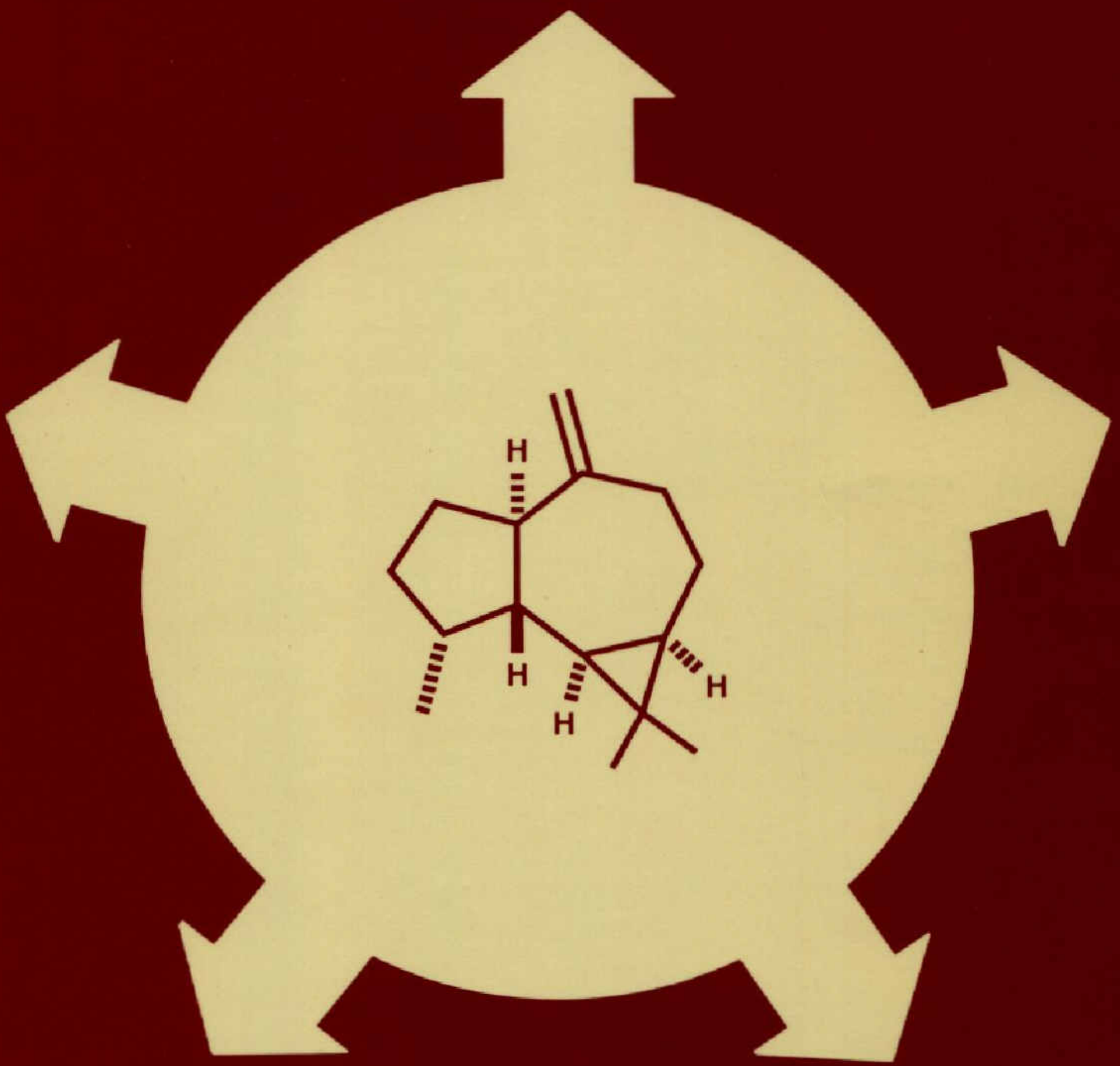
(+)-AROMADENDRENE AS CHIRAL STARTING MATERIAL FOR THE SYNTHESIS OF SESQUITERPENES



H.J.M. Gijsen

(+)-AROMADENDRENE AS CHIRAL STARTING MATERIAL FOR THE SYNTHESIS OF SESQUITERPENES

H.J.M. Gijsen

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

Stellingen

1. De namen ledene en viridiflorene, twee namen voor dezelfde stof, worden ten onrechte toegekend aan twee verschillende verbindingen die voorkomen in de knoppen van de zwarte bes (*Ribes nigrum* L.).

   J-L. Le Quere en A. Latrasse, *J. Agric. Food Chem.* **1990**, *38*, 3-10.

2. Het is onwaarschijnlijk dat de door van Loon et al. gespiegeld getekende struktuur van glucobrassicine de biologische aktiviteit heeft die eraan wordt toegekend.

   J.J.A. van Loon, A. Blaakmeer, F.C. Griepink, T.A. van Beek, L.M. Schoonhoven en Ae. de Groot, *Chemoecology* **1992**, *3*, 39-44.

3. De struktuur-correctie van de produkten verkregen na solvolyse van Westphalen-type verbinding I is niet in overeenstemming met wat men chemisch zou verwachten.

   A. Kasal en M. Budesínsky, in abstracts of papers, XV conference on isoprenoids, Zakopane, Polen 20-25 sept. 1993, blz. 45.

4. De onafhankelijkheid tussen celdood door ATP-gebrek en Ca^{2+} gemedieerde celdood wordt niet overtuigend door Kamendulis en Corcoran aangetoond.

   L.M. Kamendulis en G.B. Corcoran, *Toxicol. Lett.* **1992**, *63*, 277-287.

5. Het verschil in de bescherming van rattehepatocyten door fructose tegen CCCP, gevonden door Nieminen et al. en Snyder et al., kan ook verklaard worden door verschillen in metabole status van de gebruikte hepatocyt cultures.

   A-L. Nieminen, T.L. Dawson, G.J. Gores, T. Kawanishi, B. Herman en J.J. Lemasters, *Biochem. Biophys. Res. Commun.* **1990**, *167*, 600-606.

   J.W. Snyder, J.G. Pastorino, A.P. Thomas, J.B. Hoek en J.L. Farber, *Am. J. Physiol.* **1993**, *264*, C709-C714.

6. De bewering dat de Natural Killer Cell aktiviteit door vitamine A zuur verhoogd wordt is ongegrond. De 23% lysis die gevonden wordt wijkt niet af van de 13 tot 31% lysis, gevonden bij contrôle experimenten.

   W. Goettsch, Y. Hatori en R.P. Sharma, *Int. J. Immunopharmac.* **1992**, *14*, 143-150.

   W. Goettsch, stageverslag vakgroep Toxicologie, LUW 1989.

7. De verklaring die R.J. Cremlyn geeft voor de remming van acetylcholinesterase door het insecticide *E*-mevinphos is verwarrend en met zichzelf in tegenspraak.

   R.J. Cremlyn in: Agrochemicals, preparation and mode of action, John Wiley & Sons Ltd., Chichester, 1990, blz. 123-126.

8. Het huidige tetanus vaccin biedt naast bescherming tegen tetanus ook bescherming tegen infecties met runderhart.

9. Het verwijderen van alle afgestudeerden van de SSHW-flats maakt de huur voor studenten onbetaalbaar.

10. Het verkrijgen van goede resultaten in een rommelige werkomgeving geeft blijk van enige intelligentie.

Stellingen behorende bij het proefschrift: "(+)-aromadendrene as chiral starting material for the synthesis of sesquiterpenes".

Wageningen, 15 december 1993 H.J.M. Gijsen

Met dank aan Anton, Romano, Corike (2x), Wim, Hans, en Marcel.

H.J.M. Gijsen

(+)-AROMADENDRENE AS CHIRAL STARTING MATERIAL FOR THE SYNTHESIS OF SESQUITERPENES

Proefschrift
ter verkrijging van de graad van doctor
in de landbouw- en milieuwetenschappen
op gezag van de rector magnificus,
dr. C.M. Karssen
in het openbaar te verdedigen
op woensdag 15 december 1993
des namiddags te half twee in de aula
van de Landbouwuniversiteit te Wageningen

CIP-gegevens Koninklijke Bibliotheek, Den Haag

ISBN 90-5485-201-1

Acknowledgement

The investigations described in this thesis have been carried out under the auspices of the Netherlands Foundation for Chemical Research (SON/NWO), with financial aid from the Netherlands Technology Foundation (STW/NWO) and Quest International.

Voorwoord

Voor u ligt het resultaat van vier jaar sleutelen aan aromadendreen. Hoewel ik met enige twijfel begon aan dit onderzoek, kan ik zonder meer terugkijken op vier leuke en leerzame jaren. Bijna iedereen binnen de vakgroep organische chemie heeft wel zijn of haar steentje bijgedragen aan het tot stand komen van dit proefschrift. Hetzij via het doen van analyses, het geven van tips en adviezen, het voorzien in of het (onbewust) uitlenen van chemicalieën en glaswerk, of simpelweg door aanwezig te zijn. Allen wil ik hier hartelijk voor bedanken. Enkele personen wil ik met name noemen.

Allereerst André Stork, naast je bijdrage aan drie publikaties, beschreven in dit proefschrift, wist je het lableven aanzienlijk te veraangenamen. Al moeten mijn bureau en labtafel je soms tot wanhoop hebben gedreven, een betere zaal- en kamergenoot kon ik me niet wensen.

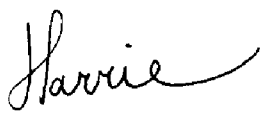
Æde de Groot, bedankt voor de mogelijkheid die jij me bood om dit onderzoek te mogen doen. De grote mate van vrijheid die ik kreeg en je voortdurende betrokkenheid heb ik zeer gewaardeerd.

Connie van Ravenswaay, jouw bijdrage tijdens je stage staan misschien niet met zoveel woorden in dit proefschrift, toch was het van grote waarde en heeft het me veel tijd bespaard.

Hans Wijnberg, bedankt voor de zeer plezierige begeleiding. Jouw nauwkeurige beoordeling van publikaties deed me iedere keer weer versteld staan. Waren er problemen waar ik niet uitkwam, jij had er altijd wel een oplossing voor.

Als laatste wil ik Corike bedanken. Jij gaf me de afgelopen twee jaar een extra stimulans om dit onderzoek te doen.

Ik wens iedereen veel plezier (u zult het nodig hebben) bij het doornemen van dit proefschrift.



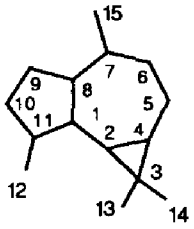
Contents

1 Everything you always wanted to know about aromadendranes

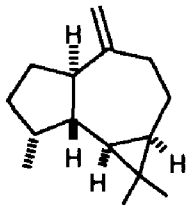
1.1 Structure and occurrence

Aromadendranes (**1**) belong to a class of sesquiterpenes, structurally characterized by a dimethyl cyclopropane ring fused to a hydroazulene skeleton, as depicted in figure 1.1. Throughout this and the following chapters the numbering of the carbon skeleton will be used as given in **1**. Next to the aromadendranes, the related sesquiterpenes with a 1,7-cycloaromadendrane, 7,8-seco-, and 9,10-secoaromadendrane skeleton will be discussed. Some alkylated aromadendranes, e.g. macrocarpals and prenylaromadendranes are also included in this overview.

Figure 1.1



1



2

The name "aromadendrane" originates from the sesquiterpene (+)-aromadendrene (**2**), the first reported sesquiterpene with this skeleton[1]. (+)-Aromadendrene is a constituent of the essential oil extracted from the wood of *Eucalyptus* trees. In earlier days the trees belonging to this genus were known as *Aromadendron* trees.

After numerous experiments, the structure of (+)-aromadendrene (**2**) was elucidated in 1953[2], but it took thirteen years before Büchi et al in 1966 established the absolute configuration of **2** through the synthesis of (–)-aromadendrene starting from (–)-perillaldehyde[3] (see chapter 1.4.1). In addition, the absolute configurations of alloaromadendrene (**3**), in which the hydroazulene skeleton is *cis*-fused, and the related tertiary C7-alcohols globulol (**4**), epiglobulol (**5**), ledol (**6**), and viridiflorol (**7**) were established.

Gurjon balsam, the resin from tropical trees belonging to the *Dipterocarpaceae* family, provided the aromadendrane (–)-α-gurjunene (**25**)[4], whose structure was determined in 1963 by Ourisson et al[5]. This hydrocarbon can be oxidized to the α,β-unsaturated ketone (–)-cyclocolorenone (**27**)[6], which has been isolated from *Pseudowintera colorata*[7]. The stereochemistry of **27** was independently determined through synthesis of its C8-epimer in 1966[8]. All the compounds mentioned so far are present in numerous plant species. Other frequently occurring aromadendranes are the tertiary C8 and C11 alcohols palustrol (**8**) and spathulenol (**31**), respectively, and the hydrocarbon ledene (**43**), also known as viridiflorene[9].

A number of other aromadendrane hydrocarbons have been isolated from the oil or resin obtained from different tree species. Gurjon balsam contains, besides α-gurjunene (**25**) also its C7 epimer **26**[10]. Tolu balsam, obtained from *Myroxylon balsamum* var. *balsamum*, was found to contain the five hydrocarbons **52-56**[11]. The aromadendrane hydrocarbon β-spathulene (**51**) is a minor component in the oil of *Schinus Molle*[12].

In many aromadendranes C7 and/or C11 are oxidized. Although less frequently, oxidation at all the other carbon atoms, except C1 and C2, is also observed. Oxygenated aromadendranes are widespread among the family of *Compositae*[13-19], with, amongst others, members of the tribes *Inulae*[20-24], and *Calendulaceae*[25-27]. From the latter and from *Pittosporum tobira*[28] glycosylated aromadendranes have been extracted. Other plants that provided oxygenated aromadendranes were *Phebalium squamulosum*[29], *Ferulago antiochia*[30], *Humulus lupulus*[31], and members of the family of *Labiatae*[32,33].

Ent-aromadendrane sesquiterpenes which have the mirror image carbon skeleton, have been found in the red alga *Laurencia subopposita*[34], soft corals (*Coelenterata, Octocorallia*), marine sponges (*Porifera*) and liverworts (*Hepaticae*) (Table 1.2). All of the abundant aromadendranes mentioned above have been found in their enantiomeric form, but also *ent*-aromadendranes without known antipodes in higher plants have been isolated.

The soft corals *Sinularia mayi*[35] and *Cespitularia* sp. aff. *asubviridis*[36,37] have been reported to contain aromadendranes with both chiralities. In the case of *C. subviridis* the isolated (+)-ledol (**6**) might actually be *ent*-(+)-ledol (**61**), because the sign of rotation is dependent on the solvent used[38]. *Ent*-aromadendranes with a new structure have been isolated from the soft corals *Clavularia koellikeri*[39] and *Xenia novae-brittaniae*[40]

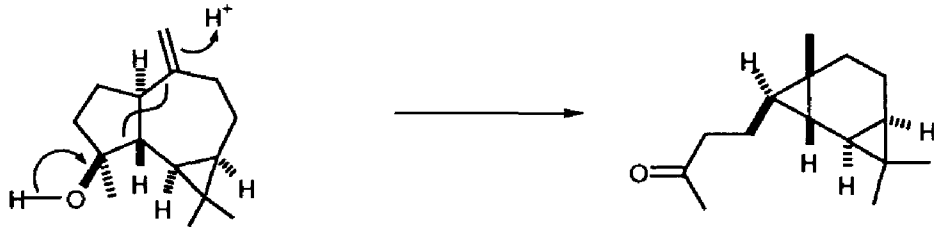
Some marine sponges contain aromadendranes with isonitrile, isothiocyanate, or formamide groups at C7 or C8. Epipolasin B (**78**) has been isolated from *Epipolasis kushimotoensis*[41]. The same structure has been proposed for axisothiocyanate-2, isolated from *Axinella cannabina*[42] and *Acanthella pulcherrima*[43]. Epipolasin B (**78**) has been proven to possess the *ent*-configuration[41]. The absolute stereochemistry of the aromadendranes from *Axinella cannabina*, including axisothiocyanate-2 is not known, but the *ent*-configuration is most likely. Aromadendranes with a nitrogen containing group at C8 have been found in *Acanthella* species[43,44]. The stereochemistry at C7 and C8, at first unclear, was proven to be β as indicated in **84-86**[37a]. Axisonitrile-2 (**77**) and axisothiocyanate-2 (**78**), found in the nudibranch *Cadlina luteomarginata*, probably originate from the sponge diet of this mollusc[45].

All aromadendranes found in liverworts (*Hepaticae*) possess the *ent*-configuration. A number of *ent*-aromadendranes, which all have known antipodal counterparts in higher plants, have been isolated from liverworts[46-51]. In a few cases, their antipodes have not been found in higher plants[24,50,52]. From the liverwort genus *Plachiogila* many *ent*-9,10-secoaromadendranes have been isolated[48,53-60] (table 1.3). The liverwort *Mylia taylorii* is a rich source of unusual sesquiterpenoids derived from *ent*-aromadendranes. Besides *ent*-aromadendranes, several *ent*-7,8-secoaromadendranes[47,61], an *ent*-nor-7,8-secoaromadendrane (**113**)[62], and several *ent*-1,7-cycloaromadendranes[47,63,64] have been isolated (table 1.4 and 1.5). Anastreptene (**118**), one of the *ent*-1,7-cycloaromadendranes is a common constituent in many liverwort species[65].

Various aromadendranes with extra alkyl substituents have been isolated (table 1.6). The dimeric *ent*-spiroterpenoid plagiospirolide E (**119**) has been isolated from *Plachiogila moritziana*[66]. This C_{30}-terpenoid is composed of an aromadendrane and an eudesmane unit. Tanzanene (**120**) is a C7-spiro benzopyranyl aromadendrane, isolated from *Uvaria tanzaniae*[67]. Prenylaromadendranes (cneorubins), consisting of an aromadendrane unit with an isopentylgroup at C13, have been isolated from *Cneorum tricoccon*[68]. *Eucalyptus globulus*[69,70] and *E. macrocarpa*[71,72] contain aromadendranes in which C11 bears an isopentyl phloroglucinol group (macrocarpals or euglobals).

Waitzia acuminata (*Compositae, Inulae*) contains a fragmentated aromadendrane sesquiterpene, waitziacuminone (**129**), probably derived from spathulenol (**31**)[22] (Scheme 1.1).

Scheme 1.1



31 **129**

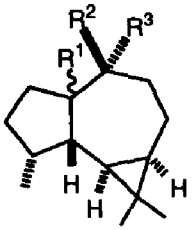
The aromadendranes known so far and the organisms from which they have been isolated for the first time, are given in tables 1.1 to 1.6. The accompanying structures are given below the respective tables. For the structures of the *ent*-aromadendranes with known antipodal counterparts is referred to the structures of the latter.

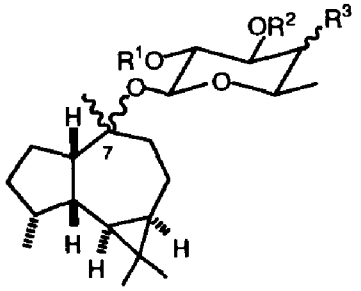
Table 1.1: natural occurring aromadendranes

	Compound	Isolated from	Ref.
2	(+)-aromadendrene	*Eucalyptus* species	1
3	(–)-alloaromadendrene	*Eucalyptus* species	73
4	(–)-globulol	*Eucalyptus globulus*	74
5	(–)-epiglobulol	*Humulus lupulus*	31
6	(–)-ledol[a]	*Ledum palustre*	75
7	(+)-viridiflorol	*Melaleuca viridiflora*	76
8	(–)-palustrol	*Ledum palustre*	76
9	(–)-8-hydroxy-alloaromadendrene	*Cassinia subtropica*	21
10	aromadendrene epoxide	*Humulus lupulus*	31
11	alloaromadendrene epoxide	*Humulus lupulus*	31
12	(–)-arvoside B	*Calendula arvensis*	25
13	(–)-ledol-β-D-fucopyranoside-2'-O-acetate	*Calendula arvensis*	25
14	(–)-ledol-β-D-fucopyranoside-2'-O-2-methylbutyrate	*Calendula arvensis*	25
15	(–)-ledol-β-D-fucopyranoside-2'-O-4-methylsenecioate	*Calendula arvensis*	25
16	(–)-ledol-β-D-fucopyranoside-2'-O-isobutyrate	*Calendula arvensis*	27
17	(–)-ledol-β-D-fucopyranoside-2'-O-angelate	*Calendula arvensis*	27
18	viridiflorol-β-D-fucopyranoside	*Calendula persica*	26
19	viridiflorol-β-D-chinovopyranoside	*Calendula persica*	26
20	viridiflorol-β-D-fucopyranoside-2'-O-4-methylsenecioate	*Calendula persica*	26
21	viridiflorol-β-D-fucopyranoside-2'-O-senecioate	*Calendula persica*	26
22	viridiflorol-β-D-chinovopyranoside-2'-O-senecioate	*Calendula persica*	26
23	(+)-pittosporanoside A1	*Pittosporum tobira*	28
24	(+)-pittosporanoside A2	*Pittosporum tobira*	28
25	(–)-α-gurjunene	Gurjon balsam	4,5
26	7-epi-α-gurjunene	Gurjon balsam	10

27	(–)-cyclocolorenone	*Pseudowintera colorata*	7
28	5α-hydroxy-α-gurjunene	*Helichrysum nudifolium*	14
29	(–)-5α-acetoxy-α-gurjunene	*Helichrysum nudifolium*	14
30	(–)-5β-acetoxy-α-gurjunene	*Helichrisum nudifolium*	14

(a) The sign of rotation of ledol is dependent on the solvent used[38].





2: $R^1 = \alpha H$ $R^2 = R^3 = CH_2$

3: $R^1 = \beta H$ $R^2 = R^3 = CH_2$

4: $R^1 = \alpha H$ $R^2 = CH_3$ $R^3 = OH$

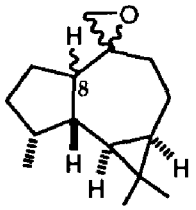
5: $R^1 = \alpha H$ $R^2 = OH$ $R^3 = CH_3$

6: $R^1 = \beta H$ $R^2 = CH_3$ $R^3 = OH$

7: $R^1 = \beta H$ $R^2 = OH$ $R^3 = CH_3$

8: $R^1 = \alpha OH$ $R^2 = H$ $R^3 = CH_3$

9: $R^1 = \beta OH$ $R^2 = R^3 = CH_2$



10: 8αH

11: 8βH

7α–glycosyl, 7β–methyl:

12: $R^1 = H$ $R^2 = H$ $R^3 = \beta OH$

13: $R^1 = Ac$ $R^2 = H$ $R^3 = \beta OH$

14: R^1= 2-MeBu $R^2 = H$ $R^3 = \beta OH$

15: R^1 = MeSen $R^2 = H$ $R^3 = \beta OH$

16: R^1 = Bu $R^2 = H$ $R^3 = \beta OH$

17: R^1 = Ang $R^2 = H$ $R^3 = \beta OH$

7α–methyl, 7β–glycosyl:

18: $R^1 = H$ $R^2 = H$ $R^3 = \beta OH$

19: $R^1 = H$ $R^2 = H$ $R^3 = \alpha OH$

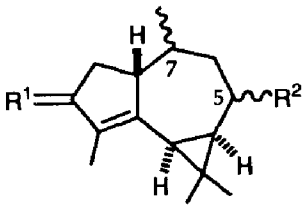
20: R^1 = MeSen $R^2 = H$ $R^3 = \beta OH$

21: R^1 = Sen $R^2 = H$ $R^3 = \beta OH$

22: R^1 = Sen $R^2 = H$ $R^3 = \alpha OH$

23: $R^1 = Ac$ R^2 = Ang $R^3 = \beta OH$

24: $R^1 = Ac$ $R^2 = H$ $R^3 = \beta$Ang



25: 7αCH$_3$ $R^1 = H_2$ $R^2 = H$

26: 7βCH$_3$ $R^1 = H_2$ $R^2 = H$

27: 7αCH$_3$ $R^1 = O$ $R^2 = H$

28: 7αCH$_3$ $R^1 = H_2$ $R^2 = \alpha OH$

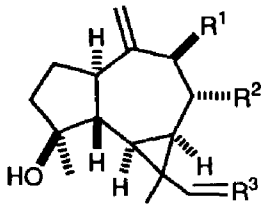
29: 7αCH$_3$ $R^1 = H_2$ $R^2 = \alpha OAc$

30: 7αCH$_3$ $R^1 = H_2$ $R^2 = \beta OAc$

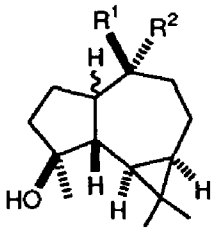
Table 1.1: Continued

	Compound	Isolated from	Ref.
31	(+)-spathulenol	*Eucalyptus spathulata*	77
32	(+)-5α-hydroxy-spathulenol	*Cineraria fruticulorum,* *Parthenium argentatum*	24 16
33	(–)-guayulin C	*Parthenium argentatum*	18
34	guayulin D	*Parthenium argentatum*	18
35	5α-benzoyloxy-spathulenol	*Ferulago antiochia*	30
36	(–)-6β-hydroxy-spathulenol	*Sideritis varoi*	33
37	(+)-6β-acetoxy-spathulenol	*Sideritis varoi*	33
38	(–)-5α,14-dihydroxy-spathulenol	*Cineraria fruticulorum*	24
39	(–)-5α-hydroxy-14-oxo-spathulenol	*Cineraria fruticulorum*	24
40	(–)-aromadendrane-7α,11β-diol	*Brasilia Sickii*	15
41[a]	(+)-alloaromadendrane-7β,11β-diol	*Ambrosia peruviana*	19
42	(–)-aromadendrane-7α,11α-diol	*Sinularia mayi*	35
43	(+)-ledene (viridiflorene)	*Melaleuca alternifolia*	9
44	(+)-isospathulenol	*Salvia sclarea*	32
45	(–)-squamulosone	*Phebalium squamulosum*	29
46	13,14-diacetoxy-9-oxo-ledene	*Gnephosis brevifolia*	20
47	(+)-15-hydroxy-viridiflorol	*Wyethia arizonica* *Pulicaria paludosa*	17 23
48	(+)-14,15-dihydroxy-viridiflorol	*Wyethia arizonica*	17
49	flourensadiol	*Flourensia cernua*	13
50	(+)-10-oxo-viridiflorol	*Helichrysum albirosulatum*	14
51	β-spathulene	*Schinus molle*	12
52	(–)-8-epi-α-gurjunene	*Myroxylon balsamum*	11
53	(+)-8(9)-aromadendrene	*Myroxylon balsamum*	11
54	(–)-6(7)-alloaromadendrene	*Myroxylon balsamum*	11
55	1(8)-10(11)-aromadendradiene	*Myroxylon balsamum*	11
56	1(11)-7(8)-aromadendranediene	*Myroxylon balsamum*	11

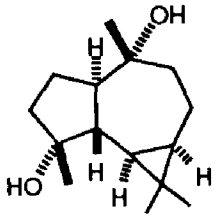
(a) Revised structure, see section 1.4, page 23[78]



31: $R^1 = H$ $R^2 = H$ $R^3 = H_2$
32: $R^1 = H$ $R^2 = OH$ $R^3 = H_2$
33: $R^1 = H$ $R^2 = OCinn$ $R^3 = H_2$
34: $R^1 = H$ $R^2 = OAnis$ $R^3 = H_2$
35: $R^1 = H$ $R^2 = OBz$ $R^3 = H_2$
36: $R^1 = OH$ $R^2 = H$ $R^3 = H_2$
37: $R^1 = OAc$ $R^2 = H$ $R^3 = H_2$
38: $R^1 = H$ $R^2 = OH$ $R^3 = OH, H$
39: $R^1 = H$ $R^2 = OH$ $R^3 = O$



40 αH $R^1 = CH_3$ $R^2 = OH$
41 βH $R^1 = OH$ $R^2 = CH_3$



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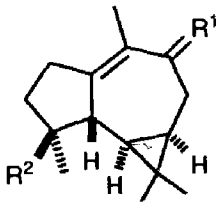
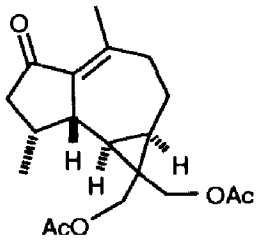


43: $R^1 = H_2$ $R^2 = H$
44: $R^1 = H_2$ $R^2 = OH$
45: $R^1 = O$ $R^2 = H$



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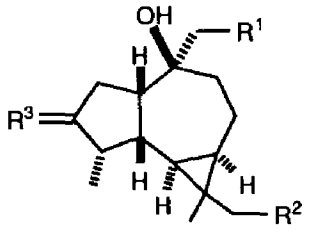
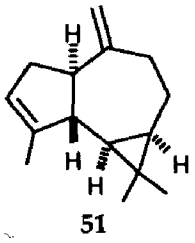


47: $R^1 = OH$ $R^2 = H$ $R^3 = H_2$
48: $R^1 = OH$ $R^2 = OH$ $R^3 = H_2$
49: $R^1 = H$ $R^2 = OH$ $R^3 = H_2$
50: $R^1 = H$ $R^2 = H$ $R^3 = O$



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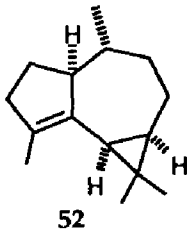

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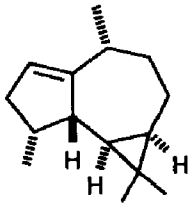

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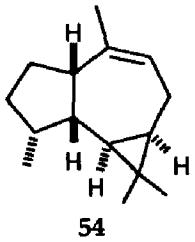

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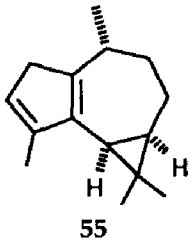

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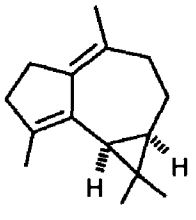


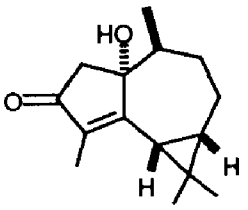
56

Table 1.2: *ent*-aromadendranes

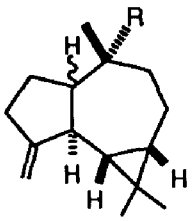
	Compound	Isolated from	Ref.
57[a]	(–)-aromadendrene	*Scapania ornithopodioides*	46
58[a]	alloaromadendrene	*Cespitularia* sp.aff. *subviridis*	36
59[a]	(+)-globulol	*Mylia taylorii*	47
60[a]	(+)-epiglobulol	*Plagiochila yokogurensis* *Diplophyllum albicans*	48 49
61[a]	(+)-ledol	*Cespitularia* sp.aff. *subviridis*	36
62[a]	(–)-viridiflorol	*Cespitularia* sp.aff. *subviridis*	36
63[a]	(+)-palustrol	*Cespitularia* sp.aff. *subviridis*	37
64[a]	(–)-spathulenol	*Plagiochila yokogurensis*	48
65[a]	(–)-ledene	*Plagiochila yokogurensis*	48
66[a]	(+)-α-gurjunene	*Porella* species	50
67[a]	(+)-cyclocolorenone	*Plagiochila acanthophylla*	51
68	(+)-8-hydroxy-cyclocolorenone	*Porella* species	50
69	(+)-11(12)-alloaromadendrene (β-gurjunene)[b]	*Porella* species	50
70	(+)-11(12)-dehydroledol	*Mylia taylorii*	47
71	(+)-11(12)-dehydroglobulol	*Mylia taylorii*	47
72[a]	(+)-aromadendrane-7β,11α-diol	*Sinularia mayi*	35
73[a]	(–)-alloaromadendrane-7α,11α-diol[c]	*Sinularia mayi*	19,35
74	(–)-tridensenone	*Bazzania tridens*	52
75[a]	(+)-8-hydroxy-alloaromadendrene	*Laurencia subopposita*	34
76	(–)-8(9)-dehydroglobulol	*Laurencia subopposita*	34
77	(+)-axisonitrile-2	*Axinella cannabina* *Cadlina luteomarginata*	42c 45
78	(+)-axisothiocyanate-2 (+)-epipolasin-B	*Axinella cannabina* *Epipolasis kushimotoensis* *Cadlina luteomarginata*	42b 41 45
79	(+)-axamide-2	*Axinella cannabina*	42b
80	epipolasinthiourea-B	*Epipolasis kushimotoensis*	41
81	(–)-7β-isocyanoalloaromadendrane	*Axinella cannabina*	42a
82	(–)-7β-isothiocyanate- alloaromadendrane	*Axinella cannabina*, *Acanthella pulcherrima*	42a 43
83	7β-formamidoalloaromadendrane	*Axinella cannabina*	42a

84	(–)-8-isocyano-7β-aromadendrane	*Acanthella acuta* *A. pulcherrima*	44b,c 43
85	(–)-8-isothiocyanate-7β-aromadendrane	*Acanthella acuta*	44b
86	8-isocyanate-7β-aromadendrane	*Acanthella acuta*	44a
87	see structure	*Clavularia koellikeri*	39
88	(+)-1(8)-aromadendren-4-ol	*Xenia novae-brittaniae*	40

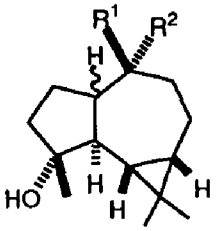
(a) Compound with known antipode, for structure see antipodal structure, table 1.1. (b) The name β-gurjuneen for **69** is incorrect. This name has already been given to 1(10)-aristolene (calarene). (c) Revised structure, see chapter 5.



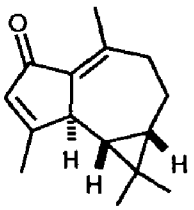
68



69: αH R = H
70: αH R = OH
71: βH R = OH



72: βH R^1 = OH R^2 = CH_3
73: αH R^1 = CH_3 R^2 = OH



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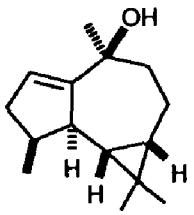

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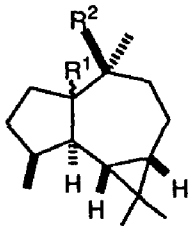
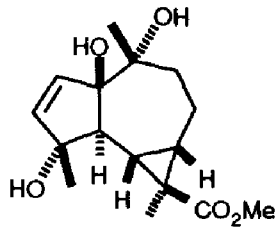


77: R^1 = βH R^2 = NC
78: R^1 = βH R^2 = NCS
79: R^1 = βH R^2 = NHCHO
80: R^1 = βH R^2 = $NHCSNHC_2H_4Ph$
81: R^1 = αH R^2 = NC
82: R^1 = αH R^2 = NCS
83: R^1 = αH R^2 = NHCHO
84: R^1 = βNC R^2 = CH_3
85: R^1 = βNCS R^2 = CH_3
86: R^1 = βNCO R^2 = CH_3



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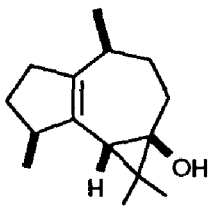
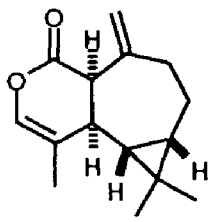


88

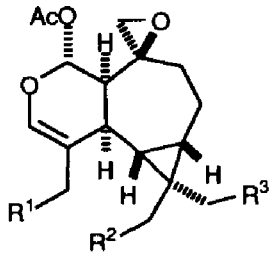
Table 1.3: *ent*-9,10-secoaromadendranes

	Compound	Isolated from	Ref.
89	(–)-plagiochilide	*plagiochila yokogurensis*	53
90	(+)-plagiochiline A	*Plagiochila yokogurensis*	53
91	(+)-plagiochiline B	*Plagiochila hattoriana*	54
92	(+)-plagiochiline D	*Plagiochila asplenioides*	57
93	(+)-plagiochiline G	*Plagiochila ovalifolia*	48
94	(+)-plagiochiline I	*Plagiochila yokogurensis*	48
95	(+)-plagiochiline E	*Plagiochila asplenioides*	57
96	(+)-plagiochiline C	*Plagiochila asplenioides*	57
	(+)-ovalifoliene	*Plagiochila semidecurrens*	55
97	(+)-plagiochiline H	*Plagiochila yokogurensis*	48
	(+)-deacetoxyovalifoliene	*Plagiochila semidecurrens*	59
98	(+)-6α-acetoxyovalifoliene	*Plagiochila semidecurrens*	59
99	(+)-ovalimethoxy I	*Plagiochila semidecurrens*	59
100	(+)-ovalimethoxy II	*Plagiochila semidecurrens*	59
a	(+)-methoxyplagiochiline C	*Plagiochila yokogurensis*	48
101	(+)-plagiochiline F	*Plagiochila asplenioides*	57
102	(+)-ovalifolienal	*Plagiochila semidecurrens*	59
103	(+)-ovalifolienalone	*Plagiochila semidecurrens*	56
104	(–)-plagiochiline J	*Plagiochila fruticosa*	60
105	plagiochiline K	*Plagiochila fruticosa*	60
106	(–)-furanoplagiochilal	*Plagiochila hattoriana*	58
107	(–)-plagiochilal A	*Plagiochila hattoriana*	58
	(–)-hanegokedial	*Plagiochila semidecurrens*	55
108	(–)-plagiochilal B	*Plagiochila fruticosa*	60
109	(+)-hanegoketrial	*Plagiochila semidecurrens*	59

(a) According to Asakawa et al the 10-methoxy compounds are artefacts, formed during isolation[48].



89



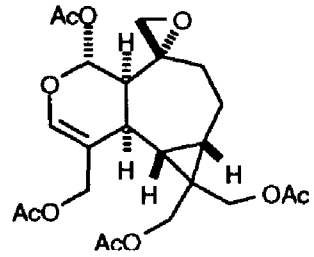
90: R^1 = OAc R^2 = H R^3 = H

91: R^1 = OAc R^2 = OAc R^3 = H

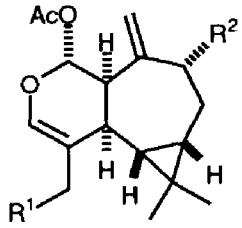
92: R^1 = OAc R^2 = OAc R^3 = OAc

93: R^1 = OAc R^2 = OAc R^3 = OH

94: R^1 = OH R^2 = H R^3 = H



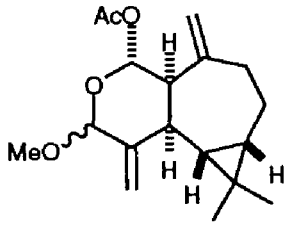
95



96: R^1 = OAc R^2 = H

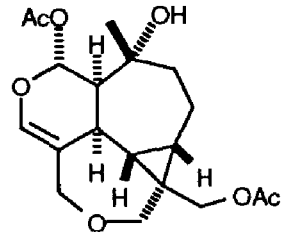
97: R^1 = H R^2 = H

98: R^1 = OAc R^2 = OAc



99: βOMe

100: αOMe



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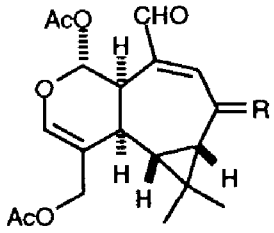
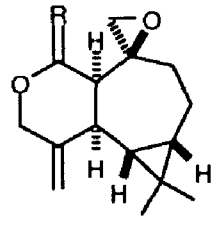


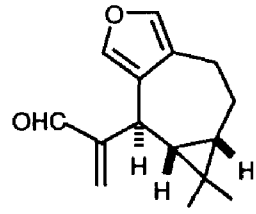
102: R = H_2

103: R = O



104: R = O

105: R = αOH, βH



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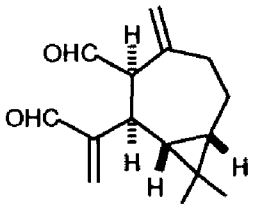

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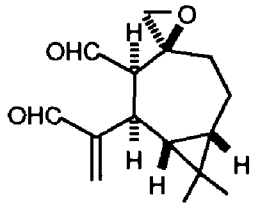

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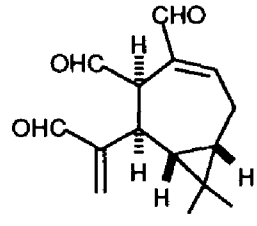


109

Table 1.4: *ent*-7,8-seco-aromadendranes

	Compound	Isolated from	Ref.
110	(–)-taylorione	*Mylia taylorii*	61
111	(–)-10-acetoxytaylorione	*Mylia taylorii*	47
112	(–)-7,10-dioxotaylori-11-ene	*Mylia taylorii*	47
113	see structure	*Mylia taylorii*	62

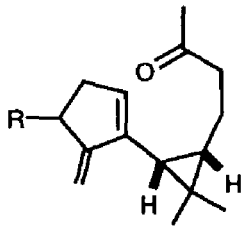
Table 1.5: *ent*-1,7-cycloaromadendranes

	Compound	Isolated from	Ref.
114	(–)-myliol	*Mylia taylorii*	63
115	(–)-10-epimyliol	*Mylia taylorii*	47
116	(+)-myli-11(12)-en-6-one	*Mylia taylorii*	47
117	(–)-dihydromylione A	*Mylia taylorii*	64
118	(+)anastreptene	*Anastrepta orcadensis*	65

Table 1.6: alkylated aromadendranes

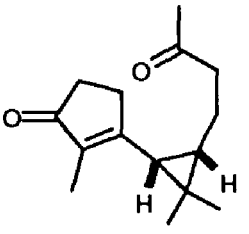
	Compound	Isolated from	Ref.
119	*ent*-(+)-plagiospirolide E	*Plagiochila moritziana*	66
120	(–)-tanzanene	*Uvaria tanzaniae*	67
121	(+)-cneorubine U	*Cneorum tricoccon*	68
122	cneorubine W1	*Cneorum tricoccon*	68
123	cneorubine W2	*Cneorum tricoccon*	68
124	(–)-cneorubine X	*Cneorum tricoccon*	68
125	(–)-euglobal V	*Eucalyptus globulus*	69
126	(–)-macrocarpal A	*Eucalyptus macrocarpa*	71
127	(–)-macrocarpal B	*Eucalyptus globulus* *Eucalyptus macrocarpa*	70 72
128	(–)-macrocarpal C (–)-macrocarpal G[a]	*Eucalyptus globulus* *Eucalyptus macrocarpa*	70 72

(a) Macrocarpal C from *E. globulus* and macrocarpal G from *E. macrocarpa* are probably identical.



110: R = H

111: R = OAc



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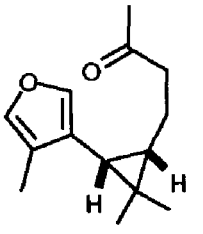

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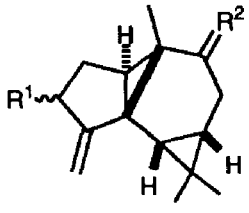
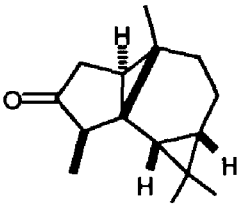


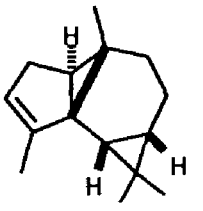
114: R^1 = βOH $R^2 = H_2$

115: R^1 = αOH $R^2 = H_2$

116: R^1 = H R^2 = O



117



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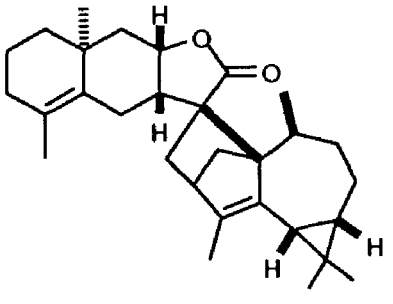

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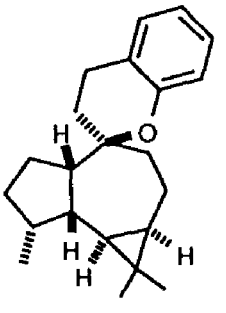

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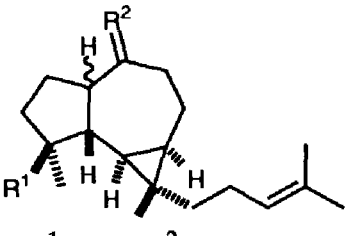
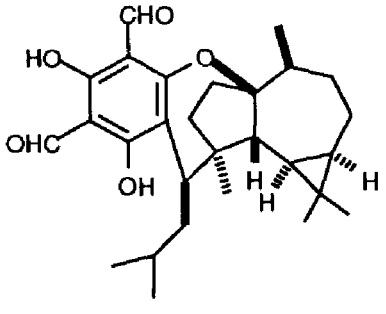


121: αH R^1 = H R^2 = βCH$_3$, αOH

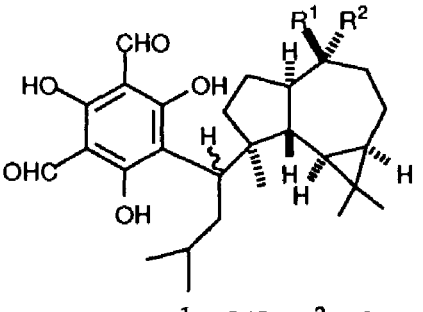
122: βH R^1 = H $R^2 = CH_2$

123: αH R^1 = H $R^2 = CH_2$

124: βH R^1 = OH $R^2 = CH_2$



125



126: αH R^1 = OH $R^2 = CH_3$

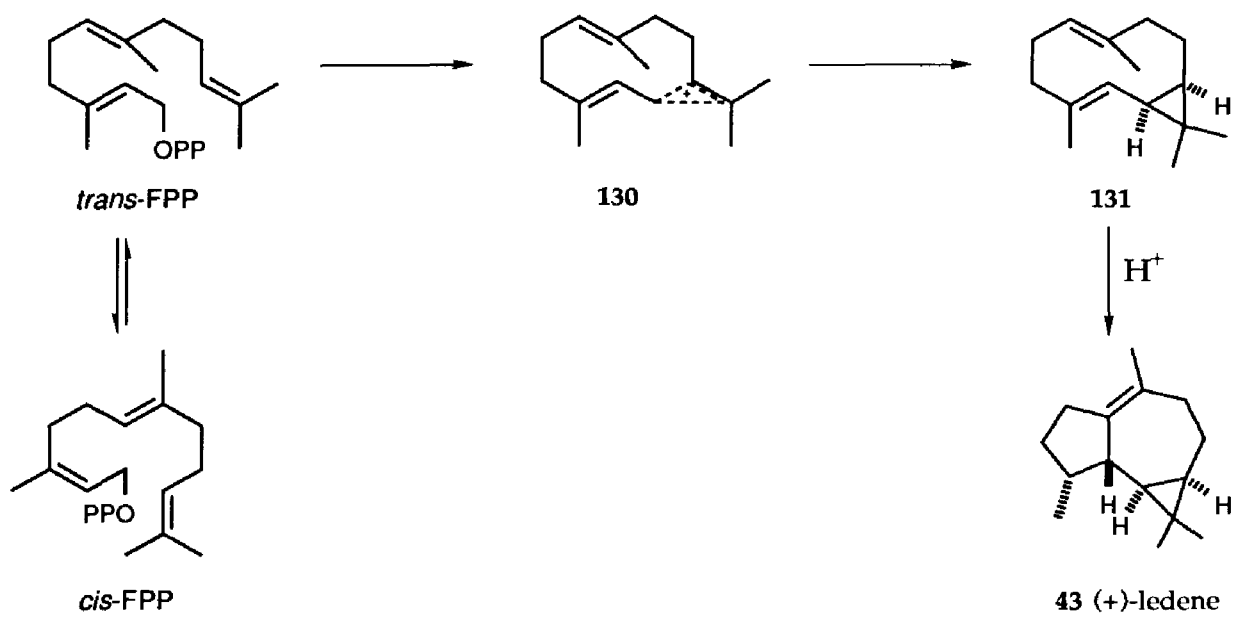
127: βH R^1 = OH $R^2 = CH_3$

128: αH $R^1 = R^2 = CH_2$

1.2 Biosynthesis

Almost all the structural classes of sesquiterpenes can be derived from *trans*-farnesylpyrophosphate (*trans*-FPP), and the *cis*-isomer (*cis*-FPP), through appropriate cyclizations and rearrangements. Enzymatic regiospecific cyclizations of *trans*-FPP and *cis*-FPP generate various monocarbocyclic cations through the intermediacy of non-classical carbocations[79]. The non-classical cation **130** obtained from *trans*-FPP gives, after a stereoselective 1,3-deprotonation, the bicyclogermacrene **131** (Scheme 1.1). The latter compound is believed to be the biosynthetic precursor of aromadendranes and maalianes[80-82]. Treatment of **131** with acid gives, among other products, the aromadendrane sesquiterpene (+)-ledene (**43**)[81]. In many plants containing aromadendranes, also (+)-bicyclogermacrene (**131**) has been identified[83]. From organisms that produce *ent*-aromadendranes often (–)-*ent*-bicyclogermacrene has been isolated[84]. The absolute stereochemistry of an aromadendrane is therefore determined by the enzymes that produce either (+)-bicyclogemacrene (**131**) or its (–)-enantiomer.

Scheme 1.1

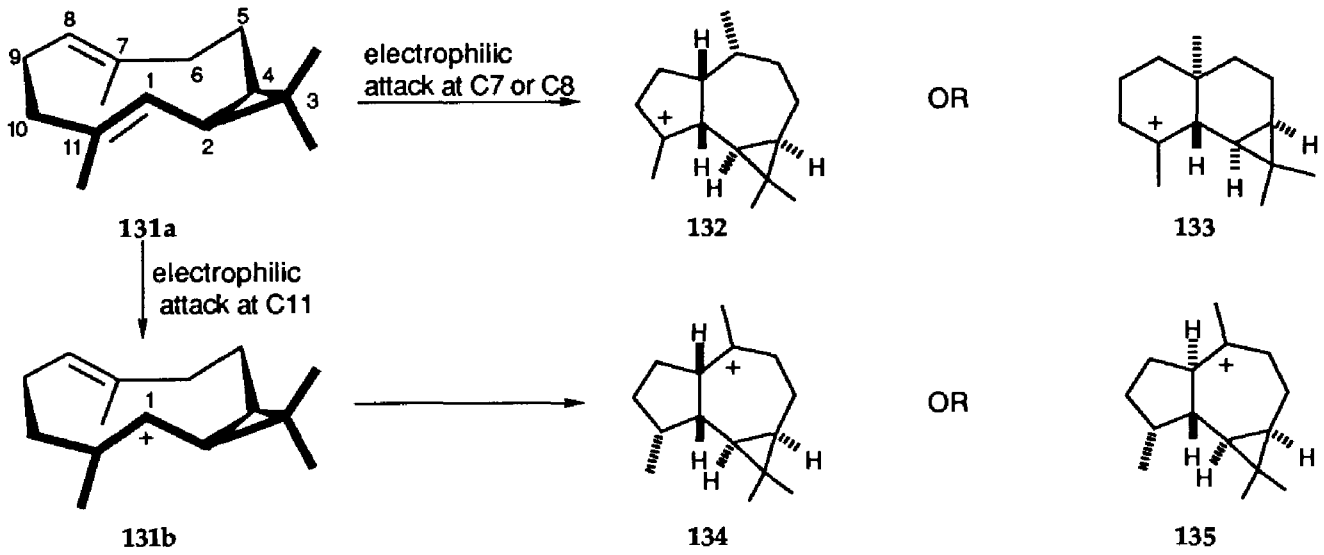


trans-FPP — **130** — **131**

cis-FPP — **43** (+)-ledene

A transannular cyclization of the most stable conformer **131a** of bicyclogermacrene[85] would produce the *cis*-fused alloaromadendrane carbocations **132** or **134** after electrophilic attack at C7 or C11, respectively[82] (Scheme 1.2). Similarly the *trans*-fused maaliane carbocation **133** can be formed after electrophilic attack at C8.

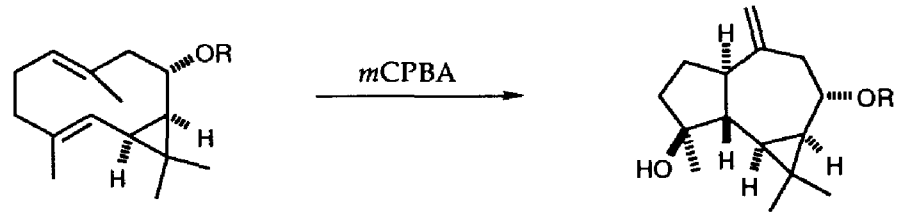
Scheme 1.2



The formation of the *trans*-fused aromadendrane carbocation **135** from **131** is more difficult to explain. A similar cyclization as described for alloaromadendranes would require a less stable conformer of **131**[82]. However, attack of an electrophile at C11, or acid-catalyzed opening of a C1-C11 epoxide in bicyclogermacrene (**131**) in anti-Markownikoff fashion would lead to a cyclopropyl carbinyl cation at C1(**131b**). With this relatively stable carbocation one can imagine cyclization towards *trans*-aromadendranes which are in general thermodynamically more favoured than their corresponding *cis*- (allo)aromadendranes[86].

Trans-aromadendranes can be produced from bicylogermacranes, as has been proven in the synthesis of guayulin C (**33**) and D (**34**) from guayulin A (**136**) and B (**137**), respectively, via epoxidation with *m*CPBA[18] (Scheme 1.3).

Scheme 1.3



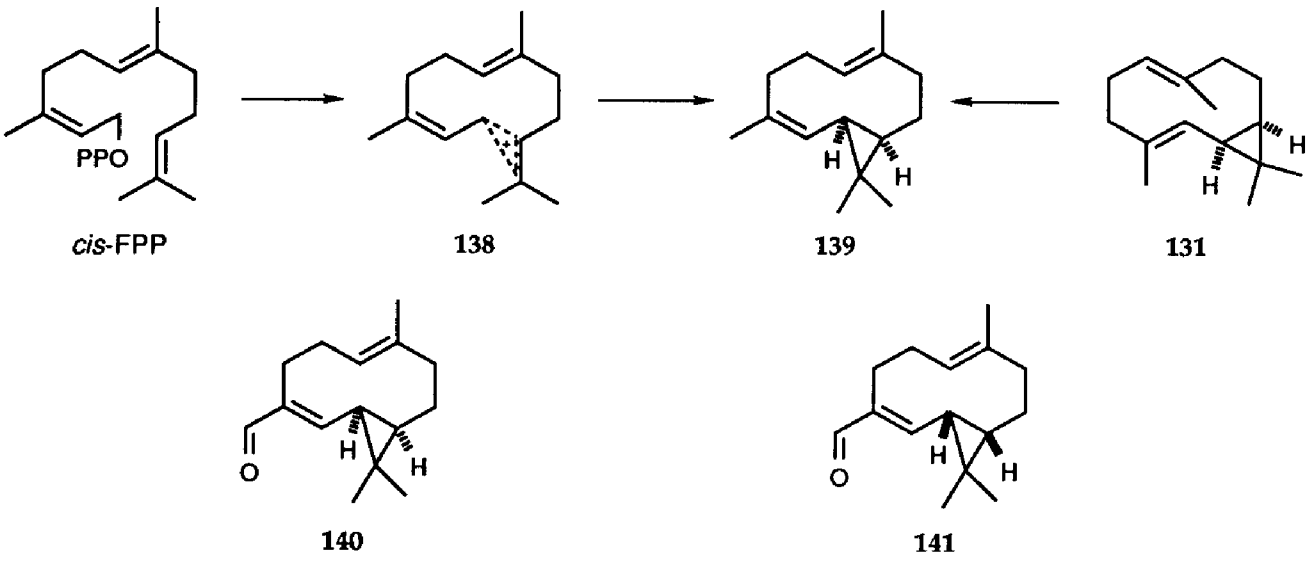
136: R = Cinnamoyl
137: R = Anisoyl

33: R = Cinnamoyl
34: R = Anisoyl

Another theory explains the formation of *trans*-aromadendranes as starting from isobicyclogermacrene (**139**)[82]. This compound can be derived from *cis*-FPP via 1,3 deprotonation of the non-classical cation **138**, in a similar way as bicyclogermacrene (**131**) from *trans*-FPP (Scheme 1.4). Also it can be formed via isomerization of **131**[81]. Cyclization of the most stable conformer of **139** should give rise to *trans*-

aromadendranes or *cis*-maalianes[82]. The fact that *cis*-maalianes have never been found in nature speaks against this cyclization process. Furthermore, up till now only two isobicyclogermacranes have been reported to occur in one or two plant species: (+)-isobicyclogermacrenal (**140**)[87] and its (–)-enantiomer (**141**)[82]. It is therefore unlikely that all the *trans*-aromadendranes are derived from isobicyclogermacrene (**139**).

Scheme 1.4

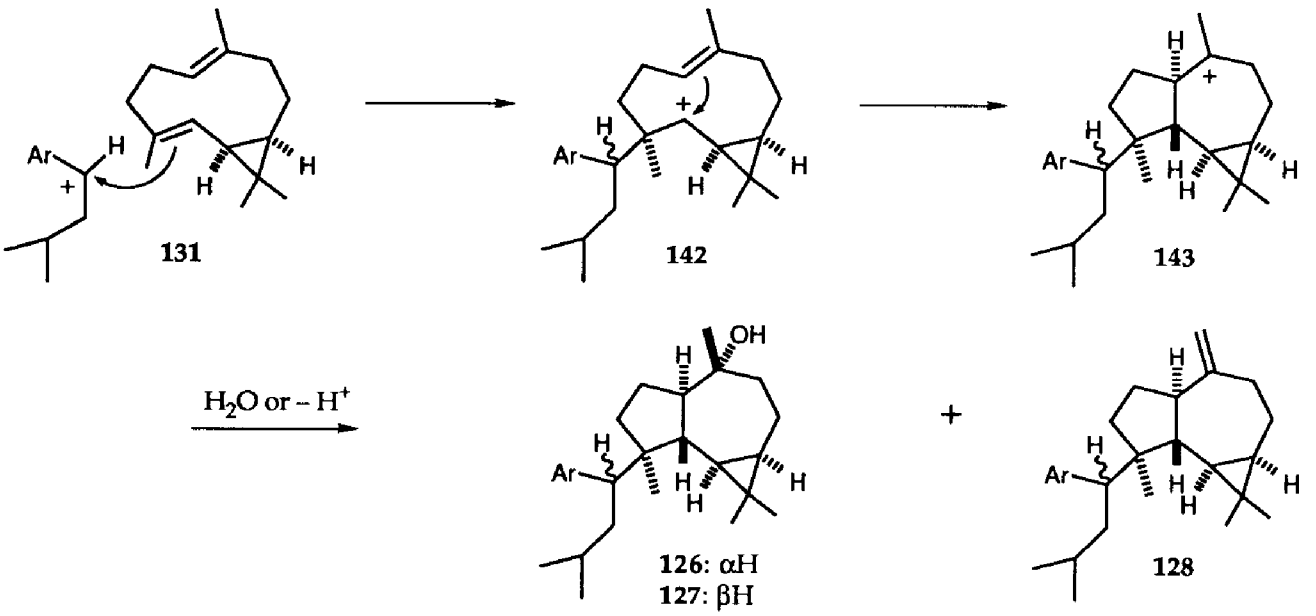


cis-FPP **138** **139** **131**

140 **141**

The biosynthesis of the *trans*-fused macrocarpals **126**, **127**, and **128** from bicyclogermacrene (**131**) and a benzylic cation has also been explained via a cyclopropyl carbinyl cation (**142**) as pictured in scheme 1.5[70].

Scheme 1.5



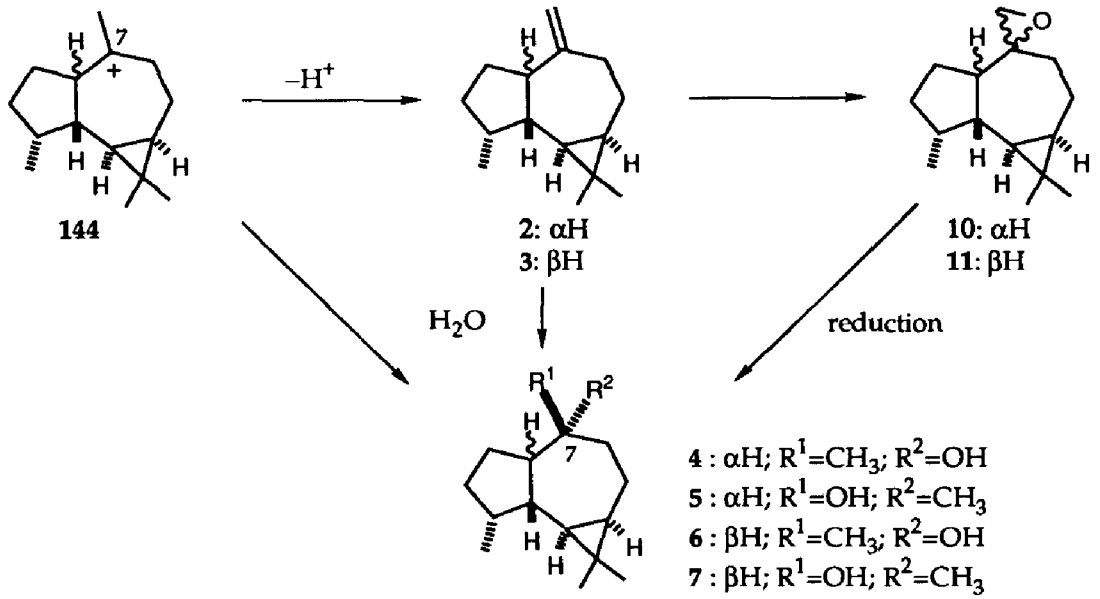
131 **142** **143**

126: αH
127: βH

128

Neutralization of the carbocations after cyclization takes place by hydrogen expulsion or reaction with a nucleophile. This process, together with oxidation steps in bicyclogermacrene or aromadendranes, leads to the functional groups found in the naturally occurring aromadendranes. For example, the presence of the tertiary alcoholgroups at C7 in **4-7** can be explained by reaction of the C7-cation **144** formed after cyclization with OH^- , or by addition of water to **2** or **3**. The reduction of the epoxides **10** and **11**, derived from aromadendrene (**2**) and alloaromadendrene (**3**), respectively, has been proposed by Tressl et al for the biosynthesis of **4-7**[31] (Scheme 1.6).

Scheme 1.6



The isonitril groups in the natural products found in sponges have been proven to originate from cyanide ions[88]. The isothiocyanate and formamide groups are subsequently derived from the isonitril function[89].

1,7-Cyclo-, 7,8-seco-[47], and 9,10-secoaromadendranes[55,59] are probably derived from the appropriate cyclization or bond cleavages in the corresponding aromadendranes.

1.3 Biological activity

From the aromadendranes listed in section 1.1 only a few have been shown to exhibit biological activity. This does not necessarily mean that biological activity is rare among aromadendranes. Most compounds have only been tested for one specific biological activity, or have not been tested at all.

Many essential oils and other plant extracts used in the fragrance and flavour industry contain aromadendranes[90]. Most of them are hydrocarbons and/or monohydroxy derivatives. Hop (*Humulus lupulus*), which gives beer its characteristic taste, contains a variety of aromadendranes[31,91].

Some medicinal plants[17,92] or plants with known biological activity[93] contain aromadendranes, but in most cases it is not known which compounds are responsible for the medicinal properties or biological activities.

Biological activities that have been reported for selected (*ent*)-aromadendranes include antifungal, antibacterial, antiviral (section 1.3.1), plant growth regulatory (section 1.3.2), antifeedant, repellent (section 1.3.3), piscicidal, and cytotoxic activities (section 1.3.4). Some miscellaneous biological activities are described in section 1.3.5.

1.3.1 Antifungal, antibacterial, and antiviral activities

Some aromadendrane mono- and dialcohols have been found to possess fungicidal activity, e.g. (–)-ledol (**6**) against *Coriolus ronatus*[94] and alloaromadendrane-7β,11β-diol (**41**) against *Cladosporium herbarium*[19,78]. The antifungal properties of (+)-spathulenol (**31**) might be responsible for its repellency against leaf cutter ants[95] (see also section 1.3.3). (–)-Cyclocolorenone (**27**) inhibits the growth of the fungi *Curvularia lunata*, *Chaetomium cochliodes*, and *Chaetomium spinusum*, but not of *Aspergillus flavus*[96]. This compound also shows antibacterial activity against several Gram-positive bacteria and, at higher concentration, against Gram-negative bacteria[96]. The isothiocyanate **82** and isonitrile **84**, isolated from *Acanthella pulcherrima*, are, among others, responsible for the growth inhibition of the Gram-positive bacteria *Bacillus subtilis*[43]. Aromadendrane containing essential oils from several plants have been found to possess antibacterial activity[92b-d]. However, the compounds responsible for this activity have not been identified. Macrocarpals A (**126**), B (**127**), and G (**128**), metabolites from *Eucalyptus macrocarpa*, show antibacterial activity against Gram-positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus*, but not against Gram-negative bacteria, yeast, or fungi[71,72].

Macrocarpals **126-128** have antiviral properties in that they inhibit the enzyme HIV-reverse transciptase[70]. The ledol glycosides, especially arvoside B (**12**), which have been extracted from the aerial parts of *Calendula arvensis*, exhibit antiviral activity against the vesicular stomatitis virus[27].

1.3.2 Plant growth regulatory activity

(+)-Globulol (**4**) shows weak activity against the germination of cress seed[97]. Alloaromadendrane-7β,11β-diol (**41**), isolated from *Ambrosia peruviana*, causes marginal reduction in the growth of cress seeds, but stimulates wood and shoot growth in lettuce at low concentrations[19,78]. (–)-Cyclocolorenone (**27**) shows good growth-inhibitory activity against etiolated wheat coleoptiles. It is also phytotoxic against greenhouse-grown corn, bean, and tobacco plants[96].

The *ent*-2,3-secoaromadendrane plagiochiline A (**90**) inhibits the germination of rice and wheat[53]. The methanol extract from *Plagiochila semidecurrens* inhibits the growth of the leaves and roots of rice seedlings[59]. The compounds responsible for this plant growth inhibition are the *ent*-2,3-secoaromadendranes ovalifoliene (plagiochiline C) (**96**)[55], ovalimethoxy I (**99**) and II (**100**), ovalifolienal (**102**), and ovalifolienalone (**103**). Especially compounds **96, 99** and **102** are very strong growth inhibitors of rice seedlings[59].

1.3.3 Antifeedant and repellent activity

Plachiochiline A (**90**), already mentioned in section 1.3.2, is a very pungent substance found in several plachiochila species. It shows a very strong antifeedant activity against the larvae of the African army worm (*Spodoptera exempta*)[58].

(+)-Spathulenol (**31**) is one of the compounds in *Melanpodium divaricatum* that has repellent properties against the leaf cutter ant (*Atta cephalotes*)[95]. It is possible that these ants discriminate against **31** because of its antifungal properties (see section 1.3.1). (–)-Alloaromadendrene (**3**) shows toxic activity against Southeast Asian termites (*Neotermes* spp.) and is probably one of the components in the crude resin of *Dipterocarpus* trees that is responsible for the insecticidal properties of this resin[98]. The viridiflorol glycosides **23** and **24** from *Pittosporum tobira* show repellent activity against the blue mussel *Mytilus edulis*[28] and might be useful as non-toxic antifouling agents[99].

The isonitrile **77** and isothiocyanate **78**, together with other metabolites found in *Axinella* species (sponges), probably secure the sponge against being eaten and

overgrown[100]. A mixture of isonitriles, including **77**, found in *Axinella* species inhibits the settlement and/or metamorphosis of the larval or juvenile invertebrates *Phidolophora pacifica* (ectoproct), *Salmacina tribranchiata* (polychaete), and *Haliotes refescens* (abalone). Metamorphosis and settlement of *Haliotes refescens* were also inhibited by a mixture of the isothiocyanates, including **78**, found in *Axinella* species[100]. Both isonitriles and isothiocyanates inhibited fish-feeding when applied to pelleted fish food for goldfish (*Carassius auratus*) and sculpin (*Clinocottus analis*)[100]. Isonitrile **77** and isothiocyanate **78**, found in the nudibranch *Cadlina luteomarginata*, might have a similar function in the nudibranch as in the sponges[45].

1.3.4 Piscicidal and other toxic activities

Treatment of killie-fish (*Oryzia latipes*) with the pungent plachiochiline A (**90**) at very low concentration kills them within a few hours[101]. Plachiochiline A also shows cytotoxicity against KB cells[101].

The mixture of isonitriles and isothiocyanates obtained from *Axinella* species, mentioned in section 1.3.3, shows piscicidal activity against goldfish (*Carassius auratus*)[100]. The isonitrile **84**, obtained from *Acanthella acuta* is toxic for guppy (*Lebistis reticulatus*)[44a,c]. Epipolasinthiourea B (**80**) shows moderate cytotoxicity against L1210 cells[41].

The essential oil of *Ledum palustre*, with (+)-ledol (**6**) as a major constituent, has been used as a medicine against various diseases and to provoke abortion. However, ledol is toxic and can cause vomitting and gastroenteritis. On digestion it can cause convulsions, followed by paralysis[102].

1.3.5 Miscellaneous activities

Plagiochilal B (**108**), isolated from *Plagiochila fruticosa*, causes acceleration of neurite sprouting and enhancement of choline acetyltransferase activity on a neuronal cell culture of fetal rat cerebral hemisphere[60]. Similar activity has been reported for plagiochilide (**89**) and a mixture of these and other plagiochilines obtained from *Plagiochila fruticosa* might be used as ingredients in nerve cell degeneration reparation agents[103].

Macrocarpals A (**126**), B (**127**), and G (**128**) have been shown to inhibit the enzyme aldose reductase from swine[104].

The extracts from the aerial parts of *Calendula arvensis*, containing ledol glycosides **12-17**[27], show anti-inflammatory activity[92a]. Euglobal V (**125**) causes strong granulation-inhibition in the fertile egg test, indicating anti-inflammatory activity[69a].

1.4 Synthesis

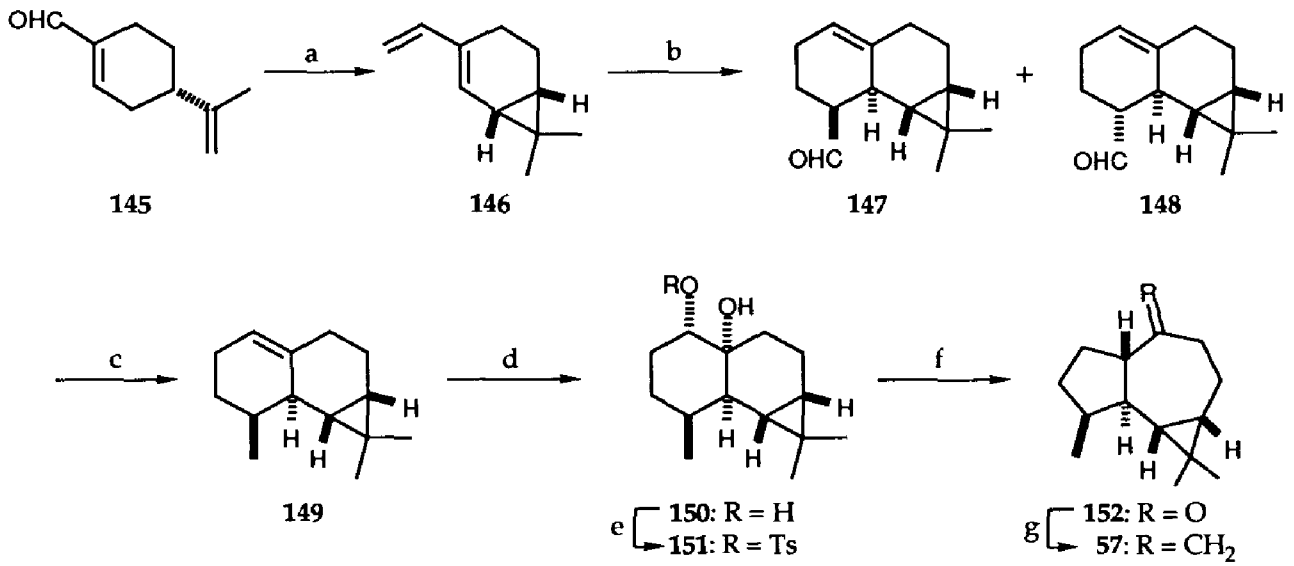
The available literature on the synthetic chemistry of aromadendranes can be devided into two parts: total synthesis of aromadendranes (section 1.4.1). and synthesis with natural aromadendranes as starting material (section 1.4.2).

1.4.1 Total synthesis of aromadendranes

Most total syntheses of aromadendranes have been based on the construction of a hydronaphthalene precursor that is subsequently rearranged to a hydroazulene ring system. The introduction of substituents in a stereoselective way is more easily achieved in the conformationally well understood hydronaphthalene system than in the hydroazulene system with its flexible cycloheptane ring. This makes the approach via hydronaphthalene systems attractive and reliable.

Several types of rearrangement from hydronaphthalene to hydroazulene skeletons have been described[105]. The well known total synthesis of (–)-aromadendrene (57) by Büchi et al uses a pinacol-type rearrangement[3] (Scheme 1.7). In this synthesis the hydronaphthalene skeleton was constructed via a Diels-Alder condensation of diene **146**, which was prepared from (–)-perillaldehyde (**145**), with acrolein. This cycloaddition gave a 5 : 1 mixture of the aldehydes **147** and **148**, respectively.

Scheme 1.7[a]

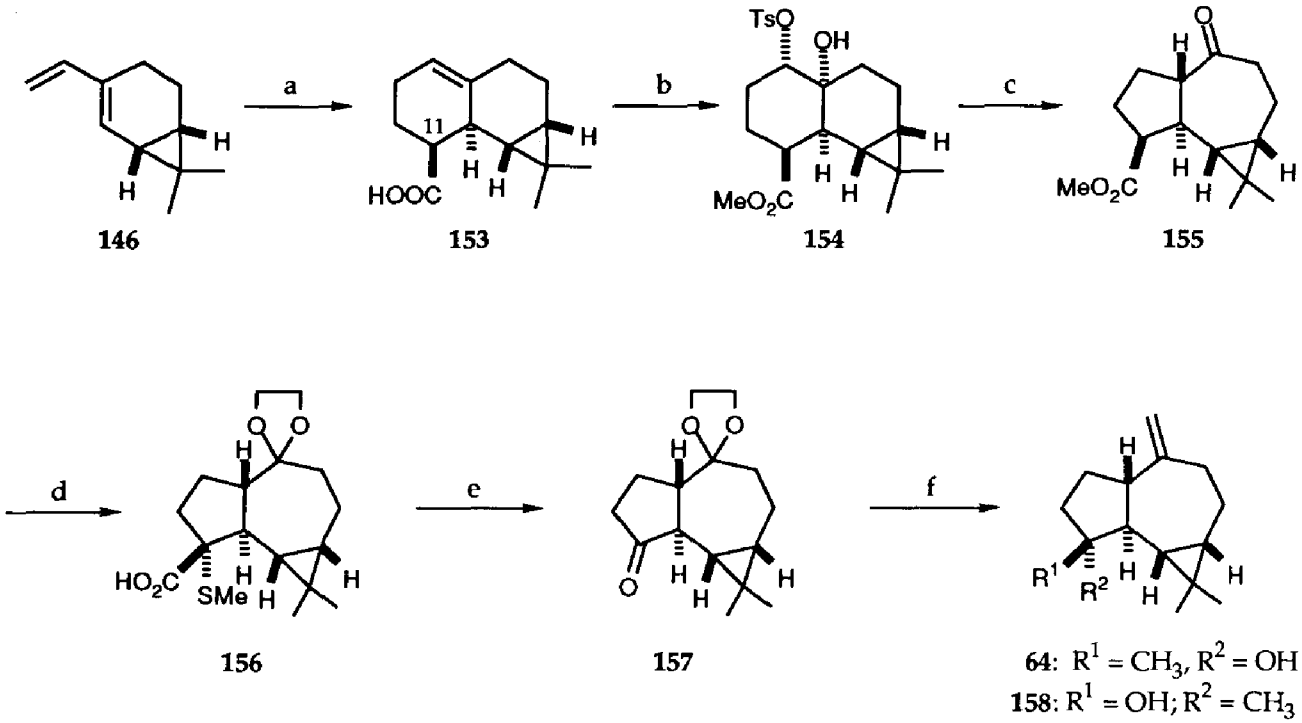


a (a) HBr; KO*t*Bu, HO*t*Am; $Ph_3P{=}CH_2$; (b) acrolein, 100°C; (c) $LiAlH_4$; MsCl; $LiAlH_4$; (d) OsO_4; (e) TsCl; (f) Al_2O_3; (g) $Ph_3P{=}CH_2$.

Reduction of the aldehyde group in **147** to the methyl group by standard procedures followed by oxidation of the double bond with OsO_4 gave a single diol **150** which was selectively tosylated to **151**. When **151** was treated with activated alumina in CH_3Cl, it readily underwent a pinacol rearrangement to give (–)-apoaromadendrone **152**. Ketone **152** was subsequently converted into (–)-aromadendrene (**57**) via a Wittig reaction.

Surburg and Mondon followed the same reaction sequence in their synthesis of (–)-spathulenol (**64**)[106] (Scheme 1.8). By using acroleic acid as dienophile, instead of acrolein, in the Diels-Alder condensation with diene **146**, hydronaphthalene **153** and its C11-epimer were obtained again in a 5 : 1 ratio, respectively.

Scheme 1.8[a]



146 **153** **154** **155**

156 **157**

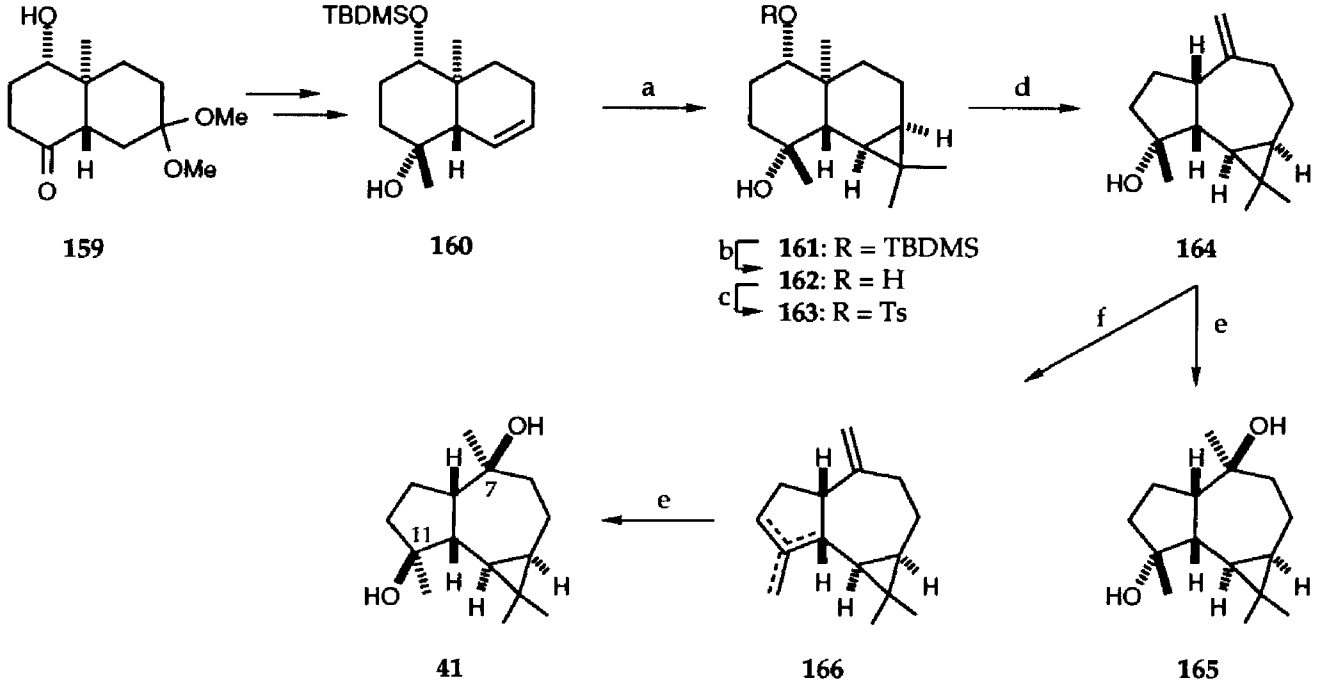
64: $R^1 = CH_3$, $R^2 = OH$
158: $R^1 = OH$; $R^2 = CH_3$

[a] (a) acroleic acid, 100°C; (b) OsO_4; CH_2N_2; TsCl; (c) KO*t*Bu, HO*t*Am; (d) ethylene glycol, *p*TsOH, benzene; LDA, Me_2S_2; KOH, ethylene glycol; (e) NCS, MeOH; aq. HCl; (f) MeMgI; aq. H_2SO_4, CH_2Cl_2; $Ph_3P{=}CH_2$.

Following the procedure of Büchi et al[3], the rearranged methyl ester **155** was prepared. After oxidative decarboxylation of its methylthio derivative **156**, ketone **157** was obtained in low yield. Grignard addition with MeMgI, followed by hydrolysis of the acetal and a Wittig reaction afforded the alcohols (–)-spathulenol (**64**) and 11-epispathulenol (**158**) in a 1 : 1 ratio.

Jenniskens et al have developed a new route to synthesize *cis*-fused hydroazulene systems via a base-induced and -directed rearrangement of substituted *trans*-perhydronaphthalene-1,4-diol monosulfonate esters[78]. This method has been applied in the total synthesis of (±)-alloaromadendrane-7β,11α-diol (**165**), supposedly isolated from *Ambrosia peruviana*[19] (Scheme 1.9). Starting from the readily available compound **159**, the *trans*-fused hydronaphthalene-1,4-diol monosulfonate ester **163** was prepared. Base-induced rearrangement of **163** with Na *t*-amylate in refluxing toluene gave, via selective intramolecular deprotonation, the alloaromadendrene derivative **164** in 70% yield.

Scheme 1.9[a]

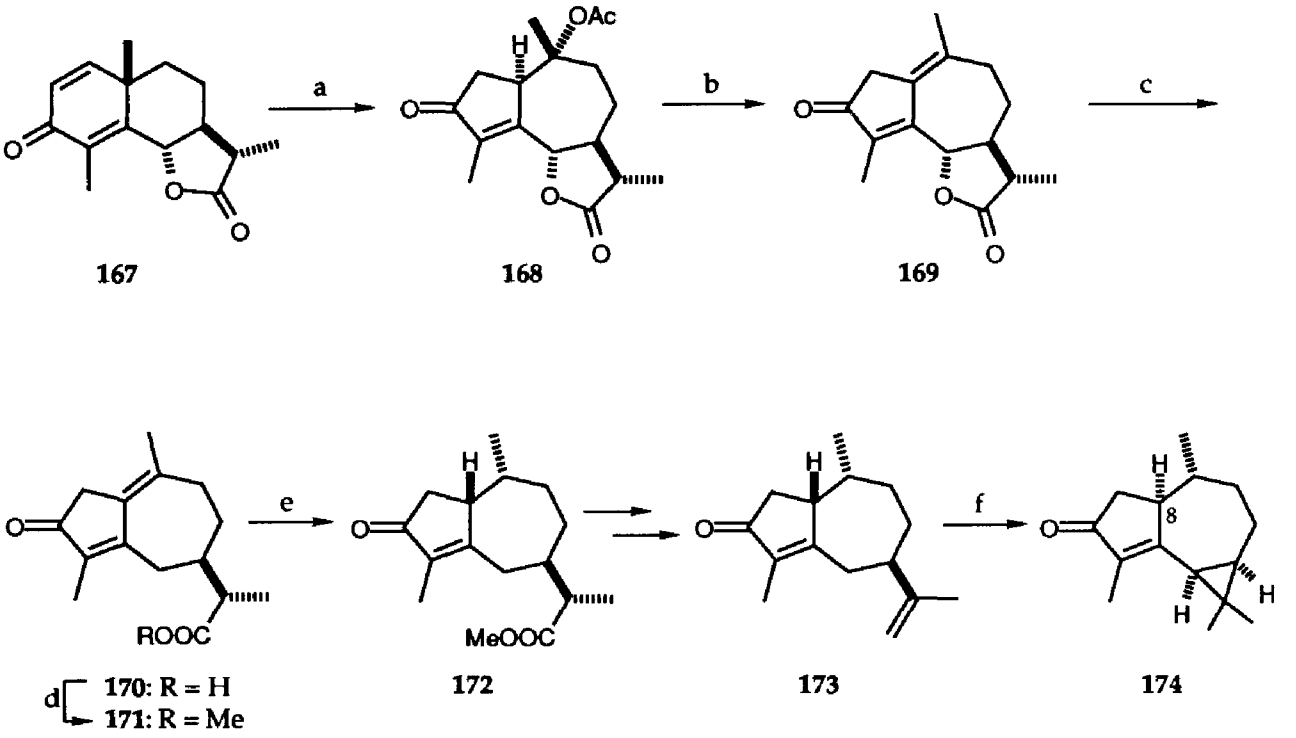


a (a) $CHBr_3$, NaO*t*Am,toluene; $(Me)_2(CuCN)Li_2$; MeI; (b) aq. HF, MeCN; (c) TsCl; (d) NaO*t*Am, toluene, Δ; (e) dimethyldioxirane; $LiAlH_4$; (f) $SOCl_2$.

Epoxidation and subsequent reduction of **164** gave (±)-alloaromadendrane-7β,11α-diol (**165**). However, its spectral data did not agree with those reported for the natural product. On the other hand, the spectral data of the epimeric 7β,11β-diol **41**, prepared from **164** via a dehydration, epoxidation, and reduction sequence, agreed very well with those of the natural product. Consequently, the natural product isolated from *A. peruviana* possesses the stereochemistry as shown in structure **41**, and not the one proposed in structure **165**.

Another approach to obtain hydroazulene products from hydronaphthalene precursors is the photochemical rearrangement of cross-conjugated hydronaphthalene dienones. α-Santonin (**167**) can be rearranged to the O-acetylisophotosantonic lactone **168** upon irradiation in aqueous AcOH[107]. This lactone has been transformed into 8-epicyclocolorenone (**174**) by Büchi et al[108] (Scheme 1.10).

Scheme 1.10[a]



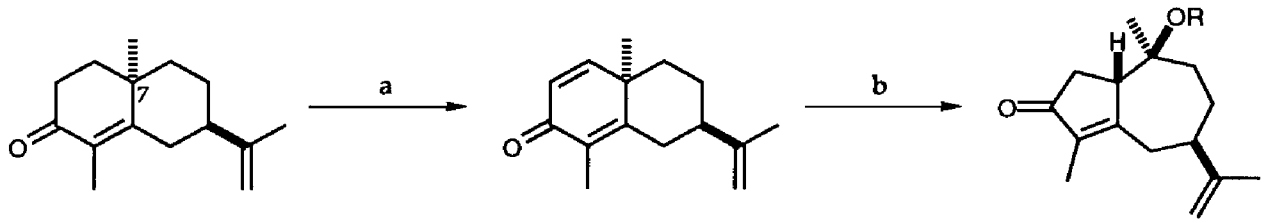
a (a) hν, AcOH; (b) H_2SO_4; (c) $CrCl_2$, AcOH; (d) CH_2N_2; (e) H_2, Pd/C; (f) HBr; KOH, MeOH.

Treatment of the acetate **168** with concentrated H_2SO_4 afforded the dienone lactone **169**. Treatment of **169** with chromous chloride in AcOH gave the carboxylic acid **170**. Partial hydrogenation of the methyl ester **171** with H_2 and Pd/C gave **172**, which could be converted into the olefin **173** in a few steps. Construction of the cyclopropane ring in **174** proceeded via treatment of the tertiary bromide, prepared from **173**, with methanolic KOH. The basic conditions used in the last step caused the C8-proton to epimerize to the α-position.

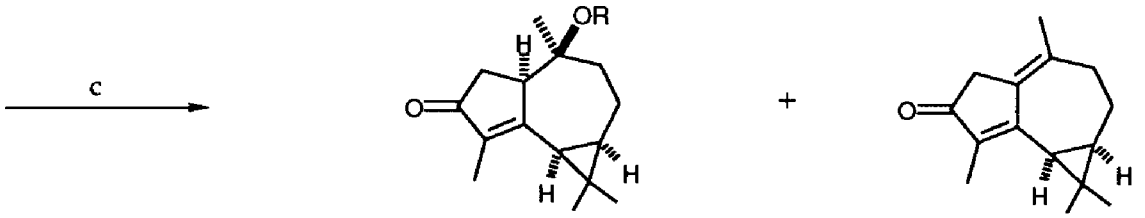
Streith and Blind used the hydronaphthalene **176**, obtained via oxidation of (–)-7-epicyperone (**175**) with DDQ, for their synthesis of cyclocolorenone derivatives[109] (Scheme 1.11). Photochemical rearrangement of **176** in AcOH gave a mixture of the

hydroazulenes **177** and **178**. Cyclopropane ring closure, as described above, gave the cyclocolorenone derivatives **179, 180,** and **181**.

Scheme 1.11[a]



175 **176** **177**: R = H
178: R = Ac



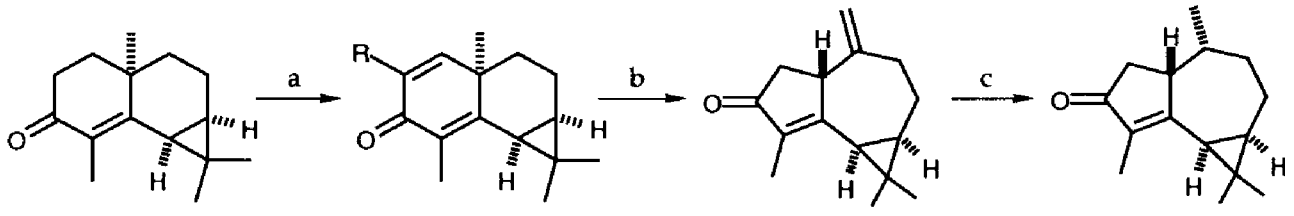
179: R = H
180: R = Ac

181

[a] (a) DDQ; (b) hν, AcOH; (c) HBr; KOH, MeOH.

A total synthesis of (–)-cyclocolorenone (**27**) itself was reported by Caine and Ingwalson[110]. Starting from (–)-maalienone (**182**), they prepared the dienone acid **183** (Scheme 1.12). Irradiation of **183** in dioxane gave the trienone **185** in 60% yield. Subsequent reduction of the exocyclic double bond with H_2 and Pd/C afforded (–)-cyclocolorenone (**27**).

Scheme 1.12[a]

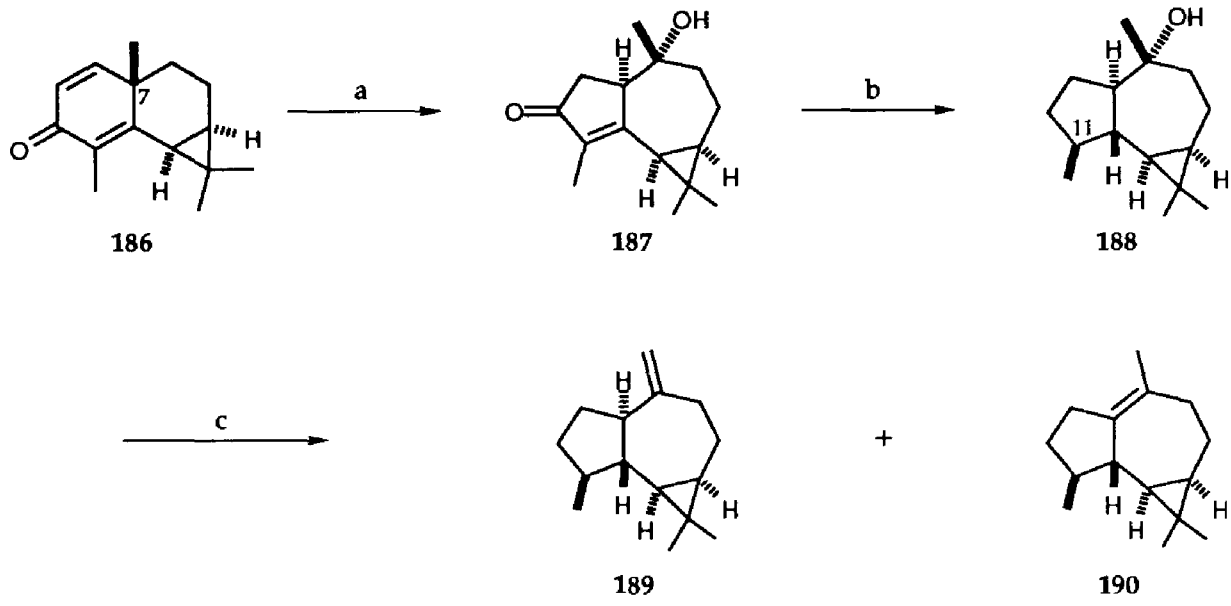


182 **183**: R = COOH
184: R = H
185 **27**

[a] (a) HCO_2Et, NaOAc; DDQ; CrO_3; (b) hν, dioxane; (c)H_2, Pd/C.

In contrast to the dienone acid **183**, the dienone **184** was photochemically stable. However, its C7-epimer **186** appeared to be photolabile and was used as a precursor in the synthesis of 11-epiglobulol (**188**) and the olefinic aromadendranes 11-epiaromadendrene (**189**) and 11-epiledene (**190**)[111] (Scheme 1.13).

Scheme 1.13[a]

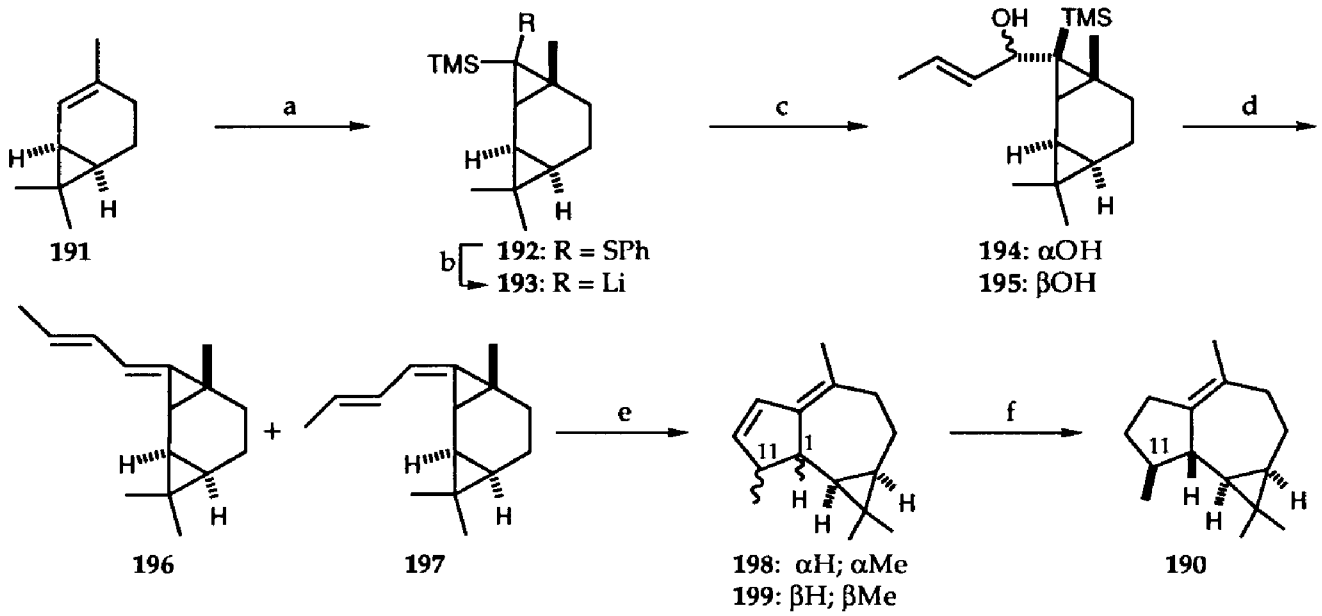


186 **187** **188** **189** **190**

[a] (a) hν, $HOAc/H_2O$; (b) Li, NH_3; Wolff-Kishner; (c) $SOCl_2$; NaOAc, HOAc.

11-Epiledene (**190**) has also been synthesized via an approach that does not involve a hydronaphthalene precusor[112]. Starting from (+)-2-carene (**191**) the phenylthio(trimethylsilyl)cyclopropyl acetal **192** was prepared (Scheme 1.14). Reductive lithiation with lithium-1-(dimethylamino)naphthalenide (LDMAN) gave the α-lithiosilane **193**, that was condensed with crotonaldehyde to give the alcohols **194** and **195** in a 7 : 1 ratio, respectively. The alcohols **194** and **195** underwent a Peterson olefination upon treatment with KH to give the allylidenecyclopropanes **196** and **197**, respectively. Upon thermolysis, both **196** and **197** gave a ca. 1 : 1 mixture of the aromadendrane dienes **198** and **199**. Hydrogenation of **198** using Wilkenson's catalyst gave 11-epiledene (**190**).

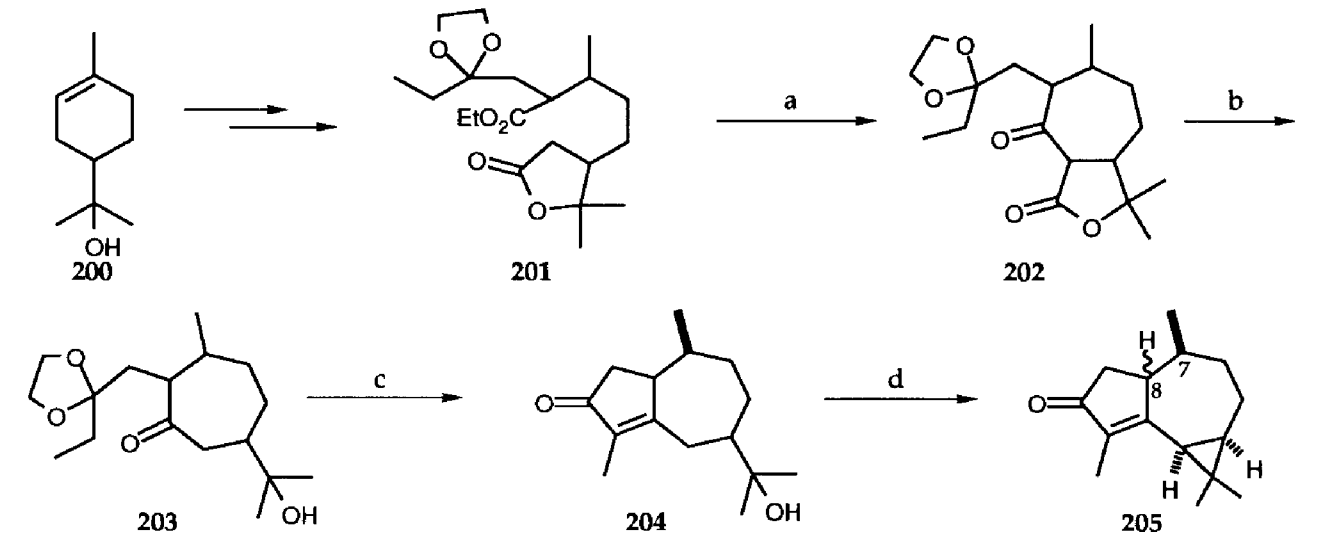
Scheme 1.14[a]



a (a) $PhSCHCl_2$, KOH; *s*BuLi; TMSCl; (b) LDMAN; (c) crotonaldehyde; H_2O; (d) KH; (e) thermolysis 190°C; (f) H_2, $(PPh_3)_3RhCl$.

A second approach to aromadendrenes that does not use a hydronaphthalene precursor is described by Narang and Dutta[113] (Scheme 1.15). Starting from (±)-terpineol (200), the 7-membered ring precursor **203** was synthesized in two steps from **201**. Hydrolysis of the acetal group followed by treatment with aqeous KOH afforded the hydroazulenic product **204**. The cyclopropane ring was constructed according to standard procedures to give in low yield compound **205**, a C7-epimer of cyclocolorenone (27) with an unknown stereochemistry at C8.

Scheme 1.15[a]

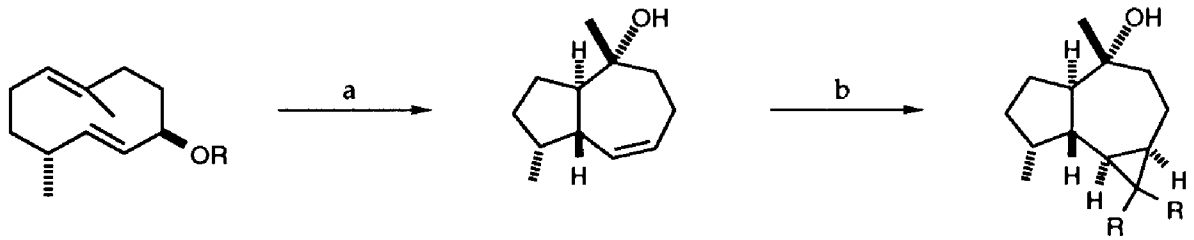


a (a) KO*t*Bu, xylene, Δ; (b) KOH, H_2O; (c) *p*TsOH; KOH, H_2O; (d) HBr; KOH, MeOH.

A biomimetic strategy towards the synthesis of aromadendranes makes use of a transannular cyclization of cyclodecane derivatives. Two examples of this approach have already been described in section 1.2 in the synthesis of ledene (**43**)[81] and guayulin C (**33**) and D (**34**)[18] from bicyclogermacrene precursors.

In a synthesis of (±)-globulol (**4**) Marshall and Ruth prepared the hydroazulenic compound **207** via a stereoselective solvolytic cyclization of the cyclodecadienol derivative **206**[114] (Scheme 1.16). Compound **207** could be converted into (±)-globulol (**4**) upon reaction with dibromocarbene, followed by treatment of the resulting dibromocyclopropane derivative **208** with lithium dimethylcuprate.

Scheme 1.16[a]

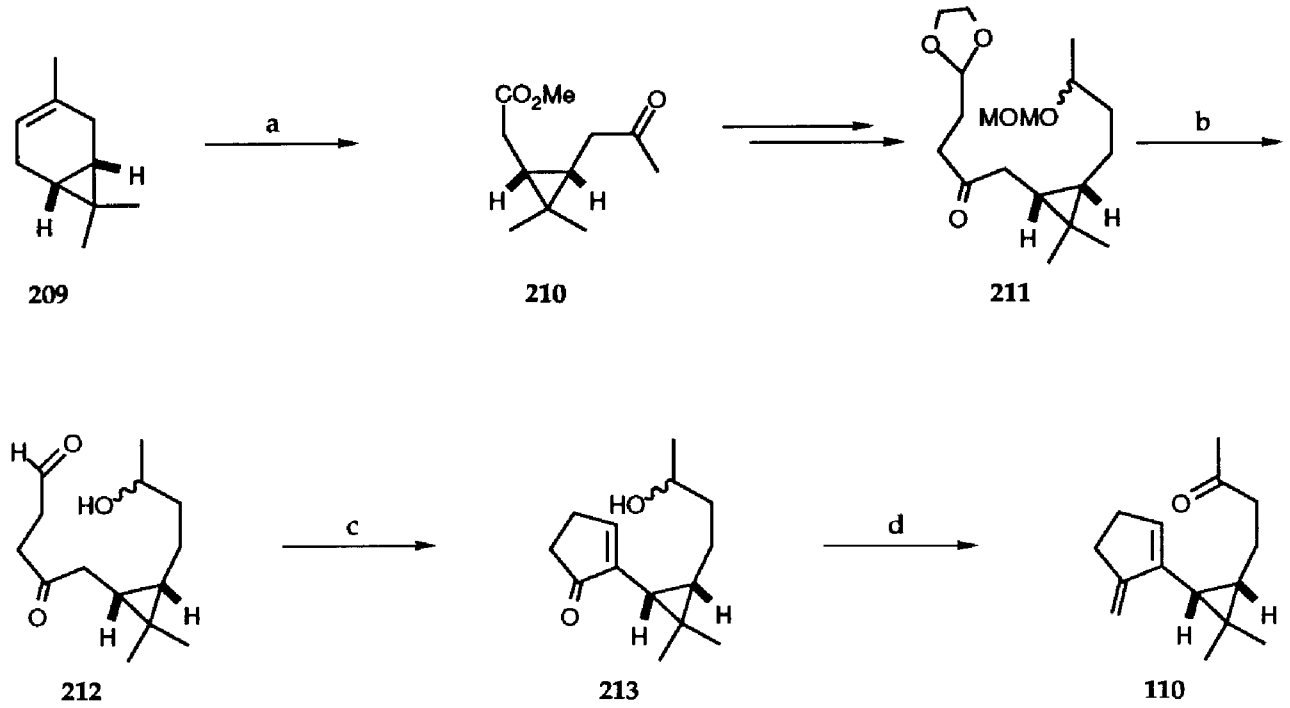


206: R = $COC_6H_4NO_2$-*p* **207** c → **208**: R = Br; **4**: R = Me

a (a) $NaHCO_3$, H_2O; (b) $PhHgCBr_3$, benzene; (c) $LiMe_2Cu$.

The 7,8-secoaromadendrane (–)-taylorione (**110**) has been synthesized by Nakayama et al, starting from Δ^3-carene (**209**)[115] (Scheme 1.17). Ozonolysis of **209** followed by oxidation and esterification gave product **210** that was transformed to product **211** in several steps. Removal of both protective groups with aqueous HCl in acetone gave the γ-keto-aldehyde **212**. Treatment of **212** with methanolic NaOH afforded the cyclisized product **213**, that was converted into (–)-taylorione (**110**) via a Wittig reaction and subsequent oxidation of the alcohol group.

Scheme 1.17[a]



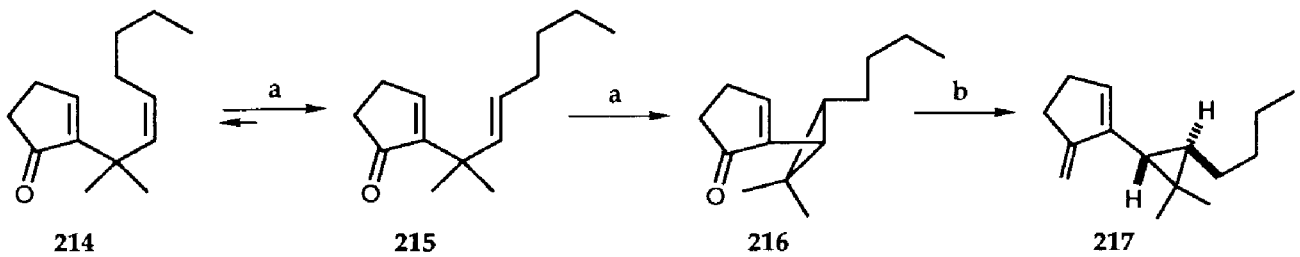
209 210 211

212 213 110

a (a) O_3; CrO_3; MeOH, HCl; (b) HCl, H_2O, acetone; (c) NaOH, MeOH; (d) $Ph_3P{=}CH_2$; DMSO, benzene, DCC, pyridine-$OCOCF_3$.

Pattenden and Whybrow tried to synthesize the taylorione skeleton via the photosensitive *Z*- and *E*-cyclopentenones **214** and **215**[116] (Scheme 1.18). Irradiation of the *E*-cyclopentenone **215** gave via a di-π-methane rearrangement the cyclopropane **216**, which was converted into *trans*-deoxytaylorione (**217**) via a Wittig reaction. Irradiation of the *Z*-cyclopentenone **214** also led to **216**, presumably via **215**, which was produced by *Z*-*E* photoisomerization.

Scheme 1.18[a]

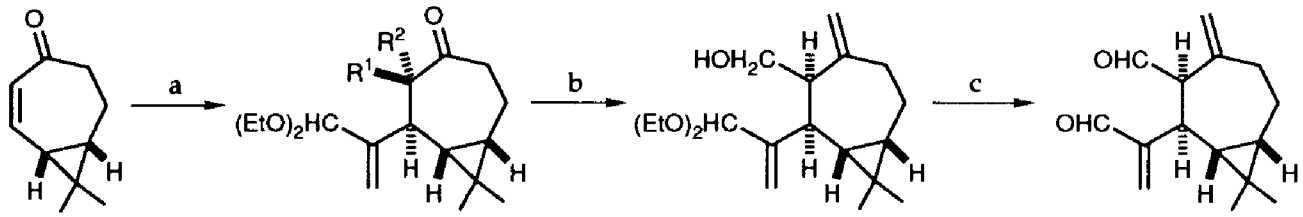


214 215 216 217

a (a) hν, hexane; (b) $Ph_3P{=}CH_2$.

The bicyclic enone **218**, available in both racemic and chiral forms[117], might be a versatile intermediate for the synthesis of (seco)aromadendranes. It has been used as starting material for the synthesis of the 9,10-secoaromadendrane (+)-hanegokedial (**107**)[118] (Scheme 1.19). Treatment of (–)-**218** with bis(1,1-diethoxy-2-propenyl) lithium cuprate in ether and quenching of the resultant enolate with formaldehyde gave the isomeric alcohols **219** and **220** in a 2 : 1 ratio, respectively. The minor alcohol **220** was converted into **221** via a Wittig reaction. Oxidation of **221**, followed by hydrolysis of the acetal gave (+)-hanegokedial (**107**). The difference between the optical rotations of natural (–)-hanegokedial[55] and the synthesized (+)-hanegokedial, respectively –10.4° and +0.5°, is probably due to the presence of impurities formed during storage of the unstable hanegokedial.

Scheme 1.19[a]



218 **219**: $R^1 = H$; $R^2 = CH_2OH$ **220**: $R^2 = CH_2OH$; $R^1 = H$ **221** **107**

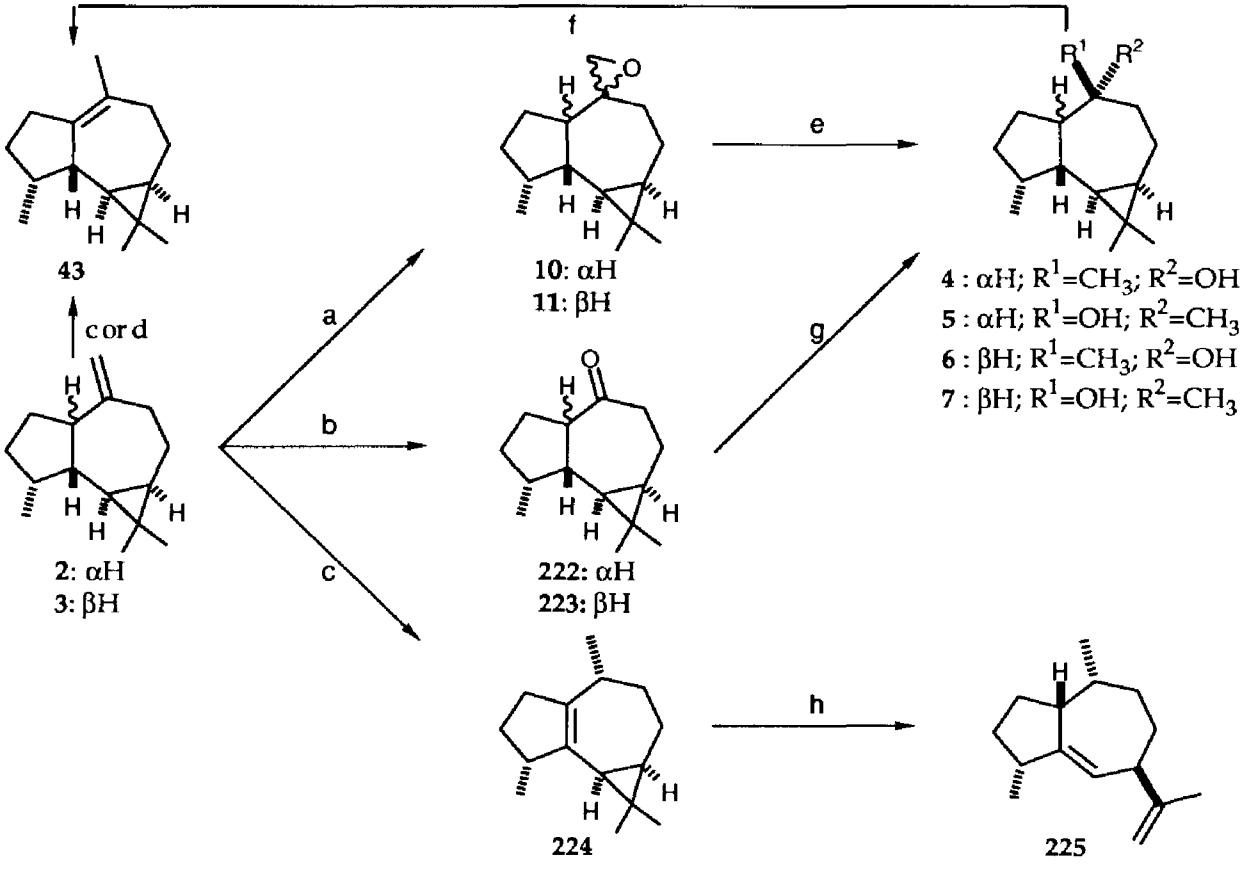
[a] (a) Li(1,1-(EtO)$_2$-2-propenyl)Cu; H_2CO; (b) $Ph_3P{=}CH_2$; (c) Collin's reagent; H_3O^+.

1.4.2 Aromadendranes as starting materials in the synthesis of sesquiterpenes

Several aromadendranes have been synthesized from more or less readily available aromadendranes. Usually, this has been done to correlate the structure and stereochemistry of newly isolated aromadendranes with those of known ones.

Epoxidation of aromadendrene (**2**) or alloaromadendrene (**3**), followed by reduction gave the tertiary alcohols globulol (**4**) and epiglobulol (**5**), or ledol (**6**) and viridiflorol (**7**), respectively[31,73,119] (Scheme 1.20). Epiglobulol could also be obtained via reaction of MeLi or MeMgI with (+)-apoaromadendrone (**222**), prepared from (+)-aromadendrene by ozonolysis[119,120]. In a similar way ledol could be prepared from alloaromadendrone (**223**)[119]. Dehydration of the tertiary alcohols **4-7** gave mainly (+)-ledene (**43**)[73]. Isomerization of (+)-aromadendrene with K/Al_2O_3 at 100°C gave (+)-ledene in 40% yield[121]. The same reaction at room temperature gave quantitatively isoledene (**224**), that could be converted into (+)-γ-gurjunene (**225**) by pyrolysis[121]. Isomerization of (+)-aromadendrene with KO*t*Bu in DMSO gave (+)-ledene in 80% yield[122].

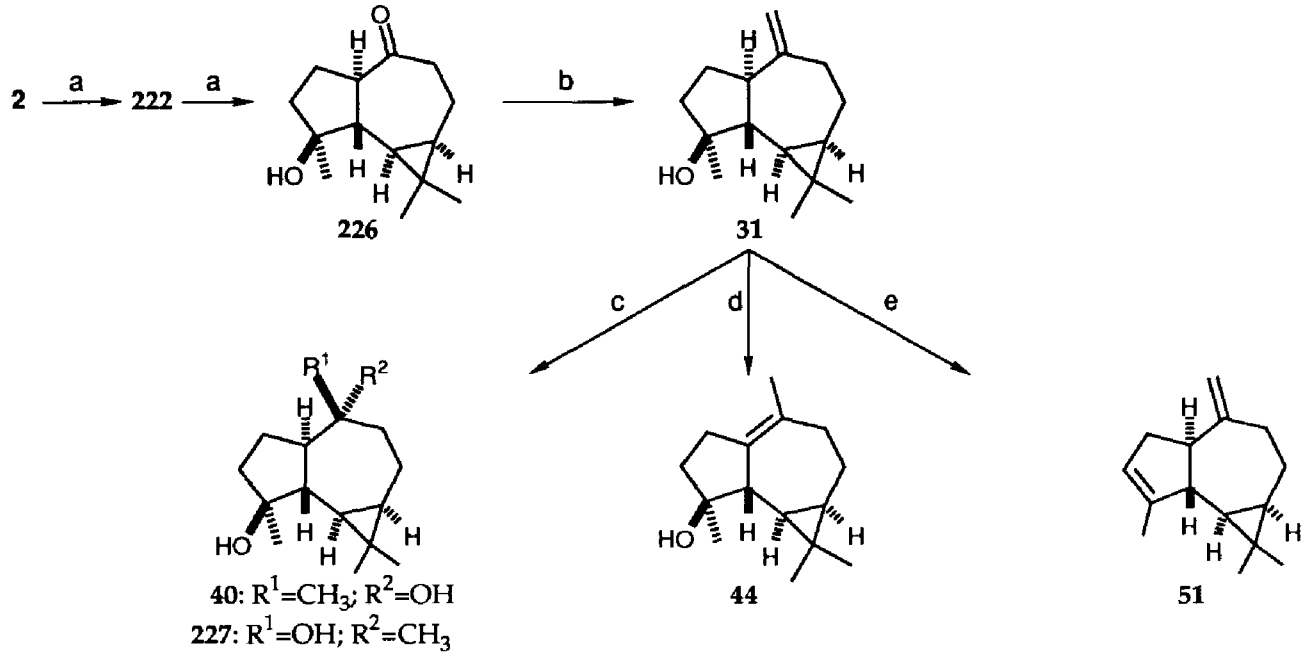
Scheme 1.20[a]



a (a) *m*CPBA; (b) O_3; (c) K/Al_2O_3, room temperature; (d) KO*t*Bu, DMSO; (e) $LiAlH_4$; (f) $SOCl_2$; (g) MeLi, or MeMgI; (h) 450°C.

The diols **40** and **227** have been prepared from spathulenol (**31**) by epoxidation and subsequent reduction[15,35] (Scheme 1.21). Spathulenol (**31**) has also been used as starting material in the synthesis of isospathulenol (**44**)[32] and β-spathulene (**51**)[12].

Scheme 1.21[a]

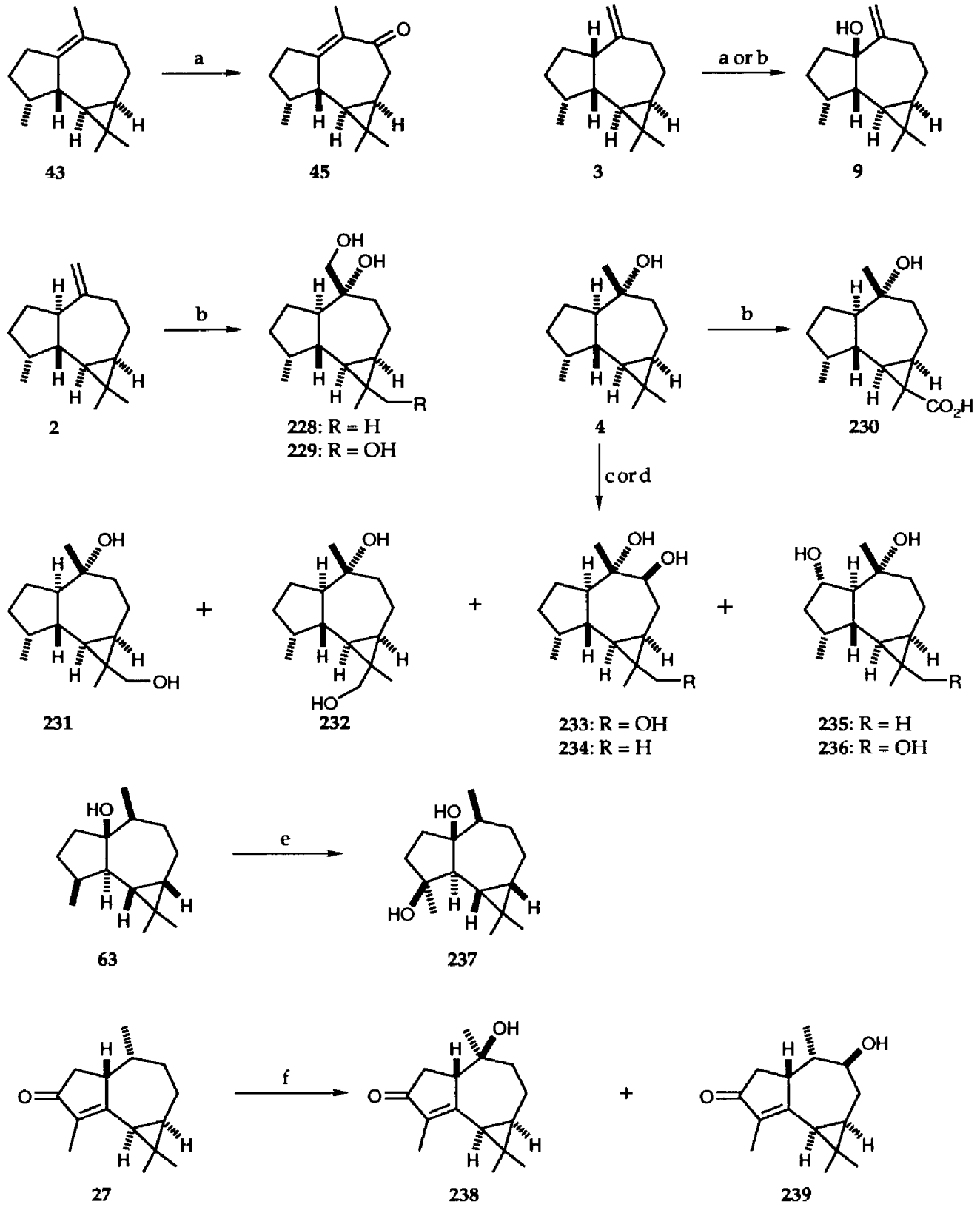


[a] (a) O_3; (b) $Ph_3P{=}CH_2$; (c) *m*CPBA; $LiAlH_4$; (d) *p*TsOH; (e) $SOCl_2$.

Since spathulenol (**31**) is not as readily available as (+)-aromadendrene (**2**), a route has been developed to synthesize **31** from **2**[123] (Scheme 1.21). A distillation tail of *Eucalyptus* oil, containing about 58% (+)-aromadendrene (**2**) has been ozonolyzed to obtain pure, crystallizable apoaromadendrone (**222**). Regio- and stereoselective oxidation of **222**, again with ozone, afforded the hydroxyketone **226** in 9% yield. Subsequently, hydroxyketone **226** was converted into (+)-spathulenol (**31**) via a Wittig reaction.

Many aromadendranes are oxidized derivatives of more common aromadendranes. Several of these oxidized derivatives have been prepared via allylic or microbial oxidation of abundant aromadendranes (Scheme 1.22). Squamulosone (**45**) has been synthesized via allylic oxidation of (+)-ledene (**43**) with SeO_2[29]. 8-Hydroxy-alloaromadendrene (**9**) has been prepared in a similar way from alloaromadendrene (**3**)[34]. Microbial hydroxylation of **3** with *Mycobacterium smegmatis* also gave **9**[124]. (+)-Aromadendrene (**2**) and globulol (**4**) were also fermentated by this microorganism. In this way the two hydroxylated products **228** and **229** were obtained from **2**, the acid **230** was obtained from **4**[124].

Scheme 1.22[a]

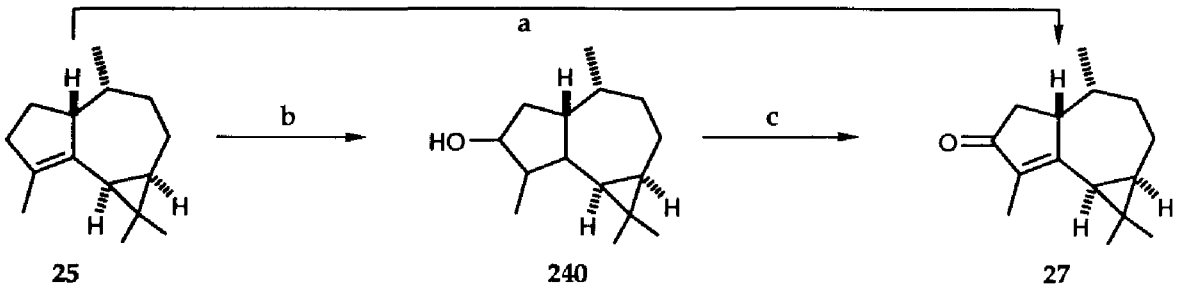


a (a) SeO_2; (b) *M. smegmatis*; (c) *D. gossypina*; (d) *B. megaterium*; (e) O_2; (f) rabbit.

Fermentation of **4** with *Diplodia gossypia* gave the three hydroxylated products **231**, **232**, and **233**[124,125]. The same products were formed by fermentation with *Bacillus megaterium*, together with three other products, **234**, **235**, and **236**[124]. The yields of these biotransformations were very low, with the exception of the formation of **230** from **4** which proceeded in 46% yield[124]. Autooxidation of (+)-palustrol (**63**) afforded the diol **237**[37a]. (–)-Cyclocolorenone (**27**) was metabolized by rabbits into the oxidized products **238** and **239**[126].

(–)-Cyclocolorenone (**27**) has been prepared from (–)-α-gurjunene (**25**) to establish the stereochemistry of α-gurjunene (Scheme 1.23)[5a,6]. Treatment of **25** with sodium peroxide gave **27** in very low yield (<2%)[5a]. Oxidative hydroboration of **25** gave the alcohol **240** in about 25% yield. Oxidation of **240** followed by bromination and dehydrobromination gave **27** in about 50% overall yield[6].

Scheme 1.23[a]

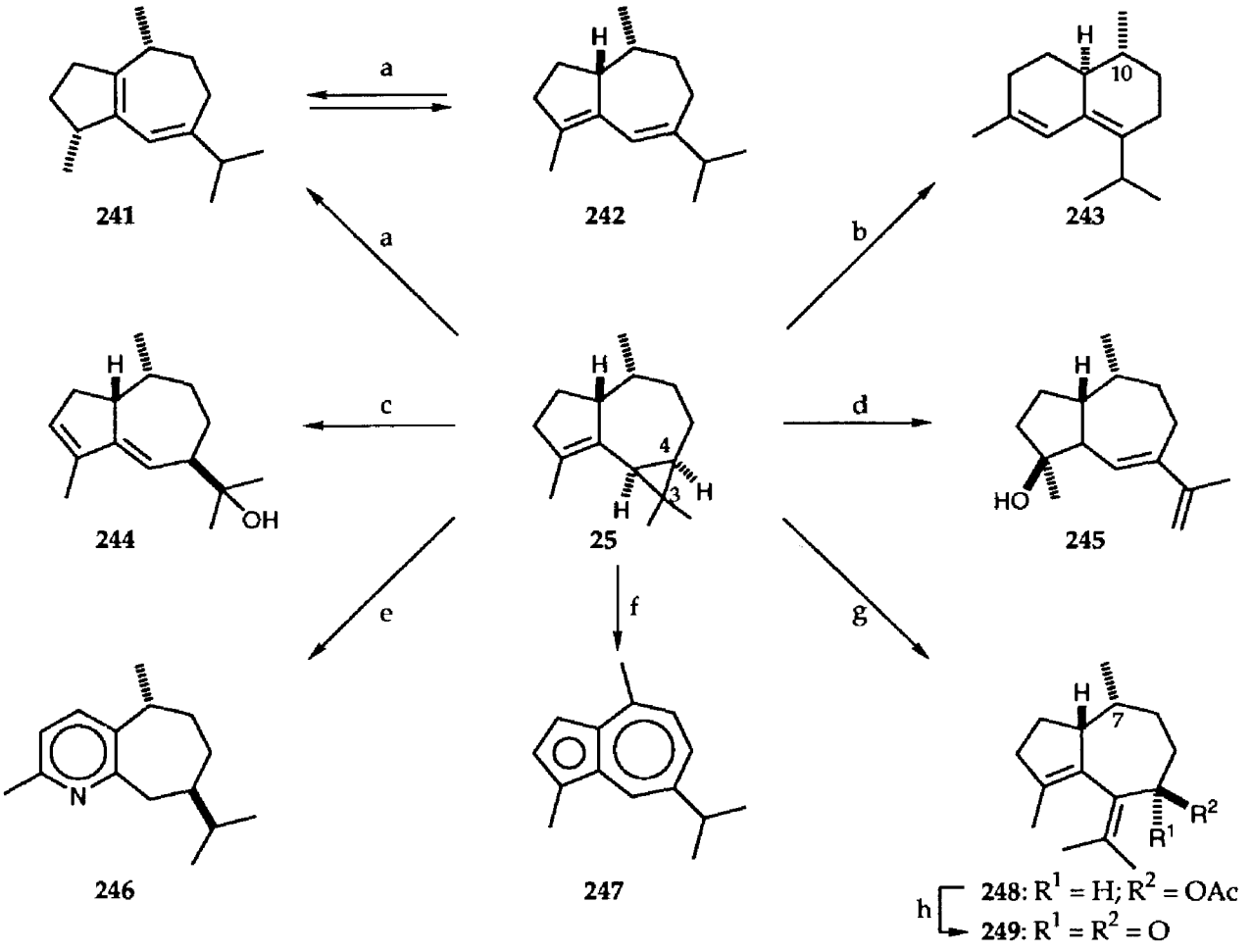


[a] (a) Na_2O_2; (b) BH_3; NaOH, H_2O_2; (c) CrO_3; $PhMe_3NBr_3$; Li_2CO_3, LiCl, DMF.

α-Gurjunene (**25**) has also been used as starting material in the synthesis of various other types of sesquiterpenes, mainly guaianes (Scheme 1.24). Treatment of **25** with acid provided a 3 : 2 mixture of the guaiane-type products **241** and **242**, respectively[127]. Guaiadiene **241** has been isolated from Tolu balsam[128]. When strongly acidic conditions (conc. H_2SO_4) were used, **25** was rearranged to 10-epizonarene (**243**) in 50% yield[129]. The insecticidal dienols **244** and **245** (γ-gurjunenol), isolated from *Dipterocarpus kerii* tree resins, have been prepared from **25** by oxidation with SeO_2 and *m*CPBA, respectively[130]. The alkaloid epiguaipyridine (**246**), isolated from patchouli oil, was synthesized from **25** in two steps[10]. Oxidative ring opening of **25** gave a diketone which, after treatment with hydroxylamine hydrochloride, gave **246** in low yield. Dehydrogenation of **25**[5a], as well as of (+)-aromadendrene (**2**)[131], with sulfur, gave the blue S-guaiazulene (**247**).

Cleavage of the C3-C4 bond of the cyclopropanering in **25** could be achieved by sensitized photooxygenation of **25**[132]. Reduction of the crude photooxygenized mixture with $NaBH_4$, followed by treatment with oxalic acid in Ac_2O/HOAc gave 10-epizieryl acetate (**248**) in low yield. After reduction of the acetate and subsequent oxidation of the alcohol function, epizierone (**249**), a C7-epimer of the naturally occurring zierone, was obtained.

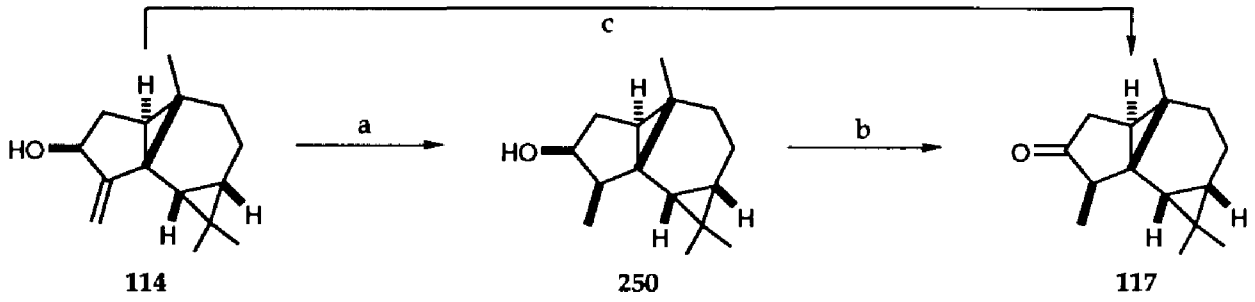
Scheme 1.24[a]



a (a) *p*TsOH, AcOH; (b) H_2SO_4; (c) SeO_2; (d) *m*CPBA; (e) O_3; $HONH_2$-HCl; (f) S, Δ; (g) hν, O_2; $NaBH_4$; oxalic acid, Ac_2O, HOAc; (h) $LiAlH_4$; CrO_3-pyridine.

The 1,7-cycloaromadendrane (–)-dihydromylione A (**117**) has been synthesized from (–)-myliol (**114**) via hydrogenation of the double bond, followed by oxidation of the hydroxyl group[64] (Scheme 1.25) Treatment of **114** with methanolic HCl gave **117** directly.

Scheme 1.25[a]



114 **250** **117**

a (a) H_2, PtO_2; (b) CrO_3; (c) HCl, MeOH.

1.5 References

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2 Introduction

2.1 General Introduction

Enantioselectivity is commonly seen in nature. Many enzymes, themselves chiral, produce compounds in an enantiospecific manner, leading to enantiopure products. The physiological activity of chemical compounds is often associated with binding to a chiral receptor site or enzyme. As a consequence, the chirality of a molecule can have considerable influence on its physiological action. Enantiomers may exhibit very different types of activity. If one enantiomer performs a specific action, the other might be inactive, have undesirable side effects, or even inhibit the action of the first enantiomer[1]. Therefore it is generally desirable to produce chemical compounds, especially pharmachemicals or agrochemicals, but also fragrances and flavours, in an enantiopure form.

Currently several approaches to synthesize chiral compounds are being used[1]. The first one is separation of a racemate into its enantiomers: resolution. The second one is asymmetric synthesis. In this approach, enantiopure products are obtained through transformation of prochiral substrates with an optically active agent, preferably used catalytically. The third approach is to start with compounds from the chiral carbon pool. This pool contains optically active (natural) products that can be used as building blocks in synthesis. To be industrially useful they must be readily available and relatively inexpensive. The three major classes of such chiral substances are the sugars[2], the amino acids[3], and the terpenes[4].

Of the terpenes mainly the highly abundant monoterpenes like limonene, 3-carene, and α- and β-pinene, have served as a source of building blocks on a large scale. Higher terpenes like sesquiterpenes have seen a more limited use sofar. In research, relative abundant sesquiterpenes, e.g. α-santonin[5], have been used as starting material for the synthesis of other terpenes, often for their structure elucidation.

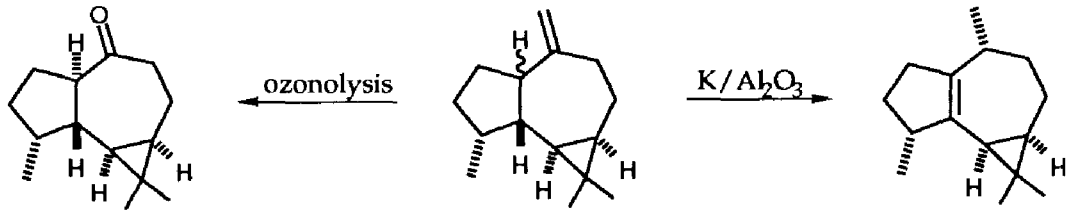
This thesis describes how the sesquiterpene (+)-aromadendrene (**2**) can be used as a chiral starting material for the synthesis of other optically active compounds.

2.2 (+)-Aromadendrene as a member of the chiral pool

One of the distillation tails of the oil of *Eucalyptus globulus*, which is commercially available[6], contains about 55-70% of (+)-aromadendrene (**2**), together with 10-15% of (–)-alloaromadendrene (**3**) and minor quantities of other sesquiterpenes. *Eucalyptus* trees are widely distributed over the world[7] and bulk quantities of the above

mentioned distillation tail are available at low price (2 US$/kg). This makes (+)-aromadendrene an attractive candidate for the chiral pool. To be useful, however, a method must be developed to isolate pure **2** from the crude distillation tail. Since the boiling points of the major compounds **2** and **3** are 261-263°C and 265-267°C, respectively, large scale distillation to obtain pure **2** is not a feasible option. Purification via derivatives is more interesting, especially if **2** and **3** can be converted into the same product. In this thesis two such purification methods will be described (Scheme 2.1).

Scheme 2.1



222 **2**: αH, **3**: βH **224**

In the literature purification has been accomplished by ozonolysis of the crude distillation tail[8]. In this way (+)-aromadendrene (**2**) is transformed to (+)-apo-aromadendrone (**222**), that crystallizes from the reaction mixture. The optimalization of this purification procedure will be described in **chapter 3**. Treatment of **2** with potassium on aluminum oxide (K/Al_2O_3) gives quantitatively (–)-isoledene (**224**)[9]. If a similar isomerization of the exocyclic double bond is possible for (–)-alloaromadendrene (**3**), treatment of the distillation tail with potassium on aluminum oxide will give an oil containing about 75% of **224**. This purification method of both **2** and **3** from the distillation tail will be described in **chapter 7**.

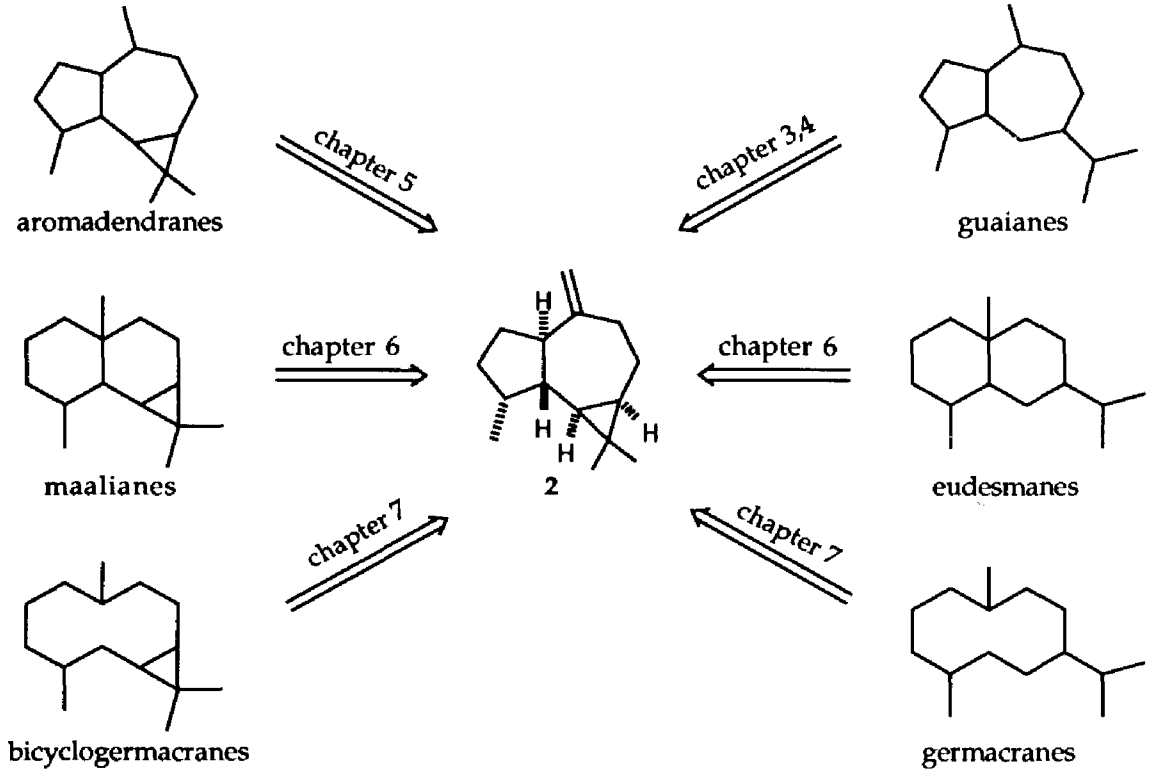
Besides the development of a purification method, it needs to be demonstrated that (+)-aromadendrene and its derivatives are useful starting compounds in the synthesis of interesting (natural) products. Several aromadendranes exhibit a variety of biological activities, as seen in chapter 1. Similar biological activities are known for other classes of sesquiterpenes. In most cases, these compounds are available from natural sources in only minute amounts. To obtain larger quantities, they have to be synthesized, for example from (+)-aromadendrene (**2**).

Some classes of sesquiterpenes have structural similarities with (+)-aromadendrene. For the synthesis of compounds with a guaiane skeleton only the cyclopropane ring in **2** has to be selectively opened in the right direction. The opening

of the cyclopropane ring in aromadendranes and the synthesis of guaianes from **2** will be described in **chapter 3** and **chapter 4**, respectively. Aromadendranes, having the same skeleton as **2**, form of course also a logic target for synthesis starting from **2**. This will be illustrated in **chapter 5**. If the hydroazulene ringsystem of aromadendrene can be rearranged to a hydronaphthalene ringsystem, the synthesis of maaliane or eudesmane sesquiterpenes might be possible. Rearrangement reactions of the aromadendrane skeleton will be described in **chapter 6**. Cleavage of the double bond in **224** gives products with a bicyclogermacrane skeleton. Subsequent cyclopropane ringopening leads to germacrane sesquiterpenes. Both the bicyclogermacrane and germacrane sesquiterpenes might be useful intermediates, since they are believed to be the biosynthetic precursors for many other classes of sesquiterpenes. The synthesis of the bicyclogermacrane skeleton from **2** via **224** and the reaction possibilities of the obtained 10-membered ring compound will be described in **chapter 7**.

In scheme 2.2 the different classes of sesquiterpenes discussed sofar are given, including the chapters where possible routes to these sesquiterpenes, starting from **2**, will be described. In most of these chapters the usefulness of (+)-aromadendrene as starting material will be further demonstrated by the synthesis of one or more natural occurring sesquiterpenes.

Scheme 2.2



The investigations described in this thesis are limited to the synthesis of sesquiterpenes. The pathways developed here and some of the synthesized intermediates, however, might be used in the synthesis of other products, like di- or triterpenes. In **chapter 8** conclusions will be made about the usefulness of (+)-aromadendrene as a member of the chiral pool, based on the results described in this thesis.

2.3 References and notes

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5 See reference 4: chapter 10.1, pp 265-283.

6 Distalaciones Bordas Chinchurreta S.A., Seville, Spain.

7 The annual production of *Eucalyptus* oil, worldwide, is estimated to be 25-32 kT, containing about 2% of (+)-aromadendrene (source: ref. 6).

8 van Lier, F.P.; Hesp, T.G.M.; van der Linde, L.M.; van der Weerdt, A.J.A. *Tetrahedron Lett.* **1985**, *26*, 2109.

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3 The conversion of natural (+)-aromadendrene into chiral synthons*

Abstract: *(+)-Apoaromadendrone (222) can be obtained easily in large quantities from (+)-aromadendrene which is the main constituent in a commercially available distillation tail of the oil of Eucalyptus globulus. Acid catalyzed selective cleavage of the C3-C4 bond of the cyclopropane ring in 222 gave (–)-isoapoaromadendrone (253) in high yield. The regioselectivity of the cyclopropane ring opening was proved by NMR spectroscopy in combination with chemical transformations. Ozonolysis of 253 afforded the keto alcohol 262 which is a suitable chiral intermediate for the syntheses of guaianes and guaianolides.*

3.1 Introduction

One of the distillation tails of the oil of *Eucalyptus globulus*, which is commercially available[1], contains about 55-70% of (+)-aromadendrene (2) together with 10-15% of alloaromadendrene (3) and minor quantities of other sesquiterpenes (see chapter 2).

Although (+)-aromadendrene seems to be an attractive starting material for the synthesis of chiral intermediates, especially in the total synthesis of guaianes and guaianolides, little work has been done in this direction[2,3]. The use of (+)-aromadendrene as chiral starting material requires a laborious isolation and purification procedure. For (+)-aromadendrene itself this process is troublesome, but after ozonolysis of the above mentioned distillation tail a mixture is obtained with the crystallizable (+)-apoaromadendrone (**222**) as the main component[3]. In this chapter will be described how **3** can be converted into synthons which might be useful for the synthesis of guaianes and gaianolides.

3.2 Results and discussion

The crude distillation tail of the oil of *Eucalyptus globulus* was ozonolyzed to give a mixture containing about 60% of (+)-apoaromadendrone (**222**) together with 15% of alloaromadendrone (**223**). Pure **222** was easily obtained in large quantities by crystallization from methanol. The easiest way to obtain pure (+)-aromadendrene (**2**) is a Wittig condensation of **222** with methylenetriphenylphosphorane in dimethyl sulfoxide.

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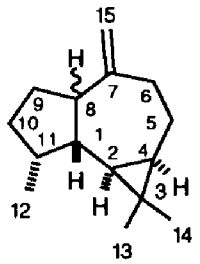
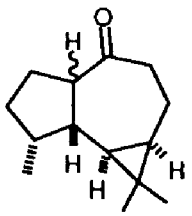
* This chapter has been published in a revised form: Gijsen, H.J.M.; Kanai, K.; Stork, G.A.; Wijnberg, J.B.P.A.; Orru, R.V.A.; Seelen, C.J.G.M.; van der Kerk, S.M.; de Groot, Ae. *Tetrahedron* **1990**, *46*, 7237.

A direct route to guaiane sesquiterpenes requires a selective cleavage of the C2-C3 bond of the aromadendrane skeleton. The unclear data in the literature[4-6] prompted us to start a renewed investigation of this ring cleavage. Treatment of **2** with concentrated aqueous HCl in refluxing ethanol invariably led to unattractive mixtures. (–)-Globulol (**4**) and (–)-epiglobulol (**5**), both prepared from **2**[7], gave similar results. Probably, the presence of acid sensitive groups (an exocyclic double bond or a tertiary hydroxyl group) in these compounds is responsible for this behaviour. To avoid acid-catalyzed side-reactions 7-noraromadendrane (**251**) was prepared via reduction of **222** with $NaBH_4$, mesylation of the hydroxyl function, and finally reduction of the mesyloxy group with lithium triethylborohydride (Super-Hydride^R)[8]. In this way **251** was obtained in an overall yield of 35%[9]; a direct Wolff-Kishner reduction of **222** gave a mixture of C8 epimers of **251**.

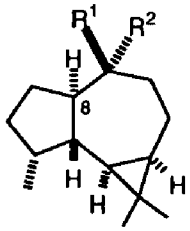
Figure 3.1



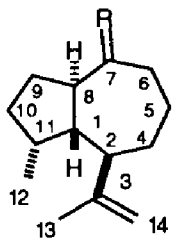
2 : αH
3 : βH



222 : αH
223 : βH



4 : $R^1 = CH_3$; $R^2 = OH$
5 : R^1 =OH; $R^2 = CH_3$
251 : $R^1 = R^2 = H$



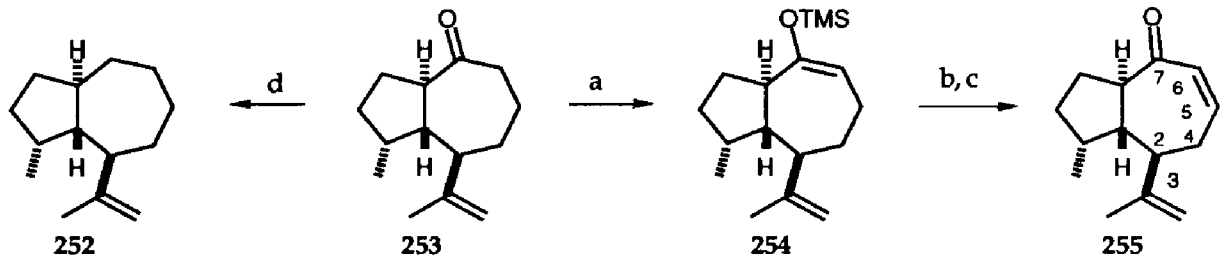
252 : R = H_2
253 : R = O

A short treatment (15 min) of **251** with concentrated aqueous HCl in refluxing ethanol gave a 4:1 mixture of **252** and a double bond isomer of **252**, respectively. Shorter reaction time led to partial recovery of the starting material, longer reaction times gave complex mixtures.

In contrast, treatment of **222** with concentrated aqueous HCl in refluxing ethanol for 1,5 h afforded (–)-isoapoaromadendrone (**253**)[4,5] in 75% yield. Probably, a competitive protonation of the carbonyl group of **222** strongly retards the double bond migration. Furthermore, it was found that mixtures of **222** and alloaromadendrone (**223**)[10] also gave **253** as the sole product upon treatment with concentrated aqueous HCl in refluxing ethanol. This means that **223** undergoes epimerization at C8 before or after ring opening. This opened up the possibility to use the mother liquor of the ozonolysis reaction as starting material in the preparation of an additional portion of **253** (see experimental section, 3.3).

The structure of **253** was elucidated by NMR spectroscopy in combination with some chemical transformations. Treatment of **253** with lithium diisopropylamide (LDA) and trimethylchlorosilane at -78°C gave the silyl enol ether **254** in quantitative yield. Bromination of **254** with N-bromosuccinimide (NBS) followed by dehydrobromination afforded the enone **255** in 38% yield (Scheme 3.1).

Scheme 3.1[a]



[a] (a) LDA, $(CH_3)_3$ SiCl, -78°C; (b) NBS, THF; (c) Li_2CO_3, LiBr, DMF, 120°C; (d) N_2H_4, diethylene glycol, 140→200°C.

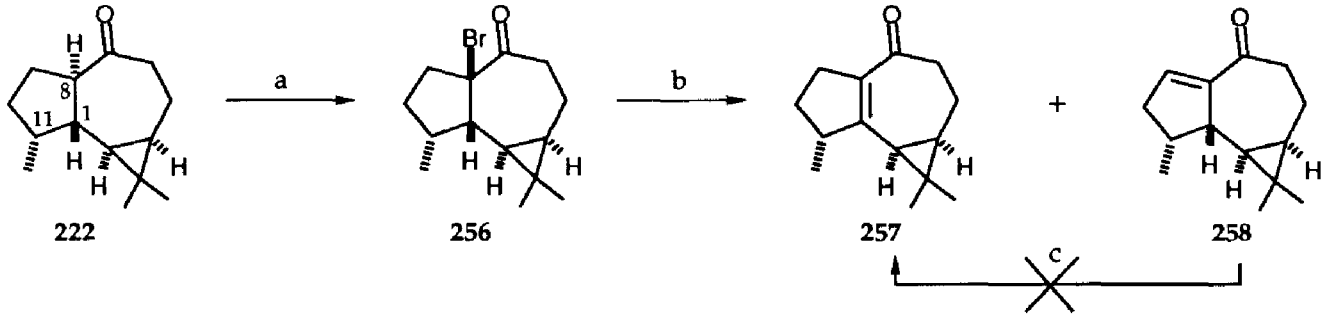
The ^1H NMR spectrum of **255** shows a signal (ddd) of the olefinic proton at C5 as a result of coupling with one proton at C6 (J = 11.8 Hz) and two protons at C4 (J = 5.5, 8.5 Hz). These data indicate that the isopropenyl group is located at C2. However, the question whether the ring junction is *cis* or *trans* could not be answered. 2D-NOE measurements on **253** yielded no information on the stereochemistry of this compound , due to the severe overlap of the signals in its ^1H NMR spectrum and the large amount of T_1 noise present in its 2D-NOE spectrum. By application of the lanthanide shift reagent Eu(fod)$_3$ both problems could be resolved simultaneously. Using a molar ratio **253** : Eu(fod)$_3$ = 1 : 0.765 in $CDCl_3$ an optimum was obtained between the demands of shift effect and retaining a reasonable line shape. In the 2D-NOE spectrum of the **253**/Eu(fod)$_3$ mixture both the diagonal peak and the corresponding cross peaks of the multiplet showing the largest down-field shift (a signal at δ 5.66) cannot be observed. It is to be expected though, that the T_1 values of protons spatially close to the Eu(fod)$_3$ moiety are considerably smaller than those of most other protons in the **253**/Eu(fod)$_3$ mixture, and smaller than the mixing time used in the 2D-NOE experiments. This was borne out by Inversion Recovery measurement of the T_1 values in the **253**/Eu(fod)$_3$ mixture: for the multiplet at δ 5.66 a T_1 of about 0.3 sec was obtained, while the T_1 values of the other protons in the molecule were found to vary between 0.9 and 1.4 sec. By recording a 2D-NOE spectrum using a much shorter mixing time, the signals belonging to the δ 5.66 resonance (both the diagonal and the cross peaks) could be made to appear. On the basis of its 2D-NOE spectrum, a series of double resonance experiments, and of all information gathered

previously (*vide supra*), it proved possible to assign the ^1H NMR spectrum of the **253**/Eu(fod)$_3$ mixture completely, including a *trans* relationship between the two bridging protons at C1 and C8, witnessing the complete absence of NOE between these protons. Having established the structure of **253** a Wolff-Kishner reduction of **253** also confirmed the structure of **252**.

The observed regioselectivity of the cyclopropane ring opening is not fully understood. Steric factors may play a role, but offer no complete explanation for the exclusive formation of **253**. The formation of a more favourable equatorial isopropenyl group could be an additional explanation for the selective cleavage of the C3-C4 bond. A similar argumentation has been used for the regioselective opening of the cyclopropane ring of maaliane[11].

An alternative way to achieve cleavage of the C2-C3 bond might be via compounds with a double bond, conjugated with the cyclopropane ring. A double bond between C1-C8 or between C1-C11 can direct ringopening towards products with a guaiane skeleton as shown for isoledene (**224**) and α-gurjunene (**25**), respectively, in section 1.4.2. Therefore it was tried to prepare the α,β-unsaturated ketone (**257**) from **222** (Scheme 3.2). Bromination of **222** with 2-carboxyethyltriphenylphosphonium perbromide[12] gave the α-bromoketone **256** in 81% yield. Dehydrobromation of **256**, using different procedures, always led to mixtures of the unsaturated ketones **257** and **258**, with **258** being the major compound. The best yield of **257** was obtained by dehydrobromination with Li_2CO_3/LiBr in DMF. This gave **257** and **258** in a 1 : 2 ratio, respectively. Isomerization of the double bond in **258** to **257** with $RhCl_3$[13] or via treatment with Pd on carbon under hydrogen atmosphere[14] was not successfull. Oxidation of the 8β-phenylselenyl derivative of **222** with H_2O_2[15] gave almost exclusively compound **258**. Since selective introduction of a double bond between C1 and C8 was not possible, this route to guaianes was abandoned.

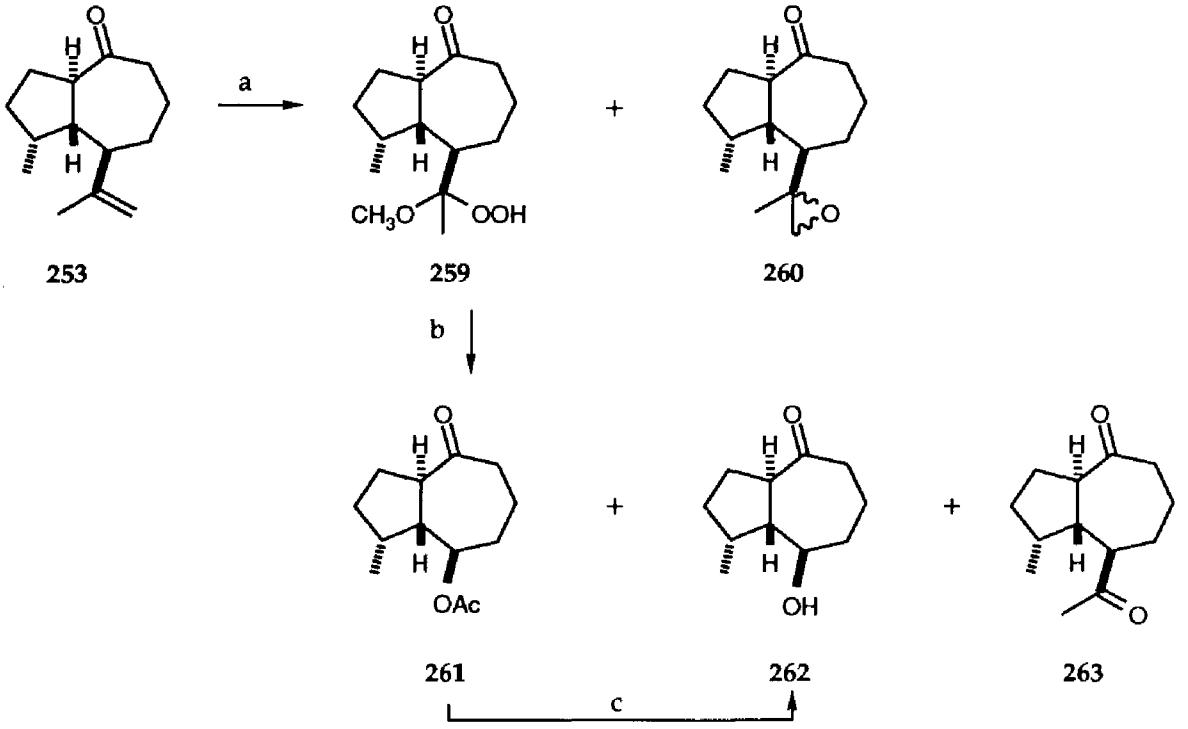
Scheme 3.2[a]



[a] (a) 2-carboxyethyltriphenylphosphonium perbromide (b) Li_2CO_3, LiBr, DMF, 100°C; (c) $RhCl_3$, or H_2, Pd on carbon.

Although the acid catalyzed, selective cleavage of the C3-C4 bond does not lead directly to compounds with a guaiane skeleton, ketone **253** remains an attractive starting material for the preparation of several chiral synthons, especially because of its simple preparation in large quantities. Its use in the synthesis of guaianes and guaianolides requires the conversion of the isopropenyl group at C2 into a hydroxyl group. The easiest way to do this is given by Schreiber et al[16]. Thus, ozonolysis of **253** in the presence of methanol and subsequent treatment of the intermediate methoxyhydroperoxide **259** with acetic anhydride should result in Criegee rearrangement and dealkylation to afford the acetate **261**. Saponification of **261** then would provide the desired alcohol **262**. However, under standard conditions[16] the main product was the diketone **263**.

Scheme 3.3[a]



[a] (a) O_3, 5:1 CCl_4/CH_3OH, -30°C; (b) Ac_2O, Et_3N, DMAP, -30°C; (c) $NaOCH_3$, CH_3OH

A much better result was obtained when the methoxyhydroperoxide **259** was treated with acetic anhydride immediately after ozonolysis at –30°C. The workup afforded, according to GC-MS analysis, a mixture of the acetate **261**, the alcohol **262**, the diketone **263**, and a 2:1 mixture of two diastereomeric epoxides **260** in a ratio of 6 : 1 : 1.5 : 3,

respectively. The amount of epoxide formed, could be diminished using carbon tetrachloride (μ = 0.0D) instead of dichloromethane (μ = 1.60D)[17]. According to GC-MS analysis, a mixture of **261, 262, 263** and **260** was obtained in a ratio of 4.5 : 1 : 1 : 1.25, respectively. Upon treatment of this mixture with sodium methoxide in methanol the acetate **261** was converted into its alcohol **262**, and now the components could be separated easily. In this manner the ketone **253** could be converted into pure alcohol **262** on a large scale in 56% overall yield.

Starting from the commercially available distillation tail of *Eucalyptus* oil large quantities of the chiral alcohol **262** can be obtained via the procedure described. In this alcohol two different functionalities are properly located for the construction of the guaiane skeleton.

3.3 Experimental section

Melting points were determined on an Olympus HSA melting point apparatus and are uncorrected. Optical rotations were obtained from $CHCl_3$ solutions on a B-S Model A polarimeter. ^1H NMR spectra were recorded at 90 MHz on a Varian EM-390, at 200 MHz on a Bruker AC-E 200, or at 300 MHz on a Bruker CXP-300 spectrometer. ^{13}C NMR spectra were recorded at 50 MHz on a Bruker AC-E200 or at 75 MHz on a Bruker CXP-300 spectrometer. Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were recorded on a HP 5970 GC/MSD system. Accurate mass measurements were performed on an AEI MS 902 spectrometer equipped with a VG ZAB console. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. 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 Merck silica gel 60 (70-230 or 230-400 mesh). 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 prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

(+)-Apoaromadendrone (222). Through a stirred solution of 60.0 g of the commercially available distillation tail of the oil of *Eucalyptus globulus*[1] in 300 mL of ethanol, cooled to -78°C, was passed an oxygen-ozone mixture. Progress of the reaction was monitored by TLC. When the starting material had disappeared (8 h) the solution was purged with nitrogen for 15 min. The reaction mixture was allowed to warm to -30°C and then a solution of 10.0 g of thiourea in 100 mL of a 9:1 mixture of ethanol/water was added. Stirring was continued at room temperature for 16 h. The white precipitate was removed by suction filtration and washed with 25 mL of ethanol. The filtrate was concentrated under reduced pressure and the remaining residue was dissolved in 400 mL of petroleum ether (bp 40-60°C). The solution was washed with 100 mL of water, 100 mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was crystallized from methanol to afford 26.0 g of pure **222**. After concentration under reduced pressure and subsequent crystallization from a 5:1 mixture of methanol/water the mother liquor gave another 2.0 g of pure **222**: mp 81-82°C (lit.[18]: 82-83°C); $[\alpha]_D$ +2.4° (c 2.54) [lit.[5]: +3.5° (c 2.70)]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.64-0.83 (m, 2H), 0.89 (d, J = 7.0 Hz, 3H), 0.91 (s, 3H), 1.02 (s, 3H), 1.19-1.81 (m, 5H), 1.89-2.13 (m, 3H), 2.26-2.45 (m, 2H), 2.73 (dt, J = 7.9, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.25 (q), 15.77 (q), 18.38 (s), 20.03 (t), 23.40 (t), 26.31 (d), 27.06 (d), 28.53 (q), 34.29 (t), 36.22 (d), 42.37 (d), 44.13 (t), 58.58 (d), 212.60 (s); mass spectrum, *m/e* (relative intensity) 206 (M^+, 83), 193 (9), 163 (22), 111 (40), 109 (37), 95 (45), 83 (35), 82 (38), 81 (37), 69 (100); calcd for $C_{14}H_{22}O$ (M^+) *m/e* 206.1671, found *m/e* 206.1671. Anal. Calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.74. Found: C, 81.24; H, 10.74.

The remaining mother liquor (33.6 g), according to GC-MS analysis a mixture of mainly **222** and **223** in a ratio of 2:3, respectively, was used for the synthesis of an additional portion of **253**.

(+)-Aromadendrene (2). To a stirred solution of 100 mL of 0.55 M dimethylsulfinylsodium in dry dimethyl sulfoxide was added 19.60 g (55.0 mmol) of methyltriphenylphosphonium bromide. The mixture was stirred at room temperature for 30 min, and then a solution of 5.65 g (25.0 mmol) of **222** in 25 mL of dry ether was added dropwise. The reaction mixture was stirred at room temperature for 2 h, and then poured into 250 mL of water. The aqueous solution was extracted with five 50-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 75 mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was chromatographed on silica gel (230-400 mesh) [5:1 petroleum ether (bp 40-60°C)/EtOAc] to give pure **2** as a colourless oil in quantitative

yield: $[\alpha]_D$ +6.9° (c 2.62) [lit.[6]: +9° (ethanol)]; the ^1H NMR, ^{13}C NMR, and mass spectrum were consistent with those reported in the literature.[19,20] Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.83. Found: C, 88.10; H, 11.96.

(–)-Globulol (4) and (–)-Epiglobulol (5). A mixture of **4** and **5** was prepared from **2** as described[7]. Flash chromatography [40:1 petroleum ether (bp 40-60°C)/EtOAc] gave pure **4** and **5.**

4: physical and spectroscopic data were consistent with those reported in the literature.[19,21]

5: $[\alpha]_D$ -37.1° (c 1.40); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.33-0.72 (m, 2H), 0.80-2.30 (m, 12H), 0.92 (d, J = 7 Hz, 3H), 0.99 (s, 3H), 1.03 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.83 (q), 16.57 (q), 19.13 (t), 20.55 (s), 26.57 (t), 27.12 (d), 28.74 (q), 28.87 (d), 31.30 (q), 34.59 (t), 35.76 (d), 37.54 (d), 42.91 (t), 55.91 (d), 72.25 (s); the mass spectrum was consistent with that reported in the literature[7]; calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found *m/e* 222.1982.

(–)-Noraromadendrane (251). To a solution of 2.02 g (9.8 mmol) of **222** in 75 mL of ethanol, cooled to 0°C, was added 0.37 g (9.8 mmol) of $NaBH_4$. The reaction mixture was allowed to stir for 3 h at 0°C, and then poured into 150 mL of water. The aqueous solution was extracted with three 50-mL portions of EtOAc. The combined organic layers were washed with 50 mL of brine, dried, and then evaporated under reduced pressure. The remaining product, according to GC analysis a 3:2 mixture, was taken up in 50 mL of pyridine and 1.3 mL (20.0 mmol) of mesyl chloride was added. The mixture was stirred at 40°C for 18 h and then concentrated under reduced pressure. The resulting residue was taken up in 100 mL of CH_2Cl_2 and washed successively with one 50-mL portion of a 10% aqueous HCl solution, two 25-mL portions of a saturated aqueous $NaHCO_3$ solution, and one 50-mL portion of brine. The organic layer was dried and the solvent was removed under reduced pressure. The crude product was flash chromatographed [15:1 petroleum ether (bp 40-60°C)/EtOAc] to give 1.91 g of an inseparable 3:2 mixture of two isomeric mesylates: ^1H NMR (main peaks, $CDCl_3$, 90 MHz) δ 3.01 (s, 3H), 4,40 (m, 0.6H), 5.15 (br d, J = 4.5 Hz, 0.4H). To a solution of this mixture of mesylates in 10 mL of dry THF, cooled to 0°C, was added 15 mL (15 mmol) of Super-Hydride® (1M in THF). The reaction mixture was allowed to stir at room temperature for 2 d. The excess Super-Hydride® was then destroyed by the careful addition of a minimum amount of a saturated aqueous Na_2SO_4 solution. After filtration through celite the solution was dried. The solvent was evaporated under reduced pressure and the remaining residue was chromatographed on silica gel (70-230

mesh) [petroleum ether (bp 40-60°C)] to give 0.87 g of crude **251** which, according to GC and ^{1}H NMR analysis, was contaminated with an unsaturated impurity. The purification of **251** was accomplished after treatment of a solution of crude **251** in 75 mL of a 2:1 mixture of ether/water with 1.00 g (2.02 mmol) of magnesium monoperoxyphtalate[22] at room temperature for 18 h. The workup and column chromatography on silica gel (70-230 mesh) [petroleum ether (bp 40-60°C)] gave 0.66 g (35%) of pure **251** as a colourless oil: $[\alpha]_D$ -29.3° (c 0.55); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.42-0.67 (m, 2H), 0.70-2.30 (m, 13H), 0.89 (d, J = 6 Hz, 3H), 1.00 (s, 6H); mass spectrum, *m/e* (relative intensity) 192 (M^+, 24), 149 (70), 108 (68), 82 (100); calcd for $C_{14}H_{24}$ (M^+) *m/e* 192.1878, found *m/e* 192.1872. Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.57. Found: C, 87.20; H, 12.58.

Wolff-Kishner Reduction of 222. A solution of 4.95 g (24.0 mmol) of **222** and 30.0 g (600 mmol) of hydrazine hydrate in 100 mL of diethylene glycol was stirred at 140°C for 1 h. Water and hydrazine were then distilled off and 8.4 g (150 mmol) of KOH was added to the remaining solution. The mixture was stirred at 200°C for 2 h. After cooling, 100 mL of ice-water was added and the aqueous mixture extracted with three 75-mL portions of ether. The combined organic layers were washed with two 25-mL portions of brine, dried, and then evaporated under reduced pressure. The resulting product was chromatographed on silica gel (230-400 mesh) [petroleum ether (bp 40-60°C)] to give 1.90 g (41%) of a colourless oil. According to GC-MS analysis, the product consisted of a mixture of **251** and an isomer [mass spectrum, *m/e* (relative intensity) 192 (M^+, 11), 149 (44), 108 (34), 82 (100)] in a ratio of 9 : 1, respectively.

(–)-Isoapoaromadendrone (253). To a solution of 20.0 g (97.1 mmol) of **222** in 300 mL of ethanol was added 100 mL of concentrated aqueous HCl solution. The mixture was heated at reflux for 1.5 h, allowed to come to room temperature, and then diluted with 300 mL of water. The aqueous solution was extracted with four 125-mL portions of CH_2Cl_2. The combined organic layers were washed with 100 mL of saturated aqueous $NaHCO_3$ solution followed by 100 mL of brine, dried, and then evaporated under reduced pressure. The resulting product was crystallized from methanol to give 15.0 g (75%) of pure **253**: mp 60-61°C (lit.[5]: 61-62°C); $[\alpha]_D$ -53.0° (c 1.55) (lit.[4]: -48.6°); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.77 (d, J = 7.0 Hz, 3H), 1.10-1.41 (m, 2H), 1.49-1.93 (m, 6H), 1.62 (br s, 3H), 2.00-2.56 (m, 5H), 3.10 (dt, J = 4.8, 10.4 Hz, 1H), 4.68 (br s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.70 (q) 19.23 (q), 22.31 (t), 23.11 (t), 32.42 (t), 35.17 (t), 37.82 (d), 43.51 (t), 50.64 (d), 50.77 (d), 51.37 (d), 110.72 (t), 148.65 (s), 214.43 (s); mass spectrum, *m/e* (relative intensity) 206 (M^+, 70), 191 (7), 165 (15), 164 (12), 163 (16), 137 (64), 125 (27), 109 (53), 73

(100), 72 (30); calcd for $C_{14}H_{22}O$ (M^+) *m/e* 206.1671, found *m/e* 206.1670. Anal. Calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.74. Found: C, 81.26; H, 10.80.

In a similar experiment starting from 33.6 g of the mother liquor obtained after ozonolysis of the distillation tail of *Eucalyptus* oil an additional portion of **253** was prepared. After the workup the dark-brown oil (30.0 g) was submitted to steam-distillation[23] to give 17.0 g of a yellow oil. Repeated crystallization from methanol afforded 7.3 g of pure **253**.

[1R-(1α,3aα,8β,8aβ)]-decahydro-1-methyl-8-(1-methylethenyl)-azulene (252). A sample of 2.50 g (12.0 mmol) of **253** was treated with hydrazine hydrate and KOH as described for the Wolff-Kishner reduction of **222**. The workup and chromatography on silica gel (230-400 mesh) [petroleum ether (bp 40-60°C)] afforded 0.20 g (9%)[24] of pure **252** as a colourless oil: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.75 (d, J = 7.5 Hz, 3H), 1.10-2.20 (m, 16H), 1.70 (br s, 3H), 4.70 (br s, 2H); mass spectrum, *m/e* (relative intensity) 192 (M^+, 7), 177 (5), 149 (38), 135 (52), 107 (68), 94 (89), 81 (87), 67 (71), 55 (54), 41 (100). Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.57. Found: C, 87.48; H, 12.73.

Acid Treatment of 251. A mixture of 3 mL of ethanol in which 0.095 g (0.5 mmol) of **251** was dissolved, and 0.5 mL of concentrated aqueous HCl solution was heated at reflux for 15 min. According to GC-MS analysis the reaction mixture consisted of mainly two compounds, **252** and a double bond isomer [^{1}H NMR (major peaks, $CDCl_3$, 90 MHz) δ 1.63 (br s, 3H), 1.69 (br s, 3H); mass spectrum, *m/e* (relative intensity) 192 (M^+, 39), 177 (6), 149 (89), 107 (81), 94 (72), 93 (71), 81 (68), 79 (58), 67 (54), 41 (100)] in a ratio of 4:1, respectively.

Trimethylsilyl Enol Ether 254. To a stirred mixture of 4.1 mL (6.5 mmol) of *n*-butyllithium (1.6 M in hexane) in 6.5 mL of dry THF, cooled at 0°C, was added dropwise 0.91 mL (6.5 mmol) of diisopropylamine. After 15 min the mixture was cooled to -78°C and then a solution of 1.03 g (5.0 mmol) of **253** in 6 mL of dry THF was added dropwise. When the addition was complete, the reaction mixture was allowed to stir for 40 min at -78°C after which time 0.88 mL (6.9 mmol) of chlorotrimethylsilane was added. The reaction mixture was allowed to come to room temperature and stirring was continued for an additional 2.5 h. After dilution with 15 mL of dry ether and subsequent filtration through a short column of basic alumina the solvents were evaporated under reduced pressure. The resulting crude **254** (1.34 g, 96%) [^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.21 (s, 9H), 0.78 (d, J = 7 Hz, 3H), 1.08-2.33 (m, 11H), 1.67 (br s, 3H), 2.76 (m, 1H), 4.67 (br s, 2H), 4.95 (dt, J = 2, 6.5 Hz, 1 H)] was used immediately for the next reaction.

Dehydroisoapoaromadendrone (255). To a stirred solution of 0.872 g (4.90 mmol) of N-bromosuccinimide in 13 mL of dry THF, cooled at 0°C, was added dropwise a solution of 1.34 g (4.87 mmol) of **254** in 7 mL of dry THF. The reaction mixture was allowed to stir for 20 min at 0°C, diluted with 30 mL of water, and then extracted with three 30-mL portions of carbon tetrachloride. The combined organic layers were washed with 50 mL of brine, dried, and then evaporated under reduced pressure to give 1.35 g (98%) of a solid bromo compound. To a solution of 1.21 g (4.24 mmol) of this bromo compound in 20 mL of dry DMF was added 0.762 g (8.76 mmol) of lithium bromide and 0.969 g (13.12 mmol) of lithium carbonate. The mixture was stirred at 120°C for 19 h, allowed to come to room temperature, and then filtered. The filtrate was diluted with 25 mL of brine and extracted with two 25-mL portions of ether. The combined organic layers were dried and evaporated under reduced pressure. The remaining residue was flash chromatographed [30:1 petroleum ether (bp 40-60°C)/EtOAc] to give 0.379 g (38%) of pure **255**: 53-54°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, J = 6.9 Hz, 3H), 1.44 (m, 1H), 1.65 (m, 1H), 1.69 (br s, 3H), 1.82 (m, 1H), 2.04 (m, 1H), 2.15 (m, 1H), 2.35-2.44 (m, 2H), 2.64-2.76 (m, 3H), 4.74 (br s, 1H) 4.76 (br s, 1H), 6.07 (dd, J = 2.2, 11.8 Hz, 1H), 6.58 (ddd, J = 5.5, 8.5, 11.8 Hz, 1H); mass spectrum, *m/e* (relative intensity) 204 (M^+, 38), 189 (23), 176 (46), 161 (50), 136 (81), 133 (63), 121 (100), 107 (58), 105 (60), 93 (94); calcd for $C_{14}H_{20}O$ (M^+) *m/e* 204.1514, found *m/e* 204.1509.

α-Bromoketone 256. To a stirred solution of 2.53 g (12.3 mmol) of **222** in 25 mL of dry THF, cooled at -78°C, was added dropwise a solution of 7.5 g (13 mmol) of 2-carboxyethyltriphenylphosphonium perbromide in 30 mL of dry THF. The reaction mixture was allowed to warm up to 0°C and stirring was continued for 4 h, during which time white crystals were formed. Then 15 mL of 10% aqueous $Na_2S_2O_3$ was added and the resulting mixture stirred for another 20 min. After addition of 100 mL of ether and separation of the layers, the organic layer was washed with 40 mL of water and 40 mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was flash chromatographed [20:1 to 10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 2.85 g (81%) of **256**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.29 (dd, J = 8.8, 11.7 Hz, 1H), 0.75 (ddd, J =5.5, 8.8, 11.2 Hz, 1H), 0.99 (s, 3H), 0.99 (d, J = 6.9 Hz, 3H), 1.03 (s, 3H), 1.28-2.99 (m, 9H), 3.51 (ddd, J = 2.8, 7.8, 15.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.37 (q), 15.67 (q), 18.97 (t), 19.10 (s), 24.89 (d), 25.11 (d), 28.09 (q), 29.84 (t), 35.01 (d), 36.70 (t), 39.51 (d), 51.55 (d), 77.75 (s), 204.32 (s).

Dehydrobromination of 256. To a solution of 636 mg (2.23 mmol) of **256** in 5 mL of dry DMF was added 290 mg (3.34 mmol) of lithium bromide and 380 mg (5.14 mmol) of lithium carbonate. The mixture was stirred at 100°C for 4 h and allowed to come to room temperature. The reaction mixture was poured into 20 mL of icewater and extracted with four 20-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried and evaporated under reduced pressure. The remaining residue was flash chromatographed on silica gel [30:1 petroleum ether (bp 40-60°C)/EtOAc] to give, in order of elution, 132 mg (29%) of **257** and 256 mg (56%) of **258**.

1,8-Dehydroaromadendrone (257): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.78-1.00 (m, 2H), 0.92 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.15 (s, 3H), 1.22-1.40 (m, 2H), 1.85-2.72 (m, 7H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.74 (q), 18.38 (q), 20.83 (t), 23.92 (s), 26.40 (d), 27.96 (q), 29.93 (d), 30.30 (2xt), 42.42 (t), 46.10 (d), 137.31 (s), 160.30 (s), 201.34 (s).

8,9-Dehydroaromadendrone (258): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.52-1.02 (m, 2H), 1.03 (s, 3H), 1.04 (d, J = 7 Hz, 3H), 1.06 (s, 3H), 1.38-1.60 (m, 1H), 1.79-2.10 (m, 2H), 2.30-2.74 (m, 5H), 6.47 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.18 (q), 15.55 (q), 18.69 (s), 18.69 (t), 24.95 (d), 25.69 (d), 28.05 (q), 34.97 (d), 38.15 (t), 42.56 (t), 42.87 (d), 139.48 (d), 149.21 (s), 202.29 (s).

Ozonolysis of 253. Through a stirred solution of 1.03 g (5.0 mmol) of **253** in 12 mL of a 5:1 mixture of carbon tetrachloride/methanol, cooled to -30°C, was passed an oxygen-ozone mixture. Progress of the reaction was monitored by GC. When the starting material had disappeared (45 min) the solution was purged with nitrogen for 10 min at -30°C. Sequentially acetic anhydride (5 mL), triethylamine (5 mL), and 0.02 g of 4-dimethylaminopyridine were added. Stirring was continued at -30°C for 10 min and then at 0°C for 1 h. The reaction mixture was poured into 30 mL of 10% aqueous HCl solution and extracted with four 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 25 mL of saturated aqueous $NaHCO_3$ solution followed by 25 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue (1.15 g) was according to GC-MS and ^{1}H NMR analysis a mixture of the acetate **261** (54%), the alcohol **262** (12%), the ketone **263** (12%), and the epoxide **260** (15%), the latter compound as a 2:1 mixture of two diastereomers. This residue was dissolved in 15 mL of 1M sodium methoxide in methanol. The reaction mixture was allowed to stir at room temperature for 16 h, and then poured into 75 mL of water. The aqueous solution was extracted with five 30-mL portions of CH_2Cl_2. The combined organic layers were washed with 50 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed (CH_2Cl_2) to give 0.56 g (61%) of pure **262**.

(–)-[1R-(1α,3aα,8β,8aβ)]-Octahydro-8-hydroxy-1-methyl-4(2*H*)-azulenone (262): mp 87-88°C (from methanol); $[\alpha]_D$ -84.7° (c 1.51); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (d, J = 7.0 Hz, 3H), 1.20-1.88 (m, 8H), 2.09-2.52 (m, 5H), 2.91 (ddd, J = 4.5, 9.5, 11.0 Hz, 1H), 3.86 (dt, J = 4.2, 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.87 (q), 19.19 (t), 22.67 (t), 32.19 (t), 36.78 (d), 38.15 (t), 42.95 (t), 48.05 (d), 54.77 (d), 73.42 (d), 213.24 (s); mass spectrum, *m/e* relative intensity) 182 (M^+, 23), 167 (3), 164 (9), 154 (7), 149 (7), 125 (17), 111 (52), 109 (100), 95 (27), 81 (56); calcd for $C_{11}H_{18}O_2$ (M^+) *m/e*, found *m/e* 182.1309. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.20; H, 9.68.

In a similar experiment starting from 25.75 g (125 mmol) of **253**, bulb-to-bulb distillation (140°C, 1 mm Hg) and subsequent crystallization from a 7:1 mixture of petroleum ether (bp 40-60°C)/EtOAc of the crude reaction product afforded 10.91 g (48%) of pure **262**. Flash chromatography of the mother liquor [10:1 to 2:1 petroleum ether (bp 40-60°C)/EtOAc] gave another 1.82 g (8%) of pure **262** and fractions with pure ketone **263** and epoxides **260** as a 2:1 mixture of two diastereomers.

(–)-[1R-(1α,3aα,8β,8aβ)]-8-acetyloctahydro-1-methyl-4(2*H*)-azulenone (263): mp 100-102°C (from methanol); $[\alpha]_D$ -51.5° (c 1.54); ^{1} NMR ($CDCl_3$, 200 MHz), δ 0.74 (d, J = 7.0 Hz, 3H), 1.13-1.46 (m, 2H), 1.52-2.52 (m, 10H), 2.15 (s, 3H), 2.62 (dt, J = 3.1, 11.3 Hz, 1H), 3.02 (dt, J = 4.7, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.42 (q), 22.14 (t), 22.66 (t), 28.17 (q), 31.89 (t), 32.48 (t), 37.12 (d), 43.03 (t), 49.12 (d), 51.07 (d), 56.52 (d), 210.90 (s), 212.78 (s); mass spectrum, *m/e* (relative intensity) 208 (M^+, 100), 165 (39), 147 (84), 127 (27), 125 (37), 109 (39), 95 (34), 84 (53), 81 (94), 41 (84); calcd for $C_{13}H_{20}O_2$ (M^+) *m/e* 208.1463, found *m/e* 208.1461. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.71; H, 9.80.

[1R-[1α,3aα,8β(R*),8aβ]]-octahydro-1-methyl-8-(2-methyloxiranyl)-4(2*H*)-azulenone and its 8β(S*)-isomer (260): ^{1}H NMR (main peaks, $CDCl_3$, 90 MHz) (major compound) δ 0.84 (d, J = 7 Hz, 3H), 1.15 (s, 3H); ^{1}H NMR (main peaks, $CDCl_3$, 90 MHz) (minor compound) δ 0.89 (d, J = 7. Hz, 3H), 1.16 (s, 3H); mass spectrum (major compound), *m/e* (relative intensity) 222 (M^+, 0.1), 204 (8), 165 (49), 147 (16), 135 (22), 123 (18), 109 (35), 93 (19), 81 (100), 67 (26); mass spectrum (minor compound), *m/e* (relative intensity) 222 (M^+, 3) 207 (6), 204 (3), 196 (6), 165 (38), 147 (13), 135 (14), 123 (14), 109 (39), 81 (100).

A pure sample of the acetate **261** was prepared by treating **262** with a 2:1 mixture of pyridine and acetic anhydride.

(–)-[1R-(1α,3aα,8β,8aβ)]-8-(acetyloxy)octahydro-1-methyl-4(2*H*)-azulenone (261): mp 51-52°C (from methanol); $[\alpha]_D$ -88.9° (c 0.99); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.74 (d, J = 7.0 Hz, 3H), 1.18-1.91 (m, 7H), 1.99 (s, 3H), 2.19-2.59 (m, 5H), 2.94 (ddd, J = 4.6, 9.6, 11.2 Hz, 1H), 4.80 (dt, J = 4.3, 10.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.85 (q), 18.99 (t), 21.18 (q), 22.63 (t), 32.06 (t), 34.15 (t), 36.83 (d), 42.89 (t), 48.14 (d), 51.72 (d), 75.56 (d), 170.27

(s), 212.46 (s); mass spectrum, *m/e* (relative intensity) 164 (M^+ -60, 100), 135 (28), 126 (22), 111 (14), 109 (30), 108 (4), 93 (17), 81 (41), 55 (17), 43 (57). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.98. Found: C, 69.56; H, 9.11.

3.4 References and notes

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4 The synthesis of (–)-kessane, starting from natural (+)-aromadendrene*

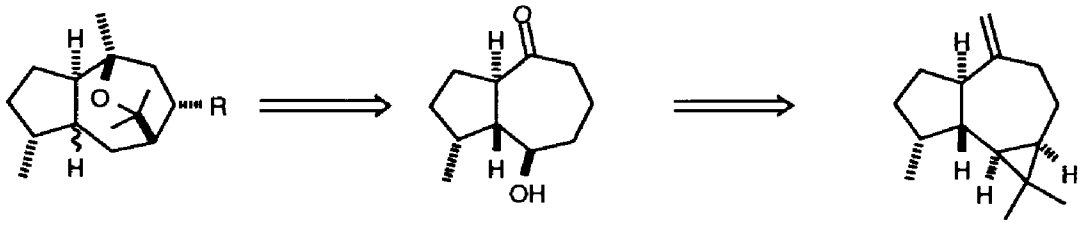
Abstract: Starting from the readily available chiral synthon 262 the guaiane sesquiterpene ether (-)-kessane (264) can be synthesized in a 9 steps reaction sequence in an overall yield of 43%.

4.1 Introduction

In the previous chapter on (+)-aromadendrene (**2**) as an attractive starting material for the synthesis of natural products, we described the large-scale preparation of keto alcohol **262**. This chiral synthon is a highly suitable starting material for the synthesis of guaianes, as demonstrated in this paper in the synthesis of (–)-kessane (**264**).

(–)-Kessane (**264**), a guaiane sesquiterpene with an unique oxido-framework, occurs in several plants, e.g. *Valeriana officinalis*[1], *Heracleum dissectum*[2], and *Bothriochloa intermedia*[3]. The synthesis of (±)-kessane[4], its *cis*-fused C1 epimer **265**[5], and (±)-kessanol (**266**)[6] have been reported in the literature. No syntheses of chiral kessane or its chiral derivatives are known.

Figure 4.1



264 : βH, R = H
265 : αH, R = H
266 : βH, R = OH

262

2

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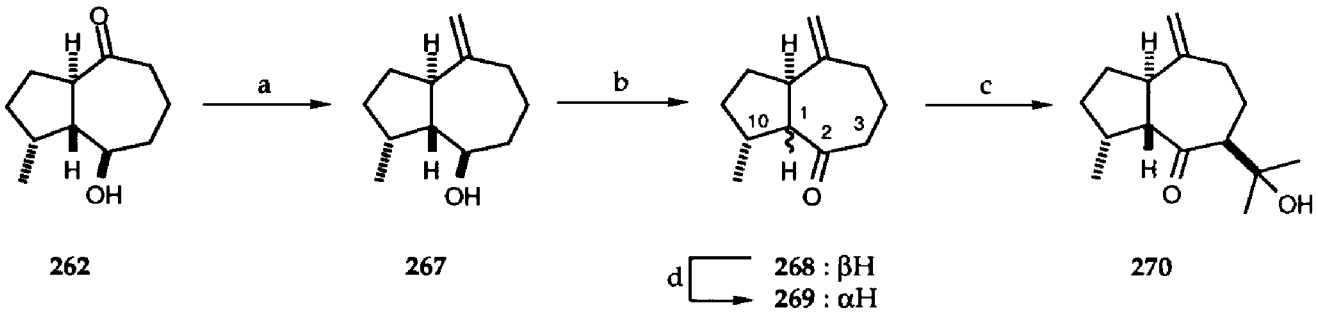
* This chapter has been published: Gijsen, H.J.M.; Wijnberg, J.B.P.A.; Stork, G.A.; de Groot, Ae. *Tetrahedron* **1991**, *47*, 4409.

4.2 Results and discussion

The first step in our synthetic approach to (–)-kessane was the introduction of an isopropyl group at C3. For this purpose the keto alcohol **262** was converted into the ketone **268** in high overall yield via a Wittig condensation with methylenetriphenylphosphorane in dimethyl sulfoxide followed by Jones oxidation (Scheme 4.1). During these reactions a small percentage (~3%) of the C1 epimerized *cis*-fused compound **269** was formed. In contrast, treatment of **268** with sodium methoxide in methanol gave **269** in almost quantitative yield.

Scheme 4.1[a]



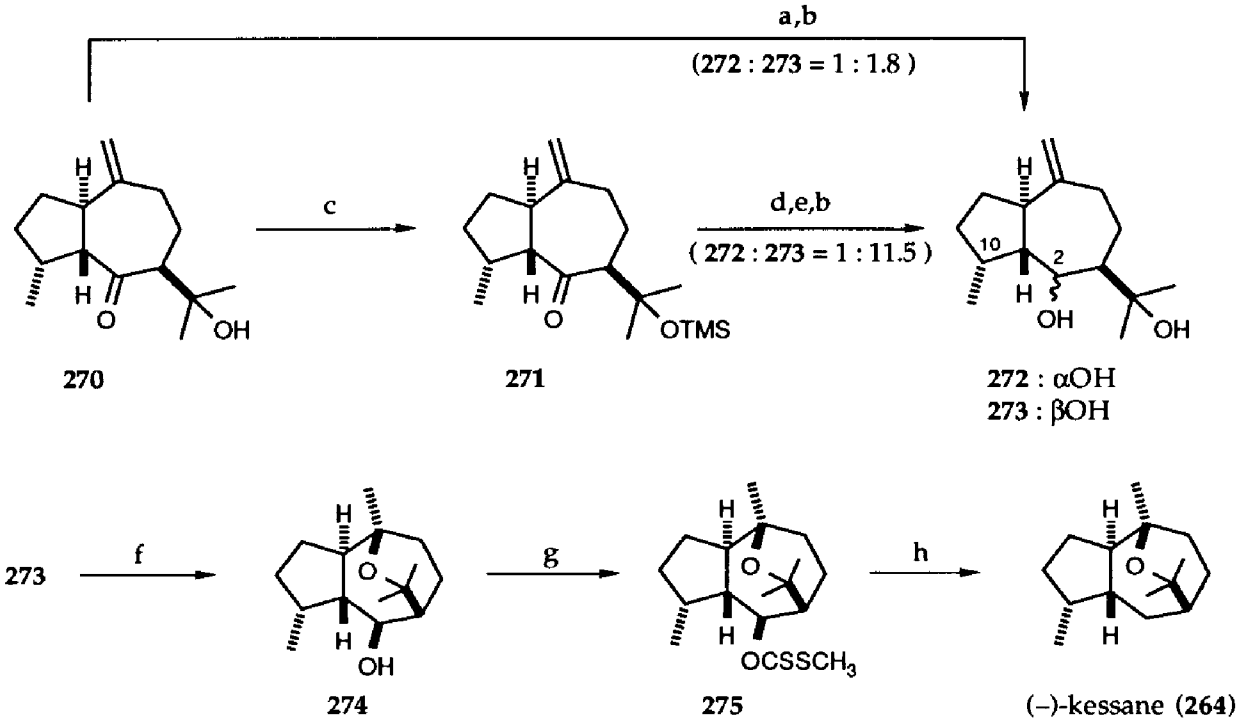
262 267 268 : βH / 269 : αH 270

[a] (a) $Ph_3P{=}CH_2$, DMSO; (b) Jones oxidation; (c) LDA, $ZnCl_2$, acetone; (d) $NaOCH_3$, CH_3OH.

The ketone **268** now possesses a suitable functional group for the introduction of the isopropyl substituent at C3. A zinc chloride assisted aldol condensation[7] of **268** with acetone afforded **270** in 85% yield as a single stereoisomer. To avoid an undesired epimerization at C1 in transformations further in the synthesis, the carbonyl function of **270** had to be reduced[5]. Furthermore, a sp^3 hybridized C2 atom will make the 7-membered ring more flexible, so that the cyclic ether formation can proceed more easily. When **270** was treated with lithium aluminum hydride partly a retrograde aldol reaction occurred. Reduction of **270** with sodium borohydride gave a mixture of the α-alcohol **272** and its β-epimer **273** in a ratio of 1:1.8, respectively. When, after separation, both alcohols were subjected to oxymercuration conditions, only the β–alcohol **273** showed a smooth reaction. The α-alcohol **272** reacted very slowly and mainly the starting material was recovered. This behaviour of **272** can be explained by assuming a strong 1,3-diaxial steric hindrance between the methyl group at C10 and

the α-hydroxyl group at C2 after ring closure. Therefore, it is necessary to reduce the ketone **270** in a more selective way. The best result was obtained by reduction of the trimethylsilyl ether **271**[8] with lithium aluminum hydride. Because of the trimethylsilyl protected hydroxyl group a retro aldol reaction was no longer possible. Also, reduction became more stereoselective because of the steric hindrance of this trimethylsilyl group. After cleavage of the trimethylsilyl ether function with tetrabutylammonium fluoride (TBAF) the β-alcohol **273** was obtained in 92% yield together with a small quantity (8%) of its α–epimer **272** (Scheme 4.2).

Scheme 4.2[a]



[a] (a) $NaBH_4$; (b) separation; (c) TMSCl, HMDS, pyridine; (d) $LiAlH_4$; (e) TBAF; (f) $Hg(OAc)_2$; $NaBH_4$, NaOH; (g) NaH, CS_2, CH_3I; (h) Bu_3SnH, AIBN.

As mentioned above the ring closure of **273** to the cyclic ether **274** proceeded in a satisfactory yield (66%). To complete the synthesis of (–)-kessane, the hydroxyl group of **274** had to be removed. The best way to do this is given by Barton et al[9]. Thus, conversion of **274** into its xanthate **275** and subsequent reduction of the dithiocarbonate group with tributyltin hydride in the presence of α,α'-azoisobutyronitril (AIBN) afforded (–)-kessane in an overall yield of 91%.

Starting from the readily available chiral synthon **262** (–)-kessane (**264**) has been synthesized in a 9 steps reaction sequence in an overall yield of 43%.

4.3 Experimental section

Melting points were determined on an Olympus HSA melting point apparatus and are uncorrected. Optical rotations were obtained from $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Bruker AC-E 200 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard in chloroform-d as the solvent. Mass spectral data were determined on an AEI MS 902 spectrometer equipped with a VG ZAB console. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. 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. 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 magnesium sulfate prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

(–)-[3R-(3α,3aβ,4β,8aα)]-Decahydro-3-methyl-8-methylene-4-azulenol (267). To a stirred solution of 100 mL of 0.83 M dimethylsulfinylsodium in dry dimethyl sulfoxide was added 29.75 g (83.0 mmol) of methyltriphenylphosphonium bromide. The mixture was stirred at room temperature for 20 min, and then a solution of 4.55 g (25.0 mmol) of **262** in 40 mL of dry dimethyl sulfoxide was added dropwise. The reaction mixture was stirred at room temperature for 45 min, and then poured into 250 mL of water. The aqueous solution was extracted with six 200-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 200 mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was flash chromatographed [10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 4.35 g (97%) of pure **267**: $[\alpha]_D$ -66°(c 1.44); ^1H NMR δ 0.91 (d, J = 7.0 Hz, 3H), 1.24-1.98 (m, 10H), 2.24-2.43 (m, 4H), 3.58 (dt, J = 3.9, 10.3 Hz, 1H), 4.72 (br s, 1H), 4.79 (br s, 1H); ^{13}C NMR δ 15.61 (q), 21.26 (t), 29.19 (t), 32.57 (t), 35.48 (d), 36.54 (t), 36.68 (t), 41.13 (d), 58.43 (d), 73.60 (d), 107.86 (t), 152.99 (s); mass spectrum, *m/e* (relative intensity) 180 (M^+, 0.5), 162 (67), 147 (100), 134 (26), 133 (68), 105 (32), 93 (34), 91 (34), 81 (68), 79 (37); calcd for $C_{12}H_{20}O$ (M^+) *m/e* 180.1514, found *m/e* 180.1509.

(–)-[3R-(3α,3aβ,8aα)]-Octahydro-3-methyl-8-methylene-4(1*H*)-azulenone (268). Jones reagent was added dropwise to a vigorously stirred solution of 3.76 g (20.9 mmol) of **267** in 120 mL of acetone. The addition was continued until the characteristic orange colour of the reagent persisted. The excess oxidizing agent was then destroyed by dropwise addition of isopropyl alcohol. After addition of 100 mL of water, the mixture was extracted with three 100-mL portions of EtOAc. The combined organic layers were washed with 100 mL of a saturated aqueous $NaHCO_3$ solution followed by 100 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [50:1 petroleum ether (bp 40-60°C)/EtOAc] to give 3.65 g (98%) of **268**[10]: $[\alpha]_D$ -185° (c 1.61); ^1H NMR δ 0.86 (d, J = 7.0 Hz, 3H), 1.30 (m, 1H), 1.49 (m, 1H), 1.63-2.08 (m, 4H), 2.11-2.37 (m, 2H), 2.42-2.74 (m, 5H), 4.79 (s, 2H); ^{13}C NMR δ 17.53 (q), 24.58 (t), 28.80 (t), 31.77 (t), 36.46 (d), 39.86 (t), 43.83 (d), 45.13 (t), 62.79 (d), 107.92 (t), 151.15 (s), 215.41 (s); mass spectrum, *m/e* (relative intensity) 178 (M^+, 47), 163 (14), 160 (6), 149 (24), 136 (100), 123 (63), 107 (53), 94 (39), 81 (39), 79 (32); calcd for $C_{12}H_{18}O$ (M^+) *m/e* 178.1358, found *m/e* 178.1355.

(+)-[3R-(3α,3aα,8aα)]-Octahydro-3-methyl-8-methylene-4(1*H*)-azulenone (269). A solution of 0.150 g (0.84 mmol) of **268** in 8 mL of 1 M sodium methoxide in methanol was stirred at room temperature for 20 min. After dilution with 10 mL of water, the reaction mixture was extracted with four 10-mL portions of EtOAc. The combined organic layers were washed with 15 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [50:1 petroleum ether (bp 40-60°C)/EtOAc)] to give 0.148 g (99%) of **269**: mp 55-56°C [from petroleum ether (bp 40-60°C)]; $[\alpha]_D$ +44° (c 0.43); ^1H NMR δ 0.95 (d, J = 6.6 Hz, 3H), 1.16 (m, 1H), 1.52-2.15 (m, 5H), 2.21-2.55 (m, 5H), 2.76 (dd, J = 8.4, 12.0 Hz, 1H), 3.00 (dt, J = 6.8, 10.7 Hz, 1H), 4.76 (s, 1H), 4.83 (s, 1H); ^{13}C NMR δ 19.57 (q), 22.56 (t), 29.95 (t), 34.19 (t), 34.51 (d), 36.18 (t), 41.80 (t), 46.06 (d), 61.88 (d), 111.56 (t), 148.80 (s), 212.00 (s); mass spectrum, *m/e* (relative intensity) 178 (M^+, 23), 163 (24), 145 (15), 135 (16), 123 (36), 107 (56), 93 (57), 81 (77), 79 (79), 41 (100); calcd for $C_{12}H_{18}O$ (M^+) *m/e* 178.1358, found *m/e* 178.1344.

(–)-[3R-(3α,3aβ,5β,8aα)]-Octahydro-5-(1-hydroxy-1-methylethyl)-3-methyl-8-methylene-4(1*H*)-azulenone (270). To a stirred solution of 21.5 mL of 1.6 M butyllithium in hexane, cooled to -78°C, was added dropwise a solution of 5.75 mL (41.0 mmol) of diisopropylamine in 25 mL of dry THF. The reaction mixture was stirred at -78°C for 40 min, and then a solution of 2.05 g (11.5 mmol) of **268** in 10 mL of

dry THF was added dropwise. Stirring was continued for an additional 45 min, allowed to come to -45°C, and then a mixture of 3.06 g (22.5 mmol) of zinc chloride in 20 mL of dry THF was added. After 5 min 10 mL of dry acetone was added. The reaction mixture was stirred at -45°C for 30 min, and then diluted with 100 mL of saturated aqueous NH_4Cl solution. The aqueous solution was extracted with four 75-mL portions of EtOAc. The combined organic layers were washed with 125 mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was flash chromatographed [25:1 to 10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 2.31 g (85%) of pure **270**: $[\alpha]_D$ -218° (c 1.70); ^1H NMR δ 0.98 (d, J = 7.1 Hz, 3H), 1.16 (s, 3H), 1.22 (m, 1H), 1.24 (s, 3H), 1.45-1.73 (m, 2H), 1.82-2.11 (m, 3H), 2.16-2.88 (m, 6H), 3.64 (br s, 1H; disappears with D_2O added), 4.74 (br s, 1H), 4.79 (br s, 1H); ^{13}C NMR δ 18.14 (q), 26.35 (t), 26.51 (q), 28.97 (q), 28.97 (t), 31.85 (t), 36.97 (d), 37.93 (t), 43.35 (d), 59.29 (d), 62.33 (d), 72.01 (s), 108.75 (t), 150.28 (s), 219.45 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 1), 221 (9), 218 (12), 203 (5), 193 (11), 178 (62), 135 (62), 123 (100), 109 (49), 107 (49); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1778.

(+)-[3R-(3α,3aα,4α,5β,8aα)]-Decahydro-4-hydroxy-α,α,3-trimethyl-8-methylene-5-azulenemethanol (272) and its 4β–isomer 273. To a stirred solution of 0.164 g (0.69 mmol) of **270** in 5 mL of methanol was added portionwise 0.045 g (1.19 mmol) of sodium borohydride over a period of 2.5 h. When the addition was complete, the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was poured into 20 mL of water, and then extracted with four 15-mL portions of EtOAc. The combined organic layers were washed with 15 mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was flash chromatographed [10:1 to 5:1 petroleum ether (bp 40-60°C)/EtOAc] to give, in order of elution, 0.045 g (27%) of pure α–alcohol **272** and 0.081 g (49%) of pure β–alcohol **273**.

272: $[\alpha]_D$ +66° (c 1.80); ^1H NMR δ 1.11 (s, 3H), 1.17 (d, J = 7.0 Hz, 3H), 1.29 (s, 3H), 1.20-1.85 (m, 9H), 1.96-2.29 (m, 2H), 2.57 (ddd, J = 2.3, 5.3, 14.7 Hz, 1H), 2.70-2.90 (m, 2H), 4.12 (dd, J = 2.9, 6.3 Hz, 1H), 4.62 (br s, 2H); ^{13}C NMR δ 14.89 (q), 24.19 (q), 26.72 (t), 28.73 (t), 30.59 (q), 35.31 (t), 37.18 (d), 40.51 (t), 42.93 (d), 47.54 (d), 58.31 (d), 71.10 (d), 74.92 (s), 104.19 (t), 153.21 (s); mass spectrum, *m/e* (relative intensity) 220 (M^+-18, 6), 187 (28), 159 (39), 146 (21), 133 (21), 105 (36), 91 (50), 79 (43), 69 (56),.59 (94), 41 (100); calcd for $C_{15}H_{26}O_2$ (M^+-18) *m/e* 220.1827, found *m/e* 220.1800.

273: mp 91-92°C [from petroleum ether (bp 40-60°C)]; $[\alpha]_D$ + 1° (c 3.0); ^{1}H NMR δ 0.94 (d, J = 7.1 Hz, 3H), 1.21 (s, 3H), 1.23-2.17 (m, 9H), 1.38 (s, 3H), 2.21-2.41 (m, 2H), 2.55 (dt, J = 5.2, 14.0 Hz, 1H), 2.69 (br s, 1H), 3.12 (br s, 1H), 4.26 (dd, J = 3.5, 9.0 Hz, 1H), 4.66 (s, 1H), 4.68 (s, 1H); ^{13}C NMR δ 15.82 (q), 20.79 (t), 28.70 (q), 28.85 (q), 29.24 (t), 33.40 (t), 34.25 (d), 36.88 (t), 43.40 (d), 49.44 (d), 54.06 (d), 71.08 (d), 73.93 (s), 107.22 (t), 152.70 (s); mass spectrum, *m/e* (relative intensity) 220 (M^+-18, 4), 202 (42), 162 (69), 159 (49), 147 (100), 134 (47), 133 (43), 107 (47), 69 (83), 59 (55); calcd for $C_{15}H_{26}O_2$ (M^+-18) *m/e* 220.1827, found *m/e* 220.1828.

[3R-(3α,3aβ,5β,8aα)]-octahydro-3-methyl-8-methylene-5-[1-methyl-1-(trimethylsilyl)oxy]-ethyl-4(2*H*)-azulenone (271). To a stirred solution of 0.832 g (3.52 mmol) of **270** in 12 mL of dry pyridine were added 2.6 mL of hexamethyldisilazane (HMDS) and 1.3 mL of chlorotrimethylsilane (TMSCl). The reaction mixture was stirred at room temperature for 15 min, and then concentrated under reduced pressure. The resulting residue was flash chromatographed [100:1 petroleum ether (bp 40-60°C)/EtOAc] to give 1.060 g (98%) of pure **271**: ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 9H), 1.03 (d, J = 7.1 Hz, 3H), 1.18-1.76 (m, 3H), 1.26 (s, 3H), 1.27 (s, 3H), 1.78-2.19 (m, 4H), 2.25-2.62 (m, 4H), 2.77 (dd, J = 9.2, 11.9 Hz, 1H), 4.69 (br s, 1H), 4.72 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 2.42 (3 x q), 17.85 (q), 26.07 (t), 27.91 (q), 28.85 (q), 29.56 (t), 33.71 (t), 36.76 (d), 37.66 (t), 48.98 (d), 58.56 (d), 64.52 (d), 75.36 (s), 107.42 (t), 151.48 (s), 216.59 (s); mass spectrum, *m/e* (relative intensity) 293 (M^+-15, 4), 250 (22), 235 (4), 208 (2), 159 (2), 147 (2), 147 (2), 131 (100), 75 (10), 73 (28); calcd for $C_{17}H_{29}O_2Si$ (M^+-15) *m/e* 293.1937, found *m/e* 293.1934.

Lithium aluminum hydride reduction of 271. To a stirred solution of 0.924 g (3.00 mmol) of **271** in 18 mL of dry THF, cooled to 0°C, was added 0.140 g of lithium aluminum hydride. The reaction mixture was allowed to stir for 45 min at 0°C. The excess lithium aluminum hydride was then destroyed by the careful addition of a minimum amount of 25% aqueous NaOH solution. The reaction mixture was stirred overnight at room temperature with anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. The remaining residue was dissolved in 5 mL of 0.5 M TBAF in THF, and this solution was stirred at room temperature for 10 min. After addition of 25 mL of water and 15 mL of EtOAc, 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 25 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [10:1 to 5:1 petroleum ether (bp 40-60°C)/EtOAc] to give, in order of elution, 0.061 g (8%) of pure α–alcohol **272** and 0.655 g (92%) of pure β-alcohol **273**.

(–)-2β-Hydroxykessane (274). To a stirred solution of 0.484 g (2.03 mmol) of **273** in 5 mL of dry THF was added 1.30 g (4.08 mmol) of mercuric acetate. The reaction mixture was stirred at 55°C for 16 h. The mixture was allowed to come to room temperature, and then 4 mL of 3 N NaOH in water was added, followed by 4.5 mL of 0.5 M $NaBH_4$ in aqueous 3 N NaOH. After stirring at room temperature for 1.5 h the reaction mixture was filtered through Celite, and the filter cake was washed with 40 mL of water and 50 mL of EtOAc. The resulting two-phase mixture was separated, and the aqueous layer was extracted with three 50-mL portions of EtOAc. The combined organic layers were washed with 75 mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was flash chromatographed [10:1 to 5:1 petroleum ether (bp 40-60°C)/EtOAc] to give 0.320 g (66%) of pure **274**: mp 130-130.5°C [from petroleum ether (bp 40-60°C)]; $[\alpha]_D$ -46° (c 0.56); ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 6.9 Hz, 3H), 1.09 (s, 3H), 1.26 (s, 3H), 1.34-2.42 (m, 13H), 1.42 (s, 3H), 3.75 (br d, J = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.77 (q), 21.25 (t), 28.11 (t), 28.39 (q), 29.10 (q), 30.83 (d), 31.17 (t), 32.05 (q), 34.19 (t), 44.34 (d), 47.21 (d), 48.30 (d), 73.60 (s), 74.52 (s), 78.24 (d); mass spectrum, *m/e* (relative intensity) 238 (M^+, 32), 223 (31), 220 (15), 205 (85), 111 (71), 109 (82), 95 (69), 81 (86), 69 (72), 43 (100); calcd for $C_{15}H_{26}O_2$ (M^+) *m/e* 238.1933, found *m/e* 238.1932.

(O-kessanyl-2)-S-methyl-dithiocarbonate (275). To a solution of 0.240 g (1.01 mmol) of **274** in 6 mL of dry THF were added a catalytic amount of imidazole and 0.050 g (1.67 mmol, as a 80% dispersion in mineral oil) of sodium hydride. The mixture was heated at reflux for 3 h, after which time 0.35 mL of carbon disulfide was added. After heating at reflux for an additional 30 min 0.35 mL of iodomethane was added. Heating at reflux was continued for 30 min and after cooling to room temperature, 0.35 mL of acetic acid was added. The reaction mixture was diluted with 25 mL of water and extracted with three 25-mL portions of CH_2Cl_2. The combined organic layers were washed successively with 25 mL of saturated aqueous $NaHCO_3$ and 25 mL of brine. The organic layer was dried, and the solvent was removed under reduced pressure. The crude product was flash chromatographed [40:1 petroleum ether (bp 40-60°C)/EtOAc] to give 0.305 g (92%) of pure **275**: ^1H NMR ($CDCl_3$) δ 0.78 (d, J = 7.0 Hz, 3H), 1.12 (s, 3H), 1.23 (s, 3H), 1.35 (s, 3H), 1.40-2.33 (m, 11H), 2.52 (s, 3H), 2.66 (dt, J = 8.2, 12.1 Hz, 1H), 5.55 (dd, J = 1.1, 11.6 Hz, 1H); ^{13}C NMR ($CDCL_3$) δ 18.36 (q), 18.57 (q), 20.10 (t), 28.28 (t), 28.28 (q), 28.83 (q), 30.96 (d), 31.23 (t), 31.56 (q), 33.92 (t), 40.22 (d), 45.52 (d), 47.40 (d), 73.63 (s), 74.22 (s), 89.51 (d), 214.80 (s); mass spectrum, *m/e* (relative intensity) 328 (M^+, 1), 303 (1), 295 (8), 211 (100), 203 (68), 163 (52), 147 (27), 95 (53), 91 (29), 43 (44); calcd for $C_{17}H_{28}O_2S_2$ (M^+) *m/e* 328.1531, found *m/e* 328.1528.

(–)-Kessane (264). To a refluxing solution of 0.7 mL (2.60 mmol) of tributyltin hydride and a catalytic amount of AIBN in 30 mL of dry toluene was added dropwise a solution of 0.535 g (1.63 mmol) of **275** in 35 mL of dry toluene over a period of 2.25 h. When the addition was complete, the reaction mixture was heated at reflux for an additional 3 h. The reaction mixture was allowed to come to room temperature and then concentrated under reduced pressure. The resulting residue was flash chromatographed [petroleum ether (bp 40-60°C) to 60:1 petroleum ether (bp 40-60°C)/EtOAc] to give 0.354 g (98%) of pure **264**: $[\alpha]_D$ -6.1° (c 4.40) (lit.[1]: -7.2°); ^{1}H NMR ($CDCl_3$) δ 0.76 (d, J = 6.5 Hz, 3H), 0.85-1.11 (m, 2H), 1.09 (s, 3H), 1.22 (s, 6H), 1.23-2.21 (m, 12H). ^{13}C NMR ($CDCl_3$) δ 18.50 (q), 24.16 (t), 28.20 (t), 28.20 (q), 28.36 (q), 31.09 (d), 32.05 (t), 32.81 (q), 33.24 (t), 34.69 (t), 35.67 (d), 41.46 (d), 50.13 (d), 73.87 (s), 74.82 (s); mass spectrum, *m/e* (relative intensity) 222 (M^+, 9), 207 (3), 204 (4), 189 (5), 164 (9), 161 (8), 149 (15), 126 (100), 108 (44), 81 (25); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1984, found *m/e* 222.1981.

4.4 References and notes

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8 The trimethylsilyl ether **271** was prepared from **270** according to the procedure as described. See: Sweely, C.C.; Bentley, R.; Mahita, M.; Wells, W.W. *J. Am. Chem. Soc.* **1963**, *85*, 2497.

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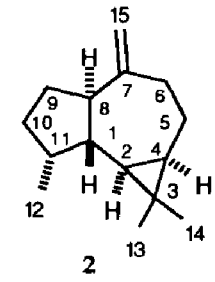
10 According to GC analysis, the purity of **268** was 96%. As a by-product a minor quantity (3.5%) of **269** was formed.

5 The synthesis of mono- and dihydroxy aromadendrane sesquiterpenes, starting from natural (+)-aromadendrene*

Abstract: *The monoalcohols (–)-globulol (**4**), (–)-epiglobulol (**5**), (–)-ledol (**6**), and (+)-viridiflorol (**7**) were synthesized from (+)-aromadendrene (**2**). The cis-fused alloaromadendrone (**223**), the key intermediate used in the synthesis of **6** and **7**, was obtained from the trans-fused apoaromadendrone (**222**) via a selective protonation of the thermodynamic enol trimethylsilylether **278**. After hydroxylation of the tertiary C11 of **222** with RuO_4, (+)-spathulenol (**31**), (–)-allospathulenol (**276**), and the aromadendrane diols **40**, **41**, **227**, and **277** could be prepared. Compounds **4-7**, **31**, **40**, **41**, **227**, **276**, and **277** were tested for antifungal properties, but their activity was only moderate.*

5.1 Introduction



In chapter 3 and 4, the large-scale conversion of (+)-aromadendrene (**2**) into a chiral synthon and its conversion into (–)-kessane were described. In this chapter the outcome of the investigations on the usefulness of **2** in the synthesis of the hydroxylated aromadendrane derivatives **4-7**, **31**, **40**, **41**, **227**, **276**, and **277** is described. In addition, the results of testing these compounds for their antifungal properties are given.

The aromadendrane C7 monoalcohols (–)-globulol (**4**), (–)-epiglobulol (**5**), (–)-ledol (**6**)[1], and (+)-viridiflorol (**7**) have been found in a broad spectrum of plant species. (+)-Spathulenol (**31**), a C11 monoalcohol, is also present in many plant genera. The dihydroxy aromadendrane sesquiterpenes are less commonly found in nature. (–)-Aromadendrane-7α,11β-diol (**40**) has been isolated from only five different plant species[2]. The structure of **40** has been determined through synthesis from **31**[2b]. From the soft coral *Sinularia mayi* (+)-**40** (**72**), (–)-aromadendrane-7α,11α-diol (**42**), and a related diol with unknown stereochemistry have been isolated[3]. An alloaromadendrane-7,11-diol, to which structure **165** was assigned, has been obtained from *Ambrosia peruviana*[4]. Direct comparison of the spectral data of **165** with those of

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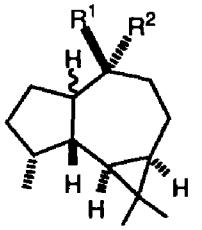
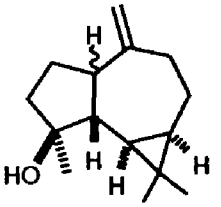
* This chapter has been published in a revised form: Gijsen, H.J.M.; Wijnberg, J.B.P.A.; Stork, G.A.; de Groot, Ae.; de Waard, M.A.; van Nistelrooy, J.G.M. *Ibid.* **1992**, *48*, 2465.

the unknown metabolite from *S. mayi* showed that these compounds are identical in every respect except in their rotation.

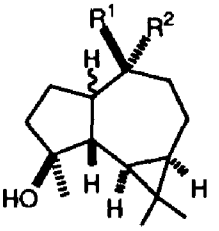
Figure 5.1



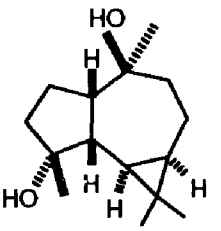
4 : αH; R^1=CH_3; R^2=OH
5 : αH; R^1=OH; R^2=CH_3
6 : βH; R^1=CH_3; R^2=OH
7 : βH; R^1=OH; R^2=CH_3



31 : αH
276 : βH



40 : αH; R^1=CH_3; R^2=OH
227 : αH; R^1=OH; R^2=CH_3
277 : βH; R^1=CH_3; R^2=OH
41 : βH; R^1=OH; R^2=CH



165

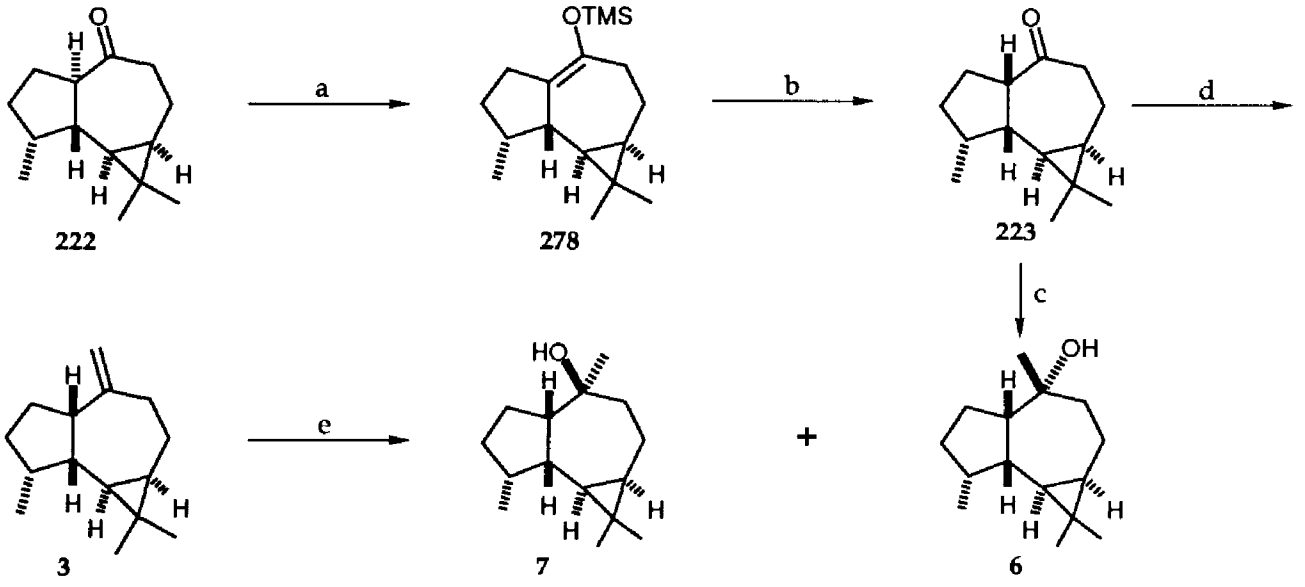
Some of the compounds mentioned above show activity as an antifungal agent, e.g. ledol against *Coriolus renatus*[5] and diol **165** against *Cladosporium herbarium*[4]. The antifungal properties of spathulenol might be responsible for its repellency against leaf cutter ants[6].

5.2 Results and discussion

Although **2** seems to be the obvious starting material for the synthesis of aromadendrane alcohols, no detailed study has been reported in this direction. As described previously, an easily separable mixture of **4** and **5** could be prepared via epoxidation of **2** with *m*-CPBA and subsequent reduction of the epoxides with $LiAlH_4$[7,8]. Treatment of (+)-apoaromadendrone (**222**), which was easily obtained in large quantities after ozonolysis of the abovementioned distillation tail[7,9], with MeLi at -78°C selectively produced **5** in 94% yield[7a]. The use of the *trans*-fused ketone **222** as the starting material for the synthesis of the *cis*-fused alcohols **6** and **7** required epimerization at C8. Treatment of **222** with NaOMe led to an equilibrium mixture of **222** and (–)-alloaromadendrone (**223**) in a ratio of 4 : 1, respectively, which was very difficult to separate by column chromatography. It was discovered however, that pure **223** could be obtained from the thermodynamic enol trimethylsilylether **278**. The crystalline **278** was prepared in 97% yield upon treatment of **222**, or a mixture of **222** and **223**, with TMSCl and triethylamine (Et_3N) in DMF at reflux temperature for 2 d. During the recrystallization of **278** from MeOH a partial conversion into **223** was

noticed. This observation led to an experiment in which **278** was treated with MeOH in the presence of Et_3N[10] at -20°C for 4 h. In this way **223** was obtained in almost quantitative yield (Scheme 5.1). This unexpected selectivity can be explained by an approach of the electrophile from the sterically less hindered β side of the molecule. Another explanation for the selective formation of **223** might be a stereoelectronically controlled ketonization of **278**[11]. The reaction of **223** with MeMgI gave a mixture of **6** and **7** in a ratio of 2 : 1, respectively. On the other hand, treatment of **223** with MeLi at -78°C afforded **6** as the sole product in 91 % yield[8a].

Scheme 5.1[a]

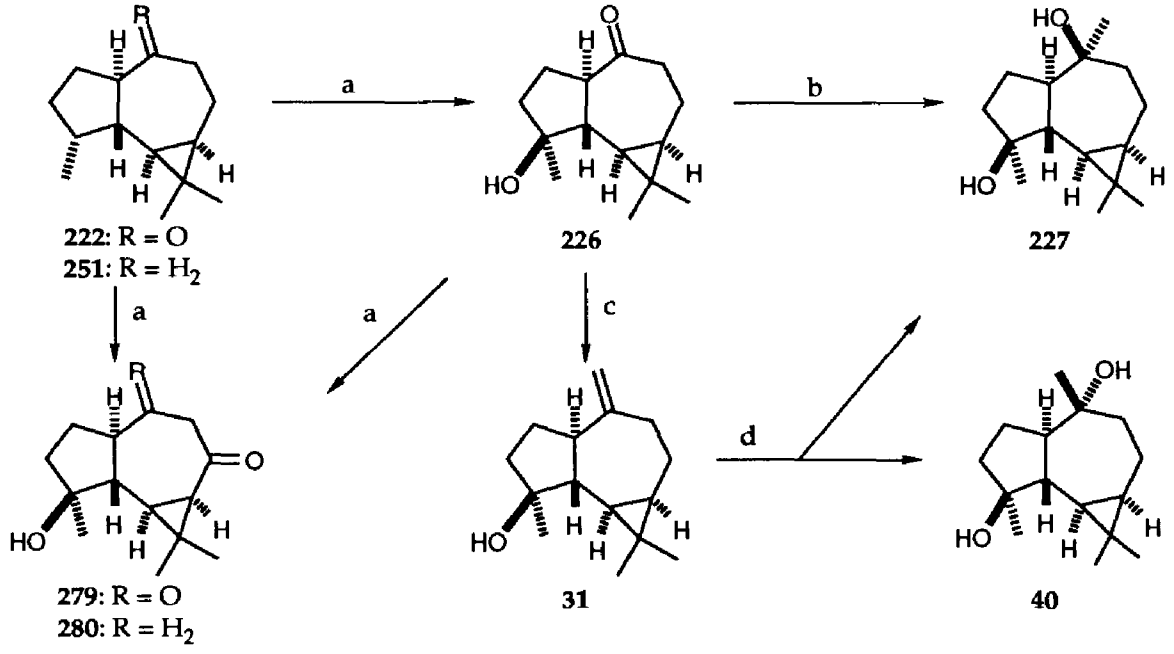


[a] (a) TMSCl, Et_3N, DMF, 130°C; (b) MeOH, Et_3N; (c) MeLi, -78°C→rt; (d) $TMSCH_2MgCl$; KH; (e) dimethyldioxirane; $LiAlH_4$.

The synthesis of **7** proceeded via (–)-alloaromadendrene (**3**). Using normal Wittig reaction conditions ($Ph_3P{=}CH_2$, DMSO) the *cis* ketone **223** only gave **2**. Evidently, **223** epimerizes at C8 under these reaction conditions and the resulting *trans* ketone **222** preferentially condenses with $Ph_3P{=}CH_2$. This epimerization could be prevented by using a Peterson olefination reaction[12]. Thus, reaction of **223** with trimethylsilylmethylmagnesium chloride ($TMSCH_2MgCl$) and subsequent treatment with KH in THF[13] afforded **3** in 91% yield. Epoxidation of **3** with *in situ* generated dimethyldioxirane[14] and reduction of the resulting mixture of epoxides with $LiAlH_4$ gave a 1 : 4 mixture of the alcohols **6** and **7** in 89% yield. Unfortunately, separation of the two isomers by column chromatography was not possible. However, preparative gas chromatography afforded pure **7** in an overall yield of 54% from **3**.

For the synthesis of the aromadendranediols **40**, **41**, **227**, and **277** the five-membered ring of the aromadendrane skeleton had to be hydroxylated at C11. The ozonization of **222** was reported to give the hydroxy ketone **226** in 9% yield[9]. The yield of **226** could be considerably improved using ruthenium(IV)oxide (RuO_2) and sodium periodate ($NaIO_4$) in a mixture of CCl_4, MeCN, and H_2O at 50°C[15]. Optimum yields (35-40%) of **226** were obtained after 50% conversion of **222** (Scheme 5.2). Completion of the reaction gave only poor yields of **226**, probably as the result of overoxidation. Higher reaction temperatures (> 60°C) also lowered the yield and led to polar, unidentified products. Overoxidation is probably mainly due to oxidation at C5 next to the cyclopropane ring, giving the 1,3-diketone **279**[16]. This easily enolizable product will be further oxidized with $RuO_2/NaIO_4$ to give carbon acids. Oxidation at C5 does take place, as was proven by treatment of (–)-noraromadendrane (**251**)[7] with $RuO_2/NaIO_4$. This gave the hydroxyketone **280** in 34% yield.

Scheme 5.2[a]



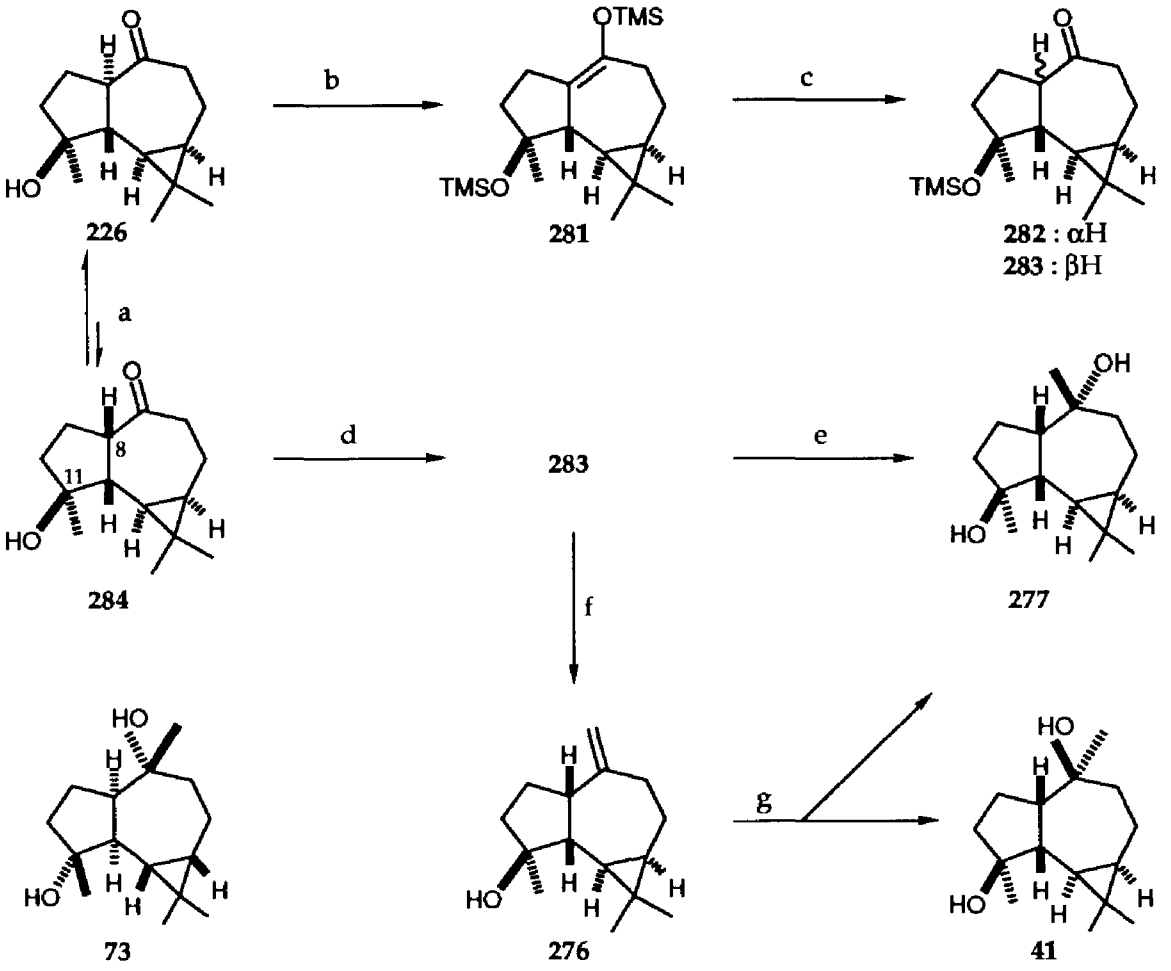
[a] (a) RuO_2, $NaIO_4$, 50°C; (b) MeMgI; (c) $TMSCH_2MgCl$; H^+, THF; (d) dimethyldioxirane; $LiAlH_4$.

Other substrates, such as **4** and **5** , which would lead directly to the *trans*-fused diols **40** and **227**, respectively, showed predominantly overoxidation with $RuO_2/NaIO_4$. Therefore, starting from the hydroxy ketone **226**, the methods outlined above for the synthesis of the monoalcohols **4-7** were employed in the synthesis of the diols **40**, **41**, **227**, and **277**. Treatment of **226** with MeMgI afforded (–)-**227** in 91% yield. For the synthesis of its C7 epimer **40** the hydroxy ketone **226** was converted into

(+)-spathulenol (**31**). A Peterson olefination reaction gave **31** in quantitative yield[17]. Epoxidation of **31** with dimethyldioxirane and subsequent reduction of the resulting mixture of epoxides led to a 1 : 1 mixture of the diols **40** and **227** in 88% yield. Careful column chromatography and crystallization from petroleum ether (bp. 80-100°C) gave a pure sample of **40**.

For the synthesis of the alloaromadendrane-7,11-diols **41** and **277** the preparation of the *cis*-fused hydroxy ketone **284** was required. In an effort to synthesize **284** via the C11 hydroxylation of **223** with $RuO_2/NaIO_4$, predominantly overoxidation was observed. Therefore, it was tried to prepare **284** in a similar way as described above for the synthesis of **223**. Treatment of **226** with TMSCl and Et_3N in DMF at reflux temperature for 22 h resulted in the formation of the enol trimethylsilylether **281** (Scheme 5.3). Unfortunately, the ketonization of **281** with MeOH in the presence of Et_3N did not proceed in a selective way. According to ^1H NMR, an inseparable 1 : 1 mixture of **282** and **283** was obtained. Probably, the β-silyloxy group at C11 of **281** sterically hinders the approach of the electrophile from the β side of the molecule. On the other hand, a short treatment of **226** with NaOMe in MeOH resulted in an equilibrium mixture of **226** and **284** in a ratio of 7 : 3, respectively. Since **226** and **284** could be easily separated by flash chromatography, this simple procedure was used to produce sufficient amounts of **284**. After three successive treatments of **226** with NaOMe, **284** was obtained in 58% overall yield. Treatment of **284** with MeMgI did not give the expected diol **277**. Instead, considerable amounts of **226** were obtained. Probably, the alcohol function at C11 is deprotonated and stimulates intramolecularly the enolization of the carbonyl group towards C8 which will prevent the addition of the Grignard reagent. After protection of the hydroxyl group as its trimethylsilylether (**284** → **283**), the reaction with MeMgI proceeded smoothly. Cleavage of the trimethylsilylether resulted in a 79% yield of (+)-allo-aromadendrane-7α,11β-diol (**277**) starting from **284**.

Scheme 5.3[a]



[a] (a) NaOMe, MeOH; (b) TMSCl, Et_3N, DMF, 130°C; (c) MeOH, Et_3N; (d) TMSCl, HMDS; (e) MeMgI; (f) $TMSCH_2MgCl$; H^+,THF; (g) dimethyldioxirane; $LiAlH_4$.

The diol **41** could be prepared from **283** in a similar reaction sequence as employed for the synthesis of **7**. A Peterson olefination reaction of **283** gave (–)-allospathulenol (**276**)[18] in 87% yield. Epoxidation of **276** followed by reduction afforded (+)-alloaromadendrane-7β,11β-diol (**41**) in 86% yield, together with 9% of **277**. Direct comparison of **41** with the aromadendranediol isolated from *A. peruviana* showed that these compounds are identical in all respects. As a consequence, the structure assigned to the natural product from *A. peruviana* must be **41**, and not **165** as proposed in the literature[4,19]. The structure of the enantiomer of **41**, isolated from *Sinularia mayi*[3,4] must then be **73**.

The compounds **4-7, 31, 40, 41, 227, 276,** and **277** were tested for antifungal activity on the fungi *Cladosporium cucumerinum* and *Penicillium italicum* via the minimal inhibitory concentration (MIC) test[20] and a thin-layer bioautography test[21]. In MIC tests the toxicity of all compounds was higher for *C. cucumerinum* than for *P. Italicum*. MIC's of all compounds to *P. Italicum* were higher than 100 $\mu g\ ml^{-1}$. Therefore, only the results obtained with *C. cucumerinum* are presented (Table 5.1). The MIC test and the thin-layer bioautography test demonstrated fungitoxicity for the monoalcohols **4, 5, 7, 31,** and **276**. The compounds **40** and **41** were only active in the thin-layer bioautography test. However, the fungitoxicity of the active compounds should be regarded as moderate, since complete growth inhibition only takes place at high ($\geq$100 $\mu g\ ml^{-1}$) concentrations of the test compounds[22].

Table 5.1. Fungitoxicity of test compounds to growth of *Cladosporium cucumerinum* in a Minimal Inhibitory Concentration (MIC) test and a Thin-layer Bioautography test.

Compound	MIC test				Bioautography test			
	Concentration ($\mu g\ mL^{-1}$)				Concentration ($\mu g\ mL^{-1}$)			
	0	1	10	100	0	10	100	1000
4	5[a]	5	5	0	3[b]	2	1	0
5	5	5	4	0	3	2	1	0
6	5	5	5	4	3	3	3	2
7	5	5	5	0	3	3	1	0
31	5	4	3	0	3	2	1	0
40	5	5	5	5	3	3	1	0
41	5	5	5	5	3	3	1	0
227	5	5	5	5	3	3	3	2
276	5	5	4	0	3	2	1	0
277	5	5	5	5	3	3	3	2

[a] Scores used for evaluation of fungal growth in MIC tests: 5 = dense mycelial growth and heavy sporulation, 4 = dense mycelial growth but slight sporulation, 3 = 100-1000 colonies per plate, 2 = idem 10-100, 1 = idem 1- 10, and 0 = no colonies present.

[b] Scores used for evaluation of fungal growth in bioautography test: 3 = normal dense growth, 2 = slight growth inhibition, 1 = strong growth inhibition, and 0 = no growth.

5.3 Experimental section

Melting points were determined on an Olympus HSA melting point apparatus and are uncorrected. Optical rotations were obtained from $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Bruker AC-E 200 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard in $CDCl_3$ as the solvent. Mass spectral data were determined on either an AEI MS 902 spectrometer or a Hewlett Packard 5970 B series MSD coupled with a Hewlett Packard 5890 A gas chromatograph with a DB-17 fused silica capillary column. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. 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. 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.

(–)-Epiglobulol (5). To a solution of 2.04 g (10.0 mmol) of **222** in 40 mL of dry ether, cooled to -78°C, was added dropwise 10 mL (15 mmol) of MeLi (1.5 M in ether). The reaction mixture was stirred for 1 h at -78°C, allowed to come to room temperature, and then carefully quenched with 15 mL of saturated aqueous NH_4Cl. The two-phase mixture was separated, and the aqueous solution was extracted with four 25-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried, and evaporated under reduced pressure. The crude product was flash chromatographed [6:1 petroleum ether (bp 40-60°C)/EtOAc] to give 2.05 g (94%) of **5** as a colourless oil. Physical and spectroscopic data were consistent with those reported in the literature[7,8b].

Enol trimethylsilylether 278. To a stirred mixture of 32 mL of DMF, 16.8 mL (192 mmol) of Et_3N, and 13.0 mL (102 mmol) of TMSCl was added 14.42 g (70.0 mmol) of **222**. The reaction mixture was heated at reflux for 48 h, allowed to come to room temperature, and then 200 mL of petroleum ether (bp 40-60°C) was added. The resulting mixture was washed twice with 50 mL of saturated aqueous $NaHCO_3$, and the combined aqueous layers were back-extracted with two 100-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. According to GC-MS analysis, the solid residue (19.42 g) consisted for 97% of **278**. Recrystallization from 350 mL of dry CH_3CN afforded 16.54 g (85%) of pure **278**: mp 57°C; $[\alpha]_D$ +76.5° (c 1.42); ^1H NMR ($CDCl_3$) δ 0.13 (s, 9H), 0.48 (ddd, J = 4.8, 9.5, 11.5 Hz, 1H), 0.67 (t, J = 9.5 Hz, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.95 (s, 3H), 1.02 (s, 3H), 1.04-2.54 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 0.53 (3·q), 15.30 (q), 15.47 (q), 17.55 (s), 20.55 (t), 24.94 (d), 28.16 (q), 29.89 (t), 30.45 (d), 32.10 (t), 35.03 (t), 37.23 (d), 37.43 (d), 126.33 (s), 141.26 (s); mass spectrum, *m/e* (relative intensity) 278 (M^+, 17), 263 (10), 235 (40), 221 (8), 195 (10), 181 (15), 145 (19), 91 (21), 73 (100), 45 (30); calcd for $C_{17}H_{30}OSi$ (M^+) *m/e* 278.2066, found *m/e* 278.2066. Anal. Calcd for $C_{17}H_{30}OSi$: C, 73.31; H, 10.85. Found: C, 73.26; H, 11.10.

Instead of pure **222**, also a mixture of **222** and **223** could be used for the synthesis of **278**.

(–)-Alloaromadendrone (223). To a solution of 751 mg (2.7 mmol) of **278** in 60 mL of dry MeOH, cooled to -20°C, was added 2 mL of Et_3N, after which the mixture was stirred for 4 h at -20°C. Evaporation of the solvent under reduced pressure gave 552 mg (99%) of crude **223**. According to GC analysis, the purity of **223** was 97%. This crude **223** could be used without further purification for the next reaction. Recrystallization from petroleum ether (bp 80-100°C) gave pure **223**: mp 75-76°C; $[\alpha]_D$ -11.7° (c 3.54); ^1H NMR ($CDCl_3$) δ 0.31 (dd, J = 9.1, 11.1 Hz, 1H), 0.60 (ddd, J = 4.9, 9.1, 11.6 Hz, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H), 0.99 (s, 3H), 1.17-2.05 (m, 6H), 2.18-2.37 (m, 2H), 2.46 (ddd, J = 7.1, 11.6, 14.4 Hz, 1H), 2.62 (ddd, J = 2.5, 7.4, 14.4 Hz, 1H), 3.15 (dt, J = 5.1, 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.90 (q), 15.15 (q), 17.55 (s), 18.64 (t), 24.09 (d), 24.23 (t), 24.94 (d), 27.94 (q), 31.42 (t), 38.62 (d), 40.06 (d), 44.03 (t), 55.14 (d), 211.62 (s); mass spectrum, *m/e* (relative intensity) 206 (M^+, 32), 191 (7), 163 (16), 145 (13), 135 (20), 107 (25), 95 (33), 83 (56), 69 (100), 55 (56), 41 (85); calcd for $C_{14}H_{22}O$ (M^+) *m/e* 206.1671, found *m/e* 206.1667. Anal. Calcd for $C_{14}H_{22}O$: C, 81.49;H, 10.74. Found: C, 81.76; H, 10.95.

(–)-Ledol (6). This compound was prepared from crude **223** (155 mg, 0.75 mmol) as described for the synthesis of **5**. The workup and flash chromatography [15:1 petroleum ether (bp 40-60°C)/EtOAc] afforded 152 mg (91%) of **6**: mp 103-104°C [from petroleum ether (bp 80-100°C)] (lit.[23]: 103-104°C); $[\alpha]_D$ -5.8° (c 1.50) (lit.[1]: -5.6°); ^{1}H NMR data were identical to those reported in the literature[23]; ^{13}C NMR ($CDCl_3$) δ 15.17 (q), 15.74 (q), 19.20 (s), 20.05 (t), 23.14 (d), 24.36 (t), 24.73 (d), 28.41 (q), 30.26 (q), 30.56 (t), 38.18 (d), 38.96 (t), 40.53 (d), 53.47 (d), 74.65 (s); the mass spectrum was consistent with that reported in the literature[23]. Anal. Calcd for $C_{15}H_{26}O$: C, 81.01; H, 11.78. Found: C, 80.67; H, 11.75.

(–)-Alloaromadendrene (3). To 438 mg (18 mmol) of Mg turnings and a crystal of I_2 in 6 mL of dry ether was added dropwise a solution of 2.58 mL (18 mmol) of $(CH_3)_3SiCH_2Cl$ in 10 mL of dry ether. The mixture was heated at reflux for 1 h, allowed to come to room temperature, and then a solution of 618 mg (3.0 mmol) of pure **223** in 10 mL of dry ether was added dropwise. After stirring for 2.5 h at room temperature, the reaction mixture was cooled to 0°C and carefully quenched with 15 mL of saturated aqueous NH_4Cl. After dilution with 25 mL of H_2O, the two-phase mixture was separated, and the aqueous layer was extracted with four 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 30 mL of brine, dried, and evaporated under reduced pressure. The remaining residue (890 mg) was dissolved in 20 mL of dry THF and added dropwise to 0.35 g of KH (8.7 mmol, freed from mineral oil) in 15 mL of dry THF. The reaction mixture was stirred at room temperature for 1 h, and then poured into 25 mL of cold saturated aqueous NH_4Cl. The resulting mixture was extracted with four 25-mL portions of ether. The combined organic layers were washed with 30 mL of brine, dried, and evaporated under reduced pressure. The crude product was flash chromatographed (pentane) to give 560 mg (91%) of pure **3** as a colourless oil: $[\alpha]_D$ -27.7° (c 1.62) (lit.[24]: -21.6°); ^{1}H NMR ($CDCl_3$) δ 0.23 (dd, J = 9.3, 10.7 Hz, 1H), 0.53 (ddd, J = 6.1, 9.3, 10.8 Hz, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.95 (s, 3H), 0.99 (s, 3H), 1.12-1.42 (m, 2H), 1.63-2.14 (m, 6H), 2.23-2.37 (m, 2H), 2.66 (br q, J = 8.0 Hz, 1H), 4.72 (br s, 2H); ^{13}C NMR ($CDCl_3$), δ 15.63 (q), 16.17 (q), 16.98 (s), 21.90 (t), 23.28 (d), 24.56 (d), 27.98 (t), 28.37 (q), 30.96 (t), 35.47 (t), 37.56 (d), 41.93 (d), 50.54 (d), 109.44 (t), 152.24 (s); mass spectrum, *m/e* (relative intensity) 204 (M^+, 18), 189 (10), 161 (32), 147 (21), 133 (30), 119 (31), 105 (48), 91 (63), 79 (46), 67 (34), 41 (100); calcd for $C_{15}H_{24}$ (M^+) *m/e* 204.1878, found *m/e* 204.1874.

(+)-Viridiflorol (7). To a solution of 430 mg (2.1 mmol) of **3** in 30 mL of CH_2Cl_2 were added 30 mL of acetone, 30 mL of water, 50 mg of 18-Crown-6, and 3.0 g of $NaHCO_3$. The mixture was vigorously stirred and 10 mL of 0.29 M Oxone (5.8 mmol of $KHSO_5$) in water was added dropwise at 0 °C. Stirring was continued for 1 hr, after which time 40 mL of saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with four 40-mL portions of CH_2Cl_2. The combined organic layers were washed with 40 mL of 10% aqueous $Na_2S_2O_3$ and 40 mL of saturated aqueous $NaHCO_3$, and then dried. After evaporation of the solvent under reduced pressure, the residue was taken up in 40 mL of dry THF and an excess $LiAlH_4$ was added. The mixture was stirred at room temperature for 18 h, diluted with 100 mL of ether, and then carefully quenched with a few drops of saturated aqueous Na_2SO_4. The mixture was dried and concentrated under reduced pressure. Flash chromatography [50:1 petroleum ether (bp 40-60°C)/EtOAc] afforded 417 mg (89%) of a 1:4 mixture of the alcohols **6** and **7**, respectively. Separation of both isomers by preparative gas chromatography, using a 9.5% Carbowax HP on Chromosorb W-HP column, 3m x 1/8" o.d., gave pure **7** in 54% yield from **3**. Also a column with a larger capacity (2m x 3/8" o.d.) could be used. Physical data of **7**: mp 75°C (from CH_3CN) (lit[24]: 75°C); $[\alpha]_D$ +4.8° (c 0.86) (lit.[24]: +4.0°); ^1H NMR[25], ^{13}C NMR[25], and MS[8b] spectroscopic data were consistent with those reported in the literature. Anal. Calcd for $C_{15}H_{26}O$: C, 81.01; H, 11.78. Found: C, 81.01; H, 11.81.

(+)-11β-Hydroxy-apoaromadendrone (226). To a bottle containing 16 mL of CCl_4, 16 mL of CH_3CN, 24 mL of H_2O, and 3.42 g (16 mmol) of $NaIO_4$ was added 824 mg (4.0 mmol) of **222** and 35 mg of $RuO_2 \cdot xH_2O$. The bottle was closed air-tight and rotated around its axis in a waterbath of 50°C until the colour of the mixture had turned from yellow to black (48 h). The reaction mixture was filtered through celite, and the filter cake was washed with 25 mL of H_2O and 40 mL of CH_2Cl_2. The combined filtrates were separated, and the aqueous layer was extracted with two 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 30 mL of aqueous 10% $Na_2S_2O_3$ and 30 mL of saturated aqueous $NaHCO_3$, and then dried. Evaporation of the solvent under reduced pressure gave a crude mixture of mainly **222** and **226**. Flash chromatography [5:1 to 3:1 petroleum ether (bp 40-60°C)/EtOAc] afforded 240 mg (28%) of **222** and 318 mg (36%) of **226**[26]: mp 103-104°C [from petroleum ether (bp 80-100°C)]; $[\alpha]_D$ +21.4° (c 1.37); ^1H NMR ($CDCl_3$) δ 0.64 (dd, J = 9.3, 10.8 Hz, 1H), 0.85 (ddd, J = 5.8, 9.3, 11.1 Hz, 1H), 0.98 (s, 3H), 1.02-1.12 (m, 1H), 1.07 (s, 3H), 1.25 (s, 3H), 1.28-1.80 (m, 5H), 1.93-2.08 (m, 1H), 2.17-2.53 (m, 3H), 2.69 (dt, J = 7.9, 11.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.98 (q), 18.73 (s), 20.08 (t), 20.93 (t), 23.60 (q), 26.20 (d), 26.51 (d), 28.59 (q), 40.84 (t),

43.97 (t), 49.53 (d), 57.82 (d), 80.04 (s), 211.35 (s); mass spectrum *m/e* (relative intensity) 222 (M^+, 100), 207 (16), 204 (59), 179 (40), 164 (69), 161 (69), 146 (75), 121 (50), 95 (65), 81 (92); calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1618. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.97. Found: C, 75.47; H, 10.17.

11β-Hydroxy-5-keto-noraromadendrane (280). (–)-Noraromadendrane **251** (768 mg, 4 mmol) was treated with 5.14 g (24 mmol) of $NaIO_4$ and 30 mg of $RuO_2 \cdot xH_2O$ as described for the synthesis of **226**. After workup, the remaining residue was flash chromatographed [3:1 petroleum ether (bp 40-60°C)/EtOAc] to give 304 mg (34%) of **280**: mp 79°C (from *n*-heptane); $[\alpha]_D$ +34.2° (c 1.71); ^1H NMR ($CDCl_3$) δ 0.78 (t, J = 10.8 Hz, 1H), 1.07 (s, 3H), 1.18 (s, 3H), 1.24 (s, 3H), 0.97-2.01 (m, 10H), 2.30-2.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.20 (q), 24.78 (q), 25.07 (s), 27.31 (d), 27.77 (q), 29.11 (t), 32.52 (t), 37.94 (d), 41.27 (t), 44.76 (t), 45.11 (d), 56.66 (d), 80.52 (s), 208.99 (s); mass spectrum, *m/e* (relative intensity) 222 (M^+, 21), 207 (31), 204 (54), 189 (53), 166 (84), 149 (95), 121 (77), 107 (100), 93 (83); calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1620. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.62; H, 10.16.

(–)-Aromadendrane-7β,11β-diol (227). To a stirred solution of 10 mL (6 mmol) of 0.6 M MeMgI in ether was added dropwise at room temperature a solution of 113.5 mg (0.51 mmol) of **226** in 7.5 mL of dry ether. After stirring for 1 h at room temperature, the reaction mixture was cooled to 0°C, and the excess MeMgI was quenched by the careful addition of saturated aqueous NH_4Cl. After addition of 25 mL of H_2O, the two-phase mixture was separated, and the aqueous layer was extracted with four 20-mL portions of CH_2Cl_2. The combined organic layers were washed with 30 mL of brine, dried, and then evaporated under reduced pressure. The crude product was flash chromatographed [3:1 petroleum ether (bp 40-60°C)/EtOAc] to give 111 mg (91%) of **227**: mp 142°C [from petroleum ether (bp 40-60°C)] (lit.[3]: 142.5-142.7°C); $[\alpha]_D$ -11.2° (c 2.20) (lit.[3]: -12.6°); ^1H NMR, ^{13}C NMR, and MS spectroscopic data were consistent with those reported in the literature[2b,3]. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.34; H, 10.95. Found: C, 75.57; H, 10.99.

(+)-Spathulenol (31). The ketone **226** (222 mg, 1.0 mmol) was treated with $(CH_3)_3SiCH_2MgCl$ for 1.5 h as described for the synthesis of **3**. After workup, the remaining residue was dissolved in 10 mL of THF, and a solution of 3 drops of concd H_2SO_4 in 10 mL of THF was added. After stirring at room temperature for 2 h, 25 mL of saturated aqueous $NaHCO_3$ was added. The two-phase mixture was separated, and the aqueous layer was extracted with 25 mL of EtOAc. The combined organic layers were washed with 25 mL of brine, dried, and evaporated under reduced pressure. The

crude product was flash chromatographed [15:1 petroleum ether (bp 40-60°C)/EtOAc] to give 220 mg (100%) of **31** as a colourless oil: $[\alpha]_D$ +9.8° (c 4.7) (lit.[2a]; +5.3°); ^{1}H NMR, ^{13}C NMR, and MS spectroscopic data were consistent with those reported in the literature[2a]. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.73; H, 10.95.

(–)-Aromadendrane-7α,11β-diol (40). The olefin **31** (220 mg, 1.0 mmol) was epoxidized and reduced as described for the synthesis of **7**. The workup gave a crude mixture of **40** and **227** in a ratio of 1:1, according to GC analysis. Flash chromatography [3:1 to 3:2 petroleum ether (bp 40-60°C)/EtOAc] afforded 209 mg (88%) of the diols **40** and **227**. Fractions containing predominantly **40** were recrystallized from petroleum ether (bp 80-100°C) to give pure **40**: mp 132-134°C (lit.[2a]: 133-134°C); $[\alpha]_D$ -21.7° (c 0.99) (lit.[2a]: -21.7°); ^{1}H NMR, ^{13}C NMR, and MS spectroscopic data were consistent with those reported in the literature[2,3]. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.33; H, 10.93.

(+)-11β-Hydroxy-alloaromadendrone (284). A solution of 1.25 g (5.6 mmol) of **226** in 10 mL of 1 M MeONa in MeOH was stirred at room temperature for 1 h. After dilution with 40 mL of H_2O, the reaction mixture was extracted with three 25-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried, and evaporated under reduced pressure. The remaining residue (1.22 g), according to GC-analysis a 7:3 mixture of **226** and **284**, respectively, was flash chromatographed [5:1 petroleum ether (bp 40-60°C)/EtOAc] to give 300 mg of pure **284**. This procedure was repeated twice with the recovered starting material **226** to give in total 450 mg (36%) of **226** and 720 mg (58%) of **284**: mp 99-100°C (from diisopropylether); $[\alpha]_D$ +1.6° (c 1.06); ^{1}H NMR ($CDCl_3$) δ 0.20 (dd, J = 9.1, 11.4 Hz, 1H), 0.64 (ddd, J = 4.8, 9.1, 11.9 Hz, 1H), 0.95 (s, 3H), 1.07 (s, 3H), 1.27 (s, 3H), 1.36 (br s, 1H), 1.48-1.90 (m, 5H), 2.14 (br t, J = 10.2 Hz, 1H), 2.31-2.71 (m, 3H), 3.47 (m, J = 5.3, 8.9, 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.57 (q), 18.00 (s), 18.80 (t), 22.31 (t), 24.01 (q), 25.14 (d), 27.07 (d), 28.17 (q), 37.95 (t), 44.07 (t), 47.90 (d), 54.09 (d), 83.46 (s), 211.59 (s); mass spectrum, *m/e* (relative intensity) 222 (M+, 9), 204 (6), 194 (6), 179 (36), 161 (21), 146 (18), 131 (15), 121 (23), 91 (30), 79 (40), 43 (100); calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1609. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.97. Found: C, 75.54; H, 10.13.

Trimethylsilylether 283. To a stirred solution of 444 mg (2.0 mmol) of **284** in 10 mL of dry pyridine was added 2.0 mL of hexamethyldisilazane (HMDS) and 1.0 mL of TMSCl. The reaction mixture was stirred at room temperature for 0.5 h, and then concentrated under reduced pressure. The resulting residue was flash chromatographed [10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 588 mg (100%) of

283 [^{1}H NMR ($CDCl_3$) δ 0.09 (s, 9H), 0.16 (dd, J = 9.1, 11.5 Hz, 1H), 0.62 (ddd, J = 4.9, 9.1, 11.8 Hz, 1H), 0.94 (s, 3H), 1.07 (s, 3H), 1.27 (s, 3H), 1.47-1.90 (m, 5H), 2.13 (dd, J = 8.8, 11.5 Hz, 1H), 2.25-2.72 (m, 3H), 3.39 (m, J = 5.4, 8.8, 9.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 2.17 (3·q), 15.57 (q), 17.78 (s), 18.60 (t), 22.27 (t), 23.31 (q), 24.79 (d), 26.90 (d), 28.04 (q), 37.65 (t), 43.76 (t), 48.98 (d), 54.20 (d), 85.86 (s), 212.04 (s)] as a colourless oil, which was used immediately for the next reactions.

Treatment of the enol trimethylsilylether **281** [^{1}H NMR ($CDCl_3$) δ 0.07 (s, 9H), 0.13 (s, 9H), 0.37-0.65 (m, 2H), 0.96 (s, 3H), 1.06 (s, 3H), 1.22 (s, 3H), 1.34-1.79 (m, 4H), 2.18-2.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 0.50 (3·q), 2.19 (3·q), 15.97 (q), 17.94 (s), 20.81 (t), 23.84 (q), 25.10 (d), 27.89 (t), 28.31 (q), 31.52 (d), 34.86 (t), 38.88 (t), 47.29 (d), 83.74 (s), 124.02 (s), 141.82 (s)], prepared from **226** as described for the synthesis of **278**, with MeOH and Et_3N gave an unseparable 1:1 mixture of **282** [^{1}H NMR (major peaks, $CDCl_3$) δ 0.05 (s, 9H), 0.94 (s, 3H), 1.05 (s, 3H), 1.21 (s, 3H)] and **283**, according to ^{1}H NMR analysis

(+)-Alloaromadendrane-7α,11β-diol (277). A sample of 294 mg (1.0 mmol) of **283** was treated with MeMgI as described for the synthesis of **227**. After workup, the remaining residue was dissolved in 10 mL of MeOH, and then 5.5 mL of 10% aqueous HOAc was added. The reaction mixture was stirred at room temperature for 18 h, after which 20 mL of saturated aqueous $NaHCO_3$ was added. Stirring was continued at room temperature for an additional 15 min. The mixture was then poured into 40 mL of H_2O and extracted with four 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 25 mL of brine, dried, and evaporated under reduced pressure. The remaining residue was crystallized from petroleum ether (bp 80-100°C) to give 189 mg (79%) of **277**: mp 155-156°C; $[\alpha]_D$ +14.0° (c 1.09); ^{1}H NMR ($CDCl_3$) δ 0.28 (dd, J = 8.8, 11.1 Hz, 1H), 0.75 (ddd, J = 5.0, 8.8, 11.6, 1H), 1.02 (s, 3H), 1.04 (s, 3H), 1.10 (s, 3H), 1.28 (s, 3H), 1.29 (m, 1H), 1.50-2.09 (m, 9H), 2.51 (br s, 1H), 2.52 (m, J = 7.8, 7.9, 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.28 (q), 20.12 (s), 20.43 (t), 23.83 (t), 24.22 (q), 24.59 (d), 26.38 (d), 28.64 (q), 30.62 (q), 38.20 (t), 39.51 (t), 48.46 (d), 49.58 (d), 74.48 (s), 83.12 (s); mass spectrum, *m/e* (relative intensity) 238 (M^+, 0.5), 220 (3), 205 (5), 187 (4), 162 (13), 147 (9), 121 (19), 107 (16), 93 (19), 79 (17), 43 (100); calcd for $C_{15}H_{26}O_2$ (M^+) *m/e* 238.1933, found *m/e* 238.1920. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.33; H, 11.02.

(–)-Allospathulenol (276). The hydroxy olefin **276** was prepared from a sample of 294 mg (1.0 mmol) of **283** as described for the synthesis of **31**. The workup and flash chromatography [20:1 petroleum ether (bp 40-60°C)/EtOAc] afforded 192 mg (87%) of **276**: $[\alpha]_D$ –11.3° (c 1.16); ^{1}H NMR ($CDCl_3$) δ 0.14 (dd, J = 9.3, 11.3 Hz, 1H), 0.52 (ddd, J =

5.7, 9.3, 11.4 Hz, 1H), 0.97 (s, 3H), 1.00 (s, 3H), 1.24 (m, 1H), 1.28 (s, 3H), 1.58-2.06 (m, 7H), 2.33-2.47 (m, 2H), 3.07 (br q, J = 8.1 Hz, 1H), 4.73 (t, J=1.9 Hz, 1H), 4.78 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.81 (q), 16.94 (s), 20.87 (t), 23.91 (d), 25.07 (q), 25.94 (d), 26.42 (t), 28.34 (q), 35.86 (t), 38.66 (t), 47.02 (d), 49.59 (d), 82.62 (s), 109.66 (t), 150.97 (s); mass spectrum, *m/e* (relative intensity) 220 (M^+, 2), 205 (22), 202 (9), 187 (10), 177 (9), 159 (20), 147 (15), 131 (15), 119 (33), 105 (29), 91 (44), 79 (31), 43 (100); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1811. Anal Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.79; H, 11.10.

(+)-Alloaromadendrane-7β,11β-diol (41). The diol **41** was prepared from **276** (180 mg, 0.8 mmol) as described for the synthesis of **7**. The workup and flash chromatography [5:1 petroleum ether (bp 40-60°C)/EtOAc] gave 17.5 mg (9%) of **277** and 167.5 mg (86%) of **41**: mp 116°C [from petroleum ether (bp 80-100°C)] (lit.[4]: 112-113°C); $[\alpha]_D$ +10.6° (c 0.87) (lit.[4]: +7°); ^1H NMR[3,4] ($CDCl_3$) δ -0.02 (t, J = 9.5 Hz, 1H), 0.60 (ddd, J = 5.6, 9.5, 11.3 Hz, 1H), 1.00 (s, 3H), 1.02 (s, 3H), 1.18 (s, 3H), 1.32 (s, 3H), 1.33-1.85 (m, 11H), 2.46 (m, 1H); ^{13}C NMR[7,8] ($CDCl_3$) δ 16.00 (q), 18.50 (t), 18.50 (s), 24.93 (t), 25.08 (d), 25.41 (q), 28.33 (q), 28.56 (d), 31.93 (q), 37.20 (t), 37.75 (t), 47.58 (d), 53.83 (d), 74.08 (s), 81.90 (s); mass spectrum[7,8], *m/e* (relative intensity) 238 (M+, 0.5), 220 (4), 205 (5), 187 (5), 177 (5), 162 (22), 147 (12), 119 (14), 107 (17), 93 (20), 79 (17), 43 (100); calcd for $C_{15}H_{26}O_2$ (M^+) *m/e* 238.1933, found *m/e* 238.1963. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.77; H, 11.30.

Fungitoxicity tests.

Minimal inhibitory concentration test. The MIC's of the compounds were determined in potato dextrose agar (PDA)[20]. Agar amended with the test compounds at various concentrations were inoculated with 10 μL of conidial suspension (10^7 conidia mL^{-1}) of both test fungi. Growth was assessed after 5 days of incubation at 25°C.

Thin-layer bioautography test. Various amounts of test compounds were applied on silicagel thin-layer plates (Merck) and sprayed with conidial suspensions (10^7 conidia mL^{-1} nutrient solution) of *C. cucumerinum*[21]. Plates were incubated in humid chambers at 25°C for 3 days, and then assessed for growth inhibition at the site were the chemicals where spotted.

5.4 References and notes

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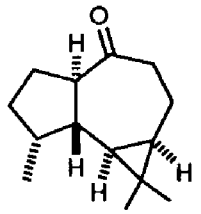
6 Rearrangement reactions of aromadendrane derivatives. The synthesis of (+)-maaliol, starting from natural (+)-aromadendrene*

Abstract: Starting from the hydroazulene α-ketol 289, which can easily be prepared from (+)-aromadendrene, two different routes to hydronaphthalene compounds with a maaliane skeleton have been developed, both proceeding in high overall yield. The first route leads to cis-fused maaliane derivatives; the second one offers access to trans-fused maaliane sesquiterpenes, as demonstrated in this chapter in the synthesis of (+)-maaliol (288). The synthesis of aristolanes or eudesmanes was not possible with the methods described here.

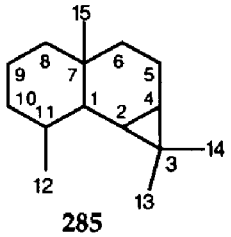
6.1 Introduction

(+)-Apoaromadendrone (222) is a suitable starting material for the synthesis of sesquiterpenes with a hydroazulene skeleton. This has been demonstrated with the synthesis of (–)-kessane (chapter 4), and a number of mono- and dihydroxy-aromadendranes (chapter 5). In this chapter is reported on the rearrangement reactions of derivatives of **222** to hydronaphthalene ringsystems. Hydronaphthalene sesquiterpenes that are closely related to the aromadendranes are the maalianes (**285**). The aristolanes (**286**) are another class of hydronaphthalene sesquiterpenes with a fused dimethyl cyclopropane ring. Selective opening of the cyclopropane ring between C2 and C3 in compounds with a maaliane skeleton would lead to compounds with an eudesmane skeleton (**287**).

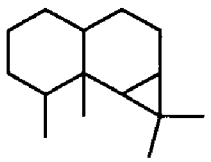
Figure 6.1



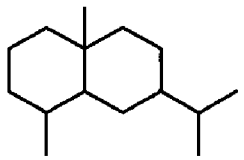
222



285



286



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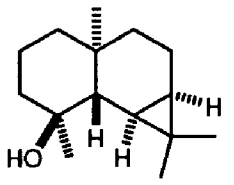
(+)-Maaliol (**288**), a representative of the maaliane sesquiterpenes, has been found in several plant species[1,2] and has been synthesized from (–)-epi-α-cyperone[3]. In this chapter the synthesis of **288** starting from (+)-aromadendrene (**2**) is described. Possible routes to synthesize aristolanes (**286**) or eudesmanes (**287**) from intermediates, obtained during the synthesis of **288**, will be described as well.



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* This chapter will be published in a revised form: Gijsen, H.J.M.; Wijnberg, J.P.B.A.; van Ravenswaay, C.; de Groot, Ae. *Tetrahedron* submitted.

6.2 Results and discussion

In the literature the rearrangement of a hydronaphthalene- to a hydrazulene skeleton is frequently seen[4]. Only a few examples are known of the reversed rearrangement reaction[5]. For aromadendrane derivatives the α-ketol rearrangement[6] of hydroazulenic α-ketol **289** to the hydronaphthalenic α-ketol **290** was investigated first.

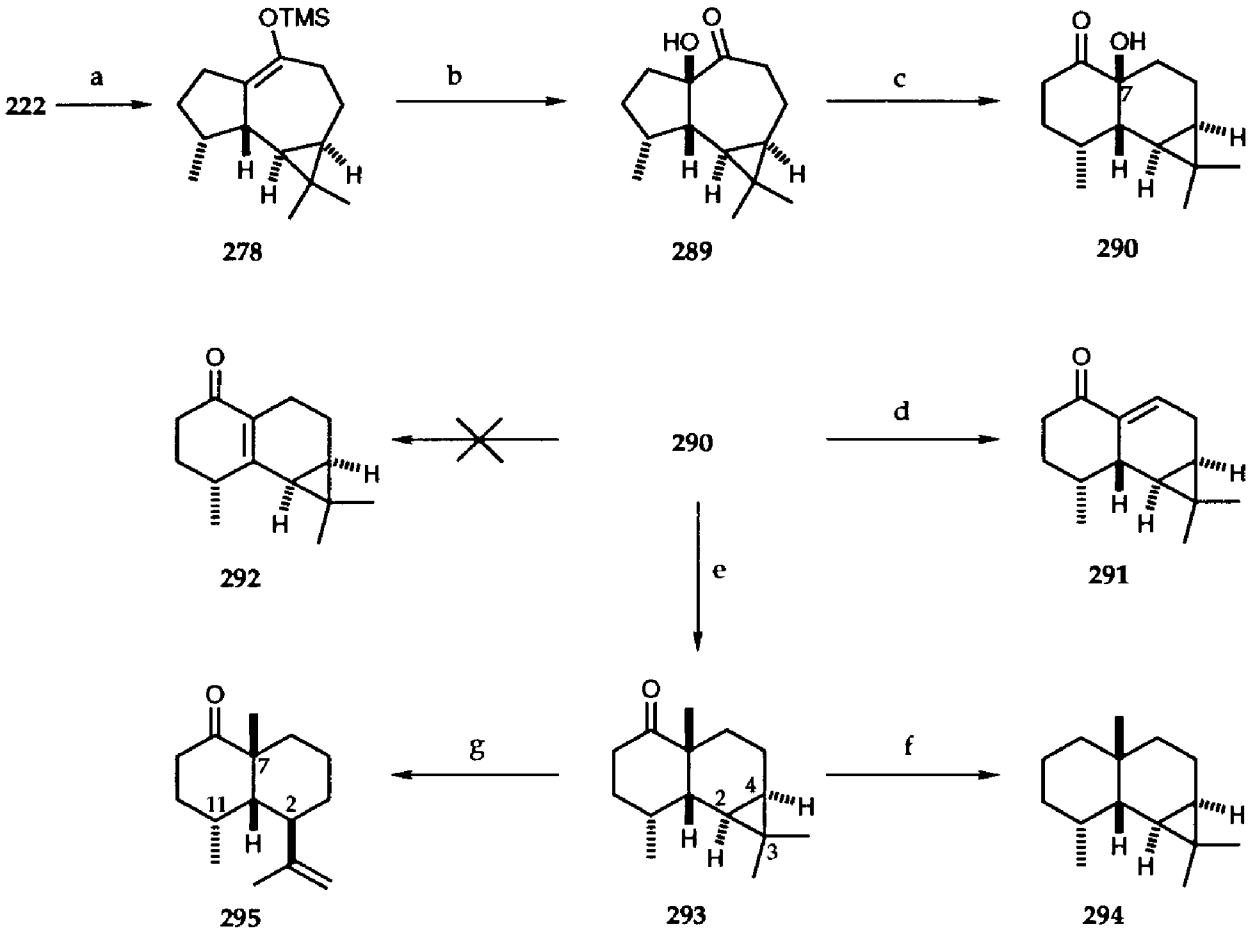
This α-ketol **289** was easily prepared from **222** via its thermodynamic enol trimethylsilylether **278**[7] (Scheme 6.1). Epoxidation with in situ generated dimethyldioxirane[8] and subsequent treatment with silica gel gave the α-ketol **289** in almost quantitative yield. The selective formation of the *cis*-fused ketol **289** must be the result of an attack from the sterically less hindered β side of the molecule[9]. Ketol **289** appeared to be unstable under gaschromatographic conditions and was partly converted into another product with, according to GC-MS analysis, the same molecular weight as **289**. This process could be imitated and improved by stirring a solution of **289** in EtOAc with neutral or basic Al_2O_3. In this way, the rearranged α-ketol **290** was obtained in 98 % yield. The stereochemistry of the hydroxyl group at C7 in **290** was confirmed by a crystal structure determination[10].

Acid-catalyzed dehydration of **290** gave the unsaturated ketone **291** as the sole product. Unfortunately, its C1-C7 double bond isomer **292** was not formed at all. Several other attempts to synthesize this compound were unsuccessful as well. Compound **292** was thought to be very useful in the synthesis of aristolanes (**286**), because introduction of an angular methyl group via a conjugate addition should give the aristolane skeleton. Also, the C1-C7 double bond in **292** would have directed cyclopropane ringopening to take place between C2 and C3, giving compounds that might have been useful in the synthesis of eudesmanes (**287**).

Replacement of the hydroxyl group of **290** by a methyl group via reaction with Li in NH_3, followed by addition of MeI[11], gave selectively the *cis*-fused ketone **293** in 72% yield. A Wolff-Kishner reduction gave the *cis*-fused maaliane **294** in 84% yield. The stereochemistry of the angular methyl group at C7 was difficult to establish. Due to overlap of the four methyl groups in the ^1H NMR spectrum of **293** and **294**, NOE measurements could not give a definite answer. After opening of the cyclopropane ring of **293** with concentrated aqueous HCl in refluxing EtOH, this problem could be solved. In the obtained product **295** the position of the isopropenyl group at C2 was determined with ^1H-^{13}C HETCOR and COSY experiments. NOE measurements on **295** showed the complete absence of a NOE between the angular methyl group at C7 and

the methyl group at C11, indicating a β position for the angular methyl group in compound **295**. From this it can be concluded that in the compounds **293** and **294** the angular methyl group also has the β position. As a consequence, this route could not be used in the synthesis of the *trans*-fused (+)-maaliol (**288**). Cyclopropane ringopening in the *cis*-maaliane derivative **293** took place between C3 and C4. This means that **293** is also not a useful intermediate for the synthesis of eudesmanes (**287**). A similar result has been found with *trans*-maaliane systems[12].

Scheme 6.1[a]

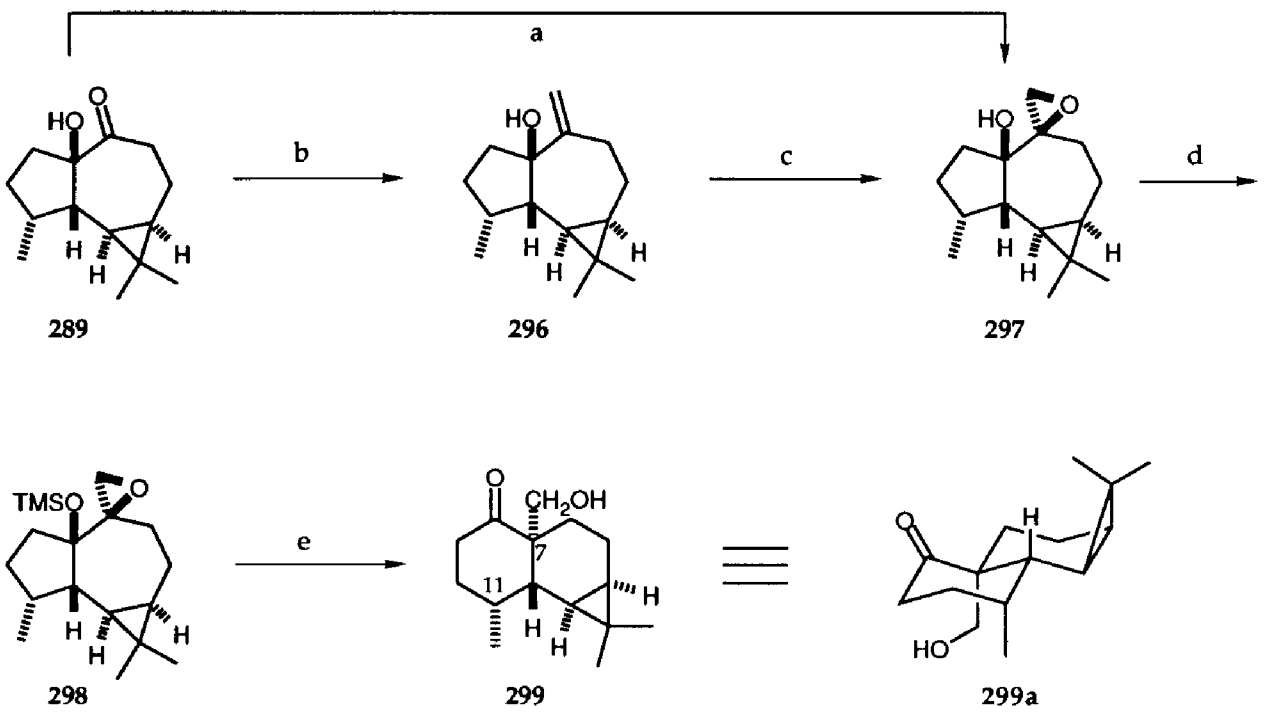


[a] (a) TMSCl, Et_3N, DMF, 130°C; (b) dimethyldioxirane; SiO_2; (c) Al_2O_3; (d);TsOH, benzene, Δ; (e) Li, NH_3, *t*BuOH; MeI; (f) N_2H_4, diethylene glycol, 100→200°C; (g) HCl, EtOH, Δ.

In a second approach towards (+)-maaliol (288) the C15 carbon atom was introduced before rearrangement of the hydroazulene skeleton. This approach is based on a recently reported reaction in which silylated 2,3-epoxy alcohols were rearranged to β-hydroxy ketones under the influence of Lewis acids[13]. The application of this method to our system required the synthesis of the epoxide **298**. This compound possesses the proper stereochemistry for the synthesis of *trans*-fused maaliane derivatives and should give the rearranged β-hydroxy ketone **299** upon treatment with a Lewis acid (Scheme 6.2).

The readily available α-ketol **289** was also the starting material in this approach. Treatment of **289** with trimethylsulfonium iodide[14] gave the epoxide **297** in a moderate yield (56 %). A much better yield of **297** was obtained when **289** was subjected to a Wittig olefination followed by a Sharpless epoxidation. The Wittig reaction required the protection of the hydroxyl group of **289** as its trimethylsilylether. Using lithium free conditions, i.e. potassium disilazide as a base[15], a high yield of the olefination product was obtained. After deprotection of the hydroxyl group with TBAF, the olefinic alcohol **296** was isolated in 96% overall yield from **289**.

Scheme 6.2[a]

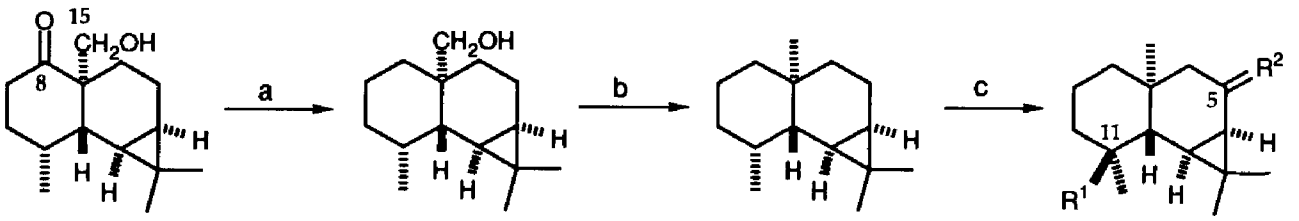


[a] (a) trimethylsulfonium iodide, KO*t*Bu, DMSO; (b) TMSCl, HMDS, pyridine; $Ph_3P{=}CH_2$; TBAF; (c) *t*BuOOH, $VO(Acac)_2$; (d) TMSCl, HMDS, pyridine; (e) $TiCl_4$, CH_2Cl_2, -78°C.

The compound **296** (8-hydroxy-alloaromadendrene) has been isolated from *Cassinia subtropica*[16] and has been synthesized previously in low yield via allylic oxidation[17] or microbial oxidation[18] of (–)-alloaromadendrene. Comparison of the spectral data of our synthetic **296** with those of the natural product shows that these compounds are identical, thus supporting our stereochemical assignments of the α-ketol **289** (vide supra). Sharpless epoxidation of **296** with *t*BuOOH/$VO(Acac)_2$[19] gave exclusively the β-epoxide **297**. Subsequent trimethylsilylation of the hydroxyl group gave **298** in 96% overall yield from **296**. Treatment of **298** with 1.1 equivalent of $TiCl_4$ in CH_2Cl_2 at -78°C afforded the rearranged product **299** in excellent yield (94%). NOE measurements on **299** showed a clear NOE between the angular hydroxymethyl group at C7 and the methyl group at C11, indicating the α-position of the angular hydroxymethyl group and a *trans*-fused ringsystem (formula **299a**).

Having established the *trans* ring junction in compound **299**, the next steps in our synthetic route towards (+)-maaliol (**288**) were the removal of the oxygen functions at C8 and C15, and the introduction of a β-hydroxyl group at C11. Our first attempt to remove the oxygen functions in **299** via reduction of the carbonyl group to a hydroxyl group, mesylation of both hydroxyl groups, and finally reduction of the mesylates failed. More successful was a stepwise removal of the oxygen functions. Conversion of **299** into its tosylhydrazone followed by reduction with $NaBH_3CN$ in the presence of $ZnCl_2$[20] afforded the alcohol **300** in 69% yield (Scheme 6.3). Although the conversion of the primary neopentyl-type hydroxyl group of **300** into its sulfonate esters (mesylate, tosylate or isopropylsulfonate[21]) proceeded smoothly, the subsequent reduction with Super-Hydride® gave only (tosylate, mesylate) or mainly (isopropylsulfonate) O-S bond cleavage. However, removal of this hydroxyl group could be achieved via reduction of its phosphordiamidate with Li in $EtNH_2$/*t*BuOH[22]. In this way the *trans*-fused maaliane **301** was obtained in 64% yield, together with 18% of **300**. Comparison of the spectral data of the maalianes **294** and **301** showed that these compounds are not identical, thus giving further evidence for our stereochemical assignments.

Scheme 6.3[a]



299 300 301

288: R^1=OH; R^2=2H
302: R^1=H; R^2=O
303: R^1=OH; R^2=O

[a] (a) tosylhydrazine, $NaBH_3CN$, $ZnCl_2$, MeOH, Δ; (b) n-butyllithium, bis(dimethylamino)chlorophosphoramidate; Li, $EtNH_2$, *t*BuOH; (c) RuO_2, $NaIO_4$, 50°C.

To complete the synthesis of (+)-maaliol (**288**), a β-hydroxyl group had to be introduced at C11 in compound **301**. It is known that tertiary C-atoms can be hydroxylated using a catalytic amount of ruthenium(IV)oxide (RuO_2) in combination with an excess of sodium periodate ($NaIO_4$)[7,23]. The application of this method to **301** afforded a mixture of three products, which was easily separated with column chromatography. GC-MS and NMR analysis of these products showed the formation of (+)-maaliol (**288**), the ketone **302**, and the hydroxy ketone **303**. Thus, oxidation had taken place at C11 as well as at C5 next to the dimethyl cyclopropane ring[24]. This has also been observed during oxidation of noraromadendrane (**251**) with $RuO_2/NaIO_4$, as described in chapter 5. When the oxidation reaction was allowed to continue long enough, the hydroxy ketone **303** was isolated as the sole product in 81% yield. Reductive removal of the carbonyl group would lead to (+)-maaliol, but this possibility has not been investigated further. Instead, the oxidation of **301** with $RuO_2/NaIO_4$ was performed with three equivalents of $NaIO_4$. In this way, an optimum yield (25%) of (+)-maaliol (**288**) was obtained, together with the starting material **301** (17%), the ketone **302** (28%), and the hydroxy ketone **303** (10%). Physical and spectroscopic data of our synthetic **288** are in agreement with those reported in the literature[2].

Starting from the readily available (+)-apoaromadendrone (**222**), two different routes to hydronaphthalene compounds with a maaliane skeleton have been developed, both in high overall yield. The first route leads to *cis*-fused maaliane derivatives; the other offers access to *trans*-fused maaliane sesquiterpenes, as demonstrated in this chapter in the synthesis of (+)-maaliol (**288**).

6.3 Experimental section

Melting points were determined on a Mettler FP80 HT and are uncorrected. Optical rotations were obtained from $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Bruker AC-E 200 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard in $CDCl_3$ as the solvent. Mass spectral data were determined on either an AEI MS 902 spectrometer or a Hewlett Packard 5970 B series MSD coupled with a Hewlett Packard 5890 A gas chromatograph with a DB-17 fused silica capillary column. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. 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. 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.

(–)-8-Hydroxy-alloaromadendrone (289). To a mixture of 400 mL of CH_2Cl_2, 400 mL of acetone, 400 mL of water, 1.0 g of 18-Crown-6, and 45 g of $NaHCO_3$ was added 300 mL of 0.29 M Oxone (87 mmol of $KHSO_5$) in water at 0°C. The mixture was stirred vigorously and then 16.68 g (60 mmol) of **278**[7] was added at 0°C. Stirring was continued for 1 h, after which time 250 mL of saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with three 250-mL portions of CH_2Cl_2. The combined organic layers were washed with 400 mL of 10% aqueous $Na_2S_2O_3$ and 400 mL of saturated aqueous $NaHCO_3$, and then dried. After evaporation of the solvent under reduced pressure, the residue was taken up in 200 mL of EtOAc and 50 g of silica gel was added. The mixture was stirred at room temperature for 18 h, filtered, and then evaporated under reduced pressure to yield 13.19 g (99%) of α-ketol **289**: mp 95°C (from methanol); $[\alpha]_D$ -76.7° (c 2.1); ^1H NMR δ 0.21 (dd, J = 9.1, 10.6 Hz, 1H), 0.72 (ddd, J = 5.2, 9.1, 12.0 Hz, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.96 (s, 3H), 0.99 (s, 3H), 1.24-1.51 (m, 3H), 1.68-2.01 (m, 3H), 2.36-2.63 (m, 3H), 2.95 (br s, 1H), 3.01 (ddd, J = 3.7, 5.1, 13.6 Hz, 1H); ^{13}C NMR δ 15.04 (q), 15.44 (q), 18.82 (s), 19.04 (t), 22.97(d), 26.93 (d), 27.96 (q), 30.50 (t), 35.93

(d), 35.93 (t) , 40.32 (t), 48.99 (d), 90.30 (s), 212.42 (s); mass spectrum, *m/e* (relative intensity) 222 (M^+, 46), 204 (32), 179 (39), 165 (85), 161 (100), 137 (79), 123 (62), 109 (71), 95 (58); calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1622. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.97. Found: C, 75.33; H, 9.92.

(+)-[1aR-(1aα,3aβ,7α,7aβ,7bα)]-Decahydro-3a-hydroxy-1,1,7-trimethyl-1*H*-cyclopropa-[a]naphthalen-4-one (290). To a solution of 7.70 g (35 mmol) of **289** in 100 mL of EtOAc was added 16 g of Al_2O_3. The reaction mixture was stirred at room temperature for 18 h, and then filtered. After evaporation of the solvent under reduced pressure, 7.56 g (98%) of **290** was obtained as a white solid: mp 104-105°C [from petroleum ether (bp 80-100°C)]; $[\alpha]_D$ +9.9° (c 0.81); ^1H NMR δ 0.28 (dd, J = 6.1, 9.2 Hz, 1H), 0.51-0.62 (m, 1H), 0.92 (s, 3H), 0.94 (d, J = 7.8 Hz, 3H), 0.99 (s, 3H), 0.99-1.14 (m, 1H), 1.34-1.54 (m, 2H), 1.67-2.13 (m, 4H), 2.10 (br s, 1H), 2.26 (ddd, J = 3.6, 5.7, 14.3 Hz, 1H), 2.44-2.66 (m, 1H), 2.78 (ddd, J = 8.0, 10.8, 14.2 Hz, 1H); ^{13}C NMR (C_6D_6) δ 15.03 (q), 16.92 (s), 16.92 (t), 17.53 (q), 18.95 (d), 19.99 (d), 27.99 (d), 27.99 (q), 29.44 (t), 32.12 (t), 36.19 (t), 44.59 (d), 75.55 (s), 210.73 (s); mass spectrum, *m/e* (relative intensity) 222 (M^+, 62), 204 (33), 179 (43), 165 (75), 161 (100), 137 (84), 123 (66), 109 (71), 95 (58); calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1623. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.97. Found: C, 75.47; H, 9.92.

(–)-[1aR-(1aα,7α,7aβ,7bα)]-1a,2,4,5,6,7,7a,7b-Octahydro-1,1,7-trimethyl-1*H*-cyclopropa-[a]naphthalen-4-one (291). To a solution of 1.10 g (5.0 mmol) of **290** in 75 mL of benzene was added 40 mg of *p*-toluenesulfonic acid. The mixture was heated at reflux for 2 h, allowed to come to room temperature, and then diluted with 40 mL of petroleum ether (bp 40-60°C). The organic layer was washed with two 50-mL portions of water, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [17:1 petroleum ether (bp 40-60°C)/EtOAc] to give 866 mg (85%) of **291**: $[\alpha]_D$ -71° (c 2.07); ^1H NMR δ 0.44 (d, J = 8.9 Hz, 1H), 0.65 (s, 3H), 0.67 (br t, J = 8.9 Hz, 1H), 0.90 (d, J = 6.9 Hz, 3H), 0.99 (s, 3H), 1.68-1.82 (m, 1H), 1.94-2.29 (m, 3H), 2.32-2.59 (m, 4H), 6.52 (dd, J = 4.1, 6.8 Hz, 1H); ^{13}C NMR δ 12.51 (q), 13.56 (q), 16.48 (s), 16.48 (d), 21.03 (t), 22.77 (d), 27.93 (q), 29.26 (t), 33.35 (d), 35.14 (d), 35.22 (t), 134.33 (d), 136.44 (s), 201.58 (s); mass spectrum, *m/e* (relative intensity) 204 (M^+, 17), 189 (8), 161 (46), 147 (25), 133 (25), 119 (22), 105 (100), 91 (68), 77 (43), 41 (63); calcd for $C_{14}H_{20}O$ (M^+) *m/e* 204.1514, found *m/e* 204.1513.

(+)-*cis*-Maali-8-one (293). To a mixture containing 630 mg (90 mmol) of lithium in 200 mL of dry NH_3 was added dropwise a solution of 4.44 g (20 mmol) of **290** and 1.88 mL (20 mmol) of dry *t*BuOH in 60 mL of dry ether over 5 min at -78°C. After stirring for 5 min, 4.4 mL (70 mmol) of MeI was added. The mixture was stirred at -78°C for 2.5 h, solid NH_4Cl was added, and NH_3 was evaporated overnight at room temperature. Then, 150 mL of water was added, and the aqueous layer was extracted with four 100-mL portions of ether. The combined organic layers were washed with 150 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [3:1 to 2:1 petroleum ether (bp 40-60°C)/CH_2Cl_2] to give 3.18 g (72%) of **293**: mp 63-64°C (from methanol); $[\alpha]_D$ +42.5° (c 1.7); ^1H NMR δ 0.25 (dd, J = 5.7, 9.3 Hz, 1H), 0.43-0.55 (m, 1H), 0.62-0.86 (m, 1H), 0.86 (s, 3H), 0.94 (s, 3H), 0.95 (d, J = 6.1 Hz, 3H), 1.13 (s, 3H), 1.20-1.37 (m, 2H), 1.68-2.04 (m, 4H), 2.16 (dt, J = 3.7, 15.4 Hz, 1H), 2.44-2.64 (m, 2H); ^{13}C NMR δ 15.13 (q), 15.45 (t), 16.48 (s), 18.25 (q), 19.38 (d), 20.04 (d), 26.53 (q), 28.58 (q), 28.73 (d), 29.51 (t), 32.22 (t), 37.15 (t), 44.36 (d), 46.50 (s), 216.05 (s); mass spectrum, *m/e* (relative intensity) 220 (M^+, 16), 205 (11), 177 (13), 159 (18), 151 (29), 125 (68), 107 (38), 93 (41), 82 (57), 41 (100); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1823. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.49; H, 11.14.

(+)-*cis*-Maaliane (294). A solution of 730 mg (3.3 mmol) of **293**, 4.2 g (75 mmol) of KOH and 2.69 mL (55 mmol) of hydrazine monohydrate in 25 mL of diethylene glycol was stirred at 100-110°C for 2.5 h. Water and hydrazine were then distilled off, and the mixture was stirred at 200°C for 4.5 h. After cooling, 100 mL of ice-water was added and the aqueous mixture extracted with three 75-mL portions of ether. The combined organic layers were washed with 75 mL of 0.4 N aqueous HCl solution, 75 mL of saturated aqueous $NaHCO_3$, 75 mL of brine, dried, and then evaporated under reduced pressure. The resulting product was flash chromatographed (n-pentane) to give 571 mg (84%) of **294**: $[\alpha]_D$ +83.1° (c 1.8); ^1H NMR δ 0.27 (dd, J = 5.0, 9.4 Hz, 1H), 0.52 (ddd, J = 1.7, 7.7, 9.4 Hz, 1H), 0.84 (d, J = 6.8 Hz, 3H), 0.87 (s, 3H), 0.89 (s, 3H), 0.98 (s, 3H), 0.91-1.65 (m, 10H), 1.65-1.87 (m, 1H), 1.90-2.12 (m, 1H); ^{13}C NMR δ 15.46 (t), 16.39 (s), 19.29 (q), 19.53 (d), 19.64 (d), 21.69 (t), 26.01 (q), 29.03 (t), 29.03 (2·q), 29.59 (d), 30.52 (t), 31.42 (s), 37.78 (t), 40.63 (d); mass spectrum, *m/e* (relative intensity) 206 (M^+, 12), 191 (8), 163 (29), 135 (14), 123 (18), 109 (76), 95 (32), 93 (32), 81 (100); calcd for $C_{15}H_{26}$ (M^+) *m/e* 206.2034, found *m/e* 206.2034.

(+)-[1R-(1α,4aβ,8β,8aβ)]-Decahydro-1,4a-dimethyl-8-(1-methylethenyl)-4(2*H*)-naphthalenone (295). To a solution of 179 mg (0.80 mmol) of **293** in 4.5 mL of ethanol was added 0.85 mL of concentrated aqueous HCl solution. The mixture was heated at reflux for 45 min, allowed to come to room temperature, and then diluted with 20 mL of ice-water. The aqueous solution was extracted with four 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of saturated aqueous $NaHCO_3$ solution followed by 20 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [20:1 petroleum ether (bp 40-60°C)/EtOAc] to give 120 mg (67%) of **295**: mp 65-65.5°C (from methanol); $[\alpha]_D$ +114° (c 0.47); ^{1}H NMR δ 0.79-0.96 (m, 1H), 1.06 (d, J = 7.3 Hz, 3H), 1.63 (s, 3H), 1.23-2.21 (m, 9H), 2.25 (ddd, J = 1.6, 5.7, 16.5 Hz, 1H), 2.41-2.68 (m, 2H), 4.58 (br s, 1H), 4.68 (br s, 1H); ^{13}C NMR δ 18.44 (q), 19.73 (q), 22.30 (t), 27.49 (t), 28.21 (q), 30.52 (d), 34.60 (t), 35.75 (t), 37.58 (t), 45.56 (d), 50.47 (s), 50.85 (d), 111.00 (t), 150.27 (s), 215.41 (s); mass spectrum, *m/e* (relative intensity) 220 (M^+, 11), 205 (4), 177 (5), 149 (11), 135 (11), 125 (100), 107 (29), 93 (34), 67 (39), 41 (72); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1827. Anal. Calcd for $C_{14}H_{22}O_2$: C, 81.76; H, 10.98. Found: C, 81.46; H, 10.95.

(–)-8-Hydroxy-alloaromadendrene (296). To a stirred solution of 5.55 g (25 mmol) of **289** in 80 ml of dry pyridine was added 18.7 mL of hexamethyldisilazane (HMDS) and 9.4 mL of TMSCl. The reaction mixture was stirred at room temperature for 15 min, and then concentrated under reduced pressure. The resulting residue was flash chromatographed [40:1 petroleum ether (bp 40-60°C)/EtOAc] to give 7.29 g (100%) of a colourless oil [^{1}H NMR δ 0.04 (s, 9H), 0.15 (dd, J = 8.9, 11.5 Hz, 1H), 0.66 (ddd, J = 5.4, 8.9, 11.4 Hz, 1H), 0.86 (d, J = 7.0 Hz, 3H), 0.92 (s, 3H), 0.97 (s, 3H), 1.15-1.93 (m, 6H), 2.20-2.43 (m, 2H), 2.61 (ddd, J = 3.2, 8.2, 13.2 Hz, 1H), 3.10 (ddd, J = 2.4, 6.8, 13.2 Hz, 1H); ^{13}C NMR δ 1.49 (3·q), 14.83 (q), 15.22 (q), 18.73 (s), 18.99 (t), 23.36 (d), 26.13 (d), 27.92 (q), 32.32 (t), 34.03 (t), 35.74 (d), 40.52 (t), 51.70 (d), 93.11 (s), 211.80 (s); mass spectrum, *m/e* (relative intensity) 294 (M^+, 38), 251 (33), 237 (81), 209 (8), 169 (10), 155 (19), 119 (12), 105 (19), 73 (100), 41 (31)] which was used immediately for the next reaction.

To a suspension of 8.75 g (24.5 mmol) of methyltriphenylphosphonium bromide in 80 mL of dry THF was added dropwise 37 mL of 0.66 M (26 mmol) potassium hexamethyldisilazide in toluene at -78°C. Then a solution of 3.86 g (13.2 mmol) of the above-mentioned colourless oil in 45 mL of dry THF and 5 mL of dry N,N'-dimethylpropylene urea (DMPU) was added slowly at -78°C. The reaction mixture was allowed to warm to room temperature over a 3-h period and then poured into 200 mL of ice-water. The aqueous solution was extracted with four 80-mL portions of petroleum

ether (bp 40-60°C). The combined organic layers were washed with 100 mL of brine, dried, and then evaporated under reduced pressure. The remaining residue was flash chromatographed [20:1 petroleum ether (bp 40-60°C)/EtOAc] to give 3.205 g (83%) of the trimethylsilylether of **296** [^{1}H NMR δ 0.04 (s, 9H), 0.08 (dd, J = 9.1, 11.8 Hz, 1H), 0.64 (br dt, J = 6.8, 9.6 Hz, 1H), 0.90 (d, J = 7.1 Hz, 3H), 0.93 (s, 3H), 0.96 (s, 3H), 1.16-2.00 (m, 6H), 2.10-2.30 (m, 2H), 2.35-2.60 (m, 2H), 4.83 (br s, 1H), 4.91 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ 1.73 (3·q), 15.75 (q), 16.41 (q), 17.56 (s), 20.97 (t), 23.03 (d), 25.05 (d), 28.36 (q), 30.03 (t), 32.09 (t), 33.57 (d), 34.89 (t), 50.87 (d), 90.65 (s), 111.73 (t), 152.41 (s); mass spectrum, *m/e* (relative intensity) 292 (M^+, 6), 277 (16), 251 (8), 223 (33), 202 (8), 187 (10), 159 (17), 117 (14), 91 (24), 73 (100)] and 0.379 g (13%) of **296**. The trimethylsilylether of **296** (3.205 g) was dissolved in 35 mL of THF and 20 mL of 1.1 M TBAF in THF was added. After stirring at room temperature for 10 min, 75 mL of water and 60 mL of petroleum ether (bp 40-60°C) were added. The two-phase mixture was separated, and the aqueous layer was extracted with two 60-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 75 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [10:1 petroleum ether (bp 40-60°C)/EtOAc] to give another 2.410 g (overall yield from **289**: 96%) of **296**: mp 55.5°C (from CH_3CN); $[\alpha]_D$ -153° (c 1.3) (lit.[17]:-105°); ^{1}H NMR data were identical to those reported in the literature[16-18]; ^{13}C NMR δ 15.58 (q), 16.33 (q), 17.81 (s), 20.94 (t), 22.99 (d), 25.05 (d), 28.28 (q), 30.27 (t), 31.75 (t), 33.97 (d), 36.17 (t), 48.71 (d), 88.23 (s), 111.41 (t), 152.61 (s); the mass spectrum was consistent with that reported in the literature[16]. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.97. Found: C, 81.44; H, 11.02.

(–)-8-Hydroxy-alloaromadendrene-β-epoxide (297). To a solution of 2.22 g (10 mmol) of **289** in 20 mL of dry DMSO was added subsequently 3.06 g (15 mmol) of trimethylsulfonium iodide and 1.40 g of KO*t*Bu. The reaction mixture was stirred at room temperature for 1.5 h, poured into 100 mL of ice-water, and extracted with four 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 75 mL of water, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [8:1 to 5:1 petroleum ether (bp 40-60°C)/EtOAc] to give 1.336 g (56%) of **297**: mp 104-105°C [from petroleum ether (bp 80-100°C)]; $[\alpha]_D$ -57.7° (c 0.8); ^{1}H NMR δ 0.20 (dd, J = 9.1, 11.5 Hz, 1H), 0.61 (ddd, J = 5.5, 9.1, 11.5 Hz, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.97 (s, 3H), 1.00 (s, 3H), 1.07-1.46 (m, 4H), 1.67-1.87 (m, 4H), 1.88 (s, 1H), 2.33-2.57 (m, 2H), 2.65 (d, J = 4.4 Hz, 1H), 2.8 (dd, J = 2.1, 4.4 Hz, 1H); ^{13}C NMR δ 15.08 (2 x q), 18.92 (s), 19.28 (t), 24.10 (d), 25.31 (d), 28.28 (q), 31.98 (t), 32.20 (t), 35.65 (d), 35.65 (t), 49.26

(d), 54.27 (t), 61.47 (s), 87.00 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 6), 218 (13), 205 (43), 193 (28), 175 (55), 163 (100), 121 (69) 107 (64), 93 (71); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1778. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 76.27; H, 10.39.

To a solution of 2.20 g (10.0 mmol) of **296** in 80 mL of benzene was added 150 mg of $VO(Acac)_2$ and 5.0 mL of 3.0 M (15 mmol) *t*BuOOH in isooctane. The reaction mixture was stirred for 2.5 h at room temperature and then 100 mL of 10% aqueous $Na_2S_2O_3$ was added. The two-phase mixture was separated, and the aqueous layer was extracted with two 50-mL portions of EtOAc. The combined organic layers were washed with 60 mL of brine, dried, and then evaporated under reduced pressure to give 2.32 g (98%) of crude **297**.

Trimethylsilylether 298. To a stirred solution of 2.32 g of crude **297** in 20 mL of dry pyridine was added 3.8 mL of hexamethyldisilazane (HMDS) and 1.9 mL of TMSCl. The reaction mixture was stirred at room temperature for 20 min, and then concentrated under reduced pressure. The resulting residue was flash chromatographed [50:1 petroleum ether (bp 40-60°C)/EtOAc] to give 2.97 g (96% from **296**) of pure **298**: ^1H NMR δ 0.10 (s, 9H), 0.16 (dd, J = 9.0, 11.6 Hz, 1H), 0.57 (ddd, J = 4.6, 9.0, 12.1 Hz, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.96 (s, 3H), 0.98 (s, 3H), 1.01-1.54 (m, 4H), 1.61-1.83 (m, 4H), 2.15-2.40 (m, 1H), 2.47-2.63 (m, 3H); ^{13}C NMR δ 2.11 (3·q), 14.84 (q), 15.03 (q), 18.74 (s), 19.54 (t), 24.70 (d), 25.66 (d), 28.31 (q), 33.11 (t), 33.40 (t), 34.85 (t), 35.73 (d), 52.42 (d), 53.23 (t), 60.73 (s), 89.94 (s); mass spectrum, *m/e* (relative intensity) 308 (M^+, 6), 278 (23), 235 (100), 209 (39), 193 (27), 183 (24), 157 (16), 131 (16), 73 (73); calcd for $C_{15}H_{32}O_2Si$ (M^+) *m/e* 308.2171, found *m/e* 308.2171.

(–)-15-Hydroxy-*trans*-maali-9-one (299). To a solution of 2.00 g (6.5 mmol) of **298** in 28 mL of dry CH_2Cl_2 was added 7.15 mL of 1.0 M (7.15 mmol) $TiCl_4$ in CH_2Cl_2 at -78°C. The reaction mixture was stirred at -78°C for 15 min, and then 40 mL of 1 N aqueous HCl solution was added. After dilution with 40 mL of water, the two-phase mixture was separated, and the aqueous layer was extracted with three 40-mL portions of CH_2Cl_2. The combined organic layers were washed with 50 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [2:1 petroleum ether (bp 40-60°C)/EtOAc] to give 1.448 g (94%) of **299**:

mp 137-138°C [from petroleum ether (bp 80-100°C)]; $[\alpha]_D$ -75.1° (c 0.7); ^1H NMR δ 0.52-0.86 (m, 2H), 0.90 (s, 3H), 0.99 (s, 3H), 1.17 (d, J = 7.3 Hz, 3H), 1.47-1.67 (m, 3H), 1.72-2.13 (m, 6H), 2.22 (dt, J = 4.0, 14.5 Hz, 1H), 2.78 (ddd, J = 6.4, 12.5, 14.5 Hz, 1H), 3.89 (br d, J = 11.4 Hz, 1H), 4.07 (br d, J = 11.4 Hz, 1H); ^{13}C NMR δ 14.88 (q), 15.26 (t), 15.37 (q), 18.35 (s), 19.39 (d), 21.67 (d), 25.30 (t), 28.96 (q), 31.08 (d), 32.64 (t), 34.38 (t), 42.74 (d), 53.69 (s), 62.85 (t), 215.65 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 4), 220 (13), 206 (42), 189 (40), 163 (75), 147 (51), 145 (51), 137 (45), 111 (56), 83 (100); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.33; H, 10.41.

(–)-15-Hydroxy-*trans*-maaliane (300). To a solution of 1.18 g (5.0 mmol) of **299** in 5 mL of MeOH was added 1.07 g (5.75 mmol) of tosylhydrazine. The mixture was heated at reflux for 2 h, and 15 mL of MeOH was added followed by a solution of 419 mg (6.67 mmol) of $NaBH_3CN$ and 467 mg (3.33 mmol) of $ZnCl_2$ in 13 mL of MeOH. After stirring at reflux temperature for 3 h, 100 mL of 0.1 N aqueous NaOH solution was added. The resulting mixture was filtered over celite, and extracted with four 60-mL portions of EtOAc. The combined organic layers were washed with 75 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 767 mg (69%) of **300**: mp 127-128°C (from n-heptane); $[\alpha]_D$ -21° (c 1.2); ^1H NMR δ 0.40 (dd, J = 6.5, 9.1 Hz, 1H), 0.51 (dt, J = 7.2, 13.2 Hz, 1H), 0.61 (t, J = 8.4 Hz, 1H), 0.64-0.83 (m, 1H), 0.94 (d, J = 7.4 Hz, 3H), 0.95 (s, 3H), 0.99 (s, 3H), 1.05 (br s, 1H), 1.17 (dd, J = 5.2, 6.4 Hz, 1H), 1.30-1.92 (m, 9H), 3.70 (br d, J = 11.0 Hz, 1H), 3.83 (br d, J = 11.0 Hz, 1H); ^{13}C NMR δ 15.10 (q), 15.60 (q), 16.00 (t), 16.94 (t), 18.03 (s), 19.76 (d), 22.04 (d), 29.31 (q), 32.10 (d), 33.54 (t), 33.62 (t), 34.06 (t), 37.20 (s), 41.93 (d), 62.09 (t); mass spectrum, *m/e* (relative intensity) 222 (M^+, 1), 204 (2), 191 (81), 161 (10), 135 (79), 121 (20), 109 (56), 91 (49), 67 (59), 41 (100); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1983, found *m/e* 222.1983. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.72; H, 11.84.

(–)-*trans*-Maaliane (301). To a solution of 666 mg (3.0 mmol) of **300** in 20 mL of dry THF and 5 mL of TMEDA was added dropwise a solution of 3.0 mL of 1.5 M n-butyllithium in hexane at 0°C. The mixture was stirred for 30 min at 0°C, and 2 h at room temperature. The resulting solution was then cooled to 0°C and 3 mL (20 mmol) of bis(dimethylamino)-chlorophosphoramidate added. The solution was allowed to warm to room temperature and stirred overnight. Then 40 mL of saturated aqueous $NaHCO_3$ solution was added at 0°C, and the mixture was extracted with four 30-mL portions of EtOAc. The combined organic layers were washed with 40 mL of brine, dried on K_2CO_3, and then evaporated under reduced pressure. The resulting phosphordiamidate was used immediately for the next reaction.

To a mixture containing 300 mg (43 mmol) of lithium in 40 mL of dry $EtNH_2$ was added dropwise a solution of the crude phosphordiamidate in 20 mL of dry THF and 0.75 mL of dry *t*BuOH over 30 min under an argon atmosphere. After stirring for an additional 10 min, sufficient solid NH_4Cl was added to destroy the excess lithium. Then, 50 mL of water was added, and the aqueous layer was extracted with four 30-mL portions of pentane. The combined organic layers were washed with 40 mL of 1 N aqueous HCl solution, 40 mL of brine, dried over K_2CO_3, and then carefully concentrated under atmospheric pressure. The resulting residue was flash chromatographed (pentane) to give 397 mg (64%) of **301** as a colourless oil: $[\alpha]_D$ -11.1° (c 0.57); ^1H NMR δ 0.40- 1.03 (m, 4H), 0.88 (s, 3H), 0.91 (s, 3H), 0.99 (s, 3H, 1.01 (d, J = 8.7 Hz, 3H), 1.22-1.93 (m, 10H); ^{13}C NMR δ 14.94 (q), 15.17 (q), 15.76 (t), 17.02 (s), 17.27 (t), 19.12 (q), 19.74 (d), 22.68 (d), 29.42 (q), 31.82 (s), 32.61 (d), 33.95 (t), 40.34 (t), 41.18 (t), 41.27 (d); mass spectrum, *m/e* (relative intensity) 206 (M^+, 8), 191 (41), 163 (21), 150 (28), 135 (34), 123 (31), 109 (70), 82 (90), 81 (100), 41 (99); calcd for $C_{15}H_{26}$ (M^+) *m/e* 206.2034, found *m/e* 206.2034. Further elution [10:1 petroleum ether (bp 40-60°C)/EtOAc] provided 120 mg (18%) of **300**.

(+)-Maaliol (288). To a bottle containing 4 mL of CCl_4, 4 mL of CH_3CN, 6 mL of H_2O, and 600 mg (2.8 mmol) of $NaIO_4$ was added 192 mg (0.93 mmol) of **301** and 10 mg of $RuO_2 \cdot xH_2O$. The bottle was closed air-tight and rotated around its axis in a waterbath of 50°C until the colour of the mixture had turned from yellow to black (5 h). The reaction mixture was filtered through celite, and the filter cake was washed with 25 mL of H_2O and 20 mL of CH_2Cl_2. The combined filtrates were separated, and the aqueous layer was extracted with three 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of aqueous 10% $Na_2S_2O_3$ and 20 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash

chromatographed [20:1 to 3:1 petroleum ether (bp 40-60°C)/EtOAc] to give, in order of elution, 33 mg (17%) of **301**, 58 mg (28%) of **302**, 52 mg (25%) of **288**, and 23 mg (10%) of **303**.

288: mp 101.5-102.5°C (from n-heptane) (lit.[2]: 103°C); $[\alpha]_D$ +35.1° (c 0.57), (lit.[2]: +32.6°), +20° (c 0.33 in ethanol) (lit.[3]: +18.4 in ethanol); ^{1}H NMR δ 0.47 (dd, J = 6.1, 9.2 Hz, 1H), 0.55-0.82 (m, 2H), 0.83 (s, 3H), 0.91 (s, 3H), 1.01 (s, 3H), 1.22 (s, 3H), 0.85-1.61 (m, 9H), 1.66-1.88 (m, 2H); ^{13}C NMR δ 15.29 (q), 15.29 (t), 17.31 (s), 18.55 (q), 18.96 (d), 19.58 (d), 19.93 (t), 22.81 (q), 28.94 (q), 32.81 (s), 39.41 (t), 41.04 (t), 42.50 (t), 49.42 (d), 72.58 (s); the mass spectrum was consistent with that reported in the literature[2]. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.89; H, 11.82.

302: $[\alpha]_D$ +220° (c 0.73); ^{1}H NMR δ 0.95 (s, 3H), 1.06 (d, J = 7.4 Hz, 3H), 1.14 (s, 3H), 1.17 (s, 3H), 1.13-1.74 (m, 10H), 1.88 (dd, J = 1.2, 16.5 Hz, 1H), 1.96-2.14 (m, 1H); ^{13}C NMR δ 14.90 (q), 16.24 (t), 16.49 (q), 20.66 (q), 28.63 (s), 29.45 (q), 31.65 (d), 32.57 (d), 33.20 (t), 36.32 (d), 39.67 (s), 39.68 (t), 41.71 (d), 58.26 (t), 209.64 (s); mass spectrum, *m/e* (relative intensity) 220 (M^+, 20), 205 (12), 177 (51) 161 (31), 149 (36), 121 (33), 109 (52), 107 (64), 96 (66), 81 (53), 67 (54), 41 (100); calcd for $C_{15}H_{24}O$ (M^+) *m/e* 220.1827, found *m/e* 220.1827.

303: mp 130-130.5°C (from n-heptane); $[\alpha]_D$ +17° (c 1.1); ^{1}H NMR δ 0.93 (s, 3H), 1.15 (s, 3H), 1.19 (br t, J = 10.8 Hz, 1H), 1.20 (s, 3H), 1.30 (s, 3H), 1.32-1.68 (m, 8H), 1.74 (d, J = 16.5 Hz, 1H), 1.82-1.93 (m, 1H), 1.99 (dd, J = 1.5, 16.5 Hz, 1H) ; ^{13}C NMR δ 16.59 (q), 19.56 (q), 19.92 (t), 22.89 (q), 28.86 (s), 29.03 (q), 30.07 (d), 35.68 (d), 38.82 (t), 40.64 (s), 42.58 (t), 49.59 (d), 57.90 (t), 72.53 (s), 208.93 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 2), 218 (68), 203 (33), 178 (50), 161 (65), 121 (46), 107 (66), 85 (63), 83 (100), 59 (89); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.96; H, 10.54.

In a similar experiment 171 mg (0.83 mmol) of **301** was treated with 2.14 g (10 mmol) of $NaIO_4$ for 96 h to yield, after workup and flash chromatography [4:1 petroleum ether (bp 40-60°C)/EtOAc], 159 mg (81%) of **303**.

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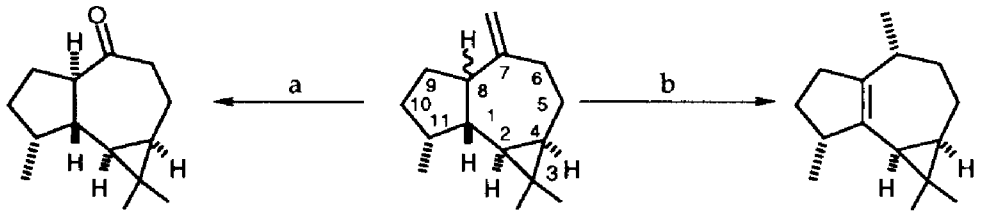
7 Thermal rearrangements of bicyclogermacrane-1,8-dione The synthesis of humulenedione and (–)-cubenol, starting from natural (+)-aromadendrene*

Abstract: *Treatment of a distillation tail of Eucalyptus globulus, containing mainly (+)-aromadendrene (2) and (–)-alloaromadendrene (3), with K/Al_2O_3 gives a quantitative conversion of 2 and 3 into isoledene (224). Oxidative cleavage of the central double bond in 224 produces (+)-bicyclogermacrane-1,8-dione (304). Thermal rearrangement of 304 gives via a homo [1,5] hydrogen shift at relatively low temperature the humulenedione 310, and at higher temperature (FVP) the products 312 and 313 both with a cadinane skeleton. The naturally occurring humulenedione (7) and (–)-cubenol (309) can be synthesized starting from 6 and 9, respectively.*

7.1 Introduction

Ozonolysis of the crude distillation tail of the oil of *Eucalyptus globulus*[1], without applying any purification procedure beforehand, can be used to obtain large quantities of pure (+)-apoaromadendrone (**222**) (see chapter 3). As described in chapter 4-6, ketone **222** has proven to be an excellent chiral starting material in the synthesis of natural products from several classes of sesquiterpenes.

Scheme 7.1[a]



222 **2**: αH, **3**: βH **224**

[a] (a) O_3; (b) K/Al_2O_3.

Isomerization of the exocyclic double bond in **2** and/or **3** might be another possibility to obtain a suitable chiral synthon for further synthesis. In the literature the isomerization of **2** to isoledene (**224**) under the influence of potassium on aluminum oxide (K/Al_2O_3) has been described[2] (Scheme 7.1). Application of this reagent on the above-mentioned, crude distillation tail might give isoledene (**224**) without laborious isolation and purification procedures.

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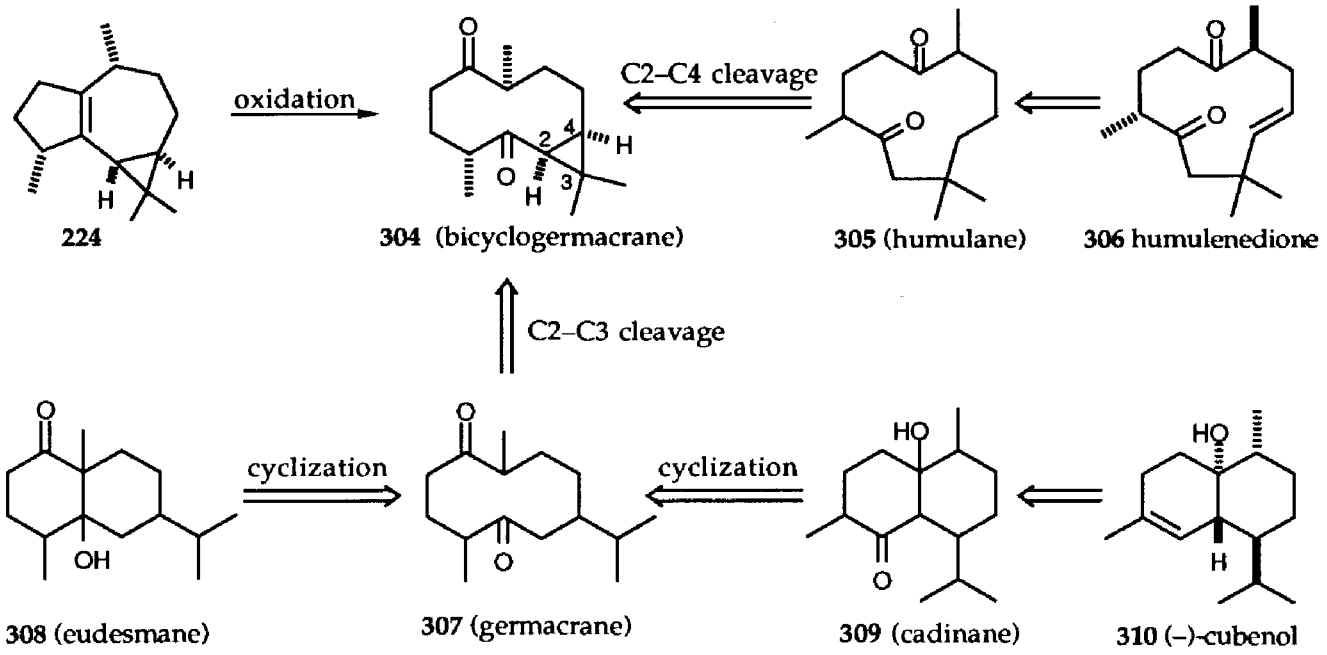
* This chapter will be published in a revised form: Gijsen, H.J.M; Wijnberg, J.B.P.A.; de Groot, Ae. *Tetrahedron* submitted.

Oxidative cleavage of the C1-C8 double bond in **224** will give the diketone **304**, which possesses the *bicyclogermacrane* skeleton. Bicyclogermacrane-1,8-dione (**304**) has the capability of being transformed into a variety of chiral derivatives and naturally occurring sesquiterpenes (Scheme 7.2). Cleavage of the C2–C3 or C2–C4 bond of the fused cyclopropane ring may lead to diones with a *germacrane* (**307**) or *humulane* (**305**) skeleton, respectively. Intramolecular aldol condensations with the dione having a germacrane skeleton should give *eudesmanes* (**308**) and/or *cadinanes* (**309**)[3]. The usefulness of this approach is demonstrated in the first syntheses of humulenedione (**306**) and (–)-cubenol (**310**). The humulane sesquiterpene **306** has been isolated from *Lippia integrifolia* recently[4]. The cadinane sesquiterpene (–)-cubenol has been found in many plant species[5]. Recently the cell-destroying activity of (–)-cubenol against red tide planktons has been reported[6].

Scheme 7.2



7.2 Results and discussion

The distillation tail of the oil of *Eucalyptus globulus*, used in the isomerization experiments, contained, according to GC analysis, 66% of **2** and 14% of **3**. Application of K/Al_2O_3 on this crude distillation tail gave an oil in 94% yield which contained, according to GC analysis, 85% of **224** (Scheme 7.1). This means that both **2** and **3** are quantitatively converted into **224**. It should be noted that the same reaction conditions applied on (–)-α-gurjunene[7] did not give any **224**. Without further purification, the

C1–C8 double bond in **224** (85% pure) was oxidized using ruthenium(IV)oxide (RuO_2) and sodium periodate ($NaIO_4$) in a mixture of CCl_4, MeCN, and H_2O at 45–50°C to give the bicyclogermacrane-1,8-dione (**304**) which was easily purified by means of flash chromatography. Via this procedure 7.8 g of pure **304** could be obtained from a 10 g-sample of the crude distillation tail and in this way a second route to a useful chiral synthon derived from the aromadendrenes in *Eucalyptus* oil is available.

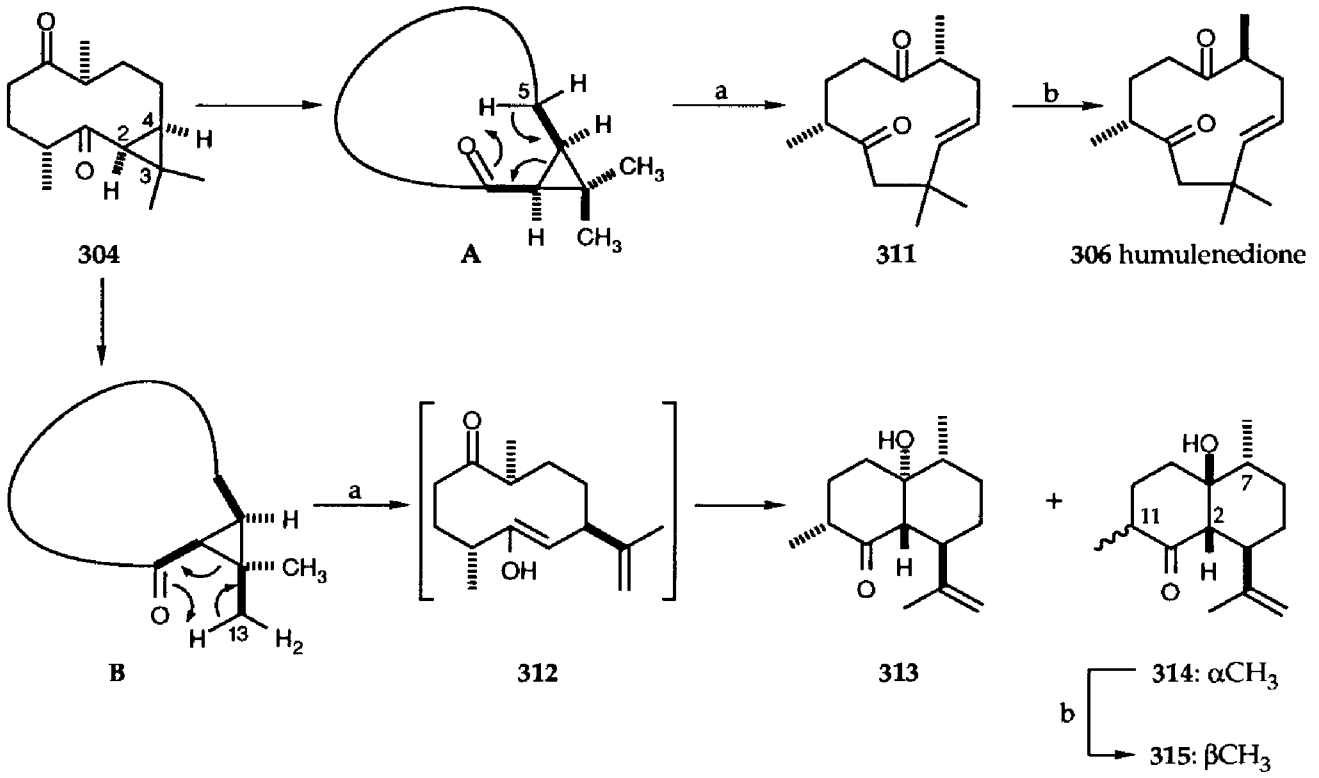
Initial experiments showed that **304** is unstable at elevated temperatures. Heating of **304** in refluxing xylene afforded a 1:1:1 mixture of **311**, **313**, and **314**. When dioxane (bp 101°C) was used instead of xylene (bp ca 140°C) for the pyrolysis of **304**, predominantly **311** was formed. After a reflux periode of 8 days, the yield of isolated **311** was 81%. The influence of higher temperatures on the thermal rearrangement of **304** was investigated with flash vacuum pyrolysis (FVP). The use of high-boiling solvents for these thermal rearrangements is unattractive because of difficulties to be expected in workup and purification procedures. With FVP at a temperature of 500°C **313** and **314** were obtained in 55 and 40%, respectively.

These results can be explained with two competing homo [1,5] hydrogen shifts[8-10], represented as in the partial structures **A** and **B** (Scheme 7.3). In both **A** and **B** the requirement of a *cis* relationship between the carbonyl and alkyl group (C5 and C13, respectively) is present. The reaction path via **A** gives directly the humulane **311** via cleavage of the C2-C4 bond of the cyclopropane ring. The ^1H NMR spectrum of **311** measured in $CDCl_3$ did not give a clear answer about the *cis* or *trans* relationship of the double bond in **311**. By using C_6D_6 as a solvent, the coupling constants of the vinylic proton signals could be established, indicating a *trans*-double bond. This was confirmed by treatment of **311** with $NaOCH_3$ in CH_3OH, giving the epimerized **306**, whose spectral data are in full agreement with those reported for the natural *trans*-humulenedione, isolated from *Lippia integrifolia*[4]. Unfortunately, during this epimerization some racemization took place.

If reaction path **B** is followed (cleavage of the C2-C3 bond of the cyclopropane ring), compound **312** with a *germacrane* skeleton must be an intermediate. A subsequent non-selective aldol cyclization of **312** leads to the cadinanes **313** and **314**. Since NMR analysis (NOE in combination with coupling constants) could not give a definite answer about the stereochemistry of the tertiary hydroxyl group in **313** as well as in **314**, the assignment was based on indications obtained from chemical experiments. Upon treatment with 1 M $NaOCH_3$ in CH_3OH **313** did not react, whereas **314** largely epimerized to **315**. From these results it was concluded that in **313** all the alkyl substituents have an equatorial orientation, and that the ring junction is *trans*. The most likely structure for **314** is thought to be the *cis*-fused isomer of **313**. The relatively

bulky isopropenyl and the methyl group at C7 both possess the equatorially orientation in this structure, the methyl group at C11, on the other hand, is axially oriented. Thus, epimerization at C11 leading to **315** will be an easy process. Epimerization at C2 is not likeky because in that case the isopropenyl group and the methyl group at C7 both should adopt the unfavorable axial orientation.

Scheme 7.3[a]

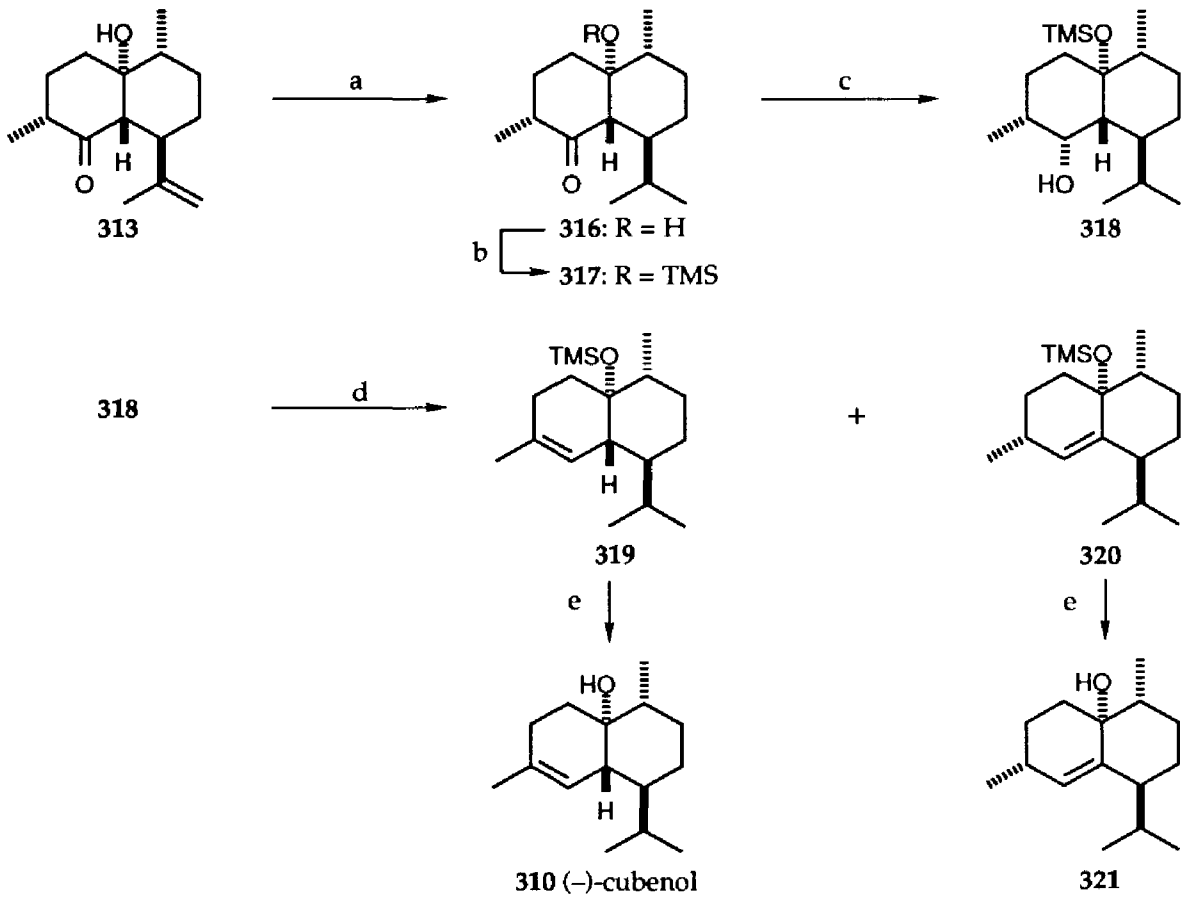


[a] (a) xylene, Δ; (b) NaOMe, MeOH.

Since the stereochemistry of **313**, as proposed here, is identical to that of (–)-cubenol (**310**), compound **313** can be considered as an ideal starting material for the synthesis of natural (–)-cubenol. Therefore, to develop an effective synthesis of **310** the yield of **313** in the thermal rearrangement reaction had to be improved. This could be done by further elevating the temperature in the FVP reaction. An optimum yield (71%) of **313** was found at a FVP temperature of 700°C. At this temperature the yield of **314** was diminished to 19%. Higher temperatures decreased the yield of **313** (and **314**) because of charring and desintegration.

The next step towards **310** was the reduction of the double bond in **313**. Upon hydrogenation with H_2 and Pt/C at 60 psi, **313** was quantitatively converted into **316** (Scheme 7.4). The planned transformation of the carbonyl group into a double bond (**316** → **310**) via the Bamford-Stevens reaction[11] was not possible because the tosylhydrazone of **316** could not be prepared. The alternative conversion of **316** into **310** via reduction and dehydration requires the protection of the angular hydroxyl group at C8. However, this axial hydroxyl group proved to be very unreactive. Various methods to prepare trimethylsilylethers were unsuccessful. Finally, it was found that this conversion could be realized after prolonged heating (5 days, 120°C) of a solution of **316** in DMF in the presence of TMSCl and Et_3N. In this way the trimethylsilylether **317** was formed in 91% yield. It should be noted that these reaction conditions have been used previously to prepare enol trimethylsilylethers from ketones (see chapter 5). In this specific case however, no enol silylether formation was observed at all, which confirmed the unreactivity of this carbonyl group. Reduction with $LiAlH_4$, however, proceeded without any difficulty and afforded the alcohol **318** in good yield.

Scheme 7.4[a]



a (a) H_2, Pt/C, 60 psi; (b) TMSCl, Et_3N, DMF, 120°C; (c) $LiAlH_4$; (d) $SOCl_2$; (e) TBAF.

Subsequent dehydration of **318** with $SOCl_2$ in pyridine gave an inseparable 3 : 2 mixture of two double bond isomers **319** and **320**, respectively. Removal of the protecting trimethylsilyl group with TBAF, followed by separation by means of column chromatography finally gave (–)-cubenol (**310**) together with its double bond isomer **321** in 44 and 31% overall yield from **317**, respectively. The physical and spectroscopic data of the synthetic **310** are in full agreement with those reported in the literature[5], thereby supporting the original assignment of the stereochemistry of **313**.

Besides the synthesis of *humulanes* or *cadinanes* like humulenedione or (–)-cubenol, respectively, it also might be possible to prepare sesquiterpenes with a *bicyclogermacrane*, a *germacrane*, or an *eudesmane* skeleton from **304**. These possibilities may considerably enlarge the synthetic applicability of synthon **304** and thus also of (+)-aromadendrene (**2**).

7.3 Experimental section

Melting points were determined on a Mettler FP80 HT and are uncorrected. Optical rotations were obtained from $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were recorded at 200 MHz on a Bruker AC-E 200 spectrometer, or, where indicated, at 500 MHz on a Bruker AMX-500. ^{13}C NMR spectra were recorded at 50 MHz on a Bruker AC-E 200 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard in $CDCl_3$ as the solvent. Mass spectral data were determined on either an AEI MS 902 spectrometer or a Hewlett Packard 5970 B series MSD coupled with a Hewlett Packard 5890 A gas chromatograph with a DB-17 fused silica capillary column. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. GC analyses were carried out on a Hewlett Packard 5890 II 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. 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, unless otherwise noted. Product solutions were dried over anhydrous $MgSO_4$ prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

Isoledene (224). To 100 g of mechanically stirred Al_2O_3 (ICN, basic, activity grade Super, dried at 250°C at reduced pressure) was added 10 g (0.25 mol) of potassium in small portions at 200°C, under an argon atmosphere (Caution!). The resulting blue powder (non pyrophoric) was allowed to come to room temperature, cooled to 0°C, and then 80 mL of dry hexane was added. To this stirred suspension 32.5 g of crude distillation tail of the oil of *Eucalyptus globulus*[1] in 50 mL of dry hexane was added. The ice-bath was removed and stirring was continued for 4 h. The green suspension was filtered through a glass-filter and the catalyst was washed carefully with an ether-hexane mixture. After removal of the solvent via distillation, 30.44 g of a colourless oil was obtained, containing, according to GC-analysis, 85% of isoledene (**224**). ^1H NMR ($CDCl_3$) δ 0.94 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.13 (s, 3H), 1.00-2.58 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 15.76 (q), 19.01 (q), 20.49 (s), 21.50 (q), 22.54 (t), 23.94 (d), 28.12 (q), 30.16 (d), 31.19 (t), 34.34 (t), 34.74 (t), 38.26 (d), 44.73 (d), 136.64 (s), 138.35 (s); mass spectrum, *m/e* (relative intensity) 204 (M^+, 25), 199 (12), 161 (83), 147 (16), 133 (31), 119 (62), 105 (100), 91 (63).

(+)-Bicyclogermacrane-1,8-dione (304). To a solution of 16.00 g of the crude oil containing 85 % (66 mmol) of **224** in 120 mL of CCl_4 were added 120 mL of CH_3CN, 180 mL of H_2O, 25 g (117 mmol) of $NaIO_4$ and 250 mg of $RuO_2 \cdot xH_2O$. The mixture was stirred at 45-50°C for 3 h and an additional 10 g (46 mmol) of $NaIO_4$ was added. After stirring for another 1.5 h the mixture was allowed to come to room temperature, and 25 mL of isopropanol was added. The mixture was stirred for 15 min, filtered through celite, and the filter cake was washed with 200 mL of H_2O and 150 mL of CH_2Cl_2. The combined filtrates were separated, and the aqueous layer was extracted with three 150-mL portions of CH_2Cl_2. The combined organic layers were washed with 250 mL of aqueous 10% $Na_2S_2O_3$ and 250 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [15:1 to 10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 13.36 g (86%) of **304**: mp 54-55°C (from CH_3CN); $[\alpha]_D$ +227° (c 1.86); ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 7.2 Hz, 3H), 1.06 (s, 3H), 1.07 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H), 1.09-1.33 (m, 2H), 1.52 (d, J = 8.5 Hz, 1H), 1.62-2.06 (m, 4H), 2.17-2.57 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.59 (q), 17.40 (q), 18.91 (q), 20.74 (t), 28.80 (q), 30.61 (t), 30.91 (s), 31.89 (t), 32.50 (d), 40.14 (t), 41.60 (d), 48.29 (d), 52.71 (d), 214.56 (s), 216.21 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 44), 221 (21), 218 (25), 208 (18), 151 (21), 137 (100), 124 (36), 111 (43), 96 (49), 84 (32); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.01; H, 10.21.

Thermolysis of 304. A solution of 472 mg (2.0 mmol) of **304** in 30 mL of *p*-xylene was heated at reflux for 18 h. Evaporation of the solvent under reduced pressure followed by flash chromatography [12:1 to 3:1 petroleum ether (bp 40-60°C)/EtOAc] of the resulting residue afforded, in order of elution, 131 mg (28%) of **311**, 142 mg (30%) of **313**, and 145 mg (31%) of **314**.

(+)-7α,11α-*trans*-Humulene-1,8-dione (311): mp 76.5-77.5°C (from n-heptane); $[\alpha]_D$ +248° (c 2.18); ^{1}H NMR ($CDCl_3$, 500MHz) δ 0.99 (d, J = 7.3 Hz, 3H), 1.01 (s, 3H), 1.15 (s, 3H), 1.19 (d, J = 7.1 Hz, 3H), 1.68-1.73 (m, 2H), 1.93 (dd, J = 1.2, 11.1 Hz, 1H), 2.03-2.16 (m, 2H), 2.39-2.53 (m, 3H), 2.56 (d, J = 11.1 Hz, 1H), 2.60-2.68 (m, 1H), 5.36-5.42 (m, 2H); ^{1}H NMR (C_6D_6, 500MHz) δ 0.79 (d, J = 7.2 Hz, 3H), 0.82 (s, 3H), 0.90 (d, J = 7.3 Hz, 3H), 1.20 (s, 3H), 1.72-1.91 (m, 5H), 2.21 (d, J = 11.1 Hz, 1H), 2.32-2.47 (m, 3H), 2.63-2.71 (m, 1H), 5.18 (dd, J = 1.5, 15.5 Hz, 1H), 5.27 (ddd, 4.4, 10.4, 15.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.95 (q), 17.89 (q), 23.57 (q), 24.68 (t), 31.04 (q), 36.85 (s), 37.51 (t), 38.10 (t), 45.57 (d), 45.85 (d), 52.05 (t), 121.07 (d), 140.22 (d), 213.76 (s), 215.29 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 46), 165 (100), 154 (22), 111 (34), 110 (29), 96 (47), 70 (26); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.11; H, 10.20.

(–)-[2R-(2α,4aα,5α,8β,8aβ)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-(1-methylethenyl)-1(2*H*)-naphthalenone (313): mp 64.5-65.5°C (from *n*-heptane); $[\alpha]_D$ -7.3° (c 2.11); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (d, J = 6.7 Hz,3H), 0.98 (d, J = 6.3 Hz, 3H), 1.12 (dq, J = 3.8, 13.1 Hz, 1H), 1.17 (s, 1H), 1.34 (dq, J = 3.4, 13.1 Hz, 1H), 1.47 (ddd, J = 3.5, 7.0, 13.1 Hz, 1H), 1.56-1.70 (m, 3H), 1.78 (s, 3H), 1.82 (ddd, J = 3.4, 7.0, 13.1 Hz, 1H), 1.96-2.07 (m, 2H), 2.36 (dt, J = 3.8, 12.0 Hz, 1H), 2.42-2.49 (m, 1H), 2.61 (d, J = 12.0 Hz, 1H), 4.50 (s, 1H), 4.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.00 (q), 14.72 (q), 22.35 (q), 29.61 (t), 31.98 (t), 32.27 (t), 35.34 (t), 38.64 (d), 40.86 (d), 45.15 (d), 60.96 (d), 79.19 (s), 107.21 (t), 150.16 (s), 211.64 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 65), 218 (44), 203 (35), 175 (44), 162 (31), 149 (42), 148 (55), 135 (100), 94 (47); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1775. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.99; H, 10.56.

(+)-[2R-(2α,4aβ,5α,8β,8aβ)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-(1-methylethenyl)-1(2*H*)-naphthalenone (314): mp 158°C [from petroleum ether (bp 80-100°C)]; $[\alpha]_D$ +62.8° (c 1.63); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.11 (d, J = 7.2 Hz, 3H), 1.20 (d, J = 7.3 Hz, 3H), 1.29 (dq, J = 3.6, 13.6 Hz, 1H), 1.31 (s, 1H), 1.34-1.39 (m, 2H), 1.58-1.66 (m, 2H), 1.69-1.76 (m, 1H), 1.80 (s, 3H), 1.94 (tt, J = 4.3, 13.6 Hz, 1H), 2.16-2.27 (m, 2H), 2.38 (dt, J = 4.3, 12.0 Hz, 1H), 2.51-2.57 (m, 1H), 3.01 (d, J = 12.0 Hz, 1H), 4.50 (s, 1H), 4.65 (s,1H); ^{13}C NMR ($CDCl_3$) δ 15.41 (q), 15.73 (q), 22.31 (q), 26.42 (t), 27.72 (t), 28.18 (t), 30.96 (t), 38.17 (d), 39.46 (d), 44.49 (d), 49.91 (d), 79.73 (s), 106.83 (t), 150.42 (s), 214.20 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 72), 218 (59), 203 (34), 175 (45), 162 (40), 149 (68), 148 (49), 135 (100), 94

(52); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.42; H, 10.41.

In another experiment, a solution of 1.18 g (5.0 mmol) of **304** in 100 mL of 1,4-dioxane was heated at reflux for 7 d. Evaporation of the solvent under reduced pressure followed by flash chromatography [15:1 petroleum ether (bp 40-60°C)/EtOAc] of the resulting residue afforded 961 mg (81%) of **311**.

(±)-7β,11α-*trans*-Humulene-1,8-dione (306). A solution of 354 mg (1.0 mmol) of **311** in 10 mL of 1 M MeONa in MeOH was stirred at room temperature for 90 h. After dilution with 40 mL of H_2O, the reaction mixture was extracted with four 25-mL portions of ether. The combined organic layers were washed with 30 mL of brine, dried, and evaporated under reduced pressure. The remaining residue (354 mg), according to GC-analysis a 1:15 mixture of **311** and **306**, respectively, was flash chromatographed [15:1 to 10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 322 mg (91%) of **306**: mp 64.5-65°C (from methanol); $[\alpha]_D$ +12.8° (c 1.2) (lit.[10]: +201°). According to GC-analysis with a chiral column (WCOT fused silica 50 m x 0.25 mm i.d. coated with CP-cyclodextrin-β-2,3,6-M-19, film thickness 0.25 μm), **306** was a mixture of two enantiomers in a 53 : 47 ratio; ^1H NMR, ^{13}C NMR, and MS spectroscopic data were consistent with those reported in the literature[4]. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.10; H, 10.48.

Flash Vacuum Pyrolysis of 304. The FVP experiments were performed using standard FVP equipment[12] with a vertically placed quartz tube of 20 cm long and 13 mm in diameter. The diketone **304** was preheated at 70°C with a Büchi TO 50 oven and pyrolyzed at a pressure of $1 \cdot 10^{-2}$ mbar using different temperatures. The products were trapped at the end of the quartz tube with a cold finger, cooled at -78°C. In this way 1.00 g (4.23 mmol) of **304** was pyrolyzed at 500°C in a 1 h period. Flash chromatography [6:1 to 3:1 petroleum ether (bp 40-60°C)/EtOAc] of the resulting product mixture afforded 550 mg (55%) of **313** and 398 mg (40%) of **314**.

In a similar experiment 118 mg (0.5 mmol) of **304** was pyrolyzed at 700°C to give 84 mg (71%) of **313** and 23 mg (19%) of **314**.

(+)-[2S-(2β,4aβ,5α,8β,8aβ)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-(1-methylethenyl)-1(2*H*)-naphthalenone (315). A solution of 236 mg (1.0 mmol) of **314** in 5 mL of 1 M MeONa in MeOH was stirred at room temperature for 60 h. After dilution with 20 mL of H_2O, the reaction mixture was extracted with four 15-mL portions of ether. The combined organic layers were washed with 20 mL of brine, dried, and evaporated

under reduced pressure. The remaining residue (236 mg), according to GC-analysis a 1:8 mixture of **314** and **315**, respectively, was flash chromatographed [5:1 petroleum ether (bp 40-60°C)/EtOAc] to give 27 mg (11%) of **314** and 205 mg (86%) of **315**: mp 120°C (from n-heptane); $[\alpha]_D$ +0.6° (c 2.79); ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.1 Hz, 3H), 1.06 (d, J = 7.1 Hz, 3H), 1.39 (s, 1H), 1.78 (s, 3H), 1.20-2.14 (m, 9H), 2.36 (dt, J = 2, 12 Hz, 1H), 2.38 (t, J = 12 Hz, 1H), 2.73 (d, J = 12 Hz), 4.49 (s, 1H), 4.63 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.07 (q), 15.38 (q), 22.44 (q), 26.31 (t), 27.74 (t), 31.63 (t), 35.88 (t), 38.64 (d), 39.32 (d), 45.31 (d), 54.90 (d), 79.90 (s), 107.20 (d), 150.39 (s), 212.00 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 71), 218 (64), 203 (27), 175 (38), 162 (34), 149 (94), 148 (56), 135 (100), 94 (50); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.33; H, 10.49.

(–)-[2R-(2α,4aα,5α,8β,8aβ)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-(1-methylethyl)-1(2*H*)-naphthalenone (316). To a solution of 4.72 g (20 mmol) of **313** in 35 mL of ethanol was added 250 mg of 10% Pt on carbon. The mixture was hydrogenated in a hydrogen atmosphere at a pressure of 60 psi for 4 h. The reaction mixture was filtered through celite and a short SiO_2-column [1:1 petroleum ether (bp 40-60°C)/EtOAc] to give 4.71 g (99%) of **316**: mp 48-49 °C (from EtOH); $[\alpha]_D$ -36.1° (c 0.95); ^{1}H NMR ($CDCl_3$) δ 0.60 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H), 1.25 (s,1H), 0.88-2.03 (m, 11H), 2.41 (d, J = 11.9 Hz, 1H), 2.37-2.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.02 (q), 14.98 (q), 15.51 (q), 21.18 (q), 22.37 (t), 26.93 (d), 29.13 (t), 32.71 (t), 35.40 (t), 36.04 (d), 41.16 (d), 45.75 (d), 59.90 (d), 79.74 (s), 212.88 (s); mass spectrum, *m/e* (relative intensity) 238 (M^+, 15), 220 (100), 195 (39), 192 (36), 175 (47), 162 (39), 151 (44), 138 (51), 128 (94), 127 (67); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 238.1933, found *m/e* 238.1933. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.47; H, 11.20.

(–)-[2R-(2α,4aα,5α,8β,8aβ)]-Octahydro-4a-trimethylsilyloxy-2,5-dimethyl-8-(1-methylethyl)-1(2*H*)-naphthalenone (317). To a solution of 3.00 g (12.6 mmol) of **316** in 20 mL of DMF and 5.0 mL (57 mmol) of Et_3N, was added 3.8 mL (30 mmol) of TMSCl. The reaction mixture was heated at 120°C for 6 d, allowed to come to room temperature, and then 75 mL of petroleum ether (bp 40-60°C) was added. The resulting mixture was washed twice with 50 mL of saturated aqueous $NaHCO_3$, and the combined aqueous layers were back-extracted with two 50-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were dried and evaporated under reduced pressure. The resulting residue was flash chromatographed [15:1 petroleum ether (bp 40-60°C)/EtOAc] to give 3.56 g (91%) of **317**: mp 91 °C (from n-heptane); $[\alpha]_D$ -2.8° (c 1.13);

^{1}H NMR ($CDCl_3$) δ 0.02 (s, 9H), 0.53 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.6 Hz, 6H), 0.93 (d, J = 6.2 Hz, 3H), 1.21-1.64 (m, 7H), 1.81-2.09 (m, 4H), 2.22 (d, J = 11.3 Hz, 1H), 2.28-2.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 2.55 (3xq), 14.26 (q), 15.51 (q), 15.90 (q), 21.16 (q), 22.57 (t), 26.52 (d), 29.14 (t), 32.43 (t), 34.92 (t), 35.55 (d), 42.29 (d), 45.02 (d), 61.12 (d), 85.22 (s), 210.68 (s); mass spectrum, *m/e* (relative intensity) 310 (M^+, 16), 295 (18), 268 (22), 267 (100), 220 (94), 199 (31), 183(28), 162 (31), 73 (59); calcd for $C_{18}H_{34}O_2Si$ (M^+) *m/e* 310.2328, found *m/e* 310.2327. Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.63; H, 11.04. Found: C, 69.23; H, 11.05.

Trimethylsilylethers of cubenol (319) and isocubenol (320). To a solution of 655 mg (2.1 mmol) of **317** in 10 mL of dry THF was added 80 mg (2.1 mmol) of $LiAlH_4$ at -78°C. The mixture was allowed to warm to -30°C over a 2-h period and then cooled again to -50°C. The mixture was diluted with 20 mL of ether, and then carefully quenched with a few drops of 4N NaOH. The resulting mixture was dried and concentrated under reduced pressure to give 659 mg of a solid, containing, according to GC-analysis, 91% of **318** [^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 0.73 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.6 Hz, 3H), 1.05 (d, J = 5.9 Hz, 3H), 1.08-2.24 (m, 13H), 3.27 (d, J = 9.4 Hz, 1H), 3.69 (br d, J = 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 2.86 (3xq), 15.11 (q), 15.54 (q), 18.52 (q), 21.51 (q), 24.03 (t), 24.14 (t), 25.39 (d), 30.06 (t), 35.70 (t), 37.50 (d), 37.61 (d), 42.73 (d), 50.17 (d), 70.24 (d), 80.88 (s); mass spectrum, *m/e* (relative intensity) 312 (M^+, 4), 269 (100), 251 (99), 205 (10), 179 (9), 149 (10), 105 (15), 73 (68)] which was used immediately for the next reaction.

To a solution of the crude **318** in 5 mL of dry pyridine was added 1.25 mL (17 mmol) of $SOCl_2$ at -20°C. The reaction mixture was stirred at -20°C for 1.5 h, poured into 40 mL of ice-water, and extracted with four 25-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 40 mL of 4N HCl, 40 mL of saturated $NaHCO_3$ and 40 mL of brine, and then dried. Evaporation of the solvent under reduced pressure gave 600 mg of a crude mixture of mainly **319** and **320**, in a 3:2 ratio, respectively. The unseparable mixture was used immediately for the next reaction.

319: ^{1}H NMR (major peaks, $CDCl_3$) δ 0.11 (s, 9H), 0.77 (d, J = 6,9 Hz, 3H), 0.90 (d, J = 6.3 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 1.71 (s, 3H), 5.42 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 2.40 (3xq), 14.71 (q), 15.43 (q), 21.23 (q), 23.39 (q), 23.93 (t), 25.69 (d), 27.28 (t), 30.12 (t), 31.65 (t), 39.19 (d), 41.13 (d), 46.56 (d), 75.74 (s), 120.45 (d), 132.22 (s); mass spectrum, *m/e* (relative intensity) 294 (M^+, 1), 279 (2), 251 (100), 161 (8), 119 (10), 105 (21), 73 (40).

320: ^{1}H NMR (major peaks, $CDCl_3$) δ 0.11 (s, 9H), 0.89 (d, J = 7 Hz, 3H), 0.90 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 5.24 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 1.95 (3xq), 14.71 (q), 18.40 (q), 21.23 (q), 22.34 (q), 26.86 (d), 27.28 (t), 28.60 (t), 30.45 (t), 30.62 (d), 34.95 (t), 43.39 (d), 44.50 (d), 74.60 (s), 125.23 (d), 143.50 (s); mass spectrum, *m/e* (relative intensity) 294 (M^+, 8), 279 (16), 251 (100), 204 (33), 161 (30), 119 (32), 105 (32), 73 (73).

(–)-Cubenol (310). The crude mixture of **319** and **320** (600 mg) was dissolved in 6 mL of THF and 5 mL of 1.1 M TBAF in THF was added. The reaction mixture was heated at 60°C for 3 h, cooled to room temperature, and then 25 mL of water and 20 mL of petroleum ether (bp 40-60°C) were added. The two-phase mixture was separated, and the aqueous layer was extracted with two 20-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 25 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was carefully flash chromatographed [22:1 petroleum ether (bp 40-60°C)/EtOAc] to give, in order of elution, 208 mg of cubenol (**310**) (44% from **317**) and 145 mg of isocubenol (**321**) (31% from **317**), both as colourless oils.

(310): $[\alpha]_D$ -30.4° (c 0.90) (lit.[5a,6]: -30°); ^{1}H NMR, ^{13}C NMR, and MS spectroscopic data were consistent with those reported in the literature[5b].

(–)-Isocubenol (321): $[\alpha]_D$ -87.5° (c 0.91); ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.1 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 7.1 Hz, 3H), 1.35 (s, 1H), 1.08-1.84 (m, 8H), 1.97-2.20 (m, 4H), 5.31 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.53 (q), 17.40 (q), 21.68 (q), 22.05 (q), 26.48 (t), 26.48 (d), 27.14 (t), 30.37 (t), 31.27 (d), 36.63 (t), 43.05 (d), 43.20 (d), 70.81 (s), 127.66 (d), 141.53 (s); mass spectrum, *m/e* (relative intensity) 222 (M^+, 2), 204 (7), 179 (100), 161 (37), 119 (8), 105 (13), 82 (8); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1983, found *m/e* 222.1983.

Acknowledgement

I thank Dr. A.J.H. Klunder and A.C.L.M. van der Waals from the University of Nijmegen for the use of their Flash Vacuum Pyrolysis apparatus.

7.4 References and notes

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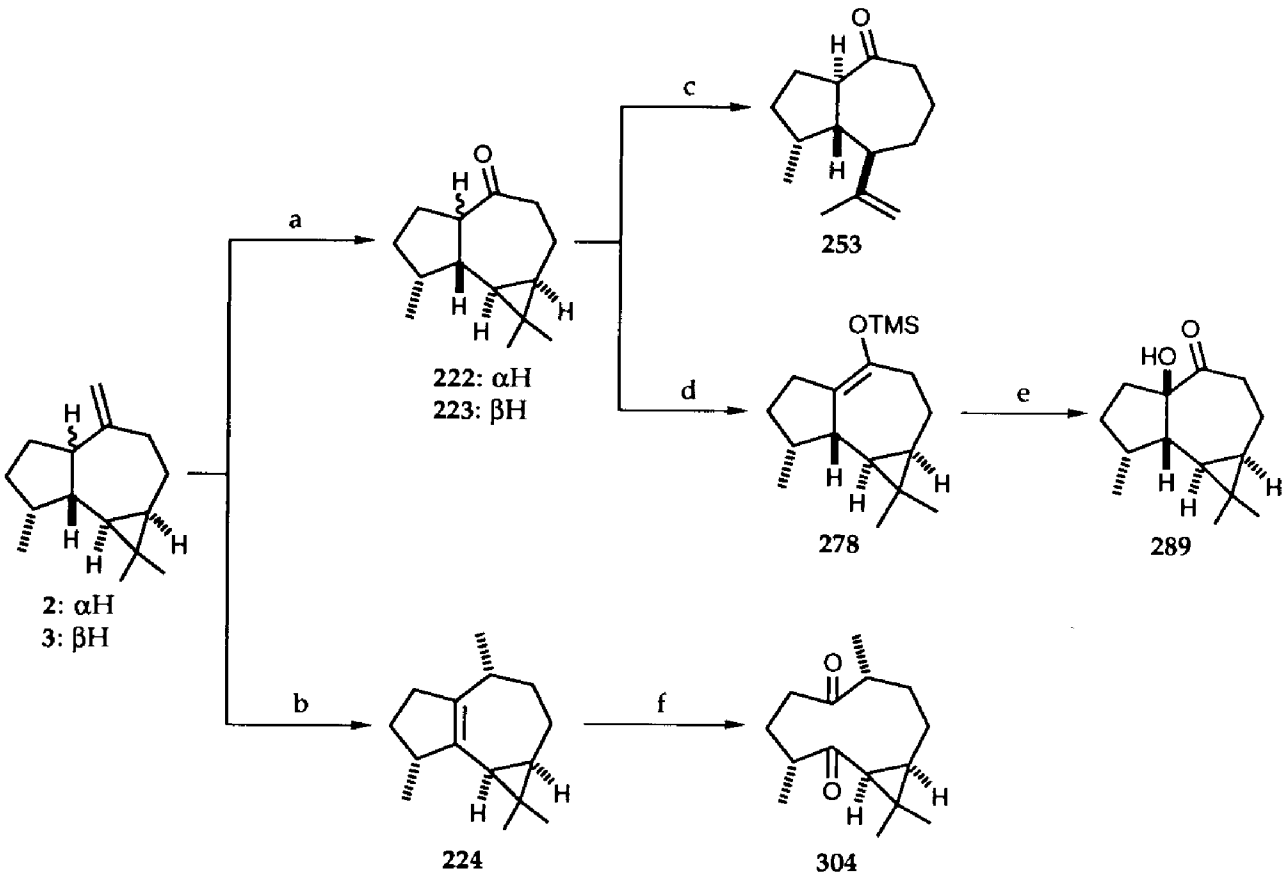
8 General discussion

(+)-Aromadendrene (**2**), is the main constituent in a commercially available distillation tail of the oil derived from *Eucalytus globulus*[1]. Because of its availability in large quantities and its low price (2 US$/kg), **2** is a potential candidate for the chiral pool, especially as starting material for the synthesis of other sesquiterpenes. In order to be useful as a chiral building block, (+)-aromadendrene (**2**) or derivatives made from **2** have to be readily available in a more or less pure form. Also it needs to be demonstrated that (+)-aromadendrene and its derivatives are useful starting compounds for the synthesis of interesting (natural) products (see chapter 2.2). The above-mentioned distillation tail contains about 55-70% of **2** besides 10-15% of alloaromadendrene (**3**). In chapter 3 and 7 two simple routes have been described to obtain pure derivatives of **2** (and **3**) from this crude distillation tail (Scheme 8.1).

Scheme 8.1[a]



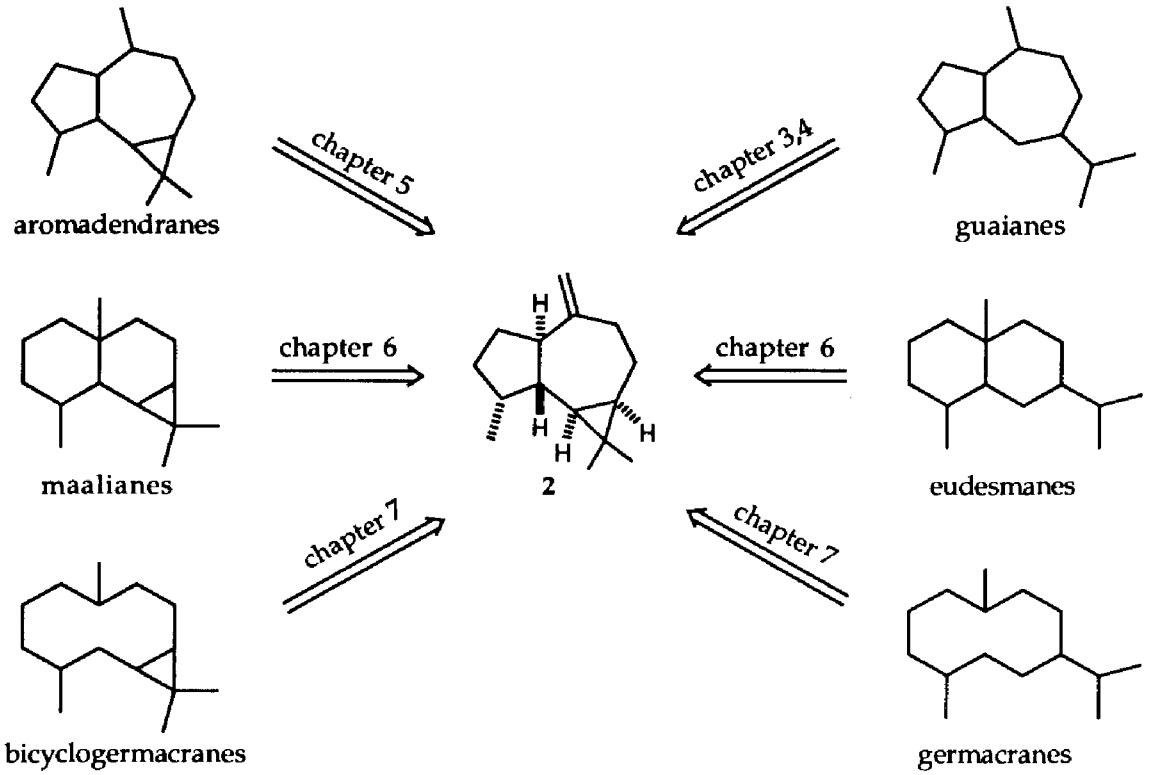
a (a) O_3; (b) K/Al_2O_3; (c) HCl, EtOH, Δ; (d) TMSCl, Et_3N, DMF, 130°C; (e) dimethyldioxirane; SiO_2; (f) RuO_2, $NaIO_4$, 50°C.

In chapter 3 is described how purification has been accomplished by ozonolysis of the crude distillation tail, giving, after reductive workup and crystallization, pure apoaromadendrone (**222**). This reaction could be done on a large scale and without purification problems. The remaining mixture of mainly apoaromadendrone (**222**) and alloaromadendrone (**223**) was also useful, because both products could be converted in either isoapoaromadendrone (**253**) (chapter 3) or the thermodynamic enol trimethylsilylether **278** (chapter 5). The carbonyl group in apoaromadendrone is a useful handle for further elaboration of the aromadendrane skeleton. An example of this is the synthesis of hydroxyketone **289**, a crucial intermediate in the synthesis of hydronaphthalene compounds (chapter 6).

The second way to obtain a pure derivative from the *Eucalyptus* distillation tail was via treatment with potassium on aluminum oxide (K/Al_2O_3) as described in chapter 7. Both aromadendrene (**2**) and alloaromadendrene (**3**) give quantitatively the same product: isoledene (**224**), making it a very interesting purification method. Preparation of the reagent K/Al_2O_3 is potentially hazardous, but by using dry and oxygen free conditions, the reaction can be done on a large scale. The obtained oil, consisting of over 80% of isoledene (**224**), has been converted into bicyclogermacrane-1,8-dione (**304**) by oxidative cleavage of the double bond with $RuO_2/NaIO_4$. Pure **304** could only be obtained after column chromatography, making large scale production difficult. However, for many subsequent reactions with **304** it might be possible to use the crude **304**, obtained after oxidation with $RuO_2/NaIO_4$. This has not been investigated yet.

To demonstrate the usefulness of (+)-aromadendrene or its derivatives **222**, **224**, and **304** as chiral synthons, compounds with carbon skeletons from several classes of sesquiterpenes have been prepared from (+)-aromadendrene. The potential classes of sesquiterpenes, which have been described in chapter 2.2, are given in scheme 8.2 (see also scheme 2.2).

Scheme 8.2

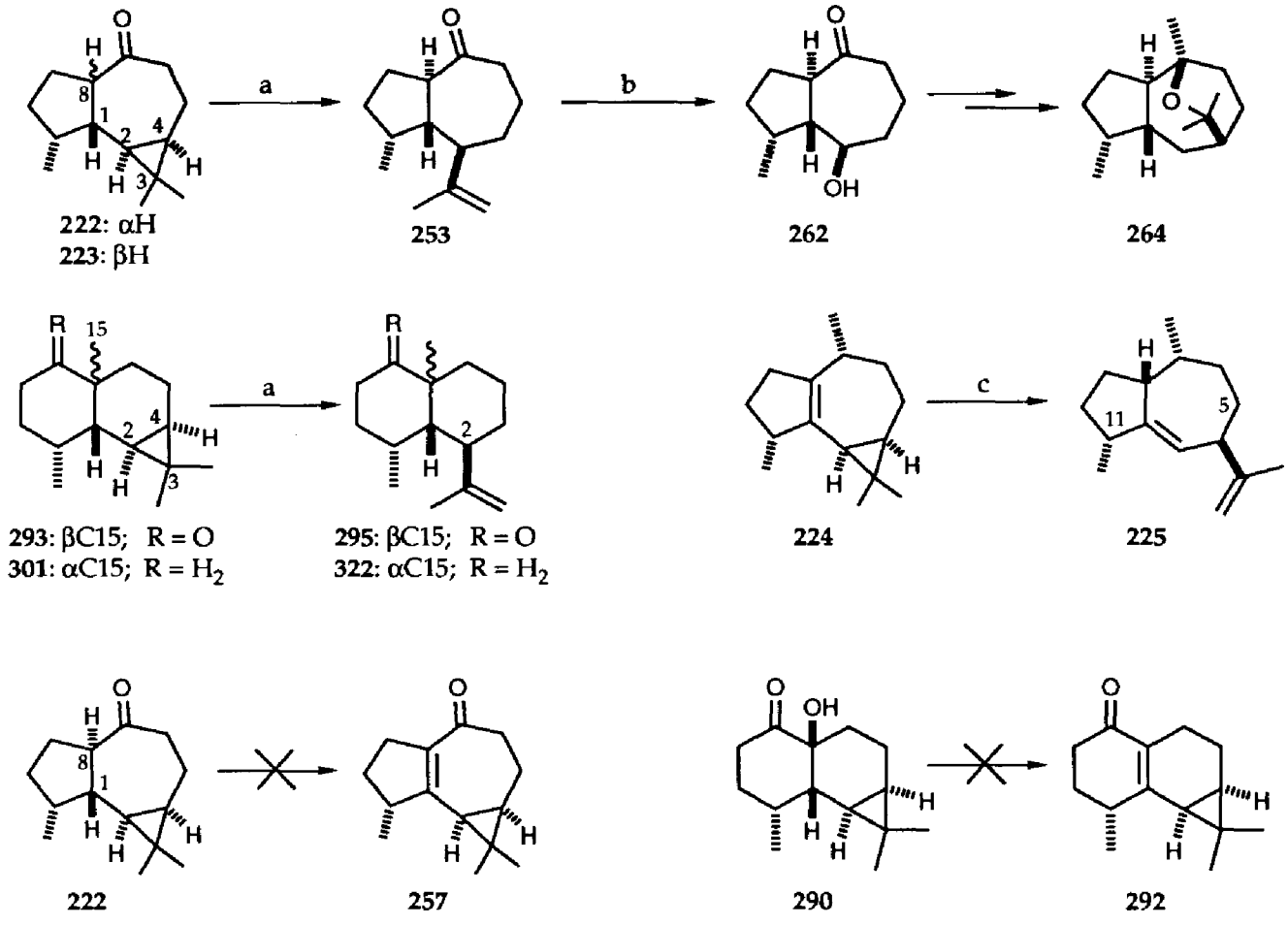


Synthesis of products from the three classes on the right, the guaianes, the eudesmanes, and the germacranes, were thought to be possible via cleavage of the C2-C3 bond in the cyclopropane ring. Unfortunately, acid-catalyzed ring opening of apoaromadendrone (**222**) and alloaromadendrone (**223**)took place exclusively between C3 and C4, giving isoapoaromadendrone (**253**). Treatment of other aromadendranes like aromadendrene, globulol, and epiglobulol with HCl all led to unattractive mixtures. The reason for the selective cleavage in **222** and **223** is not completely understood. The formation of energetically more favourable products or attack of H^+ from the less sterically hindered side may both play a role. Cyclopropane ring opening in the *cis*-maaliane compound **293** or *trans*-maaliane (**301**) also took place between C3 and C4, giving **295** and **322**[2], respectively (Scheme 8.3, see chapter 6). To explain this behaviour it might be necessary to study cyclopropane ring opening reactions with more test compounds and to perform molecular dynamics calculations on these reactions.

One way to direct ring cleavage between C2 and C3 is via a double bond between C1 and C8 as in isoledene (**224**). Pyrolysis of isoledene does give the guaiane γ-gurjunene (**225**) in 80% yield[3]. However, this product is not very useful for the synthesis of other *guaianes* because of its lack of functional groups at C5 to C11. Introduction of a double

bond between C1 and C8 via apoaromadendrone (**222**), giving the enone **257**, has not been successful in an efficient way (chapter 3). Synthesis of the enone **292**, a possible precursor for eudesmanes, from the hydroxyketone **290** has not been successful either (chapter 6).

Scheme 8.3[a]

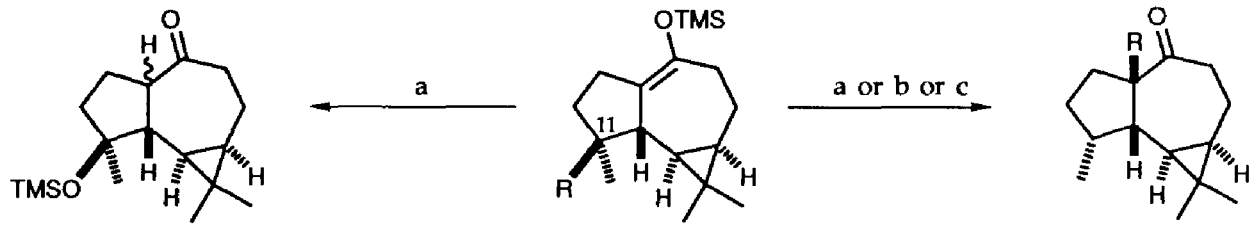


a (a) HCl; (b) O_3, MeOH; Ac_2O, Et_3N, DMAP; NaOMe, MeOH; (c) 450°C.

Isoapoaromadendrone (**253**) can be used for the synthesis of guaianes via the readily available synthon **262**. This has been demonstrated with the synthesis of the guaiane (–)-kessane (**264**), as described in chapter 4. Although **264** has been synthesized from **262** in good yield, the synthesis of a guaiane via removal of the isopropenyl group at C2 and subsequent introduction of a new isopropyl-type substituent at C4 is not a very elegant approach. Nevertheless, keto alcohol **262** might be a useful synthon for the synthesis of other compounds containing a hydrazulene fragment.

(+)-Aromadendrene is a good starting material for the synthesis of other aromadendranes as has been shown in chapter 5. *Cis*-fused aromadendranes could be obtained via β-attack of an electrophile at the thermodynamic enolsilylether **278**. Selective attack of an electrophile at the β-side of the thermodynamic enol(ate) took place during the formation of alloaromadendrone (**223**), but also during bromination of apoaromadendrone (chapter 3) and epoxidation of **278** with dimethyldioxirane (chapter 6), giving the *cis*-fused products **256** and **289**, respectively (Scheme 8.4). Protonation of **281**, with a β-trimethylsilyloxy group at C11, gave a 1:1 ratio of *trans*-fused **282** and *cis*-fused **283**. Apparantly, β-substituents at C11 hinder the attack from the β-side of the enol double bond, making the attack less selective.

Scheme 8.4[a]



282: αH
283: βH
282 : **283** = 1 : 1

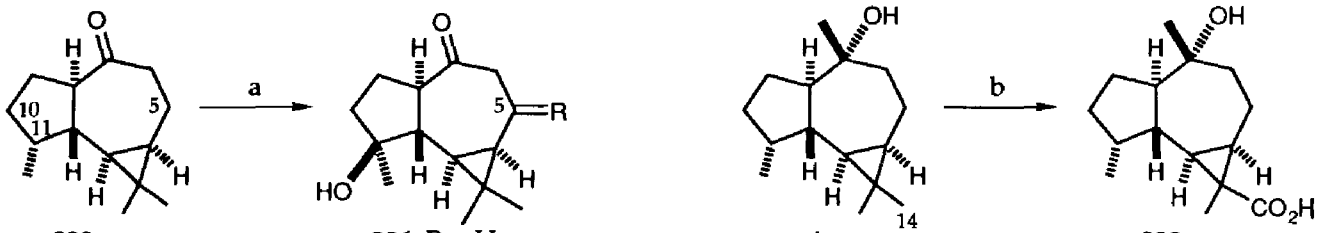
278: R = H
281: R = OTMS

223: R = H
256: R = Br
289: R = OH

[a] (a) MeOH, Et_3N; (b) Br^+; (c) dimethyldioxirane; SiO_2.

One drawback on the use of (+)-aromadendrene, in general, is its lack of functionality in the five-membered ring. Functionalization of C10 or C11 via the carbonyl function of apoaromadendrone will take too many steps to be of any interest. Functionalization of the five-membered ring in one step was achieved in reasonable yield (36%) by hydroxylation of **222** at C11 with $RuO_2/NaIO_4$, giving the hydroxy ketone **226** (Scheme 8.5). Unfortunately, the yield of **226** could not be increased further, due to overoxidation at C5, next to the cyclopropane ring (product **279**).

Scheme 8.5[a]



222

226: R = H_2
279: R = O

4

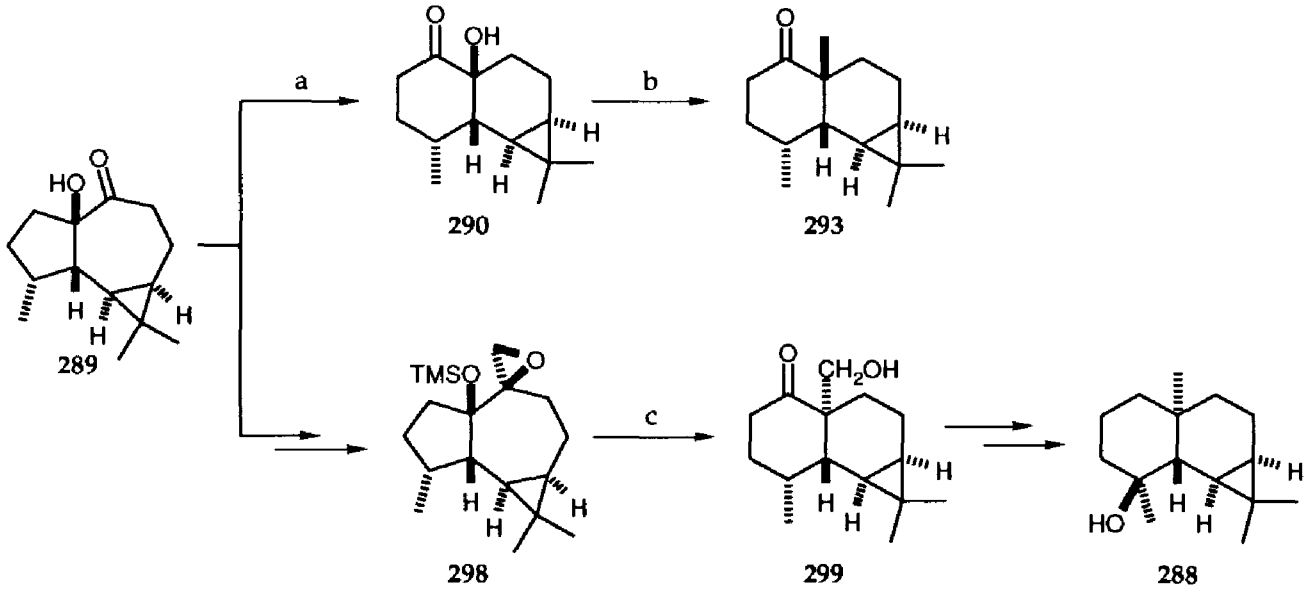
230

[a] (a) RuO_2, $NaIO_4$, 50°C; (b) *Mycobacterium smegmatis*.

During the hydroxylation of maaliane to maaliol with $RuO_2/NaIO_4$, oxidation at C5 also took place (chapter 6). When an oxygen group at C5 next to the cyclopropane ring is required, this oxidation method might be useful, assuming that no other sensitive groups, like double bonds, are present in the molecule. Further functionalization of the carbon skeleton might be achieved via microbial oxidation. As mentioned in chapter 1.4, the C14-methyl group in globulol (**4**) can be converted into a carbonacid group (**230**) in 46% yield by fermentation of **4** with *Mycobacterium smegmatis*[4].

In chapter 6 rearrangement reactions of aromadendrane derivatives to hydronaphthalene products are described. As mentioned above, the synthesis of products with an eudesmane skeleton was unsuccessful. However, the synthesis of products **293** and **299** with the *cis*- and *trans*-maaliane skeleton, respectively, from (+)-aromadendrene could be achieved efficiently (Scheme 8.6). An important intermediate for both *cis*- and *trans*-maalianes is the hydroxyketone **289**, already mentioned above.

Scheme 8.6[a]

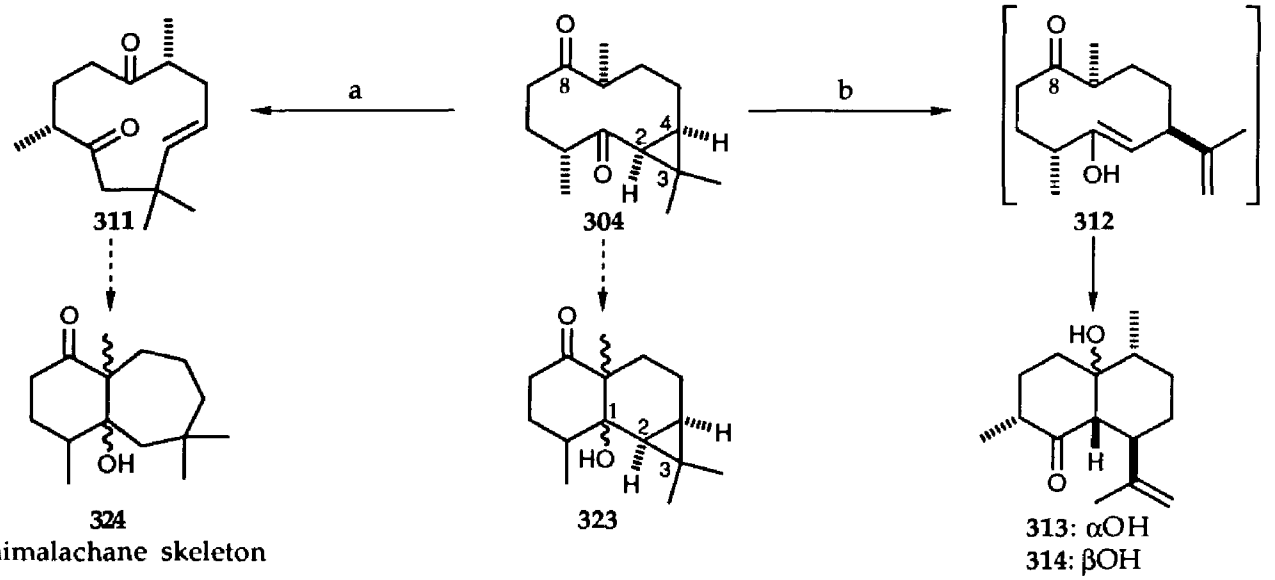


a (a) Al_2O_3; (b) Li, NH_3, *t*BuOH; MeI; (c) $TiCl_4$, CH_2Cl_2, -78°C.

The skeletons discussed so far have all been synthesized via apoaromadendrone (**222**). For the synthesis of bicyclogermacranes and germacranes, the bicyclogermacrane-1,8-dione (**304**) was thought to be the appropriate starting material (Scheme 8.7, chapter 7). The bicyclogermacranes, a small class of sesquiterpenes, are considered to be the precursors in the biosynthesis of the aromadendranes and the maalianes (see

chapter 1.2). Since aromadendrane- and maaliane-type compounds have already been synthesized from **2**, it has not been tried to synthesize naturally occurring bicyclogermacranes from **304**. For the synthesis of germacranes from **304**, again cleavage of the C2-C3 cyclopropane bond is required. Because of the directing influence of the carbonyl group, it was expected that ring opening would now proceed in the right direction, giving products with a germacrane skeleton. Treatment of **304** with acid led to unattractive mixtures. The use of high temperatures had to be avoided because of thermal rearrangements. However, these thermal rearrangements made it possible to synthesize two new types of sesquiterpene skeletons: humulanes and cadinanes. Thermal rearrangement at low temperature (100°C) gave predominantly the humulane product **311**. At temperatures above 500°C (FVP) mainly the cadinanes **313** and **314** were obtained.

Scheme 8.7[a]



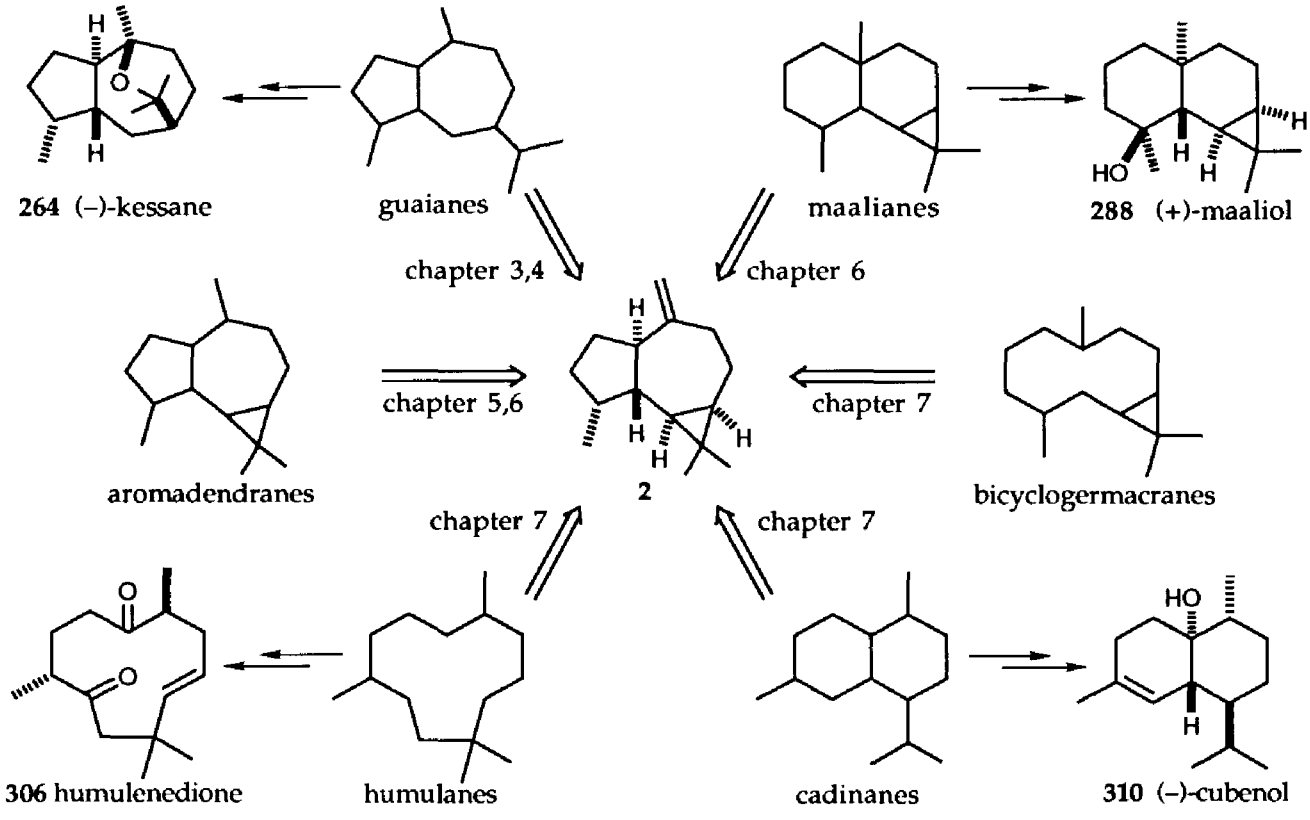
[a] (a) dioxane, Δ; (b) FVP.

The cadinanes must have been formed via the germacrane intermediate **312**. When the C8-carbonyl group in **304** can be selectively converted into another functional group, e.g. a protected alcohol or a double bond, cyclization can be avoided during pyrolysis or acidic cyclopropane ring opening. This offers the possibility to obtain germacranes and, via controlled cyclizations of these products, eudesmanes or other types of cyclized germacranes, e.g. cadinanes or guaianes. Treatment of **304** with base at low temperature might give the maaliane type products **323**. Via the hydroxyl group at C1, cyclopropane ring opening in **323** might be directed towards cleavage of the C2-C3 bond, leading to eudesmane products. An intramolecular aldol condensation in humulane derivatives of humulenedione **311** might give products with a himalachane skeleton (**324**).

8.1 Concluding remarks

Two efficient routes have been developed to purify the crude distillation tail of *Eucalyptus globulus*. Both routes lead to derivatives of (+)-aromadendrene that can be used for the synthesis of compounds with several different sesquiterpene carbon skeletons. In scheme 8.8 the different types of sesquiterpene skeletons, which have been synthesized from (+)-aromadendrene (**2**) as described in chapter 3 - 7, are given. (–)-Kessane (**264**) (chapter 4), several mono- and dihydroxy aromadendranes (chapter 5 and 6), (+)-maaliol (**288**) (chapter 6), humulenedione **306** and (–)-cubenol (**310**) (chapter 7) are naturrally occurring sesquiterpenes of these sesquiterpene classes which have been synthesized from **2**. On the basis of these results it can be concluded that (+)-aromadendrene from *Eucalyptus* oil is a versatile starting material for the synthesis of sesquiterpenes.

Scheme 8.8



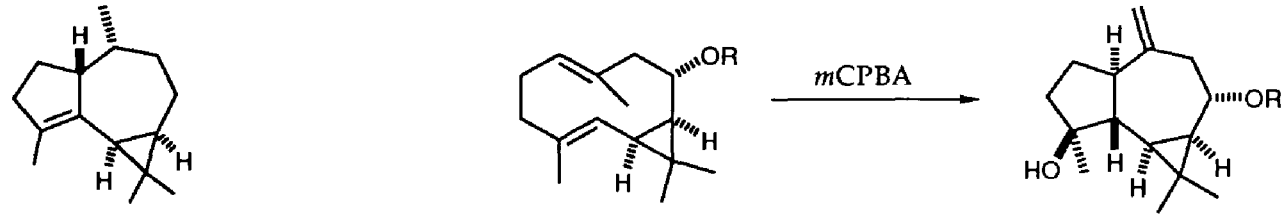
Although the synthesis of guaianes, eudesmanes, and germacranes from **2** has been difficult or unsuccessful with the methods used, it should be noted that various possibilities to synthesize these types of compounds still have to be examined. Especially bicyclogermacrane-1,8-dione (**304**) seems to be a promising synthon for further research.

8.2 Some notes on the availability of (+)-aromadendrene

As mentioned in chapter 2.1 the availability and a low price of a substance are also important factors for being an interesting member of the chiral pool. (+)-Aromadendrene is a relatively cheap material because it is a side (waste) product of the production of monoterpenes like cineol from *Eucalyptus* oil. The average amount of (+)-aromadendrene in the commercially available *Eucalyptus* oil is about 2%. Since the annual production of (+)-aromadendrene is not that high (50-60 tonnes), and is totally dependent on the production of cineol, large scale use of (+)-aromadendrene might increase its price. To avoid that the availability of (+)-aromadendrene is dependent on the cineol production, oil of *Eucalyptus* species which contain higher levels (up to 40%) of aromadendrene can be used[5].

(+)-Aromadendrene is just one of the sesquiterpenes which is available in reasonable quantities. In the class of the aromadendranes the only sesquiterpene with comparable availability is α-gurjunene (**25**). Worth mentioning might be guayulin A (**136**), a major component of the resin of the mexican rubber plant, guayule (*Parthenium argentatum*) . Because of growing interest in the production of rubber from guayule, **136** is expected to be available in the near future in 20-75 kT annually[6]. As mentioned in chapter 1.4, guayulin A can be converted into the aromadendrane guayulin C (**33**) via epoxidation with *m*CPBA in good yield[7] (Scheme 8.9). In this way guayulin C (**33**) might become an abundantly available, highly functionalized alternative for (+)-aromadendrene.

Scheme 8.9



25 **136**: R = Cinnamoyl **33**: R = Cinnamoyl

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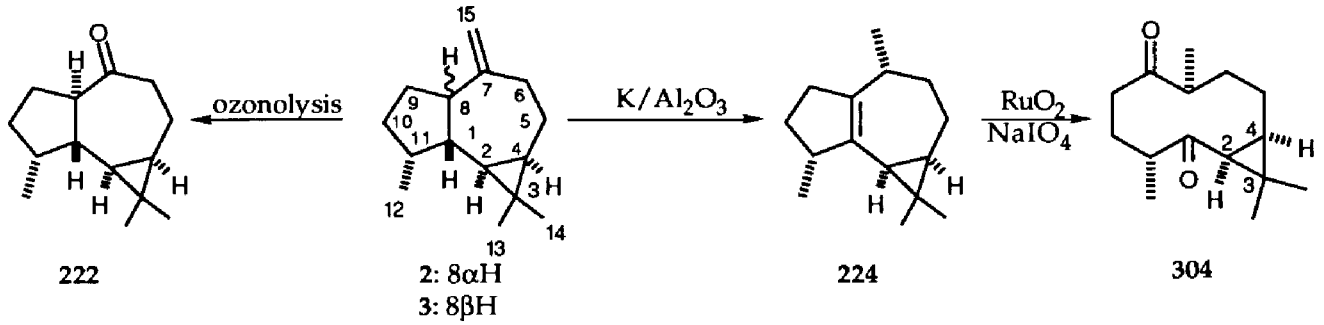
9 Summary

One of the distillation tails of the oil of *Eucalyptus globulus*, which is commercially available, contains about 55-70% of (+)-aromadendrene (**2**), together with 10-15% of alloaromadendrene (**3**). In this thesis has been described how (+)-aromadendrene from *Eucalyptus* oil can be used as a chiral starting material for the synthesis of sesquiterpenes.

Two methods have been described to purify the crude distillation tail in order to obtain pure derivatives of **2** (and **3**). In the first method, described in chapter 3, the crude distillation tail was ozonolyzed to give the crystallizable (+)-apoaromadendrone (**222**) (Scheme 9.1). In the second method, described in chapter 7, treatment of the crude distillation tail with potassium on aluminum oxide (K/Al_2O_3) gave a quantitative conversion of **2** and **3** into isoledene (**224**). Oxidative cleavage of the central double bond in **224** produced bicyclogermacrane-1,8-dione (**304**).

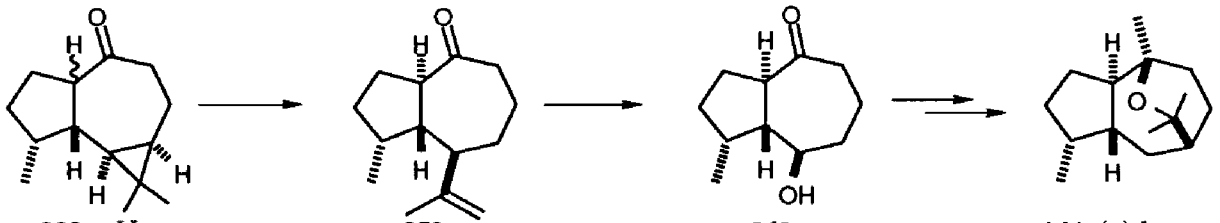
Scheme 9.1



222 — 2: 8αH, 3: 8βH — 224 — 304

Both derivatives **222** and **304** were used as starting materials for the synthesis of compounds with carbon skeletons from several classes of sesquiterpenes. Selective, acid-catalyzed cleavage of the C3-C4 bond of the cyclopropane ring in **222** (and **223**) gave (–)-isoapoaromadendrone (**253**) in high yield (chapter 3, scheme 9.2). Ozonolysis of **253** afforded the keto alcohol **262** which is a suitable chiral intermediate for the syntheses of guaianes. This was demonstrated in the synthesis of (–)-kessane (**264**), which proceeded in a 9 steps reaction sequence in an overall yield of 43% from **262** (chapter 4).

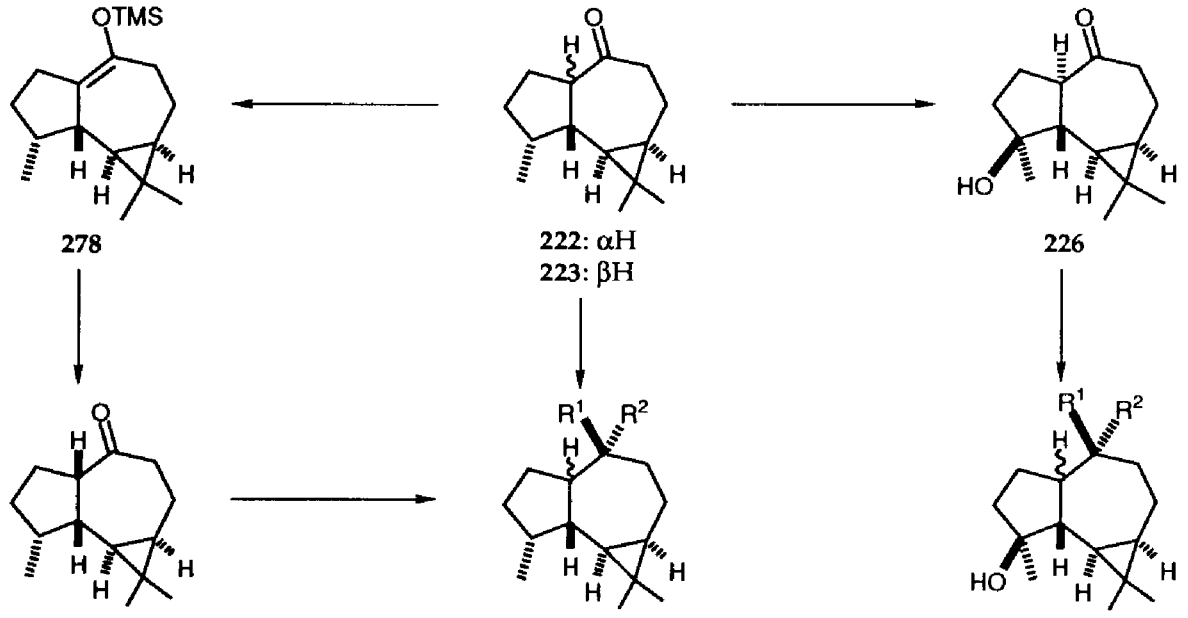
Scheme 9.2



222: αH, 223: βH — 253 — 262 — 264: (–)-kessane

The synthesis of the mono- and dihydroxy aromadendranes **4-7, 31, 40, 41, 227, 276,** and **277** from **222** has been described in chapter 5. The *cis*-fused alloaromadendrone (**223**), the key intermediate for the synthesis of (–)-ledol (**6**) and (+)-viridiflorol (**7**), was obtained from the *trans*-fused apoaromadendrone (**222**) via a selective protonation of the thermodynamic enol trimethylsilylether **278** (Scheme 9.3). Hydroxylation of the tertiary C11 of **222** with RuO_4 gave **226**, which could be transformed into (+)-spathulenol (**31**), (–)-allospathulenol (**276**), and the aromadendrane-diols **40, 41, 227,** and **277**. Compounds **4-7, 31, 40, 41, 227, 276,** and **277** were tested for antifungal properties, but their activity was only moderate.

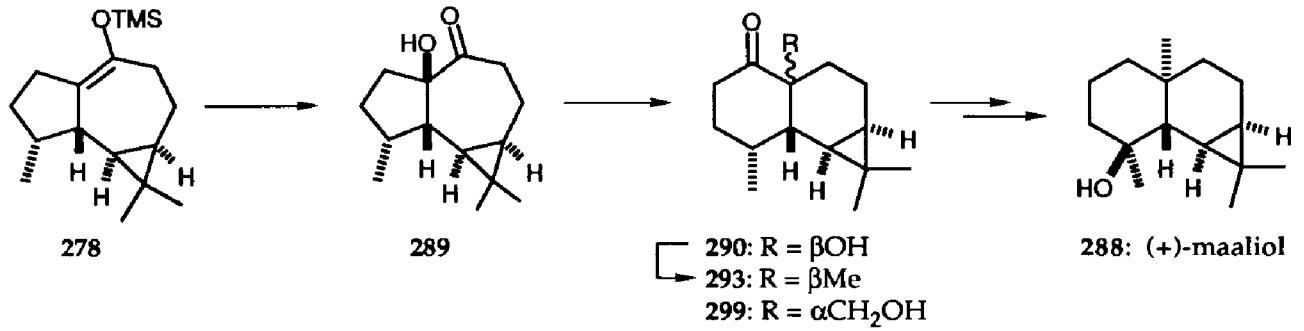
Scheme9.3[a]



A stereoselective epoxidation of the thermodynamic enol trimethylsilylether **278** gave the hydroazulene α-ketol **289** (chapter 6, scheme 9.4). Starting from this α-ketol, two different routes to hydronaphthalene compounds with a maaliane skeleton were developed, both in high overall yield. The first route via α-ketol **290** led to *cis*-fused

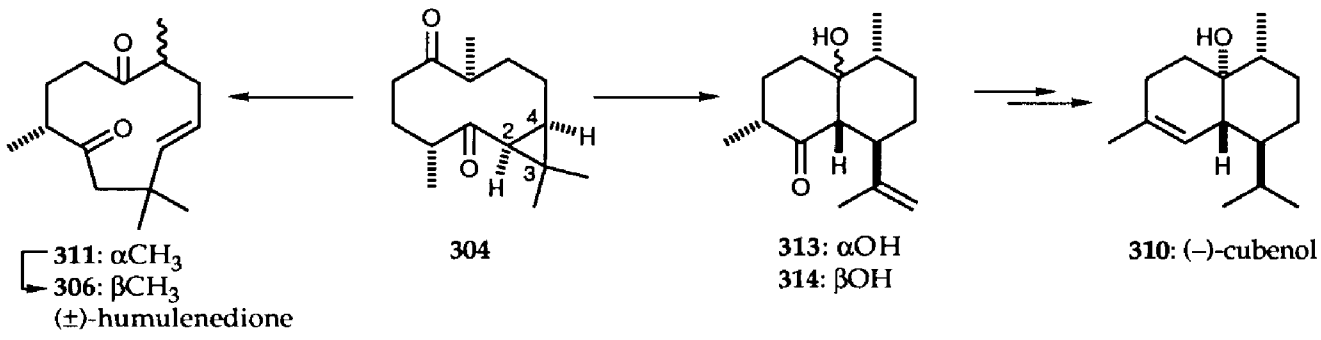
maaliane ketone **293**; the second one offered access to the *trans*-fused maaliane compound **299**. From **299** the naturally occurring (+)-maaliol (**288**) was synthesized.

Scheme 9.4



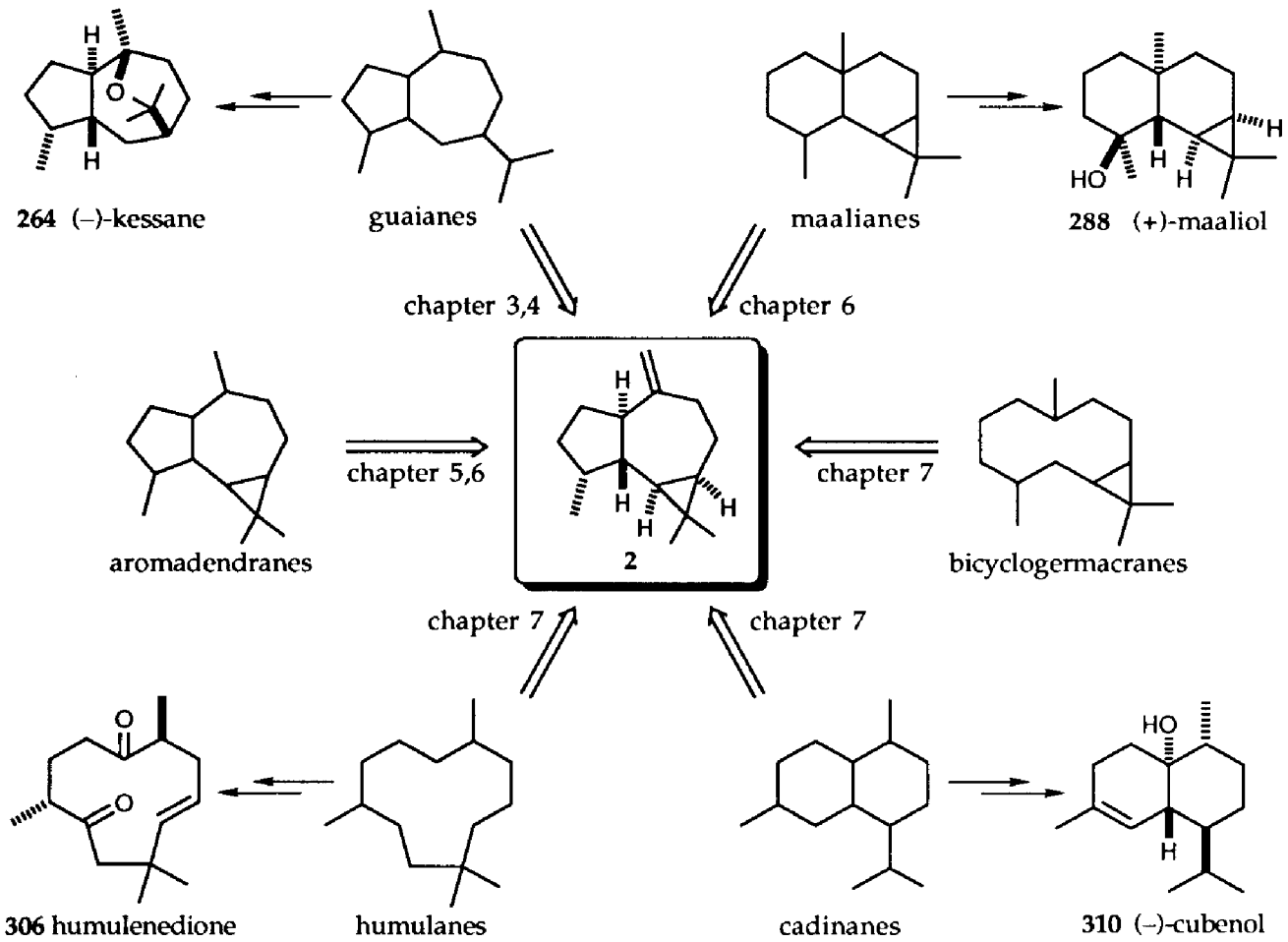
Synthon **304**, obtained via the second purification method of the crude distillation tail (*vide supra*), was used as starting material of compounds with a humulane or cadinane skeleton (chapter 7). The α-keto-cyclopropane compound **304** was found to be thermolabile. Thermal rearrangement of **304** gave via a homo [1,5] hydrogen shift at relatively low temperature (refluxing dioxane) the humulane compound **311** and at higher temperatures (Flash Vacuum Pyrolysis, 500°C and up) the products **313** and **314**, both with a cadinane skeleton (Scheme 9.5). Epimerization of **311** gave the naturally occurring humulenedione (**306**). Starting from **313**, the naturally occurring (–)-cubenol (**310**) was synthesized in a 4 steps reaction sequence.

Scheme 9.5



The results described in this thesis are shortly summarized in scheme 9.6. With (+)-aromadendrene (**2**) from *Eucalyptus* oil as starting material, compounds have been synthesized with sesquiterpene skeletons belonging to the classes of the guaianes, the aromadendranes, the maalianes, the bicyclogermacranes, the humulanes, and the cadinanes. (–)-Kessane (**264**) (chapter 4), several mono- and dihydroxy aromadendranes (chapter 5 and 6), (+)-maaliol (**288**) (chapter 6), humulenedione (**306**) (chapter 7), and (–)-cubenol (**310**) (chapter 7) are naturally occurring sesquiterpenes which have been synthesized from **2**. On the basis of these results it can be concluded that (+)-aromadendrene from *Eucalyptus* oil is a versatile chiral starting material for the synthesis of sesquiterpenes.

Scheme 9.6

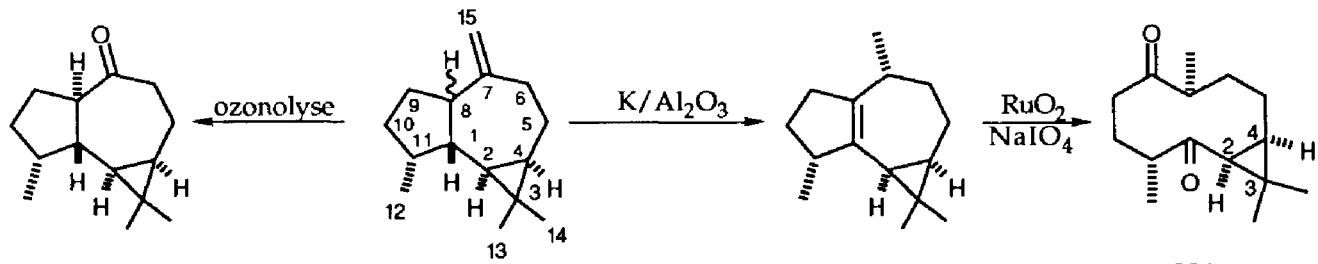


10 Samenvatting

Een commercieel verkrijgbare distillatie fractie van de olie verkregen uit *Eucalyptus globulus* bevat ongeveer 55-70% (+)-aromadendreen (**2**) en 10-15% alloaromadendreen (**3**). In dit proefschrift is een onderzoek beschreven naar de toepassingsmogelijkheden van (+)-aromadendreen uit *Eucalyptus* olie als chirale uitgangsstof voor de synthese van sesquiterpenen.

Twee methoden zijn beschreven om de ruwe distillatie fraktie te bewerken en zo zuivere derivaten van **2** (en **3**) te verkrijgen. Bij de eerste methode, beschreven in hfst. 3, werd de ruwe distillatie fraktie geozonolyseerd en ontstond het kristalliseerbare (+)-apoaromadendron (**222**) (Schema 10.1). Bij de tweede methode, beschreven in hfst. 7, werd de ruwe distillatie fraktie behandeld met kalium op aluminium oxide (K/Al_2O_3). Hierbij werden **2** en **3** quantitatief omgezet in isoledeen (**224**). Oxidatie van de centrale dubbele binding in **224** gaf bicyclogermacraan-1,8-dion (**304**).

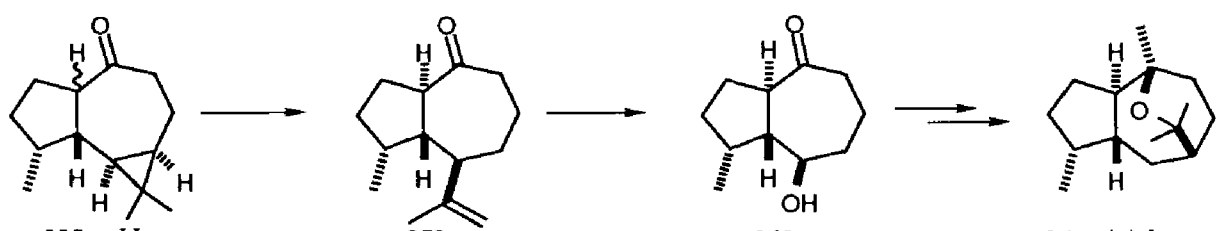
Schema 10.1



222 — **2**: 8αH, **3**: 8βH — **224** — **304**

De derivaten **222** en **304** werden beide gebruikt als uitgangsstof voor de synthese van verbindingen met het koolstof skelet van verschillende klassen sesquiterpenen. Selectieve, zuur gekatalyseerde verbreking van de C3-C4 binding van de cyclopropaan ring in **222** (en **223**) gaf (–)-isoapoaromadendron (**253**) in hoge opbrengst (hfst. 3, schema 10.2). Ozonolyse van **253** gaf de keto alcohol **262**, een geschikt chiraal intermediair voor de synthese van guaianen. Dit werd aangetoond met de synthese van (–)-kessaan (**264**) dat, uitgaande van **262**, in 9 stappen werd gesynthetiseerd in 43% totaal opbrengst.

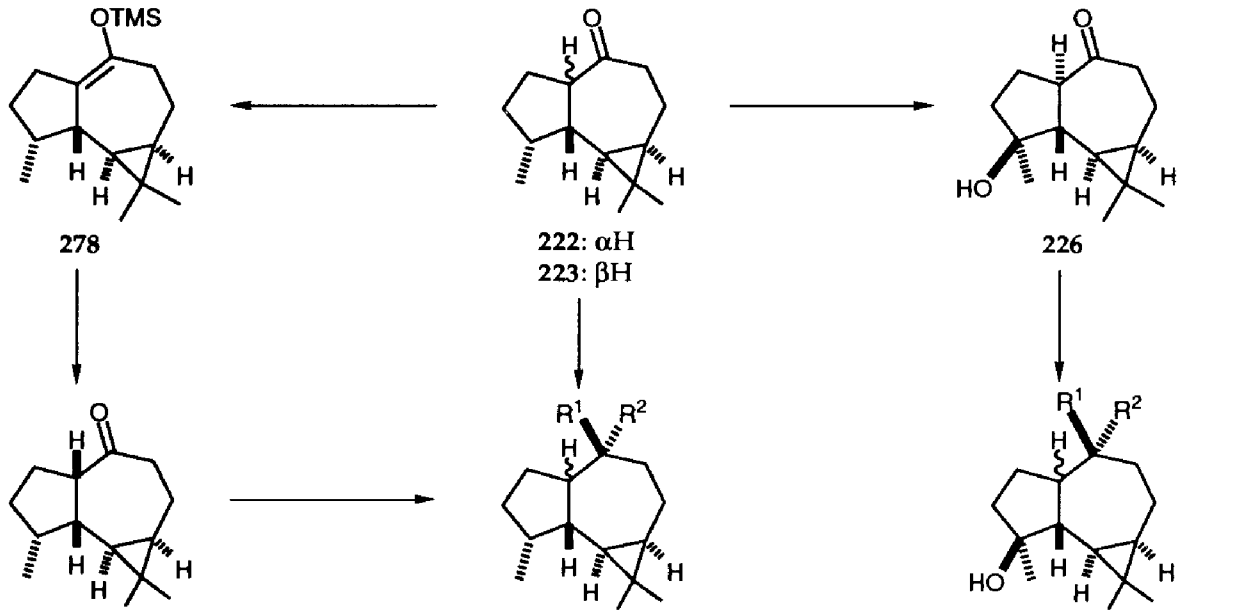
Schema 10.2



222: αH, **223**: βH — **253** — **262** — **264**: (–)-kessaan

De synthese van de mono- en dihydroxy aromadendranen **4-7, 31, 40, 41, 227, 276,** en **277**, uitgaande van **222**, is beschreven in hfst. 5. Het *cis*-verknoopte alloaromadendron (**223**), het sleutel intermediair voor de synthese van (–)-ledol (**6**) en (+)-viridiflorol (**7**), werd verkregen uit het *trans*-verknoopte apoaromadendron (**222**) via een selektieve protonering van de thermodynamische enol trimethylsilylether **278** (Schema 10.3). Hydroxylering van de tertiaire C11 in **222** met RuO_4 gaf **226**, dat kon worden omgezet in (+)-spathulenol (**31**), (–)-allospathulenol (**276**), en de aromadendraan-diolen **40, 41, 227,** en **277**. De verbindingen **4-7, 31, 40, 41, 227, 276,** en **277** werden getest op fungicide eigenschappen, maar hun werking was matig.

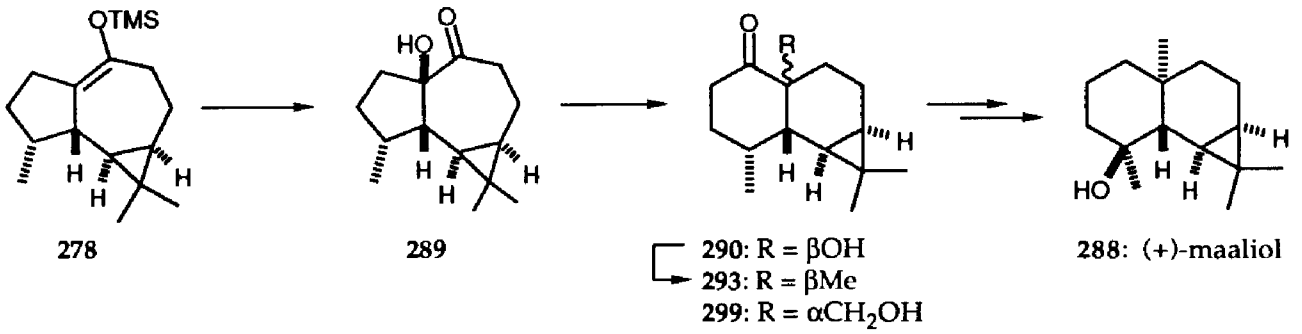
Schema 10.3



Een stereoselektieve epoxidatie van de thermodynamische enol trimethylsilylether **278** gaf het hydroazuleen α-ketol **289** (hfst. 6, schema 10.4). Uitgaande van dit α-ketol, werden twee verschillende routes naar hydronaftaleen verbindingen met een maaliaan skelet ontwikkeld, beide in hoge totaal opbrengst. De eerste route, via α-ketol **290** leidde naar het *cis*-verknoopte maaliaan keton **293**; de tweede gaf toegang tot

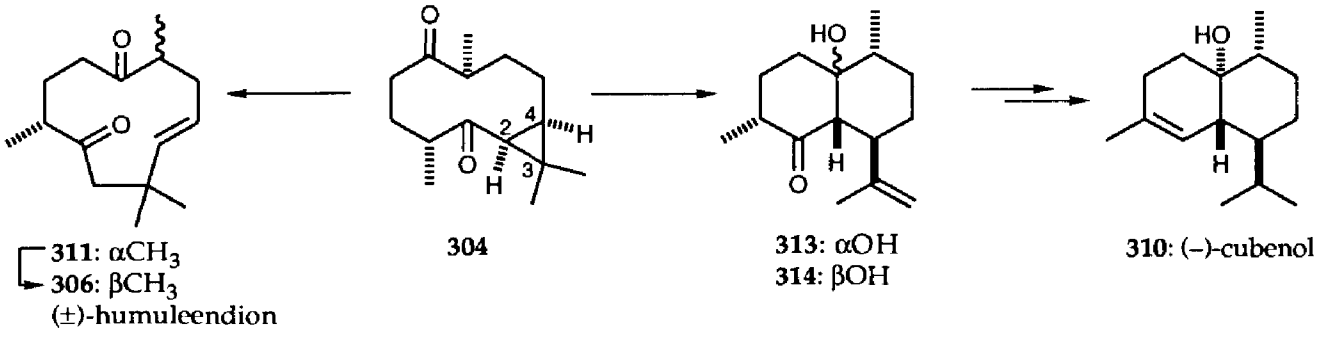
de *trans*-verknoopte maaliaan verbinding **299**. Vanuit **299** werd het natuurlijk voorkomende (+)-maaliol (**288**) gesynthetiseerd.

Schema 10.4



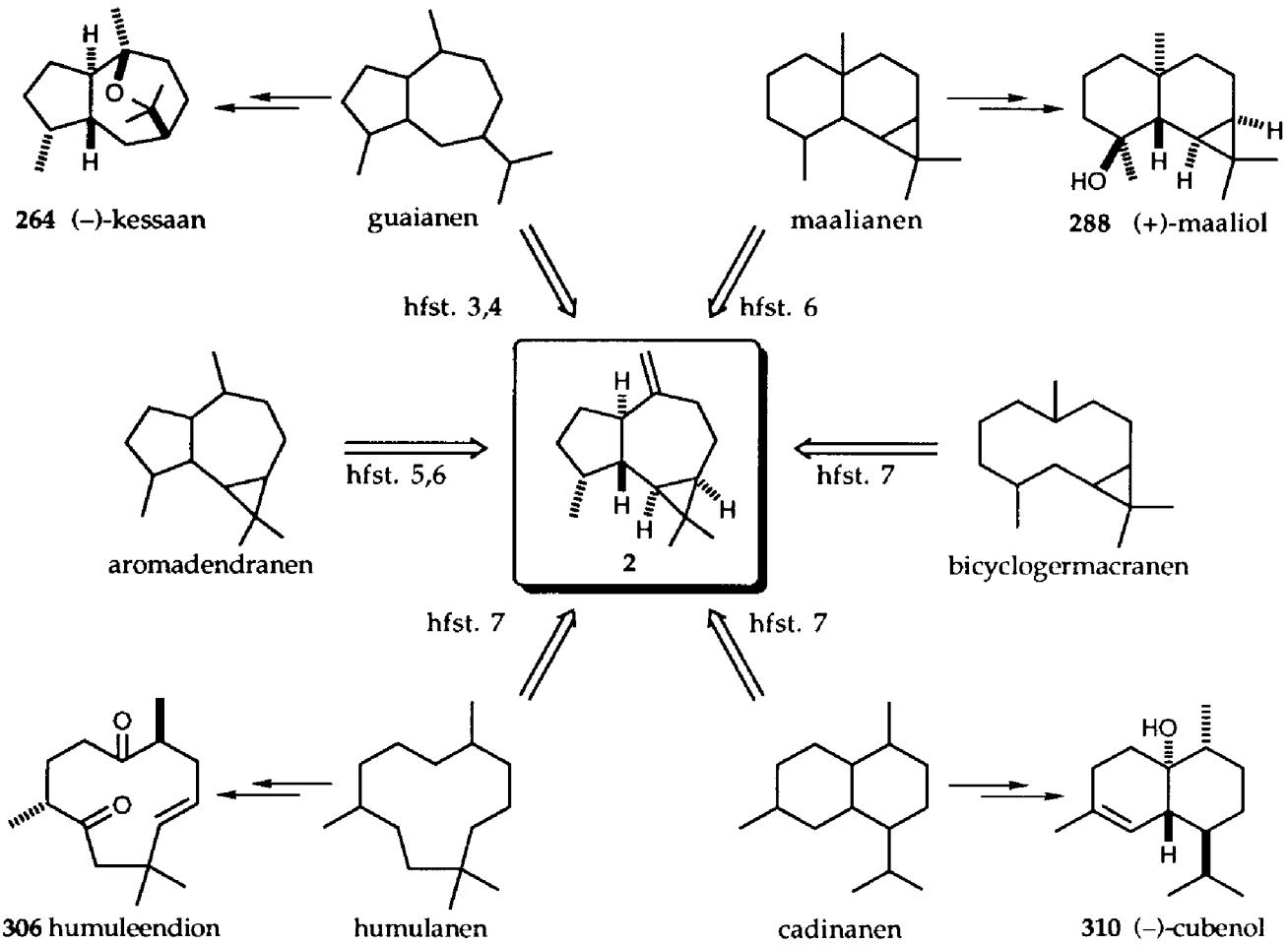
Synthon **304**, verkregen via de tweede zuiverings methode van de ruwe distillatie fraktie (*vide supra*), werd gebruikt als uitgangsstof voor verbindingen met een humulaan of cadinaan skelet (hfst. 7). De α-keto-cyclopropaan verbinding **304** bleek thermolabiel te zijn. Thermische omlegging van **304** gaf via een homo [1,5] waterstof verhuizing bij relatief lage temperatuur (refluxende dioxaan) de humulaan verbinding **311**, en bij hogere temperaturen (Flits Vacuum Pyrolyse, 500°C en hoger) de produkten **313** en **314**, beide met een cadinaan skelet (Schema 10.5). Epimerisatie van **311** gaf het natuurlijk voorkomende humuleendion (**306**). Uitgaande van **313** werd in 4 stappen het natuurlijk voorkomende (–)-cubenol (**310**) gesynthetiseerd.

Schema 10.5



De resultaten, beschreven in dit proefschrift, zijn kort samengevat in schema 10.6. Met (+)-aromadendreen (**2**) uit *Eucalyptus* olie als uitgangsstof zijn verbindingen met sesquiterpeen skeletten gesynthetiseerd die behoren tot de klassen van de guaianen, de aromadendranen, de maalianen, de bicyclogermacranen, de humulanen, en de cadinanen. (–)-Kessaan (**264**) (hfst. 4), verschillende mono- en dihydroxy aromadendranen (hfst. 5 en 6), (+)-maaliol (**288**) (hfst. 6), humuleendion **306** (hfst. 7) en (–)-cubenol (**310**) (hfst. 7) zijn natuurlijk voorkomende sesquiterpenen die gesynthetiseerd zijn, uitgaande van **2**. Op grond van deze resultaten kan geconcludeerd worden dat (+)-aromadendreen uit *Eucalyptus* olie een veelzijdige, chirale uitgangsstof is voor de synthese van sesquiterpenen.

Schema 10.6



Curriculum Vitae

Henricus Jacobus Maria (Harrie) Gijsen werd geboren op 9 september 1966 te Roermond. In 1984 behaalde hij het diploma Gymnasium-B aan het Bisschoppelijk College Broekhin te Roermond. Vanaf 1984 volgde hij de studie Molekulaire Wetenschappen aan de Landbouwuniversiteit te Wageningen. Als afstudeervakken koos hij voor Organische Chemie (dr. J.B.P.A. Wijnberg en prof. dr. Æ de Groot) en Biochemie (dr. ir. I. Rietjens). In september 1989 studeerde hij met lof af. Van juli 1989 tot juli 1993 was hij als onderzoeker in opleiding (OIO) verbonden aan de vakgroep Organische Chemie van de Landbouwuniversiteit Wageningen. Het tijdens deze periode uitgevoerde onderzoek, onder leiding van dr. J.B.P.A. Wijnberg en prof. dr. Æ de Groot, staat beschreven in dit proefschrift.