), 35.41 (t), 41.51 (t), 51.32 (d), 52.10 (d), 72.67 (s), 212.51 (s).

(±)-7-*epi*-Amiteol (VI). This compound was prepared from the lactol **125** (0.046 g, 0.21 mmol) as described for the synthesis of **II**. The workup and flash chromatography (20:1 petroleum ether (bp 40-60 °C)/EtOAc) afforded 0.045 g (99%) of **VI**: mp 112-113 °C (from diisopropyl ether); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.73-2.03 (m, 15 H), 0.99 (s, 3 H), 1.39 (s, 3 H), 1.69 (br s, 3 H), 4.65 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.26 (t), 21.09 (q), 27.18 (t), 29.40 (t), 29.40 (t), 30.50 (q), 31.15 (q), 33.99 (s), 35.25 (t) 42.96 (t), 45.32 (d), 53.03 (d), 72.81 (s), 108.02 (t), 150.82 (s); mass spectrum *m/e* (relative intensity) 222 (M+, 15), 207 (9), 204 (96), 189 (51), 161 (47), 137 (71), 135 (62), 109 (60), 95 (60), 81 (100); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found 222.1986.

(2α,4aα,8β,8aα)-(±)-1-(Decahydro-8-hydroxy-4a,8-dimethyl-2-naphthalenyl)ethanone (127). To a stirred solution of 0.224 g (2.00 mmol) of *t*-BuOK in 5 mL of dry DMSO was added at once a solution of 0.203 g (0.91 mmol) of **125** in 5 mL of dry DMSO. The reaction mixture was stirred at room temperature for 1 min and then quenched by the addition of 0.13 mL of AcOH. The reaction mixture was poured into 50 mL of water. The aqueous layer was extracted with eight 15-mL portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (10:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, 0.051 g (25%) **125** and 0.119 g (59%) of **127**.

127: mp 110-111 °C (from diisopropyl ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85-2.20 (m, 14 H), 0.85 (s, 3 H), 1.16 (s, 3 H), 2.04 (s, 3 H), 3.16 (dddd, *J* = 4, 4, 13, 13 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.28 (t), 23.04 (t), 23.67 (t), 28.12 (q), 29.09 (q), 31.16 (q), 31.61 (t), 32.56 (s), 41.46 (t), 42.51 (t), 46.46 (d), 46.86 (d), 73.27 (s), 213.79 (s); mass spectrum *m/e* (relative intensity) 224 (M^+, 8), 209 (4), 206 (82), 191 (19), 163 (31), 148 (5), 137 (24), 121 (16), 109 (40), 95 (20), 81 (32), 71 (40), 43 (100); calcd for $C_{14}H_{24}O_2$ (M^+) *m/e* 224.1776, found 224.1771.

(±)-Amiteol (V). A solution of 1.57 mL (1.57 mmol) of titanium(IV) chloride (1.0 M in THF) was added dropwise to a mixture of zinc dust (0.96 g, 14.7 mmol) and CH_2I_2 (0.64 mL, 7.95 mmol) in 20 mL of dry THF (argon atmosphere) at 0 °C. The resulting mixture was stirred at room temperature for 30 min, and then a solution of 0.086 g (0.38 mmol) of **127** in 5 mL of dry THF was added dropwise. The reaction mixture was stirred at room temperature for 3.5 h, heated at reflux for 1 h, and then allowed to come to room temperature. Stirring was continued for an additional 17 h, after which time the reaction mixture was diluted with 50 mL of 5% aqueous HCl. The two-phase mixture was separated, and the aqueous layer was extracted with three 25-mL portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (20:1 petroleum ether (bp 40-60 °C)/EtOAc) to afford 0.062 g (74%) of **V**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94 (s, 3 H), 0.96-2.09 (m, 14 H), 1.22 (s, 3 H), 1.72 (br s, 3 H), 2.64 (ddddd *J* = 13, 13, 3, 3, 1 Hz, 1 H), 4.66 (br s, 1 H), 4.68 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.39 (t), 20.92 (q), 26.50 (t), 26.60 (t), 29.49 (q), 31.23 (q), 32.47 (t), 32.79 (s), 39.62 (d), 41.76 (t), 42.57 (t), 47.66 (d), 73.46 (s), 107.56 (t), 151.75 (s); mass spectrum *m/e* (relative intensity) 204 (M^+-18, 65), 179 (27), 175 (8), 161 (26), 147 (28), 133 (14), 121 (29), 109 (100), 97

(25); calcd for $C_{15}H_{26}O$ (M^+ - 18) *m/e* 204.1878, found 204.1874. Our synthetic (±)-**V** exhibited spectra identical with those of (+)-amiteol.[26]

(±)-Evuncifer ether (128). To a stirred solution of 8.3 mL (13.28 mmol) of CH_3Li (1.6 M in ether), cooled to 0 °C, was added 0.630 g (7 mmol) of CuCN. The mixture was allowed to stir at 0 °C for 1 h, after which time it was cooled to -78 °C. To a solution of 0.152 g (0.68 mmol) of lactol **125** in 25 mL of dry ether was added 0.410 mL (3.3 mmol) of freshly distillated boron trifluoride etherate. This mixture was allowed to stand at room temperature for 2 min, and then added at once to the stirred cuprate mixture at -78 °C. The reaction mixture was allowed to stir for 3 min, and then quenched with saturated aqueous NH_4Cl. After addition of 50 mL of water, the two-phase mixture was separated, and the aqueous layer was extracted with two 25-mL portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (5:1 pentane/CH_2Cl_2) to give 0.096 g (64%)[19] of **128**: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.65-1.16 (m, 8 H), 1.00 (s, 3 H), 1.23-1.60 (m, 2 H), 1.23 (s, 3 H), 1.28 (s, 3 H), 1.33 (s, 3 H) 1.74-1.95 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.68 (t), 22.16 (t), 25.25 (t), 29.07 (q), 29.07 (q), 29.33 (t), 29.67 (q), 31.02 (q), 32.62 (s), 34.84 (d), 41.05 (t), 42.21 (t), 42.83 (d), 72.88 (s), 74.58 (s); mass spectrum *m/e* (relative intensity) 222 (M^+, 0.3), 207 (100), 189 (28), 164 (7), 149 (27), 133 (11), 123 (13), 109 (80), 93 (18), 81 (23), 43 (60); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found 222.1996. Our synthetic (±)-**128** exhibited spectra identical with those of (-)-evuncifer ether.[17]

(1α,4aα,8aα)-(±)-Decahydro-7-ethylidene-1,4a-dimethyl-1-naphthalenol (129). The olefin **129** was prepared in 88% yield from the hydroxy ketone **100** (1.59 g, 8.1 mmol) as described for the synthesis of **120a**. According to GCMS and ^1H NMR analysis, **129** was a 3:1 mixture of two geometric isomers: ^1H NMR ($CDCl_3$, 90 MHz) (major peaks) δ 1.19 (s, 6 H), 5.14 (m, 1 H); mass spectrum (major isomer) *m/e* (relative intensity) 208 (M^+, 4), 190 (31), 175 (15), 161 (13), 150 (8), 133 (11), 121 (42), 107 (14), 93 (29), 81 (31), 43 (100); mass spectrum (minor isomer) *m/e* (relative intensity) 208 (M^+, 6), 190 (31), 175 (19), 161 (6), 150 (9), 133 (6), 121 (28), 107 (19), 93 (25), 79 (31), 43 (100).

(2α,4aβ,8β,8aβ)-(±)-1-(Decahydro-8-hydroxy-4a,8-dimethyl-2-naphthalenyl)ethanone (130), and (2α,4aα,8α,8aα)-(±)-1-(Decahydro-8-hydroxy-4a,8-dimethyl-2-naphthalenyl)ethanone (131). An inseparable mixture of **130** and

131 was prepared in 87% yield from the olefin **129** (1.39 g, 6.8 mmol) as described for the oxidative hydroboration and subsequent oxidation of **120a**. According to GCMS and ^{1}H NMR analysis, the ratio of **130** and **131** was 1:2.3, respectively: ^{1}H NMR ($CDCl_3$, 90 MHz) (major peaks) δ 1.18 (s, 3 H), 1.24 (s, 3 H), 2.16 (s, 3 H). **130**: mass spectrum *m/e* (relative intensity) 224 (M^+, 1.4), 209 (1.6), 206 (22), 191 (11), 163 (9), 137 (13), 121 (9), 95 (11), 81 (13), 71 (25), 43 (100). **131**: mass spectrum *m/e* (relative intensity) 209 (M^+ - 15, 14), 206 (8), 167 (6), 163 (7), 149 (6), 139 (8), 121 (8), 95 (12), 81 (12), 71 (24), 43 (100).

(±)-5-*epi*-Paradisiol (VIII). This compound was prepared from the 1:2.3 mixture of **130** and **131** as described for the synthesis of **I**. After equilibration a 19:1 mixture (1.24 g) of **130** and **131**, respectively, was obtained. Treatment of this 19:1 mixture with $Ph_3P{=}CH_2$ gave, after chromatography and recrystallization from diisopropyl ether, 0.897 g (68%) of **VIII**: mp 83-84 °C (lit.[20] mp 77 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-2.00 (m, 15 H), 1.12 (s, 3 H), 1.17 (s, 3 H), 1.69 (br s, 3 H), 4.65 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.21 (t), 20.73 (q), 26.60 (t), 29.66 (t), 30.65 (q), 31.20 (q), 31.20 (t), 33.04 (s), 34.17 (t), 42.73 (t), 45.49 (d), 51.91 (d), 74.01 (s), 107.92 (t), 150.59 (s); mass spectrum *m/e* (relative intensity) 222 (M^+, 5), 204 (32), 189 (19), 161 (30), 135 (43), 121 (25), 109 (34), 81 (65), 43 (100); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found 222.1986. Anal. Calcd for $C_{15}H_{26}O$: C, 81.01; H, 11.78. Found: C, 80.85; H, 11.81. Our synthetic (±)-**VIII** exhibited spectra identical with those of synthetic (-)-**VIII**.[20]

(±)-5-*epi*-Neointermedeol (VII). A sample of the 1:2.3 mixture of **130** and **131** (0.061 g, 0.27 mmol) was treated with $(CH_3)_3SiCH_2Li$ and KH as described for the synthesis of **II**. The workup and flash chromatography (20:1 petroleum ether (bp 40-60 °C)/EtOAc) gave, in order of elution, 0.011 g (18%) of **VIII**, 0.009 g (15%) of a 2:1 mixture of **VII** and **VIII**, respectively, and 0.033 g (55%) of **VII** with a purity of 93% according to GC analysis. The spectroscopic data of this (±)-**VII** were identical with those of (+)-**VII** (vide infra).

[2R-[2α(S*),4aα,8aα]]-1,2,3,4,4a,5,6,8a-Octahydro-α,4a,8-trimethyl-methyl Ester, 2-Naphthaleneacetic Acid (134). The keto acid **132** (5.16 g, 20.7 mmol), prepared from commercially available (-)-α-santonin as described,[21a] was dissolved in 400 mL of CH_3OH and $(CH_3)_3SiCl$ (6.0 mL, 47 mmol) was added. The mixture was stirred at room temperature for 46 h, and then diluted with 250 mL of saturated aqueous $NaHCO_3$. After removal of CH_3OH under reduced pressure, the remaining aqueous solution was extracted with three

150-mL portions of EtOAc. The combined organic layers were dried, and evaporated. The resulting residue was flash chromatographed (4:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 4.68 g (86%) of keto ester **133**. The spectroscopic data of **133** were identical with those in the literature.[21b] A sample of **133** (2.38 g, 9.02 mmol) was converted into the *cis*-fused olefinic ester **134** in 79% yield as described.[21c]

[2R-[2α(S*),4aα,8α,8aα)]]-2-(Decahydro-8-hydroxy-α,4a,8-trimethyl-2-naphthalenyl)ethanol (135) and [2R-[2α(S*),4aα,8β,8aα)]]-2-(Decahydro-8-hydroxy-α,4a,8-trimethyl-2-naphthalenyl)ethanol (138). To a stirred solution of 0.935 g (3.74 mmol) of ester **134** in 50 mL of CH_2Cl_2 were added subsequently 50 mL of acetone, 0.081 g (0.31 mmol) of 18-crown-6, and a solution of 1.42 g (16.9 mmol) of $NaHCO_3$ in 50 mL of water. The two-phase mixture was cooled to 0 °C, and then a solution of 2.88 g (4.68 mmol) of Oxone in 16 mL of water was added dropwise. The reaction mixture was allowed to stir at 0 °C for 3.5 h, after which time 50 mL of saturated aqueous $Na_2S_2O_3$ and 100 mL of saturated aqueous $NaHCO_3$ were added. 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 dried and evaporated. The remaining residue was flash chromatographed (20:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 0.760 g (76%) of a 1:4 mixture of two epoxides, according to GCMS analysis: mass spectrum (major compound) *m/e* (relative intensity) 266 (M^+, 18), 251 (81), 178 (33), 163 (29), 135 (24), 121 (26), 107 (40), 88 (38), 55 (50), 43 (100); mass spectrum (minor compound) *m/e* (relative intensity) 266 (M^+, 26), 251 (89), 248 (5), 178 (38), 161 (38), 149 (44), 135 (28), 125 (36), 112 (42), 88 (64), 55 (63), 43 (100). To a solution of this epoxide mixture in 50 mL of dry THF was added 0.430 g (11.3 mmol) of $LiAlH_4$. The reaction mixture was heated at reflux for 20 h and, after cooling to 0 °C, quenched with saturated aqueous Na_2SO_4. After addition of 100 mL of water, the reaction mixture was extracted with five 50-mL portion of EtOAc. The combined organic layers were dried and evaporated. The remaining residue was flash chromatographed (2:1 - 1:1 petroleum ether (bp 40-60 °C)/EtOAc) to give, in order of elution, 0.139 g (20%) of **138** and 0.481 g (70%) of **135**. Physical and spectroscopic data of **135** and **138** are shown below.

135: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (d, J = 6 Hz, 3 H), 1.00-2.20 (m, 17 H), 1.03 (s, 3 H), 1.20 (s, 3 H), 3.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz)[27] δ 14.67 (q), 19.22 (t), 23.60 (t), 26.05 (t), 29.05 (q), 30.44 (q), 33.65 (s), 34.27 (t), 34.27

(d), 36.53 (t)*, 37.67 (d)*, 39.84 (t)*, 49.17 (d), 65.89 (t), 74.14 (s); mass spectrum *m/e* (relative intensity) 225 (M^+ - 15, 3), 222 (27), 207 (41), 204 (19), 189 (25), 163 (85), 137 (40), 121 (28), 109 (72), 81 (100); calcd for $C_{14}H_{25}O_2$ (M^+ - 15) *m/e* 225.1854, found 225.1845. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.94; H, 11.74. Found: C, 74.92; H, 11.82.

138: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.65-2.40 (m, 17 H), 0.86 (d, *J* = 7 Hz, 3 H), 0.90 (s, 3 H), 1.21 (s, 3 H), 3.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.83 (q), 17.20 (t), 22.91 (t), 26.07 (t), 29.26 (q), 29.41 (s), 30.95 (q), 32.18 (t), 32.78 (d), 40.94 (d), 41.51 (t), 42.10 (t), 47.54 (d), 65.99 (t), 73.29 (s); mass spectrum *m/e* (relative intensity) 222 (M^+ - 18, 17), 207 (27), 204 (15), 189 (16), 163 (81), 137 (30), 121 (26), 109 (100), 81 (49); calcd for $C_{15}H_{26}O$ (M^+ - 18) *m/e* 222.1983, found 222.1993.

[7R-[1α,4aα,7α(S*),8aα)]]-Decahydro-1-hydroxy-1,4a-dimethyl-7-[1-methyl-2-[(methylsulfonyl)oxy]ethyl]naphthalene (136). To a stirred solution of 0.412 g (1.72 mmol) of diol **135** in 20 mL of pyridine was added 0.444 g (3.88 mmol) of MsCl. The reaction mixture was stirred at 40 °C for 40 min and then concentrated under reduced pressure. The resulting residue was taken up in 50 mL of EtOAc and washed successively with 25 mL of 10% aqueous H_2SO_4, 50 mL of saturated aqueous $NaHCO_3$, and brine. The organic layer was dried and evaporated. The crude product was flash chromatographed (3:1 - 2:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 0.474 g (87%) of **136**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90-1.90 (m, 16 H), 0.95 (d, *J* = 7 Hz, 3 H), 1.02 (s, 3 H), 1.17 (s, 3 H), 2.96 (s, 3 H), 4.06 (dd, *J* = 9.5, 6.2 Hz, 1 H), 4.17 (dd, *J* = 9.5, 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz)[27] δ 14.50 (q), 19.12 (t), 23.24 (t), 25.86 (t), 29.24 (q), 30.41 (q), 33.57 (s), 34.32 (d), 34.32 (t), 34.94 (d)*, 36.53 (t)*, 37.14 (q), 39.87 (t)*, 48.78 (d), 73.38 (t), 73.80 (s); mass spectrum *m/e* (relative intensity) 303 (M^+ - 15, 3), 300 (13), 285 (29), 207 (16), 204 (70), 189 (47), 137 (44), 109 (72), 95 (65), 81 (100); calcd for $C_{15}H_{27}O_4S$ (M^+ - 15) *m/e* 303.1630, found 303.1631.

[7R-[1α,4aα,7α(S*),8aα)]]-Decahydro-1-hydroxy-1,4a-dimethyl-7-(1-methyl-2-iodoethyl)naphthalene (137). To a stirred solution of 0.441 g (1.39 mmol) of mesylate **136** in 20 mL of acetone was added 0.397 g (2.65 mmol) of NaI. The reaction mixture was heated at reflux for 48 h, allowed to come to room temperature, and then poured into 100 mL of water. The acetone was evaporated under reduced pressure, and the remaining aqueous layer was extracted with three 50-mL portions of EtOAc. The combined organic layers were dried and evaporated. The remaining residue was flash

chromatographed (10:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 0.432 g (88%) of **137**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (d, J = 6 Hz, 3 H), 0.90-1.80 (m, 16 H), 0.98 (s, 3 H), 1.18 (s, 3 H), 3.21 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz)[27] δ 18.46 (t), 18.56 (q), 19.14 (t), 23.25 (t), 25.83 (t), 29.38 (q), 30.45 (q), 33.53 (s), 34.75 (t), 35.92 (t)*, 37.16 (d), 37.16 (d), 39.53 (t)*, 48.66 (d), 73,87 (s); mass spectrum *m/e* (relative intensity) 335 (M^+ - 15, 3), 332 (11), 317 (19), 205 (50), 163 (79), 123 (21), 109 (43), 95 (49), 81 (74), 71 (100); calcd for $C_{14}H_{24}OI$ (M^+-15) *m/e* 335.0871, found 335.0867.

(+)-5-*epi*-Neointermedeol (VII). To a stirred solution of 0.232 g (0.66 mmol) of iodide **137** in 20 mL of dry *t*-BuOH was added 1.00 g (8.91 mmol) of *t*-BuOK. The reaction mixture was heated at reflux for 9 h, allowed to come to room temperature, and then diluted with 100 mL of saturated aqueous NH_4Cl. The aqueous solution was extracted with three 50-mL portions of EtOAc. The combined organic layers were dried and evaporated. The remaining residue was flash chromatographed (15:1 petroleum ether (bp 40-60 °C)/EtOAc) to give 0.144 g (98%) of **VII**: $[\alpha]_D$= +30.2 ± 0.1° (*c* = 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 3 H), 1.00-1.80 (m, 14 H), 1.23 (s, 3 H), 1.69 (d, J = 0.5 Hz, 3 H), 2.26 (m, 1 H), 4.73 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz)[27] δ 19.08 (t), 21.29 (q), 24.52 (t), 26.35 (t), 28.91 (q), 30.30 (q), 33.50 (s), 34.45 (t), 36.65 (t)*, 39.31 (d), 39.97 (t)*, 49.01 (d), 73.83 (s), 109.10 (t), 148.74 (s); mass spectrum *m/e* (relative intensity) 222 (M+, 11), 207 (3), 204 (82), 189 (100), 175 (11), 161 (68), 147 (36), 135 (71), 121 (39), 109 (74), 95 (58), 81 (88), 71 (44); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found 222.1994.

(+)-Amiteol (V). The same procedure was followed as described for the synthesis of (+)-**VII**. The diol **138** (0.132 g, 0.55 mmol) gave, *via* its mesylate **139** and iodide **140**, (+)-**V** in 58% overall yield. The physical and spectroscopic data of **139**, **140**, and (+)-**V** are shown below.

139: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 3 H), 0.93 (d, J = 7 Hz, 3 H), 1.00-2.20 (m, 16 H), 1.19 (s, 3 H), 2.96 (s, 3 H), 4.14 (d, J = 6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.39 (q), 17.34 (t), 23.76 (t), 25.99 (t), 29.31 (q), 31.19 (q), 32.07 (t), 32.76 (s), 33.30 (d), 37.25 (q), 38.58 (d), 41.60 (t), 42.39 (t), 47.59 (d), 73.19 (s), 73.58 (t); mass spectrum *m/e* (relative intensity) 300 (M^+ - 18, 6), 285 (11), 205 (17), 189 (30), 163 (22), 137 (44), 121 (24), 109 (22), 95 (60), 81 (100); calcd for $C_{16}H_{28}O_3S$ (M^+-18) *m/e* 300.1759, found 300.1748.

140: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.70-2.20 (m, 16 H), 0.88 (s, 3 H), 0.94 (m, 3 H), 1.26 (s, 3 H), 3.29 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.26 (t), 17.66 (q),

18.66 (t), 23.95 (t), 25.61 (t), 29.14 (q), 31.30 (q), 31.87 (t), 32.52 (s), 37.08 (d), 39.98 (d), 41.48 (t), 42.08 (t), 47.46 (d), 73.17 (s); mass spectrum *m/e* (relative intensity) 332 (M^+ - 18, 13), 317 (10), 205 (42), 163 (100), 135 (15), 123 (24), 109 (72), 95 (47), 81 (88), 71 (83); calcd for $C_{15}H_{25}I$ (M^+ - 18) *m/e* 332.1001, found 332.0984.

(+)-**V**: $[\alpha]_D$= +17.7 ± 0.1°, $[\alpha]_{365}$ = +60.3 ± 0.1° (*c* = 1.2, $CHCl_3$) (lit.[26] $[\alpha]_{365}$ = +8° ($CHCl_3$)). The spectroscopic data of (+)-**V** were identical with those of (±)-**V**.

6.4 REFERENCES AND NOTES

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(12) preceding chapter.

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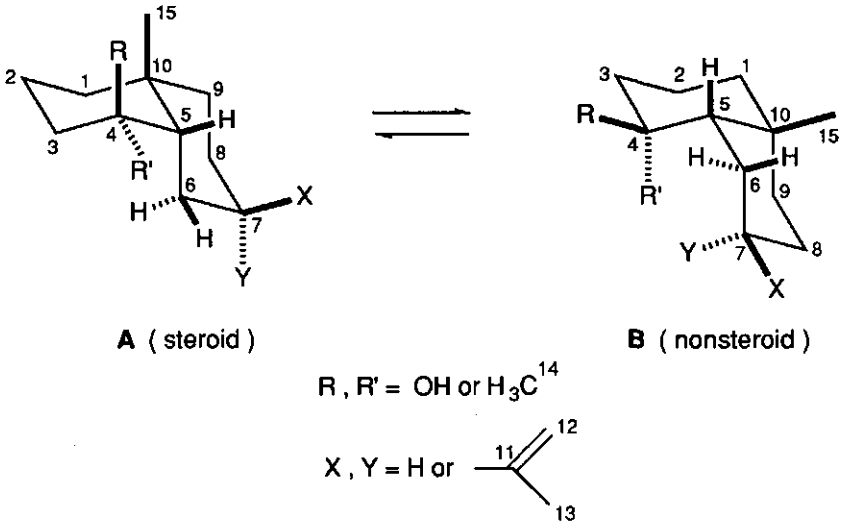
(27) Coalescence was observed for the marked signals. Increasing the temperature leads to sharpening of these signals.

7. CONFORMATIONAL ANALYSIS OF THE *CIS*-FUSED EUDESM-11-EN-4-OLS

It is already mentioned in chapter 4 that *cis*-fused decalins can occur in the steroid conformation, the nonsteroid conformation, or as an equilibrium mixture of these conformations[1] (Chart 7.1). In this equilibrium axial substituents shift to the equatorial positions and *vice versa*.

This chapter deals with the conformational analysis using NMR spectroscopy and MM2 calculations of the *cis*-fused eudesm-11-en-4-ols **V** - **VIII**. In addition, the conformational behavior of the *cis*-fused intermediates in the total synthesis of amiteol **V** and 7-*epi*-amiteol **VI** is studied to understand the stereochemical outcome of the reactions of these intermediates.[2]

Chart 7.1



7.1. CONFORMATIONAL ANALYSIS USING NMR

The first part of this paragraph describes the NMR method used during the conformational analysis. The second section deals with the conformational analysis of most of the *cis*-fused intermediates in the

synthesis of amiteol **V** and 7-*epi*-amiteol **VI**. The conformational analyses of amiteol **V**[4] and 7-*epi*-amiteol **VI** are given in the third and fourth section, respectively. The conformational behavior of 5-*epi*-paradisiol **VIII** and 5-*epi*-neointermedeol **VII** is described in the next two sections.[5] The last section of this paragraph deals with some final conclusions.

In principle, ^{1}H NMR spectroscopy can be used to distinguish between the two conformations. In the steroid conformation **A** the bridgehead proton at C-5 will have a large and a small coupling owing to an axial-axial and an axial-equatorial coupling with the α and β proton at C-6, respectively. In the nonsteroid conformer **B** these couplings are both small as a result of an equatorial-equatorial (with the α C-6 proton) and an equatorial-axial (with the β C-6 proton) coupling (Chart 7.1).

Additional information about the conformation of this type of *cis*-fused compounds can be obtained from the line width at half height of the C-7 proton ($W_{1/2}$).[3] When the $W_{1/2}$ is relatively small (± 15 Hz), as a result of two equatorial-axial and two equatorial-equatorial couplings, the C-7 substituent possesses an axial position. On the contrary, a relatively large $W_{1/2}$ (± 35 Hz) due to two axial-axial and two axial-equatorial couplings is consistent with an equatorial C-7 substituent.

In order to determine the conformation of the *cis*-fused decalins with NMR spectroscopy, the ^{1}H resonances have to be assigned. A problem is that the ^{1}H NMR spectra of the compounds investigated are complicated by extensive interproton coupling and by overlap of multiplet signals. This makes the full assignment of the ^{1}H NMR spectra using a 200 MHz spectrometer very difficult. However, in most compounds the protons at C-5 and C-7, which are very useful in determining the conformation, can be assigned using a combination of the following NMR techniques: two dimensional homonuclear correlation spectroscopy (COSY), two dimensional ^{1}H-^{13}C heteronuclear correlation spectroscopy (^{1}H-^{13}C), including the (^{13}C) cross-sections, and NOE-difference.

The procedure used in the NMR analyses of these *cis*-fused decalins started with recording the recording of the 2D COSY spectrum. In this spectrum the C-7 proton could be located because of a long range coupling with the geminal protons at C-12 (Chart 7.1). *Via* the ^{1}H-^{13}C spectrum the C-7 carbon (CH signal) was assigned. Consequently, the remaining CH signal in the ^{13}C spectum was identified as the C-5 carbon. Now, the C-5 proton could be located *via* the ^{1}H-^{13}C spectrum. In case of overlap of the multiplet signals of the C-5 and C-7 proton in the ^{1}H spectrum, cross-sections from the ^{1}H-^{13}C

spectrum gave the $W_{1/2}$ values and the (large) couplings. In some cases, the C-5 and C-7 proton signals appeared without overlap and the couplings could be measured directly in the ^{1}H NMR spectrum. The couplings (*J*) and the $W_{1/2}$ values measured for the C-5 and C-7 proton of the *cis*-fused eudesm-11-en-4-ols are listed in Table 7.1. The procedure, outlined above could not be used for 5-*epi*-neointermedeol **VII** because of coalesence effects (See paragraph 7.1.5).

Table 7.1. Chemical shifts for the C-5 and C-7 Protons[a,b]

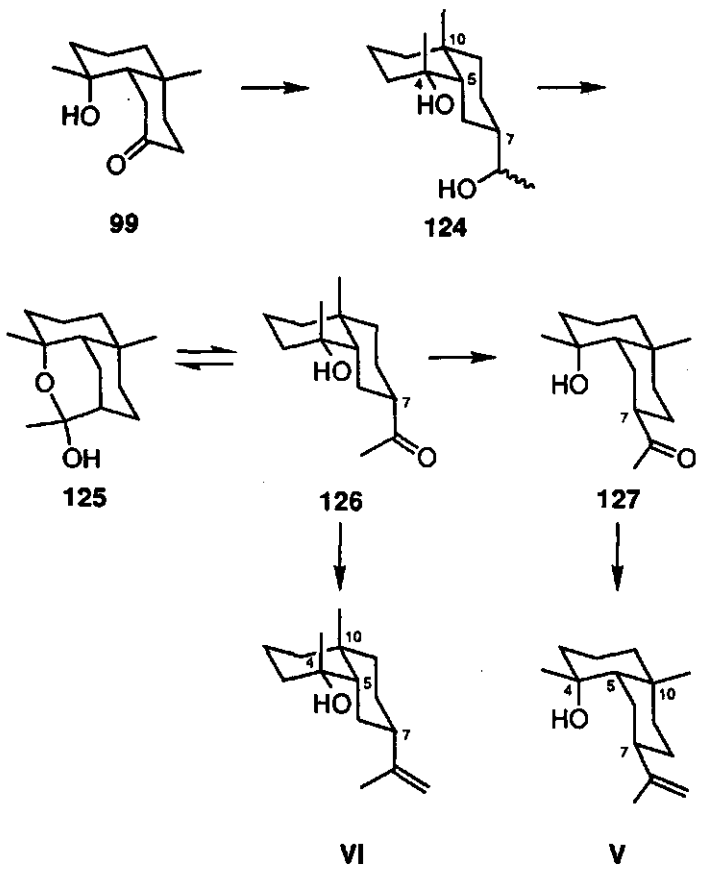
	H_{C-5}		H_{C-7}	
compound	δ	*J* (Hz)	δ	$W_{1/2}$ (Hz)
amiteol **V**	1.13	6, 3	2.62	31
7-*epi*-amiteol **VI**	1.40	16, ±3[c]	1.82	35
5-*epi*-neointermedeol **VII**[d]	-	-	2.26	-
5-*epi*-paradisiol **VIII**	1.23	14, 5	1.79	37

[a] Chemical shifts in ppm relative to the $CHCl_3$ singlet (δ 7.23).
[b] For full ^{1}H NMR spectra, see chapter 6 and 8
[c] Exact measurement of the small couplings was not possible.
[d] Coalesence effects.

7.1.1 Conformational analyses of intermediates in the synthesis of **V** and **VI**

The nonsteroid conformation of the hydroxy ketone **99**, which was used as the starting material in the synthesis of **V** and **VI**, has already been detemined in previous chapters.[6,7] The ketone **99** was converted *via* a Wittig reaction and an oxidative hydroboration into the diol **124**. The ^{1}H NMR spectrum of **124** shows two couplings of 14 and 2 Hz for the C-5 proton at δ 1.31 ppm. These values imply the steroid conformation for **124**.[8] This conformation is supported by a NOE between the C-10 methyl group at δ 0.98 ppm and the C-4 methyl group at δ 1.39 ppm. Furthermore, the $W_{1/2}$ value of 41 Hz of the C-7 proton indicates that the C-7 substituent of **124** possesses the equatorial position (Scheme 7.1). These data mean that during the conversion of ketone **99** into diol **124** a *conformational inversion* has occurred.

Scheme 7.1

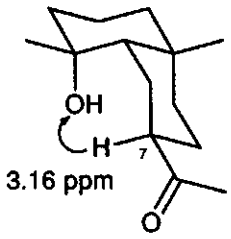


Oxidation of diol **124** gave the cyclic lactol **125**. The formation of **125** required again a *conformational inversion*. In solution the lactol **125** is in equilibrium with its open form **126**. For this reason, it is difficult to establish the conformation of **126**. Because of the structural similarities, it is likely that **126** must have the same conformation as **VI**[9] (See paragraph 7.1.3).

A short treatment of lactol **125** with a strong base gave **127**, which was converted into **V**. In the ^{1}H NMR spectrum the α C-7 proton of **127** appears at δ 3.16 ppm with two large couplings of 13 Hz. As a consequence, this proton must have the axial position. Normally, protons α to a carbonyl group appear at ± 2 ppm.[2] The deshielding of the α C-7 proton of **127** with ca. 1 ppm results from the anisotropy of the tertiary hydroxyl group. Such an

interaction is only possible when **127** possesses the nonsteroid conformation (Figure 7.1).

Figure 7.1



127 (nonsteroid)

7.1.2 Conformational analysis of Amiteol **V**

The conformation of amiteol **V** is easy to determine with NMR, because the C-5 and C-7 proton both appear separately. The C-5 proton is located at δ 1.13 ppm with small couplings of 3 and 6 Hz. The C-7 proton appears at δ 2.62 ppm with a $W_{1/2}$ value of 31 Hz. The low field location of the C-7 proton can be explained in a similar way as for the C-7 proton of the acetyl compound **127**. These data found for amiteol **V** are consistent with the nonsteroid conformation (Scheme 7.1). Further evidence was gained upon irradiation of the C-10 methyl group at δ 0.94 ppm, which yielded no NOE of the C-4 methyl group at δ 1.22 ppm. Prestwich, who studied natural amiteol **V** using a 360 MHz spectrometer, also came to the nonsteroid conformation for **V**.[4]

7.1.3 Conformational analysis of 7-*epi*-Amiteol **VI**

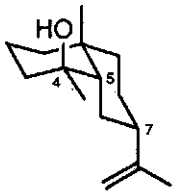
The conformation of 7-*epi*-amiteol **VI** is more difficult to determine. The protons at C-5 and C-7 give rise to overlapped signals in the ^{1}H NMR spectrum. However, the assignment of these protons is easy using the cross-sections from the ^{1}H-^{13}C spectrum. The C-5 proton appears at δ 1.40 ppm with a large coupling of 16 Hz and a small coupling of about 3 Hz. The C-7 proton is located at δ 1.82 ppm with a $W_{1/2}$ value of 35 Hz. Further information was obtained by irradiation of the C-10 methyl group at δ 0.99 ppm which gave a large NOE on the C-4 methyl group at δ 1.39 ppm. These

observations lead to the conclusion that **VI** exists in the steroid conformation (Scheme 7.1).

7.1.4 Conformational analysis of 5-*epi*-Paradisiol **VIII**

In the ^{1}H NMR spectrum of 5-*epi*-paradisiol **VIII** both the C-5 and the C-7 proton signals are overlapped by other multiplets. Again, the cross-sections of C-5 and C-7 carbons can be used for the conformational analysis. The C-5 proton is located at δ 1.23 ppm with couplings of 5 and 14 Hz. The C-7 proton appears at δ 1.79 ppm with a $W_{1/2}$ value of 37 Hz. These data are in agreement with the steroid conformation for **VIII** (Figure 7.2). The steroid conformation of **VIII** has been confirmed by a single-crystal X-Ray analysis.[10]

Figure 7.2



VIII

7.1.5 Conformational analysis of 5-*epi*-Neointermedeol **VII**

The conformational behavior of 5-*epi*-neointermedeol **VII** is different from that of the other *cis*-fused eudesm-11-en-4-ols. In the ^{13}C and ^{1}H NMR spectra exchange phenomena are observed at room temperature. Two ^{13}C signals show coalescense effects. By increasing the temperature to 55 °C these effects disappear. Decreasing the temperature to -43 °C gives an almost complete redoubling of the number of ^{13}C peaks. At lower temperature the ^{1}H NMR spectrum in $CDCl_3$ does not show sharpening of the signals. As a consequence, it is not possible to use 2D NMR techniques. These coalescense effects are attributed to the existence of an equilibrium mixture of two conformers.

Comparison of the peak areas of the ^{13}C signals[11] of **VII** at -43 °C reveals that the quaternary C-11 signal at δ 151.03 ppm and the CH signals at δ 46.10 and 38.26 ppm belong to the conformer, present in minor quantity

Table 7.2. ^{13}C NMR Data (50 MHz) for the eudesmane alcohols I-VIII in $CDCl_3$[a]

	carbon	*trans* -eudesmanes				*cis* -eudesmanes				
signal[b]	no	I	II	III	IV	V	VI	VII(minor)	VII(major)	VIII
CH	5	54.69	49.08	51.84	45.82	47.66	53.03	46.10	50.14	51.91
	7	46.19	39.25	46.67	39.13	39.62	45.32	38.26	39.67	45.49
C	11	150.49	146.61	150.75	146.90	151.75	150.82	151.03	146.16	150.59

[a] For full ^{13}C NMR spectra, see chapter 6 and 8.

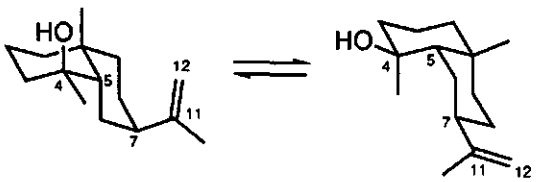
[b] Multiplets were obtained from DEPT experiment.

(minor conformer). The C-11 signal at δ 146.16 ppm and the CH signals at δ 50.14 and 39.67 ppm are assigned to the conformer, present in major quantity (major conformer). Comparison of the C-11 shifts of the eudesm-11-en-4-ols (Table 7.2) learns that these signals appear in the range of δ 150-152 ppm when the 1-methylethenyl group has an equatorial position (**I, III, V, VI,** and **VIII**). In case of an axially orientated 1-methylethenyl group, such as in **II** and **IV**, the C-11 signals appear at about δ 146 ppm.

Comparing these values with the chemical shifts of the two C-11 signals observed in the ^{13}C NMR spectrum of **VII** at -43 °C, lead to the conclusion that the 1-methylethenyl group is equatorially orientated in the minor conformer, and axially in the major conformer.

Comparison of the CH signals of the minor conformer (δ 38.26 and 46.10 ppm) with those of amiteol **V** (δ 39.62 and 47.66 ppm), which exists in the nonsteroid conformation, shows that the chemical shifts of these signals do not differ very much. From this similarity, it is concluded that the minor conformer **VIIB** is the nonsteroid conformation with an equatorial 1-methylethenyl group (Figure 7.3). As a consequence, the major conformer **VIIA** is the steroid conformation (Figure 7.3).

Figure 7.3



VIIA (major) **VIIB** (minor)

7.1.5.1 Dynamic NMR Investigation

The redoubling of the ^{13}C signals in the spectrum of **VII** at lower temperature allows the calculation of the conformational inversion barrier and the conformational energy difference between **VIIA** and **VIIB**.

The conformational inversion barrier (ΔG_{act}) can be calculated using the Eyring-equation:[12]

$$\Delta G_{act} = 19.12 \cdot T_c \, (9.97 + \log T_c/\delta\upsilon) \, (J/mol) \qquad (eq\ 1)$$

T_c is the temperature in K at which two signals of a ^{13}C nucleus are just separated from each other, and $\delta\upsilon$ is the difference in resonance frequency in Hz of this ^{13}C nucleus in the steroid and the nonsteroid conformation.

The coalescenced ^{13}C signal of C-12 is used for the calculation of ΔG_{act}. This isolated signal at δ 109 ppm is just separated at -18 °C (T_c = 255 K). In the ^{13}C NMR spectrum at - 43 °C the $\delta\upsilon$ of 146.5 Hz could be measured. Using these data in eq 1 gives a ΔG_{act} of 50 kJ/mol. This value is in good agreement with the value determined for *cis*-decalin (52 kJ/mol).[1b]

The calculation of the conformational energy difference (ΔG) between **VIIA** and **VIIB** can be achieved using the ^{13}C NMR spectrum at -43 °C. It was assumed that in the Gibbs-Helmholtz equation ($\Delta G = \Delta H - T\Delta S$) ΔG is independent of temperature, because the difference in entropy (ΔS) and in heat capacity (ΔC_p)[13] between the two conformers are both small or zero. The ΔG can then be calculated using the following formula:

$$\Delta G = -R.T.\ln K_{eq} \qquad (eq\ 2)$$

K_{eq} is the equilibrium constant, which can be gained upon measuring the ratio of the peak areas of signals of a ^{13}C nucleus in the steroid and nonsteroid conformation, T is the temperature in K at which K_{eq} is determined, and R is the gas constant.

At -43 °C (T = 230 K) a ratio of 1:2.7 (K_{eq} = 1/2.7) between the two peak areas of the C-12 signals could be measured. Using these data in the formula, a ΔG value of 2 kJ/mol is found.

7.1.6 Conclusions

It has become clear that the compounds **V**, **VI**, and **VIII** adopt a conformation in which the relatively large 1-methylethenyl group possesses an equatorial position. The orientation of the methyl group at C-4 in these compounds seems to be less important. The *conformational inversions* observed during the syntheses of **V** and **VI** can be explained in a similar way.

However, in the nonsteroid conformer **VIIB** with an equatorial 1-methylethenyl group the axial orientated C-4 methyl group is subjected to severe compression by the ajoining ring. This compression is thought to be nearly equivalent in magnitude with the 1,3-diaxial interactions of the C-4 hydroxyl and the C-7 1-methylethenyl group in the steroid conformer **VIIA**.

This counterbalance in combination with the calculated energy barrier of 50 kJ/mol, explains the observed conformational equilibrium of **VII**.

7.2 CONFORMATIONAL ANALYSIS USING MOLECULAR MECHANICS CALCULATION (MM2)

The conformational behavior of the eudesm-11-en-4-ols determined in the foregoing paragraph was simulated with molecular mechanics calculations using the MM2(87) force field valence program.[14] The procedure used was as follows: Both the steroid and the nonsteroid conformations of **V - VIII** were optimized by energy minimization with the MM2 program. During the minimization the stretch, bending, stretch bending, torsional, dipolar, and van der Waals contributions were taken into account. The difference in the calculated energies between the nonsteroid and the steroid conformer ($\Delta G = G_{nonst} - G_{st}$) was appointed.

The entropy difference between the nonsteroid and steroid conformers (ΔS) is assumed to be negligibly small. The equilibrium constant (K_{eq}) can then be calculated from ΔG using equation 2. The fraction X of the nonsteroid conformer in the equilibrium mixture can be calculated using equation 3:

$$K_{eq} = X/(1 - X) \quad \text{(eq 3)}$$

In most cases the results of the MM2 calculations were consistent with those obtained from the NMR experiments. However, for the nonsteroid conformation of 7-*epi*-amiteol **VI** an intramolecular H-bonding between the tertiary alcohol at C-4 and the double bond was found. Not any experimental evidence was found to support this intramolecular H-bonding.[15] Therefore, the H-bonding energy terms were omitted in the MM2 program.[16] In this way, the energy of the nonsteroid conformation of **VI** agrees with the experimental data. The energies of the other compounds are not affected. The calculated data are shown in Table 7.3.[17]

Table 7.3. Free Energy Calculations of the Steroid and Nonsteroid Conformers of the *Cis*-fused Eudesm-11-en-4-ols

compound	calculated results: Energy (kJ/mol) steroid conformer	nonsteroid conformer	ΔG	% non-steroid	experimental results: % non-steroid
V	125	107	-18	>>99	>97
VI	114	124	+10	~1	<3
VII	116	118	+2	26	27
VIII	104	140	+36	<<1	<3

The percentages of the nonsteroid conformer found with NMR are also listed in Table 7.3. Comparison of these results with those obtained from the MM2 calculations show that the outcome of both methods (NMR and MM2) fits very well. So MM2 calculations make a reliable prediction of the conformational behavior of eudesm-11-en-4-ols possible.

7.3 EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker 200 E at 200 MHz (^{1}H) and at 50 MHz (^{13}C). Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). NMR multiplicities are recorded by use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad; *J*, coupling constant; $W_{1/2}$, line width at half height; Hz, hertz. Typical parameters for the COSY-45 experiments are as follows: 90° pulse = 6 μs (5 mm selective probe), a spectral width of 900 Hz in t_1 and t_2 was used, and 128 experiments with 8 transients each were done. Before Fourier transformation, zero filling was used once, and no window functions were applied. For the ^{1}H-^{13}C heteronuclear shift correlation spectra: 90° carbon pulse = 6 μs, 90° proton pulse = 11 μs (5 mm dual probe). Spectral width in t_1 = 800 Hz, in t_2 = 3787.9 Hz with a size of 256·1 K. A total of 128 experiments with 128 transients each were performed. Delays used in the pulse sequence were 3.3 and 2.2 ms. Sine-bell window functions without phase shift were used for the fourier transformation. MM2(87) calculations were performed in SiliconGraphics Personal IRIS 4D/25 computer.

^{13}C NMR spectra of 5-*epi*-neointermedeol VII. ^{13}C NMR ($CDCl_3$, 50 MHz, room temperature) δ 19.08 (t), 21.29 (q), 24.52 (t), 26.35 (t), 28.91 (q), 30.30 (q), 33.50 (s), 34.45 (t), 36.65 (t)[18], 39.31 (d), 39.97 (t)[18], 49.01 (d), 73.83 (s), 109.10 (t), 148.74 (s); ^{13}C NMR ($CDCl_3$, 50 MHz, 55 °C) δ 19.06 (t), 21.06 (q), 24.63 (t), 26.46 (t), 28.84 (q), 30.22 (q), 33.48 (s), 34.62 (t), 36.77 (t), 39.45 (d), 40.03 (t), 49.15 (d), 73.59 (s), 108.98 (t), 148.67 (s); ^{13}C NMR ($CDCl_3$, 50 MHz, -43 °C) δ 18.14 (t), 19.67 (t), 20.85 (q), 22.72 (t), 25.29 (t), 25.51 (t), 27.04 (t), 27.32 (q), 29.24 (t), 29.90 (q), 31.11 (q), 32.30 (t), 33.50 (t), 33.59 (s), 36.80 (t), 38.26 (d), 39.67 (d), 41.59 (t), 44.14 (t), 46.10 (d), 50.14 (d), 73.79 (s), 108.01 (t), 110.94 (t), 146.16 (s), 151.03 (s).

7.4 REFERENCES AND NOTES

(1) (a) Browne, L. M.; Klinck, R. E.; Stothers, J. B. *Can. J. Chem.* **1979**, *57*, 803. (b) Browne, L. M.; Klinck, R. E.; Stothers, J. B. *Org. Magn. Reson.* **1979**, *12*, 561. (c) Dalling, D. K.; Grant, D. M.; Johnson, L. F. *J. Am. Chem. Soc.* **1971**, *93*, 3678. (d) see chapter 4.

(2) See chapter 6.

(3) Rao, P. N. *J. Org. Chem.* **1971**, *36*, 2426.

(4) Naya, Y.; Prestwich, G. D.; Spanton, S. G. *Tetrahedron Lett.* **1982**, 23, 3047.

(5) Confronted with inseparable product mixtures during the synthesis of **VII** and **VIII** it was not possible to perform conformational analysis because of overlap of chemical related protons in the ^{1}H MMR spectra.[2]

(6) See scheme 6.4, previous chapter.

(7) See chapter 5.

(8) The diastereoisomeric mixture of **124** was separated after carefull column chromatography. Both diastereoisomers must have the same conformation because of the small differences in chemical shifts and couplings.

(9) This assumption is supported by MM2 calculations. A ΔG = 2 kJ/mol in favor of the steroid conformer was found.

(10) Baker, R.; Organ, A. J.; Walsmley, S. A.; Webster, M.; Galas, A. M. R. *J. Chem. Res. Miniprint* **1984**, 1401.

(11) The difference in peak areas of two ^{13}C signals, which interchange environment due to conformational inversion, is a measure for the relative quantity between the two conformations when the assumption is made that the relaxation time of the ^{13}C nucleus in both conformers is in the same range.

(12) Günther, H. *NMR-Spektroskopie;* Georg Thieme Verlag: Stuttgart, 1973, 248.

(13) (a) ΔH is temperature independent when ΔC_p is small or zero. (b) Denbigh, K. *The Principles of Chemical Equilibrium;* Cambridge University: Cambridge, 1981, 144 and 150.

(14) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) Burkert, U.; Allinger, N. L. *Molecular Mechanics;* ACS Monograph 177, Washington, D. C. 1982.

(15) A decrease in intensity of the absorption band for bonded OH stretching and a concommitant increase in the intensity of the free hydroxyl absorption in the IR spectrum of **VII** was observed after dilution in CCl_4.

(16) The H-bonding parameters of O-H with C=C and O-H with C=O, (MM2 atom types, 21···2, and 21·····7, respectively) were set to zero.

(17) The calculated data of the intermediates in the synthesis of **V** and **VI** are also in good agreement with the NMR results.

(18) Coalesence of this signal was observed.

8. CHROMATOGRAPHIC AND SPECTROSCOPIC DATA OF ALL STEREOISOMERS OF EUDESM-11-EN-4-OL

Since all eight stereoisomers of eudesm-11-en-4-ol were available in pure form and in sufficient amounts it was considered worthwhile to record for all of them - under identical conditions - the retention on two different capillary GC columns and the mass-, FTIR-, ^{1}H NMR-, and ^{13}C NMR spectra and to publish these data. Thus others may be able to identify these common essential oil constituents more reliably in future, either without isolating them (by Kovats indices, GC/MS, and GC/FTIR) or after isolation (by NMR). In this chapter these data are presented and discussed shortly.

8.1 MASS SPECTRA

The MS spectra are shown in the Figures 8.1a-h. Only neointermedeol **III**, paradisiol **IV**, and amiteol **V** can be clearly distinguished. Amiteol **V** has its base peak at *m/z* 109, while all the others show their base peak at *m/z* 43. Neointermedeol **III** and paradisiol **IV**, which both possess an equatorial methyl group at C-4, show a significant peak at *m/z* 207 corresponding with the loss of a methyl group $[M-15]^{+}$. Distinction between these two compounds, which only differ in the stereochemistry at C-7, is possible by comparing the ratio between the peaks at *m/z* 135 and 125 and between *m/z* 135 and 151. For neointermedeol **III** these ratio's are 10.7 and 13.9, respectively, while for paradisiol **IV** values of 1.4 and 1.6 are observed. The same ratio's can be used to distinguish between the two other *trans*-fused C-7 epimers selin-11-en-4α-ol **I** and intermedeol **II** (9.9 and 18.2 for selin-11-en-4α-ol; 0.60 and 3.7 for intermedeol). Apart from the low *m/z* 135 to 125 ratio, intermedeol **I** may be further recognized by a high *m/z* 204 to 81 ratio. However, the spectra of selin-11-en-4α-ol **I** and 5-*epi*-neointermedeol **VII** are nearly fingerprint identical. The only significant difference lies in the *m/z* 123 to 125 ratio (4.3 and 1.9, respectively). As a pair these compounds can be distinguished from the *cis*-fused eudesmanes **VI** and **VIII** by their different *m/z* 135 to 137 ratio. For the compounds **VI** and **VIII** this ratio is 1.0, while a value of ca. 1.9 is found for the first pair. The spectra of 7-*epi*-amiteol **VI** and 5-*epi*-paradisiol **VIII** are also very similar. A small difference can be found in the ratio between the peaks at *m/z* 189 and 222 (parent peak), 9.3 and 2.5, respectively. No detailed mass spectral studies have been carried out to explain the above observed empirical differences. Without the exact spectra

Figure 8.1a: Mass spectrum of selin-11-en-4α-ol **I**.

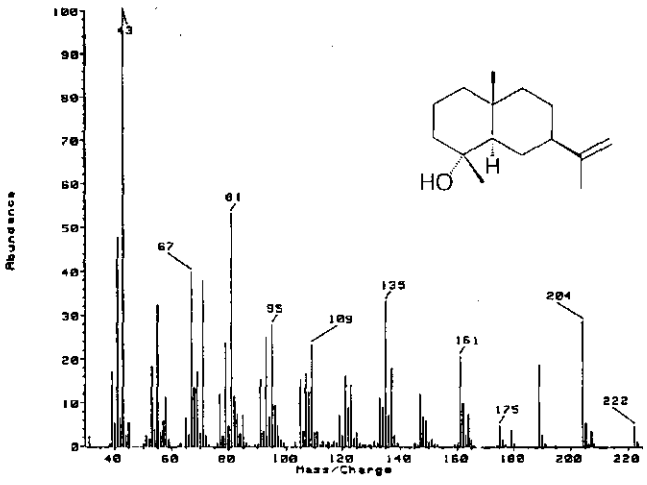


Figure 8.1b: Mass spectrum of intermedeol **II**.

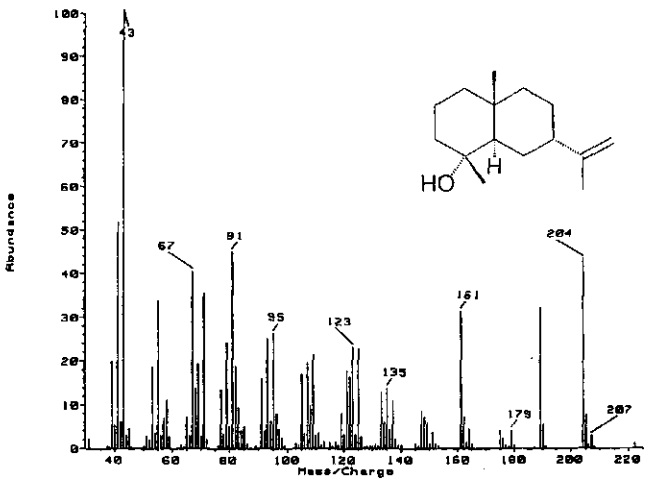


Figure 8.1c: Mass spectrum of neointermedeol **III**.

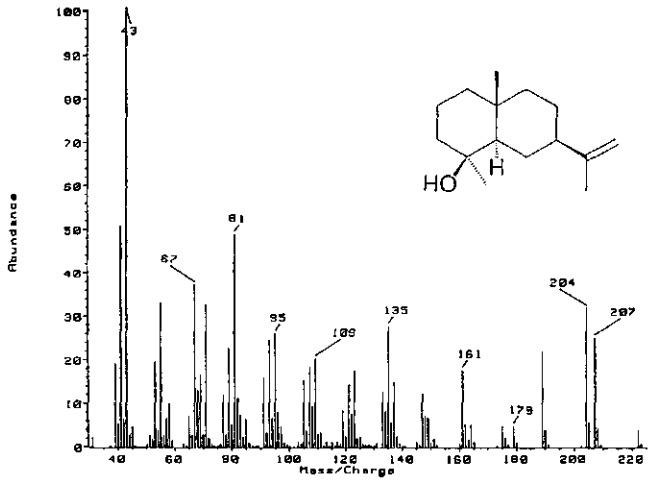


Figure 8.1d: Mass spectrum of paradisiol **IV**.

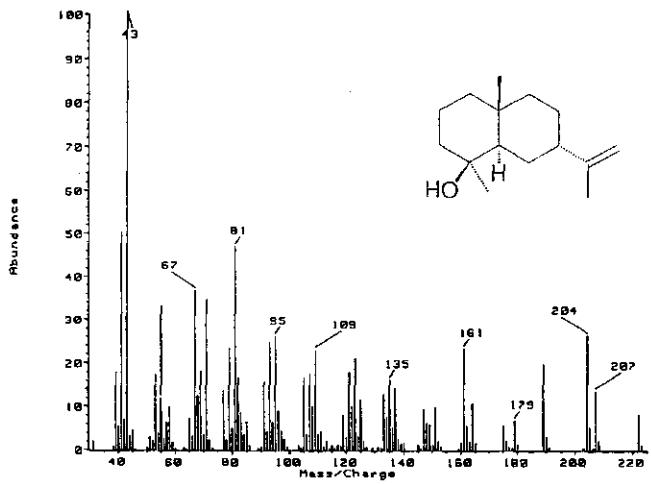


Figure 8.1e: Mass spectrum of amiteol **V**.

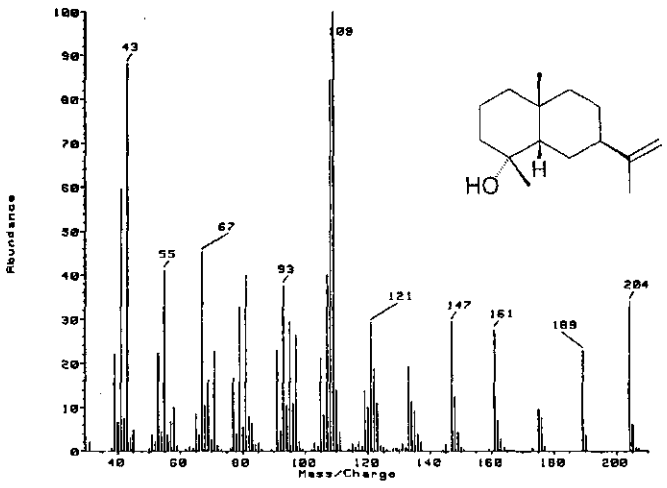


Figure 8.1f: Mass spectrum of *7-epi*-amiteol **VI**.

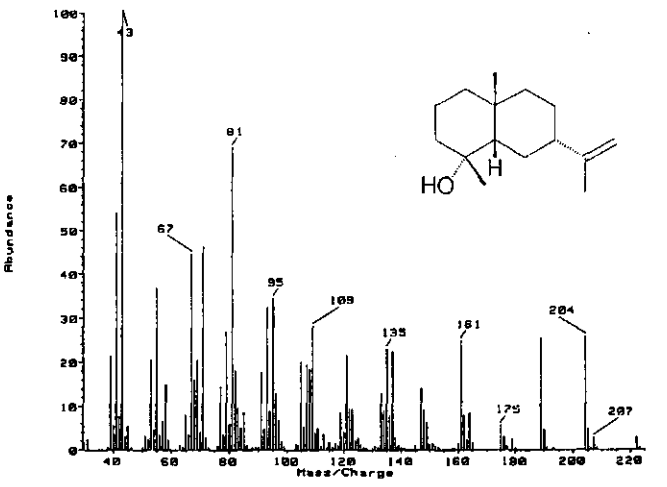


Figure 8.1g: Mass spectrum of 5-*epi*-neointermedeol VII.

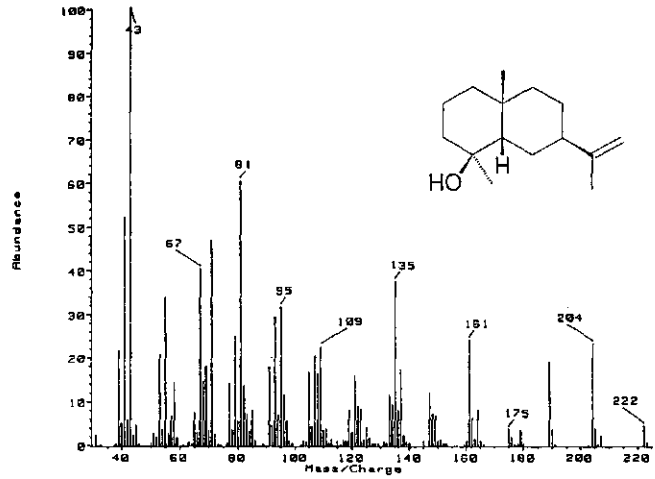
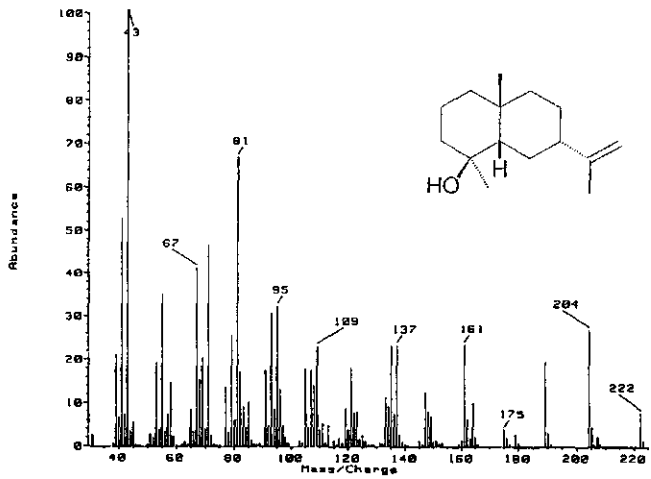


Figure 8.1h: Mass spectrum of 5-*epi*-paradisiol VIII.



as presented in Fig. 8.1a-h a distinction between selin-11-en-4α-ol **I** and the *cis*-fused compounds **VI-VIII** will be hard to make.

8.2 RETENTION INDICES

Retention indices for all eight stereoisomers on both the apolar and polar column are given in Table 8.1. As a further characteristic of each compound the difference in retention index (Δ RI) on the two columns is presented as well.

Table 8.1. Retention Indices of the Eudesm-11-en-4-ol Stereoisomers I-VIII

	Retention indices		
compound	DB-1	DB-Wax	DRI
selin-11-en-4α-ol **I**	1641	2264	623
intermedeol **II**	1647	2247	600
neointermedeol **III**	1602	2148	546
paradisiol **IV**	1627	2182	555
amiteol **V**	1587	2122	535
7-*epi*-amiteol **VI**	1646	2264	618
5-*epi*-neointermedeol **VII**	1637	2245	608
5-*epi*-paradisiol **VIII**	1600	2154	554
β-eudesmol **22**	1638	2242	-

For comparison the retention index obtained under identical conditions of the frequently occurring sesquiterpene alcohol β-eudesmol **22**[1] is also given. On the apolar methyl silicone column a clear distinction by means of retention indices can be made between selin-11-en-4α-ol **I**, paradisiol **IV**, amiteol **V**, and 5-*epi*-neointermedeol **VII**. The two pairs which are poorly separated on this column, namely intermedeol **II**/7-*epi*-amiteol **VI** and neointermedeol **III**/5-*epi*-paradisiol **VIII** can be separated on the polar polyethylene glycol column. The order of elution on the apolar column is based on the availability of the apolar groups for van der Waals interaction with each other and with the stationairy phase. The order on the polar column is determined by the relative availability of the polar hydroxyl function for polar interactions with the stationary phase. The more exposed this group is, the stronger the retention. In amiteol **V**[2] the hydroxyl group is

effectively screened by the C-4 methyl group and the α-protons at C-2, C-7, and C-9. Thus it has the lowest retention index on the polar column. In neointermedeol **III**, paradisiol **IV** and 5-*epi*-paradisiol **VIII**[3] the hydroxyl group is hindered by two methyl groups of which the C-10 methyl group is in a 1,3-diaxial position to the C-4 hydroxyl group. This hindrance is nicely illustrated by the relatively small difference in retention index between the apolar and polar column (average Δ RI = 552). In the remaining four eudesmanes the hydroxyl group is only hindered by the methyl group on the same carbon and is thus more available for interactions with the stationary phase. This causes a significantly higher difference in retention index (average Δ RI = 612).

8.3 ^{13}C AND ^{1}H NMR SPECTRA

The ^{13}C NMR data are given in Table 8.2, and the ^{1}H NMR spectra are shown in the Figures 8.2a-h. The distinction between the eight eudesmane alcohols is easy by means of ^{13}C NMR.

The resonances attributed to C-15 are diagnostic for the stereochemistry at C-5. In the *cis*-fused compounds **V-VIII** the C-15 signals resonate in the range of δ 28.9-30.7 ppm, while the corresponding resonances in the *trans*-fused compounds **I-IV** are found at about δ 18.5 ppm. The shifts of the C-14 carbons in these *trans*-fused compounds correlate well with the stereochemistry at C-4. When C-14 is β-oriented, as in neointermedeol **III** and paradisiol **IV**, the signals appear approximately at δ 22.5 ppm. In contrast, the downfield signals of C-14 at about δ 30.0 ppm in the spectra of intermedeol **II** and selin-11-en-4α-ol **I** are indicative of an α-orientation of this methyl group. Distinction between neointermedeol **III** with an equatorial substituent at C-7 and paradisiol **IV** with an axial substituent at the same carbon can be made by comparing the methine signals which appear at δ 54.69 and 46.19 ppm for neointermedeol **III**, and at δ 49.08 and 39.25 ppm for paradisiol **IV**. Similar differences are observed between selin-11-en-4α-ol **I** and intermedeol **II**. The distinction between the *cis*-fused compounds **V-VIII** is less clear. Although significant differences between amiteol **V** and 5-*epi*-neointermedeol **VII** on the one hand, and 7-*epi*-amiteol **VI** and 5-*epi*-paradisiol **VIII** on the other are observed for the methine signals, no further simple distinction by means of a single characteristic absorption can be made. For instance, the C-14 signals all have about the same shift (ca. δ 31.0 ppm). Nevertheless, by comparison of the shifts of the methylene carbons the *cis*-fused compounds **V-VIII** can be

Table 8.2. ^{13}C NMR Data of the Eudesm-11-en-4-ol Stereoisomers I-VIII in $CDCl_3$

		trans-eudesmanes				*cis*-eudesmanes			
signal	C	I	II	III	IV	V	VI	VII	VIII
CH_3	13	21.00	22.65	20.69	22.59	20.92	21.09	21.29	20.73
	14	22.58	22.21	30.23	29.78	31.23	31.15	30.30	31.20
	15	18.61	18.38	18.66	18.31	29.49	30.50	28.91	30.65
CH_2		20.03	20.06	18.03	17.81	17.39	20.26	19.08	18.21
		25.89	22.65	25.76	22.38	26.50	27.18	24.52	26.60
		26.74	23.40	26.81	23.13	26.60	29.40	26.35	29.66
		40.96	40.24	41.24	39.38	32.47	29.40	34.45	31.20
		43.23	41.25	41.56	41.01	41.76	35.25	36.65	34.17
		44.55	43.42	43.85	41.61	42.57	42.96	39.97	42.73
	12	108.06	110.72	108.31	110.37	107.56	108.02	109.10	107.92
CH	5	54.69	49.08	51.84	45.82	47.66	53.03	49.01	51.91
	7	46.19	39.25	46.67	39.13	39.62	45.32	39.31	45.49
C	10	34.49	35.21	33.66	34.14	32.79	33.99	33.50	33.04
	4	72.10	72.01	71.92	71.83	73.46	72.81	73.83	74.01
	11	150.49	146.61	150.75	146.90	151.75	150.82	148.74	150.59

Figure 8.2a: ^{1}H NMR spectrum of selin-11-en-4α-ol I.

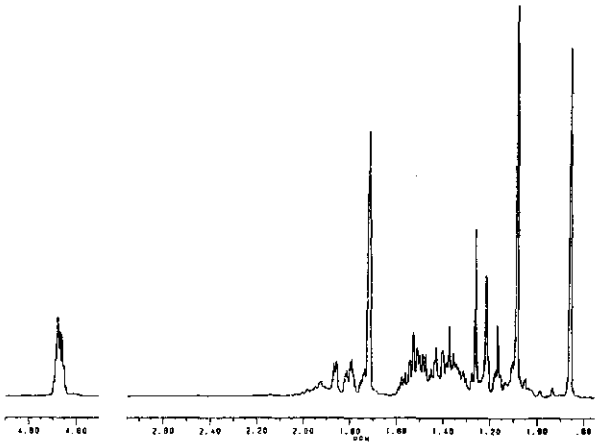


Figure 8.2b: ^{1}H NMR spectrum of intermedeol II.

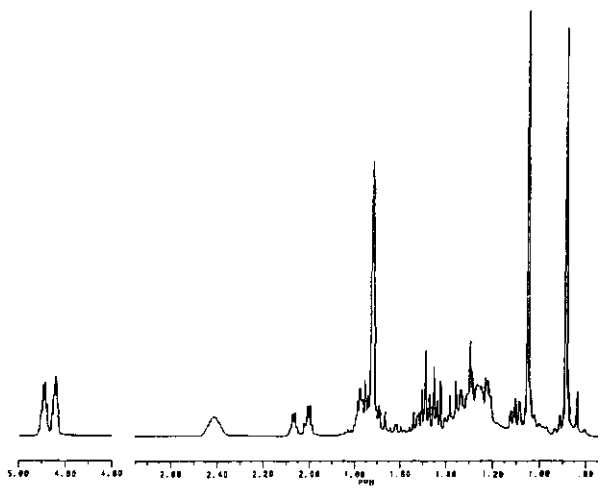


Figure 8.2c: ^{1}H NMR spectrum of neointermedeol III.

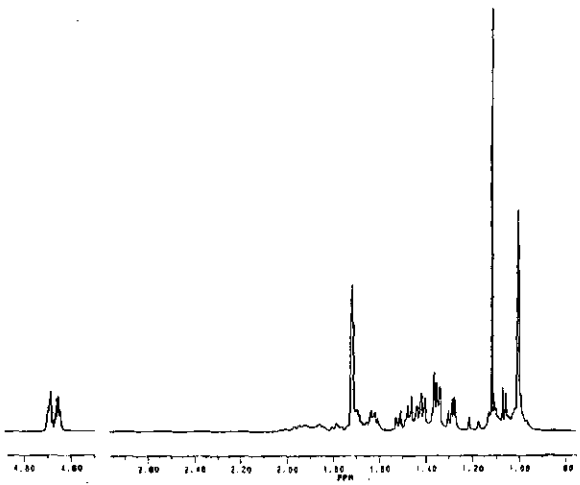


Figure 8.2d: ^{1}H NMR spectrum of paradisiol IV.

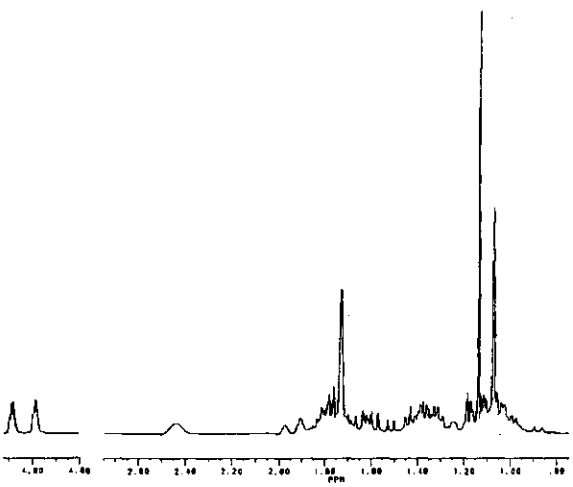


Figure 8.2e: ^{1}H NMR spectrum of amiteol **V**.

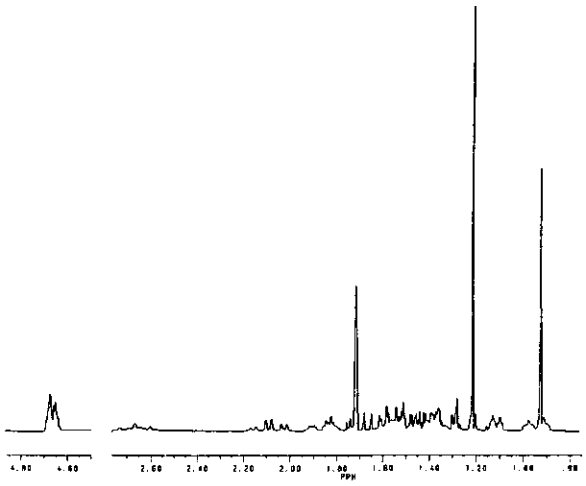


Figure 8.2f: ^{1}H NMR spectrum of *7-epi*-amiteol **VI**.

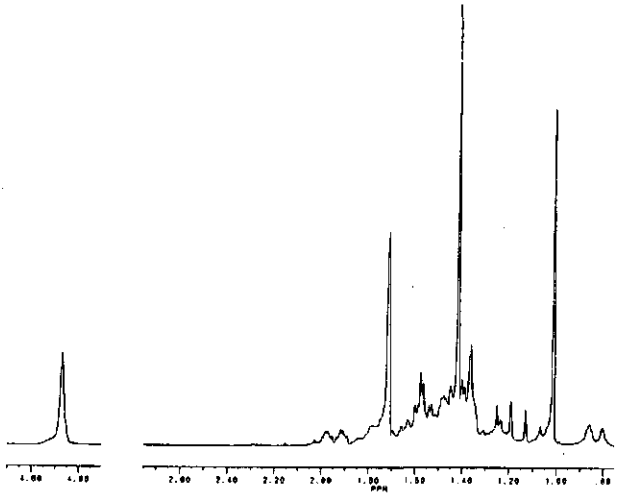


Figure 8.2g: ^{1}H NMR spectrum of 5-*epi*-neointermedeol **VII**.

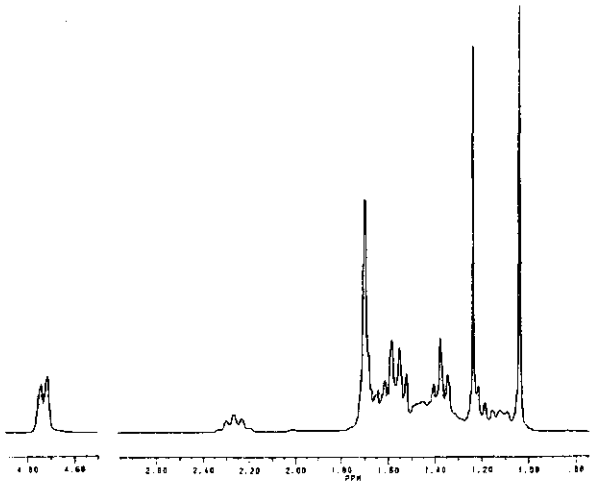
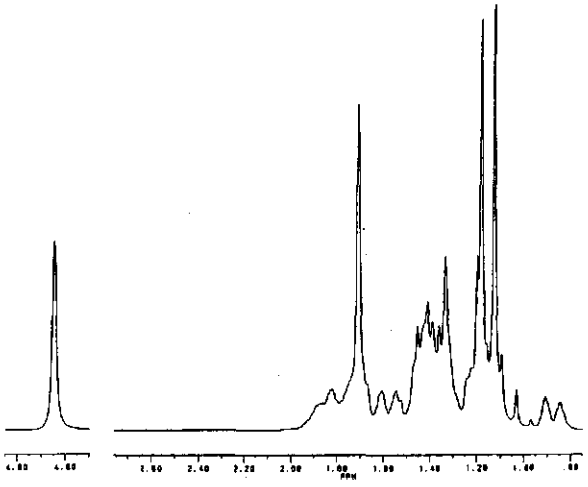


Figure 8.2h: ^{1}H NMR spectrum of 5-*epi*-paradisiol **VIII**.



reliably identified. With ^{1}H NMR, however, distinction between these compounds is much easier. The ^{1}H NMR spectrum of amiteol **V** shows a multiplet at δ 2.64 ppm, while the corresponding signal in 5-*epi*-neointermedeol **VII** appears at δ 2.26 ppm. The difference in chemical shift between the methyl groups at C-4 and C-10, 0.40 and 0.05 ppm for 7-*epi*-amiteol **VI** and 5-*epi*-paradisiol **VIII**, respectively, is useful in distinguishing between these two compounds.

8.4 FTIR SPECTRA

All the FTIR spectra of the eight stereoisomers of eudesm-11-en-4-ol are slightly different in the fingerprint area. However, it was not possible to correlate these differences with the stereochemistry of the eudesm-11-en-4-ols. Nevertheless the FTIR spectra are given for comparison (Figure 8.3a-h).

8.5 CONCLUSION

In conclusion is it possible to identify all eight stereoisomers of eudesm-11-en-4-ol by any of the five techniques discussed above. If the compounds have to be detected in mixtures (e.g. essential oils) the most reliable method is a combination of GC/MS, GC/FTIR, and capillary GC on two different columns. After isolation and purification further confirmation can be obtained with either ^{1}H NMR or ^{13}C NMR.

8.6 EXPERIMENTAL

The eight possible stereoisomers of eudesm-11-en-4-ol, namely selin-11-en-4α-ol **I**, intermedeol **II**, neointermedeol **III**, paradisiol **IV**, amiteol **V**, 7-*epi*-amiteol **VI**, 5-*epi*-neointermedeol **VII**, and 5-*epi*-paradisiol **VIII** have been synthesized as described (vide infra).[4,5,6]

GC/MS was performed at 70 eV on a Hewlett Packard 5970 B series Mass Selective Detector, coupled with a J & W DB-17 fused silica capillary column, 30 m x 0.25 mm i.d. and 0.25 μm film thickness in a Hewlett Packard 5890 A Gas Chromatograph; carrier gas He.GC was performed on a Hewlett Packard 5890 A gas chromatograph equipped with one split/splitless injection system, a 1:1 inlet splitter, two columns and two FI detectors. The two columns were

Figure 8.3a: FTIR spectrum of selin-11-en-4α-ol **I**.

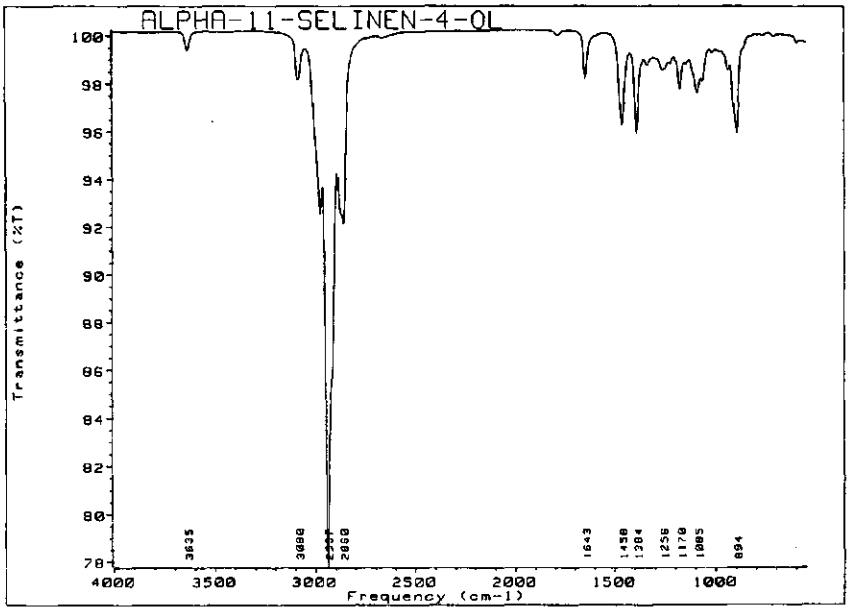


Figure 8.3b: FTIR spectrum of intermedeol **II**.

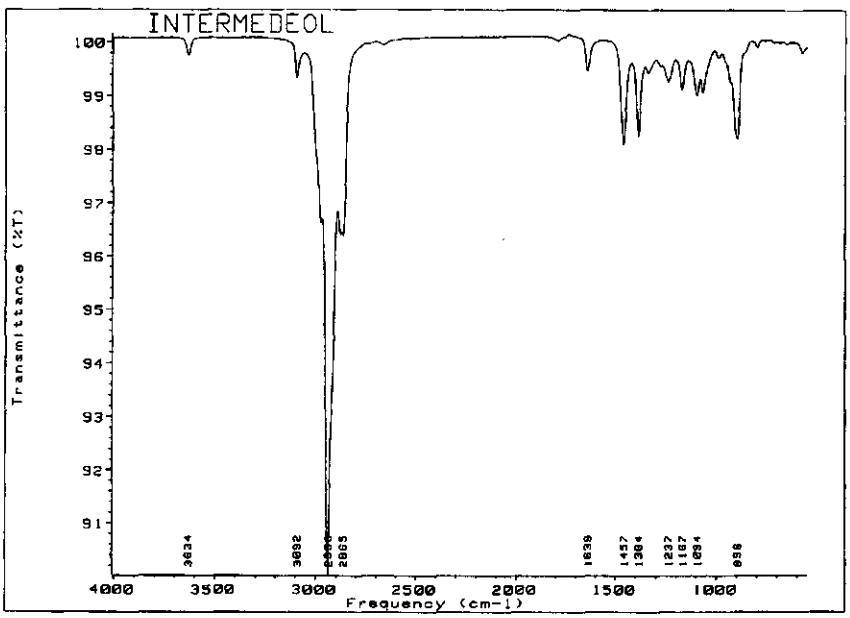


Figure 8.3c: FTIR spectrum of neointermedeol III.

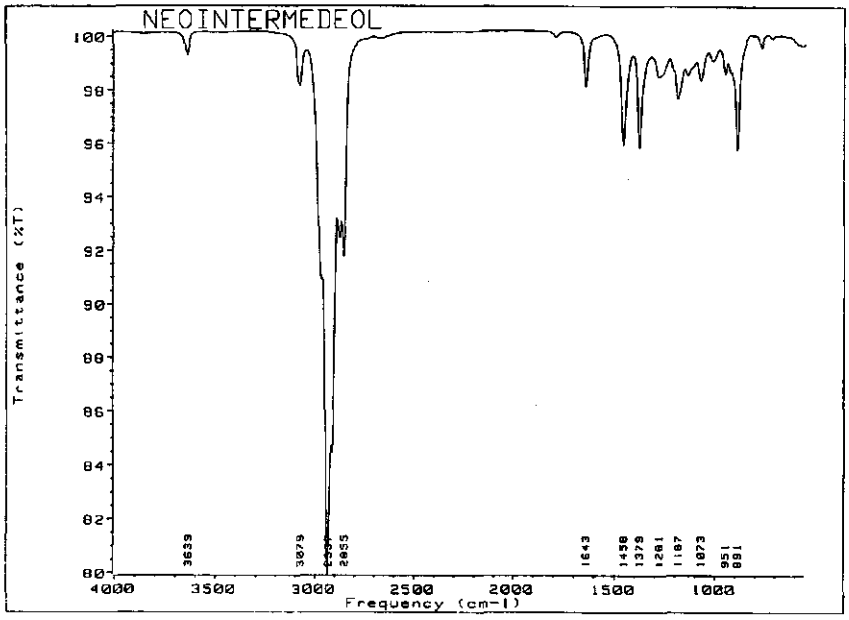


Figure 8.3d: FTIR spectrum of paradisiol IV.

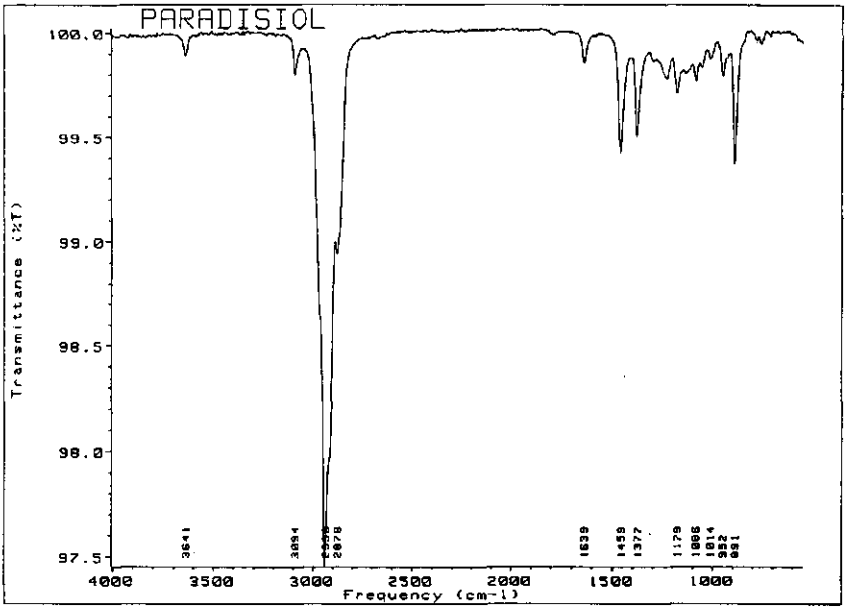


Figure 8.3e: FTIR spectrum of amiteol V.

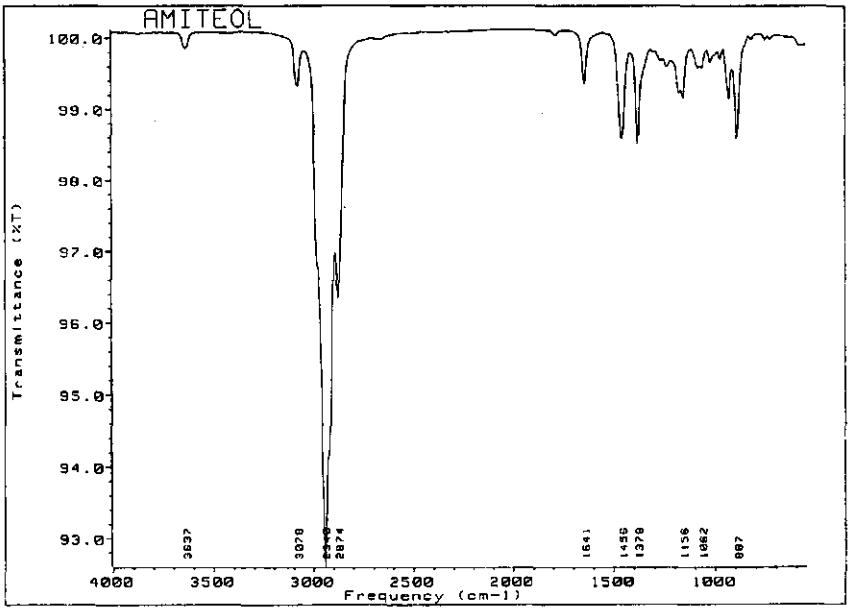


Figure 8.3f: FTIR spectrum of *7-epi*-amiteol VI.

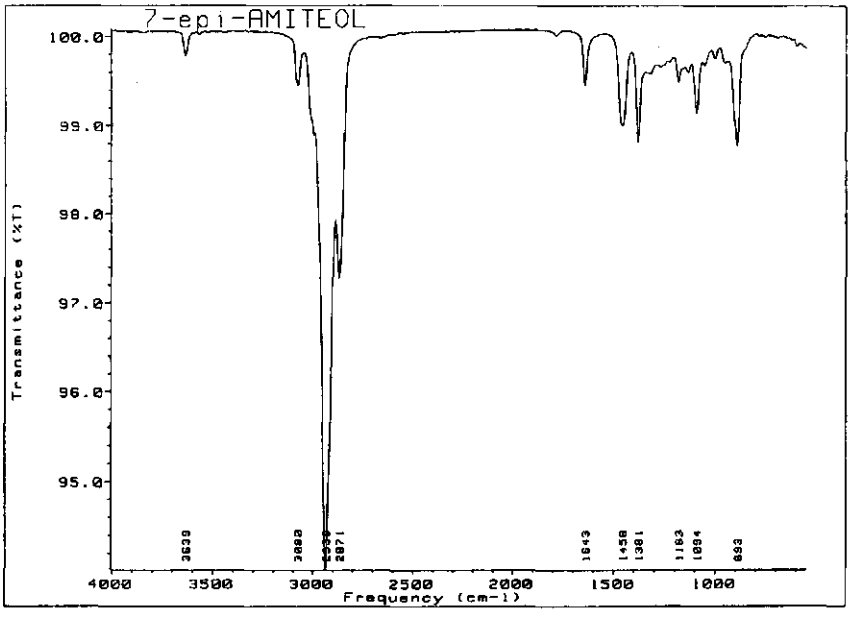


Figure 8.3g: FTIR spectrum of 5-*epi*-neointermedeol **VII**.

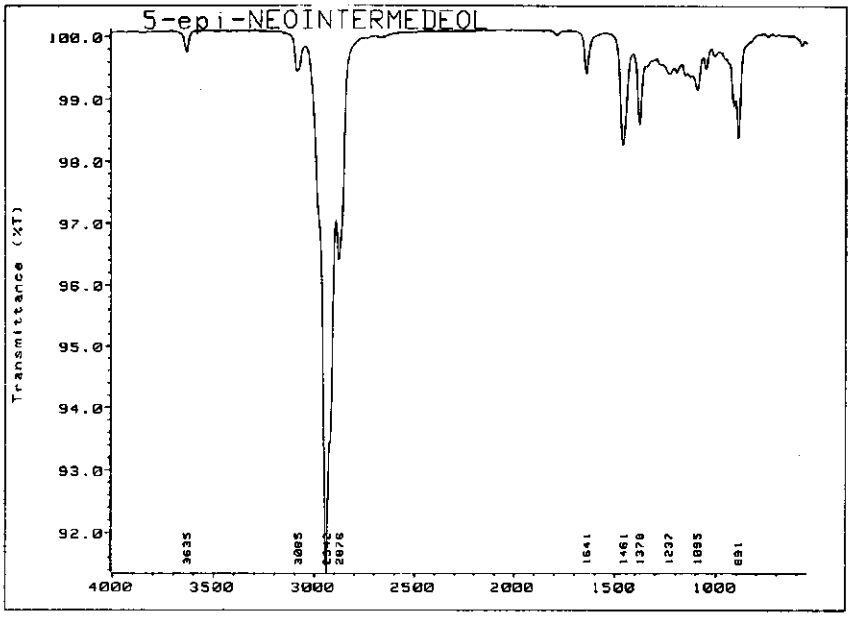
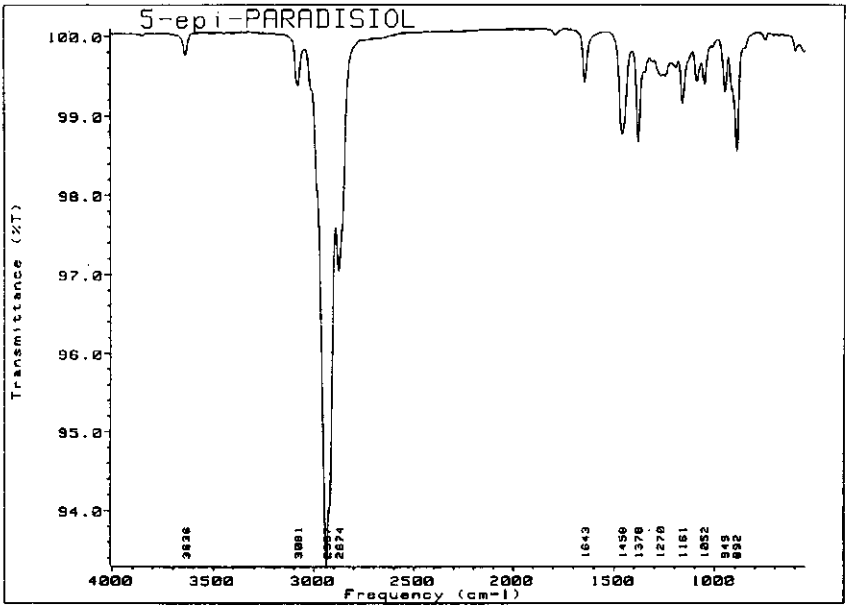


Figure 8.3h: FTIR spectrum of 5-*epi*-paradisiol **VIII**.



i.d. and 0.25 μm film thickness, respectively. Split ratio 1:100, carrier gas H_2, inlet pressure 20 psi, linear velocity 35 cm/s; temp. prog. 50°C (0 min hold) to 238°C (8 min hold) at 4°/min; inj. temp. 220°C; det. temp. 260°C.

Retention indices are Kovats indices. They were calculated by comparing the retention times of the compounds of interest with those of the C7-C23 alkanes.

NMR spectra were recorded on a Bruker 200 E at 200 MHz (^1H) and at 50 MHz (^{13}C) in $CDCl_3$ at room temperature. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ = 0.00 ppm).

^{13}C multiplicities were obtained from DEPT experiments. Assignments based on normal chemical shift rules and reference compounds were confirmed by means of COSY- and ^1H-^{13}C heteronuclear shift correlation spectra.

FTIR was performed on a Hewlett Packard 5965B Infra-Red Detector (Fourier Transform mode) coupled with a CP Sil-5 (Chrompack) fused silica column coated with methylsilicon, in a Hewlett Packard 5890 gas chromatograph. Conditions: "light-pipe" length: 100 mm x 1 mm i.d., maintained at 250 °C; transfer lines: 250 °C; injector temperature: 250 °C; oven temperature program: 60 °C to 250 °C, rate: 2 °C/min.

8.7 REFERENCES AND NOTES

(1) Isolated from the essential oil of *Amyris balsamifera*.

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(4) J. B. P. A. Wijnberg, R.P.W. Kesselmans, and Æ. de Groot, *Tetrahedron Lett.*, **1986**, *27*, 2415.

(5) R.P.W. Kesselmans, J. B. P. A. Wijnberg, N.K. de Vries, and Æ. de Groot, *J. Org. Chem.*, **1991**, *56*, 7232.

(6) R. P. W. Kesselmans, J. B. P. A. Wijnberg, A. Minnaard, R. Walinga, and Æ. de Groot, *J. Org. Chem.*, **1991**, *56*, 7237.

9. ABSTRACT & SAMENVATTING

9.1 ABSTRACT

In this thesis the total synthesis of all stereoisomers of eudesm-11-en-4-ol e.g. selin-11-en-4α-ol **I**, intermedeol **II**, neointermedeol **III**, paradisiol **IV**, amiteol **V**, 7-*epi*-amiteol **VI**, 5-*epi*-neointermedeol **VII**, and 5-*epi*-paradisiol **VIII** is described.

The natural occurrences and the difficulties encountered in the structural elucidation of these eudesmanes are described in chapter 1. The eudesm-11-en-4-ols occur in a wide range of plant species, some of which are used in medicine, or as insect repellent. However, the most spectacular occurrence of eudesm-11-en-4-ols is established in the secretion of termite soldiers. These secretions are used as chemical weapons to defend the termite colony.

In chapter 2 the strategies used in eudesmane syntheses are reported. The first part of this chapter deals with general approaches to the eudesmane skeleton. This part is organized in sections, each dealing with a number of methods under a common heading i.e. annulation, cycloaddition, intramolecular cyclization reactions, and transformations of natural sesquiterpenes. The second part of the chapter describes the reported total syntheses of intermedeol **I**, neointermedeol **III**, paradisiol **IV**, and 5-*epi*-paradisiol **VIII**. These syntheses proceed in low overall yields because of the occurrance of complex product mixtures.

The lack of spectroscopic and chromatographic data for identification, the interesting biological properties, and the availability of a good synthetic plan has been the reason for this investigation (Chapter 3). Starting from enone **101**, a large scale synthesis of the diones **95** and **96** has been developed as is described in chapter 4. The *trans*-fused dione **95** was transformed into the *cis*-fused dione **96** by treatment with trimethyl orthoformate and a catalytical amount of acid in CH_3OH. This transformation allows full stereocontrol on the C-5 bridgehead position.

An efficient method for the synthesis of the octahydro-8-hydroxy-4a,8-dimethyl-2(1*H*)-naphthalenones **97-100**, which are suitable intermediates in the total synthesis of *trans*- and *cis*-fused 4-hydroxyeudesmane sesquiterpenes is reported in chapter 5. Starting from the *trans*-fused dione **95** the corresponding hydroxy ketones **97** and **98** could be easily prepared. The *cis*-fused hydroxy ketones **99** and **100** were synthesized starting from the dione **96**. Protection of the C-7 carbonyl function of **96** as its *dimethyl* acetal

followed by treatment with CH_3Li gave the hydroxy ketone **100**. On the other hand, protection of the C-7 carbonyl function of **96** as its *ethylene* acetal and subsequent treatment with CH_3MgI afforded the hydroxy ketone **99** as the main product. NMR studies revealed that **100** exists predominantly in the steroid conformation and that **99** exists exclusively in the nonsteroid conformation.

The syntheses of the natural occurring (±)-selin-11-en-4α-ol **I**, (±)-intermedeol **II**, (±)-neointermedeol **III**, (±)-amiteol **V**, and the four remaining stereoisomers (±)-paradisiol **IV**, (±)-7-*epi*-amiteol **VI**, (±)-5-*epi*-neointermedeol **VII**, (±)-5-*epi*-paradisiol **VIII**, which not yet have been discovered in nature, are described in chapter 6. In addition the related (±)-evuncifer ether **128** has been prepared. The syntheses in this chapter started from the hydroxy ketones **97-100**. The reaction sequence employed for the synthesis of **I**, **III**, **V**, and **VIII** involved Wittig reaction, oxidative hydroboration, oxidation, equilibration, and olefination. For the synthesis of **II**, **IV**, **VI**, and **VII** the interim equilibration step was omitted. The oxidative hydroboration was the key step in these syntheses.

The conformational behavior of the *cis*-fused stereoisomers of eudesm-11-en-4-ol has been investigated using NMR and conformational energy calculations (MM2) and is reported in chapter 7. In addition, the conformational analysis of most *cis*-fused intermediates in the synthesis to **V** and **VI** are studied.

Kovats indices and mass-, GC/FTIR-, ^1H NMR-, and ^{13}C NMR data were collected for all eight stereoisomers of eudesm-11-en-4-ol in chapter 8. Differences in Kovats indices, mass spectral data, and GC/FTIR of the various isomers on one side, and ^1H NMR and ^{13}C NMR on the other, are shortly discussed. In this way other investigators may be able to identify these common essential oil constituents more reliably in future, either without isolating them (by Kovats indices, GC/MS, and GC/FTIR) or after isolation (by NMR).

9.2 SAMENVATTING

Deze dissertatie is gewijd aan de totaal-synthese van alle mogelijke stereoisomeren van eudesm-11-en-4-ol (selin-11-en-4α-ol **I**, intermedeol **II**, neointermedeol **III**, paradisiol **IV**, amiteol **V**, 7-*epi*-amiteol **VI**, 5-*epi*-neointermedeol **VII** en 5-*epi*-paradisiol **VII**).

Hun natuurlijk voorkomen en de moeilijkheden bij de struktuur toekenning worden beschreven in hoofdstuk 1. De eudesm-11-en-4-olen komen in veel plantensoorten voor. Sommige ervan worden als medicijn of als insekt verjagend middel gebruikt. Maar het meest verrassende is dat de eudesm-11-en-4-olen te vinden zijn in de secretie-vloeistof van termieten soldaten. Zij gebruiken deze secreties om hun kolonie te verdedigen.

In hoofdstuk 2 worden de strategieën beschreven die tot dusver werden gebruikt in de synthesen van eudesmanen. In het eerste deel van dit hoofdstuk worden de algemene synthetische benaderingen die leiden tot een eudesmaan skelet besproken. Het is onderverdeeld in paragrafen, waarin een aantal methoden aan de orde komt die zijn samengevat onder een algemene term, zoals annelerings-, cycloadditie-, intramoleculaire cyclizatie-reacties en omzettingen van natuurlijke sesquiterpenen. Het tweede deel van hoofdstuk 2 beschrijft de gepubliceerde totaal-synthesen van intermedeol **I**, neointermedeol **III**, paradisiol **IV** en 5-*epi*-paradisiol **VIII**. Deze synthesen gaven lage totaalopbrengsten, die meestal veroorzaakt werden door complexe produktmengsels.

Het gebrek aan spectroscopische en chromatografische gegevens voor identificatie, de interessante biologische eigenschappen en de aanwezigheid van een goed synthetisch plan liggen ten grondslag aan dit onderzoek (hoofdstuk 3). In hoofdstuk 4 wordt de synthese op grote schaal van de dionen **95** en **96** uitgaande van enon **101** beschreven. Het *trans*-verknoopte dion **95** kon in het *cis*-verknoopte dion **96** worden omgezet door behandeling met trimethyl orthoformaat en een katalytische hoeveelheid zuur in methanol. Anomere en kinetische effecten maakten deze transformatie mogelijk en dat leidde tot volledige stereocontrole op het C-5 bruggehoofd.

Een efficiënte methode voor de synthese van octahydro-8-hydroxy-4a,8-dimethyl-2(1*H*)-naftalenonen **97-100**, die als intermediairen kunnen dienen in de totaal-synthesen van *trans*- en *cis*-verknoopte 4-hydroxyeudesmanen, wordt in hoofdstuk 5 uitgewerkt. De overeenkomstige hydroxy ketonen **97** en **98** werden eenvoudig gesynthetiseerd uitgaande van het *trans*-verknoopt

dion **95**. Bij de synthesen van de *cis*-verknoopte hydroxy ketonen **99** en **100** diende het *cis*-verknoopte dion **96** als uitgangsstof. Bescherming van de C-7 carbonyl-groep van **96** als *dimethyl* acetaal gevolgd door behandeling met CH_3Li leidde tot hydroxy keton **100**, terwijl bescherming van de C-7 carbonyl-groep als *ethyleen* ketaal gevolgd door behandeling met CH_3MgI voornamelijk de vorming van hydroxy keton **99** tot gevolg had. Uit NMR-onderzoek bleek dat **100** voornamelijk voorkomt in de steroïd conformatie. Hydroxy keton **99** bestaat uitsluitend als nonsteroïd conformeer.

De synthesen van de natuurlijk voorkomende (±)-selin-11-en-4α-ol **I**, (±)-intermedeol **II**, (±)-neointermedeol **III** en (±)-amiteol **V** en de resterende, (nog) niet in de natuur gevonden, stereoisomeren (±)-paradisiol **IV**, (±)-7-*epi*-amiteol **VI**, (±)-5*epi*-neointermedeol **VII** en (±)-5-*epi*-paradisiol **VIII** vinden hun weerslag in hoofdstuk 6. Daarnaast werd de aan **VI** gerelateerde (±)-evuncifer ether **128** gesynthetiseerd. De synthesen in dit hoofdstuk beginnen met de hydroxy ketonen **97-100**. De toegepaste reactie-volgorde in de synthese van **I, III, V** en **VIII** is achtereenvolgens een Wittig reaktie, oxidatieve hydroborering, oxidatie, isomerisatie en olefinatie. De isomerisatie-stap in deze reeks werd weggelaten in de synthese van **II, IV, VI** en **VIII**. De oxidatieve hydroborering is de belangrijkste reactie in deze synthesen.

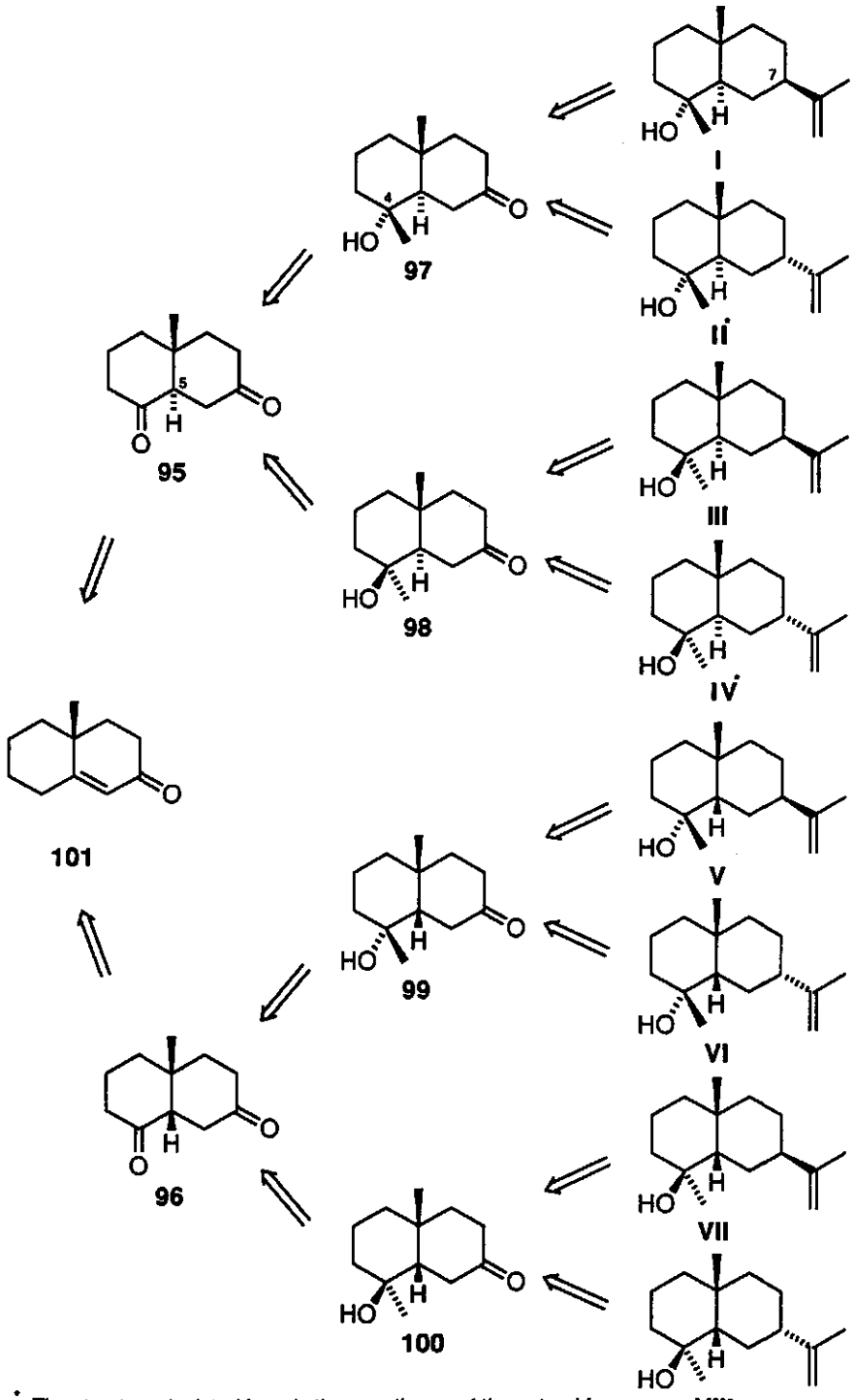
De conformaties van de *cis*-verknoopte eudesm-11-en-4-olen **V, VI, VII** en **VIII** werden bepaald met behulp van NMR-studies en conformatie energie berekeningen (MM2), zoals beschreven is in hoofdstuk 7. Ook de conformaties van de meeste *cis*-verknoopte intermediairen in de synthese van **V** and **VI** werden onderzocht.

Kovats indices, massa- en GC/FTIR-, ^1H NMR- en ^{13}C NMR-data werden voor alle stereoisomeren van eudesm-11-en-4-ol verzameld in hoofdstuk 8. Verschillen in de Kovats indices en in de massa en FTIR-spectra aan de ene en ^1H NMR- en ^{13}C NMR-spectra aan de andere kant worden kort beschreven. Op deze manier is het voor anderen mogelijk om deze componenten in vluchtige oliën op betrouwbare wijze te bepalen zonder (Kovats indices, GC/MS en GC/FTIR) of na isolatie (NMR).

CURRICULUM VITAE

Ronald Peter Wilhelmus Kesselmans werd geboren op 7 september 1963 te Panningen. Het ongedeeld VWO-diploma behaalde hij in 1981 op het Bouwens van de Boye College aldaar. Daarna is de auteur begonnen aan de studie Levensmiddelen Technologie (oude stijl) aan de toenmalige Landbouwhogeschool in Wageningen. Het kandidaatsexamen met als specialisatie Levensmiddelen Chemie legde hij af op 24 september 1985. In de doctoraalfase werden de hoofdvakken Levensmiddelen Chemie (prof. dr. ir. A.G.J. Voragen) en Organische Chemie (dr. J.B.P.A. Wijnberg en prof. dr. Ae. de Groot) gevolgd. Daarnaast werden stages bij de keuringsdienst van Waren te Maastricht (dr. P. Beljaars) en CIVO-TNO (dr. K.D. Bos) gelopen. Voor het doctoraalexamen slaagde hij op 26 juni 1987 met lof.

In de periode van juli 1987 tot december 1991 werd het in dit proefschrift beschreven onderzoek onder leiding van dr. J.B.P.A. Wijnberg en prof. dr. Ae. de Groot uitgevoerd aan de vakgroep Organische Chemie van de Landbouwuniversiteit Wageningen.



* The structure depicted here is the enantiomer of the natural form.