(+)-Aromadendrene as chiral starting material for the synthesis of fragrances and pheromones

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Yvonne

Contents

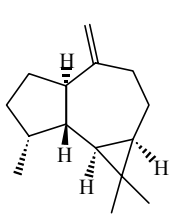
Chapter 1

Introduction

1.1 General introduction

(+)-Aromadendrene (**1**) is a sesquiterpene that belongs to the class of aromadendranes (**2**), structurally characterized by a dimethyl cyclopropane ring fused to a hydroazulene skeleton (Figure 1). The numbering of the carbon skeleton of aromadendranes as given in structure **2** will be followed throughout the text of this thesis.

Figure 1



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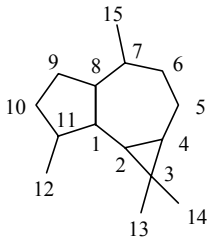

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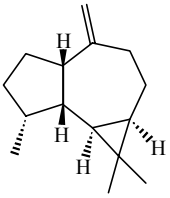

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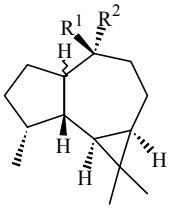


4: αH $R^1 = CH_3$ $R^2 = OH$
5: αH $R^1 = OH$ $R^2 = CH_3$
6: βH $R^1 = CH_3$ $R^2 = OH$
7: βH $R^1 = OH$ $R^2 = CH_3$

(+)-Aromadendrene is present in the essential oil of *Eucalyptus* trees, which in earlier days were known as *Aromadendron* trees. Aromadendrene is the first compound isolated with this carbon skeleton[1] and therefore its name has been used for the whole class of sesquiterpenes. The structure of (+)-aromadendrene was elucidated by Birch *et al.* in 1953.[2] Büchi *et al.* established its absolute configuration in 1966 through total synthesis of (–)-aromadendrene.[3] The same authors established the configuration of (–)-alloaromadendrene (**3**) as the C8 epimer of **1**, possessing a *cis*-fused hydroazulene skeleton.[4] Simultaneously, the absolute configurations of the tertiary C7 alcohols globulol (**4**), epiglobulol (**5**), ledol (**6**) and viridiflorol (**7**) were reported.

In 1995, a review by Gijsen *et al.* has been published which covers the occurrence, biosynthesis, and biological activity of aromadendranes, together with their synthesis and chemistry.[5] The literature in this review has been covered through September 1993. Naturally occurring aromadendranes reported more recently will be described in Paragraph 1.2.

Aromadendrene (**1**) is available in large quantities at low price as the major constituent (55-70%) of the sesquiterpene distillation tail of the oil from *Eucalyptus globulus* and is commercially available.[6] Next to **1**, this distillation tail consists of 10-15% of alloaromadendrene (**3**) and minor quantities of some other sesquiterpenes.

1.2 Isolation of aromadendranes

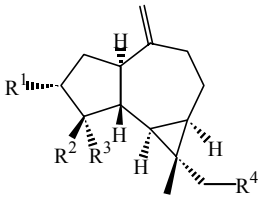
As described in the previous Paragraph, Gijsen *et al.* have published a review on aromadendranes in 1995.[5] In this review an overview is given of all naturally occurring aromadendranes reported in literature through September 1993. In this Paragraph aromadendranes and *ent*-aromadendranes reported more recently will be described. *ent*-Aromadendranes, possessing a carbon skeleton enantiomeric to that of aromadendranes, are mostly found in liverworts and marine sponges, while aromadendranes are mainly present in higher plants.

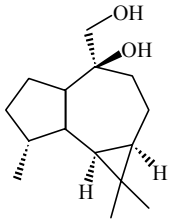
In Table 1 an overview is given of the recently reported aromadendranes and in Table 2 the *ent*-aromadendranes are listed. The structures of the compounds are given below the respective tables.

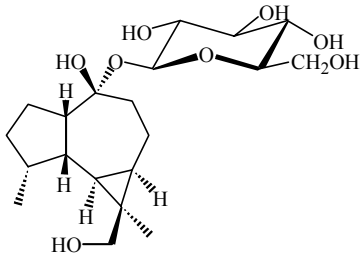
Table 1 Naturally occurring aromadendranes

Compound	Name	Isolated from	Ref.
8	(+)-14-hydroxyspathulenol	*Eriostemon brucei*	7
9	(+)-11-epispathulenol	*Taonia lacheana*	8
10	(–)-10-acetoxyspathulenol	*Parerythropodium fulvum*	9
11	alloaromadendrane-7,15-diol	*Duguetia grabriuscula*	10
12	(–)-dendroside A	*Dendrobium nobile*	11
13	(–)-aromadendrane-7,11-diol-7-monomethylether	*Sinularia maxima*	12
14	(–)-aromadendrane-7,11-diol	*Aristolochia heterophylla*	13
15	(–)-hebelodendrol	*Hebeloma longicaudum*	14
16	10,11-dehydro-epiglobulol	*Cistus ladaniferus*	15
17	(+)-aromadendra-1(11),7-dien-15-al-10-one	*Mandevilla pentlandiana*	16

Figure 2



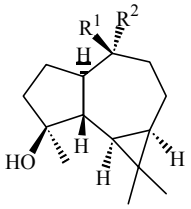


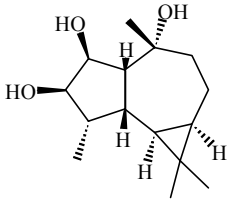


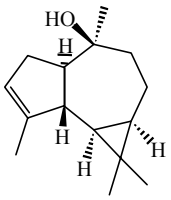
8: $R^1 = H$ $R^2 = OH$ $R^3 = CH_3$ $R^4 = OH$
9: $R^1 = H$ $R^2 = CH_3$ $R^3 = OH$ $R^4 = H$
10: $R^1 = OAc$ $R^2 = OH$ $R^3 = CH_3$ $R^4 = H$

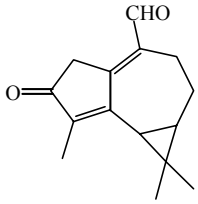
11

12









13: $R^1 = CH_3$ $R^2 = OCH_3$
14: $R^1 = OH$ $R^2 = CH_3$

15

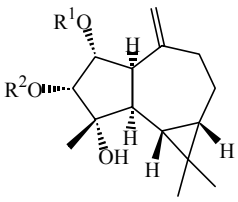
16

17

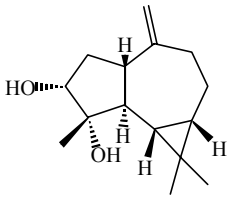
Table 2 Naturally occurring *ent*-aromadendranes

Compound	Name	Isolated from	Ref.
18	(+)-planotriol	*Heteroscyphus planus*	17
19	(+)-planotriol-9-monoacetate	*Heteroscyphus planus*	17
20	(–)-planotriol-9,10-diacetate	*Heteroscyphus planus*	17
21	(–)-10-hydroxyspathulenol	*Lepicolea ochroleuca*	18
22	(–)-aromadendrane-7,11-diol-7-monomethylether	*Sinularia maxima*	12
23	(+)-aromadendrane-7,11-diol-7-monomethylether	*Lepicolea ochroleuca*	18
24	(+)-7-isothiocyanatoalloaroma-dendrene	*Acanthella cavernosa*	19
25	(–)-aromadendr-1-ol	*Conocephalum conicum*	20
26	(+)-1,11-dehydroviridiflorol	*Calopogeia muelleriana*	21
27	(+)-aromadendr-1(11)-en-13-ol	*Conocephalum conicum*	20
28	(+)-millecrone B	*Leminda millecra*	22
29	(+)-10-hydroxyledene	*Calopogeia muelleriana*	21
30	(+)-1-hydroxyaromadendr-8-en-10-one	*Heteroscyphus coalitus*	23
31	(+)-aromadendra-8,11-dien-10-one	*Calopogeia azura*	24
32	(+)-8-hydroxyaromadendr-1(11)-en-10-one	*Heteroscyphus coalitus*	25

Figure 3



18: $R^1 = H$ $R^2 = H$
19: $R^1 = Ac$ $R^2 = H$
20: $R^1 = Ac$ $R^2 = Ac$



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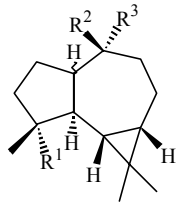
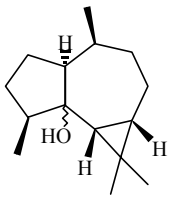


22: αH $R^1 = OH$ $R^2 = OCH_3$ $R^3 = CH_3$
23: βH $R^1 = OH$ $R^2 = OCH_3$ $R^3 = CH_3$
24: αH $R^1 = H$ $R^2 = CH_3$ $R^3 = NCS$



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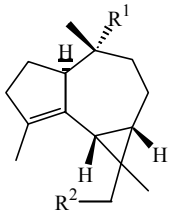
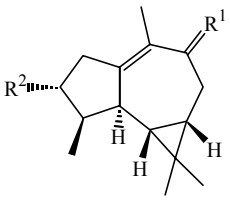
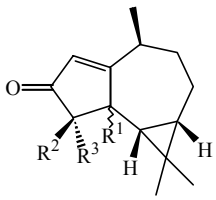


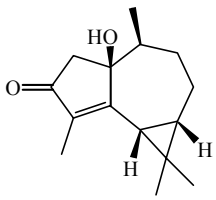
26: $R^1 = OH$ $R^2 = H$
27: $R^1 = H$ $R^2 = OH$



28: $R^1 = O$ $R^2 = H$
29: $R^1 = H_2$ $R^2 = OH$



30: $R^1 = \beta OH$ $R^2 = CH_3$ $R^3 = H$
31: $R^1 = \alpha H$ $R^2 = R^3 = CH_2$



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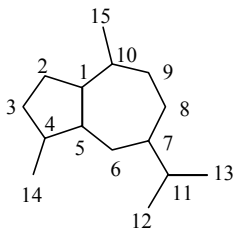
1.3 Isolation of guaianes

Sesquiterpenes strongly related to aromadendranes are the guaianes. These sesquiterpenes are structurally characterized by the substituted hydroazulene skeleton **33** (Figure 4). The numbering of the carbon skeleton of guaianes given in structure **33** will be used throughout the text of this thesis.

Figure 4



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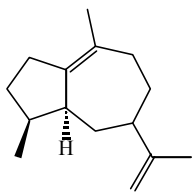

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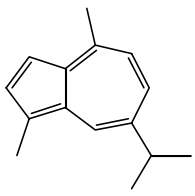

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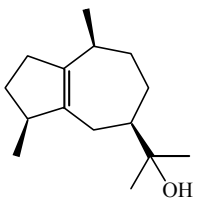

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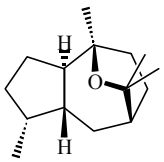

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The number of naturally occurring guaianes is very large and therefore the overview given in this Chapter is limited to guaiane hydrocarbons and mono-oxygenated guaianes. These compounds are also the ones that are used most frequently in fragrance formulations. Typical examples of guaiane hydrocarbons present in several plant species are α-bulnesene (**34**)[26-30] and guaiazulene (**35**).[31-38] The latter sesquiterpene is used as a blue pigment in cosmetics.

(–)-Guaiol (**36**) is a mono-oxygenated guaiane found in the essential oil of *Bulnesia sarmienti* (guaiac wood oil)[39] and *Pogostemon patchouli* (patchouli oil).[40] Next to guaiane alcohols, guaiane ethers are also found quite commonly in plant species. The most widespread example is (–)-kessane (**37**), which is present in *Valeriana officinalis*[41] and several other plant species.[42-44]

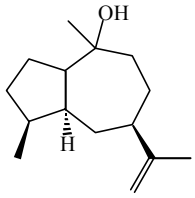
In Table 3 an overview is given of the guaiane hydrocarbons and mono-oxygenated guaianes known so far and of the organisms from which they have been isolated for the first time. The structures of the compounds are given in Figure 5 and 6.

Table 3 Naturally occurring guaianes

Compound	Name	Isolated from	Ref.
38	pogostol	*Pogostemon cablin* Benthum *Alpinia japonica*	45,46 47
39	(–)-nardol	*Nardostachys jatamansi D.C.*	48,49
36	(–)-guaiol	guaiac wood oil *(Bulnesia sarmienti)*	39
40	(–)-α-guaiene	*Bulnesia sarmienti* *Pogostemon patchouli*	26
41	(–)-rotundone	*Cyperus rotundus*	50
42	(+)-α-guaiene	*Dumortiera hirsuta*	51
43	(+)-calamusenone	*Acorus calamus, A. tatarinowii*	52
44	(+)-guai-4,10-dien-11-ol	*Viburnum awabuki* *Thuja occidentalis* L.	53 54
45	(+)-aciphyllene	*Dumortiera hirsuta*	51
46	(–)-guai-4,7(11)-dien-8-one	*Acorus calamus*	52
47	(+)-γ-gurjunene	*Dipterocarpus dyeri*	55,56
48	(+)-guai-5-en-11-ol	*Dipterocarpus* sp.	57
49	epi-γ-gurjunene	*Cumbastela hooperi*	58
50	guai-5-en-11-ol	*Tritomaria quinquedentata*	59
51	(+)-guaia-6,10-diene	*Nephthea chabrolii*	60
52	guai-6-en-4-ol	*Silphium perfoliatum*	61
53	guaia-6,10-dien-4-ol	*Athanasia dregeana* *Silphium perfoliatum*	62 61
54	(+)-alismol	*Alisma plantago-aquatica* var. *orientale*	63,64
55	guai-6-en-10-ol	*Guarea macrophylla*	65
34	(+)-α-bulnesene	*Bulnesia sarmienti* *Pogostemon patchouli*	26

Compound	Name	Isolated from	Ref.
56	(+)-bulnesol	*Bulnesia sarmienti*	66
57	(+)-guaia-1(10),11-dien-9-one	*Aquilaria agallocha*	67
58	(–)-guaia-1(10),11-dien-15-ol	*Aquilaria agallocha*	67
59	(–)-guaia-1(10),11-dien-15-al	*Aquilaria agallocha*	29
60	β-bulnesene	*Bulnesia sarmienti*	26
61	(–)-guaia-1(5),6-diene	*Halichondria* sp.	68
62	(+)-(5*R*,10*R*)-guai-1(5),6-diene	*Balsamum tolutanum*	69
63	(+)-(5*S*,10*R*)-guai-1(5),6-diene	*Balsamum tolutanum*	69
64	sclereosporal	*Sclerotinia fructicola*	70,71
65	(+)-isoguaiene	*Parthenium hysterophorus*	72
66	(–)-isoguaiene	*Dumortiera hirsuta*	51
67	(–)-guaia-4,6-diene	*Athanasia montana, A. dregeana*	62
68	(+)-guaia-4,6-dien-10-ol	*Nephthea chabrolii*	60
69	(+)-guaia-4,6-dien-11-ol	*Parthenium hysterophorus*	72
70	(–)-guaia-4,6-dien-11-ol	*Lettowianthus stellatus*	73
71	(–)-guaia-6,9-diene	*Geranium Bourbon*	74
72	(+)-guaia-6,9-diene	*Dumortiera hirsuta*	51
73	(+)-guaia-6,9-dien-4-ol	*Nephthea chabrolii*	75
74	sangol	*Lactarius sanguifluus*	76
75	guaia-1(2),3,5,7(11),9-pentaen-14-al	*Lactarius sanguifluus*	77
76	guaia-1(2),3,5,8,11-pentaen-14-ol	*Lactarius deliciosus*	78
77	delical	*Lactarius deliciosus, L. deterrimus*	79
35	guaiazulene	*Canarium strictum* Blue camphor oil *Matricaria chamomilla*	31 33,34 36
78	lactarazulene	*Lactarius deliciosus*	80
79	deterrol	*Lactarius deliciosus, L. deterrimus*	79
80	lactaroviolin	*Lactarius deliciosus*	81
81	11,12-dihydrolactaro-violin	*Lactarius deterrimus*	82

Figure 5



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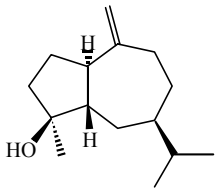

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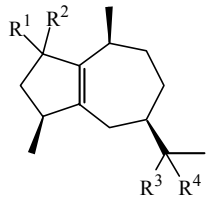
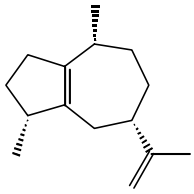
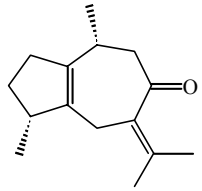




42

36: $R^1 = H$ $R^2 = H$ $R^3 = CH_3$ $R^4 = OH$
40: $R^1 = H$ $R^2 = H$ $R^3 = R^4 = CH_2$
41: $R^1 = R^2 = O$ $R^3 = R^4 = CH_2$



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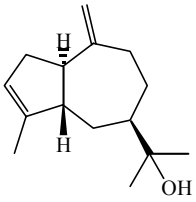

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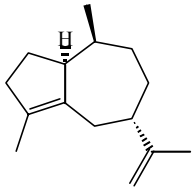

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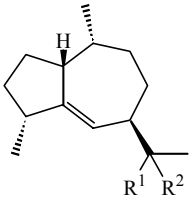
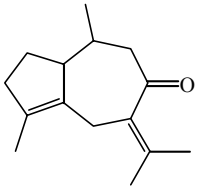


47: $R^1 = R^2 = CH_2$
48: $R^1 = CH_3$ $R^2 = OH$



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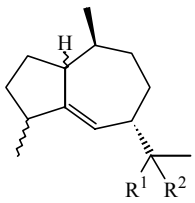
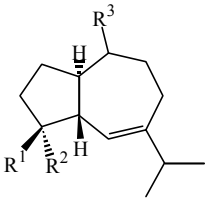
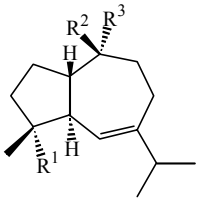


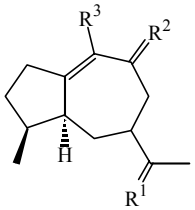
49: αMe βH $R^1 = R^2 = CH_2$
50: βMe αH $R^1 = CH_3$ $R^2 = OH$



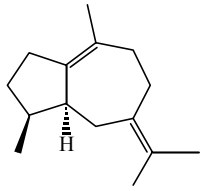
51: R^1, $R^2 = CH_3$, H $R^3 = CH_2$
52: $R^1 = CH_3$ $R^2 = OH$ $R^3 = CH_3$
53: $R^1 = CH_3$ $R^2 = OH$ $R^3 = CH_2$



54: $R^1 = OH$ $R^2 = R^3 = CH_2$
55: $R^1 = H$ $R^2 = OH$ $R^3 = CH_3$



34: $R^1 = H_2$ $R^2 = H_2$ $R^3 = CH_3$
56: R^1 = OH, H $R^2 = H_2$ $R^3 = CH_3$
57: $R^1 = H_2$ $R^2 = O$ $R^3 = CH_3$
58: $R^1 = H_2$ $R^2 = H_2$ $R^3 = CH_2OH$
59: $R^1 = H_2$ $R^2 = H_2$ $R^3 = CHO$



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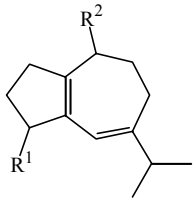
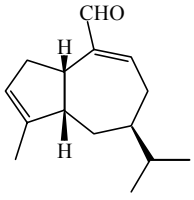


61: $R^1 = CH_3$ $R^2 = CH_3$
62: $R^1 = \alpha CH_3$ $R^2 = \alpha CH_3$
63: $R^1 = \beta CH_3$ $R^2 = \alpha CH_3$



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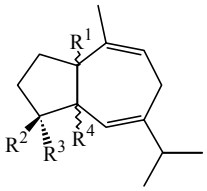
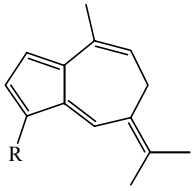
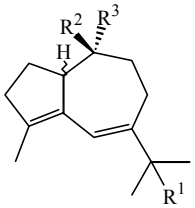


71: $R^1 = \beta H$ $R^2 = H$ $R^3 = CH_3$ $R^4 = \beta H$
72: $R^1 = \alpha H$ $R^2 = CH_3$ $R^3 = H$ $R^4 = \alpha H$
73: $R^1 = \alpha H$ $R^2 = OH$ $R^3 = CH_3$ $R^4 = \beta H$



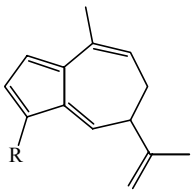
74: R = CH_2OH
75: R = CHO



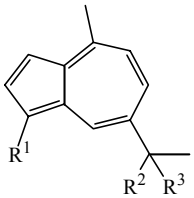
65: αH $R^1 = H$ $R^2 = CH_3$ $R^3 = H$
66: βH $R^1 = H$ $R^2 = H$ $R^3 = CH_3$
67: $R^1 = H$ R^2, $R^3 = CH_3$, H
68: αH $R^1 = H$ $R^2 = CH_3$ $R^3 = OH$
69: αH $R^1 = OH$ $R^2 = CH_3$ $R^3 = H$
70: αH $R^1 = OH$ $R^2 = H$ $R^3 = CH_3$

Compound	Name	Isolated from	Ref.
82	lactarofulvene	*Lactarius deliciosus*	83
83	(+)-1,5-epoxyguaiane	*Cyperus rotundus*	50
84	1α,5α-epoxyguai-11-ene	*Pogostemon cablin Benth*	46
85	1β,5β-epoxyguai-11-ene	*Pogostemon cablin Benth*	46
86	(+)-3,4-epoxyguai-10-ene	*Nephthea* sp.	84
87	1,10-epoxyguai-11-ene	*Pogostemon cablin Benth*	46
88	(–)-1,10-epoxyguai-11-ene	*Aquilaria agallocha*	67
89	(+)-guaioxide	*Bulnesia sarmienti*	26,85
90	(–)-liguloxide	*Ligularia fischeri*	86
91	5,11-oxaguaiane	*Ligularia* sp.	87
92	(+)-9,11-oxaguaia-4,10-diene	*Thuja occidentalis*	54
93	(–)-1,11-oxaguai-10-ene	*Eriostemon fitzgeraldii*	88
37	(–)-kessane	*Valeriana officinalis*	41

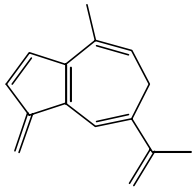
Figure 6



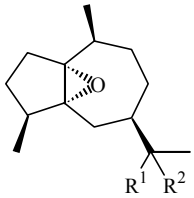
76: R = CH_2OH
77: R = CHO



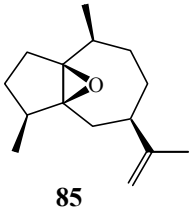
35: $R^1 = CH_3$ $R^2 = CH_3$ $R^3 = H$
78: $R^1 = CH_3$ $R^2 = R^3 = CH_2$
79: $R^1 = CH_2OH$ $R^2 = R^3 = CH_2$
80: R^1 = CHO $R^2 = R^3 = CH_2$
81: R^1 = CHO $R^2 = CH_3$ $R^3 = H$



82



83: $R^1 = CH_3$ $R^2 = H$
84: $R^1 = R^2 = CH_2$



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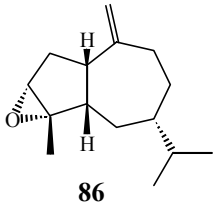

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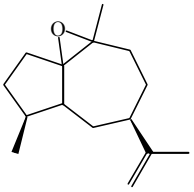
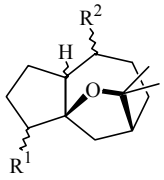
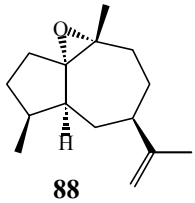




89: βH $R^1 = \beta Me$ $R^2 = \beta Me$
90: βH $R^1 = \alpha Me$ $R^2 = \beta Me$
91: αH $R^1 = \alpha Me$ $R^2 = \alpha Me$



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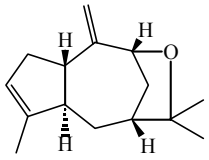

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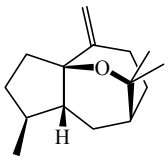

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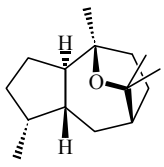


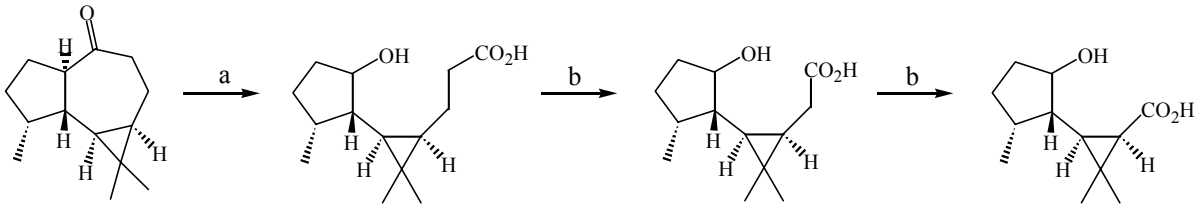
37

1.4 The chemistry of aromadendrene

Numerous reactions have been carried out in order to determine the structure of aromadendrane sesquiterpenes. In early literature about aromadendrene and its derivatives, the characterization of products was very difficult because of the limited analytical methods available, which often led to the wrong conclusions. For clarity, in this overview only the chemistry of aromadendrene (**1**) and alloaromadendrene (**3**) published after the structure of aromadendrene had been established correctly[2], is included.

Dolejs *et al.* have reported the stepwise degradation of the aromadendrane skeleton in order to establish the position of the cyclopropane ring in aromadendrene.[89] (+)-Apoaromadendrone (**94**), produced by oxidation of the double bond in aromadendrene, was subjected to a Baeyer-Villiger oxidation and subsequently hydrolyzed to hydroxy acid **95** (Scheme 1). In compound **97**, which was obtained from **95** after two subsequent Barbier-Wieland degradations, the cyclopropane ring was still present, thereby confirming its position as proposed by Birch *et al.*[2]

Scheme 1

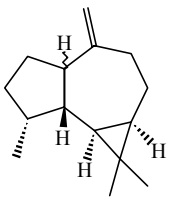


94 **95** **96** **97**

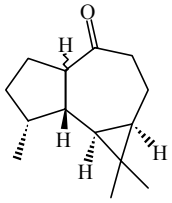
a: perphtalic acid; hydrolysis; b: Barbier-Wieland degradation.

One of the most reported reactions on aromadendrene (**1**) is its oxidation to (+)-apoaromadendrone (**94**) by ozonolysis or by treatment with $KMnO_4$ and $NaIO_4$.[90] In a similar way (–)-alloapoaromadendrone (**98**) was obtained from (–)-alloaromadendrene (**3**).[91,92] Compound **98** can be converted easily to its more stable C8 epimer **94** by heating[91] or by treatment with base.[55] Introduction of a C8-C9 double bond in **94**, leading to **99**, was achieved by bromination with NBS and subsequent dehydrobromination with LiCl in DMF.[93] Hydrogenation of **99** led selectively to the formation of alloapoaromadendrone (**98**), indicating that the β-side of **99** is the least hindered side of the molecule.

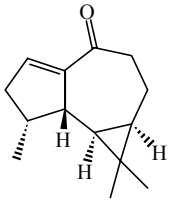
Figure 7



1



94: αH
98: βH



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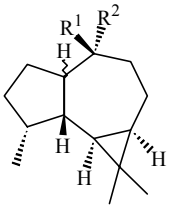
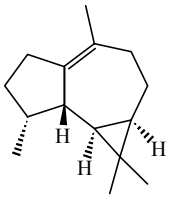


4: αH $R^1 = CH_3$ $R^2 = OH$
5: αH $R^1 = OH$ $R^2 = CH_3$
6: βH $R^1 = CH_3$ $R^2 = OH$
7: βH $R^1 = OH$ $R^2 = CH_3$



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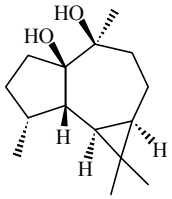


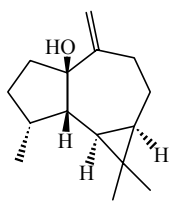
101

Epoxidation of aromadendrene and subsequent reduction with $LiAlH_4$ gave a mixture of globulol (**4**) and epiglobulol (**5**).[93] A selective formation of epiglobulol is achieved upon treatment of apoaromadendrone (**94**) with MeLi[93] or MeMgI.[90] In a similar way, a mixture of ledol (**6**) and viridiflorol (**7**) is obtained after epoxidation and reduction of alloapoaromadendrone **98**.[93,94] Ledol has been obtained selectively by treatment of **98** with MeLi[93] or MeMgI.[94]

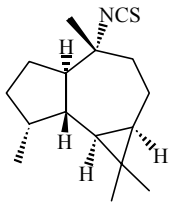
Dehydration of the alcohols **4**-**7** led to the formation of ledene (**100**) (Figure 7), which is often characterized by formation of its dihydroxylated product ledglycol (**101**).[90,94] The stereochemistry of **101** has been established as the β-diol by X-ray crystallography.[95]

The structure of an unknown aromadendrane sesquiterpene from *Laurencia subopposita* was established through reaction of alloaromadendrene (**3**) with selenium oxide to produce alcohol **102** (Figure 8). This alcohol was identical with the natural sesquiterpene.[96]

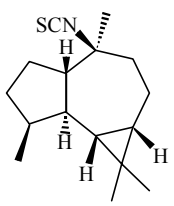
Figure 8



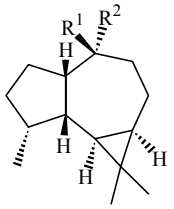
102



103



104

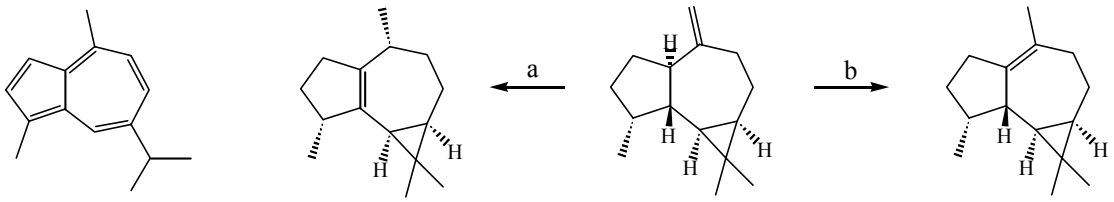


105: $R^1 = NCS$ $R^2 = CH_3$
106: $R^1 = CH_3$ $R^2 = NCS$

Conversion of aromadendrene to isothiocyanate **103** in a reaction with thiocyanic acid was used by da Silva *et al.* to establish the absolute stereochemistry of axisothiocyanate-2 (**104**), which proved to be the enantiomer of **103**.[97] Treatment of alloaromadendrene under the same conditions produces **105**, the epimer of the naturally occurring isothiocyanate **106**. More recently, compound **24** (see Figure 3), the enantiomer of **105**, has been isolated from *Acanthella cavernosa.*[19]

Dehydrogenation of aromadendranes to guaiazulene **35** (Scheme 2) with sulfur or selenium has been used as structural prove for the presence of the hydroazulene skeleton in natural products. Generally, the yield of these reactions is very low. However, treatment of aromadendrene with dithioglycolate as hydrogen acceptor under thermic or photochemical reaction conditions has led to the formation of guaiazulene in a yield up to 48%.[98] This reaction will be described in more detail in Chapter 3.

Scheme 2



35 **107** **1** **100**

a: K/Al_2O_3, 20 °C; b: K/Al_2O_3, 100 °C; c: KO*t*Bu, DMSO, 100 °C.

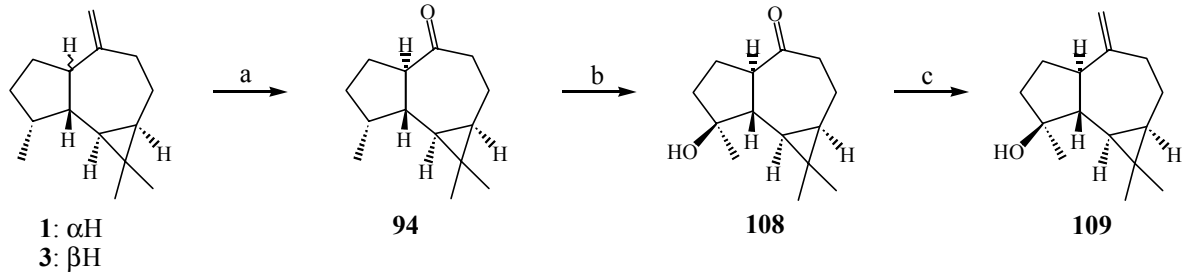
Double bond isomerization of aromadendrene has been investigated by Rienäcker and Graefe.[99] When **1** was treated with potassium on alumina (K/Al_2O_3) at room temperature, (–)-isoledene (**107**) was obtained in high yield. When the temperature of the reaction is raised to 100 °C, (+)-ledene (**100**) is formed in 42% yield, together with isoledene and other isomers. A better yield of **100** could be achieved when **1** was treated with KO*t*Bu in DMSO at 100 °C.[100]

(+)-Spathulenol (**109**), a naturally occurring fragrance, has been synthesized from (+)-aromadendrene in three steps.[101] First, a distillation fraction of *Eucalyptus globulus* (containing 58% of **1** and 12% of **3**) was ozonolyzed to a mixture of apoaromadendrone (**94**) and alloapoaromadendrone (**98**). Crystallization provided pure **94**, which upon treatment with ozone gave **108** in 9% yield (after 50% conversion). This product was converted to (+)-spathulenol by a Wittig reaction.

Gijsen *et al.* improved the yield of the reaction of **94** to **108** by using RuO_2 in the presence of $NaIO_4$.[102] The optimum yields of **108** reached to 35-40% after a

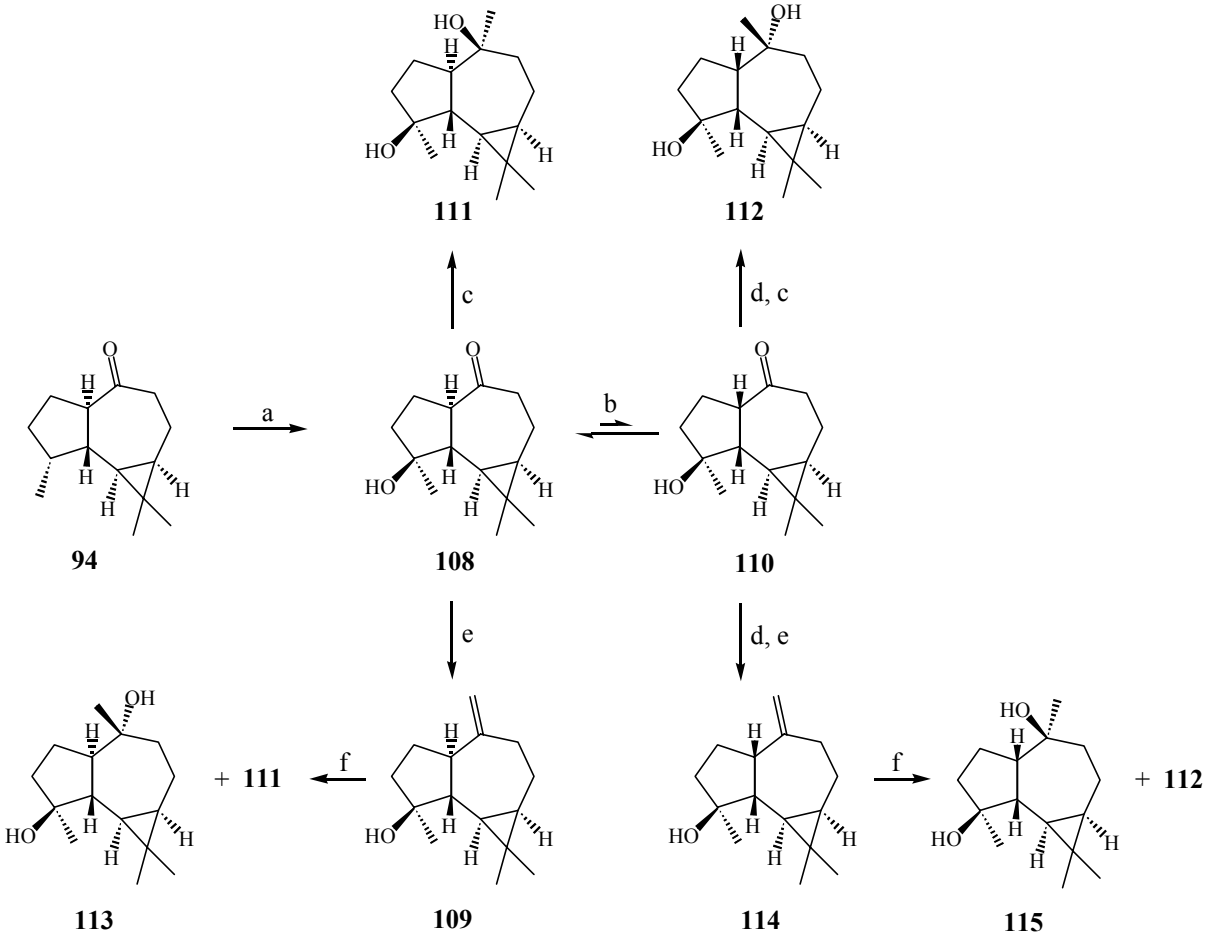
conversion of 50%. This reaction was also used in the route to the synthesis of the dihydroxyaromadendranes **111**, **112**, **113**, and **115** from aromadendrene, as depicted in Scheme 4. These four diols were tested for antifungal properties, together with the monohydroxy compounds **4**-**7**, but their activities were only moderate.

Scheme 3



a: O_3, EtOH; $P(OEt)_3$; purification; b: O_3, cyclohexane; c: Ph_3PCH_2.

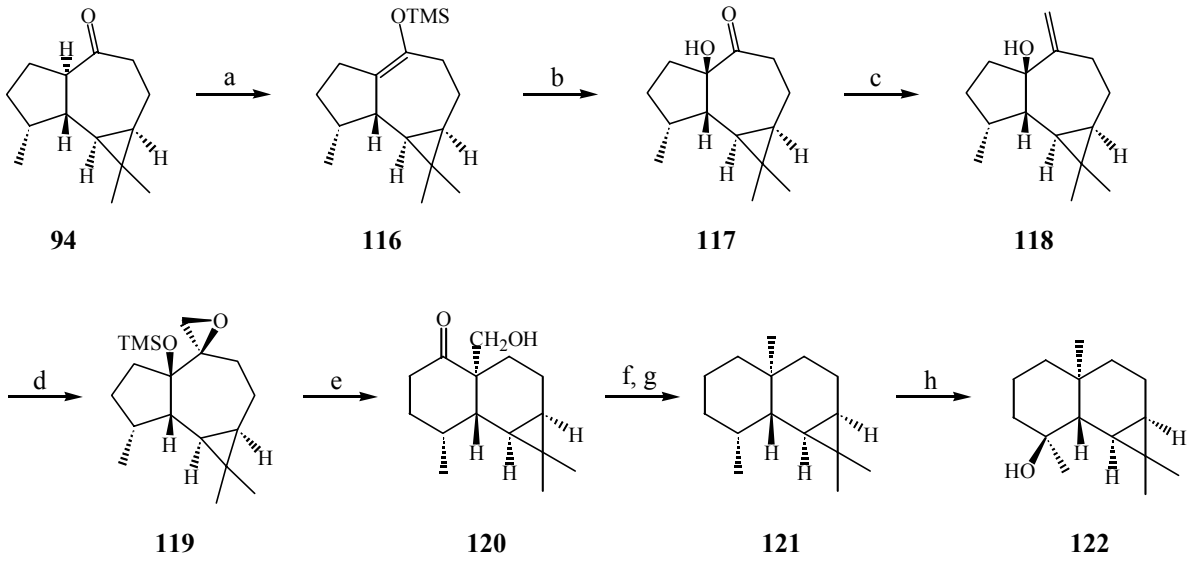
Scheme 4



a: RuO_2, $NaIO_4$; b: NaOMe, MeOH; c: MeMgI; d: TMSCl, HMDS; e: $TMSCH_2MgCl$; H^+, THF; f: dimethyldioxirane; $LiAlH_4$.

(+)-Apoaromadendrone **94** was also used as starting material for the synthesis of (+)-maaliol (**122**), a maaliane sesquiterpene found in several plant species.[103] In this approach compound **119** was synthesized first (Scheme 5). Treatment of **119** with $TiCl_4$ initiated rearrangement of the aromadendrane skeleton to the maaliane **120**. After removal of both the ketone and the alcohol function, subsequent oxidation of resulting **121** with RuO_2 and $NaIO_4$ produced (+)-maaliol.

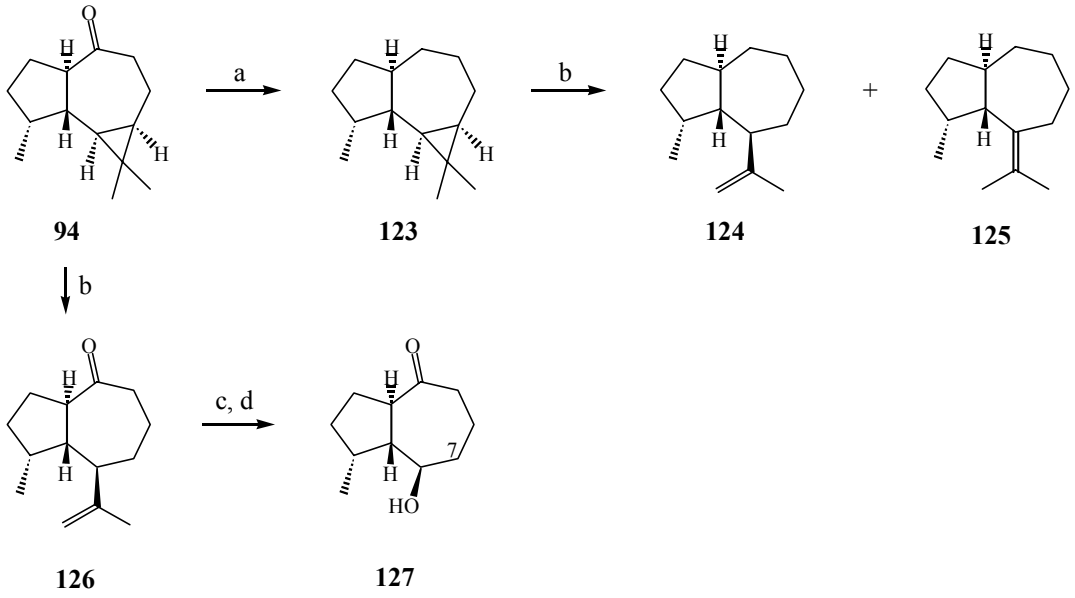
Scheme 5



a: TMSCl, Et_3N, DMF, 130 °C; b: dimethyldioxirane; SiO_2; c: TMSCl, HMDS, pyridine; Ph_3PCH_2; TBAF; d: *t*BuOOH, $VO(acac)_2$; TMSCl, HMDS, pyridine; e: $TiCl_4$, CH_2Cl_2, -78 °C; f: tosylhydrazine, $NaBH_3CN$, $ZnCl_2$, MeOH, Δ; g: *n*BuLi, bis(dimethylamino)chlorophosphoramidate; Li, $EtNH_2$, *t*BuOH; h: RuO_2, $NaIO_4$, 50 °C.

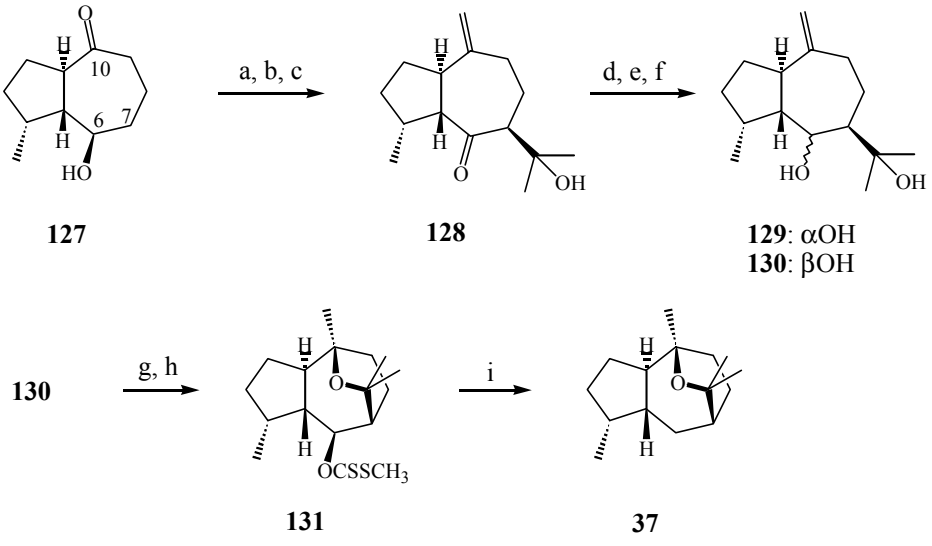
Because aromadendranes and guaianes are structurally related, selective cleavage of the C2-C3 bond in aromadendranes will be an attractive approach for a short synthesis of guaianes from aromadendrene. However, all attempts to selectively open the cyclopropane ring of aromadendrene to a guaiane failed.[104] Treatment of aromadendrene (**1**), globulol (**4**), and epiglobulol (**5**) with concentrated HCl in refluxing ethanol led to complex mixtures. When the noraromadendrane **123**, synthesized from (+)-apoaromadendrone (**94**) in three steps, was treated under the same conditions, a 4:1 mixture of **124** and its C6-C11 double bond isomer **125**, respectively, was obtained. Treatment of **94** under the same conditions led to a 75% yield of (–)-isoapoaromadendrone (**126**). This product could be converted in 56% yield to alcohol **127** through ozonolysis, Criegee rearrangement, and saponification of the acetate (Scheme 6).

Scheme 6



a: $NaBH_4$; MsCl, pyridine; $LiBEt_3H$; b: conc. HCl, EtOH, reflux; c: O_3, CCl_4, MeOH; Ac_2O, Et_3N, DMAP; d: NaOMe, MeOH.

Scheme 7

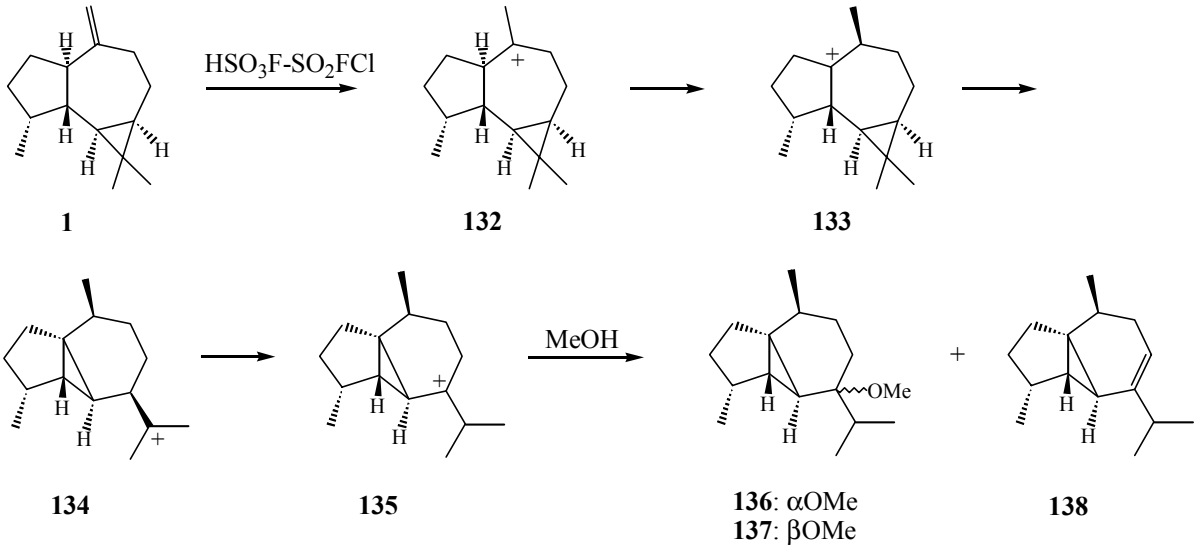


a: Ph_3PCH_2; b: Jones oxidation; c: LDA, $ZnCl_2$, acetone; d: TMSCl, HMDS, pyridine; e: $LiAlH_4$; f: TBAF; separation; g: $Hg(OAc)_2$; $NaBH_4$, NaOH; h: NaH, CS_2, MeI; i: Bu_3SnH, AIBN.

The guaiane skeleton could be obtained from aromadendrene by reintroduction of an isopropyl group at C7 in alcohol **127**. In this way, (–)-kessane (**37**) was synthesized from **127**, in an overall yield of 43% over nine steps (Scheme 7).[105] First the double bond at C10 was reinstalled and after oxidation of the alcohol at C6, the isopropyl group was introduced to obtain product **128**. This compound was almost selectively reduced to compound **130** (ratio **129**:**130** = 1:11.5). Cyclic ether formation under oxymercuration conditions and removal of the hydroxyl group easily converted **130** to (–)-kessane.

The behavior of aromadendrene in superacidic media has been reported by Polovinka *et al.*[106-108] Upon treatment of **1** with HSO_3F-SO_2FCl at –110 °C, a mixture of the products **136**, **137**, and **138** is obtained (Scheme 8).[106,107]

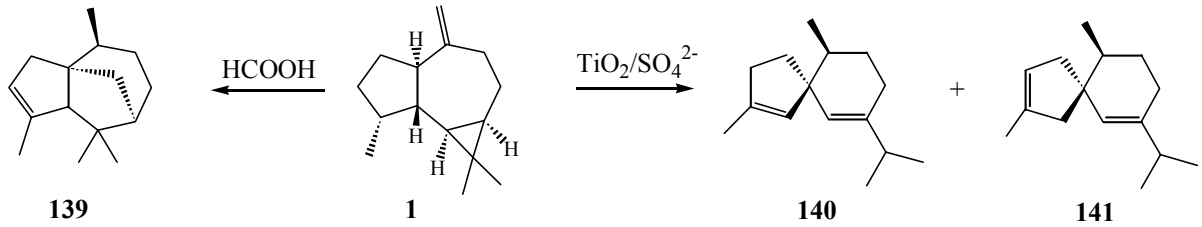
Scheme 8



The first two steps in this rearrangement of **1** are protonation of the double bond and a 1,2-H shift, resulting in the bridgehead cation **133**. This cation rearranges further to **134**, which in turn produces the cyclopropylcarbinyl cation **135**, which is the most stable one that can be obtained. Quenching of the reaction mixture with MeOH then results in the formation of the compounds **136**, **137**, and **138**.

In a later publication by the same authors[108], more reactions of aromadendrene in acidic and superacidic media have been reported. Treatment of **1** with formic acid at reflux temperature led to formation of **139**, and from the reaction of **1** with TiO_2/SO_4^{2-} a mixture of **140** and **141** was obtained (Scheme 9).

Scheme 9



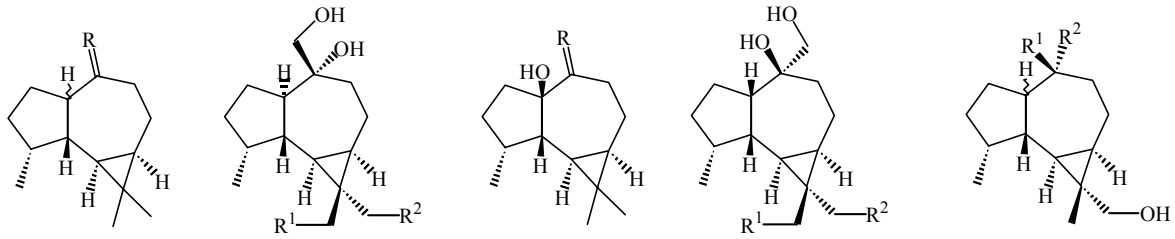
139 **1** **140** **141**

Aromadendranes have been hydroxylated at different positions by microorganisms. In Table 4 an overview is given of the outcome of microbial transformations with aromadendrene (**1**), alloaromadendrene (**3**), alloapoaromadendrone (**98**), and the diols **142** and **147** (Figure 9). In general these transformations are of little synthetic use, because the yields are very low. The only exception is the conversion of **142** to **143** by *Mucor plumbeus* in a yield of 61% (Entry 6).

Table 4 Conversion of some aromadendranes by microorganisms

Entry	Start.mat.	Microorganism	Results	Ref.
1	**1**	*Bacillus megaterium* DSM32	**1** (17%) + **142** (0.4%) + **143** (0.7%)	109
2	**1**	*Glomerella cingulata*	**1** (22%) + **143** (6%)	110
3	**1**	*Mucor plumbeus*	**1** (70%) + **143** (3%)	111
4	**3**	*Mycobacterium smegmatis*	**3** (64%) + **145** (0.8%)	109
5	**3**	*Glomerella cingulata*	**3** (12%) + **148** (3%)	110
6	**142**	*Mucor plumbeus*	**143** (61%) + **144** (0.6%)	111
7	**142**	*Cephalosporium aphidicola*	**143** (31%)	111
8	**147**	*Beauvaria densa* CMC 3240	**148** (4.6%) + **149** (38%)	112
9	**147**	*Beauvaria bassiana* ATCC 7159	**148** (28%) + **149** (28%)	112
10	**147**	*Curvularia lunata* 2380	**148** (24%) + **149** (27%)	112
11	**98**	*Beauvaria densa* CMC 3240	**150** (8.5%)	112
12	**98**	*Beauvaria bassiana* ATCC 7159	**150** (16.2%)	112
13	**98**	*Curvularia lunata* 2380	**150** (11.7%) + **151** (12.1%)	112
14	**98**	*Rhizopus* sp.	**146** (17.3%)	112

Figure 9

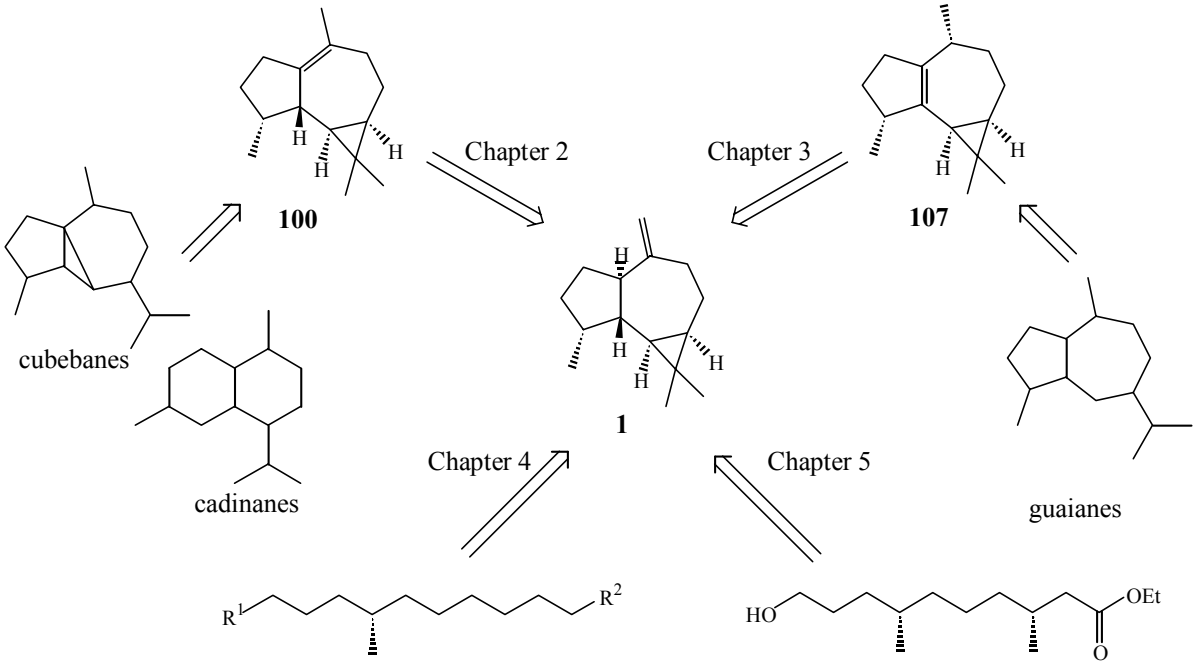


1: αH R = CH_2 **142**: R^1 = H R^2 = H **145**: R = CH_2 **147**: R^1 = H R^2 = H **150**: R^1 = R^2 = O
3: βH R = CH_2 **143**: R^1 = H R^2 = OH **146**: R = O **148**: R^1 = H R^2 = OH **151**: R^1 = OH R^2 = H
98: βH R = O **144**: R^1 = OH R^2 = H **149**: R^1 = OH R^2 = H

1.5 Scope of this thesis

As follows from the previous Paragraph, aromadendrene has several functionalities that can be used as a handle for synthetic transformations. In this thesis the use of aromadendrene **1** as starting material for the synthesis of fragrance compounds and pheromones is investigated further.

Scheme 10



In Chapter 2 the chemistry of ledene (**100**), a double bond isomer of aromadendrene, and the rearrangements of ledene epoxide will be described. These rearrangements lead to the formation of products with the cubebane and the cadinane skeleton.

Isoledene (**107**), another double bond isomer of **1** has been used as starting material for the synthesis of guaianes. The approaches to the guaiane skeleton via the rearrangement of isoledene epoxide and the synthesis of guaiazulene will be reported in Chapter 3.

Chiral linear pheromones with one or more methyl groups are found commonly in various insects. A reaction sequence, with a Baeyer-Villiger reaction and a Grob fragmentation as the key steps, has led to the formation of a chiral linear intermediate from aromadendrene. Its synthesis and the transformation to chiral linear pheromones with one methyl group are described in Chapter 4. A synthetic route toward a suitable intermediate for the synthesis of chiral pheromones with two methyl groups, is reported in Chapter 5.

In Chapter 6 the results of the research described in this thesis will be discussed.

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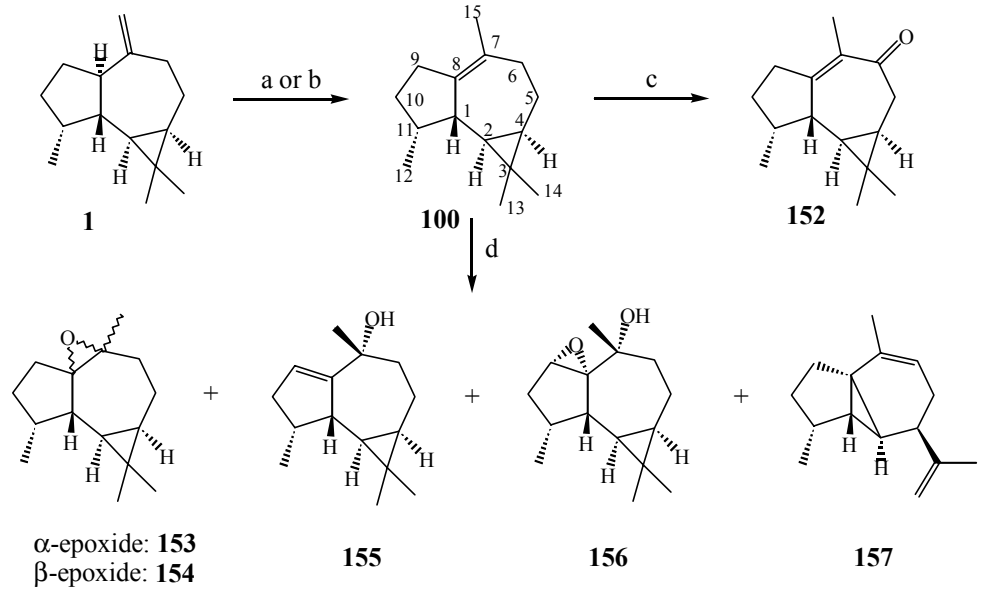
Chapter 2

(+)-Ledene as starting material for the synthesis of sesquiterpenes

2.1 The chemistry of ledene

The aromadendrane sesquiterpene (+)-ledene (**100**), also known as viridiflorene, is present in small amounts in the essential oils of *Melaleuca alternifolia*[1], *Melaleuca leucadendron*[2], *Cassina uncata*[3], *Valeriana officinalis* var. *sambucifolia*[4], and a *Prostanthera* species.[5] The most simple way to obtain ledene in large quantities is its synthesis from (+)-aromadendrene (**1**). This can be achieved in 80% by a reaction of **1** with KO*t*Bu in DMSO at 100 °C (Scheme 1).[6] In the reaction of **1** with potassium on aluminum oxide (K/Al_2O_3) at 100 °C, ledene is formed in a much lower yield (42%).[7] Ledene has been used in experiments to establish the absolute configuration of, among others, globulol and viridiflorol (see Chapter 1).

Scheme 1

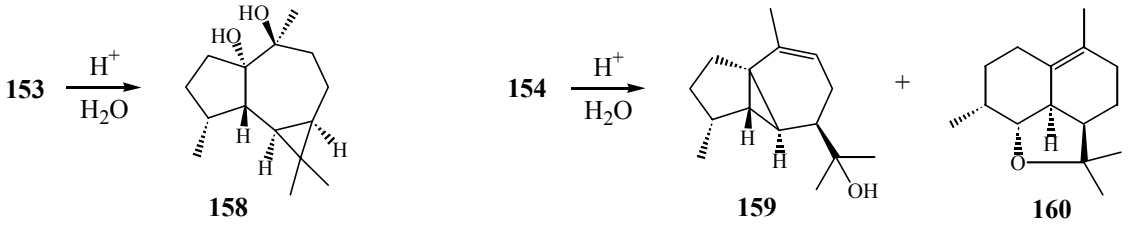


a: K/Al_2O_3, 100 °C; b: KO*t*Bu, DMSO, 100 °C; c: SeO_2; d: *m*CPBA, CH_2Cl_2.

The allylic oxidation of ledene led to squamulosone (**152**), a natural sesquiterpene found in *Phebalium squamulosum*.[8] Treatment of ledene with *m*CPBA in CH_2Cl_2 resulted in a mixture of five compounds (**153-157**).[9] The ratio between these compounds depends on the reaction temperature and the amount of *m*CPBA. When the reaction is performed at 0 °C, β-epoxide **154** is the main product (73-76%). However, at higher temperatures (room temperature or at reflux), compound **154** is not detected at all. Under these conditions, a product mixture of **153**, **155**, **156**, and **157** is formed. The highest yield of α-epoxide **153** (25%) is reached when 1.3 equivalents of *m*CPBA are used at room temperature.

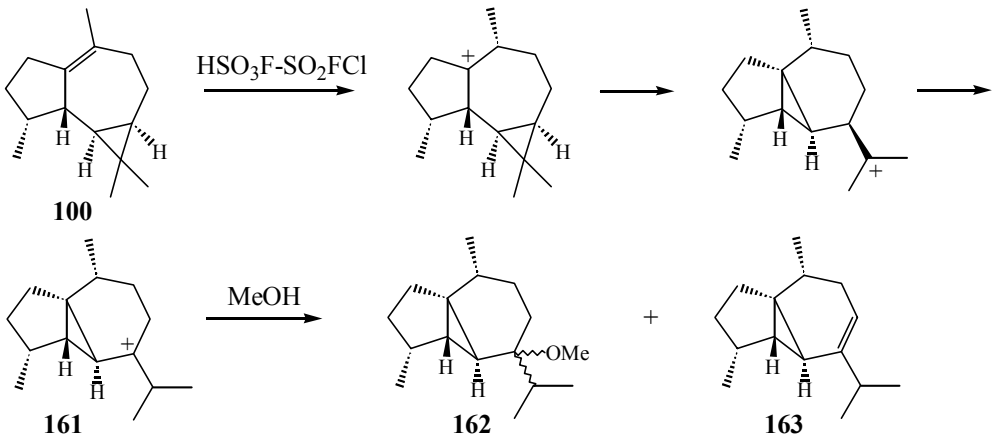
Attempts to open the epoxide ring of compounds **153** and **154** with $LiAlH_4$ were unsuccessful.[9] However, acidic workup converted the α-epoxide **153** to diol **158**, whereas the β-epoxide **154** rearranged to compounds **159** and **160**. The mechanism of this rearrangement will be discussed later in this chapter.

Scheme 2



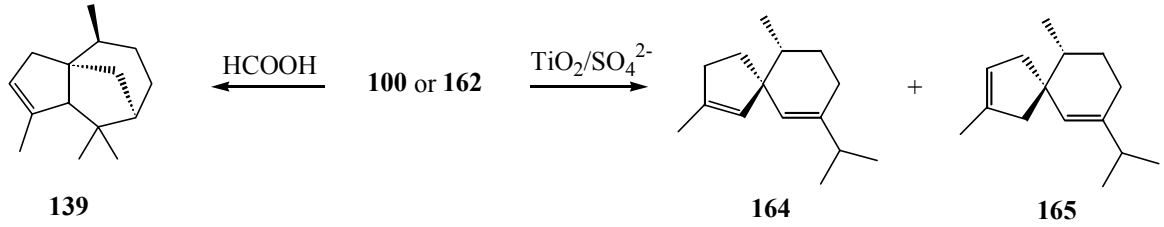
The behavior of ledene in superacidic media is similar to that of aromadendrene (see Chapter 1).[10,11] In the reaction with HSO_3F-SO_2FCl, the double bond in ledene is protonated at the β-side and a bridgehead cation is formed, leaving the methyl group at C7 in the α-position. Further rearrangement and a H shift lead to the stabilized cyclopropylcarbinyl cation **161** which, after quenching the reaction mixture with MeOH, gives a mixture of the compounds **162** and **163**.

Scheme 3



Heating of **100** or **162** in formic acid at reflux temperature leads to the formation of compound **139**.[12] This product is also formed in the reaction of aromadendrene with formic acid (see Chapter 1). Furthermore, **100** has been converted to a mixture of **164** and **165** in a reaction with TiO_2/SO_4^{2-} (Scheme 4).[12]

Scheme 4

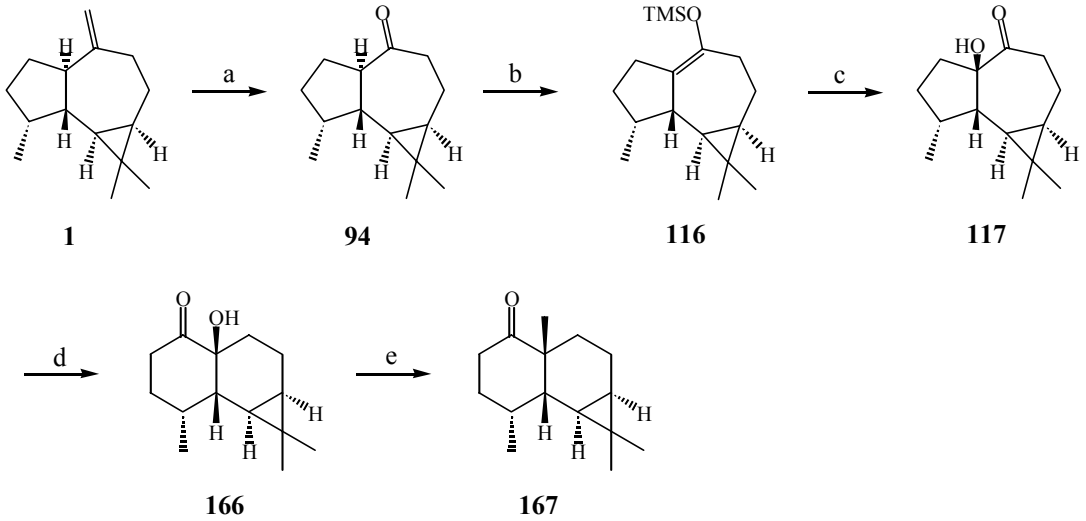


139 **164** **165**

2.2 Synthesis of a maaliane skeleton from ledene

Gijsen *et al.*[6] have described a five-step conversion of (+)-aromadendrene to the fragrance compound **167**, as depicted in Scheme 5. In this route aromadendrene is first ozonolyzed to apoaromadendrone **94**. After formation of a silyl enol ether, the double bond is epoxidized and subsequent treatment of the resulting epoxide with silica leads to α-ketol **117**. Rearrangement of the aromadendrane to the maaliane skeleton (**117→166**) takes place upon treatment with aluminum oxide. Finally, treatment of **166** with lithium in liquid ammonia, followed by addition of methyl iodide, results in the formation of compound **167**.

Scheme 5



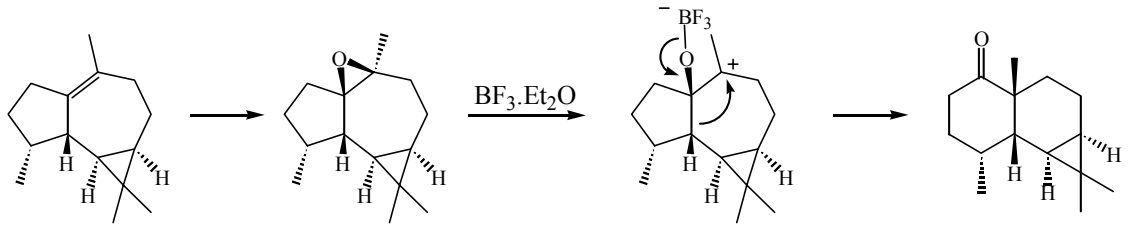
1 **94** **116** **117**

166 **167**

a: O_3; thiourea; b: TMSCl, Et_3N, DMF, 130 °C; c: dimethyldioxirane; SiO_2; d: Al_2O_3; e: Li, NH_3, *t*BuOH; MeI.

Although all steps in this route proceed smoothly and in high yield, first a carbon atom is removed and then added again in the last step of the reaction sequence. Furthermore, a reductive methylation in liquid ammonia is not feasible on an industrial scale. Because compound **167** was an interesting fragrance for perfumes, we wanted to develop an economically feasible route for it and therefore the route to **167** depicted in Scheme 6 has been investigated. The key step in this route to the fragrance compound **167** is the rearrangement of the β-epoxide **154**, derived from ledene, under the influence of BF_3-etherate. This rearrangement is in principle similar to that of **117** to **166**.

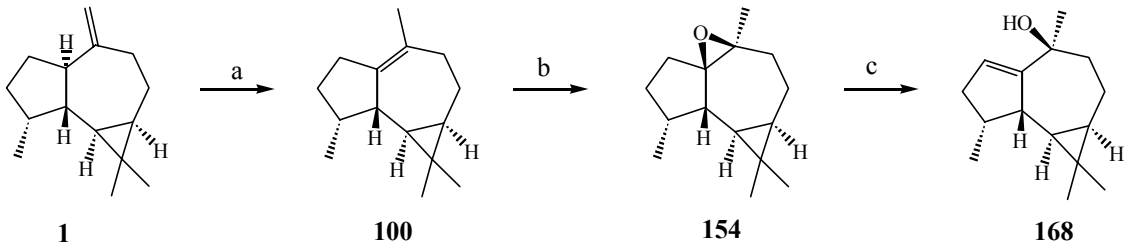
Scheme 6



2.3 Oxidations and rearrangements of ledene

Aromadendrene was converted to ledene with KO*t*Bu in DMSO. For this purpose the distillation tail of the oil of *Eucalyptus globulus* was used.[13] Since epoxidation of **100** with *m*CPBA led to a mixture of 5 compounds (see Paragraph 2.1)[9], the reaction was performed with dimethyldioxirane and in this way epoxide **154** was obtained as the sole product. The orientation of the epoxide in **154** turned out to be β. This was confirmed by a reaction of **154** with $LiNEt_2$ leading to **168**, a natural sesquiterpene with known configuration.[14]

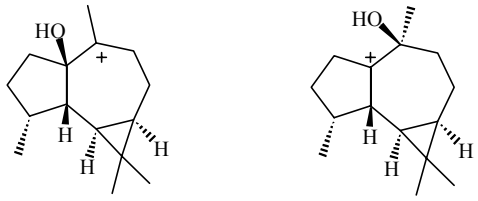
Scheme 7



a: KO*t*Bu, DMSO, 100 °C; b: dimethyldioxirane; c: $LiNEt_2$, Et_2O.

In principle two carbocations, **169** and/or **170**, can be obtained after opening of the epoxide in **154** and calculations showed that the heat of formation of **169** and **170** is very similar (–39.53 and –39.34 kcal/mole, respectively). Therefore rearrangements of epoxide **154** were investigated and it was first treated with $BF_3 \cdot Et_2O$. However, this reaction only led to a complex mixture of products, and a similar result was obtained by reaction of **154** with $MgBr_2$.

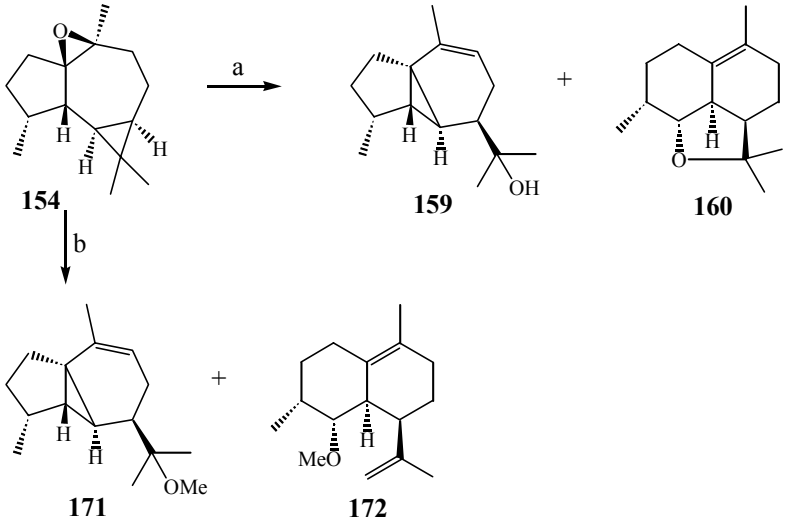
Scheme 8



169 **170**

When **154** was treated under mild acidic conditions, a more selective rearrangement took place (Scheme 9) and the compounds **159** and **160** were formed in 14 and 45% yield, respectively. Upon treatment of **154** with cerium ammonium nitrate (CAN) in MeOH, a similar rearrangement took place and the compounds **171** and **172** were formed, in 26 and 22% yield, respectively.

Scheme 9



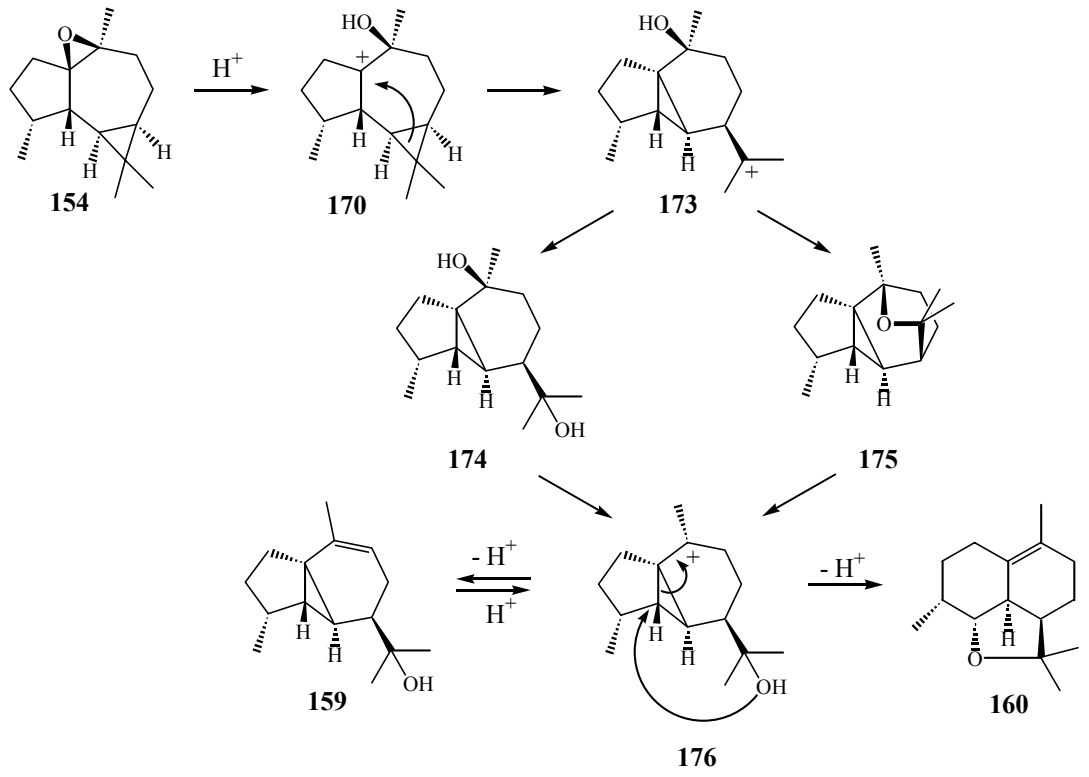
a: H_2SO_4, THF, H_2O; b: CAN, MeOH.

The formation of the products in these reactions can only be explained by the intermediary of the bridgehead carbocation **170** (Scheme 10) and subsequent opening of the cyclopropane ring in **170** to carbocation **173**. This cation **173** rearranges further

to the stable cyclopropylcarbinyl cation **176**, either via compound **174** or via ringclosure to cyclic ether **175** and subsequent ether cleavage. Carbocation **176** can undergo proton loss to give compound **159** or can rearrange further to compound **160**. The latter compound is a naturally occurring cadinane present in *Baccharis dracunculifolia*.[15] The configuration of **160** has been confirmed by 2D NMR (NOE) analysis[15] and its NMR spectra are consistent with those reported for the natural product.

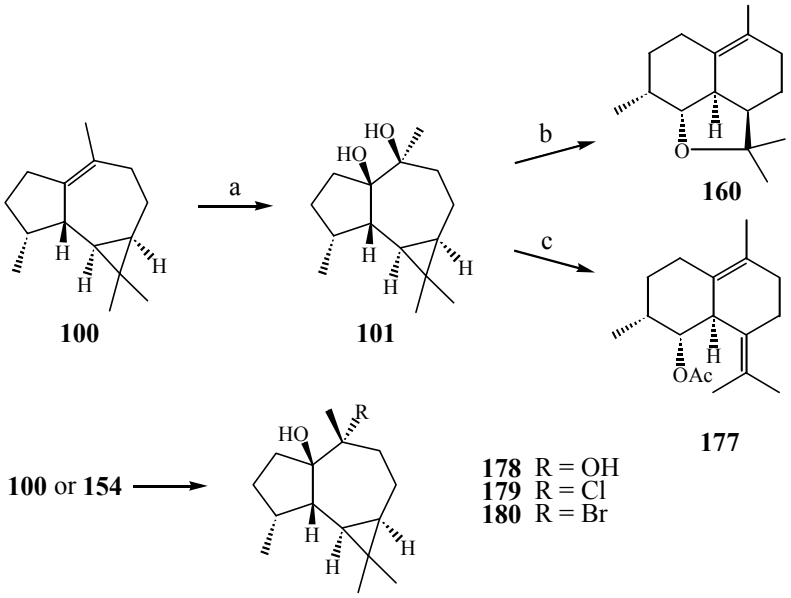
The ratio in which **159** and **160** are formed can be controlled by temperature and reaction time. At higher temperature and longer reaction times more **160** is formed. Upon treatment with acid **159** is converted to **160** indicating that both **159** and **160** are derived from the same intermediate cation. Compounds **171** and **172** are formed in a similar way from **154** with CAN in MeOH. In this case, the carbocations are trapped by MeOH instead of water.

Scheme 10



To suppress the formation of bridgehead cation **170**, attempts were made to synthesize a compound with a good leaving group at C7 and a group at C8 that would not splitt off under mild acidic conditions. This could be, for example, a protected hydroxy group which, at the same time, would stimulate the rearrangement by stabilization of the carbocation at C8.

Scheme 11



a: $KMnO_4$, EtOH; b: AcOH, H_2O, I_2; c: AcOH, I_2.

For this purpose, ledene was converted first to its cis-diol **101** by reaction with $KMnO_4$. This oxidation afforded one product, which turned out to be the β-diol.[5] This diol rearranged to compound **160** upon treatment with acetic acid in the presence of water. When no water was present during the reaction, compound **177** was formed. The formation of these products can be explained in a similar way as depicted in Scheme 10. Attempts to form the trans-diol[16] **178** from ledene or from the epoxide **154** were not successful and also the formation of a chloro- or bromohydrine[17-19] (**179** or **180**) from ledene did not work in our hands.

From these experiments it was concluded that all reactions on the double bond in ledene take place at the β-side.The formation of a carbocation at C8 is favored and further reaction results in the formation of cadinanes like **160**, **172**, or **177**. Unfortunately, we were not successful in finding an economically feasible route to fragrance compound **167** with aromadendrene as the starting material, and the route depicted in Scheme 5 is still the best one.

2.4 Experimental part

General

^1H NMR spectra (200 MHz) and ^{13}C NMR spectra (50 MHz) were recorded on a Bruker AC-E 200. $CDCl_3$ was used as solvent, unless stated otherwise, and chemical

shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). MS and HRMS data were obtained with a Finnigan Mat 95 spectrometer. MSD spectra were recorded on a HP5973 spectrometer. Analytical data were obtained using a Carlo Erba Analyzer 1106. GC analyses were carried out on a Fisons GC 8000 gas chromatograph with a flame ionization detector and a DB-17 fused silica capillary column (30 m x 0.25 mm i.d., film thickness 0.25 μm). GC peak areas were integrated electronically with a Fisons integrator DP700 or the Lab Systems X-Chrom integrating system. For dry reactions flasks were dried at 125 °C, flushed with nitrogen just before use, and kept under nitrogen atmosphere during the reaction. Column and flash chromatography were performed with ICN silica gel 60 (230-400 mesh), using mixtures of petroleum ether bp 40-60 °C (PE) and ethyl acetate (EA) as eluents, unless reported otherwise.

(1a*R*,7*R*,7a*S*,7b*R*)-1,1,4,7-Tetramethyl-1a,2,3,5,6,7,7a,7b-octahydro-1*H*-cyclopropa[*e*]azulene (Ledene) (100).

To a stirred solution of 15 g of the distillation tail of *Eucalyptus globulus*[13] in 500 mL of DMSO was added 18.1 g (0.16 mol) of KO*t*Bu. After the reaction mixture was stirred at 100 °C for 19 h, an additional portion of 3.0 g (0.03 mol) of KO*t*Bu was added and the reaction mixture was stirred for another 4 h. The mixture was allowed to come to room temperature, diluted with 750 mL of water and extracted with five 200-mL portions of PE. The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the remaining residue was column chromatographed twice (PE) to give 2.22 g (18%) of pure **100** and 5.67 g (35%) of **100** with a GC purity of 74%, both fractions as light yellow oils. The NMR and mass spectral data of **100** correspond to those reported in literature.[1,20]

(1*R*,3a*R*,4a*S*,6a*R*,7a*R*,7b*S*)-1,4a,7,7-Tetramethyldecahydrocyclopropa[7,8]-azuleno-[3a,4-*b*]oxirene (154).

To a stirred solution of 0.50 g (2.45 mmol) of **100** in 40 mL of CH_2Cl_2 were added 40 mL of acetone, 40 mL of water, 100 mg (0.38 mmol) of 18-crown-6 and 4.0 g (48 mmol) of $NaHCO_3$. The reaction mixture was cooled to 0 °C and a solution of 5.4 g of Oxone (min. 4.5% of active oxygen) in 30 mL of water was added. After stirring for 2 h at 0 °C, the reaction mixture was diluted with 200 mL of saturated aqueous $NaHCO_3$ and extracted with four 100-mL portions of CH_2Cl_2. The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure to yield 0.52 g (96%) of **154** as a colorless oil: MS *m/z* (r.i.) 220 (M^+, 49), 205 (89), 177 (100), 123 (59), 121 (53), 107 (81), 95 (47), 93 (51), 81 (48), 43 (52); HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1827. The ^1H and ^{13}C NMR data of **154** correspond to those reported in literature.[9]

(1a*R*,4*S*,7*R*,7a*S*,7b*R*)-1,1,4,7-Tetramethyl-1a,2,3,4,6,7,7a,7b-octahydro-1*H*-cyclopropa[*e*]azulen-4-ol (168).

To a solution of 80 µL (1.25 mmol) of Et_2NH in 5 mL of dry Et_2O, cooled to 0 °C, was added 0.78 mL of 1.6 M *n*BuLi in hexane. After stirring for 15 minutes, a solution of 110 mg (0.50 mmol) of **154** in 2 mL of dry Et_2O was added. After 2 h, the reaction mixture was allowed to come to room temperature. After stirring for 1 day at room temperature, the reaction mixture was diluted with 50 mL of water and extracted with four 25-mL portions of Et_2O. The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The remaining residue was column chromatographed (PE/EA 10:1) to yield 70 mg (57%) of **168** as a colorless oil: ^{13}C NMR δ 15.6 (q), 16.2 (q), 19.4 (t), 20.1 (s), 25.1 (d), 28.0 (d), 28.9 (q), 30.0 (q), 37.8 (t), 38.4 (d), 42.4 (t), 43.8 (d), 71.9 (s), 123.1 (d), 154.9 (s); MSD *m/z* (r.i.) 220 (M^+, 9), 159 (91), 125 (43), 123 (46), 117 (43), 105 (49), 95 (54), 91 (62), 77 (43), 43 (100). The ^1H NMR data of **168** correspond to those reported in literature.[14]

Treatment of 154 with H_2SO_4 at 30 °C. Synthesis of 2-[(3*R*,3a*S*,3b*R*,4*R*)-3,7-dimethyl-2,3,3a,3b,4,5-hexahydro-1*H*-cyclopenta[2,3]cyclopropa[1,2-*a*]benzen-4-yl]-2-propanol (159) and (2a*R*,8*R*,8a*R*,8b*R*)-2,2,5,8-tetramethyl-2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho [1,8-*bc*]furan (160).

To a stirred solution of 110 mg (0.50 mmol) of **154** in 6 mL of THF/H_2O 1:1 were added 2 drops of concentrated H_2SO_4. After stirring for 2 h at 30 °C, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with three 30-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 10:1) to yield 50 mg (45%) of pure **160** and 20 mg of **159** (GC purity ca. 80%), both fractions as colorless oils. The NMR and mass spectral data of **159** and **160** correspond to those reported in literature.[9,15]

Treatment of 154 with H_2SO_4 at 0 °C.

To a stirred solution of 128 mg (0.58 mmol) of **154** in 6 mL of THF/H_2O 1:1, cooled to 0 °C, were added 2 drops of concentrated H_2SO_4. After stirring for 15 minutes at 0 °C, the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with three 30-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to yield 150 mg of a mixture that consisted of 76% of **159** and 14% of **160** (GC-analysis). This mixture was used in the next reaction without purification.

Conversion of 159 to 160.

To a stirred solution of 150 mg of this mixture in 5 mL of THF/H_2O 1:1 were added 2 drops of concentrated H_2SO_4. After stirring for 1 day at room temperature, the

reaction mixture was diluted with water and extracted with three 25-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to yield 100 mg of **160** with a GC-purity of 78%.

1-[(3*R*,3a*S*,3b*R*,4*R*)-3,7-Dimethyl-2,3,3a,3b,4,5-hexahydro-1*H*-cyclopenta[2,3]-cyclopropa[1,2-*a*]benzen-4-yl]-1-methylethyl methyl ether (171) and (2*R*,8a*R*)-8-Isopropenyl-2,5-dimethyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthalenyl methyl ether (172).

To a stirred solution of 218 mg (0.64 mmol) of crude **154** (GC purity 65%) in 5 mL of MeOH was added 98 mg (0.18 mmol) of cerium ammonium nitrate (CAN). After stirring at room temperature for 30 minutes, the reaction mixture was diluted with 50 mL of water and extracted with three 25-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 10:1) to yield 60 mg (26%) of **171** as a colorless oil and 100 mg of a fraction which, after purification by column chromatography (PE/EA 20:1) yielded 50 mg (22%) of **172** also as a colorless oil.

171: ^{1}H NMR δ 0.94 (d, *J* = 6.5 Hz, 3H), 1.07 (s, 3H), 1.18 (s, 3H), 1.40 (t, d = 4.4 Hz, 1H), 1.77 (br s, 3H), 1.48-2.00 (m, 9H), 3.14 (s, 3H), 5.17 (dt, *J* = 1.6, 5.0 Hz, 1H); ^{13}C NMR δ 18.2 (q), 20.4 (d), 21.4 (q), 22.3 (q), 22.9 (t), 23.1 (q), 29.7 (t), 29.8 (t), 30.8 (s), 33.9 (d), 34.5 (d), 38.1 (d), 48.6 (q), 77.9 (s), 117.1 (d), 136.9 (s).

172: ^{1}H NMR δ 0.89 (d, *J* = 7.1 Hz, 3H), 1.23-1.35 (m, 1H), 1.51 (br s, 3H), 1.71 (br s, 3H), 1.5-2.6 (m, 10H), 3.15 (s, 3H), 3.24 (dd, *J* = 4.9, 10.5 Hz, 1H), 4.58 (br s, 1H), 4.78 (br s, 1H); ^{13}C NMR δ 11.6 (q), 19.2 (q), 23.2 (t), 24.7 (q), 25.2 (t), 28.7 (t), 29.4 (t), 29.6 (d), 40.4 (d), 41.4 (d), 56.3 (q), 81.6 (d), 110.0 (t), 126.0 (s), 129.4 (s), 146.8 (s).

(1a*R*,4*S*,4a*R*,7*R*,7a*S*,7b*R*)-1,1,4,7-Tetramethyldecahydro-4a*H*-cyclopropa[*e*]-azulene-4,4a-diol (101).

To a stirred solution of 1.65 g (8.1 mmol) of **100** in 60 mL of 96% EtOH, cooled to 0 °C, was added dropwise a solution of 1.54 g (9.7 mmol) of $KMnO_4$ in 38 mL of water, over a period of 2 h. The reaction mixture was then diluted with 200 mL of water and extracted with four 100-mL portions of CH_2Cl_2. After filtration over Celite to remove the brown impurities, the organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was recrystallized twice from PE to yield 1.03 g (54%) of **101**: MS *m/z* (r.i.) 238 (M^+, 17), 177 (62), 149 (51), 123 (61), 109 (65), 95 (51), 83 (72), 81 (47), 43 (100), 41 (54); HRMS calcd for $C_{15}H_{26}O_2$ (M^+) 238.1934, found 238.1933; Anal. calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.83; H, 11.29. The ^{1}H and ^{13}C NMR data of **101** correspond to those reported in literature.[5]

(2a*R*,8*R*,8a*R*,8b*R*)-2,2,5,8-Tetramethyl-2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho [1,8-*bc*]furan (160) from Diol 101.

To a stirred solution of 95 mg (0.40 mmol) of **101** in 4 mL of THF/H_2O 1:1, cooled to 0°C, were added 6 mL of AcOH and a few I_2 crystals. After stirring for 4 days at room temperature, the reaction mixture was diluted with 50 mL of 2% aqueous $Na_2S_2O_3$ and extracted with four 25-mL portions of CH_2Cl_2. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 10:1) to yield 40 mg of **160** with a GC purity of ca. 80%.

(2*R*,8a*R*)-2,5-Dimethyl-8-(1-methylethylidene)-1,2,3,4,6,7,8,8a-octahydro-1-naphthalenyl acetate (177).

To a stirred solution of 99 mg (0.42 mmol) of **101** in 5 mL of AcOH was added a small I_2 crystal. After 2.5 h at room temperature, another I_2 crystal was added and stirring was continued for 6 h. The reaction mixture was then diluted with 50 mL of 2% aqueous $Na_2S_2O_3$ and extracted with four 25-mL portions of CH_2Cl_2. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 10:1) to yield 40 mg (34%) of **177** as a colorless oil: ^{1}H NMR δ 0.96 (d, *J* = 7.1 Hz, 3H), 1.63 (br s, 3H), 1.66 (br s, 3H), 1.70 (br s, 3H), 1.93 (s, 3H), 1.80-2.50 (m, 9H), 3.24 (d, *J* = 11.3 Hz, 1H), 4.93 (dd, *J* = 5.1, 11.2 Hz, 1H); ^{13}C NMR δ 12.3 (q), 18.8 (q), 20.0 (q), 20.6 (q), 21.0 (q), 24.2 (t), 24.3 (t), 31.8 (t), 32.3 (d), 33.6 (t), 41.2 (d), 76.7 (d), 124.5 (s), 126.6 (s), 128.3 (s), 130.6 (s), 170.0 (s); MSD *m/z* (r.i.) 262 (M^+, 0.1), 202 (100), 187 (82), 159 (67), 145 (28), 131 (30), 119 (37), 105 (49), 91 (49), 43 (52).

2.5 References and notes

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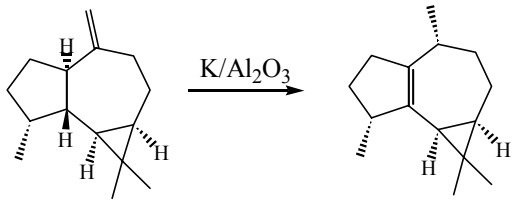
Chapter 3

(–)-Isoledene as starting material for the synthesis of sesquiterpenes

3.1 The chemistry of isoledene

(–)-Isoledene (**107**) is a sesquiterpene that has been found rarely in plant species. The only examples of isolation of isoledene are from the essential oil of *Citrus aurantifolia*[1] and *Cistus ladaniferus*[2], in which **107** is present in small amounts. On the other hand, large amounts of isoledene can be obtained from (+)-aromadendrene (**1**) in high yield upon treatment with potassium on aluminium oxide (K/Al_2O_3).[3]

Scheme 1

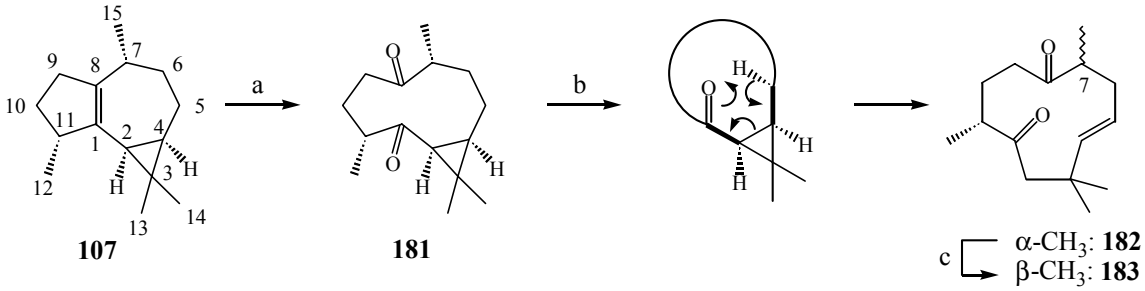


1 **107**

Isoledene has been used as starting material for the synthesis of several other natural sesquiterpenes. For the synthesis of humulenedione (**183**, Scheme 2) and (–)-cubenol (**190**, Scheme 3), the double bond in isoledene is oxidized with RuO_2 in the presence of $NaIO_4$ to obtain diketone **181**.[4] Thermal rearrangement of **181** at 100 °C leads to compound **182** via a homo [1,5] hydrogen shift (Scheme 2). An epimerization of the methyl group at C7 in **182** with NaOMe in MeOH leads to humulenedione **183**.

When **181** is heated at 700 °C under flash vacuum pyrolysis (FVP) conditions, a different homo [1,5] hydrogen shift takes place (Scheme 3) resulting in a 71% yield of **185**. A five-step reaction sequence produces (–)-cubenol (**190**) and its double bond isomer **191** in 40 and 28% overall yield, respectively, from **185**.

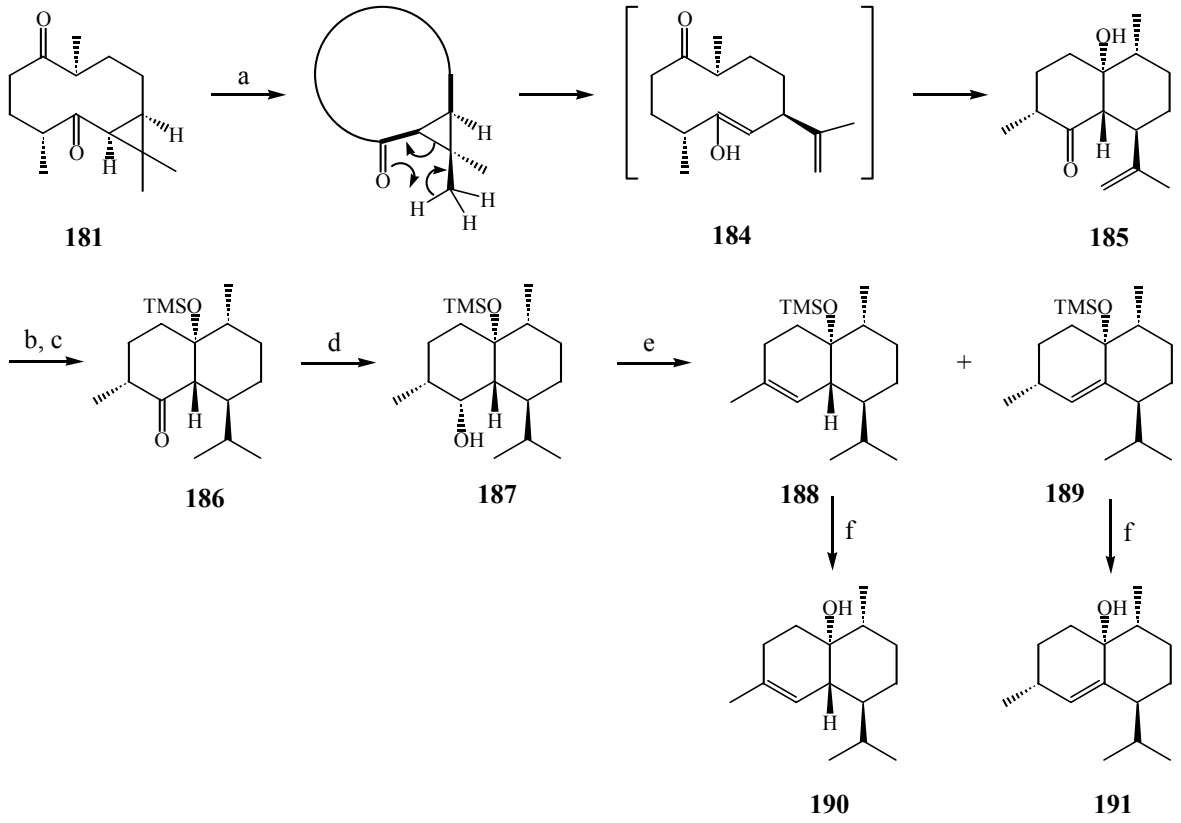
Scheme 2



107 **181**

a: RuO_2, $NaIO_4$; b: 1,4-dioxane, reflux; c: NaOMe, MeOH.

Scheme 3

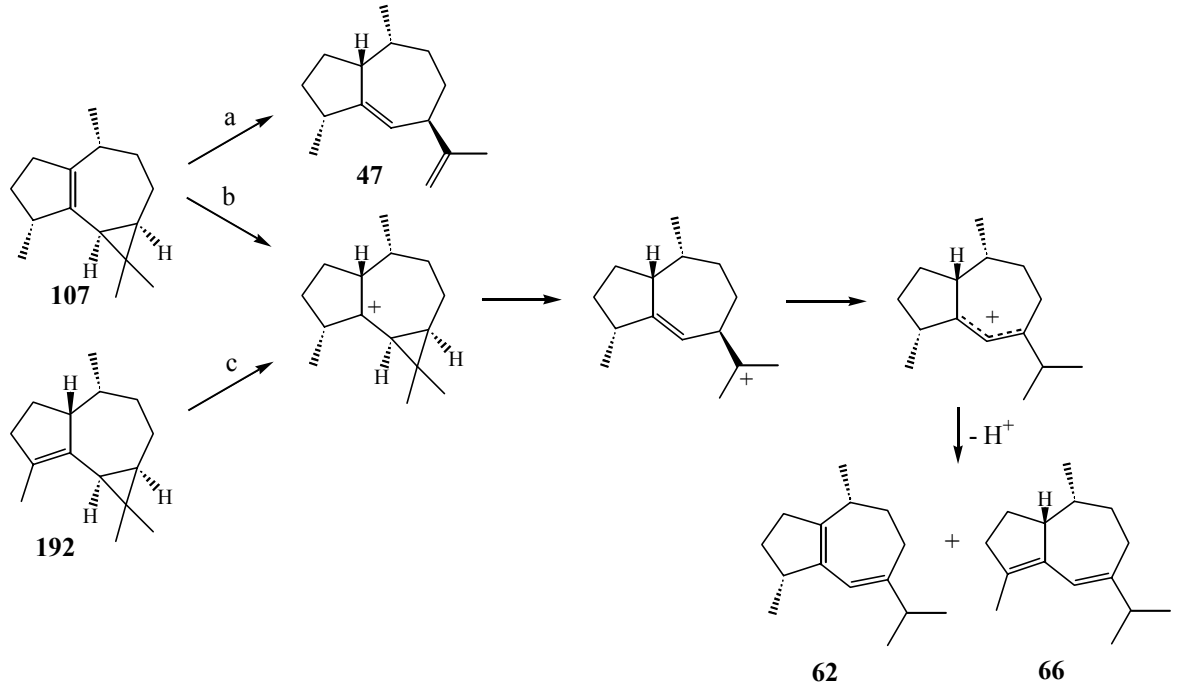


181 **184** **185** **186** **187** **188** **189** **190** **191**

a: FVP, 700 °C; b: H_2, Pt(C); c: TMSCl, Et_3N, DMF, 120 °C; d: $LiAlH_4$; e: $SOCl_2$; f: TBAF.

When isoledene (**107**) is heated at 450 °C, it is converted to the guaiane sesquiterpene γ-gurjunene (**47**).[3] The guaiane dienes **62** and **66** are obtained upon treatment of **107** with superacidic media (HSO_3F-SO_2FCl) in 15 and 7% isolated yield, respectively.[5] The same dienes are formed when α-gurjunene (**192**) is treated with TsOH in acetic acid.[6]

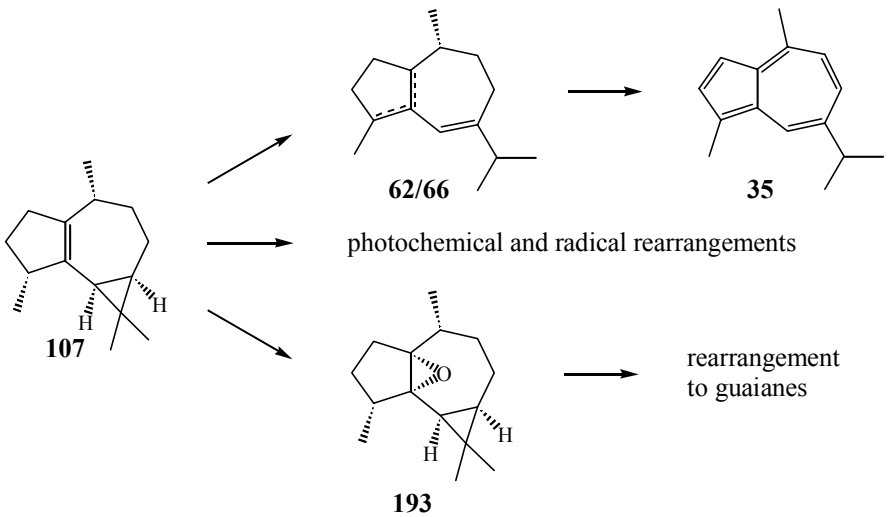
Scheme 4



a: 450 °C; b: HSO_3F-SO_2FCl; c: TsOH, AcOH.

In this Chapter, the use of isoledene as starting material for the synthesis of sesquiterpenes with a rearranged skeleton, like the guaiane or patchoulane skeleton, is further investigated (Scheme 5). The synthesis of guaiazulene (**35**) from the mixture of **62** and **66** is described in Paragraph 3.2. Attempts to rearrange isoledene photochemically or via a radical reaction are briefly discussed in Paragraph 3.3. The synthesis of isoledene epoxide (**193**) and its rearrangement to compounds with the guaiane skeleton are described in Paragraph 3.4.

Scheme 5



3.2 Synthesis of guaiazulene

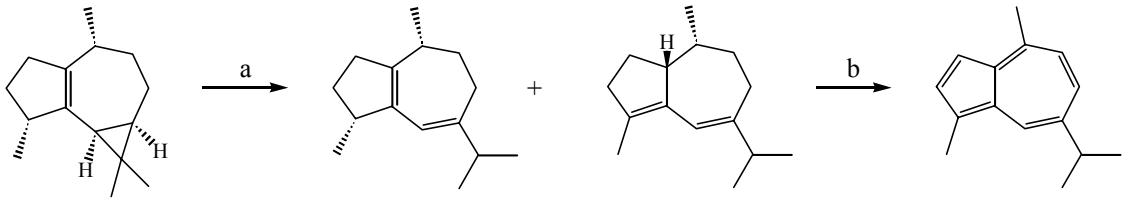
Guaiazulene (**35**), a naturally occurring guaiane with a dark blue color, is present in Blue camphor oil[7,8], in the oil of *Cinnamomum cassia*[9] and *Matricaria chamomilla*[10], and in several other plant species. Guaiazulene is approved by the American Food and Drug Administration (FDA) for use as colorant in externally applied cosmetics and therefore a cheap production of **35** will be interesting for the industry.

The conversions of several aromadendrane and guaiane sesquiterpenes to **35** are known.[6,11-16] These reactions were performed to prove the azulene skeleton of unknown compounds and only in a few cases the yields are given. The highest yield reported for the dehydrogenation of aromadendrene to guaiazulene with sulfur is 6.3%.[13]

A better yield of guaiazulene from aromadendrene may be possible when first the cyclopropane ring in the latter should be opened to a partly unsaturated guaiane skeleton. This should facilitate further unsaturation to guaiazulene.

An easy opening of the cyclopropane ring in aromadendrene to the guaiane skeleton is not known, but after conversion of aromadendrene to isoledene, in which the double bond has migrated to the "conjugated" position, such a ring opening is possible as the conversion of isoledene to a mixture of dienes in superacidic media shows.[5] From literature it is also known, that α-gurjunene gives the same mixture of dienes upon heating in acetic acid.[6] This led us to investigate the conversion of isoledene (**107**) to **62** and **66** under milder acidic conditions. Indeed, when isoledene is subjected to several acidic or Lewis acidic conditions (see Experimental part), a mixture of products is formed with **62** and **66** as the main products, together with some other apolar compounds. This product mixture was used for the synthesis of guaiazulene (**35**) without further purification.

Scheme 6



a: H^+ or $BF_3 \cdot Et_2O$; b: sulfur, mesitylene, 160 °C.

When the mixture of dienes **62** and **66** is dehydrogenated in the presence of sulfur, guaiazulene (**35**) could be isolated in 22% yield from **107** (Scheme 6). This yield is reached when the dienes are solved in mesitylene and stirred overnight at

160 °C. Attempts to dehydrogenate aromadendrene (**1**) or isoledene (**107**) under the same conditions led to the formation of a complex mixture of products, in which some **35** was present, according to GC-analysis. However, the purification of these mixtures proved to be difficult and did not lead to pure guaiazulene, because decomposition of guaiazulene in these mixtures took place on both silica gel and alumina.

An alternative method for the synthesis of guaiazulene was published by Yamin *et al.*[17] According to these authors, aromadendrene can be dehydrogenated to guaiazulene with dithioglycolate esters under thermic or photochemical conditions in a yield up to 23%. When ditertbutylperoxide was added to the reaction mixture, the yield could even be improved to 48%. However, when we tried to repeat the reaction of *n*-butyl dithioglycolate with the mixture of **62** and **66** or with the distillation tail of *Eucalyptus globulus*, almost no guaiazulene was formed.

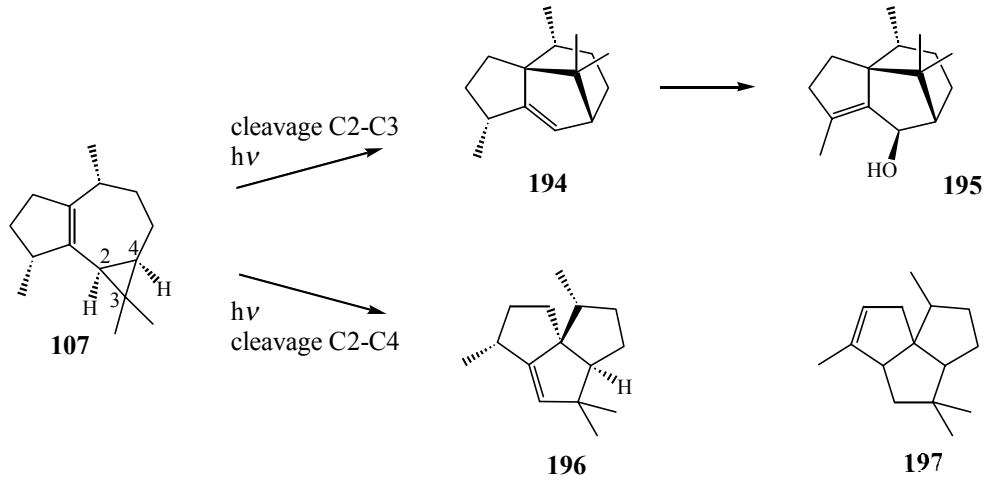
When the dehydrogenation of **62** and **66** with sulfur is compared to that of aromadendrene (**1**) or isoledene (**107**), it can be concluded that our proposition was right. After opening of the cyclopropane ring through which an extra double bond in the carbon skeleton is introduced, further dehydrogenation becomes easier and guaiazulene is obtained in a better yield.

3.3 Photochemical and radical rearrangement of isoledene

The photochemical rearrangement of vinylcyclopropanes to cyclopentenes is well known.[18-21] With isoledene (**107**) this photochemical rearrangement may give two different skeletons, depending on which cyclopropane bond is broken. When the C2-C3 bond is cleaved, isoledene can rearrange to compound **194**, which has the patchoulane skeleton. Compound **194** can be used as synthon for the synthesis of patchoulenol (**195**), a fragrance compound isolated from *Cyperus scariosus*.[22] Cleavage of the C2-C4 bond may lead to the formation of compound **196**, which has a rather unusual skeleton. The only example of a natural sesquiterpene with the same skeleton is senoxydene (**197**), isolated from *Senecio oxyodontus*[23] and *Lordhowea insularis.*[24]

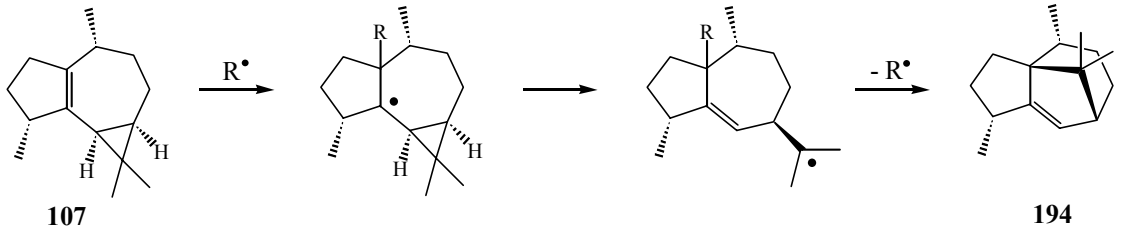
Upon irradiation of isoledene with a medium pressure mercury lamp, neither of the two rearrangements took place. A mixture of two unstable compounds was formed, which decomposed on both silica gel and alumina. From the ^{1}H and ^{13}C NMR spectra of the crude mixture it became clear, that the cyclopropane ring was opened to form an isopropenyl group. Because the mixture could not be separated by column chromatography, no further structure determination was carried out.

Scheme 7



Another way to rearrange isoledene to the patchoulane skeleton may proceed via a radical-mediated rearrangement. If a radical can be found, that can first add to the double bond in **107** and later be eliminated, a rearrangement can take place as is depicted in Scheme 8.

Scheme 8



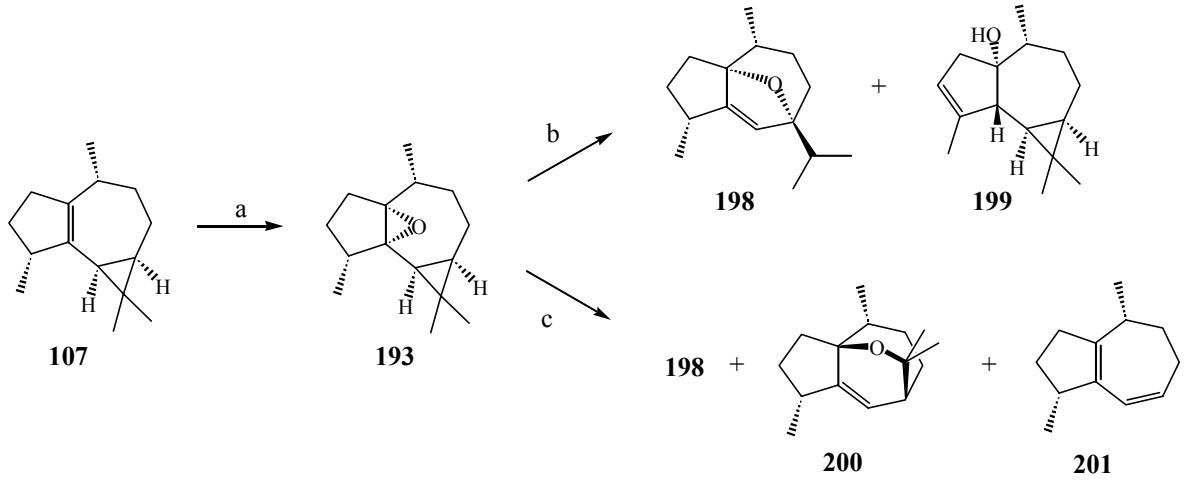
Isoledene has been reacted with several reagents (see Experimental part), but under most conditions no product was formed at all. Only the reaction with SO_2Cl_2 and AIBN in refluxing toluene led to a reaction, but under these conditions a complex mixture of products was formed.

3.4 Rearrangements of isoledene epoxide

As shown in Scheme 4 the cyclopropane ring can be opened regioselectively when a carbocation can be generated at C5[25] by protonation of a suitably positioned double bond. A second way to generate a carbocation at C5 is by opening of an epoxide and in this Paragraph the use isoledene epoxide as starting material for the synthesis of products with the guaiane skeleton is described. The first step in this approach is the epoxidation of **107** to the α-epoxide **193**. The α-configuration has been

proven by 2D NMR experiments on compounds **202** and **204** (Scheme 12), products derived from the α-ether **198**, which in turn only can be obtained from α-epoxide **193** (see Scheme 9).

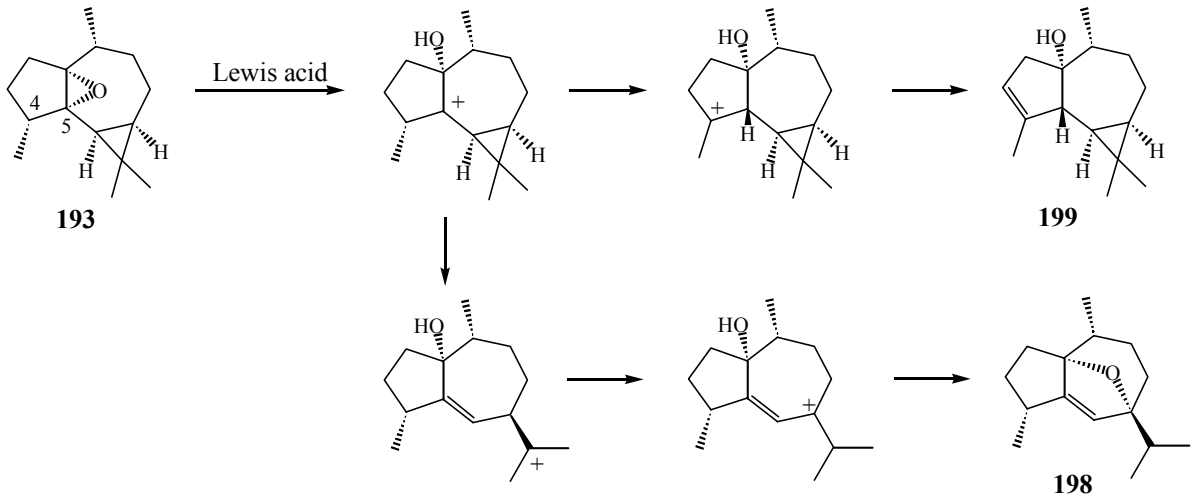
Scheme 9



a: *m*CPBA, CH_2Cl_2; b: $BF_3{\cdot}Et_2O$ or $TiCl_4$; c: TsOH, acetone.

The epoxide **193** can undergo rearrangement resulting in the formation of different products. Under Lewis acid conditions ($BF_3{\cdot}Et_2O$ or $TiCl_4$), a mixture of **198** and **199** is obtained. The product ratio depends on the amount and nature of the Lewis acid, and on the reaction temperature. Reaction at room temperature of **193** with 1.3 equivalents of $BF_3{\cdot}Et_2O$ leads to 80% yield of **198**. Lower temperatures or smaller amounts of Lewis acid lead to the formation of more **199**. Also, when $TiCl_4$ is used instead of $BF_3{\cdot}Et_2O$ more **199** is formed, but in all cases **198** remains the main product (>70% according to GC-analysis).

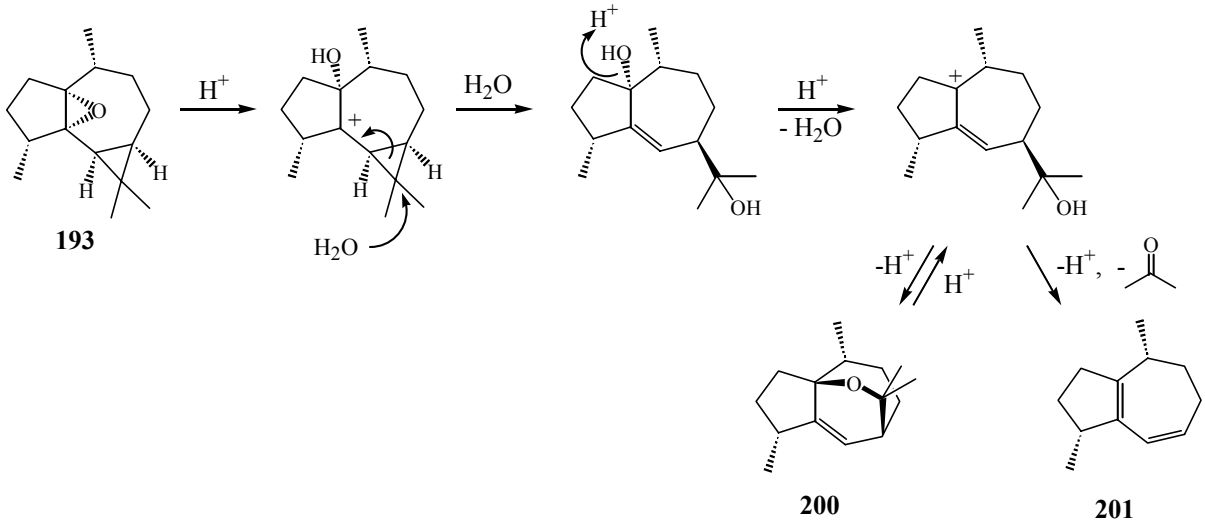
Scheme 10



The mechanism of the formation of **198** and **199** is depicted in Scheme 10. The route to **198** involves formation of a cyclopropylcarbinyl cation which, in turn, rearranges to a homoallylic cation. Then a [1,2] hydride shift takes place to a more stable allylic cation followed by ether bridge formation. A [1,2] hydride shift from C4[25] to C5 in the cyclopropylcarbinyl cation, followed by proton loss explains the formation of the minor product **199**.

A different reaction outcome is observed upon treatment of **193** with TsOH in wet acetone. Under these conditions a mixture of **200** and **201** is formed, together with ca. 10% of **198**. The ratio of **200** and **201** depends on the reaction time and the amount of acid. More **201** is formed when more acid or a longer reaction time is used. The mechanism of the reaction is shown in Scheme 11.

Scheme 11



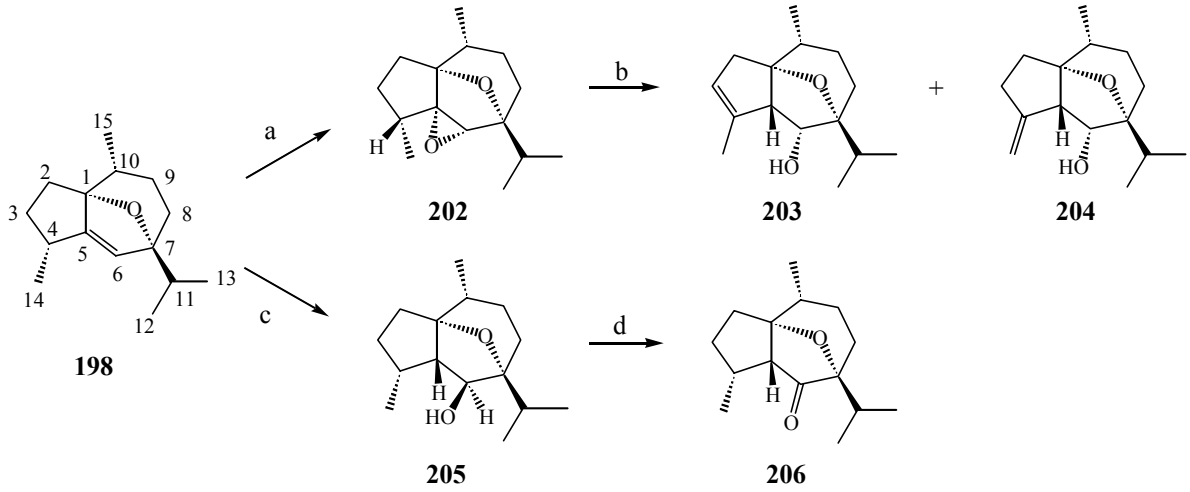
Just as with the Lewis acid-induced rearrangement, first a cyclopropylcarbinyl cation is formed. After opening of the cyclopropane ring, the resulting homoallylic cation is then attacked by water to form a diol. A small amount of water is present in the reaction mixture, because the acetone used was not dry. Elimination of water finally leads to the formation of ether **200**. Compound **201** is formed through elimination of acetone from the intermediate allylic cation. Alternatively, when **200** is stirred for a longer time under acidic conditions, also acetone is eliminated and **201** is obtained.

The ethers **198** and **200** can be obtained in good yields and several derivatives have been prepared to investigate their chemistry and their properties as fragrance compounds. The skeleton of ether **200** resembles that of patchoulane and this stimulates research in this direction. Furthermore, by 2D NMR analysis of these

derivatives the stereochemistry of the ether bridge in compound **198** and the epoxide ring in **193** can be established.

The double bond in **198** can be functionalized in different ways (Scheme 12). When **198** is epoxidized, compound **202** is formed, which can be converted to a mixture of **203** and **204** by reaction with $BF_3 \cdot Et_2O$. Opening of the epoxide ring and a 1,2-H shift from C4 to C5, followed by proton loss explains the formation of **203** and **204** from **202**.

Scheme 12



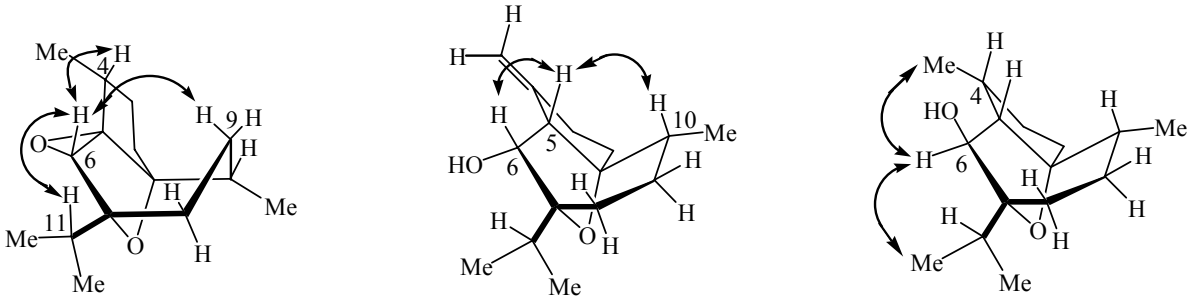
a: *m*CPBA, CH_2Cl_2; b: $BF_3 \cdot Et_2O$; c: $BH_3 \cdot DMS$; H_2O_2, NaOH; d: PCC/Al_2O_3.

The stereochemistry of **202** and **204** has been established by 2D NMR experiments on these compounds. From the COSY spectrum of **202** the positions of relevant protons were established. The NOESY spectrum of **202** shows a NOE correlation between H6 and H4, between H6 and H9β, and between H6 and H11.

From the COSY spectrum of **204** the positions of H5, H6 and H10 were established. The NOESY spectrum of **204** clearly shows a NOE correlation between H5 and H6, indicating that H6 is also β and therefore the hydroxy group at C6 is α (Figure 1). A NOE correlation is also present between H5 and H10, which is only possible when the ether bridge is in the α-position, as is depicted in Scheme 12 and Figure 1.

In this way it has been proven clearly that the ether bridge in **202** and **204** is in the α-position and therefore the ether bridge in **198**, from which these compounds are derived, is also in the α-position. Since this α-ether **198** can only result from an α-epoxide, the configuration of **193** must be α as well.

Figure 1

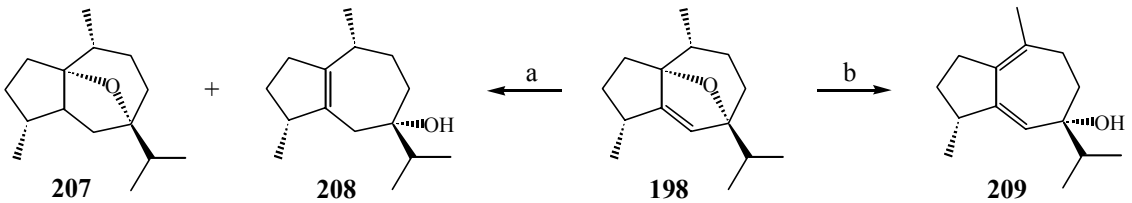


202 **204** **205**

Most relevant NOE correlations

Ketone **206** can be obtained upon hydroboration of **198** followed by oxidation of the resulting hydroxy group at C6 (Scheme 12). The hydroxyl group in **205** is most likely β-oriented, because no NOE correlation is observed between H5 and H6 in **205**. The NOE correlations between H6 and the methyl group at C4 and between H6 and one of the methyl groups of the isopropyl group support this conclusion.

Scheme 13



207 **208** **198** **209**

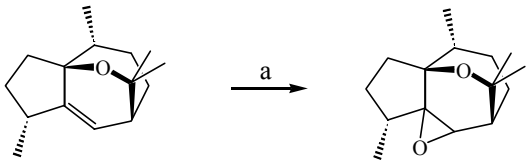
a: **198** in ethylenediamine, then Li; b: lithium ethylenediamide.

Some attempts to open the ether bridge in **198** have been undertaken. For this purpose reactions with lithium in ethylenediamine have been carried out. In these reactions the order of addition of the reagents is crucial. A reductive ring opening in **194** can be achieved when lithium is added to a solution of **198** in ethylenediamine. In this reaction addition of an electron leads to opening of the ether bridge and formation of a radical at C1. After migration of the double bond and subsequent elimination of a hydrogen radical, compound **208** is formed. Next to reductive ring opening, reduction of the double bond in **198** to compound **207** takes place. Compound **207** is also formed when **198** is treated with hydrogen and palladium charcoal. The configuration at C5 in compound **207** could not been established from its NMR spectra.

Basic ring opening resulting in a 89% yield of **209** takes place when a solution of lithium ethylenediamide is prepared first followed by addition of **198**. This formation of **209** can proceed smoothly because H10 and the C1 ether bond in **198** have an

antiperiplanar relationship, which is another proof for the α configuration of the ether bridge in **198**.

Scheme 14



200 **210**

a: *m*CPBA, CH_2Cl_2.

Functionalization of compound **200** proved to be more difficult than that of **198**. Epoxidation did take place, but the reaction time was much longer than in case of **198**. The stereochemistry of epoxide **210** could not be established from its NMR spectrum. It is likely that the epoxide is situated at the α-side, because the upper side of the molecule is shielded by the ether bridge. Hydrogenation of **200** did not work and also ether opening did not lead to good results.

The compounds depicted in Scheme 12 and 13 were tested for their use as fragrances, but they proved not to be suitable as such.

3.5 Experimental part

(1a*R*,4*R*,7*R*,7b*S*)-1,1,4,7-Tetramethyl-1a,2,3,4,5,6,7,7b-octahydro-1*H*-cyclopropa-[*e*]-azulene (Isoledene) (107).

To 100 g of mechanically stirred basic Al_2O_3 (dried at 250 °C under reduced pressure) was carefully added 10 g (0.25 mol) of potassium in small portions at 200 °C, under an argon atmosphere. The resulting blue powder was allowed to come to room temperature, cooled to 0 °C and 80 mL of dry hexane was added. To this stirred suspension a solution of 32.5 g of the distillation tail of the oil of *Eucalyptus globulus*[26] in 50 mL of dry hexane was added. The ice bath was removed and the suspension was stirred overnight. The green suspension was filtered through a glass-filter and the residue was washed carefully with an ether-hexane mixture (1:1). The filtrate was evaporated under reduced pressure to yield 31.5 g (96%) of isoledene (**107**) as a colorless oil. The ^{1}H and ^{13}C NMR data of **107** correspond to those reported in literature.[4]

Treatment of 107 with (Lewis) acids. Synthesis of (1*R*,4*R*)-7-isopropyl-1,4-dimethyl-1,2,3,4,5,6-hexahydroazulene (62) and (8*R*)-5-isopropyl-3,8-dimethyl-1,2,6,7,8,8a-hexa-hydroazulene (66).

Table 1 Conversion of 107 to dienes 62 and 66

Entry	(Lewis) acid	solvent	temperature	reaction time	ratio 62:66[27]
1	TsOH	AcOH	70 °C	3 days	27 : 26
2	CF_3CO_2H	AcOH	room temp.	3 days	27 : 21
3	CF_3CO_2H	CH_2Cl_2	room temp.	3 days	33 : 30
4	CF_3CO_2H	toluene	room temp.	3 days	34 : 38
5	$BF_3{\cdot}Et_2O$	CH_2Cl_2	room temp.	3 hours	32 : 28
6	$BF_3{\cdot}Et_2O$	$CHCl_3$	room temp.	5 days	34 : 29
7	$BF_3{\cdot}Et_2O$	CCl_4	room temp.	1 day	35 : 28

Procedure for entries 1-4:

To a stirred solution of 500 mg (2.5 mmol) of **107** in 200 mL of solvent was added a catalytic amount of acid. After completion of the reaction, the mixture was diluted with 100 mL of water and extracted with three 100-mL portions of Et_2O. The combined organic layers were washed three times with saturated aqueous $NaHCO_3$ and once with brine, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, a mixture was obtained, which consisted mainly of **62** and **66**.

Procedure for entries 5-7:

To a stirred solution of 800 mg (3.9 mmol) of **107** in 80 mL of solvent was added 0.2 mL of $BF_3{\cdot}Et_2O$. After completion of the reaction, the mixture was diluted with 50 mL of saturated aqueous $NaHCO_3$ and extracted with three 40-mL portions of Et_2O. The combined organic layers were washed twice with saturated aqueous $NaHCO_3$ and once with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE) to yield a mixture, which consisted mainly of **62** and **66**. In all cases the yield of the mixture was higher than 70%. For entry 5 the conversion of **107** to the mixture of **62** and **66** was quantitative.

Repeated column chromatography (PE) of the mixture of dienes led to a sample that consisted of 70% of **66**: ^{13}C NMR δ 14.6 (q), 21.5 (q), 21.5 (q), 21.7 (q), 28.5 (t), 29.9 (t), 36.0 (t), 36.5 (t), 38.0 (d), 39.1 (d), 54.4 (d), 117.8 (d), 136.1 (s), 136.6 (s), 148.1 (s). The ^{1}H NMR data of **66** correspond to those reported in literature.[28]

7-Isopropyl-1,4-dimethylazulene (Guaiazulene) (35).

To a stirred solution of 0.2 g of a mixture that consisted of 35% of **62** and 27% of **66** (GC-analysis) in 3 mL of mesitylene was added 0.10 g of sulfur. The mixture was stirred at 160 °C overnight. The mixture was allowed to come to room temperature and

purified over a short basic Al_2O_3 column (PE) to yield 42 mg (22%) of **35**. The ^1H and ^{13}C NMR data of **35** correspond to those reported in literature.[29,30]

Photochemical rearrangement of 107.

A stirred solution of 250 mg of **107** in 80 mL of dry hexane in a quartz flask was irradiated with a 150 W medium pressure mercury lamp for 7 h. A mixture of products was formed. The two main products decomposed when the mixture was chromatographed on silica gel or alumina.

Radical rearrangement of 107. General procedure.

To a stirred solution of **107** in dry solvent was added one equivalent of reagent and a catalytic amount of initiator (see Table 2). The reaction mixture was stirred overnight at room temperature or at reflux, but in most cases no reaction took place. Only the reaction with SO_2Cl_2 and AIBN led to a complex mixture of products after 15 min.

Table 2 Reaction of 107 under radical conditions

Entry	Reagents	Solvent	Temperature	Products
1	Bz_2O_2, cat. AIBN[31]	toluene	reflux	starting material
2	Me_2S_2, hν[32]	cyclohexane	room temp.	starting material
3	Me_2S_2, cat. AIBN[33]	toluene	reflux	starting material
4	Me_2S_2, DTBP[34]	toluene	reflux	starting material
5	SmI_2, cat. AIBN[35]	THF	reflux	starting material
6	Bu_3SnH, cat. AIBN[36]	toluene	reflux	starting material
7	SO_2Cl_2, AIBN[37]	toluene	reflux	complex mixture

(1*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-2,2,6,10-Tetramethyl-12-oxatetracyclo-[6.3.1.0^{1,3}.0^{7,11}]dodecane (193).

To a stirred solution of 12.5 g (61.3 mmol) of **107** in 250 mL of CH_2Cl_2 was added dropwise at -10 °C a solution of 22.6 g (ca. 0.10 mol) of 70-75% *m*CPBA in 250 mL of CH_2Cl_2. The reaction mixture was then allowed to warm to 0 °C. After stirring for 30 min, the mixture was diluted with 200 mL of saturated aqueous $Na_2S_2O_3$ and stirred for 30 min. Then the organic layer was separated and washed with saturated aqueous $NaHCO_3$ and brine. The combined aqueous layers were extracted twice with 100 mL of PE and these organic layers were also washed with saturated aqueous $NaHCO_3$ and brine. The combined organic layers were dried and evaporated under reduced pressure to yield 13.1 g (97%) of **193** as a colorless oil: ^1H NMR δ 0.97 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.4 Hz, 3H), 1.07 (s, 3H), 0.8-2.1 (m, 12H); ^{13}C NMR δ 14.1 (q), 18.0 (q), 18.3 (s), 19.4 (q), 23.6 (t), 25.5 (d), 27.0 (t), 28.3 (q), 28.8 (d), 30.4 (t), 31.1 (t), 38.6 (d), 39.2 (d), 74.2 (s), 75.1 (s); MS *m/z* (r.i.) 220

(M^+, 13), 205 (17), 202 (7), 177 (20), 159 (18), 123 (41), 112 (100), 83 (42); HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1821.

(1*R*,4*R*,7*R*,10*R*)-7-Isopropyl-4,10-dimethyl-11-oxatricyclo[5.3.2.0^{1,5}]undec-5-ene (198) and (1a*R*,4*R*,4a*R*,7a*R*,7b*R*)-1,1,4,7-tetramethyl-1,1a,2,3,4,5,7a,7b-octahydro-4a*H*-cyclopropa[*e*]azulen-4a-ol (199).

To a stirred solution of 1.01 g (4.61 mmol) of **193** in 500 mL of dry Et_2O was added 0.65 mL (6.18 mmol) of $BF_3{\cdot}Et_2O$. After stirring for 10 min at room temperature, the reaction mixture was cooled to 0 °C and diluted with 100 mL of saturated aqueous $NaHCO_3$. The organic layer was washed twice with saturated aqueous $NaHCO_3$ and once with brine, dried, and evaporated under reduced pressure to yield 993 mg of a yellow oil that consisted of 96% of **198** and 4% of **199** (according to GC-analysis). The oil was flash chromatographed with neutral alumina (PE) to give 812 mg (80%) of **198**. In a similar experiment using $TiCl_4$ as the Lewis acid a small amount of **199** could also be isolated.

198: ^{1}H NMR δ 0.91 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J*= 6.9 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.15-1.79 (m, 8H), 1.91-2.11 (m, 2H), 2.41 (m, 1H), 5.36 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR δ 13.7 (q), 17.2 (q), 17.6 (q), 17.7 (q), 23.5 (t), 26.0 (t), 30.6 (t), 30.9 (d), 31.3 (d), 34.6 (t), 35.6 (t), 95.9 (s), 97.5 (s), 118.0 (d), 159.7 (s).

199: ^{1}H NMR δ 0.39 (dd, *J* = 8.9, 11.0 Hz, 1H), 0.74 (ddd, *J* = 6.2, 8.9, 11.1 Hz, 1H), 0.92 (d, *J* = 6.1 Hz, 3H), 1.07 (s, 6H), 1.66 (br s, 3H), 1.0-2.3 (m, 8H), 5.33 (br s, 1H); ^{13}C NMR δ 14.8 (q), 16.0 (q), 17.4 (q), 20.1 (s), 23.6 (d), 24.5 (t), 26.7 (d), 28.9 (q), 31.8 (t), 45.4 (t), 45.5 (d), 53.6 (d), 85.3 (s), 121.5 (d), 141.1 (s).

(1*S*,4*R*,7*R*,10*R*)-4,10,12,12-Tetramethyl-11-oxatricyclo[5.3.2.0^{1,5}]dodec-5-ene (200) and (1*R*,4*R*)-1,4-dimethyl-1,2,3,4,5,6-hexahydroazulene (201).

To a stirred solution of 200 mg (0.91 mmol) of **193** in 20 mL of wet acetone was added 16 mg (0.08 mmol) of $TsOH{\cdot}H_2O$ at room temperature. After stirring for 10 min, the reaction mixture was diluted with saturated aqeous $NaHCO_3$ and extracted with three 20-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated under reduced pressure. The residue was column chromatographed (PE - PE/EA 99:1) to yield 19 mg (10%) of **198**, 83 mg (42%) of **200** and 30 mg (20%) of **201**.

200: ^{1}H NMR δ 0.81 (d, *J* = 7.1 Hz, 3H), 1.00 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.28 (s, 3H), 1.21-2.15 (m, 12H), 2.67 (m, 1H), 5.91 (dd, *J* = 2.5, 7.7 Hz, 1H); ^{13}C NMR δ 18.5 (q), 19.1 (q), 22.0 (t), 30.1 (q), 30.5 (q), 32.7 (t), 32.2 (t), 35.5 (d), 38.7 (q), 40.4 (d), 42.4 (d), 75.4 (s), 86.8 (s), 121.5 (d), 149.1 (s); IR (neat) 1453, 1375, 1141, 1019 cm^{-1}; MS *m/z* (r.i.) 220 (M^+, 67), 205 (100), 177 (32), 162 (20), 149 (20), 138 (87), 123 (40), 109 (28), 105 (22), 91 (23); HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1824.

201: ^{1}H NMR (C_6D_6) δ 1.02 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.9-2.9 (m, 10H), 5.8-6.1 (m, 2H); ^{13}C NMR (C_6D_6) δ 19.8 (q), 20.2 (q), 26.9 (t), 31.3 (t), 31.7 (t), 35.8 (d), 36.0 (t), 44.5 (d), 124.4 (d), 132.1 (d), the chemical shift of the two quaternary C atoms could not be determined; MSD *m/z* (r.i.) 162 (M^+, 54), 147 (74), 133 (19), 120 (31), 119 (40), 106 (19), 105 (100), 91 (74), 79 (23), 77 (21).

(1*S*,3*S*,4*R*,7*R*,8*R*,11*R*)-4-Isopropyl-7,11-dimethyl-2,12-dioxatetracyclo-[6.3.3.0^{1,3}.0^{1,8}]dodecane (202).

To a stirred solution of 1.1 g (5.0 mmol) of **198** in 50 mL of CH_2Cl_2 was added dropwise at 0 °C a solution of 1.5 g (ca. 6.3 mmol) of 70-75% *m*CPBA in 50 mL of CH_2Cl_2. After stirring for 1 h at 0 °C, the reaction mixture was diluted with 50 mL of saturated aqueous $Na_2S_2O_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated under reduced pressure to yield 1.15 g (97%) of **202**: ^{1}H NMR δ 0.92 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.21-1.43 (m, 3H), 1.59-2.01 (m, 6H), 2.25 (m, 1H), 2.48 (m, 1H), 3.56 (s, 1H); ^{13}C NMR δ 14.0 (q), 14.7 (q), 17.1 (q), 17.9 (q), 20.9 (t), 23.8 (t), 25.4 (d), 26.4 (t), 30.3 (d), 32.4 (d), 35.1 (t), 56.4 (d), 76.9 (s), 88.4 (s), 91.1 (s); MS *m/z* (r.i.) 236 (M^+, 11), 218 (4), 207 (8), 203 (10), 175 (10), 147 (100), 138 (54), 123 (45), 109 (64), 43 (35); HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1776.

(1*R*,5*S*,6*R*,7*R*,10*R*)-7-Isopropyl-4,10-dimethyl-11-oxatricyclo[5.3.2.0^{1,5}]-undec-3-en-6-ol (203) and (1*R*,5*S*,6*R*,7*R*,10*R*)-7-isopropyl-10-methyl-4-methylene-11-oxatricyclo-[5.3.2.0^{1,5}]undecan-6-ol (204).

To a stirred solution of 560 mg (2.37 mmol) of **202** in 100 mL of dry Et_2O was added at 0 °C, 0.3 mL (2.85 mmol) of $BF_3{\cdot}Et_2O$. After stirring for 2 h at 0 °C, the reaction mixture was diluted with 50 mL of saturated aqueous $NaHCO_3$. The organic layer was washed twice with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 19:1) to yield 403 mg (72%) of **203** and 145 mg (26%) of **204**.

203: ^{1}H-NMR (400 MHz) δ 0.87 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.15 (m, 1H), 1.43 (m, 1H), 1.44 (d, *J* = 4.5, 1H, OH), 1.52 (m, 1H), 1.71-1.79 (m, 2H), 1.83 (br s, 3H), 2.05 (septet, *J* = 6.9 Hz, 1H), 2.14 (ddt, *J* = 17.4, 4.7, 2.3 Hz, 1H), 2.35 (ddt, *J* = 17.4, 4.0, 2.0 Hz, 1H), 3.17 (d, *J* = 7.4 Hz, 1H), 4.07 (dd, *J* = 7.4, 4.5 Hz, 1H), 5.39 (br s, 1H); ^{13}C NMR (100 MHz) δ 14.0 (q), 17.7 (q), 17.9 (q), 18.0 (q), 19.8 (t), 25.6 (t), 31.4 (d), 35.4 (d), 42.1 (t), 63.4 (d), 76.3 (d), 89.8 (s), 92.8 (s), 127.8 (d), 137.9 (s); MS *m/z* (r.i.) 236 (M^+, 87), 218 (7), 175 (11), 147 (62), 132 (49), 121 (23), 120 (22), 109 (100), 43 (21); HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1779.

204: ^{1}H NMR (400 MHz) δ 0.93 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.25 (m, 1H), 1.37 (dt, *J* = 13.1, 7.4 Hz, 1H), 1.49 (m, 2H),

1.74 (m, 2H), 1.93 (d, *J* = 4.6 Hz, 1H, OH), 1.96 (dd, *J* = 13.0, 7.4 Hz, 1H), 2.12 (septet, *J* = 6.9 Hz, 1H), 2.31 (dd, *J* = 15.3, 7.3 Hz, 1H), 2.58 (m, 1H), 3.13 (d, *J* = 8.1 Hz, 1H), 4.10 (dd, *J* = 8.1, 4.6 Hz, 1H), 4.90 (br s, 1H), 5.29 (br s, 1H); ^{13}C NMR (100 MHz) δ 14.4 (q), 18.2 (q), 18.3 (q), 21.6 (t), 26.3 (t), 31.6 (d), 34.1 (t), 34.5 (t), 35.1 (d), 59.5 (d), 76.1 (d), 90.3 (s), 94.3 (s), 112.4 (t), 151.1 (s); MS *m/z* (r.i.) 236 (M^+, 64), 218 (5), 147 (54), 137 (31), 132 (14), 120 (21), 109 (100), 108 (16), 81 (18), 71 (31), 43 (30); HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1779.

(1*R*,4R,5*R*,6*R*,7*R*,10*R*)-7-Isopropyl-4,10-dimethyl-11-oxatricyclo[5.3.2.0^{1,5}]-undecan-6-ol (205).

To a stirred solution of 532 mg (2.42 mmol) of **198** in 100 mL of dry THF was added dropwise at room temperature 3.6 mL (7.26 mmol) of BH_3·DMS. After stirring for 4 h, aqueous 4M NaOH and 35% H_2O_2 were added in excess. After 30 min, solid K_2CO_3 was added until saturation and the reaction mixture was extracted with three 100-mL portions of EA. The combined organic layers were washed with brine, dried, and evaporated under reduce pressure. The residue was flash chromatographed (PE/EA 9:1) to yield 409 mg (71%) of **205** as white crystals: ^{1}H NMR δ 0.92 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.15-2.27 (m, 13H), 4.01 (br s, 1H); ^{13}C NMR δ 15.1 (q), 15.3 (q), 16.6 (q), 18.1 (q), 21.8 (t), 26.9 (t), 33.6 (t), 35.1 (d), 35.3 (t), 36.0 (d), 36.2 (d), 59.5 (d), 75.5 (d), 85.2 (s), 93.0 (s); MS *m/z* (r.i.) 238 (M^+, 56), 220 (32), 149 (62), 135 (29), 134 (79), 122 (31), 111 (100), 86 (32), 71 (31), 43 (33); HRMS calcd for $C_{15}H_{26}O_2$ (M^+) 238.1933, found 238.1938.

(1*R*,4R,5*S*,7*R*,10*R*)-7-Isopropyl-4,10-dimethyl-11-oxatricyclo[5.3.2.0^{1,5}]-undecan-6-one (206).

To a stirred solution of 244 mg (1.01 mmol) of **205** in 20 mL of CH_2Cl_2 was added an excess of PCC on alumina. After stirring for 1 h at room temperature, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 19:1) to yield 206 mg (85%) of **206**: ^{1}H NMR δ 0.91 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.8-2.4 (m, 12H); ^{13}C NMR δ 14.7 (q), 16.8 (q), 17.2 (q), 17.3 (q), 26.2 (t), 26.7 (t), 32.5 (d), 33.8 (d), 34.4 (t), 35.6 (t), 38.0 (d), 59.8 (d), 87.6 (s), 92.3 (s), 221.2 (s).

(1*R*,4*R*,7*R*,10*R*)-7-Isopropyl-4,10-dimethyl-11-oxatricyclo[5.3.2.0^{1,5}]-undecane (207) and (3*R*,5*S*,8*R*)-5-isopropyl-3,8-dimethyl-1,2,3,4,5,6,7,8-octahydro-5-azulenol (208).

To a stirred solution of 1.07 g (4.86 mmol) of **198** in 25 mL of freshly distilled dry ethylenediamine was added in portions 338 mg (48.6 mmol) of lithium at 100 °C. After stirring under nitrogen atmosphere for 1.5 h, the initially blue solution was now

colorless. The reaction mixture was cooled to room temperature and poured into water. The aqueous layer was extracted with three 25-mL portions of Et_2O, the organic layers were washed with brine, dried, and evaporated under reduced pressure. The residue was column chromatographed (PE - PE/EA 9:1) to yield 230 mg (21%) of **207** and 332 mg (31%) of **208**.

207: ^{1}H NMR δ 0.88 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 1.1-2.1 (m, 13H), 2.35 (dt, *J* = 10.0, 5.4 Hz, 1H); ^{13}C NMR δ 14.9 (q), 16.3 (q), 17.1 (q), 18.4 (q), 26.7 (t), 27.7 (t), 31.4 (t), 33.9 (t), 34.9 (t), 35.6 (d), 36.3 (d), 36.4 (d), 49.2 (d), 86.8 (s), 95.3 (s).

208: ^{1}H NMR δ 0.90 (d, *J* = 6.9 Hz, 6H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.8-2.6 (m, 13H), 2.23 (s, 1H); ^{13}C NMR δ 16.8 (q), 17.2 (q), 19.2 (q), 20.0 (q), 29.8 (t), 31.4 (t), 34.3 (t), 35.0 (d), 35.8 (t), 36.8 (d), 37.0 (t), 44.9 (d), 74.0 (s), 135.3 (s), 142.8 (s).

Hydrogenation of 198. Synthesis of 207.

To a solution of 133 mg (0.61 mmol) of **198** in 25 mL of MeOH was added 20 mg of Pd(C). The solution was hydrogenated for 1 h in a Parr apparatus under 4 atm. of H_2 and then filtered over hyflo. The filtrate was evaporated under reduced pressure and the residue was flash chromatographed (PE) to yield 132 mg (97%) of compound **207**.

(3*R*,5*R*)-5-Isopropyl-3,8-dimethyl-1,2,3,5,6,7-hexahydro-5-azulenol (209).

To 25 mL of freshly distilled dry ethylenediamine was added in portions 165 mg (24 mmol) of lithium at 100 °C. After stirring under nitrogen atmosphere for 30 min, the initially blue solution was now colorless and no more hydrogen was generated. Then, a solution of 523 mg (2.38 mmol) of **198** in 5 mL of dry ethylenediamine was added. After stirring for 1 h, the reaction mixture was cooled and poured into water. The aqueous layer was extracted with three 25-mL portions of Et_2O and the organic layers were washed with brine, dried, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 9:1) to yield 463 mg (89%) of **209**: ^{1}H NMR δ 0.97 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.95 (s, 3H), 0.9-2.7 (m, 10H), 2.87 (s, 1H), 5.75 (s, 1H); ^{13}C NMR δ 13.5 (q), 16.9 (q), 17.2 (d), 17.3 (q), 20.1 (q), 32.5 (t), 34.6 (d), 34.8 (t), 37.9 (t), 44.2 (t), 73.7 (s), 119.4 (d), 135.3 (s), 141.9 (s), 154.2 (s).

(1*S*,4*R*,5*S*,7*R*,8*R*,11*R*)-4,11,13,13-Tetramethyl-6,12-dioxatetracyclo-[6.3.2.0^{1,5}.0^{5,7}]tridecane (210).

To a stirred solution of 450 mg (2.1 mmol) of **200** in 25 mL of CH_2Cl_2 was added dropwise at room temperature a solution of 1.0 g (ca. 4.2 mmol) of 70-75% *m*CPBA in 25 mL of CH_2Cl_2. After stirring for 7 days, the reaction mixture was diluted with 50 mL of saturated aqueous $Na_2S_2O_3$. The organic layer was washed with

saturated aqueous $NaHCO_3$ and brine. The combined aqueous layers were extracted with two 25-mL portions of ether. The combined organic layers were dried and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 49:1) to yield 415 mg (86%) of **210**: ^{1}H NMR δ 0.98 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.12 (s, 3H), 1.45 (s, 3H), 1.50-2.14 (m, 11H), 3.31 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR δ 15.3 (q), 16.6 (q), 20.1 (t), 26.2 (t), 26.8 (q), 29.8 (q), 30.0 (t), 36.4 (d), 36.9 (t), 38.5 (d), 38.7 (d), 58.5 (d), 66.5 (s), 73.6 (s), 85.8 (s); MS *m/z* (r.i.) 236 (M^+, 6), 178 (62), 123 (100), 114 (57), 109 (45), 95 (43), 81 (70), 69 (42), 55 (47), 43 (62), 41 (63); HRMS calcd. for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1770.

3.6 References and notes

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(25) For clarity the numbering used for the carbon atoms in all compounds in this Paragraph will be the numbering of the guaiane skeleton as shown in Scheme 12.
(26) Destilaciones Bordas Chinchurreta, Seville, Spain.
(27) According to GC-analysis.
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Chapter 4

Synthesis of methyl-branched linear pheromones

4.1 Introduction

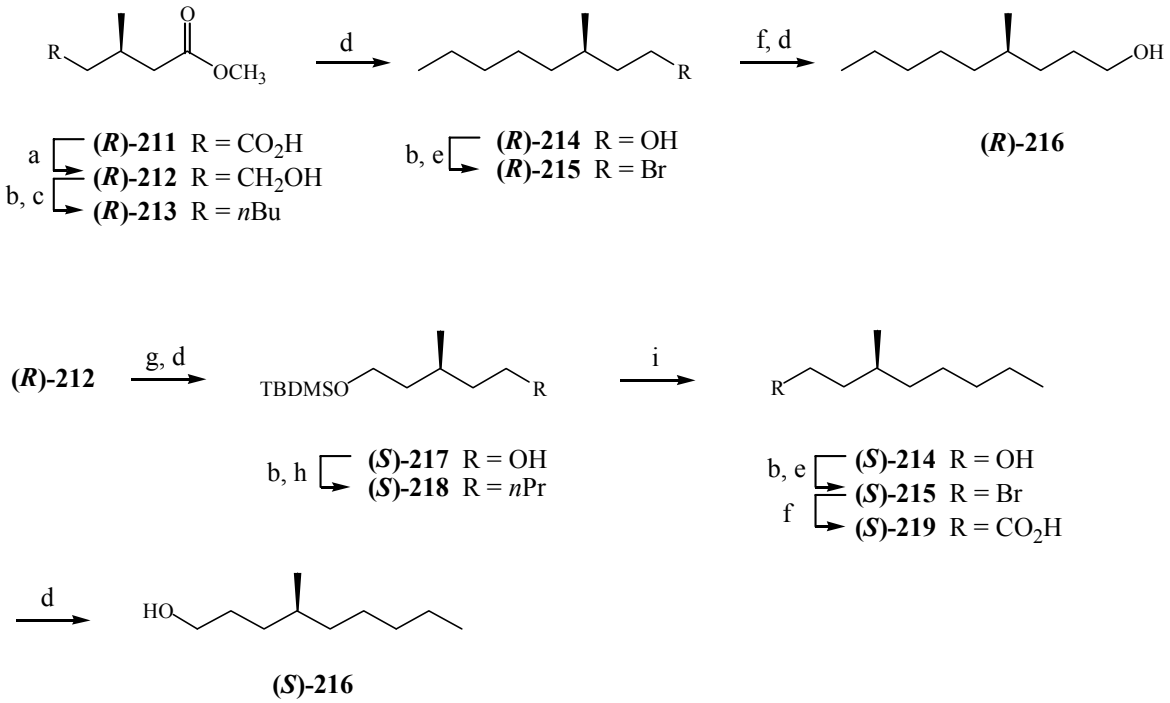
In literature, a large number of linear pheromones have been reported and many synthetic approaches have been developed for these compounds.[1,2] Next to achiral linear pheromones, many chiral derivatives have been identified and in this introduction special attention will be devoted to the synthesis of chiral linear pheromones, which are branched with one methyl group. Because the linear methyl-branched common intermediate derived from aromadendrene has its chiral center four carbon atoms away from the end of the chain (see Section 4.2), this survey will be limited to those pheromones in which the chiral center is at least four carbon atoms away from the end of the chain. The length of the chain of the synthesized pheromones can vary as a result of chain elongations. The synthesis of pheromones in which the chiral center is less than four carbon atoms away from the end of the chain has been left out of consideration in this survey. The chain lengths of the synthesized pheromones range from nine to thirtyfive carbon atoms. Furthermore, several functionalities, like double bonds, hydroxyl-, and keto groups, can be present in these pheromones. The presented examples give a good impression of the methodology that has been developed until now for the synthesis of methyl-branched pheromones.

4-Methyl-1-nonanol

The shortest pheromone, that will be described in this survey, is 4-methyl-1-nonanol (**216**), the sex pheromone of the yellow mealworm, *Tenebrio molitor*. Of the four reported syntheses of this pheromone[3-6], the method published by Carpita *et al.*[4] is the most efficient one. For this synthesis monomethyl (*R*)-3-methylglutarate ((***R*)-211**) was used as starting material for both enantiomers of **216**. The synthesis of **(*R*)-216** was achieved in eight steps and the synthesis of **(*S*)-216** took ten steps (Scheme 1), with overall yields of 21 and 24%, respectively. The exact enantiomeric purity of the synthesized pheromones has not been established. The fact that the precursors **(*R*)-212** and **(*S*)-214** had e.e. values higher than 98% led the authors to the conclusion, that the synthesized **(*R*)-216** and **(*S*)-216** also had e.e. values of at least 98%.

From biological tests it was concluded that **(*R*)-216** is the natural pheromone.[3] The racemate had about half the activity of the (*R*)-enantiomer, indicating that this enantiomer is the active one and that the (*S*)-enantiomer has no antagonistic or synergystic effect on its activity.

Scheme 1



a: BH_3·DMS, THF; b: TsCl, pyridine, 0 °C; c: $(n\text{Pr})_2\text{CuLi}$, Et_2O, -5 °C; d: $LiAlH_4$, Et_2O; e: LiBr, acetone; f: Mg; CO_2; g: TBDMSCl, imidazole, DMF; h: $(n\text{Pr})_2\text{CuLi}$, Et_2O, -45 °C; i: AcOH, THF, H_2O.

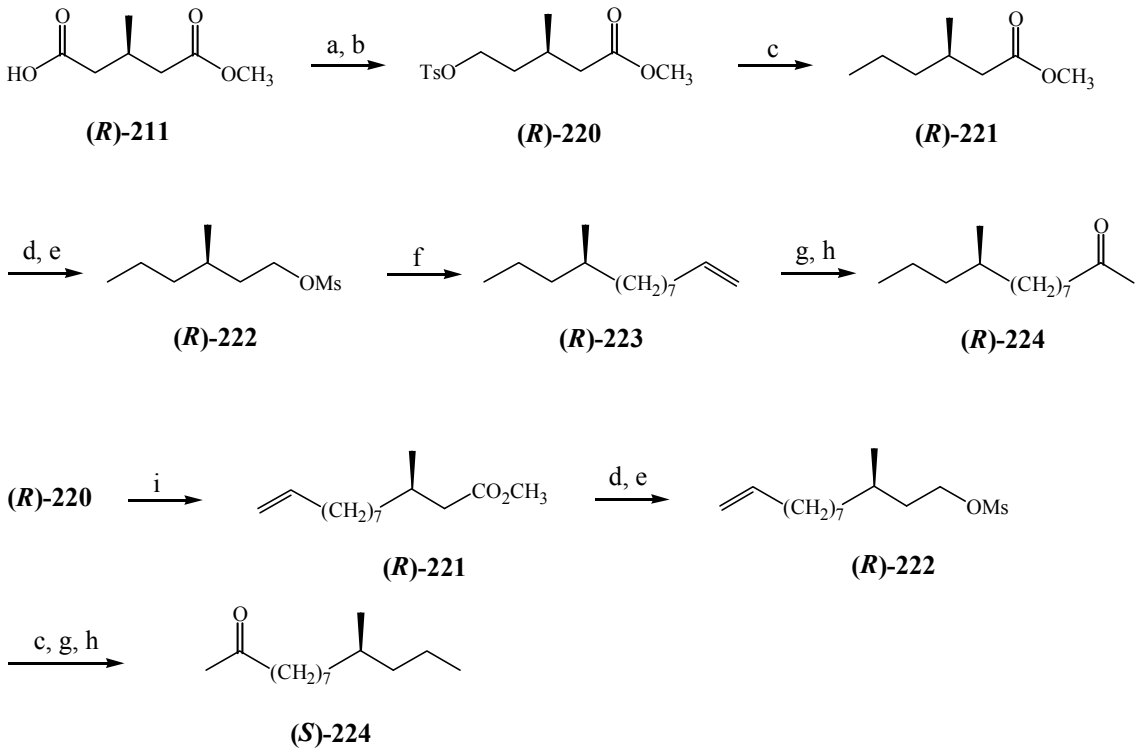
10-Methyl-2-tridecanone

Another methyl-branched linear pheromone, 10-methyl-2-tridecanone (**224**), has been synthesized by several groups.[7-13] It is the sex pheromone of the southern corn rootworm, *Diabrotica undecimpunctata* howardi Barber.[14] The most efficient synthesis of the enantiomers of **224** has been published by Nguyen Con Hao, using enantiomerically pure monomethyl (*R*)-3-methylglutarate (**(*R*)-211**) as starting material.[11] The route followed for each enantiomer consisted of eight steps and proceeded in an overall yield of 35% for **(*R*)-224** and 34% for **(*S*)-224** (Scheme 2).

The activity of the enantiomers of **224** was established by Guss *et al.*[14] Both enantiomers of **224**, a racemic mixture of **224**, and the natural pheromone from the female southern corn rootworms were tested. These experiments show, that **(*R*)-224** is the active enantiomer. The racemic mixture has a lower activity than the *R*-enantiomer.

From these experiments, it was concluded that the *S*-enantiomer does not have an antagonistic effect. Furthermore, field tests showed that also male western spotted cucumber beetles (WSCB, *Diabrotica undecimpunctata undecimpunctata* Mannerheim) and males of *Diabrotica undecimpunctata duodecimnotata* were attracted to racemic **224**, and that males of the WSCB also strongly preferred the *R*- over the *S*-enantiomer.[14]

Scheme 2

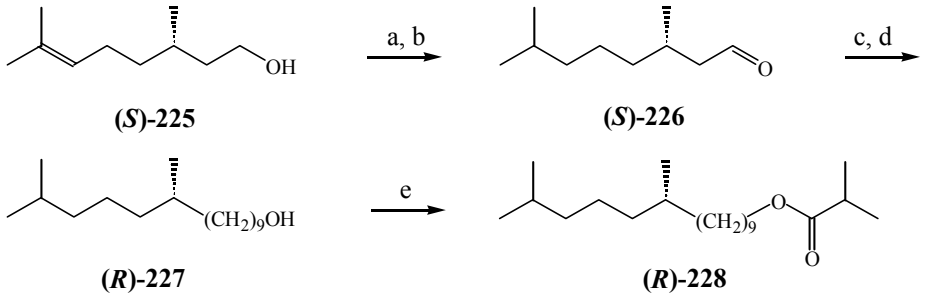


a: BH_3·DMS, THF; b: TsCl, pyridine, 0 °C; c: Me_2CuLi, Et_2O, -40 °C; d: $LiAlH_4$, Et_2O, reflux; e: MsCl, Et_3N, CH_2Cl_2, 0 °C; f: CH_2=$CH(CH_2)_5MgBr$, Li_2CuCl_4, THF, -25 °C to 0 °C; g: $Hg(OAc)_2$, THF, H_2O; $NaBH_4$, NaOH; h: $Na_2Cr_2O_7$, H_2SO_4, H_2O, Et_2O; i: $(CH_2$=$CH(CH_2)_5)_2CuLi$, Et_2O, -35 °C.

10,14-Dimethyl-1-pentadecyl isobutyrate

In order to establish the absolute configuration of the sex pheromone of the tea tussock moth (*Euproctis pseudoconspersa*), Ichikawa *et al.* synthesized both the (*R*)- and (*S*)-enantiomer of 10,14-dimethyl-1-pentadecyl isobutyrate (**228**) in five steps from (*S*)- and (*R*)-citronellol (**225**), respectively.[15] In Scheme 3 the synthesis of the (*R*)-enantiomer is depicted, which proved to be the active enantiomer of the pheromone.

Scheme 3

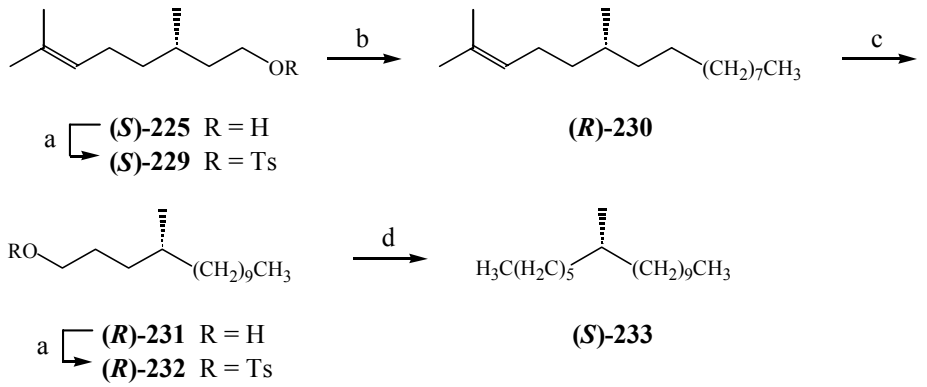


a: $LiAlH_4$, $CoCl_2$, THF; b: PCC, SiO_2, CH_2Cl_2, 0 °C; c: $HOCH_2(CH_2)_6P^+Ph_3Br^-$, NaH, DMSO, THF, 0 °C; d: $H_2NNH_2{\cdot}H_2O$, $CuSO_4$, AcOH, EtOH, $NaIO_4{\cdot}H_2O$; e: $((CH_3)_2CHCO)_2O$, pyridine.

7-Methylheptadecane

The female spring hemlock looper moth (*Lambdina athasaria*) and the female pitch pine looper moth (*Lambdina pellucidaria*) both have the same pheromones, namely 7-methyl heptadecane and 7,11-dimethylheptadecane. A synthesis of the stereoisomers of these pheromones has been published by Shiral *et al.*[16] (*R*)- and (*S*)-7-methylheptadecane (**233**) were synthesized from (*R*)- and (*S*)-citronellol (**225**), respectively. The synthesis of the (*S*)-enantiomer, which proved to be the active enantiomer, is depicted in Scheme 4. The synthesis of the pheromones took five steps and the overall yields for the (*R*)- and (*S*)-enantiomer, both obtained with an e.e. of 97%, were 57 and 74%, respectively. More recently, Díaz and Martín published another synthesis of **(*S*)-233**.[17] Their synthesis, however was less efficient with an overall yield of 32% over fifteen steps from a chiral epoxide.

Scheme 4

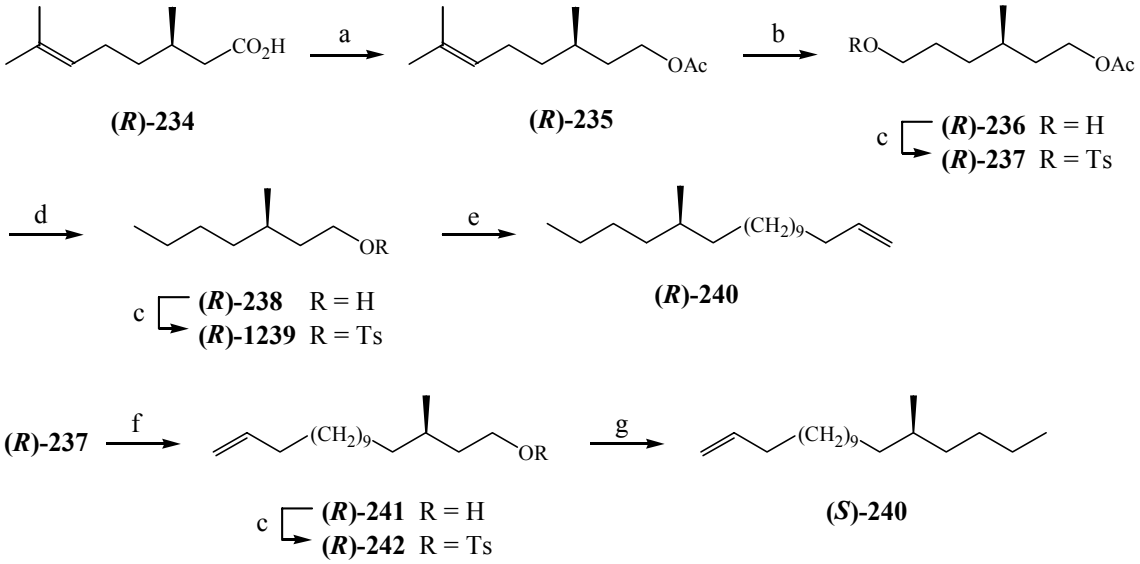


a: TsCl, pyridine; b: $CH_3(CH_2)_7MgBr$, Li_2CuCl_4, THF; c: O_3, MeOH, CH_2Cl_2, hexane; $NaBH_4$; d: *n*PrMgBr, Li_2CuCl_4, THF.

14-Methyl-1-octadecene

The peach leafminer moth, *Lyonetia clerkella* Linné is one of the most destructive pests in Japanese peach orchards. Sugie *et al.* identified the sex pheromone of the moth as 14-methyl-1-octadecene (**240**).[18] To establish the absolute configuration of the natural pheromone, Kato and Mori developed two synthetic routes to the enantiomers of **240**.[19,20] For the most efficient of the two, (*R*)-citronellic acid (**(*R*)-234**) was used as starting material for both enantiomers (Scheme 5).[20] The overall yields over six steps were 40% for **(*R*)-240** and 33% for **(*S*)-240**. The purity of the enantiomers is concluded to be 100%, because of the absolute purity of the starting material and racemization could be excluded. Biological tests with these synthesized compounds showed that the natural pheromone is **(*S*)-240**, and that there is no antagonistic activity of the (*R*)-enantiomer.[21] Two other syntheses of **240** were published more recently, but these routes were longer and had lower overall yields.[22,23]

Scheme 5

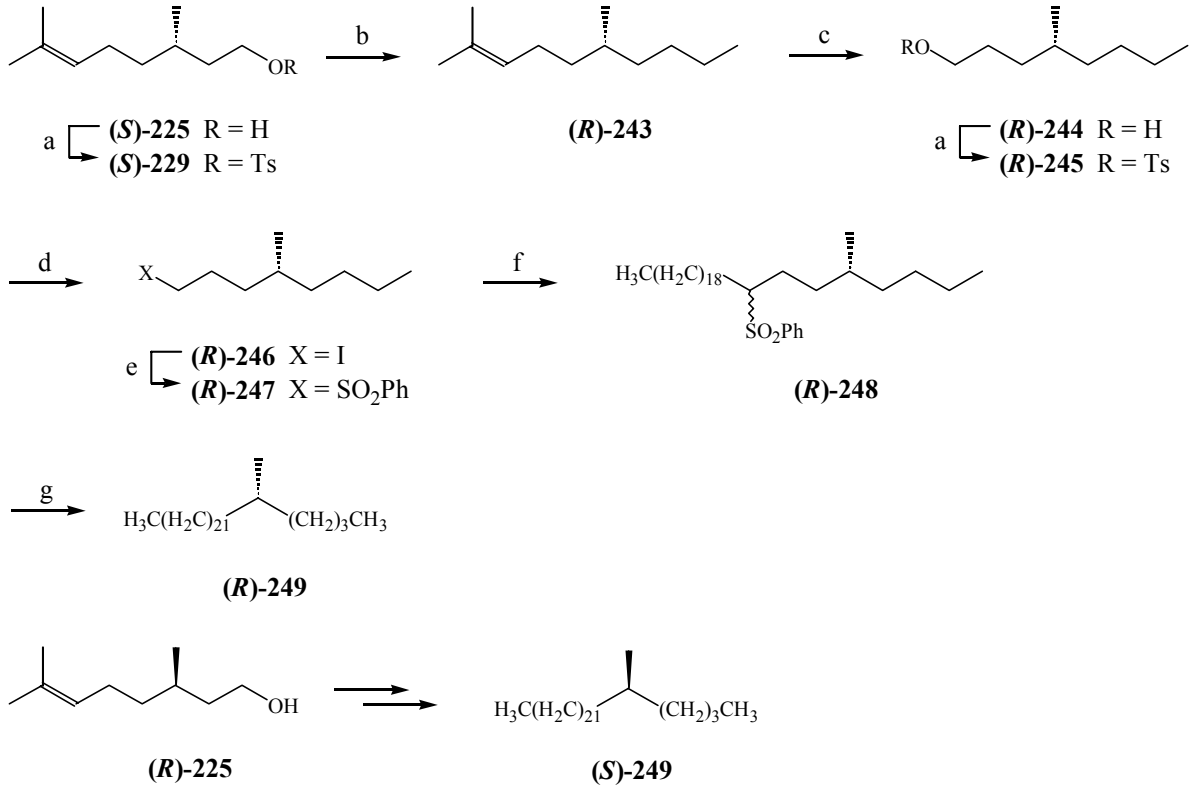


a: $LiAlH_4$; acetylation; b: O_3, MeOH, CH_2Cl_2, -70 °C; $NaBH_4$; c: TsCl, pyridine, 0 °C; d: Me_2CuLi, Et_2O, 0 °C; NaOH, MeOH, reflux; e: $(CH_2{=}CH(CH_2)_9)_2CuLi$, Et_2O, -40 °C; f: $(CH_2{=}CH(CH_2)_8)_2CuLi$, Et_2O, -40 °C; NaOH, THF, reflux; g: Et_2CuLi, Et_2O, -20 °C.

5-Methylheptacosane and 13-Methylheptacosane

A number of methyl-branched alkanes are used by ant populations (*Dicamma* species) for the recognition of their queen. Two of these compounds are 5-methylheptacosane (**249**) and 13-methylheptacosane (**254**), which have been synthesized by Marukawa *et al.*[24] As starting material for **(*R*)-249** and **(*S*)-254**, (*S*)-citronellol (**(*S*)-225**) has been used, and for **(*S*)-249** and **(*R*)-254** the starting material was (*R*)-citronellol (**(*R*)-225**). The synthesis of **(*R*)-** and **(*S*)-249**, which is depicted in Scheme 6, consisted of eight steps and had an overall yield of 22% for the (*R*)-enantiomer and 19% for the (*S*)-enantiomer.

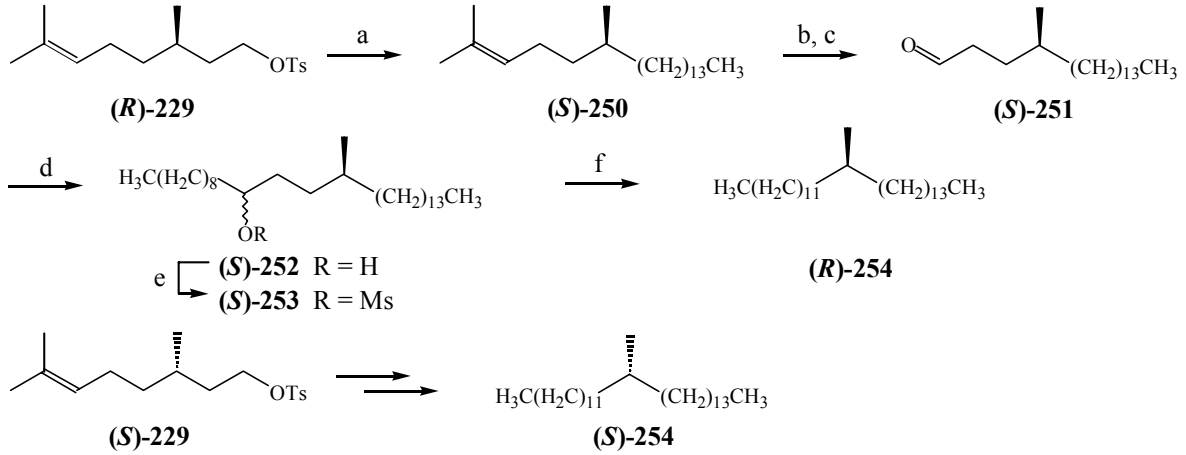
Scheme 6



a: TsCl, pyridine; b: EtMgBr, Li_2CuCl_4, THF, -78 °C to 4 °C; c: O_3, CH_2Cl_2, MeOH; $NaBH_4$; d: NaI, $NaHCO_3$, acetone, reflux; e: $PhSO_2Na{\cdot}2H_2O$, DMF; f: $CH_3(CH_2)_{18}I$, *n*BuLi, THF; g: Na(Hg), EtOH.

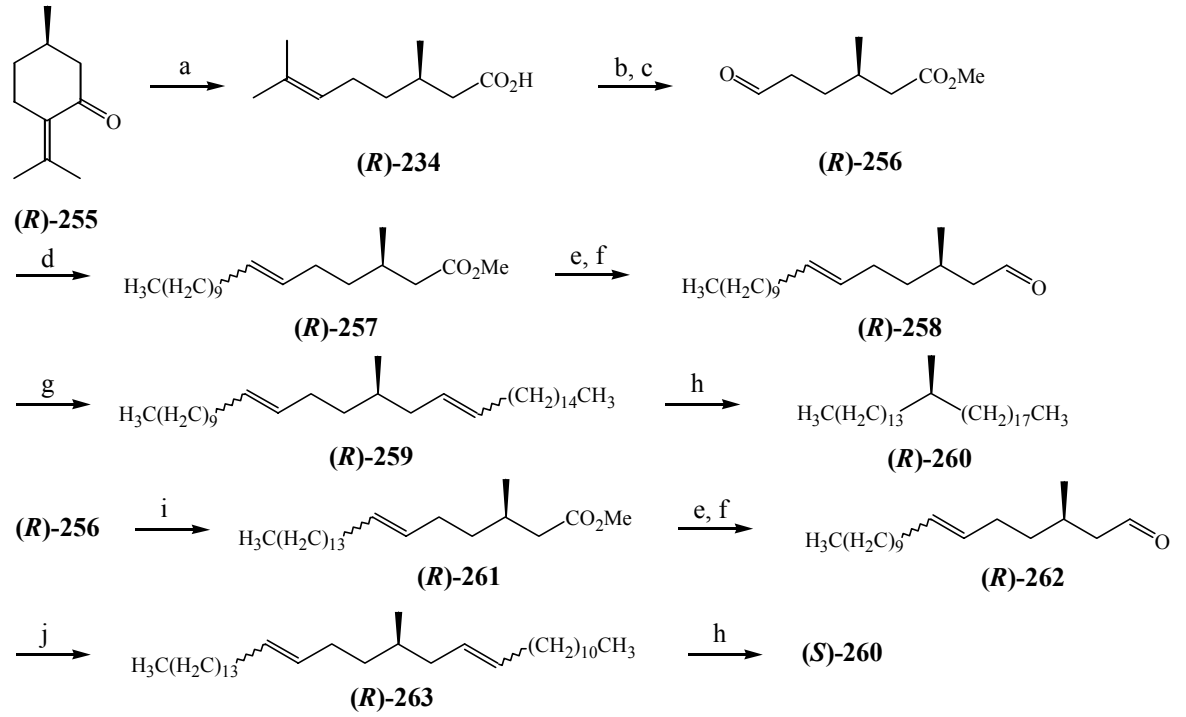
Scheme 7 shows the synthesis of **(*R*)-** and **(*S*)-254** in seven steps from citronellol, with overall yields of 37 and 32%, respectively. The enantiomeric purity of the four synthesized stereoisomers of 5- and 13-methylheptacosane was higher than 97%.

Scheme 7



a: $CH_3(CH_2)_{11}MgBr$, Li_2CuCl_4, THF, -78 °C to 4 °C; b: OsO_4, NMO, *t*BuOH, acetone, H_2O; c: $HIO_4 \cdot 2H_2O$, THF; d: $CH_3(CH_2)_8MgBr$, THF, -78 °C to rt; e: MsCl, pyridine, CH_2Cl_2; f: $LiEt_3BH$, THF.

Scheme 8



a: HCl; NaOH; b: MeOH, H_2SO_4; c: *m*CPBA, CH_2Cl_2; HIO_4, Et_2O, 10 °C; d: $[CH_3(CH_2)_{10}PPh_3]^+Br^-$, *n*BuLi, DME; e: $LiAlH_4$, Et_2O; f: PCC, CH_2Cl_2; g: $[CH_3(CH_2)_{15}PPh_3]^+Br^-$, *n*BuLi, DME; h: H_2, Pd(C), EtOH, hexane; i: $[CH_3(CH_2)_{14}PPh_3]^+Br^-$, *n*BuLi, DME; j: $[CH_3(CH_2)_{11}PPh_3]^+Br^-$, *n*BuLi, DME.

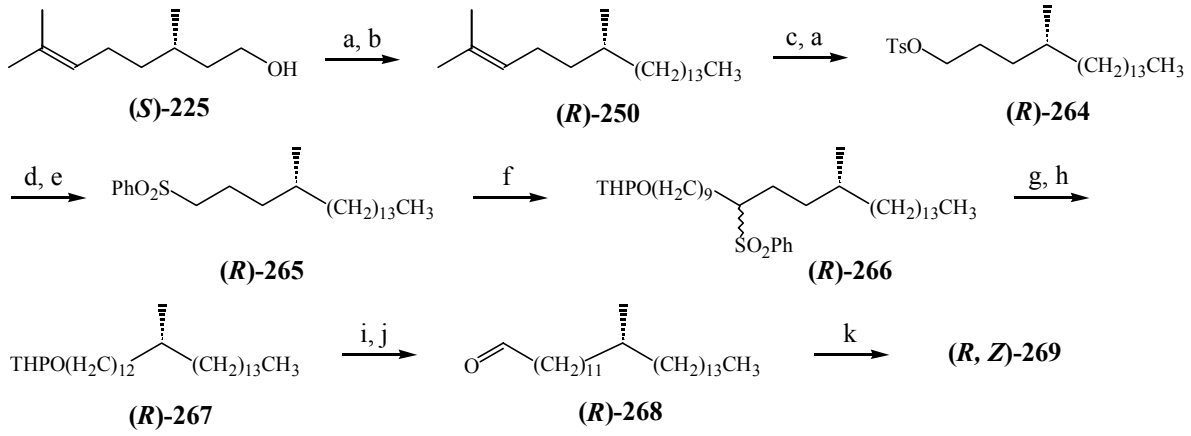
15-Methyltritriacontane

One of the longest methyl-branched linear pheromones is 15-methyltritriacontane (**260**), one of the sex pheromones of the stable fly, *Stomoxys calcitrans*. Of the two reported syntheses of the enantiomers of **130**[25,26], the synthesis published by Naoshima and Mukaidani is the most efficient one.[26] (*R*)-pulegone (**(*R*)-255**) was the starting material for this synthetic route, which consisted of eight steps (Scheme 8). The overall yield for **(*R*)-260** was 21% and for **(*S*)-260** it was 20%. The authors assume that the synthesized compounds were enantiomerically pure, because of the high enantiomeric purity of the starting material (about 100%) and the assumption that no racemization could have taken place.

21-Methyl-8-pentatriacontene

The female contact sex pheromone of the yellow-spotted longicorn beetle, *Psacothea hilaris*, has been identified as (*Z*)-21-methyl-8-pentatriacontene (**269**).[27] To establish the absolute configuration of the natural pheromone, Fukusaki *et al.* synthesized all four stereoisomers of 21-methyl-8-pentatriacontene from methyl (*R*)- and (*S*)-3-hydroxy-2-methylpropionate in overall yields from 4 to 7%.[28] A later, more efficient synthesis of the (*Z*)-enantiomers of **269** has been published by Domon *et al.*[29] As starting material, (*S*)- and (*R*)-citronellol (**(*S*)-** and **(*R*)-225**) were used for the synthesis of **(*R, Z*)-269** and **(*S, Z*)-269**, respectively. The synthesis, which consisted of twelve steps, had an overall yield of 44% for the (*R*)-enantiomer and 37% for the (*S*)-enantiomer. In Scheme 9 the synthesis of **(*R, Z*)-269** is depicted.

Scheme 9



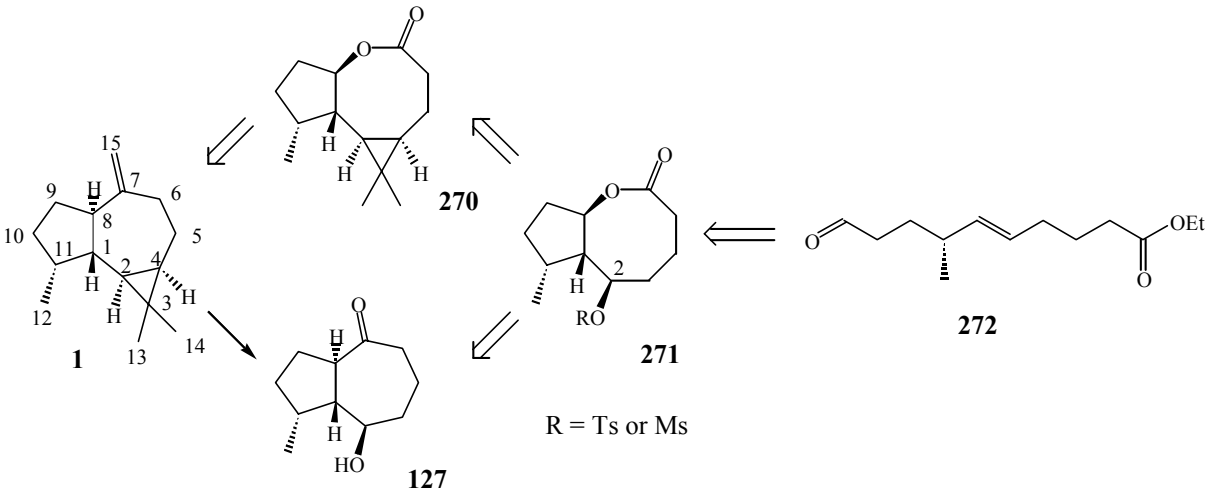
a: TsCl, pyridine, 0 °C; b: $CH_3(CH_2)_{11}MgBr$, Li_2CuCl_4, THF; c: O_3, hexane, MeOH, CH_2Cl_2, -78 °C; $NaBH_4$, 0 °C; d: NaI, $NaHCO_3$, acetone; e: $PhSO_2Na$, DMF; f: *n*BuLi, $THPO(CH_2)_9I$, THF, HMPA; g: Na(Hg), EtOH; h: H_2, PtO_2, EtOAc; i: TsOH, MeOH, CH_2Cl_2; j: PCC, mol.sieves (4 Å), CH_2Cl_2; k: $[CH_3(CH_2)_7PPh_3]^+Br^-$, NaHMDS, THF.

4.2 Synthesis of linear pheromones from aromadendrene

As shown in the previous section, a large number of synthetic routes to methyl-branched linear pheromones have been reported. For several of those syntheses natural terpenes, like citronellol and pulegone, have been used as starting material. In this Chapter, the use of aromadendrene as another cheap starting material for the synthesis of methyl-branched linear pheromones will be described.

In order to make linear products out of this tricyclic sesquiterpene, first methods have to be developed for the conversion of aromadendrene to a linear intermediate. The approaches to be investigated are depicted in Scheme 10 and rely on a Baeyer-Villiger oxidation and a Grob fragmentation as key reactions.

Scheme 10



The first approach consists of a conversion of aromadendrene (**1**) to lactone **270**, followed by opening of the cyclopropane ring. Conversion of the functionality at C2[30] to a good leaving group would lead to lactone **271**.

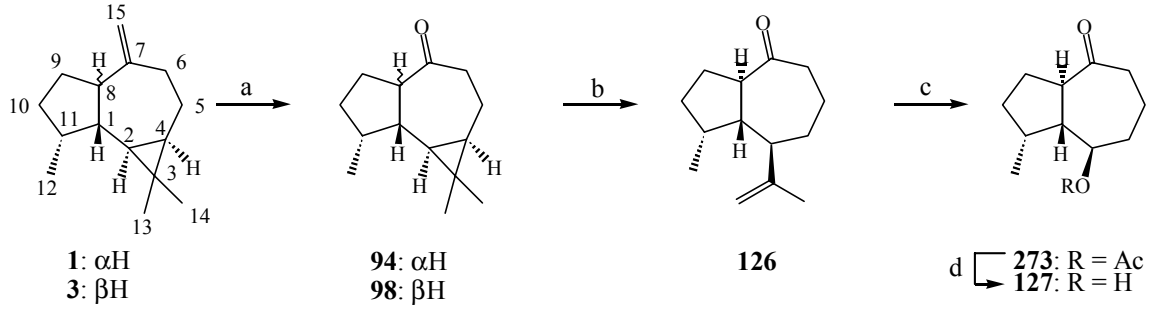
In the second approach, lactone **271** is formed in a different way. First, aromadendrene is converted to the known alcohol **127** in four steps.[31] Conversion of the hydroxyl group in **127** to a tosylate or mesylate, followed by a Baeyer-Villiger oxidation, would also lead to lactone **271**. When this lactone is subjected to strongly basic conditions, a Grob fragmentation may take place to give the linear product **272**. This product can be a versatile intermediate for the synthesis of several methyl-branched linear pheromones. Because compound **272** has two different functionalities at both ends of the chain, this chain can be elongated or shortened at either side and pheromones which vary in chain length and in the position of the chiral center, become accessible.

4.3 Synthesis of the linear intermediate

4.3.1 Baeyer-Villiger reactions on aromadendrene derivatives

In our approach to linear pheromones from aromadendrene, the Baeyer-Villiger oxidation is one of the key steps. For this reaction a carbonyl group is required at C7, and compounds possessing such a group can be prepared easily, as described by Gijsen *et al.*[31], from aromadendrene (**1**) and alloaromadendrene (**3**), both present in the distillation tail of the oil of *Eucalyptus globulus* (Scheme 11). In a four-step synthesis, the distillation tail[32] is first ozonolyzed to a mixture which consists mainly of apoaromadendrone **94** and alloapoaromadendrone **98**. Treatment of this mixture with aqueous HCl in refluxing ethanol leads to the formation of isoapoaromadendrone **126** as the sole product. This means that in compound **98**, besides ring opening, also epimerization at C8 takes place. After ozonolysis of compound **126** and subsequent Criegee rearrangement, acetate **273** is obtained. This acetate can be saponified easily with sodium methoxide to alcohol **127**.

Scheme 11



1: αH
3: βH

94: αH
98: βH

126

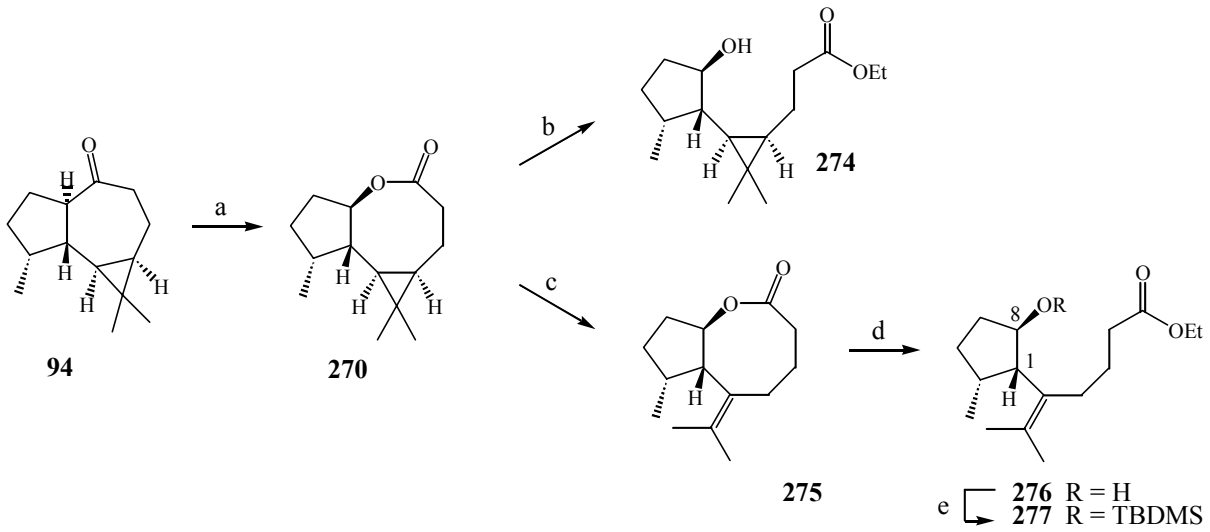
273: R = Ac
127: R = H

a: O_3, CH_2Cl_2, MeOH, -78 °C; thiourea; b: aq. HCl, EtOH, reflux; c: O_3, CCl_4, MeOH, -30 °C; Et_3N, Ac_2O, DMAP; d: NaOMe, MeOH.

The next step in the synthetic route, the Baeyer-Villiger reaction, can in principle be carried out with all ketones given in Scheme 11. The oxidation was first carried out with apoaromadendrone (**94**) to afford lactone **270** in a very high yield of 99% (Scheme 12). However, attempts to open the cyclopropane ring with concentrated HCl in ethanol only led to opening of the lactone ring and compound **274** was formed. When **270** was treated with TMSOTf in chloroform, cyclopropane ring opening to compound **275** took place, but only in a low yield. This lactone **275** proved to be unstable and therefore the lactone ring was opened with ethanol in the presence of TsOH in a one-pot reaction directly after the cyclopropane ring opening. In this way compound **276** was obtained in 36% yield from **270**. The configuration at C8 in **276** was established from the 2D NMR spectra of its TBDMS-ether **277**. From the absence

of a NOE correlation between H1 and H8 it was concluded that the hydroxyl group at C8 is β-oriented. This could also be expected, because the Baeyer-Villiger oxidation usually proceeds with retention of configuration. Further conversion of **276** to a suitable starting material for the Grob fragmentation appeared to be problematic and this fact, together with the low yield of the cyclopropane ring opening, prompted us to investigate other methods for the synthesis of lactone **271**.

Scheme 12

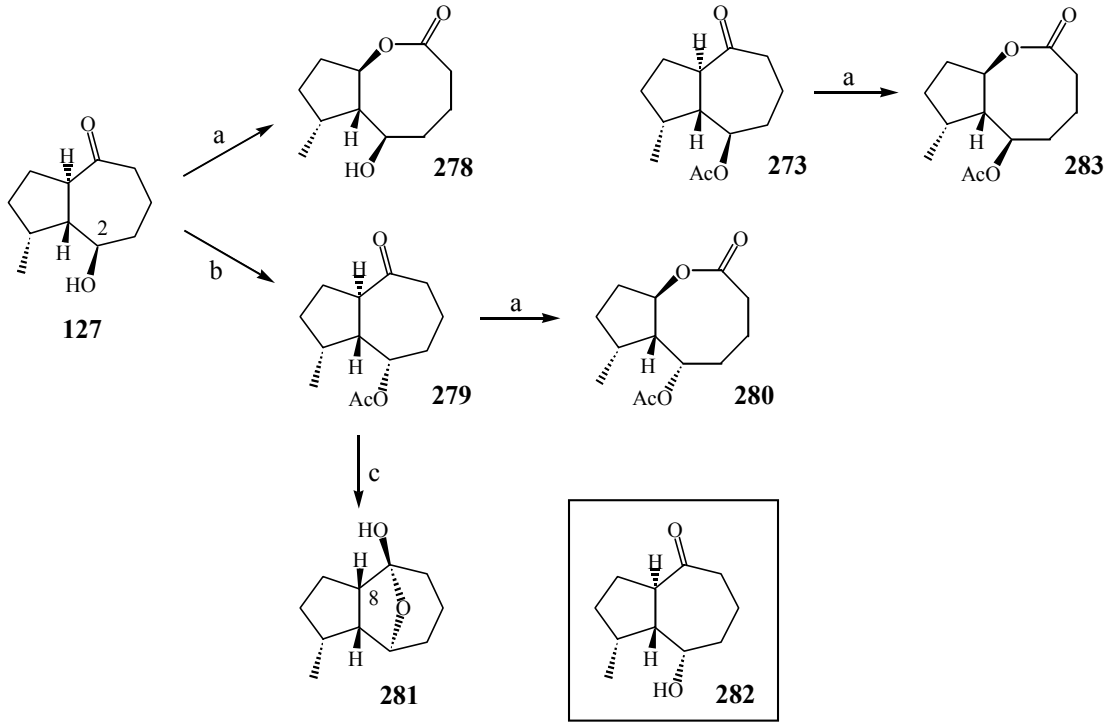


a: *m*CPBA, $NaHCO_3$, CH_2Cl_2; b: aq. HCl, EtOH; c: TMSOTf, $CHCl_3$; d: EtOH, TsOH; e: TBDMSCl, imidazole, DMF.

The suitability of isoapoaromadendrone (**126**) (see Scheme 11) as substrate for the Baeyer-Villiger reaction was doubtful, because several competing reactions could occur. Treatment of **126** with *m*CPBA would most probably also lead to the formation of epoxides, and indeed, NMR analysis of the product mixture formed upon reaction of **126** with *m*CPBA showed the complete absence of double bonds.

The Baeyer-Villiger reaction of **127** with *m*CPBA in CH_2Cl_2 also appeared problematic at first. However, when $MgSO_4$ was added to the reaction mixture, the reaction proceeded well and compound **278** was isolated in a yield of 69%. The Baeyer-Villiger reactions of several derivatives of **127** depicted in Scheme 13 show that this reaction works well under these conditions for compounds with an α- or a β-functionality at C2, in yields ranging from 65 to 74%. The reaction was not tested with the α-alcohol **282**, because the saponification of acetate **279** led to the formation of hemiacetal **281** instead of **282**. Epimerization at C8 under the basic reaction conditions used for the saponification of **279** explains the easy formation of hemiacetal **281**.[33]

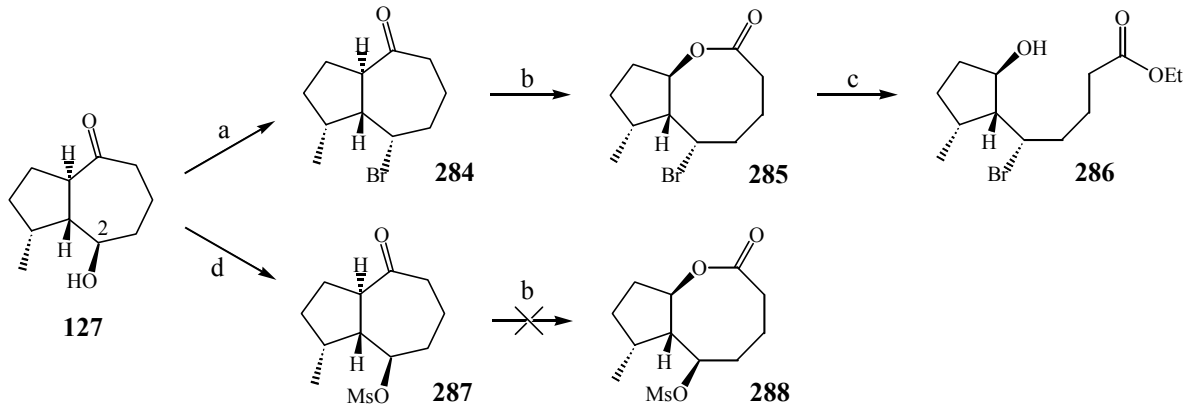
Scheme 13



a: *m*CPBA, $MgSO_4$, CH_2Cl_2; b: TsCl, pyridine; KOAc, DMSO; c: KOH, MeOH.

In order to obtain a suitable lactone as starting material for the Grob fragmentation, it is necessary to introduce a good leaving group at C2 in compound **127**. Therefore, **127** was converted to its α-bromide **284** through reaction with CBr_4 and PPh_3 (Scheme 14).

Scheme 14



a: CBr_4, PPh_3, CH_2Cl_2; b: *m*CPBA, $MgSO_4$, CH_2Cl_2; c: TsOH, EtOH; d: MsCl, pyridine.

The Baeyer-Villiger reaction of **284** also went well with *m*CPBA. It is noteworthy that with **284** the addition of $MgSO_4$ was not necessary to obtain a good result. After the Baeyer-Villiger reaction, the lactone ring is opened with ethanol in the presence of TsOH in a one-pot reaction. This is done, because the lactone **285** is not very stable and decomposes easily, even when it is stored at low temperature. The hydroxy ester **286** is more stable and, when stored at 4 °C, does not give any problems of decomposition. The stereochemistry of the lactones depicted in Scheme 13 and 14 was not established by 2D NMR, but it was assumed that the configuration at the bridgehead carbon is as shown, because the Baeyer-Villiger oxidation usually proceeds with retention of configuration.

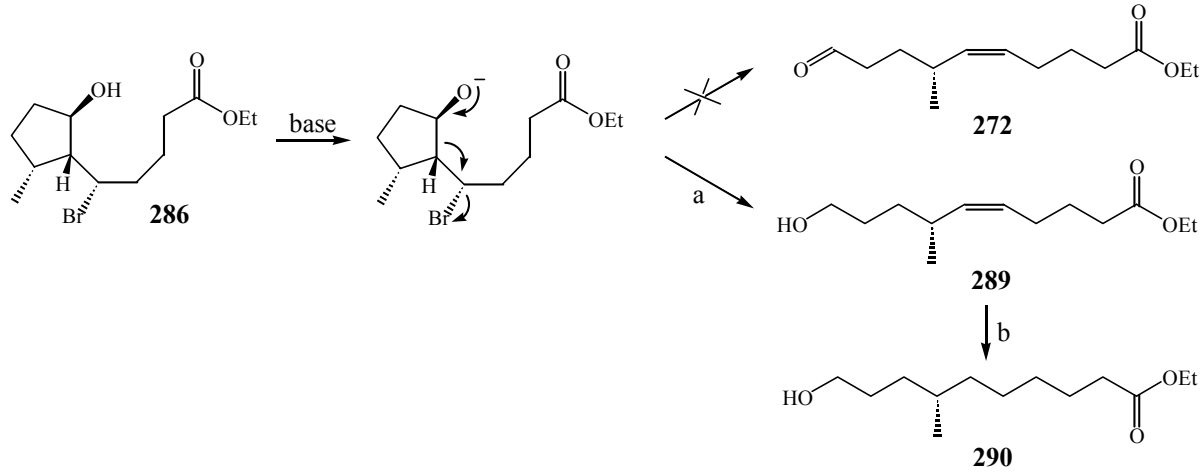
Attempts to synthesize lactone **288** with a mesylate group as leaving group were not successful. The formation of mesylate **287** from **127** proceeded in a good yield. However, when **287** was treated under Baeyer-Villiger conditions, the product decomposed before it could be isolated. The instability of lactone **288**, having a β-oriented good leaving group at C2, might be caused by through-bond orbital interactions (TBI)[34] between the oxygen functionality at C8 and the mesylate group. Because of the antiperiplanar relationship between the central C1-C8 bond and the C2-OMs bond, TBI can be transmitted efficiently as a result of which the mesylate group, as a very good leaving group, can split off easily with all its consequences. The other lactones **278** and **283** with a β-oriented hydroxy- and acetate group, respectively, at C2 are more stable, because these groups are poor leaving groups in comparison with the mesylate group. The stability of lactone **285**, having an α-oriented bromide at C2, is of equal magnitude as those of **287** and **283**, because there is no antiperiplanar relationship between C1-C8 and the C2-Br bond through which TBI is less efficient. In conclusion, hydroxy ester **286** with the α-bromide as leaving group ultimately appeared the best starting material for the Grob fragmentation, which will be described in the next section.

*4.3.2 Grob fragmentation of compound **286***

The Grob fragmentation can be used to synthesize a linear product from a monocyclic compound via fragmentation of the γ-hydroxy bromide **286**, as depicted in Scheme 15. A strong base is used to generate the alcoholate of **286**, which then can fragment to form aldehyde **272**. Several bases, like KO*t*Bu and NaOEt were tested for this fragmentation, but compound **272** could never be isolated from the reaction mixture in an acceptable yield. Under strongly basic conditions, the aldehyde appeared to be unstable and decomposed very easily to give a mixture of products.

This problem could be solved by adding a reducing agent to the reaction mixture. When the Grob fragmentation was carried out with NaOEt in EtOH in the presence of five equivalents of $NaBH_4$, alcohol **175** could be obtained in 80% yield.

Scheme 15



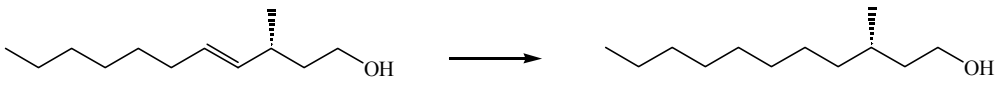
a: NaOEt, $NaBH_4$, EtOH; b: H_2, Pd (C), EtOAc.

The next step in the synthesis is the reduction of the double bond in **289**. When this reduction was carried out with hydrogen in the presence of Pd(C), the reaction went well and gave **290** in 85% yield. Sometimes partial racemization of allylic chiral centers may be expected in catalytic reductions of double bonds. However, Larcheveque *et al.*[35] have shown that this is not a serious problem in reduction with Pd(C) as catalyst (Table 1).

Table 1 Catalytic reduction of A to B

Entry	Reagent	Solvent	Yield (%)	Racemisation rate (%)[a]
1	HN=NH	EtOH	80	0
2	H_2, 10% Pd(C)	EtOH	80	3
3	$LiAlH_4$, $CoCl_2$	THF	80	6
4	H_2, 5% Rh/alumina	EtOH	80	8.5
5	H_2, PtO_2	AcOEt	90	19

[a] Racemisation rate = $(1\text{-e.e.}_B/\text{e.e.}_A) \times 100\%$



A **B**

They also showed that no racemization takes place in reduction of the double bond with diimine. However, the diimide reductions that were carried out with compound **289** did not give any satisfactory results. A similar hydrogenation with PtO_2

as a catalyst has been used in the synthesis of 14-methyl-1-octadecene by Sonnet *et al*.[22] and they claimed to have synthesized this product with an enantiomeric purity of more than 99%. However, they determined the enantiomeric purity of an intermediate in their synthesis prior to the reduction of the double bond and concluded that the end product had the same purity.

Attempts were made to establish the optical purity of **290**, but this proved to be more difficult than expected. Standard methods like measurement of optical rotation or determination of purity by GC- or HPLC-analysis can only be used when both enantiomers of the compound are known, which is not the case for compound **290**. Furthermore, attempts were made to synthesize diastereomeric esters of **290** with a chiral acid, in the hope that this would lead to a crystalline product of which the crystal structure could be established. However the reaction of **290** with camphorsulfonic acid chloride led to the formation of the chloride of **290** instead of the camphorsulfonic ester. From the reactions of **290** with (*R*)- and (*S*)-α-methoxy-α-trifluoromethyl-phenylacetic acid (MTPA), the corresponding esters were formed, but the products were oils, so no crystal structures could be determined.

4.4 Synthesis of linear pheromones from compound 290

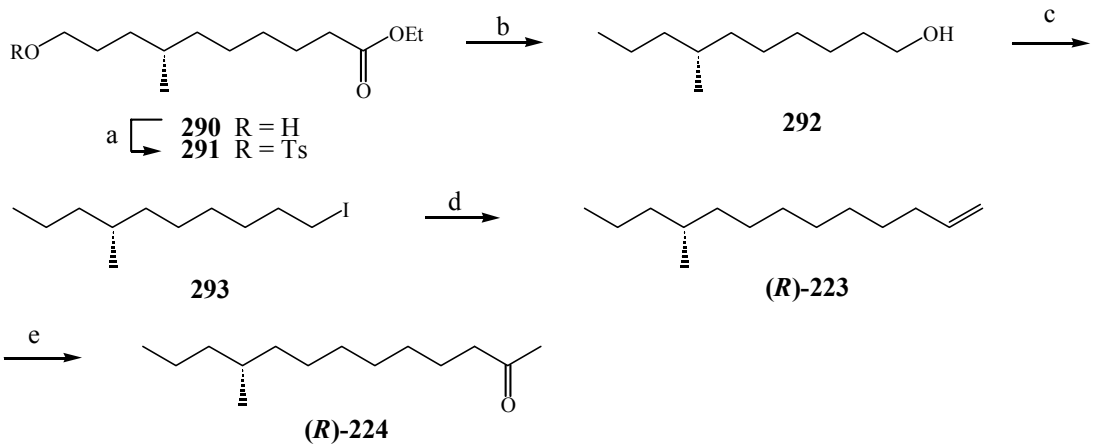
The linear intermediate **290** has been used for the synthesis of three different linear pheromones. These syntheses will be described in the following sections.

4.4.1 Synthesis of (R)-10-methyl-2-tridecanone

(*R*)-10-methyl-2-tridecanone (**(*R*)-224**) is the active pheromone of the southern corn rootworm, *Diabrotica undecimpunctata* howardi Barber. Several syntheses of this pheromone have been reported before (see Section 4.1). We used compound **290** to synthesize **(*R*)-224**, which was done in a five-step sequence with an overall yield of 57% (Scheme 16). The two different functionalities in **290**, the hydroxy group at the left side and an ester group at the right side of the chain, allow modification of both ends of the chain separately. For pheromone **(*R*)-224**, this means that at the left side the hydroxy group has to be removed and that the right side of the chain has to be elongated with a three-carbon fragment.

First the hydroxy group was converted to a good leaving tosylate group by reaction of **290** with TsCl in pyridine to give **291** in 83% yield. Subsequently, both the tosylate and the ester group were reduced affording alcohol **292** in a very good yield of 95%. Prior to introduction of the three-carbon fragment at the right side of the molecule, the hydroxy group in **292** was replaced by iodide to give **293** in 91% yield.[36] Introduction of an allylgroup and oxidation of this group[37] finally led to the formation of **(*R*)-224** in 83% yield.

Scheme 16

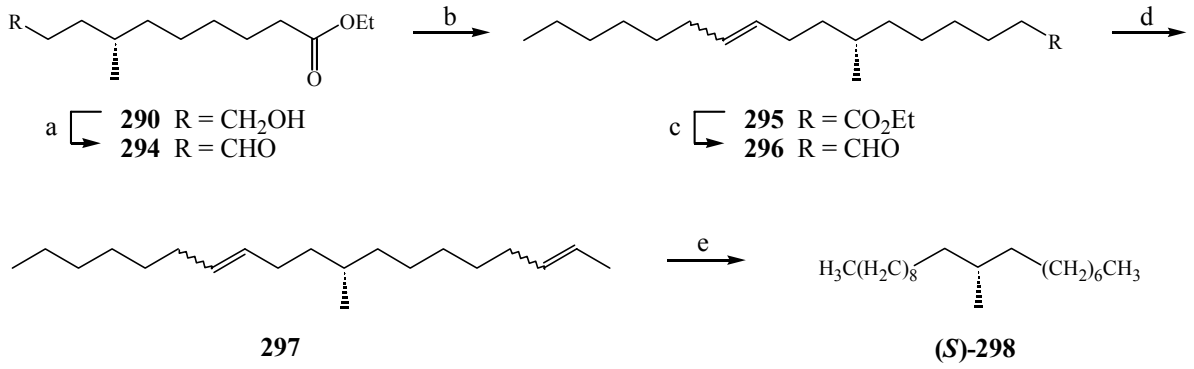


a: TsCl, pyridine; b: $LiAlH_4$, THF; c: I_2, PPh_3, imidazole, CH_2Cl_2; d: allylMgCl, THF; e: $PdCl_2$, O_2, DMF(wet).

4.4.2 Synthesis of (S)-9-methylnonadecane

(*S*)-9-Methylnonadecane (**(*S*)-298**) has been identified as one of the sex pheromones of the cotton leafworm, *Alabama argillacea.*[38] The synthetic route described below is the first synthesis of the pheromone that is reported. This route from compound **290** to **(*S*)-298**, which consists of five steps with an overall yield of 58%, is depicted in Scheme 17. For the synthesis of this pheromone from **290**, elongation at both ends of the chain is necessary. A seven- and two-carbon fragment have to be added at the left and right side, respectively.

Scheme 17



a: PCC, CH_2Cl_2; b: $[C_7H_{15}PPh_3]^+I^-$, *n*BuLi, THF, -78 °C; c: DIBALH, toluene, -78 °C; d: $[C_2H_5PPh_3]^+I^-$, *n*BuLi, THF, -78 °C; H_2, Pd(C), EtOAc.

In this synthetic route, **290** was oxidized first to aldehyde **294**. The left side of **294** was then elongated with a seven-carbon fragment via a Wittig reaction with heptyltriphenylphosphonium iodide to give a mixture of the *Z* and *E* isomers of **295** in a ratio of 3:1 (according to GC-analysis) in 76% yield over two steps. Reduction of the ester group in compound **295** resulted in the formation of aldehyde **296**[39] in 86% yield. A second Wittig reaction on **296** led to the formation of **297** as a mixture of four stereoisomers in 92% yield. The formation of these stereoisomers was no problem, because reduction of the double bonds led to a single product, pheromone **(*S*)-298**, in 95% yield.

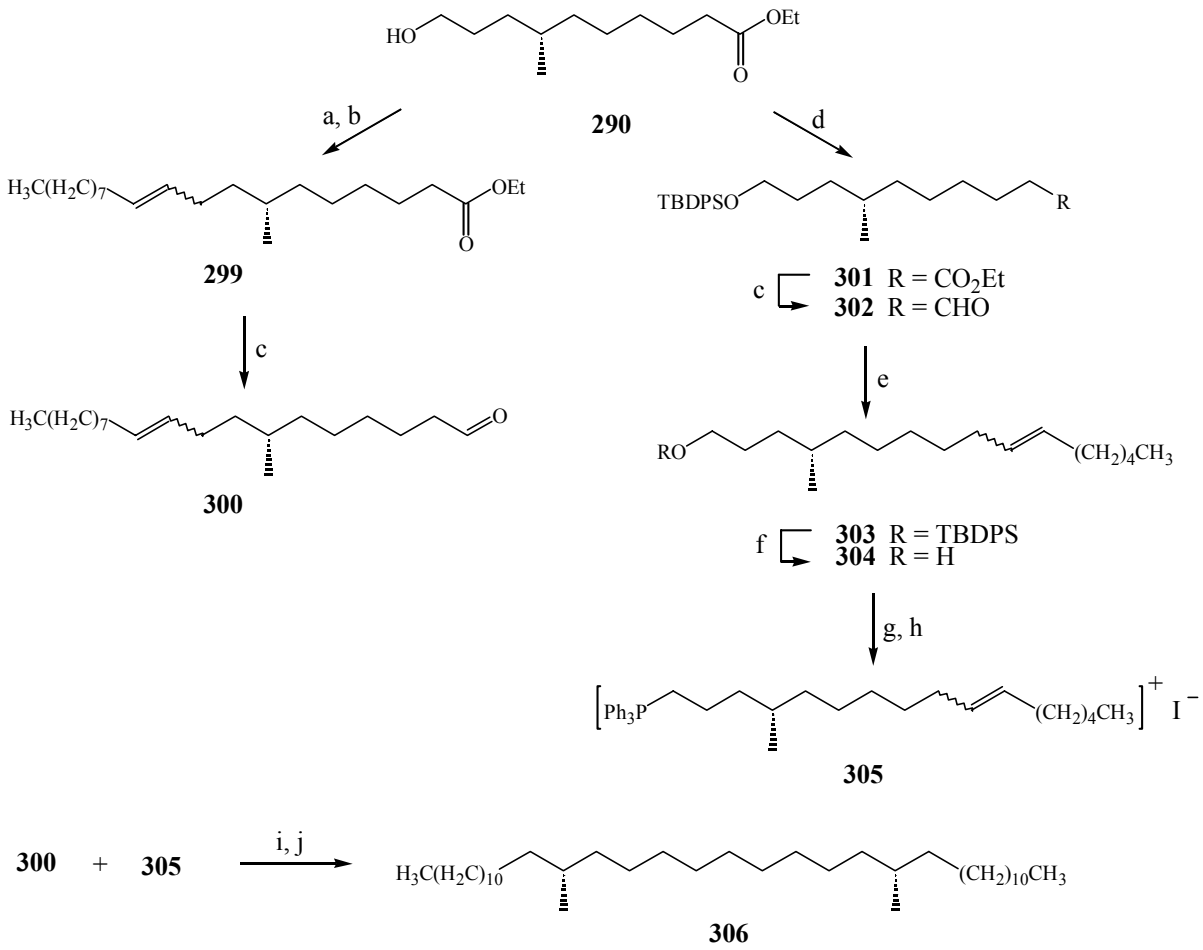
4.4.3 Synthesis of meso-13,23-dimethylpentatriacontane

Meso-13,23-dimethylpentatriacontane (**306**) has been identified as the sex pheromone of the tse tse fly, *Glossina pallidipes*.[38] In this pheromone, the two chiral centers are separated from each other by nine carbon atoms, which makes it possible to use two units of **290**, coupled head to tail, to synthesize the central part of the chain. In our synthetic route, the left and right segment of the molecule are synthesized first. Both segments are then coupled to form the chain of thirty-five carbon atoms. The left segment consists of one molecule of **290** elongated at the left side with nine carbons whereas the right segment is built up from one molecule of **290** elongated with a six-carbon segment (Scheme 18). During the Wittig reactions used for this synthesis, double bond isomers can be formed. This is not a problem, because in the last step of the synthesis the double bonds are hydrogenated and only one product, pheromone **306**, is obtained.

The left side of the molecule was synthesized via a Wittig reaction with the aldehyde **294** to give compound **299** in 89% yield. After reduction of **299** with DIBALH[39], aldehyde **300** is obtained in 85% yield.

The first steps in the synthesis of the right side of the pheromone consist of protection of the hydroxy group with a silyl group and reduction of the ester group to aldehyde **302** in 77% yield over two steps. Addition of a six-carbon fragment via a Wittig reaction (60% yield), followed by deprotection of the silyl group (94% yield), led to the formation of **304**. Prior to coupling to compound **300**, the hydroxy group of **304** had to be replaced by iodide[36], after which the phosphonium salt **305** could be prepared in 86% yield over two steps by reaction with PPh_3. Then, the left and right side of the pheromone (**300** and **305**) were coupled via a Wittig reaction (80% yield) and in the final step the double bonds in the triene were hydrogenated and the pheromone **193** was obtained in 95% yield.

Scheme 18



a: PCC, CH_2Cl_2; b: $[C_9H_{19}PPh_3]^+Br^-$, *n*BuLi, THF, -78 °C; c: DIBALH, toluene, -78 °C; d: TBDPSCl, imidazole, DMAP, DMF; e: $[C_6H_{13}PPh_3]^+I^-$, *n*BuLi, THF, -78 °C; f: TBAF, THF; g: I_2, PPh_3, imidazole, CH_3CN, Et_2O, 0 °C to rt; h: PPh_3, toluene, reflux; i: *n*BuLi, THF, -78 °C; j: H_2, Pd(C).

4.5 Experimental part

Compounds **94**, **126**, **273**, and **127** were prepared from the distillation tail of *Eucalyptus globulus* as described by Gijsen *et al*.[31]

(1*R*,3a*R*,7a*R*,8a*R*,8b*S*)-1,8,8-Trimethyldecahydro-5*H*-cyclopenta[*b*]cyclopropa-[*d*]-oxocin-5-one (270)

To a stirred solution of 13.4 g (65 mmol) of **94** in 300 mL of CH_2Cl_2, cooled to 0 °C, was added 30.7 g (125-133 mmol) of 70-75% *m*CPBA and 21 g of $NaHCO_3$. After stirring for 1 h at room temperature, 100 mL of CH_2Cl_2 was added to the suspension, because stirring became increasingly difficult. After stirring for another

1.5 h, the reaction mixture was diluted with 300 mL of water and 100 mL of saturated aqueous $NaHCO_3$. After separation of the layers, the organic layer was washed successively with 300 mL of 10% aqueous $Na_2S_2O_3$, 400 mL of saturated aqueous $NaHCO_3$, and brine, and then dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, 14.9 g (99%) of **270** was obtained as a white solid: ^{1}H NMR δ 0.35-0.54 (m, 2H), 0.82 (d, *J* = 7.2 Hz, 3H), 0.90 (s, 3H), 0.99 (s, 3H), 1.0-1.7 (m, 4H), 1.86-2.07 (m, 4H), 2.27 (dt, *J* = 4.7, 10.5 Hz, 1H), 2.56 (m, 1H), 4.89 (dt, *J* = 1.9, 9.2 Hz, 1H); ^{13}C NMR δ 15.0 (q), 18.0 (q), 19.2 (s), 21.5 (t), 25.4 (d), 27.0 (d), 28.6 (t), 28.8 (q), 30.7 (t), 31.9 (d), 35.9 (t), 47.8 (d), 84.8 (d), 179.2 (s).

Ethyl 3-{(1*R*,3*R*)-3-[(1*S*,2*R*,5*R*)-2-hydroxy-5-methylcyclopentyl]-2,2-dimethylcyclopropyl}propanoate (274)

To a stirred solution of 0.16 g (0.72 mmol) of **270** in 3 mL of EtOH was added 1 mL of concentrated aqueous HCl. After stirring for 45 min at room temperature, saturated aqueous $NaHCO_3$ was added and the reaction mixture was extracted with three 30-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 1:1) to yield 0.12 g (62%) of **274** as a colorless oil: ^{1}H NMR δ 0.25 (dd, *J* = 9.0, 11.5 Hz, 1H), 0.44 (dt, *J* = 5.6, 8.5 Hz, 1H), 0.89 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 3H), 1.01 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.45-1.56 (m, 3H), 1.75-2.40 (m, 8H), 4.04 (m, 1H), 4.10 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR δ 14.2 (q), 15.6 (q), 16.7 (q), 17.3 (s), 20.9 (t), 15.8 (d), 26.7 (d), 29.0 (q), 30.8 (t), 33.1 (t), 34.2 (d), 34.9 (t), 48.0 (d), 60.3 (t), 79.5 (d), 174.0 (s); MSD *m/z* (r.i.) 268 (M^+, 0.2), 250 (0.6), 207 (13), 169 (49), 149 (27), 137 (25), 123 (35), 107 (39), 95 (100), 81 (57), 69 (43), 55 (57), 41 (41).

Ethyl 5-[(1*S*,2*R*,5*R*)-2-hydroxy-5-methylcyclopentyl]-6-methyl-5-heptenoate (276)

To a stirred solution of 5.0 g (22.5 mmol) of **270** in 50 mL of dry CH_2Cl_2, cooled to 0 °C, was added 0.65 mL (3.4 mmol) of TMSOTf. After stirring for 3.5 h at room temperature, another portion of 0.25 mL (1.3 mmol) of TMSOTf was added. After stirring for two days, all **270** was converted to **275** and 15 mL of EtOH and a catalytic amount of $TsOH·H_2O$ were added. After stirring for one day, 200 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted with three 100-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed twice (PE/EA 5:1) to yield 2.2 g (36%) of **276** as a light yellow oil: ^{1}H NMR δ 0.67 (*J* = 7.3 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.62 (s, 3H), 1.70 (s, 3H), 1.51-2.33 (m, 12 H), 2.82 (t, *J* = 9.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.31 (q, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 14.3 (q), 17.8 (q), 20.5 (q), 21.0 (q), 24.5 (t), 31.1 (t), 31.2 (t),

34.1 (t), 34.5 (t), 35.6 (d), 54.1 (d), 60.4 (t), 74.8 (d), 129.4 (s), 130.3 (s), 174.0 (s); MSD *m/z* (r.i.) 250 (M^+-H_2O, 14), 207 (27), 161 (36), 135 (78), 109 (68), 107(55), 95 (84), 81 (56), 69 (48), 67 (34), 55 (100), 43 (64), 41 (80).

(6*R*,6a*S*,7*R*,9a*R*)-6-Hydroxy-7-methyloctahydrocyclopenta[*b*]oxocin-2(3*H*)-one (278)

To a stirred solution of 182 mg (1.0 mmol) of **127** in 10 mL of CH_2Cl_2, cooled to 0 °C, were added 1.2 g (4.9-5.2 mmol) of 70-75% *m*CPBA and 1.2 g of $MgSO_4$. After stirring for 72 h at room temperature, the reaction mixture was washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 3:2) to yield 137 mg (69%) of **278** as white crystals: M.p. 99-100 °C; $[\alpha]_D$ = –100.7° (c = 1.425, $CHCl_3$); ^{1}H NMR δ 0.86 (d, *J* = 7.2 Hz, 3H), 1.32-2.66 (m, 13 H), 4.07 (dt, *J* = 4.6, 8.1 Hz, 1H), 4.35 (dt, *J* = 3.1, 9.7 Hz, 1H); ^{13}C NMR δ 15.8 (q), 18.7 (t), 27.1 (t), 29.7 (t), 30.9 (t), 33.9 (t), 34.1 (d), 56.4 (d), 73.6 (d), 80.8 (d), 172.1 (s); MS *m/z* (r.i.) 180 (M^+-H_2O, 25), 154 (100), 99 (84), 95 (46), 82 (57), 81 (42), 71 (55), 67 (64), 55 (61), 43 (36), 41 (40); HRMS calcd. for $C_{11}H_{16}O_2$ (M-H_2O) 180.1152, found 180.1150.

(6*R*,6a*S*,7*R*,9a*R*)-7-Methyl-2-oxodecahydrocyclopenta[*b*]oxocin-6-yl acetate (283)

To a stirred solution of 0.2 g (0.9 mmol) of **273** in 12 mL of CH_2Cl_2, cooled to 0 °C, were added 1.1 g (4.5-4.8 mmol) of 70-75% *m*CPBA and 1.1 g of $MgSO_4$. After stirring for 72 h at room temperature, the reaction mixture was washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 17:3) to yield 0.14 g (65%) of **283** as a yellow oil. During NMR measurements in acetone-d_6, the product decomposed partly resulting in a mixture of compounds. The two singlets at δ 174.8 and 178.2 observed in the ^{13}C NMR spectrum pointed to the presence of a lactone ring and an acetate group.

(3*R*,3a*R*,4*S*,8a*R*)-3-Methyl-8-oxodecahydro-4-azulenyl acetate (279)

To a stirred solution of 0.9 g (4.95 mmol) of **127** in 15 mL of pyridine, cooled to 0 °C, was added 0.95 g (4.95 mmol) of TsCl. After stirring for 40 h at 35 °C, the reaction mixture was cooled to 15 °C and diluted with 100 mL of ether. The mixture was washed twice with 20 mL of ice-cold 4 M aqueous HCl, then with water, and finally with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 9:1) to yield 1.12 g (68%) of the corresponding tosylate as a white solid: ^{1}H NMR δ 0.82 (d, *J* = 7 Hz, 3H), 1.39-1.90 (m, 7H), 2.43 (s, 3H), 2.26-2.53 (m, 5H), 2.94

(ddd, *J* = 5.1, 10.1, 11.3 Hz, 1H), 4.80 (dt, *J* = 4.2, 10.4 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H).

To a stirred solution of 0.81 g (2.4 mmol) of the tosylate from the previous reaction in 20 mL of DMSO was added 5 g (51 mmol) of KOAc. After stirring for 24 h at 60 °C, 150 mL of water was added and the reaction mixture was extracted with three 50-mL portions of CH_2Cl_2. The combined organic layers were washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was flash chromatographed (PE/EA 9:1) to yield 0.15 g (28%) of **279** as a white solid: M.p. 69-70 °C; $[\alpha]_D = -28.74°$ (c = 2.035, $CHCl_3$); ^{1}H NMR δ 0.85 (d, *J* = 7 Hz, 3H), 1.21-2.62 (m, 12H), 2.06 (s, 3H), 3.48 (q, *J* = 8 Hz, 1H), 5.26 (br s, 1H); ^{13}C NMR δ 15.3 (q), 17.6 (t), 21.7 (q), 24.7 (t), 34.4 (t), 34.6 (t), 37.4 (d), 42.9 (t), 47.1 (d), 49.2 (d), 71.4 (d), 170.2 (s), 213.5 (s); MS *m/z* (r.i.) 224 (M^+, 5), 164 (100), 149 (24), 135 (14), 121 (17), 109 (29), 108 (16), 93 (16), 81 (27), 55 (14), 43 (55); HRMS calcd. for $C_{13}H_{20}O_3$ 224.1412, found 224.1412.

(6*S*,6a*S*,7*R*,9a*R*)-7-Methyl-2-oxodecahydrocyclopenta[*b*]oxocin-6-yl acetate (280)

To a stirred solution of 50 mg (0.2 mmol) of **279** in 2.5 mL of CH_2Cl_2, cooled to 0 °C, were added 0.28 g (1.1-1.2 mmol) of 70-75% *m*CPBA and 0.28 g of $MgSO_4$. After stirring for 72 h at room temperature, the reaction mixture was washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 17:3) to yield 40 mg (75%) of **280** as a yellow oil: ^{1}H NMR δ 0.81 (d, *J* = 7.2 Hz, 3H), 1.14-2.40 (m, 11H), 2.00 (s, 3H), 2.87 (dt, *J* = 6, 12.4 Hz), 4.99-5.17 (m, 2H); ^{13}C NMR δ 16.9 (q), 21.1 (q), 22.1 (t), 28.8 (t), 30.3 (t), 30.7 (t), 31.1 (t), 36.2 (d), 54.2 (d), 70.7 (d), 79.9 (d), 169.9 (s), 175.1 (s).

(1*R*,2*S*,6*R*,7*R*,10*R*)-6-Hydroxy-10-methyl-11-oxatricyclo[5,3,0^{1,7}]undecane (281)

To a stirred solution of 136 mg (0.61 mmol) of **279** in 3 mL of MeOH was added 0.2 g of KOH. After stirring for 4 h at room temperature, the MeOH was evaporated under reduced pressure and the residue was extracted with three 5-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 9:1) to yield 98 mg (89%) of **281** as a white solid: M.p. 101-102 °C; $[\alpha]_D = +24.38°$ (c = 1.575, $CHCl_3$); ^{1}H NMR δ 1.00 (d, *J* = 6.9 Hz, 3H), 1.19-2.05 (m, 11H), 2.28 (t, *J* = 7.9 Hz, 1H), 2.40 (dt, *J* = 2.4, 10.3 Hz, 1H), 2.96 (br s, 1H), 4.26 (s, 1H); ^{13}C NMR δ 15.6 (q), 18.1 (t), 26.5 (t), 29.8 (t), 34.6 (t), 36.9 (t), 38.2 (d), 49.1 (d), 50.2 (d), 74.2 (d), 104.1 (s); IR(nujol, cm^{-1}) 3346 (broad, OH), 1018 (C-O-C); MS *m/z* (r.i.) 182 (M^+, 21), 137 (24),

111 (13), 109 (30), 95 (50), 82 (20), 81 (100), 67 (22), 55 (16), 41 (13); HRMS calcd. for $C_{11}H_{18}O_2$ 182.1307, found 182.1304.

(1*R*,3a*R*,8*S*,8a*R*)-8-Bromo-1-methyloctahydro-4(1*H*)-azulenone (284)

To a stirred solution of 1.5 g (8.2 mmol) of **127** and 3.0 g (9.0 mmol) of CBr_4 in 75 mL of CH_2Cl_2 was added in small portions 4.3 g (16.4 mmol) of PPh_3, over a period of 1 h. After stirring for 15 min. at room temperature, the solvent was partially evaporated to a volume of approximately 10 mL and this mixture was column chromatographed (PE/EA 1:1) to yield 1.57 g (78%) of **284** as a light yellow oil: ^{1}H NMR δ 1.18 (d, *J* = 6.7 Hz, 3H), 1.37-2.57 (m, 12H), 3.62 (q, *J* = 8.6 Hz, 1H), 4.79 (t, *J* = 3.2 Hz, 1H); ^{13}C NMR δ 13.9 (q), 18.9 (t), 25.8 (t), 33.6 (t), 37.6 (d), 40.7 (t), 42.5 (t), 47.8 (d), 53.7 (d), 59.7 (d), 213.1 (s); MS *m/z* (r.i.) 246 (M^+, ^{81}Br, 36), 244 (M^+, ^{79}Br, 36), 165 (100), 164 (32), 162 (31), 147 (24), 137 (22), 109 (51), 95 (41), 81 (64); HRMS calcd. for $C_{11}H_{17}O^{79}Br/C_{11}H_{17}O^{81}Br$ 244.0463/246.0443, found 244.047/246.044.

Ethyl (5*S*)-5-bromo-5-[(1*R*,2*R*,5*R*)-2-hydroxy-5-methylcyclopentyl]-pentanoate (286)

To a stirred solution of 1.7 g (6.9 mmol) of **284** in 100 mL of CH_2Cl_2 was added 8.3 g (ca. 35 mmol) of 70-75% *m*CPBA. After stirring for 2 days at room temperature, 40 mL of EtOH and a catalytic amount of $TsOH·H_2O$ were added. After stirring for another day, the reaction mixture was diluted with 200 mL of saturated aqueous $NaHCO_3$. After separation of the layers, the water layer was extracted with two 100-mL portions of CH_2Cl_2. The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 1:1) to yield 1.25 g (59%) of **286** as a colorless oil and 0.16 g (10%) of starting material: ^{1}H NMR δ 0.75 (d, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.3-2.4 (m, 13H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.04-4.42 (m, 2H); ^{13}C NMR δ 14.3 (q), 14.5 (q), 22.5 (t), 31.8 (t), 31.8 (t), 33.4 (t), 37.0 (t), 37.1 (d), 59.0 (d), 60.5 (t), 60.6 (d), 77.3 (d), 173.2 (s); MS *m/z* (r.i.) 227 (M^+-Br, 28), 209 (88), 181 (100), 163 (98), 135 (81), 121 (61), 95 (70), 93 (60), 81 (92), 55 (87), 41 (56); HRMS calcd. for $C_{13}H_{23}O_3$ (M^+-Br) 227.1647, found 227.1650.

(3*R*,3a*R*,4*R*,8a*R*)-3-Methyl-8-oxodecahydro-4-azulenyl methanesulfonate (287)

To a stirred solution of 0.30 g (1.65 mmol) of **127** in 10 mL of pyridine, cooled to 0 °C, was added 0.75 mL (9.7 mmol) of MsCl. After stirring for 35 min. at room temperature, the reaction mixture was diluted with 1 M aqueous HCl and extracted three times with EA. The combined organic layers were washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, and then dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was column

chromatographed (PE/EA 1:1) to yield 0.40 g (93%) of **287**: ^{1}H NMR δ 0.83 (d, *J* = 7.0 Hz, 3H), 1.01-1.64 (m, 7H), 1.98-2.66 (m, 6H), 2.26 (s, 3H), 4.62 (dt, *J* = 4.4, 10.4 Hz, 1H); ^{13}C NMR δ 13.3 (q), 18.2 (t), 22.6 (t), 32.0 (t), 35.3 (t), 37.0 (d), 38.8 (q), 42.3 (t), 46.9 (d), 52.0 (d), 82.9 (d), 209.0 (s); MS *m/z* (r.i.) 260 (M^+, 3), 165 (30), 164 (100), 135 (40), 121 (28), 109 (81), 108 (32), 83 (31), 81 (49), 79 (34), 55 (30); HRMS calcd. for $C_{12}H_{20}O_4S$ (M^+) 260.1082, found 260.1076.

Ethyl (5Z,7R)-10-hydroxy-7-methyl-5-decenoate (289)

To a stirred solution of 0.60 g (1.95 mmol) of **286** in 70 mL of 0.5 M ethanolic NaOEt was added 0.38 g (10 mmol) of $NaBH_4$. After stirring for 2 h at room temperature, the reaction mixture was diluted with 100 mL of 1 M aqueous HCl and extracted with three 50-mL portions of CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 1:1) to yield 0.26 g (77%) of **289** as a colorless oil: ^{1}H NMR δ 0.87 (d, *J* = 5.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.30-1.69 (m, 8H), 1.95-2.02 (m, 2H), 2.2-2.4 (m, 2H), 3.55 (t, *J* = 6.5 Hz, 2H), 4.06 (q, *J*= 7.1 Hz, 2H), 5.04-5.29 (m, 2H); ^{13}C NMR δ 14.3 (q), 21.4 (q), 25.0 (t), 26.8 (t), 30.8 (t), 31.5 (d), 33.4 (t), 33.8 (t), 60.3 (t), 63.1 (t), 127.4 (d), 137.0 (d), 174 (s); MS *m/z* (r.i.) 210 (M^+-H_2O, 16), 185 (33), 152 (86), 123 (35), 99 (47), 95 (73), 81 (100), 69 (34), 67 (42), 55 (51), 41 (34); HRMS calcd. for $C_{13}H_{22}O_2$ (M^+-H_2O) 210.1620, found 210.1616.

Ethyl (7*S*)-10-hydroxy-7-methyldecanoate (290)

To a solution of 100 mg (0.44 mmol) of **289** in 5 mL of EA was added 50 mg of 10% Pd(C). The solution was hydrogenated for 1 h in a Parr apparatus under 4 atm. of H_2 and then filtrated over hyflo. The hyflo was washed with CH_2Cl_2 and the filtrate was evaporated under reduced pressure. The residue was column chromatographed (PE/EA 2:1) to yield 84 mg (83%) of **290** as a colorless oil: ^{1}H NMR δ 0.86 (d, *J* = 6.3 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.00-1.70 (m, 14H), 2.28 (t, *J* = 7.5 Hz, 2H), 3.61 (t, *J* = 6.6 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR δ 14.3 (q), 19.6 (q), 25.0 (t), 26.6 (t), 29.4 (t), 30.3 (t), 32.5 (d), 32.9 (t), 34.4 (t), 36.7 (t), 60.2 (t), 63.3 (t), 174.0 (s).

Ethyl (7*S*)-7-methyl-10-{[(4-methylphenyl)sulfonyl]oxy}decanoate (291)

To a stirred solution of 0.22 g (0.96 mmol) of **290** in 20 mL of pyridine was added 0.91 g (4.8 mmol) of TsCl. After stirring for 4 h at room temperature, the reaction mixture was diluted with 100 mL of 1 M aqueous HCl and extracted with three 50-mL portions of EA. The combined organic layers were washed with 1 M aqueous HCl and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 2:1) to yield 0.29 g (79%) of **291** as a colorless oil: ^{1}H NMR δ 0.79 (d, *J* = 6.2 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.0-1.4 (m, 8H), 1.53-1.70 (m, 5H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.68 (s, 3H), 3.99 (t, *J* = 6.5 Hz,

2H), 4.11 (q, *J* = 7.1 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR δ 14.3 (q), 19.4 (q), 21.7 (q), 25.0 (t), 26.5 (t), 26.6 (t), 29.4 (t), 32.2 (d), 32.5 (t), 34.4 (t), 36.5 (t), 60.2 (t), 71.1 (t), 127.9 (d, 2C), 129.8 (d, 2C), 133.2 (s), 144.7 (s), 173.9 (s).

(7*R*)-7-Methyl-1-decanol (292)

To a stirred solution of 0.29 g (0.76 mmol) of **291** in 25 mL of dry THF was added 0.15 g (4.0 mmol) of $LiAlH_4$. After stirring for 1.5 h at room temperature, the reaction mixture was diluted with 100 mL of 1 M aqueous HCl and extracted with three 40-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 2:1) to yield 124 mg (95%) of **292** as a colorless oil: ^{1}H NMR δ 0.85 (d, *J* = 6.3 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H), 1.04-1.65 (m, 15H), 3.65 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR δ 14.4 (q), 19.7 (q), 20.1 (t), 25.8 (t), 27.0 (t), 29.8 (t), 32.5 (d), 32.8 (t), 37.0 (t), 39.4 (t), 63.1 (t). The ^{1}H NMR spectrum corresponds to that of racemice **292** reported in literature.[40]

(7*R*)-1-Iodo-7-methyldecane (293)

To a stirred solution of 106 mg (0.62 mmol) of **292** in 20 mL of CH_2Cl_2 were added 0.32 g (1.2 mmol) of PPh_3, 90 mg (1.3 mmol) of imidazole and 0.32 g (1.3 mmol) of I_2. After stirring for 40 min at room temperature, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed twice (PE/EA 5:1) to yield 158 mg (91%) of **293** as a colorless oil: ^{1}H NMR δ 0.83 (d, *J* = 6.3 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H), 1.04-1.37 (m, 13H), 1.75-1.89 (m, 2H), 3.18 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR δ 7.4 (t), 14.4 (q), 19.7 (q), 20.1 (t), 26.9 (t), 28.9 (t), 30.6 (t), 32.4 (d), 33.6 (t), 36.9 (t), 39.4 (t); MS m/z (r.i.) 282 (M^+, 8), 155 (35), 99 (12), 85 (47), 71 (69), 69 (17), 57 (100), 55 (35), 43 (92), 41 (41), 39 (9); HRMS calcd. for $C_{11}H_{23}I$ (M^+) 282.0844, found 282.0838.

(10*R*)-10-Methyl-1-tridecene ((*R*)-223)

To a stirred solution of 32 mg (0.11 mmol) of **293** in 2 mL of dry THF, cooled to 0 °C, was added 0.22 mL of 1 M allylMgCl in THF. After stirring for 1 h at 0 °C, the reaction mixture was diluted with 1 M aqueous HCl and extracted three times with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 5:1) to yield 19 mg (83%) of **(*R*)-223** as a colorless oil: ^{1}H NMR δ 0.93-0.99 (m, 6H), 1.08-1.42 (m, 17H), 2.00-2.18 (m, 2H), 5.01-5.15 (m, 2H), 5.75-5.95 (m, 1H); ^{13}C NMR δ 14.4 (q), 19.6 (q), 20.3 (t), 27.3 (t), 29.1 (t),

29.3 (t), 29.7 (t), 30.2 (t), 32.7 (d), 34.0 (t), 37.3 (t), 39.5 (t), 114.3 (t), 139.0 (d). The ^{1}H NMR spectrum corresponds to that reported in literature.[7]

(10*R*)-10-Methyl-2-tridecanone ((*R*)-224)

A suspension of 7.8 mg (0.079 mmol) of CuCl and 1.4 mg (0.008 mmol) of $PdCl_2$ in 0.5 mL of DMF, containing one drop of water, was stirred for 2 h under oxygen atmosphere. Then, a solution of 15 mg (0.077 mmol) of **(*R*)-223** in 1 mL of DMF was added and the reaction mixture was stirred for one day. The mixture was diluted with 1 M aqueous HCl and extracted three times with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 5:1) to yield 16 mg (100%) of **(*R*)-224** as a colorless oil. The ^{1}H and ^{13}C NMR spectra correspond to those reported in literature.[12]

Ethyl (7*S*)-7-methyl-10-oxodecanoate (294)

To a stirred solution of 0.35 g (1.52 mmol) of **290** in 7 mL of CH_2Cl_2 were added 41 mg (0.5 mmol) of NaOAc and 0.49 g (2.25 mmol) of PCC. After stirring for 2.5 h at room temperature, the reaction mixture was column chromatographed directly (PE/EA 19:1) to yield 0.27 g (78%) of **294** as a colorless oil: $[\alpha]_D$ = -0.36° (c = 1.4, $CHCl_3$); ^{1}H NMR δ 0.83 (d, *J* = 6.7 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.10-1.66 (m, 11H), 2.27 (t, *J* = 7.6 Hz, 2H), 2.39 (dt, *J* = 1.8, 6.9 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 9.75 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR δ 14.3 (q), 19.3 (q), 24.9 (t), 26.6 (t), 28.8 (t), 29.3 (t), 32.3 (d), 34.3 (t), 36.5 (t), 41.7 (t), 60.2 (t), 173.9 (s), 203.1 (d); IR (neat, cm^{-1}) 1735 (C=O), 1720 (C=O), 1179 (C-O-C); MS *m/z* (r.i.) 200 (M^+-CO, 21), 185 (92), 183 (40), 172 (37), 139 (75), 101 (78), 97 (45), 88 (100), 83 (34), 69 (42), 55 (62); HRMS calcd. for $C_{12}H_{24}O_2$ (M^+-CO) 200.1776, found 200.1774.

Ethyl (7*S*)-7-methyl-10-heptadecenoate (295)

To a stirred solution of 0.73 g (1.5 mmol) of $[H_{15}C_7PPh_3]^+I^-$ in 5 mL of dry THF, cooled to 0 °C and under argon atmosphere, was added 0.94 mL (1.5 mmol) of 1.6 M *n*BuLi in hexane. After stirring for 2 h at 0°C, the solution was cooled to –78 °C and a solution of 0.27 g (1.18 mmol) of **294** in 3 mL of THF was added dropwise. After stirring for 1 h at –78 °C and 1 h at room temperature, the reaction mixture was diluted with 20 mL of water and extracted with four 20-mL portions of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 19:1) to yield 0.36 g (98%) of **295** as a mixture of *Z/E* isomers in a ratio of 3:1 (according to GC-analysis): ^{1}H NMR δ 0.85 (d, *J* = 6.3 Hz, 3H), 0.87 (t, *J* = 5.9 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.03-1.65 (m, 19H), 2.00 (m, 4H), 2.28 (t, *J* = 7.7 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 5.25-5.39 (m, 2H, *Z/E*); ^{13}C NMR δ 14.1 (q), 14.2 (q), 19.5 (q), 22.6 (t), 24.7 (t), 25.0 (t), 26.6 (t), 27.2 (t), 29.0 (t), 29.5 (t), 29.7 (t), 31.8 (t), 32.1 (d), 34.4 (t),

36.7 (t), 37.0 (t), 60.1 (t), 129.8 (d, *Z*), 130.0 (d, *Z*), 130.2 (d, *E*), 130.4 (d, *E*), 173.9 (s).

(7*S*)-7-Methyl-10-heptadecenal (296)

To a stirred solution of 0.34 g (1.1 mmol) of **295** in 30 mL of toluene, cooled to -78 °C, was added slowly 0.77 mL (1.2 mmol) of 1.5 M DIBALH in toluene. After stirring for 1 h, 3 mL of 1M aqueous AcOH was carefully added, while keeping the temperature below –65 °C, and the reaction mixture was stirred for another half hour. Then the reaction mixture was poured slowly into ice-cold 1 M aqueous HCl and extracted with three 30-mL portions of Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 97:3) to yield 0.25 (86%) of **296** as a colorless oil, which was used immediately in the next reaction.

(9*S*)-9-Methyl-2,12-nonadecadiene (297)

To a stirred solution of 0.46 g (1.2 mmol) of $[H_5C_2PPh_3]^+I^-$ in 4 mL of dry THF, cooled to 0 °C and under argon atmosphere, was added 0.70 mL (1.1 mmol) of 1.6 M *n*BuLi in hexane. After stirring for 2 h at 0°C, the solution was cooled to –78 °C and a solution of 0.25 g (0.94 mmol) of **296** in 2 mL of THF was added dropwise. After stirring for 1 h at –78 °C and 1 h at room temperature, the reaction mixture was diluted with 20 mL of water and extracted with four 20-mL portions of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (PE) to yield 0.24 g (92%) of **297** as a colorless oil. The product was a mixture of four stereoisomers: ^{1}H NMR δ 0.85 (d, *J* = 6.5 Hz, 3H), 0.85 (t, *J* = 6.0 Hz, 3H), 1.07-1.64 (m, 19H), 1.59 (d, *J* = 5.4 Hz, 3H), 1.97-2.03 (m, 6H), 5.25-5.48 (m, 4H, *Z/E*); ^{13}C NMR δ 14.2 (q, 2C), 19.6 (q), 22.7 (q), 24.8 (t), 26.9 (t), 27.2 (t), 29.0 (t), 29.6 (t, 2C), 29.8 (t), 31.8 (t), 32.4 (d), 32.6 (t), 36.9 (t), 37.1 (t), 123.6, 124.5, 129.7, 130.1, 130.9, 131.7 (all d, 4C, *Z/E*); MS *m/z* (r.i.) 278 (M^+, 30), 109 (39), 97 (53), 96 (67), 95 (37), 83 (58), 81 (43), 69 (73), 68 (46), 55 (100), 41 (38); HRMS calcd. for $C_{20}H_{38}$ (M^+) 278.2974, found 278.2971.

(9*S*)-9-Methylnonadecane ((*S*)-298)

To a solution of 0.24 g (0.86 mmol) of **297** in 35 mL of EA was added 80 mg of 10% Pd(C). The solution was hydrogenated for 1.5 h in a Parr apparatus under 4 atm. of H_2 and then filtered over silica gel. The filtrate was evaporated under reduced pressure and the residue was flash chromatographed (PE) to yield 0.23 g (95%) of **298** as a colorless oil: ^{1}H NMR δ 0.86 (d, *J* = 6.4 Hz, 3H), 0.85 (t, *J* = 8.2 Hz, 6H), 1.00-1.55 (m, 33H), ^{13}C NMR δ 14.1 (q, 2C), 19.7 (q), 22.7 (t, 2C), 27.1 (t, 2C), 29.4 (t, 3C), 29.7 (t, 3C), 30.0 (t, 2C), 31.9 (t, 2C), 32.7 (d), 37.1 (t, 2C). MS *m/z* (r.i.) 282 (M^+, 4), 168 (17), 141 (17), 140 (28), 85 (63), 71 (72), 57 (100), 56 (17), 55 (23), 43 (68), 41 (27); HRMS calcd. for $C_{20}H_{42}$ (M^+) 282.3287, found 282.3287.

Ethyl (7*S*)-7-methyl-10-nonadecenoate (299)

To a stirred solution of 0.70 g (1.5 mmol) of $[H_{19}C_9PPh_3]^+Br^-$ in 5 mL of dry THF, cooled to 0 °C and under argon atmosphere, was added 0.60 mL (1.5 mmol) of 2.5 M *n*BuLi in hexane. After stirring for 2 h at 0°C, the solution was cooled to –78 °C and a solution of 0.27 g (1.18 mmol) of **294** in 3 mL of THF was added dropwise. After stirring for 1 h at –78 °C and 1 h at room temperature, the reaction mixture was diluted with 20 mL of water and extracted with four 20-mL portions of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 19:1) to yield 0.36 g (89%) of **299** as a colorless oil. The product is a mixture of *Z/E* isomers in a ratio of 4:1 (according to GC-analysis): ^{1}H NMR δ 0.88 (d, *J* = 6.4 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.07-2.18 (m, 23H), 1.99-2.02 (m, 4H) 2.28 (t, *J* = 7.3 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 5.25-5.39 (m, 2H, *Z/E*); ^{13}C NMR δ 14.1 (q), 14.2 (q), 19.5 (q), 22.7 (t), 24.7 (t), 25.0 (t), 26.7 (t), 27.2 (t), 29.3 (t, 2C), 29.5 (t, 2C), 29.7 (t), 31.9 (t), 32.3 (d), 34.4 (t), 36.7 (t), 37.0 (t), 60.1 (t), 129.8 (d, *Z*), 123.0 (d, *Z*), 130.2 (d, *E*), 130.4 (d, *E*), 173.9 (s); MS *m/z* (r.i.) 338 (M^+, 24), 209 (54), 138 (100), 97 (65), 91 (40), 83 (66), 69 (72), 57 (49), 55 (96), 43 (52), 41 (46); HRMS calcd. for $C_{22}H_{42}O_2$ (M^+) 338.3185, found 338.3185.

(7*S*)-7-Methyl-10-nonadecenal (300)

To a stirred solution of 0.29 g (0.85 mmol) of **299** in 25 mL of toluene, cooled to -78 °C, was added slowly 0.60 mL (0.90 mmol) of 1.5 M DIBALH in toluene. After stirring for 1 h, 3 mL of 1M aqueous AcOH was carefully added, while keeping the temperature below –65 °C, and then the reaction mixture was stirred for another half hour. The reaction mixture was poured slowly into ice-cold 1 M aqueous HCl and extracted with three 30-mL portions of Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 97:3) to yield 0.20 g (80%) of **300** as a colorless oil: ^{1}H NMR δ 0.85 (d, *J* = 6.5 Hz, 3H), 0.85 (t, *J* = 6.1 Hz, 3H), 1.08-1.30 (m, 21H), 1.5-1.66 (m, 2H), 1.90-2.05 (m, 4H), 2.42 (dt, *J* = 1.9, 7.3 Hz, 2H), 5.25-5.39 (m, 2H, *Z/E*); ^{13}C NMR δ 14.2 (q), 19.5 (q), 22.1 (t), 22.7 (t), 24.8 (t), 26.8 (t), 27.2 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.7 (t), 29.8 (t), 31.9 (t), 32.3 (d), 36.7 (t), 36.9 (t), 43.9 (t), 129.8, 130.0, 130.4 (all d, 2C, *Z/E*), 203.0 (d); MS *m/z* (r.i.) 294 (M^+, 25), 135 (65), 126 (79), 109 (61), 97 (85), 83 (70), 81 (56), 69 (75), 57 (57), 55 (100), 43 (51); HRMS calcd. for $C_{20}H_{38}O$ (M^+) 294.2923, found 294.2924.

Ethyl (7*S*)-10-{[*tert*-butyl(diphenyl)silyl]oxy}-7-methyldecanoate (301)

To a stirred solution of 0.35 g (1.5 mmol) of **290**, 0.23 g (3.0 mmol) of imidazole and 30 mg of DMAP in 4 mL of DMF was added a solution of 0.42 g (1.55 mmol) of TBDPSCl in 1.5 mL of DMF. After stirring for 4 h at room temperature, the reaction mixture was diluted with 30 mL of water and extracted with one 30-mL and three

20-mL portions of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 97:3) to yield 0.61 g (81%) of **301** as a colorless oil: ^{1}H NMR δ 0.82 (d, *J* = 6.2 Hz, 3H), 1.03 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.01-1.61 (m, 13H), 2.29 (t, *J* = 7.3 Hz, 2H), 3. 64 (t, *J* = 6.5 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 7.33-7.43 (m, 6H), 7.65-7.71 (m, 4H).

(7*S*)-10-{[*tert*-Butyl(diphenyl)silyl]oxy}-7-methyldecanal (302)

To a stirred solution of 0.61 g (1.3 mmol) of **301** in 35 mL of toluene, cooled to -78 °C, was added slowly 0.92 mL (1.4 mmol) of 1.5 M DIBALH in toluene. After stirring for 1 h, 3 mL of 1M aqueous AcOH was carefully added, while keeping the temperature below –65 °C, and the reaction mixture was stirred for another half hour. Then the reaction mixture was poured slowly into ice-cold 1 M aqueous HCl and extracted with three 30-mL portions of Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 97:3) to yield 0.49 g (89%) of **302** as a colorless oil: ^{1}H NMR δ 0.83 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 9H), 1.03-1.66 (m, 13H), 2.41 (dt, *J* = 1.8, 7.3 Hz, 2H), 3.64 (t, *J* = 6.5 Hz, 2H), 7.33-7.46 (m, 6H), 7.65-7.69 (m, 4H), 9.76 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR δ 19.2 (s), 19.7 (q), 22.1 (t), 26.8 (t), 26.9 (q, 3C), 29.5 (t), 30.1 (t), 32.5 (d), 32.9 (t), 36.7 (t), 44.0 (t), 64.3 (t), 127.6 (d, 4C), 129.5 (d, 2C), 134.2 (s, 2C), 135.6 (d, 4C), 203.0 (d).

***tert*-Butyl(diphenyl)silyl (4*S*)-4-methyl-10-hexadecenyl ether (303)**

To a stirred solution of 0.58 g (1.22 mmol) of $[H_{13}C_6PPh_3]^+I^-$ in 5 mL of dry THF, cooled to 0 °C and under argon atmosphere, was added 0.75 mL (1.2 mmol) of 1.6 M *n*BuLi in hexane. After stirring for 2 h at 0°C, the solution was cooled to –78 °C and a solution of 0.47 g (0.94 mmol) of **302** in 3 mL of THF was added dropwise. After stirring for 1 h at –78 °C and 1 h at room temperature, the reaction mixture was diluted with 20 mL of water and extracted with four 20-mL portions of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 99:1) to yield 0.33 g (61%) of **303** as a colorless oil, which was used immediately in the next reaction.

(4*S*)-4-Methyl-10-hexadecen-1-ol (304)

To a stirred solution of 0.33 g (0.67 mmol) of **303** in 5.5 mL of THF was added dropwise 0.8 mL of 1.1 M TBAF in THF. After stirring for 3 h at room temperature, the reaction mixture was diluted with water and extracted with four 20-mL portions of Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 17:3) to yield 0.16 g (94%) of **304** as a colorless oil:

^{1}H NMR δ 0.85 (d, *J* = 6.3 Hz, 3H), 0.85 (t, *J* = 6.1 Hz, 3H), 1.03-1.68 (m, 20H), 1.96-2.04 (m, 4H), 3.62 (t, *J* = 6.6 Hz, 2H), 5.26-5.42 (m, 2H, *Z/E*); ^{13}C NMR δ 14.1 (q), 19.6 (q), 22.6 (t), 26.9 (t), 27.2 (t), 29.4 (t), 29.6 (t), 29.7 (t), 30.3 (t), 31.5 (t), 32.6 (d), 32.6 (t), 32.9 (t), 36.9 (t), 63.4 (t), 129.8 (d, *Z*), 129.90 (d, *Z*), 130.3 (d, *E*), 130.4 (d, *E*).

(4*S*)-4-Methyl-10-hexadecenyltriphenylphosphonium iodide (305)

To a stirred solution of 0.19 g (0.73 mmol) of PPh_3 and 57 mg (0.73 mmol) of imidazole in 3.5 mL of Et_2O/CH_3CN 5:2, cooled to 0 °C, was added 0.18 g (0.72 mmol) of I_2. The resulting slurry was stirred for 30 min at room temperature and then cooled again to 0 °C. A solution of 0.16 g (0.63 mmol) of **304** in 0.5 mL of Et_2O was added slowly and the reaction mixture was stirred for 2 h at room temperature. The mixture was flash chromatographed directly (PE/EA 99:1) to yield 0.20 g (87%) of the iodide as a colorless oil: ^{1}H NMR δ 0.85 (d, *J* = 6.3 Hz, 3H), 0.88 (t, *J* = 6.2 Hz, 3H), 1.06-1.87 (m, 19H), 1.97-2.20 (m, 4H), 3.16 (t, *J* = 7.1 Hz, 2H), 5.27-5.40 (m, 2H, *Z/E*); ^{13}C NMR δ 14.1 (q), 19.6 (q), 22.6 (t), 26.9 (t), 27.2 (t, 2C), 29.5 (t), 29.6 (t), 29.8 (t), 31.3 (t), 31.6 (t), 32.1 (t), 32.6 (d), 36.8 (t), 37.9 (t), 129.8 (d, *Z*), 129.9 (d, *Z*), 130.3 (d, *E*), 130.5 (d, *E*).

The iodide was converted quantitatively to its phosphonium salt **305** by refluxing it for 24 h in toluene in the presence of one equivalent of PPh_3.[41]

(13*R*, 23*S*)-13,23-Dimethylhexatriacontane (306)

To a stirred solution of 255 mg (0.41 mmol) of **305** in 4 mL of dry THF, cooled to 0 °C and under argon atmosphere, was added 0.25 mL (0.4 mmol) of 1.6 M *n*BuLi in hexane. After stirring for 2 h at 0°C, the solution was cooled to –78 °C and a solution of 100 mg (0.34 mmol) of **300** in 2 mL of THF was added dropwise. After stirring for 1 h at –78 °C and 1 h at room temperature, the reaction mixture was diluted with 20 mL of water and extracted with four 20-mL portions of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE) to yield 140 mg (80%) of the triene as a mixture of stereoisomers: ^{1}H NMR δ 0.85 (d, *J* = 6.6 Hz, 6H), 0.86 (t, *J* = 6.1 Hz, 6H), 1.08-1.45 (m, 40H), 1.90-2.10 (m, 12H), 5.23-5.40 (m, 6H, *Z/E*); ^{13}C NMR δ 14.1 (q, 2C), 19.6 (q, 2C), 22.6 (t), 22.7 (t), 24.8 (t, 2C), 26.9 (t, 2C), 27.2 (t, 2C), 29.3, 29.5, 29.6, 29.7, 29.8 (all t, 7C), 30.2 (t), 31.4 (t), 31.6 (t), 31.9 (t), 32.3 (t), 32.4 (d, 2C), 32.6 (t), 36.9 (t, 2C), 37.1 (t, 2C), 129.8, 129.9, 129.9, 130.1, 130.4 (all d, 6C).

To a solution of 140 mg (0.27 mmol) of the triene from the previous reaction in 50 mL of EA was added 60 mg of 10% Pd(C). The solution was hydrogenated for 1.5 h in a Parr apparatus under 4 atm. of H_2 and then filtered over silica gel. The filtrate was evaporated under reduced pressure and the residue was column chromatographed (PE) to yield 141 mg (99%) of **306** as a colorless oil, which

crystallized upon standing: M.p. 33-34 °C (lit. 29-30 °C[42]); ^{1}H NMR δ 0.85 (d, J = 6.4 Hz, 6H), 0.84 (t, J = 6.1 Hz, 6H), 1.25 (br s, 64H); ^{13}C NMR δ 14.1 (q, 2C), 19.7 (q, 2C), 22.7 (t, 2C), 27.1 (t, 4C), 29.4, 29.7, 30.0 (all t, 19C), 31.9 (t, 2C), 32.7 (d, 2C), 37.1 (t, 4C); MS *m/z* (r.i.) 520 (M^+, 4), 351 (71), 350 (41), 197 (46), 196 (100), 85 (53), 71 (69), 69 (25), 57 (90), 55 (22), 43 (43); HRMS calcd. for $C_{37}H_{76}$ 520.5947, found 520.4941. The ^{1}H NMR spectrum corresponds to that reported in literature.[42]

4.6 References and notes

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Chapter 5

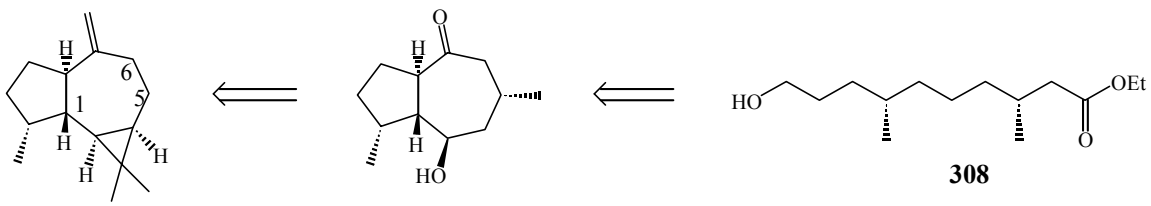
Synthesis of a linear intermediate for the synthesis of dimethyl-branched linear pheromones

5.1 Introduction

In Chapter 4 the use of aromadendrene as starting material for the synthesis of methyl-branched linear pheromones was investigated. A method was developed for the conversion of aromadendrene to a versatile linear intermediate, which has been converted to several chiral pheromones.

Because next to methyl-branched pheromones, also a large number of dimethyl-branched pheromones have been reported in literature, it was interesting to investigate the possible use of aromadendrene (**1**) for the synthesis of such pheromones as well. The second methyl group can be introduced by stereoselective conjugate addition to $\Delta^{5,6}$ enones derived from aromadendrene. The two methyl groups in the resulting intermediate will be located in a 1,5-position relative to each other and will also end up in the same relative position in the pheromones be synthesized from this intermediate. In this Chapter the results of this research, the synthesis of a dimethyl-branched linear intermediate for pheromone synthesis, will be described. The synthetic route described in the previous Chapter can be used as the basis for the synthesis of this linear intermediate **308** from aromadendrene (Scheme 1). The first part of the synthesis consists of the introduction of a methyl group at C5 in the aromadendrane skeleton to obtain **307** or a derivative of **307**, and will be described in the next Paragraph. The second part of the synthetic route, the synthesis of intermediate **308** from compound **307**, is reported in Paragraph 5.3.

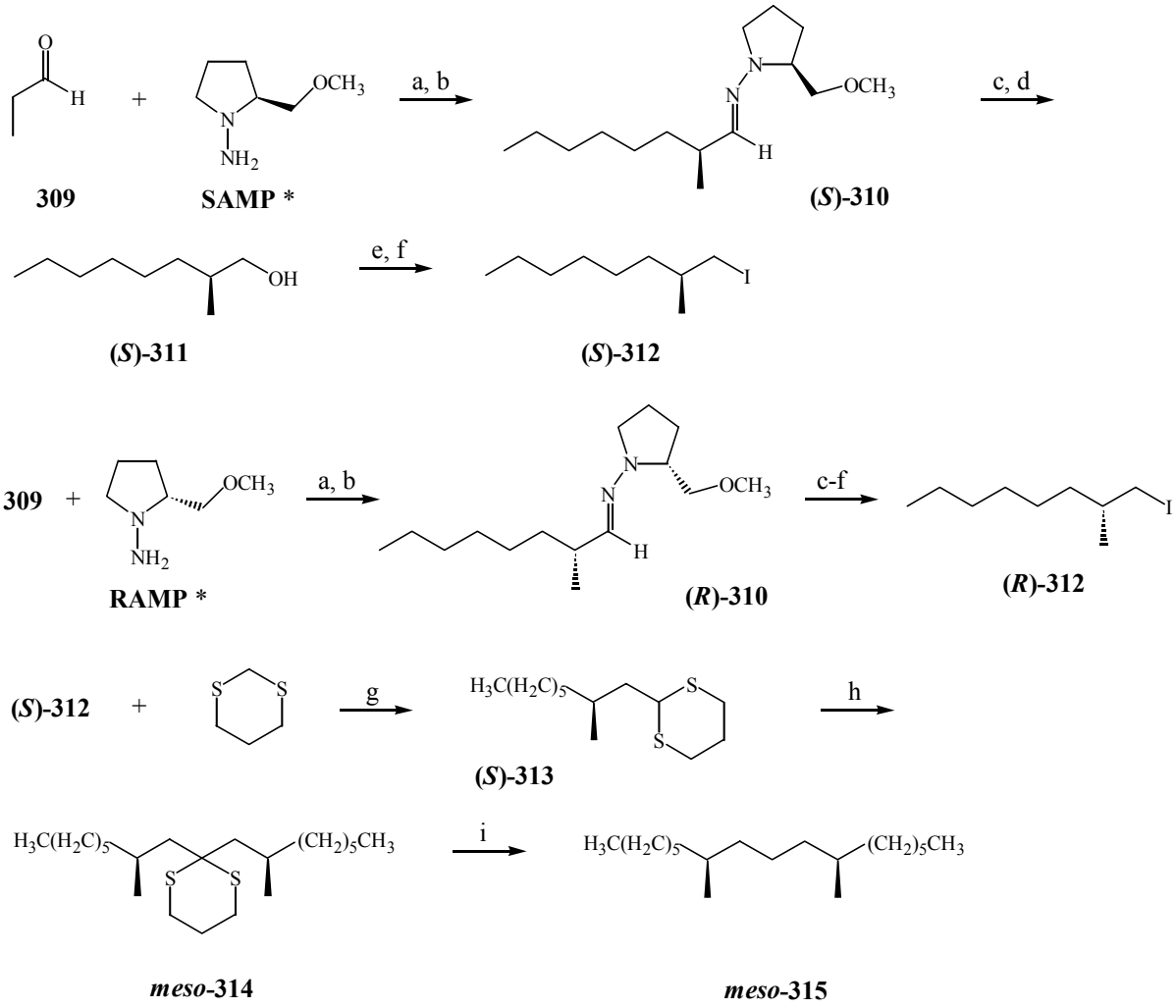
Scheme 1



1 **307** **308**

Two possible target pheromones, which may be synthesized from intermediate **308**, will be described below. These pheromones are just two examples of the many dimethyl pheromones reported in literature, which have the two methyl groups in a 1,5-position relative to each other.

Scheme 2



* SAMP/RAMP = (*S*)/(*R*)-1-amino-2-(methoxymethyl)pyrrolidine
a: rt; b: LiTMP, THF, 0 °C; $C_6H_{13}I$, -100 °C; c: HCl, pentane; d: BH_3·DMS, Et_2O; e: TsCl, pyridine, 0 °C; f: NaI, acetone, reflux; g: *t*BuLi, THF, HMPA, -78 °C to rt; h: **(*R*)-312**, *t*BuLi, THF, HMPA, -78 °C to reflux; i: Raney-Ni, H_2, *i*PrOH, reflux.

7,11-Dimethylheptadecane

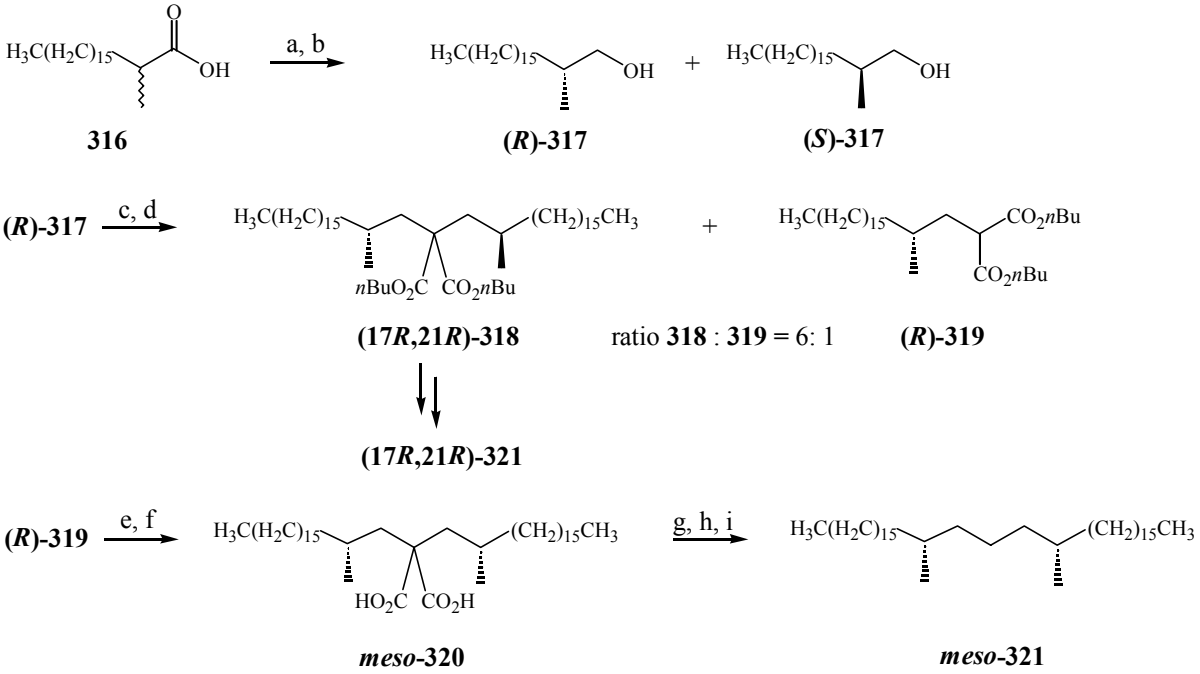
The pheromone system of the female spring hemlock looper moth (*Lambdina athasaria*) and the pitch pine looper moth (*L. pellucidaria*) consists of two compounds, 7-methylheptadecane (see Chapter 4) and 7,11-dimethylheptadecane (**315**). Of the three possible stereoisomers of the pheromone, ***meso*-315** is the active

diastereomer. Three syntheses of the diastereomers of **315** have been published.[1-3] Although the synthesis published by Shirai *et al.*[1] is the shortest one with six steps, the overall yield is very low due to the difficult separation of the diastereomers. The synthesis reported by Enders *et al.*[3], in which propanal (**309**) is used as starting material, has a much higher overall yield of 46% over fifteen steps (Scheme 2).

17,21-Dimethylheptatriacontane

The longest chiral dimethyl-branched pheromone known is 17,21-dimethylheptatriacontane (**321**), the sex pheromone of the tsetse fly, *Glossina morsitans morsitans*. The diastereomers of this pheromone have been synthesized by Ade *et al.* from racemic 2-methyloctadecanoic acid (**316**).[4] The synthesis of ***meso*-321**, which is the active diastereomer[5], is depicted in Scheme 3.

Scheme 3



a: (*R*)-phenylglycinol; separation on HPLC; H_2SO_4, dioxane; b: $LiAlH_4$; c: HI; d: $(n\text{BuO}_2\text{C})_2\text{CH}_2$, NaO*n*Bu, *n*BuOH, 50 °C; e: **(*S*)-317**; f: saponification; g: decarboxylation; h: iododecarboxylation; i: Zn, AcOH.

5.2 Introduction of a methyl group in enones derived from aromadendrene

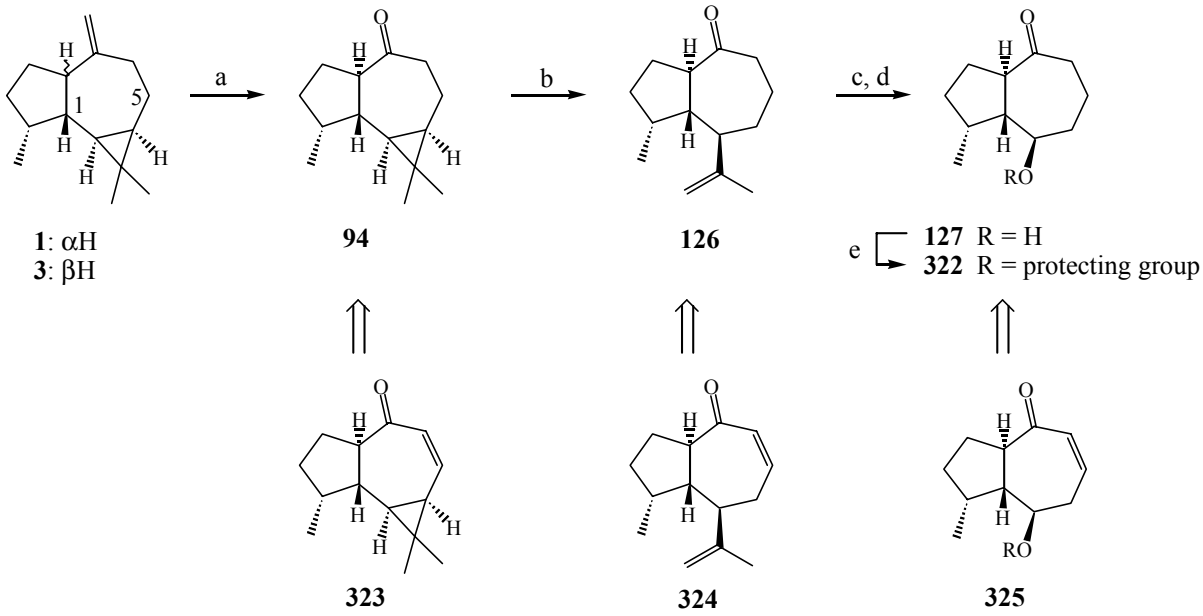
The first part of the synthetic route from aromadendrene to linear intermediate **308** consists of the introduction of a methyl group at C5 in the aromadendrane

skeleton. This can be achieved by a conjugated addition to one of the enones depicted in Scheme 4. In order to do this from the α-side with a high stereoselectivity, the upper β-side of the molecule has to be shielded sufficiently.

The synthesis of enone **324** from isoapoaromadendrone **126** has been reported by Gijsen.[6] Conversion of compound **126** to its kinetic TMS-ether, followed by bromination and elimination, led to the formation of enone **324** in 38% yield. Because this yield was not very satisfactory, together with the fact that the isopropenyl group was probably not large enough to provide enough shielding for a highly stereoselective methyl introduction, no further research was done on enone **324**.

Enone **323**, which has a dimethylcyclopropyl group to shield the β-side of the molecule, was synthesized from apoaromadendrone **94** in the same way as described above for enone **324**. However, the synthesis of **323** appeared to be problematic, since the introduction of the double bond in **94** gave the enone only in poor yields.

Scheme 4



a: O_3, CH_2Cl_2, MeOH, -78 °C; thiourea; crystallization; b: aq. HCl, EtOH, reflux; c: O_3, CCl_4, MeOH, -30 °C; Et_3N, Ac_2O, DMAP; d: NaOMe, MeOH; e: protection.

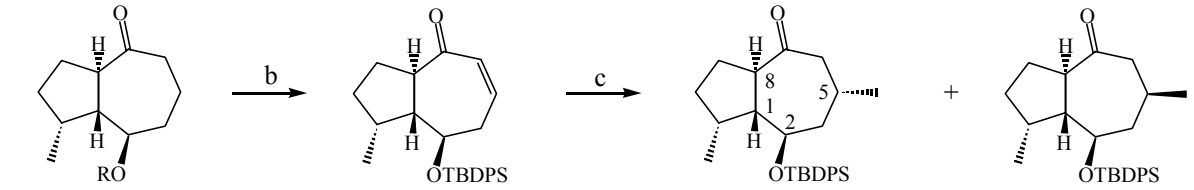
The third possibility depicted in Scheme 4 consists of the introduction of the methyl group in the protected alcohol **322**. By using a large protecting group, good conditions for a stereoselective reaction may be created. Therefore, aromadendrene (**1**) was converted first to alcohol **127** (see Chapter 4). The hydroxyl group in **127** was then protected as its TBDPS-ether **326** (Scheme 5). The synthesis of enone **327** from ketone **326** via a phenylselenyl addition, followed by oxidation and elimination, was rather troublesome. The addition of the phenylselenyl group proceeded smoothly, but

oxidation of the selenyl group and subsequent elimination appeared to be problematic. A possible explanation for this problem could be that, during the reaction, addition of nucleophiles to the double bond can take place, thereby diminishing the yield of the enone. Therefore, we shortened the reaction time of the oxidation as much as possible by quenching the reagents quickly and let the elimination take place overnight. The best result was obtained upon treatment of the phenylselenyl compound with *m*CPBA for five minutes at low temperature, followed by stirring overnight with a mixture of aqueous $Na_2S_2O_3$ and $NaHCO_3$. In this way compound **327** was obtained in 78% yield. However, this yield was difficult to reproduce, and the yield of this reaction was often much lower.

The introduction of the methyl group in **327** was carried out with lithium dimethylcuprate and proceeded in a yield of 85%. The stereoselectivity of the reaction proved to be satisfactory high; the two isomers **328** and **329** were obtained in a ratio of 5:1. Compounds **328** and **329** could be separated by repeated column chromatography. The NOE correlations observed between H1 and H5 and between H2 and H8, and the absence of a NOE correlation between H1 and H8 in the NOESY spectrum of **328** are in complete agreement with the structure assigned to **328**.

In a similar experiment, which was conducted with the enone derived from the TBDMS-ether of **127**, the stereoselectivity of the reaction was much lower. In this reaction the α- and β-methyl product were formed in a 1:1 ratio (according to GC-analysis), indicating that a very large group at the β-side of the molecule is necessary for a highly stereoselective conjugated addition.

Scheme 5



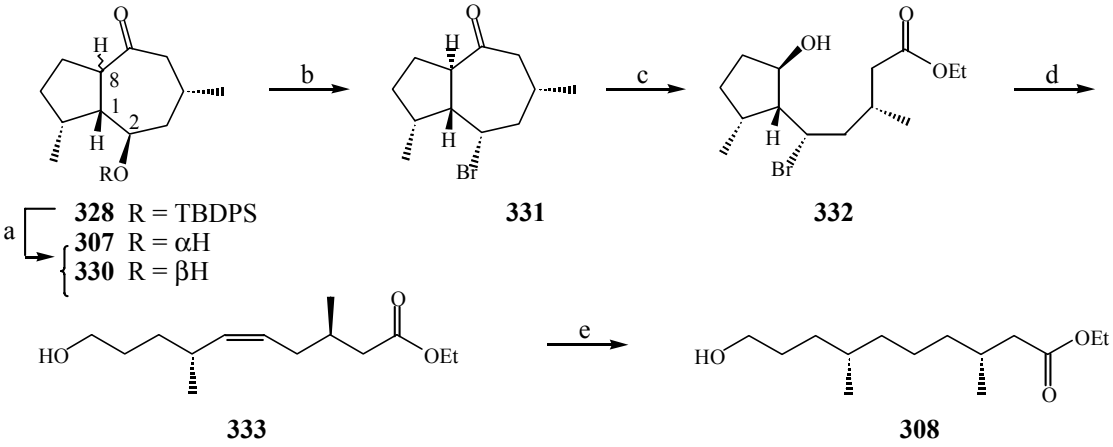
a: TBDPSCl, imidazole, DMAP, DMF, 35 °C; b: LDA, PhSeCl, THF, -78 °C; *m*CPBA, CH_2Cl_2, -10 °C; sat. aq. $NaHCO_3/Na_2S_2O_3$; c: Me_2CuLi, Et_2O, -10 °C.

5.3 Synthesis of linear intermediate 308

Compound **328** has been used for the synthesis of linear intermediate **308** in a similar way as described in Chapter 4 for the conversion of **127** to **290**. Therefore, the hydroxy group in **328** was deprotected first with TBAF in THF. This deprotection,

which normally takes place instantaneously, was only completed after 13 days at 45 °C and resulted in a mixture of **307** (53%) and its C8 epimer **330** (28%). The absence of a NOE correlation between H1 and H8 indicates that the ring system of **307** is trans-fused. When the deprotection was carried out with HF, the reaction took also a long time and no better results were obtained.

Scheme 6



a: TBAF, THF, 45 °C; b: CBr_4, PPh_3, CH_2Cl_2; c: *m*CPBA, CH_2Cl_2; TsOH, EtOH; d: NaOEt, $NaBH_4$, EtOH; e: H_2, Pd(C), EtOAc.

The alcohol **307** was converted to its bromide **331** in 76% yield. The Baeyer-Villiger reaction of **331**, followed by opening of the lactone ring, led to the formation of **332** in a yield of 19%. This is remarkably low, because when this reaction was carried out with comparable compounds, the yields were mostly around 60%. It is likely that the yield of **332** can be improved, but lack of time and starting material have prevented further investigations.

The last two reactions in the synthesis of **308** are the Grob fragmentation and the reduction of the double bond. The Grob fragmentation was again carried out in the presence of sodium borohydride in order to reduce the aldehyde function formed in the fragmentation immediately to the alcohol. The yield of this reaction was 94%. Finally, the reduction of the double bond yielded compound **308** in 93% yield.

No pheromones have been synthesized yet from this linear intermediate, but it is evident that this will be possible in a similar way as has been demonstrated for the monomethyl intermediate **290**, as described in Paragraph 4.4.

5.4 Experimental part

Compound **127** was prepared from the distillation tail of *Eucalyptus globulus* as described by Gijsen *et al.*[7]

(1*R*,3a*R*,8*R*,8a*R*)-8-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-methyloctahydro-4(1*H*)-azulenone (326)

To a stirred solution of 1.82 g (10 mmol) of **127**, 1.30 g (19 mmol) of imidazole and 0.5 g of DMAP in 20 mL of DMF was added a solution of 2.80 g (10.2 mmol) of TBDPSCl in 5 mL of DMF. After stirring for 7 days at 35 °C, the reaction mixture was diluted with 250 mL of water and extracted with three 50-mL portions of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 93:7) to yield 4.10 g (98%) of **326** as a viscous colorless oil: ^{1}H NMR δ 0.78 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 9H), 1.06-1.96 (m, 8H), 2.30 (m, 3H), 2.62 (q, *J* = 6.6 Hz, 1H), 2.82 (ddd, *J* = 4.8, 9.6, 11.2 Hz, 1H), 3.68 (dt, *J* = 4.1, 10.0 Hz, 1H), 7.31-7.49 (m, 6H), 7.63-7.77 (m, 4H); ^{13}C NMR δ 14.0 (q), 19.0 (t), 22.8 (t), 19.3 (s), 27.0 (q, 3C), 32.1 (t), 37.3 (d), 38.1 (t), 43.2 (t), 47.6 (d), 56.0 (d), 75.7 (d), 127.3 (d. 2C), 127.7 (d, 2C), 129.4 (d), 129.7 (d), 133.8 (s), 135.3 (s), 135.8 (d, 2C), 135.9 (d, 2C), 213.7 (s).

(1*R*,3a*R*,8*R*,8a*R*)-8-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-methyl-2,3,3a,7,8,8a-hexahydro-4(1*H*)-azulenone (327)

To a stirred solution of 1.40 mL of (*i*Pr)$_2$NH in 30 mL of THF, cooled to –10 °C and under argon atmosphere, was added 3.9 mL (9.8 mmol) of 2.5 M *n*BuLi in hexane. After stirring for 30 min at –10 °C, the solution was cooled to –78 °C and a solution of 4.10 g (9.8 mmol) of **326** in 40 mL of THF was added. After stirring for 1 h at –78 °C, a solution of 1.9 g (9.8 mmol) of PhSeCl in 10 mL of THF was added slowly, while maintaining the temperature below –70 °C. After stirring for 30 min at –78 °C, the reaction mixture was allowed to come to room temperature, diluted with 150 mL of saturated aqueous NH_4Cl, and extracted with four 30-mL portions of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 19:1) to yield 1.04 g (25%) of starting material **326** and 3.57 g (63%) of the desired selenyl product as a light yellow viscous oil that crystallized upon standing.

To a stirred solution of 2.1 g (3.6 mmol) of selenyl compound in 100 mL of CH_2Cl_2, cooled to –10 °C, were added 2 g of $MgSO_4$ and 1.3 g (*ca*. 5.5 mmol) of 70-75% *m*CPBA. After stirring for 5 min at –10 °C, a suspension of 3 g of $Na_2S_2O_3$ in 20 mL of saturated aqeous $NaHCO_3$ was added and the reaction mixture was allowed to come to room temperature. After stirring overnight at room temperature, the reaction mixture was diluted with 200 mL of water, the layers were separated, and the aqeous layer was extracted with three 20-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (PE/EA 19:1) to yield 1.18 g (78%) of **327** as a viscous colorless oil: $[\alpha]_D = -125.1°$ (c = 1.315, $CHCl_3$); ^{1}H NMR δ 0.64 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H), 1.42 (m, 1H), 1.69 (m, 2H), 2.10-2.56 (m, 6H), 4.15 (m, 1H), 6.13 (dd, *J* = 2.3, 11.7 Hz, 1H), 6.46 (dt, *J* = 4.9, 11.7 Hz, 1H), 7.40

(m, 6H), 7.67 (m, 4H); ^{13}C NMR δ 15.0 (q), 19.2 (s), 22.1 (t), 26.9 (q, 3C), 33.3 (t), 35.0 (d), 36.1 (t), 52.3 (d), 53.1 (d), 71.2 (d), 127.6 (d, 2C), 127.7 (d, 2C), 129.7 (d), 129.9 (d), 133.5 (d), 134.4 (s), 135.8 (d, 4C), 135.8 (s), 141.9 (d), 203.7 (s); MS *m/z* (r.i.) 363 (11), 362 (30), 361 (M^+–*t*Bu, 100), 200 (14), 199 (81), 149 (11), 145 (9), 139 (9), 32 (15), 31 (16); HRMS calcd. for $C_{23}H_{25}O_2Si$ (M^+–*t*Bu) 361.1624, found 361.1622.

(1*R*,3a*R*,6*R*,8*R*,8a*R*)-8-{[*tert*-Butyl(diphenyl)silyl]oxy}-1,6-dimethyloctahydro-4(1*H*)-azulenone (328) and (1*R*,3a*R*,6*S*,8*R*,8a*R*)-8-{[*tert*-butyl(diphenyl)-silyl]oxy}-1,6-dimethyloctahydro-4(1*H*)-azulenone (329)

To a stirred solution of Me_2CuLi, prepared from 1.66 g (5.7 mmol) of CuBr·DMS and 5.55 mL (11.1 mmol) of 2 M MeLi in 20 mL of Et_2O, cooled to –10 °C, was added dropwise a solution of 1.58 g (3.8 mmol) of **327** in 15 mL of Et_2O. After stirring for 1 h at –10 °C, the reaction mixture was diluted with 20 mL of saturated aqeous NH_4OH : NH_4Cl 1:1 and stirred at room temperature for 30 min. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was repeatedly column chromatographed (PE/EA 19:1) to yield 1.10 g (67%) of **328**, 0.17 g (10%) of **329**, and 0.13 g (8%) of a 1:1 mixture of **328** and **329**.

328: M.p. = 81-81.5 °C; $[\alpha]_D$ = +9.87° (c = 1.125, $CHCl_3$); ^{1}H NMR δ 0.59 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H), 1.28-2.58 (m, 12H), 3.99 (m, 1H), 7.42 (m, 6H), 7.69 (m, 4H); ^{13}C NMR δ 13.4 (q), 19.3 (s), 22.9 (t), 23.3 (q), 24.3 (d), 27.0 (q, 3C), 33.3 (t), 36.2 (d), 44.1 (t), 49.0 (d), 53.1 (d), 53.3 (t), 71.0 (d), 127.4 (d, 2C), 127.6 (d, 2C), 129.5 (d), 129.8 (d), 133.6 (s), 134.9 (s), 135.9 (d, 4C), 211.7 (s); MS *m/z* (r.i.) 379 (8), 378 (31), 377 (M^+–*t*Bu, 100), 335 (6), 200 (10), 199 (54), 197 (5), 161 (6), 135 (7), 105 (6); HRMS calcd. for $C_{24}H_{29}O_2Si$ (M^+–*t*Bu) 377.1937, found 337.1937.

329: M.p. = 111-113 °C; $[\alpha]_D$ = –71.35° (c = 1.18, $CHCl_3$); ^{1}H NMR δ 0.66 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 9H), 1.10-2.11 (m, 8H), 2.28 (m, 1H), 2.33 (m, 1H), 2.62 (m, 1H), 2.83 (m, 1H), 3.69 (dt, *J* = 3.6, 10.4 Hz, 1H), 7.42 (m, 6H), 7.68 (m, 4H); ^{13}C NMR δ 14.0 (q), 19.3 (s), 22.9 (t), 23.5 (q), 25.9 (d), 27.0 (q, 3C), 31.8 (t), 37.2 (d), 46.7 (t), 47.8 (d), 51.9 (t), 56.5 (d), 75.0 (d), 127.3 (d, 2C), 127.6 (d, 2C), 129.4 (d), 129.7 (d), 133.9 (s), 135.0 (s), 135.9 (d, 4C), 213.2 (s); MS *m/z* (r.i.) 379 (8), 378 (30), 377 (M^+–*t*Bu, 100), 335 (10), 200 (11), 199 (66), 161 (12), 135 (13), 105 (9), 69 (6); HRMS calcd. for $C_{24}H_{29}O_2Si$ (M^+–*t*Bu) 377.1937, found 337.1936.

(1*R*,3a*R*,6*R*,8*R*,8a*R*)-8-Hydroxy-1,6-dimethyloctahydro-4(1*H*)-azulenone (307)

To a stirred solution of 1.1 g (2.5 mmol) of **328** in 25 mL of THF was added 2.5 mL (2.5 mmol) of 1 M TBAF in THF. After stirring for 13 days at 45 °C, the

reaction mixture was diluted with water and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 3:1) to yield 264 mg (53%) of **307** and 137 mg (28%) of **330**.

307: ^{1}H NMR δ 0.92 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J*= 6.3 Hz, 3H), 1.41 (m, 1H), 1.61 (s, 1H), 1.65-2.66 (m, 11H), 4.04 (dt, *J* = 4.8, 9.9 Hz, 1H); ^{13}C NMR δ 14.5 (q), 22.9 (q), 23.5 (t), 24.9 (d), 33.0 (t), 35.9 (d), 44.8 (t), 50.1 (d), 51.7 (d), 52.4 (t), 69.2 (d), 211.6 (s).

330: ^{1}H NMR δ 0.80 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 1.46-2.51 (m, 12 H), 3.27 (m, 1H), 3.59 (m, 1H); ^{13}C NMR δ 13.9 (q), 21.9 (q), 22.9 (t), 25.8 (d), 33.1 (t), 36.0 (d), 44.2 (t), 49.1 (d), 49.5 (t), 51.5 (d), 69.1 (d), 212.4 (s).

(1*R*,3a*R*,6*S*,8*S*,8a*R*)-8-Bromo-1,6-dimethyloctahydro-4(1*H*)-azulenone (331)

To a stirred solution of 115 mg (0.59 mmol) of **307** and 195 mg (0.59 mmol) of CBr_4 in 20 mL of CH_2Cl_2 was added in small portions 0.39 g (1.49 mmol) of PPh_3. After stirring for 15 min. at room temperature, the solvent was partially evaporated to a volume of approximately 2 mL and this mixture was column chromatographed (PE/EA 10:1) to yield 116 mg (76%) of **331** as a colorless oil: ^{1}H NMR (C_6D_6) δ 0.66 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.2-2.2 (m, 10H), 2.31 (dd, *J* = 2.8, 15.3 Hz, 1H), 3.07 (dt, *J* = 7.8, 10.5 Hz, 1H), 4.04 (dt, *J* = 2.2, 7.1 Hz, 1H); ^{13}C NMR (C_6D_6) δ 13.4 (q), 23.0 (q), 25.5 (t), 28.7 (d), 33.6 (t), 37.7 (d), 44.6 (d), 46.1 (t), 51.8 (t), 52.5 (d), 56.2 (d), 207.3 (s).

Ethyl (3*S*,5*S*)-5-bromo-5-[(1*R*,2*R*,5*R*)-2-hydroxy-5-methylcyclopentyl]-3-methylpentanoate (332)

To a stirred solution of 50 mg (0.19 mmol) of **331** in 5 mL of CH_2Cl_2 were added 0.5 g of $MgSO_4$ and 0.45 g (*ca*. 1.9 mmol) of 70-75% *m*CPBA. After stirring for 3 days at room temperature, 2 mL of EtOH and a catalytic amount of $TsOH{\cdot}H_2O$ were added. After stirring for another day, the reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$. After separation of the layers, the water layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to yield 12 mg (19%) of **332** as a colorless oil: ^{1}H NMR (C_6D_6) δ 0.68 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H), 1.2-2.6 (m, 12H), 3.89-4.12 (m, 3H), 4.27-4.31 (m, 1H); ^{13}C NMR (C_6D_6) δ 14.2 (q), 14.3 (q), 20.2 (q), 28.7 (d), 32.3 (t), 33.0 (t), 37.2 (d), 39.5 (t), 44.7 (t), 58.3 (d), 58.4 (d), 60.2 (t), 76.9 (d), 172.2 (s).

Ethyl (3*R*,5*Z*,7*R*)-10-hydroxy-3,7-dimethyl-5-decenoate (333)

To a stirred solution of 33 mg (0.10 mmol) of **332** in 3 mL of 0.5 M ethanolic NaOEt was added 20 mg (0.51 mmol) of $NaBH_4$. After stirring for 2.5 h at room

temperature, the reaction mixture was diluted with 1 M aqueous HCl and extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 5:1) to yield 18 mg (94%) of **333** as a colorless oil: ^{1}H NMR (C_6D_6) δ 0.95 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 5.7 Hz, 3H), 1.00 (t, *J* = 7.1 Hz, 3H), 1.1-2.5 (m, 11H), 3.39 (t, *J* = 6.3 Hz, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 5.15-5.39 (m, 2H); ^{13}C NMR (C_6D_6) δ 14.1 (q), 19.6 (q), 21.3 (q), 30.9 (d and t), 31.5 (d), 33.6 (t), 34.3 (t), 40.9 (t), 59.8 (t), 62.6 (t), 126.2 (d), 137.8 (d), 172.3 (s).

Ethyl (3*R*,7*S*)-10-hydroxy-3,7-dimethyldecanoate (308)

To a stirred solution of 18 mg (0.074 mmol) of **333** in 4 mL of EA was added 5 mg of 10% Pd(C). The solution was hydrogenated for 1 h in a Parr apparatus under 4 atm of H_2 and then filtered over hyflo. The hyflo was washed with CH_2Cl_2 and the filtrate was concentrated under reduced pressure. The residue was column chromatographed (PE/EA 2:1) to yield 17 mg (93%) of **308** as a colorless oil: ^{1}H NMR (C_6D_6) δ 0.87 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.3 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H), 1.0-1.6 (m, 3H), 2.00-2.12 (m, 2H), 2.24 (t, *J* = 8.8 Hz, 2H), 3.41 (t, *J* = 6.2 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (C_6D_6) δ 14.1 (q), 19.6 (q), 19.7 (q), 24.4 (t), 30.4 (d), 30.4 (t), 32.6 (d), 33.0 (t), 37.0 (t), 37.2 (t), 41.7 (t), 59.7 (t), 62.8 (t), 172.03 (s).

5.5 References

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Chapter 6

Discussion

6.1 Introduction

(+)-Aromadendrene (**1**) is a chiral sesquiterpene present in 55-70% in the distillation tail of the essential oil of *Eucalyptus globulus*. This distillation tail is commercially available in large quantities and at low price and is therefore interesting as starting material for organic synthesis and a potentially valuable addition to the chiral pool. The chemistry of aromadendrene and its derivatives previously reported is described in Chapter 1. This research was mainly focussed on transformations of the functional groups in aromadendrene in short reaction sequences and on rearrangement of the aromadendrene skeleton. Two longer synthetic routes were developed for the synthesis of (+)-maaliol (**122**) and (–)-kessane (**37**) in 9 and 13 steps, respectively, from aromadendrene. These are two of the few examples in which the aromadendrane skeleton could selectively be rearranged to a single product. Rearrangements of aromadendrene under acidic or super acidic conditions usually lead to mixtures of products. No research has been reported in which aromadendrene is used for the synthesis of monocyclic or linear natural products.

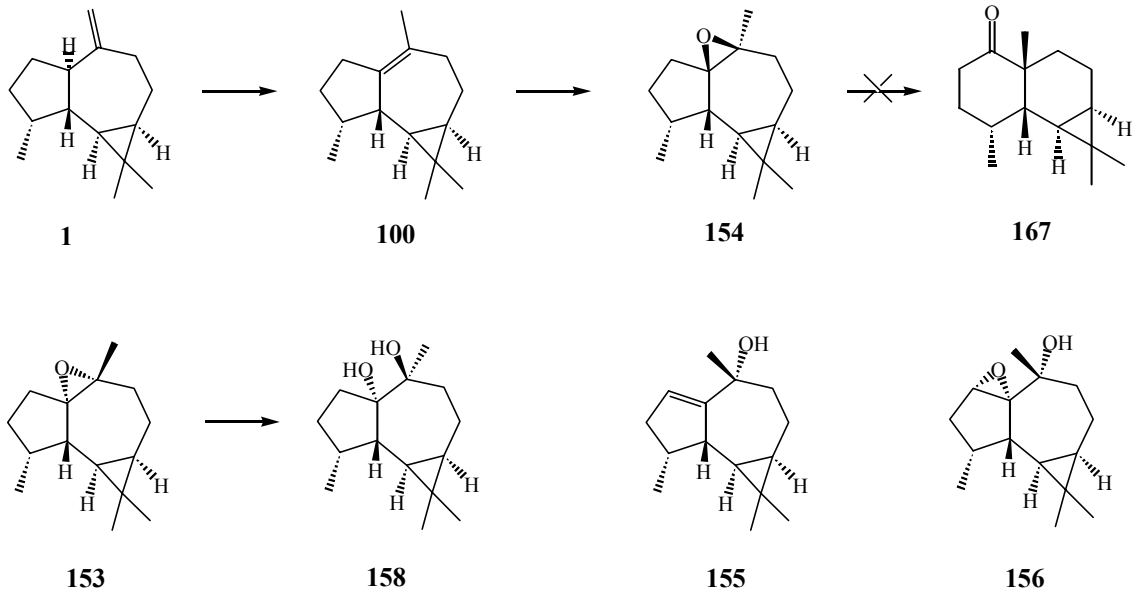
6.2 Fragrances from aromadendrene

The development of an economically feasible route to the maaliane fragrance compound **167** from aromadendrene has been investigated first (Chapter 2). The synthetic route to **167** described by Gijsen consisted of five steps.[1] Although all steps in this route proceed smoothly and in high yield, there are two disadvantages in this approach. In the first step a carbon atom is removed and reintroduced again in the last step of the synthesis. Furthermore, the reductive methylation in liquid ammonia, necessary for the reintroduction, is not feasible on an industrial scale. Through rearrangement of ledene β-epoxide **154**, easily obtainable from aromadendrene, it was hoped to find a short synthesis of maaliane **167** in which removal and reintroduction of a carbon atom could be avoided. However, this β-epoxide **154** did not show the desired rearrangement. The carbocation preferably formed through opening of the

epoxide ring in **154** appeared to be the C8 bridgehead carbocation, which rearranged further to products with cubebane and cadinane skeletons.

As an alternative substrate for rearrangement to the maaliane skeleton, ledene α-epoxide (**153**) could be investigated. The fact that under acidic conditions **153** undergoes hydrolysis to diol **158**, is an indication that reactions at C7 are possible after opening of the epoxide ring in **153**. However, α-epoxide **153** is not easily accessible because the highest yield of **153** reported for the epoxidation of ledene (**100**) is only 25%.[2] Two of the side products formed during this reaction are the compounds **155** and **156**, which must be formed via cleavage of the C8-O bond in α-epoxide **153**. So it remains doubtful whether **153** can serve as a satisfactory alternative for the rearrangement to the maaliane skeleton.

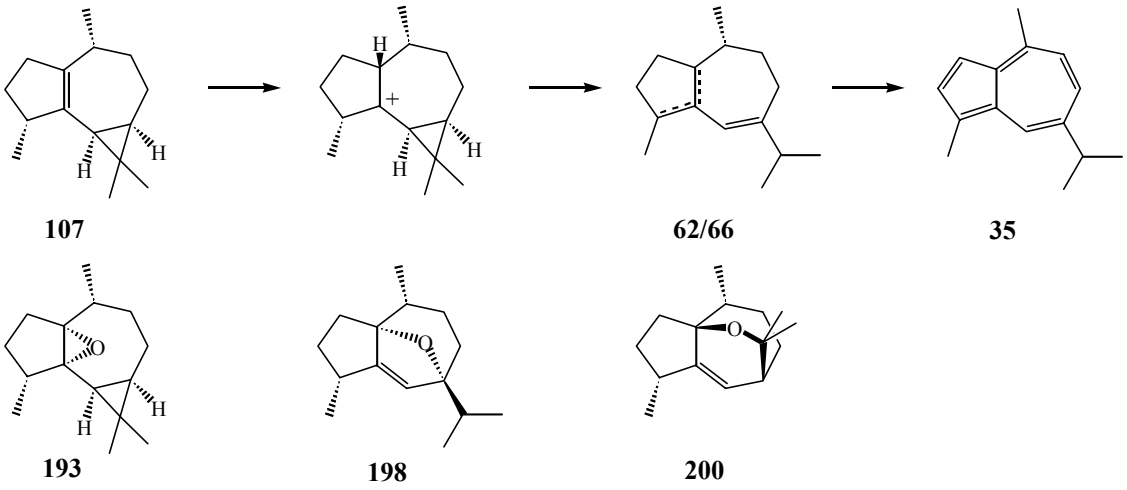
Scheme 1



In Chapter 3 the investigations on the synthesis of compounds with a guaiane skeleton from isoledene (**107**) are described. Isoledene, a double bond isomer of aromadendrene, can be obtained easily upon treatment of aromadendrene (**1**) with K/Al_2O_3. When isoledene is treated under acidic conditions, a rearrangement to the guaiane dienes **62** and **66** occurs. This clean rearrangement of isoledene to compounds with a guaiane skeleton is in sharp contrast to the acid-induced reactions of aromadendrene (**1**) and ledene (**100**), which give complex product mixtures. The reason for the much more selective reaction of isoledene (**107**) under acidic conditions is the initial formation of a relatively stable cyclopropylcarbinyl cation (Scheme 2). This cation can rearrange further to more stable carbocations with formation of the guaiane dienes **62** and **66** as the final result. A similar cyclopropylcarbinyl cation can be formed from isoledene epoxide **193** upon treatment with (Lewis) acid. Depending

on the reaction conditions, this cation can rearrange further to the compounds **198** or **200**.

Scheme 2



107 **62/66** **35**

193 **198** **200**

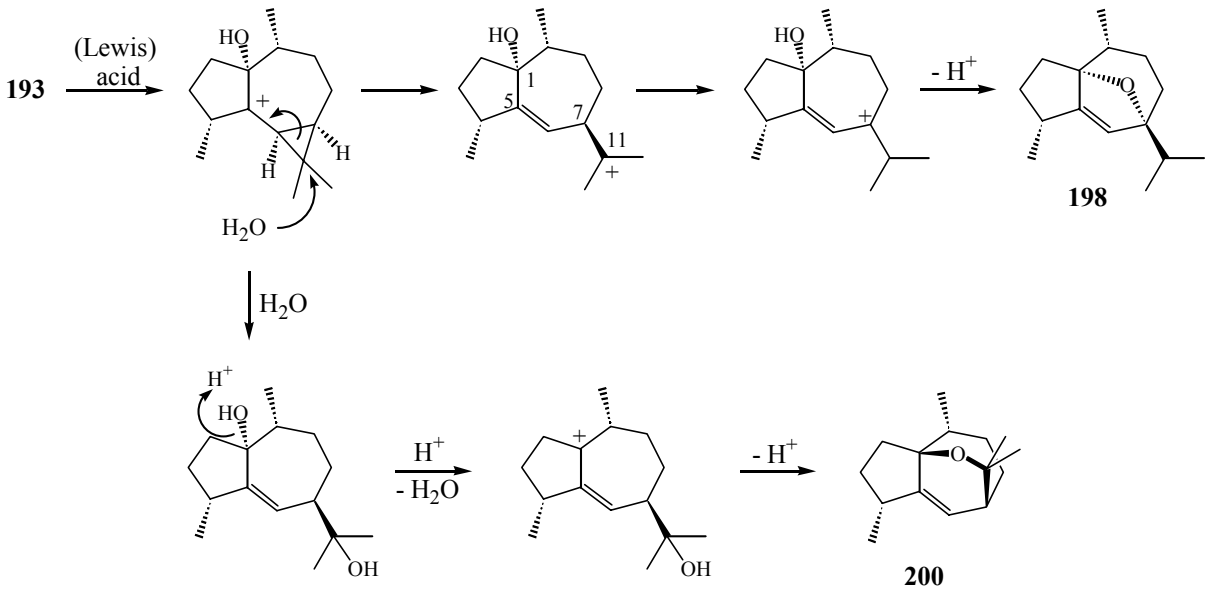
The synthesis of the blue colorant guaiazulene (**35**) was achieved in 22% isolated yield over two steps from isoledene, which is an improvement of the existing methods for the dehydrogenation of sesquiterpenes with sulfur. Whether this method is suitable for the use in an industrial process is questionable, because next to the desired product, a number of byproducts are formed through which purification will be difficult.

Synthesis of compounds with the patchoulane skeleton from isoledene could be interesting for the synthesis of patchoulenol, a natural fragrance compound. However, attempts to obtain the patchoulane skeleton by photochemical or radical rearrangement of isoledene all failed. The synthesis of the patchoulane-like compound **200**, which contains an extra oxygen in its skeleton, has been shown to be possible from isoledene epoxide (**193**) upon treatment with TsOH in acetone (Scheme 3). This compound, however, was not suitable for use in fragrances. Another rearrangement of isoledene epoxide **193** led to the formation of compound **198** possessing the guaiane skeleton with an ether bridge between C1 and C7 (Scheme 3).

These different rearrangements of compound **193** can be explained by the absence or presence of water during the reaction. When **193** was treated with Lewis acid in the absence of water, an intermediate carbocation was formed with an α-hydroxyl group at the bridgehead carbon atom (C1) and a cationic center at C11 on the β-isopropyl group. The opposite orientation of the hydroxyl group at C1 and the isopropyl group prevents formation of an ether bridge. After rearrangement to the more stable allylic cation, trapping of this cation by the oxygen function at C1 is possible, and compound **198** is formed with the ether bridge located at the α-side of the molecule. In the presence of water, as was the case in the reaction of **193** with TsOH in wet acetone, another rearrangement takes place. In this reaction a carbocation

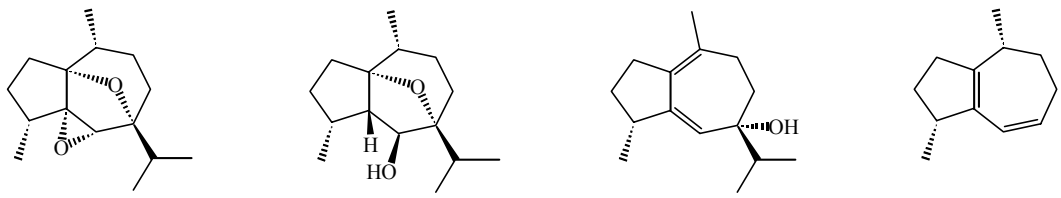
is formed with the positive charge at C1 and a hydroxyl group at C11. Trapping of the carbocationic center by the hydroxyl group now leads to the formation of compound **200** with a β-ether bridge.

Scheme 3



The chemistry of compound **198** has been investigated and epoxidation of **198** led to the formation of the α-epoxide **202**, possessing a highly strained trans-fused 5,5-ring system. The formation of the β-epoxide of **198** with a cis-fused 5,5-ring system would energetically be more favorable, but apparently the β-side of the double bond in **198** is too sterically hindered to allow approach of *m*CPBA. Treatment of **198** with BH_3 proceeded with attack from the β-side of the double bond and resulted in the formation of compound **205** with a cis-fused 5,5-ring system. Apparently BH_3 is small enough to approach the β-side of the double bond in **198**. Opening of the ether bridge in **198** was achieved with lithium ethylenediamide to give compound **209** in 89% yield. The formation of **209** proceeded smoothly because H10 and the C1 ether bond have an antiperiplanar relationship. Compound **198** and its derivatives were tested for their use as fragrances, but unfortunately they were not suitable as such.

Figure 1



202 **205** **209** **201**

Compound **200** appeared to be less reactive than compound **198**. Hydrogenation of the double bond in **200** did not work and epoxidation took much longer than in case of **198**. Under the influence of acid the ether bridge could be opened, but instead of the expected formation of a guaiane, elimination of acetone occurred leading to compound **201**.

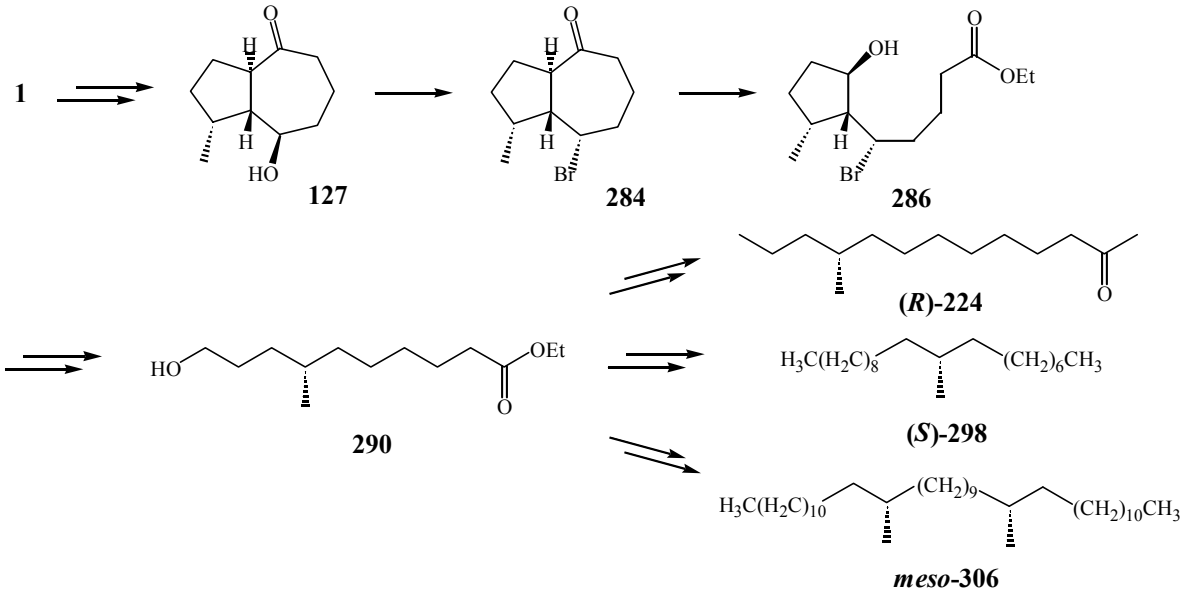
6.3 Pheromones from aromadendrene

The synthesis of methyl-branched linear pheromones from aromadendrene has been described in Chapter 4. The synthesis of products with one chiral center from a sesquiterpene which contains five chiral centers might seem to be a waste of chirality. However, the synthesis of linear products from aromadendrene has not been reported before and when these compounds can become easily accesible from a cheap starting material, they may become suitable for industrial application. Furthermore, the conversion of aromadendrene to alcohol **127** has already been reported and it was shown that this alcohol can be produced in large quantities fairly easily.[3] The synthesis of the linear intermediate **290** from this alchohol consists of only four steps. The key steps in this synthesis are the Baeyer-Villiger reaction of **284**, followed by opening of the lactone ring in a one-pot reaction to give compound **286**, and the Grob fragmentation leading to the linear product. Hydrogenation of this linear product led to the formation of **290**, which was used for the synthesis of the three methyl-branched linear pheromones **(*R*)-224**, **(*S*)-298**, and ***meso*-306**. Because **290** possesses two different functionalities at the end of its chain, either side can be elongated or shortened at will, leading to pheromones with varying chain lengths and position of their chiral center.

The suitability of this intermediate for industrial application, will differ from pheromone to pheromone. For example, the synthesis of pheromone **(*R*)-224** has been reported before by several groups (see Paragraph 4.1), and this pheromone can be synthesized in a more efficient way than the route to **(*R*)-224** decribed in this thesis. On the other hand, the synthetic route to **(*S*)-298** is the only method for the synthesis of this pheromone reported so far.

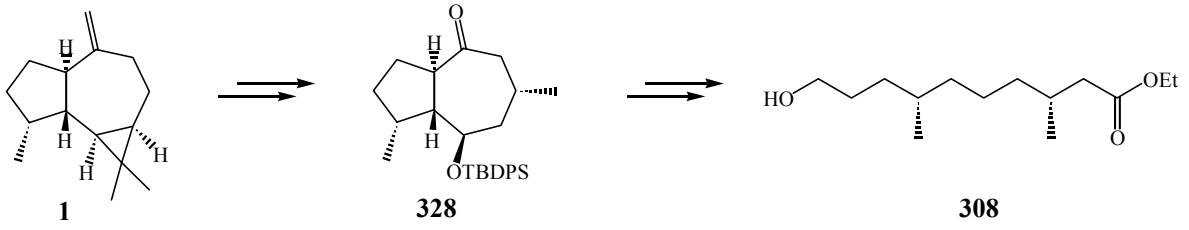
When pheromone traps are used for the monitoring of a particular insect, the amount of insecticides used for the destruction of this insect can be reduced. For the use of pheromones in this way, in this case for instance for the monitoring of *Alabama argillacea*, the amount of pheromone necessary for the use in traps is limited and the use of **(*S*)-298** synthesized as described in this thesis may be cost-effective.

Scheme 4



In Chapter 5 investigations on the synthesis of dimethyl-branched linear pheromones are reported. Via a similar route as described in Chapter 4, the synthesis of the dimethyl-branched linear intermediate (**308**) starting from aromadendrene could be realized. However, several steps in synthesis should be improved, especially the introduction of the double bond in the aromadendrane skeleton. This reaction was difficult to reproduce and gave yields from good to poor. Further research in this field will be necessary.

Scheme 5



6.4 References

(1) Gijsen, H. J. M. , PhD thesis, Wageningen Agricultural University, the Netherlands, 1993.

(2) Bombarda, I.; Gaydou, E. M.; Smadja, J.; Lageot, C.; Faure, R. *J. Agric. Food Chem.* **1996**, *44*, 1840-1846.

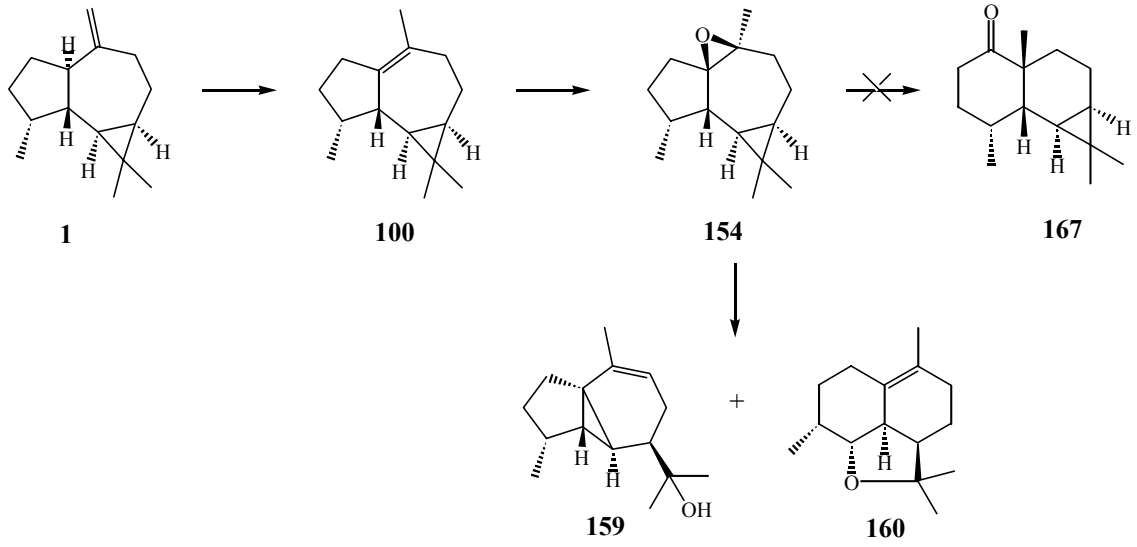
(3) Gijsen, H. J. M.; Kanai, K.; Stork, G. A.; Wijnberg, J. B. P. A.; Orrū, R. V. A.; Seelen, C. G. J. M.; van der Kerk, S. M.; de Groot, A. *Tetrahedron* **1990**, *46*, 7237-7246.

Summary

(+)-Aromadendrene (**1**) is a sesquiterpene present in the distillation tail of the oil of *Eucalyptus globulus*. This distillation tail is commercially available in large quantities at low price and is an interesting starting material for the synthesis of other chiral products. A fair amount of research has already been carried out on aromadendrene (Chapter 1). This research was mainly focussed on transformation and isomerization of the double bond, opening of the cyclopropane ring, oxidations of derivatives of aromadendrene, and rearrangement of the aromadendrene skeleton.

In this thesis, the possibilities to use aromadendrene for other synthetic strategies were explored and the first interest was the development of an economically feasible route toward the fragrance compound **167** (Chapter 2). Ledene epoxide (**154**), easily available from aromadendrene, was selected as the starting material for this route, and rearrangements of this β-epoxide were investigated. The formation of products with the cubebane (**159**) and cadinane skeleton (**160**) indicates that bridgehead carbocations are the prefered intermediates in these rearrangements. From these experiments it was concluded that the synthetic route toward **167** as published by Gijsen is the most efficient route known so far.

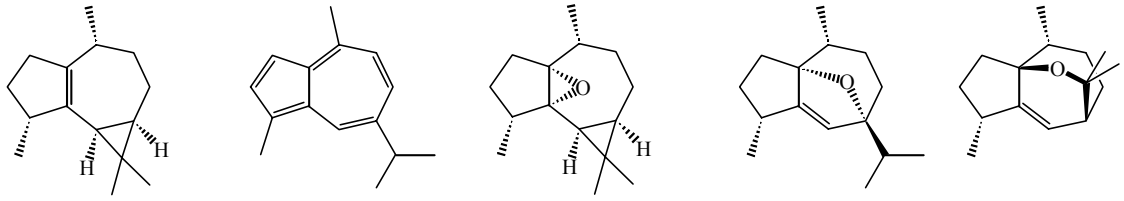
Scheme 1



Synthesis of guaiane-type compounds by opening the cyclopropane ring in aromadendrene has proven to be difficult. In Chapter 3 it was shown that the conversion of isoledene (**107**), a double bond isomer of aromadendrene, to compounds with the guaiane skeleton can be performed in a fairly easy way. The synthesis of the

blue colorant guaiazulene (**35**) in 22% isolated yield over two steps from isoledene is an improvement of the existing methods for the dehydrogenation with sulfur of aromadendrane or guaiane type sesquiterpenes.

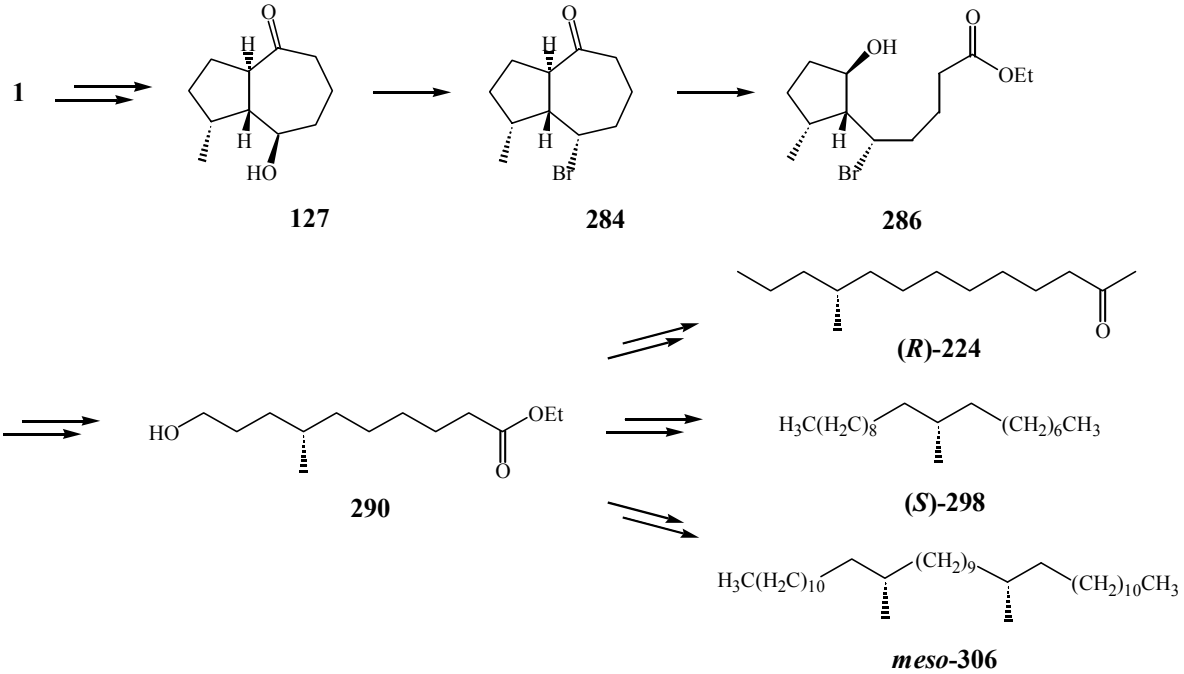
Figure 1



107 **35** **193** **198** **200**

A number of guaianes, for example the cyclic ethers **198** and **200**, were synthesized from isoledene epoxide (**193**). Isoledene epoxide can be converted by (Lewis) acid to a stabilized cyclopropylcarbinyl cation, which undergoes opening of the cyclopropane ring to a guaiane skeleton. When no water is present during the reaction, ether **198** is obtained and the presence of water leads to formation of ether **200**. Several functionalized derivatives of **198** have been prepared. These compounds were tested for their use as fragrances, but unfortunately they were not suitable as such.

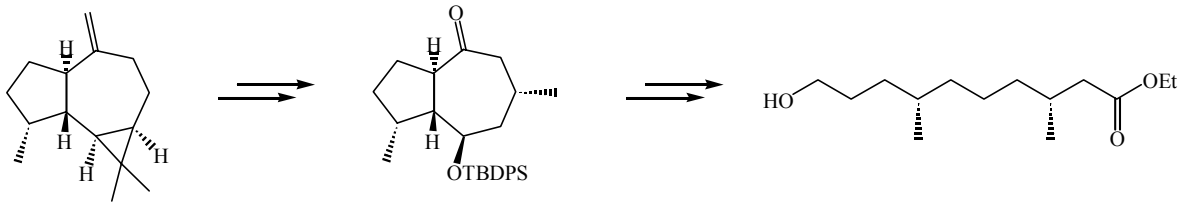
Scheme 2



A relatively new method for crop protection is the use of pheromone traps for monitoring or mass trapping of insects. By using these pheromone traps, the amount of insecticides often can be reduced considerably, which is more environmentally friendly and more selective. In Chapter 4 a method is described for the conversion of aromadendrene to methyl-branched linear pheromones. These pheromones **(*R*)-224**, **(*S*)-298**, and ***meso*-306** were all synthesized from the common linear intermediate **290**. One of the key steps in the synthesis of **290** is the Baeyer-Villiger reaction of bromide **284**, and opening of the lactone ring in a one-pot reaction to give the hydroxy ester **286**. Via a Grob fragmentation using NaOEt in the presence of $NaBH_4$ and catalytic hydrogenation, **286** was then converted to compound **290**.

In Chapter 5 investigations towards the synthesis of dimethyl-branched linear pheromones have been described. It was shown that it is possible to convert aromadendrene to the dimethyl-branched linear intermediate **308**, following a route similar to the one described in Chapter 4.

Scheme 3



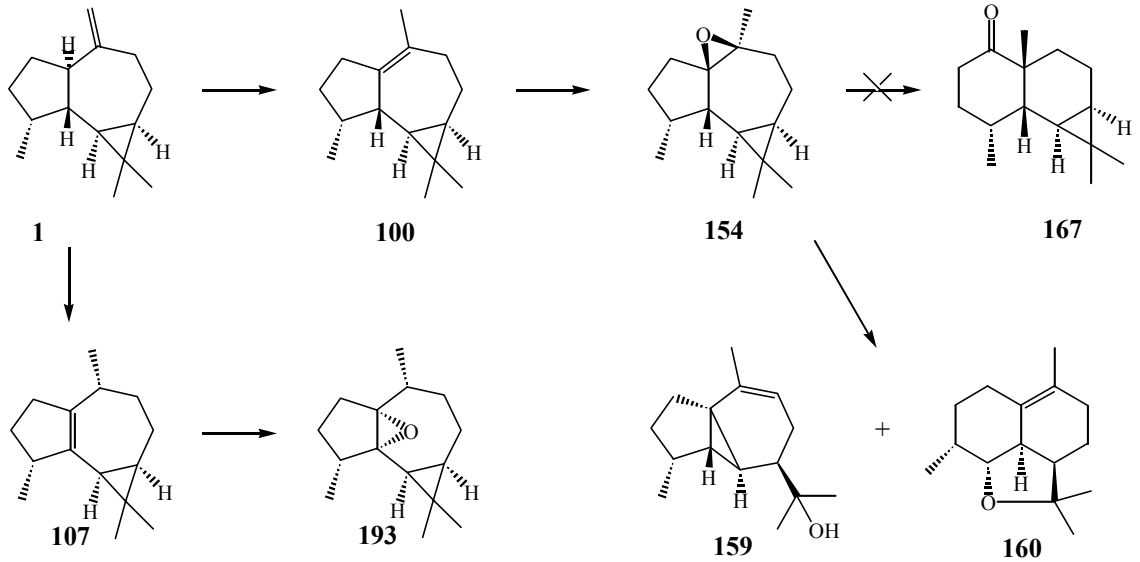
1 **328** **308**

Samenvatting

(+)-Aromadendreen (**1**) is een natuurlijk voorkomend sesquiterpeen, dat voor 55-70% aanwezig is in een van de destillatiefracties van de essentiële olie van *Eucalyptus globulus*. Deze destillatiefractie is commercieel verkrijgbaar in grote hoeveelheden tegen een lage prijs en is daardoor een interessante uitgangsstof voor de synthese van andere chirale producten. In Hoofdstuk 1 is het onderzoek beschreven, wat tot nu toe gedaan is aan aromadendreen en vooral reacties aan de dubbele band, het openen van de cyclopropaanring, de oxidatie van derivaten van aromadendreen en omleggingen van het aromadendraanskelet worden behandeld.

In dit proefschrift is het onderzoek beschreven wat gedaan is aan de ontwikkeling van nieuwe syntheseroutes uitgaande van aromadendreen. Het eerste doel van dit onderzoek was het vinden van economisch haalbare routes naar nieuwe geurstoffen zoals **167**; dit is beschreven in Hoofdstukken 2 en 3. Aromadendreen is hiervoor eerst omgezet naar ledeen (**100**) en isoledeen (**107**) en hun respectievelijke epoxiden **154** en **193**. Omleggingen van het β-epoxide **154** zijn onderzocht, maar leidden tot vorming van producten met het cubebaan- (**159**) en het cadinaanskelet (**160**). Dit geeft aan, dat carbokationen bij voorkeur op het bruggehoofd worden gevormd in deze omleggingen. Uit deze experimenten kan ook geconcludeerd worden, dat de syntheseroute naar **167** zoals die gepubliceerd is door Gijsen de meest effciënte route is tot nu toe.

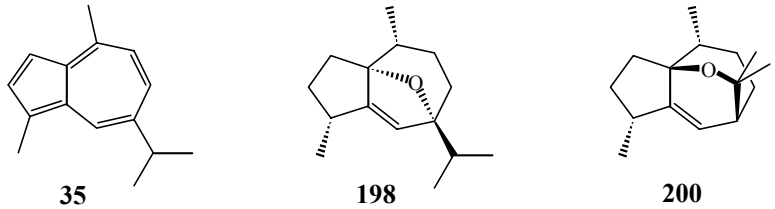
Schema 1



De synthese van verbindingen met een guaiaanskelet uit aromadendreen en ledeen is moeilijk, zoals gebleken is uit eerder onderzoek. In Hoofdstuk 3 werd aangetoond, dat de synthese van deze verbindingen uit isoledeen (**107**) relatief simpel kan worden uitgevoerd. De blauwe kleurstof guaiazuleen (**35**) kon in twee stappen gesynthetiseerd worden uit isoledeen, in een een opbrengst van 22%. Dit is een verbetering ten opzichte van de bestaande methodes voor de dehydrogenering van aromadendraan en guaiaan sesquiterpenen met zwavel.

Een aantal guaianen, zoals bijvoorbeeld de cyclische ethers **198** en **200**, zijn gesynthetiseerd uit isoledeen epoxide (**193**). Isoledeen en het epoxide kunnen gemakkelijk worden omgezet in verbindingen met een guaiaanskelet, omdat ze een gestabiliseerd cyclopropylcarbinyl kation kunnen vormen onder invloed van (Lewis) zuur. In dit kation wordt vervolgens de cyclopropaanring geopend en het guaiaanskelet gevormd. Als er geen water aanwezig is tijdens de reactie, wordt ether **198** gevormd. Wanneer er wel water aanwezig is, leidt de reactie voornamelijk tot de vorming van ether **200**. Verschillende gefunctionaliseerde derivaten van verbinding **198** zijn gesynthetiseerd en deze verbindingen zijn getest op hun gebruik als geurstof, maar bleken daar niet geschikt voor te zijn.

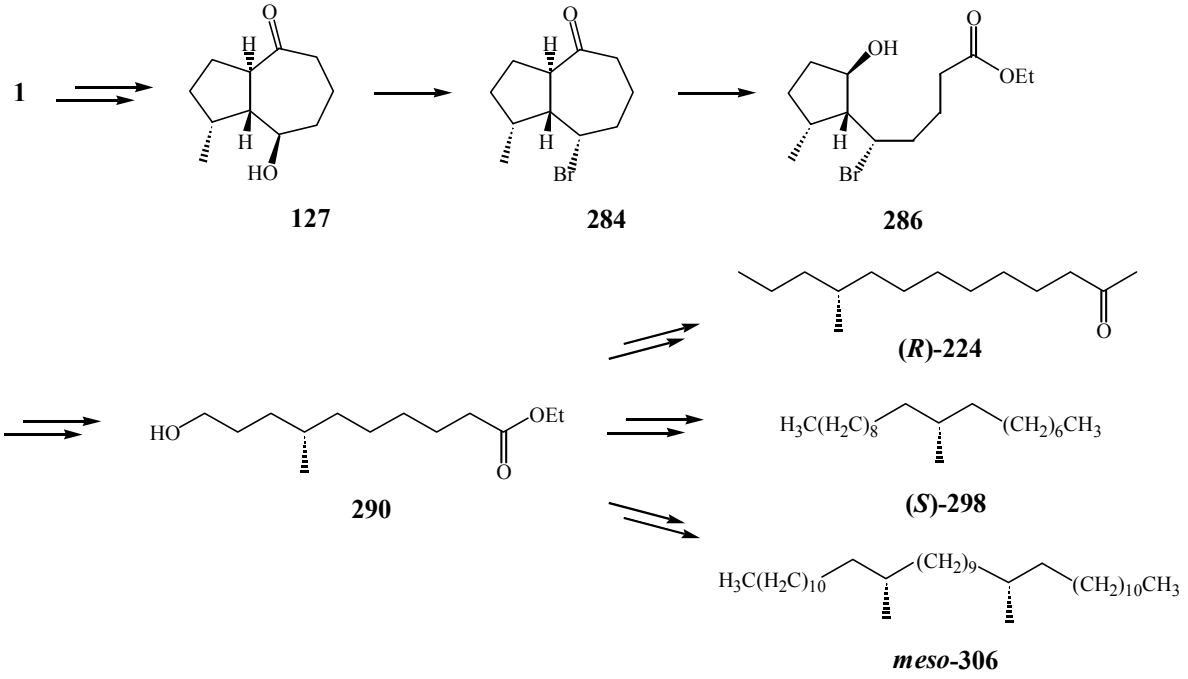
Figuur 1



35 **198** **200**

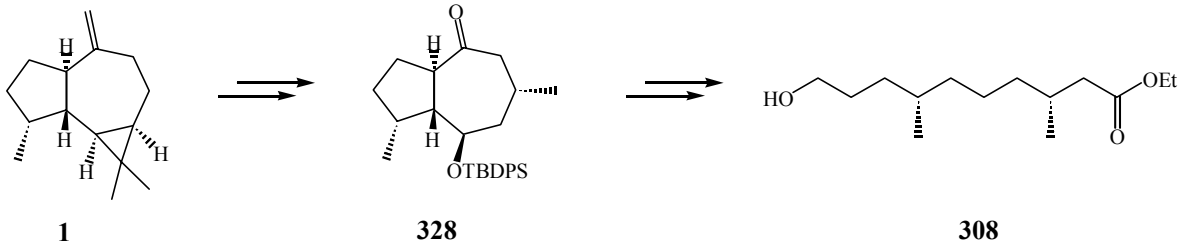
Een relatief nieuwe methode van gewasbescherming is het gebruik van feromoonvallen voor het vaststellen van de aanwezigheid van bepaalde insecten of voor het massaal vangen van deze insecten. Door het gebruik van deze feromoonvallen kan de hoeveelheid insecticiden doorgaans worden gereduceerd, wat milieuvriendelijker is en waardoor verschillende insectensoorten selectiever kunnen worden bestreden. In Hoofdstuk 4 wordt een methode beschreven voor de synthese van drie methyl-vertakte lineaire feromonen **(*R*)-224**, **(*S*)-298** en ***meso*-306**. Deze feromonen zijn gesynthetiseerd uit het gemeenschappelijke lineaire intermediair **290**, dat in een aantal stappen verkregen kan worden uit aromadendreen. Een van de belangrijkste reacties in de syntheseroute naar **290** is de Baeyer-Villiger reactie van bromide **284**, gevolgd door het openen van de lactonring, waarbij hydroxyester **286** wordt verkregen. Verbinding **290** werd uit verbinding **286** gevormd via een Grob fragmentatie met NaOEt in de aanwezigheid van $NaBH_4$, gevolgd door een katalytische hydrogenering.

Schema 2



In Hoofdstuk 5 is een aanzet tot de synthese van dimethyl-vertakte lineaire feromonen beschreven. Het is aangetoond dat aromadendreen omgezet kan worden in een gemethyleerd tussenproduct **328**. Uit dit tussenproduct kan daarna het dimethyl-vertakte lineaire intermediair **308** verkregen worden via een route, die overeenkomt met die welke is beschreven in Hoofdstuk 4.

Schema 3



Curriculum Vitae

Yvonne Maria Augusta Wilhelmina Lamers werd geboren op 8 februari 1975 te Nijmegen en is opgegroeid in het buurtschap Lienden van het stadje Batenburg. Na het behalen van haar diploma aan het Stedelijk Gymnasium Nijmegen, begon ze in september 1992 met de studie Scheikunde aan de Katholieke Universiteit Nijmegen. Tijdens deze studie werd een uitgebreide hoofdvaksstage gevolgd bij de afdeling Organische Chemie, onder begeleiding van dr. J.W. Scheeren en dr. P.H.G. Wiegerinck. Een nevenrichtingsstage werd gevolgd bij de afdeling Toxicologie, onder begeleiding van dr. J. Copius Peereboom en J. Pertijs. Het doctoraal diploma werd behaald in april 1997. Van april 1997 tot en met oktober 2001 werd promotie onderzoek uitgevoerd bij het Laboratorium voor Organische Chemie van Wageningen Universiteit, onder begeleiding van prof. dr. Aede de Groot en dr. Hans Wijnberg. Het resultaat van dit onderzoek staat beschreven in dit proefschrift. Sinds juni 2002 is zij werkzaam als intercedente bij het Intern Uitzendbureau van Kruiswerk West-Veluwe.

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